



## **Drug Safety Research Unit (DSRU)**

**AN OBSERVATIONAL POST-AUTHORIZATION SAFETY SPECIALIST  
COHORT EVENT MONITORING STUDY (SCEM) TO MONITOR THE  
SAFETY AND UTILIZATION OF RIVAROXABAN (XARELTO®) FOR THE  
PREVENTION OF STROKE IN PATIENTS WITH AF, TREATMENT OF  
DVT AND PE, AND THE PREVENTION OF RECURRENT DVT AND PE IN  
THE SECONDARY CARE HOSPITAL SETTING IN ENGLAND AND  
WALES (The ROSE Study)**

### **Final report**

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## PASS information

<b>Title</b>	An Observational Post-Authorization Specialist Cohort Event Monitoring Study (SCEM) to Monitor the Safety and Utilization of Rivaroxaban (Xarelto®) for the Prevention of Stroke in Patients with AF, Treatment of DVT and PE, and the Prevention of Recurrent DVT and PE in the Secondary Care Setting in England and Wales (The ROSE Study)
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<b>Research question and objectives</b>	<p>The primary focus of the study was to quantify the cumulative incidence (risk) of haemorrhage (within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites) occurring in the 12 weeks observation period after treatment initiation for patients treated with rivaroxaban in real life clinical practice in the secondary care hospital setting.</p> <p>The secondary focus was on</p> <p>1) advancing the understanding of the patient population prescribed rivaroxaban in the secondary care hospital setting by exploring differences between rivaroxaban and the alternative anticoagulant therapy (contextual) cohort in the prevalence of non-clinical reasons for prescribing, prognostic and clinical risk</p>

	<p>factors for the selected risks of interest; 2) describing any prescribing and use of rivaroxaban outside terms of marketing authorisation ('off-label'), for example the approved indications and/or populations with special label precaution 3) describing changes of health profile of patients, assessment of adherence, number of indication related episodes and duration, plus any alterations of the treatment programme for either cohorts during the 12 week study observation period; 4) quantifying the risk of a) other major or minor bleeding outcomes not specified in the primary objectives b) all major and minor bleeds within a composite outcome, c) haemorrhage (major bleeding during treatment (individual quantification per organ site) d) thromboembolism (recurrent and incident) and e) any other events reported in the 12 week observation period overall and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting in the UK.</p> <p>The study also included (for rivaroxaban cohort only) several exploratory analyses to 1) where possible, to quantify the incidence of other important identified ,potential and special risks and outcomes of interest (such as severe abnormal liver function) not mentioned in the primary objective, other frequently and rarely reported adverse events during treatment with rivaroxaban and to identify previously unrecognized adverse drug reactions for rivaroxaban; and 2) describe clinical features and management of cases of overdose, major bleeding, venous thromboembolism events indicating failure of anticoagulation and management of homeostasis in patients undergoing surgery (elective or urgent) during observation of the cohort exposed to rivaroxaban.</p>
<b>Country(-ies) of study</b>	England and Wales
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# **1 Abstract**

## **Title**

An Observational Post-Authorization Specialist Cohort Event Monitoring Study (SCEM) to Monitor the Safety and Utilization of Rivaroxaban (Xarelto®) for the Prevention of Stroke in Patients with AF, Treatment of DVT and PE, and the Prevention of Recurrent DVT and PE in the Secondary Care Hospital Setting in England and Wales (The ROSE study).

## **Keywords**

Rivaroxaban – Post-marketing – Safety – SCEM – ROSE

## **Rationale and background**

Rivaroxaban (XARELTO®) is a highly selective direct factor Xa inhibitor which inhibits thrombin formation and the development of thrombi. This post-marketing Specialist Cohort Event Monitoring (SCEM) safety study of rivaroxaban was carried out by the Drug Safety Research Unit (DSRU) as part of the Risk Management Plan (RMP) for rivaroxaban

## **Research question and objectives**

The primary objective was to quantify the cumulative incidence of haemorrhage (within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites) occurring during the study period in patients treated with rivaroxaban.

In addition to the primary objective there were several secondary and exploratory objectives aimed at exploring differences in the prevalence of non-clinical reasons for prescribing and prognostic and clinical risk factors for the risks of interest between rivaroxaban and an alternative anticoagulant therapy (contextual) cohort, as well as describing changes in the health profile of patients over the course of the study and the risk of non-major bleeding events.

## **Study design**

An observational, population-based cohort design of 2 cohorts (rivaroxaban and a contextual cohort (warfarin) with data collection at start of treatment (index date) and 12 weeks post-index date. The contextual and rivaroxaban cohorts had different exclusion criteria and therefore no formal comparative analyses were planned or conducted between the cohorts.



## **Setting**

Secondary care hospital setting in England and Wales.

## **Subjects and study size, including dropouts**

4846 patients provided consent to participate in the study. Baseline and 12 week questionnaires were provided for 4625 (95.4%) patients; of these four (0.1%) were ineligible leaving 4621 patients evaluable patients, of which 55.0% (n=2542) were prescribed rivaroxaban and 44.7% (n=2067) were prescribed warfarin.

## **Variables and data sources**

Patient data were derived from medical charts at index date and 12 weeks post-index date via questionnaires. Information on specialist characteristics was derived from self-reported information, supplemented from publically available professional body registration data.

## **Results**

### ***Site/HCP engagement***

1196 specialists recruited patients to the study, with no obvious differences in the geographic distribution or distribution of socioeconomic status overall between participating and non-participating trusts. For three indicators of adoption of new medicines, the proportions were higher for participating compared to non-participating trusts.

### ***Patient characteristics at baseline***

#### ***Demographics***

Demographic variables were broadly similar between the rivaroxaban and warfarin cohorts.

Although numbers were small, approximately twice as many rivaroxaban patients had a history of previous substance abuse (1.5% vs 0.8% respectively) although the history of previous alcohol misuse was similar between groups (5.1% vs 5.8% respectively).

The primary clinical condition for which anticoagulant therapy was used was similar in both cohorts. AF and DVT/PE indications accounted for the primary indication for 98.3% of patients. Consequently the other subgroups have limited data although information on these groups is presented in the report.

### *Prior and concurrent medical conditions*

Similar baseline history for important risk factors such as haemorrhage and cardiovascular disease was seen in each treatment cohort for the AF indication, although for the DVT/PE indication the baseline history of haemorrhage was higher in the warfarin treatment group.

### *Stroke and bleeding risk prediction score for all indications*

Most of the HAS-BLED indicators were similarly distributed between the two treatment groups for each indication, except that more rivaroxaban patients in the AF group had a history of stroke (30.9% rivaroxaban vs. 20.9% warfarin).

The individual criteria included within the CHA<sub>2</sub>DS<sub>2</sub>-VASc score also had broadly similar distributions within the treatment groups although there appeared to be more patients within the rivaroxaban AF group with a prior history of stroke, TIA or thromboembolism.

### **Outcomes**

Rivaroxaban group: The overall unadjusted cumulative incidence of major bleeding within gastrointestinal, urogenital and intracranial sites was 0.5% (n=13), 0.3% (n=7), and 0.1% (n=3) respectively.

Contextual Warfarin group: The overall unadjusted cumulative incidence of major bleeding within gastrointestinal, urogenital and intracranial sites was 0.2% (n=3), 0.1% (n=2) and 0.1% (n=2) respectively.

For all indications, the unadjusted cumulative risk for clinically relevant non-major bleeds, major bleeds (all) and a composite was also higher in the rivaroxaban group in relation to the contextual warfarin group 4.8% (n=121), 1.3% (n=33), 6.1% (n=154) vs. 3.2% (n=67), 0.7% (n=14), 3.9% (n=81).

### **Deaths**

41 (1.6%) patients in the rivaroxaban cohort and 35 (1.7%) patients in the warfarin cohort died within the 12-week observation period. A further patient in the warfarin treatment group (Mixed indication) died but the date of death was unknown.

Causes of death between the rivaroxaban and warfarin cohorts were similar for patients with AF but differed between the treatment groups for patients with DVT/PE.

Within the DVT/PE group there were three fatal cases of acute renal failure on rivaroxaban and one fatal case of acute renal failure on warfarin.

### **Discussion**

This study shows that rivaroxaban is largely being prescribed in accordance with prescribing recommendations and also national clinical guidelines. The estimates of risk of major bleeding at any specific site in the AF and DVT/PE rivaroxaban user populations are currently consistent with those estimated from clinical trial data and are low (<1%). An increase in the unadjusted risk of major bleeding was observed for rivaroxaban in relation to the warfarin contextual cohort; a possible explanation is the baseline differences between both cohorts. No adjusted analyses were carried out in the scope of this study.

### **Conclusion**

This study was not designed as a comparative study. The risk of gastrointestinal, urogenital or intracranial bleedings were low and in line with previous knowledge based on RCTs as well as observational studies. Rivaroxaban was in most cases used according to the label and national guidelines. This study is part of a broader literature in the safety of rivaroxaban and any conclusions on safety should be put into context with results from other post marketing studies for the product.

### **Marketing Authorisation Holder(s)**

Bayer AG, 51368, Leverkusen, Germany

### **Names and affiliations of Principal Investigators**

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## 2 List of Abbreviations

Abbreviation	Term
AC	Advisory Committee
ACS	Acute Coronary Syndrome
ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
AICC	Akaike Information Criterion correction
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
ASA	Acetylsalicylic acid
AST	Aspartate Aminotransferase
BMA	British Medical Association
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CCG	Clinical Commissioning Group
CHADS2	Congestive heart failure, Hypertension, Age $\geq 75$ years, Diabetes mellitus, and prior Stroke or transient ischemic attack
CHA2DS2-VASc	Congestive heart failure, Hypertension, Age $\geq 75$ years, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism, Vascular disease, Age 65-74 years, Sex category
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
CLRN	Local Clinical Research Networks
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
Cr	Creatinine
CRNM	Clinically Relevant Non Major Bleeds
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
CYP3A4	Cytochrome P450 3A4
d.f	Degrees of Freedom
DSRU	Drug Safety Research Unit
DVT	Deep Vein Thrombosis
ESC	European Society of Cardiology
EU	European Union
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GP	General Practitioner
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly
Hb	Haemoglobin
HCP	Healthcare Professional

<b>Abbreviation</b>	<b>Term</b>
HIV	Human Immunodeficiency Virus
ID	Incidence Density
IMD	Index of Multiple deprivation
INR	International Normalized Ratio
IR	Incidence Rate
ISTH	International Society on Thrombosis and Haemostasis
IQR	Interquartile Range
LFT	Liver Function Test
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Myocardial Infarction
MLM	Multi-Level Modelling
MOR	Median Odds Ratios
M-PEM	Modified Prescription-Event Monitoring
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR CRN	National Institute for Health Research Clinical Research Network
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratios
OTC	Over-The-Counter
PASS	Post-authorisation safety study
PCI	Percutaneous Coronary Intervention
PCV	Proportional Change in the Variance
PE	Pulmonary Embolism
PGD	Patient Group Directives
P-gp	Permeability glycoprotein 1
PH	Proportional Hazards
PSC	Project Steering Committee
PT	Prothrombin Time
RCT	Randomised Controlled Trial
RAIDAR	Rare and Iatrogenic Adverse Reactions
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SCEM	Specialist Cohort Event Monitoring
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SSRI	Selective Serotonin Reuptake Inhibitor
TA	Technology Appraisal
TIA	Transient Ischaemic Attack
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VKA	Vitamin K Antagonist
VTE	Venous thromboembolism

### 3 Investigators

<b><i>Investigator</i></b>	<b><i>Appointed person(s)</i></b>
Principal investigator	Professor Saad Shakir, Drug Safety Research Unit
Co-investigator	Dr Deborah Layton, Drug Safety Research Unit
Co-investigator	Dr Miranda Davies, Drug Safety Research Unit

### 4 Other responsible parties

<b>Responsible party</b>	<b>Appointed person(s)</b>
Marketing Authorisation holder contact	Montse Soriano-Gabarro Head of Global Epidemiology Bayer Pharma AG 13342 Berlin Germany

#### **ROSE Study Advisory Committee:**

An independent Advisory Committee (AC) was established to assist with governance of the study. The AC includes investigators as well experts in cardiology, haematology and pharmacy.

The role of the AC was to:

- provide a peer review forum for the study
- facilitate the smooth running of the project
- provide awareness of the study amongst fellow healthcare professionals
- provide scientific and technical advice when needed
- ensure adequate recruitment of patients and monitor the progress of the study through collection of data (assess specialist prescribers/cohort accrual rates, monitor and assess dropout rates)
- provide advice on and discuss any queries and issues related to the study, for example sample size calculation, prescriber and patient recruitment and questionnaires.

#### **Clinical Research Network:**

The ROSE study was adopted by the National Institute for Health Research Clinical Research Network (NIHR CRN). The CRN offers research support to researchers conducting studies within the NHS. The CRN comprises of 15 Local Clinical Research Networks (CLRN) covering England. Each CLRN delivers research across 30 clinical specialties. The ROSE study has been adopted by the Haematology, Cardiovascular, Stroke and Injuries and Emergencies Speciality groups. These

speciality groups bring together communities of clinical practice to provide national networks of research expertise. They are made up of research-interested clinicians and practitioners at both national and local levels whose role is to ensure that the studies included in their national portfolio of research receive the right support to ensure they are delivered successfully in the NHS.

## 5 Milestones

<b>MILESTONE</b>	<b>PLANNED DATE</b>	<b>ACTUAL DATE</b>	<b>COMMENTS</b>
Start of data collection	May 2013	September 2013	
End of data collection	May 2016	January 2017	Dates moved according to new start of data collection and to allow for complete follow up of events of interest.
Interim report 1	April 2015	August 2015	Dates moved according to new start of data collection
Final report of study results	January 2017	June 2017	Dates moved according to new start of data collection

## 6 Rationale and background

The aim of this study was to actively monitor the short term (up to 12 weeks) safety profile and drug utilisation of rivaroxaban as prescribed to patients for medical conditions ('medical patients' i.e. not those requiring venous thromboembolism (VTE) prophylaxis with elective surgery) requiring anticoagulation by specialist Healthcare Professionals (HCPs) in the secondary care hospital setting in England and Wales. Specifically, this study was focused on the indications of prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure (CHF), hypertension, age  $\geq$  75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE.

Rivaroxaban, a highly selective direct factor Xa inhibitor which inhibits thrombin formation and the development of thrombi, was approved by the European Commission on 30 September 2008 for the prevention of (VTE) in adult patients undergoing elective hip or knee replacements (1). On 09 December 2011, the European Commission approved the use of Xarelto in the indications prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as CHF, hypertension, age  $\geq$  75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and treatment of DVT and prevention of recurrent DVT and PE. A further variation of marketing authorisation for the treatment of PE, under the label 'Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults' was approved on 20 November 2012. Approval in the European Union (EU) was granted on 22 May 2013 for rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. A Risk Management Plan (RMP) has been developed for rivaroxaban by the Marketing Authorisation Holder (MAH). This plan includes tools designed to monitor the important risks (including class effects and off-label use) (2).

Rivaroxaban is a highly selective direct factor Xa inhibitor with high oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated. It is formulated as a film-coated tablet containing 2.5 milligram (mg), 10mg, 15mg or 20mg of active ingredient for oral administration. The absolute bioavailability of rivaroxaban is high (80% - 100%) for the 10 mg dose, with peak plasma levels attained between 2-4 hours (1)

## **6.1 Safety Profile and Undesirable Effects**

The clinical trial safety profile data for rivaroxaban for prevention of VTE in patients undergoing elective hip or knee replacement is based on the RECORD trials (3-6). For the indications of treatment of DVT and prevention of recurrent DVT and PE in adults, treatment of PE and prevention of recurrent DVT and PE in adults and prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors, additional clinical trials have been performed (7-11). The role of rivaroxaban for the treatment of VTE was investigated in three large randomised trials in the EINSTEIN programme: the EINSTEIN-DVT study was planned to probe the role



of rivaroxaban as a standalone drug for the treatment of acute DVT; the EINSTEIN-Extension study was designed to evaluate extended anticoagulation treatment with rivaroxaban in patients who have been treated for acute VTE; and the EINSTEIN-PE study evaluated the role of rivaroxaban for the treatment of acute PE. The ROCKET-AF trial was designed as double-blind, double dummy trial comparing rivaroxaban with warfarin for the prevention of stroke and thromboembolic events in people with non-valvular AF at risk of future thromboembolic events. As of 15-Sep-2016 more than 130,000 subjects have been enrolled in interventional clinical trials (completed and ongoing Phase I, Phase II, Phase III and Phase IV) including more than 71,000 subjects treated with rivaroxaban. (2). Additional information from larger numbers outside the clinical trial setting, in conditions of routine clinical practice, may be helpful to further monitor possible adverse events in users of rivaroxaban. A Risk Management Plan has been developed for rivaroxaban by the MAH. This plan includes tools designed to monitor the important risks (including class effects and off-label use). The current safety specification (important risks, potential risks, missing information) is based on the Xarelto EU RMP version 9.1 (2).

## **6.2 Considerations in initiating anticoagulation treatment, stroke and bleeding risk**

CHA2DS2-VASc score: The CHADS2 classification scheme is a clinical prediction rule (an acronym for Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus, and prior Stroke or transient ischemic attack) that estimates the risk of stroke in patients with non-rheumatic AF (12, 13). Its use is advocated by the National Institute for Health and Clinical Excellence (NICE) to determine whether or not antithrombotic therapy should be initiated based on patient-specific stroke risk (14). The classification scheme assigns a score (0 to 6; one point each for Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus and two points for prior Stroke or transient ischemic attack) based on the number of risk factors an individual patient has; a high CHADS2 score corresponds to a greater risk of stroke such that a score of 2 and above indicated the need for oral anticoagulation therapy, while a low CHADS2 score corresponds to a lower risk of stroke, whereby other risk modifiers should be considered.

To complement the CHADS2 score, by the inclusion of additional 'stroke risk modifier' risk factors, the CHA2DS2-VASc score has been proposed (12, 13, 15). These additional non-major stroke risk factors include age 65-74, female gender and vascular disease. In the CHA2DS2-VASc score, 'age 75 and above' also has extra weight, with

2 points. The CHADS-VASc risk factors have been well validated in assessing the risk of thromboembolism associated with AF. Considering the similarities of AF and VTE, it has been postulated that these factors may have a role in risk assessment of VTE (16). The review suggested that of the CHA2DS2-VASc risk factors, five appear to be associated with the occurrence of VTE; these include age, CHF, diabetes, stroke and peripheral vascular disease.

HAS-BLED: In clinical practice, bleeding risk assessment should be performed prior to initiation of oral anticoagulation therapy. A validated bleeding risk score which is included within the European Society of Cardiology (ESC) Guideline for management of AF patients is the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio (INR), Elderly, Drugs/alcohol concomitantly) bleeding risk schema, whereby a score of  $\geq 3$  indicates "high risk" and some caution and regular review of the patient is needed. Note that knowledge of INR control is needed to assess the 'labile INR' criterion; otherwise for a non-warfarin patient, this scores zero. The HAS-BLED score enables a risk estimate of major bleeds in patients with AF on vitamin K-antagonists (VKA) treatment, but has not been validated for patients with VTE. A recent study aimed to analyse whether the HAS-BLED score accurately identifies patients at high risk of major bleeds during VKA treatment for acute VTE (17). This study found that patients with acute VTE and a HAS-BLED score of three points or higher are at high risk of major bleeding events during anticoagulant treatment.

Both these scores have therefore been validated in cohorts of patients with AF, but may have some applicability to patients with VTE. Therefore in this study scores have been calculated across all indication groups.

### **6.3 Background to anticoagulant prescribing in the UK**

In the UK, anticoagulant initiation and ongoing prescribing to patients for medical conditions such as non-valvular AF or prevention/treatment of DVT and PE takes place in a range of secondary care settings, including in-patient, outpatient (hospital based and led by a medical consultant or a nurse specialist) and out-patient (community clinic based usually led by a nurse specialist). Many National Health Service (NHS) trusts in the UK have Patient Group Directives (PGD) (18). Under a PGD, patients are treated according to a set protocol, and treatment under these PGDs may be initiated by either a medical prescriber or a prescribing nurse specialist. Ongoing prescribing may then be continued by the patient's general practitioner (GP), although with warfarin there

is the requirement for regular, and initially frequent, INR review and dose management so these patients often remain under the care of outpatient services.

When the process of initiating and managing the prescription of anticoagulants to a patient is considered there is a clear hierarchy of data with patients under the care of initiating prescribers who are part of NHS trusts. Given this hierarchy of data, a multi-level modelling analysis was conducted as part of the analysis of the data from this study to identify the main factors leading to a prescription of rivaroxaban compared to warfarin. The methods used for this analysis are presented in more detail in section 9.9.2.1 and the results in section 10.6.2.

## **7 Research question and objectives**

### **7.1 Overall aim**

The overall aim of this study was to monitor the short-term (12 weeks) use and safety profile of rivaroxaban prescribed to new-user adult patients (i.e. rivaroxaban naïve who may or may not be antithrombotic therapy naïve) for the prevention of stroke and systemic embolism in adult patients with non-valvular AF, the treatment of DVT, PE, and the prevention of recurrent DVT and PE in adult patients, requiring anticoagulation under normal conditions of use in the secondary care hospital setting. In addition since it is desirable to put these observations into context and characterise a population treated with existing anticoagulant treatment to allow the variation in determinants of treatment choices to be examined in relation to risk, a similar number of evaluable patients receiving alternative anticoagulant therapy (warfarin) were monitored in order to inform on the adoption of rivaroxaban into clinical practice (final cohort split was 55% rivaroxaban, 45% warfarin). The details of the contextual cohort are provided in section 9.3.2.

### **7.2 Specific objectives**

#### ***7.2.1 The primary objective***

The primary objective was to provide timely information on:

(i) Estimation of the cumulative incidence (separately) of the following important identified risk for rivaroxaban users which is:

Haemorrhage within gastrointestinal and urogenital organ sites (which meet the criteria for a major bleed) and all intracranial sites (Table 1).

### **7.2.2 Secondary objectives**

These are given below:

(i) Prescriber and cohort accrual and the type of prescriber responsible for and the setting of initiation of treatment with either rivaroxaban or alternative anticoagulant therapy;

(ii) Prevalence of non-clinical reasons for prescribing, prognostic health factors and clinical risk factors for haemorrhage as reported in medical charts for patients undergoing anticoagulation with either rivaroxaban or alternative anticoagulant therapy in the secondary care hospital setting and the treatment programme they received to advance the understanding of the patient population prescribed rivaroxaban in actual clinical practice in the secondary care hospital setting;

(iii) Changes of health profile of patients, assessment of adherence, plus any alterations of the treatment programme during the 12 week observation period, as recorded in medical charts;

(iv) To quantify the cumulative incidence of:

(a) (separately) haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites for contextual anticoagulant therapy cohort;

(b) all major bleeding specified in primary objective for both rivaroxaban and contextual anticoagulant therapy cohort (as composite);

(c) (separately) haemorrhage (major bleeding according to Table 1) within critical organ sites other than specified in primary objective for both rivaroxaban and contextual anticoagulant therapy cohort ;

(d) all major and clinically relevant non-major bleeds (as a composite outcome);

(e) thromboembolic complications (incident and recurrent);

(f) other<sup>1</sup> events including special outcomes of interest (severe hepatic failure and abnormal LFTs above 3x ULN) as recorded in medical charts during the 12 week observation period and, if number of reports are sufficient, in patient subgroups of special interest, including:

- reported indications

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<sup>1</sup> Other than major and clinically relevant non major bleeding outcomes, or thromboembolic complications (recurrent or incident)

- elderly ( $\geq 65$  years)<sup>2</sup>, contraindicated or special groups (e.g. pregnant and breastfeeding women, patients with concurrent significant renal or hepatic impairment; patients with known VTE and/or haemorrhagic risk factors e.g. congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, active ulcerative gastrointestinal disease) and off-label groups (patients with other medical conditions);
- concomitant use of medications that are contraindicated or to be used with caution (e.g. CYP3A4 inducers/inhibitors, P-gp inhibitors, anticoagulants, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, hormone and oral contraception therapy and platelet aggregation inhibitors).

### **7.2.3 Exploratory objectives (for rivaroxaban only)**

The specific objectives that follow are all exploratory:

(i) Where possible, to quantify the incidence of other important identified and potential risks (not mentioned in objective 7.2.1), other frequently and rarely reported adverse events as recorded in the medical charts and to identify previously unrecognised Adverse Drug Reactions;

(ii) To describe clinical features and management of cases of overdose, major bleeding (according to pre-specified definition (Table 1), VTE events indicating failure of anticoagulation and management of homeostasis during surgery as recorded within the medical charts in the first 12 weeks after treatment initiation in the cohort exposed to rivaroxaban.

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<sup>2</sup> Children and adolescents aged less than 18 years of age will be excluded from the SCEM study as paediatric prescribing in secondary care usually takes place under different specialists. Since this is important missing information, data on this special population will be captured within the complementary M-PEM, if reported.

**Table 1. Haemorrhage outcomes (19)**

<b>A major<sup>†</sup> bleeding event will be defined using ISTH criteria (20) as clinically overt bleeding that is associated with:</b>				
<ul style="list-style-type: none"> <li>• A fall in haemoglobin of 2 g/dL or more, or</li> <li>• A transfusion of 2 or more units of packed red blood cells or whole blood, or</li> <li>• A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or</li> <li>• A fatal outcome</li> </ul>				
<b>A clinically-relevant non-major bleeding event is defined as an overt bleeding event not meeting the criteria for a major bleeding event, but associated with medical intervention<sup>3</sup>, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.</b>				
<b>Examples of non-major clinically relevant bleeding events are:</b>				
<ul style="list-style-type: none"> <li>• Epistaxis if it lasts for more than 5 minutes, if it is repetitive (i.e., 2 or more episodes of true bleeding, i.e., no spots on a handkerchief, within 24 hours), or leads to an intervention (packing, electrocautery, etc.)</li> <li>• Gingival bleeding if it occurs spontaneously (i.e. unrelated to tooth brushing or eating), or if it lasts for more than 5 minutes</li> <li>• Haematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract</li> <li>• Macroscopic gastrointestinal haemorrhage: at least 1 episode of melena or haematemesis, if clinically apparent</li> <li>• Rectal blood loss, if more than a few spots</li> <li>• Haemoptysis, if more than a few speckles in the sputum, or</li> <li>• Intramuscular hematoma</li> <li>• Subcutaneous hematoma if the size is larger than 25 cm<sup>2</sup> or larger than 100 cm<sup>2</sup> if provoked</li> <li>• Multiple source bleeding events</li> </ul>				

<sup>†</sup> The three organ sites included in the primary objective are gastrointestinal and, urogenital (which meet the criteria for major bleed) and intracranial. Case definition will be confirmed by project steering committee prior to patient recruitment.

## 8 Amendments and updates to the study protocol

Number	Date	Section of study protocol	Amendment or update	Reason
1 (M.A)	28/05/2013	Executive Summary; 1.2; 1.3; 1.3.2; 4.1; 4.2.1; 4.3.1; 4.4.2.2; 4.4.2.3	Document updated to reflect various changes	Document updated to reflect inclusion of Wales, approved licence indications, latest Risk Management Plan referenced, date of Study, start, and information collected on the questionnaires.

<sup>3</sup> Such as: Surgical or endoscopic intervention; decompression of a closed space to stop or control the event; protamine sulphate administration

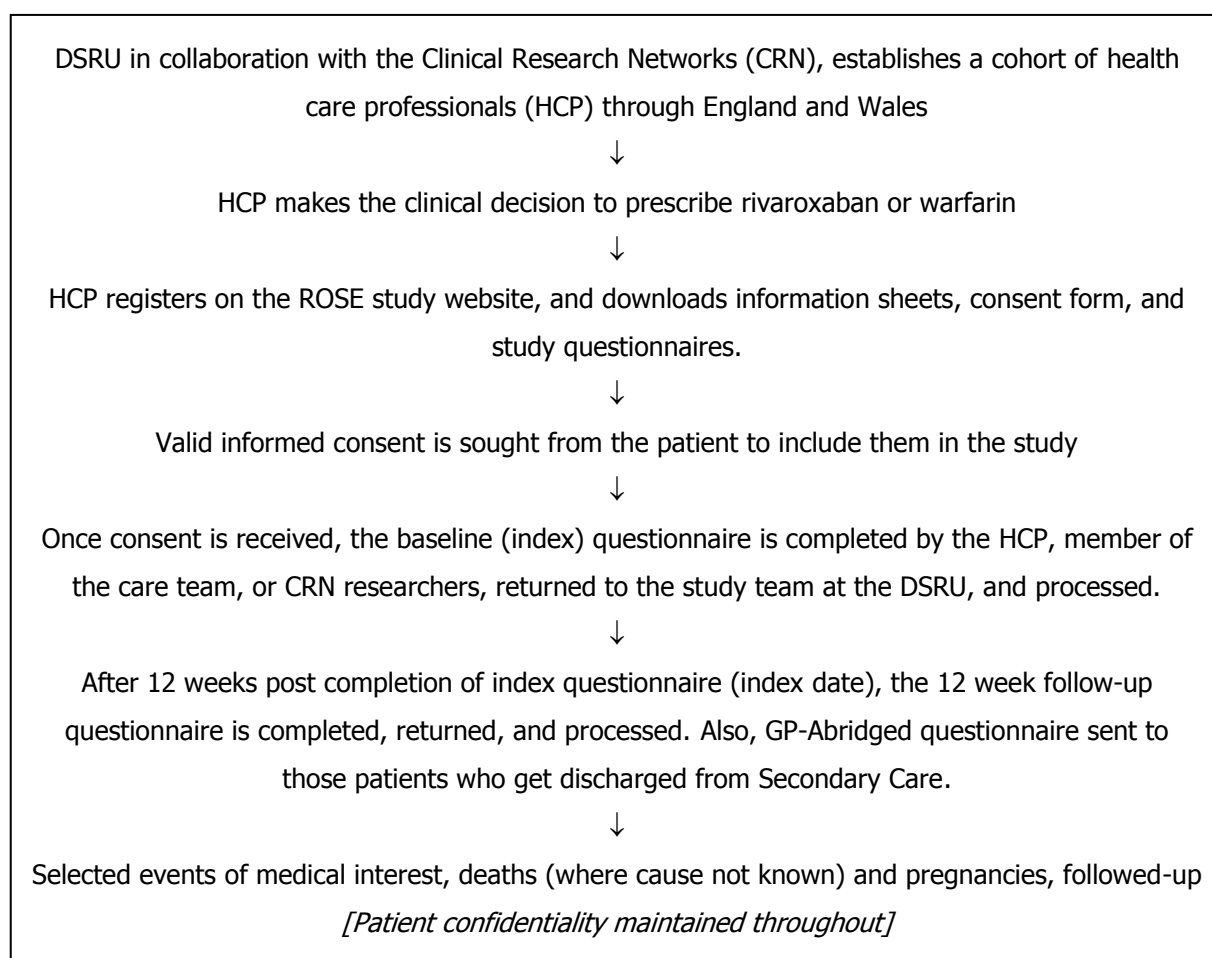
2 (S.A)	17/02/2014 (subsequently withdrawn and re- submitted as S.A 3)	3.0;3.1	Including witness signature where patient cannot sign; Including patients without mental capacity ( <i>including dysphasia/aphasia</i> )	Where a patient is unable to sign the consent form; Exclusion of patients with mental incapacity would mean exclusion of a group of potentially high risk patients
3 (S.A)	02/04/2014	3.0;3.1	Including witness signature where patient cannot sign; Including patients without mental capacity ( <i>excluding dysphasia/aphasia</i> )	Where a patient is unable to sign the consent form; Exclusion of patients with mental incapacity would mean exclusion of a group of potentially high risk patients
4	20/11/2014	Executive Summary	Removal of "any suspected drug reaction" from Event term; Use of medical "charts" rather than notes.	Definition of an event to reflect the fact that we collect information on events, not suspected drug reactions; change to terminology in keeping with the rest of the document.

## 9 Research methods

### 9.1 Study design

This observational cohort study was conducted in England and Wales, using the technique of Specialist Cohort Event Monitoring (SCEM). Figure 1 outlines the methodology used in this study.

**Figure 1. SCEM study process for ROSE**



Further information on study design and strengths of SCEM can be found in Sections 4.1 and 5.1 of the study protocol (Appendix 1).

### ***Primary, secondary and exploratory endpoints***

The primary, secondary and exploratory endpoints are listed in section 7.2 of the study statistical analysis plan (SAP) (Appendix 2).

## **9.2 Setting**

The study was conducted in the secondary care hospital setting in England and Wales in the immediate post-marketing period of rivaroxaban. Cohort accrual started in September 2013 and ended in January 2016. Recruited patients had 12 weeks of follow up.



## **9.3 Subjects**

### **9.3.1 *Specialist prescribers***

Since it is known that medicines management policies determine which trusts will prescribe new treatments, the accessible health care settings for recruitment of rivaroxaban new user patients were those for which recommendations for prescribing rivaroxaban are currently adopted in England and Wales. The framework for obtaining a representative sample of specialists is based on existing research networks, publically available data source and lists provide by NHS trusts. The aim was to recruit a representative sample of specialists practicing within both rural and urban regions.

Specialists were informed that they were participating in a study to monitor the use of rivaroxaban or warfarin. The study was adopted by the UK CRN, which provides support for health-care research within the NHS, including access to researchers and specialist health-care professionals. Specialists were invited to participate in the study prior to and since study start. They were required to register with the study co-ordinating centre (DSRU) in order to receive access to relevant study documentation. This emphasises that participating specialists were instructed to make treatment decisions independent of the study and then to evaluate whether a patient was eligible for inclusion based on entry criteria (see below). Remuneration, in line with the standard British Medical Association (BMA) rate was paid to specialists' trusts to cover time and administration costs incurred (either by themselves or associated staff) assist with consent, complete questionnaires and monitor the patients.

### **9.3.2 *Eligible patients***

Eligible patients were those patients within the accessible treated target population to which specialists have access, presenting for standard course of care as in- or out-patients for treatment of relevant indications during the study period. The identification of the actual study population occurred after the pharmacotherapeutic treatment decision regarding which of the two study oral anticoagulants should be prescribed has been made based on clinical need. Participation within the study was not required as a condition of receiving treatment. This approach was intended to reduce conscious or unconscious selection bias on the part of the specialist as to whom to invite to participate in the study, especially with regard to prognostic factors that may be related to prognosis. The patient was not asked to attend the specialist more than usual or undergo any additional treatment. Patient consent was requested after decision to start treatment had been made.

### **9.3.2.1 Eligible patient inclusion criteria**

Since this was an observational cohort study conducted in a naturalistic setting, open patient entry criteria were applied to maximise external validity. General inclusion criteria were:<sup>4</sup>

- age 18 years or above after study start<sup>5</sup>
- index date on or after study start
- signed, informed consent
- patients treated for DVT or PE
- patients with non-valvular AF (with one or more risk factors) treated for prevention of stroke and systemic embolism

### **9.3.2.2 Eligible patient exclusion criteria**

Patients who did not provide consent were excluded from the study. Patients were automatically withdrawn if the patient or specialist provided informed written or verbal notification that they no longer wished to participate at any stage of the study.

Specific exclusion criterion for the contextual alternative anticoagulant therapy cohort were:

- Any use of univalent direct thrombin inhibitor or direct factor Xa inhibitors.
- Use of anticoagulant therapy or other VKA recorded within one year prior to index date.<sup>6</sup>

These specific exclusion criteria underline that this is not a comparator cohort as the rivaroxaban cohort were more likely to have previous anticoagulant treatments than the contextual cohort

## **9.3.3 Cohort definitions**

### **9.3.3.1 Cohort entry and exit**

#### **9.3.3.1.1 Cohort entry**

Cohort entry for each patient will be defined according to the date of their first rivaroxaban or warfarin dispensation (i.e. 'index date') if all inclusion and exclusion criteria are fulfilled.

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<sup>4</sup> Any cases in which there was ambiguity relating to the indication for treatment were reviewed on a case by case basis, in order to confirm the prescribing indication/indications.

<sup>5</sup> However, a patient under the age of 18 was included in the study if, in what were expected to be rare situations, a doctor decided on the basis of his/her clinical judgement to prescribe rivaroxaban for such person.

<sup>6</sup> patients were excluded if they were being treated with antiplatelet therapy exclusively

#### 9.3.3.1.2 ***Cohort exit***

Cohort exit for each patient will be defined according to the end of study period, or at point of censoring whichever is the earliest.

#### 9.3.3.2 ***'As Assigned' Cohort***

The 'as assigned' cohort is defined as the cohort identified at cohort entry, irrespective of treatment status during the period of observation between cohort entry and cohort exit. For analysis purposes, cohort exit for this period of observation is defined according to the first of the following dates:

- End of 12 week study observation period
- Censoring from loss to follow-up
- Death

This 'as assigned' cohort definition applies to secondary objectives (i)-(iii) and exploratory objective (ii).

#### 9.3.3.3 ***'As Treated' Cohort***

The 'as treated' cohort is defined as the cohort identified at cohort entry, for whom exposure to treatment is defined between cohort entry and cohort exit. A continuous variable representing total period of treatment with either rivaroxaban or warfarin for each patient was derived from primary data on cohort entry and exit dates. Each patient is regarded as being treated between index date and last known date of treatment. The number of days will vary between patients. For event analysis purposes, this period is restricted to where cohort exit is defined according to the first of the following dates:

- End of 12 month study treatment period
- Censoring from loss to follow-up
- Death
- Censoring at first report of stopping treatment (+5 drug half-lives to account for drug elimination)
- First report of outcome of interest

For any analyses using this exposure definition, the cohorts are referred to as the 'as treated' cohorts. This exposure definition applies to the primary objective and secondary objectives (iv: a-f) and exploratory objective (i). The assumption was made that person-time exposure is continuous up to event or censor date. Denominator data is presented according to person-time treated per 1000 weeks.

## 9.4 Variables

For all eligible specialists invited to participate, information on practice type (setting) and practice location was requested from the specialist or member of the care team. Information on HCP sex, speciality and years since registration was derived from publically available professional body registration data sources.

For eligible patients the following information was obtained from the consent form, the questionnaire relating to start of treatment (index date) and the questionnaire at the end of the 12 weeks observation period.

### **Consent questionnaire included:**

- Socioeconomic factors (marital status, employment status, ethnicity, smoking and alcohol use)

### **Index questionnaire included:**

- Demographic characteristics (age, gender)
- Reasons for prescribing (clinical judgement, recommendation from NICE, expert committee guidelines, trust formulary committee guidelines, Patient Group Direction in anticoagulation clinic, potential ease of reversibility of anticoagulant, lifestyle (anticoagulant monitoring needs), patient non-adherence with prior anticoagulant therapy, side-effects with prior anticoagulant therapy)
- Which anticoagulant regimen was prescribed and start date
- Clinical condition requiring anticoagulation (indication)
- Prior oral anticoagulation treatment
- Stroke and Bleeding risk factors
  - CHF/Left Ventricular Dysfunction
  - TIA/Thromboembolism History
  - Previous History of Stroke
  - Vascular Disease History (previous Myocardial Infarction (MI), peripheral arterial disease or aortic plaque)
  - History of Hypertension
  - Current Hypertension
  - Uncontrolled Blood Pressure (BP), >160mmHg systolic at time of treatment initiation
  - Medication Usage Predisposing to Bleeding (Antiplatelet agents, non-steroidal anti-inflammatory drugs (NSAIDs))
  - Labile INR (Unstable/high INRs)

- Diabetes Mellitus
- Alcohol Abuse or Excess
- Renal Disease (Dialysis, transplant, Cr >200 µmol/L)
- Abnormal Liver Function (Cirrhosis, Bilirubin >2x Normal, AST/ALT/ALP >3x Normal)
- Prior Major Bleeding or Predisposition to Bleeding

### **12 week end of observation questionnaire included:**

- Additional information on anticoagulation treatment regimen:
  - details of prior use of oral and parenteral anticoagulant therapy (thienopyridines, aspirin, glycoprotein IIb/IIIa inhibitors, heparins)
  - If switching anticoagulant to either study drug: details of transition plan (both of prior anticoagulant and either study drug); Reasons for switching
  - Treatment regimen during the 12 weeks observation period (number of prescriptions issued (with dates, posology and duration) if known)
  - Dates and reasons for changes in anticoagulant treatment regimen during 12 week observation period<sup>7</sup>
- All relevant laboratory blood parameters during the two-week observation period pre-index date and during 12 week observation where applicable (haemoglobin, platelet count, baseline clotting screen (Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Fibrinogen Derived, D-Dimer) [*NB abnormalities would be reported as events*])
- If study drug stopped: date and reason for stopping, details of transition plan to alternative anticoagulant of study drug stopped; if required, details of reversal of anticoagulation therapy and management of bleeding complication
- Recent (< 4 weeks prior to index date) and concomitant medications (at index or during treatment):
  - not recommended for concomitant use (including azole antimycotics [e.g. ketoconazole] and HIV protease inhibitors)
  - to be used with caution (including fluconazole, strong CYP3A4 inducers, P-gp inhibitors, NSAIDs, acetylsalicylic acid, oral steroids, hormone and oral contraceptive therapy, platelet aggregation inhibitors or other antithrombotic agents)
- Medical history relevant for important potential, identified and special risks of interest (plus dates of first diagnosis/report). **For example:** past history of DVT/PE, MI, percutaneous coronary intervention (PCI), coronary artery bypass

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<sup>7</sup> for rivaroxaban only

graft (CABG), other recent surgery within three months prior to index date, malignancy, pregnancy, family and/or personal history of congestive heart failure, diabetes mellitus, hypercholesterolaemia, peripheral arterial disease, Chronic Obstructive Pulmonary Disease (COPD) etc.)

- Specific information on renal function status at index date and any changes during 12 week observation period
- Specific information on hepatic disorders present at index date (cholestasis and jaundice, hepatic failure and associated disorders, hepatic fibrosis and cirrhosis and hepatic viral infections) and any recent abnormal liver function tests
- Event reports including selected risks of interest (Protocol-Table 4)
- Cause and date of death (if died) in the first 12 weeks after starting treatment
- Reported pregnancies at start or during the first 12 weeks after starting treatment and outcome of birth
- Behaviours prior to and/or starting treatment (e.g. smoking, alcohol/substance misuse); treatment adherence

## **9.5 Data sources and measurement**

SCEM data was derived through secondary use of medical charts as abstracted onto study specific questionnaires by HCPs and GPs in England and Wales.

### **9.5.1 Recruitment**

The first phase of data collection had two parts; Part 1: Recruitment of eligible HCPs; prescriber type and setting of specialist HCPs is collected upon registration with the DSRU. Part 2: Recruitment of consenting patients initiated with the study drug under clinical care of participating specialist HCPs; date of recruitment into the study is recorded. The DSRU allocated a unique study reference number for study audit and data management processes.

### **9.5.2 Exposure/outcome data collection**

The second phase of data collection had multiple parts; Part 1: For all eligible patients invited to participate a consent form was completed. This also included optional questions to be completed by the eligible patient on selected demographic data. Part 2: For each individual consenting patient the specialist HCP was asked to collect "baseline" information (Index questionnaire) recorded within medical charts including date of start of treatment with either rivaroxaban or warfarin (index date). These

forms were then submitted to the DSRU and the data entered into the study database. Part 3: Thereafter, at least 12 weeks post index date, the specialist HCP was prompted to complete an end of observation questionnaire derived from data within existing medical charts. Part 4: For patients for whom the specialist HCP reported that the patient was discharged to primary care for continued treatment during the 12 week observation period, the patient's GP was contacted to complete an abridged end of survey 12 week questionnaire using data recorded within primary care medical charts. All information requested on this specifically designed questionnaire is detailed in Section 9.4 (Variables). Part 5: Reported data were examined for clinical events of medical interest and serious adverse event reports [classified using the International Conference on Harmonisation definitions] (21). Events of interest were followed-up using event-specific questionnaires which captured additional information required to characterise the event and patient (listed in the protocol). This included all Rare and Iatrogenic Adverse reactions (RAIDAR) events compiled by the DSRU (listed in the protocol). The questionnaires were sent to the specialist HCP and all returned initial questionnaires were reviewed by a DSRU Research Fellow.

### **9.5.3 Data coding**

Following review by a Research Fellow, all information on the SCEM and follow up questionnaires was entered into the DSRU database including events collected as free-text which were coded onto the database using the MedDRA dictionary, as detailed in the protocol (Appendix 1).

## **9.6 Bias**

An association between drug and an outcome demonstrated by cohort studies is more likely to be causal than one demonstrated by other epidemiological methods such as the 'case-control', as patients are recruited on the basis of exposure or non-exposure to a drug and their subsequent event course examines temporal relationships (22). Like other observational epidemiological studies, we recognise several potential sources of bias in our study. Possible sources of bias are discussed further in section 11.2 of this report and section 5.2 of the study protocol.

In terms of the study design, the most important consideration is of the influence of selection bias on study findings and the possibility that the cohort was not representative of the target population with relevant indication for treatment. This may be introduced as a result of external influences such as local formulary decisions

and local research governance frameworks which are beyond the ability of the study investigators to control. Selection bias may also be introduced because of the nature of patient recruitment, whereby some participating specialist HCPs are aware of some form of remuneration (regardless of how and when payment is made). However, key points about the study, which were emphasised to specialist HCPs, are that: the specialist HCPs were asked to make the decisions whether to use rivaroxaban or warfarin based on their clinical judgement prior to the decision to include the patient in the study; and that payments do not go to individual specialist HCPs, but the employing trust. It is possible that for patients with acute presentations requiring parenteral anticoagulation the time between initiation of parenteral anticoagulant and start of oral therapy may differ between the rivaroxaban and contextual cohort. These data were not captured. It is also acknowledged that this study was not designed to look at the comparative early safety of rivaroxaban in the context of initiations of other anticoagulants; but explored comparative characteristics of patients prescribed rivaroxaban compared to warfarin to inform on the extent of selection bias.

It is possible that specialist HCPs who participated in the study may have shared some characteristics. This study explored available characteristics of specialist HCPs in terms of decision to prescribe and extent of selection bias of specialist HCP who prescribed either treatment group. However we do not believe that this selection bias affected the types or number of events experienced and reported by a patient after treatment was initiated. Furthermore, since this study was national in scale, it aimed to include a broad range of specialists HCP across many regions. Detailed information on prescriber characteristics is provided in section 10.1.2.

An important point to consider in studies designed to follow patients over time is information bias whereby under- and mis-reporting of outcomes can be possible; specialist HCPs' notes may be incomplete with regard to medical history and non-cardiovascular related outcomes associated with current treatment. The two-phase data capture approach was intended to facilitate compliance with data recording and reporting as well as spreading workload for specialist HCPs.

Failure to control for relevant confounders in the estimates of risk is possible since data abstracted from patient medical charts held by specialist HCPs are likely to be biased towards recording events within secondary care and may not contain data on variables that are relevant to the study that have been reported elsewhere. However, the study asked specialist HCPs to provide data where available and report events affecting all body symptoms. Since patient consent was also obtained to access



primary medical records, the researchers were also able to contact the GP of each individual patient if necessary to obtain data on outcomes relevant to the study during the observation period.

## **9.7 Study size**

For this SCEM study, a minimum sample size of 1700 evaluable patients for rivaroxaban was considered desirable to ensure the minimum of 1005 and 561 patients was achieved for each of the two indications with 12 weeks observation period sufficient to estimate cumulative incidence of specified primary outcomes of interest with desired precision. A similar number of evaluable new user alternative anticoagulant therapy patients was collected for the internal contextual cohort.

Further information on study sample size can be found in the study protocol Section 4.2 (Appendix 1).

## **9.8 Data transformation**

There were very few data transformations performed. Some quantitative continuous variables such as age were grouped for some of the tables, but in those cases means (sd) and medians (Interquartile Range (IQR)) are also provided. Age groupings were introduced using 5 year age bands as this gave sufficient numbers in each band but also allowed for good discrimination between different age groups. Categorical variables such as deprivation scores and disease scores have been generally described without transformation, except in some of the exploratory analyses where a categorisation of the CHADSVASC score and the HAS-BLED score is used to define low, medium and high risk groups.

In order to define meaningful indication groupings, a combined AF group was derived which contained patients with non valvular AF or AF.

Similarly a combined DVT/PE grouping was defined that contained patients treated for any form of DVT or PE.

The two remaining indication groups were "Mixed" which contains patients with both AF and a DVT/PE, and "Other" which contained patients with indications outside of these three groupings. These latter two groups contained very small numbers of patients.

## **9.9 Statistical methods**

A full description of the main statistical summary measures and main statistical methods for this final report is provided in the study SAP (Appendix 2). There are four main analysis sections in the report as follows: (1) Multi level modelling to understand the impact of the patient, prescriber, NHS trust hierarchical relationship (2) Demographic information on the prescriber and patient cohorts (3) Outcome assessments for the primary, secondary and exploratory endpoints (4) Incidence density analysis to investigate the events reported on the follow up forms that were not part of the primary secondary or exploratory analyses. The sections below provide high level information on each of the four main analysis sections in the report.

### ***9.9.1 Main statistical summary measures***

#### ***9.9.1.1 Multi-Level Modelling (MLM) analyses***

The detailed report on the MLM analysis is contained in Appendix 3 and contains detailed methods and results tables. Fixed effects are reported via odds ratios (OR) and their associated 95% confidence intervals (CIs). Random effects are reported as the estimated variance components and their associated standard errors. Median odds ratios (MOR) have also been calculated for the variance components, to allow interpretation on the OR scale and direct comparison with the ORs of the patient, prescriber and trust characteristics.

#### ***9.9.1.2 Demographics***

Demographic information is tabulated and provided as counts and percentages for categorical variables. In some instances, where this is meaningful, medians and IQR are also provided for categorical variables. Continuous variables are provided as means with standard deviations, and as medians with IQR.

#### ***9.9.1.3 Primary, secondary and exploratory outcome assessments***

The primary, secondary and some exploratory outcome measures are presented as unadjusted cumulative incidence, and unadjusted cumulative incidence rates. The primary outcome is also presented as hazard functions. Further detail is provided in section 9.6 of the SAP.

Exploratory analyses for risk factors associated with the event analyses are presented as ORs using a case-noncase design within the rivaroxaban cohort, and stratum-specific estimates of hazard functions according to those selected covariates are also

presented. Where there are zero events in the reference group ORs have not been calculated.

#### **9.9.1.4 Incidence density event analyses**

For this analysis, incidence densities (IDs) will be calculated for each two-week treatment period of the 12 week study period (ID<sub>w1-2</sub>, ID<sub>w3-4</sub> etc) and all twelve weeks combined in the observation period (ID<sub>A</sub>). The calculation is described in the methods section below and in the SAP section 9.6.6.3.

### **9.9.2 Main statistical methods**

The main statistical methods were applied to the overall cohorts and to the indication stratified cohorts.

#### **9.9.2.1 MLM**

A multilevel logistic regression analysis with three levels (namely, patients clustered within prescribers clustered within trusts) was explored to study the influence of patient, prescriber and trust characteristics on rivaroxaban and warfarin use, and also the variance in prescribing at the prescriber and trust levels. The outcome variable is the binary treatment choice of rivaroxaban versus warfarin. Multilevel modelling techniques can be employed to explore sources of variability within healthcare, such as prescribing factors, within hierarchical data (23).

As part of the multi-level modelling univariate analysis was conducted. The univariate analysis provides results on the potential associations observed between individual patient characteristics, for example, and the odds of a prescription of rivaroxaban vs. warfarin. In addition, univariate analyses provide a summary of the characteristics of the study population and provide a complete list of the candidate characteristics considered in the multiple variable modelling. For the prescriber and trust-level variables, the summaries are split by prescribers or trusts where all patients were prescribed warfarin, all rivaroxaban or where a mixture of warfarin/rivaroxaban prescriptions were made. Importantly, the results of the univariate analyses do not account for the effects of the other variables and therefore could be subject to confounding – this would be evident if variables that were significant in the univariate analyses subsequently dropped out of the multiple variable modelling.

The multilevel model allows for grouping of patient prescriptions within prescribers, and prescribers within trusts, by including residuals at the trust, prescriber and patient level. Thus the residual variance is partitioned into a between trust component, a within trust between prescriber component and a within prescriber component (the variance of the patient-level residuals). By including random effects for prescribers and trusts, we are recognising the hierarchical structure of the data, preventing us from underestimating the standard errors of the regression coefficients.

#### **9.9.2.2 Demographics**

Descriptive statistics were applied to the demographic data, no formal statistical testing was conducted.

#### **9.9.2.3 Outcomes analysis for bleeds**

Analyses of events identified within the primary objective were explored using unadjusted overall and indication-specific cumulative incidence (percent of total 'as assigned' cohort exposed at the beginning of the observation period) with 95% Binomial exact CI, of targeted haemorrhage events of interest that occur during the 12-week study period. For these event analyses, right censoring at the end of the 12 weeks observation was undertaken. Where events were reported but with no supporting event date, these patients were excluded from numerator and denominator of this primary analysis. Incidence rates were not calculated where the number of events was less than ten. as per the SAP..

Unadjusted Cox proportional hazards regression was used to conduct the time to event analyses for the various primary outcomes where there were at least ten cases. Estimates of the hazard function were also modelled for the total rivaroxaban cohort and the indication specific cohorts by fitting a parametric Weibull time to event model to see whether there was evidence of changing rate over time. The risk factors for the primary outcome measures were investigated using ORs calculated using a case/non-case design. The secondary and exploratory outcomes for the rivaroxaban and the contextual cohorts were evaluated using incidence and incidence rate.

#### **9.9.2.4 Other event analyses using incidence densities**

Calculating and ranking crude IDs<sup>8</sup> - is one of a number of standard quantitative evaluations used in event monitoring methodology for descriptive analysis of multiple events as part of initial inspection of all event data for general safety surveillance. For purposes of this analysis, IDs were calculated for all other events to be evaluated as part of the secondary objectives:

- Thromboembolic complications
- All other events (excluding bleeding outcomes) including severe hepatic failure and abnormal LFTs above 3x ULN.

The numerator is the first reports of events reported as occurring after the index date and during treatment.<sup>9</sup> Data on events may have been recorded in response to specific tick box questions presented according to MedDRA terminology on the 12 week questionnaire. Events may also have been reported as free text in response to open questions; such data were coded using MedDRA. Where recurrent episodes or occurrences of events have been reported, only the first report (in chronological date order) in an individual patient was used. New onset events were defined as those where there was no evidence on the questionnaire to support a prior medical history of that same event.

The denominator used in calculating IDs was in accordance with the 'as treated' cohort and it is assumed that the pattern of use was continuous. IDs are usually expressed as the number of first reports of an event per 1000 patient-weeks of treatment for the cohort for the period under evaluation. The number of patient-weeks of treatment relates to a specific time period chronologically – e.g., the denominator for weeks 1-2 (D<sub>1-2</sub>) relates to the first 14 days of treatment for individual patients.

The calculations for an ID for a two week period were follows:

$$\text{IDt} = \frac{\text{Number of first reports of an event *during treatment* for period t} \times 1000}{\text{Number of patient-weeks of treatment for period t}}$$

$$\text{Thus, IDt} = \frac{Nt}{Dt} \times 1000$$

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<sup>8</sup> It should be noted such quantification of rate does not only reflect the rate attributable to the drug but also reflects the background rate in the general population and rate attributable to other factors such as age or other disease risk factors

<sup>9</sup> Ideally, the exposure time would be censored at the time of the first event. However, since there are a large number of health outcomes of interest and the censoring would be different for each outcome, the denominator for the crude ID will not initially include censoring at the time of event. If an elevated crude ID is identified in this monitoring analysis, a subsequent analysis with appropriately censored denominator will be performed for that outcome.

where:  $N_t$  = Number of first reports of an event during treatment for period  $t$ ,

and  $D_t$  = Number of patient-days of treatment for period  $t$

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### **9.9.3 Missing values**

#### **9.9.3.1 MLM**

No imputation for missing values was conducted. If there were missing identifiers at the patient, prescriber or trust level then those records were deleted from the MLM analysis. If a variable was missing for more than 10% of patients then this variable was dropped which avoided the need to drop a large number of patients. If less than 10% of patients had missing data on a variable then those patients were excluded from that univariate analysis. This is described in detail in the full MLM report in Appendix 3.

#### **9.9.3.2 Demographics**

All evaluable patients with data for a specific variable were included in the demographic tabulations. Patients with missing demographic data were excluded from the analysis for that specific variable.

#### **9.9.3.3 Time to event analyses**

All evaluable patients in the “as treated” cohort were included. No imputation for missing data on explanatory variables was conducted.

#### **9.9.3.4 Incidence densities**

All evaluable data was included.

### **9.9.4 Sensitivity analyses**

#### **9.9.4.1 MLM**

As a sensitivity analysis, for the overall model (across all indications), the inclusion of interactions, i.e., effect modifications, between each fixed effect retained in the model at each step and patient clinical indication was explored.

A further sensitivity analysis, for each set of modelling results, was also undertaken considering the inclusion of the HAS-BLED and CHADS2VASC disease scores (both as discrete scores and as grouped, categorical variables), rather than just the individual

patient factors that contribute to these scores, which were already included in the main analysis.

#### ***9.9.4.2 Demographics***

No sensitivity analyses were conducted.

#### ***9.9.4.3 Time to event analyses***

Since the primary analysis was run only to include confirmed cases of incident gastrointestinal, or urogenital or all intracranial major bleeding, the analysis was replicated to examine the impact of exclusion of cases with missing event dates on estimate of cumulative incidence.

#### ***9.9.4.4 Incidence densities***

No sensitivity analysis was conducted.

#### ***9.9.5 Amendments to the statistical analysis plan***

Amendments are listed in section 4 of the SAP (Appendix 2).

### **9.10 Quality control**

The DSRU have Quality Assurance procedures for data entry and coding which are fully documented.

For the ROSE data entry system, a software testing phase was undertaken to ensure the system could accurately capture data to the quality standards required. Data entry interfaces have appropriate 'on screen' validation to ensure data is within specified parameters. Validation messages generated are either 'Error' or 'Warning' type messages. Errors are always corrected or the coder cannot exit the system. Warnings are provided if data conflicted or were out of range, allowing the coder to check relevant values and correct if necessary. If the value conflicted or was out of range it would be entered as such and handled accordingly in the analysis stage. For the final study report, double entry was conducted on 100% of questionnaires for each questionnaire type in accordance with the ROSE Protocol.

## 10 Results

### 10.1 Participants

#### 10.1.1 *Site (trust) engagement*

For this study, the desire was to obtain a representative sample of new user patients for rivaroxaban and the contextual cohort across England and Wales. In accordance with secondary objective (i), data on the 87 investigative sites (trusts) participating in this study were collected from the registering site (trust) investigator and supported by publically available relevant National Health Service websites. These data were also collected for 69 non-participating acute trusts and compared with participating trusts to explore representativeness (Table 2). Geographical regions were based on NHS Public Health Centres and Welsh Health Trusts (2017). There was no obvious difference in the geographic distribution of participating and non-participating trusts (see also Figure 2). The area with the highest proportion of participating trusts was in the North West region (n=16, 18.4%) followed closely by the South West (n=15, 17.2%) and London (n=14, 16.1%).

The type of trust was explored since economic factors are known to influence adoption of new medicines by physicians (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4283087/>). In the UK, there are different types of trusts including Foundation trusts (not-for profit public corporations) and Acute trusts (trusts commissioned to provide service by clinical commissioning groups (CCGs)). In this study, two-thirds of participating trusts were Foundation trusts (n=56, 64.4%) and one-third were acute trusts (n=30, 34.5%). The distribution of the types of trusts between participating and non-participating trusts were similar.<sup>10</sup> Another factor that has been identified as independently associated with adoption of new medicines is affiliation to academic institutions. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4283087/>). The proportions of trusts with at least one hospital with Teaching status was also similar between participating and non-participating trust.

Hospital density (number of hospitals per trust), population density (number of population served) and rivaroxaban sales were chosen as indicators of adoption of new medicines. For each of these three indicators, the proportions were higher for participating compared to non-participating trusts<sup>11</sup> and guidelines for use of

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<sup>10</sup> It should be noted that Foundation and acute trusts may be affiliated with more than one trust. For these analysis each trust has been counted only once. Furthermore during the study period some trusts have merged or changed affiliation, therefore these data represent a snapshot of trusts current as of 2017.

<sup>11</sup> Based on NOAC sales <https://www.england.nhs.uk/wp-content/uploads/2014/06/pub-tab-5-med-trust.xlsx>



rivaroxaban were available for all but two participating trusts (n=85, 97.7%). A slightly lower proportion was observed for non-participating trusts (n=63, 91.3%).

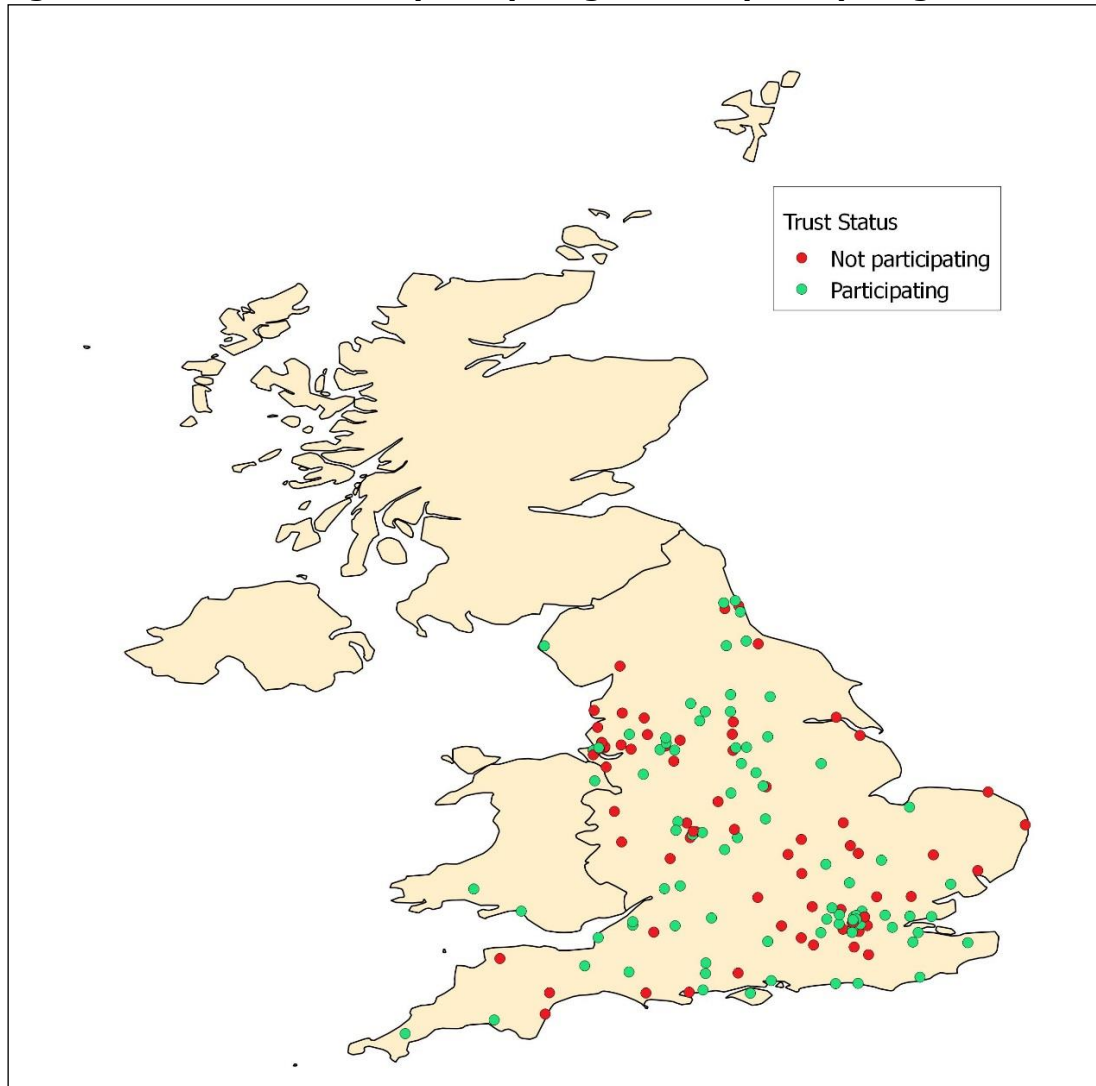
**Table 2. Participating and non-participating trust characteristics**

Characteristics (n %)		Participating trust (N=87)		Non-participating trust (N=69)		p-value	All trusts (N=156)	
		n	%	n	%		n	%
Geographical region <sup>a</sup>								
	East of England	9	10.3	13	18.8	Chi <sup>2</sup> (df7) p=0.257	22	14.1
	London	14	16.1	8	11.6		22	14.1
	North West	16	18.4	20	29.0		36	23.1
	South East	8	9.2	4	5.8		12	7.7
	South West	15	17.2	10	14.5		25	16.0
	Wales	3	3.5	0	0.0		3	1.9
	West Midlands	12	13.8	10	4.5		22	14.1
	Yorkshire and Humber	10	11.5	4	5.8		14	9.0
Trust Type								
	Acute	30	34.5	25	36.2	Chi <sup>2</sup> (df2) p=0.661	55	35.3
	Foundation	56	64.4	44	63.8		100	64.1
	Integrated	1	1.2	0	0.0		1	0.6
	<i>Not specified</i>	-		-			-	
Trust population density (per million)								
	<100001	2	2.3	11	16.2	Ranksum p<0.001	13	8.9
	100001, <200001	3	3.5	16	23.5		19	12.2
	200001, <300001	25	28.7	16	23.5		41	26.5
	300001, <400000	20	23.0	10	14.7		30	19.4
	400001, <500001	10	11.5	8	11.8		18	11.6
	500001, <600000	10	11.5	4	5.9		14	9.0
	600001, <700001	9	10.3	1	1.5		10	6.5
	700001, <800000	2	2.3	2	2.9		4	2.6
	800001, < 900001	5	5.8	0	0.0		5	3.2
	900001 +	1	1.2	0	0.0		1	0.7
	Median (IQR)	358675 (275784, 519947)		260217 (158115.5, 373147.5)			320055 (219054, 468767)	
	<i>Not available</i>	-		1			-	
Socioeconomic status of trust population served (IMD rank decile)								
	1	5	5.8	8	11.6	Ranksum p=0.764	13	8.3
	2	7	8.1	6	8.7		13	8.3
	3	15	17.2	4	5.8		19	12.2
	4	14	16.1	10	14.5		24	15.4
	5	9	10.3	8	11.6		17	10.9
	6	11	12.6	8	11.6		19	12.2
	7	4	4.6	6	8.7		10	6.4
	8	11	12.6	12	17.4		23	14.7
	9	6	6.9	5	7.3		11	7.1
	10	5	5.8	2	2.9		7	4.5
	Median IMD decile (IQR)	5 (3,8)		5 (3,8)			5 (3,8)	
	<i>Not available</i>	-		-			-	

Characteristics (n %)			Participating trust (N=87)		Non-participating trust (N=69)		p-value	All trusts (N=156)	
			n	%	n	%		n	%
Trust hospital density									
	✕ 1-4		36	41.4	45	65.2	Chi² (df4) p=0.005	81	51.9
	5 -9		35	40.2	15	21.7		50	32.1
	10-14		16	18.4	6	8.7		22	14.1
	15-19		0	0.0	2	2.9		2	1.3
	20+		0	0.0	1	1.5		1	0.7
Hospital Type									
Teaching:									
	At least one		37	42.5	25	36.2	Chi² (df1) p=0.425	62	39.7
	None <sup>b</sup>		50	57.5	44	63.8		94	60.3
General:									
	At least one		76	87.4	55	79.7	Chi² (df1) p=0.196	131	84.0
	None <sup>c</sup>		11	12.6	14	20.3		25	16.0
Trust Rivaroxaban Sales (mg purchased per 100,000 hospital days)									
	0		0	0.0	4	6.4		4	2.8
	>0,<5000		6	7.5	6	9.5		12	8.4
	5000, <10000		7	8.8	5	7.9		12	8.4
	10000, <15000		7	8.8	5	7.9		12	8.4
	15000, <20000		5	6.3	7	11.1		12	8.4
	20000, <25000		2	2.5	5	7.9		7	4.9
	25000, <30000		2	2.5	6	9.5		8	5.6
	30000 +		51	63.8	25	39.7		76	53.2
	Median (IQR)		47914.2 (15757.4, 107396.0)		23011.5 (11118.9, 67613.0)		Ranksum p=0.020	35475.7 (12768.5, 87523.7)	
	Not available		7		6				
Trust anticoagulant prescribing guideline publically available									
	Yes		85	97.7	63	91.3	Chi² (df1) p=0.072	148	94.9
	No		2	2.3	6	8.7		8	5.1

<sup>a</sup>: NHS Public Health Centre reported for sites in England <sup>b</sup>: More than one teaching hospital per trust possible, the category of None refers to other hospital types including General hospitals; <sup>c</sup>: more than one general hospital per trust possible, the category of None refers to other hospital types including Teaching hospitals

**Figure 2. Distribution of participating and non-participating trusts**

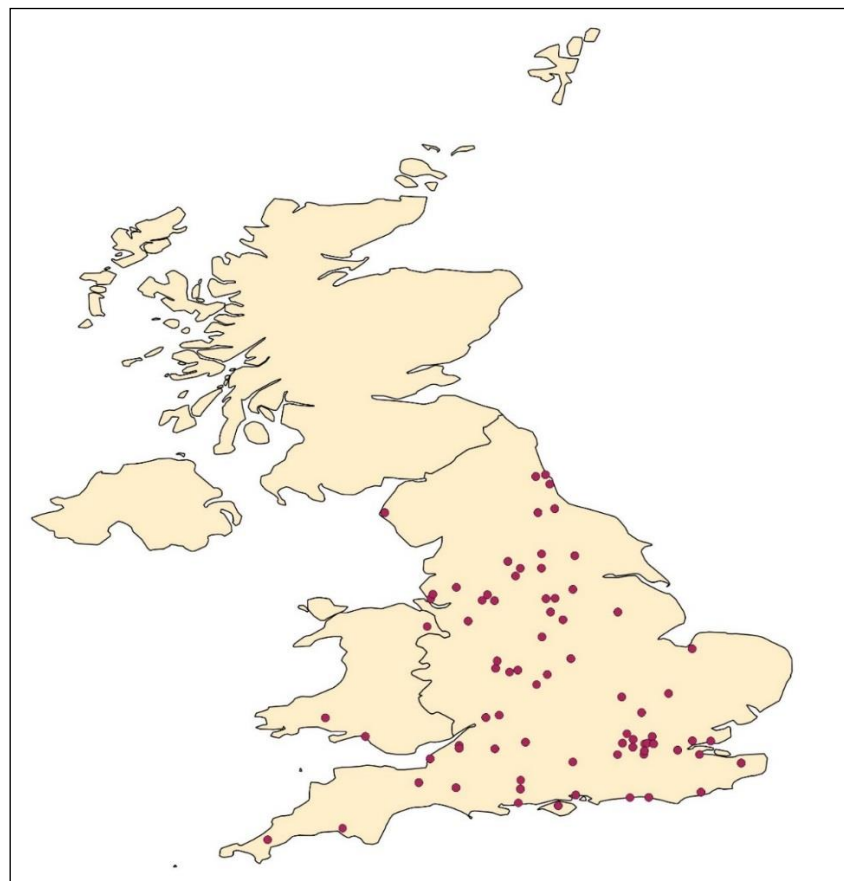


### **10.1.2 HCP Recruitment**

Specialist HCPs responsible for prescribing Rivaroxaban or Warfarin treatment for the licensed indications as outlined in the protocol were systematically identified by the DSRU and invited to participate in the study prior to the study start. Continued invitations were made and participants welcomed throughout the study. Routes of identifying relevant specialist HCPs within these settings included the use of existing clinical research networks and support networks provided by allied healthcare professionals, such as hospital pharmacists.

Data on the HCPs responsible<sup>12</sup> for the patients included in the cohort is presented in Figure 3 and Table 3. Geographical regions were based on NHS Public Health Centres and Welsh Health Trusts (2017). The areas with the highest proportion of participating HCPs were in the North West of England (n=285, 23.8%) and South West of England regions (n=285, 23.8%). Where specified, a higher proportion of participating HCPs were male (57.4%). The majority of HCPs (91.2%) reported "Medical Clinician" as their professional qualification and, of all participating HCPs, the largest single percentage were registered for less than five years although the data are highly skewed (21.6%; median number of years registered (IQR) 17.3 (6.6, 24.9). Where relevant information was provided, the majority of HCPs were in a senior role (60.8%). Where an HCP had reported to be a specialist, the largest proportion had been registered as a specialist for less than five years (36.3%; Median number of years as a specialist (IQR) 7.7 (3.7, 13.5)). The main clinical therapeutic area of participating HCPs was General Medicine (22.1%).

**Figure 3. Distribution of participating HCP practice settings of HCP cohort**



Note: There are multiple prescribers per HCP practice setting.

<sup>12</sup> The recruiter may or may not be the prescribing HCP. However it is assumed that they have permission from the responsible HCP to engage with the eligible patient. For purposes of determining representativeness, the characteristics of the responsible HCP will be explored.

**Table 3. Healthcare professional characteristics**

Characteristics		n (1196)	% where specified
Geographical region <sup>a</sup>			
	East of England	95	7.9
	London	105	8.8
	North West	285	23.8
	South East	113	9.5
	South West	285	23.8
	Wales	60	5.0
	West Midlands	114	9.5
	Yorkshire and Humber	139	11.6
Sex			
	Male	686	57.4
	Female	427	38.4
	<i>Not specified</i>	83	
Professional qualification:			
	Medical Clinician	1088	91.2
	Pharmacist	1	0.1
	Nurse	98	8.2
	<i>Other</i>	6	0.5
Years registered:			
	<5	221	21.6
	5, <10	88	8.6
	10, <15	137	13.4
	15, <20	160	15.6
	20, <25	169	16.5
	25, <30	99	9.7
	30, <35	89	8.7
	35, <40	40	3.9
	40, <45	16	1.6
	45 +	5	0.5
	Median (IQR)	17.3 (6.6, 24.9)	
	<i>Not available</i>	421	
Career level <sup>b</sup> :			
	Senior	596	60.8
	Middle	202	20.6
	Junior	182	18.6
	<i>Not available</i>	216	
Specialist award:			
	Yes	591	49.4
	No	605	50.6
	<i>Not specified</i>	-	
Years as specialist:			% of specialist where specified
	<5	166	36.3
	5, <10	109	23.9
	10, <15	89	19.5
	15, <20	91	19.9
	20+	2	0.4
	Median (IQR)	7.7 ( 3.7, 13.5)	

Characteristics	n (1196)	% where specified
<i>Not available</i>	134	
Clinical therapeutic area:		
Neurology/Stroke	142	13.9
Anticoagulation/Haematology	121	11.8
A&E/Acute Medicine	158	15.4
Cardiology	153	15.0
General Medicine	226	22.1
Other <sup>c</sup>	223	21.8
<i>Not available</i>	173	

<sup>a</sup>: NHS Public Health Centre reported for sites in England <sup>b</sup> assessed on years' experience, and/or name prefix; <sup>c</sup> Other is comprised of care of the Elderly (n=62), Endocrinology(n=18), Gastroenterology (n=26), Respiratory (n=105) and Research (n=12)

### 10.1.3 Patient Recruitment

Table 4 below presents data regarding the patient cohort, by treatment group. Following consent, it was found that some patients were not eligible to be included (Table 5 shows the reasons for ineligibility) and so these patients were excluded from further analyses. The number of patients with index questionnaires returned is shown in Table 4, and following receipt of the index questionnaire, data were reviewed to determine how many patients were considered evaluable, with data that can be analysed. This information is also shown for all 12-week questionnaires returned. The reasons why patients were not eligible for inclusion at 12-weeks are also described within Table 5. The demographic characteristics of those patients excluded were examined in relation to those patients classified as evaluable to assess any potential for selection bias (Table 6).

For this study, evaluable patients are those patients who have provided consent and for whom analysable clinical data has been provided in the data collection questionnaire at baseline and at 12 week (from either the specialist HCP and/or GP).<sup>13</sup> A very small proportion of the contextual cohort included other treatments. For the final report these were excluded from the contextual cohort and a summary of characteristics and events is provided in Appendix 4 of the final report.

From the accessible target population treated by specialists in England and Wales a total of 4846 patients, irrespective of treatment (rivaroxaban, warfarin or other),

<sup>13</sup> This is a protocol deviation. The per protocol statement was: `

*Evaluable patients are those patients who have provided consent and for whom analysable clinical data has been provided in the data collection questionnaires. Evaluable patients for whom the second phase (12 week) survey questionnaire (from BOTH specialist HCP and GP) is returned blank (contain no clinical information) or has not been returned will only be included for analysis of secondary objectives (i) and, (ii). However since important baseline prognostic data is also collected on the 12 week questionnaire, the per-protocol definition is no longer meaningful*

provided consent to participate in the study (Table 4, Figure 4). Thirteen (0.3%) of these patients had initially provided consent but later withdrew their consent to participate in the study. Furthermore, twenty of the consented patients (0.4%) were ineligible following consent. For the remaining 99.3% (n=4813) patients, 99.7% (n=4799) baseline (index) questionnaires were returned, of which 106 were considered ineligible (87 patients identified incorrectly; 13 patients did not start treatment; four had the decision to treat made in primary care; one had index questionnaire incomplete; one had enrolled in another study). Of the remaining 4693 patients, 12-week follow-up questionnaires were returned for 4625 (98.6%) patients, of which four (0.1%) were ineligible (all four patients identified incorrectly). Thus 4621 patients were evaluable, of which 55.0% (n=2542) were prescribed rivaroxaban and 44.7% (n=2067) were prescribed warfarin. A further 12 patients (0.3%) were prescribed other treatments (Appendix 4).

**Table 4. Patient cohort – evaluable patients, by treatment group**

Cohort data	Denominator Source	Rivaroxaban		Warfarin		Other		Total	
		n	%	n	%	n	%	n	%
Number of patients consented	Undefined							4846	-
Number of eligible patients	Number of consented patients							4813	99.3
Number of Index questionnaires returned	Number of eligible patients	2633	-	2,150	-	15	-	4799	99.7
Number of eligible patients at baseline	Number of index questionnaire returned	2592	98.4	2,089	97.2	12	80.0	4693	97.8
Number of 12-week follow-up questionnaires returned	Number of evaluable patients at baseline	2542	98.1	2,071	99.1	12	100.0	4625	98.6
Number of eligible patients at 12-weeks	Number of 12-week follow-up questionnaires returned	2542	100.0	2,067	99.8	12	100.0	4621	99.9
Number of GP-Abridged follow-up questionnaires returned	Number of evaluable patients at 12-week	799	31.4	487	23.6	0	0.0	1286	27.8
Number of evaluable patients at 12-weeks after all questionnaires returned	Number of eligible patients at 12-weeks	2542	100.0	2,067	100.0	12	100.0	4621	100.0

Of the 225 patients who provided consent to participate in the study but were subsequently found to be ineligible for participation, 36.9% (n = 83) had insufficient clinical information provided (HCPs for 68 patients did not return a 12-week questionnaire; HCPs for 13 patients did not return an index or 12-week questionnaire; the HCP for one patient did not return an index questionnaire but did return a 12-week questionnaire and the HCP for one patient returned an incomplete index questionnaire). A further 56.0% (n = 126) of ineligible patients were identified incorrectly, one patient was enrolled in another study and two patients were duplicates of patients already included in the study. Thirteen patients (5.8%) withdrew their consent to participate in the study (Table 5).

**Table 5. Reasons for ineligibility post consent, by treatment group**

Cohort data – reasons for ineligibility	Rivaroxaban N=93		Warfarin N=86		Other N=3		Unknown N=43		Total N=225	
	n	%	n	%	n	%	n	%	n	%
Insufficient clinical information <sup>a</sup>	51	54.8	18	20.9	0	0.0	14	32.6	83	36.9
Patient incorrectly identified <sup>b</sup>	41	44.1	66	76.7	3	100.0	16	37.2	126	56.0
Patient enrolled in other study	1	1.1	0	0.0	0	0.0	0	0.0	1	0.4
Duplicate patient	0	0.0	2	2.3	0	0.0	0	0.0	2	0.9
Consent withdrawn	0	0.0	0	0.0	0	0.0	13	30.2	13	5.8
Total	93	100.0	86	100.0	3	100.0	43	100.0	225	100.0

<sup>a</sup> Complete set of questionnaires not returned or questionnaire incomplete

<sup>b</sup> Relates to exclusion criteria: if age at index date <18 years, or study drug treatment index date <01/09/2013 (study start date), or any use of univalent direct thrombin inhibitor or direct factor Xa inhibitors/anticoagulant therapy or other vitamin K antagonists recorded within one year prior to index date, or any ineligible (labelled) primary diagnosis

Comparison of age at index and gender between excluded (n = 212) and evaluable patients (n = 4621) (Table 6) shows similar proportions between the two groups of cases (gender: excluded 57.4% male, evaluable 54.8% male, OR=1.1; age: most frequently reported age group 70-79 years in both groups, 30.7% of excluded cases, 25.9% of evaluable cases).

**Table 6. Comparison of demographic characteristics of excluded patients with evaluable patients**

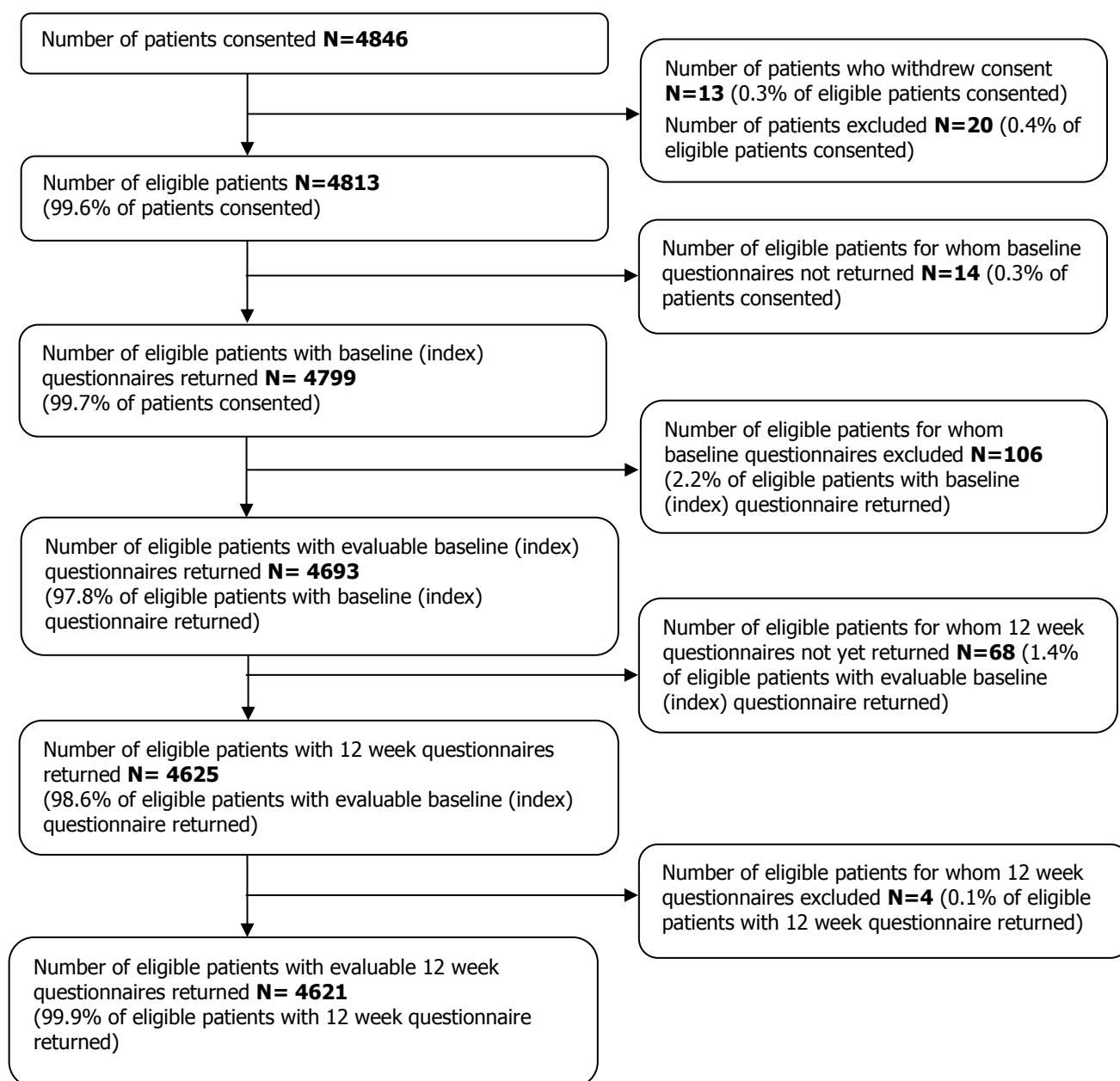
Characteristic (%)		Excluded* Cases N=212		Evaluable cases N=4621		OR (95%CI <sup>a</sup> ) [P-value]
		n	% cases where values reported	n	% non-cases where values reported	
Gender						
	Male	121	57.4	2534	54.8	1.1 (0.8; 1.5) [p=0.47]
	Female	90	42.7	2087	45.2	
	Missing	1	-	0	-	
Age at index (years)						
	<18	2	0.9	0	0.0	1.1 (1.0; 1.2) [p=0.13]
	18-29	5	2.4	132	2.9	
	30-39	9	4.3	220	4.8	
	40-49	17	8.0	424	9.2	
	50-59	20	9.4	611	13.2	
	60-69	41	19.3	1043	22.6	
	70-79	65	30.7	1196	25.9	
	80+	53	25.0	995	21.5	
	Missing	0	-	0	-	

<sup>a</sup> 95%CI calculated using Binomial exact

\* Does not include patients who withdrew consent



**Figure 4. STROBE flowchart of the number of patients recruited over the course of the study**



The accessible study population is that proportion of the target population of interest to whom participating specialist HCPs have access. The identification of the actual study population (which was a subset of the accessible study population) was through (non-probability) systematic sampling. All consecutively identified <sup>14</sup> eligible new user patients treated by a participating specialist HCP who provided consent have been enrolled. Patients were enrolled in the study after the pharmacotherapeutic treatment decision had been made that either rivaroxaban or warfarin treatment is the most appropriate treatment based on clinical need.

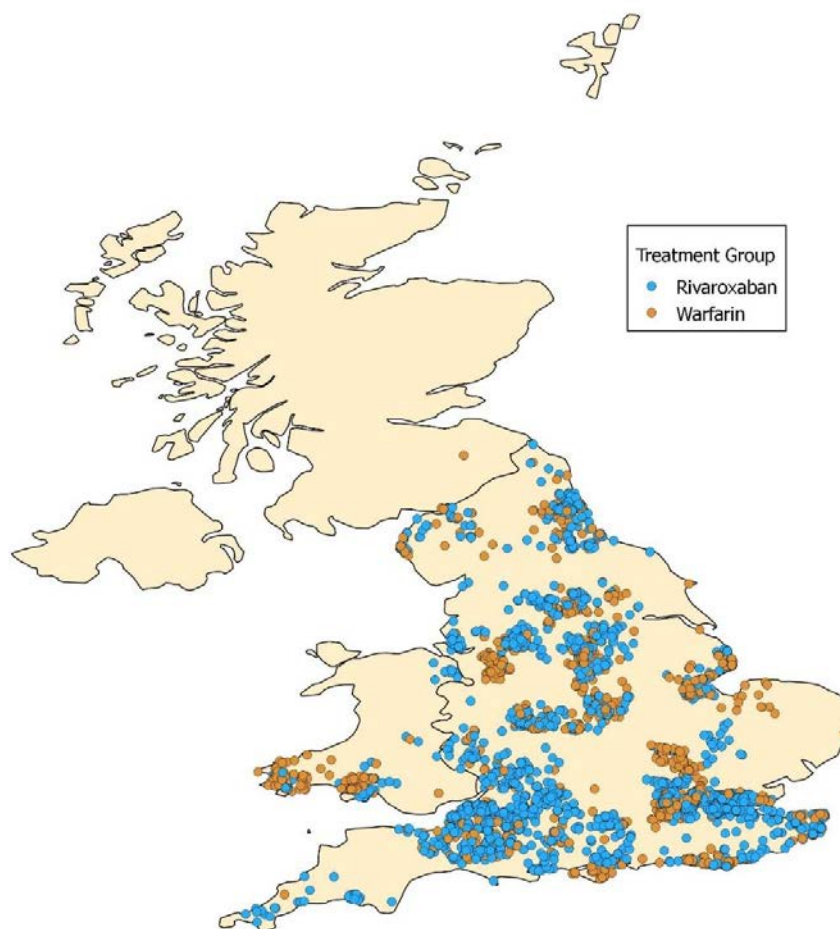
<sup>14</sup> As relevant to the date that the specialist HCP registers to participate in the study

The highest proportion of patient recruited, irrespective of treatment group, came from London and South East (n=1462, 31.7%) however, when broken down into treatment groups, the highest proportion of rivaroxaban patients were recruited from the South West and South Wales (n=879, 34.6%) (Table 7 and Figure 5).

**Table 7. Geographical distribution of recruited patients, by treatment group**

Geographical distribution – region	Rivaroxaban N=2542		Warfarin N=2067		Total N=4609	
	n	%	n	%	n	%
North	507	19.9	537	26.0	1044	22.7
Midlands and North Wales	462	18.2	457	22.1	919	19.9
South West and South Wales	879	34.6	305	14.8	1184	25.7
London and South East	694	27.3	768	37.2	1462	31.7
Total	2542	100.0	2067	100.0	4609	100.0

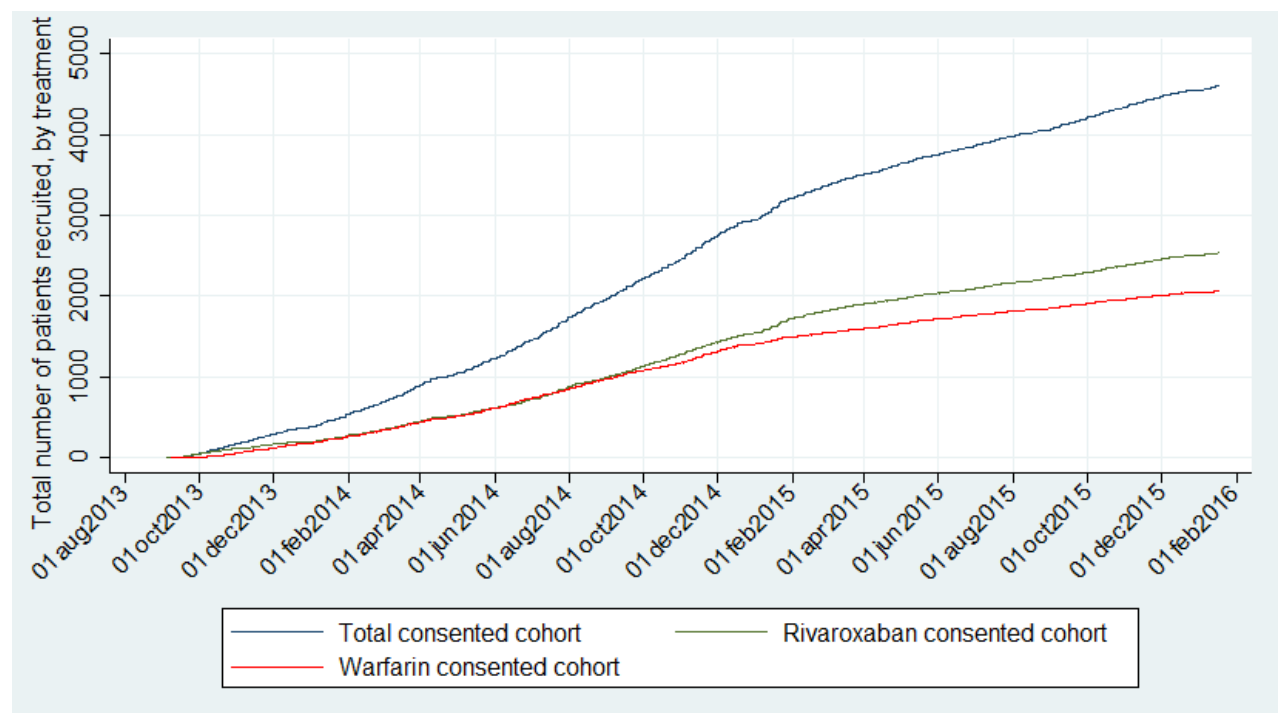
**Figure 5. Distribution of consented patients throughout England and Wales, by exposure group**



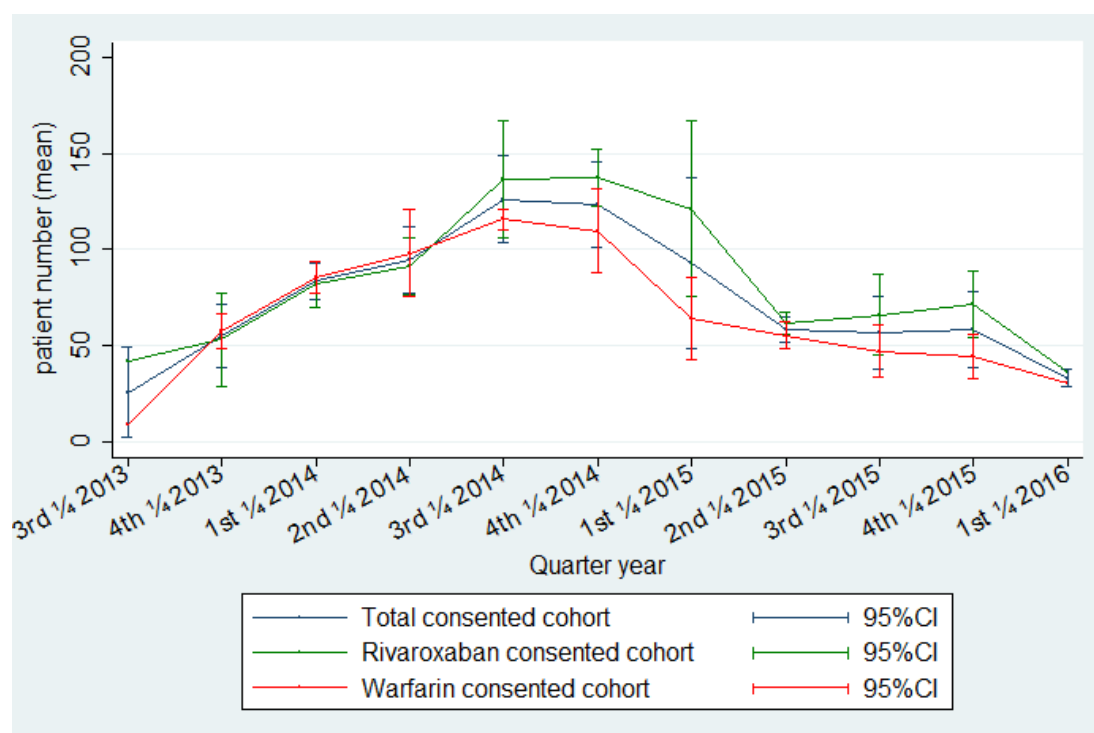
It is of interest to analyse any trend over time of patients identified. Figure 6 shows the number of consented evaluable patients recruited over the course of the study, overall and by treatment group irrespective of indication and shows a relatively steady patient accrual over time, tapering off in 2015.

This is also reflected in Figure 7 which shows a plot of the three month moving average of consented evaluable patients for the whole cohort and by treatment group. Recruitment was initially slow as investigators registered to participate and the required NHS trust approvals were sought. The mean number of patients consented by quarter year appears to decrease in the first quarter of 2015 which coincides with the target number of AF patients being reached and recruitment to the AF arm of the study for both the rivaroxaban and warfarin cohorts being terminated.

**Figure 6. Number of evaluable patients consented over the course of the study, overall, and by treatment group**



**Figure 7. Mean number of evaluable patients consented by quarter year (+95%CI) overall, and by treatment group**



## 10.2 Descriptive data

### 10.2.1 Patient Characteristics at baseline

#### 10.2.1.1 Patient Demographics

Patient demographics by cohort and overall are provided in the tables below. These demographics provide information on the baseline comparability of the rivaroxaban and warfarin cohorts and also help to identify potential biases due to channelling.

Table 8 to Table 10 will be summarised here. Table 8 provides the age and gender composition by treatment group, and it can be seen that these are broadly comparable, both categorically and by summary statistics as described below. The mean age (SD) for the rivaroxaban group was 67.8 years (17.1) for females and 64.6 years (15.4) for males; for the warfarin group the mean age (SD) was 67.1 (17.2) for females and 64.9 (14.5) for males. The median (IQR) age for the rivaroxaban group was 72 (58, 81) for females and 67 (54, 76) for males. For warfarin it was 71 (59, 80) for females and 67 (56, 76) for males.

Table 9 provides the estimated socioeconomic status of patients based on their postcode, and as for the previous demographics, these are broadly similar between the cohorts, although there was more missing information in the warfarin group than

the rivaroxaban group (10.2% vs 5.7%). The marital status of patients given in Table 10 also is broadly comparable between cohorts, although as for Table 9, there was more missing information on warfarin patients than rivaroxaban patients (16.0% vs 9.0%).

This pattern is repeated in Table 11 and Table 12 (self-reported employment status and self-reported ethnicity respectively) where the information as provided is broadly comparable between the cohorts but in each case there is more missing information on warfarin patients than on rivaroxaban patients.

**Table 8. Age/Sex counts and percentages stratified by treatment group**

Age Group	Rivaroxaban N=2542						Warfarin N=2067					
	Female		Male		Total		Female		Male		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
18-24	21	0.8	11	0.4	32	1.3	17	0.8	7	0.3	24	1.2
25-29	17	0.7	21	0.8	38	1.5	22	1.1	16	0.8	38	1.8
30-34	27	1.1	29	1.1	56	2.2	28	1.4	22	1.1	50	2.4
35-39	26	1.0	42	1.7	68	2.7	19	0.9	27	1.3	46	2.2
40-44	43	1.7	51	2.0	94	3.7	42	2.0	37	1.8	79	3.8
45-49	73	2.9	83	3.3	156	6.1	29	1.4	66	3.2	95	4.6
50-54	52	2.1	113	4.5	165	6.5	43	2.1	80	3.9	123	5.9
55-59	52	2.1	119	4.7	171	6.7	38	1.8	111	5.4	149	7.2
60-64	83	3.3	143	5.6	226	8.9	85	4.1	124	6.0	209	10.1
65-69	115	4.5	190	7.5	305	12.0	109	5.3	188	9.1	297	14.4
70-74	151	5.9	176	6.9	327	12.9	114	5.5	152	7.4	266	12.8
75-79	165	6.5	171	6.7	336	13.2	126	6.1	138	6.7	264	12.8
80-84	165	6.5	117	4.6	281	11.1	121	5.9	114	5.5	236	11.4
85-89	120	4.7	89	3.5	209	8.2	95	4.6	48	2.3	143	7.0
90-94	38	1.5	23	0.9	61	2.4	29	1.4	17	0.8	46	2.3
>94	12	0.5	4	0.2	16	0.6	1	0.1	2	0.1	3	0.1
Total	1160	45.6	1382	54.4	2542	100.0	918	44.4	1149	55.6	2067	100.0

**Table 9. Patient socioeconomic status stratified by treatment group**

Index of Deprivation Decile	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
1	176	6.9	141	6.8
2	188	7.4	174	8.4
3	246	9.7	225	10.9
4	246	9.7	190	9.2
5	278	10.9	203	9.8
6	249	9.8	206	10.0
7	261	10.3	176	8.5
8	257	10.1	184	8.9
9	279	11.0	182	8.8
10	217	8.5	176	8.5
Missing	145	5.7	210	10.2
Total	2542	100.0	2067	100.0

**Table 10. Patient self-reported marital status stratified by treatment group**

Self-reported marital status	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
Married	1276	50.2	982	47.5
Co-habiting	122	4.8	100	4.8
Single	260	10.2	190	9.2
Separated	34	1.3	31	1.5
Divorced	171	6.7	117	5.7
Widowed	446	17.6	312	15.1
Other	5	0.2	5	0.2
Unknown	228	9.0	330	16.0
Total	2542	100.0	2067	100.0

**Table 11. Patient self-reported employment status stratified by treatment group**

Self-reported employment status	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
Full time	473	18.6	328	15.9
Part time	115	4.5	93	4.5
Unemployed	151	5.9	89	4.3
Student	10	0.4	4	0.2
House husband/wife	82	3.2	57	2.8
Self-employed	94	3.7	79	3.8
Other	5	0.2	3	0.2
Unknown	322	12.7	420	20.3
Retired	1249	49.1	968	46.8
Volunteer	3	0.1	5	0.2
Carer	9	0.4	2	0.1
Pensioner	3	0.1	4	0.2
Disabled	14	0.6	8	0.4
Sick leave	11	0.4	4	0.2
Mother/maternity leave	1	0.0	3	0.2
Total	2542	100.0	2067	100.0

**Table 12. Patient self-reported ethnic background stratified by treatment group**

Self-reported ethnicity	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
White	2231	87.8	1667	80.7
African	13	0.5	9	0.4
Caribbean	29	1.1	10	0.5
Black - Other	4	0.2	6	0.3
Indian	20	0.8	35	1.7
Pakistani	11	0.4	7	0.3
Bangladeshi	2	0.1	1	0.1
Chinese	5	0.2	4	0.2
Other	18	0.7	9	0.4
Unknown	209	8.2	319	15.4
Total	2542	100.0	2067	100.0

Table 13 and Table 14 examine the “risk seeking” behaviours that may be associated with different prescribing behaviours. In this study the risk seeking behaviours are defined as those that may indicate a history of prior substance or alcohol misuse, as these may introduce confounding if there are specific reasons why one of the treatments would be used preferentially in an at risk group.

Table 13 shows that approximately twice as many rivaroxaban patients as warfarin patients had a history of prior substance misuse, although the numbers are small. The proportion with a history of prior alcohol misuse was similar between groups.

Table 14 provides further information on these patients and the type of substance misuse in the patient history. Whilst the proportion of patients with a history of alcohol misuse alone is similar, the proportion with a history of alcohol + substance misuse, or substance abuse alone is much higher for rivaroxaban patients compared to warfarin patients (11.3 % vs 5.4% respectively).

Of the substances misused, IV drug use was referenced for 29% of the 150 rivaroxaban patients with a history of substance or alcohol misuse compared with 17.7% of the 129 warfarin patients with such a history. Heroin, methadone, cannabis and opiates were the top four listed substances.

**Table 13. Specialist recorded history of risk seeking behaviours stratified by treatment group**

Risk seeking behaviour	Rivaroxaban		Warfarin	
	n	% of total (2542)	n	% of total (2067)
Prior alcohol misuse	129	5.1	119	5.8
Prior substance misuse	38	1.5	17	0.8

**Table 14 Most frequently reported substances misused**

Substance misused	Rivaroxaban		Warfarin	
	n	% of patients with any misuse <sup>15</sup>	n	% of patients with any misuse <sup>16</sup>
Any substance/alcohol abuse	150		129	
Alcohol only	112	74.7	112	86.8
Alcohol + other substances	17	11.3	7	5.4
Other substances <sup>17</sup>				
IV drug use	11	29.0	3	17.7
Heroin	8	21.1	2	11.8
Methadone	6	15.8	1	5.9
Cannabis	7	18.4	2	11.8
Opiate	1	2.6	2	11.8

#### **10.2.1.2 Diagnosis and reasons for prescribing**

At the time the study was initiated, rivaroxaban was licensed in the UK for the prevention of stroke in patients with AF, treatment of DVT and PE and the prevention of recurrent DVT and PE, and the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery (patients treated for the latter indication are not included in this study).

<sup>15</sup> refers to % of patients with reported substance/alcohol abuse

<sup>16</sup> refers to % of patients with reported substance/alcohol abuse

<sup>17</sup> Reported substances where more than 1 patient is reported in either treatment group. These are not mutually exclusive groups so a patient may have a history of substance abuse of more than 1 substance



**Table 15. Primary clinical condition for which anticoagulant therapy (rivaroxaban or warfarin treatment) was indicated by treatment group**

Indication	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
AF	965	38.0	794	38.4
DVT/PE <sup>18</sup>	1532	60.3	1212	58.6
<i>Treatment DVT</i>	860	56.1	632	52.2
<i>Treatment of DVT+PE</i>	505	33.0	380	31.4
<i>Prevent recurrent DVT/PE</i>	83	5.4	25	2.1
<i>Other DVT/PE indication</i>	121	7.9	194	16.0
Mixed	23	0.9	27	1.3
Other*	22	0.9	34	1.6
Total	2542	100.0	2067	100.0

\* All other indications are listed in Appendix 5 of the final report.

As can be seen from Table 15, the primary clinical condition for which anticoagulant therapy was indicated was very similar between the two cohorts of patients although rivaroxaban seemed to be more likely to be used for prevention of recurrent DVT/PE within the DVT/PE group than warfarin, and warfarin was more likely to be used outside of these categorisations in DVT/PE patients. Further details on the “Other” categories are provided in Appendix 5. The indications “Mixed” and “Other” both contain very few patients and as such it will be difficult to identify any meaningful differences in these two treatment groups. Table 16 and Table 17 break the indication information down further by age group and gender, and again very few consistent differences between cohorts emerge.

<sup>18</sup> Sub categories of All DVT/PE are not mutually exclusive or included in “Total %”; % denominator is subgroup “All DVT/PE”

**Table 16. Age/Sex counts and percentages for rivaroxaban and primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

Age group	Rivaroxaban(female) N=1160										Rivaroxaban (male) N=1382									
	AF		DVT/PE		Mixed		Other		Total		AF		DVT/PE		Mixed		Other		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
18-24	0	0.0	20	2.9	0	0.0	1	14.3	21	1.8	0	0.0	11	1.3	0	0.0	0	0.0	11	0.8
25-29	1	0.2	16	2.3	0	0.0	0	0.0	17	1.5	1	0.2	19	2.3	0	0.0	1	6.7	21	1.5
30-34	0	0.0	27	3.9	0	0.0	0	0.0	27	2.3	2	0.4	27	3.2	0	0.0	0	0.0	29	2.1
35-39	1	0.2	25	3.6	0	0.0	0	0.0	26	2.2	1	0.2	41	4.9	0	0.0	0	0.0	42	3.0
40-44	2	0.5	41	5.9	0	0.0	0	0.0	43	3.7	2	0.4	49	5.9	0	0.0	0	0.0	51	3.7
45-49	7	1.6	64	9.2	1	11.1	1	14.3	73	6.3	8	1.6	74	8.9	0	0.0	1	6.7	83	6.0
50-54	4	0.9	46	6.6	0	0.0	2	28.6	52	4.5	18	3.5	94	11.2	0	0.0	1	6.7	113	8.2
55-59	11	2.5	41	5.9	0	0.0	0	0.0	52	4.5	26	5.0	87	10.4	3	21.4	3	20.0	119	8.6
60-64	23	5.1	59	8.5	0	0.0	1	14.3	83	7.2	49	9.5	90	10.8	1	7.1	3	20.0	143	10.4
65-69	34	7.6	79	11.4	1	11.1	1	14.3	115	9.9	71	13.7	114	13.6	2	14.3	3	20.0	190	13.8
70-74	64	14.3	85	12.2	2	22.2	0	0.0	151	13.0	80	15.5	93	11.1	3	21.4	0	0.0	176	12.7
75-79	92	20.5	71	10.2	1	11.1	1	14.3	165	14.2	107	20.7	59	7.1	3	21.4	2	13.3	171	12.4
80-84	91	20.3	73	10.5	1	11.1	0	0.0	165	14.2	76	14.7	40	4.8	0	0.0	1	6.7	117	8.5
85-89	86	19.2	32	4.6	2	22.2	0	0.0	120	10.3	59	11.4	30	3.7	0	0.0	0	0.0	89	6.4
90-94	24	5.4	14	2.0	0	0.0	0	0.0	38	3.3	14	2.7	8	1.0	1	7.1	0	0.0	23	1.7
≥95	8	1.8	3	0.4	1	11.1	0	0.0	12	1.0	3	0.6	0	0.0	1	7.1	0	0.0	4	0.3
Total	448	100.0	696	100.0	9	100.0	7	100.0	1160	100.0	517	100.0	836	100.0	14	100.0	15	100.0	1382	100.0

**Table 17. Age/Sex counts and percentages for warfarin and primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

Age group	Warfarin (female) N=918										Warfarin (male) N=1149									
	AF		DVT/PE		Mixed		Other		Total		AF		DVT/PE		Mixed		Other		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	N	%
18-24	1	0.3	15	2.7	0	0.0	1	6.7	17	1.9	0	0.0	7	1.1	0	0.0	0	0.0	7	0.6
25 -29	0	0.0	21	3.8	0	0.0	1	6.7	22	2.4	2	0.5	13	2.0	0	0.0	1	5.3	16	1.4
30 -34	0	0.0	27	4.9	0	0.0	1	6.7	28	3.1	0	0.0	22	3.3	0	0.0	0	0.0	22	1.9
35 -39	1	0.3	18	3.3	0	0.0	0	0.0	19	2.1	2	0.5	24	3.6	0	0.0	1	5.3	27	2.4
40 - 44	1	0.3	41	7.5	0	0.0	0	0.0	42	4.6	4	0.9	32	4.8	0	0.0	1	5.3	37	3.2
45 - 49	1	0.3	25	4.6	0	0.0	3	20.0	29	3.2	9	2.0	57	8.6	0	0.0	0	0.0	66	5.7
50 - 54	11	3.2	32	5.9	0	0.0	0	0.0	43	4.7	13	2.9	64	9.6	1	5.9	2	10.5	80	7.0
55 -59	7	2.0	30	5.5	0	0.0	1	6.7	38	4.1	33	7.4	72	10.8	4	23.5	2	10.5	111	9.7
60 - 64	20	5.8	64	11.7	1	10.0	0	0.0	85	9.3	46	10.3	74	11.1	0	0.0	4	21.1	124	10.8
65 -69	38	11.0	69	12.6	1	10.0	1	6.7	109	11.9	84	18.8	96	14.4	4	23.5	4	21.1	189	16.4
70 - 74	45	13.0	64	11.7	0	0.0	5	33.3	114	12.4	72	16.1	77	11.6	1	5.9	2	10.5	152	13.2
75 - 79	69	19.9	56	10.2	1	10.0	0	0.0	126	13.7	74	16.5	58	8.7	4	23.5	2	10.5	139	12.0
80 - 84	79	22.8	37	6.8	5	50.0	0	0.0	121	13.2	64	14.3	47	7.1	3	17.7	0	0.0	115	9.9
85 - 89	56	16.2	36	6.6	1	10.0	2	13.3	95	10.4	33	7.4	15	2.3	0	0.0	0	0.0	49	4.2
90 - 94	17	4.9	11	2.0	1	10.0	0	0.0	29	3.2	10	2.2	7	1.1	0	0.0	0	0.0	17	1.5
≥95	0	0.0	1	0.2	0	0.0	0	0.0	1	0.1	2	0.5	0	0.0	0	0.0	0	0.0	2	0.2
Total	346	100.0	547	100.0	10	100.0	15	100.0	918	100.0	448	100.0	665	100.0	17	100.0	19	100.0	1149	100.0

Investigators were asked to provide the supporting reasons for prescribing either treatment for the clinical diagnosis indicated. Table 18 – Table 21 provide the reasons for prescribing associated with external forces and/or non-medical patient factors. Investigators could have reported more than one reason for prescribing and so counts are not mutually exclusive and each category is presented as percentage of relevant indication group. For the AF and DVT/PE groups, clinical judgement was the overwhelming reason for treatment choice followed by various guidelines/recommendations from expert groups such as NICE, and formulary committees. The impact of expert advice/formulary guidance seemed to be particularly relevant for the choice of warfarin in AF. For example, for AF, NICE guidance was cited as a supporting reason for 43.3% of AF warfarin patients compared to 20.7% of rivaroxaban patients. As mentioned previously the small number of patients in the “Mixed” and “Other” groups precludes meaningful assessment of any differences.

**Table 18. Supporting Reasons for prescribing for the primary diagnosis of AF, by treatment group**

Supporting Reason	Rivaroxaban N=965		Warfarin N=794	
	n	% <sup>19</sup>	n	%
Clinical Judgement	849	88.0	672	84.6
NICE Recommendation	200	20.7	344	43.3
Expert Committee Guidelines	56	5.8	133	16.8
Trust Formulary Committee	133	13.8	254	32.0
Patient Group Direction in anticoagulant clinic	26	2.7	55	6.9
Potential ease of reversibility of anticoagulant	7	0.7	68	8.6
Lifestyle	236	24.5	42	5.3
Patient non-adherence with prior anticoagulant	22	2.3	0	0.0
Side effects with prior anticoagulant	39	4.0	2	0.3
Aberrant behaviour	3	0.3	0	0.0
Poor control of anticoagulation	17	1.8	0	0.0
Patient preference	63	6.5	6	0.8
Other*	2	0.2	0	0.0
Total	965		794	

\* All other reasons are listed in Appendix 6 of the final report.

<sup>19</sup> % refers to % of patients where supporting reason is given

**Table 19. Supporting Reasons for prescribing for the primary diagnosis of DVT/PE, by treatment group**

Supporting Reason	Rivaroxaban N=1532		Warfarin N=1212	
	n	%	n	%
Clinical Judgement	1283	83.8	1057	87.2
NICE Recommendation	588	38.4	465	38.4
Expert Committee Guidelines	203	13.3	275	22.7
Trust Formulary Committee Guidelines	338	22.1	322	26.6
Patient Group Direction in anticoagulant clinic	266	17.4	38	3.1
Potential ease of reversibility of anticoagulant	6	0.4	77	6.4
Lifestyle	573	37.4	25	2.1
Patient non-adherence with prior anticoagulant	15	1.0	2	0.2
Side effects with prior anticoagulant	38	2.5	4	0.3
Aberrant behaviour	4	0.3	1	0.1
Poor control of anticoagulation	16	1.0	0	0.0
Patient preference	140	9.1	44	3.6
Other*	5	0.3	0	0.0
Total	1532		1212	

\*All other reasons are listed in Appendix 6 of the final report.

**Table 20. Supporting Reasons for prescribing for the primary diagnosis of Mixed (AF & DVT/PE) indications, by treatment group**

Supporting Reason	Rivaroxaban N=23		Warfarin N=27	
	n	%	n	%
Clinical Judgement	13	56.5	18	66.7
NICE Recommendation	6	26.1	10	37.0
Expert Committee Guidelines	2	8.7	3	11.1
Trust Formulary Committee Guidelines	6	26.1	10	37.0
Patient Group Direction in anticoagulant clinic	0	0.0	1	3.7
Potential ease of reversibility of anticoagulant	0	0.0	3	11.1
Lifestyle	11	47.8	1	3.7
Patient non-adherence with prior anticoagulant	2	8.7	0	0.0
Side effects with prior anticoagulant	4	17.4	0	0.0
Aberrant behaviour	0	0.0	0	0.0
Poor control of anticoagulation	3	13.0	0	0.0
Patient preference	4	17.4	0	0.0
Total	23		27	

**Table 21. Supporting Reasons for prescribing for the primary diagnosis of Other indications, by treatment group (% refers to % where supporting reason is given)**

Supporting Reason	Rivaroxaban N=22		Warfarin N=34	
	n	%	n	%
Clinical Judgement	18	81.8	27	79.4
NICE Recommendation	5	22.7	12	35.3
Expert Committee Guidelines	4	18.2	3	8.8
Trust Formulary Committee Guidelines	8	36.4	6	17.7
Patient Group Direction in anticoagulant clinic	0	0.0	1	2.9
Potential ease of reversibility of anticoagulant	0	0.0	2	5.9
Lifestyle	5	22.7	0	0.0
Patient non-adherence with prior anticoagulant	1	4.6	0	0.0
Side effects with prior anticoagulant	3	13.6	0	0.0
Aberrant behaviour	0	0.0	0	0.0
Poor control of anticoagulation	1	4.6	0	0.0
Patient preference	0	0.0	0	0.0
Total	22		34	

Other outcomes known to determine prescribing decisions include the history of the clinical indication. In this study, history of the clinical indication was measured according to time since first diagnosed by prescribing physician for the current indication.

The number of months prior to the index date that patients were first diagnosed with the current primary condition for treatment, if pre-existing, are presented in Table 22 for rivaroxaban and warfarin. These show very similar patterns for the AF and DVT/PE cohorts, and as previously the "Mixed" and "Other" cohorts have insufficient numbers for any meaningful comparison. For this analysis it is important to note that rivaroxaban initiators may have previously been taking warfarin for this indication, whereas warfarin initiators could not have been on any univalent thrombin inhibitor or direct factor Xa inhibitor, or have received anticoagulant therapy or other VKA therapy with the past 12 months since this would have rendered them ineligible for the study. This meant that rivaroxaban patients potentially had a greater opportunity for a longer previous medical history for chronic conditions which seems to be reflected in Table 22 results with 30.4% of rivaroxaban AF patients having a prior history of more than seven months compared to 15.7% of warfarin patients.

**Table 22. Months prior to index date that reported indication first diagnosed (where data are available), for the Rivaroxaban and Warfarin cohort by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

Months prior to index date	Rivaroxaban								Warfarin							
	AF N=938		DVT/PE N=1521		Mixed N=23		Other N=20		AF N=783		DVT/PE N=1203		Mixed N=27		Other N=32	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
≥7	285	30.4	96	6.3	13	56.5	4	20.0	123	15.7	16	1.3	11	40.7	2	6.3
6 to <7	8	0.9	9	0.6					3	0.4	3	0.3				
5 to <6	11	1.2	5	0.3	1	4.4	1	5.0	10	1.3						
4 to <5	12	1.3	9	0.6	2	8.7			16	2.0	2	0.2				
3 to <4	16	1.7	10	0.7					30	3.8	10	0.8			1	3.1
2 to <3	22	2.4	12	0.8			1	5.0	38	4.9	12	1.0			1	3.1
1 to <2	49	5.2	38	2.5					89	11.4	13	1.1	2	7.4	4	12.5
0 to <1	405	43.2	563	37.0	4	17.4	8	40.0	385	49.2	590	49.0	11	40.7	22	68.8
<1 month after treatment start	126	13.4	776	51.0	3	13.0	6	30.0	89	11.4	557	46.3	3	11.1	2	6.3
More than 1 month after treatment start	4	0.4	3	0.2												

### 10.2.1.3 Prior and concurrent medical conditions

Investigators were asked to indicate if the patient had any of the pre-specified events or conditions (as described below) prior to starting treatment within two time periods: within three months prior to starting treatment AND including date of treatment initiation to capture information on any recent acute events or newly diagnosed conditions that may impact on individual patient baseline risk; and if the event/condition had been recorded at any time prior to the three month period immediately in advance of starting treatment to capture information on chronic conditions. More than one event or condition could be reported for each patient and so counts are not mutually exclusive. The prevalence of each medical condition is presented in Table 23 – Tables 34, by period of interest. For analysis purposes, binary dummy variables were derived from tick box responses by specialist HCPs on the 12 week observation questionnaire; bleeding events (Table 23 and Table 26) have not been classified according to ISTH classification presented previously (Table 1).

In the AF group (Table 23) the most common bleed prior to treatment start on rivaroxaban or warfarin was gastrointestinal haemorrhage with 32 (3.3%) and 29 (3.7%) patients who had experienced one in any period prior, respectively. Fifty-four patients (3.1% of the total cohort) had experienced the gastrointestinal haemorrhage over three months prior to starting their treatment while only 10 patients (0.6% of the total cohort) had the bleed within the three months prior to starting their respective anti-coagulation therapy. Only nine (0.5%) patients in the whole cohort population required a transfusion following a prior bleeding event (of ≥2 units of packed red cells

or whole blood), with one patient needing a transfusion both in the past (over three months prior to treatment start) and recently (within the three months prior to index date).

In the DVT/PE group (Table 24) the two most common bleeding events that occurred prior to the index date were gastrointestinal and urogenital haemorrhages with a total of 88 (3.2%) patients for each haemorrhagic group. There were 26 (1.7%) patients on rivaroxaban and 36 (3.0%) patients on warfarin that had a gastrointestinal haemorrhage in their past medical history (over three months prior to treatment start) and 15 (1.0%) patients on rivaroxaban and another 18 (1.5%) on warfarin who had the same event in their more recent medical history (within three months prior to starting the anti-coagulation treatment of interest).



**Table 23. History of haemorrhagic related events prior to start of treatment for AF, by treatment group**

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban N=965		Warfarin N=794		Total N=1759		Rivaroxaban N=965		Warfarin N=794		Total N=1759		Rivaroxaban N= 965		Warfarin N= 794		Total N=1759		Rivaroxaban N=965		Warfarin N=794		Total N=1759	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Haemorrhage into following body sites:																								
Intracranial	7	0.7	9	1.1	16	0.9	9	0.9	4	0.5	13	0.7	0	0.0	0	0.0	0	0.0	16	1.7	12	1.5	28	1.6
Gastrointestinal	31	3.2	23	2.9	54	3.1	1	0.1	9	1.1	10	0.6	1	0.1	0	0.0	1	0.1	32	3.3	29	3.7	61	3.5
Urogenital	19	2.0	15	1.9	34	1.9	6	0.6	4	0.5	10	0.6	0	0.0	0	0.0	0	0.0	25	2.6	18	2.3	43	2.4
Intraocular	2	0.2	2	0.3	4	0.2	1	0.1	1	0.1	2	0.1	0	0.0	0	0.0	0	0.0	3	0.3	3	0.4	6	0.3
Spinal cord	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Pericardial	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1
Intraarticular	0	0.0	1	0.1	1	0.1	0	0.0	2	0.3	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	3	0.4	3	0.2
Intramuscular	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Retroperitoneal	2	0.2	1	0.1	3	0.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.2	1	0.1	3	0.2
Other bleeds*	8	0.8	7	0.9	15	0.9	7	0.7	10	1.3	17	1.0	1	0.1	0	0.0	1	0.1	41	4.3	43	5.4	84	4.8
Haemorrhage-related events which led to:																								
Decreased haemoglobin	15	1.6	14	1.8	29	1.7	16	1.7	13	1.6	29	1.7	0	0.0	0	0.0	0	0.0	24	2.5	21	2.6	45	2.6
Bleeding requiring a transfusion	2	0.2	3	0.4	5	0.3	3	0.3	2	0.3	5	0.3	0	0.0	0	0.0	0	0.0	4	0.4	5	0.6	9	0.5
A fatal outcome	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.1
Other haemorrhage-related events:																								
Injury/Trauma	11	1.1	5	0.6	16	0.9	4	0.4	7	0.9	11	0.6	0	0.0	0	0.0	0	0.0	12	1.2	12	1.5	24	1.4
On coumarin with INR > 3	17	1.8	0	0.0	17	1.0	9	0.9	6	0.8	15	0.9	0	0.0	0	0.0	0	0.0	21	2.2	6	0.8	27	1.5
Overdose	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.1
Stopping of therapy for bleeding	4	0.4	0	0.0	4	0.2	2	0.2	3	0.4	5	0.3	0	0.0	0	0.0	0	0.0	6	0.6	3	0.4	9	0.5
Bleeding leading to reversal of treatment	2	0.2	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.2	0	0.0	2	0.1

\*Other bleeds are listed in Appendix 7

**Table 24. History of haemorrhagic related events prior to start of treatment for DVT/PE, by treatment group**

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban		Warfarin		Total		Rivaroxaban		Warfarin		Total		Rivaroxaban		Warfarin		Total		Rivaroxaban		Warfarin		Total	
	N=1532		N=1212		N=2744		N=1532		N=1212		N=2744		N=1532		N=1212		N=2744		N=1532		N=1212		N=2744	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Haemorrhage into following body sites:																								
Intracranial	7	0.5	8	0.7	15	0.6	4	0.3	1	0.1	5	0.2	0	0.0	0	0.0	0	0.0	11	0.7	9	0.7	20	0.7
Gastrointestinal	26	1.7	36	3.0	62	2.3	15	1.0	18	1.5	33	1.2	2	0.1	0	0.0	2	0.1	37	2.4	51	4.2	88	3.2
Urogenital	35	2.3	37	3.1	72	2.6	17	1.1	12	1.0	29	1.1	0	0.0	0	0.0	0	0.0	42	2.7	46	3.8	88	3.2
Intraocular	1	0.1	1	0.1	2	0.1	0	0.0	2	0.2	2	0.1	0	0.0	0	0.0	0	0.0	1	0.1	3	0.3	4	0.2
Spinal cord	0	0.0	2	0.2	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.2	2	0.1
Pericardial	1	0.1	0	0.0	1	0.0	1	0.1	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.0
Intraarticular	0	0.0	4	0.3	4	0.2	0	0.0	1	0.1	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	4	0.3	4	0.2
Intramuscular	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.0
Retroperitoneal	3	0.2	5	0.4	8	0.3	1	0.1	4	0.3	5	0.2	0	0.0	0	0.0	0	0.0	3	0.2	6	0.5	9	0.3
Other bleeds*	16	1.0	15	1.2	31	1.1	17	1.1	17	1.4	34	1.2	1	0.1	0	0.0	1	0.0	57	3.7	61	5.0	118	4.3
Haemorrhage-related events which led to:																								
Decreased haemoglobin	38	2.5	19	1.6	57	2.1	58	3.8	33	2.7	91	3.3	0	0.0	0	0.0	0	0.0	80	5.2	46	3.8	126	4.6
Bleeding requiring a transfusion	13	0.9	5	0.4	18	0.7	10	0.7	12	1.0	22	0.8	0	0.0	0	0.0	0	0.0	22	1.4	16	1.3	38	1.4
A fatal outcome	1	0.1	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.0
Other haemorrhage-related events:																								
Injury/Trauma	35	2.3	35	2.9	70	2.6	41	2.7	41	3.4	82	3.0	0	0.0	0	0.0	0	0.0	70	4.6	67	5.5	137	5.0
On coumarin with INR > 3	24	1.6	13	1.0	37	1.4	12	0.8	16	1.3	28	1.0	0	0.0	0	0.0	0	0.0	29	1.9	25	2.1	54	2.0
Overdose	6	0.4	1	0.1	7	0.3	0	0.0	1	0.1	1	0.0	0	0.0	0	0.0	0	0.0	6	0.4	2	0.2	8	0.3
Stopping of therapy for bleeding	4	0.3	3	0.3	7	0.3	4	0.3	3	0.3	7	0.3	0	0.0	0	0.0	0	0.0	8	0.5	6	0.5	14	0.5
Bleeding leading to reversal of treatment	2	0.1	1	0.1	3	0.1	1	0.1	2	0.2	3	0.1	0	0.0	0	0.0	0	0.0	3	0.2	3	0.3	6	0.2

\*Other bleeds are listed in Appendix 7

The cohort of patients with a Mixed indication of both AF and DVT/PE (Table 25), was much smaller than the cohorts AF only and DVT/PE only patients (Table 23 and Table 24, respectively). Accordingly the number of patients experiencing any bleeding events at any point in their prior medical history is smaller and the impact of a single event on the proportions is correspondingly high, but not robust. For example, while a total of six patients (12.0%) experienced a gastrointestinal haemorrhage (the most common bleeding event) at any point prior to index date, it only accounts for three patients in the rivaroxaban sub-group and three patients in the warfarin sub-group.

The count of events was even lower in the cohort treated for Other indications (Table 26); two patients (3.6%) experienced an intracranial bleed, another two patients (3.6%) had a gastrointestinal haemorrhage, while only one patient had experienced another haemorrhage at any other body site.

**Table 25. History of haemorrhagic related events prior to start of treatment for Mixed (AF & DVT/PE) indications, by treatment group**

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban N=23		Warfarin N=27		Total N=50		Rivaroxaban N=23		Warfarin N=27		Total N=50		Rivaroxaban N=23		Warfarin N=27		Total N=50		Rivaroxaban N=23		Warfarin N=27		Total N=50	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Haemorrhage into following body sites:																								
Intracranial	1	4.4	0	0.0	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.4	0	0.0	1	2.0
Gastrointestinal	1	4.4	3	11.1	4	4.0	2	8.7	1	3.7	3	6.0	0	0.0	1	3.7	1	2.0	3	13.0	3	11.1	6	12.0
Urogenital	1	4.4	0	0.0	1	2.0	2	8.7	1	3.7	3	6.0	0	0.0	0	0.0	0	0.0	2	8.7	1	3.7	3	6.0
Intraocular	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	1	2.0
Spinal cord	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Pericardial	1	4.4	0	0.0	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.4	0	0.0	1	2.0
Intraarticular	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Intramuscular	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Retroperitoneal	1	4.4	0	0.0	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.4	0	0.0	1	2.0
Other bleeds*	3	13.0	0	0.0	3	6.0	3	13.0	0	0.0	3	6.0	0	0.0	0	0.0	0	0.0	5	21.7	3	11.1	8	16.0
Haemorrhage-related events which led to:																								
Decreased haemoglobin	1	4.4	1	3.7	2	4.0	0	0.0	1	3.7	1	2.0	0	0.0	0	0.0	0	0.0	1	4.4	1	3.7	2	4.0
Bleeding requiring a transfusion	1	4.4	1	3.7	2	4.0	0	0.0	1	3.7	1	2.0	0	0.0	0	0.0	0	0.0	1	4.4	1	3.7	2	4.0
A fatal outcome	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other haemorrhage-related events:																								
Injury/Trauma	1	4.4	0	0.0	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.4	0	0.0	1	2.0
On coumarin with INR > 3	3	13.0	0	0.0	3	6.0	1	4.4	0	0.0	1	2.0	0	0.0	0	0.0	0	0.0	3	13.0	0	0.0	3	6.0
Overdose	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Stopping of therapy for bleeding	0	0.0	0	0.0	0	0.0	1	4.4	1	3.7	2	4.0	0	0.0	0	0.0	0	0.0	1	4.4	1	3.7	2	4.0
Bleeding leading to reversal of treatment	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	1	2.0

\*Other bleeds are listed in Appendix 7

**Table 26. History of haemorrhagic related events prior to start of treatment for Other indications, by treatment group**

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban		Warfarin		Total		Rivaroxaban		Warfarin		Total		Rivaroxaban		Warfarin		Total		Rivaroxaban		Warfarin		Total	
	N=22		N=34		N=56		N=22		N=34		N=56		N=22		N=34		N=56		N=22		N=34		N=56	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Haemorrhage into following body sites:																								
Intracranial	0	0.0	0	0.0	0	0.0	2	9.1	0	0.0	2	3.6	0	0.0	0	0.0	0	0.0	2	9.1	0	0.0	2	3.6
Gastrointestinal	0	0.0	0	0.0	0	0.0	0	0.0	2	5.9	2	3.6	0	0.0	0	0.0	0	0.0	0	0.0	2	5.9	2	3.6
Urogenital	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Intraocular	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Spinal cord	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Pericardial	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Intraarticular	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Intramuscular	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Retroperitoneal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other bleeds*	0	0.0	1	2.9	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	1.8
Haemorrhage-related events which led to:																								
Decreased haemoglobin	0	0.0	1	2.9	1	1.8	0	0.0	4	11.8	4	7.1	0	0.0	0	0.0	0	0.0	0	0.0	5	14.7	5	8.9
Bleeding requiring a transfusion	0	0.0	0	0.0	0	0.0	0	0.0	2	5.9	2	3.6	0	0.0	0	0.0	0	0.0	0	0.0	2	5.9	2	3.6
A fatal outcome	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other haemorrhage-related events:																								
Injury/Trauma	0	0.0	1	2.9	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	1.8
On coumarin with INR > 3	1	4.6	0	0.0	1	1.8	1	4.6	1	2.9	2	3.6	0	0.0	0	0.0	0	0.0	1	4.6	1	2.9	2	3.6
Overdose	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Stopping of therapy for bleeding	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Bleeding leading to reversal of treatment	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

\*Other bleeds are listed in Appendix 7

Investigators were asked to indicate whether the patient had any history of the cardiovascular disorders and other conditions and events listed in the tables below (Table 27 – Table 34).

In the group with an indication of AF, the most common prior cardiovascular disorder (Table 27) was arrhythmia in 1,059 (60.2%) patients, of the rivaroxaban treated patients, 561 patients (58.1%) had arrhythmia at index date and 498 of the warfarin prescribed patients (62.7%) had arrhythmia at index date. The least common disorder was pulmonary embolism in 25 (1.4%) patients overall; 15 patients in the rivaroxaban cohort (1.6%) and 10 patients (1.3%) in the warfarin cohort.

There were 549 (31.2%) patients in the AF cohort overall who had arrhythmias recorded in their past medical history (over three months prior to treatment start); in the cohort later prescribed rivaroxaban there were 300 patients (31.1%) while in the cohort later prescribed warfarin there were 249 patients (31.4%). In the more recent prior medical history (within the three months prior to index date), 744 patients overall (42.3%) were recorded with arrhythmias. This includes 549 (31.2%) of the patients who were treated with rivaroxaban and 371 of the patients (46.7%) treated with warfarin.

**Table 27. History of cardiovascular disorder prior to start of treatment for indication AF, by treatment group\***

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban N= 965		Warfarin N= 794		Total N=1759		Rivaroxaban N= 965		Warfarin N= 794		Total N=1759		Rivaroxaban N= 965		Warfarin N= 794		Total N=1759		Rivaroxaban N= 965		Warfarin N= 794		Total N=1759	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Cerebrovascular accident	102	10.6	53	6.7	155	8.8	225	23.3	125	15.7	350	19.9	0	0.0	0	0.0	0	0.0	298	30.9	166	20.9	464	26.4
Deep Vein Thrombosis	21	2.6	22	2.8	43	2.4	2	0.2	5	0.6	7	0.4	0	0.0	0	0.0	0	0.0	24	2.5	26	3.3	50	2.8
Pulmonary embolism	13	1.4	8	1.0	21	1.2	2	0.2	3	0.4	5	0.3	0	0.0	0	0.0	0	0.0	15	1.6	10	1.3	25	1.4
Hypertension	340	35.2	357	45.0	697	39.6	135	14.0	104	13.1	239	13.6	0	0.0	0	0.0	0	0.0	372	38.6	376	47.4	748	42.5
Raised blood pressure	260	26.9	210	26.5	470	26.7	158	16.4	143	18.0	301	17.1	0	0.0	0	0.0	0	0.0	288	29.8	233	29.4	521	29.6
Myocardial Infarction	72	7.5	72	9.1	144	8.2	14	1.5	12	1.5	26	1.5	0	0.0	0	0.0	0	0.0	85	8.8	79	10.0	164	9.3
Congestive Heart Failure	70	7.3	69	8.7	139	7.9	47	4.9	68	8.6	115	6.5	2	0.2	0	0.0	2	0.1	141	14.6	143	18.0	284	16.2
Peripheral artery disease	19	2.0	18	2.3	37	2.1	7	0.7	9	1.1	16	0.9	0	0.0	0	0.0	0	0.0	21	2.2	23	2.9	44	2.5
Transient Ischaemic Attack	80	8.3	55	6.9	135	7.7	72	7.5	38	4.8	110	6.3	1	0.1	0	0.0	1	0.1	138	14.3	83	10.5	221	12.6
Arrhythmia	300	31.1	249	31.4	549	31.2	373	38.7	371	46.7	744	42.3	1	0.1	5	0.6	6	0.3	561	58.1	498	62.7	1059	60.2
Hypercholesterolaemia	249	25.8	230	29.0	479	27.2	109	11.3	88	11.1	197	11.2	0	0.0	0	0.0	0	0.0	272	28.2	249	31.4	521	29.6
Diabetes	161	16.7	155	19.5	316	18.0	77	8.0	78	9.8	155	8.8	0	0.0	0	0.0	0	0.0	181	18.8	168	21.2	349	19.8
Chronic obstructive pulmonary disease	70	7.3	66	8.3	136	7.7	39	4.0	33	4.2	72	4.1	1	0.1	0	0.0	1	0.1	71	7.4	72	9.1	143	8.1

\* all other events reported as freetext are listed in Appendix 7

In the AF cohort the most common other event overall (Table 28) was hospitalisation in 329 (18.7%) patients; of the rivaroxaban treated patients 187 patients (19.4%) had a prior history of hospitalisation at index date and 142 of the patients prescribed warfarin (17.9%) had a history of hospitalisation at index date. The least common conditions were renal failure and thrombocytopenia with 8 (0.5%) patients each.

There were 230 (13.1%) patients who were hospitalised more than three months prior to the index date; in the cohort later prescribed rivaroxaban there were 135 patients (14.0%) while in the cohort later prescribed warfarin there were 95 patients (12.0%). In the three months period prior to the study start, a total of 149 (8.5%) patients were hospitalised. This includes 78 patients (8.1%) in the cohort later prescribed rivaroxaban and 71 patients (8.9%) later prescribed warfarin.



**Table 28. History of other conditions/events prior to start of treatment for indication AF, by treatment group\***

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban N= 965		Warfarin N= 794		Total N=1759		Rivaroxaban N= 965		Warfarin N= 794		Total N=1759		Rivaroxaban N= 965		Warfarin N= 794		Total N=1759		Rivaroxaban N= 965		Warfarin N= 794		Total N=1759	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Liver Disorder	6	0.6	15	1.9	21	1.2	3	0.3	4	0.5	7	0.4	0	0.0	0	0.0	0	0.0	9	0.9	16	2.0	25	1.4
Abnormal liver function tests	30	3.1	41	5.2	71	4.0	33	3.4	47	5.9	80	4.6	0	0.0	0	0.0	0	0.0	50	5.2	68	8.6	118	6.7
Renal Failure	1	0.1	6	0.8	7	0.4	1	0.1	1	0.1	2	0.1	0	0.0	0	0.0	0	0.0	2	0.2	6	0.8	8	0.5
Renal disease stage 3/4	69	7.2	66	8.3	135	7.7	45	4.7	37	4.7	82	4.7	0	0.0	0	0.0	0	0.0	74	7.7	69	8.7	143	8.1
Renal disease stage 1/2	28	2.9	16	2.0	44	2.5	19	2.0	14	1.8	33	1.9	0	0.0	0	0.0	0	0.0	32	3.3	23	2.9	55	3.1
Immobility	20	2.1	23	2.9	43	2.4	46	4.8	30	3.8	76	4.3	0	0.0	0	0.0	0	0.0	54	5.6	44	5.5	98	5.6
Thrombophilia	4	0.4	2	0.3	6	0.3	2	0.2	1	0.1	3	0.2	0	0.0	0	0.0	0	0.0	5	0.5	3	0.4	8	0.5
Coagulation disorder	4	0.4	1	0.1	5	0.3	2	0.2	3	0.4	5	0.3	0	0.0	0	0.0	0	0.0	6	0.6	3	0.4	9	0.5
Thrombocytopenia	1	0.1	5	0.6	6	0.3	1	0.1	4	0.5	5	0.3	0	0.0	0	0.0	0	0.0	2	0.2	7	0.9	9	0.5
Malignancies	92	9.5	94	11.8	186	10.6	23	2.4	17	2.1	40	2.3	3	0.3	4	0.5	7	0.4	103	10.7	97	12.2	200	11.4
Pregnancies	1	0.1	1	0.1	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	2	0.1
Breastfeeding	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1
Menorrhagia	5	0.5	3	0.4	8	0.5	1	0.1	1	0.1	2	0.1	0	0.0	0	0.0	0	0.0	6	0.6	3	0.4	9	0.5
Coronary artery bypass graft	26	2.7	45	5.7	71	4.0	2	0.2	6	0.8	8	0.5	0	0.0	0	0.0	0	0.0	27	2.8	51	6.4	78	4.4
Percutaneous coronary intervention	28	2.9	36	4.5	64	3.6	5	0.5	7	0.9	12	0.7	0	0.0	0	0.0	0	0.0	32	3.3	42	5.3	74	4.2
Implanted prosthetic heart valve	7	0.7	6	0.8	13	0.7	0	0.0	1	0.1	1	0.1	0	0.0	1	0.1	1	0.1	7	0.7	7	0.9	14	0.8
Surgery	65	6.7	62	7.8	127	7.2	14	1.5	18	2.3	32	1.8	4	0.4	1	0.1	5	0.3	75	7.8	75	9.5	150	8.5
Hospitalisation	135	14.0	95	12.0	230	13.1	78	8.1	71	8.9	149	8.5	0	0.0	1	0.1	1	0.1	187	19.4	142	17.9	329	18.7

\* all other events reported as freetext are listed in Appendix 7

In the cohort with an indication of DVT/PE, the two most common cardiovascular disorders (Table 29) reported by the investigators were DVT with a total of 1268 (46.3%) patients and PE with 851 (31.0%) patients. Of patients prescribed rivaroxaban at index date, 712 (46.5%) had a history of DVT prior to the start date while 557 patients (46.0%) prescribed warfarin had a history of DVT prior to the start date.

Furthermore, the total number of patients with a history of DVT more than doubled in the three months prior to the treatment initiation compared to the period of over three months prior to treatment initiation: 946 (34.5%) patients up from 440 (16.0%) patients respectively.

In the subset of the DVT/PE cohort with a history of PE, the number of patients that developed the condition in the most recent history (n=662, 24.1%) was almost three times that from the past period (n=244, 8.9%) over three months prior to treatment start.

**Table 29. History of other cardiovascular disorders prior to start of treatment for indication DVT/PE, by treatment group\***

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban N=1532		Warfarin N=1212		Total N=2744		Rivaroxaban N=1532		Warfarin N=1212		Total N=2744		Rivaroxaban N=1532		Warfarin N=1212		Total N=2744		Rivaroxaban N=1532		Warfarin N=1212		Total N=2744	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Cerebrovascular accident	44	2.9	46	3.8	90	3.3	30	2.0	22	1.8	52	1.9	1	0.1	1	0.1	2	0.1	70	4.6	65	5.4	135	4.9
Deep Vein Thrombosis	270	17.6	170	14.0	440	16.0	493	32.2	453	37.4	946	34.5	6	0.4	0	0.0	6	0.2	712	46.5	557	46.0	1,269	46.3
Pulmonary embolism	141	9.2	103	8.5	244	8.9	324	21.2	338	27.9	662	24.1	3	0.2	0	0.0	3	0.1	444	29.0	407	33.6	851	31.0
Hypertension	286	18.7	242	20.0	528	19.2	89	5.8	91	7.5	180	6.6	0	0.0	0	0.0	0	0.0	307	20.0	254	21.0	561	20.4
Raised blood pressure	234	15.3	196	16.2	430	15.7	121	7.9	126	10.4	247	9.0	0	0.0	0	0.0	0	0.0	253	16.5	213	17.6	466	17.0
Myocardial Infarction	47	3.1	56	4.6	103	3.8	7	0.5	8	0.7	15	0.6	0	0.0	0	0.0	0	0.0	55	3.6	63	5.2	118	4.3
Congestive Heart Failure	27	1.8	41	3.4	68	2.5	18	1.2	34	2.8	52	1.9	0	0.0	0	0.0	0	0.0	51	3.3	70	5.8	121	4.4
Peripheral arterial disease	16	1.0	19	1.6	35	1.3	5	0.3	12	1.0	17	0.6	1	0.1	0	0.0	1	0.0	16	1.0	20	1.7	36	1.3
Transient Ischaemic Attack	32	2.1	31	2.6	63	2.3	3	0.2	4	0.3	7	0.3	0	0.0	0	0.0	0	0.0	35	2.3	32	2.6	67	2.4
Arrhythmia	61	4.0	64	5.3	125	4.6	49	3.2	52	4.3	101	3.7	0	0.0	0	0.0	0	0.0	91	5.9	90	7.4	181	6.6
Hypercholesterolaemia	198	12.9	182	15.0	380	13.9	72	4.7	80	6.6	152	5.5	0	0.0	0	0.0	0	0.0	212	28.2	187	15.4	399	14.5
Diabetes	131	8.6	138	11.4	269	9.8	65	4.2	84	6.9	149	5.4	0	0.0	1	0.1	1	0.0	154	10.1	161	13.3	315	11.5
Chronic obstructive pulmonary disease	93	6.1	94	7.8	187	6.8	50	3.3	53	4.4	103	3.8	1	0.1	1	0.1	2	0.1	98	6.4	98	8.1	196	7.1

\* all other events reported as freetext are listed in Appendix 7

Similar to the group with an indication of AF, the most common other condition/event in the DVT/PE group was hospitalisation with a total of 717 (26.1%) patients being hospitalised in their past medical history (Table 30). Of these patients, 427 (15.6%) patients had a history of hospitalisation more than three months prior to the index date ('past' in Table 30 below) while 414 (15.1%) patients had been hospitalised during the three months period preceding the index date.

Breaking this information on the DVT/PE group down by treatment cohort, 26.4% of patients who were prescribed rivaroxaban at index date had a history of hospitalisation (n=404) compared with 25.8% of patients prescribed warfarin (n=313). The second most common condition/event reported for this group prior to receiving the anticoagulants of interest was undergoing surgery reported for a total of 409 patients (14.9%). In the rivaroxaban group of DVT/PE patients, 212 patients (13.8%) had this event reported compared with 197 (16.3%) patients in the warfarin group.

**Table 30. History of other conditions/events prior to start of treatment for indication DVT/PE, by treatment group\***

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban N=1532		Warfarin N=1212		Total N=2744		Rivaroxaban N=1532		Warfarin N=1212		Total N=2744		Rivaroxaban N=1532		Warfarin N=1212		Total N=2744		Rivaroxaban N=1532		Warfarin N=1212		Total N=2744	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Liver Disorder	36	2.4	27	2.2	63	2.3	18	1.2	11	0.9	29	1.1	0	0.0	0	0.0	0	0.0	46	3.0	33	2.7	79	2.9
Abnormal liver function tests	83	5.4	52	4.3	135	4.9	120	7.8	73	6.0	193	7.0	0	0.0	0	0.0	0	0.0	170	11.1	107	8.8	277	10.1
Renal Failure	4	0.3	4	0.3	8	0.3	2	0.1	3	0.3	5	0.2	0	0.0	0	0.0	0	0.0	6	0.4	5	0.4	11	0.4
Renal disease stage 3/4	73	4.8	91	7.5	164	6.0	43	2.8	57	4.7	100	3.6	0	0.0	0	0.0	0	0.0	77	5.0	100	8.3	177	6.5
Renal disease stage 1/2	36	2.4	22	1.8	58	2.1	26	1.7	18	1.5	44	1.6	0	0.0	0	0.0	0	0.0	46	3.0	27	2.2	73	2.7
Immobility	81	5.3	53	4.4	134	4.9	187	12.2	125	10.3	312	11.4	2	0.1	0	0.0	2	0.1	221	14.4	150	12.4	371	13.5
Thrombophilia	27	1.8	30	2.5	57	2.1	14	0.9	21	1.7	35	1.3	1	0.1	2	0.2	3	0.1	29	1.9	33	2.7	62	2.3
Coagulation disorder	13	0.9	15	1.2	28	1.0	8	0.5	8	0.7	16	0.6	0	0.0	0	0.0	0	0.0	16	1.0	18	1.5	34	1.2
Thrombocytopenia	4	0.3	4	0.3	8	0.3	3	0.2	4	0.3	7	0.3	1	0.1	0	0.0	1	0.0	7	0.5	6	0.5	13	0.5
Malignancies	149	9.7	155	12.8	304	11.1	48	3.1	44	3.6	92	3.4	12	0.8	14	1.2	26	1.0	162	10.6	171	14.1	333	12.1
Pregnancies	15	1.0	24	2.0	39	1.4	7	0.5	21	1.7	28	1.0	0	0.0	2	0.2	2	0.1	19	1.2	34	2.8	53	1.9
Breastfeeding	3	0.2	6	0.5	9	0.3	3	0.2	8	0.7	11	0.4	0	0.0	0	0.0	0	0.0	4	0.3	11	0.9	15	0.6
Menorrhagia	9	0.6	15	1.2	24	0.9	11	0.7	6	0.5	17	0.6	0	0.0	0	0.0	0	0.0	15	1.0	16	1.3	31	1.1
Coronary artery bypass graft	15	1.0	16	1.3	31	1.1	5	0.3	3	0.3	8	0.3	0	0.0	0	0.0	0	0.0	20	2.8	19	1.6	39	1.4
Percutaneous coronary intervention	25	1.6	28	2.3	53	1.9	5	0.3	4	0.3	9	0.3	0	0.0	0	0.0	0	0.0	29	1.9	30	2.5	59	2.2
Implanted prosthetic heart valve	4	0.3	3	0.3	7	0.3	1	0.1	2	0.2	3	0.1	0	0.0	0	0.0	0	0.0	5	0.3	4	0.3	9	0.3
Surgery	141	9.2	110	9.1	251	9.2	87	5.7	104	8.6	191	7.0	3	0.2	5	0.4	8	0.3	212	13.8	197	16.3	409	14.9
Hospitalisation	249	16.3	178	14.7	427	15.6	224	14.6	190	15.7	414	15.1	4	0.3	1	0.1	5	0.2	404	26.4	313	25.8	717	26.1

\* all other events reported as freetext are listed in Appendix 7

The cohort with a Mixed indication of AF and DVT/PE was much smaller with only 50 patients (Table 31). The two most common cardiovascular disorders prior to treatment start were arrhythmias and pulmonary embolism with 33 (66.0%) patients and 26 (52.0%) patients, respectively, while the least common disorder was peripheral arterial disease with only three (6.0%) patients. In the period over three months prior to the index date, 20 patients (40.0%) of this cohort had a diagnosis of arrhythmia while 25 patients (50.0%) had this diagnosis in the three months prior to index date.

Of the patients treated with rivaroxaban, 18 (78.3%) had a history of arrhythmia compared to 15 (55.6%) prescribed warfarin.

In that same group, the two most common other conditions (Table 32) were hospitalisation and malignancies with 17 (34.0%) and nine (18.0%) patients respectively.

For the most common condition of hospitalisation, 12 (24.0%) patients had a history of hospitalisation over three months prior to the index date while nine (18.0%) were admitted to hospital at some point in the three months leading up to the start of the anticoagulation treatment.

Of the rivaroxaban patients in this indication group eight (34.8%) had a history of hospitalisation over three months prior to the index date compared with four patients (14.8%) in the warfarin group. This compares with three patients in the rivaroxaban group (13.0%) and six patients in the warfarin group (22.2%) with a history of hospitalisation in the three months prior to the index date.

**Table 31. History of other cardiovascular disorders prior to start of treatment for Mixed (AF & DVT/PE) indications, by treatment group\***

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban N=23		Warfarin N=27		Total N=50		Rivaroxaban N=23		Warfarin N=27		Total N=50		Rivaroxaban N=23		Warfarin N=27		Total N=50		Rivaroxaban N=23		Warfarin N=27		Total N=50	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Cerebrovascular accident	4	17.4	2	7.4	6	12.0	1	4.4	4	14.8	5	10.0	0	0.0	0	0.0	0	0.0	4	17.4	5	18.5	9	18.0
Deep Vein Thrombosis	8	34.8	3	11.1	11	22.0	2	8.7	8	29.6	10	20.0	0	0.0	0	0.0	0	0.0	10	43.5	11	40.7	21	42.0
Pulmonary embolism	7	30.4	6	22.2	13	26.0	4	17.4	11	40.7	15	30.0	0	0.0	0	0.0	0	0.0	12	52.2	14	51.9	26	52.0
Hypertension	8	34.8	12	44.4	20	40.0	6	26.1	0	0.0	6	12.0	0	0.0	0	0.0	0	0.0	8	34.8	12	44.4	20	40.0
Raised blood pressure	10	43.5	7	25.9	17	34.0	7	30.4	3	11.1	10	20.0	0	0.0	0	0.0	0	0.0	10	43.5	7	25.9	17	34.0
Myocardial Infarction	5	21.7	4	14.8	9	18.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	5	21.7	4	14.8	9	18.0
Congestive Heart Failure	4	17.4	3	11.1	7	14.0	1	4.4	2	7.4	3	6.0	0	0.0	0	0.0	0	0.0	4	17.4	4	14.8	8	16.0
Peripheral arterial disease	2	8.7	1	3.7	3	6.0	1	4.4	0	0.0	1	2.0	0	0.0	0	0.0	0	0.0	2	8.7	1	3.7	3	6.0
Transient Ischaemic Attack	1	4.4	2	7.4	3	6.0	0	0.0	1	3.7	1	2.0	0	0.0	0	0.0	0	0.0	1	4.4	3	11.1	4	8.0
Arrhythmia	12	52.2	8	29.6	20	40.0	13	56.5	12	44.4	25	50.0	0	0.0	0	0.0	0	0.0	18	78.3	15	55.6	33	66.0
Hypercholesterolaemia	7	30.4	3	11.1	10	20.0	3	13.0	3	11.1	6	12.0	0	0.0	0	0.0	0	0.0	7	30.4	5	18.5	12	24.0
Diabetes	5	21.7	4	14.8	9	18.0	4	17.4	2	7.4	6	12.0	0	0.0	0	0.0	0	0.0	5	21.7	4	14.8	9	18.0
Chronic obstructive pulmonary disease	4	17.4	0	0.0	4	8.0	2	8.7	0	0.0	2	4.0	0	0.0	0	0.0	0	0.0	5	21.7	0	0.0	5	10.0

\* all other events reported as freetext are listed in Appendix 7

**Table 32. History of other conditions/events prior to start of treatment for Mixed (AF & DVT/PE) indications, by treatment group\***

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban N=23		Warfarin N=27		Total N=50		Rivaroxaban N=23		Warfarin N=27		Total N=50		Rivaroxaban N=23		Warfarin N=27		Total N=50		Rivaroxaban N=23		Warfarin N=27		Total N=50	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Liver Disorder	0	0.0	1	3.7	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	1	2.0
Abnormal liver function tests	3	13.0	1	3.7	4	8.0	3	13.0	0	0.0	3	6.0	0	0.0	0	0.0	0	0.0	3	13.0	1	3.7	4	8.0
Renal Failure	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Renal disease stage 3/4	1	4.4	4	14.8	5	10.0	1	4.4	1	3.7	2	4.0	0	0.0	0	0.0	0	0.0	1	4.4	4	14.8	5	10.0
Renal disease stage 1/2	0	0.0	2	7.4	2	4.0	1	4.4	1	3.7	2	4.0	0	0.0	0	0.0	0	0.0	1	4.4	2	7.4	3	6.0
Immobility	2	8.7	0	0.0	2	4.0	1	4.4	4	14.8	5	10.0	0	0.0	0	0.0	0	0.0	2	8.7	4	14.8	6	12.0
Thrombophilia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Coagulation disorder	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Thrombocytopenia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Malignancies	4	17.4	5	18.5	9	18.0	0	0.0	1	3.7	1	2.0	0	0.0	0	0.0	0	0.0	4	17.4	5	18.5	9	18.0
Pregnancies	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Breastfeeding	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Menorrhagia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Coronary artery bypass graft	2	8.7	3	11.1	5	10.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	8.7	3	11.1	5	10.0
Percutaneous coronary intervention	1	4.4	2	7.4	3	6.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.4	2	7.4	3	6.0
Implanted prosthetic heart valve	0	0.0	0	0.0	0	0.0	1	4.4	0	0.0	1	2.0	0	0.0	0	0.0	0	0.0	1	4.4	0	0.0	1	2.0
Surgery	3	13.0	1	3.7	4	8.0	1	4.4	1	3.7	2	4.0	0	0.0	0	0.0	0	0.0	4	17.4	2	7.4	6	12.0
Hospitalisation	8	34.8	4	14.8	12	24.0	3	13.0	6	22.2	9	18.0	0	0.0	0	0.0	0	0.0	9	39.1	8	29.6	17	34.0

\* all other events reported as freetext are listed in Appendix 7



The last cohort of 56 patients were patients that were treated with the anticoagulants of interest but whose indication was neither of the ones described above. Of these, 16 patients (28.6%) had a history of hypercholesterolaemia and 14 patients (25.0%) had a history of hypertension (Table 33).

For the most common condition, 15 (26.8%) patients had hypercholesterolaemia recorded in their medical records more than three months prior to the index date while six (10.7%) were recorded to have the condition in the three months leading up to the treatment start.

Of the rivaroxaban treated patients, five (22.7%) had a 'past' history of hypercholesterolaemia compared with three patients (13.6%) with a recent history.

Of the warfarin treated patients 10 (29.4%) had a 'past' history of hypercholesterolaemia compared with three (8.8%) with a recent history.

**Table 33. History of other cardiovascular disorders prior to start of treatment for Other indications, by treatment group\***

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban N=22		Warfarin N=34		Total N=56		Rivaroxaban N=22		Warfarin N=34		Total N=56		Rivaroxaban N=22		Warfarin N=34		Total N=56		Rivaroxaban N=22		Warfarin N=34		Total N=56	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Cerebrovascular accident	2	9.1	3	8.8	5	8.9	4	18.2	5	14.7	9	16.1	0	0.0	0	0.0	0	0.0	5	22.7	7	20.6	12	21.4
Deep Vein Thrombosis	3	13.6	1	2.9	4	7.1	1	4.6	2	5.9	3	5.4	0	0.0	0	0.0	0	0.0	3	13.6	3	8.8	6	10.7
Pulmonary embolism	2	9.1	1	2.9	3	5.4	1	4.6	3	8.8	4	7.1	0	0.0	0	0.0	0	0.0	2	9.1	4	11.8	6	10.7
Hypertension	4	18.2	9	26.5	13	23.2	1	4.6	2	5.9	3	5.4	0	0.0	0	0.0	0	0.0	5	22.7	9	26.5	14	25.0
Raised blood pressure	4	18.2	7	20.6	11	19.6	4	18.2	4	11.8	8	14.3	0	0.0	0	0.0	0	0.0	5	22.7	8	23.5	13	23.2
Myocardial Infarction	3	13.6	3	8.8	6	10.7	0	0.0	3	8.8	3	5.4	0	0.0	0	0.0	0	0.0	3	13.6	5	14.7	8	14.3
Congestive Heart Failure	1	4.6	4	11.8	5	8.9	1	4.6	2	5.9	3	5.4	0	0.0	0	0.0	0	0.0	4	18.2	5	14.7	9	16.1
Peripheral arterial disease	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Transient Ischaemic Attack	0	0.0	2	5.9	2	3.6	0	0.0	2	5.9	2	3.6	0	0.0	0	0.0	0	0.0	0	0.0	3	8.8	3	5.4
Arrhythmia	3	13.6	4	11.8	7	12.5	3	13.6	8	23.5	11	19.6	0	0.0	0	0.0	0	0.0	4	18.2	9	26.5	13	23.2
Hypercholesterolaemia	5	22.7	10	29.4	15	26.8	3	13.6	3	8.8	6	10.7	0	0.0	0	0.0	0	0.0	6	27.3	10	29.4	16	28.6
Diabetes	4	18.2	7	20.6	11	19.6	3	13.6	2	5.9	5	8.9	0	0.0	0	0.0	0	0.0	4	18.2	7	20.9	11	19.6
Chronic obstructive pulmonary disease	0	0.0	1	2.9	1	1.8	1	4.6	2	5.9	3	5.4	0	0.0	0	0.0	0	0.0	1	4.6	2	5.9	3	5.4

\* all other events reported as freetext are listed in Appendix 7

Similar to the Other indication groups, the most common other condition/event (Table 34) for this cohort was hospitalisation with 15 (26.8%) patients having been hospitalised prior to starting the treatment of interest. Of the 15 patients who were hospitalised pre-treatment, seven (12.5%) were admitted more than three months prior to start treatment while 13 (23.2%) were hospitalised in the three months prior to index date.

For the rivaroxaban treated patients five patients (22.7%) had a history of hospitalisation more than three months from the index date, compared with six patients (27.3%) with a recent history of hospitalisation.

For the warfarin treated patients two patients (5.9%) had a history of hospitalisation more than three months from the index date, compared with seven patients (20.6%) with a recent history of hospitalisation.

**Table 34. History of other conditions/events prior to start of treatment for Other indications, by treatment group\***

	Past (>3 months)						Recent (<3 months)						Period unknown <sup>a</sup>						Any period prior					
	Rivaroxaban N=22		Warfarin N=34		Total N=56		Rivaroxaban N=22		Warfarin N=34		Total N=56		Rivaroxaban N=22		Warfarin N=34		Total N=56		Rivaroxaban N=22		Warfarin N=34		Total N=56	
	n	%	n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%
Liver Disorder	1	4.6	1	2.9	2	3.6	1	4.6	0	0.0	1	1.8	0	0.0	1	2.9	1	1.8	1	4.6	1	2.9	2	3.6
Abnormal liver function tests	1	4.6	1	2.9	2	3.6	0	0.0	1	2.9	1	1.8	0	0.0	0	0.0	0	0.0	1	4.6	2	5.9	3	5.4
Renal Failure	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Renal disease stage 3/4	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	1.8
Renal disease stage 1/2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Immobility	2	9.1	0	0.0	2	3.6	4	18.2	0	0.0	4	7.1	0	0.0	0	0.0	0	0.0	4	18.2	0	0.0	4	7.1
Thrombophilia	0	0.0	1	2.9	1	1.8	1	4.6	1	2.9	2	3.6	0	0.0	0	0.0	0	0.0	1	4.6	1	2.9	2	3.6
Coagulation disorder	1	4.6	0	0.0	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.6	0	0.0	1	1.8
Thrombocytopenia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Malignancies	1	4.6	5	14.7	6	10.7	1	4.6	2	5.9	3	5.4	0	0.0	1	2.9	1	1.8	1	4.6	5	14.7	6	10.7
Pregnancies	0	0.0	1	2.9	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	1.8
Breastfeeding	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Menorrhagia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Coronary artery bypass graft	0	0.0	3	8.8	3	5.4	0	0.0	1	2.9	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0	4	11.8	4	7.1
Percutaneous coronary intervention	0	0.0	2	5.9	2	3.6	0	0.0	1	2.9	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0	3	8.8	3	5.4
Implanted prosthetic heart valve	0	0.0	1	2.9	1	1.8	0	0.0	1	2.9	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0	2	5.9	2	3.6
Surgery	4	18.2	4	11.8	8	14.3	2	9.1	3	8.8	5	8.9	0	0.0	0	0.0	0	0.0	4	18.2	6	17.7	10	17.9
Hospitalisation	5	22.7	2	5.9	7	12.5	6	27.3	7	20.6	13	23.2	0	0.0	0	0.0	0	0.0	8	36.4	7	20.6	15	26.8

\*all other events reported as freetext are listed in Appendix 7

#### 10.2.1.4 Prior medication use

Investigators were asked to indicate if the patient had been prescribed any medications within 28 days prior to starting treatment with either rivaroxaban or warfarin to capture information on any recent use or newly prescribed medications that may impact on individual patient baseline risk. More than one medication could be reported for each patient and so counts are not mutually exclusive. Note that for all medications, prevalence estimates are reported of evaluable cohort, by treatment group. This approach was justified in that physicians are more likely to record prescribing or use of a medication rather than confirm non-use. The prevalence of use of each therapeutic class of medicines is presented in Table 35 – Table 38.

In the AF group (Table 35), 642 (66.5%) and 514 (64.7%) patients had used one or more antithrombotic medications in the 28 days prior to starting rivaroxaban or warfarin respectively. The most frequently reported agents were antiplatelet drugs with aspirin use reported in 396 (41.0%) patients in the rivaroxaban group and 378 (47.6%) patients in the warfarin group. In the rivaroxaban group, 156 (16.2%) patients were reported to have used warfarin in the 28 days prior to starting treatment with rivaroxaban.

**Table 35. Antithrombotic medication use history within 28 days prior to start of treatment for indication AF, by treatment group**

Medication	Rivaroxaban N=965		Warfarin N=794	
	n	%	n	%
<b>Any Antithrombotic Medication</b>	<b>642</b>	<b>66.5</b>	<b>514</b>	<b>64.7</b>
<b>Oral Anticoagulants</b>				
Warfarin	156	16.2	N/A <sup>f</sup>	
Phenindione	0	0.0	N/A <sup>f</sup>	
Nicoumalone	2	0.2	N/A <sup>f</sup>	
Dabigatran	5	0.5	N/A <sup>g</sup>	
Apixaban	1	0.1	N/A <sup>g</sup>	
Other <sup>a</sup>	0	0.0	N/A <sup>g</sup>	
Any (at least one) oral anticoagulant	163	16.1	N/A	
<b>Parenteral Anticoagulants</b>				
Bivalirudin	0	0.0	N/A <sup>g</sup>	0.0
Unfractionated heparin <sup>b</sup>	7	0.7	8 <sup>+</sup>	1.0
Low molecular weight heparin <sup>c</sup>	151	15.6	169 <sup>+</sup>	21.3
Fondaparinux	7	0.7	12 <sup>+</sup>	1.5
Other <sup>d</sup>	4	0.4	1 <sup>+</sup>	0.1
Any (at least one) parenteral anticoagulant	163	16.9	176 <sup>+</sup>	22.2
<b>Antiplatelets</b>				
Aspirin (<=300mg)	396	41.0	378	47.6
Clopidogrel	138	14.3	133	16.8
Abciximab	0	0.0	0	0.0
Dipyridamole	13	1.3	4	0.5
Eptifibatide	0	0.0	0	0.0

Medication	Rivaroxaban N=965		Warfarin N=794	
	n	%	n	%
Tirofiban	0	0.0	0	0.0
Other <sup>e</sup>	8	0.8	2	0.3
Any (at least one) antiplatelet	469	48.6	444	55.9

<sup>a</sup> to be listed; <sup>b</sup> including monaparin, monaparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>†</sup> as part of treatment of current indication only

In the DVT/PE group (Table 36), 1001 (65.3%) and 875 (72.2%) patients were reported to have used one or more antithrombotic medications in the 28 days prior to starting rivaroxaban or warfarin respectively. The most frequently reported drugs in this group were low molecular weight heparins (n=862, 56.3% in rivaroxaban group; n=831, 68.6% in warfarin group). In the rivaroxaban group, 96 (6.3%) patients were reported to have used warfarin in the 28 days prior to starting treatment with rivaroxaban.

**Table 36. Antithrombotic medication use history within 28 days prior to start of treatment for indication DVT/PE, by treatment group**

Medication	Rivaroxaban N=1532		Warfarin N=1212	
	n	%	n	%
<b>Any Antithrombotic Medication</b>	<b>1001</b>	<b>65.3</b>	<b>875</b>	<b>72.2</b>
<b>Oral Anticoagulants</b>				
Warfarin	96	6.3	N/A <sup>f</sup>	
Phenindione	0	0.0	N/A <sup>f</sup>	
Nicoumalone	1	0.1	N/A <sup>f</sup>	
Dabigatran	4	0.3	N/A <sup>g</sup>	
Apixaban	3	0.2	N/A <sup>g</sup>	
Other <sup>a</sup>	2	0.1	N/A <sup>g</sup>	
Any (at least one) oral anticoagulant	106	6.9	N/A	
<b>Parenteral Anticoagulants</b>				
Bivalirudin	0	0.0	0	0.0
Unfractionated heparin <sup>b</sup>	27	1.8	35 <sup>†</sup>	2.9
Low molecular weight heparin <sup>c</sup>	862	56.3	831 <sup>†</sup>	68.6
Fondaparinux	20	1.3	19 <sup>†</sup>	1.6
Other <sup>d</sup>	15	1.0	6 <sup>†</sup>	0.5
Any (at least one) parenteral anticoagulant	879	57.4	841 <sup>†</sup>	69.4
<b>Antiplatelets</b>				
Aspirin (<=300mg)	184	12.0	140	11.6
Clopidogrel	79	5.2	66	5.4
Abciximab	1	0.1	0	0.0
Dipyridamole	2	0.1	3	0.2
Eptifibatide	1	0.1	0	0.0
Tirofiban	0	0.0	0	0.0
Other <sup>e</sup>	2	0.1	2	0.2
Any (at least one) antiplatelet	227	14.8	174	14.4

<sup>a</sup> to be listed; <sup>b</sup> including monaparin, monaparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>†</sup> as part of treatment of current indication only

In the Mixed indication group (Table 37), 19 (82.6%) and 22 (81.5%) patients were reported to have used one or more antithrombotic medications in the 28 days prior to starting rivaroxaban or warfarin respectively. The most frequently reported drugs in this group were low molecular weight heparins (n=10, 43.5% in rivaroxaban group; n=18, 66.7% in warfarin group). In the rivaroxaban group, seven (30.4%) patients were reported to have used warfarin in the 28 days prior to starting treatment with rivaroxaban.

**Table 37. Antithrombotic medication use history within 28 days prior to start of treatment for Mixed (AF & DVT/PE) indications, by treatment group**

Medication	Rivaroxaban N=23		Warfarin N=27	
	n	%	n	%
<b>Any Antithrombotic Medication</b>	<b>19</b>	<b>82.6</b>	<b>22</b>	<b>81.5</b>
<b>Oral Anticoagulants</b>				
Warfarin	7	30.4	N/A <sup>f</sup>	
Phenindione	0	0.0	N/A <sup>f</sup>	
Nicoumalone	1	4.3	N/A <sup>f</sup>	
Dabigatran	0	0.0	N/A <sup>g</sup>	
Apixaban	0	0.0	N/A <sup>g</sup>	
Other <sup>a</sup>	0	0.0	N/A <sup>g</sup>	
Any (at least one) oral anticoagulant	8	34.8	N/A	
<b>Parenteral Anticoagulants</b>				
Bivalirudin	0	0.0	0	0.0
Unfractionated heparin <sup>b</sup>	0	0.0	0 <sup>+</sup>	0.0
Low molecular weight heparin <sup>c</sup>	10	43.5	18 <sup>+</sup>	66.7
Fondaparinux	0	4.3	1 <sup>+</sup>	3.7
Other <sup>d</sup>	1	0.0	0 <sup>+</sup>	0.0
Any (at least one) parenteral anticoagulant	11	47.8	19 <sup>+</sup>	70.4
<b>Antiplatelets</b>				
Aspirin (<=300mg)	7	30.4	10	37.0
Clopidogrel	3	13.0	6	22.2
Abciximab	0	0.0	0	0.0
Dipyridamole	0	0.0	0	0.0
Eptifibatide	0	0.0	0	0.0
Tirofiban	1	4.3	0	0.0
Other <sup>e</sup>	0	0.0	0	0.0
Any (at least one) antiplatelet	9	39.1	14	51.9

<sup>a</sup> none reported <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> includes fibrinolytic drugs <sup>e</sup> includes prasugrel, ticagrelor; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

In the Other indication group (Table 38), 16 (72.7%) and 28 (82.4%) patients were reported to have used one or more antithrombotic medications in the 28 days prior to starting rivaroxaban or warfarin respectively. In the warfarin group, the most frequently reported drugs were low molecular weight heparins (16, 47.1%). In the rivaroxaban

group, eight (36.4%) patients were reported to have used warfarin in the 28 days prior to starting treatment with rivaroxaban.

**Table 38. Antithrombotic medication use history within 28 days prior to start of treatment for Other indications, by treatment group**

Medication	Rivaroxaban N=22		Warfarin N=34	
	n	%	n	%
<b>Any Antithrombotic Medication</b>	<b>16</b>	<b>72.7</b>	<b>28</b>	<b>82.4</b>
<b>Oral Anticoagulants</b>				
Warfarin	8	36.4	N/A <sup>f</sup>	
Phenindione	0	0.0	N/A <sup>f</sup>	
Nicoumalone	0	0.0	N/A <sup>f</sup>	
Dabigatran	0	0.0	N/A <sup>g</sup>	
Apixaban	0	0.0	N/A <sup>g</sup>	
Other <sup>a</sup>	0	0.0	N/A <sup>g</sup>	
Any (at least one) oral anticoagulant	8	36.4	N/A	
<b>Parenteral Anticoagulants</b>				
Bivalirudin	0	0.0	1	2.9
Unfractionated heparin <sup>b</sup>	1	4.5	4 <sup>+</sup>	11.7
Low molecular weight heparin <sup>c</sup>	5	22.7	16 <sup>+</sup>	47.1
Fondaparinux	0	0.0	1 <sup>+</sup>	2.9
Other <sup>d</sup>	0	0.0	0 <sup>+</sup>	0.0
Any (at least one) parenteral anticoagulant	6	27.3	19 <sup>+</sup>	55.9
<b>Antiplatelets</b>				
Aspirin (<=300mg)	5	22.7	14	41.2
Clopidogrel	3	13.6	7	20.6
Abciximab	0	0.0	0	0.0
Dipyridamole	0	0.0	0	0.0
Eptifibatide	0	0.0	0	0.0
Tirofiban	0	0.0	0	0.0
Other <sup>e</sup>	0	0.0	1	2.9
Any (at least one) antiplatelet	6	27.3	17	50.0

<sup>a</sup> none reported; <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> none reported; <sup>e</sup> includes ticagrelor; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

Prescribers were asked to indicate which of the medications reported as being used within 28 days prior (Table 35 – Table 38) had been specifically switched (and assumed then stopped) onto rivaroxaban or warfarin, for those patients for whom such switching had been reported (Table 39 and Table 42).

In the AF cohort, 555 (57.5%) of the 965 patients in the rivaroxaban group and 302 (38.0%) of the 794 patients in the warfarin group were reported to have switched directly from another anti-thrombotic agent (Table 39). The majority of these patients switched directly from an antiplatelet drug. Over half of those switching directly to rivaroxaban or warfarin; switched from aspirin and around a quarter of the rivaroxaban patients switched directly from warfarin.



**Table 39. Anticoagulant/Antiplatelet switching for AF indication group prior to starting rivaroxaban or warfarin.**

Medication	Rivaroxaban N=555		Warfarin N=302	
	n	%	n	%
<b>Oral Anticoagulants</b>				
Warfarin	137	24.7	N/A <sup>f</sup>	
Phenindione	0	0.0	N/A <sup>f</sup>	
Nicoumalone	2	0.4	N/A <sup>f</sup>	
Dabigatran	5	0.9	N/A <sup>g</sup>	
Apixaban	1	0.2	N/A <sup>g</sup>	
Other <sup>a</sup>	0	0.0	N/A	
Any (at least one) oral anticoagulant	144	25.9	N/A	
<b>Parenteral Anticoagulants</b>				
Bivalirudin	0	0.0	0	0.0
Unfractionated heparin <sup>b</sup>	4	0.7	2 <sup>+</sup>	0.7
Low molecular weight heparin <sup>c</sup>	91	16.4	92 <sup>+</sup>	30.5
Fondaparinux	4	0.7	3 <sup>+</sup>	1.0
Other <sup>d</sup>	0	0.0	0 <sup>+</sup>	0.0
Any (at least one) parenteral anticoagulant	99	17.8	95 <sup>+</sup>	31.5
<b>Antiplatelets</b>				
Aspirin (<=300mg)	289	52.1	180	59.6
Clopidogrel	88	15.9	68	22.5
Abciximab	0	0.0	0	0.0
Dipyridamole	7	1.3	2	0.7
Eptifibatide	0	0.0	0	0.0
Tirofiban	0	0.0	0	0.0
Other <sup>e</sup>	5	0.9	0	0.0
Any (at least one) antiplatelet	359	64.7	235	77.8
Prior switch drug not specified	5	0.9	2	0.7

<sup>a</sup> none reported; <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> none reported; <sup>e</sup> includes prasugrel and ticagrelor; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

In the DVT/PE cohort, 831 (54.2%) of the 1532 patients in the rivaroxaban group and 540 (44.6%) of the 1212 patients in the warfarin group were reported to have switched directly from another anti-thrombotic agent (Table 40). The majority of these patients switched directly from a low molecular weight heparin.

**Table 40. Anticoagulant/Antiplatelet switching for DVT/PE indication group prior to starting rivaroxaban or warfarin.**

Medication	Rivaroxaban N=831		Warfarin N=540	
	n	%	n	%
<b>Oral Anticoagulants</b>				
Warfarin	80	9.6	N/A <sup>f</sup>	
Phenindione	0	0.0	N/A <sup>f</sup>	
Nicoumalone	1	0.1	N/A <sup>f</sup>	
Dabigatran	3	0.4	N/A <sup>g</sup>	
Apixaban	2	0.2	N/A <sup>g</sup>	
Other <sup>a</sup>	0	0.0	N/A	
Any (at least one) oral anticoagulant	86	10.3	N/A	
<b>Parenteral Anticoagulants</b>				
Bivalirudin	0	0.0	0	0.0
Unfractionated heparin <sup>b</sup>	9	1.1	15 <sup>+</sup>	2.8
Low molecular weight heparin <sup>c</sup>	707	85.1	517 <sup>+</sup>	95.7
Fondaparinux	7	0.8	6 <sup>+</sup>	1.1
Other <sup>d</sup>	6	0.7	4 <sup>+</sup>	0.7
Any (at least one) parenteral anticoagulant	721	86.8	528 <sup>+</sup>	97.8
<b>Antiplatelets</b>				
Aspirin (<=300mg)	59	7.1	36	6.7
Clopidogrel	33	4.0	16	3.0
Abciximab	0	0.0	0	0.0
Dipyridamole	1	0.1	0	0.0
Eptifibatide	0	0.0	0	0.0
Tirofiban	0	0.0	0	0.0
Other <sup>e</sup>	0	0.0	1	0.2
Any (at least one) antiplatelet	78	9.4	48	8.9
Prior switch drug not specified	4	0.5	0	0.0

<sup>a</sup> none reported; <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> includes fibrinolytics, argobatran monohydrate <sup>e</sup> ticagrelor; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

In the Mixed indication cohort, 18 (78.3%) of the 23 patients in the rivaroxaban group and 16 (59.3%) of the 27 patients in the warfarin group were reported to have switched directly from another anti-thrombotic agent (Table 41). Of these, the majority of patients in the warfarin group switched directly from a low molecular weight heparin while in the rivaroxaban group, a range of drugs were reported to have been used, including seven patients (38.9%) who switched directly from warfarin to rivaroxaban.

**Table 41. Anticoagulant/Antiplatelet switching for Mixed indication group prior to starting rivaroxaban or warfarin.**

Medication	Rivaroxaban N=18		Warfarin N=16	
	n	%	n	%
<b>Oral Anticoagulants</b>				
Warfarin	7	38.9	N/A <sup>f</sup>	
Phenindione	0	0.0	N/A <sup>f</sup>	
Nicoumalone	1	5.6	N/A <sup>f</sup>	
Dabigatran	0	0.0	N/A <sup>g</sup>	
Apixaban	0	0.0	N/A <sup>g</sup>	
Other <sup>a</sup>	0	0.0	N/A	
Any (at least one) oral anticoagulant	8	44.4	N/A	
<b>Parenteral Anticoagulants</b>				
Bivalirudin	0	0.0	0	0.0
Unfractionated heparin <sup>b</sup>	0	0.0	0 <sup>+</sup>	0.0
Low molecular weight heparin <sup>c</sup>	6	33.3	12 <sup>+</sup>	75.0
Fondaparinux	0	0.0	0 <sup>+</sup>	0.0
Other <sup>d</sup>	0	0.0	0 <sup>+</sup>	0.0
Any (at least one) parenteral anticoagulant	6	33.3	12 <sup>+</sup>	75.0
<b>Antiplatelets</b>				
Aspirin (<=300mg)	5	27.8	6	37.5
Clopidogrel	3	16.7	4	25.0
Abciximab	0	0.0	0	0.0
Dipyridamole	0	0.0	0	0.0
Eptifibatide	0	0.0	0	0.0
Tirofiban	0	0.0	0	0.0
Other <sup>e</sup>	0	0.0	0	0.0
Any (at least one) antiplatelet	7	38.9	8	50.0
Prior switch drug not specified	0	0.0	1	6.3

<sup>a</sup> none reported; <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> none reported <sup>e</sup> none reported <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

In the Other indication cohort, 15 (68.2%) of the 22 patients in the rivaroxaban group and 19 (55.9%) of the 34 patients in the warfarin group were reported to have switched directly from another anti-thrombotic agent (Table 42). Of these, the majority of patients in the warfarin group switched directly from a low molecular weight heparin, while in the rivaroxaban group, almost half of patients switched directly from warfarin.

**Table 42. Anticoagulant/Antiplatelet switching for Other indication group prior to starting rivaroxaban or warfarin.**

Medication	Rivaroxaban N=15		Warfarin N=19	
	n	%	n	%
<b>Oral Anticoagulants</b>				
Warfarin	7	46.7	N/A <sup>f</sup>	
Phenindione	0	0.0	N/A <sup>f</sup>	
Nicoumalone	0	0.0	N/A <sup>f</sup>	
Dabigatran	0	0.0	N/A <sup>g</sup>	
Apixaban	0	0.0	N/A <sup>g</sup>	
Other <sup>a</sup>	0	0.0	N/A	
Any (at least one) oral anticoagulant	7	46.7	N/A	
<b>Parenteral Anticoagulants</b>				
Bivalirudin	0	0.0	0	0.0
Unfractionated heparin <sup>b</sup>	1	6.7	3 <sup>+</sup>	15.8
Low molecular weight heparin <sup>c</sup>	2	13.3	10 <sup>+</sup>	52.6
Fondaparinux	0	0.0	0 <sup>+</sup>	0.0
Other <sup>d</sup>	0	0.0	0 <sup>+</sup>	0.0
Any (at least one) parenteral anticoagulant	3	20.0	11 <sup>+</sup>	57.9
<b>Antiplatelets</b>				
Aspirin (<=300mg)	3	20.0	6	31.6
Clopidogrel	3	20.0	2	10.5
Abciximab	0	0.0	0	0.0
Dipyridamole	0	0.0	0	0.0
Eptifibatide	0	0.0	0	0.0
Tirofiban	0	0.0	0	0.0
Other <sup>e</sup>	0	0.0	0	0.0
Any (at least one) antiplatelet	6	40.0	8	42.1
Prior switch drug not specified	1	6.7	0	0.0

<sup>a</sup> none reported; <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> none reported <sup>e</sup> none reported <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

Investigators were asked to provide the supporting reasons for switching treatment onto either rivaroxaban or warfarin; these are summarised in Table 43. Investigators could have reported more than one reason so counts are not mutually exclusive.

The most frequently reported reasons for switching to rivaroxaban from another oral anticoagulant were similar in the different indication groups and included doctor decisions, lifestyle issues and INR fluctuations (Table 43).

**Table 43. Reasons for Anticoagulant or Antiplatelet switches immediately prior to start of rivaroxaban or warfarin, by indication and treatment group**

Reason for switching from oral anticoagulant onto rivaroxaban	n	%	Reason for switching from oral anticoagulant onto warfarin	n	%
<b>AF (N=144)</b>			<b>AF</b>	<b>NA</b>	
Doctor decision	33	22.9			
Refusal of treatment by pt.	24	16.7			
Doctor Preference	14	9.7			
Lifestyle issues	11	7.6			
Reason not provided	9	6.3			
Cerebrovascular accident	9	6.3			
INR fluctuation	9	6.3			
Treatment noncompliance	8	5.6			
Anticoagulation drug level below therapeutic	5	3.5			
Other*	47	32.6			
<b>DVT/PE (N=86)</b>			<b>DVT/PE</b>	<b>NA</b>	
Lifestyle issues	19	22.1			
Doctor decision	15	17.4			
INR fluctuation	12	14.0			
Refusal of treatment by pt.	9	10.5			
Deep vein thrombosis	5	5.8			
Treatment noncompliance	5	5.8			
Other*	43	50.0			
<b>Mixed (N=8)</b>			<b>Mixed (AF &amp; DVT/PE)</b>	<b>NA</b>	
Lifestyle issues	2	25.0			
Alopecia	1	12.5			
Cerebrovascular accident	1	12.5			
Doctor decision	1	12.5			
Epistaxis	1	12.5			
Gingival bleeding	1	12.5			
INR fluctuation	1	12.5			
Prescribing guidelines	1	12.5			
Reason not provided	1	12.5			
<b>Other Indications (N=7)</b>			<b>Other Indications</b>	<b>NA</b>	
INR fluctuation	2	28.6			
Alopecia	1	14.3			
Doctor decision	1	14.3			
Drug ineffective	1	14.3			
Drug therapy changed	1	14.3			
End of course	1	14.3			
Lifestyle issues	1	14.3			
Poor venous access	1	14.3			

\*An abridged list of reasons for switching are presented here; all reasons for direct switching are described in Appendix 8.

The most frequently reported reasons for switching to rivaroxaban or warfarin from a parenteral anticoagulant were also similar in the different indication groups and included doctor and patient-related reasons and indication-related reasons such 'anticoagulant therapy', 'atrial fibrillation' and 'deep vein thrombosis'. (Table 44)

**Table 44. Reasons for Parenteral Anticoagulant switches immediately prior to start of rivaroxaban or warfarin, by indication and treatment group**

Reason for switching from parenteral anticoagulant onto rivaroxaban	n	%	Reason for switching from parenteral anticoagulant onto warfarin	n	%
<b>AF (n=99)</b>			<b>AF (n=95)</b>		
Doctor decision	25	25.3	Anticoagulant therapy	19	20.0
Reason not provided	23	23.2	Reason not provided	14	14.7
Atrial fibrillation	17	17.2	Lifestyle issues	13	13.7
Anticoagulant therapy	6	6.1	Doctor decision	11	11.6
Dr Preference	6	6.1	International normalised ratio	11	11.6
Stroke risk	6	6.1	Anticoagulation drug level above therapeutic	8	8.4
Refusal of treatment by pt.	5	5.1	Atrial fibrillation	8	8.4
Other*	21	21.2	Other*	19	20.0
<b>DVT/PE (n=721)</b>			<b>DVT/PE (n=528)</b>		
Reason not provided	115	16.0	Anticoagulant therapy	132	25.0
Anticoagulant therapy	83	11.7	Reason not provided	55	10.4
Drug therapy changed	82	11.5	Secondary care advice, formulary or guideline	50	9.5
Doctor decision	69	9.6	Pulmonary embolism	46	8.7
Prescribing guidelines	58	8.0	Doctor decision	44	8.3
Lifestyle issues	56	7.8	Deep vein thrombosis	38	7.2
Deep vein thrombosis	54	7.5	International normalised ratio	30	5.7
Pulmonary embolism	49	6.8	Anticoagulation drug level above therapeutic	28	5.3
Secondary care advice, formulary or guideline	29	4.0	Drug therapy changed	25	4.7
Refusal of treatment by pt.	29	4.0	Lifestyle issues	25	4.7
Other*	172	23.9	Other*	131	24.8
<b>Mixed (n=6)</b>			<b>Mixed (n=12)</b>		
Drug therapy changed	2	33.3	Anticoagulant therapy	4	33.3
Refusal of treatment by pt.	2	33.3	Lifestyle issues	2	16.7
Reason not provided	1	16.7	Other*	7	58.3
Doctor decision	1	16.7			
Lifestyle issues	1	16.7			
<b>Other Indications (n=3)</b>			<b>Other Indications (n=11)</b>		
Reason not provided	1	33.3	Secondary care advice, formulary or guideline	3	27.3
Drug therapy changed	1	33.3	Reason not provided	2	18.2
Refusal of treatment by pt.	1	33.3	Therapy regimen changed	2	18.2
			Other*	6	54.5

\*An abridged list of reasons are presented here; all reasons for direct switching are described in Appendix 8.

Again, the most frequently reported reasons for switching to rivaroxaban or warfarin from an antiplatelet were similar in the different indication groups and included doctor and patient-related reasons and indication-related reasons. (Table 45)

**Table 45. Reasons for Antiplatelet switches immediately prior to start of rivaroxaban or warfarin, by indication and treatment group**

Reason for switching from antiplatelet onto rivaroxaban	n	%	Reason for switching from antiplatelet onto warfarin	n	%
<b>AF (n=359)</b>			<b>AF (n=235)</b>		
Atrial fibrillation	146	60.2	Atrial fibrillation	95	40.4
Doctor decision	84	34.4	Doctor decision	30	12.8
Reason not given	30	12.0	Reason not provided	23	9.8
Dr Preference	23	10.0	Anticoagulant therapy	23	9.8
Cerebrovascular accident	21	8.9	Prescribing guidelines	17	7.2
Anticoagulant therapy	21	8.1	Cerebrovascular accident	15	6.4
Stroke risk	14	5.8	Dr Preference	11	4.7
Prescribing guidelines	12	4.6	International normalised ratio	11	4.7
Drug therapy changed	13	5.0	Anticoagulation drug level above therapeutic	9	3.8
Transient ischaemic attack	11	4.2	Secondary care advice, formulary or guideline	8	3.4
Other*	64	17.8	Other*	62	26.4
<b>DVT/PE (n=78)</b>			<b>DVT/PE (n=48)</b>		
Reason not provided	15	19.2	Reason not provided	11	22.9
Drug therapy changed	14	17.9	Deep vein thrombosis	9	18.8
Pulmonary embolism	14	17.9	Drug therapy changed	5	10.4
Doctor decision	11	14.1	Pulmonary embolism	5	10.4
Deep vein thrombosis	10	12.8	Secondary care advice, formulary or guideline	5	10.4
Anticoagulant therapy	7	9.0	Anticoagulant therapy	4	8.3
Acute myocardial infarction	3	3.8	Doctor decision	3	6.3
Practice advice, formulary or guideline	3	3.8	International normalised ratio	2	4.2
Prescribing guidelines	3	3.8	Pre-existing condition improved	2	4.2
Secondary care advice, formulary or guideline	3	3.8	Short course only	2	4.2
Other*	13	16.7	Other*	9	18.8
<b>Mixed (n=7)</b>			<b>Mixed (n=8)</b>		
Pulmonary embolism	4	57.1	Anticoagulant therapy	2	25.0
Reason not provided	2	28.6	Anticoagulation drug level above therapeutic	2	25.0
Atrial fibrillation	2	28.6	NICE guidelines	2	25.0
Doctor decision	2	28.6	Reason to provided	1	12.5
Drug therapy changed	1	14.3	Deep vein thrombosis	1	12.5
			Drug therapy changed	1	12.5
			Post thrombotic syndrome	1	12.5
			Pulmonary embolism	1	12.5
<b>Other Indications (n=6)</b>			<b>Other Indications (n=8)</b>		
Reason not provided	3	50.0	Atrial fibrillation	2	25.0
Doctor decision	2	33.3	Atrial flutter	2	25.0
Carotid artery thrombosis	1	16.7	Arterial thrombosis	1	12.5
Embolic stroke	1	16.7	Cerebrovascular accident	1	12.5
			Dr Preference	1	12.5
			International normalised ratio	1	12.5
			Lifestyle issues	1	12.5
			Prescribing guidelines	1	12.5

\*An abridged list of reasons are presented here; all reasons for direct switching are described in Appendix 8.

Investigators were also asked to provide the titration details of the treatment switched onto for either rivaroxaban or warfarin; Table 46 and Table 47 provide details of the total daily dose of the drug(s) from which patients were directly switched to rivaroxaban or warfarin. For the majority of patients the dose titration details were not specified, therefore median and IQR are not presented. Where the dose frequency was not given, this was assumed to be once daily.

**Table 46. Titration details of anticoagulant/antiplatelet switch onto rivaroxaban**

Drug/Class	No. switched	Total daily dose at start of switch interval	n	%
<b>Oral Anticoagulants</b>				
Apixaban	3	>=10, <20mg	1	33.3
		>=20mg	1	33.3
		Dose not specified	1	33.3
Dabigatran	8	<=300mg	1	12.5
		Dose not specified	7	87.5
Nicoumalone	4	Dose not specified	4	100.0
Warfarin	231	<2.5mg	5	2.2
		>=2.5, <5mg	23	10.0
		>=5.0, <10mg	11	4.8
		>=10, <20mg	5	2.2
		>=20, <30mg	1	0.4
		Dose not specified	186	80.5
<b>Parenteral Anticoagulants</b>				
Alteplase	6	10mg	1	16.7
		Dose not specified	5	83.3
Heparin	14	>=10,000 iu <20,000iu	1	7.1
		>=20,000 iu	2	14.2
		Dose not specified	11	78.6
LMWH (drug not specified)	112	Dose not specified	112	100.0
Dalteparin sodium	264	<5,000iu	3	1.1
		>=5,000 iu <10,000iu	17	6.4
		>=10,000 iu <20,000iu	105	39.8
		Dose not specified	139	52.7
Enoxaparin	357	<50mg	17	4.8
		>=50mg <100mg	17	4.8
		>=100mg <200mg	135	37.8
		>=200mg	7	2.0
		Dose not specified	181	50.7
Fondaparinux sodium	11	2.5mg	4	36.4
		Dose not specified	7	63.6
Tinzaparin	74	<5,000iu	2	2.7
		>=5,000 iu <10,000iu	1	1.4
		>=10,000 iu <20,000iu	13	17.6
		>=20,000	3	4.1
		Dose not specified	55	74.3



Drug/Class	No. switched	Total daily dose at start of switch interval	n	%
<b>Antiplatelets</b>				
Aspirin	356	75mg	84	23.6
		>75mg <=300mg	124	34.8
		Dose not specified	148	41.6
Clopidogrel	127	75mg	54	42.5
		>75mg <=300mg	5	3.9
		Dose not specified	68	53.4
Dipyridamole	8	200mg	1	12.5
		400mg	2	25.0
		Dose not specified	5	62.5
Prasugrel	1	Dose not specified	1	100.0
Ticagrelor	2	180mg	1	50.0
		Dose not specified	1	50.0

**Table 47. Titration details of anticoagulant/antiplatelet switch onto warfarin**

Drug/Class	No. switched	Total daily dose at start of switch interval	n	%
<b>Parenteral Anticoagulants</b>				
Alteplase	2	Dose not specified	2	100.0
Argobatran monohydrate	1	Dose not specified	1	100.0
Heparin	20	<10,000	4	20.0
		Dose not specified	16	80.0
LMWH (drug not specified)	34	Dose not specified		100.0
Dalteparin sodium	172	<5,000iu	0	0.0
		>=5,000 iu <10,000iu	3	21.5
		>=10,000 iu <20,000iu	89	51.7
		>=20,000	2	1.2
		Dose not specified	78	45.3
Enoxaparin	292	<50mg	7	2.4
		>=50mg <100mg	19	6.5
		>=100mg <200mg	116	39.7
		>=200mg	2	0.7
		Dose not specified	148	50.7
Fondaparinux sodium	9	2.5mg	3	33.3
		Dose not specified	6	66.7
Tenecteplase	1	Dose not specified	1	100.0
Tinzaparin	137	<5,000iu	8	5.8
		>=5,000 iu <10,000iu	0	0.0
		>=10,000 iu <20,000iu	44	32.1
		>=20,000	12	8.8
		Dose not specified	73	53.3
<b>Antiplatelets</b>				
Aspirin	228	75mg	41	18.0
		>75mg <=300mg	45	19.7
		Dose not specified	142	62.3
Clopidogrel	90	75mg	22	24.4
		>75mg <=300mg	2	2.2
		Dose not specified	66	73.3
Dipyridamole	2	400mg	2	100.0
Ticagrelor	1	180mg	1	100.0

Investigators were asked to indicate whether the patient had used any of the other selected therapeutic classes of medications in the month prior to the index date. Aggregate counts are provided according to tick box responses in Table 48 – Table 51, grouped by study drug and indication.

In the AF cohort, the proportions of patients using the drugs or drug classes listed in Table 48 were broadly similar in the rivaroxaban and warfarin groups. A larger proportion of patients were using prescribed medication in the 28 days prior to starting warfarin (n=593, 74.7%) compared to those starting rivaroxaban (n=559, 57.9%). Prior use of aspirin (>300mg) was reported in 145 (15.0%) rivaroxaban users and 161 (20.3%) warfarin users. It is possible that this is a reporting error in that respondents reported low dose aspirin use within this category. Prior use of medication that may predispose to bleeding (such as NSAIDs or SSRIs) or drugs that may interact with anticoagulant medications (such as anticonvulsants, azole antifungals) was reported in less than 5% of patients in the AF cohort.

**Table 48. Other medication history within 28 days a of initiation prior to start of treatment for indication AF, by treatment group**

Rivaroxaban N=965				Warfarin N=794			
Medication	n	%		Medication	n	%	
Analgesics & Antiinflammatory Agents				Analgesics & Antiinflammatory Agents			
Paracetamol	217	22.5		Paracetamol	184	23.2	
Aspirin (>300mg)	145	15.0		Aspirin (>300mg)	161	20.3	
NSAID	32	3.3		NSAID	26	3.3	
Other	133	13.8		Other	111	14.0	
Anti-convulsants				Anti-convulsants			
Phenytoin	2	0.2		Phenytoin	2	0.3	
Phenobarbital	0	0.0		Phenobarbital	1	0.1	
Carbamazepine	7	0.7		Carbamazepine	3	0.4	
Primidone	0	0.0		Primidone	0	0.0	
Other	17	1.8		Other	13	1.6	
Anti-infectives				Anti-infectives			
Ketoconazole	1	0.1		Ketoconazole	0	0.0	
Itraconazole	1	0.1		Itraconazole	0	0.0	
Posaconazole	1	0.1		Posaconazole	0	0.0	
Ritonavir	1	0.1		Ritonavir	0	0.0	
Clarithromycin	17	1.8		Clarithromycin	18	2.3	
Erythromycin	2	0.2		Erythromycin	1	0.1	
Rifampicin	1	0.1		Rifampicin	0	0.0	
Sulfamethoxazole	1	0.1		Sulfamethoxazole	0	0.0	
Metronidazole	4	0.4		Metronidazole	2	0.3	
Griseofulvin	1	0.1		Griseofulvin	0	0.0	
Other	98	10.2		Other	68	8.6	
Antidepressants				Antidepressants			
Tricyclic and related <sup>a</sup>	25	2.6		Tricyclic and related <sup>a</sup>	27	3.4	

Rivaroxaban N=965				Warfarin N=794			
Medication	n	%		Medication	n	%	
MAOI	1	0.1		MAOI	0	0.0	
SSRI	39	4.0		SSRI	36	4.5	
St John's Wort	0	0.0		St John's Wort	0	0.0	
Other	24	2.5		Other	25	3.1	
Female hormone products				Female hormone products			
Oestrogen and/or progestogen	4	0.4		Oestrogen and/or progestogen	3	0.4	
Hormone replacement therapies <sup>a</sup>	3	0.3		Hormone replacement therapies <sup>a</sup>	6	0.8	
Other Female hormone products <sup>a</sup>	5	0.5		Other Female hormone products <sup>a</sup>	3	0.4	
Other Medications				Other Medications			
Prescribed <sup>a</sup>	559	57.9		Prescribed <sup>a</sup>	593	74.7	
OTC <sup>a</sup>	22	2.3		OTC <sup>a</sup>	15	1.9	
Herbal/Food supplements <sup>a</sup>	30	3.1		Herbal/Food supplements <sup>a</sup>	32	4.0	
Juices	5	0.5		Juices	3	0.4	
Other <sup>a</sup>	65	6.7		Other <sup>a</sup>	66	8.3	

<sup>a</sup> See Appendix 9; where the period of exposure to a drug was not specified, these are identified in this appendix as 'any use' of the respective medication.

In the DVT/PE cohort, the proportions of patients using the drugs or drug classes listed in Table 49 were also broadly similar in the rivaroxaban and warfarin groups. The proportion of patients using analgesics and anti-inflammatory drugs in the DVT/PE group was higher than that of the AF cohort, with a higher proportion using NSAIDs (approximately 10% in both treatment groups). A relative minority of patients were using medications that may interact with warfarin or rivaroxaban (<5%).

**Table 49. Other medication history within 28 days a of initiation prior to start of treatment for indication DVT/PE, by treatment group**

Rivaroxaban N=1532				Warfarin N=1212			
Medication	n	%		Medication	n	%	
Analgesics & Antiinflammatory Agents				Analgesics & Antiinflammatory Agents			
Paracetamol	519	33.9		Paracetamol	415	34.2	
Aspirin (>300mg)	58	3.8		Aspirin (>300mg)	56	4.6	
NSAID	158	10.3		NSAID	116	9.6	
Other	373	24.3		Other	335	27.6	
Anti-convulsants				Anti-convulsants			
Phenytoin	3	0.2		Phenytoin	12	1.0	
Phenobarbital	2	0.1		Phenobarbital	0	0.0	
Carbamazepine	7	0.5		Carbamazepine	10	0.8	
Primidone	0	0.0		Primidone	0	0.0	
Other	38	2.5		Other	34	2.8	
Anti-infectives				Anti-infectives			
Ketoconazole	1	0.1		Ketoconazole	0	0.0	
Itraconazole	1	0.1		Itraconazole	1	0.1	
Posaconazole	0	0.0		Posaconazole	0	0.0	
Ritonavir	0	0.0		Ritonavir	0	0.0	

Rivaroxaban N=1532				Warfarin N=1212			
Medication	n	%		Medication	n	%	
Clarithromycin	45	2.9		Clarithromycin	42	3.5	
Erythromycin	3	0.2		Erythromycin	6	0.5	
Rifampicin	1	0.1		Rifampicin	0	0.0	
Sulfamethoxazole	1	0.1		Sulfamethoxazole	0	0.0	
Metronidazole	11	0.7		Metronidazole	10	0.8	
Griseofulvin	1	0.1		Griseofulvin	1	0.1	
Other	255	16.6		Other	199	16.4	
Antidepressants				Antidepressants			
Tricyclic and related <sup>a</sup>	74	4.8		Tricyclic and related <sup>a</sup>	49	4.0	
MAOI	4	0.3		MAOI	0	0.0	
SSRI	83	5.4		SSRI	71	5.9	
St John's Wort	0	0.0		St John's Wort	0	0.0	
Other	67	4.4		Other	54	4.5	
Female hormone products				Female hormone products			
Oestrogen and/or progestogen	26	1.7		Oestrogen and/or progestogen	37	3.1	
Hormone replacement therapies <sup>a</sup>	13	0.8		Hormone replacement therapies <sup>a</sup>	20	1.7	
Other Female hormone products <sup>a</sup>	15	1.0		Other Female hormone products <sup>a</sup>	11	0.9	
Other Medications				Other Medications			
Prescribed <sup>a</sup>	871	56.9		Prescribed <sup>a</sup>	731	60.3	
OTC <sup>a</sup>	47	3.1		OTC <sup>a</sup>	26	2.1	
Herbal/Food supplements <sup>a</sup>	66	4.3		Herbal/Food supplements <sup>a</sup>	28	2.3	
Juices	17	1.1		Juices	4	0.3	
Other <sup>a</sup>	82	5.4		Other <sup>a</sup>	94	7.8	

<sup>a</sup> See Appendix 9; where the period of exposure to a drug was not specified, these are identified in this appendix as 'any use' of the respective medication.

In the Mixed indication cohort (Table 50), the proportion of patients using prescribed medication in the 28 days prior to starting rivaroxaban (n=18, 78.3%) was higher than those starting warfarin (n=21, 77.8%). Again, a relative minority of patients were using medications that may predispose to bleeding or interact with warfarin or rivaroxaban (<5%).

**Table 50. Other medication history within 28 days a of initiation prior to start of treatment for Mixed (AF & DVT/PE) indications, by treatment group**

Rivaroxaban N=23				Warfarin N=27			
Medication	n	%		Medication	n	%	
Analgesics & Antiinflammatory Agents				Analgesics & Antiinflammatory Agents			
Paracetamol	8	34.8		Paracetamol	14	51.9	
Aspirin (>300mg)	2	8.7		Aspirin (>300mg)	5	18.5	
NSAID	0	0.0		NSAID	2	7.4	
Other	3	13.0		Other	4	14.8	

<b>Rivaroxaban N=23</b>				<b>Warfarin N=27</b>			
<b>Medication</b>	<b>n</b>	<b>%</b>		<b>Medication</b>	<b>n</b>	<b>%</b>	
Phenytoin	0	0.0		Phenytoin	0	0.0	
Phenobarbital	0	0.0		Phenobarbital	0	0.0	
Carbamazepine	0	0.0		Carbamazepine	1	3.7	
Primidone	0	0.0		Primidone	0	0.0	
Other	0	0.0		Other	0	0.0	
Anti-infectives				Anti-infectives			
Ketoconazole	0	0.0		Ketoconazole	0	0.0	
Itraconazole	0	0.0		Itraconazole	0	0.0	
Posaconazole	0	0.0		Posaconazole	0	0.0	
Ritonavir	0	0.0		Ritonavir	0	0.0	
Clarithromycin	1	4.3		Clarithromycin	1	3.7	
Erythromycin	0	0.0		Erythromycin	0	0.0	
Rifampicin	0	0.0		Rifampicin	0	0.0	
Sulfamethoxazole	0	0.0		Sulfamethoxazole	0	0.0	
Metronidazole	0	0.0		Metronidazole	1	3.7	
Griseofulvin	0	0.0		Griseofulvin	0	0.0	
Other	2	8.7		Other	5	18.5	
Antidepressants				Antidepressants			
Tricyclic and related <sup>a</sup>	0	0.0		Tricyclic and related <sup>a</sup>	2	7.4	
MAOI	0	0.0		MAOI	0	0.0	
SSRI	1	4.3		SSRI	2	7.4	
St John's Wort	0	0.0		St John's Wort	0	0.0	
Other	1	4.3		Other	2	7.4	
Female hormone products				Female hormone products			
Oestrogen and/or progestogen	0	0.0		Oestrogen and/or progestogen	0	0.0	
Hormone replacement therapies <sup>a</sup>	0	0.0		Hormone replacement therapies <sup>a</sup>	0	0.0	
Other Female hormone products <sup>a</sup>	0	0.0		Other Female hormone products <sup>a</sup>	0	0.0	
Other Medications				Other Medications			
Prescribed <sup>a</sup>	18	78.3		Prescribed <sup>a</sup>	21	77.8	
OTC <sup>a</sup>	1	4.3		OTC <sup>a</sup>	0	0.0	
Herbal/Food supplements <sup>a</sup>	2	8.7		Herbal/Food supplements <sup>a</sup>	0	0.0	
Juices	0	0.0		Juices	0	0.0	
Other <sup>a</sup>	3	13.0		Other <sup>a</sup>	4	14.8	

<sup>a</sup> See Appendix 9; where the period of exposure to a drug was not specified, these are identified in this appendix as 'any use' of the respective medication.

In the Other indication cohort (Table 51), the proportion of patients using prescribed medication in the 28 days prior to starting rivaroxaban (n=12, 54.5%) was lower than those starting warfarin (n=20, 58.8%). Again, a relative minority of patients were using medications that may predispose to bleeding or interact with warfarin or rivaroxaban (<5%).

**Table 51. Other medication history within 28 days a of initiation prior to start of treatment for Other indications, by treatment group**

Rivaroxaban N=22			Warfarin N=34		
Medication	n	%	Medication	n	%
Analgesics & Antiinflammatory Agents			Analgesics & Antiinflammatory Agents		
Paracetamol	8	36.4	Paracetamol	14	41.2
Aspirin (>300mg)	5	22.7	Aspirin (>300mg)	3	8.8
NSAID	4	18.2	NSAID	1	2.9
Other	6	27.3	Other	7	20.6
Anti-convulsants			Anti-convulsants		
Phenytoin	0	0.0	Phenytoin	0	0.0
Phenobarbital	0	0.0	Phenobarbital	0	0.0
Carbamazepine	0	0.0	Carbamazepine	0	0.0
Primidone	0	0.0	Primidone	0	0.0
Other	2	9.1	Other	2	5.9
Anti-infectives			Anti-infectives		
Ketoconazole	0	0.0	Ketoconazole	0	0.0
Itraconazole	0	0.0	Itraconazole	0	0.0
Posaconazole	0	0.0	Posaconazole	0	0.0
Ritonavir	0	0.0	Ritonavir	0	0.0
Clarithromycin	0	0.0	Clarithromycin	0	0.0
Erythromycin	0	0.0	Erythromycin	0	0.0
Rifampicin	0	0.0	Rifampicin	0	0.0
Sulfamethoxazole	0	0.0	Sulfamethoxazole	0	0.0
Metronidazole	0	0.0	Metronidazole	2	5.9
Griseofulvin	0	0.0	Griseofulvin	0	0.0
Other	4	18.2	Other	8	23.5
Antidepressants			Antidepressants		
Tricyclic and related <sup>a</sup>	0	0.0	Tricyclic and related <sup>a</sup>	1	2.9
MAOI	0	0.0	MAOI	0	0.0
SSRI	2	9.1	SSRI	1	2.9
St John's Wort	0	0.0	St John's Wort	0	0.0
Other	1	4.5	Other	2	5.9
Female hormone products			Female hormone products		
Oestrogen and/or progestogen	0	0.0	Oestrogen and/or progestogen	0	0.0
Hormone replacement therapies <sup>a</sup>	0	0.0	Hormone replacement therapies <sup>a</sup>	1	2.9
Other Female hormone products <sup>a</sup>	0	0.0	Other Female hormone products <sup>a</sup>	1	2.9
Other Medications			Other Medications		
Prescribed <sup>a</sup>	12	54.5	Prescribed <sup>a</sup>	20	58.8
OTC <sup>a</sup>	0	0.0	OTC <sup>a</sup>	0	0.0
Herbal/Food supplements <sup>a</sup>	2	9.1	Herbal/Food supplements <sup>a</sup>	1	2.9
Juices	0	0.0	Juices	0	0.0
Other <sup>a</sup>	2	9.1	Other <sup>a</sup>	1	2.9

<sup>a</sup> See Appendix 9; where the period of exposure to a drug was not specified, these are identified in those appendix as 'any use' of the respective medication.

### 10.2.1.5 Therapy Plan – Treatment Initiation

Outpatient setting was the most frequently reported treatment setting for patients with AF indication (n=1022, 58.1%, Table 52), in both the rivaroxaban (n=517, 53.6%) and warfarin (n=505, 63.6%) cohorts. Similarly, DVT/PE patients were most frequently treated in the outpatient setting (n=1598, 58.2%), in both the rivaroxaban (n=936, 61.1%) and warfarin (n=662, 54.6%) cohorts. Patients with Other indications were most frequently treated in the outpatient setting (n=31, 55.4%), but only in the rivaroxaban (n=15, 68.2%) cohort. Inpatient setting was the most frequently reported treatment setting for patients with Mixed indication (n=28, 56.0%), but only in the warfarin (n=17, 63.0%) cohort.

**Table 52. Treatment setting at index date, by indication and treatment group**

Setting	Rivaroxaban N=2542		Warfarin N=2067		Total N=4609	
	n	%	n	%	n	%
Indication:						
AF						
Inpatient	443	45.9	287	36.2	730	41.5
Outpatient	517	53.6	505	63.6	1022	58.1
Unknown	5	0.5	2	0.3	7	0.4
Total	965	100.0	794	100.0	1759	100.0
DVT/PE						
Inpatient	587	38.3	547	45.1	1134	41.3
Outpatient	936	61.1	662	54.6	1598	58.2
Unknown	9	0.6	3	0.3	12	0.4
Total	1532	100.0	1212	100.0	2744	100.0
Mixed (AF & DVT/PE)						
Inpatient	11	47.8	17	63.0	28	56.0
Outpatient	12	52.2	10	37.0	22	44.0
Unknown	0	0.0	0	0.0	0	0.0
Total	23	100.0	27	100.0	50	100.0
Other						
Inpatient	7	31.8	17	50.0	24	42.9
Outpatient	15	68.2	16	47.1	31	55.4
Unknown	0	0.0	1	3.0	1	1.8
Total	22	100.0	34	100.0	56	100.0

In the rivaroxaban evaluable cohort (n=2542), AF patients most frequently initiated treatment with a total daily dose between 20mg and 30mg (79.5% where specified, Table 53). DVT/PE patients most frequently initiated treatment with a total daily dose of  $\geq 30$ mg (76.8% where specified). Patients with Other and Mixed indications most frequently initiated treatment with a total daily dose of  $\geq 20$ mg but  $< 30$ mg (56.5% Mixed indication where specified; 73.7% Other indication where specified).

In the warfarin evaluable cohort (n=2067), AF patients most frequently initiated treatment with a total daily dose of  $\geq 2.5$ mg but  $< 5$ mg (47.9% where specified). DVT/PE patients most frequently initiated treatment with a total daily dose of  $\geq 5$ mg but  $< 10$ mg (54.7% where specified). Patients with Other and Mixed indications most frequently initiated treatment with a total daily dose of  $\geq 5$ mg but  $< 10$ mg (50.0% Mixed indication where specified; 67.7% Other indication where specified).

**Table 53. Posology (total daily dose) at index date by indication and treatment group**

Start dose	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
Indication:				
AF				
<2.5	1	0.1	122	16.3
>=2.5, <5	1	0.1	359	47.9
>=5.0, <10	0	0.0	206	27.5
>=10, <20	176	18.6	61	8.2
>=20, <30	750	79.5	0	0.0
>=30	16	1.7	1	0.1
Number patients with Missing information	21	-	45	-
Median (IQR)	20 (20, 20)		3 (3, 5)	
Mean (SD)	19.2 (2.6)		4.1 (2.6)	
DVT/PE				
<2.5	0	0.0	29	2.5
>=2.5, <5	0	0.0	88	7.6
>=5.0, <10	0	0.0	631	54.7
>=10, <20	156	10.4	405	35.1
>=20, <30	193	12.8	0	0.0
>=30	1154	76.8	0	0.0
Number patients with Missing information	29	-	59	-
Median (IQR)	30 (30, 30)		5 (5, 10)	
Mean (SD)	27.2 (5.4)		6.8 (2.6)	
Mixed (AF & DVT/PE)				
<2.5	0	0.0	2	7.7
>=2.5, <5	0	0.0	4	15.4
>=5.0, <10	0	0.0	13	50.0
>=10, <20	3	13.0	7	26.9
>=20, <30	13	56.5	0	0.0
>=30	7	30.4	0	0.0
Number patients with Missing information	0	-	1	-
Median (IQR)	20 (20, 30)		5 (5, 10)	
Mean (SD)	22.4 (5.4)		6.3 (2.8)	
Other				
<2.5	0	0.0	2	6.5



Start dose	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
>=2.5, <5	0	0.0	2	6.5
>=5.0, <10	0	0.0	21	67.7
>=10, <20	1	5.3	6	19.4
>=20, <30	14	73.7	0	0.0
>=30	4	21.1	0	0.0
Number patients with Missing information	3	-	3	-
Median (IQR)	20 (20, 20)		5 (5, 8)	
Mean (SD)	21.8 (4.5)		6.0 (2.4)	

Investigators were asked to indicate whether the patient had used any of the selected therapeutic classes of medications concurrently with rivaroxaban or warfarin. Aggregate counts are provided according to tick box responses in Table 54 – Table 57, grouped by study drug and indication. (NB. this includes information on concurrent low dose (<300mg) daily aspirin use).

In the AF cohort, the most frequently reported medication used in the 12 weeks after starting anticoagulant treatment were other prescribed medicines, analgesic and anti-inflammatory agents and anti-infectives for both rivaroxaban and warfarin users (Table 54).

**Table 54. Medication use at index date or within 12 weeks of starting treatment<sup>a</sup> for indication AF, by treatment group**

Rivaroxaban N=965			Warfarin N=794		
Medication	n	%	Medication	n	%
Analgesics & Anti-inflammatory Agents			Analgesics & Anti-inflammatory Agents		
Paracetamol	206	21.3	Paracetamol	175	22.0
Aspirin (>300mg)	37	3.8	Aspirin (>300mg)	65	8.2
NSAID <sup>a</sup>	23	2.4	NSAID <sup>a</sup>	17	2.1
Other <sup>a</sup>	124	12.8	Other <sup>a</sup>	114	14.4
Anti-convulsants			Anti-convulsants		
Phenytoin	1	0.1	Phenytoin	1	0.1
Phenobarbital	0	0.0	Phenobarbital	1	0.1
Carbamazepine	6	0.6	Carbamazepine	2	0.3
Primidone	0	0.0	Primidone	0	0.0
Other <sup>a</sup>	19	2.0	Other <sup>a</sup>	9	1.1
Anti-infectives			Anti-infectives		
Ketoconazole	0	0.0	Ketoconazole	0	0.0
Itraconazole	0	0.0	Itraconazole	0	0.0
Posaconazole	0	0.0	Posaconazole	0	0.0
Ritonavir	0	0.0	Ritonavir	0	0.0
Clarithromycin	20	2.1	Clarithromycin	18	2.3
Erythromycin	3	0.3	Erythromycin	1	0.1

Rivaroxaban N=965				Warfarin N=794			
Medication	n	%		Medication	n	%	
Rifampicin	0	0.0		Rifampicin	0	0.0	
Sulfamethoxazole	0	0.0		Sulfamethoxazole	0	0.0	
Metronidazole	8	0.8		Metronidazole	9	1.1	
Griseofulvin	0	0.0		Griseofulvin	0	0.0	
Other <sup>a</sup>	111	11.5		Other <sup>a</sup>	83	10.5	
Antidepressants				Antidepressants			
Tricyclic and related <sup>a</sup>	20	2.1		Tricyclic and related <sup>a</sup>	24	3.0	
MAOI	2	0.2		MAOI	0	0.0	
SSRI	35	3.6		SSRI	33	4.2	
St John's Wort	0	0.0		St John's Wort	1	0.1	
Other <sup>a</sup>	26	2.7		Other <sup>a</sup>	18	2.3	
Female hormone products				Female hormone products			
Oestrogen and/or progestogen	4	0.4		Oestrogen and/or progestogen	1	0.1	
Hormone replacement therapies <sup>a</sup>	1	0.1		Hormone replacement therapies <sup>a</sup>	4	0.5	
Other Female hormone products <sup>a</sup>	5	0.5		Other Female hormone products <sup>a</sup>	3	0.4	
Other Medications				Other Medications			
Prescribed <sup>a</sup>	488	50.6		Prescribed <sup>a</sup>	451	56.8	
OTC <sup>a</sup>	12	1.2		OTC <sup>a</sup>	15	1.9	
Herbal/Food supplements <sup>a</sup>	29	3.0		Herbal/Food supplements <sup>a</sup>	33	4.2	
Juices	5	0.5		Juices	1	0.1	
Other <sup>a</sup>	55	5.7		Other <sup>a</sup>	55	6.9	

<sup>a</sup> See Appendix 9; where the period of exposure to a drug was not specified, these are identified in this appendix as 'any use' of the respective medication.

In the DVT/PE cohort, approximately half of the warfarin and rivaroxaban cohorts were using other prescribed medication. The proportion of patients using analgesics and anti-inflammatory agents or anti-infectives was higher in the DVT/PE cohort compared to the AF cohort (Table 55).

**Table 55. Medication use at index date or within 12 weeks of starting treatment<sup>a</sup> for indication DVT/PE, by treatment group**

Rivaroxaban N=1532				Warfarin N=1212			
Medication	n	%		Medication	n	%	
Analgesics & Anti-inflammatory Agents				Analgesics & Anti-inflammatory Agents			
Paracetamol	515	33.6		Paracetamol	469	38.7	
Aspirin (>300mg)	39	2.5		Aspirin (>300mg)	21	1.7	
NSAID <sup>a</sup>	111	7.2		NSAID <sup>a</sup>	78	6.4	
Other <sup>a</sup>	353	23.0		Other <sup>a</sup>	346	28.5	
Anti-convulsants				Anti-convulsants			
Phenytoin	3	0.2		Phenytoin	11	0.9	
Phenobarbital	2	0.1		Phenobarbital	0	0.0	
Carbamazepine	6	0.4		Carbamazepine	9	0.7	
Primidone	1	0.1		Primidone	0	0.0	
Other <sup>a</sup>	32	2.1		Other <sup>a</sup>	28	2.3	
Anti-infectives				Anti-infectives			

Rivaroxaban N=1532				Warfarin N=1212			
Medication	n	%		Medication	n	%	
Ketoconazole	1	0.1		Ketoconazole	1	0.1	
Itraconazole	1	0.1		Itraconazole	3	0.2	
Posaconazole	0	0.0		Posaconazole	1	0.1	
Ritonavir	0	0.0		Ritonavir	1	0.1	
Clarithromycin	48	3.1		Clarithromycin	42	3.5	
Erythromycin	3	0.2		Erythromycin	5	0.4	
Rifampicin	1	0.1		Rifampicin	2	0.2	
Sulfamethoxazole	1	0.1		Sulfamethoxazole	1	0.1	
Metronidazole	20	1.3		Metronidazole	12	1.0	
Griseofulvin	2	0.1		Griseofulvin	1	0.1	
Other <sup>a</sup>	267	17.4		Other <sup>a</sup>	228	18.8	
Antidepressants				Antidepressants			
Tricyclic and related <sup>a</sup>	68	4.4		Tricyclic and related <sup>a</sup>	50	4.1	
MAOI	3	0.2		MAOI	0	0.0	
SSRI	82	5.4		SSRI	60	5.0	
St John's Wort	0	0.0		St John's Wort	0	0.0	
Other <sup>a</sup>	53	3.5		Other <sup>a</sup>	50	4.1	
Female hormone products				Female hormone products			
Oestrogen and/or progestogen	23	1.5		Oestrogen and/or progestogen	24	2.0	
Hormone replacement therapies <sup>a</sup>	6	0.4		Hormone replacement therapies <sup>a</sup>	12	1.0	
Other Female hormone products <sup>a</sup>	11	0.7		Other Female hormone products <sup>a</sup>	10	0.8	
Other Medications				Other Medications			
Prescribed <sup>a</sup>	756	49.3		Prescribed <sup>a</sup>	656	54.1	
OTC <sup>a</sup>	35	2.3		OTC <sup>a</sup>	24	2.0	
Herbal/Food supplements <sup>a</sup>	67	4.4		Herbal/Food supplements <sup>a</sup>	36	3.0	
Juices	11	0.7		Juices	3	0.2	
Other <sup>a</sup>	71	4.6		Other <sup>a</sup>	72	5.9	

<sup>a</sup> See Appendix 9; where the period of exposure to a drug was not specified, these are identified in this appendix as 'any use' of the respective medication.

Similar patterns of use of other medication were observed in the Mixed and Other indication groups (Table 56 and Table 57).

**Table 56. Medication use at index date or within 12 weeks of starting treatment<sup>a</sup> for indication Mixed, by treatment group**

Rivaroxaban N=23			Warfarin N=27		
Medication	n	%	Medication	n	%
Analgesics & Anti-inflammatory Agents			Analgesics & Anti-inflammatory Agents		
Paracetamol	7	30.4	Paracetamol	14	51.9
Aspirin (>300mg)	0	0.0	Aspirin (>300mg)	0	0.0
NSAID <sup>a</sup>	0	0.0	NSAID <sup>a</sup>	0	0.0
Other <sup>a</sup>	3	13.0	Other <sup>a</sup>	6	22.2
Anti-convulsants			Anti-convulsants		
Phenytoin	0	0.0	Phenytoin	0	0.0
Phenobarbital	0	0.0	Phenobarbital	0	0.0
Carbamazepine	0	0.0	Carbamazepine	1	3.7

Rivaroxaban N=23				Warfarin N=27			
Medication		n	%	Medication		n	%
Anti-infectives	Primidone	0	0.0	Anti-infectives	Primidone	0	0.0
	Other <sup>a</sup>	0	0.0		Other <sup>a</sup>	0	0.0
	Ketoconazole	0	0.0		Ketoconazole	0	0.0
	Itraconazole	0	0.0		Itraconazole	0	0.0
	Posaconazole	0	0.0		Posaconazole	0	0.0
	Ritonavir	0	0.0		Ritonavir	0	0.0
	Clarithromycin	0	0.0		Clarithromycin	3	11.1
	Erythromycin	1	4.3		Erythromycin	1	3.7
	Rifampicin	0	0.0		Rifampicin	1	3.7
	Sulfamethoxazole	0	0.0		Sulfamethoxazole	1	3.7
Antidepressants	Metronidazole	1	4.3	Antidepressants	Metronidazole	3	11.1
	Griseofulvin	0	0.0		Griseofulvin	1	3.7
	Other <sup>a</sup>	2	8.7		Other <sup>a</sup>	8	29.6
	Tricyclic and related <sup>a</sup>	0	0.0		Tricyclic and related <sup>a</sup>	2	7.4
	MAOI	0	0.0		MAOI	0	0.0
	SSRI	0	0.0		SSRI	2	7.4
	St John's Wort	0	0.0		St John's Wort	0	0.0
	Other <sup>a</sup>	1	4.3		Other <sup>a</sup>	2	7.4
	Female hormone products				Female hormone products		
	Oestrogen and/or progestogen	0	0.0		Oestrogen and/or progestogen	0	0.0
Other Medications	Hormone replacement therapies <sup>a</sup>	0	0.0	Other Medications	Hormone replacement therapies <sup>a</sup>	0	0.0
	Other Female hormone products <sup>a</sup>	0	0.0		Other Female hormone products <sup>a</sup>	0	0.0
	Prescribed <sup>a</sup>	15	65.2		Prescribed <sup>a</sup>	16	59.3
	OTC <sup>a</sup>	0	0.0		OTC <sup>a</sup>	0	0.0
	Herbal/Food supplements <sup>a</sup>	3	13.0		Herbal/Food supplements <sup>a</sup>	1	3.7
	Juices	0	0.0		Juices	0	0.0
	Other <sup>a</sup>	1	4.3		Other <sup>a</sup>	3	11.1

<sup>a</sup> See Appendix 9; where the period of exposure to a drug was not specified, these are identified in this appendix as 'any use' of the respective medication.

**Table 57. Medication use at index date or within 12 weeks of starting treatment<sup>a</sup> for indication Other, by treatment group**

Rivaroxaban N=22				Warfarin N=34			
Medication		n	%	Medication		n	%
Analgesics & Anti-inflammatory Agents	Paracetamol	8	36.4	Analgesics & Anti-inflammatory Agents	Paracetamol	10	29.4
	Aspirin (>300mg)	1	4.5		Aspirin (>300mg)	2	5.9
	NSAID <sup>a</sup>	2	9.1		NSAID <sup>a</sup>	1	2.9
	Other <sup>a</sup>	4	18.2		Other <sup>a</sup>	4	11.8
Anti-convulsants	Phenytoin	0	0.0	Anti-convulsants	Phenytoin	0	0.0
	Phenobarbital	0	0.0		Phenobarbital	0	0.0
	Carbamazepine	0	0.0		Carbamazepine	0	0.0
	Primidone	0	0.0		Primidone	0	0.0

Rivaroxaban N=22				Warfarin N=34			
Medication		n	%	Medication		n	%
Other <sup>a</sup>		2	9.1	Other <sup>a</sup>		1	2.9
Anti-infectives				Anti-infectives			
Ketoconazole		0	0.0	Ketoconazole		0	0.0
Itraconazole		0	0.0	Itraconazole		0	0.0
Posaconazole		0	0.0	Posaconazole		0	0.0
Ritonavir		0	0.0	Ritonavir		0	0.0
Clarithromycin		0	0.0	Clarithromycin		0	0.0
Erythromycin		0	0.0	Erythromycin		0	0.0
Rifampicin		0	0.0	Rifampicin		0	0.0
Sulfamethoxazole		0	0.0	Sulfamethoxazole		0	0.0
Metronidazole		0	0.0	Metronidazole		1	2.9
Griseofulvin		0	0.0	Griseofulvin		0	0.0
Other <sup>a</sup>		3	13.6	Other <sup>a</sup>		6	17.6
Antidepressants				Antidepressants			
Tricyclic and related <sup>a</sup>		0	0.0	Tricyclic and related <sup>a</sup>		1	2.9
MAOI		0	0.0	MAOI		0	0.0
SSRI		1	4.5	SSRI		2	5.9
St John's Wort		0	0.0	St John's Wort		0	0.0
Other <sup>a</sup>		1	4.5	Other <sup>a</sup>		2	5.9
Female hormone products				Female hormone products			
Oestrogen and/or progestogen		0	0.0	Oestrogen and/or progestogen		0	0.0
Hormone replacement therapies <sup>a</sup>		0	0.0	Hormone replacement therapies <sup>a</sup>		1	2.9
Other Female hormone products <sup>a</sup>		0	0.0	Other Female hormone products <sup>a</sup>		1	2.9
Other Medications				Other Medications			
Prescribed <sup>a</sup>		12	54.5	Prescribed <sup>a</sup>		18	52.9
OTC <sup>a</sup>		0	0.0	OTC <sup>a</sup>		0	0.0
Herbal/Food supplements <sup>a</sup>		1	4.5	Herbal/Food supplements <sup>a</sup>		0	0.0
Juices		0	0.0	Juices		0	0.0
Other <sup>a</sup>		2	9.1	Other <sup>a</sup>		2	5.9

<sup>a</sup> See Appendix 9; where the period of exposure to a drug was not specified, these are identified in this appendix as 'any use' of the respective medication.

#### 10.2.1.6 Stroke and bleeding risk prediction scores for all indications

All patients were categorised according to both the HAS-BLED and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score to identify whether there was any channelling of a particular treatment to patients who may be either at higher risk of a major bleeding event (HAS-BLED) or stroke (CHA<sub>2</sub>DS<sub>2</sub>-VASc score) and also to provide a composite score for use in regression analyses. The HAS-BLED score was abridged for this study as one element (labile INR) would only be measured in patients using warfarin.

Table 58 provides frequency information for the various HAS-BLED indicator variables by treatment group and indication. There are some differences in the distributions of the indicator variables between the treatment groups in the atrial fibrillation group. For example more warfarin patients seem to have a history of hypertension and prior bleed,

and more rivaroxaban patients a history of stroke. However these differences are not seen in the DVT/PE group, and the Mixed and Other groups are too small to make meaningful comparisons.

**Table 58. Baseline patient HAS-BLED score categories, by treatment group**

Clinical feature		Rivaroxaban N=2542		Warfarin N=2067	
		n	%	n	%
<b>AF</b>					
	Hypertension	372	38.6	376	47.3
	Abnormal renal function	15	1.6	26	3.3
	Abnormal liver function	10	1.0	13	1.6
	History Stroke	298	30.9	166	20.9
	History of Bleeding or predisposition	162	16.8	196	24.7
	Labile INR	NA	NA	NA	NA
	Age >=65 years	808	83.8	644	81.0
	Drug therapy	498	51.7	477	59.9
	Alcohol ( 8 drinks/week)	37	3.8	49	6.2
<b>DVT/PE</b>					
	Hypertension	307	20.0	254	21.0
	Abnormal renal function	26	1.7	32	2.6
	Abnormal liver function	33	2.2	21	1.7
	History Stroke	70	4.6	65	5.4
	History of Bleeding or predisposition	322	21.0	324	26.7
	Labile INR	NA	NA	NA	NA
	Age >=65 years	701	45.8	574	47.4
	Drug therapy	388	25.3	267	22.0
	Alcohol ( 8 drinks/week)	89	5.8	67	5.5
<b>Mixed</b>					
	Hypertension	8	34.8	12	44.4
	Abnormal renal function	1	4.4	1	3.7
	Abnormal liver function	0	0.0	0	0.0
	History Stroke	4	17.4	5	18.5
	History of Bleeding or predisposition	11	47.8	9	33.3
	Labile INR	NA	NA	NA	NA
	Age >=65 years	18	78.3	21	77.8
	Drug therapy	10	43.5	15	55.6
	Alcohol ( 8 drinks/week)	0	0.0	2	7.4
<b>Other</b>					
	Hypertension	5	22.7	9	26.5
	Abnormal renal function	2	9.1	1	2.9
	Abnormal liver function	1	4.6	1	2.9
	History Stroke	6	27.3	9	26.5
	History of Bleeding or predisposition	4	18.2	6	17.7
	Labile INR	NA	NA	NA	NA
	Age >=65 years	8	36.4	16	47.1
	Drug therapy	8	36.4	18	52.9
	Alcohol ( 8 drinks/week)	3	13.6	1	2.9

Table 59 provides the frequency information for the overall (abridged) HAS-BLED score, together with summary statistics. For this table the percentages are calculated within treatment group. For example, 29.0% of patients with AF treated with rivaroxaban are in category 1, compared with 19.3% of patients with AF treated with warfarin. This is reversed for category 2 (22.6% vs 27.0% respectively), and otherwise the distribution is very similar between treatment groups for each of the indications, as reflected in the distributions, the summary statistics and Figure 8.

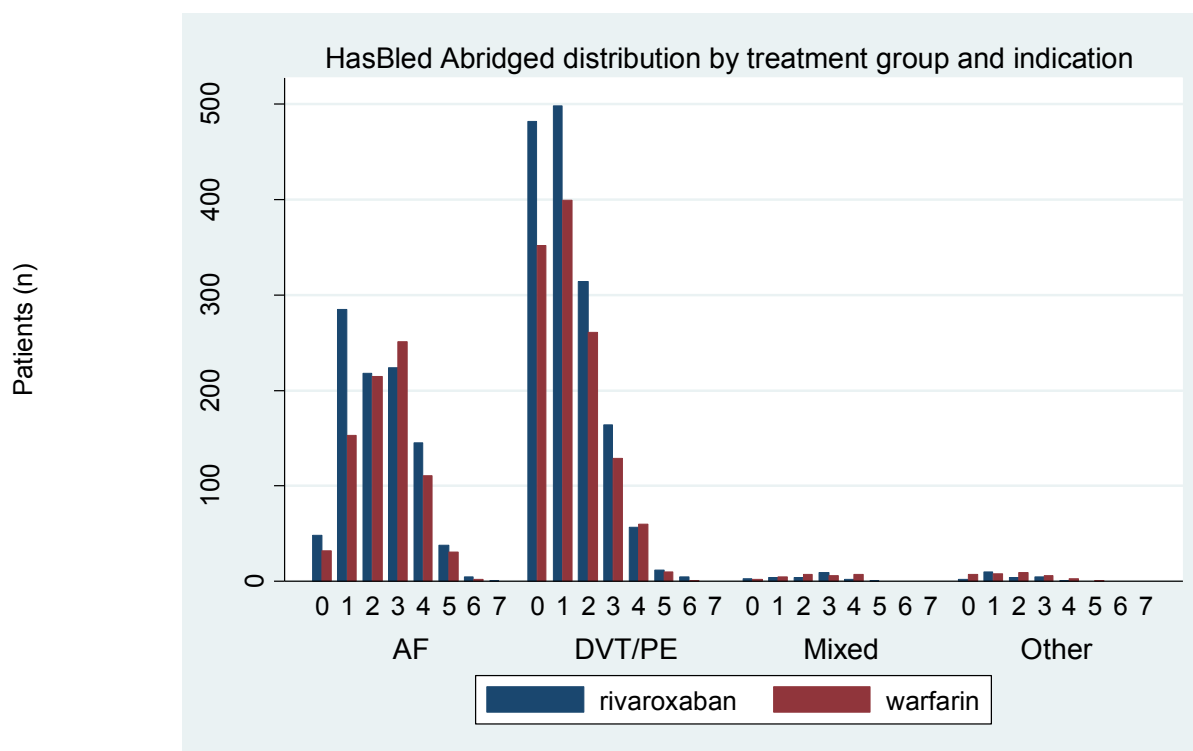
Overall, for each indication the median HAS-BLED score for rivaroxaban patients was quite low at 2 (IQR: 1-3) for AF, 1 (0-2) for DVT/PE, 3 (1-3) for Mixed indications and 1 (0-3) for Other. For warfarin patients these values were similar at 2 (IQR: 2-3) for AF, 1 (0-2) for DVT/PE, 2 (1-4) for Mixed indications and 2 (1-3) for Other.

**Table 59. Baseline patient HAS-BLED risk score, by indication and treatment group**

Indication	Score	Rivaroxaban N=2542		Warfarin N=2067	
		n	%	n	%
AF	0	48	5.0	32	4.0
	1	285	29.0	153	19.3
	2	218	22.6	215	27.0
	3	224	23.2	251	31.6
	4	145	15.0	111	14.0
	5	38	3.9	31	3.9
	6	5	0.5	2	0.3
	7	1	0.1	0	0.0
	8	0	0.0	0	0.0
	Median (IQR)	2 (1,3)		2 (2,3)	
DVT/PE	0	482	31.5	352	29.0
	1	498	32.5	399	33.0
	2	314	20.5	261	21.5
	3	164	10.7	129	10.6
	4	57	3.7	60	5.0
	5	12	0.8	10	0.8
	6	5	0.3	1	0.1
	7	0	0.0	0	0.0
	8	0	0.0	0	0.0
	Median (IQR)	1 (0,2)		1 (0,2)	
Mixed	0	3	13.0	2	7.4
	1	4	17.4	5	18.5
	2	4	17.4	7	25.9
	3	9	39.1	6	22.2
	4	2	8.7	7	25.9
	5	1	4.4	0	0.0
	6	0	0.0	0	0.0
	7	0	0.0	0	0.0
	8	0	0.0	0	0.0

Indication	Score	Rivaroxaban N=2542		Warfarin N=2067	
		n	%	n	%
Other	Median (IQR)	3 (1,3)		2 (1,4)	
	0	2	9.1	7	20.6
	1	10	45.5	8	23.5
	2	4	18.2	9	26.5
	3	5	22.7	6	17.7
	4	1	4.6	3	8.8
	5	0	0.0	1	2.9
	6	0	0.0	0	0.0
	7	0	0.0	0	0.0
	8	0	0.0	0	0.0
	Median (IQR)	1 (1,3)		2 (1,3)	

**Figure 8. Distribution of baseline patient HAS-BLED score categories (excluding labile INR), by indication and treatment group\***



\* HAS-BLED abridged scores range was 0-8, no patients had a score of 8

Figure 9 provides for each HAS-BLED category and indication the percentage of patients by treatment group. This plot is useful to identify imbalances between treatment groups for any particular HAS-BLED category, but the impact needs to take account of the numbers of patients as per Table 59 and Figure 8. For example Table 59 shows that 48 (5.0%) rivaroxaban patients treated for AF have a HAS-BLED score of 0 whereas 32 (4.0%) warfarin patients treated for AF have a HAS-BLED score of 0. Figure 9 shows



that within the AF indication, across HAS-BLED category 0, 60% of patients were treated with rivaroxaban and 40% with warfarin.

**Figure 9. Percent of patients in each HAS-BLED score category (excluding labile INR), by treatment group and indication**

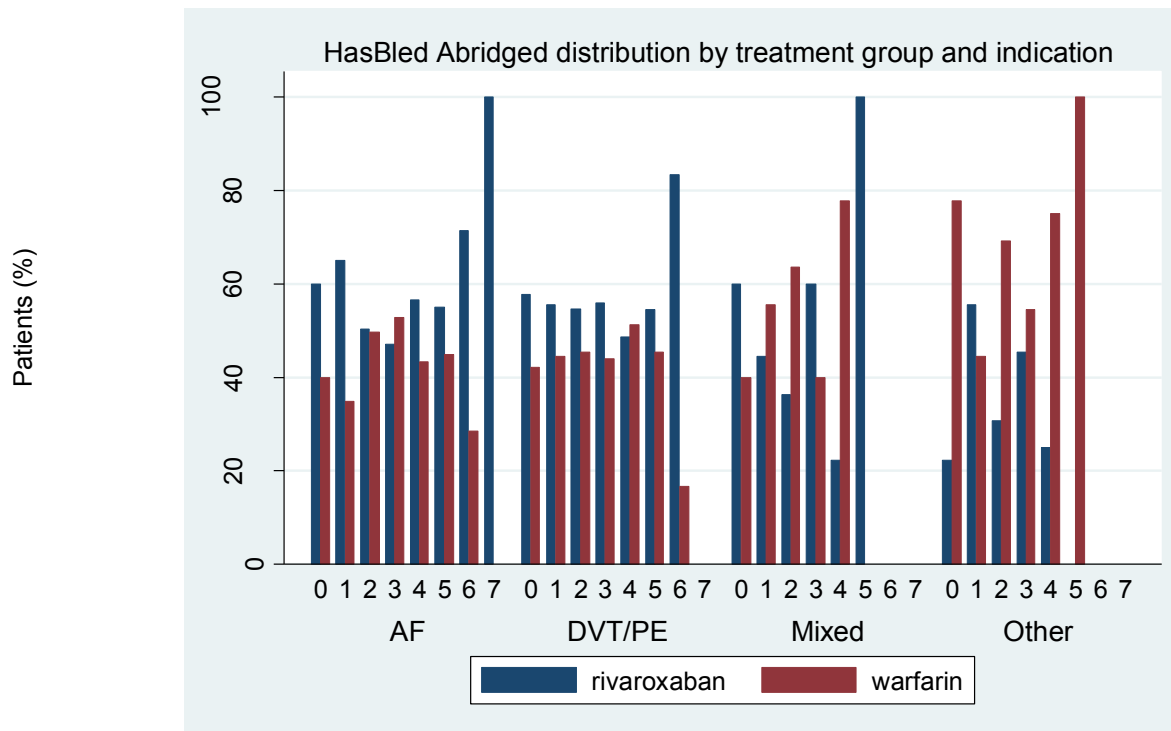


Table 60 provides frequency information for the various CHA<sub>2</sub>DS<sub>2</sub>-VASc indicator variables by treatment group and indication. There are no major differences in the distributions of the indicator variables between the treatment groups in any of the indications.

**Table 60. Baseline patient CHA<sub>2</sub>DS<sub>2</sub>-VASc score categories, by indication and treatment group**

Clinical feature	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
<b>AF</b>				
Age 65-74 years (1) OR	249	25.8	239	30.1
Age >75 (2)	559	58.0	405	50.9
Female Sex (1)	448	46.5	346	43.5
History Congestive heart failure/left ventricular dysfunction (1)	141	14.6	142	17.9
History Hypertension (1)	706	73.2	667	83.9
History Stroke, TIA or Thromboembolism (2)	452	46.9	266	33.5
Vascular Disease (1)	259	26.9	185	23.8

Clinical feature	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
Diabetes Mellitus (1)	181	18.8	168	21.1
<b>DVT/PE</b>				
Age 65-74 years (1) OR	371	24.2	306	25.3
Age >75 (2)	330	21.5	268	22.1
Female Sex (1)	696	45.4	547	45.1
History Congestive heart failure/left ventricular dysfunction (1)	51	3.3	71	5.9
History Hypertension (1)	628	41.0	522	43.1
History Stroke,TIA orThromboembolism (2)	110	7.2	106	8.8
Vascular Disease (1)	100	6.5	108	8.9
Diabetes Mellitus (1)	154	10.1	160	13.2
<b>Mixed</b>				
Age 65-74 years (1)OR	8	34.8	6	22.2
Age >75 (2)	10	43.5	15	55.6
Female Sex (1)	9	39.1	10	37.0
History Congestive heart failure/left ventricular dysfunction (1)	4	17.4	4	14.8
History Hypertension (1)	17	73.9	21	77.8
History Stroke,TIA orThromboembolism (2)	6	26.1	9	33.3
Vascular Disease (1)	8	34.8	6	22.2
Diabetes Mellitus (1)	5	21.7	4	14.8
<b>Other</b>				
Age 65-74 years (1) OR	4	18.2	12	35.3
Age >75 (2)	4	18.2	4	11.8
Female Sex (1)	7	31.8	15	44.1
History Congestive heart failure/left ventricular dysfunction (1)	4	18.2	5	14.7
History Hypertension (1)	14	63.6	21	61.8
History Stroke,TIA orThromboembolism (2)	7	31.8	11	32.4
Vascular Disease (1)	6	27.3	14	41.2
Diabetes Mellitus (1)	4	18.2	7	20.6

Table 61 provides the frequency information for the overall CHA<sub>2</sub>DS<sub>2</sub>-VASc score, together with summary statistics. For this table the percentages are calculated within treatment group. For example, 7.2% of patients with AF treated with rivaroxaban are in category 1, compared with 7.2% of patients with AF treated with warfarin. The distribution is very similar between treatment groups for each of the indications, as reflected in the distributions, the summary statistics and Figure 10.

The median CHA<sub>2</sub>DS<sub>2</sub>-VASc score for rivaroxaban patients was quite low at 4 (IQR: 3-6) for AF, 2 (1-3) for DVT/PE, 3 (2-5) for Mixed indications and 3 (2-4) for Other. For

warfarin patients these values were very similar at 4 (IQR: 3-5) for AF, 2 (1-3) for DVT/PE, 3 (2-5) for Mixed indications and 3 (2-4) for Other.

**Table 61. Baseline patient CHA2DS2-VASc score categories, by treatment group**

Indication	Score	Rivaroxaban N=2542		Warfarin N=2067	
		n	%	n	%
AF	0	8	0.8	10	1.3
	1	69	7.2	57	7.2
	2	107	11.1	103	12.9
	3	168	17.4	174	21.9
	4	195	20.2	159	20.0
	5	171	17.7	152	19.1
	6	164	17.0	90	11.3
	7	58	6.0	40	5.0
	8	22	2.3	7	0.9
	9	2	0.2	4	0.5
	Median (IQR)	4 (3,6)		4 (3,5)	
DVT/PE	0	362	23.6	232	19.1
	1	400	26.1	348	28.6
	2	279	18.2	217	17.9
	3	222	14.5	173	14.2
	4	150	9.8	127	10.5
	5	70	4.6	67	5.5
	6	40	2.6	36	3.0
	7	6	0.4	10	0.8
	8	3	0.2	5	0.4
	9	0	0.0	0	0.0
	Median (IQR)	2 (1,3)		2 (1,3)	
Mixed	0	1	4.4	2	7.4
	1	3	13.0	1	3.7
	2	3	13.0	5	18.5
	3	6	13.1	6	22.2
	4	4	17.4	5	18.5
	5	2	8.7	3	11.1
	6	1	4.4	2	7.4
	7	1	4.4	1	3.7
	8	1	4.4	2	7.4
	9	1	4.4	0	0.0
	Median (IQR)	3 (2,5)		3 (2,5)	
Other	0	3	13.6	3	8.8
	1	3	13.6	5	14.7
	2	4	18.2	2	5.9
	3	3	13.6	11	32.4
	4	5	22.7	6	17.7
	5	3	13.6	5	14.7
	6	1	4.6	1	2.9
	7	0	0.0	1	2.9

Indication	Score	Rivaroxaban N=2542		Warfarin N=2067	
		n	%	n	%
	8	0	0.0	0	0.0
	9	0	0.0	0	0.0
	Median (IQR)	3 (1,4)		3 (2,4)	

**Figure 10. Distribution of baseline patient CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score, by indication and treatment group**

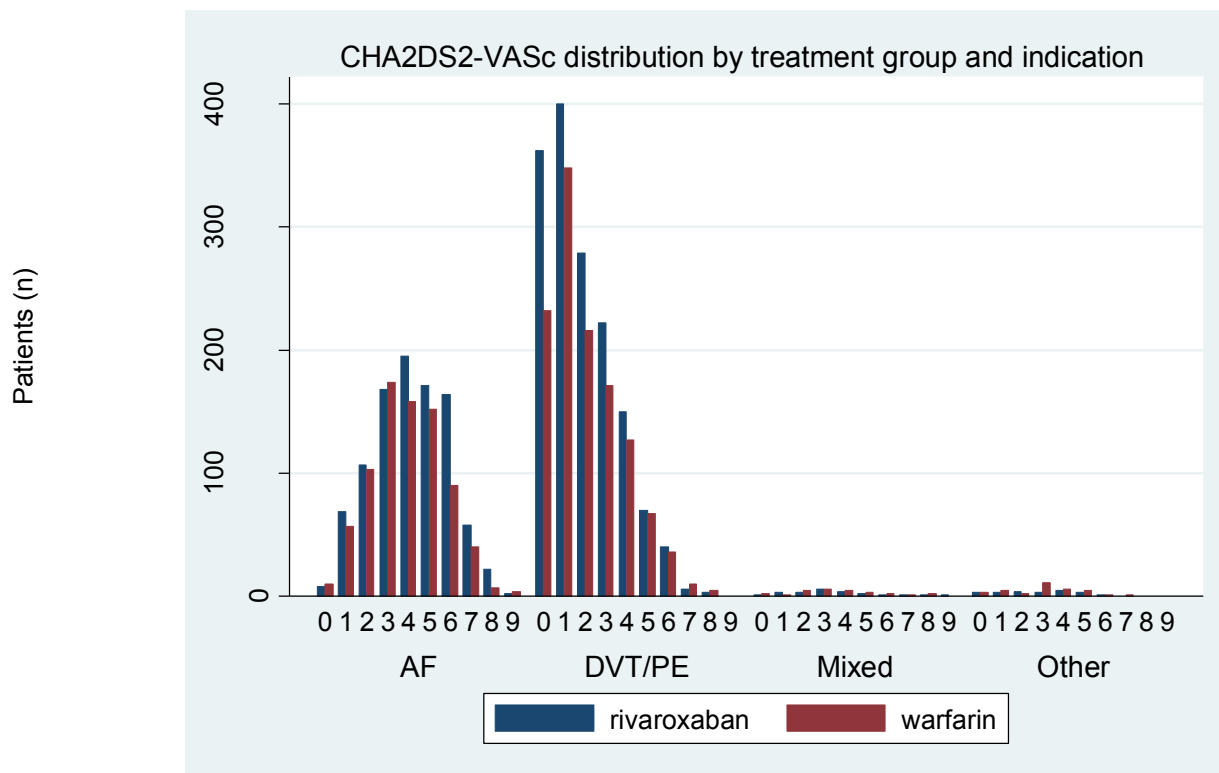
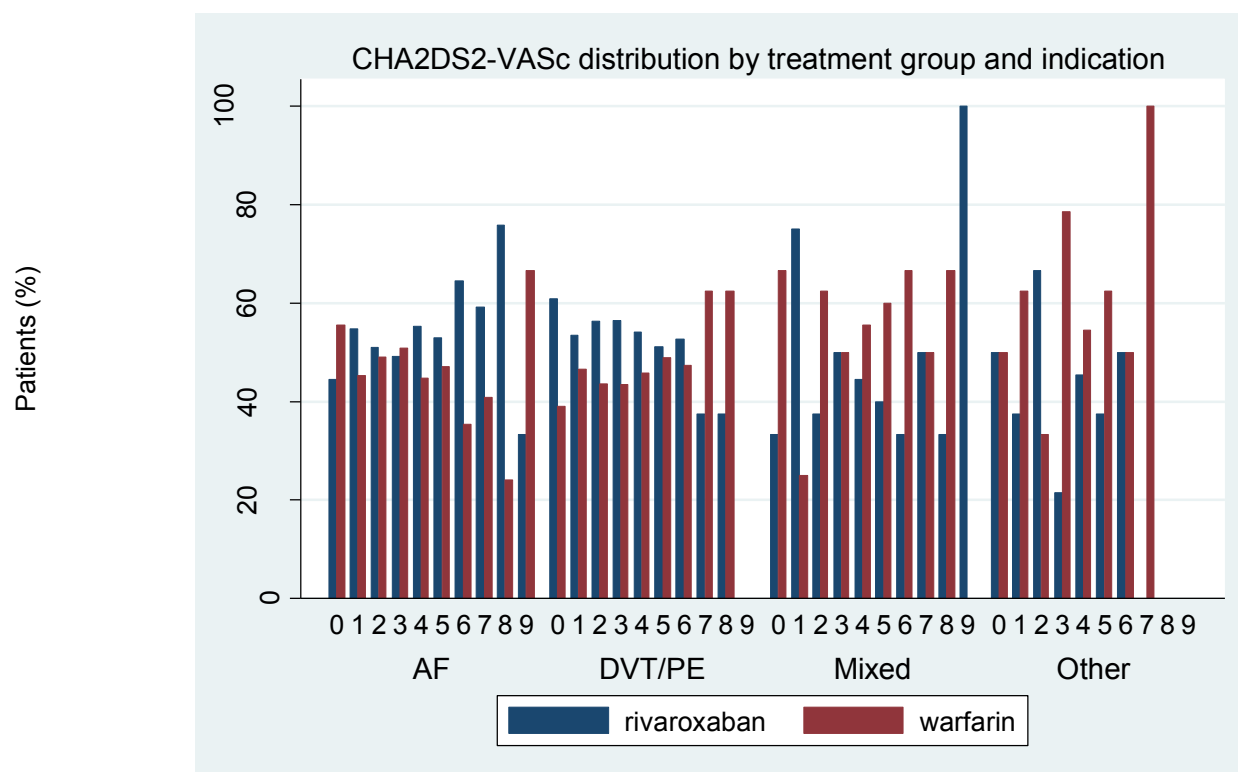


Figure 11 shows for each CHA<sub>2</sub>DS<sub>2</sub>-VASc category and indication the percentage of patients by treatment group. This plot is useful to identify imbalances between treatment groups for any particular CHA<sub>2</sub>DS<sub>2</sub>-VASc, but the impact needs to take account of the numbers of patients as per Table 61 and Figure 10. For example Table 61 shows that 8 (0.8%) rivaroxaban patients treated for AF have a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 whereas 10 (1.3%) warfarin patients treated for AF have a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0. Figure 11 shows that, across CHA<sub>2</sub>DS<sub>2</sub>-VASc category 0, 44.4% of patients were treated with rivaroxaban and 55.6% with warfarin.

**Figure 11. Percent of patients in each baseline CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score, by indication and treatment group**



### 10.3 Indicators of use

#### 10.3.1 Special populations

This section describes specific characteristics of interest in the patients receiving treatment in the study, in particular patient characteristics in the context of the Summary of Product Characteristics (SmPC).

Table 62 presents the number (%) of patients prescribed rivaroxaban who have a baseline condition/medication that is either a contraindication, a special warning/precaution for use or a potential drug-drug interaction according to the rivaroxaban SmPC.

In the AF and DVT/PE indication groups the most frequently reported contraindication for use of rivaroxaban was concomitant treatment with other anticoagulants (3.4% and 2.2%, respectively), while a lesion or condition considered a significant risk for major bleeding was the most frequently reported in the Mixed and Other indication groups (4.4% and 9.1%, respectively).

The most frequently reported special warning and precaution for use was uncontrolled severe arterial hypertension in all indication groups. The most frequently reported drug-drug interaction was concomitant treatment with CYP3A4 inhibitors in the AF, DVT/PE and Mixed indication groups (6.3%, 5.8% and 4.4%, respectively), while the most frequently reported drug-drug interaction in the Other indication group was concomitant use with NSAIDs (9.1%).

**Table 62. Prevalence of criteria and categories identifying special population users of rivaroxaban, by indication group and pooled cohort**

Clinical feature (points)	AF N=965		DVT/PE N=1532		Mixed (AF & DVT) N=23		Other N=22		TOTAL N=2542	
	n	%	n	%	n	%	n	%	n	%
Indicators of Contraindicated use										
Treatment for medical indications other than licensed indications	0	0.0	0	0.0	0	0.0	22	100.0	22	0.9
Hypersensitivity to the active substance or to any of the excipients	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Lesion or condition considered a significant risk for major bleeding	31	3.2	33	2.2	1	4.4	2	9.1	67	2.6
Concomitant treatment with other anticoagulants (other than for switching anticoagulant therapy)	33	3.4	33	2.2	0	0.0	0	0.0	66	2.6
Use in pregnancy and lactation	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Indicators of Special Warning/Precautions for use										
Renal impairment (patients with creatinine clearance $\geq 15$ , $\leq 59$ ml/min)	74	7.7	55	5.0	1	4.4	0	0.0	152	6.0
End stage renal failure (patients with creatinine clearance $\leq 15$ ml/min)	2	0.2	6	0.4	0	0.0	0	0.0	8	0.3
Congenital or acquired bleeding disorders	3	0.3	7	0.5	0	0.0	0	0.0	10	0.4
Uncontrolled severe arterial hypertension	372	38.6	307	20.0	8	34.8	5	22.7	692	27.2
Other GI disease without active ulceration (IBD, oesophagitis, gastritis and GORD)	19	2.0	66	4.3	2	8.7	1	4.6	88	3.5
Vascular retinopathy	3	0.3	3	0.2	0	0.0	0	0.0	6	0.2
Bronchiectasis or history of pulmonary bleeding.	3	0.3	8	0.5	1	4.4	0	0.0	12	0.5
Patients with AF and a prosthetic heart valve	7	0.7	0	0.0	0	0.0	0	0.0	7	0.3
Indicators of Drug-Drug Interactions										
Concomitant treatment with CYP3A4 inhibitors	61	6.3	89	5.8	1	4.4	1	4.6	152	94.0
Concomitant treatment with CYP3A4 inducers	7	0.7	11	0.7	0	0.0	0	0.0	18	0.7
Concomitant treatment with P-gp inhibitors	48	5.0	67	4.4	0	0.0	0	0.0	115	4.5
Concomitant use with NSAIDs	20	2.1	108	7.1	0	0.0	2	9.1	130	5.1
Concomitant use with platelet aggregation inhibitors	23	2.4	19	1.2	0	0.0	0	0.0	42	1.7

Table 63 and Figure 12 provide the distribution of the number of different contraindications, special warnings/precautions and drug-drug interactions per patient. The maximum number of contraindications per patient was two, which was observed in the AF indication group for two patients and the Other indication group for two patients.

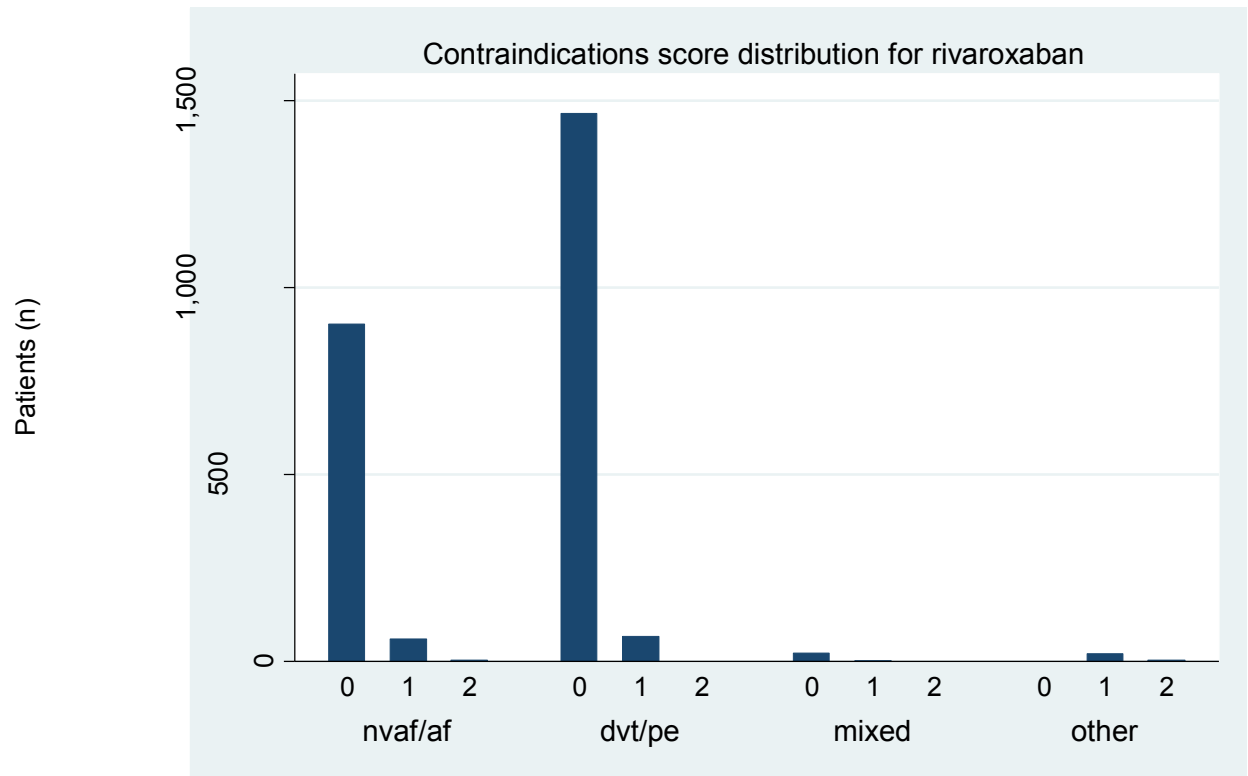
Likewise, Table 63 and Figure 13 provide the maximum number of special warnings and precautions for use observed per patient was four, which was observed for one patient in the AF indication group

The maximum number of drug-drug interactions observed per patient was two, which was observed for 11 patients in the AF indication group, 10 patients in the DVT/PE indication group and one patient in the Other indication group (Table 63 and Figure 14)

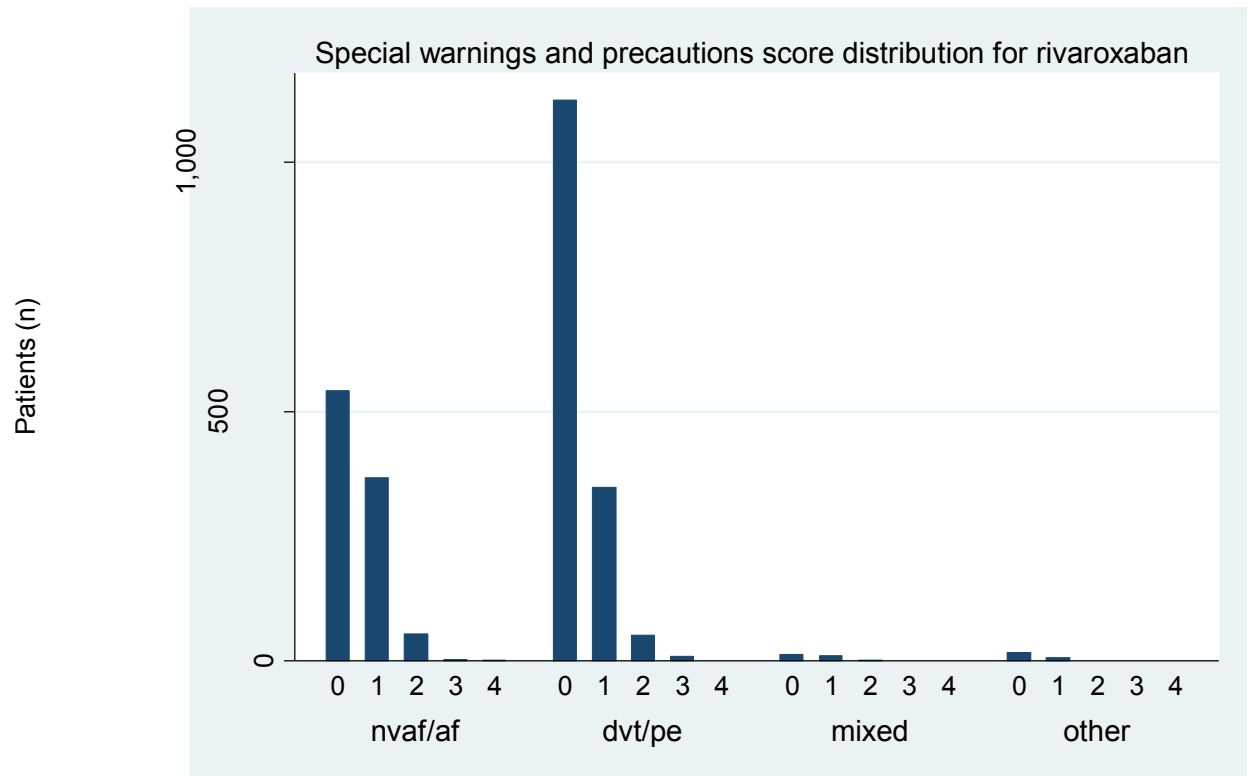
**Table 63. Special population users of rivaroxaban score distribution, by indication group and pooled cohort**

Clinical feature (points)	AF N=965		DVT/PE N=1532		Mixed (AF & DVT) N=23		Other N=22		TOTAL N=2542	
	n	%	n	%	n	%	n	%	n	%
Indicators of Contraindicated use										
0 (min)	903	93.6	1466	95.7	22	95.7	0	0.0	2391	94.1
1	60	6.2	66	4.3	1	4.4	20	90.9	147	5.8
2	2	0.2	0	0.0	0	0.0	2	9.1	4	0.2
3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
5 (max)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Median (IQR)	0 (0,0)		0 (0,0)		0 (0,0)		1 (1,1)		0 (0,0)	
Indicators of Special Warning/Precautions for use										
0 (min)	542	56.2	1125	73.4	12	52.2	16	72.7	1695	66.7
1	367	38.0	348	22.7	10	43.5	6	27.3	731	28.8
2	53	5.5	51	3.3	1	4.4	0	0.0	105	4.1
3	2	0.2	8	0.5	0	0.0	0	0.0	10	0.4
4	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1
5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
8 (max)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Median (IQR)	0 (0,1)		0 (0,1)		0 (0,1)		0 (0,1)		0 (0,1)	
Indicators of Drug-Drug Interactions										
0 (min)	847	87.8	1307	85.3	22	95.7	20	90.9	2196	86.4
1	107	11.1	215	14.0	1	4.4	1	4.6	324	12.8
2	11	1.1	10	0.7	0	0.0	1	4.6	22	0.9
3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
5 (max)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Median (IQR)	0 (0, 0)		0 (0, 0)		0 (0, 0)		0 (0, 0)		0 (0, 0)	

**Figure 12. Contraindications score distribution for rivaroxaban**

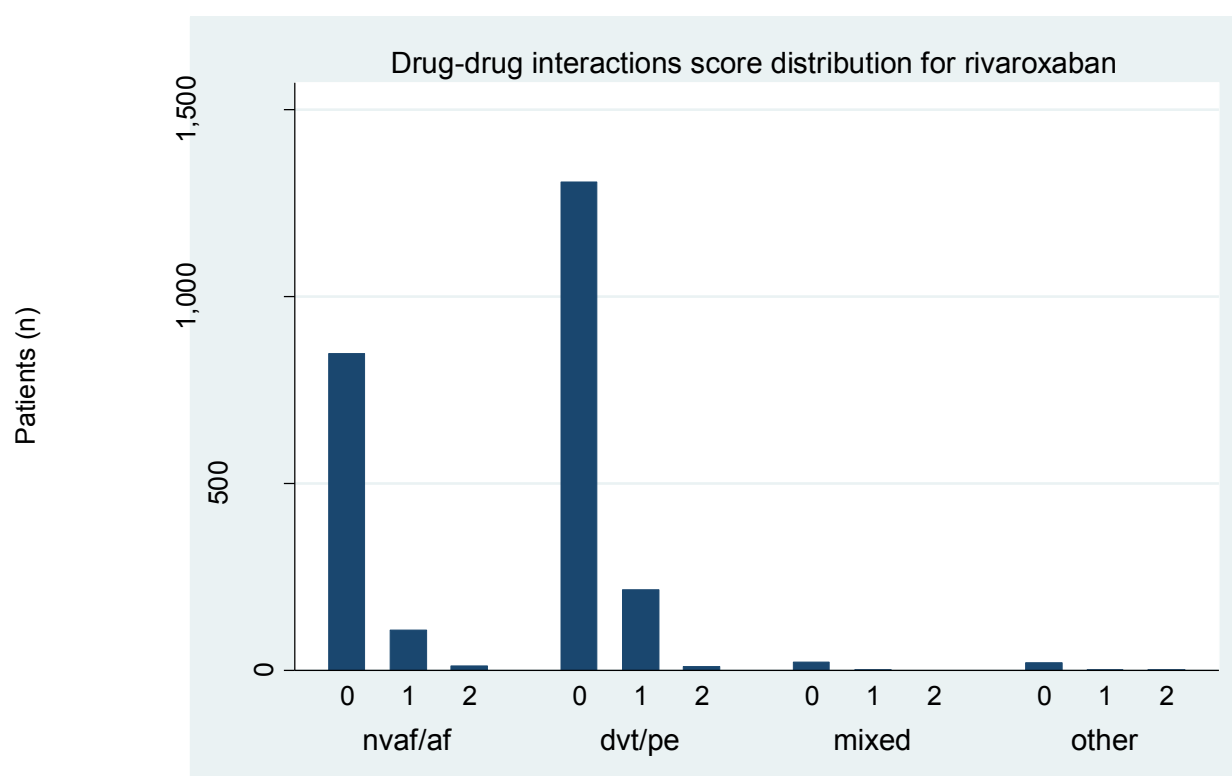


**Figure 13. Special warnings and precautions score distribution for rivaroxaban**





**Figure 14. Drug-drug interactions score distribution for rivaroxaban**



## 10.4 Outcome data

### 10.4.1 Haemorrhage events

#### 10.4.1.1 Classification of haemorrhage events

The reports of haemorrhagic events were categorised using 12 week and event follow-up information, where available, and classified according to case definitions below. All bleeds were classified into major (as per ISTH, Table 1), Clinically Relevant Non Major (CRNM) ((20), Table 1) and/or Other Non-Major (20).

- a) Major – Gastrointestinal site
- b) Major – Urogenital site
- c) Major – all Intracranial
- d) Major – all other major bleeds within critical organ sites (excluding all intracranial)
- e) Major - all other major bleeds in non-critical organ sites
- f) CRNM bleeds
- g) Other Non-Major bleeds (excluding CRNM)
- h) Unclassifiable - bleeds which cannot be classified into one of the above categories

For the three organ sites specified in the primary outcome, each of the individual components of the major bleeding criteria (a fall in haemoglobin of 2 g/dL or more, or

a transfusion of two or more units of packed red blood cells or whole blood, or a fatal outcome) has been summarised in the case series table (Table 81)

In some cases, the prescriber may have reported multiple criterion and/or multiple bleeding episodes within the same site e.g. gastrointestinal. These were followed up to identify all dates and the bleeding event of interest was that indicative of the most serious episode of bleeding within a given site. It is this bleeding event, its associated event date and classification which is evaluated in the subsequent analyses.

Overall 29 bleeding events (19 rivaroxaban and 10 warfarin) were unclassifiable even after follow-up information was requested.

## **10.5 Main results**

### ***10.5.1 Cumulative incidence of the important identified risk of haemorrhage for rivaroxaban***

The following relates to primary objective (i) for rivaroxaban only and relates to haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites.

Table 64 and Table 66 include all incident reports of major bleeding episodes that were reported on treatment with rivaroxaban during the 12 week observation period. The number of major bleeds were small and preclude detailed analyses of differences between indications. Major bleeding within the gastrointestinal tract was the most frequently reported type of bleed across all indications and also within the DVT/PE group. A sensitivity analysis was performed which included events that occurred within the 12 week observation period but for which the event date was either missing or the treatment exit date was unknown; this is shown in Table 65 and demonstrates no differences with the results seen in Table 64.

**Table 64. Number of rivaroxaban patients reporting new onset haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites and cumulative incidence estimates (+95% CI<sup>a</sup>)**

Haemorrhage Event		All incident reports (on treatment + 3 days after stopping)		
		n	%	(95% CI)
All indications N=2542				
	Major - Gastrointestinal site	13	0.5	(0.3,0.9)
	Major - Urogenital site	7	0.3	(0.1,0.6)
	Major - all Intracranial	3	0.1	(0.0,0.4)
AF N=965				
	Major - Gastrointestinal site	2	0.2	(0.0,0.8)
	Major - Urogenital site	2	0.2	(0.0,0.8)
	Major - all Intracranial	2	0.2	(0.0,0.8)
DVT/PE N=1532				
	Major - Gastrointestinal site	11	0.7	(0.4,1.3)
	Major - Urogenital site	5	0.3	(0.1,0.8)
	Major - all Intracranial	1	0.1	(0.0,0.4)
Mixed (AF & DVT/PE) N=23				
	Major - Gastrointestinal site	0	0.0	
	Major - Urogenital site	0	0.0	
	Major - all Intracranial	0	0.0	
Other N=22				
	Major - Gastrointestinal site	0	0.0	
	Major - Urogenital site	0	0.0	
	Major - all Intracranial	0	0.0	

Percentages for all incident reports have been calculated out of the number of rivaroxaban patients, for each indication; Cumulative incidence = (Total number of new cases during 12 week observation period / Population initially at risk) \*100. Note, where events are reported with no supporting event date or treatment exit date, these have been excluded from the numerator of the cumulative risk calculation for that bleed type. Where patients have haemorrhage events but all event date information is missing or treatment exit date is missing they have been excluded from the cumulative risk denominator for all bleed types;<sup>a</sup> 95% CI calculated using Binomial exact

**Table 65. (Sensitivity Analysis) Number of rivaroxaban patients reporting new onset haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites and cumulative incidence estimates (+95% CI<sup>a</sup>)**

Haemorrhage Event		All incident reports (on treatment + 3 days after stopping)		
		n	%	(95% CI)
All indications N=2542				
	Major - Gastrointestinal site	13	0.5	(0.3,0.9)
	Major - Urogenital site	7	0.3	(0.1,0.6)
	Major - all Intracranial	3	0.1	(0.0,0.3)
AF N=965				
	Major - Gastrointestinal site	2	0.2	(0.0,0.8)
	Major - Urogenital site	2	0.2	(0.0,0.8)
	Major - all Intracranial	2	0.2	(0.0,0.8)
DVT/PE N=1532				
	Major - Gastrointestinal site	11	0.7	(0.4,1.3)
	Major - Urogenital site	5	0.3	(0.1,0.8)
	Major - all Intracranial	1	0.1	(0.0,0.4)
Mixed (AF & DVT/PE) N=23				
	Major - Gastrointestinal site	0	0.0	
	Major - Urogenital site	0	0.0	
	Major - all Intracranial	0	0.0	
Other N=22				
	Major - Gastrointestinal site	0	0.0	
	Major - Urogenital site	0	0.0	
	Major - all Intracranial	0	0.0	

Percentages for all incident reports have been calculated out of the number of rivaroxaban patients, for each indication; Cumulative incidence = (Total number of new cases during 12 week observation period / Population initially at risk) \*100. Note, where event date is missing, or treatment exit date is unknown but an event occurred within the observation period, these events have been included in the cumulative incidence for this sensitivity analysis; <sup>a</sup> 95% CI calculated using Binomial exact

**Table 66. Cumulative Incidence rates (IR) of new onset haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (+95% CI<sup>a</sup>) in rivaroxaban cohort**

Haemorrhage Event	Number of events	Total person-time (100 years)	IR (95% CI)
All indications N=2542			
Major - Gastrointestinal site	13	4.7	2.8 (1.5,4.7)
Major - Urogenital site	7	4.7	N/A*
Major - all Intracranial	3	4.7	N/A*
AF N=965			

Haemorrhage Event	Number of events	Total person-time (100 years)	IR (95% CI)	
DVT/PE N=1532	Major - Gastrointestinal site	2	1.8	N/A*
	Major - Urogenital site	2	1.8	N/A*
	Major - all Intracranial	2	1.8	N/A*
	Major - Gastrointestinal site	11	2.8	3.9 (2.0,7.1)
	Major - Urogenital site	5	2.8	N/A*
	Major - all Intracranial	1	2.8	N/A*
Mixed (AF & DVT/PE) N=23	Major - Gastrointestinal site	0	0.0	N/A*
	Major - Urogenital site	0	0.0	N/A*
	Major - all Intracranial	0	0.0	N/A*
Other N=22	Major - Gastrointestinal site	0	0.0	N/A*
	Major - Urogenital site	0	0.0	N/A*
	Major - all Intracranial	0	0.0	N/A*

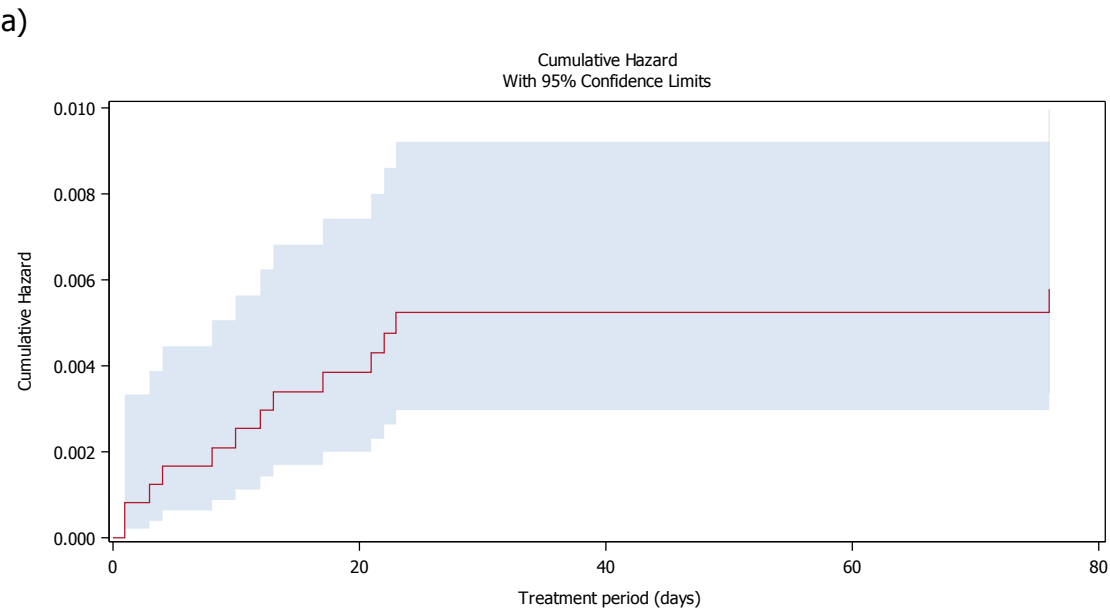
Incidence Rate (IR) = (Number of events / Total person-time) where person-time is derived from index date until the earliest of time until event of interest, date at which patient is censored or end of 12 week observation period; Total person-time (100 years) = Total person-time / (365.25\*100); \*rates have not been calculated where event count  $n \leq 10$ ;

<sup>a</sup> 95% CI calculated using Poisson exact

### 10.5.2 Time to event analysis for haemorrhage

For each primary objective outcome where there were at least 10 cases, a semi-parametric Proportional Hazards (PH) regression model was derived using the 'as treated' cohort to describe the time to event, which is presented graphically for the rivaroxaban cohort to examine its shape. A smoothed estimate of empirical hazard function was also plotted using an Epanechnikov kernel. These will be used to describe how the baseline risk of an event changes over time for the total cohort. These are provided and described below. Figure 15 provides the Nelson Aalen cumulative hazard function and the smoothed hazard function for Major Gastrointestinal bleeds for all indications. The smoothed hazard function is not very informative due to the sparse data. Whilst there is a suggestion of a bi-modal distribution, the unadjusted plot does not suggest that there are robust data to support this.

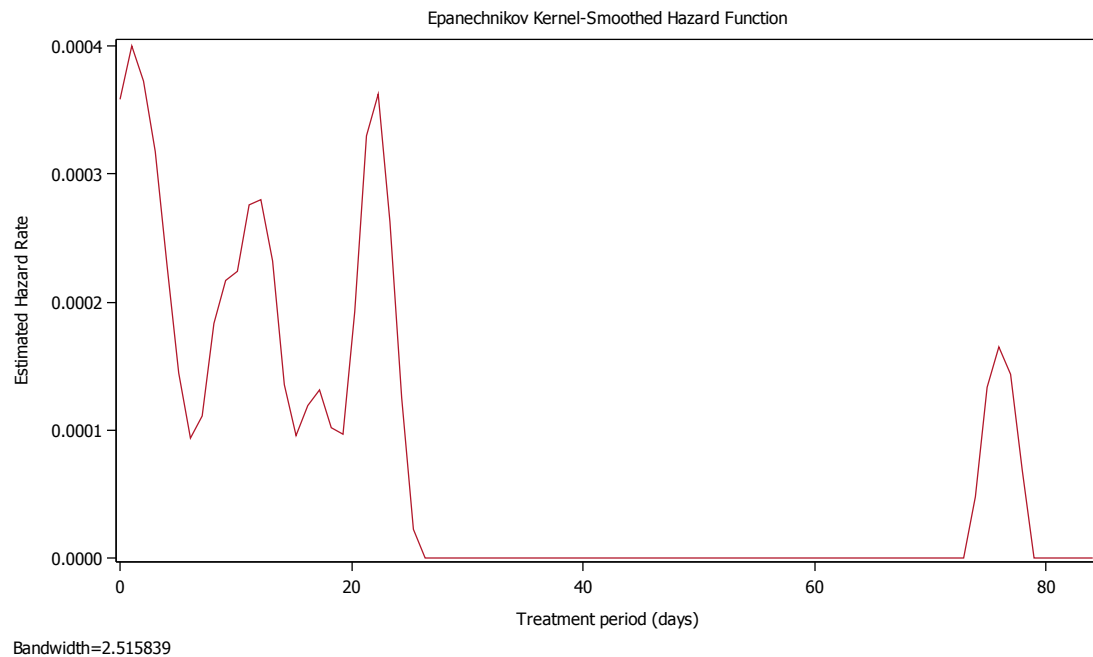
**Figure 15. Unadjusted time to event graph for study outcome (Major bleed– Gastrointestinal site ) in rivaroxaban cohort presented as a) Nelson-Aalen cumulative hazard function and b) smoothed hazard function**



Number of patients at risk					
Days	0	20	40	60	80
<hr/>					
#	2478	2223	2030	1896	1776

The Cumulative Hazard is shown as the red line, the blue outline displays the 95% confidence limits for the Cumulative Hazard

b)



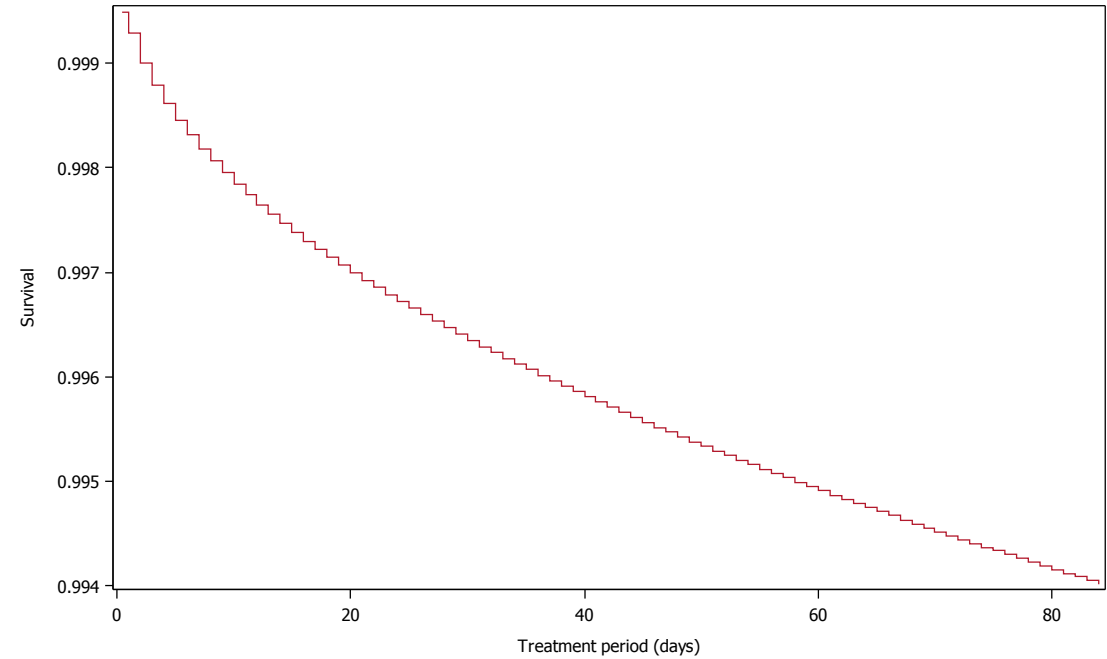
Only patients with a valid event or censor date have been included in the analysis

The Weibull semi parametric model shown in Figure 16 depicts the same data as shown in Figure 15 for the study outcome of major gastrointestinal bleed for all indications, fitted to a semi-parametric model. This suggests that the hazard function is decreasing over time in this dataset, and the goodness of fit (Figure 16d) is reasonable given the sparse data.

Figure 17 provides the subset of data for the DVT/PE subgroup of patients and shows similar results.

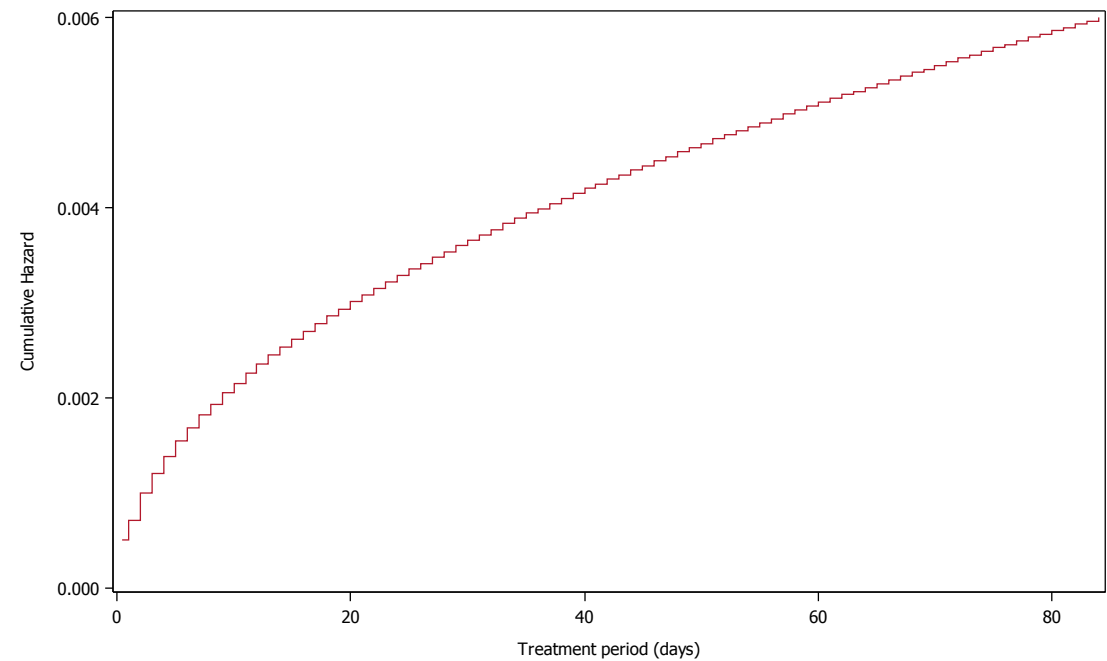
**Figure 16. Weibull unadjusted model of study primary outcome for all indications (Major bleed– Gastrointestinal) of interest (a) survival, (b) cumulative hazard, (c) hazard and (d) goodness of fit**

a) All indications



Note: Only patients with a valid event or censor date have been included in the analysis

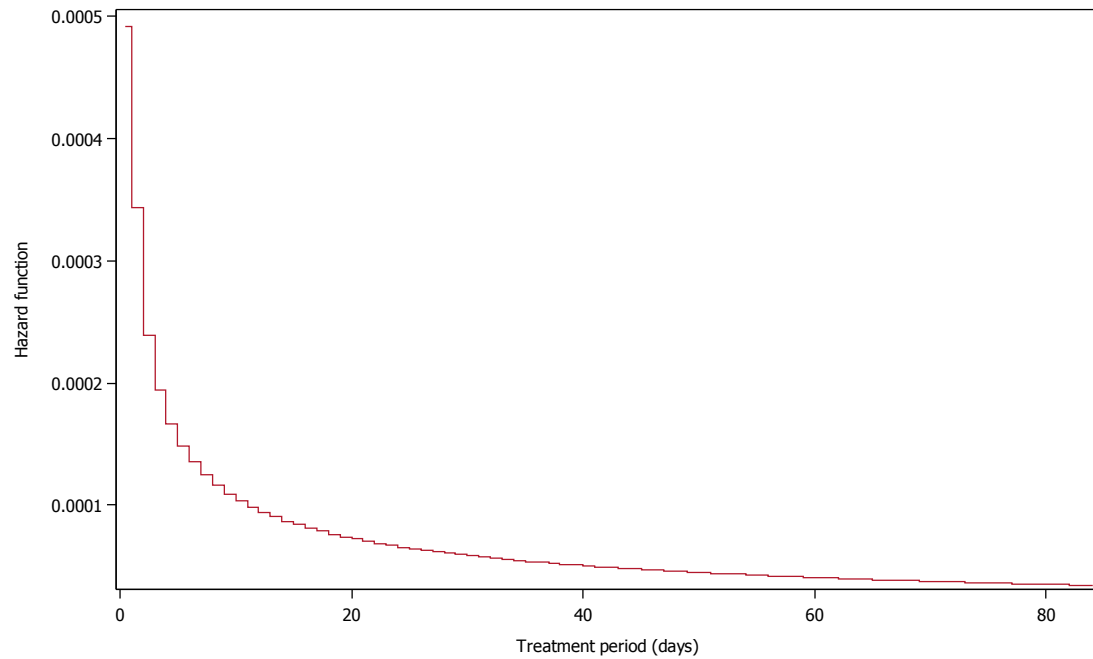
b) All indications



Note: Only patients with a valid event or censor date have been included in the analysis

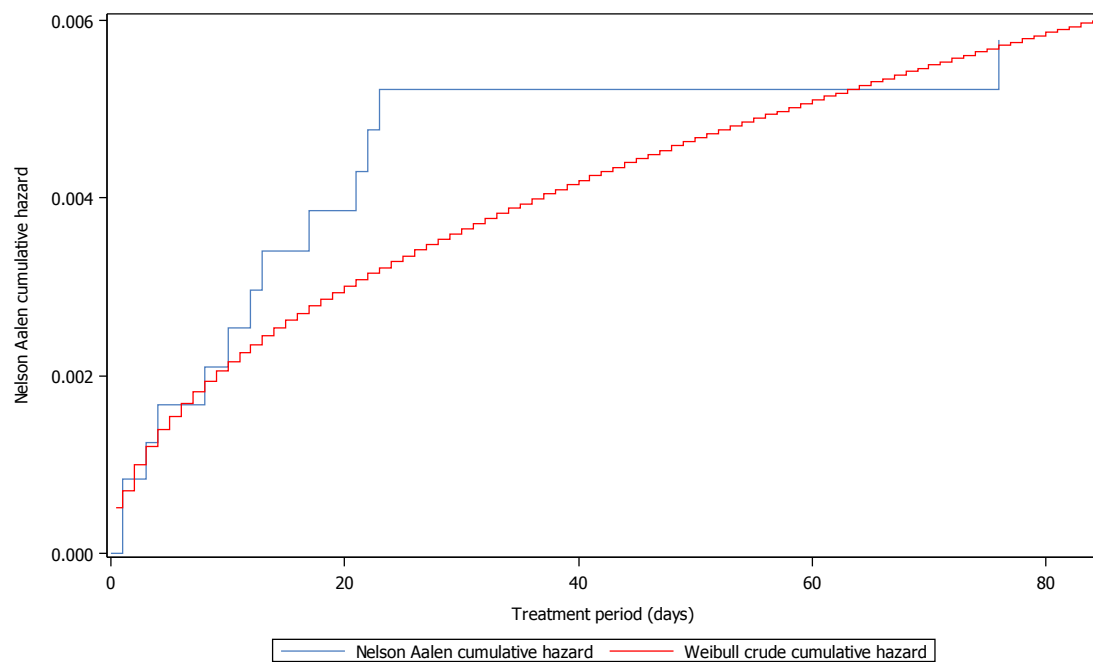


c) All indications



Note: Only patients with a valid event or censor date have been included in the analysis

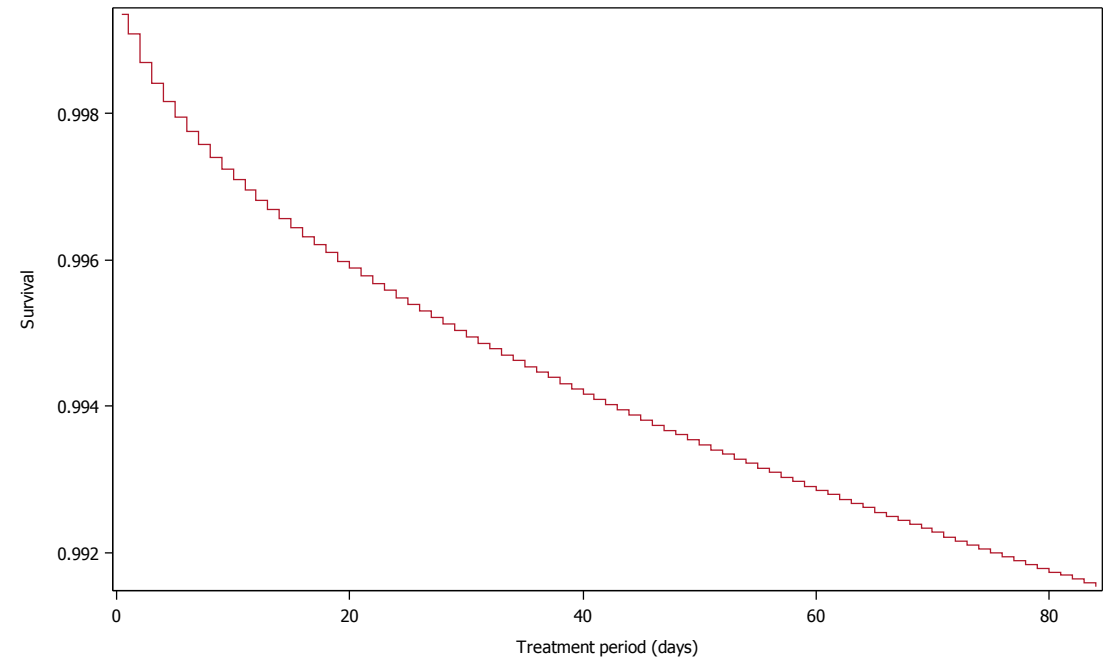
d) All indications



Note: Only patients with a valid event or censor date have been included in the analysis

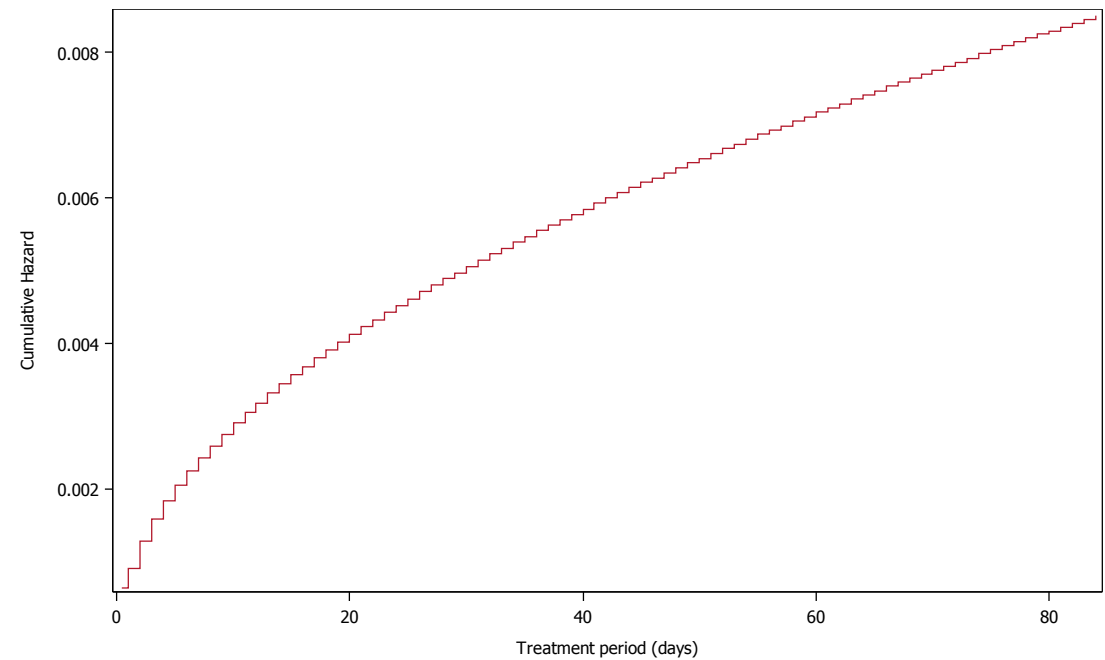
**Figure 17. Weibull unadjusted model of study primary outcome for DVT/PE group (Major bleed– Gastrointestinal) of interest (a) survival, (b) cumulative hazard, (c) hazard and (d) goodness of fit**

a) Indication= DVT/PE



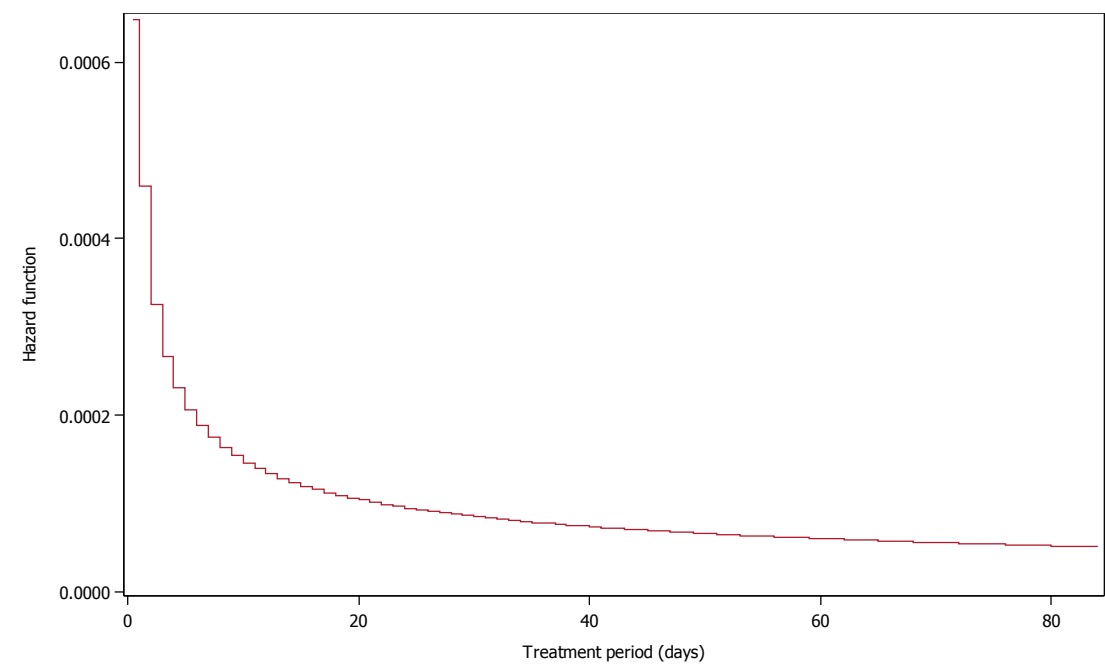
Note: Only indication groups with 10 or more events of interest have been displayed; only patients with a valid event or censor date have been included in the analysis

b) Indication= DVT/PE



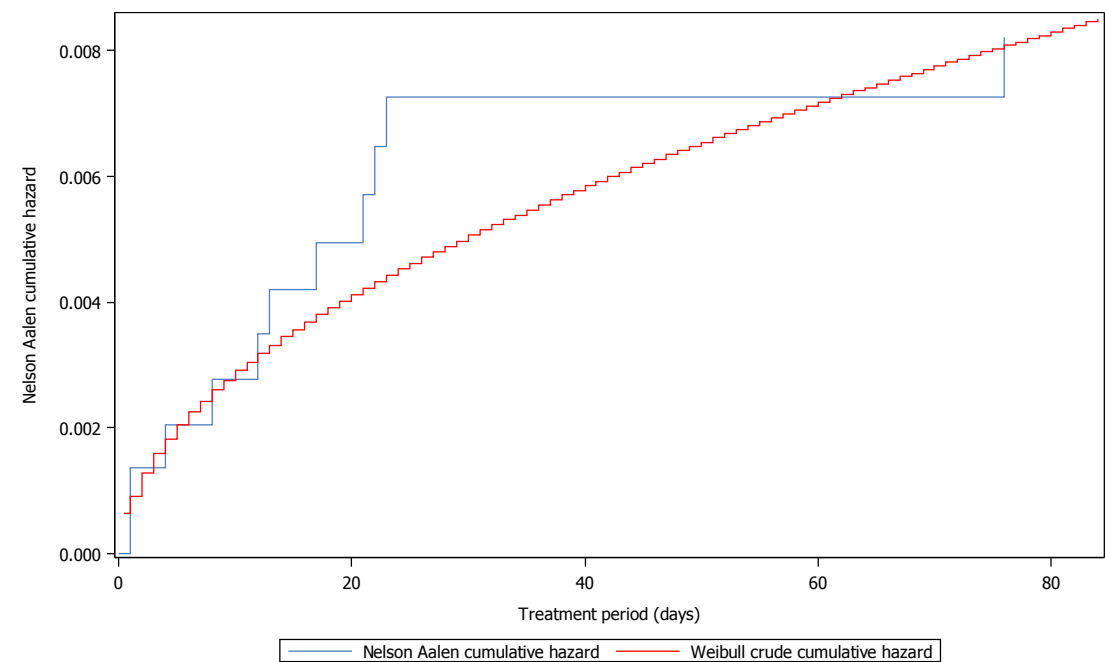
Note: Only indication groups with 10 or more events of interest have been displayed; only patients with a valid event or censor date have been included in the analysis

c) Indication= DVT/PE



Note: Only indication groups with 10 or more events of interest have been displayed; only patients with a valid event or censor date have been included in the analysis

d) Indication= DVT/PE



Note: Only indication groups with 10 or more events of interest have been displayed; only patients with a valid event or censor date have been included in the analysis

Table 67 provides the shape parameter for the Weibull distribution, which confirms that the hazard rate for major gastrointestinal bleed for both all indications and the DVT/PE subgroup is decreasing as the coefficient is less than one. The AICC suggests that the DVT/PE model fits the DVT/PE data better than the all indications model.

**Table 67. Unadjusted parametric model for study primary outcome (Major bleed– Gastrointestinal) of interest, with AICC value**

Model Parameter	Weibull	
	All indications	DVT/PE
Hazard <sup>a</sup>		
Coefficient	15.1	13.9
Std Error	3.0	2.9
P-Value	< 0.001	< 0.001
95% CI (lower)	9.3	8.3
95% CI (upper)	20.9	19.5
Shape <sup>b</sup>		
Coefficient	0.5	0.5
Std Error	0.1	0.1
95% CI (lower)	0.3	0.3
95% CI (upper)	0.8	0.9
Log Likelihood	-103.1	-82.9
AICC	210.2	169.8

Only indication groups with 10 or more events of interest have been displayed; The Hazard<sup>a</sup> parameter is the untransformed intercept, and the shape<sup>b</sup> parameter is the weibull shape parameter, both obtained with the unadjusted weibull model, from the SAS proc lifereg procedure. The hazard function is calculated using the equation:  $\alpha t^{(\gamma-1)}$  where  $\alpha = \exp(-(\mu\gamma))$ ,  $\mu = \text{intercept}^a$  value from SAS, and  $\gamma = \text{Weibull shape}^b$  parameter. Only patients with a valid event or censor date have been included in the analysis

### **10.5.3 Exploring predictors of risk of primary outcomes**

Table 68 includes baseline characteristics of patients with a major gastrointestinal bleed (cases) and baseline characteristics of patients for whom no major gastrointestinal bleed was reported (non-cases). OR with 95% CIs were calculated to identify any baseline characteristics for which a possible significant difference existed between cases and non-cases, where there were sufficient counts. For major gastrointestinal bleeds, the only significant result was for hypertension; the OR with 95% CI was 10.4 (1.5, 446.2) with an associated p value of 0.004. This suggests the odds of a patient with a major gastrointestinal bleed having baseline hypertension were approximately ten times the odds of a patient having baseline hypertension in whom no bleeding event occurred. This is consistent with known risk factors for bleeding outcomes (HAS-BLED, see section (6.2) in which baseline hypertension is included.

**Table 68. Baseline characteristics of patients with a Major bleed – gastrointestinal site (cases) and non-cases**

Characteristic (%)		Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
		n	% cases where values reported	n	% non-cases where values reported	
Gender						
	Male <sup>d</sup>	8	0.6	1374	99.4	1
	Female	5	0.4	1155	99.6	0.7 (0.2,2.6) [0.782]
	Missing	0	0.0	0	0.0	N/A
Age at index (years) <sup>e</sup>						
	<18 <sup>d</sup>	0	0.0	4	100.0	
	19-29	0	0.0	66	100.0	N/A
	30-39	0	0.0	124	100.0	N/A
	40-49	1	0.4	249	99.6	
	50-59	3	0.9	333	99.1	
	60-69	2	0.4	529	99.6	
	70-79	3	0.5	660	99.5	
	80+	4	0.7	564	99.3	
	Missing	0	0.0	0	0.0	N/A
	Median (IQR)	74.0 (54.0-84.0)		69.0 (56.0-78.0)		[0.709]
	Age <65 years <sup>d</sup>	4	0.4	1002	99.6	1
	Age 65-74 years	3	0.5	629	99.5	1.2 (0.2,7.1) [1.000]
	Age 75+ years	6	0.7	898	99.3	1.7 (0.4,8.1) [0.531]
Ethnicity						
	White <sup>d</sup>	10	0.4	2221	99.6	1
	African	0	0.0	13	100.0	N/A
	Caribbean	1	3.4	28	96.6	7.9 (0.2,59.1) [0.133]
	Black - Other	0	0.0	4	100.0	N/A
	Indian	0	0.0	20	100.0	N/A
	Pakistani	0	0.0	11	100.0	N/A
	Bangladeshi	0	0.0	2	100.0	N/A
	Chinese	0	0.0	5	100.0	N/A
	Other	0	0.0	18	100.0	N/A
	Unknown	2	1.0	207	99.0	2.1 (0.2,10.2) [0.275]
	Missing	0	0.0	0	0.0	N/A

Characteristic (%)	Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
	n	% cases where values reported	n	% non-cases where values reported	
Index of Multiple Deprivation Rank Decile					
1 (most deprived) <sup>d</sup>	1	0.6	175	99.4	1
2	2	1.1	186	98.9	1.9 (0.1,111.6) [1.000]
3	2	0.8	244	99.2	1.4 (0.1,85.1) [1.000]
4	2	0.8	244	99.2	1.4 (0.1,85.1) [1.000]
5	1	0.4	277	99.6	0.6 (0.0,49.9) [1.000]
6	1	0.4	248	99.6	0.7 (0.0,55.7) [1.000]
7	2	0.8	259	99.2	1.4 (0.1,80.2) [1.000]
8	0	0.0	257	100.0	N/A
9	1	0.4	278	99.6	0.6 (0.0,49.7) [1.000]
10 (least deprived)	0	0.0	217	100.0	N/A
Missing	1	0.7	144	99.3	1.2 (0.0,95.9) [1.000]
Median (IQR)	4.0 (2.5-6.5)		6.0 (3.0-8.0)		[0.173]
BMI (mg/kg2) <sup>e</sup>					
<18.5 (Below Normal) <sup>d</sup>	0	0.0	35	100.0	
18.5-24.9 (Normal)	3	0.5	563	99.5	
25.0-29.9 (Overweight)	2	0.3	684	99.7	
30.0-39.9 (Obese)	4	0.7	571	99.3	
40.0+ (Morbidly Obese)	1	0.9	110	99.1	
Missing	3	0.5	566	99.5	
Median (IQR)	30.0 (24.4-35.5)		27.7 (24.4-32.0)		[0.493]
Indication					
AF <sup>d</sup>	2	0.2	963	99.8	1
DVT/PE	11	0.7	1521	99.3	3.5 (0.8,32.4) [0.095]
Mixed (AF & DVT/PE)	0	0.0	23	100.0	N/A
Other	0	0.0	22	100.0	N/A
Prior/ at baseline history of:					
CVA Yes	1	0.3	377	99.7	0.5 (0.0,3.2) [0.706]
No <sup>d</sup>	12	0.6	2152	99.4	1
DVT Yes	8	0.7	1060	99.3	2.2 (0.6,8.6) [0.169]
No <sup>d</sup>	5	0.3	1469	99.7	1
Abnormal Liver Function Yes	0	0.0	44	100.0	N/A

Characteristic (%)		Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
		n	% cases where values reported	n	% non-cases where values reported	
	No <sup>d</sup>	13	0.5	2485	99.5	1
	Renal Disease Yes	1	2.3	43	97.7	4.8 (0.1,33.9) [0.204]
	No <sup>d</sup>	12	0.5	2486	99.5	1
	Diabetes Mellitus Yes	3	0.9	341	99.1	1.9 (0.3,7.5) [0.403]
	No <sup>d</sup>	10	0.5	2188	99.5	1
	Congestive Heart Failure Yes	1	0.5	199	99.5	1.0 (0.0,6.7) [1.000]
	No <sup>d</sup>	12	0.5	2330	99.5	1
	Vascular disease Yes	2	0.5	372	99.5	1.1 (0.1,4.9) [1.000]
	No <sup>d</sup>	11	0.5	2157	99.5	1
	Hypertension <sup>b</sup> Yes	12	0.9	1353	99.1	10.4 (1.5,446.2) [0.004]
	No <sup>d</sup>	1	0.1	1176	99.9	1
	Condition associated with predisposition to bleeding Yes	5	1.0	495	99.0	2.6 (0.7,9.0) [0.151]
	No <sup>d</sup>	8	0.4	2034	99.6	1
	Excessive alcohol consumption/alcohol misuse Yes	2	1.6	127	98.4	3.4 (0.4,16.0) [0.138]
	No <sup>d</sup>	11	0.5	2402	99.5	1
	Medications predisposing to bleeds Yes	5	0.6	900	99.4	1.1 (0.3,4.0) [0.781]
	No <sup>d</sup>	8	0.5	1629	99.5	1
	Smoking Yes	6	0.9	667	99.1	2.4 (0.7,8.3) [0.119]
	No <sup>d</sup>	7	0.4	1862	99.6	1
	Substance misuse prior Yes	0	0.0	38	100.0	N/A
	No <sup>d</sup>	13	0.5	2491	99.5	1
HAS-BLED score <sup>c</sup>						
	0 (low risk) <sup>d</sup>	5	0.4	1327	99.6	1
	1-2 (moderate risk)	3	0.6	537	99.4	1.5 (0.2,7.6) [0.697]
	3 + (high risk)	5	0.7	665	99.3	2.0 (0.5,8.7) [0.317]
	Missing	0	0.0	0	0.0	N/A
CHADS2VASC score <sup>e</sup>						
	0 (low risk) <sup>d</sup>	0	0.0	374	100.0	
	1 (moderate risk)	2	0.4	473	99.6	
	2 + (high risk)	11	0.6	1682	99.4	
	Missing	0	0.0	0	0.0	N/A
Patient-specific prescribing reasons as reported by physician:						

Characteristic (%)	Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
	n	% cases where values reported	n	% non-cases where values reported	
Lifestyle choice Yes	4	0.5	821	99.5	0.9 (0.2,3.3) [1.000]
No <sup>d</sup>	9	0.5	1708	99.5	1
Non-adherence with prior anticoagulant Yes	0	0.0	40	100.0	N/A
No <sup>d</sup>	13	0.5	2489	99.5	1
Side-effects with prior anticoagulant Yes	0	0.0	84	100.0	N/A
No <sup>d</sup>	13	0.5	2445	99.5	1
Patient preference Yes	1	0.5	206	99.5	0.9 (0.0,6.4) [1.000]
No <sup>d</sup>	12	0.5	2323	99.5	1
Poor control Yes	0	0.0	37	100.0	N/A
No <sup>d</sup>	13	0.5	2492	99.5	1
Aberrant health behaviours Yes	0	0.0	7	100.0	N/A
No <sup>d</sup>	13	0.5	2522	99.5	1
Influences on prescribing as reported by physician:					
Clinical Judgement Yes	11	0.5	2152	99.5	1.0 (0.2,9.0) [1.000]
No <sup>d</sup>	2	0.5	377	99.5	1
NICE recommendations Yes	5	0.6	794	99.4	1.4 (0.4,4.8) [0.561]
No <sup>d</sup>	8	0.5	1735	99.5	1
Expert Guidelines Yes	2	0.8	263	99.2	1.6 (0.2,7.2) [0.638]
No <sup>d</sup>	11	0.5	2266	99.5	1
Hospital Formulary Yes	3	0.6	482	99.4	1.3 (0.2,5.0) [0.723]
No <sup>d</sup>	10	0.5	2047	99.5	1
Patient group Direction Yes	1	0.3	291	99.7	0.6 (0.0,4.4) [1.000]
No <sup>d</sup>	12	0.5	2238	99.5	1
Ease of reversibility Yes	0	0.0	13	100.0	N/A
No <sup>d</sup>	13	0.5	2516	99.5	1

<sup>a</sup> 95% CI calculated using Fisher's exact; <sup>b</sup> according to CHADS2VASC definition; <sup>c</sup> excluding labile INR

<sup>d</sup> Reference category for Odds Ratios; <sup>e</sup> Odds ratios are non-evaluable for this strata due to 0 count for reference group



Table 69 includes baseline characteristics of patients with a major urogenital bleed (cases) and baseline characteristics of patients for whom no major urogenital bleed was reported (non-cases). OR with 95% CIs were calculated to identify any baseline characteristics for which a possible significant difference existed between cases and non-cases, where there were sufficient counts. For major urogenital bleeds, the only significant result was for prior history of stroke; the OR with 95% CI was 7.7 (1.3, 52.7) with an associated p value of 0.012. This suggests the odds of a patient with a major urogenital bleed having a prior history of stroke were approximately seven times the odds of a patient having a prior history of stroke in whom no bleeding event occurred. This is also consistent with known risk factors for bleeding outcomes (HAS-BLED, see section 6.2) in which prior history of stroke is included.

**Table 69. Baseline characteristics of patients with a Major bleed – urogenital site (cases) and non-cases**

Characteristic (%)		Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
		n	% cases where values reported	n	% non-cases where values reported	
Gender	Male <sup>d</sup>	4	0.3	1378	99.7	1
	Female	3	0.3	1157	99.7	0.9 (0.1,5.3) [1.000]
	Missing	0	0.0	0	0.0	N/A
Age at index (years) <sup>e</sup>	<18 <sup>d</sup>	0	0.0	4	100.0	
	19-29	0	0.0	66	100.0	N/A
	30-39	1	0.8	123	99.2	
	40-49	1	0.4	249	99.6	
	50-59	1	0.3	335	99.7	
	60-69	3	0.6	528	99.4	
	70-79	0	0.0	663	100.0	N/A
	80+	1	0.2	567	99.8	
	Missing	0	0.0	0	0.0	N/A
	Median (IQR)	66.0 (46.0-69.0)		69.0 (56.0-78.0)		[0.076]
	Age <65 years <sup>d</sup>	3	0.3	1003	99.7	1
	Age 65-74 years	3	0.5	629	99.5	1.6 (0.2,12.0) [0.682]
	Age 75+ years	1	0.1	903	99.9	0.4 (0.0,4.6) [0.627]
Ethnicity	White <sup>d</sup>	6	0.3	2225	99.7	1
	African	0	0.0	13	100.0	N/A
	Caribbean	0	0.0	29	100.0	N/A
	Black - Other	0	0.0	4	100.0	N/A
	Indian	0	0.0	20	100.0	N/A
	Pakistani	0	0.0	11	100.0	N/A
	Bangladeshi	0	0.0	2	100.0	N/A
	Chinese	0	0.0	5	100.0	N/A
	Other	0	0.0	18	100.0	N/A
	Unknown	1	0.5	208	99.5	1.8 (0.0,14.8) [0.466]
	Missing	0	0.0	0	0.0	N/A
Index of Multiple Deprivation Rank Decile <sup>e</sup>	1 (most deprived) <sup>d</sup>	0	0.0	176	100.0	
	2	2	1.1	186	98.9	
	3	1	0.4	245	99.6	

Characteristic (%)	Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
	n	% cases where values reported	n	% non-cases where values reported	
	4	1	245	99.6	
	5	0	278	100.0	N/A
	6	1	248	99.6	
	7	1	260	99.6	
	8	0	257	100.0	N/A
	9	0	279	100.0	N/A
	10 (least deprived)	0	217	100.0	N/A
	Missing	1	144	99.3	
	Median (IQR)	3.5 (2.0-6.0)	6.0 (3.0-8.0)		[0.283]
BMI (mg/kg2)	<18.5 (Below Normal) <sup>d</sup>	1	34	97.1	1
	18.5-24.9 (Normal)	2	564	99.6	0.1 (0.0,7.3) [0.165]
	25.0-29.9 (Overweight)	0	686	100.0	N/A
	30.0-39.9 (Obese)	0	575	100.0	N/A
	40.0+ (Morbidly Obese)	1	110	99.1	0.3 (0.0,25.0) [0.423]
	Missing	3	566	99.5	0.2 (0.0,10.0) [0.213]
	Median (IQR)	21.4 (18.6-37.4)	27.7 (24.4-32.0)		[0.218]
Indication	AF <sup>d</sup>	2	963	99.8	1
	DVT/PE	5	1527	99.7	1.6 (0.3,16.6) [0.713]
	Mixed (AF & DVT/PE)	0	23	100.0	N/A
	Other	0	22	100.0	N/A
Prior/ at baseline history of:	CVA Yes	4	374	98.9	7.7 (1.3,52.7) [0.012]
	No <sup>d</sup>	3	2161	99.9	1
	DVT Yes	1	1067	99.9	0.2 (0.0,1.9) [0.250]
	No <sup>d</sup>	6	1468	99.6	1
	Abnormal Liver Function Yes	1	43	97.7	N/A
	No <sup>d</sup>	6	2492	99.8	1
	Renal Disease Yes	0	44	100.0	N/A
	No <sup>d</sup>	7	2491	99.7	1
	Diabetes Mellitus Yes	0	344	100.0	N/A
	No <sup>d</sup>	7	2191	99.7	1
	Congestive Heart Failure Yes	0	200	100.0	N/A
	No <sup>d</sup>	7	2335	99.7	1
	Vascular disease Yes	1	373	99.7	1.0 (0.0,8.0) [1.000]

Characteristic (%)		Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
		n	% cases where values reported	n	% non-cases where values reported	
	No <sup>d</sup>	6	0.3	2162	99.7	1
	Hypertension <sup>b</sup> Yes	3	0.2	1362	99.8	0.6 (0.1,3.8) [0.711]
	No <sup>d</sup>	4	0.3	1173	99.7	1
	Condition associated with predisposition to bleeding Yes	3	0.6	497	99.4	3.1 (0.4,18.2) [0.142]
	No <sup>d</sup>	4	0.2	2038	99.8	1
	Excessive alcohol consumption/alcohol misuse Yes	1	0.8	128	99.2	3.1 (0.1,26.1) [0.306]
	No <sup>d</sup>	6	0.2	2407	99.8	1
	Medications predisposing to bleeds Yes	4	0.4	901	99.6	2.4 (0.4,16.5) [0.255]
	No <sup>d</sup>	3	0.2	1634	99.8	1
	Smoking Yes	3	0.4	670	99.6	2.1 (0.3,12.4) [0.390]
	No <sup>d</sup>	4	0.2	1865	99.8	1
	Substance misuse prior Yes	0	0.0	38	100.0	N/A
	No <sup>d</sup>	7	0.3	2497	99.7	1
HAS-BLED score <sup>c</sup>						
	0 (low risk) <sup>d</sup>	2	0.2	1330	99.8	1
	1-2 (moderate risk)	1	0.2	539	99.8	1.2 (0.0,23.7) [1.000]
	3 + (high risk)	4	0.6	666	99.4	4.0 (0.6,44.2) [0.101]
	Missing	0	0.0	0	0.0	N/A
CHADS2VASC score <sup>e</sup>						
	0 (low risk) <sup>d</sup>	0	0.0	374	100.0	
	1 (moderate risk)	2	0.4	473	99.6	
	2 + (high risk)	5	0.3	1688	99.7	
	Missing	0	0.0	0	0.0	N/A
Patient-specific prescribing reasons as reported by physician:						
	Lifestyle choice Yes	3	0.4	822	99.6	1.6 (0.2,9.3) [0.689]
	No <sup>d</sup>	4	0.2	1713	99.8	1
	Non-adherence with prior anticoagulant Yes	0	0.0	40	100.0	N/A
	No <sup>d</sup>	7	0.3	2495	99.7	1
	Side-effects with prior anticoagulant Yes	0	0.0	84	100.0	N/A
	No <sup>d</sup>	7	0.3	2451	99.7	1
	Patient preference Yes	1	0.5	206	99.5	1.9 (0.0,15.6) [0.449]
	No <sup>d</sup>	6	0.3	2329	99.7	1
	Poor control Yes	0	0.0	37	100.0	N/A
	No <sup>d</sup>	7	0.3	2498	99.7	1
	Aberrant health behaviours Yes	0	0.0	7	100.0	N/A
	No <sup>d</sup>	7	0.3	2528	99.7	1

Characteristic (%)	n	Cases % cases where values reported	n	Non-Cases % non-cases where values reported	OR (+95% CI <sup>a</sup> ) [P-value]
Influences on prescribing as reported by physician:					
Clinical Judgement Yes	5	0.2	2158	99.8	0.4 (0.1,4.6) [0.281]
No <sup>d</sup>	2	0.5	377	99.5	1
NICE recommendations Yes	3	0.4	796	99.6	1.6 (0.2,9.7) [0.685]
No <sup>d</sup>	4	0.2	1739	99.8	1
Expert Guidelines Yes	0	0.0	265	100.0	N/A
No <sup>d</sup>	7	0.3	2270	99.7	1
Hospital Formulary Yes	1	0.2	484	99.8	0.7 (0.0,5.8) [1.000]
No <sup>d</sup>	6	0.3	2051	99.7	1
Patient group Direction Yes	1	0.3	291	99.7	1.3 (0.0,10.6) [0.575]
No <sup>d</sup>	6	0.3	2244	99.7	1
Ease of reversibility Yes	0	0.0	13	100.0	N/A
No <sup>d</sup>	7	0.3	2522	99.7	1

<sup>a</sup> 95% CI calculated using Fisher's exact; <sup>b</sup> according to CHADS2VASC definition; <sup>c</sup> excluding labile INR

<sup>d</sup> Reference category for Odds Ratios; <sup>e</sup> Odds ratios are non-evaluable for this strata due to 0 count for reference group

Table 70 includes baseline characteristics of patients with an intracranial bleed (cases) and baseline characteristics of patients for whom no intracranial bleed was reported (non-cases). OR with 95% CIs were calculated to identify any baseline characteristics for which a possible significant difference existed between cases and non-cases, where there were sufficient counts. For intracranial bleeds, the only significant result was for the physician reported influence on prescribing of 'ease of reversibility'; the OR with 95% CI was 105.3 (1.6, 2096.6) with an associated p value of 0.015. This suggests the odds of ease of reversibility representing a prescriber influence amongst cases of intracranial bleed were approximately one hundred times the odds of a physician reporting this as an influence amongst patients in whom no bleeding event occurred. However this result should be treated with caution as the associated 95% CI is extremely wide. It may reflect physicians' preference for prescribing an anticoagulant for which a reversal agent is available amongst patients perceived to be at higher risk of bleeding.

**Table 70. Baseline characteristics of patients with a Major bleed – intracranial site (cases) and non-cases**

Characteristic (%)		Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
		n	% cases where values reported	n	% non-cases where values reported	
Gender	Male <sup>d</sup>	2	0.1	1380	99.9	1
	Female	1	0.1	1159	99.9	0.6 (0.0,11.5) [1.000]
	Missing	0	0.0	0	0.0	N/A
Age at index (years) <sup>e</sup>	<18 <sup>d</sup>	0	0.0	4	100.0	
	19-29	0	0.0	66	100.0	N/A
	30-39	0	0.0	124	100.0	N/A
	40-49	0	0.0	250	100.0	N/A
	50-59	0	0.0	336	100.0	N/A
	60-69	0	0.0	531	100.0	N/A
	70-79	2	0.3	661	99.7	
	80+	1	0.2	567	99.8	
	Missing	0	0.0	0	0.0	N/A
	Median (IQR)	75.0 (70.0-83.0)		69.0 (56.0-78.0)		[0.074]
	Age <65 years <sup>d</sup>	0	0.0	1006	100.0	
	Age 65-74 years	1	0.2	631	99.8	
	Age 75+ years	2	0.2	902	99.8	
Ethnicity	White <sup>d</sup>	2	0.1	2229	99.9	1
	African	0	0.0	13	100.0	N/A
	Caribbean	0	0.0	29	100.0	N/A
	Black - Other	0	0.0	4	100.0	N/A
	Indian	1	5.0	19	95.0	58.7 (0.9,1152.5) [0.026]
	Pakistani	0	0.0	11	100.0	N/A
	Bangladeshi	0	0.0	2	100.0	N/A
	Chinese	0	0.0	5	100.0	N/A
	Other	0	0.0	18	100.0	N/A
	Unknown	0	0.0	209	100.0	N/A
	Missing	0	0.0	0	0.0	N/A
Index of Multiple Deprivation Rank Decile <sup>e</sup>	1 (most deprived) <sup>d</sup>	0	0.0	176	100.0	
	2	0	0.0	188	100.0	N/A

Characteristic (%)	Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
	n	% cases where values reported	n	% non-cases where values reported	
	3	0	246	100.0	N/A
	4	2	244	99.2	
	5	0	278	100.0	N/A
	6	1	248	99.6	
	7	0	261	100.0	N/A
	8	0	257	100.0	N/A
	9	0	279	100.0	N/A
	10 (least deprived)	0	217	100.0	N/A
	Missing	0	145	100.0	N/A
	Median (IQR)	4.0 (4.0-6.0)	6.0 (3.0-8.0)		[0.360]
BMI (mg/kg2) <sup>e</sup>					
	<18.5 (Below Normal) <sup>d</sup>	0	35	100.0	
	18.5-24.9 (Normal)	3	563	99.5	
	25.0-29.9 (Overweight)	0	686	100.0	N/A
	30.0-39.9 (Obese)	0	575	100.0	N/A
	40.0+ (Morbidly Obese)	0	111	100.0	N/A
	Missing	0	569	100.0	N/A
	Median (IQR)	23.7 (23.6-24.1)	27.7 (24.4-32.0)		[0.033]
Indication					
	AF <sup>d</sup>	2	963	99.8	1
	DVT/PE	1	1531	99.9	0.3 (0.0,6.1) [0.563]
	Mixed (AF & DVT/PE)	0	23	100.0	N/A
	Other	0	22	100.0	N/A
Prior/ at baseline history of:					
	CVA Yes <sup>e</sup>	3	375	99.2	N/A
	No <sup>d</sup>	0	2164	100.0	N/A
	DVT Yes	2	1066	99.8	2.8 (0.1,163.2) [0.576]
	No <sup>d</sup>	1	1473	99.9	1
	Abnormal Liver Function Yes	0	44	100.0	N/A
	No <sup>d</sup>	3	2495	99.9	1
	Renal Disease Yes	0	44	100.0	N/A
	No <sup>d</sup>	3	2495	99.9	1
	Diabetes Mellitus Yes	1	343	99.7	3.2 (0.1,61.6) [0.354]
	No <sup>d</sup>	2	2196	99.9	1
	Congestive Heart Failure Yes	0	200	100.0	N/A
	No <sup>d</sup>	3	2339	99.9	1



Characteristic (%)	Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
	n	% cases where values reported	n	% non-cases where values reported	
Vascular disease Yes	2	0.5	372	99.5	11.7 (0.6,687.7) [0.058]
No <sup>d</sup>	1	0.0	2167	100.0	1
Hypertension <sup>b</sup> Yes <sup>e</sup>	3	0.2	1362	99.8	N/A
No <sup>d</sup>	0	0.0	1177	100.0	N/A
Condition associated with predisposition to bleeding Yes	1	0.2	499	99.8	2.0 (0.0,39.3) [0.482]
No <sup>d</sup>	2	0.1	2040	99.9	1
Excessive alcohol consumption/alcohol misuse Yes	1	0.8	128	99.2	9.4 (0.2,181.6) [0.145]
No <sup>d</sup>	2	0.1	2411	99.9	1
Medications predisposing to bleeds Yes	1	0.1	904	99.9	0.9 (0.0,17.4) [1.000]
No <sup>d</sup>	2	0.1	1635	99.9	1
Smoking Yes	1	0.1	672	99.9	1.4 (0.0,26.7) [1.000]
No <sup>d</sup>	2	0.1	1867	99.9	1
Substance misuse prior Yes	0	0.0	38	100.0	N/A
No <sup>d</sup>	3	0.1	2501	99.9	1
HAS-BLED score <sup>c e</sup>					
0 (low risk) <sup>d</sup>	0	0.0	1332	100.0	
1-2 (moderate risk)	0	0.0	540	100.0	N/A
3 + (high risk)	3	0.4	667	99.6	
Missing	0	0.0	0	0.0	N/A
CHADS2VASC score <sup>e</sup>					
0 (low risk) <sup>d</sup>	0	0.0	374	100.0	
1 (moderate risk)	0	0.0	475	100.0	N/A
2 + (high risk)	3	0.2	1690	99.8	
Missing	0	0.0	0	0.0	N/A
Patient-specific prescribing reasons as reported by physician:					
Lifestyle choice Yes	1	0.1	824	99.9	1.0 (0.0,20.0) [1.000]
No <sup>d</sup>	2	0.1	1715	99.9	1
Non-adherence with prior anticoagulant Yes	0	0.0	40	100.0	N/A
No <sup>d</sup>	3	0.1	2499	99.9	1
Side-effects with prior anticoagulant Yes	0	0.0	84	100.0	N/A
No <sup>d</sup>	3	0.1	2455	99.9	1
Patient preference Yes	0	0.0	207	100.0	N/A
No <sup>d</sup>	3	0.1	2332	99.9	1
Poor control Yes	0	0.0	37	100.0	N/A
No <sup>d</sup>	3	0.1	2502	99.9	1
Aberrant health behaviours Yes	0	0.0	7	100.0	N/A

Characteristic (%)		Cases		Non-Cases		OR (+95% CI) <sup>a</sup> [P-value]
		n	% cases where values reported	n	% non-cases where values reported	
Influences on prescribing as reported by physician:						
	No <sup>d</sup>	3	0.1	2532	99.9	1
	Clinical Judgement Yes <sup>e</sup>	3	0.1	2160	99.9	N/A
	No <sup>d</sup>	0	0.0	379	100.0	N/A
	NICE recommendations Yes	0	0.0	799	100.0	N/A
	No <sup>d</sup>	3	0.2	1740	99.8	1
	Expert Guidelines Yes	0	0.0	265	100.0	N/A
	No <sup>d</sup>	3	0.1	2274	99.9	1
	Hospital Formulary Yes	1	0.2	484	99.8	2.1 (0.0,40.8) [0.470]
	No <sup>d</sup>	2	0.1	2055	99.9	1
	Patient group Direction Yes	0	0.0	292	100.0	N/A
	No <sup>d</sup>	3	0.1	2247	99.9	1
	Ease of reversibility Yes	1	7.7	12	92.3	105.3 (1.6,2096.6) [0.015]
	No <sup>d</sup>	2	0.1	2527	99.9	1

<sup>a</sup> 95% CI calculated using Fisher's exact; <sup>b</sup> according to CHADS2VASC definition; <sup>c</sup> excluding labile INR

<sup>d</sup> Reference category for Odds Ratios; <sup>e</sup> Odds ratios are non-evaluable for this strata due to 0 count for reference group

### **10.5.4 Cumulative Incidence and rate of events reported in the 12 week observation period in both the rivaroxaban and contextual cohort and in patient subgroups of special interest.**

#### **10.5.4.1 Estimating the cumulative incidence of major bleeding for the warfarin cohort**

Table 71 and Table 72 include all incident reports of major bleeding episodes that were reported on treatment with warfarin during the 12 week observation period. The only major bleeding reported within the gastrointestinal and urogenital sites occurred within the DVT/PE group, whilst the only intracranial bleeds reported in patients taking warfarin occurred within the AF group.

**Table 71. Number of warfarin patients reporting new onset haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites and cumulative risk estimates (+95% CI<sup>a</sup>)**

Targeted Event		All incident reports (on treatment + 7 days after stopping)		(95% CI)
		n	%	
All indications N=2067				
	Major - Gastrointestinal site	3	0.2	(0.0,0.4)
	Major - Urogenital site	2	0.1	(0.0,0.4)
	Major - all Intracranial	2	0.1	(0.0,0.4)
AF N=794				
	Major - Gastrointestinal site	0	0.0	
	Major - Urogenital site	0	0.0	
	Major - all Intracranial	2	0.3	(0.0,0.9)
DVT/PE N=1212				
	Major - Gastrointestinal site	3	0.3	(0.1,0.7)
	Major - Urogenital site	2	0.2	(0.0,0.6)
	Major - all Intracranial	0	0.0	
Mixed (AF & DVT/PE) N=27				
	Major - Gastrointestinal site	0	0.0	
	Major - Urogenital site	0	0.0	
	Major - all Intracranial	0	0.0	
Other N=34				
	Major - Gastrointestinal site	0	0.0	
	Major - Urogenital site	0	0.0	
	Major - all Intracranial	0	0.0	

Percentages for all incident reports have been calculated out of the number of warfarin patients, for each indication; Cumulative incidence = (Total number of new cases during 12 week observation period / Population initially at risk) \*100. Note, where events are reported with no supporting event date or treatment exit date, these have been excluded from the numerator of the cumulative incidence calculation for that bleed type. Where patients have haemorrhage events but all event date information is missing or treatment exit date is missing they have been excluded from the cumulative incidence denominator for all bleed types; <sup>a</sup> 95% CI calculated using Binomial exact.

**Table 72. Cumulative Incidence Rates (IR) of new onset haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (+95% CI<sup>a</sup>) in warfarin cohort**

Targeted Event	Number of events	Total person-time (100 years)	IR (95% CI)
All indications N=2067			
Major - Gastrointestinal site	3	3.8	N/A*
Major - Urogenital site	2	3.8	N/A*
Major - all Intracranial	2	3.8	N/A*
AF N=794			
Major - Gastrointestinal site	0	1.5	N/A*
Major - Urogenital site	0	1.5	N/A*
Major - all Intracranial	2	1.5	N/A*
DVT/PE N=1212			
Major - Gastrointestinal site	3	2.2	N/A*
Major - Urogenital site	2	2.2	N/A*
Major - all Intracranial	0	2.2	N/A*
Mixed (AF & DVT/PE) N=27			
Major - Gastrointestinal site	0	0.0	N/A*
Major - Urogenital site	0	0.0	N/A*
Major - all Intracranial	0	0.0	N/A*
Other N=34			
Major - Gastrointestinal site	0	0.1	N/A*
Major - Urogenital site	0	0.1	N/A*
Major - all Intracranial	0	0.1	N/A*

Incidence Rate (IR) = (Number of events / Total person-time) where person-time is derived from index date until the earliest of time until event of interest, date at which patient is censored or end of 12 week observation period; Total person-time (100 years) = Total person-time / (365.25\*100);

\*rates have not been calculated where event count  $n \leq 10$ ;

<sup>a</sup> 95% CI calculated using Poisson exact

#### **10.5.4.2 Estimating the cumulative incidence of other major or non-major clinically relevant bleeding outcomes not specified in the primary objectives for the rivaroxaban and warfarin cohorts**

In accordance with secondary objectives (iv) regarding a) a composite of all major bleeding specified in the primary objective for both rivaroxaban and warfarin, b) major bleeding within critical organ sites (excluding all intracranial) for both rivaroxaban and warfarin, and c) a composite of all major and CRNM bleeds for rivaroxaban and warfarin, the analysis specified in the SAP section 9.6.2 was also applied. Of note, patients may have experienced more than one type of bleeding (e.g. major and clinically relevant non-major) within different sites, and so these counts are not mutually exclusive. As described previously, in cases where multiple bleeding episodes have been reported within the same site, the most serious episode of bleeding was

classified, and this bleeding classification with its associated event date was included in incidence density analyses.

Table 73 and Table 74 include all incident reports of major bleeding, CRNM bleeds and a composite of both these outcomes, reported on treatment with rivaroxaban and warfarin respectively during the 12 week observation period.

Across all indication groups, with the exception of major bleeds reported within critical organ sites (excluding all intracranial), the cumulative risk of major and CRNM would appear to be higher in the rivaroxaban group.

With the exception of major bleeds reported within critical organ sites (excluding all intracranial), Table 73 shows the cumulative risk of major and CRNM bleeds in rivaroxaban to be higher amongst the DVT/PE group, however there is some overlap in 95% CI between both groups.

**Table 73. Number of rivaroxaban patients reporting other new onset major or non-major clinically relevant bleeding outcomes and cumulative incidence estimates (+95% CIa)**

Haemorrhage Event		All incident reports (on treatment + 3 days after stopping)		(95% CI)
		n	%	
All indications N=2542				
	Major bleed (Gastrointestinal, Urogenital, all Intracranial)	23	0.9	(0.6,1.4)
	Major bleed – all other within critical organ sites (excluding all intracranial)	1	0.0	(0.0,0.2)
	Clinically relevant non-major bleeds	121	4.8	(4.0,5.7)
	Major bleed (All) <sup>b</sup>	33	1.3	(0.9,1.8)
	Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	154	6.1	(5.2,7.1)
AF N=965				
	Major bleed (Gastrointestinal, Urogenital, all Intracranial)	6	0.6	(0.2,1.4)
	Major bleed – all other within critical organ sites (excluding all intracranial)	1	0.1	(0.0,0.6)
	Clinically relevant non-major bleeds	41	4.3	(3.1,5.8)
	Major bleed (All) <sup>b</sup>	10	1.0	(0.5,1.9)
	Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	51	5.3	(4.0,7.0)
DVT/PE N=1532				
	Major bleed (Gastrointestinal, Urogenital, all Intracranial)	17	1.1	(0.7,1.8)
	Major bleed – all other within critical organ sites (excluding all intracranial)	0	0.0	
	Clinically relevant non-major bleeds	75	4.9	(3.9,6.1)
	Major bleed (All) <sup>b</sup>	23	1.5	(1.0,2.3)
	Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	98	6.4	(5.3,7.8)
Mixed (AF & DVT/PE) N=23				
	Major bleed (Gastrointestinal, Urogenital, all Intracranial)	0	0.0	
	Major bleed – all other within critical organ sites (excluding all intracranial)	0	0.0	
	Clinically relevant non-major bleeds	4	17.4	(5.0,38.8)

Haemorrhage Event	All incident reports (on treatment + 3 days after stopping)		(95% CI)
	n	%	
Other N=22	Major bleed (All) <sup>b</sup>	0	0.0
	Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	4	17.4
	Major bleed (Gastrointestinal, Urogenital, all Intracranial)	0	0.0
	Major bleed – all other within critical organ sites (excluding all intracranial)	0	0.0
	Clinically relevant non-major bleeds	1	4.6
	Major bleed (All) <sup>b</sup>	0	0.0
	Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	1	4.6

Percentages for all incident reports have been calculated out of the number of rivaroxaban patients, for each indication; Cumulative incidence = (Total number of new cases during 12 week observation period / Population initially at risk) \*100. Note, where events are reported with no supporting event date or treatment exit date, these have been excluded from the numerator of the cumulative incidence calculation for that bleed type. Where patients have haemorrhage events but all event date information is missing or treatment exit date is missing they have been excluded from the cumulative incidence denominator for all bleed types; <sup>a</sup> 95% CI calculated using Binomial exact; <sup>b</sup> at least one major haemorrhagic event (irrespective of site); <sup>c</sup> at least one of the following- major haemorrhagic event (irrespective of site) and/or a clinically relevant non-major bleed

Likewise, the cumulative incidence of major and CRNM bleeds in warfarin would appear to be higher amongst the DVT/PE group, however there is some overlap in 95% CI between both groups (Table 74).

**Table 74. Number of warfarin patients reporting other new onset major or non-major clinically relevant bleeding outcomes and cumulative risk estimates (+95% CIa)**

Haemorrhage Event	All incident reports (on treatment + 7 days after stopping)		(95% CI)
	n	%	
All indications N=2067			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	7	0.3	(0.1,0.7)
Major bleed – all other within critical organ sites (excluding all intracranial)	4	0.2	(0.1,0.5)
Clinically relevant non-major bleeds	67	3.2	(2.5,4.1)
Major bleed (All) <sup>b</sup>	14	0.7	(0.4,1.1)
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	81	3.9	(3.1,4.9)
AF N=794			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	2	0.3	(0.0,0.9)
Major bleed – all other within critical organ sites (excluding all intracranial)	1	0.1	(0.0,0.7)
Clinically relevant non-major bleeds	22	2.8	(1.8,4.2)
Major bleed (All) <sup>b</sup>	5	0.6	(0.2,1.5)
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	27	3.4	(2.3,4.9)
DVT/PE N=1212			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	5	0.4	(0.1,1.0)
Major bleed – all other within critical organ sites (excluding all intracranial)	3	0.3	(0.1,0.7)
Clinically relevant non-major bleeds	44	3.6	(2.7,4.9)
Major bleed (All) <sup>b</sup>	9	0.7	(0.3,1.4)
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	53	4.4	(3.3,5.7)

Haemorrhage Event		All incident reports (on treatment + 7 days after stopping)		
		n	%	(95% CI)
Mixed (AF & DVT/PE) N=27				
	Major bleed (Gastrointestinal, Urogenital, all Intracranial)	0	0.0	
	Major bleed – all other within critical organ sites (excluding all intracranial)	0	0.0	
	Clinically relevant non-major bleeds	0	0.0	
	Major bleed (All) <sup>b</sup>	0	0.0	
	Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	0	0.0	
Other N=34				
	Major bleed (Gastrointestinal, Urogenital, all Intracranial)	0	0.0	
	Major bleed – all other within critical organ sites (excluding all intracranial)	0	0.0	
	Clinically relevant non-major bleeds	1	2.9	(0.1,15.3)
	Major bleed (All) <sup>b</sup>	0	0.0	
	Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	1	2.9	(0.1,15.3)

Percentages for all incident reports have been calculated out of the number of warfarin patients, for each indication; Cumulative incidence = (Total number of new cases during 12 week observation period / Population initially at risk) \*100. Note, where events are reported with no supporting event date or treatment exit date, these have been excluded from the numerator of the cumulative incidence calculation for that bleed type. Where patients have haemorrhage events but all event date information is missing or treatment exit date is missing they have been excluded from the cumulative incidence denominator for all bleed types; <sup>a</sup> 95% CI calculated using Binomial exact; <sup>b</sup> at least one major haemorrhagic event (irrespective of site); <sup>c</sup> at least one of the following- major haemorrhagic event (irrespective of site) and/or a clinically relevant non-major bleed

Table 75 and Table 76 include all incident rates of major bleeding, CRNM bleeds and a composite of both these outcomes, reported on treatment with rivaroxaban and warfarin respectively during the 12 week observation period.

Across all indication groups and where sufficient counts of events permitted an incident rate to be calculated, it would appear that higher rates of bleeding were observed within the rivaroxaban group, although the warfarin group is a contextual not a comparator cohort.

Where sufficient counts of events permitted an incidence rate to be calculated in the rivaroxaban group i.e. with respect to CRNM bleeds and the composite outcome, it would appear that higher rates of bleeding were observed within the DVT/PE group, however there is some overlap in 95% CI between both groups (Table 75).

**Table 75. Cumulative Incidence rates (IR) of new onset major or non-major clinically relevant bleeding outcomes and cumulative risk estimates (+95% CI<sup>a</sup>) in the rivaroxaban cohort**

Haemorrhage Event	n	Total person-time (100 years)	IR (95% CI)
All indications N=2542			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	23	4.7	4.9 (3.1,7.4)
Major bleed – all other within critical organ sites (excluding all intracranial)	1	4.7	N/A*
Clinically relevant non-major bleeds	121	4.6	26.3 (21.8,31.4)
Major bleed (All) <sup>b</sup>	33	4.7	7.1 (4.9,9.9)
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	154	4.6	33.6 (28.5,39.3)
AF N=965			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	6	1.8	N/A*
Major bleed – all other within critical organ sites (excluding all intracranial)	1	1.8	N/A*
Clinically relevant non-major bleeds	41	1.8	22.7 (16.3,30.8)
Major bleed (All) <sup>b</sup>	10	1.8	5.5 (2.6,10.1)
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	51	1.8	28.2 (21.0,37.1)
DVT/PE N=1532			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	17	2.8	6.1 (3.6,9.8)
Major bleed – all other within critical organ sites (excluding all intracranial)	0	2.8	N/A*
Clinically relevant non-major bleeds	75	2.7	27.6 (21.7,34.6)
Major bleed (All) <sup>b</sup>	23	2.8	8.3 (5.3,12.5)
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	98	2.7	36.2 (29.4,44.1)
Mixed (AF & DVT/PE) N=23			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	0	0.0	N/A*
Major bleed – all other within critical organ sites (excluding all intracranial)	0	0.0	N/A*
Clinically relevant non-major bleeds	4	0.0	N/A*
Major bleed (All) <sup>b</sup>	0	0.0	N/A*
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	4	0.0	N/A*
Other N=22			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	0	0.0	N/A*
Major bleed – all other within critical organ sites (excluding all intracranial)	0	0.0	N/A*
Clinically relevant non-major bleeds	1	0.0	N/A*
Major bleed (All) <sup>b</sup>	0	0.0	N/A*
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	1	0.0	N/A*

Incidence Rate (IR) = (Number of events / Total person-time) where person-time is derived from index date until the earliest of time until event of interest, date at which patient is censored or end of 12 week observation period;

Total person-time (100 years) = Total person-time / (365.25\*100);

\*rates will not be calculated where event count n<=10;

<sup>a</sup> 95% CI calculated using Poisson exact; <sup>b</sup> at least one major haemorrhagic event (irrespective of site);

<sup>c</sup> at least one of the following- major haemorrhagic event (irrespective of site) and/or a clinically relevant non-major bleed



Where sufficient counts of events permitted an incidence rate to be calculated in the warfarin group i.e. with respect to CRNM bleeds and the composite outcome, it would appear that higher rates of bleeding were observed within the DVT/PE group, however there is some overlap in 95% CI between both groups (Table 76).

**Table 76. Cumulative Incidence rates (IR) of new onset major or non-major clinically relevant bleeding outcomes and cumulative risk estimates (+95% CI<sup>a</sup>) in the warfarin cohort**

Haemorrhage Event	n	Total person-time (100 years)	IR (95% CI)
All indications N=2067			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	7	3.8	N/A*
Major bleed – all other within critical organ sites (excluding all intracranial)	4	3.8	N/A*
Clinically relevant non-major bleeds	67	3.8	17.8 (13.8,22.6)
Major bleed (All) <sup>b</sup>	14	3.8	3.7 (2.0,6.2)
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	81	3.8	21.6 (17.2,26.8)
AF N=794			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	2	1.5	N/A*
Major bleed – all other within critical organ sites (excluding all intracranial)	1	1.5	N/A*
Clinically relevant non-major bleeds	22	1.5	14.7 (9.2,22.3)
Major bleed (All) <sup>b</sup>	5	1.5	
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	27	1.5	18.1 (11.9,26.4)
DVT/PE N=1212			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	5	2.2	N/A*
Major bleed – all other within critical organ sites (excluding all intracranial)	3	2.2	N/A*
Clinically relevant non-major bleeds	44	2.2	20.4 (14.8,27.4)
Major bleed (All) <sup>b</sup>	9	2.2	
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	53	2.1	24.7 (18.5,32.3)
Mixed (AF & DVT/PE) N=27			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	0	0.0	N/A*
Major bleed – all other within critical organ sites (excluding all intracranial)	0	0.0	N/A*
Clinically relevant non-major bleeds	0	0.0	N/A*
Major bleed (All) <sup>b</sup>	0	0.0	N/A*
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	0	0.0	N/A*
Other N=34			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)	0	0.1	N/A*
Major bleed – all other within critical organ sites (excluding all intracranial)	0	0.1	N/A*
Clinically relevant non-major bleeds	1	0.1	N/A*
Major bleed (All) <sup>b</sup>	0	0.1	N/A*
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>	1	0.1	N/A*

Incidence Rate (IR) = (Number of events / Total person-time) where person-time is derived from index date until the earliest of time until event of interest, date at which patient is censored or end of 12 week observation period;

Total person-time (100 years) = Total person-time /(365.25\*100);

\*rates will not be calculated where event count n<=10;

<sup>a</sup> 95% CI calculated using Poisson exact; <sup>b</sup> at least one major haemorrhagic event (irrespective of site);  
<sup>c</sup> at least one of the following- major haemorrhagic event (irrespective of site) and/or a clinically relevant non-major bleed

### 10.5.5 Incidence density calculations for targeted events

In the rivaroxaban cohort, a total of 24449 person-weeks of exposure was observed overall (Table 77) with a slightly smaller person-time denominator in the warfarin group (19862 person-weeks) (Table 78). Person-time was highest in the DVT/PE cohort in line with the higher number of patients in this group.

**Table 77. Denominators for rivaroxaban cohort (in person weeks)**

Time Period	Weeks 1&2	Weeks 3&4	Weeks 5&6	Weeks 7&8	Weeks 9&10	Weeks 11&12	All Weeks
All (D <sub>i</sub> )	4679	4384	4113	3940	3753	3580	24449
AF (D <sub>AFi</sub> )	1778	1699	1606	1544	1479	1429	9536
DVT/PE (D <sub>DVT/PEi</sub> )	2820	2605	2432	2330	2214	2096	14496
Mixed (D <sub>MIXED</sub> )	44	44	40	32	29	27	215
Other (D <sub>OTHERi</sub> )	38	36	35	34	31	28	202

D<sub>i</sub> – The amount of patient-time at risk within time period i

**Table 78. Denominators for warfarin cohort (in person weeks)**

Time Period	Weeks 1&2	Weeks 3&4	Weeks 5&6	Weeks 7&8	Weeks 9&10	Weeks 11&12	All Weeks
All (D <sub>i</sub> )	3857	3510	3353	3190	3048	2904	19862
AF (D <sub>AFi</sub> )	1493	1387	1326	1268	1220	1171	7864
DVT/PE (D <sub>DVT/PEi</sub> )	2248	2018	1925	1830	1741	1651	11413
Mixed (D <sub>MIXED</sub> )	52	45	44	39	36	34	250
Other (D <sub>OTHERi</sub> )	64	61	58	54	50	48	335

D<sub>i</sub> – The amount of patient-time at risk within time period i

Table 79 and Table 80 include IDs for the targeted events of CVA, DVT and PE. IDs are presented for both recurrent and incident events. Recurrent and incident event IDs have been stratified by indication group. In the rivaroxaban group, the majority of recurrent strokes reported during the study occurred within the AF group (there were no incident events of stroke reported within the rivaroxaban AF group), whilst all of the recurrent DVT and PE events occurred within the DVT/PE group, in addition to eleven incident reports [DVT (n=1) and PE (n=10)]. There were two recurrent strokes reported in the warfarin group overall ); one of these occurred within the AF group and one within the Other indication group, in addition to three reports of incident stroke within the warfarin AF group. Almost all of the recurrent events of DVT and PE

were reported within the DVT/PE group, with a further 12 reports of incident PE in this group.

In the rivaroxaban group, recurrent stroke within the AF group had an ID<sub>A</sub> of 0.9 across the observation period, compared to the ID<sub>A</sub> for recurrent stroke within the warfarin group of 0.1. IDs for recurrent DVT and PE amongst the DVT/PE group were also slightly higher amongst the rivaroxaban group; the ID<sub>A</sub> for recurrent DVT and PE in this group were 1.1 and 1.2 in the rivaroxaban group vs. 1.1 and 0.5 in the warfarin group. The ID<sub>A</sub> for incident PE in the DVT/PE groups were similar in both treatment groups (0.7 and 1.1 in the rivaroxaban and warfarin groups respectively).

There were no reports of incident hepatic failure in either study group. There was one report of incident abnormal LFTs (greater than 3 X upper limit of normal) within the rivaroxaban group and two reports within the warfarin group.

IDs were also calculated for all other events reported as freetext (excluding those already captured within a targeted event definition) and these are presented in Appendix 10.

**Table 79. Incidence Densities of targeted events<sup>a</sup> (excluding haemorrhage events) in rivaroxaban cohort, by two-week period and for total 12 week period**

Event <sup>b</sup>		N	N	N	N	N	N	ID	ID	ID	ID	ID	ID	N <sub>A</sub>	ID <sub>A</sub>
		w1&2	w3&4	w5&6	w7&8	w9&10	w11&12	w1&2	w3&4	w5&6	w7&8	w9&10	w11&12		
Recurrent thromboembolic events, by indication															
AF	Cerebrovascular Accident	4	3	1	0	1	0	2.3	1.8	0.6	0.0	0.7	0.0	9	0.9
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Pulmonary Embolism	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
DVT/PE	Cerebrovascular Accident	0	1	1	1	0	0	0.0	0.4	0.4	0.4	0.0	0.0	3	0.2
	Deep Vein Thrombosis	5	1	3	1	2	3	1.8	0.4	1.2	0.4	0.9	1.4	16	1.1
	Pulmonary Embolism	6	2	4	2	2	2	2.1	0.8	1.6	0.9	0.9	1.0	18	1.2
Mixed indication	Cerebrovascular Accident	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Pulmonary Embolism	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
Other indication	Cerebrovascular Accident	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Pulmonary Embolism	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
All indications	Cerebrovascular Accident	4	4	2	1	1	0	0.9	0.9	0.5	0.3	0.3	0.0	12	0.5
	Deep Vein Thrombosis	5	1	3	1	2	3	1.1	0.2	0.7	0.3	0.5	0.8	16	0.7
	Pulmonary Embolism	6	2	4	2	2	2	1.3	0.5	1.0	0.5	0.5	0.6	18	0.7
Incident thromboembolic events, by indication															
AF	Cerebrovascular Accident	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Pulmonary Embolism	2	1	0	0	0	1	1.1	0.6	0.0	0.0	0.0	0.7	4	0.4

Event <sup>b</sup>		N	N	N	N	N	N	ID	ID	ID	ID	ID	ID	NA	IDA
		w1&2	w3&4	w5&6	w7&8	w9&10	w11&12	w1&2	w3&4	w5&6	w7&8	w9&10	w11&12		
DVT/PE															
	Cerebrovascular Accident	4	1	0	0	0	0	1.4	0.4	0.0	0.0	0.0	0.0	5	0.3
	Deep Vein Thrombosis	0	0	0	0	1	0	0.0	0.0	0.0	0.0	0.5	0.0	1	0.1
	Pulmonary Embolism	7	3	0	0	0	0	2.5	1.2	0.0	0.0	0.0	0.0	10	0.7
Mixed indication															
	Cerebrovascular Accident	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Pulmonary Embolism	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
Other indication															
	Cerebrovascular Accident	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Pulmonary Embolism	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
All indications															
	Cerebrovascular Accident	4	1	0	0	0	0	0.9	0.2	0.0	0.0	0.0	0.0	5	0.2
	Deep Vein Thrombosis	0	0	0	0	1	0	0.0	0.0	0.0	0.0	0.3	0.0	1	0.0
	Pulmonary Embolism	9	4	0	0	0	1	1.9	0.9	0.0	0.0	0.0	0.3	14	0.6
Incident other events															
	Hepatic Failure	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Abnormal LFTs 3x ULN	1	0	0	0	0	0	0.2	0.0	0.0	0.0	0.0	0.0	1	0.0

N=Number of Events, ID=Incidence Density; NA = Number of first reports of an event during all twelve weeks observation; IDA = ID for all twelve weeks observation <sup>a</sup> Targeted events misreported as –free text general events and/or reasons for stopping will be included in event counts for calculation of IDs; <sup>b</sup> Counts not mutually exclusive as patients may have experienced more than one type of event

**Table 80. Incidence Densities of targeted events<sup>a</sup> (excluding haemorrhage events) in warfarin cohort, by two-week period and for total 12 week period**

Event <sup>b</sup>		N	N	N	N	N	N	ID	ID	ID	ID	ID	ID	NA	IDA
		w1&2	w3&4	w5&6	w7&8	w9&10	w11&12	w1&2	w3&4	w5&6	w7&8	w9&10	w11&12		
Recurrent thromboembolic events, by indication															
AF															
	Cerebrovascular Accident	0	0	0	0	1	0	0.0	0.0	0.0	0.0	0.8	0.0	1	0.1
	Deep Vein Thrombosis	0	0	1	0	0	0	0.0	0.0	0.8	0.0	0.0	0.0	1	0.1
	Pulmonary Embolism	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
DVT/PE															
	Cerebrovascular Accident	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Deep Vein Thrombosis	5	1	3	1	1	0	2.2	0.5	1.6	0.5	0.6	0.0	12	1.1
	Pulmonary Embolism	2	2	0	1	1	0	0.9	1.0	0.0	0.5	0.6	0.0	6	0.5
Mixed indication															
	Cerebrovascular Accident	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Pulmonary Embolism	1	0	0	0	0	0	19.2	0.0	0.0	0.0	0.0	0.0	1	4.0
Other indication															
	Cerebrovascular Accident	0	0	1	0	0	0	0.0	0.0	17.3	0.0	0.0	0.0	1	3.0
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Pulmonary Embolism	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
All indications															
	Cerebrovascular Accident	0	0	1	0	1	0	0.0	0.0	0.3	0.0	0.3	0.0	2	0.1
	Deep Vein Thrombosis	5	1	4	1	1	0	1.3	0.3	1.2	0.3	0.3	0.0	13	0.7
	Pulmonary Embolism	3	2	0	1	1	0	0.8	0.6	0.0	0.3	0.3	0.0	7	0.4
Incident thromboembolic events, by indication															
AF															
	Cerebrovascular Accident	3	0	0	0	0	0	2.0	0.0	0.0	0.0	0.0	0.0	3	0.4
	Deep Vein Thrombosis	0	0	1	0	0	0	0.0	0.0	0.8	0.0	0.0	0.0	1	0.1
	Pulmonary Embolism	0	0	0	1	0	0	0.0	0.0	0.0	0.8	0.0	0.0	2	0.3
DVT/PE															
	Cerebrovascular Accident	1	0	0	1	2	0	0.4	0.0	0.0	0.5	1.1	0.0	4	0.4
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Pulmonary Embolism	7	4	1	0	0	0	3.1	2.0	0.5	0.0	0.0	0.0	12	1.1
Mixed indication															
	Cerebrovascular Accident	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0

Event <sup>b</sup>		N	N	N	N	N	N	ID	ID	ID	ID	ID	ID	NA	IDA
		w1&2	w3&4	w5&6	w7&8	w9&10	w11&12	w1&2	w3&4	w5&6	w7&8	w9&10	w11&12		
Other indication	Pulmonary Embolism	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Cerebrovascular Accident	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Deep Vein Thrombosis	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
All indications	Pulmonary Embolism	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Cerebrovascular Accident	4	0	0	1	2	0	1.0	0.0	0.0	0.3	0.7	0.0	7	0.4
	Deep Vein Thrombosis	0	0	1	0	0	0	0.0	0.0	0.3	0.0	0.0	0.0	1	0.1
	Pulmonary Embolism	7	4	1	1	0	0	1.8	1.1	0.3	0.3	0.0	0.0	14	0.7
Incident other events															
	Hepatic Failure	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
	Abnormal LFTs 3x ULN	2	0	0	0	0	0	0.5	0.0	0.0	0.0	0.0	0.0	2	0.1

N=Number of Events, ID=Incidence Density; NA = Number of first reports of an event during all twelve weeks observation; IDA = ID for all twelve weeks observation <sup>a</sup> Targeted events misreported as –free text general events and/or reasons for stopping will be included in event counts for calculation of IDs; <sup>b</sup> Counts not mutually exclusive as patients may have experienced more than one type of event

### **10.5.6 Quantitative case series summary for selected events**

#### **10.5.6.1 Clinical features and management of major bleeding reported in the first 12 weeks after treatment initiation in the cohort exposed to rivaroxaban**

In total, two major gastrointestinal bleeds were observed in the AF indication group and 11 were observed in DVT/PE indication group. Most of these events were observed during treatment and were the reason for stopping treatment. In addition, most of these events were related to other pre-existing conditions. Further details on cases and other types of major bleeds are provided in Table 81.

**Table 81. Characteristics\* and management\* of rivaroxaban patients for whom major bleeding was reported, by indication**

Indication	AF										DVT/PE										Mixed (AF & DVT/PE)		
Major Bleeding	GI		Urogenital		Intracranial		Other critical organ <sup>h</sup>		Other non-critical organ <sup>i</sup>		GI		Urogenital		Intracranial		Other critical organ <sup>h</sup>		Other non-critical organ <sup>i</sup>		Other critical organ <sup>h</sup>		
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Events during observation (N)	2		1		2		1		5		11		5		1		2		6		1		
Events during treatment (n/N, %)	2	100.0	1	100.0	1	50.0	1	100.0	3	60.0	10	90.9	1	100.0	0	0.0	1	50.0	5	83.3	1	100.0	
Sex <sup>a</sup> (n/n; %)																							
	Male	2	100.0	1	100.0	1	50.0	0	0.0	4	80.0	6	54.6	2	40.0	1	100.0	1	50.0	4	66.7	0	0.0
	Female	0	0.0	0	0.0	1	50.0	1	100.0	1	20.0	5	45.5	3	60.0	0	0.0	1	50.0	2	33.3	1	100.0
Age <sup>a</sup> (years) Median (IQR)	75, 84		69		75, 83		86		71 (69, 76)		69 (52, 85)		50 (46, 68)		70		69, 85		53.5 (40, 63)		81		
Dose at event (mg/day)																							
	0-10	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	>10-20	2	100.0	1	100.0	2	100.0	1	100.0	5	100.0	5	45.5	3	60.0	0	0.0	0	0.0	4	66.7	1	100.0
	>20	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	6	54.6	2	40.0	1	100.0	2	100.0	2	33.3	0	0.0
Exposure duration (days) <sup>b</sup> Median (IQR)	3, 10		81		37, 64		10		48 (41, 57)		13 (4, 22)		13 (12, 20)		34		0, 7		23 (7, 29)		84		
Event as Reason for stopping <sup>c</sup> (n/n; %)	2	100.0	0	0.0	2	100.0	1	100.0	1	20.0	9	81.8	1	20.0	0	0.0	2	100.0	5	83.3	1	100.0	
Event had Fatal outcome (n/n; %)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
Event reported with decreased haemoglobin (>2g/dL) (n/n; %)	2	100.0	1	100.0	0	0.0	0	0.0	3	60.0	10	90.9	5	100.0	0	0.0	0	0.0	5	83.3	0	0.0	
Event required a transfusion of >2 units of packed red cells or whole blood (n/n; %)	1	50.0	0	0.0	0	0.0	0	0.0	2	40.0	5	45.5	1	20.0	0	0.0	1	50.0	3	50.0	0	0.0	
Event required reversal of anticoagulation therapy for bleeding (n/n; %)	0	0.0	0	0.0	1	50.0	0	0.0	0	0.0	1	9.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
Prior history (or present at start of treatment) of bleed within same site (n/n; %)	0	0.0	0	0.0	0	0.0	0	0.0	1	20.0	2	18.2	1	20.0	1	100.0	0	0.0	1	16.7	0	0.0	
Event was related to other pre-existing conditions which were risk factors for bleeding <sup>d</sup> (n/n; %)	2	100.0	1	100.0	2	100.0	1	100.0	5	100.0	10	90.9	5	100.0	1	100.0	2	100.0	5	83.3	1	100.0	
Concomitant meds prescribed at event (n/n; %)	2	100.0	1	100.0	1	50.0	1	100.0	4	80.0	10	90.9	4	80.0	1	100.0	2	100.0	6	100.0	1	100.0	

Indication	AF										DVT/PE										Mixed (AF & DVT/PE)	
	GI		Urogenital		Intracranial		Other critical organ <sup>h</sup>		Other non-critical organ <sup>i</sup>		GI		Urogenital		Intracranial		Other critical organ <sup>h</sup>		Other non-critical organ <sup>i</sup>		Other critical organ <sup>h</sup>	
Major Bleeding	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Concomitant meds predisposing to bleeds prescribed at event <sup>e</sup> (n/n; %)	0	0.0	0	0.0	0	0.0	0	0.0	1	20.0	1	9.1	1	20.0	0	0.0	0	0.0	4	66.7	0	0.0
Patient HAS-BLED Score <sup>f</sup>																						
0-1	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	5	45.5	2	40.0	0	0.0	2	100.0	3	50.0	0	0.0
2	0	0.0	0	0.0	0	0.0	0	0.0	2	40.0	3	27.3	1	20.0	0	0.0	0	0.0	2	33.3	0	0.0
3+	2	100.0	1	100.0	2	100.0	0	0.0	3	60.0	3	27.3	2	40.0	1	100.0	0	0.0	1	16.7	1	100.0

\*information available from SCeM and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender); <sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for bleeding: thrombocytopenia, excessive alcohol consumption or abuse, prior history of conditions associated with increased risk of bleeding, injury/trauma, percutaneous coronary intervention, other recent major surgery, malignancy, pregnancy <sup>e</sup> concomitant medication at event- anticoagulants, antiplatelets, NSAIDs; <sup>f</sup> HAS-BLED risk of major bleeding score (0=low risk, 1-2=moderate risk, 3 + =high risk ); <sup>g</sup> CHA<sub>2</sub>DS<sub>2</sub>VASc risk of stroke score (0=low risk, 1=moderate risk, 2 +=high risk ); <sup>h</sup> Other critical organ: major bleed in critical organ sites (excluding intracranial); <sup>i</sup> Other non-critical organ: major bleed in non-critical organ site . isch: Ischaemic CVA; haem: haemorrhagic CVA

***10.5.6.2 Clinical features and management of cases of overdose, VTE events indicating failure of anticoagulation and management of haemostasis in patients undertaking surgery (elective or urgent) reported in the first 12 weeks after treatment initiation in the cohort exposed to rivaroxaban***

There was one case of an overdose of rivaroxaban reported in addition to a bleed, which was unclassifiable (Table 82). The event occurred 36 days after starting treatment in a female DVT/PE patient in their forties who had a prior history of bleeding within the same site as well as other pre-existing conditions which were risk factors for bleeding. The patient was on concomitant medications but not any known to be predisposing to bleeds. The patient had a HAS-BLED score of 1-2 denoting a moderate risk of major bleeding.



**Table 82. Characteristics\* and management\* of haemostasis in rivaroxaban patients for whom overdose (reported as event or dose <50mg/day) was reported in addition to a bleed, by type of bleed and indication group (N=1)**

Indication	AF								DVT/PE								Mixed (AF & DVT/PE)								Other							
	All Major		CRNM		Other non-major		UC		All Major		CRNM		Other non-major		UC		All Major		CRNM		Other non-major		UC		All Major		CRNM		Other non-major		UC	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
Bleeding Type (Incident event)																																
Events during observation (N)	0		0		0		0		0		0		0		1		0		0		0		0		0		0		0			
Events during treatment (n/N, %)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
Sex <sup>a</sup>																																
Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
Age <sup>a</sup> (years)	-		-		-		-		-		-		-		45-49		-		-		-		-		-		-		-			
Dose at event (mg/day)																																
0-10	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
>10-20	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
20	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
Exposure duration (days) <sup>b</sup>	-		-		-		-		-		-		-		36		-		-		-		-		-		-		-			
Event as Reason for stopping <sup>c</sup>	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
(n/n: %)																																
Event had Fatal outcome	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
(n/n: %)																																
Event reported with decreased haemoglobin (>2g/dL)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	DK	DK	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
(n/n: %)																																
Event required a transfusion of >2 units of packed red cells or whole blood	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
(n/n: %)																																
Event required reversal of anticoagulation therapy for bleeding	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
(n/n: %)																																
Prior history (or present at start of treatment) of bleed within same site	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
(n/n: %)																																
Event was related to other pre-existing conditions which were risk factors for bleeding <sup>d</sup>	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
(n/n: %)																																

Indication Bleeding Type (Incident event)	AF								DVT/PE								Mixed (AF & DVT/PE)								Other							
	All Major		CRNM		Other non-major		UC		All Major		CRNM		Other non-major		UC		All Major		CRNM		Other non-major		UC		All Major		CRNM		Other non-major		UC	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Concomitant meds prescribed at event (n/n; %)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Concomitant meds predisposing to bleeds prescribed at event <sup>e</sup> (n/n; %)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other clinical sequelae (n/n; %)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Patient HAS-BLED Score <sup>f</sup>	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	1-2	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	3+	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender); <sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for bleeding: thrombocytopenia, excessive alcohol consumption or abuse, prior history conditions associated with increased risk of bleeding, injury/trauma, percutaneous coronary intervention, other recent major surgery, malignancy, pregnancy <sup>e</sup> concomitant medication at event- anticoagulants, antiplatelets, NSAIDs; <sup>f</sup> HAS-BLED risk of major bleeding score (0=low risk, 1-2=moderate risk, 3 + =high risk ); UC= unclassifiable; DK=Don't Know

In total there were three cases of injury/trauma reported in addition to a bleeding event (Table 83). In one case, occurring in a female AF patient in their sixties, the bleeding event was classified as major according to ISTH (Table 1) The event occurred 73 days after starting treatment with rivaroxaban and required a transfusion of >2 units of packed red cells or whole blood. The patient was on concomitant medications but not any known to be predisposing to bleeds. The patient had a HAS-BLED score of 1-2 denoting moderate risk of major bleeding. The two other cases of injury/trauma resulted in bleeds with were classified as clinically relevant non-major (Table 1). Both occurred within DVT/PE patients, one male in their fifties and one female in their seventies. The exposure duration was 58 and 69 days respectively. The HAS-BLED scores were between 1-2 (male) and 3+ (female) denoting a moderate and high risk of major bleeding respectively.

There were no cases of bleeds in patients reported with events of surgery.

**Table 83. Characteristics\* and management\* of haemostasis in rivaroxaban with injury/trauma requiring acute medical/surgical treatment (with or without) hospitalisation patients, by type of bleed and indication (N=3)**

Indication	AF				DVT/PE				Mixed (AF & DVT/PE)				Other			
	All Major		CRNM		Other non-major		UC		All Major		CRNM		Other non-major		UC	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Bleeding Type (Incident event)																
Events during observation (N)	1		0		0		0		0		0		0		0	
Events during treatment (n/N, %)	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	2	100.0	0	0.0	0	0.0
Sex <sup>a</sup>																
Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	50.0	0	0.0	0	0.0
Female	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	1	50.0	0	0.0	0	0.0
Age <sup>a</sup> (years)																
65-69			-		-		-		-		50-54		-		-	
											75-79					
Dose at event (mg/day)																
0-10	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
>10-20	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	2	100.0	0	0.0	0	0.0
>20	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Exposure duration (days) <sup>b</sup>																
73			-		-		-		-		58, 69		-		-	
Event as Reason for stopping <sup>c</sup>	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
(n/n: %)																
Event had Fatal outcome	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
(n/n: %)																
Event reported with decreased haemoglobin (>2g/dL)	DK	DK	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
(n/n: %)																
Event required a transfusion of >2 units of packed red cells or whole blood	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
(n/n: %)																
Event required reversal of anticoagulation therapy for bleeding	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
(n/n: %)																
Prior history (or present at start of treatment) of bleed within same site	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
(n/n: %)																
Event was related to other pre-existing conditions which were risk factors for bleeding <sup>d</sup>	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
(n/n: %)																

Indication	AF								DVT/PE								Mixed (AF & DVT/PE)								Other							
Bleeding Type (Incident event)	All Major		CRNM		Other non-major		UC		All Major		CRNM		Other non-major		UC		All Major		CRNM		Other non-major		UC		All Major		CRNM		Other non-major		UC	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
Concomitant meds prescribed at event (n/n; %)	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
Concomitant meds predisposing to bleeds prescribed at event <sup>e</sup> (n/n; %)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
Other clinical sequelae (n/n; %)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
Patient HAS-BLED Score <sup>f</sup>																																
0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
1-2	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	1	50.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
3+	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	50.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		

\*information available from SCEN and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender); <sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for bleeding: thrombocytopenia, excessive alcohol consumption or abuse, prior history of bleeding, predisposition to bleeding, injury/trauma, percutaneous coronary intervention, other recent major surgery, malignancy, pregnancy <sup>e</sup> concomitant medication at event- anticoagulants, antiplatelets, NSAIDs; <sup>f</sup> HAS-BLED risk of major bleeding score (0=low risk, 1-2=moderate risk, 3 + =high risk ); UC= unclassifiable

In total, there were 17 VTE events reported for the rivaroxaban treatment group during the observation period; 12 of these were DVT events and five were PE events (Table 84). All of these events occurred within the DVT/PE indication group. The majority of events occurred during treatment with rivaroxaban and within male patients. The median age of those with a PE event was higher than for those with a DVT event (68 years vs 53 years), though median exposure duration was longer for those with a DVT event than a PE event (16.5 days vs 7 days). The majority of patients had a prior history of VTE.

**Table 84. Characteristics\* and management\* of rivaroxaban patients for whom VTE (DVT/PE) was reported, indication.**

Indication		DVT/PE					
VTE type		All <sup>f</sup> (DVT/PE)		DVT		PE	
		n	%	n	%	n	%
Events during observation (N)		17		12		5	
Events during treatment (n/N, %)		13	76.5	9	75.0	4	80.0
Sex <sup>a</sup>		(n/n; %)					
	Male	10	58.8	7	58.3	3	60.0
	Female	7	41.2	5	41.7	2	40.0
Age <sup>a</sup> (years)	Median (IQR)	57 (50, 68)		53 (45.5, 64.5)		68 (62, 74)	
Dose at event (mg/day)							
	0-10	0	0.0	0	0.0	0	0.0
	>10-20	5	31.3	5	45.5	0	0.0
	>20	11	68.8	6	54.6	5	100.0
Exposure duration (days) <sup>b</sup>		14		16.5		7	
	Median (IQR)	(7, 30)		(8, 45)		(4, 22)	
Event as Reason for stopping <sup>c</sup>		6	35.3	5	41.7	1	20.0
	(n/n; %)						
Event had Fatal outcome		3	17.6	0	0.0	3	60.0
	(n/n; %)						
Patient had prior history (or present at start of treatment) of DVT and/or PE		14	82.4	9	75.0	5	100.0
	(n/n; %)						
Event was related to other pre-existing conditions which were risk factors for VTE <sup>d</sup>		11	68.8	7	58.3	4	80.0
	(n/n; %)						
Concomitant meds prescribed at event <sup>e</sup>		11	68.8	7	58.3	4	80.0
	(n/n; %)						

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender); <sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for VTE: cardiac disorders (myocardial infarction, congestive heart failure, peripheral arterial disease, cardiac arrhythmias), immobility, surgery requiring general anaesthesia, malignancy, oestrogen containing product, travel for a prolonged period of time, trauma, other recent major surgery, thrombophilia disorder, other coagulation disorder, pregnancy; <sup>e</sup> concomitant medication at event (tbc); <sup>f</sup> first incident event;

In total, there were eight CVA events reported in those with an indication of AF within the 12 week observation period (Table 85). Of these, six were ischaemic, one was haemorrhagic and one was considered unclassifiable. In addition, there were two CVA events reported in those with an indication of DVT/PE within the 12 week observation period, both of which were ischaemic.

Within the AF indication group, the majority of CVA events occurred during treatment and those with an ischaemic stroke type had a higher median age than those with haemorrhagic stroke (82.5 years vs 75 years). Median exposure duration was longer for haemorrhagic stroke than ischaemic stroke (8.5 days vs 37 days) and all patients had a prior history of CVA.

Within the DVT/PE indication group, both CVA events occurred during treatment and patient ages were 68 and 89 years. Exposure duration was 22 and 55 days and both patients had a prior history of CVA.

There were no CVA events reported during the observation period for the Mixed and Other indication groups.

**Table 85. Characteristics\* and management\* of rivaroxaban patients for whom CVA was reported, by indication.**

Indication		AF								DVT/PE							
CVA type		AIl <sup>f</sup>		Isch		Heam		UC		AIl <sup>f</sup>		Isch		Heam		UC	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Events during observation (N)		8		6		1		1		2		2		0		0	
Events during treatment (n/N, %)		7	87.5	5	83.3	1	100.0	1	100.0	2	100.0	2	100.0	0	0.0	0	0.0
Sex <sup>a</sup>																	
	Male	4	50.0	4	66.7	0	0.0	0	0.0	1	50.0	1	50.0	0	0.0	0	0.0
	Female	4	50.0	2	33.3	1	100.0	1	100.0	1	50.0	1	50.0	0	0.0	0	0.0
Age <sup>a</sup> (years)																	
	Median (IQR)	80.5 (75, 83.5)		82.5 (75, 84)		75		79		68, 89		68, 89		-		-	
Dose at event (mg/day)																	
	0-10	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	>10-20	7	87.5	6	100.0	1	100.0	0	0.0	2	100.0	2	100.0	0	0.0	0	0.0
	>20	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Exposure duration (days) <sup>b</sup>																	
	Median (IQR)	8.5 (5, 22)		8.5 (5, 16)		37		5		22, 55		22, 55		-		-	
Event as Reason for stopping <sup>c</sup>																	
	(n/n; %)	3	37.5	2	33.3	1	100.0	0	0.0	2	100.0	2	100.0	0	0.0	0	0.0
Event had Fatal outcome																	
	(n/n; %)	2	25.0	2	33.3	0	0.0	0	0.0	1	50.0	1	50.0	0	0.0	0	0.0
Patient had prior history (or present at start of treatment) of stroke																	
		8	100.0	6	100.0	1	100.0	1	100.0	2	100.0	2	100.0	0	0.0	0	0.0
Event was related to other pre-existing conditions which were risk factors for stroke <sup>d</sup>																	
	(n/n; %)	8	100.0	6	100.0	1	100.0	1	100.0	2	100.0	2	100.0	0	0.0	0	0.0
Concomitant medications prescribed at event																	
	(n/n; %)	5	62.5	5	83.3	0	0.0	0	0.0	2	100.0	2	100.0	0	0.0	0	0.0
Other clinical sequelae (incl. moderate-severe disability)																	
	(n/n; %)	3	37.5	3	50.0	0	0.0	0	0.0	1	50.0	1	50.0	0	0.0	0	0.0
Patient CHA <sub>2</sub> DS <sub>2</sub> VASc Score <sup>e</sup>																	
	0																
	1																
	2	8	100.0	6	100.0	1	100.0	1	100.0	2	100.0	2	100.0	0	0.0	0	0.0

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender); <sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for stroke; <sup>e</sup> CHA<sub>2</sub>DS<sub>2</sub>VASc risk of stroke score (0=low risk, 1=moderate risk, 2 +=high risk ); <sup>f</sup> first incident event; isch: Ischaemic CVA; haem: haemorrhagic CVA; UC: unclassifiable



### 10.5.7 Aggregate Assessment of Drug-Relatedness of Selected Events in the cohort exposed to rivaroxaban

Table 86 below provides an assessment of drug relatedness for selected events listed in the protocol (Appendix 1). This drug relatedness assessment utilised all the relevant information on the questionnaire.

There were 16 events of acute kidney injury in the rivaroxaban cohort which were evaluated further; 12 occurred during treatment and four resulted in a fatal outcome (Table 86). Ten cases were assessed as unlikely to be related to rivaroxaban, two cases were assessed as possibly related and four cases were considered unassessable.

**Table 86. Case series relatedness assessments of acute kidney injury reported for rivaroxaban patients for further evaluation**

Event term			Acute kidney injury	
			n	%
<b>Event details</b>				
Events during observation (N)			16	
Events during treatment (n/N, %)			12/16	75.0
Event had Fatal outcome (n/n; %)			4/16	25.0
<b>Patient demographics</b>				
Sex <sup>a</sup>				
	Female	(n/n; %)	4/16	25.0
	Male	(n/n; %)	12/16	75.0
Age <sup>a</sup> (years)			69.5	
Median (IQR)			(67, 79)	
Indication				
	AF	(n/n; %)	7/16	43.8
	DVT/PE	(n/n; %)	9/16	56.3
	Mixed (AF & DVT/PE)	(n/n; %)	0/16	0.0
	Other	(n/n; %)	0/16	0.0
<b>Relatedness Assessment criteria <sup>b</sup></b>				
Pharmacological plausibility (n/n; %)			16/16	100.0
Temporality (n/n; %)			10/16	62.5
	Exposure duration (days) <sup>c</sup>		14.5	
	Median (IQR)		(7, 46)	
Dose relationship (n/n; %)			0/16	0.0
	Dose at event (mg/day)			
	0-10 (n/n; %)		0/16	0.0
	>10-20 (n/n; %)		8/16	50.0
	>20 (n/n; %)		8/16	50.0
Prior history same event and or present on starting (n/n; %)			4/16	25.0

Event term	Acute kidney injury	
	n	%
Risk factors (Other pre-existing conditions <sup>d</sup> and/or concomitant meds <sup>e</sup> ) (n/n; %)	16/16	100.0
Positive Dechallenge (Reason for stopping) <sup>f</sup> (n/n; %)	1/16	6.3
Positive rechallenge (n/n; %)	0/16	0.0
<b>Drug Relatedness Assessment decision<sup>g</sup></b>		
Probable (n/n; %)	0/16	0.0
Possible (n/n; %)	2/16	12.5
Unlikely (n/n; %)	10/16	62.5
Unassessable (n/n; %)	4/16	25.0

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; a demographic characteristics (age, gender); b Austin-Bradford Hill criteria; c derived from time to onset analysis; d co-morbidities associated with event of interest; e concomitant medication associated with event of interest; f derived from information on treatment cessation; g (24)

There were five events of cardiac arrhythmias in the rivaroxaban cohort that were evaluated further; all occurred during treatment and none had a fatal outcome (Table 87. It was noted that two of these patients subsequently died from cardiac arrest. All five cases were assessed as unlikely to be related to rivaroxaban.

**Table 87. Case series relatedness assessments of cardiac arrhythmia reported for rivaroxaban patients for further evaluation**

Event term	Cardiac arrhythmia	
	n	%
<b>Event details</b>		
Events during observation (N)	5	
Events during treatment (n/N, %)	5/5	100.0
Event had Fatal outcome (n/n; %)	0/5	0.0 <sup>h</sup>
<b>Patient demographics</b>		
Sex <sup>a</sup>		
Female (n/n; %)	1/5	20.0
Male (n/n; %)	4/5	80.0
Age <sup>a</sup> (years)	62 (46, 67)	
Median (IQR)		
Indication		
AF (n/n; %)	4/5	80.0
DVT/PE (n/n; %)	1/5	20.0
Mixed (AF & DVT/PE) (n/n; %)	0/5	0.0
Other (n/n; %)	0/5	0.0
<b>Relatedness Assessment criteria<sup>b</sup></b>		
Pharmacological plausibility (n/n; %)	0/5	0.0

Event term	Cardiac arrhythmia	
	n	%
Temporality (n/n; %)	4/5	80.0
Exposure duration (days) <sup>c</sup> Median (IQR)	55 (23, 119)	
Dose relationship (n/n; %)	0/5	0.0
Dose at event (mg/day)		
0-10 (n/n; %)	0/5	0.0
>10-20 (n/n; %)	4/5	80.0
>20 (n/n; %)	1/5	20.0
Prior history same event and or present on starting (n/n; %)	3/5	60.0
Risk factors (Other pre-existing conditions <sup>d</sup> and/or concomitant meds <sup>e</sup> ) (n/n; %)	5/5	100.0
Positive Dechallenge (Reason for stopping) <sup>f</sup> (n/n; %)	0/5	0.0
Positive rechallenge (n/n; %)	0/5	0.0
<b>Drug Relatedness Assessment decision <sup>g</sup></b>		
Probable (n/n; %)	0/5	0.0
Possible (n/n; %)	0/5	0.0
Unlikely (n/n; %)	5/5	100.0
Unassessable (n/n; %)	0/5	0.0

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; a demographic characteristics (age, gender); b Austin-Bradford Hill criteria; c derived from time to onset analysis; d co-morbidities associated with event of interest; e concomitant medication associated with event of interest; f derived from information on treatment cessation; g (24); h two patients died from cardiac arrest

There were two events of liver disorder in the rivaroxaban cohort that were evaluated further; both occurred during treatment and neither were fatal (Table 88). One event was assessed as probably related to rivaroxaban and the other event was assessed as unlikely to be related.

**Table 88. Case series relatedness assessments of liver disorder reported for rivaroxaban patients for further evaluation**

Event term	Liver disorder	
	n	%
<b>Event details</b>		
Events during observation (N)	2	
Events during treatment (n/N, %)	2/2	100.0
Event had Fatal outcome (n/n; %)	0/2	0.0
<b>Patient demographics</b>		
Sex <sup>a</sup>		

Event term	Liver disorder	
	n	%
Age <sup>a</sup> (years) (IQR) Indication	<i>Female</i> (n/n; %)	1/2 50.0
	<i>Male</i> (n/n; %)	1/2 50.0
	Median	38, 52
	<i>AF</i> (n/n; %)	0/2 0.0
	<i>DVT/PE</i> (n/n; %)	2/2 100.0
	<i>Mixed (AF &amp; DVT/PE)</i> (n/n; %)	0/2 0.0
	<i>Other</i> (n/n; %)	0/2 0.0
<b>Relatedness Assessment criteria <sup>b</sup></b>		
Pharmacological plausibility (n/n; %)	2/2	100.0
Temporality (n/n; %)	1/2	50.0
	<i>Exposure duration (days) <sup>c</sup></i> Median (IQR)	2, 11
Dose relationship (n/n; %)	0/2	0.0
	<i>Dose at event (mg/day)</i>	
	0-10 (n/n; %)	0/2 0.0
	>10-20 (n/n; %)	0/2 0.0
	>20 (n/n; %)	2/2 100.0
Prior history same event and or present on starting (n/n; %)	1/2	50.0
Risk factors (Other pre-existing conditions <sup>d</sup> and/or concomitant meds <sup>e</sup> ) (n/n; %)	0/2	0.0
Positive Dechallenge (Reason for stopping) <sup>f</sup> (n/n; %)	1/2	50.0
Positive rechallenge (n/n; %)	0/2	0.0
<b>Drug Relatedness Assessment decision <sup>g</sup></b>		
Probable (n/n; %)	1/2	50.0
Possible (n/n; %)	0/2	0.0
Unlikely (n/n; %)	1/2	50.0
Unassessable (n/n; %)	0/2	0.0

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; a demographic characteristics (age, gender); b Austin-Bradford Hill criteria; c derived from time to onset analysis; d co-morbidities associated with event of interest; e concomitant medication associated with event of interest; f derived from information on treatment cessation; g (24)

There were two events of pancreatitis in the rivaroxaban cohort that were evaluated further; both occurred during treatment and neither was fatal (Table 89). Both of these events were assessed as unlikely to be related to rivaroxaban.

**Table 89. Case series relatedness assessments of pancreatitis reported for rivaroxaban patients for further evaluation**

Event term	Pancreatitis	
	n	%
<b>Event details</b>		
Events during observation (N)		2
Events during treatment (n/N, %)	2/2	100.0
Event had Fatal outcome (n/n; %)	0/2	0.0
<b>Patient demographics</b>		
Sex <sup>a</sup>		
Female (n/n; %)	2/2	100.0
Male (n/n; %)	0/2	0.0
Age <sup>a</sup> (years)		46, 64
Median (IQR)		
Indication		
AF (n/n; %)	0/2	0.0
DVT/PE (n/n; %)	2/2	100.0
Mixed (AF & DVT/PE) (n/n; %)	0/2	0.0
Other (n/n; %)	0/2	0.0
<b>Relatedness Assessment criteria <sup>b</sup></b>		
Pharmacological plausibility (n/n; %)	0/2	0.0
Temporality (n/n; %)	2/2	100.0
Exposure duration (days) <sup>c</sup> Median (IQR)		40, 45
Dose relationship (n/n; %)	0/2	0.0
Dose at event (mg/day)		
0-10 (n/n; %)	0/2	0.0
>10-20 (n/n; %)	0/2	0.0
>20 (n/n; %)	2/2	100.0
Prior history same event and or present on starting (n/n; %)	1/2	50.0
Risk factors (Other pre-existing conditions <sup>d</sup> and/or concomitant meds <sup>e</sup> ) (n/n; %)	2/2	100.0
Positive Dechallenge (Reason for stopping) <sup>f</sup> (n/n; %)	0/2	0.0
Positive rechallenge (n/n; %)	0/2	0.0
<b>Drug Relatedness Assessment decision <sup>g</sup></b>		
Probable (n/n; %)	0/2	0.0
Possible (n/n; %)	0/2	0.0
Unlikely (n/n; %)	2/2	100.0
Unassessable (n/n; %)	0/2	0.0

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; a demographic characteristics (age, gender);b Austin-Bradford Hill criteria; c derived from time to onset

analysis; d co-morbidities associated with event of interest; e concomitant medication associated with event of interest; f derived from information on treatment cessation; g (24)

There were seven events of thrombocytopenia in the rivaroxaban cohort that were evaluated further; six of these occurred during treatment and none were fatal (Table 90). Six cases were assessed as unlikely to be related to rivaroxaban and one case was assessed as possibly related.

**Table 90. Case series relatedness assessments of thrombocytopenia reported for rivaroxaban patients for further evaluation**

Event term			Thrombocytopenia	
			n	%
<b>Event details</b>				
Events during observation (N)			7	
Events during treatment (n/N, %)			6/7	85.7
Event had Fatal outcome (n/n; %)			0/7	0.0
<b>Patient demographics</b>				
Sex <sup>a</sup>				
	Female	(n/n; %)	2/7	28.6
	Male	(n/n; %)	5/7	71.4
Age <sup>a</sup> (years)			66 (50, 76)	
Median (IQR)				
Indication				
	AF	(n/n; %)	1/7	14.3
	DVT/PE	(n/n; %)	6/7	85.7
	Mixed (AF & DVT/PE)	(n/n; %)	0/7	0.0
	Other	(n/n; %)	0/7	0.0
<b>Relatedness Assessment criteria <sup>b</sup></b>				
Pharmacological plausibility (n/n; %)			7/7	100.0
Temporality (n/n; %)			6/7	85.7
	Exposure duration (days) <sup>c</sup>		55	
	Median (IQR)		(20, 66)	
Dose relationship (n/n; %)			0/7	0.0
	Dose at event (mg/day)			
	0-10 (n/n; %)		0/7	0.0
	>10-20 (n/n; %)		3/7	42.9
	>20 (n/n; %)		4/7	57.1
Prior history same event and or present on starting (n/n; %)			0/7	0.0
Risk factors (Other pre-existing conditions <sup>d</sup> and/or concomitant meds <sup>e</sup> ) (n/n; %)			6/7	85.7
Positive Dechallenge (Reason for stopping) <sup>f</sup> (n/n; %)			0/7	0.0
Positive rechallenge (n/n; %)			0/7	0.0

Event term	Thrombocytopenia	
	n	%
<b>Drug Relatedness Assessment decision <sup>g</sup></b>		
Probable (n/n; %)	0/7	0.0
Possible (n/n; %)	1/7	14.3
Unlikely (n/n; %)	6/7	85.7
Unassessable (n/n; %)	0/7	0.0

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; a demographic characteristics (age, gender); b Austin-Bradford Hill criteria; c derived from time to onset analysis; d co-morbidities associated with event of interest; e concomitant medication associated with event of interest; f derived from information on treatment cessation; g (24)

Finally, there were a further three single reports of selected outcomes of interest. These included aplastic anaemia, multi-organ failure and sudden death, each of which is described briefly below:

#### *Aplastic anaemia:*

This female patient in her eighties started rivaroxaban in October 2013 for an indication of AF. Approximately seven weeks later the patient died and causes of death reported included pneumonia, aplastic anaemia and rheumatoid arthritis. The patient was reported to have a prior history of aplastic anaemia and had been taking regular methotrexate. This event was considered unlikely to be related to rivaroxaban, as it was pre-existing with alternative risk factors identified.

#### *Multi-organ failure:*

This male patient in his seventies was started on rivaroxaban in January 2015 for treatment of a pulmonary embolus. Approximately four weeks later the patient died; causes of death included multi-organ failure and multiple aspiration pneumonias. Approximately two months prior to the commencement of rivaroxaban the patient had been "admitted with stroke, had been thrombolysed which had resulted in a bleed, suffered 3 x aspiration pneumonia and systemic sepsis leading to death". This event was considered unlikely to be related to rivaroxaban, as it was considered more likely to be as a result of multiple episodes of pneumonia and systemic sepsis.

#### *Sudden death:*

This male patient in his eighties was started on rivaroxaban in May 2015 for an indication of AF. Approximately five months later the patient was admitted to hospital with epigastric pain and died. The cause of death was unknown, and the death was

considered sudden and unexpected, and hence referred to the coroner. This event was considered to be unassessable due to insufficient information about the case.

### **10.5.8 Cohort exposure, dose patterns over time and treatment cessation**

In the rivaroxaban evaluable cohort (n=2542), total daily dose at the end of the 12 week observation period was most frequently  $\geq 20\text{mg}$  but  $< 30\text{mg}$  in all indication groups (Table 91); AF 78.4% where specified; DVT/PE 64.8% where specified; Mixed indication 65.2% where specified and Other indication 89.5% where specified).

In the warfarin evaluable cohort (n=2067), total daily dose at the end of the 12 week observation period was most frequently  $\geq 2.5\text{mg}$  but  $< 5\text{mg}$  in AF patients (48.1% where specified);  $\geq 5\text{mg}$  but  $< 10\text{mg}$  in DVT/PE patients (55.0% where specified), Mixed indication patients (42.3% where specified) and Other indication patients (65.6% where specified).

**Table 91. Posology (total daily dose) at end of 12 week observation period by indication and treatment group**

End of observation total daily dose	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
Indication:				
AF				
<2.5	1	0.1	133	17.7
$\geq 2.5$ , <5	1	0.1	361	48.1
$\geq 5.0$ , <10	0	0.0	199	26.5
$\geq 10$ , <20	190	20.1	56	7.5
$\geq 20$ , <30	742	78.4	0	0.0
$\geq 30$	12	1.3	1	0.1
Number patients with Missing information	19	-	44	-
Median (IQR)	20 (20, 20)		3 (3, 5)	
Mean (SD)	19.0 (2.6)		4.1 (2.5)	
DVT/PE				
<2.5	0	0.0	38	3.3
$\geq 2.5$ , <5	0	0.0	108	9.3
$\geq 5.0$ , <10	0	0.0	637	55.0
$\geq 10$ , <20	81	5.4	375	32.4
$\geq 20$ , <30	981	64.8	0	0.0
$\geq 30$	451	29.8	0	0.0
Number patients with Missing information	19	-	54	-
Median (IQR)	20 (20, 30)		5 (5, 10)	
Mean (SD)	22.8 (5.0)		6.7 (2.7)	
Mixed (AF & DVT/PE)				
<2.5	0	0.0	3	11.5
$\geq 2.5$ , <5	0	0.0	7	26.9



End of observation total daily dose	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
>=5.0, <10	0	0.0	11	42.3
>=10, <20	3	13.0	5	19.2
>=20, <30	15	65.2	0	0.0
>=30	5	21.7	0	0.0
Number patients with Missing information	0	-	1	-
Median (IQR)	20 (20, 20)		5 (4, 8)	
Mean (SD)	21.5 (4.9)		5.5 (2.8)	
Other				
<2.5	0	0.0	3	9.4
>=2.5, <5	0	0.0	2	6.3
>=5.0, <10	0	0.0	21	65.6
>=10, <20	0	0.0	6	18.8
>=20, <30	17	89.5	0	0.0
>=30	2	10.5	0	0.0
Number patients with Missing information	3	-	2	-
Median (IQR)	20 (20, 20)		5 (5, 7)	
Mean (SD)	21.1 (3.2)		5.8 (2.6)	

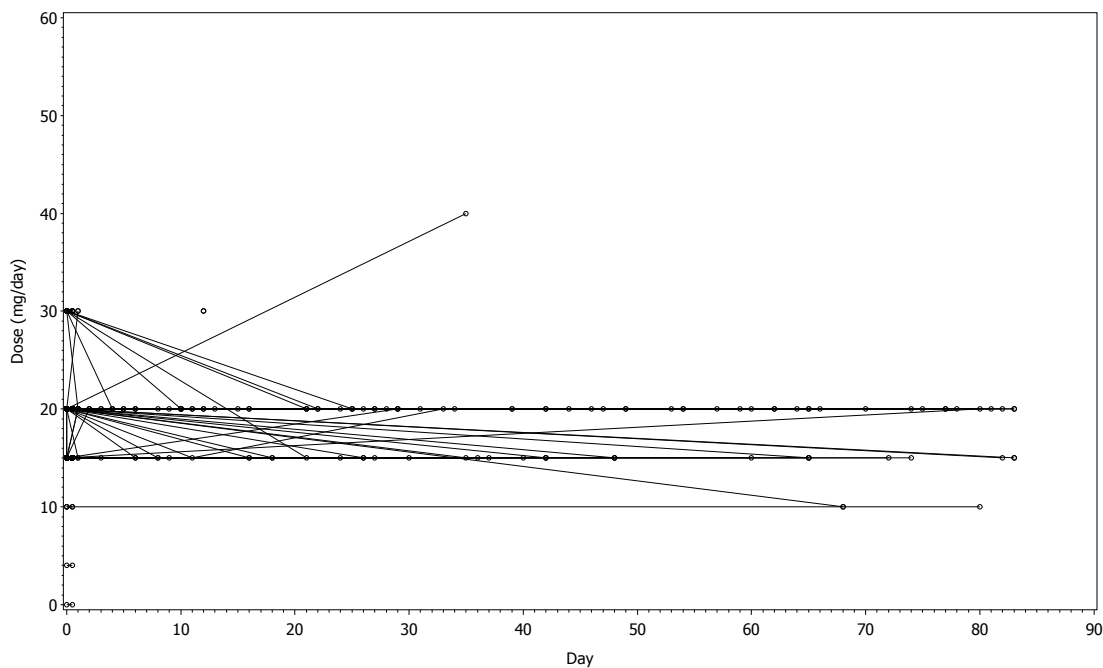
Figure 18a shows at the individual patient level the dose trajectories for rivaroxaban patients by indication. For AF patients the posology in the SmPC is 20mg per day. There is no clear overall pattern of increase or decrease in the individual patient data. For the DVT/PE patients there is a clear pattern visible for patients starting at 30mg and decreasing to 20mg in line with the stated posology for rivaroxaban in this indication which is for patients to commence at 15 mg twice daily for three weeks and then to reduce to 20mg. The data for the Mixed and Other groups are too sparse to be meaningful.

Figure 18b provides the least squares fitted dose trajectory for the individual data. The fitted slope for the AF indication shows a very slight decline from the intercept of 19.2mg daily. The fitted slope for the DVT/PE indication shows a rate of change of -0.2mg per day from an intercept of 26mg.

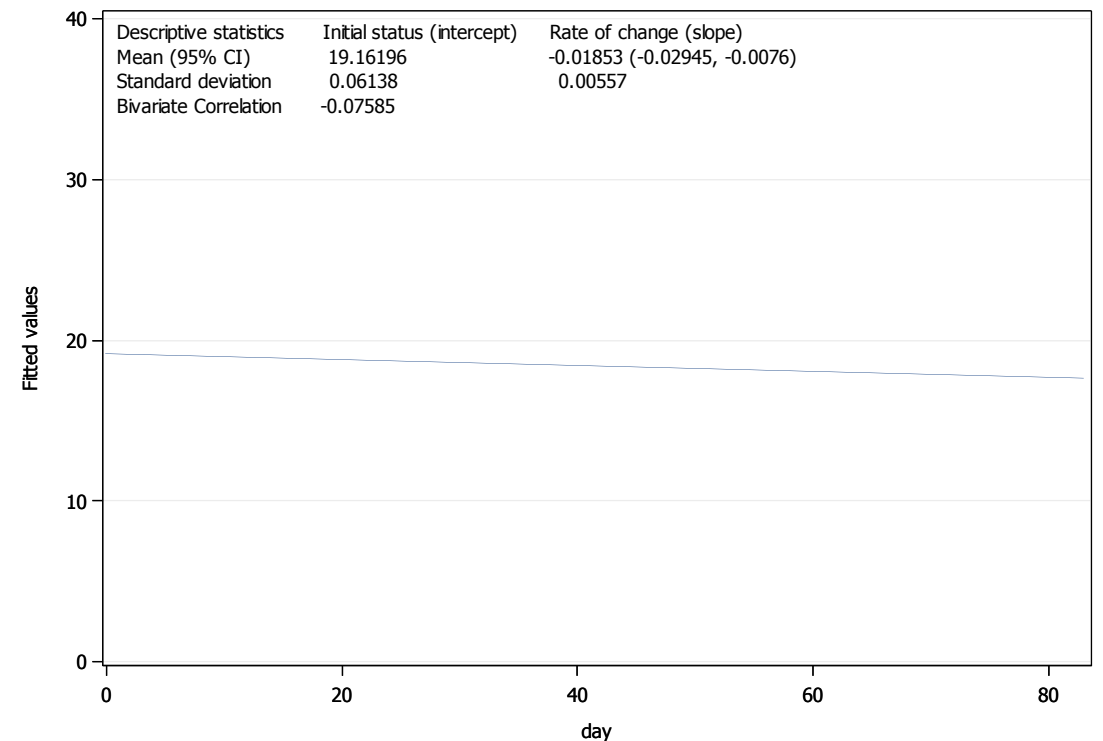
Overall these results suggest that the SmPC posology for the different indications is being used.

**Figure 18. a) Empirical and b) OLS fitted dose trajectories of 12 week observation period, by indication**

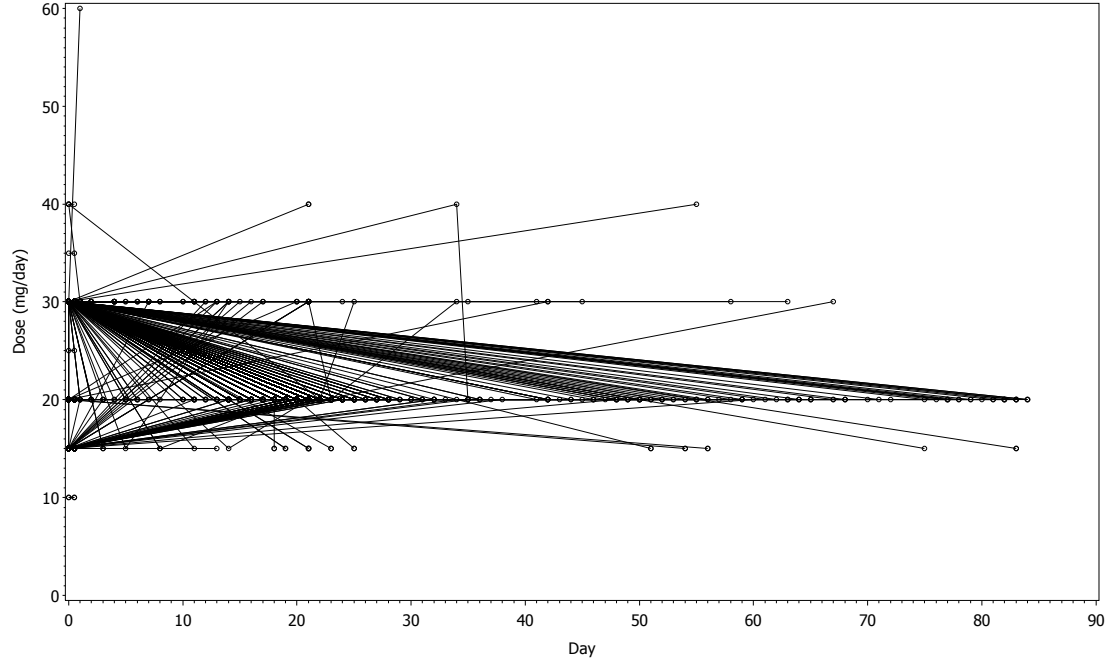
a) Empirical dose trajectories for indication=AF



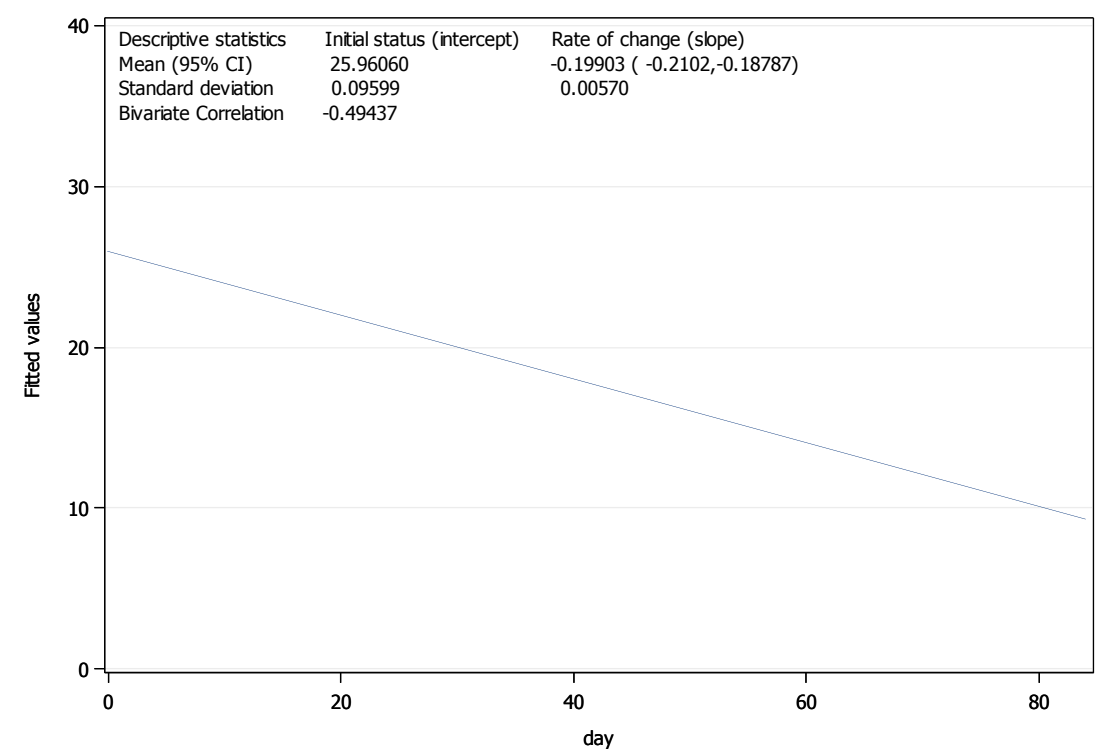
b) OLS fitted dose trajectories for indication=AF



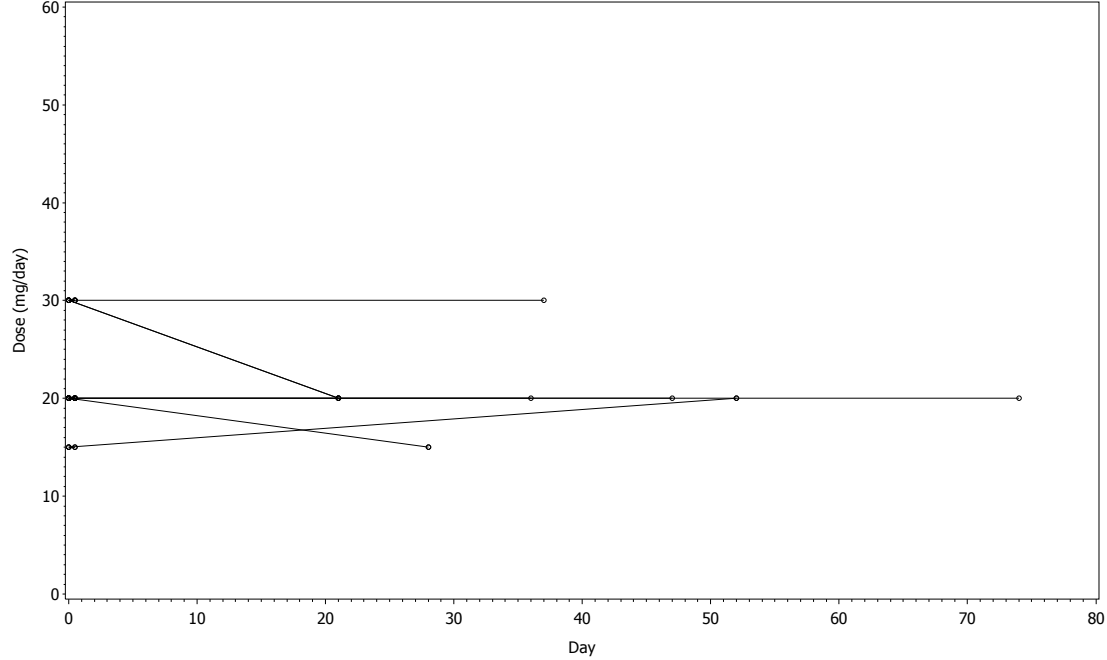
a) Empirical dose trajectories for indication=DVT/PE



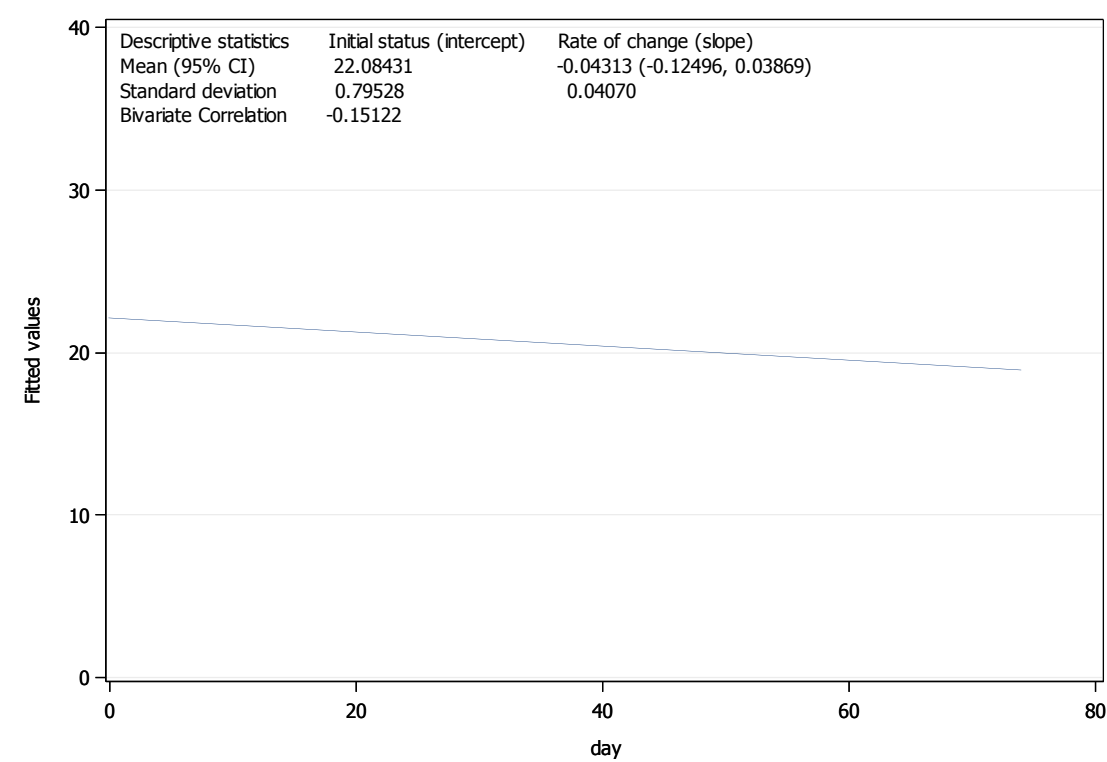
b) OLS fitted dose trajectories for indication=DVT/PE



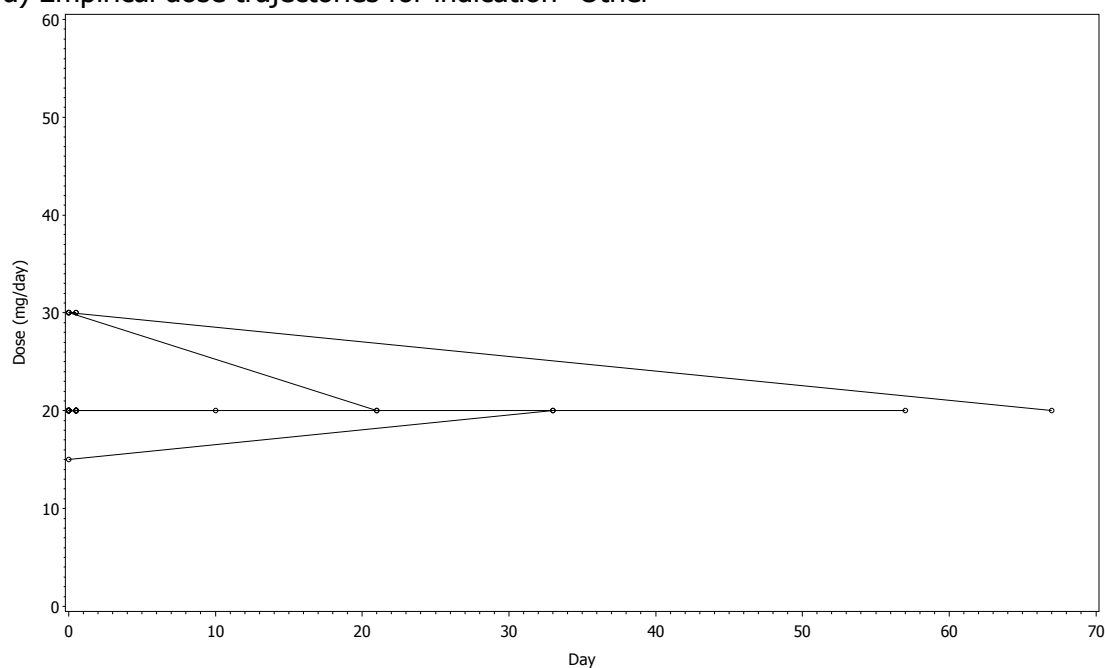
a) Empirical dose trajectories for indication=Mixed



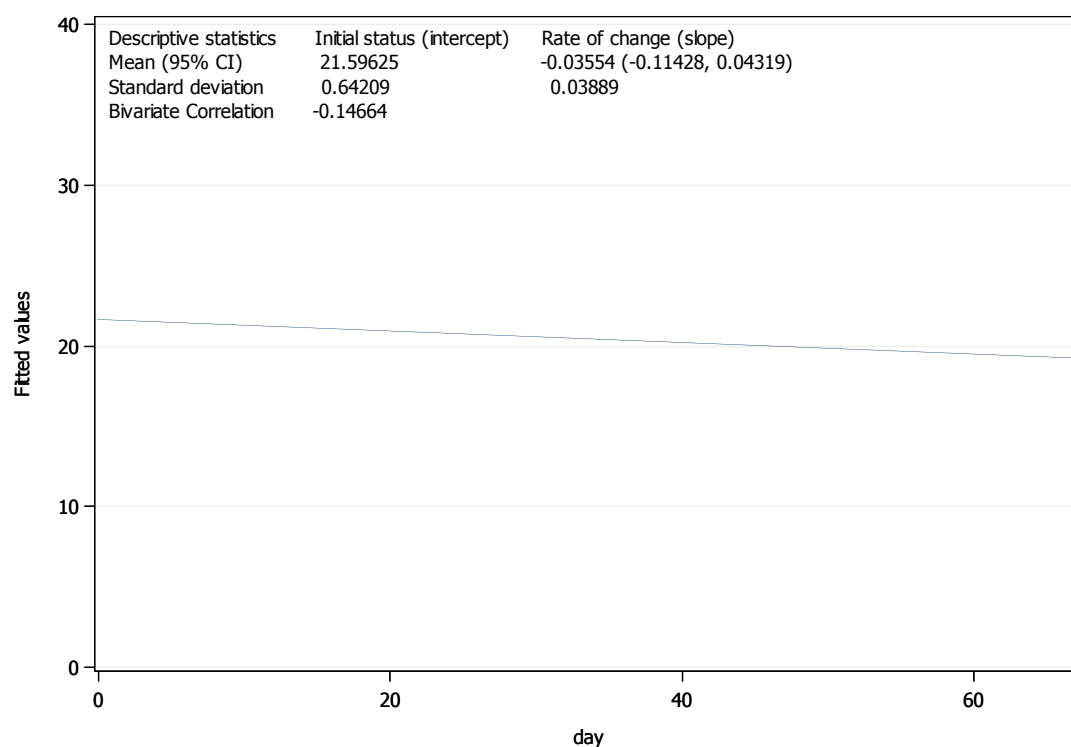
b) OLS fitted dose trajectories for indication=Mixed



a) Empirical dose trajectories for indication=Other



b) OLS fitted dose trajectories for indication=Other



In the rivaroxaban evaluable cohort (n=2542), five AF patients reported a dose increase during treatment (Table 92). Five reasons for dose increases were provided in three patients in the AF indication group and two patients did not specify a reason for dose increase. In the DVT/PE indication group, 88 patients reported a dose increase during

treatment; 16 reasons for dose increases were provided in 76 patients and 12 patients did not specify a reason for dose increase. The most frequently reported reason for dose increase in the DVT/PE patients was prescribing guidelines (n=35, 39.8% of DVT/PE patients where a dose increase was reported). In both the Mixed indication group and Other indication group, a single patient reported a dose increase and both reported prescribing guidelines as the reason for dose increase.

**Table 92. Reasons for first reported rivaroxaban dose increase where treatment has not stopped, by indication and treatment group**

Rivaroxaban		
Reason for dose increase	n	% of patients where dose increase reported
AF N=5		
GFR abnormal	1	20.0
GFR increased	1	20.0
Incorrect dose administered	1	20.0
Prescribing guidelines	1	20.0
Therapy regimen changed	1	20.0
Not specified	2	40.0
DVT/PE N=88		
Prescribing guidelines	35	39.8
Therapy regimen changed	10	11.4
Doctor decision	8	9.1
Local prescribing policy	8	9.1
Local protocol	7	8.0
Hospital advised	2	2.3
Oedema peripheral	2	2.3
Dispensing policy	1	1.1
Drug regimen changed	1	1.1
Hospital decision	1	1.1
Manufacturer advice or guidelines	1	1.1
Pharmacist decision	1	1.1
Planned duration	1	1.1
Policy change	1	1.1
Practice protocol	1	1.1
Prescribing advisor advice	1	1.1
Not specified	12	13.6
Mixed (AF & DVT/PE) N=1		
Prescribing guidelines	1	100.0
Other N=1		
Prescribing guidelines	1	100.0

In the rivaroxaban evaluable cohort (n=2542), 22 AF patients reported a dose decrease during treatment (Table 93). Thirteen reasons for dose decreases were provided in 18 patients in the AF indication group and four patients did not specify a reason for dose decrease. The most frequently reported reason for dose decrease in the AF patients was prescribing guidelines (n = 4, 18.2% AF patients where a dose decrease was reported). In the DVT/PE indication group, 737 patients reported a dose decrease during treatment; 38 reasons for dose decreases were provided in 676 patients and 61 patients did not specify a reason for dose decrease. The most frequently reported reason for dose decrease in the DVT/PE patients was prescribing guidelines (n = 393, 53.3% of DVT/PE patients where a dose decrease was reported). In the Mixed indication group, three patients reported a dose decrease during treatment; two reasons for dose decreases were provided in these three patients.

In the Other indication group, a single patient reported a dose decrease and provided a single reason for this change.

**Table 93. Reasons for first reported dose decrease where treatment has not stopped, by indication and treatment group**

Rivaroxaban		
Reason for dose decrease	n	(% of patients where dose decrease reported)
AF N=22		
Prescribing guidelines	4	18.2
Renal impairment	3	13.6
Doctor decision	2	9.1
Glomerular filtration rate abnormal	2	9.1
Therapy regimen changed	2	9.1
Atrial fibrillation	1	4.6
Blood creatinine decreased	1	4.6
Blood creatinine increased	1	4.6
Body temperature increased	1	4.6
Contusion	1	4.6
Gingival bleeding	1	4.6
Hospital decision	1	4.6
Infection	1	4.6
Thrombosis	1	4.6
Not specified	4	18.2
DVT/PE N=737		
Prescribing guidelines	393	53.3
Therapy regimen changed	59	8.0
Local protocol	45	6.1
Local prescribing policy	42	5.7
Doctor decision	25	3.4
NICE guidelines	20	2.7

Rivaroxaban		
Reason for dose decrease	n	(% of patients where dose decrease reported)
Practice advice, formulary or guideline	15	2.0
Hospital advised	14	1.9
Lifestyle issues	11	1.5
Manufacturer advice or guidelines	10	1.4
Secondary care advice, formulary or guidelines	10	1.4
Dispensing policy	7	1.0
Planned duration R for stopping	6	0.8
Drug regimen changed	5	0.7
Prescribing advisor advice	5	0.7
Deep vein thrombosis	4	0.5
Pulmonary embolism	4	0.5
Drug regulator advice or guidelines	3	0.4
Practice protocol	3	0.4
Renal impairment	3	0.4
Anticoagulation drug level above therapeutic	2	0.3
Hospital decision	2	0.3
Practice policy	2	0.3
Refusal of treatment by patient	2	0.3
Blood creatinine decreased	1	0.1
Contusion	1	0.1
Dr Preference	1	0.1
Drug level	1	0.1
Embolism	1	0.1
End of course	1	0.1
Haemorrhage	1	0.1
Haemorrhage prophylaxis	1	0.1
Pharmacist decision	1	0.1
Planned duration	1	0.1
Pre-existing condition improved	1	0.1
Prophylaxis	1	0.1
Thrombolysis	1	0.1
Thrombosis	1	0.1
Not specified	61	8.3
Mixed (AF & DVT/PE)		
N=3		
Prescribing guidelines	2	66.7
Renal impairment	1	33.3
Other		
N=1		
Routine follow up	1	100.0

In the rivaroxaban evaluable cohort (n=2542), total daily dose on stopping treatment was most frequently  $\geq 20\text{mg}$  but  $< 30\text{mg}$  in all indication groups (Table 94); AF 74.8% where specified; DVT/PE 58.1% where specified; Mixed indication 80.0% where specified and Other indication 100.0% where specified).



In the warfarin evaluable cohort (n=2067), total daily dose on stopping treatment was most frequently  $\geq 2.5\text{mg}$  but  $< 5\text{mg}$  in AF patients (37.7% where specified) and Mixed indication patients (44.4% where specified);  $\geq 5\text{mg}$  but  $< 10\text{mg}$  in DVT/PE patients (55.5% where specified).

**Table 94. Posology (total daily dose) on stopping, by indication and treatment group**

Total daily dose on stopping	Rivaroxaban N=2542		Warfarin N=2067	
	n	%	n	%
Indication:				
AF				
<2.5	0	0.0	20	26.0
$\geq 2.5$ , <5	0	0.0	29	37.7
$\geq 5.0$ , <10	0	0.0	22	28.6
$\geq 10$ , <20	25	24.3	6	7.8
$\geq 20$ , <30	77	74.8	0	0.0
$\geq 30$	1	1.0	0	0.0
Number patients with Missing information	13	-	44	-
Median (IQR)	20 (20, 20)		3.5 (2, 5)	
Mean (SD)	18.9 (3.1)		4.1 (2.4)	
DVT/PE				
<2.5	0	0.0	12	8.2
$\geq 2.5$ , <5	0	0.0	25	17.1
$\geq 5.0$ , <10	0	0.0	81	55.5
$\geq 10$ , <20	9	4.1	28	19.2
$\geq 20$ , <30	129	58.1	0	0.0
$\geq 30$	84	37.8	0	0.0
Number patients with Missing information	25	-	74	-
Median (IQR)	20 (20, 30)		5 (4, 8)	
Mean (SD)	23.8 (5.7)		6.0 (2.9)	
Mixed (AF & DVT/PE)				
<2.5	0	0.0	2	22.2
$\geq 2.5$ , <5	0	0.0	4	44.4
$\geq 5.0$ , <10	0	0.0	2	22.2
$\geq 10$ , <20	0	0.0	1	11.1
$\geq 20$ , <30	4	80.0	0	0.0
$\geq 30$	1	20.0	0	0.0
Number patients with Missing information	0	-	2	-
Median (IQR)	20 (20, 20)		4 (3, 5)	
Mean (SD)	22.0 (4.5)		4.4 (2.9)	
Other				
<2.5	0	0.0	1	33.3
$\geq 2.5$ , <5	0	0.0	1	33.3
$\geq 5.0$ , <10	0	0.0	1	33.3
$\geq 10$ , <20	0	0.0	0	0.0
$\geq 20$ , <30	3	100.0	0	0.0
$\geq 30$	0	0.0	0	0.0
Number patients with Missing information	1	-	1	-

<b>Total daily dose on stopping</b>	<b>Rivaroxaban N=2542</b>		<b>Warfarin N=2067</b>	
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
Median (IQR)	20 (20, 20)		4.5 (0.5, 5)	
Mean (SD)	20 (0.0)		3.3 (2.5)	

In the AF cohort, 105 (90.5%) of the 116 patients reported to have stopped rivaroxaban provided one or more reasons for stopping. The most frequently reported reasons in this subgroup were 'doctor decision' and 'hospitalisation' (Table 95). Rectal haemorrhage (five patients) and haemorrhage (five patients) were also among the most frequently reported reasons for stopping in this subgroup. Of the 121 patients in the AF cohort who stopped warfarin, 111 (91.7%) provided one or more reasons for stopping. The most frequently reported reasons in this subgroup were 'INR increased', 'treatment non-compliance' and 'INR fluctuation'. The full range of reasons for stopping for the AF cohort are provided in Appendix 11.

In the DVT/PE cohort, 225 (91.1%) of the 247 patients who stopped rivaroxaban provided one or more reasons for stopping (Table 95). In this subgroup, the most frequently reported reasons were due to completion of the course and hospitalisation. Bleeding events such as rectal haemorrhage (10 patients), epistaxis (eight patients), gastrointestinal haemorrhage (seven patients) and melaena (six patients) were also among the most frequently reported reasons for stopping rivaroxaban in this subgroup. Of the 220 patients stopping warfarin, 195 (88.6%) provided one or more reason for stopping. In this subgroup, the most frequently reported reasons were due to 'INR increased' and 'doctor decision'. The full range of reasons for stopping for the DVT/PE cohort are provided in Appendix 11.

In the Mixed indication cohort, four (80.0%) of the five patients who stopped rivaroxaban and 10 (90.9%) of the 11 patients who stopped warfarin provided reasons for stopping therapy. In the Other indication cohort, three (75.0%) of the four patients who stopped rivaroxaban and two (50.0%) of the four patients who stopped warfarin provided reasons for stopping therapy. Reasons for stopping in these subgroups are presented in Appendix 11.

**Table 95. Most frequently reported reasons for stopping, by indication treatment group\***

Rivaroxaban			Warfarin		
Reason for stopping	n	%	Reason for stopping	n	%
<b>AF (N=116)</b>			<b>AF (N=121)</b>		
Reason not provided	11	9.5	INR increased	31	25.6
Doctor decision	7	6.0	Reason not provided	10	8.3
Hospitalisation	7	6.0	Treatment noncompliance	7	5.8
Rectal haemorrhage	5	4.3	INR fluctuation	6	5.0
Refusal of treatment by pt.	5	4.3	Refusal of treatment by pt.	6	5.0
Surgery	5	4.3	Doctor decision	5	4.1
Haemorrhage	5	4.3	Hospitalisation	5	4.1
<b>DVT/PE (N=247)</b>			<b>DVT/PE (N=220)</b>		
Course Completed	23	9.3	INR increased	32	14.5
End of course	22	8.9	Reason not provided	25	11.4
Reason not provided	22	8.9	Doctor decision	12	5.5
Hospitalisation	19	7.7	Course completed	9	4.1
Rectal haemorrhage	10	4.0	Refusal of treatment by pt.	9	4.1
Doctor decision	9	3.6	Drug therapy changed	9	4.0
Nausea	8	3.2	Lifestyle issues	8	3.6
Epistaxis	8	3.2	INR	8	3.6
GI haemorrhage	7	2.8	INR fluctuation	7	3.2
Vomiting	7	2.8	Pre-existing cond'n improved	5	2.3
Pre-existing cond'n improved	7	2.8	Epistaxis	5	2.3
Dizziness	7	2.8			
Refusal of treatment by pt.	7	2.8			
Treatment noncompliance	7	2.8			
Melaena	6	2.4			
Haemoglobin decreased	6	2.4			

\* an abridged list is presented here where count is  $\geq 5$ ; all reasons for stopping are presented in Appendix 11. INR: international normalised ration; GI: gastrointestinal; pt.: patient; cond'n: condition

Overall, 173 (6.8%) patients in the rivaroxaban group and 189 (9.1%) patients in the warfarin group were reported to have switched to another anticoagulant or antiplatelet after stopping treatment. In the AF cohort, rivaroxaban patients most frequently switched to warfarin, apixaban or aspirin while warfarin patients most frequently switched to rivaroxaban, low molecular weight heparin or aspirin (Table 96).

**Table 96. Anticoagulant/Antiplatelet switches immediately post treatment cessation for indication AF, by treatment group**

Medication	Rivaroxaban (N=50)		Warfarin (N=53)	
	n	%	n	%
<b>Anticoagulants</b>				
Oral				
Warfarin	15	30.0	0	0.0
Rivaroxaban	0	0.0	21	39.6
Phenindione	0	0.0	0	0.0
Nicoumalone	0	0.0	0	0.0
Dabigatran	7	14.0	3	5.7
Apixaban	11	22.0	0	0.0

Medication	Rivaroxaban (N=50)		Warfarin (N=53)	
	n	%	n	%
Parenteral				
Bivalirudin	0	0.0	0	0.0
Unfractionated heparin	0	0.0	1	1.9
Low molecular weight heparin <sup>a</sup>	7	14.0	19	35.8
Fondaparinux	1	2.0	1	1.9
<b>Antiplatelets</b>				
Aspirin (<=300mg)	10	20.0	9	17.0
Clopidogrel	3	6.0	1	1.9
Abciximab	0	0.0	0	0.0
Dipyridamole	0	0.0	0	0.0
Eptifibatide	0	0.0	0	0.0
Tirofiban	0	0.0	0	0.0

<sup>a</sup> Includes enoxaparin, tinzaparin or dalteparin

In the DVT/PE cohort, patients who switched to another drug most frequently switched to a low molecular weight heparin (n=82, 69.5% in rivaroxaban group and n=56 (44.4%) in the warfarin group). A further 62 (49.2%) warfarin patients switched to rivaroxaban on stopping while 33 (28.0%) switched from rivaroxaban to warfarin after stopping (Table 97).

**Table 97. Anticoagulant/Antiplatelet switches immediately post treatment cessation for indication DVT/PE, by treatment group**

Medication	Rivaroxaban (N=118)		Warfarin (N=126)	
	n	%	n	%
<b>Anticoagulants</b>				
Oral				
Warfarin	33	28.0	0	0.0
Rivaroxaban	0	0.0	62	49.2
Phenindione	0	0.0	0	0.0
Nicoumalone	0	0.0	1	0.8
Dabigatran	0	0.0	0	0.0
Apixaban	6	5.1	5	4.0
Parenteral				
Bivalirudin	0	0.0	0	0.0
Unfractionated heparin	2	1.7	4	3.2
Low molecular weight heparin <sup>a</sup>	82	69.5	56	44.4
Fondaparinux	0	0.0	0	0.0
Other <sup>b</sup>	1	0.8	0	0.0
<b>Antiplatelets</b>				
Aspirin (<=300mg)	2	1.7	3	2.4
Clopidogrel	1	0.8	1	0.8
Abciximab	0	0.0	0	0.0
Dipyridamole	0	0.0	0	0.0
Eptifibatide	0	0.0	0	0.0
Tirofiban	0	0.0	0	0.0

<sup>a</sup> Includes enoxaparin, tinzaparin and dalteparin <sup>b</sup> Tenecteplase

In the Mixed and Other indication cohorts, the numbers of patients of switching to another anticoagulant after stopping were too small to provide meaningful interpretation (Table 98 and Table 99).

**Table 98. Anticoagulant/Antiplatelet switches immediately post treatment cessation for indication Mixed, by treatment group**

Medication		Rivaroxaban (N=2)		Warfarin (N=9)	
		n	%	n	%
<b>Anticoagulants</b>					
Oral					
	Warfarin	0	0.0	0	0.0
	Rivaroxaban	0	0.0	5	55.6
	Phenindione	0	0.0	0	0.0
	Nicoumalone	0	0.0	0	0.0
	Dabigatran	0	0.0	0	0.0
	Apixaban	1	50.0	2	22.2
Parenteral					
	Bivalirudin	0	0.0	0	0.0
	Unfractionated heparin	1	50.0	0	0.0
	Low molecular weight heparin <sup>a</sup>	0	0.0	2	22.2
	Fondaparinux	0	0.0	0	0.0
<b>Antiplatelets</b>					
	Aspirin (<=300mg)	0	0.0	0	0.0
	Clopidogrel	0	0.0	0	0.0
	Abciximab	0	0.0	0	0.0
	Dipyridamole	0	0.0	0	0.0
	Eptifibatide	0	0.0	0	0.0
	Tirofiban	0	0.0	0	0.0

<sup>a</sup> Includes enoxaparin, tinzaparin or dalteparin

**Table 99. Anticoagulant/Antiplatelet switches immediately post treatment cessation for indication Other, by treatment group**

Medication		Rivaroxaban (N=3)		Warfarin (N=1)	
		n	%	n	%
<b>Anticoagulants</b>					
Oral					
	Warfarin	3	100.0	0	0.0
	Rivaroxaban	0	0.0	0	0.0
	Phenindione	0	0.0	0	0.0
	Nicoumalone	0	0.0	0	0.0
	Dabigatran	0	0.0	0	0.0
	Apixaban	0	0.0	0	0.0
Parenteral					
	Bivalirudin	0	0.0	0	0.0
	Unfractionated heparin	0	0.0	0	0.0
	Low molecular weight heparin <sup>a</sup>	0	0.0	1	100.0
	Fondaparinux	0	0.0	0	0.0

Medication	Rivaroxaban (N=3)		Warfarin (N=1)	
	n	%	n	%
<b>Antiplatelets</b>				
Aspirin (<=300mg)	1	33.3	0	0.0
Clopidogrel	1	33.3	0	0.0
Abciximab	0	0.0	0	0.0
Dipyridamole	0	0.0	0	0.0
Eptifibatide	0	0.0	0	0.0
Tirofiban	0	0.0	0	0.0

<sup>a</sup> Includes enoxaparin, tinzaparin or dalteparin

Overall, 372 (14.6%) patients in the rivaroxaban group and 356 (17.2%) patients in the warfarin group stopped treatment within the 12 week observation period. The date of stopping was missing for 64 patients in the rivaroxaban group and for 30 in the warfarin group.

Overall, patients stopped treatment earlier in the warfarin group compared to those in the rivaroxaban group. Of those patients who stopped treatment, 25% had stopped treatment by Day 10 in the rivaroxaban group compared to Day 5 in the warfarin group (Table 100). In both treatment groups, patients who stopped treatment did so earlier in the DVT/PE cohort than in the AF cohort.

**Table 100. Summary Statistics to show number of days to treatment cessation for 10th, 25th and 50th percentiles, by indication and treatment group**

Treatment		Number of days on treatment (percentile) among patients who stopped*		
	Indication	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>
Rivaroxaban				
	AF	3	10	33
	DVT/PE	2	10	24
	Mixed (AF & DVT/PE)	36	36.5	42
	Other	10	10	57
	Total	2	10	28
Warfarin				
	AF	3	7	20
	DVT/PE	2	4	14
	Mixed (AF & DVT/PE)	3	5	37
	Other	3	3	52
	Total	2	5	17

\* Excludes patients with missing stop date; Only the first report of stopping within the observation period is included in this analysis.

At the end of the 12 week observation period, 1735 (70.0%) patients in the rivaroxaban group and 1402 (68.8%) patients in the warfarin group remained on treatment after considering both treatment cessation and losses to follow up (Table 101). The number of patients remaining on treatment at 12 weeks was slightly higher in the AF cohort

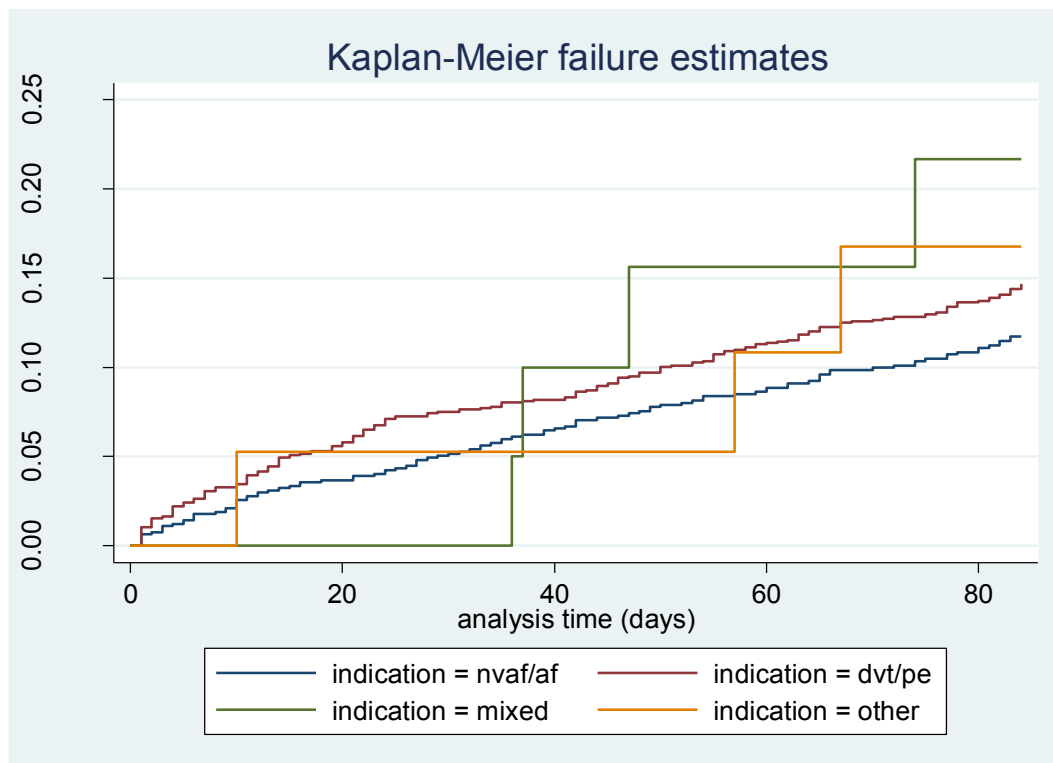
(n=695, 72.9% in the rivaroxaban group; n=569, 72.6% in the warfarin group) than in the DVT/PE cohort (n=1013, 68.3% in the rivaroxaban group; n=794, 66.6% in the warfarin group).

**Table 101. Count and percent of number of days exposed prior to stopping (by week), by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

Days On Treatment	AF		DVT/PE		Mixed		Other		Total	
	n	%	n	%	n	%	n	%	n	%
<b>Rivaroxaban</b>										
Date missing	13	-	49	-	1	-	1	-	64	-
Total non-missing	952	100.0	1483	100.0	22	100.0	21	100.0	2478	100.0
7	881	92.5	1394	94.0	22	100.0	19	90.5	2316	93.5
14	863	90.7	1359	91.6	22	100.0	18	90.5	2262	91.3
21	851	89.4	1311	88.4	22	100.0	18	90.5	2202	88.9
28	826	87.8	1240	83.6	22	100.0	18	90.5	2106	85.0
35	799	93.8	1214	81.9	20	90.9	18	85.7	2051	82.8
42	786	82.6	1194	80.5	17	77.3	17	85.7	2014	81.3
49	772	81.1	1161	78.3	15	68.2	17	85.7	1965	79.3
56	755	79.3	1132	76.3	15	68.2	17	81.0	1919	77.4
63	737	77.4	1105	74.5	15	68.2	15	71.4	1872	75.5
70	724	76.1	1077	72.6	14	63.6	15	71.4	1829	73.8
77	715	75.1	1052	70.9	13	59.1	15	71.4	1794	72.4
84	695	72.9	1013	68.3	13	59.1	14	66.7	1735	70.0
<b>Warfarin</b>										
Date missing	10	-	19	-	0	-	1	-	30	-
Total non-missing	784	100.0	1193	100.0	27	100.0	33	100.0	2037	100.0
7	729	93.0	1068	89.5	23	85.2	31	93.9	1851	90.9
14	703	89.7	1022	85.7	22	81.5	31	93.9	1778	87.3
21	680	86.7	996	83.5	22	81.5	30	90.9	1728	84.8
28	666	84.9	976	81.8	22	81.5	30	90.9	1694	83.2
35	654	83.4	957	80.2	22	81.5	29	87.9	1662	81.6
42	642	81.9	932	78.1	19	70.4	28	84.8	1621	79.6
49	628	80.1	907	76.0	19	70.4	27	81.8	1581	77.6
56	618	78.8	883	74.0	18	66.7	25	75.8	1544	75.8
63	606	77.3	863	72.3	17	63.0	25	75.8	1511	74.2
70	597	76.1	846	70.7	17	63.0	24	72.7	1484	72.9
77	582	74.2	823	69.0	17	63.0	24	72.7	1446	71.0
84	569	72.6	794	66.6	16	59.3	23	69.7	1402	68.8

The cumulative incidence curves of treatment cessation for rivaroxaban suggests rate of stopping was higher in the DVT/PE cohort than in the AF cohort, however, this was not statistically significant (Log rank test:  $\chi^2$  (3 d.f.) =4.85; p=0.183) (Figure 19). Numbers of patients in the Mixed and Other indication cohorts were too small to make any meaningful interpretation.

**Figure 19. Cumulative incidence of treatment cessation within 12 weeks observation period for 'as treated' rivaroxaban cohort, by indication**

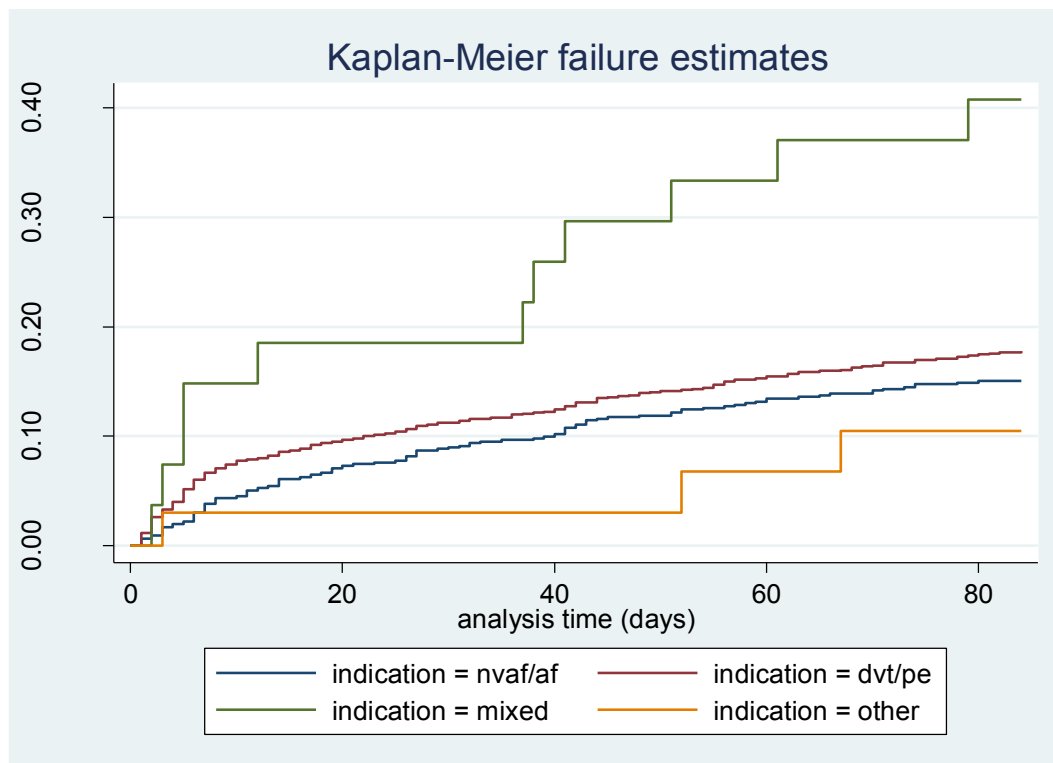


Log rank test:  $\text{Chi}^2$  (3 d.f.) =4.85;  $p=0.183$

The cumulative incidence curves of treatment cessation for warfarin suggests that there were differences in the rate of stopping between the different indication groups (log rank test:  $\text{Chi}^2$  (3 d.f.) =15.98;  $p=0.001$ ) (Figure 20). The rate of stopping was higher in the DVT/PE cohort than in the AF cohort. Numbers in the Mixed and Other indication cohorts were too small to make any meaningful interpretation.



**Figure 20. Cumulative incidence curve of treatment cessation within 12 weeks observation period for 'as treated' warfarin cohort, by indication**



log rank test:  $\chi^2$  (3 d.f.) = 15.98;  $p=0.001$

### **10.5.9 Assessment of adherence**

Prevalence of criteria identifying aberrant general health behaviours was low in all indication groups; the most frequently reported was new onset of smoking in 76 patients (3.0% of pooled cohort; Table 102).

Prevalence of criteria identifying poor anticoagulant medication compliance was also low in all indication groups; the most frequently reported was missed clinical review appointments in 67 patients (2.6% of pooled cohort; Table 102).

**Table 102. Prevalence of criteria and categories identifying aberrant general health behaviours and poor anticoagulant medication compliance in users of rivaroxaban, by indication group and pooled cohort**

Indicator (points)	AF N=965		DVT/PE N=1532		Mixed (AF & DVT) N=23		Other N=22		TOTAL N=2542	
	n	%	n	%	n	%	n	%	n	%
<b>New onset aberrant general health behaviours</b>										
Alcohol misuse (1)	2	0.2	16	1.0	0	0.0	1	4.6	19	0.8
Smoker (1)	15	1.6	58	3.8	0	0.0	3	13.6	76	3.0
Substance misuse (1)	0	0.0	4	0.3	0	0.0	1	4.6	5	0.2
<b>Poor anticoagulant medication compliance</b>										
Overall general poor medication taking behaviour (1)	9	0.9	13	0.9	0	0.0	1	4.6	23	0.9
Missed clinical review appointments (1)	15	1.6	47	3.1	1	4.4	4	18.2	67	2.6
Missed anticoagulant doses (1)	9	0.9	25	1.6	0	0.0	1	4.6	35	1.4
Extra anticoagulant doses (1)	3	0.3	4	0.3	0	0.0	0	0.0	7	0.3
Demonstrated poor understanding of need for regular use (1)	3	0.3	5	0.3	0	0.0	0	0.0	8	0.3
Disclosed high dietary intake of foods high in Vitamin K (1)	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1

General health behaviour risk scores were zero for the majority of patients in the cohort (n=2458, 96.7% of pooled cohort; Table 103 and Figure 21a). There were two patients in the AF indication and one patient in the Other indication group who had the maximum risk score of three.

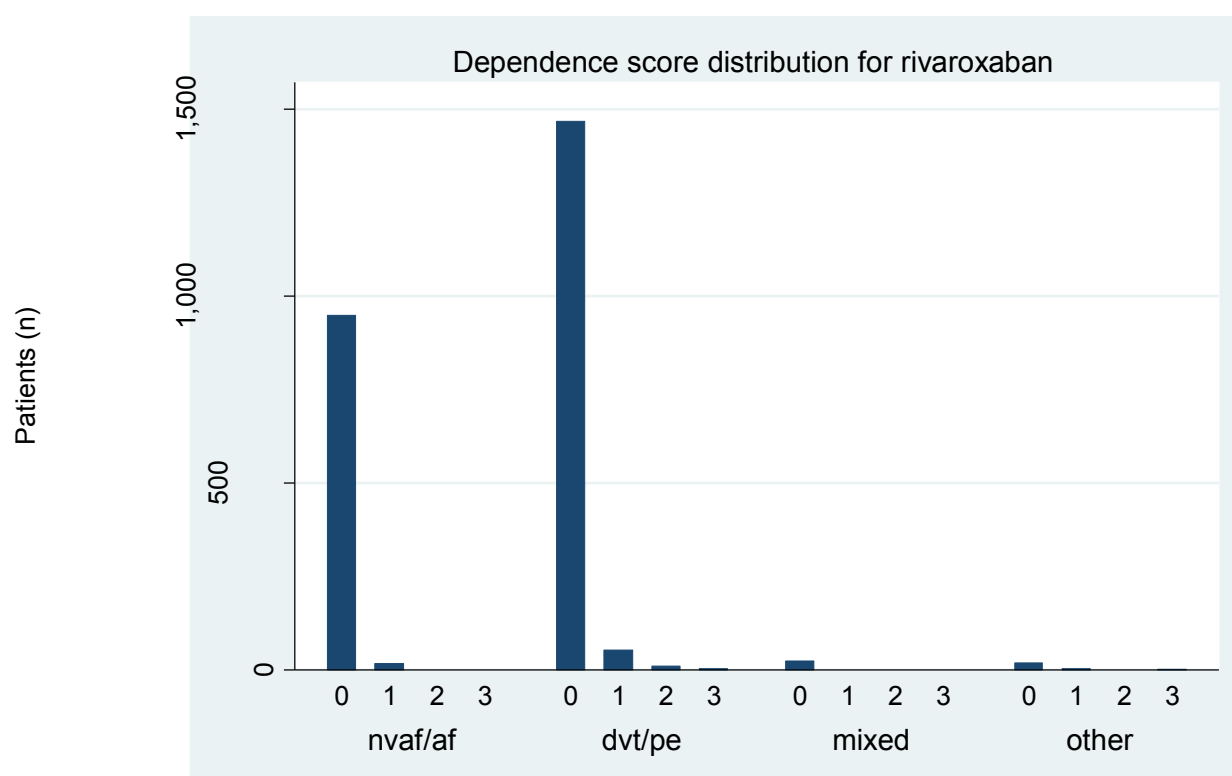
Medication compliance risk scores were zero for the majority of patients in the cohort (n=2432, 95.7% of pooled cohort; Table 103 and Figure 21b). There were no patients who had the maximum risk score of six. Two patients in the DVT/PE indication group had the highest reported risk score of four.

**Table 103. Behaviour indicator score distribution, by indication group and pooled cohort**

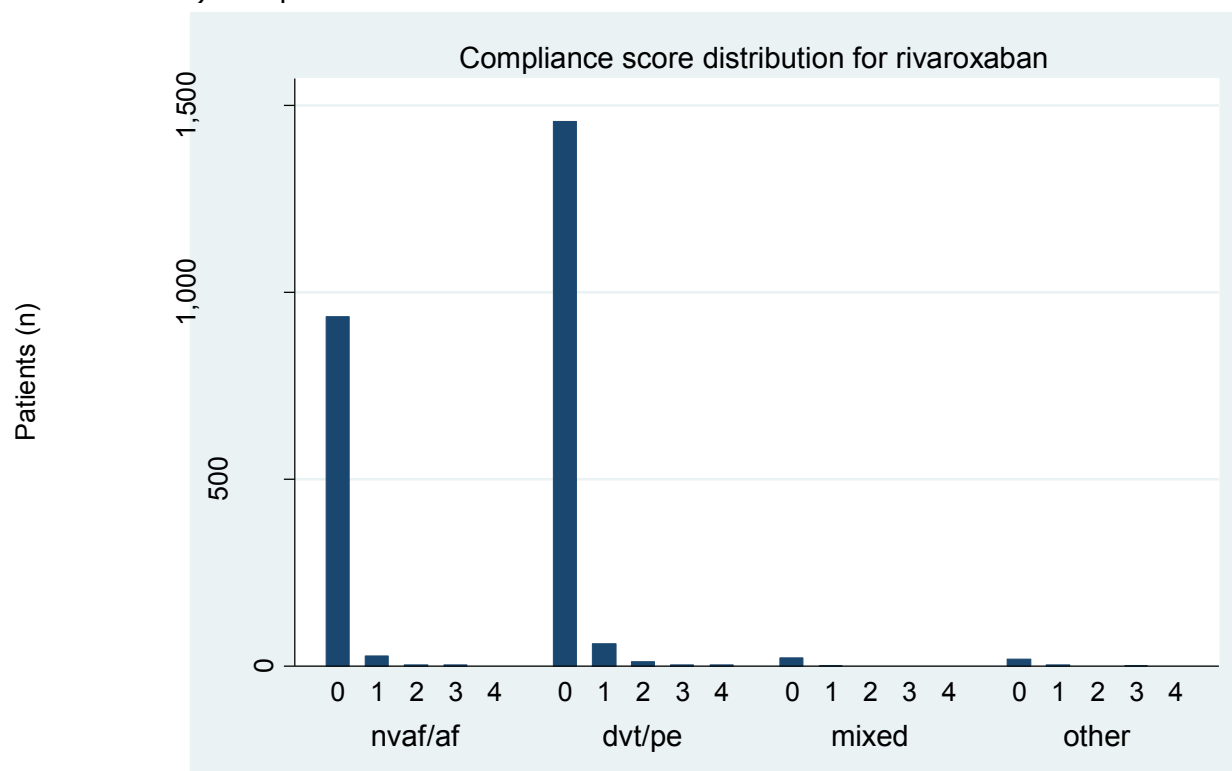
Indicator (points)	AF N=965		DVT/PE N=1532		Mixed (AF & DVT) N=23		Other N=22		TOTAL N=2542	
	n	%	n	%	n	%	n	%	n	%
New onset aberrant general health behaviours										
0 (min)	948	98.2	1468	95.8	23	100.0	19	86.4	2458	96.7
1	17	1.8	52	3.4	0	0.0	2	9.1	71	2.8
2	0	0.0	10	0.7	0	0.0	0	0.0	10	0.4
3 (max)	0	0.0	2	0.1	0	0.0	1	4.6	3	0.1
Median (IQR)	0 (0, 0)		0 (0, 0)		0 (0, 0)		0 (0, 0)		0 (0, 0)	
Poor anticoagulant medication compliance										
0 (min)	934	96.8	1458	95.2	22	95.7	18	81.8	2432	95.7
1	26	2.7	59	3.9	1	4.4	3	13.6	89	3.5
2	2	0.2	11	0.7	0	0.0	0	0.0	13	0.5
3	3	0.3	2	0.1	0	0.0	1	4.6	6	0.2
4	0	0.0	2	0.1	0	0.0	0	0.0	2	0.1
5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
6 (max)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Median (IQR)	0 (0, 0)		0 (0, 0)		0 (0, 0)		0 (0, 0)		0 (0, 0)	

**Figure 21. Behaviour indicator score distribution, by indication group and pooled cohort**

a) Dependence score distribution for rivaroxaban



b) Compliance score distribution for rivaroxaban



### 10.5.10 Pregnancies

**Table 104. Number and outcomes of confirmed pregnancies in women of child-bearing age (12-60 years) in rivaroxaban cohort**

Exposure to rivaroxaban	Total	Live birth	Spontaneous abortion	Therapeutic termination	Stillborn	Neonatal death	NS
Drug stopped before last menstrual period	1	0	0	0	0	0	1
Drug taken in first trimester	0	0	0	0	0	0	0
Drug taken in second trimester	0	0	0	0	0	0	0
Exposure uncertain	0	0	0	0	0	0	0
<b>Total</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>

There was one pregnancy reported in the rivaroxaban cohort, which occurred 96 days after treatment was stopped in a 25 year old patient in the DVT/PE indication group (Table 104). A supplementary questionnaire was not returned for this patient and so the outcome of pregnancy is unknown.

There were no pregnancies reported in the warfarin cohort (Table 105).

**Table 105. Number and outcomes of confirmed pregnancies in women of child-bearing age (12-60 years) in warfarin cohort**

<b>Exposure to warfarin</b>	<b>Total</b>	<b>Live birth</b>	<b>Spontaneous abortion</b>	<b>Therapeutic termination</b>	<b>Stillborn</b>	<b>Neonatal death</b>	<b>NS</b>
Drug stopped before last menstrual period	0	0	0	0	0	0	0
Drug taken in first trimester	0	0	0	0	0	0	0
Drug taken in second trimester	0	0	0	0	0	0	0
Exposure uncertain	0	0	0	0	0	0	0
<b>Total</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

### **10.5.11 Deaths**

In total, 41 (1.6%) patients in the rivaroxaban cohort (n=11 for AF, n=28 for DVT/PE and n=2 for Mixed indications) and 35 (1.7%) patients in the warfarin cohort (n=21 for AF, n=13 for DVT/PE and n=1 for Other indications) died within the 12-week observation period. A further patient in the warfarin treatment group (Mixed indication) died but the date of death was unknown. Multiple causes of death may have been reported per patient including underlying conditions leading to death. Cause of death was not specified for seven patients. In the rivaroxaban cohort, 23 causes of death in 11 patients were reported during the 12 week observation period for the AF indication group, 73 causes of death in 28 patients were reported for the DVT/PE indication group and five in 2 patients were reported in the Mixed indication group (Table 106). In the AF indication group, the most frequently reported cause of death was pneumonia (n=3, 13.0%). Within the DVT/PE indication group, the most frequently reported cause of death was pulmonary embolism (n=11, 15.3%).

In the warfarin cohort, 30 causes of death in 21 patients were reported during the 12 week observation period for the AF indication group, 14 causes of death in 13 patients were reported for the DVT/PE indication group and one cause of death in 1 patient was reported in the Other indication group (Table 106). In the AF indication group, the most frequently reported cause of death was Sepsis (n=4, 13.8%).

Causes of death between the rivaroxaban and warfarin treatment groups were similar for those with an indication of AF. However, causes of death reported for the rivaroxaban treatment group for the indication of DVT/PE differed to those in the warfarin treatment group. Many of these deaths were indication related or appeared to be related to older age. Of note, there were three fatal cases of acute renal failure on rivaroxaban within this indication group and a single fatal case of acute renal failure reported within the warfarin DVT/PE group. The proportion of rivaroxaban treated DVT/PE patients with renal disease

at baseline were 3%, 5% and 0.4% for renal disease stage 1/2, renal disease stage 3/4 and renal failure respectively compared with 2.2%, 8.3% and 0.4% for warfarin treated DVT/PE patients. All causes of death, stratified by observation period, are presented in Appendix 12.

**Table 106. Most frequently reported causes of death\* during 12 week observation period by indication and treatment group**

<b>Rivaroxaban</b>			<b>Warfarin</b>		
<b>No. of deaths = 41</b>			<b>No. of deaths = 35</b>		
<b>Cause of death</b>	<b>n</b>	<b>%</b>	<b>Cause of death</b>	<b>n</b>	<b>%</b>
<b>AF (N=11 patients)</b>	<b>N=23</b>		<b>AF (N=21 patients)</b>	<b>N=30</b>	
Pneumonia	3	13.0	Sepsis	4	13.8
Cerebrovascular accident	2	8.7	Pneumonia	3	10.3
Alveolitis fibrosing	1	4.4	Cardiac arrest	2	6.9
Aplastic anaemia	1	4.4	Cerebrovascular accident	2	6.9
Atrial fibrillation	1	4.4	Death	2	6.9
B-cell lymphoma	1	4.4	Lung neoplasm malignant	2	6.9
Blood pressure increased	1	4.4	Multi-organ failure	2	6.9
Bronchiectasis	1	4.4	Atrial fibrillation	1	3.4
			Chronic obstructive pulmonary disease	1	3.4
Bronchopneumonia	1	4.4	Haemoptysis	1	3.4
Cerebral infarction	1	4.4			
Chronic obstructive pulmonary disease	1	4.4	Haemorrhage Intracranial	1	3.4
Death	1	4.4	Hepatic failure	1	3.4
Klebsiella sepsis	1	4.4	Hypertension	1	3.4
Lymphadenopathy	1	4.4	Left ventricular failure	1	3.4
Lymphadenopathy mediastinal	1	4.4	Lower respiratory tract infection	1	3.4
Respiratory failure	1	4.4	Myocardial infarction	1	3.4
Rheumatoid arthritis	1	4.4	Pneumonia aspiration	1	3.4
Sepsis	1	4.4	Renal failure	1	3.4
Abdominal Lymphadenopathy	1	4.4	Renal failure acute	1	3.4
Urinary tract infection	1	4.4	Respiratory failure	1	3.4
<b>DVT/PE (N=28 patients)</b>	<b>N=73</b>		<b>DVT/PE (N=13 patients)</b>	<b>N=14</b>	
Pulmonary embolism	11	15.3	Clostridial infection	1	7.7
Pneumonia	6	8.3	Enterocolitis infectious	1	7.7
Chronic obstructive pulmonary disease	4	5.6			
Myocardial infarction	3	4.2	Interstitial lung disease	1	7.7
Pancreatic carcinoma metastatic	3	4.2	Lobar pneumonia	1	7.7
Renal failure acute	3	4.2	Lung neoplasm malignant	1	7.7
Cerebrovascular accident	2	2.8	Metastasis	1	7.7
Diabetes mellitus	2	2.8	Oesophageal cancer metastatic	1	7.7
Ischaemic stroke	2	2.8	Pancreatic carcinoma	1	7.7
Metastatic neoplasm	2	2.8	Pneumonia	1	7.7
Renal failure chronic	2	2.8	Pneumonia aspiration	1	7.7
Adenocarcinoma	1	1.4	Pulmonary fibrosis	1	7.7
Asthenia	1	1.4	Renal failure acute	1	7.7
Asthma	1	1.4	Respiratory failure	1	7.7
Atrial fibrillation	1	1.4	Sepsis	1	7.7
Breast cancer metastatic	1	1.4			
Bronchopneumonia	1	1.4			
Cardiac failure congestive	1	1.4			

Rivaroxaban No. of deaths = 41			Warfarin No. of deaths = 35		
Cause of death	n	%	Cause of death	n	%
Cerebrovascular disorder	1	1.4			
Clostridial infection	1	1.4			
<b>Mixed (AF &amp; DVT/PE) (N=2 patients)</b>	<b>N=5</b>		<b>Mixed (AF &amp; DVT/PE)</b>	<b>N=0</b>	
Asthenia	1	20.0			
Cerebrovascular disorder	1	20.0			
Elderly	1	20.0			
Renal failure chronic	1	20.0			
Right ventricular failure	1	20.0			
<b>Other</b>	<b>N=0</b>		<b>Other (N=1 patient)</b>	<b>N=1</b>	
			Congestive cardiomyopathy	1	100.0

\*Multiple causes of death may have been reported per patient, including underlying conditions leading to death  
Cause of death was not specified for 7 patients

## 10.6 Other analyses

### 10.6.1 Other outcomes

#### 10.6.1.1 Change in general health parameters

Information on anthropometric measures (BMI and weight) were collected at baseline and also at the end of the 12 week observation period to determine whether any change had been reported, since these factors were considered to have a time-dependent effect on any subsequent estimates of risk. For each characteristic both baseline and 12 week data are presented and summarised for completeness, with BMI and weight categories for both rivaroxaban and warfarin cohorts, by indication, presented in Table 107 and Table 108. Change in the median values of BMI and weight (bars represent IQR) during the 12 week observation period, stratified by indication group, are presented in Figure 22 and Figure 23.

In the AF rivaroxaban treated cohort, prescribers did not know or did not complete the patients BMI for 221 patients at baseline (22.9%) and 858 patients at 12-weeks (88.9%). In the rivaroxaban AF cohort, the mean BMI at baseline was 28.1 and at 12-weeks it was 27.6. In the AF warfarin treated cohort, prescribers did not know or did not complete the patients BMI for 231 patients at baseline (29.1%) and 662 patients at 12-weeks (83.4%). In the warfarin AF cohort, the mean BMI at baseline was 28.7 and at 12-weeks it was 28.3. Overall, in both AF cohorts there was little change in mean BMI between baseline and 12-weeks.

In the DVT/PE rivaroxaban treated cohort, prescribers did not know or did not complete the patients BMI for 337 patients at baseline (22.9%) and 1298 patients at 12-weeks (84.7%). In the rivaroxaban DVT/PE cohort, the mean BMI at baseline was 29.3 and

at 12-weeks it was 28.7. In the DVT/PE warfarin treated cohort, prescribers did not know or did not complete the patients BMI for 331 patients at baseline (27.3%) and 997 patients at 12-weeks (82.3%). In the warfarin DVT/PE cohort, the mean BMI at baseline was 29.4 and at 12-weeks it was 29.9. Overall, in both DVT/PE cohorts there was little change in mean BMI between baseline and 12-weeks.

In the Mixed (AF & DVT/PE) rivaroxaban treated cohort, prescribers did not know or did not complete the patients BMI for six patients at baseline (26.1%) and 19 patients at 12-weeks (82.6%). In the rivaroxaban Mixed cohort, the mean BMI at baseline was 25.6 and at 12-weeks it was 25.9. In the Mixed warfarin treated cohort, prescribers did not know or did not complete the patients BMI for six patients at baseline (22.2%) and 19 patients at 12-weeks (70.4%). In the warfarin Mixed cohort, the mean BMI at baseline was 28.0 and at 12-weeks it was 26.4, corresponding to a 1.6kg/m<sup>2</sup> decrease in mean BMI. However, this result should be interpreted with caution due to small sample sizes in this specific cohort.

In the Other rivaroxaban treated cohort, prescribers did not know or did not complete the patients BMI for five patients at baseline (22.7%) and 21 patients at 12-weeks (95.4%). In the rivaroxaban Other cohort, the mean BMI at baseline was 27.4 and at 12-weeks it was 27.0. In the Other warfarin treated cohort, prescribers did not know or did not complete the patients BMI for nine patients at baseline (26.5%) and 29 patients at 12-weeks (85.3%). In the warfarin Other cohort, the mean BMI at baseline was 27.7 and at 12-weeks it was 30.5, corresponding to a 2.8kg/m<sup>2</sup> increase in mean BMI. However, this result should be interpreted with caution due to small sample sizes in this specific cohort.

There was no obvious trend for change in BMI values over the observation period. Since the proportion of patients with missing information is high, caution is recommended in generalising results to similar groups of treated patients.



**Table 107. BMI categories at baseline and 12-week follow up, by indication and treatment group**

BMI (kg/m2)		Rivaroxaban N=2542				Warfarin N=2067			
		Baseline		12-Week*		Baseline		12-Week*	
		n	%	n	%	n	%	n	%
AF									
<18.5 (Below Normal)		17	1.8	2	0.2	8	1.0	3	0.4
18.5-24.9 (Normal)		247	25.6	37	3.8	176	22.2	39	4.9
25.0-29.9 (Overweight)		250	25.9	32	3.3	189	23.8	51	6.4
30.0-39.9 (Obese)		193	20.0	32	3.3	157	19.8	28	3.5
40.0+ (Morbidly Obese)		37	3.8	4	0.4	33	4.2	11	1.4
Not specified		221	22.9	858	88.9	231	29.1	662	83.4
Median (IQR)		27.1 (23.9-31.1)		27.0 (23.0-30.8)		27.5 (24.0-32.0)		27.0 (24.0-31.5)	
Mean (SD)		28.1 (6.3)		27.6 (6.4)		28.7 (6.7)		28.3 (6.6)	
Median of differences (IQR) <sup>a</sup>		-0.1 (-1.3-1.1)				-0.03 (-0.6-0.7)			
DVT/PE									
<18.5 (Below Normal)		16	1.0	6	0.4	13	1.1	3	0.3
18.5-24.9 (Normal)		308	20.1	66	4.3	218	17.9	51	4.2
25.0-29.9 (Overweight)		420	27.4	73	4.8	306	25.3	74	6.1
30.0-39.9 (Obese)		378	24.7	76	4.9	288	23.8	67	5.5
40.0+ (Morbidly Obese)		73	4.8	13	0.9	56	4.6	20	1.7
Not specified		337	22.0	1298	84.7	331	27.3	997	82.3
Median (IQR)		28.2 (24.8-32.6)		28.1 (24.0-32.4)		28.3 (24.8-32.7)		28.5 (24.9-33.4)	
Mean (SD)		29.3 (6.6)		28.7 (6.3)		29.4 (6.9)		29.9 (7.4)	
Median of differences (IQR) <sup>a</sup>		-0.0 (-0.5-0.8)				0.1 (-0.2-1.0)			
Mixed (AF & DVT/PE)									
<18.5 (Below Normal)		1	4.4	0	0	2	7.4	0	0
18.5-24.9 (Normal)		7	30.4	0	0	6	22.2	4	14.8
25.0-29.9 (Overweight)		7	30.4	4	17.4	6	22.2	1	3.7
30.0-39.9 (Obese)		2	8.7	0	0	5	18.5	3	11.1
40.0+ (Morbidly Obese)		0	0.0	0	0	2	7.4	0	0
Not specified		6	26.1	19	82.6	6	22.2	19	70.4
Median (IQR)		26.1 (21.5-28.4)		25.9 (25.4-26.3)		26.8 (23.0-31.4)		26.5 (21.2-31.0)	

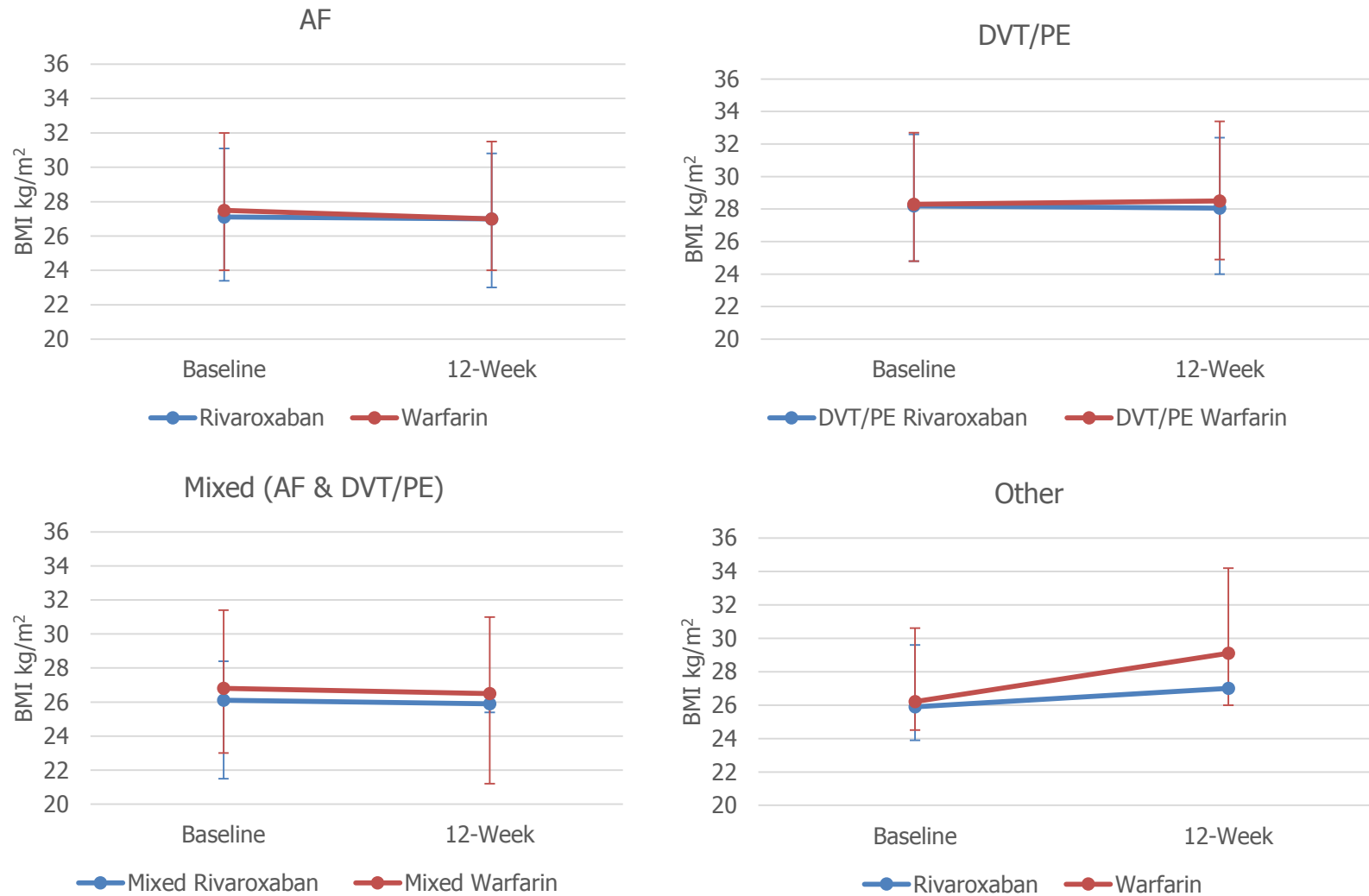
BMI (kg/m2)	Rivaroxaban N=2542				Warfarin N=2067			
	Baseline		12-Week*		Baseline		12-Week*	
	n	%	n	%	n	%	n	%
<i>Mean (SD)</i>	25.6 (5.0)		25.9 (0.7)		28.0 (7.2)		26.4 (5.9)	
Median of differences (IQR) <sup>a</sup>			-1.2 (-3.0-0.2)				-0.0 (-1.1-1.9)	
Other								
<18.5 (Below Normal)	1	4.6	0	0	0	0	0	0.0
18.5-24.9 (Normal)	4	18.2	0	0	10	29.4	1	2.9
25.0-29.9 (Overweight)	9	40.9	1	4.6	7	20.6	2	5.9
30.0-39.9 (Obese)	2	9.1	0	0	7	20.6	1	2.9
40.0+ (Morbidly Obese)	1	4.6	0	0	1	2.9	1	2.9
Not specified	5	22.7	21	95.4	9	26.5	29	85.3
<i>Median (IQR)</i>	25.9 (23.9-29.6)		27.0 <sup>b</sup>		26.2 (24.5-30.6)		29.1 (26.0-34.2)	
<i>Mean (SD)</i>	27.4 (6.9)		27.0 <sup>b</sup>		27.7 (5.2)		30.5 (8.0)	
Median of differences (IQR) <sup>a</sup>			1.6 <sup>b</sup>				-0.4 (-1.3-1.4)	

<sup>a</sup> paired analysis; approach will be dependent on distribution of data variable; where data are Normal, paired t-test will apply; where data are skewed, the median of differences will be calculated as the 50 percentile of all individual differences (change from baseline (<http://onbiostatistics.blogspot.co.uk/2015/12/median-of-differences-versus-difference.html>))

\* value closest to the end of the 12-week observation period after starting treatment

<sup>b</sup> IQR not presented as only one 12 week value for Other indication group

**Figure 22. Change of median BMI (kg/m<sup>2</sup>) during 12-week observation period, stratified by indication group**



In the AF rivaroxaban treated cohort, prescribers did not know or did not complete the patient's weight for 192 patients at baseline (19.9%) and 790 patients at 12-weeks (81.9%). In the rivaroxaban AF cohort, the mean weight at baseline was 80.4kg and at 12-weeks it was 80.2kg. In the AF warfarin treated cohort, prescribers did not know or did not complete the patients weight for 214 patients at baseline (26.9%) and 606 patients at 12-weeks (76.3%). In the warfarin AF cohort, the mean weight at baseline was 82.8kg and at 12-weeks it was 81.9kg. Overall, in both AF cohorts there was little change in mean weight between baseline and 12-weeks.

In the DVT/PE rivaroxaban treated cohort, prescribers did not know or did not complete the patients weight for 317 patients at baseline (20.7%) and 1255 patients at 12-weeks (81.9%). In the rivaroxaban DVT/PE cohort, the mean weight at baseline was 86.5kg and at 12-weeks it was 84.0kg, corresponding to a 2.9% decrease in mean weight. In the DVT/PE warfarin treated cohort, prescribers did not know or did not complete the patients weight for 310 patients at baseline (25.6%) and 969 patients at 12-weeks (79.9%). In the warfarin DVT/PE cohort, the mean weight at baseline was 86.4kg and at 12-weeks it was 86.0kg. Overall, in both DVT/PE cohorts there was little change in mean weight between baseline and 12-weeks.

In the Mixed (AF & DVT/PE) rivaroxaban treated cohort, prescribers did not know or did not complete the patients weight for five patients at baseline (21.7%) and 19 patients at 12-weeks (82.6%). In the rivaroxaban Mixed cohort, the mean weight at baseline was 72.4kg and at 12-weeks it was 75.1kg, corresponding to a 3.7% increase in mean weight. In the Mixed warfarin treated cohort, prescribers did not know or did not complete the patients weight for six patients at baseline (22.2%) and 18 patients at 12-weeks (66.7%). In the warfarin Mixed cohort, the mean weight at baseline was 86.2kg and at 12-weeks it was 78.7kg, corresponding to a 8.7% decrease in mean weight. However, these results should be interpreted with caution due to small sample sizes in these specific cohorts.

In the Other rivaroxaban treated cohort, prescribers did not know or did not complete the patients weight for four patients at baseline (18.2%) and 20 patients at 12-weeks (90.9%). In the rivaroxaban Other cohort, the mean weight at baseline was 82.4kg and at 12-weeks it was 74.9kg, corresponding to a 9.1% decrease in mean weight. In the Other warfarin treated cohort, prescribers did not know or did not complete the

patients weight for nine patients at baseline (26.5%) and 29 patients at 12-weeks (85.3%). In the warfarin Other cohort, the mean weight at baseline was 79.4kg and at 12-weeks it was 84.7kg, corresponding to a 6.7% increase in mean weight. However, these results should be interpreted with caution due to small sample sizes in these specific cohorts.

There was no obvious trend for change in weight values over the observation period. Since the proportion of patients with missing information is high, caution is recommended in generalising results to similar groups of treated patients.

**Table 108. Weight (kg) categories at baseline and 12-week follow up, by indication and treatment group**

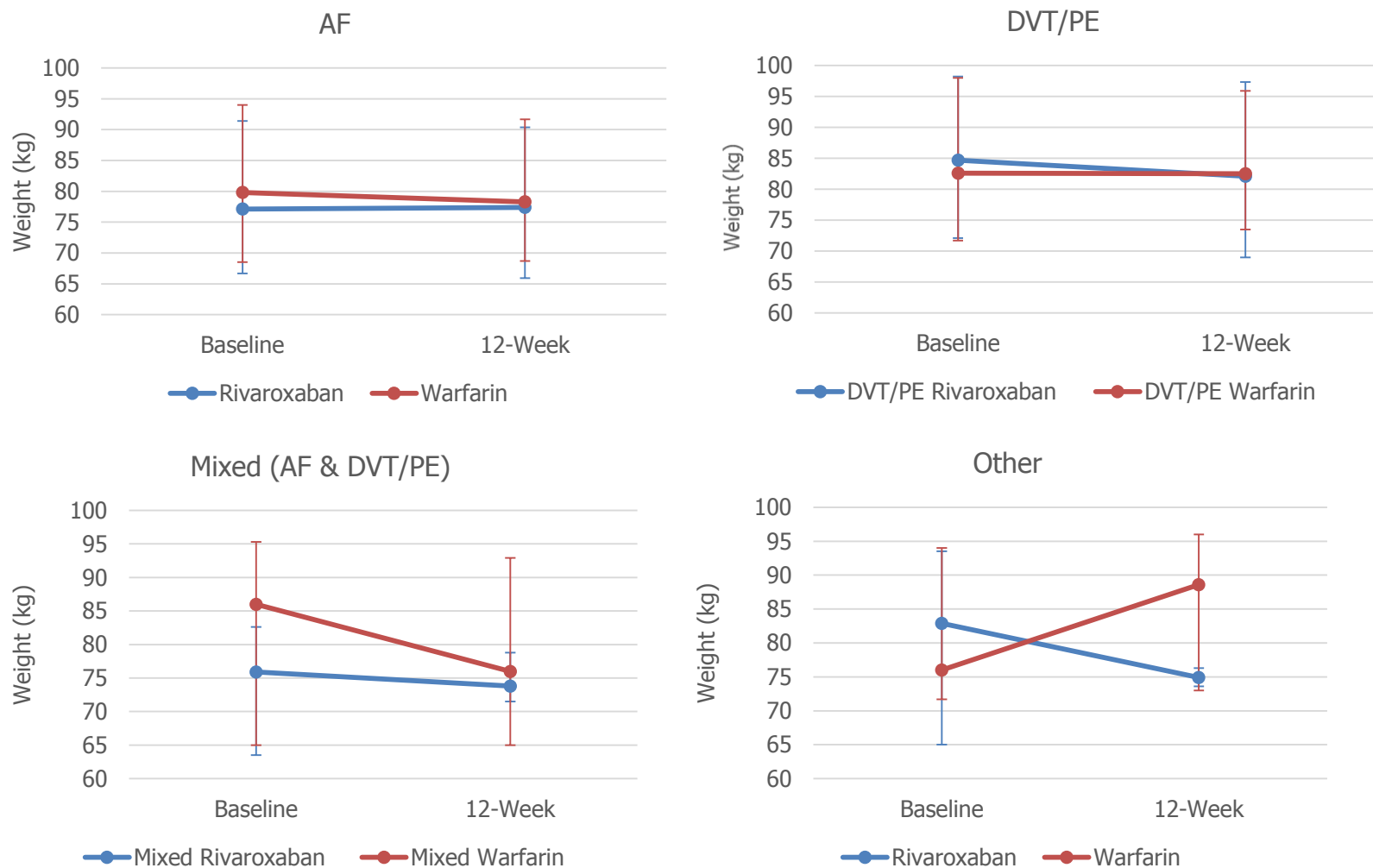
Weight (kg)		Rivaroxaban N=2542				Warfarin N=2067			
		Baseline		12-Week*		Baseline		12-Week*	
		n	%	N	%	n	%	n	%
AF									
	<50	25	2.6	10	1.0	14	1.8	6	0.8
	50-69.9	235	24.4	46	4.8	167	21.0	48	6.1
	70-89.9	309	32.0	75	7.8	220	27.7	85	10.7
	90-109.9	142	14.7	28	2.9	114	14.4	27	3.4
	110+	62	6.4	16	1.7	65	8.2	22	2.8
	Not specified	192	19.9	790	81.9	214	26.9	606	76.3
	Median (IQR)	77.1 (66.7-91.4)		77.4 (65.9-90.4)		79.8 (68.5-94.0)		78.3 (68.7-91.7)	
	Mean (SD)	80.4 (20.3)		80.2 (21.3)		82.8 (21.5)		81.9 (20.5)	
	Median of differences (IQR) <sup>a</sup>	-0.1 (-2.3-2.0)				0.0 (-2.6-1.0)			
DVT/PE									
	<50	16	1.0	9	0.6	14	1.2	5	0.4
	50-69.9	256	16.7	66	4.3	180	14.9	40	3.3
	70-89.9	477	31.1	107	6.9	379	31.3	107	8.8
	90-109.9	317	20.7	65	4.2	216	17.8	64	5.3
	110+	149	9.7	30	1.9	113	9.3	27	2.2
	Not specified	317	20.7	1255	81.9	310	25.6	969	79.9
	Median (IQR)	84.7 (72.1-98.2)		82.1 (69.0-97.3)		82.6 (71.7 – 98.0)		82.5 (73.5-95.9)	
	Mean (SD)	86.5 (21.2)		84.0 (21.4)		86.4 (21.9)		86.0 (21.7)	
	Median of differences (IQR) <sup>a</sup>	0.0 (-1.2-1.7)				0.6 (-0.7-3.1)			
Mixed (AF & DVT/PE)									
	<50	1	4.4	0	0	1	3.7	1	3.7
	50-69.9	6	26.1	0	0	6	22.2	3	11.1
	70-89.9	11	47.8	4	17.4	7	25.9	2	7.4
	90-109.9	0	0	0	0	4	14.8	2	7.4
	110+	0	0	0	0	3	11.1	1	3.7

Weight (kg)		Rivaroxaban N=2542				Warfarin N=2067			
		Baseline		12-Week*		Baseline		12-Week*	
		n	%	N	%	n	%	n	%
Not specified		5	21.7	19	82.6	6	22.2	18	66.7
Median (IQR)		75.9 (63.5-82.6)		73.8 (71.5-78.8)		86.0 (65.0-95.3)		76.0 (65.0-92.9)	
Mean (SD)		72.4 (13.3)		75.1 (5.6)		86.2 (28.7)		78.7 (20.9)	
Median of differences (IQR) <sup>a</sup>		-3.3 (-12.3-4.9)				-0.6 (-3.1-6.9)			
Other									
<50		0	0	0	0	0	0	0	0
50-69.9		5	22.7	0	0	6	17.7	1	2.9
70-89.9		7	31.8	2	9.1	11	32.4	2	5.9
90-109.9		5	22.7	0	0	8	23.5	2	5.9
110+		1	4.6	0	0	0	0	0	0
Not specified		4	18.2	20	90.9	9	26.5	29	85.3
Median (IQR)		82.9 (65.0-93.5)		74.9 (73.6-76.3)		76.0 (71.7-94.0)		88.6 (73.0-96.0)	
Mean (SD)		82.4 (19.9)		74.9 (1.9)		79.4 (15.3)		84.7 (14.5)	
Median of differences (IQR) <sup>a</sup>		-0.8 (-1.7-0.1)				0.3 (-2.9-1.6)			

<sup>a</sup> paired analysis; approach will be dependent on distribution of data variable; where data are Normal, paired t-test will apply; where data are skewed, the median of differences will be calculated as the 50 percentile of all individual differences (change from baseline (<http://onbiostatistics.blogspot.co.uk/2015/12/median-of-differences-versus-difference.html>))

\* value closest to the end of the 12-week observation period after starting treatment

**Figure 23. Change of weight (kg) during 12-week observation period, stratified by indication group**





#### ***10.6.1.2 Changes in laboratory test results***

Investigators were asked to provide results of haemoglobin levels at baseline and closest to the end of the 12 week observation period (Table 109, Figure 24). Within the rivaroxaban evaluable cohort, where haemoglobin values were provided, 78 (70.9%) AF, 335 (83.3%) DVT/PE, two (66.7%) Mixed indication and six (100.0%) Other indication males fell within guideline normal values at baseline and 58 (65.2%) AF, 153 (76.9%) DVT/PE, five (71.4%) Mixed indication and three (100.0%) Other indication males had normal haemoglobin values at 12 weeks. Correspondingly 61 (64.9%) AF, 212 (70.7%) DVT/PE, two (100.0%) Mixed indication and three (100.0%) Other indication females fell within normal values at baseline and 47 (62.7%) AF, 123 (71.1%) DVT/PE and four (100.0%) Other indication females had normal haemoglobin values at 12 weeks.

Within the warfarin evaluable cohort, where haemoglobin values were provided, 134 (72.8%) AF, 281 (78.5%) DVT/PE, six (66.7%) Mixed indication and nine (90.0%) Other indication males fell within guideline normal values at baseline and 55 (59.1%) AF, 136 (69.7%) DVT/PE, three (42.9%) Mixed indication and four (66.7%) Other indication males had normal haemoglobin values at 12 weeks. Correspondingly 85 (68.0%) AF, 197 (65.4%) DVT/PE, three (75.0%) Mixed indication and one (20.0%) Other indication females fell within normal values at baseline and 49 (55.1%) AF, 91 (64.5%) DVT/PE and three (75.0%) Mixed indication and three (60.0%) Other indication females had normal haemoglobin values at 12 weeks.

There was no obvious trend for change in haemoglobin values over the observation period. Since the proportion of patients with missing information is high, caution is recommended in generalising results to similar groups of treated patients.

**Table 109. Haemoglobin (g/dL) at baseline and 12-week follow up, by indication and treatment group**

a)

Haemoglobin (g/dL)		Rivaroxaban N=2542				Warfarin N=2067			
		Baseline		12-Week*		Baseline		12-Week*	
		n	%	n	%	N	%	n	%
AF									
Male									
<13		31	28.2	30	33.7	49	26.6	38	40.9
≥13 & <18		78	70.9	58	65.2	134	72.8	55	59.1
≥18		1	0.9	1	1.1	1	0.5	0	0.0
Not specified		407	-	428	-	264	-	355	-
Median (IQR)		14.2 (12.9, 15.2)		13.9 (12.5, 14.9)		14.1 (12.9, 15.1)		13.5 (12.2, 14.6)	
Mean (SD)		14.1 (1.7)		13.6 (1.8)		13.9 (1.8)		13.3 (1.8)	
Median/mean of differences <sup>a</sup>		-0.3 (-1.2, 0.4) N=61				-0.1 (-1.0, 0.6) N=65			
Female									
<12		22	23.4	21	28.0	32	25.6	37	41.6
≥12 & <15		61	64.9	47	62.7	85	68.0	49	55.1
≥15		11	11.7	7	9.3	8	6.4	3	3.4
Not specified		354	-	373	-	221	-	257	-
Median (IQR)		13.3 (12.2, 14.2)		13.1 (11.8, 13.9)		13.1 (11.9, 14.0)		12.5 (11.2, 13.8)	
Mean (SD)		13.1 (1.7)		12.8 (1.6)		13.0 (1.5)		12.4 (1.7)	
Median/mean of differences <sup>a</sup>		-0.1 (-1.1, 0.6) N=57				0.0 (-0.7, 0.6) N=55			
DVT/PE									
Male									
<13		62	15.4	43	21.6	70	19.6	58	29.7
≥13 & <18		335	83.3	153	76.9	281	78.5	136	69.7
≥18		5	1.2	3	1.5	7	2.0	1	0.5
Not specified		434	-	637	-	307	-	470	-
Median (IQR)		14.7 (13.5, 15.5)		14.5 (13.1, 15.3)		14.3 (13.2, 15.3)		14.0 (12.7, 15.2)	
Mean (SD)		14.5 (1.6)		14.6 (6.1)		14.2 (1.9)		13.7 (2.0)	
Median/mean of differences <sup>a</sup>		-0.1 (-0.7, 0.5) N=158				0.0 (-0.8, 0.8) N=165			
Female									
<12		71	23.7	46	26.6	92	30.6	47	33.3
≥12 & <15		212	70.7	123	71.1	197	65.4	91	64.5
≥15		17	5.7	4	2.3	12	4.0	3	2.1
Not specified		396	-	523	-	246	-	406	-
Median (IQR)		13.0 (12.0, 13.8)		12.9 (11.8, 13.6)		12.8 (11.7, 13.8)		12.7 (11.4, 13.5)	
Mean (SD)		12.8 (1.6)		12.6 (1.5)		12.7 (1.8)		12.4 (1.6)	
Median/mean of differences <sup>a</sup>		0.0 (-0.6, 0.7) N=135				0.0 (-0.6, 0.6) N=114			

Note: Haemoglobin (g/L) guideline normal values 130-180 g/L adult males; 120-150g/L adult females

<sup>a</sup> paired analysis; approach will be dependent on distribution of data variable; where data are Normal, paired t-test will apply; where data are skewed, the median of differences will be calculated as the 50 percentile of all individual differences (change from baseline

(<http://onbiostatistics.blogspot.co.uk/2015/12/median-of-differences-versus-difference.html>)

\* value closest to the end of the 12-week observation period after starting treatment

b)

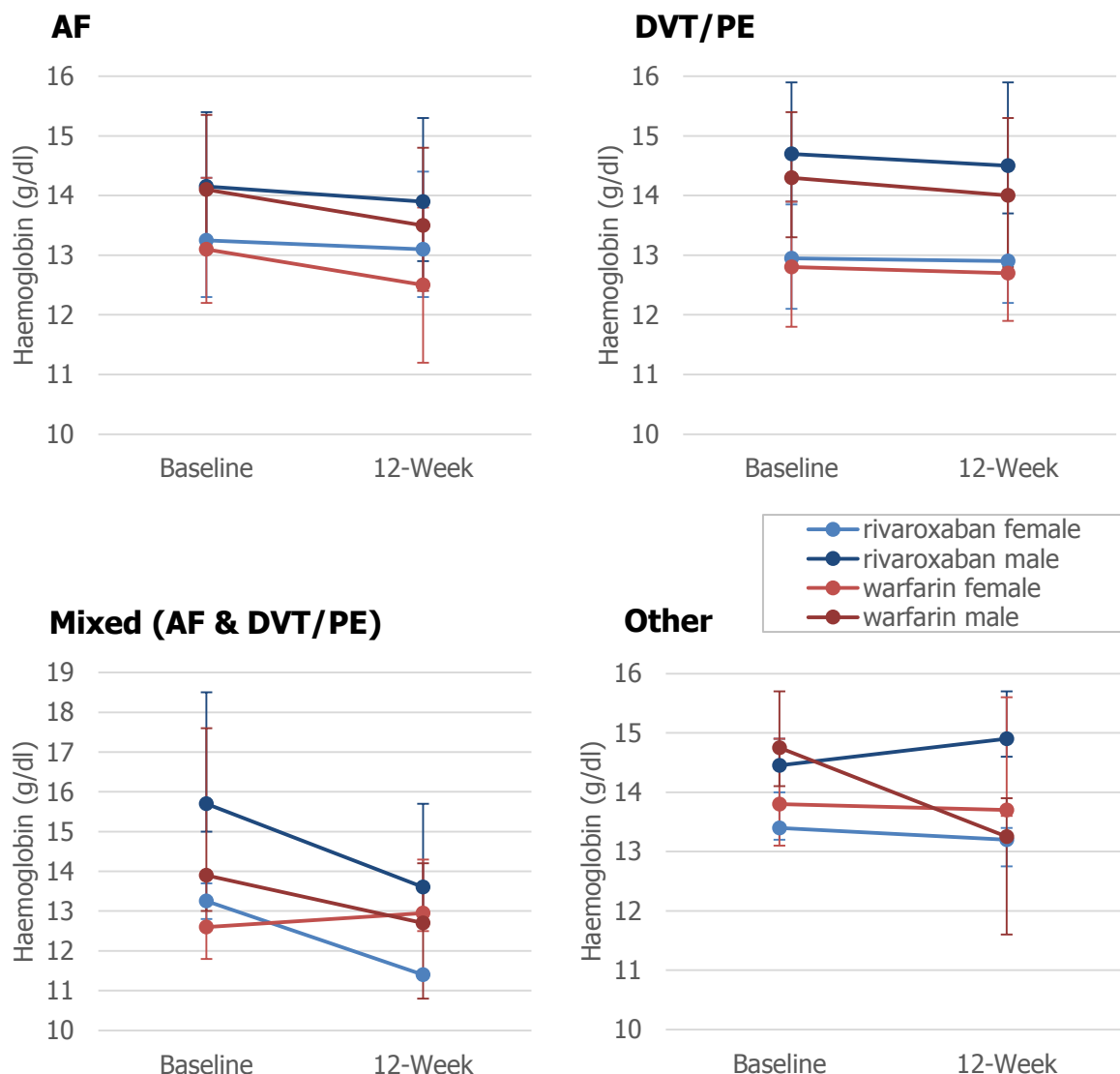
Haemoglobin (g/dL)		Rivaroxaban N=2542				Warfarin N=2067			
		Baseline		12-Week*		Baseline		12-Week*	
		n	%	n	%	N	%	n	%
Mixed (AF & DVT/PE)									
Male									
<13		1	33.3	2	28.6	3	33.3	4	57.1
≥13 & <18		2	66.7	5	71.4	6	66.7	3	42.9
≥18		0	0.0	0	0.0	0	0.0	0	0.0
Not specified		11	-	7	-	8	-	10	-
Median (IQR)		15.7 (12.9, 16.4)		13.6 (11.5, 14.3)		13.9 (10.2, 14.8)		12.7 (11.2, 14.6)	
Mean (SD)		15.0 (1.8)		13.2 (1.3)		12.9 (3.0)		12.9 (1.9)	
Median/mean of differences <sup>a</sup>		-				0.7 (0.2, 2.4)			
		N=2				N=5			
Female									
<12		0	0.0	1	100.0	1	25.0	1	25.0
≥12 & <15		2	100.0	0	0.0	3	75.0	3	75.0
≥15		0	0.0	0	0.0	0	0.0	0	0.0
Not specified		7	-	8	-	6	-	6	-
Median (IQR)		-		-		-		-	
Mean (SD)		-		-		-		-	
Median/mean of differences <sup>a</sup>		-				-			
		N=0				N=3			
Other									
Male									
<13		0	0.0	0	0.0	1	10.0	2	33.3
≥13 & <18		6	100.0	3	100.0	9	90.0	4	66.7
≥18		0	0.0	0	0.0	0	0.0	0	0.0
Not specified		9	-	12	-	9	-	13	-
Median (IQR)		14.5 (14.0, 14.5)		-		14.8 (13.8, 15.4)		13.3 (12.6, 14.9)	
Mean (SD)		14.5 (1.0)		-		14.5 (1.2)		13.8 (1.6)	
Median/mean of differences <sup>a</sup>		-				-0.1 (-2.6, 0.3)			
		N=2				N=6			
Female									
<12		0	0.0	0	0.0	4	80.0	2	40.0
≥12 & <15		3	100.0	4	100.0	1	20.0	3	60.0
≥15		0	0.0	0	0.0	0	0.0	0	0.0
Not specified		4	-	3	-	10	-	10	-
Median (IQR)		-		-		13.8 (12.7, 14.5)		13.7 (11.8, 13.8)	
Mean (SD)		-		-		14.0 (1.6)		12.9 (1.4)	
Median/mean of differences <sup>a</sup>		-				-			
		N=3				N=2			

Note: Haemoglobin (g/L) guideline normal values 130-180 g/L adult males; 120-150g/L adult females

<sup>a</sup> paired analysis; approach will be dependent on distribution of data variable; where data are Normal, paired t-test will apply; where data are skewed, the median of differences will be calculated as the 50 percentile of all individual differences (change from baseline  
(<http://onbiostatistics.blogspot.co.uk/2015/12/median-of-differences-versus-difference.html>)

\* value closest to the end of the 12-week observation period after starting treatment

**Figure 24. Change of Haemoglobin (g/DL) during 12-week observation period, stratified by indication group**



Investigators were asked to provide results of platelet levels at baseline and closest to the end of the 12 week observation period (Table 110, Figure 25). Within the rivaroxaban evaluable cohort, where platelet values were provided, 167 (89.8%) AF, 521 (88.5%) DVT/PE, three (75.0%) Mixed indication and eight (88.9%) Other indication patients fell within guideline normal values at baseline. At 12 weeks (or closest to 12 weeks) 134 (89.9%) AF, 301 (91.2%) DVT/PE, five (71.4%) Mixed indication and six (100.0%) Other indication patients fell within guideline normal values. Within the warfarin evaluable cohort, where platelet values were provided, 246 (87.5%) AF, 534 (88.6%) DVT/PE, 10 (100.0%) Mixed indication and 12 (92.3%) Other indication patients fell within guideline normal values at baseline. At 12 weeks (or closest to 12 weeks) 145 (87.3%) AF, 290 (93.2%) DVT/PE, eight (80.0%) Mixed

indication and 10 (90.9%) Other indication patients fell within guideline normal values. There was no obvious trend for change in platelet values over the 12 week observation period. Since the proportion of patients with missing information is high, caution is recommended in generalising results to similar groups of treated patients.

**Table 110. Platelets (x10<sup>9</sup>/L) at baseline and 12-week follow up, by indication and treatment group**

Platelets (x10 <sup>9</sup> /L)	Rivaroxaban N=2542				Warfarin N=2067			
	Baseline		12-Week*		Baseline		12-Week*	
	n	%	n	%	n	%	n	%
AF								
<150	16	8.6	13	8.7	26	9.3	16	9.6
≥150 & <450	167	89.8	134	89.9	246	87.5	145	87.3
≥450	3	1.6	2	1.3	9	3.2	5	3.0
Not specified	779	-	816	-	513	-	628	-
Median (IQR)	223.5 (186.0, 301.0)		250.0 (189.0, 290.0)		227.0 (185.0, 276.0)		224.5 (194.0, 283.0)	
Mean (SD)	245.8 (87.4)		246.4 (76.7)		240.9 (83.0)		243.7 (89.4)	
Median/mean of differences <sup>a</sup>	-9.5 (-36.0, 31.0)				-2.0 (-23.0, 28.0)			
DVT/PE								
<150	49	8.3	14	4.2	53	8.8	13	4.2
≥150 & <450	521	88.5	301	91.2	534	88.6	290	93.2
≥450	19	3.2	15	4.5	16	2.7	8	2.6
Not specified	943	-	1202	-	609	-	901	-
Median (IQR)	235.0 (192.0, 285.0)		250.0 (207.0, 301.0)		229.9 (185.0, 288.0)		255.0 (204.0, 315.0)	
Mean (SD)	247.4 (83.2)		267.3 (100.1)		244.4 (86.0)		266.5 (87.8)	
Median/mean of differences <sup>a</sup>	11.0 (-18.5, 48.0)				19.0 (-16.0, 68.0)			
Mixed (AF & DVT/PE)								
<150	1	25.0	1	14.3	0	0.0	1	10.0
≥150 & <450	3	75.0	5	71.4	10	100.0	8	80.0
≥450	0	0.0	1	14.3	0	0.0	1	10.0
Not specified	19	-	16	-	17	-	17	-
Median (IQR)	233.5 (168.5, 303.5)		202.0 (150.0, 274.0)		241.0 (219.0, 259.0)		265.5 (245.0, 356.0)	
Mean (SD)	236.0 (83.6)		244.7 (135.9)		238.1 (48.7)		302.2 (138.0)	
Median/mean of differences <sup>a</sup>	24.5 (-1.0, 50.0)				19.0 (-34.0, 67.0)			
Other								
<150	1	11.1	0	0.0	1	7.7	1	9.1
≥150 & <450	8	88.9	6	100.0	12	92.3	10	90.9
≥450	0	0.0	0	0.0	0	0.0	0	0.0
Not specified	13	-	16	-	21	-	23	-
Median (IQR)	227.0 (174.0, 257.0)		251.5 (195.0, 290.0)		226.0 (203.0, 277.0)		234.0 (185.0, 285.0)	
Mean (SD)	209.9 (88.5)		251.2 (55.1)		237.1 (61.3)		241.0 (64.2)	
Median/mean of differences <sup>a</sup>	2.0 (-18.0, 42.0)				10.5 (-29.5, 38.5)			

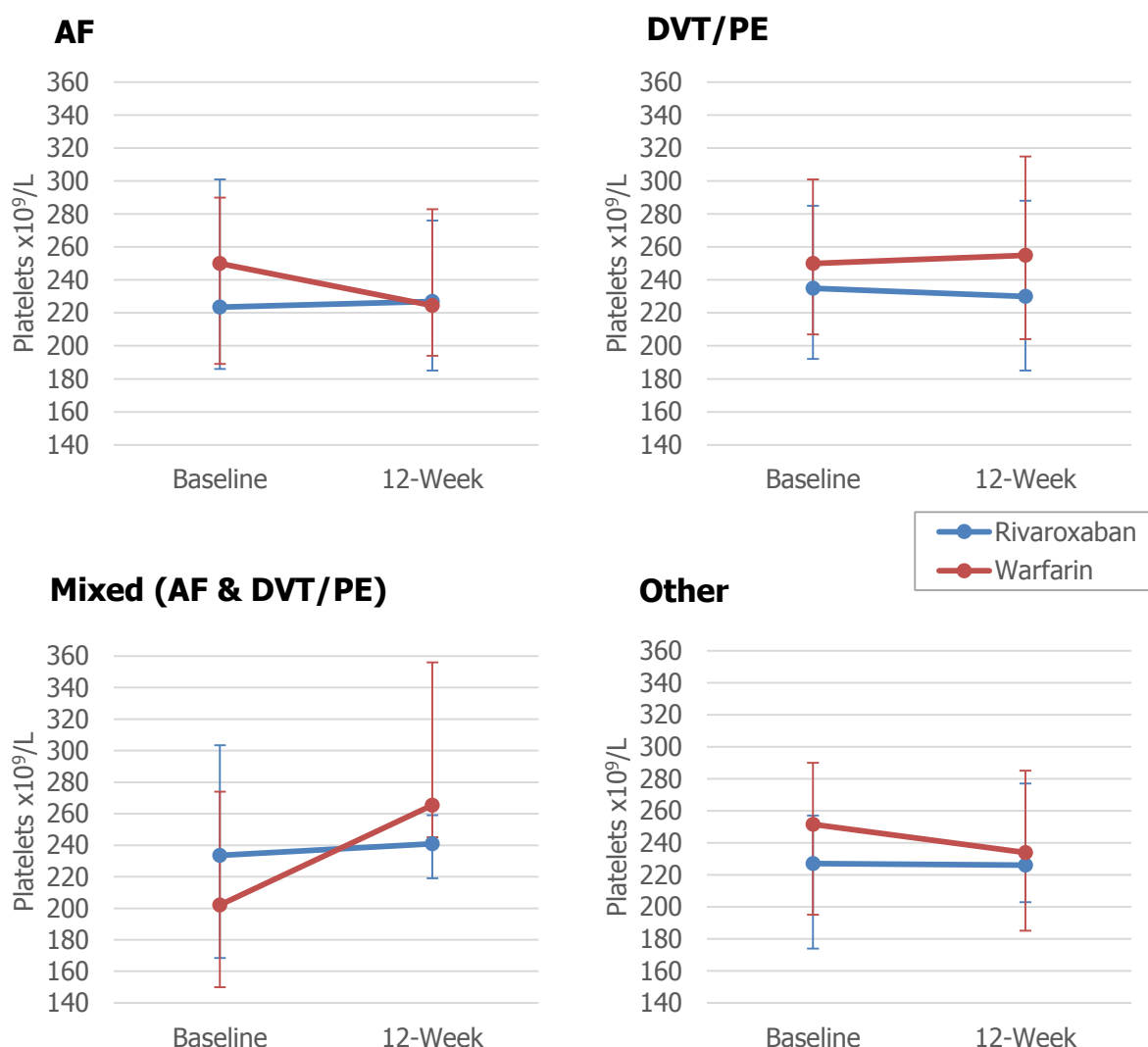
**Note:** Platelets (x10<sup>9</sup>/L) guideline normal range 150-450

<sup>a</sup> paired analysis; approach will be dependent on distribution of data variable; where data are Normal, paired t-test will apply; where data are skewed, the median of differences will be calculated as the 50 percentile of all individual differences (change from baseline

(<http://onbiostatistics.blogspot.co.uk/2015/12/median-of-differences-versus-difference.html>)

\* value closest to the end of the 12-week observation period after starting treatment

**Figure 25. Change of Platelets ( $\times 10^9/\text{L}$ ) during 12-week observation period, stratified by indication group**



Investigators were asked to provide results of coagulation parameter values at the time of treatment initiation (Table 111, Figure 26, Figure 27, Figure 28 and Figure 29). Within the rivaroxaban evaluable cohort, where values were provided, median PT (Prothrombin Time) for all indications was 11.5 seconds (IQR 10.7, 13.0); AF 11.8 seconds (11.0, 13.0); DVT/PE 11.4 seconds (10.7, 13.0). Median APTT (activated partial thromboplastin time) for all indications was 27.2 seconds (24.0, 30.9); AF 26.4 seconds (24.0, 30.0); DVT/PE 27.6 seconds (24.1, 30.9). Median Fibrinogen-derived for all indications was 4.2 g/l (3.3, 5.2); AF 3.6 g/l (3.0, 4.3); DVT/PE 4.5 g/l (3.6, 5.4). Median D-Dimer for DVT/PE indications was 2.0 ug FEU/ml (1.1, 4.3). Within the warfarin evaluable cohort, where values were provided, median PT for all indications was 11.3 seconds (IQR 10.6, 13.0); AF 11.4 seconds (10.7, 13.3); DVT/PE 11.3 seconds (10.6, 12.9). Median APTT for all indications was 28.1 seconds (25.0, 31.9); AF 29.0 seconds

(25.0, 32.0); DVT/PE 28.0 seconds (25.0, 31.9). Median Fibrinogen-derived for all indications was 3.9 g/l (3.0, 4.8); AF 3.4 g/l (2.9, 4.3); DVT/PE 4.1 g/l (3.2, 5.0). Median D-Dimer for DVT/PE indications was 1.4 ug FEU/ml (0.9, 4.8). Since the proportion of patients with missing information is high, caution is recommended in generalising results to similar groups of treated patients.

**Table 111. Coagulation parameter values present at the time of treatment initiation with rivaroxaban or warfarin, by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

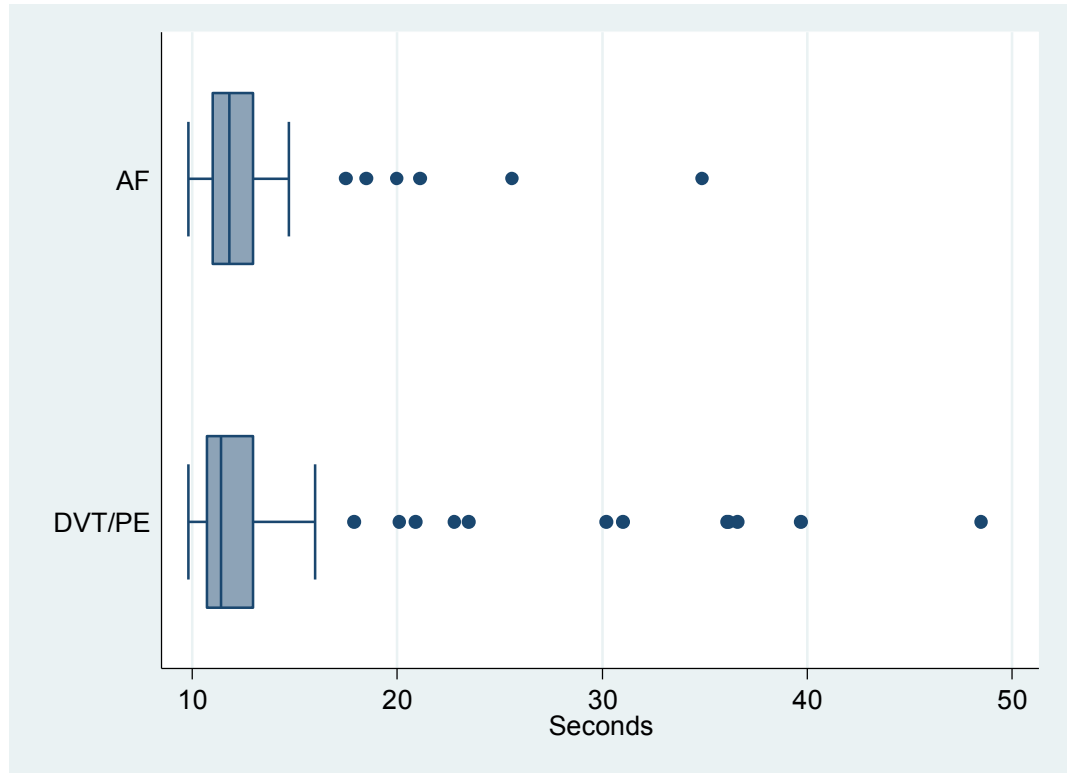
Clotting parameter [median (IQR)]	Rivaroxaban				
	AF	DVT/PE	Mixed (AF & DVT/PE)	Other	Total
PT (seconds)	11.8 (11.0, 13.0) N=74	11.4 (10.7, 13.0) N=327	- N=4	- N=2	11.5 (10.7, 13.0) N=407
APTT (seconds)	26.4 (24.0, 30.0) N=62	27.6 (24.1, 30.9) N=298	- N=3	- N=2	27.2 (24.0, 30.9) N=365
Fibrinogen derived (g/l)	3.6 (3.0, 4.3) N=39	4.5 (3.6, 5.4) N=152	- N=2	- N=1	4.2 (3.3, 5.2) N=194
D-Dimer (if DVT) ug FEU/ml	n/a	2.0 (1.1, 4.3) N=77	- N=0	n/a	2.0 (1.1, 4.3) N=77

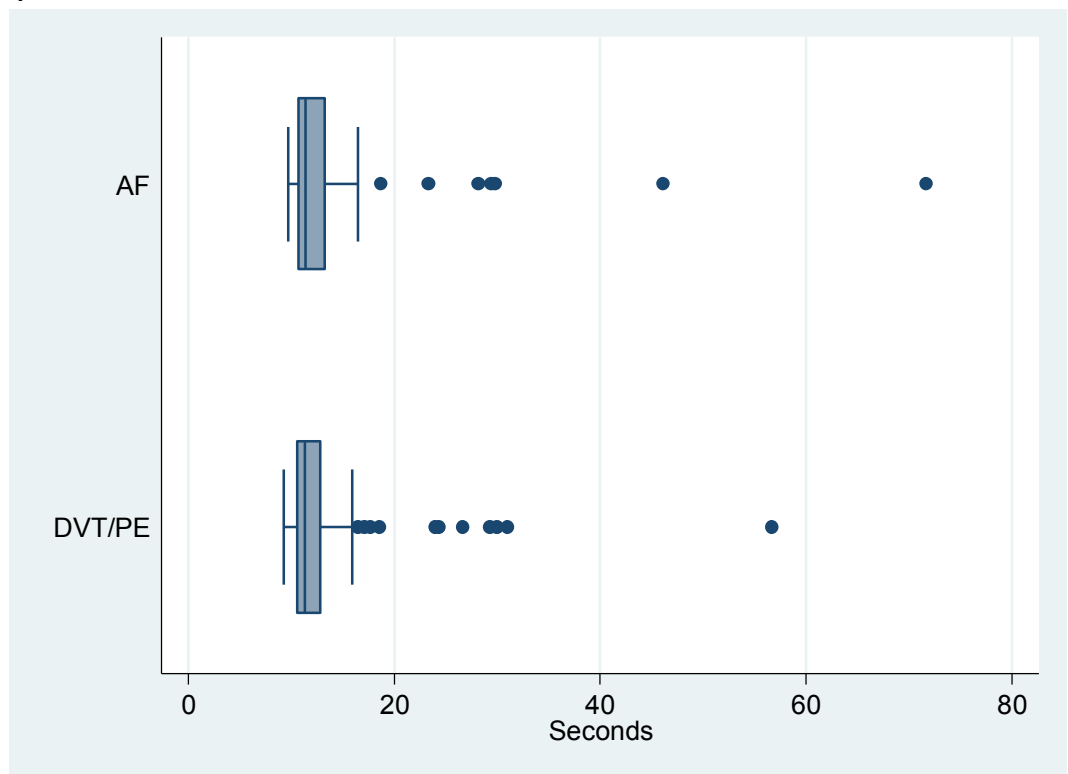
Clotting parameter [median (IQR)]	Warfarin				
	AF	DVT/PE	Mixed (AF & DVT/PE)	Other	Total
PT (seconds)	11.4 (10.7, 13.3) N=134	11.3 (10.6, 12.9) N=306	- N=2	- N=4	11.3 (10.6, 13.0) N=446
APTT (seconds)	29.0 (25.0, 32.0) N=101	28.0 (25.0, 31.9) N=264	- N=1	- N=3	28.1 (25.0, 31.9) N=369
Fibrinogen derived (g/l)	3.4 (2.9, 4.3) N=78	4.1 (3.2, 5.0) N=147	- N=1	- N=2	3.9 (3.0, 4.8) N=228
D-Dimer (if DVT) ug FEU/ml	n/a	1.4 (0.9, 4.8) N=83	- N=1	n/a	1.4 (0.9, 4.8) N=84

**Figure 26. Boxplot Coagulation parameters (PT) at the time of treatment initiation a) rivaroxaban and b) warfarin cohort, by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

a)



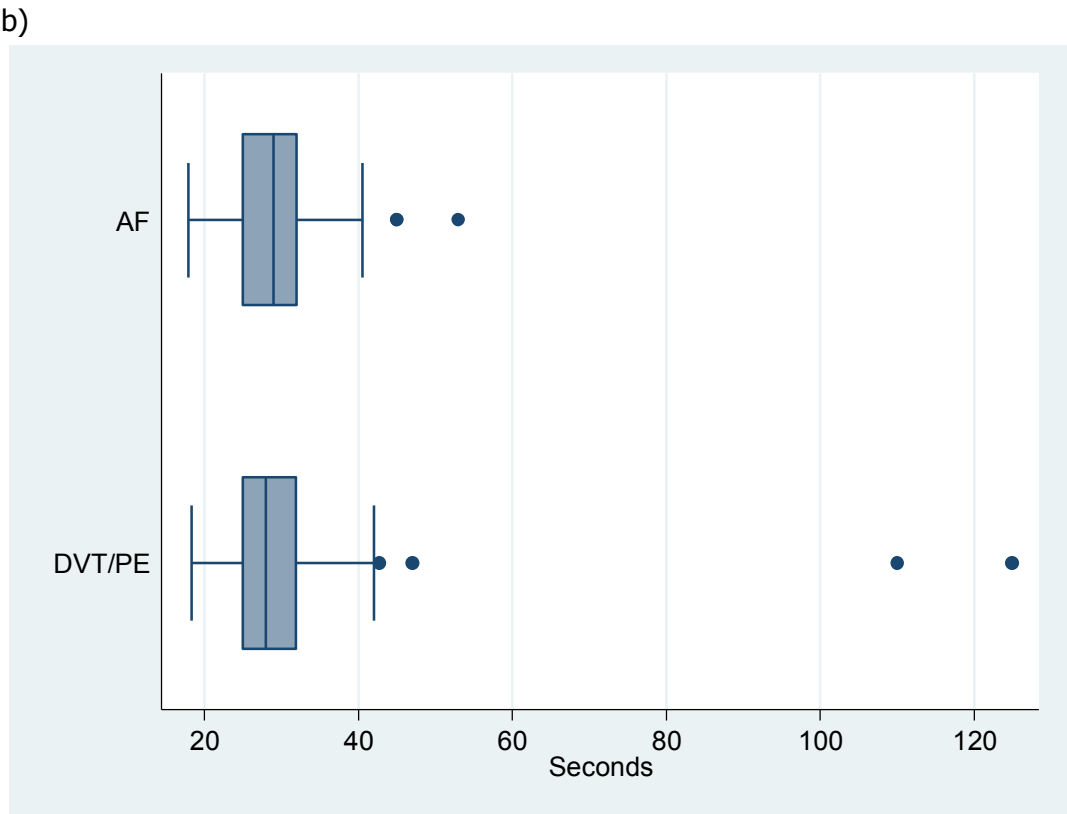
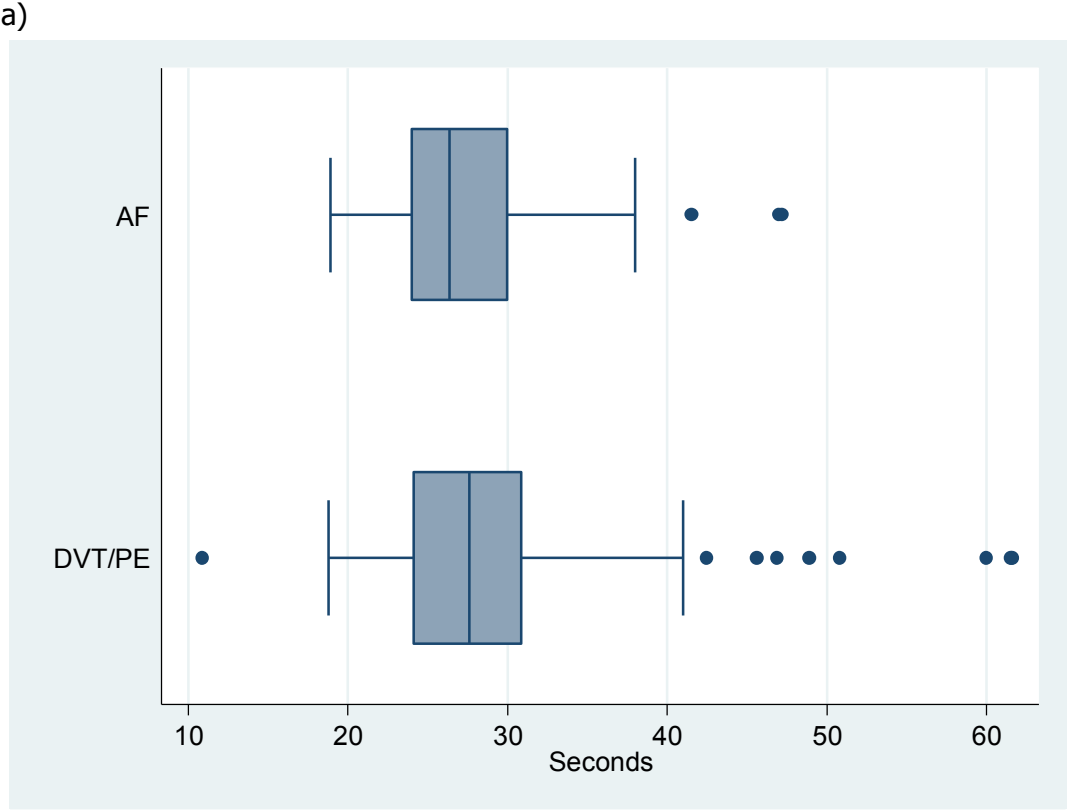
b)



\*Too few observations to plot Mixed (AF & DVT/PE) and Other indications

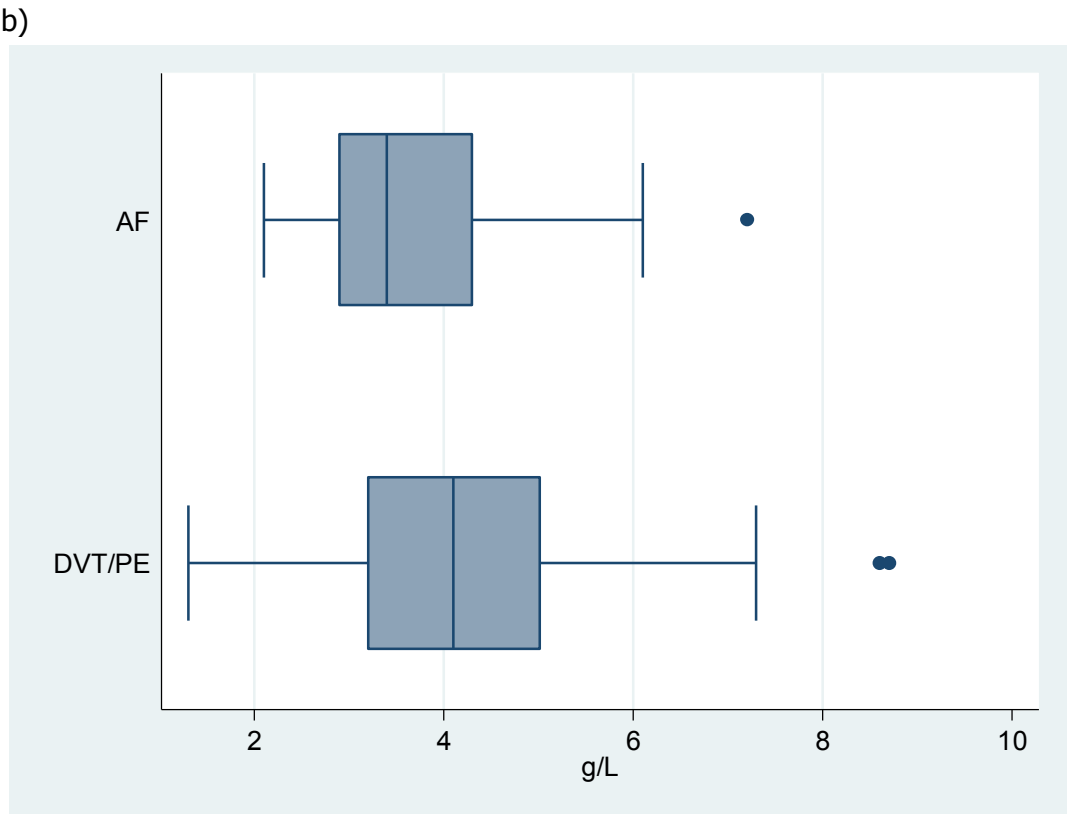
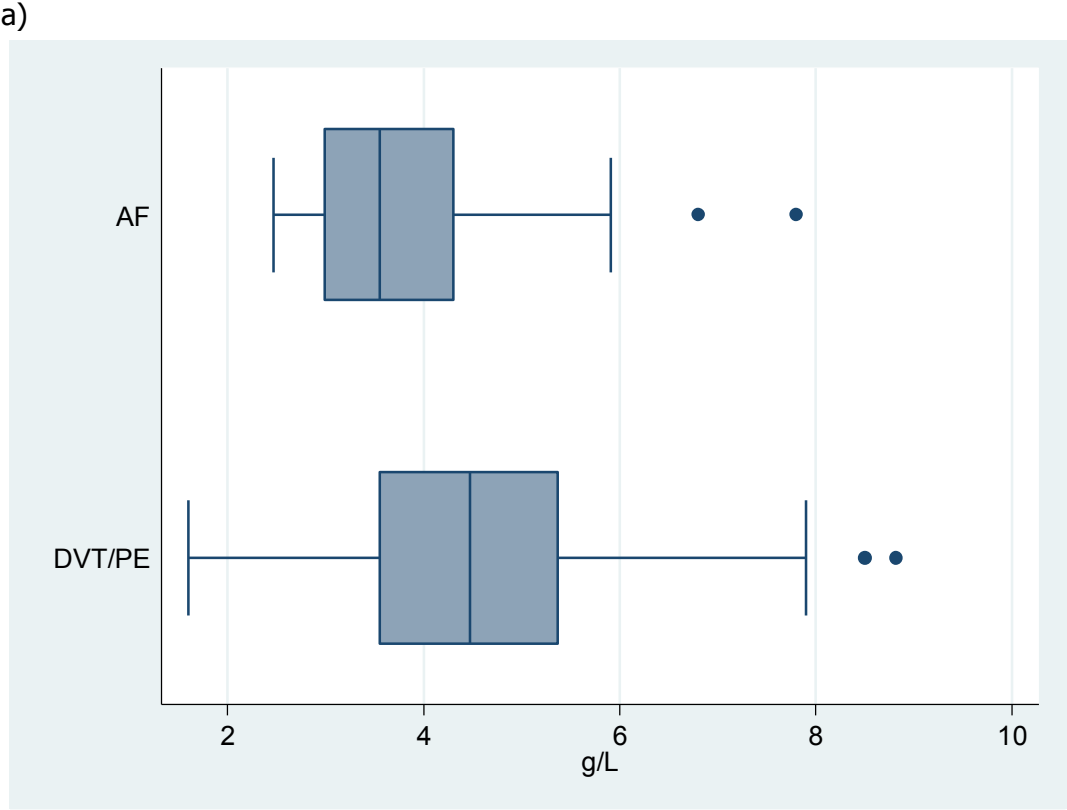


**Figure 27. Boxplot Coagulation parameters ( APPT) at the time of treatment initiation a) rivaroxaban and b) warfarin cohort, by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**



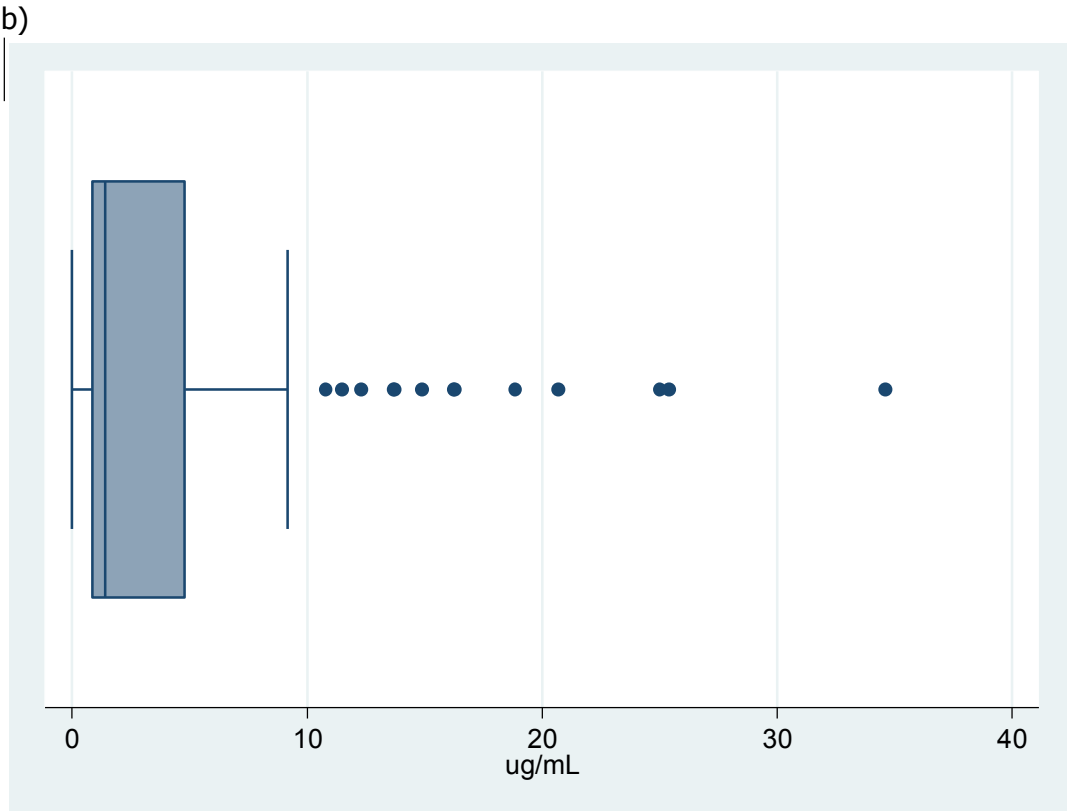
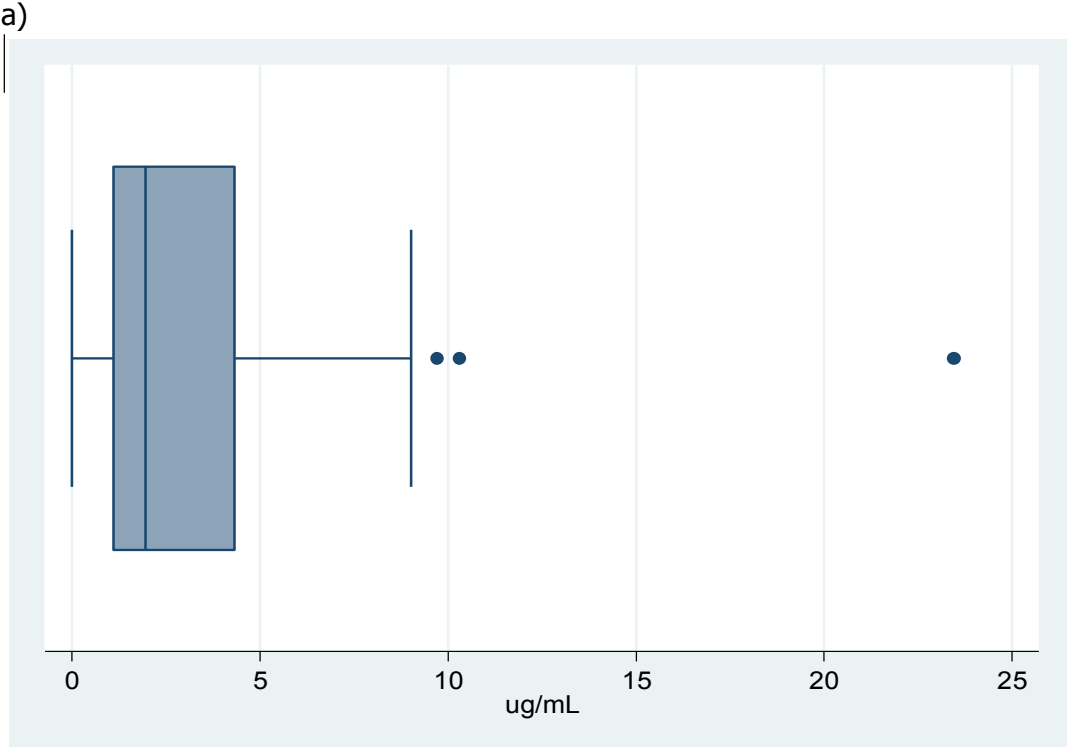
\*Too few observations to plot Mixed (AF & DVT/PE) and Other indications

**Figure 28.   Boxplot Coagulation parameters (Fibrinogen) at the time of treatment initiation a) rivaroxaban and b) warfarin cohort, by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**



\*Too few observations to plot Mixed (AF & DVT/PE) and Other indications

**Figure 29.   Boxplot Coagulation parameters (D-Dimer) at the time of treatment initiation a) rivaroxaban and b) warfarin cohort, by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

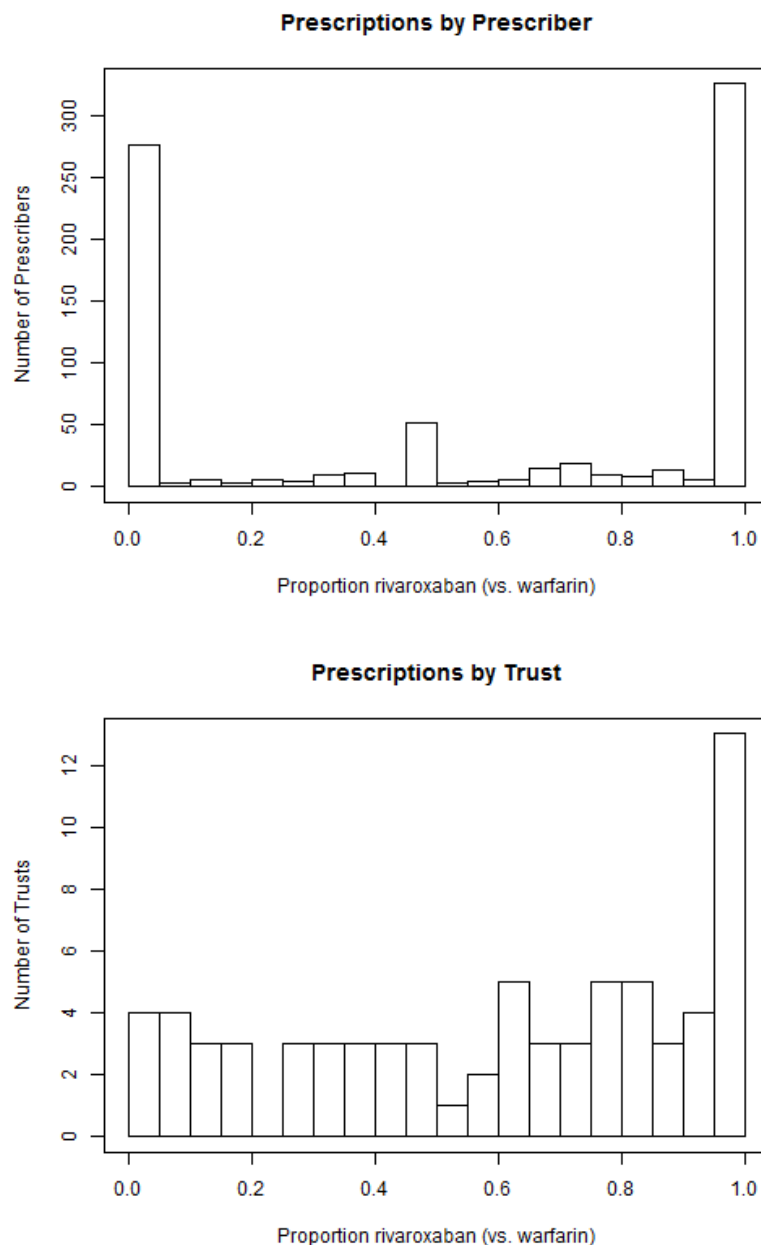


\*Too few observations to plot Mixed (AF & DVT/PE) indication

### 10.6.2 Multi-level modelling analysis

Following the data processing described in the study report in Appendix 3, the data available for multilevel regression analysis included 3574 patients, 1468 (41.1%) of whom were prescribed warfarin and 2106 (58.9%) rivaroxaban. These patients were associated with 780 different prescribers, with between 1 and 115 patients within a prescriber (mean of 4.6). There were 73 trusts, with between 1 and 47 prescribers within a trust (mean of 11). The proportion of patients with rivaroxaban vs warfarin prescriptions reported by prescriber and trust is visualised in Figure 30.

**Figure 30. Histograms of the proportion of patients prescribed with rivaroxaban (vs. warfarin) by prescriber and trust.**



Of the 3574 patients with complete data available for analysis, the majority had a clinical indication of DVT/PE (n=2014; 56.4%), closely followed by AF (n=1474; 41.2%), with a small proportion of patients having indications of Mixed (i.e., AF & DVT/PE composite: n=41; 1.1%) and Other (i.e., off-label: n=45; 1.3%) (Table 113).

Summaries of the numbers of patients per prescriber, and patients and prescribers per trust, by indication, are provided in Table 112.

**Table 112. Summaries of the numbers of patients, prescribers and trusts, by clinical indication**

Indication	Summary	Mean	Median (Range)
<b>Overall</b>	Patients by Trust (n=73)	49.0	35 (1-254)
	Prescribers (n=780) by Trust	11.0	7 (1-47)
	Patients (n=3574) by Prescriber	4.6	1 (1-115)
<b>DVT/PE</b>	Patients by Trust (n=64)	31.5	22 (1-150)
	Prescribers (n=569) by Trust	9.1	5.5 (1-35)
	Patients (n=2014) by Prescriber	3.5	1 (1-76)
<b>Mixed</b>	Patients by Trust (n=26)	1.6	1 (1-3)
	Prescribers (n=37) by Trust	1.4	1 (1-3)
	Patients (n=41) by Prescriber	1.1	1 (1-3)
<b>AF</b>	Patients by Trust (n=62)	23.8	15 (1-148)
	Prescribers (n=336) by Trust	5.5	3 (1-21)
	Patients (n=1474) by Prescriber	4.4	1 (1-79)
<b>Other</b>	Patients by Trust (n=23)	2	2 (1-6)
	Prescribers (n=36) by Trust	1.6	1 (1-5)
	Patients (n=45) by Prescriber	1.2	1 (1-4)

The observed prescription rates of rivaroxaban versus warfarin (per patient), by indication group, are given in Table 113.

**Table 113. Prescription rates (rivaroxaban versus warfarin) by patient clinical indication**

	Warfarin		Prescription Rivaroxaban		Total	
	n	%	n	%	n	%
<b>DVT/PE</b>	800	39.7	1214	60.3	2014	100.0
<b>Mixed</b>	22	53.7	19	46.3	41	100.0
<b>AF</b>	618	41.9	856	58.1	1474	100.0
<b>Other</b>	28	62.2	17	37.8	45	100.0
<b>Overall</b>	1468	41.1	2106	58.9	3574	100.0

#### **10.6.2.1 Univariate Analyses**

In general, the prescriber and trust-level characteristics were constant within a prescriber and trust, respectively. For example, a male prescriber always had a prescriber gender of male, across all of their patients. However, for the prescriber

professional years registered (experience), this variable varied slightly between patients within a prescriber, depending on the time in the study that the prescriber saw that patient. Therefore, this variable was considered in the patient univariate analyses, despite experience being a prescriber characteristic.

#### 10.6.2.1.1 **All Indications**

The univariate analysis results are provided in Appendix 3. In particular, the overall univariate results (across all indications) are shown in Table 6, Table 7 and Table 8 of the appendix (Appendix 3) for the patient, prescriber and trust-level characteristics, respectively. Effects that were significant at the 5% level and comparisons between categorical variable groupings where the CI does not contain one are highlighted in particular.

For the patient-level characteristics, the univariate analyses across all indications provide some evidence of patients with prior/at baseline history of congestive heart failure, hypertension (CHADS2VASC) and bleeding predisposition, and a CHADS2VASC score group of moderate or high compared with low risk being associated with a lower odds of being prescribed rivaroxaban. A patient with a clinical indication of Other (off-label) is also estimated to have a lower odds of being prescribed rivaroxaban compared with DVT/PE. Conversely, patients with prior substance misuse, and a patient-specific prescriber reason for prescribing of lifestyle choice, non-adherence with prior anticoagulant, side-effects with prior anticoagulant, patient preference, and poor control, are estimated to have a higher odds of being prescribed rivaroxaban.

For the prescriber-level characteristics, the univariate analyses across all indications provide some evidence of prescribers with a clinical specialism of care of elderly, endocrinology, gastroenterology, other and respiratory being associated with a lower odds of prescribing rivaroxaban than a haematology specialism (which was the most common clinical specialism observed). Prescribers with a higher percentage of patients with a reason for prescribing of expert guidelines and potential ease of reversibility were also estimated to have a lower odds of prescribing rivaroxaban.

At the trust level, across all indications, there was no evidence (at the 5% level) that any of the characteristics considered were individually associated with the odds of prescribing rivaroxaban.

#### 10.6.2.1.2 **DVT/PE**

The univariate results for the DVT/PE clinical indication are given in Appendix 3 (Table 9, Table 10 and Table 11) for the patient, prescriber and trust-level characteristics, respectively.

For the patient-level characteristics, the univariate analyses for DVT/PE provide some evidence of patients with prior/at baseline history of CHF, vascular disease and hypertension (CHADS2VASC), and a higher CHADS2VASC score, or CHADS2VASC score group of high compared with low risk, being associated with a lower odds of being prescribed rivaroxaban. Whereas, patients with a patient-specific prescriber reason for prescribing of lifestyle choice, side-effects with prior anticoagulant, patient preference, and poor control, are estimated to have a higher odds of being prescribed rivaroxaban.

For the prescriber-level characteristics, the univariate analyses for DVT/PE provide some evidence of prescribers with a clinical specialism of care of elderly, endocrinology, gastroenterology, general medicine, other and respiratory being associated with a lower odds of prescribing rivaroxaban than a haematology specialism (which was the most common observed). Prescribers with a higher percentage of patients with a reason for prescribing of clinical judgement and potential ease of reversibility were also estimated to have a lower odds of prescribing rivaroxaban. Whereas, prescribers with specialist status, and prescribers with a higher percentage of patients with a reason for prescribing of patient group direction were estimated to have a higher odds of prescribing rivaroxaban.

At the trust level, for DVT/PE, trusts that had a higher percentage of hospitals that are other hospitals (i.e., not general or teaching hospitals) were estimated to have a higher odds of prescribing rivaroxaban.

#### 10.6.2.1.3 **AF**

The univariate results for the AF clinical indication are given in Appendix 3 (Table 12, Table 13 and Table 14) for the patient, prescriber and trust-level characteristics, respectively.

For the patient-level characteristics, the univariate analyses for AF provide some evidence of patients with a prior/at baseline history of CVA and a patient-specific prescriber reason for prescribing of lifestyle choice, non-adherence with prior anticoagulant, side-effects with prior anticoagulant, patient preference, and poor control, having a higher odds of being prescribed rivaroxaban.

For the prescriber-level characteristics, the univariate analyses for AF provide some evidence of prescribers with a clinical specialism of anticoagulation being associated with a lower odds of prescribing rivaroxaban than a haematology specialism (which was the most common observed) and similarly for prescribers with nurse as their professional qualification rather than medic. Prescribers with a higher percentage of patients with a reason for prescribing of NICE recommendations, expert guidelines, hospital formulary and potential ease of reversibility, and prescribers with a higher number of professional years registered were also estimated to have a lower odds of prescribing rivaroxaban. Prescribers with a higher percentage of patients with a reason for prescribing of clinical judgement and prescribers with a specialism of stroke compared with haematology were estimated to have a higher odds of prescribing rivaroxaban.

At the trust level, for AF, there was insufficient evidence (at the 5% level) that any of the characteristics considered were individually associated with the odds of prescribing rivaroxaban.

#### ***10.6.2.2 Multiple Variable Analyses***

A summary of the results of the multiple variable multilevel logistic regression modelling across all indications, DVT/PE and AF is provided in Table 114, Table 115 and Table 116 respectively. This includes the intercept coefficient, ORs for the fixed effects (patient, prescriber and trust characteristics), variance components, median odds ratios (MOR) for the model fitted in each step, as well as the proportional change in the variance (PCV) between models.



**Table 114. Summary of the results of the multiple variable multilevel logistic regression analysis for all indications**

		Step 1: Empty Model	Step 2: + Patient Characteristics	Step 3: + Prescriber Characteristics	Step 4: + Trust Characteristics
Explanatory Variables; Fixed Effects					
Intercept (SE) [95% CI]		0.6 (0.3) [0.1, 1.1]	-0.2 (0.3) [-0.7, 0.4]	-0.3 (0.3) [-0.8, 0.2]	-1.0 (0.4) [-1.8, -0.3]
Patient Characteristics; OR (95% CI)					
Patient-specific prescriber reason for prescribing: non-adherence with prior anticoagulant	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		20.3 (4.1, 70.7)	22.6 (5.2, 74.7)	22.8 (4.7, 81.8)
Prior/at baseline history of congestive heart failure	No		Reference; LRT p=0.041	Reference; LRT p=0.041	Reference; LRT p=0.047
	Yes		0.7 (0.4, 1.0)	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)
Prior/at baseline history of CVA	No		Reference; LRT p=0.042	<dropped>	
	Yes		1.4 (1.0, 1.9)		
Prior/at baseline history of hypertension	No		Reference; LRT p=0.028	Reference; LRT p=0.024	Reference; LRT p=0.026
	CHADS2VASC		0.7 (0.6, 1.0)	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)
	CHADS2VASC & HAS-BLED		1.1 (0.8, 1.4)	1.1 (0.9, 1.5)	1.1 (0.8, 1.5)
Indication	DVT/PE		Reference; LRT p=0.017	Reference; LRT p=0.017	Reference; LRT p=0.018
	Mixed		0.4 (0.2, 1.1)	0.4 (0.2, 1.1)	0.4 (0.12, 1.0)
	AF		0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	1.0 (0.7, 1.3)
	Other		0.3 (0.1, 0.7)	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)
Patient-specific prescriber reason for prescribing: lifestyle choice	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		49.2 (28.4, 73.4)	50.4 (29.2, 76.3)	50.8 (29.4, 77.6)
Patient-specific prescriber reason for prescribing: poor control	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		65.2 (9.2, 171.2)	68.3 (9.7, 157.4)	72.6 (12.2, 169.7)
Patient-specific prescriber reason for prescribing: patient preference	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		4.0 (2.1, 7.2)	4.6 (2.5, 8.1)	4.7 (2.6, 7.9)
Patient-specific prescriber reason for prescribing: side-effects with prior anticoagulant	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		34.5 (10.1, 80.5)	41.6 (13.1, 104.8)	43.5 (13.9, 109.7)
Prescriber Characteristics					

		Step 1: Empty Model	Step 2: + Patient Characteristics	Step 3: + Prescriber Characteristics	Step 4: + Trust Characteristics
Percentage of patients with reason for prescribing: expert guidelines				Reference; LRT p=0.008 1.0 (1.0, 1.0)	Reference; LRT p=0.004 1.0 (1.0, 1.0)
Percentage of patients with reason for prescribing: potential ease of reversibility				Reference; LRT p<0.001 0.9 (0.9, 1.0)	Reference; LRT p<0.001 0.9 (0.9, 1.0)
Type of Trust	Acute Foundation Integrated				Reference; LRT p=0.02 3.0 (1.2, 7.3) 0.1 (0.0, 2.9)
Variance Components					
Between-prescriber variance (SE)		1.8 (0.1)	1.8 (0.1)	1.6 (0.1)	1.7 (0.1)
SD (95% CI)		1.4 (1.0, 1.4)	1.3 (1.0, 1.4)	1.3 (0.9, 1.4)	1.3 (0.9, 1.4)
MOR		3.6	3.6	3.4	3.5
PCV			-1.9%	-8.8%	2.4%
Between-Trust variance (SE)		3.7 (0.2)	3.9 (0.2)	3.4 (0.23)	2.7 (0.2)
SD (95% CI)		1.9 (1.4, 2.3)	2.0 (1.5, 2.4)	1.8 (1.4, 2.2)	1.7 (1.2, 1.9)
MOR		6.2	6.5	5.8	4.9
PCV			4.7%	-12.7%	-18.7%

CI = Confidence Interval (Parametric Bootstrap); SE = Standard Error (Wald); MOR = Median Odds Ratio; PCV = Proportional Change in the Variance; LRT = Likelihood Ratio Test

**Table 115. Summary of the results of the multiple variable multilevel logistic regression analysis for DVT/PE**

		Step 1: Empty Model	Step 2: + Patient Characteristics	Step 3: + Prescriber Characteristics	Step 4: + Trust Characteristics
Explanatory Variables; Fixed Effects					
Intercept (SE) [95% CI]		0.6 (0.3); [0.0, 1.1]	-0.2 (0.3); [-0.8, 0.4]	-0.7 (0.3); [-1.3, -0.0]	-1.2 (0.4); [-2.0, -0.4]
Patient Characteristics; OR (95% CI)					
Prior/at baseline history of congestive heart failure	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		0.3 (0.2, 0.6)	0.3 (0.1, 0.6)	0.3 (0.2, 0.6)
Patient-specific prescriber reason for prescribing: lifestyle choice	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		71.1 (32.8, 114.7)	82.8 (38.5, 141.6)	82.6 (37.7, 149.6)
Patient-specific prescriber reason for prescribing: poor control	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		29.9 (2.7, 70.4)		27.9 (2.2, 48.7)
Patient-specific prescriber reason for prescribing: patient preference	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		3.0 (1.5, 5.4)	3.5 (1.8, 6.6)	3.7 (1.8, 7.3)
Patient-specific prescriber reason for prescribing: side-effects with prior anticoagulant	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		31.8 (6.4, 87.7)	42.5 (6.9, 134.9)	45.78 (8.9, 103.1)
Percentage of patients with reason for prescribing: clinical judgement				Reference; LRT p=0.020 1.0 (1.0, 1.0)	Reference; LRT p=0.019 1.0 (1.0, 1.0)
Percentage of patients with reason for prescribing: potential ease of reversibility				Reference; LRT p<0.001 1.0 (0.9, 1.0)	Reference; LRT p<0.001 1.0 (1.0, 1.0)
Specialist status	No			Reference; LRT p=0.029 1.7 (1.1, 2.6)	<dropped>
	Yes				
Trust Characteristics					
Percentage of hospitals within Trust that are other hospitals					Reference; LRT p=0.003 1.0 (1.0, 1.0)
Type of Trust	Acute				Reference; LRT p=0.019 4.0 (1.5, 9.9) 0.3 (0.1, 6.2)
	Foundation				
	Integrated				
Variance Components					
Between-prescriber variance (SE)		1.1 (0.1)	1.2 (0.2)	1.0 (0.2)	1.0 (0.2)

	Step 1: Empty Model	Step 2: + Patient Characteristics	Step 3: + Prescriber Characteristics	Step 4: + Trust Characteristics
SD (95% CI)	1.1 (0.6, 1.1)	1.1 (0.5, 1.2)	1.0 (0.5, 1.1)	1.0 (0.5, 1.1)
MOR	2.7	2.8	2.6	2.6
PCV		3.8%	-15.4%	3.4%
Between-Trust variance (SE)	4.2 (0.3)	4.1 (0.3)	4.0 (0.3)	2.8 (0.2)
SD (95% CI)	2.0 (1.4, 2.5)	2.0 (1.4, 2.4)	2.0 (1.4, 2.4)	1.7 (1.1, 2.0)
MOR	7.0	7.0	6.8	4.9
PCV		-0.6%	-2.9%	-30.2%

CI = Confidence Interval (Parametric Bootstrap); SE = Standard Error (Wald); MOR = Median Odds Ratio; PCV = Proportional Change in the Variance; LRT = Likelihood Ratio Test

**Table 116. Summary of the results of the multiple variable multilevel logistic regression analysis for AF**

		Step 1: Empty Model	Step 2: + Patient Characteristics	Step 3: + Prescriber Characteristics	Step 4: + Trust Characteristics	Step 5: + Disease Scores (Sensitivity Analysis)
Explanatory Variables; Fixed Effects						
Intercept (SE); [95% CI]		0.5 (0.3) [-0.2, 1.1]	-0.8 (0.4) [-1.6, -0.2]	-0.6 (0.4) [-1.3, 0.1]	-0.1 (0.7) [-1.3, 0.7]	0.2 (0.7) [-1.1, 1.2]
Patient Characteristics OR (95% CI)						
Patient-specific prescriber reason for prescribing: non-adherence with prior anticoagulant	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		47.9 (4.1, 98.9)	40.9 (3.1, 71.7)	46.1 (4.0, 55.6)	48.2 (4.4, 70.6)
Prior/at baseline history of CVA	No		Reference; LRT p=0.003	Reference; LRT p=0.005	Reference; LRT p=0.013	Reference; LRT p=0.002
	Yes		2.3 (1.4, 3.5)	2.1 (1.4, 3.2)	2.0 (1.3, 3.0)	2.4 (1.6, 3.8)
Prior/at baseline history of hypertension (HAS-BLED)	No		Reference; LRT p=0.045	Reference; LRT p=0.0312	Reference; LRT p=0.029	Reference; LRT p=0.004
	Yes		1.5 (1.1, 2.3)	1.6 (1.1, 2.2)	1.6 (1.1, 2.3)	2.1 (1.3, 3.2)
HAS-BLED score						Reference; LRT p=0.047 0.8 (0.7, 1.0)
Patient-specific prescriber reason for prescribing: lifestyle choice	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		20.9 (9.8, 37.2)	19.2 (9.1, 34.0)	20.1 (9.2, 35.8)	20.1 (9.6, 36.4)
Patient-specific prescriber reason for prescribing: poor control	No		Reference; LRT p<0.001	Reference; LRT p=0.001	Reference; LRT p=0.001	Reference; LRT p=0.001
	Yes		30.5 (2.9, 64.1)	28.7 (3.3, 59.2)	27.3 (2.9, 71.6)	25.9 (2.8, 56.5)
Patient-specific prescriber reason for prescribing: patient preference	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p=0.001	Reference; LRT p=0.001
	Yes		11.7 (3.0, 38.4)	12.4 (2.8, 34.7)	11.7 (2.7, 40.2)	11.6 (3.0, 39.9)
Patient-specific prescriber reason for prescribing: side-effects with prior anticoagulant	No		Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001	Reference; LRT p<0.001
	Yes		30.21 (5.5, 91.2)	25.3 (5.0, 77.9)	25.1 (4.6, 70.3)	27.0 (5.6, 81.2)
Prescriber Characteristics						

		Step 1: Empty Model	Step 2: + Patient Characteristics	Step 3: + Prescriber Characteristics	Step 4: + Trust Characteristics	Step 5: + Disease Scores (Sensitivity Analysis)
Professional years registered				Reference; LRT p=0.020 1.0 (0.1.0, 1.0)	<dropped>	<dropped>
Percentage of patients with reason for prescribing: NICE recommendations				Reference; LRT p=0.0013 1.0 (0.1.0, 1.0)	Reference; LRT p=0.0003 1.0 (0.1.0, 1.0)	Reference; LRT p=0.0003 1.0 (0.1.0, 1.0)
Percentage of patients with reason for prescribing: potential ease of reversibility				Reference; LRT p=0.003 1.0 (0.1.0, 1.0)	Reference; LRT p=0.002 0.9 (0.9, 1.0)	Reference; LRT p=0.002 0.9 (0.9, 1.0)
Professional qualification	Medic			Reference; LRT p=0.007 0.2 (0.1, 0.7)	Reference; LRT p<0.001 0.1 (0.0, 0.5)	Reference; LRT p<0.001 0.1 (0.0, 0.4)
	Nurse					
Trust Characteristics						
Geographic region	East of England				Reference; LRT p=0.015	Reference; LRT p=0.0114
	London				0.1 (0.0, 0.5)	0.01 (0.0, 0.6)
	North West				0.6 (0.2, 3.1)	0.7 (0.12, 3.5)
	South East				1.6 (0.4, 8.0)	1.7 (0.4, 7.9)
	South West				2.7 (0.8, 10.4)	2.9 (0.7, 12.3)
	West Midlands				0.5 (0.1, 2.8)	0.5 (0.1, 3.3)
	Yorkshire and Humber				0.6 (0.2, 3.6)	0.7 (0.1, 3.5)
Variance Components						
Between-prescriber variance (SE)		2.2 (0.2)	2.3 (0.2)	2.1 (0.2)	2.4 (0.2)	2.4 (0.2)
SD (95% CI)		1.5 (0.9, 1.7)	1.5 (0.9, 1.7)	1.4 (0.8, 1.6)	1.5 (0.9, 1.8)	1.5 (0.9, 1.8)
MOR		4.1	4.3	3.9	4.4	4.3
PCV			5.2%	-11.4%	16.3%	-1.3%
Between-Trust variance (SE)		4.0 (0.3)	3.8 (0.3)	3.2 (0.3)	1.7 (0.3)	1.6 (0.3)
SD (95% CI)		2.0 (1.4, 2.4)	2.0 (1.3, 2.4)	1.8 (1.1, 2.3)	1.3 (0.5, 1.6)	1.3 (0.2, 1.5)
MOR		6.8	6.5	5.5	3.5	3.4
PCV			-5.2%	-15.9%	-47.2%	-4.4%

CI = Confidence Interval (Parametric Bootstrap); SE = Standard Error (Wald); MOR = Median Odds Ratio; PCV = Proportional Change in the Variance; LRT = Likelihood Ratio Test

#### 10.6.2.2.1 **All Indications**

The PCV between models suggests that accounting for possible differences in the patient characteristics has limited impact on the variance explained by differences in prescribing practice between prescribers and between trusts. However, the addition of the prescriber effects was estimated to reduce the prescriber and trust variance components, and the addition of the trust effects was estimated to further reduce the trust variance component.

For all indications, variability in prescribing was shown to be dominated by the variability at the trust level compared with the prescriber level – in each model the between-trust variance (final model variance: 2.7) is estimated to be greater than the between-prescriber variance (final model variance: 1.7).

Though the MOR for the trust variance component (final model MOR: 4.9) is large relative to a number of the fixed patient, prescriber and trust effects, a larger effect on the odds of prescribing rivaroxaban was estimated for patients with a patient-specific prescriber reason for prescribing of non-adherence with prior anticoagulant, lifestyle choice, poor control and side-effects with prior anticoagulant (final model OR: 22.8, 50.8, 72.6 and 43.5, respectively, in favour of rivaroxaban), having controlled for the other characteristics available, although these larger odds applied to a small subset of patients within the study.

Other variables that are estimated to have a relatively large, independent effect on the odds of prescribing rivaroxaban vs. warfarin are the patient characteristic prior/at baseline history of congestive heart failure (final model OR: 0.7, in favour of warfarin) and an indication of Other (off-label) rather than DVT/PE (0.3, in favour of warfarin); and the trust characteristic type of trust (3.0 for foundation vs. acute).

#### 10.6.2.2.2 **DVT/PE**

The PCV between models, suggests that accounting for possible differences in the patient characteristics has limited impact on the variance explained by differences in prescribing practice between prescribers and between trusts. However, the addition of the prescriber effects is estimated to reduce the prescriber variance component, and the addition of the trust effects is estimated to reduce the trust variance component.

For the DVT/PE patient subgroup, variability in prescribing was shown to be dominated by the variability at the trust level compared with the prescriber level – in each model the between-trust variance (final model variance: 2.8) was estimated to be greater than the between-prescriber variance (final model variance: 1.0).

Though, the MOR for the trust variance component (final model MOR: 4.9) is large relative to many of the fixed patient, prescriber and trust effects, a larger effect on the odds of prescribing rivaroxaban was estimated for the small number of patients with a patient-specific prescriber reason for prescribing of lifestyle choice, poor control and side-effects with prior anticoagulant (final model OR: 82.6, 27.9 and 45.8, respectively, in favour of rivaroxaban), having controlled for the other characteristics available.

Other variables that are estimated to have a relatively large, independent effect on the odds of prescribing rivaroxaban vs warfarin are the patient characteristic prior/at baseline history of congestive heart failure (final model OR: 0.3, in favour of warfarin), a patient-specific prescriber reason for prescribing of patient preference (3.7, in favour of rivaroxaban); and the trust characteristic type of trust (4.0 for foundation vs acute).

#### 10.6.2.2.3 **AF**

The PCV between models suggests that accounting for possible differences in the patient characteristics has limited impact on the variance explained by differences in prescribing practice between prescribers and between trusts. However, the addition of the prescriber effects was estimated to reduce the prescriber and trust variance components, and the addition of the trust effects was estimated to further reduce the trust variance component (though, the prescriber variance component estimate increases in this step).

For the final model, having accounted for the trust effects, variability in prescribing was estimated to be dominated by the variability at the prescriber level (final model variance: 2.4) compared with the trust level (final model variance: 1.7).

Though, the MORs for the prescriber and trust variance components (final model MOR: 4.4 and 3.5, respectively) are smaller than many of the fixed patient, prescriber and trust effects. For example, we see a larger, independent effect on the odds of prescribing rivaroxaban for patients with a patient-specific prescriber reason for prescribing of non-adherence with prior anticoagulant, lifestyle choice, poor control, patient preference and side-effects with prior anticoagulant (final model OR: 46.1, 20.1, 27.3, 11.7 and 25.1, respectively, in favour of rivaroxaban); the prescriber characteristic nurse rather than medic as a professional qualification (0.1, in favour of warfarin); and the trust characteristic region being London versus East of England (0.1, in favour of warfarin).



### **10.6.2.3 Sensitivity Analyses**

#### **10.6.2.3.1 Interactions with Indication**

In each modelling step, for the overall model (across all indications), interactions with the fixed effects retained in the model were considered as additional candidate variables in the modelling.

The results of this sensitivity analysis, in terms of the estimated variance components, were very similar to those from the main, overall model (final model variance: 1.7 and 2.8 at the prescriber and trust levels for the sensitivity analysis, compared with 1.7 and 2.7 for the main model, respectively). Furthermore, the interpretation of the fixed effects, in terms of whether there was evidence of these being associated with higher rivaroxaban or warfarin prescription rates, were broadly consistent with the results obtained in the main analysis (summarised in Table 114, Table 115 and Table 116).

All of those variables retained in the overall model (across all indications) from the main analysis (see Table 114) were also present in the model including interactions with indication, with the same direction of effect (i.e., in favour of rivaroxaban or warfarin), except for patient prior/at baseline history of hypertension which was dropped.

Where interactions with indication were retained in the sensitivity analysis, these were also evident when comparing the main overall results with those stratified by indication. For example, a patient-specific prescriber reason for prescribing of lifestyle choice was estimated to be associated with an increase in the odds of a rivaroxaban prescription, but with a smaller effect for AF than for DVT/PE. This was also evident from the corresponding odds ratios for lifestyle choice for the AF (final model OR: 20.1, 95% CI = 9.2, 35.8) and DVT/PE (82.6, 95% CI = 37.7, 149.6) stratified model results.

Given the consistency of the outputs for this sensitivity analysis with those of the main analysis, tables of these results have not been presented.

#### **10.6.2.3.2 Disease Scores**

A further sensitivity analysis, for each set of modelling results, was also undertaken considering the inclusion of the patient HAS-BLED and CHADS2VASC disease scores. In this case, the disease scores were considered as the combined, grouped variables (no bleed risk/moderate bleed risk/high bleed risk, and no stroke risk/moderate stroke risk/high stroke risk, respectively) and also discrete, count variables, rather than just the individual patient factors that contribute to these scores, which were included in

the main analysis (such as prior/at baseline history of hypertension which features in both scores).

Exploring the inclusion of these scores for each of the final models from the main analysis, only the discrete HAS-BLED score was retained and only for the stratified model for the AF clinical indication. The model estimates for this extended model are given in Table 116. A one point increase in the HAS-BLED score was estimated to be associated with a 19.6% decrease in the odds of a patient being prescribed rivaroxaban (OR: 0.8, 95% CI = 0.7, 1.0). However, it should be noted that the model also includes the individual prior/at baseline history of hypertension variable that contributes to the HAS-BLED score. Hypertension has the opposite effect – presence of hypertension is estimated to be associated with an increase in the odds of a rivaroxaban prescription (OR: 2.1, 95% CI = 1.3, 3.2).

## **10.7 Adverse events/adverse reactions**

Not applicable.

## **11 Discussion**

This final study report summarises data on patients prescribed rivaroxaban in the secondary care setting in England and Wales in the ROSE SCEM Study conducted as a Post-authorisation Safety Study (PASS) in the EU. Within the study the rivaroxaban cohort is a group of new users of rivaroxaban comprised of both anticoagulant naïve and prior anticoagulant users. The contextual warfarin cohort are new warfarin users defined as no prior use of univalent direct thrombin inhibitor or direct factor Xa inhibitors and/or no use of anticoagulant therapy or other VKA recorded within one year prior to index date. Data analyses were performed on all patients for whom both baseline and 12 week data from specialists were available (n=4609), [55.2% (n=2542) rivaroxaban users and 44.8% (n=2067) warfarin users] identified in the study period from September 2013 to January 2016.

### **11.1 Key results and interpretation**

The primary objective of the study was to estimate the unadjusted cumulative incidence (separately) of the following important identified risk for rivaroxaban users which is haemorrhage within the gastrointestinal and urogenital sites (which meets the criteria for a major bleed (Table 1) and all intracranial sites. Secondary objectives

included the corresponding estimation of unadjusted cumulative incidence amongst warfarin users (a contextual cohort), and further quantification of bleeding risk in both user groups (composite outcome of major bleeding [alone and in combination with CRNM bleeds], quantification of additional critical organ bleeding sites). In addition there were a number of exploratory objectives and analyses made possible due to the large amount of data collected on these patients. There is a relatively large body of literature looking at the risk of bleeding on rivaroxaban compared to warfarin, both from clinical trials and observational research. The results from this study will be considered alongside other research results.

### *Major Bleeds*

In this study, the cumulative incidence of major bleeding as defined in the primary objective within the sites of gastrointestinal, urogenital and intracranial for all indications within the rivaroxaban group was 0.5% (n=13), 0.3% (n=7), and 0.1% (n=3) respectively. Within the warfarin group, the cumulative incidence of major bleeding within these sites across all indications was 0.2% (n=3), 0.1% (n=2) and 0.1% (n=2) respectively. For all indications, the cumulative incidence for clinically relevant non-major bleeds, major bleeds (all) and a composite (major plus CRNM) was also higher amongst the rivaroxaban group compared to the warfarin group 4.8% (n=121), 1.3% (n=33), 6.1% (154) vs 3.2% (n=67), 0.7% (n=14), 3.9% (n=81) respectively. These results suggest that the risk of major bleeds with rivaroxaban during the 12 week treatment period may be slightly higher than with warfarin. These unadjusted results differ to results from a retrospective cohort study in the US which examined the rates of gastrointestinal bleeding with rivaroxaban compared to warfarin (for any indication). This US study found that there was no statistically significant difference (adjusted hazard ratio= 0.98, 95% CI: 0.36, 2.69). The unadjusted rates of gastrointestinal bleeding in this US study were found to be 3.41 per 100 person years for rivaroxaban and 7.02 per 100 person years for warfarin i.e. higher in warfarin than rivaroxaban (25). Thus, although the unadjusted incidence rates were markedly different, the adjusted hazard ratio was 0.98 indicating the importance of statistical adjustment. In our study the unadjusted rates of gastrointestinal bleeding were 4.7 per 100 person years for rivaroxaban and 3.8 per 100 person years for the warfarin cohort. The rate for warfarin is clearly lower than in the US study. In this context it is also important to consider what the impact of different exclusion criteria for warfarin and rivaroxaban patients may have been as the warfarin cohort was not designed to be comparator cohort in this study. Whereas rivaroxaban treated patients may have been previously treated with other anticoagulants, warfarin patients were anticoagulant naïve.

### *Atrial fibrillation*

The observed cumulative incidence of major bleeding (inclusive of gastrointestinal, urogenital and all intracranial) within the AF group on rivaroxaban was 0.6% (0.2, 1.4; n=6). This is similar to that estimated from the ROCKET-AF study (0.7%) assuming 12 weeks of treatment rather than the reported ROCKET-AF study median duration of treatment exposure of 590 days, as described in the study protocol section 4.2.1 (2).

Within the rivaroxaban AF group, the cumulative incidence of major bleeding within the gastrointestinal site was 0.2% (0.0, 0.8; n=2). No major gastrointestinal bleeds were reported within the warfarin AF group. Rates of gastrointestinal bleeding found in other rivaroxaban studies are quite variable. In the ROCKET AF trial, the rate of major gastrointestinal bleeding was significantly more in rivaroxaban patients than warfarin patients (2.00 per 100 patient years vs 1.24 per 100 patient-years; HR=1.66, 95% CI: 1.34, 2.05). However the ROCKET AF study had a median duration of treatment exposure of 590 days, and the median follow-up period was 707 days, which is therefore not comparable to our study (10). In the XANTUS study, the incidence rate of major gastrointestinal bleeding was 0.9 (0.6-1.1) events per 100 patient years for rivaroxaban. The incidence was 0.8% although this was a one year study (26). A meta-analysis of real-world studies of rivaroxaban in AF patients found that the pooled rate of major gastrointestinal bleeding with rivaroxaban was 2.41 per 100 patient years (95% CI: 1.25–3.56). Three of the six studies did not use ISTH major bleeding definitions, in those that did the rates were 0.9, 0.7 and 0.19 per 100 patient years (27). A retrospective cohort study in Denmark found an unadjusted event rate for any gastrointestinal bleeding of 1.0 and 0.6 per 100 person years for 15mg and 20mg rivaroxaban in AF patients, respectively (28).

In this study, the cumulative incidence of major bleeding within the urogenital site was 0.2% (0.0, 0.8; n=2). No major urogenital bleeds were reported within the warfarin AF group. The only urogenital site major bleed reported within the ROCKET AF study was for macroscopic haematuria, which was reported within the rivaroxaban and warfarin groups at a cumulative incidence of 0.4% and 0.3% respectively. This is comparable to the rates seen in our study.

The third bleeding site included within the primary objective of the ROSE study within the rivaroxaban group was for intracranial bleeds; in the AF group these were reported

at cumulative incidence of 0.2% (0.0, 0.8; n=2). Within the warfarin AF group, the cumulative incidence of intracranial bleeds was 0.3% (0.0, 0.9; n=2). This is lower than the risk of intracranial bleeding reported within the rivaroxaban and warfarin groups within the ROCKET study of 0.8% and 1.2% respectively, although this was a longer study (10). An electronic data base cohort study including 44,793 patients on rivaroxaban for AF with an observation period of 2.5-years reported an incident rate per 100 person years of 0.23 (0.19–0.28) (29). In the XANTUS study the incidence rate was 0.4 (0.3–0.6) per 100 patients years. The incidence was 0.4% although this was a one year study (26).

The incidence of clinically relevant non-major bleeds (CRNM), major bleeds (all) and the composite outcome of major plus clinically relevant non-major bleeds were all higher amongst the rivaroxaban AF group compared to the warfarin AF group [CRNM bleeds 4.3% (n=41) vs 2.8% (n=22), major bleed (all) 1.0% (n=10) vs 0.6% (n=5), composite 5.3% (n=51) vs 3.4% (n=27) respectively]. A meta-analysis of real-world studies of rivaroxaban in AF patients concluded that pooled rates of major bleeding with rivaroxaban were generally low (3.32 per 100 patient years, 95% CI: 2.28–4.25) and consistent with those reported in its pivotal randomized controlled trial (27). In the ROSE study we found a cumulative incidence rate of 5.5 (2.6, 10.1) per 100 person years in the AF indication group, which is slightly higher than the rate found in the meta-analysis. The incidence of CRNM bleeding amongst an AF cohort of rivaroxaban users was reported as 6.88% within a rivaroxaban cohort of 6817 patients, with a median follow-up of 173 days (30). In the ROSE study we found a slightly lower incidence of CRNM at 4.3% in the AF indication group.

#### *DVT/PE*

The observed cumulative incidence of major bleeding (inclusive of gastrointestinal, urogenital and all intracranial) within the DVT/PE group on rivaroxaban was 1.1% (0.7, 1.8; n=17) which is higher than the clinical trial incidence in this population (0.4%), as described in the study protocol section 4.2.1.

Within this study in the rivaroxaban DVT/PE group, the cumulative incidence of major bleeding within the gastrointestinal site was 0.7% (0.4, 1.3; n=11), and the cumulative incident rate was 3.9 (2.0, 7.1) per 100 person years. Within the warfarin DVT/PE group, the cumulative incidence of major gastrointestinal bleeding was 0.3% (0.1, 0.7; n=3). In the EINSTEIN trial, the risk of all major bleeding within the rivaroxaban and warfarin groups was 0.8% and 1.2% respectively; major bleeds were not further reported by individual site (31). In the XALIA study, a non-interventional study of

patients with DVT, which included patients taking rivaroxaban and standard anticoagulation therapy for at least 3 months, the risk of major gastrointestinal bleeding in the rivaroxaban group was 0.1% vs 0.8% in the standard anticoagulation therapy group.

In this study, the cumulative incidence of major bleeding within the urogenital site in the rivaroxaban DVT/PE group was 0.3% (0.1, 0.8; n=5), whilst the cumulative incidence of major bleeding within urogenital sites in the warfarin DVT/PE group was 0.2 % (0.0, 0.6; n=2). A retrospective chart review study in Belgium examined incidence of abnormal uterine bleeding with rivaroxaban in female VTE patients compared to VKA. The study found that incidence of bleeding was 73% for rivaroxaban and 67% for VKA, which was not statistically significantly different (32). The third bleeding site included within the primary objective of the ROSE study was intracranial bleeds; these were reported at cumulative incidence of 0.1% (0.0, 0.4; n=1) within the rivaroxaban DVT/PE group. There were no intracranial bleeds within the warfarin DVT/PE group. In XALIA, major bleeding in the CNS (including intracranial, subdural, subarachnoid, or cerebral) was 0.2% in both treatment groups (33).

Viewing the results overall, the incidence of CRNM bleeds, major bleeds (all) and the composite outcome of major plus clinically relevant non-major bleeds in this study were all higher amongst the rivaroxaban DVT/PE group compared to the warfarin DVT/PE group [CRNM bleeds 4.9% (3.9, 6.1; n=75) vs 3.6% (2.7, 4.9; n=44), major bleed (all) 1.5% (1.0, 2.3; n=23) vs 0.7% (0.3, 1.4; n=9), composite 6.4% (5.3, 7.8; n=98) vs 4.4% (3.3, 5.7; 53) respectively]. REMOTEV was a prospective, non-interventional study of patients with acute symptomatic VTE, treated with oral rivaroxaban, VKA or parenteral heparin/fondaparinux alone for at least three months and followed up for six months (34). Major and non-major clinically significant bleeding occurred in 4.7% of patients in the rivaroxaban group vs 5.6% in the VKA group; major bleeding was reported within the rivaroxaban cohort at 1.1% vs 3.1% in the VKA group. The results from the REMOTEV study contrast with the results from the ROSE study which indicate higher levels of bleeding within the rivaroxaban DVT/PE group compared to the warfarin DVT/PE group. The reasons for this are not clear, but may possibly be related to the nature of the contextual warfarin cohort. The risk of major, CRNM and composite bleeding would appear to be lower in the ROSE warfarin DVT/PE group compared to the REMOTEV warfarin group; bleeding risk within the ROSE rivaroxaban DVT/PE group is consistent with the REMOTEV rivaroxaban group study findings, if not slightly higher [ROSE rivaroxaban DVT/PE group CRNM bleeds 4.9% vs REMOTEV rivaroxaban CRNM 4.3%, ROSE rivaroxaban DVT/PE major bleeds 1.5% vs

REMOTEV rivaroxaban major 1.1%, ROSE rivaroxaban DVT/PE gastrointestinal major bleeds 0.7% vs REMOTEV rivaroxaban gastrointestinal major 0.4%].

#### *HAS-BLED and CHA2DS2-VASc*

Both the HAS-BLED and the CHA2DS2-VASc scores can be used together to evaluate an approach to treatment in patients with AF. CHA2DS2-VASc Scores of 0, 1, or  $\geq 2$  indicate low, moderate, or high stroke risk, respectively. The updated 2012 European Society of Cardiology guidelines and the National Institute for Health and Care Excellence guidelines recommend that patients with at least one risk factor included in the CHA2DS2-VASc score be considered for anticoagulation therapy (excluding female patients under age 65 years with lone atrial fibrillation), and that anticoagulation should be offered to patients with atrial fibrillation and a CHA2DS2-VASc score of 2 or more (35). Decision-making for thromboprophylaxis needs to balance the risk of stroke against the risk of major bleeding, especially ICH, which is the most feared complication of anticoagulation therapy and confers a high risk of death and disability. Thus, a formal bleeding risk assessment is recommended for all patients with AF, and in patients with a HAS-BLED score  $\geq 3$ , caution and regular review are appropriate, as well as efforts to correct the potentially reversible risk factors for bleeding.

#### HAS-BLED:

This study reported on the frequency for the various HAS-BLED indicator variables by treatment group and indication. Most of the indicators were similarly distributed between the two groups, however more rivaroxaban patients had a history of stroke (30.9% amongst rivaroxaban group vs 20.9% amongst warfarin group) within the AF group. This may reflect some channelling of patients in whom previous anticoagulant treatment with a VKA for stroke prevention was ineffective. Overall, within the AF group the median HAS-BLED score for both rivaroxaban and warfarin patients was 2, reflecting a moderate risk for major bleeding ( $\sim 2/100$  patient-years). This is consistent with the HAS-BLED score calculated for a retrospective new-user cohort study of 118891 patients, in which the majority of patients taking rivaroxaban for non-valvular AF scored a HAS-BLED of 2 points (54%), (36), and is broadly consistent with the findings of a Norwegian database study in which 47% of patients taking rivaroxaban for AF scored a Modified HAS-BLED score of  $\geq 3$  (30). In this study within the AF group, fewer patients with a HAS-BLED score of 3 were taking rivaroxaban compared to the warfarin group (23.2% vs 31.6%), although the distribution was similar at HAS-BLED scores in excess of 3. This may reflect clinicians' reluctance to prescribe rivaroxaban amongst patients with a higher risk of bleeding due to the current lack of an antidote.

Not surprisingly the median HAS-BLED score for both groups within the DVT/PE reflected a lower bleeding risk [median 1 (IQR 0, 2)]; this score has not been validated within this patient group.

#### CHA2DS2-VASc:

Within this study, the individual criteria included within the CHA2DS2-VASc score had broadly similar distributions within the rivaroxaban and warfarin treatment groups. There appeared to be more patients within the rivaroxaban AF group with a prior history of stroke, TIA or thromboembolism. This may reflect some channelling of patients in whom previous anticoagulant treatment with a VKA for stroke prevention was ineffective. Overall in this study the median CHA2DS2-VASc score within the AF group was 4 in both treatment groups, reflecting a high risk of stroke. In the ROCKET AF trial, the CHADS2 score was used to assess the baseline risk of stroke, in contrast to this study in which the CHA2DS2-VASc score was applied. The mean and median CHADS2 within the ROCKET AF trial were 3.5 and 3.0 for both rivaroxaban and warfarin groups. Most patients within the ROCKET study had a CHADS2 score of 3, [rivaroxaban n=3058, 42.9% and warfarin n= 3158, 44.3%], with approximately a third of patient scoring a value of 4. In the ROSE study there were some differences between the two treatment groups but broadly speaking there were a greater number of patients within each treatment group with higher CHA2DS2-VASc scores compared to the CHADS2 scores reported in ROCKET AF trial. This is not surprising as the CHA2DS2-VASc model includes additional risk factors which are likely to result in higher scores. The median CHA2DS2-VASc score of 4 is similar to CHA2DS2-VASc scores reported in other observational studies; a study which included 44793 patients taking rivaroxaban identified from electronic medical records reported that across the entire study cohort, patients with major bleeding had a median CHA2DS2-VASc score of 4 (quartile 1, quartile 3: 4, 5) compared with 3 (quartile 1, quartile 3: 2, 5) among those without major bleeding (29). Further observational studies reported similar mean CHA2DS2-VASc scores of 2.62 (SD1.65) (37) and 2.94 (30) respectively.

Not surprisingly, there were a greater number of patients within each treatment group for the DVT/PE indication with CHA2DS2-VASc scores of 0 and 1, reflecting the lower stroke risk in this population.

#### *Other targeted events*

Recurrent/Incident thromboembolic events:



An additional targeted outcome within this study was to examine the risk of incident and recurrent thromboembolic events, including CVA, DVT and PE, in order to assess effectiveness of treatment.

Within the rivaroxaban AF group, the risk of recurrent stroke was 0.9%, with no incident reports of stroke within this group. Within the warfarin AF group the risk of recurrent stroke was lower at 0.1% and the risk of incident stroke was 0.4%. The rivaroxaban group results are in contrast to results seen in a retrospective new-user cohort study of 66651 patients with nonvalvular AF who were taking rivaroxaban, in which the risk of thromboembolic stroke was 0.2% (36). It is of note however that in this study the outcome of stroke included both ischaemic and haemorrhagic types.

Within the rivaroxaban DVT/PE group, the risk of recurrent DVT and PE was 1.0% and 1.2% respectively; the results for recurrent DVT and PE within the warfarin DVT/PE group were similar for the risk of recurrent DVT (1.0%) and lower for the risk of recurrent PE (0.5%). The risk of recurrent DVT and PE in the rivaroxaban group in this study were consistent with results from the REMOTEV observational study, in which the risk of recurrent VTE within six months in the rivaroxaban group was 1.4%. However the results in this study for the risk of recurrent DVT and PE within the warfarin group would appear to be lower than reported in the REMOTEV study (REMOTEV warfarin risk of recurrent VTE within six months was 3.1%) (34). Again this may reflect the nature of the contextual cohort as the rivaroxaban cohort may have had a longer history of anticoagulation and associated comorbidities than the warfarin cohort. In this study, the risk of incident PE was similar in both rivaroxaban and warfarin DVT/PE groups (0.7% and 1.0% respectively).

#### *Patient determinants of prescribing*

The secondary focus of this study was to advance the understanding of the patient population prescribed rivaroxaban in the secondary care hospital setting by exploring differences between rivaroxaban and the alternative anticoagulant therapy (warfarin) cohort with regard to the prevalence of non-clinical reasons for prescribing, prognostic and clinical risk factors for the selected outcomes of interest. In addition to the descriptive assessment of baseline patient characteristics, we also conducted a multi-level regression analysis to investigate the key drivers for rivaroxaban vs warfarin prescribing, utilising the hierarchical nature of prescribing decisions in the NHS.

In terms of prescribing decisions, for the AF and DVT/PE groups, clinical judgement was the overwhelming reason for treatment choice followed by various

guidelines/recommendations from expert groups such as NICE, and formulary committees. The impact of expert advice/formulary guidance seemed to be particularly relevant for the choice of warfarin in AF (NICE guidance was cited as a supporting reason for 43.4% of AF warfarin patients compared to 20.6% of AF rivaroxaban patients). The characteristics of the patients (demographic, general health, selected prior and concurrent medical conditions and events) were collected, since these data may identify vulnerable patients at risk and/or are considered important risk factors for outcomes of interest. In terms of patient characteristics, irrespective of indication, there were very few differences in the demographics or socio-economic variables either overall or in the specific indication subgroups.

Where specified, the prevalence of prescriber-reported risk seeking behaviours (substance misuse and alcohol abuse) was low in both cohorts (<2% and <6% respectively). Approximately twice as many rivaroxaban patients as warfarin patients had a history of prior substance misuse, although the proportion with a history of prior alcohol misuse was comparable between groups.

Information on concomitant use of specific therapeutic drug classes was also obtained (including analgesics/anti-inflammatory agents, anti-convulsants, anti-infectives, antidepressants, female hormone products), in addition to information on the use of OTC medication, herbal agents and juices, in order to identify patients at possible risk of drug interactions. These data have been explored according to the indication groups and are summarised below for both the AF and DVT/PE groups only since the "Mixed" and "Other" indications both contained very few patients and as such it was difficult to identify any meaningful differences in these two treatment groups.

#### AF Cohort:

In patients with AF, the age and sex distributions of rivaroxaban and warfarin cohorts were similar, with the majority of females being older than 75 years of age (67.2% rivaroxaban; 63.9% warfarin vs 50% males, rivaroxaban; 41% males, warfarin). This is consistent with the known increasing prevalence of AF with age; 2.9% of the total estimated AF in the population is likely to occur in people aged under 45, 16.6% in people aged 45-65 and 80.5% in people aged over 65 (38). There were also slightly more males in the AF cohort than females (516 males vs 448 females) which is consistent with the estimated prevalence of AF in which the prevalence of AF is higher in men than in women, (2.8% versus 2.0%) (38).

The highest percentage of patients in both cohorts for whom treatment was being initiated had been diagnosed with AF in the month prior to the start of treatment (rivaroxaban 43.2% and warfarin 49.2%).

The prevalence of prior medical history of haemorrhagic events appears to be similar between both AF rivaroxaban and warfarin treatment groups; the most prevalent being gastrointestinal bleed (3.3% vs 3.7%, respectively). There were however some differences in the prevalence of some known risk factors for both stroke and bleeding in the rivaroxaban AF cohort compared to the warfarin AF cohort. With respect to risk factors for stroke, the prevalence of a prior history of CVA and TIA was higher amongst rivaroxaban users compared to warfarin users (CVA; 30.9% vs 20.9%, TIA 14.3% vs 10.5%), however the prevalence of other risk factors for CVA including prior history of CHF, hypertension, MI, and diabetes mellitus were all lower amongst rivaroxaban users (CHF 14.6% vs 18.0%, hypertension 38.6% vs 47.4%, MI 8.8% vs 10.0%, diabetes mellitus 18.8% vs 21.2%).

With respect to possible risk factors for bleeding, the prevalence of a prior history of the following conditions were lower amongst rivaroxaban users (Hypertension 38.6% vs 47.4%, liver disorder 0.9% vs 2.0%, abnormal liver function tests 5.2% vs 8.6%, and renal impairment stage 3-4 7.7% vs 8.7%).

Some concomitant medications may predispose the patient to bleeding; there was a lower percentage of rivaroxaban patients prescribed aspirin (3.8% vs 8.2%) but a slightly higher percentage of rivaroxaban patients prescribed NSAIDs (2.4% vs 2.1%). Prescriber reported rates of a history of alcohol misuse were also slightly lower amongst rivaroxaban users (5.1% vs 5.8%) however this was not indication specific. In contrast, a prior history of stroke (an additional risk factor for bleeding) was higher amongst rivaroxaban users (30.9% vs 20.9%). As stated above, prior bleeding risk was broadly similar within both cohorts.

The pattern of concomitant use of other selected medications of interest was broadly similar in both the rivaroxaban and warfarin AF cohorts; the most frequently reported medication used in the 12 weeks after starting anticoagulant treatment were prescribed medicines, analgesic and anti-inflammatory agents and anti-infectives. Amongst the named anti-infectives, clarithromycin was most frequently reported (rivaroxaban 2.1% vs warfarin 2.3%). Concomitant use of antidepressants was also common for both groups. Concomitant use of herbal agents and/or food supplements was lower amongst rivaroxaban users compared to warfarin users (3.0% vs 4.2%).

respectively), which is of interest given the well documented food interactions that may occur with warfarin.

#### DVT/PE Group:

The age and sex distributions of rivaroxaban and warfarin treated patients in the DVT/PE group were similar although the DVT/PE cohort was younger than the AF cohort. In the rivaroxaban group 69.1% of males and 72.3% of females were less than 75 years of age and in the warfarin group 61.8% of males and of 74.2% females were less than 75 years of age with slightly more males than females in each group respectively (54.6%, 54.9%). Although published data suggest no consistent differences in the incidence of VTE among men and woman, the incidence of first-time VTE rises exponentially with age from <5 per 100,000 per year among children < 15 years of age to values in the range of 450 to 600 per 100,000 per year among individuals over the age of 80 years; the incidence increasing dramatically after age 60 years (39).

As with the AF cohort, the highest percentage of patients for whom treatment with warfarin was being initiated had been diagnosed with DVT/PE in the month prior to the start of treatment (49.0%). However in the rivaroxaban cohort, the majority of patients had been diagnosed with DVT/PE less than one month after treatment start (51.0%).

In the DVT/PE group, the most prevalent prior medical history of haemorrhagic events within body sites in the warfarin group was gastrointestinal bleed (4.2%) which was higher than for the rivaroxaban group (4.2% vs 2.4%) The most prevalent prior medical history of haemorrhagic events within body sites in the rivaroxaban group was urogenital bleed which was lower than for the warfarin group (2.7% vs 3.8%). Bleeding risk factors relevant to this patient population may be different to those identified and validated within an AF population; criteria that may predispose patients to bleeding within this indication include history of malignancy, the prevalence of which was higher amongst warfarin users (14.1%) compared to rivaroxaban users (10.6%) (40).

With respect to possible risk factors for bleeding in the DVT/PE group, the prevalence of a prior history of renal impairment stage 3-4 was lower amongst rivaroxaban users (5.0% vs 8.3%) and the prevalence of a prior history of abnormal liver function tests was higher amongst rivaroxaban users (11.1% vs 8.8%).

A further risk factor is the presence of anaemia; overall the prevalence of baseline anaemia amongst males and females (defined as a haemoglobin of less than the lower limit of normal i.e. <130g/L and <120 g/L respectively) was lower amongst rivaroxaban users than warfarin users (Males 15.4% vs 19.6%; Females 23.7% vs 30.6%)

With respect to prescribing of concomitant medications which may predispose the patient to bleeding, there was a higher percentage of rivaroxaban patients prescribed aspirin (2.5% vs 1.7%) and NSAIDS (7.2% vs 6.4%).

The pattern of concomitant use of other selected medications of interest was broadly similar in both the rivaroxaban and warfarin cohorts; approximately half of the cohort were using other prescribed medication. The proportions of patients using analgesics and anti-inflammatory agents or anti-infectives were higher in the DVT/PE cohort compared to the AF cohort. Concomitant use of antidepressants was also common for both groups. The concomitant use of herbal agents and/or food supplements was higher amongst rivaroxaban users (4.4%) compared to warfarin users (3.0%), which is consistent with the well documented food interactions that may occur with warfarin.

#### *Socioeconomic data*

Although there was no obvious difference in the distribution of socioeconomic status overall (according to the Index of Multiple deprivation (IMD)<sup>20</sup>) between participating and non-participating trusts, importantly the North West, North East and London regions are associated with high levels of deprivation. Furthermore social deprivation is negatively associated with cardiovascular disease (CVD) such that people from economically deprived areas being more likely to have CVD events, such as stroke, than those from least deprived areas. Therefore the overall pattern of site participation appears to be representative not only of social deprivation in England ([https://www.stroke.org.uk/sites/default/files/stroke\\_statistics\\_2015.pdf](https://www.stroke.org.uk/sites/default/files/stroke_statistics_2015.pdf)) but also CVD mortality and morbidity (<https://www.bhf.org.uk/-/media/files/publications/.../bhf-cvd-statistics-2015-final.pdf>)

Indicator data for adoption of new medicines based on hospital density, population density and rivaroxaban sales were higher for participating compared to non-participating sites. Whilst these indicator data are not available for each year of the

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<sup>20</sup> Indices of deprivation scores are a measure of deprivation using 10 domains from census data across England and Wales; unemployment, overcrowding, car ownership and social class  
41. Morgan O BA. Measuring deprivation in England and Wales using 2001 Carstairs scores. Health Stat Q. 2006;31:28-33.

study, as surrogate measures these observations align with recent the publication of a systematic review which reported that high volumes of patient flow and high prescribing volume for prescribers are each associated with a higher likelihood of adoption of a new medicines, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4283087/>. Therefore it is not unexpected that trusts with high hospital and/or population density and rivaroxaban sales were more likely to participate in this study than those with lower volumes, respectively.

It is also known that medicines management policies determine which trusts will prescribe new treatments. In this study guidelines for use of rivaroxaban were available for all but two participating trusts (n=85, 97.70%). A slightly lower proportion was observed for non-participating trusts (n=63, 91.30%). These observations align with expected medicines management practice in the UK for rivaroxaban. Importantly, an evidence based national Technology Appraisal (TA) for the use of rivaroxaban in the prevention of stroke and embolism in people with atrial fibrillation was first issued by NICE in May 2012; whilst a TA for the use of rivaroxaban in treating pulmonary embolism and preventing recurrent VTE were published by NICE in June 2013. In the UK, the NHS is legally bound to fund and resource medicines and treatments recommended by NICE TAs.

#### *Multi level regression analysis*

The multi-level modelling analysis was conducted as an exploratory analysis not specifically related to the safety outcomes for rivaroxaban, except to the extent that any systematic channelling of the drug based on prescribing guidelines may create systematic imbalances in risk factor groups associated with the primary outcomes between rivaroxaban and the contextual cohort. The analysis aimed to understand the main drivers for rivaroxaban prescribing, whilst acknowledging and modelling the hierarchical nature of prescribing decisions for such drugs in the UK healthcare system.

In that context the results showed that, for all indications, the main drivers for prescription of rivaroxaban or warfarin are trust prescribing guidelines. However, differences in trust level and prescriber level variance was observed following stratification by indication. For the subgroup of DVT/PE patients, the main drivers for prescription of rivaroxaban or warfarin are trust prescribing guidelines. However for patients with AF, the main drivers for prescription of rivaroxaban or warfarin were observed at the Prescriber level (within Trusts). This may highlight differences in trust

level guidelines for the treatment of DVT/PE compared with AF, as well as differences in the management and treatment care pathways for these diseases.

The large ORs identified for some patient specific prescriber reasons (e.g. lifestyle choice; OR = 50.78; all indications) indicate that for those patients these factors may be highly important. Although the patient groups impacted are small, the imbalances are clearly quite large and are generally in the direction of favouring rivaroxaban prescription. These factors may indicate situations such as lifestyle issues, for example regular travel commitments, which render it difficult for patients to accept or comply with the regular monitoring requirements associated with warfarin.

Results also suggest that warfarin prescription is favoured over rivaroxaban for patients with a prior or baseline history of CHF, hypertension (according to CHADS2VASC) or other indication. For the AF patient subgroup, a prior or baseline history of CVA or hypertension (according to HAS-BLED) favours the prescribing of rivaroxaban. These treatment decisions may be associated with the reversibility and close monitoring associated with warfarin, as well as the management and treatment care pathways for these diseases.

Nurse prescribers were shown to favour warfarin prescribing for patients in the AF subgroup. This may suggest an NHS HCP category in which the use of well-established standard treatment is preferred over novel treatments, or may reflect the impact of PGDs. At the trust level, foundation trusts were observed to favour rivaroxaban prescribing for all indications and for the DVT/PE subgroup. This may reflect differences in prescribing autonomy between foundation, acute and integrated trusts. At the geographic regional level, results suggest that trusts within London favour warfarin prescribing for AF patients, when compared to the East of England. This may highlight trust level differences due to geographical region.

## **11.2 Limitations**

Like other observational epidemiological studies, we recognise several potential sources of bias in our study (22).

A potential source of bias in this study is non-response bias. It is unknown whether the prescribing patterns and/or patients of specialist HCP who returned the questionnaire are different to those of the specialist HCPs who did not return the questionnaire, as is the potential selection bias in terms of representativeness of

patients included in this cohort. However, we do not believe that selection bias affects the types or number of events experienced and reported by a patient after treatment was initiated although differences introduced by the different exclusion criteria may impact the expected rate of event in each cohort. Furthermore, widespread recognition of national and local clinical guidelines regarding prescribing of these anticoagulants contributes to some extent to reducing the selection bias. Around 50% of prescribers contributed only 1 patient however, which may make it more difficult to control selective reporting.

There is also a further potential bias where specialist HCPs may under-report or over-report particular events in particular patients. The direction of any bias within this study is unknown. This bias and misclassification bias is addressed by use of follow up questionnaires which aim to gather additional information on reported events.

In SCEM, exposure is based on prescription data as recorded in medical charts. However, as with many observational studies, the degree of patient compliance in taking the prescribed medication cannot be fully ascertained.

In this study information was collected on cases of selected events including haemorrhage events and other medical conditions. It is acknowledged that these conditions may have been present prior to commencing rivaroxaban or warfarin, as specific information was not collected regarding baseline screening for these events prior to starting therapy. However, these events have been described and specific information on relevant risk factors and patient characteristics will be presented in case series format in order to support generation of hypotheses for further evaluation.

A key factor of interest for these targeted events was the temporal relationship with treatment. New onset events that develop within the first three months of drug treatment could be suggestive of a possible causal relationship; however, individual drug relatedness assessments are not able to be performed for all events of interest, as often multiple risk factors exist, placing the patient at an elevated risk independent of drug exposure which precludes individual assessments being performed to determine relatedness.

Information on relevant confounders in the estimates of risk and rate may be missing or incomplete since data abstracted from patient medical records held by specialist HCPs are likely to be biased towards recording cardiovascular-related medical events for the acute period of care and may not contain data on all variables for the full 12



week observation period that are relevant to the study. However, the study asked HCPs to provide data where available and report events affecting all body symptoms, without making any prior assessment on relatedness.

Misclassification and under-reporting of events is also possible. All relevant cases of haemorrhage were adjudicated and if necessary additional information was requested from the specialist HCP. The study also requested such data from the GPs of patients who were discharged from the care of the specialist HCP prior to the end of the 12 week observation period.

As this is an observational study, information on patient characteristics i.e. reported medication use is only as reported by patients. However there no reason to suspect this would differ between rivaroxaban and contextual cohorts.

Another important consideration that could have introduced bias is that the SCEM rivaroxaban cohort is a group comprised of both anticoagulant naïve and prior anticoagulant users. Selection bias could have arisen because patients who failed to respond or could not tolerate warfarin were prescribed rivaroxaban. The estimates of incidence and reasons for treatment withdrawal (through depletion of susceptibles) may differ between the two treatment cohorts. In acknowledgement of this important source of bias, this SCEM study is designed to capture information on prior use of anticoagulants in rivaroxaban users because of the complex treatment patterns for patients requiring acute anticoagulation and the likely switching of formulations, for the purposes of further exploration of possible safety signals. However the analyses conducted are unadjusted and so comparisons between the rivaroxaban and warfarin cohorts need to be viewed with caution.

Another potential source of bias would occur if there is any time differential between switching patients from parenteral to oral anticoagulation. This was a potential concern for acute PE treatment but NICE CK guidelines do not suggest such a differential is current clinical practice.

### **11.3 Generalisability**

The study aimed to recruit Specialist HCPs and patients from across England and Wales from both urban and rural areas. The geographical distribution of all prescribers and evaluable patients participating in the SCEM study corresponds generally to those urbanised areas where prevalence of health service utilisation is likely to be more

prevalent. There is no reason to believe that the evaluable cohort is likely to be systematically different to the population in England and Wales treated with rivaroxaban for similar indications within secondary care. Evaluation of regional and local differences in the ROSE study population were examined in this report but no major differences were seen that impact the evaluable cohort. However, this study is part of a broader literature in the safety of rivaroxaban and any conclusions on safety should be put into context with results from other post-marketing studies for the product.

## **12 Other information**

None.

## **13 Conclusion**

The SCEM design provides a framework suitable to evaluate the safety of newly marketed medicines in secondary care setting. The analysis of The ROSE Study data shows that rivaroxaban is largely being prescribed to populations in accordance with prescribing recommendations and national clinical guidelines. In terms of the primary outcome risk of major bleeding, the estimates of risk in the AF and DVT/PE rivaroxaban user populations are overall low and consistent with those estimated from clinical trial data. There is some evidence that the risk of major bleeding in rivaroxaban patients may be higher than in warfarin patients. However, due to the small number of bleeding cases, lack of adjustment for baseline differences, and different exclusion criteria in the two cohorts, a direct comparison is not warranted. This study is part of a broader literature on the safety of rivaroxaban and any conclusions on safety should be put into context with results from other post marketing studies for the product.

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## **15 Appendices**

### **Annex 1. List of stand-alone documents**

None

## **Annex 2. Additional information**

Appendix 1: Study protocol

Appendix 2: Statistical Analysis Plan

Appendix 3: Multi-level modelling analysis

Appendix 4: Other treatments for the contextual cohort

Appendix 5: Other indications for treatment

Appendix 6: Other supporting reasons for prescribing

Appendix 7: Other medical history prior to starting

Appendix 8: Reasons for switching medications prior to starting

Appendix 9: Other medication use

Appendix 10: Incidence densities for other events

Appendix 11: Reasons for stopping

Appendix 12: All causes of death

## **Appendix 1. Study Protocol**

### **FULL STUDY PROTOCOL**

#### **AN OBSERVATIONAL POST-AUTHORIZATION SAFETY SPECIALIST COHORT EVENT MONITORING STUDY (SCEM) TO MONITOR THE SAFETY AND UTILIZATION OF RIVAROXABAN (XARELTO®) FOR THE PREVENTION OF STROKE IN PATIENTS WITH AF, TREATMENT OF DVT AND PE, AND THE PREVENTION OF RECURRENT DVT AND PE IN THE SECONDARY CARE HOSPITAL SETTING IN ENGLAND AND WALES**

**November 2014**

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## Appendix 1. Study Protocol

### Glossary of terms

Abbreviation	Term
A & E	Accident and Emergency
ADR	Adverse Drug Reaction
ACS	Acute coronary syndrome
AE	Adverse Event
AF	Atrial fibrillation
ALT	alanine aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	aspartate aminotransferase
BMA	British Medical Association
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CHADS <sub>2</sub>	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and prior Stroke or transient ischemic attack
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CYP2CP	Cytochrome P450 2C9
CYP P450	Cytochrome P-450
DMP	Data Management Plan
DSRU	Drug Safety Research Unit
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drugs Administration
FDR	False Discovery Rate
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GP	General Practitioner
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HLT	Higher Level Term
ID	Incidence Density
INR	International normalized ratio
IRAS	Integrated Research Application System
ISTH	International Society on Thrombosis and Haemostasis
IQR	Interquartile Range
LFT	Liver Function Test
LLT	Lower Level Term
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
M-PEM	Modified Prescription-Event Monitoring

## Appendix 1. Study Protocol

NDA	New Drug Application
NHS	National Health Service
NHSRxS	National Health Service Prescription Services
NICE	National Institute for Health and Clinical Excellence
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over-The-Counter
PCI	Percutaneous coronary insert
PE	Pulmonary embolism
PEM	Prescription Event Monitoring
PIP	Paediatric Investigation Plan
PS	Propensity Scores
PSC	Project Steering Committee
RCT	Randomised Controlled Trial
RAIDAR	Rare and Iatrogenic Adverse Reactions
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SCEM	Specialist Cohort Event Monitoring
SOC	System Organ Class
SOP	Standard Operating Procedure
SPAF	Stroke Prevention in Atrial Fibrillation
SPC	Summary of Product Characteristics
TIA	Transient Ischaemic Attack
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VKA	Vitamin K Antagonist
VKORC1	Vitamin K epoxide reductase complex subunit 1
VTE	Venous thromboembolism

## Appendix 1. Study Protocol

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### **EXECUTIVE SUMMARY**

Rivaroxaban, a highly selective direct factor Xa inhibitor which inhibits thrombin formation and the development of thrombi, was approved by the European Commission on 30 September 2008 for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacements.[1] On 19 December 2011, the European Commission approved the use of Xarelto in the indications prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure, hypertension, age  $\geq$  75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) [2] A further variation of marketing authorisation for the treatment of PE, under the label ‘Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults’ was approved on 20 November 2012 [3] More recently, a marketing application has been approved in the EU for rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.[4] A Risk Management Plan (RMP) has been developed for rivaroxaban by the manufacturer. This plan includes tools designed to monitor the important risks (including class effects and off-label use). [5]

This postmarketing safety study of rivaroxaban (XARELTO®) is to be carried out by the Drug Safety Research Unit (DSRU) as part of a broader Post-Authorisation Commitment requested by the Committee for Medicinal Products for Human Use (CHMP) to further investigate the safety profile of rivaroxaban in clinical practice. This study, which is designed to monitor the safety profile and drug utilisation of rivaroxaban as prescribed by specialist Healthcare Professionals (HCP) for medical indications requiring anticoagulation (i.e. not the licensed surgical indications for prevention of VTE in adult patients undergoing elective major hip or knee replacement surgery) and used in the secondary care hospital setting in England and Wales, is one of two complementary studies conducted by the DSRU. The other, based in primary care, is a Modified Prescription-Event Monitoring (PEM) Study, the aim of which is to proactively capture safety profile and drug utilisation data in the post-marketing phase of license approval of rivaroxaban as prescribed to patients by general practitioners (GP) in England.

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The aim of this Specialist Cohort Event Monitoring (SCEM) study is to monitor the short-term (up to 12 weeks) safety profile and drug utilisation of rivaroxaban as prescribed to patients for medical conditions requiring anticoagulation by specialist HCPs in the secondary care hospital setting in England and Wales. A registry-based observational, population based cohort study with a contextual cohort, utilising the technique of cohort-event-monitoring will be used (section 4) for this purpose. In the three-year post approval period, the study aims to collect exposure and outcome data for a cohort of at least 1700 evaluable patients (each observed for a minimum of 12 weeks), comprising of a minimum of 561 and 1005 patients treated with rivaroxaban for the prevention of stroke and systemic embolism in adult patients with non-valvular AF (with one or more risk factors, such as congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, prior stroke or transient ischaemic attack), and for the treatment of DVT and PE and prevention of recurrent thromboembolic events, respectively. In addition to the desire to study the use of rivaroxaban in a population that is more heterogeneous than those observed in clinical trials, it is desirable to put these observations into context. To characterise a population treated with existing anticoagulant therapy will allow the variation in determinants of treatment choices to be examined in relation to risk. Therefore, a similar number (at least 1700) of evaluable new user patients receiving alternative anticoagulant therapy will be recruited concurrently as an internal contextual cohort in order to characterise the adoption of rivaroxaban into clinical practice and explore possible differences in factors such as setting, prevalence of (non-clinical)\* reasons for prescribing, physician prescribing preference factors<sup>†</sup> and those clinical characteristics which are known risk factors for the primary outcomes of interest.[6] This study will not inform on relative measure of risk of primary outcome between rivaroxaban and the internal contextual cohort. The key purpose of this internal contextual cohort is to explore the variation in the distribution and determinants of prognostic and clinical risk factors. The purpose is not to compare risk of primary outcome between the rivaroxaban and the internal contextual cohort; a much larger study is required for that.

Specialist HCP prescribers of anticoagulants from within the secondary care hospital setting will be systematically identified across the country, facilitated by existing clinical research

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\* Non-clinical reasons for prescribing include: factors associated with accumulation of authoritative evidence (formulary committee approval; recommendation from NICE; expert committee guidelines); patient request and/or prescriber expertise and history of clinical success with similar treatments .

<sup>†</sup> type of novel anticoagulant prescribed by the specialist HCP in previous calendar month; proportion of novel anticoagulant use of all anticoagulants prescribed in clinical setting in previous calendar month.

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networks, and will be invited to participate in the study prior to study start (exact date to be determined). These specialist HCPs will be informed that they will be participating in a cohort study which will monitor the use of a new entity oral antithrombotic agent (rivaroxaban) in accordance with requirements within the Risk Management Plan, [5] and existing therapy in patients with medical conditions that require anticoagulation. Data collection will be in two phases. After the clinical decision to start treatment with rivaroxaban or alternative anticoagulant therapy has been made by the HCP specialist, patients will be invited to participate in the study, be provided with patient study documentation and consent will be obtained. The specialist HCP will complete a summary of treatment details (including actual start date of anticoagulant treatment (hereafter denoted 'index date'), and demographic data as captured from existing medical charts. At least 12 weeks after index date a data collection end-of-observation questionnaire will be completed to collect information recorded in existing medical charts about early utilisation of rivaroxaban or alternative anticoagulant therapy and safety during the first 12 weeks of observation.

This study will enable the systematic collection and aggregated safety data reporting on patients newly initiated on treatment with rivaroxaban or alternative anticoagulant therapy in the secondary care hospital setting, with a particular focus on obtaining information on patients who stop taking rivaroxaban or switch to another anticoagulant prior to transfer of care to their GP. Its purpose will be to provide information on a large number of such patients and the treatment they received in the secondary care hospital setting.

The primary focus of the study will be to quantify the cumulative incidence (risk) of haemorrhage (within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed (Table 2)) and all intracranial sites) occurring in the 12 weeks observation period after treatment initiation for patients treated with rivaroxaban in real life clinical practice in the secondary care hospital setting. The secondary focus will be on 1) advancing the understanding of the patient population prescribed rivaroxaban in the secondary care hospital setting by exploring differences between rivaroxaban and the alternative anticoagulant therapy (contextual) cohort in the prevalence of non-clinical reasons for prescribing, prognostic and clinical risk factors for the selected risks of interest; 2) describing any prescribing and use of rivaroxaban outside terms of marketing authorisation ('off-label'), for example the approved indications and/or populations with special label precautions; 3) describing changes of health profile of patients, assessment of adherence, number of indication related episodes and duration, plus any alterations of the treatment programme for



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either cohorts during the 12 week study observation period; 4) quantifying the risk of a) other major or minor bleeding outcomes not specified in the primary objectives b) all major and minor bleeds within a composite outcome, c) Haemorrhage (major bleeding during treatment (individual quantification per organ site) d) thromboembolism (recurrent and incident) and e) any other events<sup>‡</sup> reported in the 12 week observation period overall and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting in the UK.

The study also includes (for rivaroxaban cohort only) several exploratory analyses to 1) where possible, to quantify the incidence of other important identified ,potential and special risks and outcomes of interest (such as severe abnormal liver function) not mentioned in the primary objective, other frequently and rarely reported adverse events during treatment with rivaroxaban and to identify previously unrecognized adverse drug reactions for rivaroxaban; and 2) describe clinical features and management of cases of overdose, major bleeding, VTE events indicating failure of anticoagulation and management of homeostasis in patients undergoing surgery (elective or urgent) during observation of the cohort exposed to rivaroxaban.

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<sup>‡</sup> The term 'event', as used in this study, is defined as, “any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter in the patient's medical charts.”

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### **1.0 BACKGROUND**

#### **1.1 Post-marketing surveillance**

The clinical safety information available when a new medicine is marketed relates to a limited number of patients.[7] This applies to new formulations of licensed medicines. Pre-marketing data will usually give little information on drug utilisation and safety post-marketing. There has been general agreement for more than 50 years of the importance of postmarketing adverse event monitoring and postmarketing safety studies in providing complementary information on the clinically necessary understanding of the safety profile of a drug. This has resulted in not only the establishment of voluntary systems for reporting suspected adverse drug reactions (ADRs), but the development of a range of other methods to monitor and study postmarketing drug safety. In the UK, the Yellow Card spontaneous reporting scheme and a prescription based monitoring process (Prescription-Event Monitoring (PEM) [8]) provide complementary systems of post-marketing surveillance on a national scale of newly marketed drugs prescribed by general practitioners (GPs) in the primary care setting. The theoretical basis for establishing a system to monitor events regardless of relatedness to drug exposure was proposed by Finney in 1965.[9] The principle of ‘event monitoring’ has since been adapted to monitor the use and safety profile of a new drug prescribed to a patient population under the care of specialist HCPs in the secondary care hospital setting (termed ‘Specialist care Event Monitoring’ (SCEM) studies).

#### **1.2 Study rationale**

The aim of this study is to actively monitor the short term (up to 12 weeks) safety profile and drug utilisation of rivaroxaban as prescribed to patients for medical conditions (‘medical patients’ - i.e. not those requiring VTE prophylaxis with elective surgery) requiring anticoagulation by specialist HCPs in the secondary care hospital setting in England and Wales. In the UK, often the choice of drugs prescribed in primary care is guided by clinical experience and recommendations from experts and therapeutic committees in secondary care hospital setting. The patient population who are under the care of specialist HCPs, include those who may be more complex in terms of underlying disease, co-morbidities and concomitant medications than in the general disease population. In particular, this methodology enables the capture of important information on patients who may discontinue treatment prior to transfer of care to general practitioners in the primary care setting and

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therefore, risk estimates will be less subject to the influence of selection bias based on concurrent health status/disease severity by capturing first ever prescriptions from secondary care HCPs. Also, this method enables more reliable examination of exposures in relation to outcomes.

For this study, monitoring the target patient population will be achieved through an active research network of HCPs, established and maintained by the administration team at the DSRU and study research nurses/facilitators. Healthcare professionals responsible for prescribing anticoagulants (hereafter denoted 'specialist HCPs) in the secondary care hospital setting will be systematically identified directly by the DSRU and also through existing clinical research networks and will be invited to participate in the study prior to study start (February 2013 - exact date to be determined). Specialist HCPs will be informed that they will be participating in a cohort study which will monitor the extension of licence of a recently introduced oral antithrombotic agent (rivaroxaban), in accordance with requirements within the Risk Management Plan. [5]

Medical patients will be seen by specialist HCPs within the standard course of care (section 1.4) when initiating anticoagulant therapy. In the UK, the usual care pathway is such that it is anticipated that the initial follow-up of each individual patient will be handled by the specialist HCP. The patient may then continue to be managed by the specialist HCP and seen by them for their follow-up appointments on an 'out-patient' basis within the secondary care hospital setting, or they may be discharged and ongoing care transferred to their primary care physician (GP). This depends on factors specific to each individual case. Once the pharmacotherapeutic treatment decision has been made, and either rivaroxaban or alternative anticoagulant therapy prescribed as the most appropriate treatment, the patient will be invited to participate in the study. Consent will be required for access to information from existing secondary care hospital charts, and also to enable contact with their GP to access information from existing general practice primary care charts. The patient observation period will be for the first 12 weeks after starting anticoagulant treatment ('index date') to capture initial use in all target subsets of interest, and similarly for new user anticoagulant therapy patients.

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### **1.3 Rivaroxaban formulation and licensed prescribing indications**

Rivaroxaban, a highly selective direct factor Xa inhibitor, was approved by the European Commission on 30 September 2008 for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacements. [1] On 19 December 2011, the European Commission approved the use of Xarelto for the indication prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure, hypertension, age  $\geq$  75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.[2] A further variation of marketing authorisation for the treatment of PE, under the label ‘Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults’ was approved on 20 November 2012 [3] More recently, a marketing application has been approved in the EU for rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.[4]

Rivaroxaban is a highly selective direct factor Xa inhibitor with high oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated. It is formulated as a film-coated tablet containing 10 milligram (mg), 15mg or 20mg of active ingredient for oral administration. The absolute bioavailability of rivaroxaban is high (80 % - 100 %) for the 10 mg dose, with peak plasma levels attained between 2-4 hours.[1]

#### ***1.3.1 Dosage and duration***

Duration depends on individual risk of patient for VTE and stroke, which is determined by indication for treatment (Table 1).

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**Table 1. Dosage and duration of treatment with rivaroxaban according to licensed and proposed indications. [1;5;10-12]**

Indication	Initial dose (mg)	Maintenance / maximum dose	Duration	Food intake
Prevention of VTE in adult patients undergoing elective major hip or knee replacement surgery	10 Initial dose should be taken 6 to 10 hours after surgery provided that haemostasis has been established	10	For patients undergoing major hip surgery, -5 weeks For patients undergoing major knee surgery - 2 weeks	Can be taken with or without food
Treatment of DVT and prevention of recurrent DVT and PE in adults	15 (twice daily for first 3 weeks)	20 (daily)	Continued treatment	To be taken with food
Treatment of PE and prevention of recurrent DVT and PE in adults	15 (twice daily for first 3 weeks)	20 (daily)	Continued treatment	To be taken with food
Treatment of DVT and prevention of recurrent DVT and PE in adults (in patients with moderate or severe renal impairment) §	15 (twice daily for first 3 weeks)	15 (daily)	Continued treatment	To be taken with food
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age $\geq 75$ years, diabetes mellitus, prior stroke or transient ischaemic attack	20 (daily)	20 (daily)	Continued treatment	To be taken with food
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age $\geq 75$ years,	15 (daily)	15 (daily)	Continued treatment	To be taken with food

§ In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:  
For the treatment of DVT and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily based on PK modelling

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diabetes mellitus, prior stroke or transient ischaemic attack (in patients with moderate or severe renal impairment)				
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### *1.3.2 Safety Profile and Undesirable Effects*

The clinical trial safety profile data for rivaroxaban for prevention of VTE in patients undergoing elective hip or knee replacement is based on the RECORD trials [13] [14-16] For the new indications of treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) in adults, treatment of PE and prevention of recurrent DVT and PE in adults and prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, additional clinical trials have been performed. [10;17-20] The role of rivaroxaban for the treatment of VTE was investigated in three large randomised trials in the EINSTEIN programme: the EINSTEIN-DVT study was planned to probe the role of rivaroxaban as a standalone drug for the treatment of acute DVT; the EINSTEIN-Extension study was designed to evaluate extended anticoagulation treatment with rivaroxaban in patients who have been treated for acute VTE; and the EINSTEIN-PE study evaluated the role of rivaroxaban for the treatment of acute PE. The ROCKET-AF trial was designed as double-blind, double dummy trial comparing rivaroxaban with warfarin for the prevention of stroke and thromboembolic events in people with non-valvular atrial fibrillation at risk of future thromboembolic events. Approximately 80,000 individuals (receiving rivaroxaban, comparator and placebo) have been recruited to rivaroxaban clinical studies to date. [5] Additional information from larger numbers outside the clinical trial setting, in conditions of routine clinical practice, may be helpful to further monitor possible adverse events in users of rivaroxaban. A Risk Management Plan has been developed for rivaroxaban by the MAH. This plan includes tools designed to monitor the important risks (including class effects and off-label use). The current safety specification (important risk, potential risk, missing information) is based on the Xarelto EU RMP version 7.5. [5]

Important identified risks, including class effects, are

- Haemorrhage

Important potential risks, including class effects, are

- Embryo-foetal toxicity

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Important missing information includes:

- Patients undergoing major orthopaedic surgery **OTHER** than the approved indication “elective hip or knee replacement surgery<sup>\*\*</sup>”
- Patients with severe renal impairment (CrCl <30ml/min)
- Patients receiving concomitant systemic treatment with CYP3A4 or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV protease inhibitors (e.g. ritonavir)
- Remedial pro-coagulant therapy for excessive haemorrhage
- Pregnant or breast-feeding women
- Patients with AF and a prosthetic heart valve
- long term therapy with rivaroxaban in treatment of DVT, PE and SPAF in real-life setting.
- Patients < 18 years

Outcomes of special interest

- Increase in liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST)], Gamma-Glutamyl Transferase (GGT)] and bilirubin
- Management of homeostasis in patients with the indications of interest who also undergo surgery (elective or urgent) during the observation period in this study.

The safety profile and efficacy of rivaroxaban in children aged <18 years have not been established. No data are available. Therefore, rivaroxaban is not recommended for use in children below 18 years of age. [1] A Paediatric Investigation Plan (PIP) has been agreed with EMA, the aim of which is to contribute to the insight in the efficacy and safety profile of rivaroxaban in paediatric populations.

Off label prescribing of rivaroxaban (in terms of medical indication, dose etc) is possible so any data relating to off label use will be examined in this study.

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<sup>\*\*</sup> This study is not designed to monitor the safety and use of rivaroxaban in this group of off-label **surgical** patients. However since there is a need to inform on off-label use in non-orthopaedic medical conditions requiring anticoagulation, data from any patients within this latter category will be eligible for inclusion and evaluated as part of the secondary objective (ii) in Section 2.2.2

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### **1.4 Anticoagulant Therapy**

In the UK, evidence based guidelines provide recommendations to practitioners to support pharmacotherapeutic decision making. These are summarised in the sections below.

#### ***1.4.1 Atrial Fibrillation***

For the diagnosis and management of patients with AF who are either post-stroke, or have had a TIA the following standard pharmacotherapeutic treatments are recommended:

- warfarin should be administered as the most effective thromboprophylactic agent
- aspirin or dipyridamole should not be administered as thromboprophylactic agents unless indicated for the treatment of comorbidities or vascular disease. [21]

#### ***1.4.2 DVT/PE***

A choice of low molecular weight heparin (LMWH) or fondaparinux should be offered to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs with the following exceptions:

- For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m<sup>2</sup>) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.
- For patients with an increased risk of bleeding consider UFH.
- For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy.

The LMWH, fondaparinux or UFH should be started as soon as possible and continued for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]) is 2 or above for at least 24 hours, whichever is longer.[22]

The Scottish Intercollegiate Guidelines recommend that after the first episode of limb deep vein thrombosis, continuation of anticoagulation with an oral anticoagulant (warfarin) is required as maintenance treatment. The aim is to minimise the risks of PE, recurrent DVT and post thrombotic syndrome (PTS) [23]

The British guideline on oral anticoagulation with warfarin recommends that:



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- first episodes of VTE should be treated with an INR target of 2.5 - the target range should not be lowered for patients who require anticoagulation beyond 3 months
- recurrent VTE whilst anticoagulated and within the therapeutic range should be managed by increasing the INR target to 3.5
- patients with proximal DVT or PE should be treated for at least 3 months to prevent extension of thrombus and recurrence. [24]

### **1.5 Considerations in initiating anticoagulation treatment, stroke and bleeding risk**

For this study, it is important to capture information on a patient's stroke and bleeding risk score as derived from information within existing medical records relating to index date and end of observation, so that any changes in risk of either can be examined in relation to changes in factors associated with clinical condition.

The CHADS<sub>2</sub> classification scheme is a clinical prediction rule (an acronym for Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus, and prior Stroke or transient ischemic attack) that estimates the risk of stroke in patients with non-rheumatic atrial fibrillation.[25;26] Its use is advocated by the National Institute for Health and Clinical Excellence (NICE) to determine whether or not antithrombotic therapy should be initiated based on patient-specific stroke risk.[27] The classification scheme assigns a score (0 to 6; one point each for Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus and two points for prior Stroke or transient ischemic attack) based on the number of risk factors an individual patient has; a high CHADS<sub>2</sub> score corresponds to a greater risk of stroke such that a score of 2 and above indicated the need for oral anticoagulation therapy, while a low CHADS<sub>2</sub> score corresponds to a lower risk of stroke, whereby other risk modifiers should be considered.

To complement the CHADS<sub>2</sub> score, by the inclusion of additional 'stroke risk modifier' risk factors, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score has been proposed. [25;26;28] These additional non-major stroke risk factors include age 65-74, female gender and vascular disease. In the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, 'age 75 and above' also has extra weight, with 2 points.

In clinical practice, bleeding risk assessment should be performed prior to initiation of oral anticoagulation therapy. A validated bleeding risk score which is included within the European Society of Cardiology (ESC) Guideline for management of AF patients is the HAS-

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bled (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly) bleeding risk schema, whereby a score of  $\geq 3$  indicates "high risk" and some caution and regular review of the patient is needed. Note that knowledge of INR control is needed to assess the 'labile INR' criterion; otherwise for a non-warfarin patient, this scores zero.

In the UK, a NICE clinical guideline is available which outlines assessment of risks of VTE and bleeding in medical patients admitted to hospital. [29] It advocates a form of benefit risk assessment of offering VTE prophylaxis to medical, surgical and /or patients with trauma balanced against risk of VTE and bleeding. It also states that choice of pharmacological VTE prophylaxis should be based on local policy, clinical condition and patient preference. Thus it is important to examine whether the likely hierarchical clustering of patients –by region geographically and by medical institution has any impact on either bleeding risk assessment or incidence of haemorrhage.

### **2.0 AIMS AND OBJECTIVES OF STUDY**

#### **2.1 Overall aim:**

To monitor the short-term (12 weeks) use and safety profile of rivaroxaban prescribed to new-user adult patients (i.e. rivaroxaban naïve who may or may not be antithrombotic therapy naïve) for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, the treatment of DVT, PE, and the prevention of recurrent DVT and PE in adult patients, requiring anticoagulation under normal conditions of use in the secondary care hospital setting. In addition since it is desirable to put these observations into context and characterise a population treated with existing anticoagulant treatment to allow the variation in determinants of treatment choices to be examined in relation to risk, a similar number of evaluable patients receiving alternative anticoagulant therapy will be monitored in order to inform on the adoption of rivaroxaban into clinical practice.

#### **2.2 Specific objectives:**

##### **2.2.1 The primary objective**

Its purpose is to provide timely information on:

(i) Estimation of the cumulative incident risk (separately) of the following important identified risk for rivaroxaban users which is:

- Haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (Table 2))

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### 2.2.2 Secondary Objectives

These are given below. Their purpose is to provide timely information on:

- (i) Prescriber and cohort accrual and the type of prescriber responsible for, and the setting of initiation of treatment with either rivaroxaban or alternative anticoagulant therapy.
- (ii) Prevalence of non-clinical reasons for prescribing, prognostic health factors and clinical risk factors for haemorrhage as reported in medical charts for patients undergoing anticoagulation with either rivaroxaban or alternative anticoagulant therapy in the secondary care hospital setting and the treatment programme they received to advance the understanding of the patient population prescribed rivaroxaban in actual clinical practice in the secondary care hospital setting
- (iii) Changes of health profile of patients, assessment of adherence, plus any alterations of the treatment programme during the 12 week observation period, as recorded in medical charts.
- (iv) To quantify the risk of:
  - (a) (separately) haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites for contextual anticoagulant therapy cohort
  - (b) all major bleeding specified in primary objective for both rivaroxaban and contextual anticoagulant therapy cohort (as composite)
  - (c) (separately) haemorrhage (major bleeding according to Table 2) within critical organ sites other than specified in primary objective for both rivaroxaban and contextual anticoagulant therapy cohort
  - (d) all major and clinically relevant non-major bleeds (as a composite outcome)
  - (e) thromboembolic complications (incident and recurrent)
  - (f) other<sup>††</sup> events including special outcomes of interest (severe hepatic failure and abnormal LFTs above 3x ULN) as recorded in medical charts during the 12 week observation period and, if number of reports are sufficient, in patient subgroups of special interest, including:
    - reported indications
    - elderly ( $\geq 65$  years)<sup>‡‡</sup>, other contraindicated or special groups (e.g. pregnant and breastfeeding women, patients with concurrent significant renal or hepatic

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<sup>††</sup> Other than major and clinically relevant non major bleeding outcomes, or thromboembolic complications (recurrent or incident)

<sup>‡‡</sup> Children and adolescents aged less than 18 years of age will be excluded from the SCEM study. Since this is important missing information, data on this special population will be captured within the complementary M-PEM, if reported.

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impairment; patients with known VTE and/or haemorrhagic risk factors e.g. congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, active ulcerative gastrointestinal disease) and off-label groups (patients with other non-orthopaedic medical conditions )

- concomitant use of medications that are contraindicated or to be used with caution (e.g. CYP3A4 inducers/inhibitors, P-gp inhibitors, anticoagulants, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, hormone and oral contraception therapy and platelet aggregation inhibitors)

### ***2.2.3 Exploratory objectives (for rivaroxaban only)***

The specific objectives that follow are all exploratory. The purposes of these objectives are:

- (i) Where possible, to quantify the incidence of other important identified and potential risks (not mentioned in objective 2.2.1), other frequently and rarely reported adverse events as recorded in the medical charts and to identify previously unrecognised ADRs
- (ii) To describe clinical features and management of cases of overdose, major bleeding (according to pre-specified definition (Table 2), VTE events indicating failure of anticoagulation and management of homeostasis during surgery as recorded reporting the medical charts in the first 12 weeks after treatment initiation in the cohort exposed to rivaroxaban.

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**Table 2. Haemorrhage outcomes[30]**

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**A major<sup>†</sup> bleeding event will be defined using ISTH criteria (21) as clinically overt bleeding that is associated with:**

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- A fall in haemoglobin of 2 g/dL or more, or
  - A transfusion of 2 or more units of packed red blood cells or whole blood, or
  - A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
  - A fatal outcome
- 

**A clinically-relevant non-major bleeding event is defined as an overt bleeding event not meeting the criteria for a major bleeding event, but associated with medical intervention<sup>§§</sup>, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.**

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**Examples of non-major clinically relevant bleeding events are:**

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- Epistaxis if it lasts for more than 5 minutes, if it is repetitive (i.e., 2 or more episodes of true bleeding, i.e., no spots on a handkerchief, within 24 hours), or leads to an intervention (packing, electrocautery, etc.)
  - Gingival bleeding if it occurs spontaneously (i.e. unrelated to tooth brushing or eating), or if it lasts for more than 5 minutes
  - Haematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract
  - Macroscopic gastrointestinal haemorrhage: at least 1 episode of melena or haematemesis, if clinically apparent
  - Rectal blood loss, if more than a few spots
  - Haemoptysis, if more than a few speckles in the sputum, or
  - Intramuscular hematoma
  - Subcutaneous hematoma if the size is larger than 25 cm<sup>2</sup> or larger than 100 cm<sup>2</sup> if provoked
  - Multiple source bleeding events
- 

<sup>†</sup> The three organ sites included in the primary objective are gastrointestinal and, urogenital (which meet the criteria for major bleed) and intracranial. Case definition will be confirmed by project steering committee prior to patient recruitment.

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<sup>§§</sup> Such as: Surgical or endoscopic intervention; decompression of a closed space to stop or control the event; protamine sulphate administration

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### **3.0 ETHICAL CONSIDERATIONS**

All studies carried out by at the DSRU will be conducted in accordance with national and international guidelines. [31;32] For this cohort study, ethics approval via IRAS (integrated research application system) in the UK will be required. Participating specialist HCPs will be asked to provide patients with documentation (with a unique study reference code). Patient study documentation will include an patient information sheet about the study which will describe that their secondary care medical charts will be accessed during the time-frame of active study data collection by the specialist HCP and/or DSRU research staff in order to extract exposure and outcome data relevant to the 12 week observation period, <sup>\*\*\*</sup> and also that their primary care medical charts may be accessed (*contact details to be provided on the consent form*), if they are discharged to the care of their GP within the 12 week observation period. It will also provide contact details of the DSRU study team if they have any questions.

Specialist HCPs will provide patients with a consent form so that patients can consider and give consent for their participation within this project. The consent form will stress confidentiality, that no specific details of their treatment will be released to external parties, that the patient may withdraw consent at any time by contacting either the specialist HCP or the DSRU study research team directly, and that the patient will not be asked to attend clinics more than usual or undergo any additional treatment or questioning. The consent form will also request information to be provided on patient ethnicity, current marital status, current employment status, smoking and alcohol use. This is optional and will be used to inform on representativeness of study cohort. Three signed copies are required. Those patients who wish to inform the DSRU immediately of their decision will give the signed consent form to the specialist HCP. They in turn will send the original to the DSRU, retain one copy for their records and issue a copy to the patient. Where a patient is unable to sign the consent form (e.g. because of weakness of the dominant hand following stroke), consent will be confirmed orally in the presence of a witness (an individual other than the person taking consent) who will sign the consent form on behalf of the participant.

For those patients who wish to have a further opportunity to reflect on their participation, the specialist HCP will ask the patient to complete a ‘consent to contact’ form, which will enable DSRU study research staff to contact the patient through their preferred route of contact (surface post, email, or telephone) after a period of at least two days to obtain consent. This

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<sup>\*\*\*</sup> The exception will be if a female patient becomes pregnant, the outcome of the birth will be requested.

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will be the only point at which DSRU research staff will contact the eligible patients directly. If the patient agrees to participate, they will sign the consent form, retain a copy and send the original and one further copy via surface mail to the DSRU study coordinating centre, or, if preferred, to the specialist HCP (who will then submit the original form to the DSRU). Receipt of the signed consent to contact form or the fully completed consent form (if patient provides immediate consent) by the DSRU study team should be within 4 weeks after index date, if possible.

In addition, within the same time frame, the specialist HCP will be asked to summarise selected data from the medical charts (non-clinical reasons for prescribing, demographic and treatment details) using a simple questionnaire (anonymised using the patient's allocated study reference number) and send these data to the DSRU coordinating centre either through a secure electronic website, or via surface mail.

### **3.1 Consent for patients without mental capacity**

We wish to include patients who do not have mental capacity and who are therefore unable to consent for themselves. This would include patients who have had a stroke, have cognitive impairment, dementia and/or learning difficulties. Due to the nature of the indication for use, many patients with these conditions may be prescribed rivaroxaban and these are patients who may be unable to consent for themselves but are still at risk of adverse events and therefore should be included. Exclusion of patients with mental incapacity would mean exclusion of a group of potentially high risk patients.

For potential patients who lack mental capacity to consent to research, a medically qualified member of the care team will identify a personal consultee to approach and discuss the study with. This will be a person who is in a position to advise on the wishes and feelings of the potential patient in relation to taking part in this research project. It is anticipated that the personal consultee would be a family member or friend. In the situation where no family member or friend is willing and able to act as a consultee, a nominated consultee will be sought following the local arrangements in situ. This will be a person who has no connection with the project and who is willing to be consulted about the participation of the person who lacks capacity in the research project. In the situation where consent is being sought out of hours and there is no nominated consultee available, the process can wait until a suitable person is available.

The identified consultee will be provided with a consultee information sheet (there will not be a separate information sheet for the nominated consultee, if they wish to view a copy then they can request a copy of the personal consultee information sheet) and will also have an opportunity to ask

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questions. The consultee will then be asked to complete a consultee declaration form if they believe the patient would have no objection to taking part in the study.

If a patient regains capacity during their participation in the study, they will be informed about the study, given a patient information sheet and asked to provide their own consent in the normal way. If a patient does not wish to continue in the study, they will be withdrawn.

### **4.0 METHODS**

#### **4.1 Study Design & Time frame**

This study will be a registry-based observational, population-based cohort study with an internal contextual cohort utilising the technique of cohort event monitoring to study the short-term (up to 12 weeks) safety profile and use of rivaroxaban prescribed by specialist HCPs in the secondary care hospital setting in the immediate post-marketing period for the licence extension. Twelve weeks observation is regarded as a period of time sufficient for data from all relevant patient populations (which informs on any post start of observation health events related to short-term exposure that they might have experienced) to be recorded in the patient's medical charts by specialist HCP. Randomisation will not be required. Once the pharmacotherapeutic treatment decision has been made, and either rivaroxaban or the alternative anticoagulation therapy prescribed as the most appropriate treatment based on clinical need, a patient will be invited to participate in the study and consent obtained for access to information from medical charts (see section 3.0).

Study start is defined as the date that the first patient is recruited into the study, which is anticipated to begin May 2013 (*exact date to be confirmed*) and continue for a maximum of 36 months, or until the target sample size for both cohorts has been achieved (whichever is the soonest); see section 4.2. The final cohort sizes, period of observation and the duration of the SCEM study will be dependent on the level of prescribing of rivaroxaban by specialist HCPs in England and Wales (see section 4.2). Data collected during later time periods can be compared with earlier periods to identify any trends that may be emerging. Slow uptake may impact on the ability to meet the study objectives; in this instance the need to continue data collection, extend the observation period and the feasibility of study completion within the proposed time frame should be open to re-evaluation.



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Period of observation for analyses will commence from index date (i.e. actual start date of anticoagulant treatment, not the date first seen by the specialist) and continue for 12 weeks (or less if patient discontinues to be under the care of the specialist HCP; to be established via the 12 week end of observation questionnaire) in order to allow for detection of outcomes associated with oral anticoagulant treatment initiation as recorded in medical charts. This study will also collect information on exposure to any other medicines (including those given as part of acute care management within the four calendar weeks prior to index date) as recorded in medical charts in order to explore impact of those treatments on outcomes of interest. Since patient care is likely to be shared between secondary and primary care for most patients during the 12 week observation period, the patient's GP will be contacted<sup>†††</sup> to complete a simple questionnaire to collect any information on outcomes of interest that have been recorded in the patient's medical charts held in primary care during the 12 week observation period to minimise under-reporting on selected outcomes. Where additional outcomes are identified that have not be reported by the initiating prescriber, these will be followed-up with the GP to ascertain further information.

### 4.2 Sample size

#### ***4.2.1 Sample size for primary outcome (haemorrhage – within intracranial, gastrointestinal and urogenital critical organ sites) where expected cumulative incidence is known***

Where studies, such as clinical trials, have already estimated the impact of the exposure on the outcome of interest, the one objective of this observational study is to be able to estimate the measure of frequency so that it lies within a range (margin of error) close to the estimate from the RCT, assuming this represents the true value. Ideally this margin of error (also called precision) should be as narrow as possible, so that the frequency is estimated as precisely as possible [33], for example the margin of error is equal to half the width of the confidence interval. for the frequency estimate As such, in this study it is more appropriate to choose a sample size that will yield a confidence interval of a predefined width for those identified risks defined within the primary outcome which are of greatest clinical and medical importance i.e. major bleeding outcomes (Section 2.2.1). Table 3 displays the samples sizes (95% confidence intervals) across a range of expected incidences and levels of precision.

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<sup>†††</sup> Overlap of data collection between SCEM and M-PEM should minimise any under-reporting of events of interest associated with the primary objective. However due consideration should be given to a) possible non-response of GPs for the long-term M-PEM study that might arise from the GP's knowledge that the patient is participating in the SCEM and b) that some patients are managed by specialist GPs purely on an outpatient basis and thus may never be officially admitted to hospital . The emphasis must be made that the two studies are complementary and participation in both is highly desirable.

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From rivaroxaban clinical trial data, the cumulative incidence of each of the primary outcome major bleeding events (GI, urogenital and intracranial) in patients taking rivaroxaban for DVT and prevention of recurrent DVT and PE over 12 weeks of treatment was approximately 0.2%, 0.1% and 0.0%, respectively. Since information on the reported incidence for intracranial major bleeding outcomes within the first 12 weeks of treatment is limited, the reported incidence of intracranial haemorrhage with enoxaparin/vitamin K antagonist (VKA) from RCTs of 0.1% within 12 weeks will be used as an estimate of the incidence of that event in this population for rivaroxaban. From clinical trial data, the cumulative incidence of the primary outcome major bleeding events was similar in patients taking rivaroxaban for PE (~0.3%). As such, we do not expect any difference in cumulative incidence of bleeding between PE and DVT patients.

The formula used to calculate the sample size based on an estimation of the proportion of patients who will experience major bleeding outcomes is[33]:

$$\text{Sample size} = \frac{3.84 \times p(1-p)}{(\text{precision})^2} \quad \text{where } p = \text{estimated proportion (cumulative incidence)}$$

Thus in this population of patients taking rivaroxaban for the treatment of DVT and PE and prevention of recurrent DVT and PE, in order to estimate the expected (true) cumulative incidence of the primary outcomes of major bleeding (GI, urogenital and intracranial) of 0.4% (0.2%, 0.1% and 0.1%, respectively), within +/- 0.39%, we would need a sample size of 1005 patients (Epi Info v6).

The cumulative incidence of each of the primary outcome major bleeding events (GI, urogenital and intracranial) in patients taking rivaroxaban for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation over 12 weeks of treatment was approximately 0.5%, 0.1% and 0.1%,<sup>\*\*\*</sup> respectively. [5] Thus, in this population of patients taking rivaroxaban for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, in order to estimate the expected (true) cumulative incidence of the primary outcomes of major bleeding (GI, urogenital and

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<sup>\*\*\*</sup> Approximate estimates of cumulative incidence in 12 weeks of treatment, based on steady increase in incidence over time and overall cumulative incidence from a median of 590 days treatment exposure (90/590\*N)

## Appendix 1. Study Protocol

intracranial) of 0.7% (0.5%, 0.1% and 0.1%, respectively), within +/- 0.69%, we would need a sample size of 561 patients.

Thus, in summary, for this study, a minimum sample size of 1700 evaluable patients for rivaroxaban is desirable to ensure the minimum of 1005 and 561 patients is achieved for each of the two indications described above for each drug, based on ratio of 1:2 respectively, with 12 weeks observation period sufficient to estimate cumulative incidence of specified primary outcomes of interest with desired precision. A similar number of evaluable new user alternative anticoagulant therapy patients will be collected for the internal contextual cohort.

In this study, sample size has been calculated such that the study estimate of cumulative incidence of major bleeding within each indication should fall with a pre-specified proportion which is relative to the true value. There is no ideal precision which should be used when calculating sample size, so use of proportion as an indicator of relative precision ensures the margin of error remains appropriate to the estimated size of cumulative incidence of major bleeding events.

**Table 3. Sample sizes of evaluable patients required to estimate the expected (true) cumulative incidence of a specified adverse event with 95% confidence intervals of different precisions (0.2% to 5%).**

<b>Incidence from RCT (%)</b>	<b>Precision 0.20%</b>	<b>Precision 0.39%</b>	<b>Precision 0.50%</b>	<b>Precision 0.69%</b>	<b>Precision 1%</b>	<b>Precision 2%</b>	<b>Precision 3%</b>	<b>Precision 5%</b>
<b>0.10</b>	958	252	153	81	38	10	4	2
<b>0.20</b>	1913	504	307	161	77	19	9	3
<b>0.30</b>	2864	755	459	241	115	29	13	5
<b>0.40</b>	3812	1005	612	321	153	38	17	6
<b>0.50</b>	4755	1255	764	401	191	48	21	8
<b>0.70</b>	6631	1752	1067	561	267	67	30	11
<b>0.80</b>	7564	2000	1218	640	305	76	34	12
<b>1.00</b>	9418	2494	1519	798	380	95	42	15
<b>2.00</b>	18475	4926	3003	1579	752	188	84	30
<b>3.00</b>	27187	7296	4452	2342	1117	279	124	45
<b>4.00</b>	35566	9605	5866	3089	1473	369	164	59
<b>5.00</b>	43627	11854	7246	3818	1821	456	203	73

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### ***4.2.2 Sample size for general safety surveillance of other events (aside from the primary outcome) where background rate is unknown.***

For purposes of general safety surveillance (for events arising from exploratory objective (Section 2.2.3 (iii)) for the population of interest (i.e. those prescribed rivaroxaban according to labelled new indications), it is possible to estimate a sample size necessary to detect a minimum of three cases<sup>§§§</sup> based on an assumed rate in that exposed sub-group and assuming the background rate is zero. [35] For this study, a sample size of at least 1700 evaluable patients (see section 4.3.2.3) should allow for the detection of at least three cases of an event if it occurs with a rate of at least one in 200, with 99% probability. [35]

## **4.3 Study Population**

### ***4.3.1 Phase 1: Selection of specialist HCP***

Since it is known that managed entry of rivaroxaban into the NHS exists (to assist organisations in developing medicines management policies and to inform prescribing decisions) the accessible secondary care settings will be those for which recommendations for prescribing rivaroxaban have been adopted. Thus the actual secondary care hospital settings will be a subset of all secondary care hospital settings in England and Wales. A representative sample <sup>\*\*\*\*</sup> of specialist healthcare professionals responsible for prescribing anticoagulants ('specialist HCP') for medical conditions that require anticoagulation within those accessible settings will be systematically identified by the DSRU and will be invited to participate in the study prior to study start (anticipated May 2013, to be determined). This non-probability sampling method will be used because a probability sampling framework is not feasible as stated above.

Routes of identifying relevant specialist HCPs within these accessible settings will include the use of the existing clinical research networks and support networks provided by allied healthcare professionals, including hospital pharmacists, some of whom are highly specialised anticoagulation pharmacists working in secondary care hospital settings across England and Wales.

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– §§§ In many situations involving rare reactions it is assumed that the frequency of the event is small, so that the occurrence of the event follows a Poisson distribution and the 95% confidence interval (CI) calculated based on the number of events. If no events are observed in a study of X individuals then one can be 95% certain that the event occurs no more often than  $3/X$ . [34]

\*\*\*\* Representativeness of specialist HCPs will be considered in terms of geography, secondary care setting (teaching, general, private, outpatient only).

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Specialist HCPs will be informed that they will be participating in a cohort study which will monitor the extension of licence of a recently introduced oral antithrombotic agent (rivaroxaban), in accordance with requirements within the Risk Management Plan for that product. Using a bespoke website, specialist HCPs will be required to register online with the study co-ordinating centre (DSRU) in order to receive access to relevant study documentation. Each participating specialist HCP will be requested to make treatment decisions independent of the study and then to evaluate whether a patient is eligible for inclusion based on broad entry criteria (see below).

Remuneration, in line with the standard British Medical Association (BMA) rate will be paid to the NHS trust to cover time and administration costs incurred (either by specialist HCPs or associated staff) to assist with obtaining consent and completing questionnaires.

### ***4.3.2 Phase 2: Selection of patients***

The accessible study population will be that portion of the target population of interest to whom participating specialist HCPs have access. The identification of the actual study population, (which will be a subset of the accessible study population) will be through (non-probability) systematic sampling whereby all consecutively identified<sup>††††</sup> eligible new user patients treated by any specialist HCP (after the pharmacotherapeutic treatment decision has been made that one of the two study oral anticoagulants is the most appropriate treatment based on clinical need) and who provide consent ( see section 3.0) will be enrolled until the desired sample size is reached. This method will be used because a probability sampling framework is not feasible and because participation within the study is not required as a condition of receiving treatment. This approach is intended to reduce conscious or unconscious selection bias on the part of the specialist HCP as to whom to invite to participate in the study, especially with regard to prognostic factors that may be related to prognosis.

New users of rivaroxaban will be comprised of rivaroxaban naïve patients, who may or may not be antithrombotic or anticoagulant treatment naïve patients newly initiated by specialist HCPs. The patient may then have medicines management transferred to the GP in primary care. Thus, the GP may take on the primary role of monitoring treatment, providing prescriptions and altering the dose when necessary, with the option of referral to secondary

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<sup>††††</sup> As relevant to the date that the specialist HCP registers to participate in the study

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care if and when required. Alternatively, the patient may be primarily managed within the secondary care setting alone.

The contextual cohort will be comprised of patients for whom no exposure to anticoagulation therapy has occurred within the 12 months prior to initiation by the Specialist HCP for the current study. Clinical care pathway will be the same as that outlined above for rivaroxaban patients.

Since this is a new user inception or incidence rivaroxaban cohort that is being identified, this study avoids the introduction of a number of biases associated with existing users (including incidence/prevalence bias, survivorship bias, and follow-up bias) which may impact on the measure of frequency of primary objective. Data will also be available for the internal contextual cohort which will have been collected during the same calendar period, for similar indications using the same data collection methods, and all subject to the same protocol. This minimises effect of bias from non-random measurement error. However, whilst users of anticoagulant therapy appear to provide a 'logical' contextual cohort that may be similar with regard to some clinical risk factors, they may also differ with respect to other important confounding factors such as disease severity. The key purpose of this contextual cohort is to explore the variation in the distribution and determinants of prognostic and clinical risk factors. It is not to compare risk of primary outcome between the two groups.

The first part of the second phase of the study will involve participating specialist HCPs capturing (in anonymised format using patient unique identifier) brief summary data (e.g. sex, age, indication, bleeding/stroke risk score and non-clinical reasons for prescribing) as recorded in the medical charts for **all** individuals invited to participate (including those who declined) for whom the clinical decision to prescribe rivaroxaban or alternative anticoagulant therapy was made under conditions of real life practice. These data will help examine the representativeness of the study population.

Cohort recruitment will be examined regularly to monitor the number of evaluable patients included, so as to ensure that the desired ratio of 1:1 rivaroxaban: contextual cohort patients with the relevant indications is achieved in the final overall study cohort for secondary objective analysis.

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### **4.3.2.1 Patient Inclusion Criteria**

Since this is an observational cohort study conducted in a naturalistic setting, open patient entry criteria apply to maximise external validity. General inclusion criteria are: \*\*\*\*

- age 18 years or above after study start<sup>§§§§</sup>
- index date on or after study start
- signed, informed consent
- patients treated for DVT or PE
- patients with non-valvular AF ( with one or more risk factors) treated for prevention of stroke and systemic embolism

### **4.3.2.2 Patient Exclusion Criteria**

Specific exclusion criterion for the alternative anticoagulant therapy cohort is:

- Any use of univalent direct thrombin inhibitor or direct factor Xa inhibitors.
- use of anticoagulant therapy or other vitamin K antagonists recorded within one year prior to index date.<sup>\*\*\*\*\*</sup>

### **4.3.2.3 Evaluable patients.**

Evaluable patients are those patients who have provided consent and for whom analysable clinical data has been provided in the data collection questionnaires. Evaluable patients for whom the second phase (12 week) survey questionnaire (from BOTH specialist HCP and GP) is returned blank (contain no clinical information) or has not been returned will only be included for analysis of secondary objectives (i) and, (ii).

Consented patients will not be considered evaluable if the specialist HCP reports that the patient did not take rivaroxaban or alternative anticoagulant therapy. If there is evidence to suggest duplication of patients, either through inadvertent duplication between different specialist HCPs within the same clinical setting, or if a patient was switched from rivaroxaban to alternative anticoagulant therapy, or there is a significant delay (>1 month) in receipt of phase 1 survey form then the patients identified will be considered for inclusion on a case by case basis by the study manager and/or project advisory committee.

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\*\*\*\* Any cases in which there is ambiguity relating to the indication for treatment will be reviewed on a case by case basis, in order to confirm the prescribing indication/indications.

§§§§ However, a patient under the age of 18 will be included in the study if, in what is expected to be rare situations, a doctor decides on the basis of his/her clinical judgement to prescribe rivaroxaban for such person.

\*\*\*\*\* patients will be excluded if they are being treated with antiplatelet therapy exclusively

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Patients will be automatically withdrawn if the patient or specialist HCP provides informed written or verbal notification that they no longer wish to participate at any stage of the study.

### **4.4 Data Collection**

Medical charts-based data collection in this study will be conducted in various phases; relevant documentation (such as information leaflets, questionnaire, consent forms, etc) will be available both as hard copies and electronically for download by the participating specialist HCP.

#### ***4.4.1 Data Collection Methods***

##### ***4.4.1.1 Recruitment***

The first phase will have two parts.

Part 1: Recruitment of eligible specialist HCP.

Demographic and prescribing preference data on specialist HCPs (see below) will be collected upon registration with the DSRU. The DSRU will allocate a unique HCP study reference number to each participating specialist HCP for study audit and data management processes.

Part 2: Recruitment of eligible patients initiated with the study drug under clinical care of participating specialist HCP.

For all eligible patients invited to participate, the specialist HCP will be asked to create a patient log to record anonymously (using the study patient reference number provided on patient study documentation issued), demography (age and sex), indication, treatment given and presence of known pre-existing risk factors for stroke and bleeding as derived from data within existing medical charts. This log will be submitted to the DSRU coordinating centre either through a secure online website, or via surface mail. . The unique study reference number allocated to each patient will be used for study audit and data management processes.

##### ***4.4.1.2 Exposure/outcome data collection***

The second phase will also have two parts.

Part 1: At least twelve weeks post index date, the specialist HCP will be prompted to complete a questionnaire which will gather information recorded within medical charts on medical history and medication use prior to or present on index date; changes on general health and medications during treatment, clinical events of medical interest and serious adverse event reports [classified using the International Conference on Harmonisation definitions [36]]. For patients for whom the specialist HCP reports that the patient was



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discharged to primary care for continued treatment during the 12 week observation period, the patient's GP will be contacted to complete an abridged end of survey 12 week questionnaire using data recorded within primary care medical charts.

Part 2. Events of interest will undergo aggregate assessment of drug-relatedness, which may include follow-up using event-specific questionnaires sent to the specialist HCP (see 4.4.2.3) or GP. These events will be assessed for drug-relatedness by DSRU staff.[37] With the exception of these enquiries for additional information on selected events, no further monitoring of patients for purposes of data collection for this study from medical charts will occur post the survey period.

### ***4.4.2 Data Collection***

#### ***4.4.2.1 Specialist HCP***

The following data will be collected for specialist HCPs upon recruitment into the study

1. Demographic characteristics; (age, sex, ethnicity, year of first registration as HCP and awarding institution, year of first registration as specialist and awarding institution, year of start of employment at current institution)
2. Setting- (e.g. inpatient hospital ward, outpatient clinic);
3. Institution type (teaching, general, private) and region of location
4. Specialist HCP preference factors (type of novel anticoagulants prescribed in previous calendar month; proportion of novel anticoagulant use of all anticoagulants prescribed in previous calendar month)
5. Participation response/non-response rates (of eligible specialist HCPs within relevant existing research networks where available).

#### ***4.4.2.2 Eligible patient index date information***

For all eligible patients invited to participate, the following anonymised information will be collected using information contained within medical charts.

- demographic characteristics (age, gender)
- Reasons for prescribing (clinical judgement, recommendation from NICE, expert committee guidelines, trust formulary committee guidelines, Patient Group Direction in anticoagulation clinic, potential ease of reversibility of anticoagulant, lifestyle (anticoagulant monitoring needs), patient non-adherence with prior anticoagulant therapy, side-effects with prior anticoagulant therapy.
- which anticoagulant regimen was prescribed and start date

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- clinical condition requiring anticoagulation (indication)
- Prior anticoagulation treatment
- Stroke and Bleeding risk factors
  - Congestive Heart Failure/Left Ventricular Dysfunction
  - TIA/Thromboembolism History
  - Previous History of Stroke
  - Vascular Disease History (previous MI, peripheral arterial disease or aortic plaque)
  - History of Hypertension
  - Current Hypertension
  - Uncontrolled BP, > 160mmHg systolic at time of treatment initiation
  - Medication Usage Predisposing to Bleeding (Antiplatelet agents, NSAIDs)
  - Labile INR (Unstable/high INRs)
  - Diabetes Mellitus
  - Alcohol Abuse or Excess<sup>††††</sup>
  - Renal Disease (Dialysis, transplant, Cr >200 µmol/L)
  - Abnormal Liver Function (Cirrhosis, Bilirubin >2x Normal, AST/ALT/ALP >3x Normal)
  - Prior Major Bleeding or Predisposition to Bleeding

### 4.4.2.3 Patient 12 week end of observation questionnaire

For evaluable patients providing consent and for whom a completed index date questionnaire has been received by the DSRU, after at least 12 weeks of observation, a second questionnaire will be systematically generated to collect clinical information relevant to start of observation and any clinical events of medical interest (including serious adverse event reports [classified using the International Conference on Harmonisation definitions [36]] as recorded in the medical charts during the first 12 weeks of observation.

Data obtained from the 12-week end of observation questionnaire will include:

- Additional information on anticoagulation treatment regimen:
  - details of prior use of oral and parenteral anticoagulant therapy (thienopyridines, aspirin, glycoprotein IIb/IIa inhibitors, heparins)

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<sup>††††</sup> Alcohol abuse/excess is classified as intake greater than current recommendation by the NHS guidelines of > 21 units for men or > 14 units for women per week

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- If switching anticoagulant to either study drug: details of transition plan (both of prior anticoagulant and either study drug); Reasons for switching.
- Treatment regimen during the 12 weeks observation period (number of prescriptions issued (with dates, posology and duration) if known)
- Dates and reasons for changes in anticoagulant treatment regimen during 12 week observation period\*\*\*\*
- All relevant laboratory blood parameters during two-week observation period pre-index date and during 12 week observation where applicable (haemoglobin, platelet count, baseline clotting screen (PT, APTT, Fibrinogen Derived, D-Dimer) [*NB abnormalities would be reported as events*])
- If study drug stopped: date and reason for stopping, details of transition plan to alternative anticoagulant of study drug stopped; if required, details of reversal of anticoagulation therapy and management of bleeding complication.
- Recent ( < 4 weeks prior to index date) and concomitant medications (at index or during treatment):
  - not recommended for concomitant use (including azole antimycotics [e.g. ketoconazole] and HIV protease inhibitors)
  - to be used with caution (including fluconazole, strong CYP3A4 inducers, P-gp inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, oral steroids, hormone and oral contraceptive therapy, platelet aggregation inhibitors or other antithrombotic agents)
- Medical history relevant for important potential, identified and special risks of interest (plus dates of first diagnosis/report). **For example:** past history of DVT/PE, myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), other recent surgery within 3 months prior to index date, malignancy, pregnancy, family and/or personal history of congestive heart failure, diabetes mellitus, hypercholesterolaemia, peripheral arterial disease, COPD etc.)
- Specific information on renal function status at index date and any changes during 12 week observation period
- Specific information on hepatic disorders present at index date (cholestasis and jaundice, hepatic failure and associated disorders, hepatic fibrosis and cirrhosis and hepatic viral infections) and any recent abnormal liver function tests.
- event reports including selected risks of interest (Table 4)

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\*\*\*\* for rivaroxaban only

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- cause and date of death (if died) in the first 12 weeks after starting treatment;
- reported pregnancies at start or during the first 12 weeks after starting treatment and outcome of birth.
- behaviours prior to and/or starting treatment (e.g. smoking, alcohol/substance misuse); treatment adherence

**Table 4. Selected events of interest requiring further evaluation**

Risk/Missing Information	Proposed data capture	Comment
<b>IDENTIFIED, POTENTIAL AND SPECIAL RISKS AND OUTCOMES for targeted data collection on SCEM questionnaires</b>		
Major bleeding episode (into a critical organ sites )	Targeted outcome questions on critical sites	Selected risk factors collected on SCEM questionnaire. Further data on severity, management and risk factors to be collected via follow-up.
Clinically relevant minor bleeding episodes	Targeted outcome question to specify details	Selected risk factors collected on SCEM questionnaire. Not for follow-up
Incident and recurrent thromboembolic complications (DVT, PE, Stroke)	Targeted outcome questions	Selected risk factors collected on SCEM questionnaire. Further data on symptoms, severity, management and risk factors to be collected via follow-up.
Overdose, accidental trauma and Reversal of anticoagulation therapy	Targeted outcome question	Events of overdose (dose > 50mg/day) and accidental trauma are those of clinical medical importance which require acute medical/surgical treatment (with or without) hospitalisation Further data to be collected via follow-up
Management of homeostasis	Targeted outcome question	Data on management of homeostasis in patients reported with events of surgery (elective or urgent ) during the observation period will be collected via follow-up
Increased liver transaminases and Gamma-Glutamyl Transferase (GGT)	Targeted outcome question	Data on diagnosis of hepatic failure and where abnormal laboratory results indicate 3 X ULN relevant parameters will be collected via follow-up.
Concomitant use of contraindicated medications and medications to be used with caution	Targeted outcome question on other medications to gather duration and changes	Further data may be collected via follow-up
<b>IMPORTANT MISSING INFORMATION for general surveillance</b>		
Use during pregnancy and lactation	General event report	Further data to be collected via follow-up

### 4.4.2.4 Abridged 12 week end of observation questionnaire for GP

For each evaluable patient recorded as having been discharged from under the care of the specialist HCP to the care of their GP during the 12 week observation period, their GP will be contacted and invited to complete an abridged end of observation SCEM questionnaire which will gather information on clinical events of medical interest and serious adverse event reports [classified using the International Conference on Harmonisation definitions [36]] reported since date of discharge from secondary care up to end of the 12 week observation period, and recorded within primary care medical charts. Data obtained from this abridged 12 week SCEM questionnaire will include:

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- Anticoagulant treatment regimen as prescribed in primary care
- event reports of selected risks of interest (Table 4)
- cause and date of death (if died);
- reported pregnancies and outcome of birth.
- date and reasons for stopping (if stopped) including switching
- any newly prescribed concomitant treatments

### 4.4.2.5 Follow-up Questionnaires

During the course of the study, selected outcomes of interest (arising from Section 2.2) may undergo further evaluation for aggregate assessment of drug-relatedness to inform on any unusual features/manifestations, relevant risk factors, clinical course and behaviours (see section 4.8). Where necessary, a supplementary follow-up questionnaire which is bespoke to the outcome of interest may gather additional relevant information where recorded within medical charts. [37]

With the exception of these enquiries for additional information on selected events, no further monitoring of patients for purposes of data collection will occur post the survey period. In accordance with Good Pharmacovigilance Practice (GVP) sections VI.C.1.2.1 and VI.C.2.2.2, [38] data will be analysed at aggregate level partially at the time of compiling the interim report (because all information may be available then) and at study completion. Such aggregate analyses can help formulate possible hypotheses which then require further analytic study. Because of the epidemiological nature of the design of this cohort study, any *conclusions* on drug-relatedness will be made on aggregate basis at study milestones, i.e. when the interim and final reports are written (see Section 4.9.2 on Communications).

If any other safety issues become apparent during the conduct of this study, additional events and/or event categories may be added to the list of events for follow up and this will be documented accordingly.

Specific events of interest for further evaluation:

1. Pregnancies: All reported pregnancies will be followed-up using a supplementary questionnaire to describe the outcome of pregnancy<sup>§§§§§</sup>.
2. Deaths: All reported deaths will be followed-up to try to establish the cause of death.

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§§§§§ Drug-relatedness assessments of abnormal birth outcomes are not conducted by the DSRU

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3. Events: Selected events of interest as defined in Table 4 may be followed-up for additional information on relevant risk factors, where insufficient information is provided on the questionnaire. The event of switching given as a reason for stopping rivaroxaban (although not defined in Table 4) will undergo further evaluation.
4. Adverse events: Other adverse events deemed of medical importance by the DSRU which are considered to be possible safety signals (either arising from literature reports post marketing, or subsequent to interim data analysis) may also be followed-up for additional information on relevant risk factors for signal strengthening purposes.
5. Adverse events: Events within the list of Rare and Iatrogenic Adverse Reactions (RAIDAR) compiled by the DSRU (Appendix 2) will be automatically followed up if a more likely alternative explanation for their occurrence is not given.

### ***4.4.3 Methods to Maximise Questionnaire Response Rate***

#### ***4.4.3.1 Patient 12 week end of observation questionnaire***

A proportion of Specialist HCPs or GPs are likely to fail to submit these questionnaires. Methods to maximise response rates will include prompts from study facilitators by phone, email and personal contact and reminder questionnaires targeted at those who have not responded within one month of the date the initial questionnaire was sent.

#### ***4.4.3.2 Specific event follow-up questionnaires***

A duplicate event follow-up questionnaire will be sent to specialist HCPs or GPs for the specific patient(s) for whom they have not responded to the initial follow-up questionnaire; within six weeks of the date the initial event follow-up questionnaire was sent. Specialist HCPs and GPs will be offered remuneration for each follow-up questionnaire that is completed and returned to the DSRU.

## **4.5 Data processing**

Specialist HCP/ GP/patient identifiable information will be stored within a unique database. All original documents and individual correspondence from HCPs will be stored for 15 years at the DSRU, with considerable care taken to preserve patient confidentiality (see below).

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### ***4.5.1 Review of data***

All returned questionnaires with clinical data will be coded onto the study database. Medically important adverse events that have been selected for follow-up will be coded as a priority. There will be a regular monthly review of both the number of patients identified and study questionnaires returned, processed, and classified as void. This will assist in determining the point at which the final cohort size will be achieved. Aggregate data will be reviewed at interim and end of study milestones.

### ***4.5.2 Coding of data***

Data on indications, exposure, relevant medical history and medication use plus events of interest will be coded directly from targeted closed format questions on the questionnaire (which reference Medical Dictionary for Regulatory Activities (MedDRA) terminology) and coded onto the bespoke study database. Other events reported on the questionnaires as free text will be coded onto this database using the DSRU Event Dictionary Doctor Summary Term synonym list that is mapped to MedDRA, in order to enable consistent reporting to be provided using MedDRA terminology.

Study specific coding procedures will facilitate consistency in coding the data. An SOP will be created upon development of the study specific SCEM database and will be maintained within the DSRU. Regular meetings of DSRU staff will be held to discuss study questionnaires that are difficult to code. A consensus opinion will be reached by medically qualified staff.

Methods to handle issues of missing or conflicting data, will be summarised within the detailed study specific Data Management Plan (DMP) which will be constructed to assist database development and data analysis.

Completed questionnaires will be examined upon receipt for data completeness. Missing data are those where a variable is directly reported as missing or unavailable, where a variable observation is blank, where the reported data may not be interpretable, or where the value must be imputed to be missing because of data inconsistency or out-of-range results. The individual responsible for completing the questionnaire will be contacted to obtain the missing or correct information and data corrected when possible.

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The degree of data completeness will be summarized at interim stage. The distribution of observed variables for patients with missing data will be compared to patients with complete data to gain insight into whether there is any non-random systematic missing information. The most appropriate method to handle missing data for final analysis will be determined by the Project Steering committee at Interim stage.

### **4.5.3 Confidentiality procedures**

All DSRU staff sign confidentiality agreements and the DSRU is registered with the office of the Data Protection Registrar (Registration No. Z5438861).

DSRU information security policies are in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. These include ensuring the premises provides suitable physical and environmental security, all DSRU equipment is secure and protected against malicious software, the network can only be accessed by authorised DSRU staff, telecommunication lines to the DSRU premises are protected from interception by being routed overhead or underground and personal receive training regarding security awareness.

All original documents, individual correspondence from specialist HCPs, will be stored for 15 years at the DSRU, with considerable care taken to preserve the confidentiality of data. The DSRU databases are well protected. To ensure patient anonymity, the names and addresses of patients will be deleted from the DSRU database at an appropriate time point (provisionally this is at datalock or earlier if patients have provided informed notification that they wish to withdraw from the study, but the DSRU will request an extension to this to comply with CHMP requirements). Until this time, only appointed staff would have access to such data.

## **4.6 Quality Assurance**

Good clinical data management is a high priority at the DSRU. A number of strategies exist to minimise biased event monitoring study results. The DSRU has a set of rules and processes associated with the conduct of pharmacoepidemiological studies. Data quality is assured through a number of methods based on error-prevention, data monitoring, data cleaning and documentation. These include:

- Operator training;
- Vigilance of operators at the various stages of processing,



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- On screen validation during data entry,
- Adoption of and adherence to study-specific data coding conventions,
- Coding review meetings,
- Code list and algorithms
- Double entry (100% of questionnaires), error reporting and correction of discrepancies between the entries by quality assurance staff
- Coding of questionnaires are randomly reviewed by a quality assurance assessor.
- Routine data cleaning to screen for errors, missing values and extreme values and diagnose their cause; this being supported by bespoke software with objective, standardised logical checks and undertaken by the DSRU data manager or allocated staff.
- Relevant maintenance of reference tables, e.g., Event Dictionary
- Pilot testing of study documentation

### **4.7 Data analysis**

#### ***4.7.1 Cohort accrual, the type of specialist HCP responsible for, the setting of initiation of treatment, specialist HCP preference factors and non-clinical reasons for prescribing***

The following relates to Section 2.2.2 Secondary objectives (i) and (ii). Data on specialist HCP response rates will be presented, as will data on prescriber demography, type, setting and institution, specialist HCP preference factors and non-clinical reasons for prescribing. These data will be used to inform on cohort accrual and study timelines to target sample size.

Cohort accrual will be summarised with description of losses to follow-up and withdrawals. [39] Patients who decline to participate will be compared to those who provide consent (through use of data collected on the invitation log) in terms of demographic variables to assess potential for selection bias through non-participation. Similarly, patients who are lost to the study because of withdrawal of consent, or because of attrition will be compared to those who remain in the study to examine whether there are any systematic differences in demographic or treatment variables which may affect internal validity or generalisability.

#### ***4.7.2 To estimate the cumulative incidence of the important identified risk of haemorrhage for rivaroxaban.***

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The following relates to Section 2.2.1 primary objective (i) for rivaroxaban only and relates to haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (as defined in Table 2)..

For the three organ sites specified in the primary outcome, each of the individual components of the major bleeding criteria ( a fall in haemoglobin of 2 g/dL or more, or a transfusion of 2 or more units of packed red blood cells or whole blood, or a fatal outcome - as per table 2) will be summarised. Where an individual has one or more criterion for an individual organ site of interest, this will also be summarised – in such individuals the first report will be regarded as the incident event. The cumulative incidence (risk) of the primary outcomes reported during treatment within the 12 week observation period will be explored by estimating the cumulative incidence of incident reports (plus 95% CI) and cumulative hazard rates (plus 95%CI) of incident events over time. For purposes of this analysis the denominator (person-period at risk) is defined as the 12 week observation period (i.e., the time from the date the first prescription was issued for rivaroxaban (treatment index date) until the date of stopping (+ 2 days) or at 12 weeks if patient did not stop, whichever occurs first). The numerator will comprise of reports of incident major bleeding events during that 12 week observation period. These which have been adjudicated by expert review (using all available information from SCEM questionnaires, follow-up and any additional documentation). Where such information reveals that the event was misreported, that patient will be excluded as a case from the analysis, but contribute person-time exposed.

The cumulative incidence will be calculated according to the formula:

$$\frac{\text{Total number of new cases during 12 week observation period}}{\text{Population initially at risk}} \times 100$$

If the observed cumulative incidence from the SCEM study falls within the range expected as set by the precision limits of cumulative incidence from clinical trial data, then the null hypothesis (of no difference) will not be rejected. Cumulative hazard rate methods account for truncation of exposure time and censoring; for these analyses the exposure time would be censored at the time of the first event. Kaplan-Meier plots will be presented to describe time-to event as well as smoothed hazard plots to describe how the baseline risk of an event changes over time. Estimates of the hazard function will also be modelled to determine whether the baseline hazard (risk) of the event increases or decreases with time. A constant

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hazard over time may be consistent with a background (not caused by the drug) event rate, whereas a non-constant hazard over time may be an indicator of a drug-event relationship. The null hypothesis that the hazard rate of the selected event in patients prescribed rivaroxaban will be constant during the 12 week period following the start of treatment will be tested by fitting a parametric time to event model (e.g. Weibull). Such models have a shape parameter that indicates whether the hazard is significantly increasing or decreasing over time. At least five reports of an event are deemed necessary for modelling purposes.\*\*\*\*\*\*

Several sensitivity analyses will be performed: In one, observation start date will be imputed to be the same as the diagnosis date (i.e the index date will be shifted backwards in time) for those patients for whom a lag period between diagnosis and receiving rivaroxaban treatment was reported. The application of time-varying covariates methodology will enable examination of the impact of any transition from other treatments given as part of initial standard care on the results. In addition, since the primary analysis will be run only to include confirmed cases of incident major bleeding, it will be necessary to explore the reasons for exclusion of incomplete cases and examine their impact on the estimated measure of frequency.

Where possible, data will be stratified according to relevant strong risk factors (e.g. gender, age ( $\leq 60$ ,  $60-74$ ,  $\geq 75$  years), indication and past history of haemorrhage or VTE) and stratum-specific incidence rates examined.

Graphs of cumulative counts of events of interest, by month over the study period, will be examined for possible change in reporting over calendar time.

### ***4.7.3. To describe the health profile of patients at index date prescribed treatment with rivaroxaban in the secondary care hospital setting and the treatment programme they received to advance the understanding of the rivaroxaban patient population in actual clinical practice in relation to the contextual cohort.***

The following relates to Section 2.2.2 secondary objective (ii). Valid cohort demography (patient self-reported: age, gender, ethnicity, socioeconomic index) will be presented separately for both rivaroxaban and the contextual cohort, as reported at index date using all

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\*\*\*\*\* e.g. when the shape parameter ( $p$ ) for the Weibull model is equal to one, the hazard is estimated to be constant over time, if  $p$  is greater than one the hazard is increasing, if  $p$  is less than one the hazard is decreasing. The hazard function will be determined as non-constant if the 95% CI excludes the value one

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available information from questionnaires (completed by patient and specialist HCP). Other patient self-reported general health factors [BMI, weight, height, smoking and alcohol use] and indication-related characteristics [primary (and secondary if provided) diagnosis/decision, date and duration since first ever recorded; stroke and reported bleeding risk factors; pattern of most recent INR/APTT levels if switching from prior anticoagulant]; anticoagulant treatment initiation programme by specialist HCP (index date, dose and frequency) and non-clinical prescribing reasons. A synopsis of pre-index and concurrent relevant morbidities and medication use will also be provided.

For rivaroxaban cohort only, patient subgroups of special interest (Table 5 – ‘off-label’ use defined as arising from contraindications and those for which: a) precautions for use are recommended; b) appropriate clinical monitoring is recommended; c) limited information is available; and d) selected concomitant drug use) will be summarised in order to inform on real-life use of rivaroxaban. The proportion of patients within each special population subgroup prescribed rivaroxaban who had *one or more* relevant characteristics/conditions/co-prescribed medications at index date will also be summarised within each indicator group by simple aggregation of counts (Table 5).

Further stratification within-cohort by calendar period *may* also be undertaken to identify any cohort effects or trends that may be emerging.

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**Table 5. Special population Indicators of Use for Rivaroxaban**

5a) Indicators of Contraindicated Use ( <i>Patients can have up to 5 indicators</i> )
Treatment for medical indications other than licensed indications
Clinically significant active bleeding
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
Use in pregnancy and lactation
Hypersensitivity to the active substance or to any of the excipients
5b) Indicators of Use with Special Warnings or Precautions ( <i>Patients can have up to 11 indicators</i> )
Patients with liver cirrhosis with moderate hepatic impairment (classified as Child Pugh B), not associated with coagulopathy
Severe renal impairment (patients with creatinine clearance < 30 ml/min)
Moderate renal impairment (patients with creatinine clearance 30-49 ml/min)
Congenital or acquired bleeding disorders
Uncontrolled severe arterial hypertension
Active ulcerative gastrointestinal disease
Recent gastrointestinal ulcerations
Vascular retinopathy
Recent intracranial or intracerebral haemorrhage
Intraspinal or intracerebral vascular abnormalities
Recent brain, spinal or ophthalmological surgery.
5c). Indicators of Use in Patients with Limited Information ( <i>Patients can have up to 1 indicators</i> )
Patients with AF and a prosthetic heart valve
Children aged $\leq 15$ years
5d) Indicators of Use with Potential Drug-Drug Interactions ( <i>Patients can have up to 4 indicators</i> )
Concomitant systemic treatment with azole-antimycotics, e.g ketoconazole or HIV protease inhibitors
Concomitant treatment with CYP3A4 inhibitors/inducers or P-gp inhibitors
Concomitant treatment with other anticoagulants
Concomitant use with NSAIDs and platelet aggregation inhibitors

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### ***4.7.4 To describe changes of health profile of patients, assessment of adherence; number of indication related episodes and duration, plus any alterations of the treatment programme during the 12 week observation period.***

The following relates to Section 2.2.2 secondary objective (iii) Status of indication-related characteristics (alteration of diagnosis, stroke (CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc) and bleeding risk score (HAS BLED) if available) will be summarised, plus pattern of anticoagulant treatment adherence at the end of the 12 week observation period (as estimated from Medication Possession Ratio<sup>†††††</sup>) will be summarised. The frequency and reasons for attendance to clinics for review and management of anticoagulation and/or acute hospitalisations (including hospital referrals) will also be summarised, where reported. Alterations in treatment programme (change in dose, other drugs) will be described, as will any reason(s) for stopping treatment (including switching) and transition plans to other anticoagulants.

Changes in these indication-related characteristics and treatment details will be examined by comparing values at index and at 12 weeks post index date. Exploratory analysis may include data mining and descriptive measures for describing alterations in treatment programme.

The number of pregnancies, trimester of first exposure and details of births, terminations and miscarriages will be presented. The number of deaths (as recorded in medical charts) in the total cohort for each month of exposure will be calculated. Causes of death will also be described by system-organ class.

Sensitivity analyses will examine any under-reporting using data provided from the patients GP.

### ***4.7.5 To quantify the incidence risk and rate of events reported in the 12 week observation period in both the rivaroxaban and contextual cohort and in patient subgroups of special interest.***

The following relates to Section 2.2.2 secondary objectives (i) and (iv) regarding a) major bleeding outcomes as specified in the primary objective for the contextual cohort, b) other

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<sup>†††††</sup> For this study, MPR will be defined as:  $\frac{\text{No. days supply held during treatment}}{\text{No. days supply expected during treatment}} \times 100$

Where no. days held will be calculated from information derived from 12 week questionnaire on number of prescriptions and average treatment length of prescriptions (usually given in 7, 14, 28, 56 day repeats); no. days supply expected will assume chronic use from start to end of study observation or treatment stop date (if stopped)

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major or non-major clinically relevant bleeding outcomes not specified in the primary objectives , c) thromboembolism (recurrent and incident) and d) any other events reported in the 12 week observation period .

For major bleeding events not specified in the primary outcome, each of the individual components of the major bleeding criteria ( a fall in haemoglobin of 2 g/dL or more, or a transfusion of 2 or more units of packed red blood cells or whole blood, or a fatal outcome - as per table 2) will be summarised. Where an individual has one or more criterion for an individual organ site of interest, this will also be summarised – in such individuals the first report will be regarded as the incident event.

For clinically relevant non-major bleeding events, each of the individual associated components (as per table 2 such as requiring medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life) will be summarised. Where an individual has one or more criterion for a clinically relevant non-major bleeding event, this will also be summarised – in such individuals the first event report will be regarded as the incident event.

Analysis of event data for purposes of signal detection includes exploring overall risk and rate for the observation period and time to onset profiles. The methodology provides a numerator (the number of reports of an event) and a denominator (person-time at risk), both collected within a known time frame. This allows for the calculation of crude risks (percent of total valid cohort exposed) and rates (Incidence Densities-ID; person-time incidence rates) for each event separately. Each event may be reported in response to a closed question (for example information on each individual major and/or clinically relevant non-major bleeding risk component), or as free text in response to open questions on the data collection forms. Such analyses will be performed using ‘Higher-level’ event terms from the MedDRA dictionary where possible. The risk profile of the overall cohorts and sub-group of interest (based on index date characteristics, including whether anticoagulant naïve, rivaroxaban naïve or past (other anticoagulant user) will be described by presenting summary tabulations (by rank) of counts and incidence risk of reported events, and crude event rates (IDs).

Calculating and ranking crude ID rates is one of a number of standard quantitative evaluations used in event monitoring methodology for signal generation purposes as part of initial

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inspection of all event data for general safety surveillance. It is used as a means of alerting early potential signals as priorities for further evaluation. Medical judgment however is also part of this evaluation and prioritization process. Crude Incidence Densities (ID) <sup>\*\*\*\*\*</sup> can be calculated by week in order to quantify rates of events. IDs will be calculated, for each given time period (t), for all events reported in patients who continue to take rivaroxaban for a given time period, or for whom the date of stopping is known. Only the first report of an event in an individual patient is used in the calculation of IDs. They are usually expressed as the number of first reports of an event per 1000 patient-weeks. This assumes the pattern of use is continuous. The numerator will be the first reports of events reported as occurring after the index date and during treatment.<sup>§§§§§§</sup> For this study, IDs will be calculated for each event for each week as follows:

$$ID_t = \frac{\text{Number of first reports of an event during treatment for period } t \times 1000}{\text{Number of patient-weeks of treatment for period } t}$$

$$\text{Thus, } ID_t = \frac{N_t \times 1000}{D_t}$$

where:  $N_t$  = Number of first reports of an event during treatment for period t,

and  $D_t$  = Number of patient-days of treatment for period t / 7

IDs will also be calculated for each event for all 12 weeks during treatment combined ( $ID_A$ ), and the first week after stopping ( $ID_{SW1}$ ) if patient stopped (and where patients are recorded as remaining on treatment for at least 1 week) after index date.

Sensitivity analyses will examine any under-reporting by including events of interest recorded in primary care medical charts and confirmed on follow-up for those patients discharged to primary care, during the 12 week observation period.

As IDs for the overall cohort may sometimes mask significant signals in specific risk groups, the subgroups defined by specific characteristics (e.g. previous history of VTE or haemorrhage, previous/concurrent use of selected medications, off-label indication groups,

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<sup>\*\*\*\*\*</sup> It should be noted such quantification of rate does not only reflect the rate attributable to the drug but also reflects the background rate in the general population and rate attributable to other factors such as age or other disease risk factors

<sup>§§§§§§</sup> Ideally, the exposure time would be censored at the time of the first event. However, since there are a large number of health outcomes of interest and the censoring would be different for each outcome, the denominator for the crude ID will not initially include censoring. If an elevated crude ID is identified in this monitoring analysis, a subsequent analysis with appropriately censored denominator will be performed for that outcome.



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rivaroxaban naïve or past user) will have IDs calculated and compared according to strata for relevant events, where appropriate.

It is possible to explore the time taken for an event of interest using parametric time to event models (e.g. Weibull) as described previously, thus providing an additional tool for signal generation purposes. This approach will be explored for events of interest, where counts  $\geq 5$ . If undertaken, a sensitivity analysis will be performed to include in the numerator events reported within 7 days of stopping, and extend the denominator by 7 days

### ***4.7.6 To characterise differences in prevalence of prognostic factors and clinical risk factors for haemorrhage associated with rivaroxaban in comparison with contextual cohort as reported during the first 12 weeks after starting treatment in routine secondary care hospital setting in UK.***

This relates to Section 2.2.1 secondary objective (v), the aim of which is to explore the effect of important predictors (prognostics characteristics, selected relevant risk factors and oral anticoagulant on the primary outcomes of interest (haemorrhage), **only if sufficient numbers of cases of primary outcome are reported**. The effect of physician anticoagulant prescribing preference factors (type of novel anticoagulants prescribed in previous calendar month; proportion of novel anticoagulant use of all anticoagulants prescribed in previous calendar month), medical education, setting and institution will be explored as a suitable conditioning (instrumental) variable for modelling..[40] Since, data are likely to be hierarchical the application of a multilevel model for discrete response data will be considered. Odds ratios and 95% confidence intervals will be calculated.

### ***4.7.7 To describe clinical features and management of cases of overdose, major bleeding, VTE events indicating failure of anticoagulation and management of homeostasis in patients undertaking surgery (elective or urgent) reported in the first 12 weeks after treatment initiation in the cohort exposed to rivaroxaban.***

The following relates to Section 2.2.3 exploratory objective (ii) . A qualitative assessment of these cases will include evaluation of patient demographic characteristics, treatment details, the detection and clinical features and management of events of interest, resolution, relevant investigations prior to and during therapy, the patient's relevant medical history and concurrent medication and any sequelae. Data will be derived from the SCEM and follow up questionnaires sent to gather other relevant essential information for construction of a case-series summary descriptive table.

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### ***4.7.8 Multiple comparison adjustments***

The methods of signal surveillance require a large number of multiple comparisons on adverse events, which involve inferring statistical significance on multiple  $p$ -values. To control for an excess of false positive signals, suitable multiple comparison adjustments will be made with the false discovery rate (FDR) approach. [41] The Simes method [42;43] in addition to the double FDR method [41] will be implemented to maintain the false discovery rate at the acceptable 10% level for all statistical tests. Such approaches would allow for a balance between false positive and false negative signals.

### **4.8 Aggregate Assessment of Drug- Relatedness of Selected Events**

As described previously (section 4.4.1.3) selected events of interest (Table 4) that require further characterisation and evaluation may be followed-up via a questionnaire sent to the responsible specialist HCP or patient's GP seeking further information. The information received at follow-up for events of medical significance or those which require further clarification will facilitate further evaluation at the aggregate level, including collective assessment of drug-relatedness, by experienced research staff at the DSRU (two qualified members of staff, independently, with a third adjudicator if necessary). The aim of the collective drug-relatedness assessment for groups of events during the analysis of the interim and final reports, is to put events in context regarding temporality co-morbidity, pre-existing disease and concomitant medications. This aggregate assessment of event data occurs at interim or final report for cases for which all requested information (i.e. index date questionnaire, 12 week end of observation questionnaire, and follow-up questionnaire if applicable) has been received. In the process of aggregate assessment of event data, the application of elements of the Austin Bradford Hill criteria, when the necessary information is available and the use of the method is considered appropriate, will be used (see Box 1) .[44]

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### Box 1. Points for consideration in collective evaluation of reported events

- *The distribution of time to onset (temporal relationship);*
- *The principle clinical and pathological characteristics of the group of events;*
- *The pharmacological plausibility based on previous knowledge of the drug and the therapeutic class if appropriate;*
- *Similar reports in medical literature*
- *patient's clinical characteristics, including:*
  - *previous medical history, such as history of drug allergies, presence of renal or hepatic impairment, etc.*
  - *concomitant medications or medications taken prior to and during treatment;*
- *Management and remedial action;*

The collective drug-relatedness of selected groups of events of interest will be categorised in terms of proportions of reports assessed within the following four categories: 1) probable<sup>\*\*\*\*\*</sup>, 2) possible<sup>+++++</sup>, 3) unlikely<sup>++++</sup>, and 4) not assessable<sup>\$\$\$\$\$</sup>. [45]

## 4.9 Data Monitoring

### 4.9.1 Project Steering Committee

A Project Steering Committee (PSC) will be set up to be comprised of the study investigators and other experts. The role of the PSC will be to oversee the smooth running of the project and provide scientific, statistical and technical advice when needed and will meet at regular intervals (3 to 12 monthly depending on the stage of the study, either in person or by teleconference).

The PSC is broadly analogous to a Safety Monitoring Committee or Review Board, but the purpose may be slightly different such that the PSC includes investigators and also oversees the effective progress of the study. The first PSC meeting will orientate the project team members and establish the logistics for specialist and patient recruitment and confirm patient inclusion criteria. Subsequent PSC meetings will clarify the understanding of the ongoing

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\*\*\*\*\* Events are assessed as 'probable' if the event is well defined clinically and pathologically, if there is a reasonable time sequence, if it is more likely to be attributed to the study drug rather than to a concurrent disease or concomitant medication, if there is a positive dechallenge, rechallenge or response to dose increase, and if there are other supporting criteria (e.g. on the basis of lab tests or histological findings).

+++++ Events are assessed as 'possible' if the event has a reasonable clinical and pathological definition, if there is a reasonable time sequence, if it could also be explained by concurrent disease or concomitant medication, but dechallenge, rechallenge and confirmatory investigations are inconclusive or not fully available. Medical judgement will be necessary in some cases.

++++ Events are assessed as unlikely if the event had a temporal relationship to the study drug administration that made a causal relationship improbable, or if concurrent disease or concomitant medication provided a far more plausible explanation.

\$\$\$\$\$ Events are unassessable if insufficient information about the event has been provided and an appropriate evaluation is therefore not possible.

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project requirements, monitor progress through assessment of data within the interim reports [specialist/cohort accrual rates, preliminary analyses of individual variable responses on questionnaires], consider any additional proposed inclusion criteria, and act as a forum to review and discuss any queries.

### ***4.9.2 Communications***

Progress reports (relevant to specialist and patient cohort accrual) will be produced in time for inclusion in the scheduled Periodic Safety Update Reports for the product (i.e., every six months for the first two years after launch and then annually thereafter) or regular updates of the RMP for as long as the study continues. Examination of aggregate event data will be limited to one interim report based on the evaluable study cohort achieved at approximately 18 months post date of first patient recruited, and a detailed final report based on the evaluable study cohort achieved at approximately 36 months post date of first patient recruited. It is anticipated that the final cohort for analysis will be comprised of 3400 evaluable patients with relevant indications. However the final sample size achieved within this timeframe will be governed by application of NICE guidance (which can vary) between secondary care trusts and managed entry, therefore the possibility of a requirement to extend the study period must be acknowledged.

### ***4.9.3 Adverse event /reaction reporting***

This registry-based, observational, non-interventional cohort study is based on secondary use of data, therefore adverse reactions reporting is not required. Reports of adverse events/reactions will be summarised in the study report, where applicable. The DSRU shall, on an ongoing basis, notify the MAH when they consider, based on their evaluation, that any issues or matters of interest relating to the Study or its outcomes are of importance and shall provide the MAH with related results of the study and analyses thereof.

Since the clinicians are prescribing a licensed product, they will be reminded in the study documentation that it is their responsibility to report any suspected adverse reactions (including serious<sup>\*\*\*\*\*</sup> adverse drug reactions) to the company and/or to the MHRA (using

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#### **\*\*\*\*\* Definition of Serious Adverse Event**

"Serious Adverse Event means an adverse event which is fatal or life-threatening, results in persistent or significant disability, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

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Yellow Cards) as they would normally do in their practice in support of routine pharmacovigilance. In cases where the DSRU receives, by mistake, such reports it will forward them to the MHRA and/or the MAH as appropriate.

### **5.0 STRENGTHS AND LIMITATIONS**

#### **5.1. Strengths**

- The observational and inclusive design allows for the surveillance of a diverse patient population under the care of specialist HCP, particularly those that are more complex in terms of underlying disease, co-morbidities and concomitant medications that would not have been included in clinical trials, and also would not be comparable to the general disease population. Thus error introduced through selection based on disease severity or type will be minimised; there are no specific exclusion criteria. The approach also allows for surveillance of rivaroxaban when used off-label.
- The prescribing of relevant pharmacological therapy should not be affected because of participation in this study therefore the observational non-interventional nature of the study design is maintained.
- Data is collected on large numbers of rivaroxaban and warfarin users in conditions of routine clinical practice.
- Special populations can be characterised
- Time-dependent effects can be examined .This method is prospective and thus will enable more reliable examination of exposures in relation to outcomes.
- By obtaining patient consent, additional information from medical charts from other clinical specialities may be examined for selected outcomes.
- Extension to monitor long-term safety is possible.
- The DSRU has established networks of specialists in the UK to conduct such studies.

#### **5.2 Limitations**

- Possible delay in new user cohort accrual if adoption by secondary care hospital trusts and specialists is low.
- Since this is an observational epidemiological study, we recognise several potential sources of bias. The most important is selection bias and the possibility that the cohorts will not be representative of the general population for whom anticoagulation

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is clinically desirable. Because of the prospective nature of patient recruitment, bias in recruitment may be introduced by some participating specialist HCPs through awareness of some form of remuneration (regardless of how and when payment is made). This study does not look at the comparative early safety profile of rivaroxaban in the context of initiations of other novel anticoagulants; therefore the extent of selection bias cannot be established in regard to those treatments. However the same number of patients treated with warfarin for similar indications will be collected to explore factors which may contribute to selection bias. Furthermore, the characteristics of patients providing consent to those who do not will be compared in order to identify possible systematic differences between such patients.

- Knowledge of which patients will be participating may affect the non-interventional nature of observational research. Exclusion of patients initiated on treatment between date of market launch and study start may also add to selection bias. Nevertheless patient identification (case ascertainment) is likely to be more complete than through retrospective methodology; this may also minimise bias introduced by non-participation of patients. It is also possible that specialist HCPs who participate in the study will be a self-selected group, but we do not believe that this selection bias will affect the types or number of events experienced and reported by a patient after treatment has been initiated. An instrumental variable reflecting physician prescribing preference will be explored to control for unmeasured confounding possibly associated with treatment decisions.
- Confounding by indication is a form of selection bias where the disease that forms the indication being treated (irrespective of severity) is not only associated with treatment but also an independent risk factor for selected outcomes (events of interest) in patients not exposed to antithrombotic agents. This needs to be examined since such channelling may result in apparent association of increased risk of such events in this population. It may be introduced through prescribing of treatment based on certain characteristics of a patient. For this study, patients for whom prior alternative treatment was poorly tolerated or ineffective may be selectively prescribed the new treatment.
- Confounding by severity is possible and needs to be accounted for.
- Under- and mis- reporting of outcomes is possible; specialist HCPs' notes may be incomplete with regard to medical history and non-cardiovascular related outcomes of interest associated with current treatment. The two-phase data capture approach could facilitate compliance with data reporting as well as spreading workload for specialist

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HCPs. By obtaining patient consent at the start of treatment to facilitate communication with the Patient's GP and access to primary medical charts, under ascertainment of outcomes can be minimised. In contrast, overreporting and overrecording of health related events in the period following the administration of the index questionnaire are possible due to increased specialist HCPs' attention to special populations of interest (e.g. SPAF) as detailed in the questionnaire, however since information is being abstracted from medical charts such bias is unlikely. Where similar information is obtained from primary care medical charts by GPs who were not involved in treatment initiation, a sensitivity analysis may inform on the impact of such bias, if it exists.

- Regarding the definition of bleeding, in this study case definitions are based on acceptable agreed clinical standards and aim to address specific regulatory questions in the context of the risk management plan for the product.
- Immortal time bias is possible arising from misclassification of exposure to the study OAC.
- With this patient population, patient attrition and loss to follow-up may introduce selection bias, however, the relatively short period of observation should mitigate this possibility at least to some extent.
- Misclassification bias will be minimised by well defined outcome and follow-up of medically important events. Patients with selected events of interest will be followed-up with regard to co-prescribed medicines and concurrent illness. Events that represent features of the respective indications will be taken into account when signals of potential ADRs to rivaroxaban are investigated (i.e., confounding by indication).
- Time bias may also become an issue if the study collection period, and thus the observation period, is extended because of low prescribing rates.
- Furthermore unidentified poor adherence may also lead to misclassification of exposure. However, as with many observational studies, the degree of patient compliance in taking the prescribed medication cannot be ascertained. Whilst it is not possible to be sure the patient used the medication, it is almost certain that the patient received it since starting treatment is required for study participation.

### **6.0 STUDY SPONSORSHIP**

This study is being undertaken by the DSRU as part of the Risk Management Plan for the product at the request of the Committee for Medicinal Products for Human Use (CHMP). The Drug Safety Research Trust is a registered independent charity (No, 327206) operating in

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association with the University of Portsmouth and is the sponsor of the study. For this study, the DSRU (the academic sponsor) receives support from Bayer.



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### (Appendix 1. UK SPC for rivaroxaban)

#### Bayer plc

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**Before you contact this company:** often several companies will market medicines with the same active ingredient.

Please check that this is the correct company before contacting them. Why?

Summary of Product Characteristics last updated on the eMC: 18/06/2012

#### Xarelto 10 mg film-coated tablets

##### 1. Name of the medicinal product

Xarelto ▼ 10 mg film-coated tablets

##### 2. Qualitative and quantitative composition

Each film-coated tablet contains 10 mg rivaroxaban.

##### Excipients with known effect:

Each film-coated tablet contains 27.9 mg lactose monohydrate, see section 4.4.

For the full list of excipients, see section 6.1.

##### 3. Pharmaceutical form

Film-coated tablet (tablet).

Light red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and "10" and a triangle on the other side.

##### 4. Clinical particulars

###### 4.1 Therapeutic indications

Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

###### 4.2 Posology and method of administration

###### Posology

The recommended dose is 10 mg rivaroxaban taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established.

The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

- For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended.

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- For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.

If a dose is missed the patient should take Xarelto immediately and then continue the following day with once daily intake as before.

#### *Converting from Vitamin K Antagonists (VKA) to Xarelto*

When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

#### *Converting from Xarelto to Vitamin K antagonists (VKA)*

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is  $\geq 2.0$ . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both Xarelto and VKA, the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto. Once Xarelto is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

#### *Converting from parenteral anticoagulants to Xarelto*

For patients currently receiving a parenteral anticoagulant, Xarelto should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

#### *Converting from Xarelto to parenteral anticoagulants*

Give the first dose of parenteral anticoagulant at the time the next Xarelto dose would be taken.

#### Special populations

##### *Renal impairment*

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min) (see section 5.2).

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased, therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance  $< 15$  ml/min (see sections 4.4 and 5.2).

##### *Hepatic impairment*

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

##### *Elderly population*

No dose adjustment (see section 5.2).

##### *Body weight*

No dose adjustment (see section 5.2).

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#### *Gender*

No dose adjustment (see section 5.2).

#### *Paediatric population*

The safety and efficacy of Xarelto in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto is not recommended for use in children below 18 years of age.

#### Method of administration

For oral use. Xarelto can be taken with or without food (see section 4.5 and 5.2).

#### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically significant active bleeding.

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast feeding (see section 4.6).

#### **4.4 Special warnings and precautions for use**

##### Haemorrhagic risk

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

##### Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6-fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

Xarelto is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

##### Interaction with other medicinal products

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

##### Other haemorrhagic risk factors

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Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- recent gastrointestinal ulcerations
- vascular retinopathy
- recent intracranial or intracerebral haemorrhage
- intraspinal or intracerebral vascular abnormalities
- recent brain, spinal or ophthalmological surgery
- bronchiectasis or history of pulmonary bleeding.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.1 and 5.2).

#### Hip fracture surgery

Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, rivaroxaban is not recommended in these patients.

#### Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

An epidural catheter is not to be removed earlier than 18 hours after the last administration of rivaroxaban. The next rivaroxaban dose is to be administered not earlier than 6 hours after the removal of the catheter.

If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

#### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban  $C_{max}$ , with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment



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with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in  $C_{max}$ . This increase is not considered clinically relevant.

Erythromycin (500 mg three times a day) which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and  $C_{max}$ . This increase is not considered clinically relevant.

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean  $C_{max}$ . This increase is not considered clinically relevant.

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

#### Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see section 4.4).

#### NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

#### Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the  $C_{trough}$  of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

#### CYP3A4 inducers

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Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

#### Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

No clinically relevant interaction with food was observed (see section 4.2).

#### Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

#### 4.6 Pregnancy and lactation

##### Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of childbearing potential should avoid becoming pregnant during treatment with rivaroxaban.

##### Breast feeding

Safety and efficacy of Xarelto have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

##### Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

#### 4.7 Effects on ability to drive and use machines

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope and dizziness have been reported to be common (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

#### 4.8 Undesirable effects

##### Summary of the safety profile

The safety of rivaroxaban has been evaluated in eight phase III studies including 16,041 patients exposed to rivaroxaban (see Table 1).

**Table 1: Number of patients studied, maximum daily dose and treatment duration in phase III studies**

Indication	Number of patients*	Maximum daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days

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Treatment of DVT and prevention of recurrent DVT and PE	2,194	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

\*Patients exposed to at least one dose of rivaroxaban

In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 24% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery, bleeding events occurred in approximately 6.8% of patients and anaemia occurred in approximately 5.9% of patients. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately 1.8% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years.

#### Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

common ( $\geq 1/100$  to  $< 1/10$ )

uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Not known: cannot be estimated from the available data.

**Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies (prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (VTE-P), treatment of DVT and prevention of recurrent DVT and PE (DVT-T), and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF))**

Common	Uncommon	Rare	Not Known
<b>Blood and lymphatic system disorders</b>			
Anaemia (incl. respective laboratory parameters)	Thrombocythemia (incl. platelet count increased) <sup>A</sup>		
<b>Immune system disorders</b>			
	Allergic reaction, dermatitis allergic		
<b>Nervous system disorders</b>			
Dizziness, headache, syncope	Cerebral and intracranial haemorrhage		
<b>Eye disorders</b>			
Eye haemorrhage (incl. conjunctival haemorrhage)			
<b>Cardiac disorders</b>			
Tachycardia			
<b>Vascular disorders</b>			

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Hypotension, haematoma			Pseudoaneurysm formation following percutaneous intervention*
<b>Respiratory, thoracic and mediastinal disorders</b>			
Epistaxis	Haemoptysis		
<b>Gastrointestinal disorders</b>			
Gastrointestinal tract haemorrhage (incl. gingival bleeding and rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth		
<b>Hepatobiliary disorders</b>			
	Hepatic function abnormal	Jaundice	
<b>Skin and subcutaneous tissue disorders</b>			
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis	Urticaria, cutaneous and subcutaneous haemorrhage		
<b>Musculoskeletal and connective tissue disorders</b>			
Pain in extremity <sup>A</sup>	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
<b>Renal and urinary disorders</b>			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia <sup>B</sup> )	Renal impairment (incl. blood creatinine increased, blood urea increased) <sup>A</sup>		Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
<b>General disorders and administration site conditions</b>			
Fever <sup>A</sup> , peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise), localised oedema <sup>A</sup>		
<b>Investigations</b>			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased LDH <sup>A</sup> , increased lipase <sup>A</sup> , increased amylase <sup>A</sup> , increased GGT <sup>A</sup>	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
<b>Injury, poisoning and procedural complications</b>			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion <sup>A</sup>			

A: observed in VTE-P after major orthopaedic surgery of the lower limbs

B: observed in DVT-T as very common in women < 55 years

\*) These reactions occurred in other clinical studies than the phase III studies in patients undergoing major orthopaedic surgery of the lower limbs, patients treated for DVT and prevention of recurrent DVT and PE, or patients treated for the prevention of stroke and systemic embolism

Description of selected adverse reactions

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Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

#### 4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

#### Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

### 5. Pharmacological properties

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antithrombotic agents, ATC code: B01AX06

#### Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

#### Pharmacodynamic effects

Dose-dependent inhibition of Factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent

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way with a close correlation to plasma concentrations ( $r$  value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 s (baseline values before surgery 12 to 15s).

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.2).

#### Clinical efficacy and safety

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of VTE, i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs. Over 9,500 patients (7,050 in total hip replacement surgery and 2,531 in total knee replacement surgery) were studied in controlled randomised double-blind phase III clinical studies, the RECORD-programme.

Rivaroxaban 10 mg once daily (od) started no sooner than 6 hours post-operatively was compared with enoxaparin 40 mg once daily started 12 hours pre-operatively.

In all three phase III studies (see table 3), rivaroxaban significantly reduced the rate of total VTE (any venographically detected or symptomatic DVT, non fatal PE and death) and major VTE (proximal DVT, non fatal PE and VTE-related death), the pre-specified primary and major secondary efficacy endpoints. Furthermore, in all three studies the rate of symptomatic VTE (symptomatic DVT, non-fatal PE, VTE-related death) was lower in rivaroxaban treated patients compared to patients treated with enoxaparin.

The main safety endpoint, major bleeding, showed comparable rates for patients treated with rivaroxaban 10 mg compared to enoxaparin 40 mg.

**Table 3: Efficacy and safety results from phase III clinical studies**

	RECORD 1			RECORD 2			RECORD 3		
Study Population	4,541 patients undergoing total hip replacement surgery			2,509 patients undergoing total hip replacement surgery			2,531 patients undergoing total knee replacement surgery		
Treatment dose and duration after surgery	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 35 ± 4 days	p	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 12 ± 2 days	p	Rivaroxaban 10 mg od 12 ± 2 days	Enoxaparin 40 mg od 12 ± 2 days	p
Total VTE	18 (1.1 %)	58 (3.7 %)	< 0.001	17 (2.0 %)	81 (9.3 %)	< 0.001	79 (9.6 %)	166 (18.9 %)	< 0.001
Major VTE	4 (0.2 %)	33 (2.0 %)	< 0.001	6 (0.6 %)	49 (5.1 %)	< 0.001	9 (1.0 %)	24 (2.6 %)	0.01
Symptomatic VTE	6 (0.4 %)	11 (0.7 %)		3 (0.4 %)	15 (1.7 %)		8 (1.0 %)	24 (2.7 %)	
Major bleedings	6 (0.3 %)	2 (0.1 %)		1 (0.1 %)	1 (0.1 %)		7 (0.6 %)	6 (0.5 %)	

The analysis of the pooled results of the phase III trials corroborated the data obtained in the individual studies regarding reduction of total VTE, major VTE and symptomatic VTE with rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily.

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric population in the treatment of thromboembolic events. The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events. See section 4.2 for information on paediatric

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use.

#### 5.2 Pharmacokinetic properties

##### Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 10 mg dose. Rivaroxaban 10 mg tablets can be taken with or without food. Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %, apart from the day of surgery and the following day when variability in exposure is high (70 %).

##### Distribution

Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with  $V_{ss}$  being approximately 50 litres.

##### Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

##### Special populations

###### *Gender*

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

###### *Elderly population*

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

###### *Different weight categories*

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.

###### *Inter-ethnic differences*

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

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#### *Hepatic impairment*

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of Factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

#### *Renal impairment*

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

#### Pharmacokinetic data in patients

In patients receiving rivaroxaban for prevention of VTE 10 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 101 (7 - 273) and 14 (4 - 51) µg/l, respectively.

#### Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (Factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and Factor Xa activity was best described by an E<sub>max</sub> model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects. In patients, baseline Factor Xa and PT were influenced by the surgery resulting in a difference in the concentration-PT slope between the day post-surgery and steady state.

#### Paediatric population

Safety and efficacy have not been established for children and adolescents up to 18 years.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased



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IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

#### 6. Pharmaceutical particulars

##### 6.1 List of excipients

###### Tablet core:

Microcrystalline cellulose

Croscarmellose sodium

Lactose monohydrate

Hypromellose

Sodium laurilsulfate

Magnesium stearate

###### Film-coat:

Macrogol 3350

Hypromellose

Titanium dioxide (E171)

Iron oxide red (E172)

##### 6.2 Incompatibilities

Not applicable.

##### 6.3 Shelf life

3 years

##### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

##### 6.5 Nature and contents of container

PP/Aluminium foil blisters or PVC/PVDC/Aluminium foil blisters in cartons of 5, 10 or 30 tablets or perforated unit dose blisters in cartons of 10 x 1 or 100 x 1 tablets.

Not all pack sizes may be marketed.

##### 6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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#### 7. Marketing authorisation holder

Bayer Pharma AG

13342 Berlin

Germany

#### 8. Marketing authorisation number(s)

EU/1/08/472/001-010

#### 9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 30 September 2008

#### 10. Date of revision of the text

05/2012

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Distributed in the United Kingdom by:

Bayer plc

Bayer House

Strawberry Hill

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**Before you contact this company:** often several companies will market medicines with the same active ingredient.

Please check that this is the correct company before contacting them. **Why?**

Summary of Product Characteristics last updated on the eMC: 18/06/2012

### Xarelto 15mg film-coated tablets

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#### 1. Name of the medicinal product

Xarelto ▼ 15 mg film-coated tablets

#### 2. Qualitative and quantitative composition

Each film-coated tablet contains 15 mg rivaroxaban.

##### Excipients with known effect:

Each 15 mg film-coated tablet contains 25.4 mg lactose monohydrate, see section 4.4.

For the full list of excipients, see section 6.1.

#### 3. Pharmaceutical form

Film-coated tablet (tablet).

Red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and “15” and a triangle on the other side.

#### 4. Clinical particulars

##### 4.1 Therapeutic indications

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, prior stroke or transient ischaemic attack.

Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

##### 4.2 Posology and method of administration

###### Posology

###### *Prevention of stroke and systemic embolism*

The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Xarelto should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding (see section 4.4).

If a dose is missed the patient should take Xarelto immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

###### *Treatment of DVT and prevention of recurrent DVT and PE*

The recommended dose for the initial treatment of acute DVT is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE, as indicated in the table below.

	Dosing schedule	Maximum daily dose
Day 1 - 21	15 mg twice daily	30 mg
Day 22 and onwards	20 mg once daily	20 mg

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

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Short duration of therapy (3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT. Experience with Xarelto in this indication for more than 12 months is limited.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Xarelto immediately to ensure intake of 30 mg Xarelto per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take Xarelto immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

#### *Converting from Vitamin K Antagonists (VKA) to Xarelto*

For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Xarelto therapy should be initiated when the INR is  $\leq 3.0$ .

For patients treated for DVT and prevention of recurrent DVT and PE, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is  $\leq 2.5$ .

When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

#### *Converting from Xarelto to Vitamin K antagonists (VKA)*

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is  $\geq 2.0$ . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both Xarelto and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto. Once Xarelto is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

#### *Converting from parenteral anticoagulants to Xarelto*

For patients currently receiving a parenteral anticoagulant, Xarelto should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

#### *Converting from Xarelto to parenteral anticoagulants*

Give the first dose of parenteral anticoagulant at the time the next Xarelto dose would be taken.

#### Special populations

##### *Renal impairment*

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see section 5.2).

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).

- For the treatment of DVT and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks.

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Thereafter, the recommended dose is 15 mg once daily based on PK modelling (see sections 4.4 and 5.2).

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased, therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

#### *Hepatic impairment*

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

#### *Elderly population*

No dose adjustment (see section 5.2).

#### *Body weight*

No dose adjustment (see section 5.2).

#### *Gender*

No dose adjustment (see section 5.2).

#### *Paediatric population*

The safety and efficacy of Xarelto in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto is not recommended for use in children below 18 years of age.

#### Method of administration

For oral use. The tablets are to be taken with food (see section 5.2).

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically significant active bleeding.

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast feeding (see section 4.6).

### 4.4 Special warnings and precautions for use

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

#### Haemorrhagic risk

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

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Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

#### Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

Xarelto should be used with caution in patients with renal impairment concomitantly receiving other medicinal products that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) as PK modelling shows increased rivaroxaban concentrations in these patients.

#### Interaction with other medicinal products

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

#### Other haemorrhagic risk factors

Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- recent gastrointestinal ulcerations
- vascular retinopathy
- recent intracranial or intracerebral haemorrhage
- intraspinal or intracerebral vascular abnormalities
- recent brain, spinal or ophthalmological surgery
- bronchiectasis or history of pulmonary bleeding.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.1 and 5.2).

#### Patients with prosthetic valves

Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

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#### Patients with acute pulmonary embolism

Xarelto is not recommended in the treatment of acute pulmonary embolism.

#### Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Xarelto should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Xarelto should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see section 5.2).

#### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### 4.5 Interaction with other medicinal products and other forms of interaction

#### CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban  $C_{max}$ , with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in  $C_{max}$ . This increase is not considered clinically relevant.

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and  $C_{max}$ . This increase is not considered clinically relevant.

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean  $C_{max}$ . This increase is not considered clinically relevant.

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

#### Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see section 4.4).

#### NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg

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acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

#### Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and HepTest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the  $C_{trough}$  of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

#### CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

#### Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

#### Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

#### 4.6 fertility, pregnancy and breast feeding

##### Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

##### Breast feeding

Safety and efficacy of Xarelto have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding



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or to discontinue/abstain from therapy.

#### Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

#### 4.7 Effects on ability to drive and use machines

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope and dizziness have been reported to be common (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

#### 4.8 Undesirable effects

##### Summary of the safety profile

The safety of rivaroxaban has been evaluated in eight phase III studies including 16,041 patients exposed to rivaroxaban (see Table 1).

**Table 1: Number of patients studied, maximum daily dose and treatment duration in phase III studies**

Indication	Number of patients*	Maximum daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Treatment of DVT and prevention of recurrent DVT and PE	2,194	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

\*Patients exposed to at least one dose of rivaroxaban

In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 24% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery, bleeding events occurred in approximately 6.8% of patients and anaemia occurred in approximately 5.9% of patients. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately 1.8% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years.

##### Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

common ( $\geq 1/100$  to  $< 1/10$ )

uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Not known: cannot be estimated from the available data.

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Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies (prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (*VTE-P*), treatment of DVT and prevention of recurrent DVT and PE (*DVT-T*), and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (*SPAF*))

Common	Uncommon	Rare	Not known
<b>Blood and lymphatic system disorders</b>			
Anaemia (incl. respective laboratory parameters)	Thrombocythemia (incl. platelet count increased) <sup>A</sup>		
<b>Immune system disorders</b>			
	Allergic reaction, dermatitis allergic		
<b>Nervous system disorders</b>			
Dizziness, headache, syncope	Cerebral and intracranial haemorrhage		
<b>Eye disorders</b>			
Eye haemorrhage (incl. conjunctival haemorrhage)			
<b>Cardiac disorders</b>			
Tachycardia			
<b>Vascular disorders</b>			
Hypotension, haematoma			Pseudoaneurysm formation following percutaneous intervention*
<b>Respiratory, thoracic and mediastinal disorders</b>			
Epistaxis	Haemoptysis		
<b>Gastrointestinal disorders</b>			
Gastrointestinal tract haemorrhage (incl. gingival bleeding and rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth		
<b>Hepatobiliary disorders</b>			
	Hepatic function abnormal	Jaundice	
<b>Skin and subcutaneous tissue disorders</b>			
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis	Urticaria, cutaneous and subcutaneous haemorrhage		
<b>Musculoskeletal and connective tissue disorders</b>			
Pain in extremity <sup>A</sup>	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
<b>Renal and urinary disorders</b>			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia <sup>B</sup> )	Renal impairment (incl. blood creatinine increased, blood urea increased) <sup>A</sup>		Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
<b>General disorders and administration site conditions</b>			
Fever <sup>A</sup> , peripheral oedema, decreased general strength and	Feeling unwell (incl. malaise), localised oedema <sup>A</sup>		

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energy (incl. fatigue and asthenia)			
<b>Investigations</b>			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased LDH <sup>A</sup> , increased lipase <sup>A</sup> , increased amylase <sup>A</sup> , increased GGT <sup>A</sup>	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
<b>Injury, poisoning and procedural complications</b>			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion <sup>A</sup>			

A: observed in VTE-P after major orthopaedic surgery of the lower limbs

B: observed in DVT-T as very common in women < 55 years

\*) These reactions occurred in other clinical studies than the phase III studies in patients undergoing major orthopaedic surgery of the lower limbs, patients treated for DVT and prevention of recurrent DVT and PE, or patients treated for the prevention of stroke and systemic embolism

#### Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

#### **4.9 Overdose**

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

#### Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However,

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there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

#### 5. Pharmacological properties

##### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antithrombotic agents, ATC code: B01AX06

##### Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

##### Pharmacodynamic effects

Dose-dependent inhibition of Factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of DVT and prevention of recurrent DVT and PE, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 16 to 33 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 25 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 21 s.

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.2).

##### Clinical efficacy and safety

##### *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation*

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to Xarelto 20 mg once daily (15 mg once daily in patients with creatinine clearance 30 - 49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.

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Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 – 0.96;  $P < 0.001$  for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 – 1.03;  $P < 0.001$  for non-inferiority;  $P = 0.117$  for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 3.

Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles ( $P = 0.74$  for interaction). Within the highest quartile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 4).

**Table 3: Efficacy results from phase III ROCKET AF**

•	• ITT analyses of efficacy in patients with non-valvular atrial fibrillation		
Treatment, dosage	Xarelto	Warfarin	Hazard ratio (95% CI)
	20 mg od	titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)	p-value, test for superiority
	(15 mg od in patients with moderate renal impairment)		
	Event rate (100 pt-yr)	Event rate (100 pt-yr)	
Stroke and non-CNS systemic embolism	269  (2.12%)	306  (2.42%)	0.88  (0.74 - 1.03)  0.117
Stroke, non-CNS systemic embolism and vascular death	572  (4.51%)	609  (4.81%)	0.94  (0.84 - 1.05)  0.265
Stroke, non-CNS systemic embolism, vascular death and Myocardial infarction	659  (5.24%)	709  (5.65%)	0.93  (0.83 - 1.03)  0.158
Stroke	253  (1.99%)	281  (2.22%)	0.90  (0.76 - 1.07)  0.221
Non-CNS systemic embolism	20  (0.16%)	27  (0.21%)	0.74  (0.42 - 1.32)  0.308
Myocardial infarction	130	142	0.91

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	(1.02%)	(1.11%)	(0.72 - 1.16)
			0.464

**Table 4: Safety results from phase III ROCKET AF**

• Study population	• Patients with non-valvular atrial fibrillation <sup>a</sup>		
Treatment dosage	Xarelto	Warfarin	Hazard ratio (95% CI)
	20 mg once a day	titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)	p-value
	(15 mg once a day in patients with moderate renal impairment)		
	Event rate (100 pt-yr)	Event rate (100 pt-yr)	
Major and non-major clinically relevant bleeding events	1,475  (14.91%)	1,449  (14.52%)	1.03 (0.96 - 1.11)  0.442
Major bleeding events	395  (3.60%)	386  (3.45%)	1.04 (0.90 - 1.20)  0.576
Death due to bleeding*	27  (0.24%)	55  (0.48%)	0.50 (0.31 - 0.79)  0.003
Critical organ bleeding*	91  (0.82%)	133  (1.18%)	0.69 (0.53 - 0.91)  0.007
Intracranial haemorrhage*	55  (0.49%)	84  (0.74%)	0.67 (0.47 - 0.93)  0.019
Haemoglobin drop*	305  (2.77%)	254  (2.26%)	1.22 (1.03 - 1.44)  0.019
Transfusion of 2 or more units of packed red blood cells or whole blood*	183  (1.65%)	149  (1.32%)	1.25 (1.01 - 1.55)  0.044
Non-major clinically relevant bleeding events	1,185  (11.80%)	1,151  (11.37%)	1.04 (0.96 - 1.13)  0.345
All cause mortality	208  (1.87%)	250  (2.21%)	0.85 (0.70 - 1.02)  0.073

a) Safety population, on treatment

\* Nominally significant

#### *Treatment of DVT and prevention of recurrent DVT and PE*

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto in the initial and continued treatment of acute DVT and prevention of recurrent DVT and PE.

Over 4,600 patients were studied in two randomised controlled phase III clinical studies (Einstein DVT and Einstein Extension). The overall

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combined treatment duration in both studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

The comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range ( $\geq 2.0$ ). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Xarelto 20 mg once daily was compared with placebo.

Both phase III studies used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all cause mortality.

In the Einstein DVT study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ( $p < 0.0001$  (test for non-inferiority); hazard ratio: 0.680 (0.443 - 1.042),  $p=0.076$  (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.67 ((95% CI= 0.47 - 0.95), nominal p value  $p=0.027$ ) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2 - 3) in the equally sized tertiles and the incidence of the recurrent VTE ( $P=0.932$  for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.69 (95% CI, 0.35 - 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

In the Einstein Extension study (see Table 6) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

In both the Einstein DVT and Einstein Extension studies, patients with moderate renal impairment (creatinine clearance 30 -- 49 ml/min) were treated with the same dose as patients with creatinine clearance above 50 ml/min (i.e. 15 mg twice daily for the first three weeks and 20 mg once daily from day 22 onwards).

**Table 5: Efficacy and safety results from phase III Einstein DVT**

Study Population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment dosage and duration	Xarelto <sup>a</sup>	Enoxaparin/VKA <sup>b</sup>
	3, 6 or 12 months	3, 6 or 12 months
	N=1,731	N=1,718
Symptomatic recurrent VTE*	36  (2.1%)	51  (3.0%)
Symptomatic recurrent PE	20	18

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	(1.2%)	(1.0%)
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/Death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days followed by VKA

\*  $p < 0.0001$  (non-inferiority); hazard ratio: 0.680 (0.443 - 1.042),  $p=0.076$  (superiority)

**Table 6: Efficacy and safety results from phase III Einstein Extension**

Study Population	1,197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment dosage and duration	Xarelto <sup>a</sup>  6 or 12 months  N=602	Placebo  6 or 12 months  N=594
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Fatal PE/Death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)

a) Rivaroxaban 20 mg once daily

\*  $p < 0.0001$  (superiority), hazard ratio: 0.185 (0.087 - 0.393)

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric



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population in the treatment of thromboembolic events. The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events. See section 4.2 for information on paediatric use.

#### 5.2 Pharmacokinetic properties

##### Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When Xarelto 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Xarelto 15 mg and 20 mg are to be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions Xarelto 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

##### Distribution

Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with  $V_{ss}$  being approximately 50 litres.

##### Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

##### Special populations

###### *Gender*

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

###### *Elderly population*

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

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#### *Different weight categories*

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.

#### *Inter-ethnic differences*

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

#### *Hepatic impairment*

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of Factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

#### *Renal impairment*

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

#### Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) µg/l, respectively.

#### Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (Factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and Factor Xa activity was best described by an E<sub>max</sub> model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

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#### Paediatric population

Safety and efficacy have not been established for children and adolescents up to 18 years.

#### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

#### Tablet core:

Microcrystalline cellulose

Croscarmellose sodium

Lactose monohydrate

Hypromellose

Sodium laurilsulfate

Magnesium stearate

#### Film-coat:

Macrogol 3350

Hypromellose

Titanium dioxide (E171)

Iron oxide red (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

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#### 6.5 Nature and contents of container

PP/Aluminium foil blisters in cartons of 14, 28, 42 or 98 film-coated tablets or perforated unit dose blisters in cartons of 10 x 1 or 100 x 1 film-coated tablets.

Not all pack sizes may be marketed.

#### 6.6 Special precautions for disposal and other handling

No special requirements for disposal.

#### 7. Marketing authorisation holder

Bayer Pharma AG

13342 Berlin

Germany

#### 8. Marketing authorisation number(s)

EU/1/08/472/011- 016

#### 9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 30 September 2008

#### 10. Date of revision of the text

05/2012

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Distributed in the United Kingdom by:

Bayer plc

Bayer House

Strawberry Hill

Newbury

Berkshire

RG14 1JA



### Bayer plc

Bayer House, Strawberry Hill, Newbury, Berkshire, RG14 1JA

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**Before you contact this company:** often several companies will market medicines with the same active ingredient.

Please check that this is the correct company before contacting them. Why?

Summary of Product Characteristics last updated on the eMC: 18/06/2012

### Xarelto 20mg film-coated tablets

#### 1. Name of the medicinal product

Xarelto ▼ 20 mg film-coated tablets

#### 2. Qualitative and quantitative composition

Each film-coated tablet contains 20 mg rivaroxaban.

Excipients with known effect:

Each 20 mg film-coated tablet contains 22.9 mg lactose monohydrate, see section 4.4.

For the full list of excipients, see section 6.1.

#### 3. Pharmaceutical form

Film-coated tablet (tablet).

Brown-red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and “20” and a triangle on the other side.

#### 4. Clinical particulars

##### 4.1 Therapeutic indications

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, prior stroke or transient ischaemic attack.

Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

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#### 4.2 Posology and method of administration

##### Posology

##### *Prevention of stroke and systemic embolism*

The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Xarelto should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding (see section 4.4).

If a dose is missed the patient should take Xarelto immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

##### *Treatment of DVT and prevention of recurrent DVT and PE*

The recommended dose for the initial treatment of acute DVT is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE, as indicated in the table below.

	Dosing schedule	Maximum daily dose
Day 1-21	15 mg twice daily	30 mg
Day 22 and onwards	20 mg once daily	20 mg

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

Short duration of therapy (3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT. Experience with Xarelto in this indication for more than 12 months is limited.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Xarelto immediately to ensure intake of 30 mg Xarelto per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take Xarelto immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

##### *Converting from Vitamin K Antagonists (VKA) to Xarelto*

For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Xarelto therapy should be initiated when the INR is  $\leq 3.0$ .

For patients treated for DVT and prevention of recurrent DVT and PE, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is  $\leq 2.5$ .

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When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

#### *Converting from Xarelto to Vitamin K antagonists (VKA)*

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is  $\geq 2.0$ . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both Xarelto and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto. Once Xarelto is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

#### *Converting from parenteral anticoagulants to Xarelto*

For patients currently receiving a parenteral anticoagulant, Xarelto should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

#### *Converting from Xarelto to parenteral anticoagulants*

Give the first dose of parenteral anticoagulant at the time the next Xarelto dose would be taken.

#### *Special populations*

##### *Renal impairment*

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see section 5.2).

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).

- For the treatment of DVT and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily based on PK modelling (see sections 4.4 and 5.2).

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance  $< 15$  ml/min (see sections 4.4 and 5.2).

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#### *Hepatic impairment*

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

#### *Elderly population*

No dose adjustment (see section 5.2).

#### *Body weight*

No dose adjustment (see section 5.2).

#### *Gender*

No dose adjustment (see section 5.2).

#### *Paediatric population*

The safety and efficacy of Xarelto in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto is not recommended for use in children below 18 years of age.

#### Method of administration

For oral use. The tablets are to be taken with food (see section 5.2).

#### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically significant active bleeding.

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast feeding (see section 4.6).

#### **4.4 Special warnings and precautions for use**

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

#### Haemorrhagic risk

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during



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long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

#### Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

Xarelto should be used with caution in patients with renal impairment concomitantly receiving other medicinal products that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) as PK modelling shows increased rivaroxaban concentrations in these patients.

#### Interaction with other medicinal products

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

#### Other haemorrhagic risk factors

Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- recent gastrointestinal ulcerations
- vascular retinopathy

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- recent intracranial or intracerebral haemorrhage
- intraspinal or intracerebral vascular abnormalities
- recent brain, spinal or ophthalmological surgery
- bronchiectasis or history of pulmonary bleeding.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.1 and 5.2).

#### Patients with prosthetic valves

Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

#### Patients with acute pulmonary embolism

Xarelto is not recommended in the treatment of acute pulmonary embolism.

#### Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Xarelto should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Xarelto should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see section 5.2).

#### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban  $C_{max}$ , with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment

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with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in  $C_{max}$ . This increase is not considered clinically relevant.

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and  $C_{max}$ . This increase is not considered clinically relevant.

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean  $C_{max}$ . This increase is not considered clinically relevant.

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

#### Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see section 4.4).

#### NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

#### Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects

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on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C<sub>trough</sub> of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

#### CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

#### Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

#### Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

#### 4.6 Fertility, pregnancy and breast feeding

##### Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

##### Breast feeding

Safety and efficacy of Xarelto have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding

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or to discontinue/abstain from therapy.

#### Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

#### 4.7 Effects on ability to drive and use machines

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope and dizziness have been reported to be common (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

#### 4.8 Undesirable effects

##### Summary of the safety profile

The safety of rivaroxaban has been evaluated in eight phase III studies including 16,041 patients exposed to rivaroxaban (see Table 1).

**Table 1: Number of patients studied, maximum daily dose and treatment duration in phase III studies**

Indication	Number of patients*	Maximum daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Treatment of DVT and prevention of recurrent DVT and PE	2,194	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

\*Patients exposed to at least one dose of rivaroxaban

In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 24% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery, bleeding events occurred in approximately 6.8% of patients and anaemia occurred in approximately 5.9% of patients. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately 1.8% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years.

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#### Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

common ( $\geq 1/100$  to  $< 1/10$ )

uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Not known: cannot be estimated from the available data.

**Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies (prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (*VTE-P*), treatment of DVT and prevention of recurrent DVT and PE (*DVT-T*), and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (*SPAF*))**

Common	Uncommon	Rare	Not known
<b>Blood and lymphatic system disorders</b>			
Anaemia (incl. respective laboratory parameters)	Thrombocythemia (incl. platelet count increased) <sup>A</sup>		
<b>Immune system disorders</b>			
	Allergic reaction, dermatitis allergic		
<b>Nervous system disorders</b>			
Dizziness, headache, syncope	Cerebral and intracranial haemorrhage		
<b>Eye disorders</b>			
Eye haemorrhage (incl. conjunctival haemorrhage)			
<b>Cardiac disorders</b>			
Tachycardia			
<b>Vascular disorders</b>			

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Hypotension, haematoma			Pseudoaneurysm formation following percutaneous intervention*
<b>Respiratory, thoracic and mediastinal disorders</b>			
Epistaxis	Haemoptysis		
<b>Gastrointestinal disorders</b>			
Gastrointestinal tract haemorrhage (incl. gingival bleeding and rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth		
<b>Hepatobiliary disorders</b>			
	Hepatic function abnormal	Jaundice	
<b>Skin and subcutaneous tissue disorders</b>			
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis	Urticaria, cutaneous and subcutaneous haemorrhage		
<b>Musculoskeletal and connective tissue disorders</b>			
Pain in extremity <sup>A</sup>	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
<b>Renal and urinary disorders</b>			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia <sup>B</sup> )	Renal impairment (incl. blood creatinine increased, blood urea increased) <sup>A</sup>		Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
<b>General disorders and administration site conditions</b>			
Fever <sup>A</sup> , peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise), localised oedema <sup>A</sup>		
<b>Investigations</b>			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased LDH <sup>A</sup> , increased	Bilirubin conjugated increased (with or without concomitant increase of ALT)	

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	lipase <sup>A</sup> , increased amylase <sup>A</sup> , increased GGT <sup>A</sup>		
<b>Injury, poisoning and procedural complications</b>			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion <sup>A</sup>			

A: observed in VTE-P after major orthopaedic surgery of the lower limbs

B: observed in DVT-T as very common in women < 55 years

\*) These reactions occurred in other clinical studies than the phase III studies in patients undergoing major orthopaedic surgery of the lower limbs, patients treated for DVT and prevention of recurrent DVT and PE, or patients treated for the prevention of stroke and systemic embolism

#### Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

#### **4.9 Overdose**

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

#### Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should



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be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

### 5. Pharmacological properties

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antithrombotic agents, ATC code: B01AX06

##### Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

##### Pharmacodynamic effects

Dose-dependent inhibition of Factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of DVT and prevention of recurrent DVT and PE, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 16 to 33 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 25 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 21 s.

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.2).

##### Clinical efficacy and safety

##### *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation*

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto for the prevention of stroke and systemic embolism in patients

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with non-valvular atrial fibrillation.

In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to Xarelto 20 mg once daily (15 mg once daily in patients with creatinine clearance 30 - 49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.

Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 – 0.96; P<0.001 for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 – 1.03; P<0.001 for non-inferiority; P=0.117 for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 3.

Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles (P=0.74 for interaction). Within the highest quartile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 4).

**Table 3: Efficacy results from phase III ROCKET AF**

	• ITT analyses of efficacy in patients with non-valvular atrial fibrillation		
Treatment, dosage	Xarelto 20 mg od (15 mg od in patients with moderate renal impairment)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)	Hazard ratio (95% CI) p-value, test for superiority
	Event rate (100 pt-yr)	Event rate (100 pt-yr)	
Stroke and non-CNS systemic embolism	269 (2.12%)	306 (2.42%)	0.88 (0.74 - 1.03) 0.117
Stroke, non-CNS systemic embolism and vascular death	572 (4.51%)	609 (4.81%)	0.94 (0.84 - 1.05) 0.265
Stroke, non-CNS systemic embolism, vascular death and Myocardial infarction	659 (5.24%)	709 (5.65%)	0.93 (0.83 - 1.03) 0.158
Stroke	253 (1.99%)	281 (2.22%)	0.90 (0.76 - 1.07) 0.221
Non-CNS systemic embolism	20 (0.16%)	27 (0.21%)	0.74

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			(0.42 - 1.32)
			0.308
Myocardial infarction	130 (1.02%)	142 (1.11%)	0.91 (0.72 - 1.16)
			0.464

**Table 4: Safety results from phase III ROCKET AF**

• Study population	• Patients with non-valvular atrial fibrillation*		
Treatment, dosage	Xarelto 20 mg once a day (15 mg once a day in patients with moderate renal impairment)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)	Hazard ratio (95% CI) p-value
	Event rate (100 pt-yr)	Event rate (100 pt-yr)	
Major and non-major clinically relevant bleeding events	1,475 (14.91%)	1,449 (14.52%)	1.03 (0.96 - 1.11) 0.442
Major bleeding events	395 (3.60%)	386 (3.45%)	1.04 (0.90 - 1.20) 0.576
Death due to bleeding*	27 (0.24%)	55 (0.48%)	0.50 (0.31 - 0.79) 0.003
Critical organ bleeding*	91 (0.82%)	133 (1.18%)	0.69 (0.53 - 0.91) 0.007
Intracranial haemorrhage*	55 (0.49%)	84 (0.74%)	0.67 (0.47 - 0.93) 0.019
Haemoglobin drop*	305 (2.77%)	254 (2.26%)	1.22 (1.03 - 1.44) 0.019
Transfusion of 2 or more units of packed red blood cells or whole blood*	183 (1.65%)	149 (1.32%)	1.25 (1.01 - 1.55) 0.044
Non-major clinically relevant bleeding events	1,185 (11.80%)	1,151 (11.37%)	1.04 (0.96 - 1.13) 0.345
All cause mortality	208 (1.87%)	250 (2.21%)	0.85 (0.70 - 1.02) 0.073

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a) Safety population, on treatment

\* Nominally significant

#### *Treatment of DVT and prevention of recurrent DVT and PE*

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto in the initial and continued treatment of acute DVT and prevention of recurrent DVT and PE.

Over 4,600 patients were studied in two randomised controlled phase III clinical studies (Einstein DVT and Einstein Extension). The overall combined treatment duration in both studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

The comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range ( $\geq 2.0$ ). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Xarelto 20 mg once daily was compared with placebo.

Both phase III studies used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all cause mortality.

In the Einstein DVT study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ( $p < 0.0001$  (test for non-inferiority); hazard ratio: 0.680 (0.443 - 1.042),  $p=0.076$  (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.67 ((95% CI= 0.47–0.95), nominal  $p$  value  $p=0.027$ ) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2 - 3) in the equally sized tertiles and the incidence of the recurrent VTE ( $P=0.932$  for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.69 (95% CI, 0.35 to 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

In the Einstein Extension study (see Table 6) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

In both the Einstein DVT and Einstein Extension studies, patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) were treated with the same dose as patients with creatinine clearance above 50 ml/min (i.e. 15 mg twice daily for the first three weeks and 20 mg once daily from day 22 onwards).

**Table 5: Efficacy and safety results from phase III Einstein DVT**

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Study Population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment dosage and duration	Xarelto <sup>a</sup>  3, 6 or 12 months  N=1,731	Enoxaparin/VKA <sup>b</sup>  3, 6 or 12 months  N=1,718
Symptomatic recurrent VTE*	36  (2.1%)	51  (3.0%)
Symptomatic recurrent PE	20  (1.2%)	18  (1.0%)
Symptomatic recurrent DVT	14  (0.8%)	28  (1.6%)
Symptomatic PE and DVT	1  (0.1%)	0
Fatal PE/Death where PE cannot be ruled out	4  (0.2%)	6  (0.3%)
Major or clinically relevant non-major bleeding	139  (8.1%)	138  (8.1%)
Major bleeding events	14  (0.8%)	20  (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days followed by VKA

\* p < 0.0001 (non-inferiority); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (superiority)

**Table 6: Efficacy and safety results from phase III Einstein Extension**

Study Population	1,197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment dosage and duration	Xarelto <sup>a</sup>  6 or 12 months  N=602	Placebo  6 or 12 months  N=594
Symptomatic recurrent VTE*	8  (1.3%)	42  (7.1%)
Symptomatic recurrent PE	2  (0.3%)	13  (2.2%)
Symptomatic recurrent DVT	5	31

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	(0.8%)	(5.2%)
Fatal PE/Death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)

a) Rivaroxaban 20 mg once daily

\*  $p < 0.0001$  (superiority), hazard ratio: 0.185 (0.087 - 0.393)

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric population in the treatment of thromboembolic events. The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events. See section 4.2 for information on paediatric use.

#### 5.2 Pharmacokinetic properties

##### Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When Xarelto 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Xarelto 15 mg and 20 mg are to be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions Xarelto 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

##### Distribution

Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with  $V_{ss}$  being approximately 50 litres.

##### Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and

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hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

#### Special populations

##### *Gender*

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

##### *Elderly population*

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

##### *Different weight categories*

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.

##### *Inter-ethnic differences*

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

##### *Hepatic impairment*

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of Factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

##### *Renal impairment*

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

## Appendix 1. Study Protocol

### (Appendix 1. UK SPC for rivaroxaban)

Use is not recommended in patients with creatinine clearance < 15 ml/min. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

#### Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) µg/l, respectively.

#### Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (Factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and Factor Xa activity was best described by an E<sub>max</sub> model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

#### Paediatric population

Safety and efficacy have not been established for children and adolescents up to 18 years.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

#### Tablet core:

Microcrystalline cellulose

Croscarmellose sodium

Lactose monohydrate

Hypromellose

Sodium laurilsulfate

Magnesium stearate



## **Appendix 1. Study Protocol**

### **(Appendix 1. UK SPC for rivaroxaban)**

#### Film-coat:

Macrogol 3350

Hypromellose

Titanium dioxide (E171)

Iron oxide red (E172)

#### **6.2 Incompatibilities**

Not applicable.

#### **6.3 Shelf life**

3 years

#### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

#### **6.5 Nature and contents of container**

PP/Aluminium foil blisters in cartons of 14, 28 or 98 film-coated tablets or perforated unit dose blisters in cartons of 10 x 1 or 100 x 1 film-coated tablets.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal and other handling**

No special requirements for disposal.

#### **7. Marketing authorisation holder**

Bayer Pharma AG

13342 Berlin

Germany

#### **8. Marketing authorisation number(s)**

EU/1/08/472/017-021

#### **9. Date of first authorisation/renewal of the authorisation**

Date of first authorisation: 30 September 2008

#### **10. Date of revision of the text**

05/2012

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Distributed in the United Kingdom by:

Bayer plc

Bayer House

## **Appendix 1. Study Protocol**

### **(Appendix 1. UK SPC for rivaroxaban)**

Strawberry Hill

Newbury

Berkshire

RG14 1JA



## **Appendix 1. Study Protocol**

### **(Appendix 2. Rare Adverse Events which are Serious and a high Proportion are due to drug)**

Agranulocytosis  
Alveolitis  
Anaemia aplastic  
Anaphylaxis  
Angioneurotic oedema  
Arrhythmia  
Bone marrow abnormal  
Congenital abnormality  
Dermatitis exfoliative  
Disseminated intravascular coagulation  
Erythema multiforme  
Erythroderma  
Guillain-Barre syndrome  
Hepatic failure  
Hepatitis  
Jaundice  
Leucopenia  
Multiorgan failure  
Nephritis  
Nephrotic syndrome  
Neuroleptic malignant syndrome  
Neutropenia  
Pancreatitis  
Pancytopenia  
Pseudomembranous colitis  
Renal failure acute  
Retroperitoneal fibrosis  
Rhabdomyolysis  
Stevens Johnson syndrome  
Sudden Unexpected Death  
Thrombocytopenia  
Torsades de pointe  
Toxic epidermal necrolysis

## **Appendix 1. Study Protocol**

**(Appendix 2. Rare Adverse Events which are Serious and a high Proportion are due to drug)**

Any event for which there is a positive rechallenge

## **Appendix 2. Statistical Analysis Plan**

### **STATISTICAL ANALYSIS PLAN**

#### **VERSION 1**

**FOR STUDY PROTOCOL: AN OBSERVATIONAL POST-AUTHORIZATION SAFETY SPECIALIST COHORT EVENT MONITORING STUDY (SCM) TO MONITOR THE SAFETY AND UTILIZATION OF RIVAROXABAN (XARELTO®) FOR THE PREVENTION OF STROKE IN PATIENTS WITH AF, TREATMENT OF DVT AND PE, AND THE PREVENTION OF RECURRENT DVT AND PE IN THE SECONDARY CARE HOSPITAL SETTING IN ENGLAND AND WALES**

#### **Investigators**

Members of the Drug Safety Research Unit (DSRU), Southampton, SO31 1AA, UK:

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A Evans PhD, Study Manager

D Layton PhD, Principal Research Fellow

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## Appendix 2. Statistical Analysis Plan

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## Appendix 2. Statistical Analysis Plan

### 1.0 LIST OF ABBREVIATIONS

Abbreviation	Term
A & E	Accident and Emergency
ADR	Adverse Drug Reaction
ACS	Acute coronary syndrome
AE	Adverse Event
AF	Atrial fibrillation
ALT	alanine aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	aspartate aminotransferase
BMA	British Medical Association
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CHA <sub>2</sub> DS <sub>2</sub> -VASc	Congestive heart failure, Hypertension, Age ≥75 years, or age 65-75 years, Diabetes mellitus, and prior Stroke or transient ischemic attack or thromboembolism, Vascular Disease, female sex.
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CYP2CP	Cytochrome P450 2C9
CYP P450	Cytochrome P-450
DMP	Data Management Plan
DSRU	Drug Safety Research Unit
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drugs Administration
FDR	False Discovery Rate
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GP	General Practitioner
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HLT	Higher Level Term
ID	Incidence Density
INR	International normalized ratio
IRAS	Integrated Research Application System
ISTH	International Society on Thrombosis and Haemostasis
IQR	Interquartile Range



## Appendix 2. Statistical Analysis Plan

LFT	Liver Function Test
LLT	Lower Level Term
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
M-PEM	Modified Prescription-Event Monitoring
NDA	New Drug Application
NHS	National Health Service
NHSRxS	National Health Service Prescription Services
NICE	National Institute for Health and Clinical Excellence
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over-The-Counter
PCI	Percutaneous coronary insert
PE	Pulmonary embolism
PEM	Prescription Event Monitoring
PIP	Paediatric Investigation Plan
PS	Propensity Scores
PSC	Project Steering Committee
RCT	Randomised Controlled Trial
RAIDAR	Rare and Iatrogenic Adverse Reactions
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SCEM	Specialist Cohort Event Monitoring
SOC	System Organ Class
SOP	Standard Operating Procedure
SPAF	Stroke Prevention in Atrial Fibrillation
SPC	Summary of Product Characteristics
TIA	Transient Ischaemic Attack
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VKA	Vitamin K Antagonist
VKORC1	Vitamin K epoxide reductase complex subunit 1
VTE	Venous thromboembolism

## 2.0 RESPONSIBLE PARTIES

Responsible party	Appointed person(s)
Principal investigator	Professor Saad Shakir, Drug Safety Research Unit
Co-principal investigator	
Marketing Authorisation holder contact	

## **Appendix 2. Statistical Analysis Plan**

### **3.0 ABSTRACT**

This document describes the outline statistical analysis plan for the proposal from the Drug Safety Research Unit (DSRU) for a Specialist Cohort Event Monitoring study (SCEM) Study to monitor the safety and utilization of rivaroxaban (Xarelto®) for the prevention of stroke in patients with AF, treatment of DVT and PE, and the prevention of recurrent DVT and PE.

### **4.0 AMENDMENTS AND UPDATES**

#### **Document Change Record**

Date	Version	Author	Change Details
03/12/2013	Draft 1	Ian Ratcliffe	Creation
06/06/2014	Draft 2	Vicki Osborne	Additional tables
02/02/2015	Draft 3	Sarah Marley	Statistical updates
13/03/2015	Draft 4	Deborah Layton	Restructure of flow
18/03/2015	Draft 5	Deborah Layton	Statistical updates
05/11/2016	Draft 6	Deborah Layton	Restructure of tables
27/01/2017	Draft 7	Deborah Layton	Updates to all sections following Bayer review
23/02/2017	Draft 8	Deborah Layton	Updates to all sections following review of Data Management Plan (DMP)
08/03/2017	Draft 9	Deborah Layton	Further updates following revision to DMP

### **5.0 MILESTONES**

Not applicable.

### **6.0 RATIONALE AND BACKGROUND**

Please refer to the study protocol for background details of the study methodology and the drug under surveillance.

### **7.0 RESEARCH QUESTION AND OBJECTIVES**

#### **7.1 Overall Aim**

To monitor the short-term (12 weeks) use and safety profile of rivaroxaban prescribed to new-user adult patients (i.e. rivaroxaban naïve who may or may not be

## **Appendix 2. Statistical Analysis Plan**

antithrombotic therapy naïve) for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, the treatment of DVT, PE, and the prevention of recurrent DVT and PE in adult patients, requiring anticoagulation under normal conditions of use in the secondary care hospital setting. In addition since it is desirable to put these observations into context and characterise a population treated with existing anticoagulant treatment to allow the variation in determinants of treatment groups to be examined in relation to risk, a similar number of evaluable patients receiving alternative anticoagulant therapy (contextual cohort- warfarin) will be monitored in order to inform on the adoption of rivaroxaban into clinical practice.

### **7.2 Specific Objectives**

#### ***7.2.1 The primary objective***

Its purpose is to provide timely information on:

(i) Estimation of the cumulative incident risk (separately) of the following important identified risk for rivaroxaban users which is:

- Haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites, Box 1)

#### ***7.2.2 Secondary Objectives***

These are given below. Their purpose is to provide timely information on:

(i) Prescriber and cohort accrual and the type of prescriber responsible for, and the setting of initiation of treatment with either rivaroxaban or alternative anticoagulant therapy.

(ii) Prevalence of non-clinical reasons for prescribing, prognostic health factors and clinical risk factors for haemorrhage as reported in medical charts for patients undergoing anticoagulation with either rivaroxaban or alternative anticoagulant therapy in the secondary care hospital setting and the treatment programme they received to advance the understanding of the patient population prescribed rivaroxaban in actual clinical practice in the secondary care hospital setting

(iii) Changes of health profile of patients, assessment of adherence, plus any alterations of the treatment programme during the 12 week observation period, as recorded in medical charts.

(iv) To quantify the risk of:

- (a) (separately) haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites for warfarin anticoagulant therapy cohort

## Appendix 2. Statistical Analysis Plan

- (b) all major bleeding specified in primary objective for both rivaroxaban and warfarin anticoagulant therapy cohort (as composite)
- (c) (separately) haemorrhage (major bleeding according to Box 1) within critical organ sites other than specified in primary objective for both rivaroxaban and warfarin anticoagulant therapy cohort
- (d) all major and clinically relevant non-major bleeds (as a composite outcome)
- (e) thromboembolic complications (incident and recurrent)
- (f) other<sup>1</sup> events including special outcomes of interest (severe hepatic failure and abnormal LFTs above 3x ULN) as recorded in medical charts during the 12 week observation period and, if number of reports are sufficient, in patient subgroups of special interest<sup>2</sup>, including:
  - reported indications
  - elderly ( $\geq 65$  years)<sup>3</sup>, other contraindicated or special groups (e.g. pregnant and breastfeeding women, patients with concurrent significant renal or hepatic impairment; patients with known VTE and/or haemorrhagic risk factors e.g. congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, active ulcerative gastrointestinal disease) and off-label groups (patients with other non-orthopaedic medical conditions )
  - concomitant use of medications that are contraindicated or to be used with caution (e.g. CYP3A4 inducers/inhibitors, P-gp inhibitors, anticoagulants, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, hormone and oral contraception therapy and platelet aggregation inhibitors)

### ***7.2.3 Exploratory objectives (for rivaroxaban only)***

The specific objectives that follow are all exploratory. The purposes of these objectives are:

- (i) Where possible, to quantify the incidence of other important identified and potential risks (not mentioned in objective 3.2.1), other frequently and rarely

---

<sup>1</sup> Other than major and clinically relevant non major bleeding outcomes, or thromboembolic complications (recurrent or incident)

<sup>2</sup> Groups of special interest will be those common to both cohorts, such as the HASBLED criteria. Off-label indications contraindications and warnings and precautions for use will not be systematically assessed for the contextual cohort.

<sup>3</sup> Children and adolescents aged less than 18 years of age will be excluded from the SCeM study. Since this is important missing information, data on this special population will be captured within the complementary M-PEM, if reported.

## Appendix 2. Statistical Analysis Plan

reported adverse events as recorded in the medical charts and to identify previously unrecognised ADRs

(ii) To describe clinical features and management of cases of overdose, major bleeding (according to pre-specified definition (Box 1), VTE events indicating failure of anticoagulation and management of haemostasis during surgery as recorded reporting the medical charts in the first 12 weeks after treatment initiation in the cohort exposed to rivaroxaban.

### **Box 1. Haemorrhage outcomes(1)**

**A major bleeding event will be defined using ISTH criteria as clinically overt bleeding that is associated with:**

- A fall in haemoglobin of 2 g/dL or more, or
- A transfusion of 2 or more units of packed red blood cells or whole blood, or
- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome

**A clinically-relevant non-major bleeding event is defined as an overt bleeding event not meeting the criteria for a major bleeding event, but associated with medical intervention<sup>4</sup>, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life. Examples of non-major clinically relevant bleeding events are:**

- Epistaxis if it lasts for more than 5 minutes, if it is repetitive (i.e., 2 or more episodes of true bleeding, i.e., number of spots on a handkerchief, within 24 hours), or leads to an intervention (packing, electrocautery, etc.)
- Gingival bleeding if it occurs spontaneously (i.e. unrelated to tooth brushing or eating), or if it lasts for more than 5 minutes
- Haematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract
- Macroscopic gastrointestinal haemorrhage: at least 1 episode of melena or haematemesis, if clinically apparent
- Rectal blood loss, if more than a few spots
- Haemoptysis, if more than a few speckles in the sputum, or
- Intramuscular hematoma
- Subcutaneous hematoma if the size is larger than 25 cm<sup>2</sup> or larger than 100 cm<sup>2</sup> if provoked
- Multiple source bleeding events

## **8.0 METHODS**

Please refer to the protocol for further details of methods (study design, setting, study period, study population inclusion/exclusion criteria). In brief, exposure, outcome and covariate data<sup>5</sup> will be collected using the bespoke Specialist Cohort Monitoring Study (SCM) study questionnaire. This questionnaire will seek

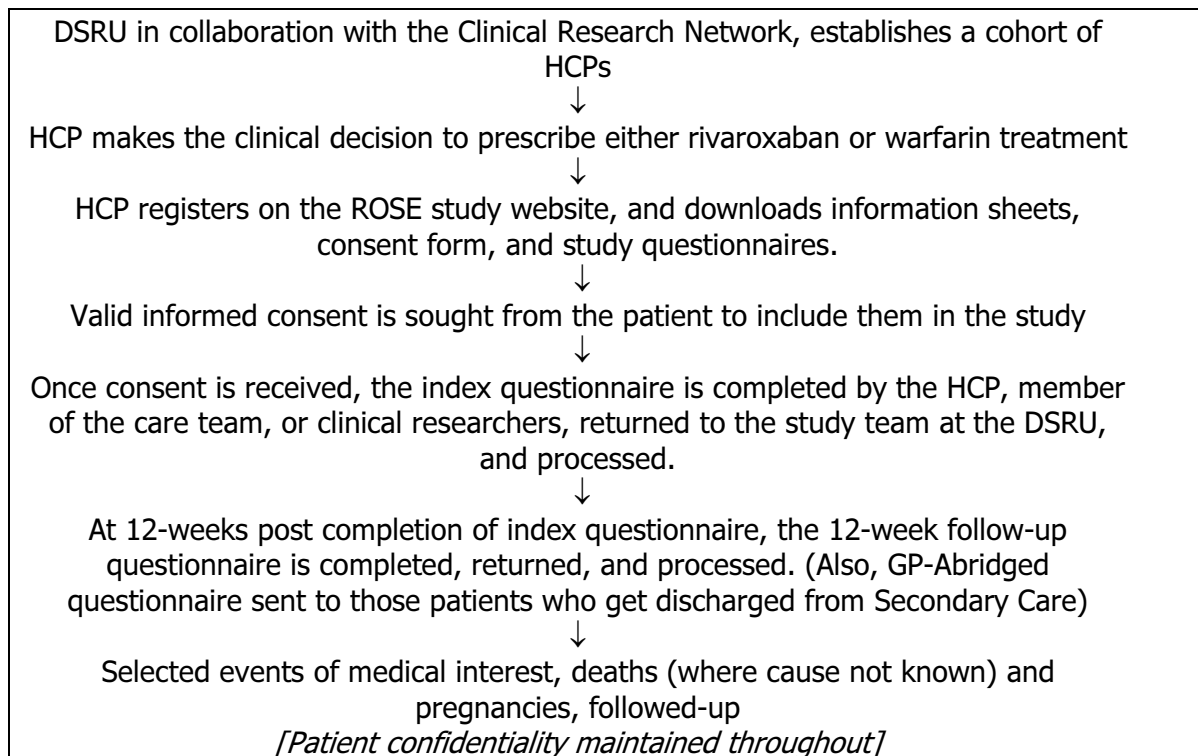
<sup>4</sup> Such as: Surgical or endoscopic intervention; decompression of a closed space to stop or control the event; protamine sulphate administration

<sup>5</sup> Derivation of each variable is outlined in section 9.

## Appendix 2. Statistical Analysis Plan

information on how rivaroxaban is prescribed in daily secondary care practice. Patient data to be captured for this study is summarised in Figure 1.

**Figure 1. SCEM Study of rivaroxaban (Xarelto®)**



## 9.0 DATA ANALYSIS

Data on response rates, patient demography and baseline health characteristics of the evaluable<sup>6</sup> patient cohort will be summarised using univariate descriptive statistics, including measures of central tendency and dispersion for continuous variables (mean, standard deviation, median, range, and percentiles) and frequencies with proportions for categorical variables, where a response is specified. All data analyses will be performed using STATA v12 (Special Edition).

### 9.1 Health Care Professional and Patient Recruitment

<sup>6</sup> Patients excluded from the evaluable cohort are those meeting either (1) the standard exclusion criteria per protocol and (2) study specific exclusions where patients with no evidence of having used Rivaroxaban defined by a start date before market launch date.

## Appendix 2. Statistical Analysis Plan

In accordance with secondary objective (i), recruitment and distribution of both the HCP and patient cohorts will be described. Investigative site (trust-level) characteristics will also be presented.

### 9.1.1 Site (trust) engagement

Data on the investigative site (trusts) participating in this study, to which participating HCP are affiliated will include region, type of trust, catchment population density served (2013), socioeconomic status of population served, number of hospitals per trust and types (teaching/general), trust rivaroxaban sales volume (2013), availability of trust anticoagulant prescribing guidelines. These data will be derived from self-reported information from the registering site (trust) investigator supported by publically available relevant National Health Service websites. These data will also be collected for non-participating acute trusts and compared with participating trusts to explore representativeness

The following data will be presented in tabulations and figures.

**Table 1. Site (trust) characteristics**

<b>Data Description</b>	<b>Source</b>	<b>Result Reference</b>
<b>Geographic setting – count and percent by region</b>	In-House Database	Table 1A, Figure 2
<b>Trust type -count and percent of type</b>	In-House Database, else NHS Choices website; e.g <a href="http://www.nhs.uk/Services/hospitals/Overview/DefaultView.aspx?id=245">http://www.nhs.uk/Services/hospitals/Overview/DefaultView.aspx?id=245</a>	Table 1A
<b>Trust catchment population density served- median (IQR)</b>	trust website specific, else from <a href="http://www.apho.org.uk/resource/item.aspx?RID=178648">http://www.apho.org.uk/resource/item.aspx?RID=178648</a>	Table 1A
<b>Socioeconomic status of trust population served</b>	Post code from In-House Database ; Index Multiple deprivation from : <a href="http://imd-by-postcode.opendatacommunities.org/">http://imd-by-postcode.opendatacommunities.org/</a>	Table 1A
<b>Trust Hospital density – count, median (IQR)</b>	In-House Database, else NHS Choices website; e.g <a href="http://www.nhs.uk/Services/hospitals/Overview/DefaultView.aspx?id=245">http://www.nhs.uk/Services/hospitals/Overview/DefaultView.aspx?id=245</a>	Table 1A
<b>Trust hospital type (teaching/general) : count</b>	NHS Choices website; e.g <a href="http://www.nhs.uk/Services/hospitals/Overview/DefaultView.aspx?id=245">http://www.nhs.uk/Services/hospitals/Overview/DefaultView.aspx?id=245</a>	Table 1A

## Appendix 2. Statistical Analysis Plan

<b>Trust Rivaroxaban Sales (mg purchased), count; median (IQR)</b>	Proxy indicator of trust use) <a href="https://www.england.nhs.uk/wp-content/uploads/2014/06/pub-tab-5-med-trust.xlsx">https://www.england.nhs.uk/wp-content/uploads/2014/06/pub-tab-5-med-trust.xlsx</a>	Table 1A
<b>Trust anticoagulant prescribing guideline</b>	trust website specific, else from <a href="http://www.apho.org.uk/resource/it-em.aspx?RID=178648">http://www.apho.org.uk/resource/it-em.aspx?RID=178648</a>	Table 1A

**Table 1A. Participating and non-participating trust characteristics**

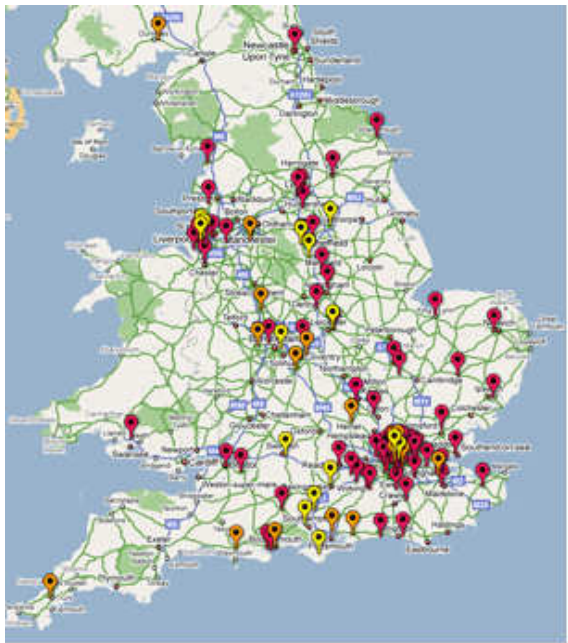
Characteristics (n %)	Participating trust	Non-participating trust	p-value	All trusts (n=154)
Geographical distribution – region			Chi <sup>2</sup> (df2)	
North			p=	
Midlands and North Wales				
South West and South Wales				
London and South East				
Trust Type			Chi <sup>2</sup> (df2)	
Acute			p=	
Foundation				
Integrated				
<i>Not specified</i>				
Trust population density (per million)			Ranksum	
<1			p=	
1, <2				
3, <4				
4, <5				
.....				
10+				
Median (IQR)				
<i>Not available</i>				
Socioeconomic status of trust population served (IMD rank decile)			Ranksum	
1			p=	
...				
10				
Median (IQR)				
<i>Not available</i>				
Trust hospital density			Chi <sup>2</sup> (df2)	
<5			p=	
5, <10				
10+				
<i>Not available</i>				
Hospital Type			Chi <sup>2</sup> (df1)	
Teaching			p=	
General				
Trust Rivaroxaban Sales (mg			Ranksum	



**Appendix 2. Statistical Analysis Plan**

purchased per 100,000 hospital days)	p=
<50000	
50000, <100000	
.....	
250000, <300000	
300000 +	
Not available	
Trust anticoagulant prescribing guideline publicly available	Chi <sup>2</sup> (df1)
	p=
Yes	
No	
Not available	

**Figure 2. Example of: Distribution of participating and non-participating trusts**



**9.1.2 HCP Recruitment**

Data on the health care professional responsible<sup>7</sup> for the patients included in the cohort will be presented. These will include: affiliate region, sex, profession, years of experience, career level, specialist status, type of speciality, years of specialism.<sup>8</sup>

<sup>7</sup> The recruiter may or may not be the prescribing HCP. However it is assumed that they have permission from the responsible HCP to engage with the eligible patient. For purposes of determining representativeness, the characteristics of the responsible HCP will be explored.

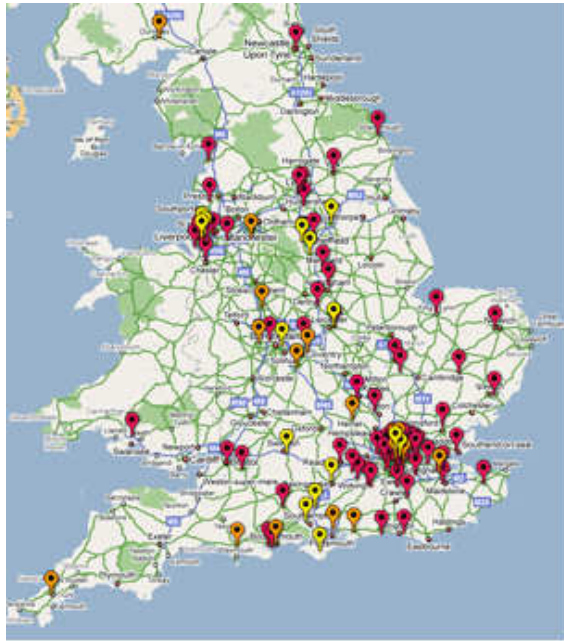
<sup>8</sup> Additional information will be derived for each prescribing HCP from aggregate patient-level clustered data such as: rivaroxaban prescribing preference (% rivaroxaban prescribed

## Appendix 2. Statistical Analysis Plan

These data will be derived from self-reported information from the responsible prescriber supported by publically available relevant professional body membership details.

The following data will be presented in tabulations and figures.

**Figure 3. Example of: Distribution of participating HCP practice settings of HCP cohort**



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to patients recruited, most common factors influencing decision such as clinical judgement, nice guidelines, other expert group guidelines, trust formulary). These will be presented as part of the multi-level analysis

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**Table 2. HCP responsible for patient: characteristics**

<b>Data Description</b>	<b>Source</b>	<b>Result Reference</b>
Geographic region	In-House Database	Table 2A, Figure 3
HCP sex -count and percent of type	In-House Database	Table 2A
HCP professional qualification- -count and percent of type	In-house database Professional registers: <a href="http://www.gmc-uk.org/doctors/register/LRMP.asp">http://www.gmc-uk.org/doctors/register/LRMP.asp</a> ; from GPhC website: <a href="https://www.pharmacyregulation.org/registration">https://www.pharmacyregulation.org/registration</a> ; from <a href="https://www.nmc.org.uk/registration/search-the-register/">https://www.nmc.org.uk/registration/search-the-register/</a>	
HCP years registered- -count and percent of type; median (IQR)	Professional registers	
HCP career level	In-House Database	
HCP specialist status - count and percent type	Professional register data	
HCP specialism (Clinical area)- count and percent by type	In-House Database	
HCP years as specialist- count and percent of type; median (IQR)	Professional register data	

Specialist healthcare professionals responsible for prescribing Rivaroxaban or Warfarin treatment for the licensed indications as outlined in the protocol have been systematically identified by the DSRU and invited to participate in the study prior to the study start. Continued invitations were made and participants welcomed throughout the study. Routes of identifying relevant specialist HCPs within these settings included the use of existing clinical research networks and support networks provided by allied healthcare professionals, such as hospital pharmacists.

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**Table 2A. Healthcare professional characteristics**

Characteristics	N	%
Geographical distribution – region		
	North	
	Midlands and North Wales	
	South West and South Wales	
	London and South East	
Sex		
	Male	
	Female	
	<i>Not specified</i>	
Professional qualification:		
	Medical Clinician	
	Pharmacist	
	Nurse	
	<i>Not specified</i>	
Years registered:		
	<5	
	5, <10	
	10, <15	
	15, <20	
	20, <25	
	25+	
	Median (IQR)	
	<i>Not available</i>	
Career level <sup>a</sup> :		
	Senior	
	Middle	
	Junior	
	<i>Not available</i>	
Specialist award:		
	Yes	
	No	
	<i>Not specified</i>	
Years as specialist:		
	<5	
	5, <10	
	10, <15	
	15, <20	
	20, <25	
	25+	
	Median (IQR)	
	<i>Not available</i>	
Specialism type:		
	Neurology/Stroke	
	Haematology	
	Geriatrics	
	Surgery	
	Gastroenterology	
	Endocrinology	
	Cardiology	

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Acute care  
Accident and emergency  
Other  
*Not available*

<sup>a</sup> assessed on years' experience, and/or name prefix

### 9.1.3 Patient Recruitment

In accordance with secondary objective (i), data on accrual rates for the cohort will be presented. Following patient consent, questionnaires are completed and returned at baseline and at 12-weeks post index date. The following data will be presented in tabulations and figures.

**Table 3. Patient Recruitment**

Data description	Source	Result reference
Treatment group	Index Questionnaire (Q3)	N/A text
Count and percentage for patients consented, index and 12-week questionnaires returned.	In-House Database	Table 3A
Reasons for classification of ineligible patients.	Database coded data Communications to study team	Table 3B , Figure 4
Geographic distribution of cohort	In-House Database	Table 3C, Figure 5
Number of patients recruited over the course of the study	In-House Database	Figure 6a
Number of patients recruited by month (moving average with 95% confidence interval)	In-House Database	Figure 6b
Dates of first and last patients in valid cohort, and last form returned.	In-House Database	N/A Text

Table 3A below presents data regarding the patient cohort, by treatment. Following consent, it was found that some patients were not eligible to be included (Table 3B shows the reasons for ineligibility) The number of patients with index questionnaires returned is shown in Table 3A, and following receipt of the index questionnaire, data are reviewed to determine how many patients are considered evaluable, with data that can be analysed. This information is also shown for all 12-week questionnaires

## Appendix 2. Statistical Analysis Plan

returned. The reasons why patients were not eligible for inclusion at 12-weeks are also described within Table 3B. The demographic characteristics of those patients excluded will be examined in relation to those patients classified as evaluable to assess any potential for selection bias (Table 3C)

For this study, evaluable patients are those patients who have provided consent and for whom analysable clinical data has been provided in the data collection questionnaire at baseline and at 12 week (from either the specialist HCP and/or GP).<sup>9</sup>

**Table 3A. Patient cohort – evaluable patients, by treatment group**

Cohort data	Denominator Source	Rivaroxaban N%	Warfarin N%	Other <sup>a</sup> N%
Number of patients consented	Undefined	-		
Number of eligible patients	Number of consented patients			
Number of Index questionnaires returned	Number of eligible patients			
Number of eligible patients at baseline	Number of index questionnaire returned			
Number of 12-week follow-up questionnaires returned	Number of evaluable patients at baseline			
Number of evaluable patients at 12-weeks	Number of 12-week follow-up questionnaires returned			
Number of GP-Abridged follow-up questionnaires returned	Number of evaluable patients at 12-week			
Number of evaluable patients at 12-weeks after all questionnaires returned	Number of GP Abridged questionnaires returned			

<sup>a</sup>: name to be confirmed

<sup>9</sup> This is a protocol deviation. The per protocol statement was: ‘

*Evaluable patients are those patients who have provided consent and for whom analysable clinical data has been provided in the data collection questionnaires. Evaluable patients for whom the second phase (12 week) survey questionnaire (from BOTH specialist HCP and GP) is returned blank (contain no clinical information) or has not been returned will only be included for analysis of secondary objectives (i) and, (ii). However since important baseline prognostic data is also collected on the 12 week questionnaire, the per-protocol definition is no longer meaningful*

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A very small proportion of the contextual cohort includes other treatments. For the final report these will be excluded from the contextual cohort and a summary of characteristics and events provided in an appendix of the final report.

**Table 3B. Reasons for ineligibility post consent, by treatment group**

Cohort data – reasons for ineligibility	Rivaroxaban N%	Warfarin N%	Total N%
e.g Insufficient clinical information			
Patient incorrectly identified <sup>a</sup>			
Patient withdrawn			
Specialist withdrawn			

<sup>a</sup>: **relates to exclusion criteria:** if age at index date <18 years, or study drug treatment index date <01/09/2013 (study start date), or any use of univalent direct thrombin inhibitor or direct factor Xa inhibitors/anticoagulant therapy or other vitamin K antagonists recorded within one year prior to index date, or any ineligible (labelled) primary diagnosis

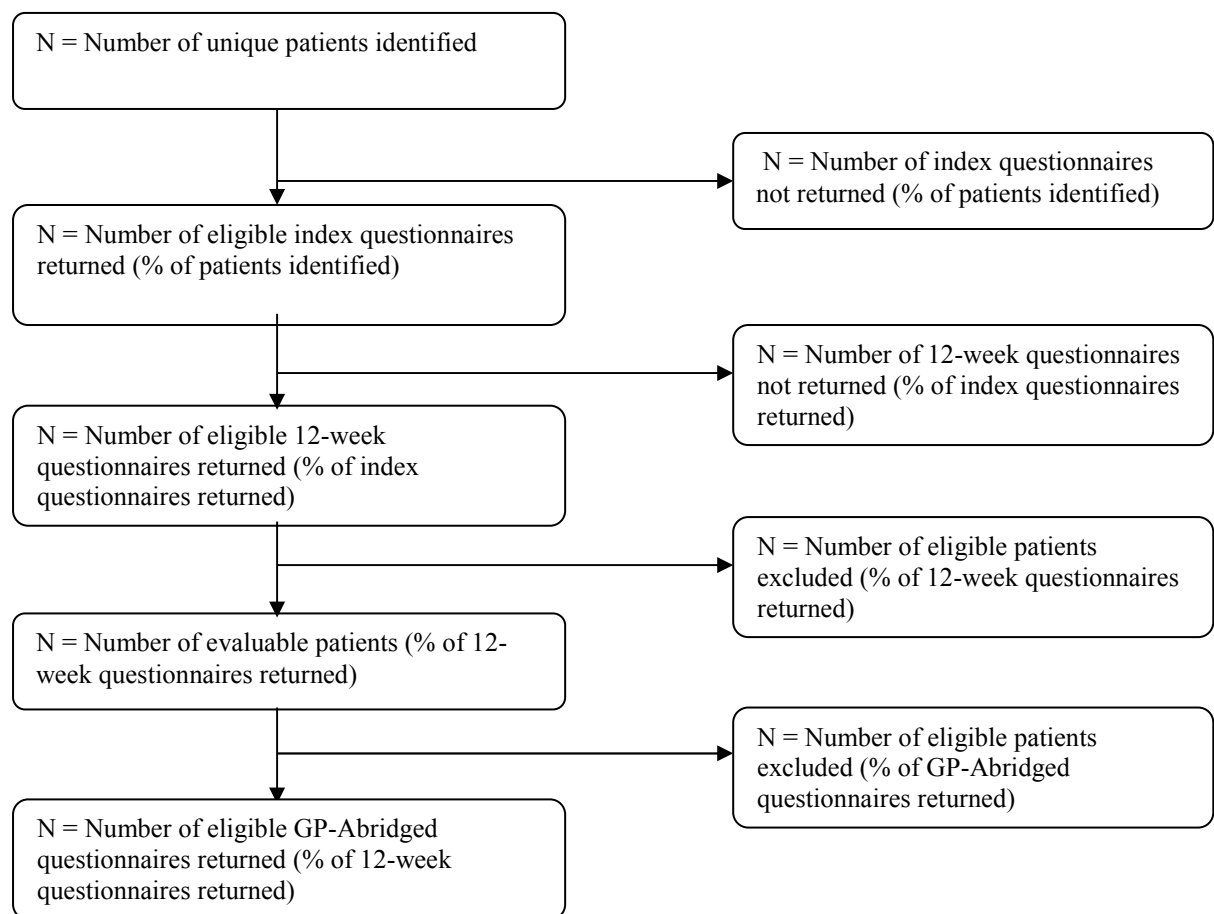
**Table 3C. Comparison of demographic characteristics of excluded patients with evaluable patients**

Characteristic (%)	Excluded Cases		Evaluable cases		OR (+95%CI <sup>a</sup> ) [P-value]
	N	% cases where values reported	N	% non-cases where values reported	
Gender					
Male					
Female					
Missing					
Age at index (years)					
<18					
19-29					
30-39					
40-49					
50-59					
60-69					
70-79					
80+					
Missing					

<sup>a</sup> 95%CI calculated using Binomial exact

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**Figure 4. Example: STROBE flowchart of the number of patients recruited over the course of the study**



The accessible study population is that proportion of the target population of interest to whom participating specialist health care professionals (HCPs) have access. The identification of the actual study population (which will be a subset of the accessible study population) has been through (non-probability) systemic sampling whereby all consecutively identified <sup>10</sup> eligible new user patients treated by any specialist HCP (after the pharmacotherapeutic treatment decision has been made that either rivaroxaban or warfarin treatment is the most appropriate treatment based on clinical need) and who provide consent have been enrolled.

<sup>10</sup> As relevant to the date that the specialist HCP registers to participate in the study

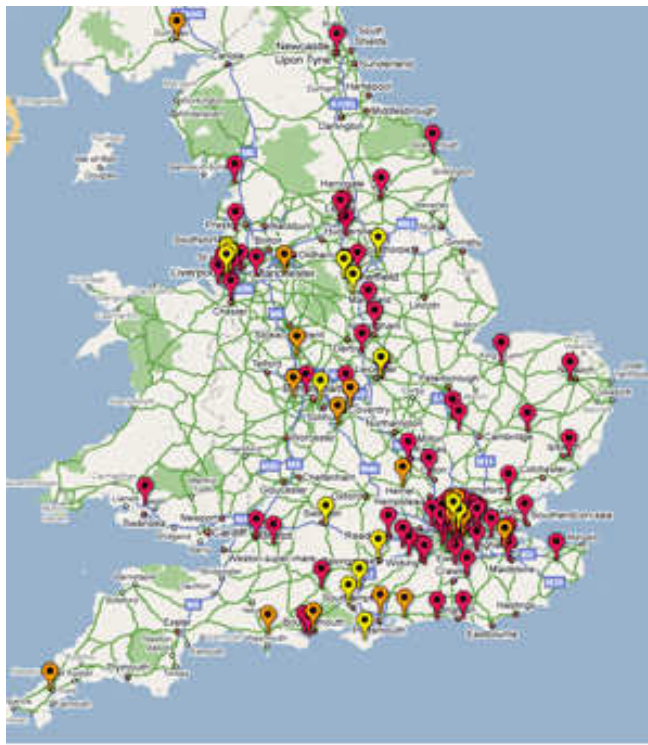


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**Table 3D. Geographical distribution of recruited patients, by treatment group**

Geographical distribution – region	Rivaroxaban N%	Warfarin N%	Total N%
North			
Midlands and North Wales			
South West and South Wales			
London and South East			
<b>Total</b>			

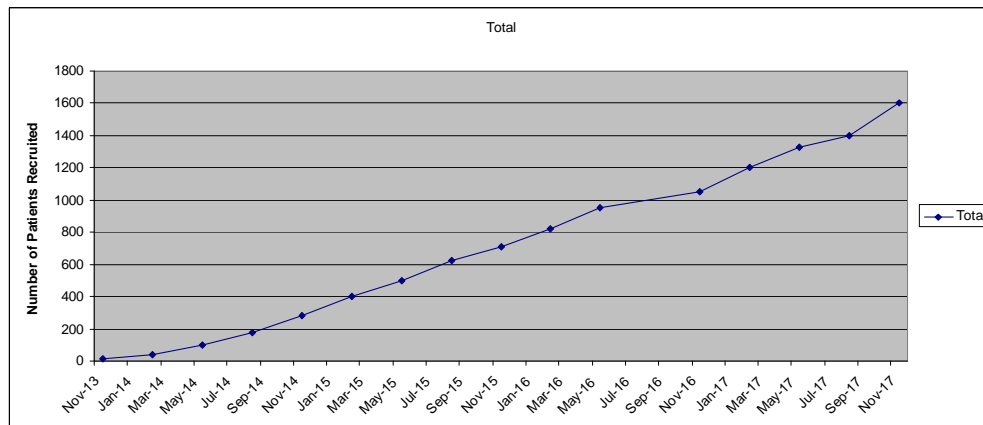
**Figure 5. Example of: Distribution of consented patients throughout England, by exposure group**



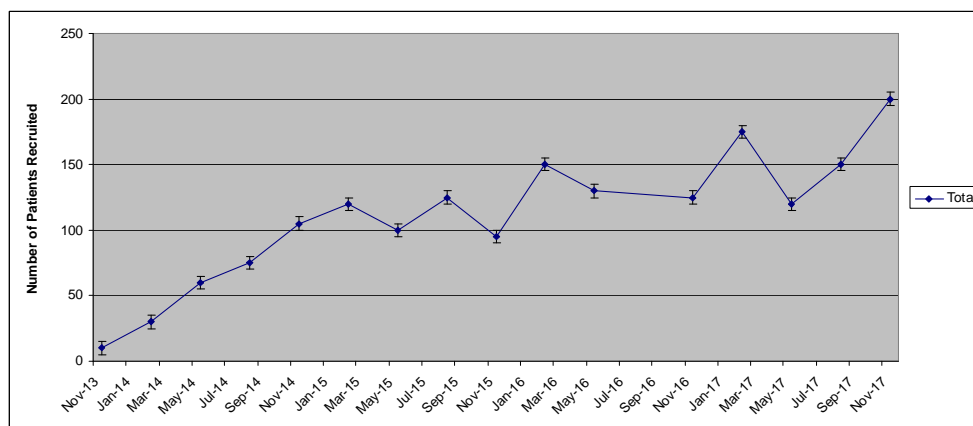
It is of interest to analyse any trend over time of patients recruited into the study, by exposure group. This can indicate if any recruitment initiatives had a positive (or negative) response on the number of patients being recruited. Figure 6 shows an example plot of the moving average of patients being recruited by month; it also highlights the point in time where any recruitment initiative took place.

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**Figure 6(a). Example of the number of patients recruited over the course of the study**



**Figure 6(b). Number of Patients recruited by month. Moving average with 95% confidence intervals**



## 9.2 Drug Utilization

This section will describe patient demographics, diagnosis and factors affecting HCP decision to prescribe, patient medical history and concomitant medications at the point of rivaroxaban/warfarin treatment initiation.

### 9.2.1 Cohort entry and exit

#### 9.2.1.1 Cohort entry

Cohort entry for each patient will be defined according to the date of their first rivaroxaban or warfarin dispensation (hereafter known as 'index date') if all inclusion and exclusion criteria are fulfilled.

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### **9.2.1.2 Cohort exit**

Cohort exit for each patient will be defined according to the end of study period, or at point of censoring whichever is the earliest.

### **9.2.1.3 'As Assigned' Cohort**

The 'as assigned' cohort is defined as the cohort identified at cohort entry, irrespective of treatment status during the period of observation between cohort entry and cohort exit. For analysis purposes, cohort exit for this period of observation is defined according to the first of the following dates:

- End of 12 week study observation period
- Censoring from loss to follow-up
- Death

This 'as assigned' cohort definition applies to secondary objectives (i)-(iii) and exploratory objective (ii).

### **9.2.1.4 'As Treated' Cohort**

The 'as treated' cohort is defined as the cohort identified at cohort entry, for whom exposure to treatment is defined between cohort entry and cohort exit. A continuous variable representing total period of treatment with either rivaroxaban or warfarin for each patient will be derived from primary data on cohort entry and exit dates. Each patient will be regarded as being treated between index date and last known date of treatment. The number of days will vary between patients. For event analysis purposes, this period will be restricted to where cohort exit is defined according to the first of the following dates:

- End of 12 month study treatment period
- Censoring from loss to follow-up
- Death
- Censoring at first report of stopping treatment (+5 half-lives to account for drug elimination)
- First report of outcome of interest.<sup>11</sup>

For any analyses using this exposure definition, the cohorts will be referred to as the 'as treated' cohorts. This exposure definition applies to the primary objective and secondary objectives (iv: a-f) and exploratory objective (i). The assumption will be

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<sup>11</sup> Applies to each event analysis separately. Competing risks will not be accounted for.

## Appendix 2. Statistical Analysis Plan

made for that person-time exposure will be continuous up to event or censor date. Denominator data will be presented according to person-time treated per 1000 weeks.

### ***9.2.2 Patient Characteristics at baseline***

Characteristics of the evaluable rivaroxaban or warfarin cohorts at the start of treatment (index date) will be described, including patient demographics, the proposed primary clinical diagnosis and reasons for prescribing rivaroxaban or warfarin treatment, previous medical history, and concurrent medications. Patient characteristics will be stratified by exposure group and also indication group where appropriate.

#### **9.2.2.1 Patient Demographics**

In accordance with secondary objective (ii), patient demographics as captured at baseline, or start of treatment, will be presented. Demographic data including age and sex, will be presented for both rivaroxaban and warfarin treatment cohorts.

**Table 4. Patient demographics**

<b>Data description</b>	<b>Source</b>	<b>Result reference</b>
Age by sex counts and percentages	Index Questionnaire (Q1)	Table 4A
Age distribution summary statistics: mean, standard deviation, median, maximum, minimum. Stratified by sex,	Index Questionnaire (Q1)	N/A. Presented as text.
Socioeconomic status (IMD rank)	Optional Consent Form (Q2)	Table 4B
Marital Status: Counts and Percent	Optional Consent Form (Q2)	Table 4C
Employment Status: Count and Percent	Optional Consent Form (Q3)	Table 4D
Ethnic Background: Count and Percent	Optional Consent Form (Q4)	Table 4E
Risk seeking behaviours and substances reported	12-week questionnaire (Q18)	Table 4F & 4G

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**Table 4A. Age/Sex counts and percentages stratified by treatment group**

Age (yr) Range	Rivaroxaban			Warfarin		
	Male N%	Female N%	Total N%	Male N%	Female N%	Total N%
18-24						
25-29						
30-34						
35-39						
Thereafter in bands of 5 years						
Median (IQR)						
mean (SD)						
Not specified						
<b>Total</b>						

**Table 4B. Patient socioeconomic status<sup>12</sup> stratified by treatment group**

Index of Multiple Deprivation rank	Rivaroxaban		Warfarin	
	N	%	N	%
1				
2				
3				
4				
...				
10				
Median (IQR)				
Not specified				

**Table 4C. Patient self-reported marital status stratified by treatment group**

Marital Status	Rivaroxaban		Warfarin	
	N	%	N	%
Married				
Separated				
Co-Habiting				
Divorced				
Single				
Widowed				
Other <sup>a</sup>				
Not Specified				

<sup>a</sup> example (n=); etc.

<sup>12</sup> Socioeconomic status is based on the patient's postcode using the Index of Multiple deprivation (2015 <http://imd-bypostcode.opendatacommunities.org/>)

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**Table 4D. Patient self-reported employment status stratified by treatment group**

Employment Status	Rivaroxaban		Warfarin	
	N	%	N	%
Self-employed				
Full-Time				
Unemployed				
Part-Time				
Student				
House Husband/Wife				
Other <sup>b</sup>				
Not specified				

<sup>b</sup> example (n=); etc.

**Table 4E. Patient self-reported ethnic background stratified by treatment group**

Ethnicity	Rivaroxaban		Warfarin	
	N	%	N	%
White				
Indian				
Black African				
Pakistani				
Black Caribbean				
Bangladeshi				
Black - Other <sup>c</sup>				
Chinese				
Other <sup>d</sup> Ethnic Group				
Not specified				

<sup>c</sup> example (n=); etc.; <sup>d</sup> example (n=); etc.

**Table 4F. Specialist recorded history of risk seeking behaviours stratified by treatment group**

Risk-Seeking Behaviour	Rivaroxaban		Warfarin	
	Prior to or present at index date		Prior to or present at index date	
	N	%	N	%
Substance Misuse				
Alcohol misuse <sup>a</sup>				
Smoker (ever)				

<sup>a</sup> refer to HAS-BLED criteria (section 9.3)

## Appendix 2. Statistical Analysis Plan

**Table 4G. Most frequently reported substances misused**

Substance name	Rivaroxaban		Warfarin	
	N	%	N	%
<b>Total</b>				

### 9.2.2.2 Diagnosis and reasons for prescribing

In accordance with secondary objective (ii), the primary clinical condition, for which rivaroxaban or warfarin treatment is indicated, as reported on the index questionnaire, will be presented together with reasons for prescribing and patient demographic characteristics.

**Table 5. Diagnosis**

Data Description	Source	Result Reference
Primary clinical condition for prescribing, by treatment group	Index Questionnaire (Q2)	Tables 5A. Note Other refer only to off-label indications (e.g where not possible to allocate to relevant category AF or DVT/PE and unlabelled indications)
Patient demographic characteristics present at the time of prescribing Rivaroxaban or Warfarin treatment, by Indication	Index Questionnaire (Q1)	Table 5B
Supporting Reasons for prescribing Rivaroxaban or Warfarin treatment, by Indication AF	Index Questionnaire (Q5)	Table 5C
Supporting Reasons for prescribing Rivaroxaban or Warfarin treatment, by Indication DVT/PE	Index Questionnaire (Q5)	Table 5D
Supporting Reasons for prescribing Rivaroxaban or Warfarin treatment, by Indication Mixed (AF & DVT/PE)	Index Questionnaire (Q5)	Table 5E
Supporting Reasons for	Index Questionnaire (Q5)	Table 5F

## Appendix 2. Statistical Analysis Plan

prescribing Rivaroxaban or  
Warfarin treatment, by  
Indication Other

Months prior to prescription      Index Questionnaire (Q2)      Table 5G  
that indication was  
diagnosed, by indication

**Table 5A. Primary clinical condition for which anticoagulant therapy (rivaroxaban or warfarin treatment) was indicated by treatment group**

Indication	Rivaroxaban		Warfarin	
	N	%	N	%
Non-Valvular AF				
All DVT/PE				
Treatment of DVT				
Treatment of DVT + PE				
Prevention of recurrent DVT + PE				
Mixed (AF & DVT/PE)				
Other*				

\* All other indications will be list in an Appendix of the final report. Other indications are 'off-label'

**Table 5B. Age/Sex counts and percentages by treatment group and primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

	AF	Rivaroxaban				Total	AF	Warfarin			Total
		DVT/ PE	Mixed	Other				DVT/ PE	Mixed	Other	
Age (yr)	N%	N%	N%	N%	N%	N%	N%	N%	N%	N%	N%
18-24											
25-29											
30-34											
35-39											
Thereafter											
in bands of											
5 years											
Median											
(IQR)											
mean (SD)											
Not											
specified											
<b>Total</b>											



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**Table 5C. Supporting Reasons for prescribing for the primary diagnosis of AF, by treatment group**

Supporting Reason	Rivaroxaban		Warfarin	
	N	%	N	%
Clinical Judgement				
NICE Recommendation				
Expert Committee Guidelines				
Trust Formulary Committee Guidelines				
Patient Group Direction in anticoagulant clinic				
Potential ease of reversibility of anticoagulant				
Lifestyle				
Patient non-adherence with prior anticoagulant				
Side effects with prior anticoagulant				
Aberrant behaviour				
Poor control of anticoagulation				
Patient preference				
Other*				
Not specified				

\* All other supporting reasons will be list in an Appendix of the final report

**Table 5D. Supporting Reasons for prescribing for the primary diagnosis of DVT/PE, by treatment group**

Supporting Reason	Rivaroxaban		Warfarin	
	N	%	N	%
Clinical Judgement				
NICE Recommendation				
Expert Committee Guidelines				
Trust Formulary Committee Guidelines				
Patient Group Direction in anticoagulant clinic				
Potential ease of reversibility of anticoagulant				
Lifestyle				
Patient non-adherence with prior anticoagulant				
Side effects with prior anticoagulant				
Aberrant behaviour				
Poor control of anticoagulation				
Patient preference				
Other*				
Not specified				

## Appendix 2. Statistical Analysis Plan

**Table 5E. Supporting Reasons for prescribing for the primary diagnosis of Mixed (AF & DVT/PE) indications, by treatment group**

Supporting Reason	Rivaroxaban		Warfarin	
	N	%	N	%
Clinical Judgement				
NICE Recommendation				
Expert Committee Guidelines				
Trust Formulary Committee Guidelines				
Patient Group Direction in anticoagulant clinic				
Potential ease of reversibility of anticoagulant				
Lifestyle				
Patient non-adherence with prior anticoagulant				
Side effects with prior anticoagulant				
Aberrant behaviour				
Poor control of anticoagulation				
Patient preference				
Other*				
Not specified				

**Table 5F. Supporting Reasons for prescribing for the primary diagnosis of Other indications, by treatment group**

Supporting Reason	Rivaroxaban		Warfarin	
	N	%	N	%
Clinical Judgement				
NICE Recommendation				
Expert Committee Guidelines				
Trust Formulary Committee Guidelines				
Patient Group Direction in anticoagulant clinic				
Potential ease of reversibility of anticoagulant				
Lifestyle				
Patient non-adherence with prior anticoagulant				
Side effects with prior anticoagulant				
Aberrant behaviour				
Poor control of anticoagulation				
Patient preference				
Other*				
Not specified				

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**Table 5G. Months prior to index date that reported indication first diagnosed, for the Rivaroxaban and Warfarin cohort by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

Months prior to index date	Rivaroxaban					Warfarin				
	AF	DVT/PE	Mixed	Other	Total	AF	DVT/PE	Mixed	Other	Total
	N%	N%	N%	N%	N%	N%	N%	N%	N%	N%
7+										
6										
Descending to the month post-start										
Not specified										
<b>Total</b>										

### 9.2.2.3 Prior and concurrent medical conditions

In accordance with secondary objectives (ii) and to support secondary objective (iv), data showing the cohorts' medical history prior to or concurrent with initiation of Rivaroxaban or warfarin treatment will be presented. For analysis purposes, recent/concurrent conditions are defined as those diagnosed within 3 months prior to and including treatment initiation.

Binary dummy variables are derived from tick box responses by specialists on 12 week observation questionnaire.

**Table 6. Medical history**

Data Description	Source	Result Reference
Bleeding Events before the start of anticoagulant therapy, less than & greater than three months; by Rivaroxaban & Warfarin treatment for indication AF	Index Questionnaire (Q6) & 12-Week Questionnaire (Q13, Q15.1 – Q15.4 & Q16).	Table 6A
Bleeding Events before the start of anticoagulant therapy, less than & greater than three months; by Rivaroxaban & Warfarin treatment, for indication DVT/PE	Index Questionnaire (Q6) & 12-Week Questionnaire (Q13, Q15.1 – Q15.4 & Q16).	Tables 6B
Bleeding Events before the start of	Index Questionnaire (Q6)	Tables 6C

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anticoagulant therapy, less than & greater than three months; by Rivaroxaban & Warfarin treatment, for Mixed (AF & DVT/PE) indications	& 12-Week Questionnaire (Q13, Q15.1 – Q15.4 & Q16).	
Bleeding Events before the start of anticoagulant therapy, less than & greater than three months; by Rivaroxaban & Warfarin treatment, for Other indications	Index Questionnaire (Q6) & 12-Week Questionnaire (Q13, Q15.1 – Q15.4 & Q16).	Tables 6D
Other Events before the start of anticoagulant therapy, less than & greater than three months; by Rivaroxaban & Warfarin treatment, for indication AF	Index Questionnaire (Q1) & 12-Week Questionnaire (Q13, Q15.5 – Q15.6 & Q16)	Table 6E
Other Events before the start of anticoagulant therapy, less than & greater than three months; by Rivaroxaban & Warfarin treatment, for indication DVT/PE	Index Questionnaire (Q1) & 12-Week Questionnaire (Q13, Q15.5 – Q15.6 & Q16)	Table 6F
Other Events before the start of anticoagulant therapy, less than & greater than three months; by Rivaroxaban & Warfarin treatment for Mixed (AF & DVT/PE) indications	Index Questionnaire (Q1) & 12-Week Questionnaire (Q13, Q15.5 – Q15.6 & Q16)	Table 6G
Other Events before the start of anticoagulant therapy, less than & greater than three months; by Rivaroxaban & Warfarin treatment for other indications	Index Questionnaire (Q1) & 12-Week Questionnaire (Q13, Q15.5 – Q15.6 & Q16)	Table 6H

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**Appendix 2. Statistical Analysis Plan**

**Table 6A. History of haemorrhagic related events prior to start of treatment for AF, by treatment group**

	Past (>3 months)			Recent (<3 months)			Period unknown <sup>a</sup>			Any period prior		
	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%
Haemorrhage into following body sites:												
Intracranial												
Gastrointestinal												
Urogenital												
Etc...												
Haemorrhage-related events which led to:												
Decreased haemoglobin												
Bleeding requiring a transfusion												
A fatal outcome												
Other haemorrhage- related events:												
Stopping of anticoagulation therapy for bleeding												
Etc...												
Other bleeding events:												
*												

\*The ten most frequent other bleeding events will be included in the main table. All other bleeding events will be described in an Appendix;

<sup>a</sup>: information on date and/or period not reported

**Appendix 2. Statistical Analysis Plan**

**Table 6B. History of haemorrhagic related events prior to start of treatment for DVT/PE, by treatment group**

	Past (>3 months)			Recent (<3 months)			Period unknown <sup>a</sup>			Any period prior		
	Rivaroxaban	Warfarin	Total	Rivaroxaban	Warfarin	Total	Rivaroxaban	Warfarin	Total	Rivaroxaban	Warfarin	Total
	N%	N%	N%	N%	N%	N%	N%	N%	N%	N%	N%	N%
Haemorrhage into following body sites:												
Intracranial												
Gastrointestinal												
Urogenital												
Etc...												
Haemorrhage-related events which led to:												
Decreased haemoglobin												
Bleeding requiring a transfusion												
A fatal outcome												
Other haemorrhage-related events:												
Stopping of anticoagulation therapy for bleeding												
Etc...												
Other bleeding events:												
*												

\*The ten most frequent other bleeding events will be included in the main table. All other bleeding events will be described in an Appendix.

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**Table 6C. History of haemorrhagic related events prior to start of treatment for Mixed (AF & DVT/PE) indications, by treatment group**

	Past (>3 months)			Recent (<3 months)			Period unknown <sup>a</sup>			Any period prior		
	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%
Haemorrhage into following body sites:												
Intracranial												
Gastrointestinal												
Urogenital												
Etc...												
Haemorrhage-related events which led to:												
Decreased haemoglobin												
Bleeding requiring a transfusion												
A fatal outcome												
Other haemorrhage- related events:												
Stopping of anticoagulation therapy for bleeding												
Etc...												
Other bleeding events:												
*												

\*The ten most frequent other bleeding events will be included in the main table. All other bleeding events will be described in an Appendix.

**Appendix 2. Statistical Analysis Plan**

**Table 6D. History of haemorrhagic related events prior to start of treatment for Other indications, by treatment group**

	Past (>3 months)			Recent (<3 months)			Period unknown <sup>a</sup>			Any period prior		
	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%
Haemorrhage into following body sites:												
Intracranial												
Gastrointestinal												
Urogenital												
Etc...												
Haemorrhage-related events which led to:												
Decreased haemoglobin												
Bleeding requiring a transfusion												
A fatal outcome												
Other haemorrhage- related events:												
Stopping of anticoagulation therapy for bleeding												
Etc...												
Other bleeding events:												
*												

\*The ten most frequent other bleeding events will be included in the main table. All other bleeding events will be described in an Appendix.



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**Table 6E. History of other events/ conditions prior to start of treatment for indication AF, by treatment group**

	Past (>3 months)			Recent (<3 months)			Period unknown <sup>a</sup>			Any period prior		
	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%
Cardiovascular Disorders:												
Cerebrovascular accident												
Deep Vein Thrombosis												
Pulmonary embolism												
Etc...												
Other Conditions:												
Liver Disorder												
Abnormal liver function tests												
Renal Failure												
Etc...												
Other events:												
Injury/Trauma												
On coumarin with INR > 3												
*												

\*Full list of other prior medical conditions will be presented in an appendix

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Table 6F. History of other events/ conditions prior to start of treatment for indication DVT/PE, by treatment group

	Past (>3 months)			Recent (<3 months)			Period unknown <sup>a</sup>			Any period prior		
	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%
Cardiovascular Disorders:												
Cerebrovascular accident												
Deep Vein Thrombosis												
Pulmonary embolism												
Etc...												
Other Conditions:												
Liver Disorder												
Abnormal liver function tests												
Renal Failure												
Etc...												
Other events:												
Injury/Trauma												
On coumarin with INR > 3												
*												

\*Full list of other prior medical conditions will be presented in an appendix

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**Table 6G. History of other events/ conditions prior to start of treatment for Mixed (AF & DVT/PE) indications, by treatment group**

	Past (>3 months)			Recent (<3 months)			Period unknown <sup>a</sup>			Any period prior		
	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%
Cardiovascular Disorders:												
Cerebrovascular accident												
Deep Vein Thrombosis												
Pulmonary embolism												
Etc...												
Other Conditions:												
Liver Disorder												
Abnormal liver function tests												
Renal Failure												
Etc...												
Other events:												
Injury/Trauma												
On coumarin with INR > 3												
*												

\*Full list of other prior medical conditions will be presented in an appendix

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**Table 6H. History of other events/ conditions prior to start of treatment for other indications, by treatment group**

	Past (>3 months)			Recent (<3 months)			Period unknown <sup>a</sup>			Any period prior		
	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%	Rivaroxaban N%	Warfarin N%	Total N%
Cardiovascular Disorders:												
Cerebrovascular accident												
Deep Vein Thrombosis												
Pulmonary embolism												
Etc...												
Other Conditions:												
Liver Disorder												
Abnormal liver function tests												
Renal Failure												
Etc...												
Other events:												
Injury/Trauma												
On coumarin with INR > 3												
*												

\*Full list of other prior medical conditions will be presented in an appendix

## Appendix 2. Statistical Analysis Plan

### 9.2.2.4 Prior medication use

In accordance with secondary objectives (ii) and to support secondary objective (iv), data showing the cohorts' medication history prior to or concurrent with initiation of Rivaroxaban or warfarin treatment will be presented, summarised according to ATC dictionary. For analysis purposes, recent use is defined use within 28 days prior to treatment initiation. Any relevant additional information from follow-up questionnaires will be considered for inclusion as appropriate. Anticoagulant and anti-platelet products for which Rivaroxaban or the warfarin cohort was switched will be presented, with reasons for switch and treatment transition details summarised where information available.

**Table 7. Medication history**

<b>Data Description</b>	<b>Source</b>	<b>Result Reference</b>
Anticoagulation or antiplatelet use within 28 days prior , but not including index date by Rivaroxaban & Warfarin treatment	12-Week Questionnaire (Q12 & Q13)	Tables 7A -7D. Counts will account for responses in Q13
Count and percent of number of patients who switched directly from other anticoagulant or antiplatelet therapy treatment onto Rivaroxaban or warfarin treatment.	12-Week Questionnaire (Q13)	Table 7E-7H. Counts should be a sub-set of Tables 7A-7D
Count and percent of reasons for switching prior to initiation of Rivaroxaban or warfarin treatment.	12-week questionnaire (Q13)	Table 7I.Counts should be a sub-set of 7E-7H
Transition details (dose at initiation of switch) of switched medication prior to initiation of Rivaroxaban or warfarin treatment.	12-week questionnaire (Q13)	Table 7J & 7K. Counts should be a sub-set of 7E-7H
Other medication use within 28 days prior , but not including index date by Rivaroxaban & Warfarin treatment	12-Week Questionnaire (Q14) Route assumed oral unless otherwise stated	Tables 7L – 7O

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**Table 7A. Anticoagulation medication use history within 28 days prior to start of treatment for indication AF, by treatment group**

Medication	Rivaroxaban N%	Warfarin N%
<b>Anticoagulants</b>		
Oral		
Warfarin		N/A <sup>f</sup>
Phenindione		N/A <sup>f</sup>
Nicoumalone		N/A <sup>f</sup>
Dabigatran		N/A <sup>g</sup>
Apixaban		N/A <sup>g</sup>
Other <sup>a</sup>		N/A <sup>g</sup>
Any (at least one) oral anticoagulant		
Parenteral		
Bivalirudin		N/A <sup>g</sup>
Unfractionated heparin <sup>b</sup>		†
Low molecular weight heparin <sup>c</sup>		†
Fondaparinux		†
Other <sup>d</sup>		
Any (at least one) parenteral anticoagulant		
<b>Antiplatelets</b>		
Aspirin (<=300mg)		
Clopidogrel		
Abciximab		
Dipyridamole		
Eptifibatide		
Tirofiban		
Other <sup>e</sup>		
Any (at least one) antiplatelet		

<sup>a</sup> to be listed; <sup>b</sup> including monaparin, monaparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; † as part of treatment of current indication only

**Table 7B. Anticoagulation medication use history within 28 days prior to start of treatment for indication DVT/PE, by treatment group**

Medication	Rivaroxaban N%	Warfarin N%
<b>Anticoagulants</b>		
Oral		
Warfarin		N/A <sup>f</sup>
Phenindione		N/A <sup>f</sup>
Nicoumalone		N/A <sup>f</sup>
Dabigatran		N/A <sup>g</sup>
Apixaban		N/A <sup>g</sup>
Other <sup>a</sup>		N/A <sup>g</sup>
Any (at least one) oral anticoagulant		
Parenteral		
Bivalirudin		N/A <sup>g</sup>
Unfractionated heparin <sup>b</sup>		†
Low molecular weight heparin <sup>c</sup>		†
Fondaparinux		†
Other <sup>d</sup>		

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Any (at least one) parenteral anticoagulant  
**Antiplatelets**

Aspirin ( $\leq 300\text{mg}$ )  
 Clopidogrel  
 Abciximab  
 Dipyridamole  
 Eptifibatide  
 Tirofiban  
 Other <sup>e</sup>

Any (at least one) antiplatelet

<sup>a</sup> to be listed; <sup>b</sup> including monaparin, monaparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

**Table 7C. Anticoagulation medication use history within 28 days prior to start of treatment for Mixed (AF & DVT/PE) indications, by treatment group**

Medication	Rivaroxaban N%	Warfarin N%
<b>Anticoagulants</b>		
Oral		
Warfarin		N/A <sup>f</sup>
Phenindione		N/A <sup>f</sup>
Nicoumalone		N/A <sup>f</sup>
Dabigatran		N/A <sup>g</sup>
Apixaban		N/A <sup>g</sup>
Other <sup>a</sup>		N/A <sup>g</sup>
Any (at least one) oral anticoagulant		
Parenteral		
Bivalirudin		N/A <sup>g</sup>
Unfractionated heparin <sup>b</sup>		+
Low molecular weight heparin <sup>c</sup>		+
Fondaparinux		+
Other <sup>d</sup>		
Any (at least one) parenteral anticoagulant		
<b>Antiplatelets</b>		
Aspirin ( $\leq 300\text{mg}$ )		
Clopidogrel		
Abciximab		
Dipyridamole		
Eptifibatide		
Tirofiban		
Other <sup>e</sup>		
Any (at least one) antiplatelet		

<sup>a</sup> to be listed; <sup>b</sup> including monaparin, monaparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

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**Table 7D. Anticoagulation medication use history within 28 days prior to start of treatment for Other indications, by treatment group**

Medication	Rivaroxaban N%	Warfarin N%
<b>Anticoagulants</b>		
Oral		
Warfarin		N/A <sup>f</sup>
Phenindione		N/A <sup>f</sup>
Nicoumalone		N/A <sup>f</sup>
Dabigatran		N/A <sup>g</sup>
Apixaban		N/A <sup>g</sup>
Other <sup>a</sup>		N/A <sup>g</sup>
Any (at least one) oral anticoagulant		
Parenteral		
Bivalirudin		N/A <sup>g</sup>
Unfractionated heparin <sup>b</sup>		+
Low molecular weight heparin <sup>c</sup>		+
Fondaparinux		+
Other <sup>d</sup>		
Any (at least one) parenteral anticoagulant		
<b>Antiplatelets</b>		
Aspirin (<=300mg)		
Clopidogrel		
Abciximab		
Dipyridamole		
Eptifibatide		
Tirofiban		
Other <sup>e</sup>		
Any (at least one) antiplatelet		

<sup>a</sup> to be listed; <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

**Table 7E. Anticoagulant/Antiplatelet switching for AF indication group prior to starting rivaroxaban or warfarin.**

Medication	Rivaroxaban N%	Warfarin N%
<b>Anticoagulants</b>		
Oral		
Warfarin		N/A <sup>f</sup>
Phenindione		N/A <sup>f</sup>
Nicoumalone		N/A <sup>f</sup>
Dabigatran		N/A <sup>g</sup>
Apixaban		N/A <sup>g</sup>
Other <sup>a</sup>		N/A <sup>g</sup>
Any (at least one) oral anticoagulant		
Parenteral		
Bivalirudin		N/A <sup>g</sup>
Unfractionated heparin <sup>b</sup>		+
Low molecular weight heparin <sup>c</sup>		+
Fondaparinux		+



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Other <sup>d</sup>
Any (at least one) parenteral anticoagulant
<b>Antiplatelets</b>
Aspirin (<=300mg)
Clopidogrel
Abciximab
Dipyridamole
Eptifibatide
Tirofiban
Other <sup>e</sup>
Any (at least one) antiplatelet

<sup>a</sup> to be listed; <sup>b</sup> including monaparin, monaparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

**Table 7F. Anticoagulant/Antiplatelet switching for DVT/PE indication group prior to starting rivaroxaban or warfarin.**

Medication	Rivaroxaban N%	Warfarin N%
<b>Anticoagulants</b>		
Oral		
Warfarin		N/A <sup>f</sup>
Phenindione		N/A <sup>f</sup>
Nicoumalone		N/A <sup>f</sup>
Dabigatran		N/A <sup>g</sup>
Apixaban		N/A <sup>g</sup>
Other <sup>a</sup>		N/A <sup>g</sup>
Any (at least one) oral anticoagulant		
Parenteral		
Bivalirudin		N/A <sup>g</sup>
Unfractionated heparin <sup>b</sup>		+
Low molecular weight heparin <sup>c</sup>		+
Fondaparinux		+
Other <sup>d</sup>		
Any (at least one) parenteral anticoagulant		
<b>Antiplatelets</b>		
Aspirin (<=300mg)		
Clopidogrel		
Abciximab		
Dipyridamole		
Eptifibatide		
Tirofiban		
Other <sup>e</sup>		
Any (at least one) antiplatelet		

<sup>a</sup> to be listed; <sup>b</sup> including monaparin, monaparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

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### 7G. Anticoagulant/Antiplatelet switching for Mixed (AF & DVT) indication group, prior to starting rivaroxaban or warfarin.

Medication	Rivaroxaban N%	Warfarin N%	
<b>Anticoagulants</b>			
Oral			
Warfarin		N/A <sup>f</sup>	
Phenindione		N/A <sup>f</sup>	
Nicoumalone		N/A <sup>f</sup>	
Dabigatran		N/A <sup>g</sup>	
Apixaban		N/A <sup>g</sup>	
Other <sup>a</sup>		N/A <sup>g</sup>	
Any (at least one) oral anticoagulant			
Parenteral			
Bivalirudin		N/A <sup>g</sup>	
Unfractionated heparin <sup>b</sup>			+
Low molecular weight heparin <sup>c</sup>			+
Fondaparinux			+
Other <sup>d</sup>			
Any (at least one) parenteral anticoagulant			
<b>Antiplatelets</b>			
Aspirin (<=300mg)			
Clopidogrel			
Abciximab			
Dipyridamole			
Eptifibatide			
Tirofiban			
Other <sup>e</sup>			
Any (at least one) antiplatelet			

<sup>a</sup> to be listed; <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

**Table 7H. Anticoagulant/Antiplatelet switching for Other indication group prior to starting rivaroxaban or warfarin**

Medication	Rivaroxaban N%	Warfarin N%	
<b>Anticoagulants</b>			
Oral			
Warfarin		N/A <sup>f</sup>	
Phenindione		N/A <sup>f</sup>	
Nicoumalone		N/A <sup>f</sup>	
Dabigatran		N/A <sup>g</sup>	
Apixaban		N/A <sup>g</sup>	
Other <sup>a</sup>		N/A <sup>g</sup>	
Any (at least one) oral anticoagulant			
Parenteral			
Bivalirudin		N/A <sup>g</sup>	
Unfractionated heparin <sup>b</sup>			+
Low molecular weight heparin <sup>c</sup>			+
Fondaparinux			+

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Any (at least one) parenteral anticoagulant	Other <sup>d</sup>
<b>Antiplatelets</b>	
	Aspirin (<=300mg)
	Clopidogrel
	Abciximab
	Dipyridamole
	Eptifibatide
	Tirofiban
	Other <sup>e</sup>
Any (at least one) antiplatelet	

<sup>a</sup> to be listed; <sup>b</sup> including monaparin, monaparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed; <sup>f</sup> Patient exclusion from warfarin cohort if < 12 months prior to cohort entry date; <sup>g</sup> Patient exclusion from warfarin cohort ever use; <sup>+</sup> as part of treatment of current indication only

**Table 7I. Reasons for Anticoagulant or Antiplatelet switches immediately prior to start of rivaroxaban or warfarin, by indication and treatment group**

<b>Reason for switching from anticoagulant onto rivaroxaban</b>	<b>N%</b>	<b>Reason for switching from anticoagulant onto warfarin</b>	<b>N%</b>
AF e.g. Poor response Intolerance Poor compliance etc Other*		AF e.g. Poor response Intolerance Poor compliance etc Other*	
DVT/PE e.g. Poor response Intolerance Poor compliance etc Other*		DVT/PE e.g. Poor response Intolerance Poor compliance etc Other*	
Mixed (AF & DVT/PE) e.g. Poor response Intolerance Poor compliance etc Other*		Mixed (AF & DVT/PE) e.g. Poor response Intolerance Poor compliance etc Other*	
Other Indications e.g. Poor response Intolerance Poor compliance etc Other*		Other Indications e.g. Poor response Intolerance Poor compliance etc Other*	
<b>Reason for switching from antiplatelet onto rivaroxaban</b>	<b>N%</b>	<b>Reason for switching from antiplatelet onto warfarin</b>	<b>N%</b>
AF e.g. Poor response Intolerance Poor compliance etc Other*		AF e.g. Poor response Intolerance Poor compliance etc Other*	
DVT/PE e.g. Poor response Intolerance Poor compliance etc		DVT/PE e.g. Poor response Intolerance Poor compliance etc	

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Other*	Other*
Mixed (AF & DVT/PE)	Mixed (AF & DVT/PE)
e.g. Poor response	e.g. Poor response
Intolerance	Intolerance
Poor compliance etc	Poor compliance etc
Other*	Other*
Other Indications	Other Indications
e.g. Poor response	e.g. Poor response
Intolerance	Intolerance
Poor compliance etc	Poor compliance etc
Other*	Other*

\*The Top 10 reasons for switching will be included in the main final report. All other reasons for switching will be described in an Appendix of the final report

**Table 7J. Titration details of anticoagulant / antiplatelet switch onto rivaroxaban**

Anticoagulant	N (% switched)
e.g Warfarin	
Total daily dose at start of switch interval	
<2.5mg	
>=2.5, <5mg	
>=5.0, <10mg	
>=10, <20mg	
>=20, <30mg	
>=30mg	
Median (IQR)mg	
<i>Number patients with Missing information</i>	
Antiplatelet	N (% switched)
e.g aspirin	
Total daily dose at start of switch interval	
<75mg	
75mg	
150mg	
300mg	
Other	
Median (IQR)	
<i>Number patients with Missing information</i>	

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**Table 7K. Titration details of anticoagulant / antiplatelet switch onto warfarin**

Anticoagulant	N (% switched)
e.g parenteral heparin	
Total daily dose at start of switch interval	
	tbc
	Median (IQR)mg
<i>Number patients with Missing information</i>	
Antiplatelet	N (% switched)
e.g aspirin	
Total daily dose at start of switch interval	
	<75mg
	75mg
	150mg
	300mg
	Other
	Median (IQR)
<i>Number patients with Missing information</i>	

**Table 7L. Other medication history within 28 days <sup>a</sup> of initiation prior to start of treatment for indication AF, by treatment group**

Rivaroxaban		Warfarin	
Medication	N%	Medication	N%
Analgesics		Analgesics	
	Paracetamol		Paracetamol
	Etc...		Etc...
Anti-Inflammatory		Anti-Inflammatory	
	Aspirin (>300mg)		Aspirin (>300mg)
	NSAID		NSAID
	Etc...		Etc...
Anti-convulsants		Anti-convulsants	
	Phenytoin		Phenytoin
	Phenobarbital		Phenobarbital
	Carbamazepine		Carbamazepine
	Etc...		Etc...
Anti-infective		Anti-infective	
	Ketoconazole		Ketoconazole
	Itraconazole		Itraconazole
	Posaconazole		Posaconazole
	Etc...		Etc...
Antidepressants		Antidepressants	
	Tricyclic and related <sup>a</sup>		Tricyclic and related <sup>a</sup>
	MAOI		MAOI
	SSRI		SSRI
	Etc...		Etc...
Female hormone products		Female hormone products	
	Oestrogen and/or progestogen		Oestrogen and/or progestogen
	Hormone replacement therapies <sup>a</sup>		Hormone replacement therapies <sup>a</sup>

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Other Female hormone products <sup>a</sup>	Other Female hormone products <sup>a</sup>
Other Medications	Other Medications
Prescribed <sup>a</sup>	Prescribed <sup>a</sup>
OTC <sup>a</sup>	OTC <sup>a</sup>
Herbal/Food supplements <sup>a</sup>	Herbal/Food supplements <sup>a</sup>
Juices	Juices
Other <sup>a</sup>	Other <sup>a</sup>

<sup>a</sup> When a questionnaire asks for drugs to be specified these will be reported in an appendix of the final report and presented according to the Anatomical Therapeutic Chemical (ATC) Classification System; where the period of exposure to a drug is not specified, these will be identified in those appendices and no assumption will be made regarding exposure period for the primary analysis

**Table 7M. Other medication history within 28 days <sup>a</sup> of initiation prior to start of treatment for indication DVT/PE, by treatment group**

Rivaroxaban		Warfarin	
Medication	N%	Medication	N%
Analgesics		Analgesics	
Paracetamol		Paracetamol	
Etc...		Etc...	
Anti-Inflammatory		Anti-Inflammatory	
Aspirin (>300mg)		Aspirin (>300mg)	
NSAID		NSAID	
Etc...		Etc...	
Anti-convulsants		Anti-convulsants	
Phenytoin		Phenytoin	
Phenobarbital		Phenobarbital	
Carbamazepine		Carbamazepine	
Etc...		Etc...	
Anti-infective		Anti-infective	
Ketoconazole		Ketoconazole	
Itraconazole		Itraconazole	
Posaconazole		Posaconazole	
Etc...		Etc...	
Antidepressants		Antidepressants	
Tricyclic and related <sup>a</sup>		Tricyclic and related <sup>a</sup>	
MAOI		MAOI	
SSRI		SSRI	
Etc...		Etc...	
Female hormone products		Female hormone products	
Oestrogen and/or progestogen		Oestrogen and/or progestogen	
Hormone replacement therapies <sup>a</sup>		Hormone replacement therapies <sup>a</sup>	
Other Female hormone products <sup>a</sup>		Other Female hormone products <sup>a</sup>	
Other Medications		Other Medications	
Prescribed <sup>a</sup>		Prescribed <sup>a</sup>	
OTC <sup>a</sup>		OTC <sup>a</sup>	
Herbal/Food supplements <sup>a</sup>		Herbal/Food supplements <sup>a</sup>	
Juices		Juices	
Other <sup>a</sup>		Other <sup>a</sup>	

<sup>a</sup> When a questionnaire asks for drugs to be specified these will be reported in an appendix of the final report and presented according to the ATC Classification System; where the period of exposure to a drug is not specified, these will be identified in those appendices and no assumption will be made regarding exposure period for the primary analysis

## Appendix 2. Statistical Analysis Plan

**Table 7N. Other medication history within 28 days <sup>a</sup> of initiation prior to start of treatment for mixed (AF & DVT/PE) indications, by treatment group**

Rivaroxaban		Warfarin	
Medication	N%	Medication	N%
Analgesics		Analgesics	
Paracetamol		Paracetamol	
Etc...		Etc...	
Anti-Inflammatory		Anti-Inflammatory	
Aspirin (>300mg)		Aspirin (>300mg)	
NSAID		NSAID	
Etc...		Etc...	
Anti-convulsants		Anti-convulsants	
Phenytoin		Phenytoin	
Phenobarbital		Phenobarbital	
Carbamazepine		Carbamazepine	
Etc...		Etc...	
Anti-infective		Anti-infective	
Ketoconazole		Ketoconazole	
Itraconazole		Itraconazole	
Posaconazole		Posaconazole	
Etc...		Etc...	
Antidepressants		Antidepressants	
Tricyclic and related <sup>a</sup>		Tricyclic and related <sup>a</sup>	
MAOI		MAOI	
SSRI		SSRI	
Etc...		Etc...	
Female hormone products		Female hormone products	
Oestrogen and/or progestogen		Oestrogen and/or progestogen	
Hormone replacement therapies <sup>a</sup>		Hormone replacement therapies <sup>a</sup>	
Other Female hormone products <sup>a</sup>		Other Female hormone products <sup>a</sup>	
Other Medications		Other Medications	
Prescribed <sup>a</sup>		Prescribed <sup>a</sup>	
OTC <sup>a</sup>		OTC <sup>a</sup>	
Herbal/Food supplements <sup>a</sup>		Herbal/Food supplements <sup>a</sup>	
Juices		Juices	
Other <sup>a</sup>		Other <sup>a</sup>	

<sup>a</sup> When a questionnaire asks for drugs to be specified these will be reported in an appendix of the final report and presented according to the ATC Classification System; where the period of exposure to a drug is not specified, these will be identified in those appendices and no assumption will be made regarding exposure period for the primary analysis

## Appendix 2. Statistical Analysis Plan

**Table 70. Other medication history within 28 days <sup>a</sup> of initiation prior to start of treatment for Other indications, by treatment group**

Rivaroxaban		Warfarin	
Medication	N%	Medication	N%
Analgesics		Analgesics	
Paracetamol		Paracetamol	
Etc...		Etc...	
Anti-Inflammatory		Anti-Inflammatory	
Aspirin (>300mg)		Aspirin (>300mg)	
NSAID		NSAID	
Etc...		Etc...	
Anti-convulsants		Anti-convulsants	
Phenytoin		Phenytoin	
Phenobarbital		Phenobarbital	
Carbamazepine		Carbamazepine	
Etc...		Etc...	
Anti-infective		Anti-infective	
Ketoconazole		Ketoconazole	
Itraconazole		Itraconazole	
Posaconazole		Posaconazole	
Etc...		Etc...	
Antidepressants		Antidepressants	
Tricyclic and related <sup>a</sup>		Tricyclic and related <sup>a</sup>	
MAOI		MAOI	
SSRI		SSRI	
Etc...		Etc...	
Female hormone products		Female hormone products	
Oestrogen and/or progestogen		Oestrogen and/or progestogen	
Hormone replacement therapies <sup>a</sup>		Hormone replacement therapies <sup>a</sup>	
Other Female hormone products <sup>a</sup>		Other Female hormone products <sup>a</sup>	
Other Medications		Other Medications	
Prescribed <sup>a</sup>		Prescribed <sup>a</sup>	
OTC <sup>a</sup>		OTC <sup>a</sup>	
Herbal/Food supplements <sup>a</sup>		Herbal/Food supplements <sup>a</sup>	
Juices		Juices	
Other <sup>a</sup>		Other <sup>a</sup>	

<sup>a</sup> When a questionnaire asks for drugs to be specified these will be reported in an appendix of the final report and presented according to the ATC Classification System; where the period of exposure to a drug is not specified, these will be identified in those appendices and no assumption will be made regarding exposure period for the primary analysis

### 9.2.2.5 Therapy Plan – Treatment Initiation

In accordance with secondary objective (i) and (ii), this section will describe details of treatment setting, the therapy plan given to the patients at index date and all medication being used on start (at index date), and /or during first 12 weeks of treatment with rivaroxaban or Warfarin treatment.



## Appendix 2. Statistical Analysis Plan

**Table 8. Treatment initiation**

<b>Data description</b>	<b>Source</b>	<b>Result reference</b>
Treatment setting (Inpatient or outpatient)	Index questionnaire (Q3)	Table 8A
Summary statistics for dose at index: mean, standard deviation, median, minimum & maximum	Index questionnaire (Q3) and 12-Week Questionnaire (Q9, Q10 & Q11)	Table 8B
Medications used on start (at index date), and /or during first 12 weeks of treatment, by Rivaroxaban & Warfarin treatment and indication.	12-Week Questionnaire (Q14)	Tables 8C – 8F

**Table 8A. Treatment setting at index date, by indication and treatment group**

<b>Setting</b>	<b>Rivaroxaban N%</b>	<b>Warfarin N%</b>	<b>Total N%</b>
Indication: AF			
Inpatient			
Outpatient			
Unknown			
Total			
DVT/PE			
Inpatient			
Outpatient			
Unknown			
Total			
Mixed (AF & DVT/PE)			
Inpatient			
Outpatient			
Unknown			
Total			
Other			
Inpatient			
Outpatient			
Unknown			
Total			

## Appendix 2. Statistical Analysis Plan

**Table 8B. Posology (total daily dose) at index date by indication and treatment group**

Start dose	Rivaroxaban N%	Warfarin N%
Indication:		
IAF		
	<2.5	
	>=2.5, <5	
	>=5.0, <10	
	>=10, <20	
	>=20, <30	
	>=30	
Number patients with Missing information		
Median (IQR)		
Mean (SD)		
DVT/PE		
	<2.5	
	>=2.5, <5	
	>=5.0, <10	
	>=10, <20	
	>=20, <30	
	>=30	
Number patients with Missing information		
Median (IQR)		
Mean (SD)		
AF & DVT/PE		
	<2.5	
	>=2.5, <5	
	>=5.0, <10	
	>=10, <20	
	>=20, <30	
	>=30	
Number patients with Missing information		
Median (IQR)		
Mean (SD)		
Other		
	<2.5	
	>=2.5, <5	
	>=5.0, <10	
	>=10, <20	
	>=20, <30	
	>=30	
Number patients with Missing information		
Median (IQR)		
Mean (SD)		

## Appendix 2. Statistical Analysis Plan

**Table 8C. Medication use at index date or during 12 weeks of treatment<sup>a</sup> for indication AF, by treatment group**

Rivaroxaban		Warfarin	
Medication	N%	Medication	N%
Analgesics		Analgesics	
Paracetamol		Paracetamol	
Etc...		Etc...	
Anti-Inflammatory		Anti-Inflammatory	
Aspirin (>300mg)		Aspirin (>300mg)	
NSAID		NSAID	
Etc...		Etc...	
Anti-convulsants		Anti-convulsants	
Phenytoin		Phenytoin	
Phenobarbital		Phenobarbital	
Carbamazepine		Carbamazepine	
Etc...		Etc...	
Anti-infective		Anti-infective	
Ketoconazole		Ketoconazole	
Itraconazole		Itraconazole	
Posaconazole		Posaconazole	
Etc...		Etc...	
Antidepressants		Antidepressants	
Tricyclic and related <sup>a</sup>		Tricyclic and related <sup>a</sup>	
MAOI		MAOI	
SSRI		SSRI	
Etc...		Etc...	
Female hormone products		Female hormone products	
Oestrogen and/or progestogen		Oestrogen and/or progestogen	
Hormone replacement therapies <sup>a</sup>		Hormone replacement therapies <sup>a</sup>	
Other Female hormone products <sup>a</sup>		Other Female hormone products <sup>a</sup>	
Other Medications		Other Medications	
Antiplatelets <sup>a</sup>		Antiplatelets <sup>a</sup>	
Anticoagulants <sup>a</sup>		Anticoagulants <sup>a</sup>	
Other Prescribed <sup>a</sup>		Other Prescribed <sup>a</sup>	
OTC <sup>a</sup>		OTC <sup>a</sup>	
Herbal/Food supplements <sup>a</sup>		Herbal/Food supplements <sup>a</sup>	
Juices		Juices	
Other <sup>a</sup>		Other <sup>a</sup>	

<sup>a</sup> When a questionnaire asks for drugs to be specified these will be reported in an appendix of the final report and presented according to the ATC Classification System; where the period of exposure to a drug is not specified, these will be identified in those appendices and no assumption will be made regarding exposure period for the primary analysis.

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**Table 8D. Medications use at index date or during 12 weeks of treatment<sup>a</sup> for indication DVT/PE, by treatment group**

Rivaroxaban		Warfarin	
Medication	N%	Medication	N%
Analgesics		Analgesics	
Paracetamol		Paracetamol	
Etc...		Etc...	
Anti-Inflammatory		Anti-Inflammatory	
Aspirin (>300mg)		Aspirin (>300mg)	
NSAID		NSAID	
Etc...		Etc...	
Anti-convulsants		Anti-convulsants	
Phenytoin		Phenytoin	
Phenobarbital		Phenobarbital	
Carbamazepine		Carbamazepine	
Etc...		Etc...	
Anti-infective		Anti-infective	
Ketoconazole		Ketoconazole	
Itraconazole		Itraconazole	
Posaconazole		Posaconazole	
Etc...		Etc...	
Antidepressants		Antidepressants	
Tricyclic and related <sup>a</sup>		Tricyclic and related <sup>a</sup>	
MAOI		MAOI	
SSRI		SSRI	
Etc...		Etc...	
Female hormone products		Female hormone products	
Oestrogen and/or progestogen		Oestrogen and/or progestogen	
Hormone replacement therapies <sup>a</sup>		Hormone replacement therapies <sup>a</sup>	
Other Female hormone products <sup>a</sup>		Other Female hormone products <sup>a</sup>	
Other Medications		Other Medications	
Antiplatelets <sup>a</sup>		Antiplatelets <sup>a</sup>	
Anticoagulants <sup>a</sup>		Anticoagulants <sup>a</sup>	
Other Prescribed <sup>a</sup>		Other Prescribed <sup>a</sup>	
OTC <sup>a</sup>		OTC <sup>a</sup>	
Herbal/Food supplements <sup>a</sup>		Herbal/Food supplements <sup>a</sup>	
Juices		Juices	
Other <sup>a</sup>		Other <sup>a</sup>	

<sup>a</sup> When a questionnaire asks for drugs to be specified these will be reported in an appendix of the final report and presented according to the ATC Classification System; where the period of exposure to a drug is not specified, these will be identified in those appendices and no assumption will be made regarding exposure period for the primary analysis

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**Table 8E. Medications use at index date or during 12 weeks of treatment<sup>a</sup> for Mixed (AF & DVT/PE) indications, by treatment group**

Rivaroxaban		Warfarin	
Medication	N%	Medication	N%
Analgesics		Analgesics	
Paracetamol		Paracetamol	
Etc...		Etc...	
Anti-Inflammatory		Anti-Inflammatory	
Aspirin (>300mg)		Aspirin (>300mg)	
NSAID		NSAID	
Etc...		Etc...	
Anti-convulsants		Anti-convulsants	
Phenytoin		Phenytoin	
Phenobarbital		Phenobarbital	
Carbamazepine		Carbamazepine	
Etc...		Etc...	
Anti-infective		Anti-infective	
Ketoconazole		Ketoconazole	
Itraconazole		Itraconazole	
Posaconazole		Posaconazole	
Etc...		Etc...	
Antidepressants		Antidepressants	
Tricyclic and related <sup>a</sup>		Tricyclic and related <sup>a</sup>	
MAOI		MAOI	
SSRI		SSRI	
Etc...		Etc...	
Female hormone products		Female hormone products	
Oestrogen and/or progestogen		Oestrogen and/or progestogen	
Hormone replacement therapies <sup>a</sup>		Hormone replacement therapies <sup>a</sup>	
Other Female hormone products <sup>a</sup>		Other Female hormone products <sup>a</sup>	
Other Medications		Other Medications	
Antiplatelets <sup>a</sup>		Antiplatelets <sup>a</sup>	
Anticoagulants <sup>a</sup>		Anticoagulants <sup>a</sup>	
Other Prescribed <sup>a</sup>		Other Prescribed <sup>a</sup>	
OTC <sup>a</sup>		OTC <sup>a</sup>	
Herbal/Food supplements <sup>a</sup>		Herbal/Food supplements <sup>a</sup>	
Juices		Juices	
Other <sup>a</sup>		Other <sup>a</sup>	

<sup>a</sup> When a questionnaire asks for drugs to be specified these will be reported in an appendix of the final report and presented according to the ATC Classification System; where the period of exposure to a drug is not specified, these will be identified in those appendices and no assumption will be made regarding exposure period for the primary analysis

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**Table 8F. Medications use at index date or during 12 weeks of treatment<sup>a</sup> for indication other indications, by treatment group**

Rivaroxaban		Warfarin	
Medication	N%	Medication	N%
Analgesics		Analgesics	
Paracetamol		Paracetamol	
Etc...		Etc...	
Anti-Inflammatory		Anti-Inflammatory	
Aspirin (>300mg)		Aspirin (>300mg)	
NSAID		NSAID	
Etc...		Etc...	
Anti-convulsants		Anti-convulsants	
Phenytoin		Phenytoin	
Phenobarbital		Phenobarbital	
Carbamazepine		Carbamazepine	
Etc...		Etc...	
Anti-infective		Anti-infective	
Ketoconazole		Ketoconazole	
Itraconazole		Itraconazole	
Posaconazole		Posaconazole	
Etc...		Etc...	
Antidepressants		Antidepressants	
Tricyclic and related <sup>a</sup>		Tricyclic and related <sup>a</sup>	
MAOI		MAOI	
SSRI		SSRI	
Etc...		Etc...	
Female hormone products		Female hormone products	
Oestrogen and/or progestogen		Oestrogen and/or progestogen	
Hormone replacement therapies <sup>a</sup>		Hormone replacement therapies <sup>a</sup>	
Other Female hormone products <sup>a</sup>		Other Female hormone products <sup>a</sup>	
Other Medications		Other Medications	
Antiplatelets <sup>a</sup>		Antiplatelets <sup>a</sup>	
Anticoagulants <sup>a</sup>		Anticoagulants <sup>a</sup>	
Other Prescribed <sup>a</sup>		Other Prescribed <sup>a</sup>	
OTC <sup>a</sup>		OTC <sup>a</sup>	
Herbal/Food supplements <sup>a</sup>		Herbal/Food supplements <sup>a</sup>	
Juices		Juices	
Other <sup>a</sup>		Other <sup>a</sup>	

<sup>a</sup> When a questionnaire asks for drugs to be specified these will be reported in an appendix of the final report and presented according to the ATC Classification System; where the period of exposure to a drug is not specified, these will be identified in those appendices and no assumption will be made regarding exposure period for the primary analysis

### 9.3 Stroke and bleeding risk prediction

Calculations of specific risks scores (HAS-BLED and CHA<sub>2</sub>DS<sub>2</sub>-VASc) will be presented for all indication groups, by treatment choice.

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**Table 10. Stroke and bleeding risk prediction**

<b>Data Description</b>	<b>Source</b>	<b>Result Reference</b>
Baseline HAS-BLED score categories by indication group	Index Questionnaire (Q1, Q6) 12 week (Q13, Q15, Q16, Q18, Q21)	Table 10A
Baseline HAS-BLED risk score by indication group	Index Questionnaire (Q1, Q2, Q6) 12 week (Q13, Q15, Q16, Q18, Q21)	Table 10B, Figure 10
Baseline CHA <sub>2</sub> DS <sub>2</sub> -VASc score categories by indication group	Index Questionnaire (Q1, Q6) 12 week (Q13, Q14, Q15, Q16)	Table 10C
Baseline CHA <sub>2</sub> DS <sub>2</sub> -VASc risk score by indication group	Index Questionnaire (Q1, Q6) 12 week (Q13, Q14, Q15, Q16)	Table 10D, Figure 11

**Table 10A. Baseline patient HAS-BLED score categories, by treatment group**

<b>Clinical feature (points)</b>	<b>Rivaroxaban</b>		<b>Warfarin</b>	
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
AF				
Hypertension (1)				
Abnormal renal function (1)				
Abnormal liver function (1)				
History Stroke (1)				
History of Bleeding or predisposition (1)				
Labile INR (1)		n/a		
Age >=65 years (1)				
Drug therapy (1)				
Alcohol ( 8 drinks/week) (1)				
DVT/PE				
Hypertension (1)				
Abnormal renal function (1)				
Abnormal liver function (1)				
History Stroke (1)				
History of Bleeding or predisposition (1)				
Labile INR (1)		n/a		
Age >=65 years (1)				
Drug therapy (1)				
Alcohol ( 8 drinks/week) (1)				
Mixed (AF & DVT)				
Hypertension (1)				
Abnormal renal function (1)				
Abnormal liver function (1)				
History Stroke (1)				
History of Bleeding or				

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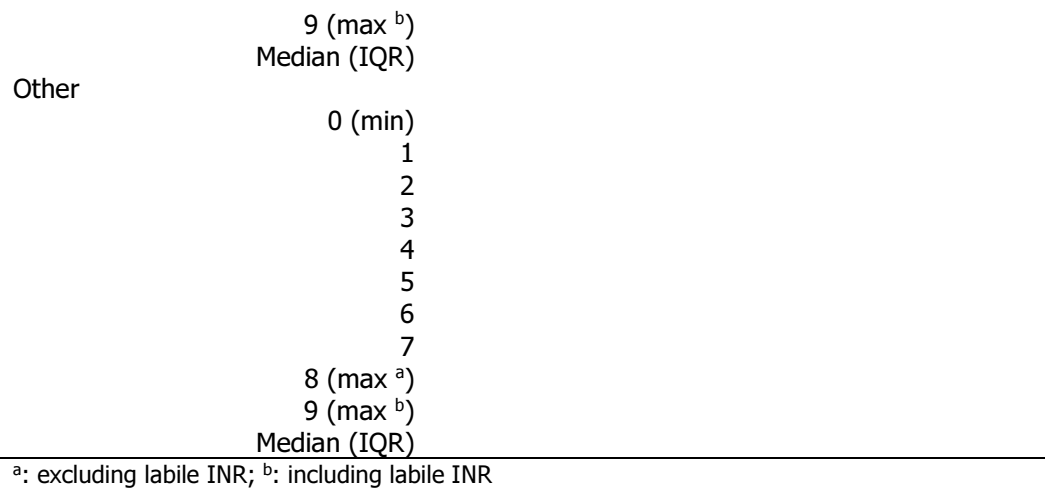
	predisposition (1)	
	Labile INR (1)	n/a
	Age >=65 years (1)	
	Drug therapy (1)	
	Alcohol ( 8 drinks/week) (1)	
Other		
	Hypertension (1)	
	Abnormal renal function (1)	
	Abnormal liver function (1)	
	History Stroke (1)	
	History of Bleeding or predisposition (1)	
	Labile INR (1)	n/a
	Age >=65 years (1)	
	Drug therapy (1)	
	Alcohol ( 8 drinks/week) (1)	

**Table 10B. Baseline patient HAS-BLED risk score, by indication and treatment group**

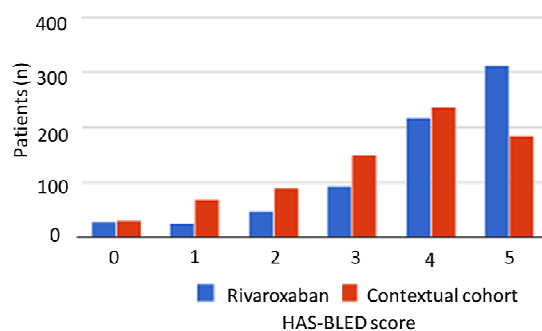
Score	Rivaroxaban		Warfarin	
	N <sup>a</sup>	%	N <sup>a</sup> %	N <sup>b</sup> %
AF				
	0 (min)			
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8 (max <sup>a</sup> )			
	9 (max <sup>b</sup> )			
	Median (IQR)			
DVT/PE				
	0 (min)			
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8 (max <sup>a</sup> )			
	9 (max <sup>b</sup> )			
	Median (IQR)			
Mixed (AF & DVT/PE)				
	0 (min)			
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8 (max <sup>a</sup> )			



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**Figure 10. Distribution of baseline patient HAS-BLED score categories (excluding labile INR), by indication and treatment group**



**Table 10C. Baseline patient CHA<sub>2</sub>DS<sub>2</sub>-VASc score categories, by indication and treatment group**

Clinical feature (points)	Rivaroxaban		Warfarin	
	N	%	N	%
AF				
Age 65-74 years (1), or >75 (2)				
Female Sex (1)				
History Congestive heart failure/left ventricular dysfunction (1)				
History Hypertension (1)				
History Stroke, TIA or Thromboembolism (2)				
Vascular Disease (1)				
Diabetes Mellitus (1)				
DVT/PE				
Age 65-74 years (1), or >75 (2)				
Female Sex (1)				
History Congestive heart failure/left ventricular				

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dysfunction (1)
History Hypertension (1)
History Stroke,TIA orThromboembolism (2)
Vascular Disease (1)
Diabetes Mellitus (1)
Mixed (AF & DVT/PE)
Age 65-74 years (1), or >75 (2)
Female Sex (1)
History Congestive heart failure/left ventricular dysfunction (1)
History Hypertension (1)
History Stroke,TIA orThromboembolism (2)
Vascular Disease (1)
Diabetes Mellitus (1)
Other
Age 65-74 years (1), or >75 (2)
Female Sex (1)
History Congestive heart failure/left ventricular dysfunction (1)
History Hypertension (1)
History Stroke,TIA orThromboembolism (2)
Vascular Disease (1)
Diabetes Mellitus (1)

**Table 10D. Baseline patient CHA<sub>2</sub>DS<sub>2</sub>-VASc score categories, by treatment group**

Score	Rivaroxaban		Warfarin	
	N	%	N	%
AF	0 (min)			
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9(max)			
	Median (IQR)			
DVT/PE	0 (min)			
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9(max)			
	Median (IQR)			
Mixed (AF & DVT/PE)	0 (min)			

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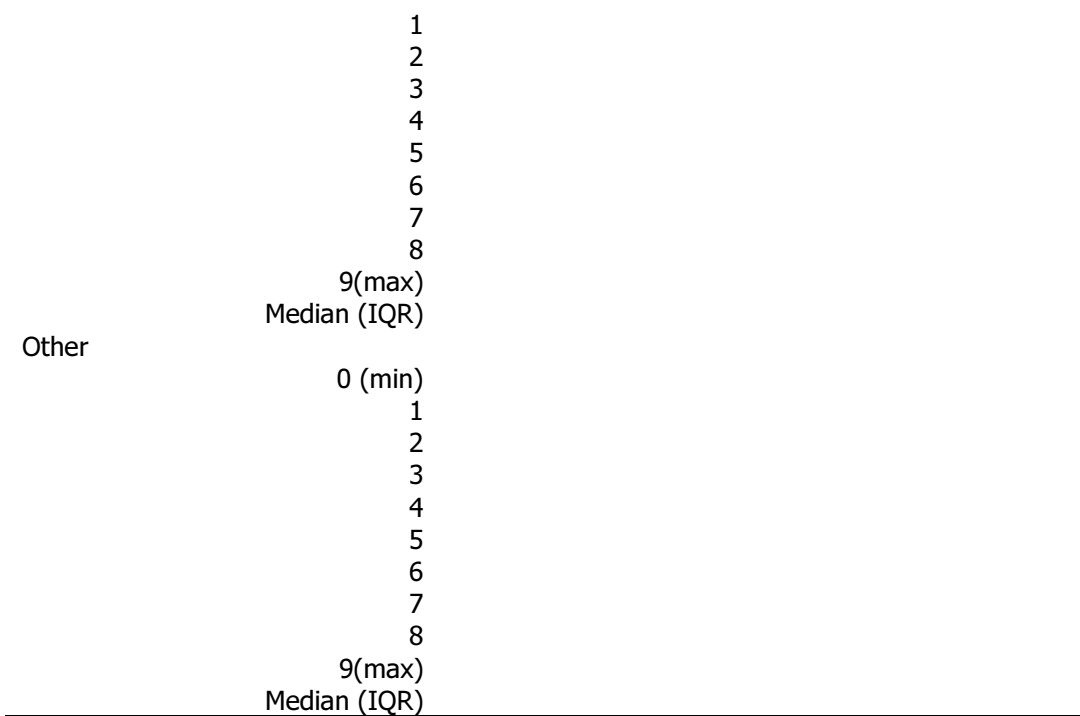
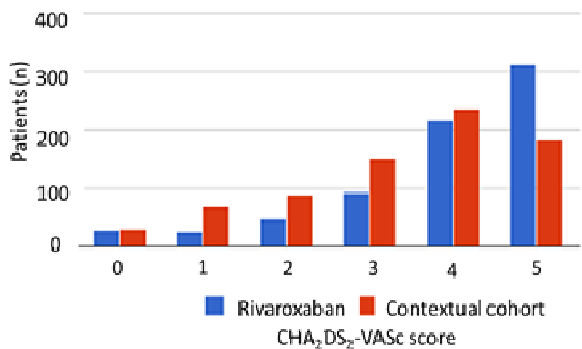


Figure 11. Distribution of baseline patient CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score, by indication and treatment group



9.4 Indicators of use

9.4.1 Special populations

Data analysis will provide summary tabulations of the derived variables representing categories of special populations defined within the SmPC for rivaroxaban. For each

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special population indicator operational definitions will be constructed from tick box responses and free text information in accordance with known clinical definitions (ICD-10 terminology) (Table 11). Missing data will be treated as a negative response.

A simple unweighted indicator score will be derived for each category (where more than one criteria apply). The summary distribution and prevalence of each criteria, by category, of patients prescribed rivaroxaban will be summarised for the rivaroxaban cohort and by indication group (Table 11A).

**Table 11. Special population indicators of use for rivaroxaban cohort**

<b>Data description</b>	<b>Source</b>	<b>Result reference</b>
<b>Indicators of Contraindicated use (patients can have up to 7 indicators)</b>		
Treatment for medical indications other than licensed indications	Index questionnaire (Q2)	Table 11A
Hypersensitivity to the active substance or to any of the excipients	12 week questionnaire (Q15 & Q16)	
Clinically significant active bleeding	Index questionnaire (Q6) & 12 week questionnaire (Q15 & Q16)	
Lesion or condition considered a significant risk for major bleeding which may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities	12 week questionnaire (Q15 & Q16)	
Concomitant treatment with other anticoagulants (other than for switching anticoagulant therapy)	12 week questionnaire (Q14)	
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	12 week questionnaire (Q15 & Q16)	
Use in pregnancy and lactation	12 week questionnaire (Q15 & Q16)	
<b>Indicators of Special Warning/Precautions for use (patients can have up to 9 indicators)</b>		
Moderate to severe renal impairment (patients with creatinine clearance $\geq 15$ - $\leq 59$ ml/min)	Index questionnaire (Q6) & 12 week questionnaire (Q15 & Q16)	Table 11A
End stage renal failure (patients with creatinine clearance $\leq 15$ ml/min)	Index questionnaire (Q6) & 12 week questionnaire (Q15 & Q16)	
Patients with liver cirrhosis with moderate hepatic impairment (classified as Child Pugh B), not associated with coagulopathy	Index questionnaire (Q6) & 12 week questionnaire (Q15 & Q16)	

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Congenital or acquired bleeding disorders	Index questionnaire (Q6) & 12 week questionnaire (Q15 & Q16)
Uncontrolled severe arterial hypertension	Index questionnaire (Q6) & 12 week questionnaire (Q15 & Q16)
Other GI disease without active ulceration (IBD, oesophagitis, gastritis and GORD)	12 week questionnaire (Q15 & Q16)
Vascular retinopathy	12 week questionnaire (Q15 & Q16)
Bronchiectasis or history of pulmonary bleeding.	12 week questionnaire (Q16)
Patients with AF and a prosthetic heart valve	Index questionnaire (Q2) & 12 week questionnaire (Q15 & Q16)

### Indicators of use in patients with limited information

Children aged < 18 years NA due to exclusion criteria

### Indicators of drug-drug interactions (patients can have up to 5 indicators)

Concomitant treatment with CYP3A4 inhibitors	12 week questionnaire (Q14)	Table 11A
Concomitant treatment with CYP3A4 inducers		
Concomitant treatment with P-gp inhibitors		
Concomitant use with NSAIDs		
Concomitant use with platelet aggregation inhibitors		
Score of Indicators of Contraindicated use: count and percent of categories 0-7; median (IQR)	Table 12A	Table 11B, Figures 12 a-e
Score of Indicator of Special Warning/Precautions for use: count and percent of categories 0-9; median (IQR)		
Score of Indicator of Drug-Drug interactions: count and percent of categories 0-5; median (IQR)		

**Table 11A. Prevalence of criteria and categories identifying special population users of rivaroxaban, by indication group and pooled cohort**

Clinical feature (points)	AF		DVT/PE		Mixed (AF & DVT)		Other		TOTAL	
	N	%	N	%	N	%	N	%	N	%
<b>Indicators of Contraindicated use</b>										
Treatment for medical indications other than licensed indications										
Hypersensitivity to the active substance or to any of the excipients										
Clinically significant active bleeding										
Lesion or condition considered a significant risk for major bleeding										
Concomitant treatment with other										

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anticoagulants (other than for switching anticoagulant therapy)
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
Use in pregnancy and lactation
<b>Indicators of Special Warning/Precautions for use</b>
Renal impairment (patients with creatinine clearance $\geq 15$ , $\leq 59$ ml/min)
End stage renal failure (patients with creatinine clearance $\leq 15$ ml/min)
Patients with liver cirrhosis with moderate hepatic impairment (classified as Child Pugh B), not associated with coagulopathy
Congenital or acquired bleeding disorders
Uncontrolled severe arterial hypertension
Other GI disease without active ulceration (IBD, oesophagitis, gastritis and GORD)
Vascular retinopathy
Bronchiectasis or history of pulmonary bleeding.
Patients with AF and a prosthetic heart valve
<b>Indicators of Drug-Drug Interactions</b>
Concomitant treatment with CYP3A4 inhibitors
Concomitant treatment with CYP3A4 inducers
Concomitant treatment with P-gp inhibitors
Concomitant use with NSAIDs
Concomitant use with platelet aggregation inhibitors

**Table 11B. Special population users of rivaroxaban score distribution, by indication group and pooled cohort**

Clinical feature (points)	AF		DVT/PE		Mixed (AF & DVT)		Other		TOTAL	
	N	%	N	%	N	%	N	%	N	%
Indicators of Contraindicated use										
0 (min)										
1										
2										
3										
4										
5										
6										
7 (max)										
Median (IQR)										
Indicators of Special Warning/Precautions for use										
0 (min)										
1										
2										
3										
4										
5										
6										
7										
8										
9 (max)										
Median (IQR)										

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Indicators of Drug-Drug Interactions

0 (min)  
1  
2  
3  
4  
5 (max)  
Median (IQR)

---

**Figure 12. Special population users of rivaroxaban score distribution, by indication group and pooled cohort**

(see figure 10 for example)

### 9.5 Multilevel regression analysis of prescribing variability

In accordance with secondary objective (ii) is to explore the effect of important predictors (prognostics characteristics, selected relevant risk factors and oral anticoagulant on the primary outcomes of interest (haemorrhage). Prescribing of medications in clinical practice is also influenced by factors that are not directly associated with the patient. These include physician level factor such as prescribing preference and experience, as factors above the level of the prescriber, such as hospital and/or trust levels factors such as prescribing policy.

A multilevel model (MLM) can provide insight into sources of variability in healthcare, where hierarchical structures exist. The results of such analysis may then be used to inform on selection of appropriate instrumental variables for modelling potential associations between rivaroxaban and warfarin use with primary outcome of interest.

For this study, this planned sub-analysis will utilise a multilevel logistic regression analysis with three levels (namely, patients clustered within prescribers, clustered within Trusts) will be explored to study both the influence of patient, prescriber and Trust characteristics on rivaroxaban and warfarin treatment use, and also the variance in prescribing at the prescriber and Trust levels. The outcome variable will be the binary treatment group of rivaroxaban versus warfarin treatment. Evaluable patient characteristics will include:

- Age
- Gender
- Marital Status
- Employment Status
- Ethnicity

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- Index of Multiple Deprivation rank
- Indication
- Prior/at baseline history of
  - CVA
  - DVT
  - Abnormal Liver Function
  - Renal Disease
  - Diabetes Mellitus
  - Congestive Heart Failure
  - Vascular Disease
  - Hypertension
  - Bleeding Predisposition
  - Excessive Alcohol Consumption/ alcohol misuse
  - Medications predisposing to bleeds
- BMI (kg/m<sup>2</sup>)
- Smoking Prior
- Substance Misuse Prior
- HAS-BLED Score (for sensitivity analysis- excluding labile INR)
- CHADS<sub>2</sub>VASC Score ( for sensitivity analysis)
- Patient-specific prescribing reasons as reported by physician:
  - Lifestyle choice
  - Non-adherence with prior anticoagulant
  - Side-effects with prior anticoagulant
  - Patient preference
  - Poor control
  - Aberrant health behaviours

Prescriber characteristics will include:

- Sex
- Professional qualification
- Professional years registered
- Career Level
- Specialist status
- Specialist Experience
- Specialism
  - Neurology &/or stroke
  - Haematology
  - Geriatrics



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- Surgery
- Gastroenterology
- Endocrinology
- Cardiology
- Acute Care
- A&E
- Other
- Influences in prescribing (% of patients treated)
  - Clinical Judgement
  - NICE recommendations
  - Expert guidelines
  - Hospital Formulary
  - Patient group direction
  - Potential ease of reversibility
- Prescribing preference (% of evaluable patients treated with rivaroxaban)

Participating Trust characteristics will include:

- Catchment population density served
- Geographic region
- Socioeconomic status of trust population served (Rank)
- Trust Hospital density
- Type of Trust (Acute, Foundation, Integrated)
- %Teaching hospital
- Trust anticoagulant prescribing guideline
- Rivaroxaban Trust use (sales data)
- Number Hospitals Participating in ROSE study

The analysis will be completed in several steps to differentiate between the influence of patient, prescriber and Trust characteristics. In step 1, the “empty” model will include only random effects for the prescriber and Trust, without including any fixed effects to account for patient, prescriber or Trust characteristics. This model will provide estimates of the components of variance in prescribing at the prescriber and Trust levels, allowing comparison of their relative contributions in terms of the proportion of the total variance explained. In step 2, patient characteristics (and interaction terms) will be added to the model. This model will account for any difference that might exist in the groups of patients associated with each prescriber and Trust. The variance components in step 2 will then estimate the remaining variance explained by differences in prescribing practice between prescribers and

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between Trusts, whilst accounting for differences in the patient characteristics. Step 2 will also allow determination of the patient characteristics that are associated with prescription of rivaroxaban or warfarin treatment, along with estimates of the size and direction of those effects. In step 3, prescriber characteristics will be added to the model to account for, and estimate the effects of, prescriber characteristics associated with the prescription of rivaroxaban or warfarin treatment. Similarly, in step 5, Trust characteristics will also be added to the model.

Only those fixed effects found to have a significant effect on the performance of the models will be retained in each step. The fixed effects structure of models will be compared using F-tests, which assess the statistical significance of the effect of each variable on prescribing practice. The approach of Kenward and Roger (1997), which is appropriate for unbalanced models, will be applied.(2)

Fixed effects will be reported via odds ratios (OR) and their associated 95% confidence intervals, calculated from the regression coefficients and their standard errors (Table 12). Random effects will be reported as the estimated variance components and their associated standard errors. Median odds ratios (MOR) will also be calculated for the variance components, to allow interpretation on the OR scale and direct comparison with the ORs of patient, prescriber and Trust characteristics. The variance components in each step will be compared with those estimated in the previous step and summarised in terms of the proportional change in the variance (PCV) between models.

**Table 12. Example of multilevel model of prescribing**

	Model Parameter	Linear Model A	Multilevel Model B	Model C	Model D	Model E	Model F	Model G	Model H
Fixed effects									
Intercept	$\beta_{0ij}$								
Covariate n	$B_{1j}$								
Covariate n+1	$B_{2j}$								
Covariate n+2	$B_{3j}$								
Interaction term m	$B_{4j}$								
Etc..									
Residual Variance Components									
Within prescriber (patient) Level 1	$\sigma^2_o$								
Between prescriber Level 2	$\sigma^2_u$								
Between trust Level 3									
Covariance	$\sigma_{uo1}$								
	$\sigma_{uo3}$								

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$\sigma_{u13}$

---

Goodness of Fit  
Deviance

---

For example: Model A: Simple linear regression model, controlling for selected covariates; Model B random intercept one-level model of patients; Model C random effects two-level nested model of patients by prescriber; Models D-F random effects two-level nested model of patients by prescriber where effect of covariates and interaction terms allowed to vary on slope individually ; Models G random effects two-level nested model of patients by prescriber where effect of selected covariates allowed to vary on slope simultaneously ; Model H random effects three-level nested model of patients by prescriber by trust where effect of covariates allowed to vary on slope simultaneously

### 9.6 Event analysis

#### 9.6.1 Haemorrhage events

##### 9.6.1.1 Classification of haemorrhage events

All bleeding events reported will be classified within the categories listed below (Box 2) , as outlined in the protocol. All bleeds are classified into major (as per ISTH), clinically relevant non major (3) and/or Other Non-Major (4) (included in Box 1).

#### Box 2. Haemorrhage classification

- a) Major – Gastrointestinal site
- b) Major – Urogenital site
- c) Major – all Intracranial
- d) Major – all other major bleeds within critical organ sites (excluding all intracranial)
- e) Major - all other major bleeds in non-critical organ sites
- f) Clinically Relevant Non Major Bleeds (CRNM)
- g) Other Non Major bleeds (excluding CRNM)
- h) Unclassifiable - bleeds which cannot be classified into one of the above categories
- i) Major Bleed I (Composite a-c)
- j) Major Bleeds II (Composite a-e)
- k) All CRNM and Major Bleeds II (Composite f & j)

Information provided on the 12 week CRFs (secondary care and GP), in addition to any supplementary information obtained will be used for this purpose

For the three organ sites specified in the primary outcome, each of the individual components of the major bleeding criteria ( a fall in haemoglobin of 2 g/dL or more, or a transfusion of 2 or more units of packed red blood cells or whole blood, or a fatal outcome - as per table 2) will be summarised in an appendix of the final report. Similarly for CRNM, each of the individual associated components will be summarised in an appendix of the final report.

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In some cases, the prescriber may have reported multiple criterion and/or multiple bleeding episodes within the same site e.g gastrointestinal. The responding physician will be asked to indicate the dates for all events/episodes where available. In this scenario, the bleeding event of interest is that indicative of the most serious episode of bleeding within this site, and will be classified according to the categories identified above. It is this bleeding event, its associated event date and classification which will be analysed in accordance with primary objective and secondary objectives (iv: a-f).

These events will be regarded as new onset, i.e. with no previous record of the same classification of bleeding event at any time prior to initiation of rivaroxaban (or warfarin) therapy (index date), as reported by the responding physician on the SCEM CRF. Where no event is reported, the assumption is that the event did not occur. Furthermore, for these analyses, event occurrence is considered to be independent of other events, so no adjustments are made for competing risks.

Data on events may be recorded in response to specific tick box questions presented according to MedDRA terminology on the CRF (12 week). Events may also be reported as free text in response to open questions; such data are coded using MedDRA. Primary outcome events reported incorrectly elsewhere as free text general events and/or reasons for stopping will be included in event counts for calculation of cumulative risks and rates. All bleeding events will be adjudicated by expert review (using all available information from SCEM questionnaires, follow-up and any additional documentation). During adjudication where such information reveals that the event did not occur (misreported), that patient will be excluded as a case from the analysis, but contribute to the 'as assigned' cohort denominator.

### ***9.6.2 Estimating the cumulative incidence of the important identified risk of haemorrhage for rivaroxaban***

The following relates to primary objective (i) for rivaroxaban only and relates to haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites.

Analyses of events identified within the primary objective will be the exploration of crude and indication-specific cumulative incidence risk (percent of total 'as assigned' cohort exposed at the beginning of the observation period) with 95% Binomial exact Confidence Intervals (CI), of targeted haemorrhage events of interest that occur during the 12-week study period, as per protocol (Table 13). For these event

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analyses, right censoring at the end of the 12 weeks observation will be undertaken. Where event are reported but with no supporting event date, these pts will be excluded from numerator and denominator of this primary analysis

If the observed cumulative incidence from the SCEM study falls within the range expected as set by the precision limits (95%CI) of cumulative incidence from clinical trial data, then the null hypothesis (of no difference) will not be rejected.

The cumulative incidence rate (hazard) in the 'as treated' cohort (per 1000 patient weeks exposed), with 95% Poisson exact Confidence Intervals (CI) will also be calculated (Table 14).

**Table 13. Number of rivaroxaban patients reporting new onset haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites and cumulative risk estimates (+95% CI <sup>a</sup>)**

Targeted Event	All incident reports (on treatment + 2 days after stopping) N (%)	Cumulative risk (95% CI)
ALL indications		
Major – Gastrointestinal site		
Major – Urogenital site		
Major – all Intracranial		
AF		
Major – Gastrointestinal site		
Major – Urogenital site		
Major – all Intracranial		
DVT/PE		
Major – Gastrointestinal site		
Major – Urogenital site		
Major – all Intracranial		
Mixed (AF & DVT/PE)		
Major – Gastrointestinal site		
Major – Urogenital site		
Major – all Intracranial		
Other		
Major – Gastrointestinal site		
Major – Urogenital site		
Major – all Intracranial		

<sup>a</sup> 95%CI calculated using Binomial exact; <sup>b</sup> at least one major haemorrhagic event

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**Table 14. Cumulative Incidence rates (IR) of new onset haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (+95% CI <sup>a</sup>) in rivaroxaban cohort**

Targeted Event	Number of events	Total person-time (1000 weeks)	IR (95% CI)
ALL indications			
Major – Gastrointestinal site			
Major – Urogenital site			
Major – all Intracranial			
AF			
Major – Gastrointestinal site			
Major – Urogenital site			
Major – all Intracranial			
DVT/PE			
Major – Gastrointestinal site			
Major – Urogenital site			
Major – all Intracranial			
Mixed (AF & DVT/PE)			
Major – Gastrointestinal site			
Major – Urogenital site			
Major – all Intracranial			
Other			
Major – Gastrointestinal site			
Major – Urogenital site			
Major – all Intracranial			

<sup>a</sup> 95%CI calculated using Poisson exact; rates will not be calculated where event count  $n \leq 10$ ; <sup>b</sup> at least one major haemorrhagic event

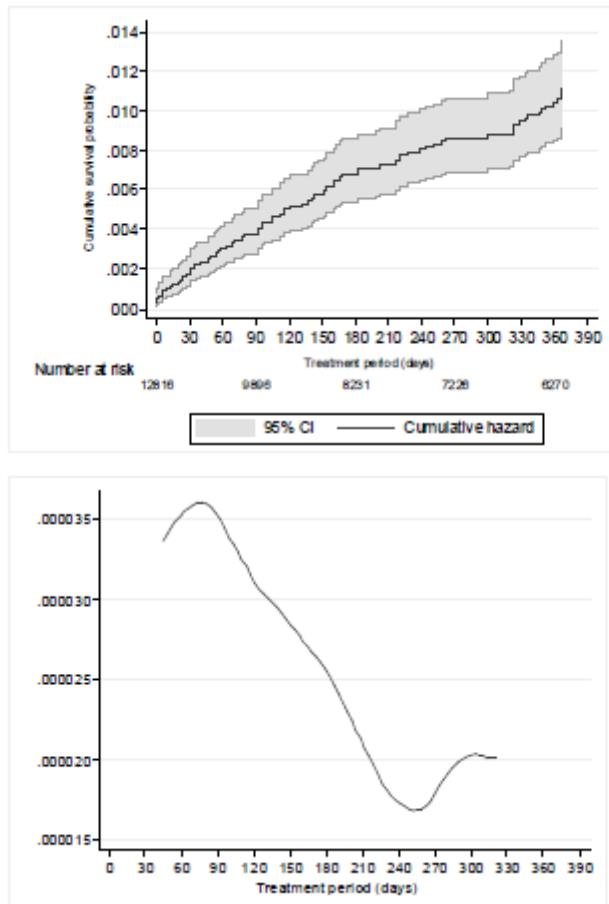
### 9.6.3 Time to event

For each primary objective outcome, a semi-parametric Proportional Hazards (PH) Regression model will also be derived using the 'as treated' cohort to describe the time to event, which will be presented graphically for the rivaroxaban cohort to examine its shape (Figure 13a)

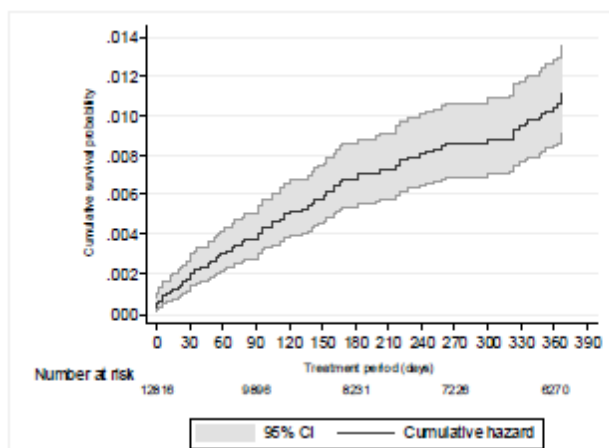
At least 10 cases will be required per event for crude estimates. A smoothed estimate of empirical hazard function will also be plotted using an epanechnikov kernel (bandwidth to be determined empirically from data) (Figure 13b). These will be used to describe how the baseline risk of an event changes over time for the total cohort

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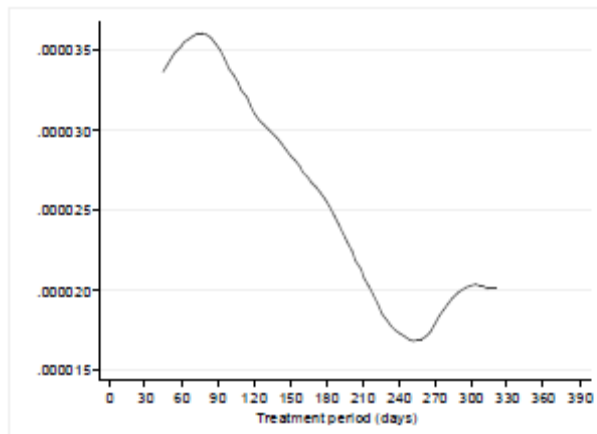
**Figure 13A.** Example of crude time to event graph for study outcome (*Major bleed– Gastrointestinal site*) in rivaroxaban cohort presented as a) Nelson-Aalen cumulative hazard function and b) smoothed hazard function



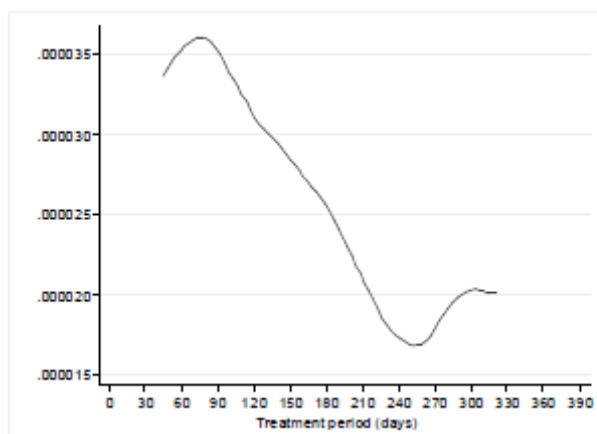
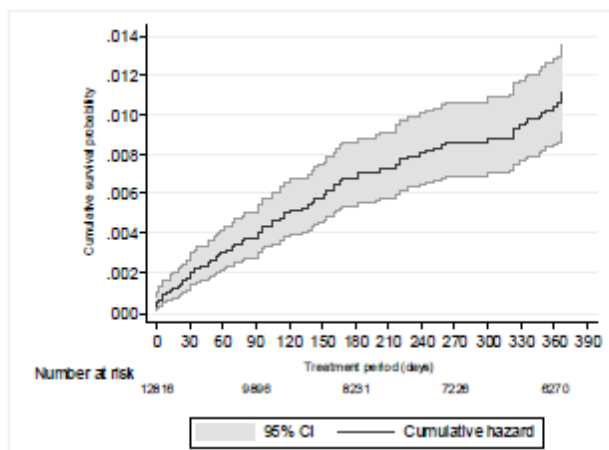
**Figure 13B.** Example of crude time to event graph for study outcome (*Major bleed– urogenital site*) in rivaroxaban cohort presented as a) Nelson-Aalen cumulative hazard function and b) smoothed hazard function



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**Figure 13C. Example of crude time to event graph for study outcome ( *Major bleed– intracranial site* ) in rivaroxaban cohort presented as a) Nelson-Aalen cumulative hazard function and b) smoothed hazard function**



Estimates of the hazard function for each primary objective event will also be modelled for the total rivaroxaban cohort and by indication group by fitting a parametric Weibull time to event model to determine whether the baseline hazard (risk) of the event increases or decreases with time. A constant hazard over time may be consistent with a background (not caused by the drug) event rate, whereas a non-constant hazard over time may be an indicator of a drug-event relationship.

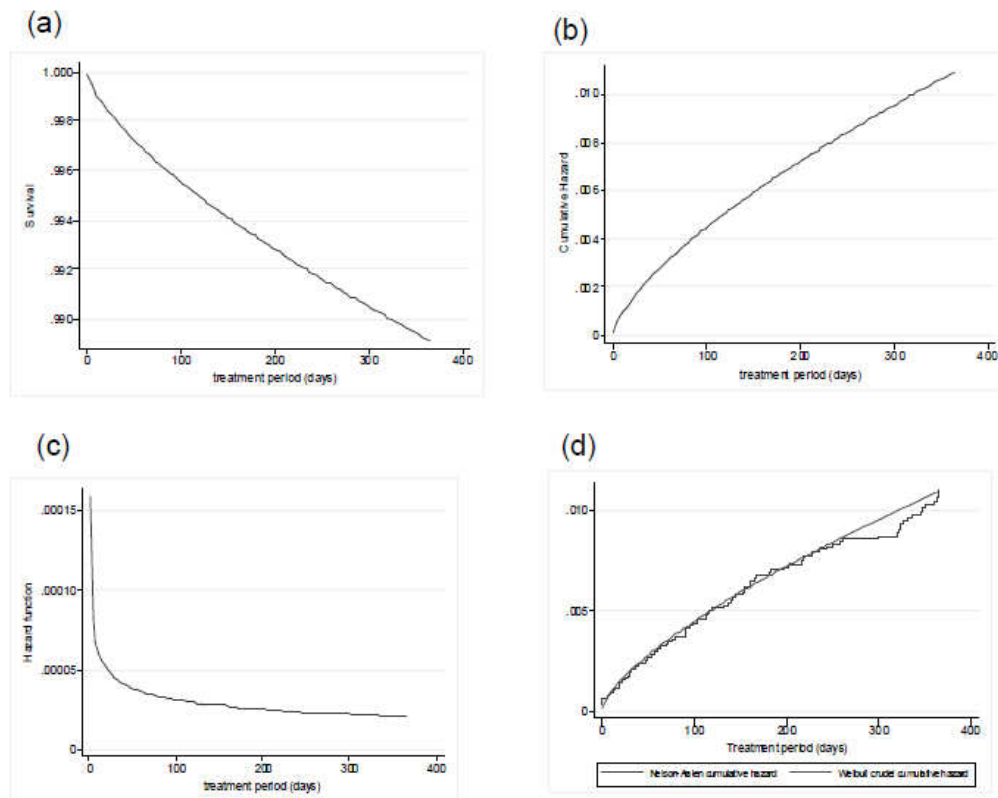


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The null hypothesis that the hazard rate of the selected event in patients prescribed rivaroxaban will be constant during the 12 week period following the start of treatment. Such models have a shape parameter that indicates whether the hazard is significantly increasing or decreasing over time (Figure 14; Table 15). At least ten reports of an event are deemed necessary for modelling purposes.

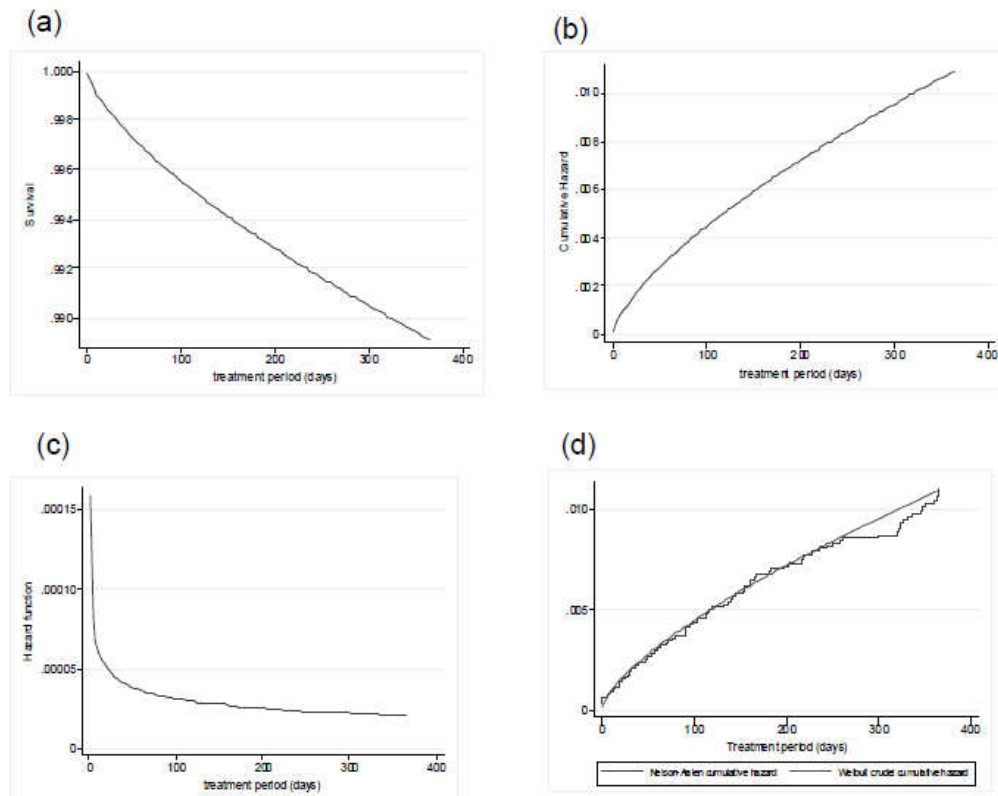
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**Figure 14A. Weibull crude model of study primary outcome (e.g *Major bleed– Gastrointestinal site*) of interest (a) survival, (b) cumulative hazard, (c) hazard and (d) goodness of fit**

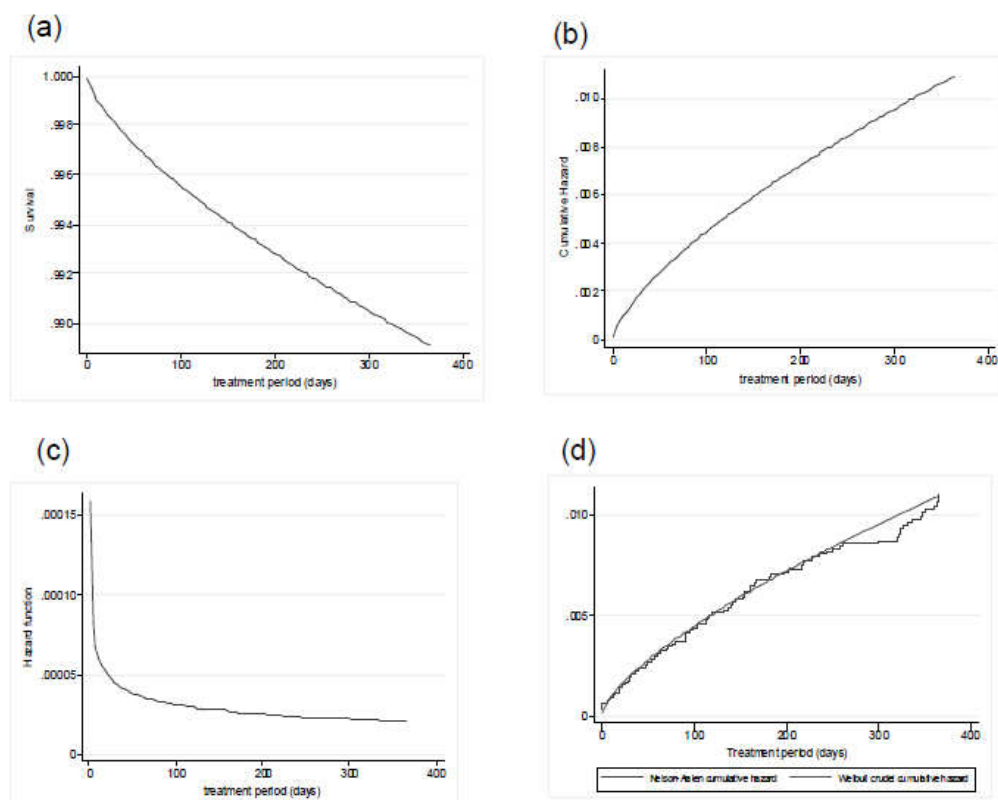


**Figure 14B. Weibull crude model of study primary outcome (e.g *Major bleed– urogenital site*) of interest (a) survival, (b) cumulative hazard, (c) hazard and (d) goodness of fit**

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**Figure 14C. Weibull crude model of study primary outcome (e.g *Major bleed– intracranial site*) of interest (a) survival, (b) cumulative hazard, (c) hazard and (d) goodness of fit**



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**Table 15A. Example of crude parametric model for study primary outcome**  
**(Major bleed– Gastrointestinal site) of interest, with AICC value**

Model Parameter	Weibull
Hazard	
	<i>Coefficient</i>
	<i>Std Error</i>
	<i>P-value</i>
	<i>95% CI</i>
Shape	
	<i>Coefficient</i>
	<i>Std.Error</i>
	<i>95%CI</i>
	<i>Log Likelihood</i>
AICC	

**Table 15B. Example of crude parametric model for study primary outcome**  
**(Major bleed– urogenital site) of interest, with AICC value**

Model Parameter	Weibull
Hazard	
	<i>Coefficient</i>
	<i>Std Error</i>
	<i>P-value</i>
	<i>95% CI</i>
Shape	
	<i>Coefficient</i>
	<i>Std.Error</i>
	<i>95%CI</i>
	<i>Log Likelihood</i>
AICC	

**Table 15C. Example of crude parametric model for study primary outcome**  
**(Major bleed– intracranial site) of interest, with AICC value**

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Model Parameter	Weibull
Hazard	
	<i>Coefficient</i>
	<i>Std Error</i>
	<i>P-value</i>
	<i>95% CI</i>
Shape	
	<i>Coefficient</i>
	<i>Std.Error</i>
	<i>95%CI</i>
	<i>Log Likelihood</i>
AICC	

### 9.6.4 Sensitivity analyses

The following sensitivity analyses will be performed:

- I. Since the primary analysis will be run only to include confirmed cases of incident GI, or urogenital or all intracranial major bleeding, the analysis will be replicated to examine the impact of exclusion of cases with missing event dates on estimate of cumulative incidence. Estimates of cumulative risk and rate will be presented in accordance with Tables 12 & 13.

### 9.6.5 Exploring predictors of risk of primary outcomes

The following also relates to primary objective (i to support further evaluation of baseline risk characteristics that may influence risk and time to onset of the individual primary events of interest (*Major bleed– Gastrointestinal, urogenital or all intracranial site*) within the rivaroxaban cohort. This analysis will be undertaken by performing a univariate case/non-case analysis to explore associations between patient characteristics (at index date) with each primary objective outcome of interest. Crude Odds ratios (OR) and 95% CI will be calculated and presented as shown in Table 16.

**Table 16A. Example table for baseline characteristics of patients with a**

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### Major bleed – gastrointestinal site (cases) and non-cases

Characteristic (%)	Cases		Non-cases		OR (+95%CI <sup>a</sup> ) [P-value]
	N	% cases where values reported	N	% non-cases where values reported	
<b>Gender</b>					
Male					ref
Female					
Missing					
<b>Age at index (years)</b>					
<18					ref
19-29					
30-39					
40-49					
50-59					
60-69					
70-79					
80+					
Missing					
Median (IQR)					Ranksum test p-value
Age >65 years					
Age 65-74 years					
Age 75+ years					
<b>Ethnicity</b>					
White					ref
African					
Caribbean					
Black-Other					
Indian					
Pakistani					
Bangladeshi					
Chinese					
Other					
Missing					
<b>Index of Multiple Deprivation Rank Decile</b>					
1 (most deprived)					ref
2					
3					
4					
5					
6					
7					
8					
9					
10 (least deprived)					
Missing					
Median (IQR)					Ranksum test p-value
<b>BMI (mg/kg<sup>2</sup>)</b>					
<18.5 (Below Normal)					ref
18.5-24.9 (Normal)					
25.0-29.9 (Overweight)					
30.0-39.9 (Obese)					
40.0+ (Morbidly Obese)					

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	<i>Missing</i>	
	<i>Median (IQR)</i>	
<b>Indication</b>		
	<i>AF</i>	ref
	<i>DVT/PE</i>	
	<i>Mixed (AF &amp; DVT/PE)</i>	
	<i>Other</i>	
<b>Prior/ at baseline history of:</b>		
	CVA <i>Yes</i>	
	<i>No</i>	ref
	DVT <i>Yes</i>	
	<i>No</i>	ref
Abnormal Liver Function	<i>Yes</i>	
	<i>No</i>	ref
Renal Disease	<i>Yes</i>	
	<i>No</i>	ref
Diabetes Mellitus	<i>Yes</i>	
	<i>No</i>	ref
Congestive Heart Failure	<i>Yes</i>	
	<i>No</i>	ref
Vascular disease	<i>Yes</i>	
	<i>No</i>	ref
Hypertension <sup>b</sup>	<i>Yes</i>	
	<i>No</i>	ref
Condition associated with predisposition to bleeding		ref
	<i>Yes</i>	
	<i>No</i>	
Excessive alcohol consumption/alcohol misuse		
	<i>Yes</i>	
	<i>No</i>	ref
Medications predisposing to bleeds	<i>Yes</i>	
	<i>No</i>	ref
Smoking	<i>Yes</i>	
	<i>No</i>	ref
Substance misuse prior	<i>Yes</i>	
	<i>No</i>	ref
<b>HAS-BLED score <sup>c</sup></b>		
	0 (low risk)	ref
	1-2 (moderate risk)	
	3 + (high risk)	
	<i>Missing</i>	
<b>CHADS<sub>2</sub>VASC Score score</b>		
	0 (low risk)	ref
	1 (moderate risk)	
	2 + (high risk)	
	<i>Missing</i>	
<b>Patient-specific prescribing reasons as reported by physician:</b>		
	Lifestyle choice <i>Yes</i>	
	<i>No</i>	ref
Non-adherence with prior anticoagulant	<i>Yes</i>	

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	<i>No</i>	ref
Side-effects with prior anticoagulant	<i>Yes</i>	
	<i>No</i>	ref
Patient preference	<i>Yes</i>	
	<i>No</i>	ref
Poor control	<i>Yes</i>	
	<i>No</i>	ref
Aberrant health behaviours	<i>Yes</i>	
	<i>No</i>	ref
<b>Influences on prescribing as reported by physician:</b>		
Clinical Judgement	<i>Yes</i>	
	<i>No</i>	ref
NICE recommendations	<i>Yes</i>	
	<i>No</i>	ref
Expert Guidelines	<i>Yes</i>	
	<i>No</i>	ref
Hospital Formulary	<i>Yes</i>	
	<i>No</i>	ref
Patient group Direction	<i>Yes</i>	
	<i>No</i>	ref
Ease of reversibility	<i>Yes</i>	
	<i>No</i>	ref

<sup>a</sup> 95%CI calculated using Binomial exact; <sup>b</sup> according to CHADS<sub>2</sub>VASC definition; <sup>c</sup> excluding labile INR

**Table 16B. Example table for baseline characteristics of patients with a Major bleed – urogenital site (cases) and non-cases**

Characteristic (%)	Cases		Non-cases		OR (+95%CI <sup>a</sup> ) [P-value]
	N	% cases where values reported	N	% non-cases where values reported	
<b>Gender</b>					
	Male				ref
	Female				
	Missing				
<b>Age at index (years)</b>					
	<18				ref
	19-29				
	30-39				
	40-49				
	50-59				
	60-69				
	70-79				
	80+				
	Missing				
	Median (IQR)				Ranksum test p-value
	Age >65 years				
	Age 65-74 years				
	Age 75+ years				
<b>Ethnicity</b>					
	White				ref



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African	
Caribbean	
Black-Other	
Indian	
Pakistani	
Bangladeshi	
Chinese	
Other	
<i>Missing</i>	
<b>Index of Multiple Deprivation Rank Decile</b>	
1 (most deprived)	ref
2	
3	
4	
5	
6	
7	
8	
9	
10 (least deprived)	
<i>Missing</i>	
<i>Median (IQR)</i>	Ranksum test p-value
<b>BMI (mg/kg<sup>2</sup>)</b>	
<18.5 (Below Normal)	ref
18.5-24.9 (Normal)	
25.0-29.9 (Overweight)	
30.0-39.9 (Obese)	
40.0+ (Morbidly Obese)	
<i>Missing</i>	
<i>Median (IQR)</i>	
<b>Indication</b>	
<i>AF</i>	ref
<i>DVT/PE</i>	
<i>Mixed (AF &amp; DVT/PE)</i>	
<i>Other</i>	
<b>Prior/ at baseline history of:</b>	
CVA <i>Yes</i>	
<i>No</i>	ref
DVT <i>Yes</i>	
<i>No</i>	ref
Abnormal Liver Function <i>Yes</i>	
<i>No</i>	ref
Renal Disease <i>Yes</i>	
<i>No</i>	ref
Diabetes Mellitus <i>Yes</i>	
<i>No</i>	ref
Congestive Heart Failure <i>Yes</i>	
<i>No</i>	ref
Vascular disease <i>Yes</i>	
<i>No</i>	ref
Hypertension <sup>b</sup> <i>Yes</i>	
<i>No</i>	ref
Condition associated with predisposition to bleeding	ref

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	<i>Yes</i>	
	<i>No</i>	
Excessive alcohol consumption/alcohol misuse	<i>Yes</i>	
	<i>No</i>	ref
Medications predisposing to bleeds	<i>Yes</i>	
	<i>No</i>	ref
Smoking	<i>Yes</i>	
	<i>No</i>	ref
Substance misuse prior	<i>Yes</i>	
	<i>No</i>	ref
<b>HAS-BLED score <sup>c</sup></b>		
	0 (low risk)	ref
	1-2 (moderate risk)	
	3 + (high risk)	
	<i>Missing</i>	
<b>CHADS<sub>2</sub>VASC Score score</b>		
	0 (low risk)	ref
	1 (moderate risk)	
	2 + (high risk)	
	<i>Missing</i>	
<b>Patient-specific prescribing reasons as reported by physician:</b>		
Lifestyle choice	<i>Yes</i>	
	<i>No</i>	ref
Non-adherence with prior anticoagulant	<i>Yes</i>	
	<i>No</i>	ref
Side-effects with prior anticoagulant	<i>Yes</i>	
	<i>No</i>	ref
Patient preference	<i>Yes</i>	
	<i>No</i>	ref
Poor control	<i>Yes</i>	
	<i>No</i>	ref
Aberrant health behaviours	<i>Yes</i>	
	<i>No</i>	ref
<b>Influences on prescribing as reported by physician:</b>		
Clinical Judgement	<i>Yes</i>	
	<i>No</i>	ref
NICE recommendations	<i>Yes</i>	
	<i>No</i>	ref
Expert Guidelines	<i>Yes</i>	
	<i>No</i>	ref
Hospital Formulary	<i>Yes</i>	
	<i>No</i>	ref
Patient group Direction	<i>Yes</i>	
	<i>No</i>	ref
Ease of reversibility	<i>Yes</i>	
	<i>No</i>	ref

<sup>a</sup> 95%CI calculated using Binomial exact; <sup>b</sup> according to CHADS<sub>2</sub>VASC definition; <sup>c</sup> excluding labile INR

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**Table 16C. Example table for baseline characteristics of patients with a Major bleed – intracranial site (cases) and non-cases**

Characteristic (%)	Cases		Non-cases		OR (+95%CI <sup>a</sup> ) [P-value]
	N	% cases where values reported	N	% non-cases where values reported	
<b>Gender</b>					
Male					ref
Female					
Missing					
<b>Age at index (years)</b>					
<18					ref
19-29					
30-39					
40-49					
50-59					
60-69					
70-79					
80+					
Missing					
Median (IQR)					Ranksum test p-value
Age >65 years					
Age 65-74 years					
Age 75+ years					
<b>Ethnicity</b>					
White					ref
African					
Caribbean					
Black-Other					
Indian					
Pakistani					
Bangladeshi					
Chinese					
Other					
Missing					
<b>Index of Multiple Deprivation Rank Decile</b>					
1 (most deprived)					ref
2					
3					
4					
5					
6					
7					
8					
9					
10 (least deprived)					
Missing					
Median (IQR)					Ranksum test p-value
<b>BMI (mg/kg<sup>2</sup>)</b>					
<18.5 (Below Normal)					ref
18.5-24.9 (Normal)					

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25.0-29.9 (Overweight)	
30.0-39.9 (Obese)	
40.0+ (Morbidly Obese)	
<i>Missing</i>	
<i>Median (IQR)</i>	
<b>Indication</b>	
<i>AF</i>	ref
<i>DVT/PE</i>	
<i>Mixed (AF &amp; DVT/PE)</i>	
<i>Other</i>	
<b>Prior/ at baseline history of:</b>	
CVA <i>Yes</i>	
<i>No</i>	ref
DVT <i>Yes</i>	
<i>No</i>	ref
Abnormal Liver Function <i>Yes</i>	
<i>No</i>	ref
Renal Disease <i>Yes</i>	
<i>No</i>	ref
Diabetes Mellitus <i>Yes</i>	
<i>No</i>	ref
Congestive Heart Failure <i>Yes</i>	
<i>No</i>	ref
Vascular disease <i>Yes</i>	
<i>No</i>	ref
Hypertension <sup>b</sup> <i>Yes</i>	
<i>No</i>	ref
Condition associated with predisposition to bleeding	ref
<i>Yes</i>	
<i>No</i>	
Excessive alcohol consumption/alcohol misuse	
<i>Yes</i>	
<i>No</i>	ref
Medications predisposing to bleeds <i>Yes</i>	
<i>No</i>	ref
Smoking <i>Yes</i>	
<i>No</i>	ref
Substance misuse prior <i>Yes</i>	
<i>No</i>	ref
<b>HAS-BLED score <sup>c</sup></b>	
0 (low risk)	ref
1-2 (moderate risk)	
3 + (high risk)	
<i>Missing</i>	
<b>CHADS<sub>2</sub>VASC Score score</b>	
0 (low risk)	ref
1 (moderate risk)	
2 + (high risk)	
<i>Missing</i>	
<b>Patient-specific prescribing reasons as reported by physician:</b>	
Lifestyle choice <i>Yes</i>	

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	<i>No</i>	ref
Non-adherence with prior anticoagulant	<i>Yes</i>	
	<i>No</i>	ref
Side-effects with prior anticoagulant	<i>Yes</i>	
	<i>No</i>	ref
Patient preference	<i>Yes</i>	
	<i>No</i>	ref
Poor control	<i>Yes</i>	
	<i>No</i>	ref
Aberrant health behaviours	<i>Yes</i>	
	<i>No</i>	ref
<b>Influences on prescribing as reported by physician:</b>		
Clinical Judgement	<i>Yes</i>	
	<i>No</i>	ref
NICE recommendations	<i>Yes</i>	
	<i>No</i>	ref
Expert Guidelines	<i>Yes</i>	
	<i>No</i>	ref
Hospital Formulary	<i>Yes</i>	
	<i>No</i>	ref
Patient group Direction	<i>Yes</i>	
	<i>No</i>	ref
Ease of reversibility	<i>Yes</i>	
	<i>No</i>	ref

<sup>a</sup> 95%CI calculated using Binomial exact; <sup>b</sup> according to CHADS<sub>2</sub>VASC definition; <sup>c</sup> excluding labile INR

For each covariate of interest identified as a potential predictor from the univariate case-non case analysis, stratum specific estimates of cumulative incidence (risk) of each of the first occurrence for each of the primary outcomes reported during treatment over the 12 week observation period in the 'as treated cohort' will be presented as shown in Table 17 (where number of cases >10 per stratum). In addition, stratum specific incidence rates for each of the primary outcomes will be also be reported as shown in Table 18, for the 'as treated' cohort.

**Table 17A. Example Number of patients reporting a new onset Major Bleed- gastrointestinal site and cumulative risk estimates (+95% CI) in rivaroxaban cohort, by covariate of interest**

Major Bleed – gastrointestinal site	All incident reports (on treatment + 2 days after stopping) n (%)	Cumulative risk (95% CI <sup>a</sup> )
Gender		
Male		
Female		
Missing		
Age at index (years)		

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<18
19-29
30-39
40-49
50-59
60-69
70-79
80+
<i>Missing</i>
HASBLED
<i>Etc...</i>

<sup>a</sup> 95%CI calculated using Binomial exact

**Table 17B. Example Number of patients reporting a new onset Major Bleed- urogenital site and cumulative risk estimates (+95% CI) in rivaroxaban cohort, by covariate of interest**

Major Bleed – gastrointestinal site	All incident reports (on treatment + 2 days after stopping) n (%)	Cumulative risk (95% CI <sup>a</sup> )
Gender		
Male		
Female		
<i>Missing</i>		
Age at index (years)		
<18		
19-29		
30-39		
40-49		
50-59		
60-69		
70-79		
80+		
<i>Missing</i>		
HASBLED		
<i>Etc...</i>		

<sup>a</sup> 95%CI calculated using Binomial exact

**Table 17C. Example Number of patients reporting a new onset Major Bleed- intracranial site and cumulative risk estimates (+95% CI) in rivaroxaban cohort, by covariate of interest**

Major Bleed – gastrointestinal site	All incident reports (on treatment + 2 days after stopping) n (%)	Cumulative risk (95% CI <sup>a</sup> )
Gender		
Male		
Female		
<i>Missing</i>		
Age at index (years)		

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<18
19-29
30-39
40-49
50-59
60-69
70-79
80+
<i>Missing</i>
HASBLED
<i>Etc...</i>

<sup>a</sup> 95%CI calculated using Binomial exact

**Table 18A. Incidence rates of new onset Major Bleeds- gastrointestinal site during the first 12 months after starting treatment with rivaroxaban (+95% CI)**

Major Bleeding	N	Total person-time (1000 weeks)	IR (95% CI <sup>a</sup> )
Gender			
	Male		
	Female		
	<i>Missing</i>		
Age at index (years)			
	<18		
	19-29		
	30-39		
	40-49		
	50-59		
	60-69		
	70-79		
	80+		
	<i>Missing</i>		
HASBLED			
	<i>Etc..</i>		

<sup>a</sup> 95%CI calculated using Poisson exact; rates will not be calculated where event count n<=10

**Table 18B. Incidence rates of new onset Major Bleeds- urogenital site during the first 12 months after starting treatment with rivaroxaban (+95% CI)**

Major Bleeding	N	Total person-time (1000 weeks)	IR (95% CI <sup>a</sup> )
Gender			
	Male		

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Female  
*Missing*  
 Age at index (years)  
     <18  
     19-29  
     30-39  
     40-49  
     50-59  
     60-69  
     70-79  
     80+  
     *Missing*  
 HASBLED  
     *Etc..*

---

<sup>a</sup> 95%CI calculated using Poisson exact; rates will not be calculated where event count  $n \leq 10$

**Table 18C. Incidence rates of new onset Major Bleeds- intracranial site during the first 12 months after starting treatment with rivaroxaban (+95% CI)**

Major Bleeding	N	Total person-time (1000 weeks)	IR (95% CI <sup>a</sup> )
Gender			
Male			
Female			
<i>Missing</i>			
Age at index (years)			
<18			
19-29			
30-39			
40-49			
50-59			
60-69			
70-79			
80+			
<i>Missing</i>			
HASBLED			
<i>Etc..</i>			

---

<sup>a</sup> 95%CI calculated using Poisson exact; rates will not be calculated where event count  $n \leq 10$

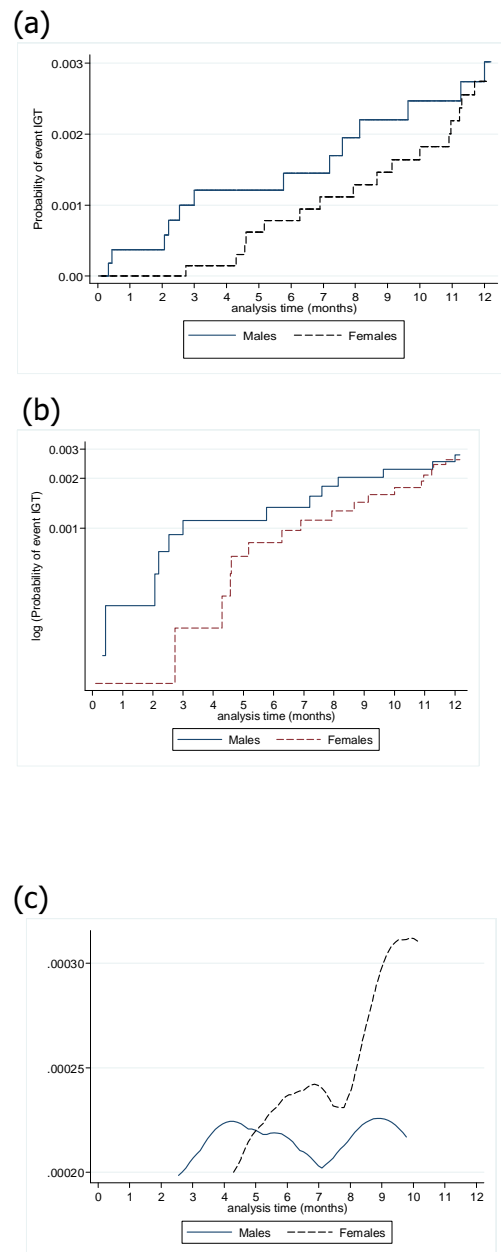
### 9.6.5.1 Stratified time to event analysis of primary outcomes

Stratum-specific estimates of hazard function according to those selected covariates that are considered significant from the univariate case-non case analysis will be presented as shown in Figure 15 (Log Rank test will also be provided), for the 'as treated' cohort.



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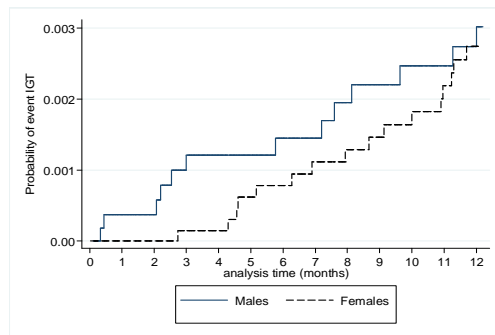
**Figure 15A. Example of time to event graph for primary study outcome (Major Bleed- gastrointestinal site) stratified by risk factor, presented as a) Nelson-Aalen cumulative hazard function (linear scale) b) Nelson-Aalen cumulative hazard function (log scale) , and c) smoothed hazard function**



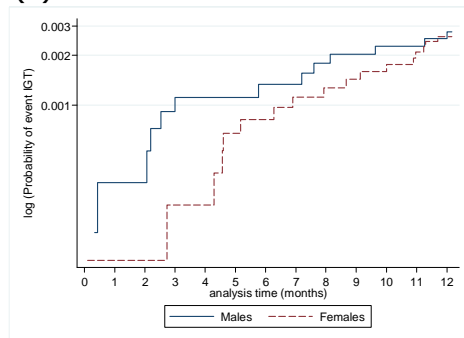
**Figure 15B. Example of time to event graph for primary study outcome (Major Bleed- urogenital site) stratified by risk factor, presented as a) Nelson-Aalen cumulative hazard function (linear scale) b) Nelson-Aalen cumulative hazard function (log scale) , and c) smoothed hazard function**

(a)

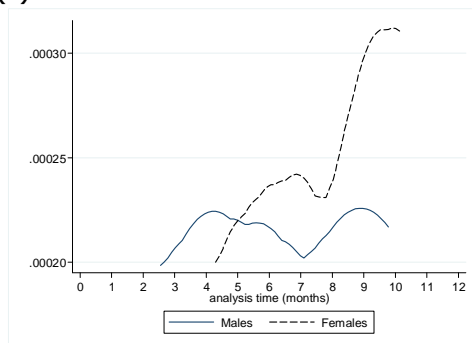
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(b)

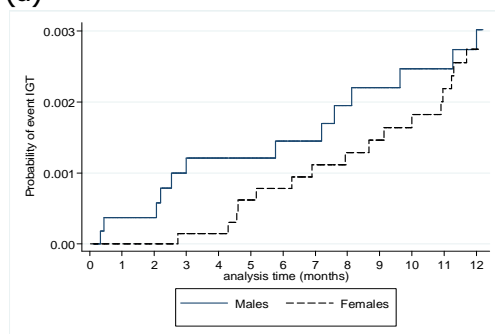


(c)



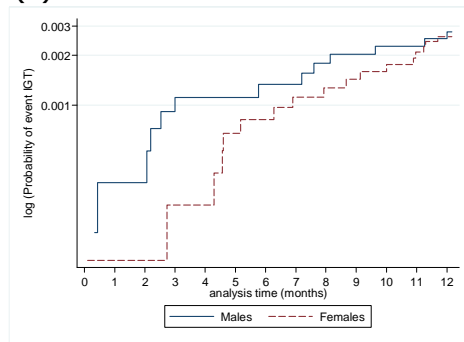
**Figure 15C. Example of time to event graph for primary study outcome (Major Bleed- intracranial site) stratified by risk factor, presented as a) Nelson-Aalen cumulative hazard function (linear scale) b) Nelson-Aalen cumulative hazard function (log scale) , and c) smoothed hazard function**

(a)

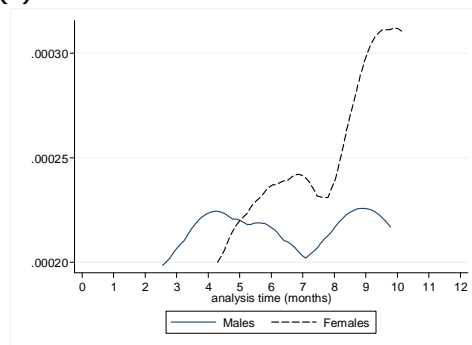


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(b)



(c)



### ***9.6.6 To quantify the incidence risk and rate of events reported in the 12 week observation period in both the rivaroxaban and contextual cohort and in patient subgroups of special interest.***

The following relates to secondary objectives (iv) regarding a) major bleeding outcomes as specified in the primary objective for the contextual warfarin cohort, b) a composite of all major bleeding specified in the primary objective for both rivaroxaban and warfarin, c) major bleeding within critical organ sites (excluding all intracranial) for both rivaroxaban and warfarin, d) a composite of all major and CRNM bleeds for rivaroxaban and warfarin, e) thromboembolism (recurrent and incident) for rivaroxaban and warfarin, and d) any other events reported in the 12 week observation period for rivaroxaban and warfarin.

#### **9.6.6.1 Estimating the cumulative incidence of major bleeding for the warfarin cohort**

In accordance with secondary objective (iv) regarding major bleeding outcomes as specified in the primary objective for the contextual warfarin cohort, the analysis

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specified in section 9.5.2 will apply to the warfarin cohort. Estimates of cumulative risk will be presented in as shown in Tables 19 .The cumulative incidence rate (hazard) in the 'as treated' cohort (per 1000 patient weeks exposed), with 95% Poisson exact Confidence Intervals (CI) will also be calculated and presented as shown in (Table 21).

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**Table 19. Number warfarin patients reporting new onset haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites and cumulative risk estimates (+95% CI <sup>a</sup>)**

Targeted Event	All incident reports (on treatment + 2 days after stopping) N (%)	Cumulative risk (95% CI)
ALL indications		
Major – Gastrointestinal site		
Major – Urogenital site		
Major – all Intracranial		
AF		
Major – Gastrointestinal site		
Major – Urogenital site		
Major – all Intracranial		
DVT/PE		
Major – Gastrointestinal site		
Major – Urogenital site		
Major – all Intracranial		
Mixed (AF & DVT/PE)		
Major – Gastrointestinal site		
Major – Urogenital site		
Major – all Intracranial		
Other		
Major – Gastrointestinal site		
Major – Urogenital site		
Major – all Intracranial		

<sup>a</sup> 95%CI calculated using Binomial exact; <sup>b</sup> at least one major haemorrhagic event

**Table 20. Cumulative Incidence rates (IR) of new onset haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (+95% CI <sup>a</sup>) in warfarin cohort**

Targeted Event	Number of events	Total person-time (1000 weeks)	IR (95% CI)
ALL indications			
Major – Gastrointestinal site			
Major – Urogenital site			
Major – all Intracranial			
AF			
Major – Gastrointestinal site			
Major – Urogenital site			
Major – all Intracranial			
DVT/PE			
Major – Gastrointestinal site			
Major – Urogenital site			

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	Major – all Intracranial
Mixed (AF & DVT/PE)	
	Major – Gastrointestinal site
	Major – Urogenital site
	Major – all Intracranial
Other	
	Major – Gastrointestinal site
	Major – Urogenital site
	Major – all Intracranial

---

<sup>a</sup> 95%CI calculated using Poisson exact; rates will not be calculated where event count  $n \leq 10$ ; <sup>b</sup> at least one major haemorrhagic event

### 9.6.6.2 Estimating the cumulative incidence of other major or non-major clinically relevant bleeding outcomes not specified in the primary objectives for the rivaroxaban and warfarin cohorts.

In accordance with secondary objectives (iv) regarding a) a composite of all major bleeding specified in the primary objective for both rivaroxaban and warfarin, b) major bleeding within critical organ sites (excluding all intracranial) for both rivaroxaban and warfarin, and c) a composite of all major and CRNM bleeds for rivaroxaban and warfarin, the analysis specified in section 9.6.2 will also apply. For completeness additional categories as specified in Box 2 of: CRNM, Major Bleed II will also be presented. Estimates of cumulative risk and rates will be presented in as shown in Tables 21 -24, respectively. Of note, patients may have experienced more than one type of bleeding (e.g. major and clinically relevant non major) within different sites, and so these counts are not mutually exclusive. As described previously, in cases where multiple bleeding episodes have been reported within the same site, the most serious episode of bleeding will be classified, and this bleeding classification with its associated event date will be included in incidence density analyses.

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**Table 21. Number of rivaroxaban patients reporting other new onset major or non-major clinically relevant bleeding outcomes and cumulative risk estimates (+95% CI <sup>a</sup>)**

Haemorrhage Event	All incident reports (on treatment + 2 days after stopping) N (%)	Cumulative risk (95% CI)
ALL indications		
Major bleed (Gastrointestinal, Urogenital, all Intracranial)		
Major bleed – all other within critical organ sites (excluding all intracranial)		
Clinically relevant non-major bleeds		
Major bleed (All) <sup>b</sup>		
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>		
AF		
Major bleed (Gastrointestinal, Urogenital, all Intracranial)		
Major bleed – all other within critical organ sites (excluding all intracranial)		
Clinically relevant non-major bleeds		
Major bleed (All) <sup>b</sup>		
Major bleed (all) and clinically relevant non-major bleeds <sup>c</sup>		
DVT/PE		
Major bleed (Gastrointestinal, Urogenital, all Intracranial)		
Major bleed – all other within critical organ sites (excluding all intracranial)		
Clinically relevant non-major bleeds		
Major bleed (All) <sup>b</sup>		
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>		
Mixed (AF & DVT/PE)		
Major bleed (Gastrointestinal, Urogenital, all Intracranial)		
Major bleed – all other within critical organ sites (excluding all intracranial)		
Clinically relevant non-major bleeds		
Major bleed (All) <sup>b</sup>		
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>		
Other		
Major bleed (Gastrointestinal, Urogenital, all Intracranial)		
Major bleed – all other within critical organ sites (excluding all intracranial)		
Clinically relevant non-major bleeds		
Major bleed (All) <sup>b</sup>		
Major bleed (All) and clinically relevant		

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non-major bleeds <sup>c</sup>

<sup>a</sup> 95%CI calculated using Binomial exact; <sup>b</sup> at least one major haemorrhagic event (irrespective of site);

<sup>c</sup> at least one of the following- major haemorrhagic event (irrespective of site) and/or a clinically relevant non-major bleed

**Table 22. Number of warfarin patients reporting other new onset major or non-major clinically relevant bleeding outcomes and cumulative risk estimates (+95% CI <sup>a</sup>)**

Haemorrhage Event	All incident reports (on treatment + 2 days after stopping) N (%)	Cumulative risk (95% CI)
ALL indications		
Major bleed (Gastrointestinal, Urogenital, all Intracranial)		
Major bleed – all other within critical organ sites (excluding all intracranial)		
Clinically relevant non-major bleeds		
Major bleed (All) <sup>b</sup>		
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>		
AF		
Major bleed (Gastrointestinal, Urogenital, all Intracranial)		
Major bleed – all other within critical organ sites (excluding all intracranial)		
Clinically relevant non-major bleeds		
Major bleed (All) <sup>b</sup>		
Major bleed (all) and clinically relevant non-major bleeds <sup>c</sup>		
DVT/PE		
Major bleed (Gastrointestinal, Urogenital, all Intracranial)		
Major bleed – all other within critical organ sites (excluding all intracranial)		
Clinically relevant non-major bleeds		
Major bleed (All) <sup>b</sup>		
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>		
Mixed (AF & DVT/PE)		
Major bleed (Gastrointestinal, Urogenital, all Intracranial)		
Major bleed – all other within critical organ sites (excluding all intracranial)		
Clinically relevant non-major bleeds		
Major bleed (All) <sup>b</sup>		
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>		
Other		
Major bleed (Gastrointestinal, Urogenital, all Intracranial)		
Major bleed – all other within critical organ sites (excluding all intracranial)		



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Clinically relevant non-major bleeds

Major bleed (All) <sup>b</sup>

Major bleed (All) and clinically relevant  
non-major bleeds <sup>c</sup>

<sup>a</sup> 95%CI calculated using Binomial exact; <sup>b</sup> at least one major haemorrhagic event (irrespective of site);

<sup>c</sup> at least one of the following- major haemorrhagic event (irrespective of site) and/or a clinically relevant non-major bleed

**Table 23. Cumulative Incidence rates (IR) of new onset major or non-major clinically relevant bleeding outcomes and cumulative risk estimates (+95% CI <sup>a</sup>) in the rivaroxaban cohort**

Haemorrhage Event	N	Total person-time (1000 weeks)	IR (95% CI)
ALL indications			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)			
Major bleed – all other within critical organ sites (excluding all intracranial)			
Clinically relevant non-major bleeds			
Major bleed (All) <sup>b</sup>			
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>			
AF			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)			
Major bleed – all other within critical organ sites (excluding all intracranial)			
Clinically relevant non-major bleeds			
Major bleed (All) <sup>b</sup>			
Major bleed (all) and clinically relevant non-major bleeds <sup>c</sup>			
DVT/PE			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)			
Major bleed – all other within critical organ sites (excluding all intracranial)			
Clinically relevant non-major bleeds			
Major bleed (All) <sup>b</sup>			
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>			
Mixed (AF & DVT/PE)			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)			
Major bleed – all other within critical organ sites (excluding all intracranial)			
Clinically relevant non-major bleeds			
Major bleed (All) <sup>b</sup>			
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>			
Other			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)			
Major bleed – all other within critical			

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organ sites (excluding all intracranial)  
 Clinically relevant non-major bleeds  
 Major bleed (All) <sup>b</sup>  
 Major bleed (All) and clinically relevant  
 non-major bleeds <sup>c</sup>

<sup>a</sup> 95%CI calculated using Poisson exact; <sup>b</sup> at least one major haemorrhagic event (irrespective of site);

<sup>c</sup> at least one of the following- major haemorrhagic event (irrespective of site) and/or a clinically relevant non-major bleed

**Table 24. Cumulative Incidence rates (IR) of new onset major or non-major clinically relevant bleeding outcomes and cumulative risk estimates (+95% CI <sup>a</sup>) in the warfarin cohort**

Haemorrhage Event	N	Total person-time (1000 weeks)	IR (95% CI)
ALL indications			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)			
Major bleed – all other within critical organ sites (excluding all intracranial)			
Clinically relevant non-major bleeds			
Major bleed (All) <sup>b</sup>			
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>			
AF			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)			
Major bleed – all other within critical organ sites (excluding all intracranial)			
Clinically relevant non-major bleeds			
Major bleed (All) <sup>b</sup>			
Major bleed (all) and clinically relevant non-major bleeds <sup>c</sup>			
DVT/PE			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)			
Major bleed – all other within critical organ sites (excluding all intracranial)			
Clinically relevant non-major bleeds			
Major bleed (All) <sup>b</sup>			
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>			
Mixed (AF & DVT/PE)			
Major bleed (Gastrointestinal, Urogenital, all Intracranial)			
Major bleed – all other within critical organ sites (excluding all intracranial)			
Clinically relevant non-major bleeds			
Major bleed (All) <sup>b</sup>			
Major bleed (All) and clinically relevant non-major bleeds <sup>c</sup>			
Other			
Major bleed (Gastrointestinal, Urogenital,			

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all Intracranial)  
Major bleed – all other within critical  
organ sites (excluding all intracranial)  
Clinically relevant non-major bleeds  
Major bleed (All) <sup>b</sup>  
Major bleed (All) and clinically relevant  
non-major bleeds <sup>c</sup>

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<sup>a</sup> 95%CI calculated using Poisson exact; <sup>b</sup> at least one major haemorrhagic event (irrespective of site); <sup>c</sup> at least one of the following- major haemorrhagic event (irrespective of site) and/or a clinically relevant non-major bleed

### 9.6.6.3 Incidence density calculations

Calculating and ranking crude Incidence Densities<sup>13</sup> - (ID) is one of a number of standard quantitative evaluations used in event monitoring methodology for descriptive analysis of multiple events as part of initial inspection of all event data for general safety surveillance. For purposes of this analysis, IDs will be calculated for all other events to be evaluated as part of the secondary objectives:

- Thromboembolic complications
- All other events (excluding bleeding outcomes) including severe hepatic failure and abnormal LFTs above 3x ULN.

The numerator will be the first reports of events reported as occurring after the index date and during treatment.<sup>14</sup> Data on events may be recorded in response to specific tick box questions presented according to MedDRA terminology on the CRF (12 week). Events may also be reported as free text in response to open questions; such data are coded using MedDRA. Where recurrent episodes or occurrences of events have been reported, only the first report (in chronological date order) in an individual patient is used. New onset events are defined as those where there is no evidence on the CRF to support a prior medical history of that same event.

The denominator used in calculating IDs will be in accordance with the 'as treated' cohort and it is assumed that the pattern of use is continuous. IDs are usually expressed as the number of first reports of an event per 1000 patient-weeks of treatment for the cohort for the period under evaluation. The number of patient-weeks of treatment may relate to a specific time period chronologically – e.g., the

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<sup>13</sup> It should be noted such quantification of rate does not only reflect the rate attributable to the drug but also reflects the background rate in the general population and rate attributable to other factors such as age or other disease risk factors

<sup>14</sup> Ideally, the exposure time would be censored at the time of the first event. However, since there are a large number of health outcomes of interest and the censoring would be different for each outcome, the denominator for the crude ID will not initially include censoring at the time of event. If an elevated crude ID is identified in this monitoring analysis, a subsequent analysis with appropriately censored denominator will be performed for that outcome.

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denominator for weeks 1-2 ( $D_{1-2}$ ) relates to the first 14 days of treatment for individual patients.

The calculations for an ID for a two week period are as follows:

$$ID_t = \frac{\text{Number of first reports of an event *during treatment* for period } t}{\text{Number of patient-weeks of treatment for period } t} \times 1000$$

$$\text{Thus, } ID_t = \frac{N_t}{D_t} \times 1000$$

where:  $N_t$  = Number of first reports of an event during treatment for period  $t$ ,

and  $D_t = \frac{\text{Number of patient-days of treatment for period } t}{14}$

For this analysis, IDs will be calculated for each two-week treatment period of the 12 week study period ( $ID_{w1-2}$ ,  $w3-4$  etc) and all twelve weeks combined in the observation period ( $ID_A$ ), as shown in Tables 28 and 29.

Summary tabulations of counts of reported events, risk and event rates (IDs), for the pooled cohort (irrespective of indication). Stratum specific estimate for each indication may be calculated, only in where event counts  $\geq 10$  (AF, DVT/PE, Mixed (AF & DVT/PE) and Other).

**Table 25. Denominators for rivaroxaban cohort**

Time Period	Weeks 1&2	Weeks 3&4	Weeks 5&6	Weeks 7&8	Weeks 9&10	Weeks 11&12	All Weeks
All Denominator ( $D_i$ )	$rD_1$	$rD_2$	$rD_3$	$rD_4$	$rD_5$	$rD_6$	$rD_A$
AF Denominator ( $D_{AFi}$ )	$rD_{AF1}$	$rD_{AF2}$	$rD_{AF3}$	$rD_{AF4}$	$rD_{AF5}$	$rD_{AF6}$	$rD_{AFA}$
DVT/PE Denominator ( $D_{DVT/PEi}$ )	$rD_{DVT/PE1}$	$rD_{DVT/PE2}$	$rD_{DVT/PE3}$	$rD_{DVT/PE4}$	$rD_{DVT/PE5}$	$rD_{DVT/PE6}$	$rD_{DVT/PEA}$
DVT/PE Denominator ( $D_{MIXED}$ )	$rD_{MIXED1}$	$rD_{MIXED2}$	$rD_{MIXED3}$	$rD_{MIXED4}$	$rD_{MIXED5}$	$rD_{MIXED6}$	$rD_{MIXEDA}$
Other Denominator ( $D_{OTHERi}$ )	$rD_{OTHER1}$	$rD_{OTHER2}$	$rD_{OTHER3}$	$rD_{OTHER4}$	$rD_{OTHER5}$	$rD_{OTHER6}$	$rD_{OTHERA}$

$D_i$  – The amount of patient-time at risk at the beginning of time period  $i$

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**Table 26. Denominators for warfarin cohort**

Time Period	Weeks 1&2	Weeks 3&4	Weeks 5&6	Weeks 7&8	Weeks 9&10	Weeks 11&12	All Weeks
All Denominator (D <sub>i</sub> )	wD <sub>1</sub>	wD <sub>2</sub>	wD <sub>3</sub>	wD <sub>4</sub>	wD <sub>5</sub>	wD <sub>6</sub>	wD <sub>A</sub>
AF Denominator (D <sub>AFi</sub> )	wD <sub>AF1</sub>	wD <sub>AF2</sub>	wD <sub>AF3</sub>	wD <sub>AF4</sub>	wD <sub>AF5</sub>	wD <sub>AF6</sub>	wD <sub>AFA</sub>
DVT/PE Denominator (DVT/PE <sub>i</sub> )	wD <sub>DVT/PE1</sub>	wD <sub>DVT/PE2</sub>	wD <sub>DVT/PE3</sub>	wD <sub>DVT/PE4</sub>	wD <sub>DVT/PE5</sub>	wD <sub>DVT/PE6</sub>	wD <sub>DVT/PEA</sub>
DVT/PE Denominator (MIXED)	wD <sub>MIXED1</sub>	wD <sub>MIXED2</sub>	wD <sub>MIXED3</sub>	wD <sub>MIXED4</sub>	wD <sub>MIXED5</sub>	wD <sub>MIXED6</sub>	wD <sub>MIXEDA</sub>
Other Denominator (D <sub>OTHERi</sub> )	wD <sub>OTHER1</sub>	wD <sub>OTHER2</sub>	wD <sub>OTHER3</sub>	wD <sub>OTHER4</sub>	wD <sub>OTHER5</sub>	wD <sub>OTHER6</sub>	wD <sub>OTHERA</sub>

D<sub>i</sub> – The amount of patient-time at risk at the beginning of time period i

Targeted events reported incorrectly elsewhere as free text general events and/or reasons for stopping will be included in event counts for calculation of IDs. All targeted events will be adjudicated by expert review (using all available information from SCEM questionnaires, follow-up and any additional documentation). During adjudication where such information reveals that the event did not occur (misreported, that patient will be excluded as a case from the analysis, but contribute to the 'as assigned' cohort denominator.

As IDs for each treatment cohort may sometimes mask significant signals in specific risk groups, stratum specific IDs will be calculated for those sub-groups defined by indication group and b) patients characteristics identified as special populations (section 9.4.1) where sufficient events (>10) per stratum apply.

**Table 27. Targeted events <sup>a</sup>**

Data Description	Source	Result Reference
Number of targeted events for each two week period and Incidence Densities in rivaroxaban cohort	12-week Questionnaire (Q15), and follow-up questionnaires;	Table 27A
Number of targeted events for each two week period and Incidence Densities in warfarin cohort	12-week Questionnaire (Q15), and follow-up questionnaires;	Table 27B

<sup>a</sup> Additional tables using same format will be presented for subsets defined by indication group (tables not shown)

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**Table 27A. Incident Densities of targeted events<sup>a</sup> (excluding haemorrhage events) in rivaroxaban cohort, by two-week period and for total 12 week period**

Event <sup>b</sup>	N	N	N	N	N	N	ID	ID	ID	ID	ID	ID	N <sub>A</sub>	ID <sub>A</sub>
	w1&2	w3&4	w5&6	w7&8	w9&10	w11&12	w1&2	w3&4	w5&6	w7&8	w9&10	w11&12		
Cardiovascular Disorders:														
Cerebrovascular accident														
Deep Vein Thrombosis														
Pulmonary embolism														
Etc...														
Other Conditions:														
Liver Disorder														
Abnormal liver function tests														
Renal Failure														
Etc...														
Other events:														
Hospitalisation														

N=Number of Events, ID=Incidence Density; <sup>a</sup> Targeted events misreported as –free text general events and/or reasons for stopping will be included in event counts for calculation of IDs; <sup>b</sup> Counts not mutually exclusive as patients may have experienced more than one type of event

**Table 27B. Incident Densities of targeted events<sup>a</sup> (excluding haemorrhage events) in warfarin cohort, by two-week period and for total 12 week period**

Event <sup>b</sup>	N	N	N	N	N	N	ID	ID	ID	ID	ID	ID	N <sub>A</sub>	ID <sub>A</sub>
	w1&2	w3&4	w5&6	w7&8	w9&10	w11&12	w1&2	w3&4	w5&6	w7&8	w9&10	w11&12		
Cardiovascular Disorders:														
Cerebrovascular accident														
Deep Vein Thrombosis														
Pulmonary embolism														
Etc...														
Other Conditions:														
Liver Disorder														
Abnormal liver function tests														
Renal Failure														
Etc...														
Other events:														
Hospitalisation														

N=Number of Events, ID=Incidence Density; <sup>a</sup> Targeted events misreported as –free text general events and/or reasons for stopping will be included in event counts for calculation of IDs; <sup>b</sup> Counts not mutually exclusive as patients may have experienced more than one type of event.

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### 9.7 Quantitative case series summary for selected events requiring further evaluation

#### ***9.7.1 To describe the clinical features and management of major bleeding reported in the first 12 weeks after treatment initiation in the cohort exposed to rivaroxaban***

The following supports the exploratory objective (ii), based on the events of major bleeding for the rivaroxaban cohort. A qualitative assessment of these cases will include evaluation of patient demographic characteristics, treatment details, the detection and clinical features and management of events of interest, resolution, relevant investigations prior to and during therapy, the patient's relevant medical history and concurrent medication and any sequelae. Data will be derived from the SCEM and follow up questionnaires sent to gather other relevant essential information for construction of a case-series summary descriptive table for each indication group (as shown in Table 28A). The cases series format will involve aggregate summaries for these events (e.g. mean, standard deviation, median, range, and percentile values or frequencies) where the number of case  $\geq 5$ . Should the number of cases be fewer than 5, then ranges will be given (e.g. age 40-50 years) to prevent identification of individual patients.

**Table 28.**

<b>Data description</b>	<b>Source</b>	<b>Result reference</b>
Quantitative case series summary of major bleeding reported in the rivaroxaban cohort	Coded data and follow-up questionnaires. <i>NB For analysis purposes, dose at event will be coded according to last known dose reported prior to/at event from 12 week questionnaire and follow-up questionnaire if available.</i>	Table 28A

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**Table 28A. Characteristics\* and management\* of rivaroxaban patients for whom major bleeding was reported, by indication.**

Indication	AF					DVT/PE					Mixed (AF & DVT/PE)					Other				
	GI	Uro- geni- tal	Intra- cran- ial	Other critical organ <sup>h</sup>	Other non- critical organ <sup>i</sup>	GI	Uro- geni- tal	Intracr- anial	Other critical organ <sup>h</sup>	Other non- critical organ <sup>i</sup>	GI	Uro- geni- tal	Intracr- anial	Other critical organ <sup>h</sup>	Other non- critical organ <sup>i</sup>	GI	Uro- geni- tal	Intracr- anial	Other critical organ <sup>h</sup>	Other non- critical organ <sup>i</sup>
<b>Major Bleeding</b>																				
Events during observation (N)																				
Events during treatment (n/N, %)																				
Sex <sup>a</sup>																				
Age <sup>a</sup> (years)																				
Median (IQR)																				
Dose at event (mg/day)																				
Exposure duration (days) <sup>b</sup>																				
Median (IQR)																				
Event as Reason for stopping <sup>c</sup>																				
(n/n; %)																				
Event had Fatal outcome																				
(n/n; %)																				
Event reported with decreased haemoglobin (>2g/dL)																				
(n/n; %)																				
Event required a transfusion of >2 units of packed red cells or whole blood																				
(n/n; %)																				
Event required reversal of anticoagulation therapy for bleeding																				
(n/n; %)																				
Prior history (or present at start of treatment) of bleed within same site																				
(n/n; %)																				
Event was related to other pre-existing																				



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conditions which were risk factors for  
bleeding <sup>d</sup>

(n/n; %)

Concomitant meds prescribed at event

(n/n; %)

Concomitant meds predisposing to bleeds  
prescribed at event <sup>e</sup>

(n/n; %)

Patient HAS BLED Score <sup>f</sup>

0

1-2

3+

---

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender); <sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for bleeding: thrombocytopenia, excessive alcohol consumption or abuse, prior history of conditions associated with increased risk of bleeding, injury/trauma, percutaneous coronary intervention, other recent major surgery, malignancy, pregnancy <sup>e</sup> concomitant medication at event- anticoagulants, antiplatelets, NSAIDs; <sup>f</sup> HASBLED risk of major bleeding score (0=low risk, 1-2=moderate risk, 3 + =high risk ); <sup>g</sup> CHA<sub>2</sub>DS<sub>2</sub>VASc risk of stroke score (0=low risk, 1=moderate risk, 2 +=high risk ); <sup>h</sup> Other critical organ: major bleed in critical organ sites (excluding intracranial); <sup>i</sup> Other non-critical organ: major bleed in non-critical organ site . isch: Ischaemic CVA; haem: haemorrhagic CVA

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### ***9.7.2 To describe clinical features and management of cases of overdose, VTE events indicating failure of anticoagulation and management of haemostasis in patients undertaking surgery (elective or urgent) reported in the first 12 weeks after treatment initiation in the cohort exposed to rivaroxaban***

The following relates to exploratory objective (ii). The events of CVA and injury/trauma will also be summarised. Data will be derived from the index, 12-week and supplementary questionnaires (if relevant information was not available on the study questionnaires); which are summarised in a case series matrix template. For events where stratum specific count >5, range of values will be reported (individual counts will not be summarised).

**Table 29. Case series for events of interest**

<b>Data description</b>	<b>Source</b>	<b>Result reference</b>
Quantitative case series summary of management of haemostasis in pts with overdose associated with bleeding	Coded data and follow-up questionnaires.	Tables 29A
Quantitative case series summary of management of haemostasis in patients undertaking surgery (elective or urgent)	Coded data and follow-up questionnaires.	Tables 29B
Quantitative case series summary of management of haemostasis in patients with accidental trauma of clinical medical importance which required acute medical/surgical treatment (with or without) hospitalisation	Coded data and follow-up questionnaires.	Tables 29C
Quantitative case series summary of (DVT/PE indicating failure of anticoagulation	Coded data and follow-up questionnaires.	Tables 29D
Quantitative case series summary of CVA indicating failure of anticoagulation	Coded data and follow-up questionnaires.	Tables 29E

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**Table 29A. Characteristics\* and management\* of haemostasis in rivaroxaban patients for whom overdose (reported as event or dose <50mg/day) was reported in addition to a bleed, by type of bleed and indication group**

Indication	AF				DVT/PE				Mixed (AF & DVT/PE)				Other			
	All Major	CRNM	Other non-major	UC	All Major	CRNM	Other non-major	UC	All Major	CRNM	Other non-major	UC	All Major	CRNM	Other non-major	UC
Bleeding Type (Incident event)																
Events during observation (N)																
Events during treatment (n/N, %)																
Sex <sup>a</sup>	(n/n; %)															
	Male															
	Female															
Age <sup>a</sup> (years)	Median (IQR)															
Dose at event (mg/day)																
	0-10															
	>10-20															
	>20															
Exposure duration (days) <sup>b</sup>	Median (IQR)															
Event as Reason for stopping <sup>c</sup>	(n/n; %)															
Event had Fatal outcome	(n/n; %)															
Event reported with decreased haemoglobin (>2g/dL)	(n/n; %)															
Event required a transfusion of >2 units of packed red cells or whole blood	(n/n; %)															
Event required reversal of anticoagulation therapy for bleeding	(n/n; %)															
Prior history (or present at start of treatment) of bleed within same site	(n/n; %)															
Event was related to other pre-existing																

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conditions which were risk factors for  
bleeding <sup>d</sup>

(n/n; %)

Concomitant meds prescribed at event

(n/n; %)

Concomitant meds predisposing to bleeds  
prescribed at event <sup>e</sup>

(n/n; %)

Other clinical sequelae

(n/n; %)

Patient HAS BLED Score <sup>f</sup>

0

1-2

3+

---

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender); <sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for bleeding: thrombocytopenia, excessive alcohol consumption or abuse, prior history conditions associated with increased risk of bleeding, injury/trauma, percutaneous coronary intervention, other recent major surgery, malignancy, pregnancy <sup>e</sup> concomitant medication at event- anticoagulants, antiplatelets, NSAIDs; <sup>f</sup> HASBLED risk of major bleeding score (0=low risk, 1-2=moderate risk, 3 + =high risk ); UC= unclassifiable

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**Table 29B. Characteristics\* and management\* of haemostasis in rivaroxaban patients peri/post surgery (elective or acute), by type of bleed and indication**

Indication	AF				DVT/PE				Mixed (AF & DVT/PE)				Other			
Bleeding Type (Incident event)	All Major	CRNM	Other non-major	UC	All Major	CRNM	Other non-major	UC	All Major	CRNM	Other non-major	UC	All Major	CRNM	Other non-major	UC
Events during observation (N)																
Events during treatment (n/N, %)																
Sex <sup>a</sup>	(n/n; %)															
	Male															
	Female															
Age <sup>a</sup> (years)	Median (IQR)															
Dose at event (mg/day)																
	0-10															
	>10-20															
	>20															
Exposure duration (days) <sup>b</sup>	Median (IQR)															
Event as Reason for stopping <sup>c</sup>	(n/n; %)															
Event had Fatal outcome	(n/n; %)															
Event reported with decreased haemoglobin (>2g/dL)	(n/n; %)															
Event required a transfusion of >2 units of packed red cells or whole blood	(n/n; %)															
Event required reversal of anticoagulation therapy for bleeding	(n/n; %)															
Prior history (or present at start of treatment) of bleed within same site	(n/n; %)															
Event was related to other pre-existing																

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conditions which were risk factors for  
bleeding <sup>d</sup>

(n/n; %)

Concomitant meds prescribed at event

(n/n; %)

Concomitant meds predisposing to bleeds  
prescribed at event <sup>e</sup>

(n/n; %)

Other clinical sequelae

(n/n; %)

Patient HAS BLED Score <sup>f</sup>

0

1-2

3+

---

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender); <sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for bleeding: thrombocytopenia, excessive alcohol consumption or abuse, prior history of bleeding, predisposition to bleeding, injury/trauma, percutaneous coronary intervention, other recent major surgery, malignancy, pregnancy <sup>e</sup> concomitant medication at event- anticoagulants, antiplatelets, NSAIDs; <sup>f</sup> HASBLED risk of major bleeding score (0=low risk, 1-2=moderate risk, 3 + =high risk ); UC= unclassifiable

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**Table 29C. Characteristics\* and management\* of haemostasis in rivaroxaban with injury/trauma requiring acute medical/surgical treatment (with or without) hospitalisation patients, by type of bleed and indication**

Indication	AF				DVT/PE				Mixed (AF & DVT/PE)				Other			
Bleeding Type (Incident event)	All Major	CRNM	Other non-major	UC	All Major	CRNM	Other non-major	UC	All Major	CRNM	Other non-major	UC	All Major	CRNM	Other non-major	UC
Events during observation (N)																
Events during treatment (n/N, %)																
Sex <sup>a</sup>	(n/n; %)															
	Male															
	Female															
Age <sup>a</sup> (years)	Median (IQR)															
Dose at event (mg/day)																
	0-10															
	>10-20															
	>20															
Exposure duration (days) <sup>b</sup>	Median (IQR)															
Event as Reason for stopping <sup>c</sup>	(n/n; %)															
Event had Fatal outcome	(n/n; %)															
Event reported with decreased haemoglobin (>2g/dL)	(n/n; %)															
Event required a transfusion of >2 units of packed red cells or whole blood	(n/n; %)															
Event required reversal of anticoagulation therapy for bleeding	(n/n; %)															
Prior history (or present at start of treatment) of bleed within same site	(n/n; %)															
Event was related to other pre-existing conditions which were risk factors for																

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bleeding <sup>d</sup>	(n/n; %)
Concomitant meds prescribed at event	(n/n; %)
Concomitant meds predisposing to bleeds prescribed at event <sup>e</sup>	(n/n; %)
Other clinical sequelae	(n/n; %)
Patient HAS BLEED Score <sup>f</sup>	
	0
	1-2
	3+

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender);<sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for bleeding: thrombocytopenia, excessive alcohol consumption or abuse, prior history of bleeding, predisposition to bleeding, injury/trauma, percutaneous coronary intervention, other recent major surgery, malignancy, pregnancy <sup>e</sup> concomitant medication at event- anticoagulants, antiplatelets, NSAIDs; <sup>f</sup> HASBLED risk of major bleeding score (0=low risk, 1-2=moderate risk, 3 + =high risk ); UC= unclassifiable



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**Table 29D. Characteristics\* and management\* of rivaroxaban patients for whom VTE (DVT/PE) was reported, indication.**

Indication	AF			DVT/PE			Mixed (AF & DVT/PE)			Other		
	All f(DVT /PE)	PE	DVT	All f(DVT /PE)	PE	DVT	All f(DVT /PE)	PE	DVT	All f(DVT /PE)	PE	DVT
Events during observation (N)												
Events during treatment (n/N, %)												
Sex <sup>a</sup> (n/n; %)												
Age <sup>a</sup> (years) (IQR)												
Dose at event (mg/day)												
Exposure duration (days) <sup>b</sup> Median (IQR)												
Event as Reason for stopping <sup>c</sup> (n/n; %)												
Event had Fatal outcome (n/n; %)												
Patient had prior history (or present at start of treatment) of DVT and/or PE (n/n; %)												
Event was related to other pre- existing conditions which were risk factors for VTE <sup>d</sup> (n/n; %)												

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%)

Concomitant meds prescribed at event<sup>e</sup>

(n/n;

%)

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender);<sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for VTE: cardiac disorders (myocardial infarction, congestive heart failure, peripheral arterial disease, cardiac arrhythmias), immobility, surgery requiring general anaesthesia, malignancy, oestrogen containing product, travel for a prolonged period of time, trauma, other recent major surgery, thrombophilia disorder, other coagulation disorder, pregnancy; <sup>e</sup> concomitant medication at event (tbc); <sup>f</sup> first incident event;

**Table 29E. Characteristics\* and management\* of rivaroxaban patients for whom CVA was reported, by indication.**

Indication		AF				DVT/PE				Mixed (AF & DVT/PE)				Other			
CVA type		All <sup>f</sup>	Isch	Heam	UC	All <sup>f</sup>	Isch	Heam	UC	All <sup>f</sup>	Isch	Heam	UC	All <sup>f</sup>	Isch	Heam	UC
Events during observation (N)																	
Events during treatment (n/N, %)																	
Sex <sup>a</sup>	(n/n; %)																
	Male																
	Female																
Age <sup>a</sup> (years)	Median (IQR)																
Dose at event (mg/day)																	
	0-10																
	>10-20																
	>20																
Exposure duration (days) <sup>b</sup>																	
	Median (IQR)																
Event as Reason for stopping <sup>c</sup>																	
	(n/n; %)																
Event had Fatal outcome																	
	(n/n; %)																
Patient had prior history (or present at start of treatment) of stroke																	
Event was related to other pre-existing conditions which were risk factors for stroke																	
<sup>d</sup>																	

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	(n/n; %)
Concomitant medications prescribed at event	
	(n/n; %)
Other clinical sequelae (incl. moderate-severe disability)	
	(n/n; %)
Patient CHA <sub>2</sub> DS <sub>2</sub> VASc Score <sup>e</sup>	
	0
	1
	2

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; <sup>a</sup> demographic characteristics (age, gender);<sup>b</sup> derived from time to onset analysis; <sup>c</sup> derived from information on treatment cessation and targeted event; <sup>d</sup> other risk factors for stroke: tbc; <sup>e</sup> CHA<sub>2</sub>DS<sub>2</sub>VASc risk of stroke score (0=low risk, 1=moderate risk, 2 +=high risk ); <sup>f</sup> first incident event; isch: Ischaemic CVA; haem: haemorrhagic CVA; UC: unclassifiable

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### ***9.7.3 Aggregate Assessment of Drug-Relatedness of Selected Events in the cohort exposed to rivaroxaban***

The following relates to secondary objective (iv). Data will be derived from the index, 12-week and supplementary questionnaires (if relevant information was not available on the study questionnaires); which are summarised in a case series matrix template. For events where stratum specific count >5, range of values will be reported (individual counts will not be summarised).

As per protocol, selected targeted events of interest will undergo further evaluation at the aggregate level, including assessment of drug relatedness where appropriate, to explore temporal relationship with starting treatment and clinical characteristics of the event, patient characteristics and presence of concomitant risk factors which may confound the association, de/rechallenge (where reported), management and sequelae (where reported).

Data will have been derived from the index, 12-week and supplementary questionnaires (if relevant information was not available on the study questionnaires); which are summarised in a case series matrix template – the basic structure shown in Table 30. This assessment will apply to the following events:

(tbc from RAIDR)

For events where stratum specific count >5, range of values will be reported (individual counts will not be summarised).

**Table 30. Case series relatedness assessments of selected events reported for rivaroxaban patients for further evaluation**

Event term		
<b>Event details</b>		
Events during observation (N)		
Events during treatment (n/N, %)		
Event had Fatal outcome (n/n; %)		
<b>Patient demographics</b>		
Sex <sup>a</sup>	Female	(n/n; %)
	Male	(n/n; %)
Age <sup>a</sup> (years) (IQR)	Median	

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Indication

*AF (n/n; %)*  
*DVT/PE (n/n; %)*  
*Mixed (AF & DVT/PE) (n/n; %)*  
*Other (n/n; %)*

### Relatedness Assessment criteria <sup>b</sup>

Recognised Association

*(n/n; %)*

Pharmacological plausibility

*(n/n; %)*

Temporality

*(n/n; %)*

*Exposure duration (days) <sup>c</sup>*

*Median (IQR)*

Dose relationship

*(n/n; %)*

*Dose at event (mg/day)*

*0-10 (n/n; %)*

*>10-20 (n/n; %)*

*>20 (n/n; %)*

Prior history same event and or present on starting

*(n/n; %)*

Risk factors

*Other pre-existing conditions<sup>d</sup> (n/n; %)*

*Concomitant meds<sup>e</sup> (n/n; %)*

Positive Dechallenge (Reason for stopping) <sup>f</sup>

*(n/n; %)*

Positive rechallenge

*(n/n; %)*

### Drug Relatedness Assessment decision <sup>g</sup>

Probable

*(n/n; %)*

Possible

*(n/n; %)*

Unlikely

*(n/n; %)*

Unassessable

*(n/n; %)*

---

\*information available from SCEM and supplementary questionnaires; IQR: Interquartile range; a demographic characteristics (age, gender);b Austin-Bradford Hill criteria; c derived from time to onset analysis; de co-morbidities associated with event of interest; e concomitant medication associated with event of interest; f derived from information on treatment cessation; g Shakir S. Causality and correlation in pharmacovigilance. In: Talbot J, Waller P, editors. Stephens' Detection of New Adverse Drug Reactions. 5 ed. Chichester: John Wiley & Sons Ltd.; 2004. p. 329-43

## 9.8 Cohort exposure, dose patterns over time and treatment cessation

In accordance with secondary objective (iii), this section will describe details of changes in the treatment plan during the 12 week observation period. Empirical and fitted dose trajectories will be presented to describe dose patterns over time. Reasons for dose changes

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will also be summarised. Information concerning changes of treatment and/or stopping treatment, i.e. frequency of treatment cessation will be summarised. Figures 17 and 18 are survival curves for the time to treatment cessation (for rivaroxaban and warfarin 'as treated' cohort by indication, respectively), which will be produced via the Kaplan-Meier method. (5) within the first 12 weeks post index date (see section 9.2.1.3) For such analyses the outcome of interest is the first report of stopping treatment.

**Table 31. Cohort exposure and dose patterns over time**

<b>Data description</b>	<b>Source</b>	<b>Result reference</b>
Summary statistics for treatment status and dose at 12 week: count and percent, mean, standard deviation, median, minimum & maximum	Index questionnaire (Q3) and 12-Week Questionnaire (Q9, Q10 & Q11). <i>End of period dose will be based on last known dose reported during the 12 week observation period</i>	Table 31A; Figure 16
Reasons for dose increase/decrease- count and percent of patients where dose change reported and dose specified (BUT NOT STOPPED)	12-Week Questionnaire (Q10 & Q11)	Tables 31B & C
Posology on stopping; dose, frequency and total daily dose - count and percent of patients who stopped and dose specified	12-Week Questionnaire (Q9 & Q11) includes patients who switched 12-week Questionnaire (Q9.1 & 11.1)	Table 31D
Reason for stopping if stopped: count and percent of RFS and percent patients who stopped, ranked by frequency, by indication	12-Week Questionnaire (Q9 & Q11) includes patients who switched 12-week Questionnaire (Q9.1 & 11.1)	Table 31E
Other anticoagulant prescribed after stopping ; count and percent	12-week Questionnaire (Q9.1 & 11.1). ATC code to be applied to free text reports	Table 31F – I
Person-time to treatment cessation (up to 12 weeks)	Index questionnaire (Q3) and 12-Week questionnaire (Qs 5, 8, 9 & 11)	Tables 31J & K; Figures 17 & 18

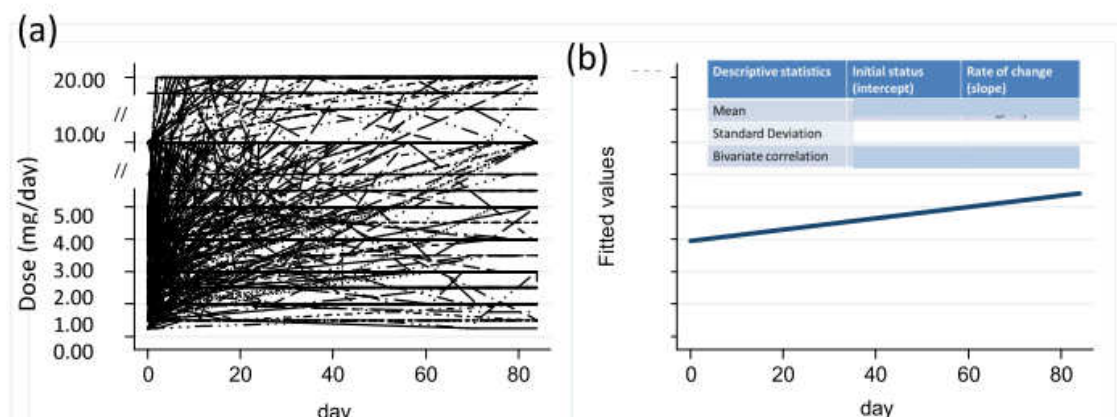
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**Table 31A. Posology (total daily dose) at end of 12 week observation period by indication and treatment group**

End of observation total daily dose		Rivaroxaban	Warfarin
		N%	N%
Indication:			
AF			
		<2.5	
		>=2.5, <5	
		>=5.0, <10	
		>=10, <20	
		>=20, <30	
		>=30	
Number patients with Missing information			
Median (IQR)			
Mean (SD)			
DVT/PE			
		<2.5	
		>=2.5, <5	
		>=5.0, <10	
		>=10, <20	
		>=20, <30	
		>=30	
Number patients with Missing information			
Median (IQR)			
Mean (SD)			
Mixed (AF & DVT/PE)			
		<2.5	
		>=2.5, <5	
		>=5.0, <10	
		>=10, <20	
		>=20, <30	
		>=30	
Number patients with Missing information			
Median (IQR)			
Mean (SD)			
Other			
		<2.5	
		>=2.5, <5	
		>=5.0, <10	
		>=10, <20	
		>=20, <30	
		>=30	
Number patients with Missing information			
Median (IQR)			
Mean (SD)			

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**Figure 16. Example empirical and OLS fitted dose trajectories of 12 week observation period, by indication and treatment group**



**Table 31B. Reasons for first reported dose increase where treatment has not stopped, by indication and treatment group**

Rivaroxaban		Warfarin	
Reason for dose increase	N%	Reason for dose increase	N%
AF		AF	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	
DVT/PE		DVT/PE	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	
Mixed (AF & DVT/PE)		Mixed (AF & DVT/PE)	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	
Other		Indications	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	



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**Table 31C. Reasons for first reported dose decrease where treatment has not stopped, by indication and treatment group**

Rivaroxaban		Warfarin	
Reason for dose increase	N%	Reason for dose increase	N%
AF		AF	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	
DVT/PE		DVT/PE	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	
Mixed (AF & DVT/PE)		Mixed (AF & DVT/PE)	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	
Other		Other	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	

**Table 31D. Posology (total daily dose) on stopping, by indication and treatment group**

Total daily dose on stopping	Rivaroxaban N%	Warfarin N%
Indication:		
AF		
	<2.5	
	>=2.5, <5	
	>=5.0, <10	
	>=10, <20	
	>=20, <30	
	>=30	
Number patients with Missing information		
Median (IQR)		
Mean (SD)		
DVT/PE		
	<2.5	
	>=2.5, <5	
	>=5.0, <10	
	>=10, <20	
	>=20, <30	
	>=30	
Number patients with Missing information		
Median (IQR)		
Mean (SD)		
Mixed (AF & DVT/PE)		

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	<2.5
	>=2.5, <5
	>=5.0, <10
	>=10, <20
	>=20, <30
	>=30
Number patients with Missing information	
Median (IQR)	
Mean (SD)	
Other	
	<2.5
	>=2.5, <5
	>=5.0, <10
	>=10, <20
	>=20, <30
	>=30
Number patients with Missing information	
Median (IQR)	
Mean (SD)	

**Table 31E. 20 most frequently reported reasons for stopping, by indication and treatment group**

Rivaroxaban		Warfarin	
Reason for stopping	N%	Reason for stopping	N%
AF		AF	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	
DVT/PE		DVT/PE	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	
Mixed (AF & DVT/PE)		Mixed (AF & DVT/PE)	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	
Other		Other	
e.g. Poor response		e.g. Poor response	
Intolerance		Intolerance	
Poor compliance etc		Poor compliance etc	
Other reasons*		Other reasons*	

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**Table 31F. Anticoagulant/Antiplatelet switches immediately post treatment cessation for indication AF, by treatment group**

Medication	Rivaroxaban N%	Warfarin N%
<b>Anticoagulants</b>		
Oral		Warfarin Phenindione Nicoumalone Dabigatran Apixaban Other <sup>a</sup>
Parenteral		Bivalirudin Unfractionated heparin <sup>b</sup> Low molecular weight heparin <sup>c</sup> Fondaparinux Other <sup>d</sup>
<b>Antiplatelets</b>		
	Aspirin (<=300mg) Clopidogrel Abciximab Dipyridamole Eptifibatide Tirofiban Other <sup>e</sup>	

<sup>a</sup> to be listed; <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed;

**Table 31G. Anticoagulant/Antiplatelet switches immediately post treatment cessation for indication DVT/PE, by treatment group**

Medication	Rivaroxaban N%	Warfarin N%
<b>Anticoagulants</b>		
Oral		Warfarin Phenindione Nicoumalone Dabigatran Apixaban Other <sup>a</sup>
Parenteral		Bivalirudin Unfractionated heparin <sup>b</sup> Low molecular weight heparin <sup>c</sup> Fondaparinux Other <sup>d</sup>
<b>Antiplatelets</b>		
	Aspirin (<=300mg) Clopidogrel Abciximab Dipyridamole	

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Eptifibatide  
Tirofiban  
Other <sup>e</sup>

<sup>a</sup> to be listed; <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed;

**Table 31H. Anticoagulant/Antiplatelet switches immediately post treatment cessation for Mixed (AF & DVT/PE) indications, by treatment group**

Medication	Rivaroxaban N%	Warfarin N%
<b>Anticoagulants</b>		
Oral		
	Warfarin	
	Phenindione	
	Nicoumalone	
	Dabigatran	
	Apixaban	
	Other <sup>a</sup>	
Parenteral		
	Bivalirudin	
	Unfractionated heparin <sup>b</sup>	
	Low molecular weight heparin <sup>c</sup>	
	Fondaparinux	
	Other <sup>d</sup>	
<b>Antiplatelets</b>		
	Aspirin (<=300mg)	
	Clopidogrel	
	Abciximab	
	Dipyridamole	
	Eptifibatide	
	Tirofiban	
	Other <sup>e</sup>	

<sup>a</sup> to be listed; <sup>b</sup> including monoparin, monoparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed;

**Table 31I. Anticoagulant/Antiplatelet switches immediately post treatment cessation for Other indications, by treatment group**

Medication	Rivaroxaban N%	Warfarin N%
<b>Anticoagulants</b>		
Oral		
	Warfarin	
	Phenindione	
	Nicoumalone	
	Dabigatran	
	Apixaban	
	Other <sup>a</sup>	
Parenteral		
	Bivalirudin	
	Unfractionated heparin <sup>b</sup>	
	Low molecular weight heparin <sup>c</sup>	

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<b>Antiplatelets</b>	Fondaparinux
	Other <sup>d</sup>
	Aspirin (<=300mg)
	Clopidogrel
	Abciximab
	Dipyridamole
	Eptifibatide
	Tirofiban
	Other <sup>e</sup>

<sup>a</sup> to be listed; <sup>b</sup> including monaparin, monaparin calcium and multiparin; <sup>c</sup> including bemiparin, enoxaparin, tinzaparin and dalteparin; <sup>d</sup> to be listed; <sup>e</sup> to be listed;

**Table 31J. Summary Statistics to show number of days to treatment cessation for 10<sup>th</sup>, 25<sup>th</sup> and 50<sup>th</sup> percentiles, by indication and treatment group**

Treatment	Indication	Number of days on treatment (percentile)		
		10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>
Rivaroxaban	AF			
	DVT/PE			
	Mixed (AF & DVT/PE)			
	Other			
	Total			
Warfarin cohort	AF			
	DVT/PE			
	Mixed (AF & DVT/PE)			
	Other			
	Total			

**Table 31K. Count and percent of number of days exposed prior to stopping (by week), by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

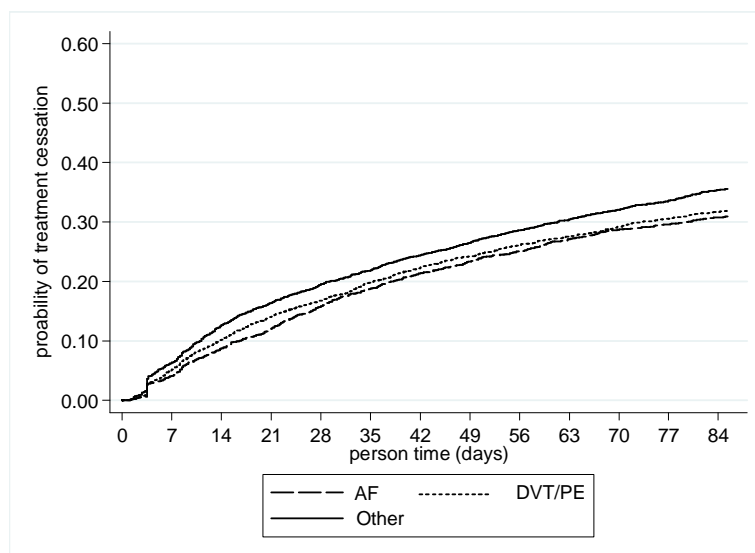
Days On Treatment	AF (N,%)	DVT/PE (N,%)	Mixed (AF & DVT/PE) (N,%)	Other (N,%)	Total (N,%)
Rivaroxaban					
7					
14					
21					
28					
35					
42					
49					
56					
63					
70					
77					
84					
Total					
Warfarin					

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7  
14  
21  
28  
35  
42  
49  
56  
63  
70  
77  
84  
Total

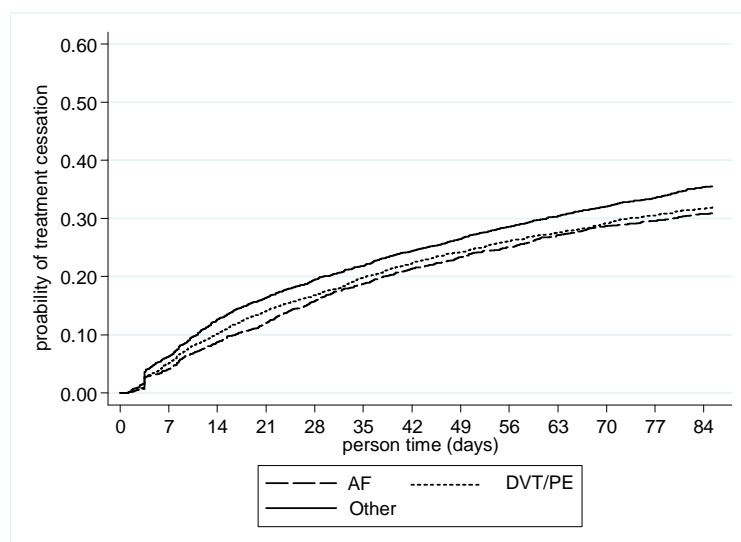
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**Figure 17. Example of cumulative incidence curve of treatment cessation within 12 weeks observation period for 'as treated' rivaroxaban cohort, by indication**



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**Figure 18. Example of cumulative incidence curve of treatment cessation within 12 weeks observation period for 'as treated' warfarin cohort, by indication**



### 9.9 Assessment of adherence

In accordance with secondary objective (iii)<sup>15</sup>, the assessment of factors associated with poor medication compliance will be presented for the rivaroxaban cohort only.

Data analysis will provide summary tabulations of the categories representing aberrant general health behaviours reported after starting rivaroxaban treatment as well as indicators of poor anticoagulation medication compliance, as shown in Table 32. Operational definitions for a binary variable representing each criteria will be constructed from tick box responses by reporting physicians in accordance with medical records notes. Missing data will be treated as a negative response. A simple unweighted indicator score will be derived for each category. The summary distribution and prevalence of each criteria, by category, of patients prescribed rivaroxaban will be summarised (Table 32A). Criteria and category specific prevalence estimates will be provided for the whole cohort and by indication group (Table 32B).

<sup>15</sup> Estimates of the Medication Possession ratios for each patient will not be summarised. This is a deviation from protocol due to the lack of information provided on the number of prescriptions issued and the average length of the interval between refills.

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**Table 32. Assessment of adherence after starting rivaroxaban treatment**

<b>New onset aberrant general health behaviours</b>	<b>Source</b>	<b>Result reference</b>
alcohol misuse: count, % smoking: count, % substance misuse: count, %	12 week questionnaire Q18	Table 32A
<b>Indicators of poor anticoagulant medication compliance</b> (count, % of known responses): Overall general poor medication taking behaviour Missed clinical review appointments Missed anticoagulant doses Extra anticoagulant doses Demonstrated poor understanding of need for regular use Disclosed high dietary intake of foods high in Vitamin K	12 week questionnaire Q19	Table 32A
Score of New onset aberrant general health behaviours count and frequency of categories 0-3*		Table 32B; Figure 19a
Score of Indicators of poor anticoagulant medication compliance count and frequency of categories 0-6*		Table 32B; Figure 19b

**Table 32A. Prevalence of criteria and categories identifying aberrant general health behaviours and poor anticoagulant medication compliance in users of rivaroxaban, by indication group and pooled cohort**

<b>Indicator (points)</b>	<b>AF</b>		<b>DVT/PE</b>		<b>Mixed (AF &amp; DVT)</b>		<b>Other</b>		<b>TOTAL</b>	
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
<b>New onset aberrant general health behaviours</b>										
Alcohol misuse (1)										
Smoker (1)										
Substance misuse (1)										
<b>Poor anticoagulant medication compliance</b>										
Overall general poor medication taking behaviour (1)										
Missed clinical review appointments (1)										
Missed anticoagulant doses (1)										
Extra anticoagulant doses (1)										
Demonstrated poor understanding of need for regular use (1)										
Disclosed high dietary intake of foods high in Vitamin K (1)										



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**Table 32B. Behaviour indicator score distribution, by indication group and pooled cohort**

Indicator (points)	AF		DVT/PE		Mixed (AF & DVT)		Other		TOTAL	
	N	%	N	%	N	%	N	%	N	%
New onset aberrant general health behaviours										
0 (min)										
1										
2										
3 (max)										
Median (IQR)										
Poor anticoagulant medication compliance										
0 (min)										
1										
2										
3										
4										
5										
6 (max)										
Median (IQR)										

**Figure 19a & b. Behaviour indicator score distribution, by indication group and pooled cohort**

(see figure 10 for example)

### 9.10 Pregnancies

This section will describe any outcomes of pregnancies in the rivaroxaban and warfarin treatment cohorts. The number and outcome of pregnancies in each cohort will be reported. Any reports of congenital abnormalities will be summarised via case narratives.

**Table 33. Pregnancies**

Data description	Source	Result reference
Pregnant on starting and/or during use: count and percent of known females of childbearing age (12 – 60)	12-week questionnaire (Q15)	Table 33A, Table 33B
Outcomes of pregnancy (count and percent, by trimester exposed: live birth, spontaneous abortion termination still born congenital abnormalities	Pregnancy event follow-up questionnaire	

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**Table 33A. Number and outcomes of confirmed pregnancies in women of child-bearing age (12-60 years) in rivaroxaban cohort**

<b>Exposure to rivaroxaban</b>	<b>Total</b>	<b>Live birth</b>	<b>Spontaneous abortion</b>	<b>Therapeutic termination</b>	<b>Stillborn</b>	<b>Neonatal death</b>	<b>NS</b>
Drug stopped before last menstrual period							
Drug taken in first trimester							
Drug taken in second trimester							
Exposure uncertain							
<b>Total</b>							

**Table 33B. Number and outcomes of confirmed pregnancies in women of child-bearing age (12-60 years) in warfarin cohort**

<b>Exposure to warfarin</b>	<b>Total</b>	<b>Live birth</b>	<b>Spontaneous abortion</b>	<b>Therapeutic termination</b>	<b>Stillborn</b>	<b>Neonatal death</b>	<b>NS</b>
Drug stopped before last menstrual period							
Drug taken in first trimester							
Drug taken in second trimester							
Exposure uncertain							
<b>Total</b>							

### 9.11 Deaths

This section will summarise causes of deaths in each cohort during the study period. The twenty most frequent cause of death will be presented by indication and treatment group as shown in Table 34A. A complete list, including underlying cause of death (described by MedDRA Preferred terms) will be provided in appendices as presented in Tables 34B and C).

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**Table 34. Deaths**

<b>Data description</b>	<b>Source</b>	<b>Result reference</b>
Top twenty most frequently reported deaths post index date: count ranked by preferred term, for total 12 week observation period	12-week follow up questionnaire Q5 & Death Follow-up questionnaire	Table 34A
All deaths reported after index date: count by preferred term, for every two weeks post index date.in rivaroxaban cohort	12-week follow up questionnaire Q5 & Death Follow-up questionnaire	Table 34B
All deaths reported after index date: count by preferred term, for every two weeks post index date.in warfarin treatment cohort	12-week follow up questionnaire Q5 & Death Follow-up questionnaire	Table 34C

**Table 34A. Most frequently reported causes of death during 12 week observation period by indication and treatment group**

<b>Rivaroxaban</b>		<b>Warfarin</b>	
<b>Cause of death</b>	<b>N%</b>	<b>Cause of death</b>	<b>N%</b>
AF		AF	
Hypertension		Hypertension	
Hepatic Failure		Hepatic Failure	
Old age		Old age	
Etc.		Etc.	
DVT/PE		DVT/PE	
Hypertension		Hypertension	
Hepatic Failure		Hepatic Failure	
Old age		Old age	
Etc.		Etc.	
Mixed (AF & DVT/PE)		Mixed (AF & DVT/PE)	
Hypertension		Hypertension	
Hepatic Failure		Hepatic Failure	
Old age		Old age	
Etc.		Etc.	
Other		Other	
Hypertension		Hypertension	
Hepatic Failure		Hepatic Failure	
Old age		Old age	
Etc.		Etc.	

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**Table 34B. Causes of death during observation period in rivaroxaban cohort ranked by total number of deaths and grouped by System Organ Class and preferred term**

Cause of death	Period Weeks	1 1&2	2 3&4	3 5&6	4 7&8	5 9&10	6 11&12	Not known
<i>For example:</i>								
<b>Cardiac Disorders</b>								
Hypertension								
								Sub-total
<b>Hepatic Disorders</b>								
Hepatic Failure								
								Sub-total
<i>Etc</i>								

**Table 34C. Causes of death during observation period in warfarin treatment cohort ranked by total number of deaths and grouped by System Organ Class and preferred term**

Cause of death	Period Weeks	1 1&2	2 3&4	3 5&6	4 7&8	5 9&10	6 11&12	Not known
<i>For example:</i>								
<b>Cardiac Disorders</b>								
Hypertension								
								Sub-total
<b>Hepatic Disorders</b>								
Hepatic Failure								
								Sub-total
<i>Etc</i>								

### 9.12 Other outcomes

The following other outcomes relate to secondary objective (iii) to describe changes in the health profile of patients

#### **9.12.1 Change in general health parameters**

For this study, Anthropometric measures (BMI ( $\text{kg/m}^2$ ), weight (kg)) at two time points: baseline and 12-weeks will be summarised and compared to inform on potential change in general health. Binary dummy variables will be created to identify those regarded as having clinically significant weight change (3% or more from index measure) and/or clinically significant BMI change ( $1\text{kg/m}^2$  or more) over the 12 week observation period.

## Appendix 2. Statistical Analysis Plan

**Table 35. General health status of cohort**

Data description	Source	Result reference
BMI (kg/m <sup>2</sup> ) category: count and percent at baseline and 12 weeks by indication and treatment group. BMI (kg/m <sup>2</sup> ) (as continuous variable) descriptive statistics (Mean (SD) /median + IQR) change over 12 week observation period , by indication and treatment group	Consent form (patient –self reports) and 12-week Questionnaire (Q20- HCP reports) <i>Standard categories apply (below normal, normal, overweight, obese, morbidity obese).</i>	Table 35A, Figure 20
Weight (kg) category: count and percent at baseline and 12 weeks, by indication and treatment group Weight (kg) (as continuous variable) descriptive statistics (Mean (SD) /median + IQR) change over 12 week observation period , by indication and treatment group	Consent form (patient self reports) and 12-week Questionnaire (Q20- HCP reports)	Table 35B, Figure 21

**Table 35A. BMI categories at baseline and 12-week follow up, by indication and treatment group**

BMI (kg/m <sup>2</sup> )	Rivaroxaban		Warfarin	
	Baseline N (%)	12-Week N (%)	Baseline N (%)	12-Week N (%)
AF				
<18.5 (Below Normal)				
18.5-24.9 (Normal)				
25.0-29.9 (Overweight)				
30.0-39.9 (Obese)				
40.0+ (Morbidly Obese)				
Not specified				
<b>Median (IQR)</b>				
<b>Mean (SD)</b>				
<b>Median/mean of differences <sup>a</sup></b>				
DVT/PE				
<18.5 (Below Normal)				
18.5-24.9 (Normal)				
25.0-29.9 (Overweight)				
30.0-39.9 (Obese)				
40.0+ (Morbidly Obese)				
Not specified				
<b>Median (IQR)</b>				
<b>Mean (SD)</b>				
<b>Median/mean of differences <sup>a</sup></b>				
Mixed (AF & DVT/PE)				
<18.5 (Below Normal)				
18.5-24.9 (Normal)				
25.0-29.9 (Overweight)				
30.0-39.9 (Obese)				

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40.0+ (Morbidly Obese)

Not specified

**Median (IQR)**

**Mean (SD)**

**Median/mean of differences <sup>a</sup>**

Other

<18.5 (Below Normal)

18.5-24.9 (Normal)

25.0-29.9 (Overweight)

30.0-39.9 (Obese)

40.0+ (Morbidly Obese)

Not specified

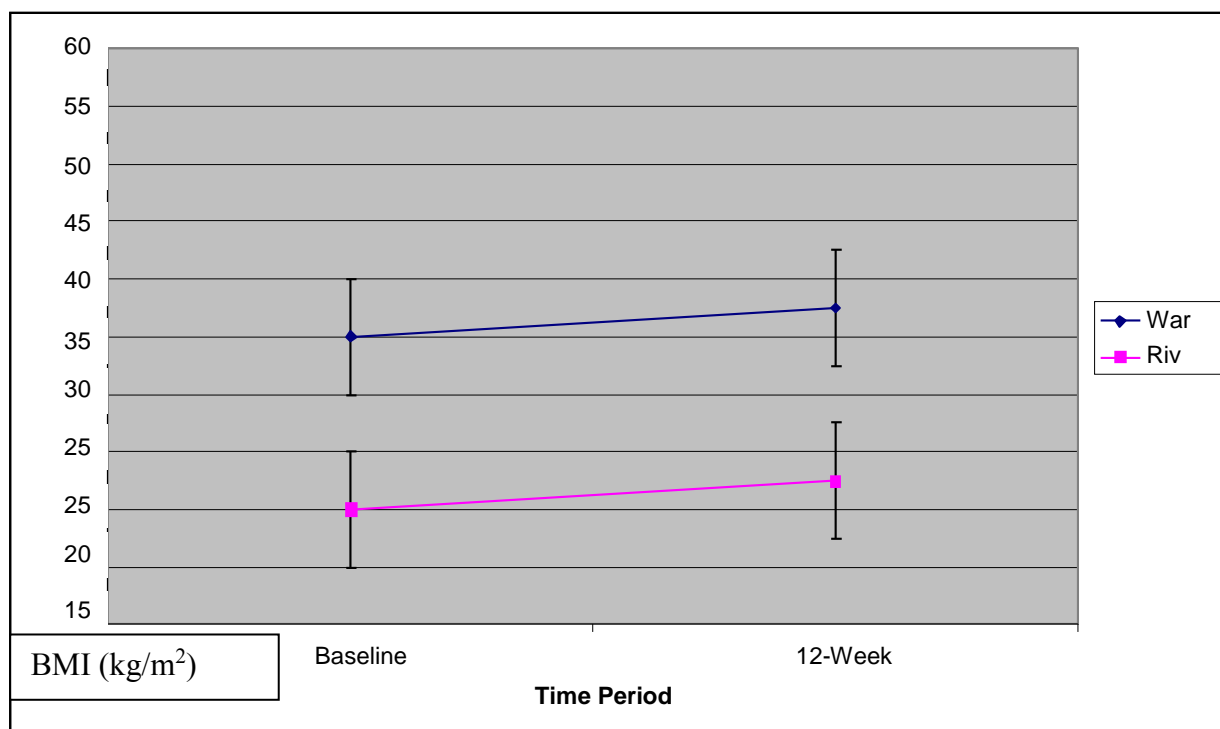
**Median (IQR)**

**Mean (SD)**

**Median/mean of differences <sup>a</sup>**

<sup>a</sup> paired analysis; approach will be dependent on distribution of data variable; where data are Normal, paired t-test will apply; where data are skewed, the median of differences will be calculated as the 50 percentile of all individual differences (change from baseline (<http://onbiostatistics.blogspot.co.uk/2015/12/median-of-differences-versus-difference.html>))

**Figure 20. Change of BMI (kg/m<sup>2</sup>) during 12-week observation period, stratified by indication group**



## Appendix 2. Statistical Analysis Plan

**Table 35B. Weight (kg) categories at baseline and 12-week follow up, by indication and treatment group**

Weight (kg)	Rivaroxaban		Warfarin	
	Baseline N (%)	12-Week N (%)	Baseline N (%)	12-Week N (%)
AF				
Quintiles tbc				
Not specified				
<b>Median (IQR)</b>				
<b>Mean (SD)</b>				
<b>Median/mean of differences <sup>a</sup></b>				
DVT/PE				
Quintiles tbc				
Not specified				
<b>Median (IQR)</b>				
<b>Mean (SD)</b>				
<b>Median/mean of differences <sup>a</sup></b>				
Mixed (AF & DVT/PE)				
Quintiles tbc				
Not specified				
<b>Median (IQR)</b>				
<b>Mean (SD)</b>				
<b>Median/mean of differences <sup>a</sup></b>				
Other				
Quintiles tbc				
Not specified				
<b>Median (IQR)</b>				
<b>Mean (SD)</b>				
<b>Median/mean of differences <sup>a</sup></b>				

<sup>a</sup> paired analysis; approach will be dependent on distribution of data variable; where data are Normal, paired t-test will apply; where data are skewed, the median of differences will be calculated as the 50 percentile of all individual differences (change from baseline (<http://onbiostatistics.blogspot.co.uk/2015/12/median-of-differences-versus-difference.html>))

## Appendix 2. Statistical Analysis Plan

### Figure 21. Change of weight (kg) during 12-week observation period, stratified by indication group

See Figure 20

#### 9.12.2 Changes in laboratory test results

For this study, laboratory tests results (Haemoglobin (g/L)), Platelets ( $\times 10^9/L$ ) at two time points: baseline and 12-weeks will be summarised and compared to inform on potential change. Dummy variables will be created to identify subjects within normal ranges<sup>16</sup>. Results of baseline clotting screen are also presented, if performed.

**Table 36. Laboratory parameters**

Data description	Source	Result reference
Haemoglobin (g/DL) category: count and percent at baseline and 12 weeks by indication and treatment group Haemoglobin (g/DL) (as continuous variable) descriptive statistics (Mean (SD) /median + IQR) change over 12 week observation period , by indication and treatment group	12-week Questionnaire (Q21)	Table 36A, Figure 22
Platelets category: count and percent at baseline and 12 weeks, by indication and treatment group Platelets (as continuous variable) descriptive statistics (Mean (SD) /median + IQR) change over 12 week observation period , by indication and treatment group	12-week Questionnaire (Q21)	Table 36B, Figure 23
Baseline clotting screen	12 week questionnaire (Q22)	Table 36C, Figures 24-28

<sup>16</sup> Haemoglobin: Men: 13.8 to 18.0 g/dL (138 to 180 g/L, or 8.56 to 11.17 mmol/L); Women: 12.1 to 15.1 g/dL (121 to 151 g/L, or 7.51 to 9.37 mmol/L). Platelets: The normal range (99% of population analyzed) for platelets in healthy Caucasians is 150,000 to 450,000 per cubic millimeter <sup>[22]</sup>(a mm<sup>3</sup> equals a microliter). or 150–400  $\times 10^9$  per litre.



## Appendix 2. Statistical Analysis Plan

**Table 36A. Haemoglobin (g/DL) at baseline and 12-week follow up, by indication and treatment group**

Haemoglobin (g/DL)	Rivaroxaban		Warfarin	
	Baseline N (%)	12-Week N (%)	Baseline N (%)	12-Week N (%)
AF				
Quintiles tbc				
Not specified				
<b>Median (IQR)</b>				
<b>Mean (SD)</b>				
<b>Median/mean of differences <sup>a</sup></b>				
DVT/PE				
Quintiles tbc				
Not specified				
<b>Median (IQR)</b>				
<b>Mean (SD)</b>				
<b>Median/mean of differences <sup>a</sup></b>				
Mixed (AF & DVT/PE)				
Quintiles tbc				
Not specified				
<b>Median (IQR)</b>				
<b>Mean (SD)</b>				
<b>Median/mean of differences <sup>a</sup></b>				
Other				
Quintiles tbc				
Not specified				
<b>Median (IQR)</b>				
<b>Mean (SD)</b>				
<b>Median/mean of differences <sup>a</sup></b>				

<sup>a</sup> paired analysis; approach will be dependent on distribution of data variable; where data are Normal, paired t-test will apply; where data are skewed, the median of differences will be calculated as the 50 percentile of all individual differences (change from baseline (<http://onbiostatistics.blogspot.co.uk/2015/12/median-of-differences-versus-difference.html>))

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**Figure 22. Change of Haemoglobin (g/DL) during 12-week observation period, stratified by indication group**

See figure 20

**Table 36B. Platelets ( $\times 10^9/L$ ) at baseline and 12-week follow up, by indication and treatment group**

Platelets ( $\times 10^9/L$ )		Rivaroxaban		Warfarin	
		Baseline N (%)	12-Week N (%)	Baseline N (%)	12-Week N (%)
AF	Quintiles tbc				
	Not specified				
	<b>Median (IQR)</b>				
	<b>Mean (SD)</b>				
	<b>Median/mean of differences <sup>a</sup></b>				
DVT/PE	Quintiles tbc				
	Not specified				
	<b>Median (IQR)</b>				
	<b>Mean (SD)</b>				
	<b>Median/mean of differences <sup>a</sup></b>				
Mixed (AF & DVT/PE)	Quintiles tbc				
	Not specified				
	<b>Median (IQR)</b>				
	<b>Mean (SD)</b>				
	<b>Median/mean of differences <sup>a</sup></b>				
Other	Quintiles tbc				
	Not specified				
	<b>Median (IQR)</b>				
	<b>Mean (SD)</b>				
	<b>Median/mean of differences <sup>a</sup></b>				

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<sup>a</sup> paired analysis; approach will be dependent on distribution of data variable; where data are Normal, paired t-test will apply; where data are skewed, the median of differences will be calculated as the 50 percentile of all individual differences (change from baseline (<http://onbiostatistics.blogspot.co.uk/2015/12/median-of-differences-versus-difference.html>))

### Figure 23. Change of Platelets (x 10<sup>9</sup>/L) during 12-week observation period, stratified by indication group

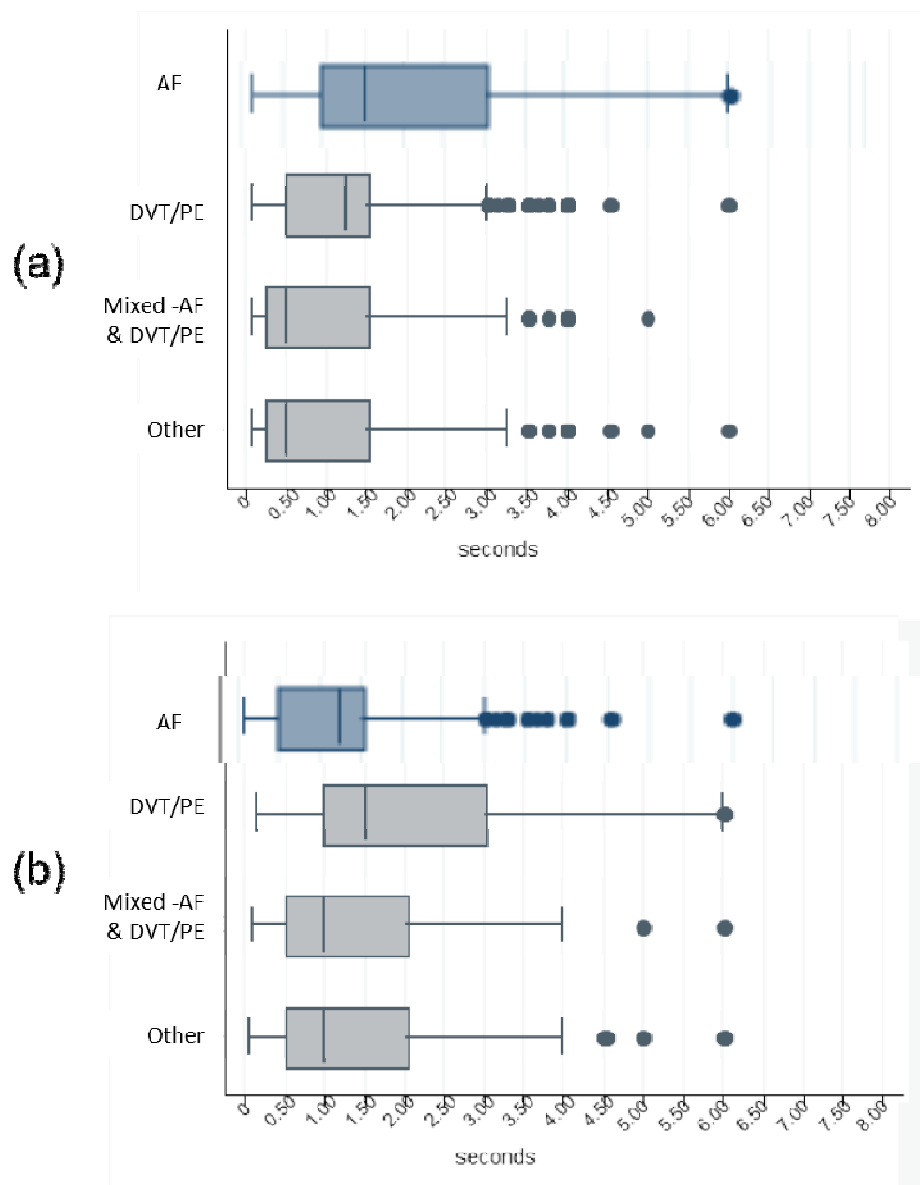
See figure 20

**Table 36C Coagulation parameter values present at the time of treatment initiation with rivaroxaban or warfarin, by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

Clotting parameter [median (IQR)]	AF	DVT/PE	Rivaroxaban Mixed (AF& DVT/PE)	Other	Total	AF	DVT/PE	Warfarin Mixed (AF& DVT/PE)	Other	Total
PT (seconds)										
APTT (seconds)										
Fibrinogen derived (mg/dl)										
D-Dimer (if DVT) mcgg FEU/ml										

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**Figure 24. Example Boxplot Coagulation parameters (PT) at the time of treatment initiation a) rivaroxaban and b) warfarin cohort, by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**



**Figure 25. Boxplot Coagulation parameters ( APPT) at the time of treatment initiation a) rivaroxaban and b) warfarin cohort, by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

See figure 24

**Figure 26. Boxplot Coagulation parameters ( Fibrinogen) at the time of treatment initiation a) rivaroxaban and b) warfarin cohort, by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

See figure 24

## **Appendix 2. Statistical Analysis Plan**

**Figure 27. Boxplot Coagulation parameters (D-Dimer) at the time of treatment initiation a) rivaroxaban and b) warfarin cohort, by primary diagnosis (AF, DVT/PE, Mixed (AF & DVT/PE), Other)**

See figure 24

### **10.0 REFERENCES**

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**Rivaroxaban Observational Safety Evaluation (ROSE) Multilevel  
Modelling of Prescribing Variability  
Final analysis**

## **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

### **Introduction**

In the statistical analysis plan (SAP) for the ROSE SCEM study, to supplement the main aims and objectives, a multilevel regression analysis of prescribing variability was included as a potential additional output. The purpose of this supplementary ad-hoc study was to explore the effect of patient, prescriber and trust characteristics on treatment choice, i.e., rivaroxaban or warfarin prescription.

In this report, we summarise the approach taken and report the results obtained for this multilevel modelling analysis of prescribing variability applied to the final study data, the summary of which appears in the main report.

### **Data Management**

#### **Exclusions**

##### ***Missing Identifiers***

The raw dataset contained data on 4,609 patients. However, two (0.04%) of these patients had no trust identifier (ID) and were therefore dropped from the analysis dataset.

One prescriber ID ("81A3051E"; associated with 15 [0.33%] patients) was also excluded, as it is understood that this identifier was assigned to a research nurse, rather than to the patients' prescribers, and therefore it was not possible to identify the individual prescribers in these cases.

A further 134 (134/4,592; 2.9%) patients were excluded where their prescriber ID was missing, leaving us with 4,458 patients for analysis (associated with 1,193 prescribers and 78 trusts), up to this point.

##### ***Missing Characteristics***

Where a variable had a considerable amount of missing data, i.e., being missing for more than 10% of patients, this characteristic was entirely excluded from the analysis. This allows us to avoid the need to exclude a large proportion of patients from the analysis. There were two variables dropped in this way: patient body mass index (both a continuous and a categorised version), with missing values for 1,128 (1,128/4,458; 25.3%) of the patients; and prescriber years of specialist experience, with missing values for 633 of those patients where their prescriber was a specialist and therefore this variable was applicable (633/3,263; 19.4%).

For those variables with a relatively small amount of missing data (<10%), the individual patients with missing values were excluded from the analysis (rather than dropping that



### **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

variable entirely). Four patients (4/4,458; 0.09%) had a prescriber with a missing profession. Fourteen patients (14/4,458; 0.31%) had a missing value for the number of hospitals in their corresponding trust that were participating in the ROSE study (this corresponded with one trust, with an ID of "RCX"). One-hundred and sixteen (116/4,458; 2.6%) patients had a prescriber with a missing clinical specialism. Two-hundred and ninety-one (291/4,458; 6.5%) patients had a prescriber with a missing career level. Three-hundred and forty-one (341/4,458; 7.6%) patients had a missing index of multiple deprivation rank/rank decile. Eighty-nine (89/4,458; 2.0%) patients had a prescriber where their gender was not stated. Three-hundred and nine (309/4,458; 6.9%) patients had a prescriber with a missing value for their professional years registered.

Following the above exclusions, 3,580 patients remained for analysis (note that some patients had missing values for multiple variables). Of these patients, only 3 (0.08%) were observed to be in a trust in the Wales geographic region; and only 3 (0.08%) had a prescriber whose professional qualification was as a pharmacist. Therefore, in the absence of there being another category to merge these responses with, these patients were also excluded from the analysis. Therefore there were 3,574 patients with a complete set of data available for the analysis.

Only 5 (5/3,580; 0.14%) of these patients were reported by their prescriber to have had aberrant health behaviours as a reason for their choice of prescription. Given the rarity of this patient-specific prescribing reason, this variable was also excluded from the analysis (as a binary variable it was not possible to collapse the categories further).

Aside from the variables excluded above, we also discounted the trust-level variable recording whether the trust had anticoagulant prescribing guidelines available, as it is understood that all trusts included in the ROSE study did so. Similarly, trust-level rivaroxaban sales presence/absence data (i.e., capturing whether a trust had any rivaroxaban sales) were also excluded as all trusts had rivaroxaban sales. Furthermore, continuous rivaroxaban sales data (per 100,000 bed days) were also excluded. Though sales may be associated with the odds of a patient in a trust being prescribed rivaroxaban, this could be a result of the fact that (perhaps lots of) patients had been prescribed it, i.e., due to demand driving sales, rather than being a driver of patients being prescribed it, i.e., sales driving demand. In which case, this would "account for" (i.e., remove the effect of) some of the variability in treatment choice in the analysis, but wouldn't necessarily explain that variability in any meaningful way.

The approach detailed above, aside from the exclusion of particular characteristics, is often described as a complete case analysis.

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Multiple imputation may help to avoid biased estimates if data may be missing at random (but not completely at random). However, if the missing data are missing not at random, multiple imputation results may also be biased, and perhaps more so than complete case analysis results.

If data are missing completely randomly, i.e., the probability of data being missing is unrelated to any of the variables included in the analysis, a complete case analysis will be unbiased (the subset of complete cases represents a random, albeit smaller, sample from the original data). If the complete cases are systematically different from the sample as a whole (i.e. different to the incomplete cases), i.e., the data are not missing completely randomly, analysing only the complete cases can lead to biased estimates. However, by applying a regression model, the approach will give unbiased estimates so long as the chance of being a complete case is independent of the outcome (treatment choice), conditional on the explanatory variables included in the model.

#### **Merging of Sparse Categories**

There were a number of examples of sparse categories for some rare levels of the categorical variables available in the data. In these cases it is unlikely that there would have been sufficient observations to estimate the effect (and its uncertainty) of that category reliably. Therefore, to retain as many data points as possible and have a more parsimonious model, avoiding potential estimation problems, we re-categorised these variables to remove the sparse groupings.

Groups were merged where we felt that these could be reasonably be combined, i.e., where the combinations did not merge levels that were very different with respect to the outcome (prescribing preference) and, where possible, represented contextually homogeneous groups.

A list of the relevant variables and categories that have been merged is given below.

- Patient marital status:
  - Other and Unknown.
- Patient self-reported employment status:
  - House husband/wife and Mother/maternity leave.
  - Disabled and Sick leave.
  - Pensioner and Retired.
  - Carer, Other, Volunteer, and Student.
- Patient ethnicity:
  - Bangladeshi, Chinese, Indian, and Pakistani (relabelled "Asian")
  - African, Black - Other, and Caribbean

## **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

### **Derived Variables**

In addition to a continuous patient age at index variable, three binary variables were provided classifying patients as being <65 or not, 65 to 74 (inclusive) or not, and ≥75 or not. To aid interpretation, these binary variables were combined into a single categorical patient age at index variable prior to analysis, with categories of: <65; 65 to 74 inclusive, and ≥75.

Two variables were provided as indicators of a patient's prior/at baseline history of hypertension based on the HAS-BLED and CHADS2VASC disease score components, where the HAS-BLED variable offers a narrower definition of hypertension. An additional categorical variable combining these two definitions of hypertension was created prior to analysis, with categories of: No, CHADS2VASC, and CHADS2VASC & HAS-BLED hypertension. Note: It is not possible for a patient to have a HAS-BLED definition of hypertension and not a CHADS2VASC definition of hypertension.

The trust-level characteristics provided included the number of hospitals in the trust along with the number of hospitals in the trust participating in the ROSE study. Taking the ratio of these variables, we also included the proportion of hospitals within a trust participating in the ROSE study as a proxy for the level of engagement of the trust with the study.

### **Methods**

A multilevel logistic regression analysis with three levels (namely, patients clustered within prescribers, clustered within trusts) was explored to study the influence of patient, prescriber and trust characteristics on rivaroxaban and warfarin use, and also the variance in prescribing at the prescriber and trust levels. The outcome variable is the binary treatment choice of rivaroxaban versus warfarin.

The multilevel model (sometimes known as a mixed-effect model) simply allows for grouping of patient prescriptions within prescribers, and prescribers within Trusts, by including residuals at the trust, prescriber and patient level. Thus the residual variance is partitioned into a between trust component, a within trust between prescriber component and a within prescriber component (the variance of the patient-level residuals). By including random effects for prescribers and trusts, we are recognising the hierarchical structure of the data, preventing us from underestimating the standard errors of the regression coefficients.

The analysis was completed in several steps to differentiate between the influence of the patient, prescriber and trust characteristics. In step 1, the "empty" model included only random effects for the prescriber and trust, without including any fixed effects to account for

### **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

patient, prescriber or trust characteristics. This model provides estimates of the components of variance in prescribing at the prescriber and trust levels, allowing comparison of their relative contributions in terms of the proportion of the total variance explained. In step 2, patient characteristics were added to the model. This model accounts for any difference that might exist in the groups of patients associated with each prescriber and trust (captured by the available patient characteristics). The variance components in step 2 then estimate the remaining variance explained by differences in prescribing practice between prescribers and between trusts, whilst accounting for possible differences in the patient characteristics (in the data available). Step 2 also allows determination of patient characteristics that are associated with the prescription of rivaroxaban or warfarin, along with estimates of the size and direction of those effects. In step 3, prescriber characteristics were added to the model to account for, and estimate the effects of, prescriber characteristics associated with the prescription of rivaroxaban or warfarin. Similarly, in step 4, trust characteristics were added to the model.

Only those fixed effects that were found to have a significant effect (at the 5% level) on the performance of the models were retained in each step. The fixed effects structures of the models were compared using Likelihood Ratio Tests (which are appropriate for both mixed effect and generalised linear models). At each step, the characteristics were added to the model via a forward-backward stepwise procedure, i.e., the most informative variables were added to the previous model, one at a time, checking at each step that the variables previously added remained significant (if not these were removed).

By including in the (step 4) model, all the covariates that are available (and that the data supports) we have attempted to account for imbalances between the prescribers and trusts. However, we are not able to account for any differences not contained within the available data so we are unable to guarantee to have eliminated all confounding effects (i.e., factors that are associated with a patient both belonging to a particular prescriber (or trust) and their prescription outcome).

Fixed effects are reported via odds ratios (OR) and their associated 95% confidence intervals (further details of how these are calculated are given below). Random effects are reported as the estimated variance components and their associated standard errors. Median odds ratios (MOR) have also been calculated for the variance components, to allow interpretation on the OR scale and direct comparison with the ORs of the patient, prescriber and trust characteristics. If two patients (with the same characteristics) were randomly chosen from different prescribers (or trusts) this would be the median OR between the patient with a higher propensity to be prescribed rivaroxaban versus the patient with the lower propensity. So, this captures the increased (median) odds of being prescribed rivaroxaban if a patient was to

### **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

change to a prescriber (or trust, respectively) with a higher propensity to prescribe rivaroxaban.

The variance components in each step are also compared with those estimated in the previous step and summarised in terms of the proportional change in the variance (PCV) between models.

A complete list of the patient, prescriber and trust-level characteristics considered as candidate variables in the modelling can be found in Table 6, Table 7 and Table 8, respectively. Note however, that the combined disease score variables (for HAS-BLED and CHADS2VASC) were only included as part of a sensitivity analysis, as described below.

Any combination of explanatory variables may interact with each other so the number of potential interactions is enormous, therefore it was not possible to consider all possible effect modifications in the modelling. In order to make the variable selection and model fitting more practicable, we considered limiting the potential interactions to pairwise interactions between the main effects retained in the model at each step, but this still proved infeasible due to the sparsity of the data and computational demands. An alternative approach is to consider adding a small number of clinically meaningful interactions that might be considered likely a priori. Clinical indication was highlighted as a likely effect modifier. Therefore, as noted below, it was agreed to carry out a sensitivity analysis considering interactions with indication and to stratify the main analysis by indication.

Note: A similar analysis (on drivers of asthma medication prescriptions for children) is presented in Leufkens *et al.* (2009).

#### **Stratification by Indication**

As well as carrying out the modelling described above across all patients (including clinical indication as a patient characteristic), the analysis was stratified by indication, i.e., the modelling was repeated separately for the two main indication groups, namely: deep vein thrombosis and pulmonary embolism (DVT/PE), and non-valvular atrial fibrillation and atrial fibrillation (NVAf/AF).

#### **Sensitivity Analyses**

As a sensitivity analysis, for the overall model (across all indications), the inclusion of interactions, i.e., effect modifications, between each fixed effect retained in the model at each step and patient clinical indication was explored.

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

A further sensitivity analysis, for each set of modelling results, was also undertaken considering the inclusion of the HAS-BLED and CHADS2VASC disease scores (both as discrete scores and as grouped, categorical variables), rather than just the individual patient factors that contribute to these scores, which were already included in the main analysis.

#### Model Specification

The model described above can be specified, mathematically, in the following way. We model the probability of being prescribed rivaroxaban, for patient  $k$ , with prescriber  $j$ , in trust  $i$ , via a generalised linear mixed-effects model as follows.

$$p_{ijk} = \text{logit}^{-1}(\alpha + \beta_1 x_{1ijk} + \beta_2 x_{2ijk} + \dots + \gamma_1 z_{1ij} + \gamma_2 z_{2ij} + \dots + \delta_1 v_{1i} + \delta_2 v_{2i} + \dots + b_{ij} + b_i) + \delta_{ijk}$$

Excluding the residuals ( $\delta_{ijk}$ ), the linear predictor for the log-odds of being prescribed rivaroxaban is then as follows.

$$\text{logit}(p_{ijk}) = \log\left(\frac{p_{ijk}}{1 - p_{ijk}}\right) = \alpha + \beta_1 x_{1ijk} + \beta_2 x_{2ijk} + \dots + \gamma_1 z_{1ij} + \gamma_2 z_{2ij} + \dots + \delta_1 v_{1i} + \delta_2 v_{2i} + \dots + b_{ij} + b_i$$

Where  $\alpha$  is the intercept, the  $\beta$  coefficients are fixed patient effects, the  $\gamma$  coefficients are fixed prescriber effects, the  $\delta$  coefficients are fixed trust effects, and the  $b$  coefficients are the random effects (i.e.,  $b_{ij}$  is the prescriber-level random effect;  $b_i$  is the trust-level random effect). The  $x$ ,  $z$  and  $v$  variables may be continuous or categorical variables (represented by dummy indicators). The random effects capture the variation between prescribers (within trusts) and between trusts, respectively, that is not accounted for by the fixed effects, and are assumed to be Normally distributed as follows (i.e., with the mean and variance given in brackets).

$$b_{ij} \sim N(0, \sigma_2^2), \text{ and} \\ b_i \sim N(0, \sigma_1^2).$$

(Note: The logistic link is symmetric, so exactly the same [reparameterised] model would be obtained if we were to model the probability of being prescribed warfarin as opposed to rivaroxaban.)

#### Separation

Some cases of (partial/quasi) "separation" were present in the final dataset. Separation occurs where the outcome variable (i.e., warfarin vs. rivaroxaban prescription) can be separated by an explanatory variable. For example, for the patient characteristic "Patient-specific prescriber

### **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

reason for prescribing: poor control”, 100% of those patients with a history of poor control were prescribed with rivaroxaban in the study. (The separation is partial rather than complete as the converse is not true – not all of the patients without a history of poor control were prescribed warfarin in the study.) In the presence of separation, logistic regression models fitted via maximum likelihood can produce infinite or biased estimates (i.e., with extremely large coefficients and standard errors). One option for dealing with this would be to apply Firth’s bias reducing, penalised maximum likelihood logistic regression (Firth, D. (1992); Firth, D. (1993); Heinze, G. (1999); Heinze, G., Schemper, M. (2002); Heinze, G., Ploner M. (2004); Ploner M, Dunkler D, Southworth H, Heinze G (2013)). However, it’s not possible to incorporate random effects within Firth’s logistic regression model. Therefore, we have applied a Bayesian logistic mixed-effect model which provides us with a more flexible framework that enables us to deal with the separation issue but also to include the random effects in the model to account for the repeated observations within prescribers and trusts (Chung, Y., Rabe-Hesketh, S., Dorie, V., Gelman, A., and Liu, J. (2013); Y. Fong, H. Rue and J. Wakefield (2010); Y. Zhao, J. Staudenmayer, B. A. Coull and M. P. Wand (2006)). We include a weakly informative Normal prior distribution for the fixed effects (and flat priors for the random effects) which regularise the coefficient estimates, i.e., penalising the likelihood expression and pushing the estimates away from singularity.

Parametric bootstrap confidence intervals are provided, which are likely to be more reliable than the more commonly presented Wald intervals (i.e., estimate  $\pm$  percentile\*standard error of estimate). The occasions when these are likely to differ are in the presence of separation (e.g., patient history of poor control) or when the sample size is low, in which case the bootstrap confidence intervals are likely to be narrower. In these cases, the assumptions that the Wald intervals are based on (likelihood profiles quadratic on the variance scale) are unlikely to be well met for the coefficients.

#### **Univariate Analyses**

Prior to carrying out the multiple variable multilevel logistic regression analyses, we agreed to run through some univariate analyses. For each characteristic (patient, prescriber and trust) one-by-one, we have fitted a Bayesian logistic mixed-effect model, including the random effects for prescriber and trust (so that the variance is decomposed appropriately), and a single explanatory variable for the characteristic in question. We have then carried out a Likelihood Ratio Test to assess the overall significance of that variable, as well as producing odds ratios and their confidence intervals for each coefficient (an OR>1 indicates a tendency for being prescribed rivaroxaban as opposed to warfarin).

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All analyses were performed in the statistical software package R version 3.3.1 (R Core Team (2016)). The *bglmer* function in the *blme* package was used to implement the Bayesian logistic mixed-effect modelling (Vincent Dorie (2014)).

## **Results**

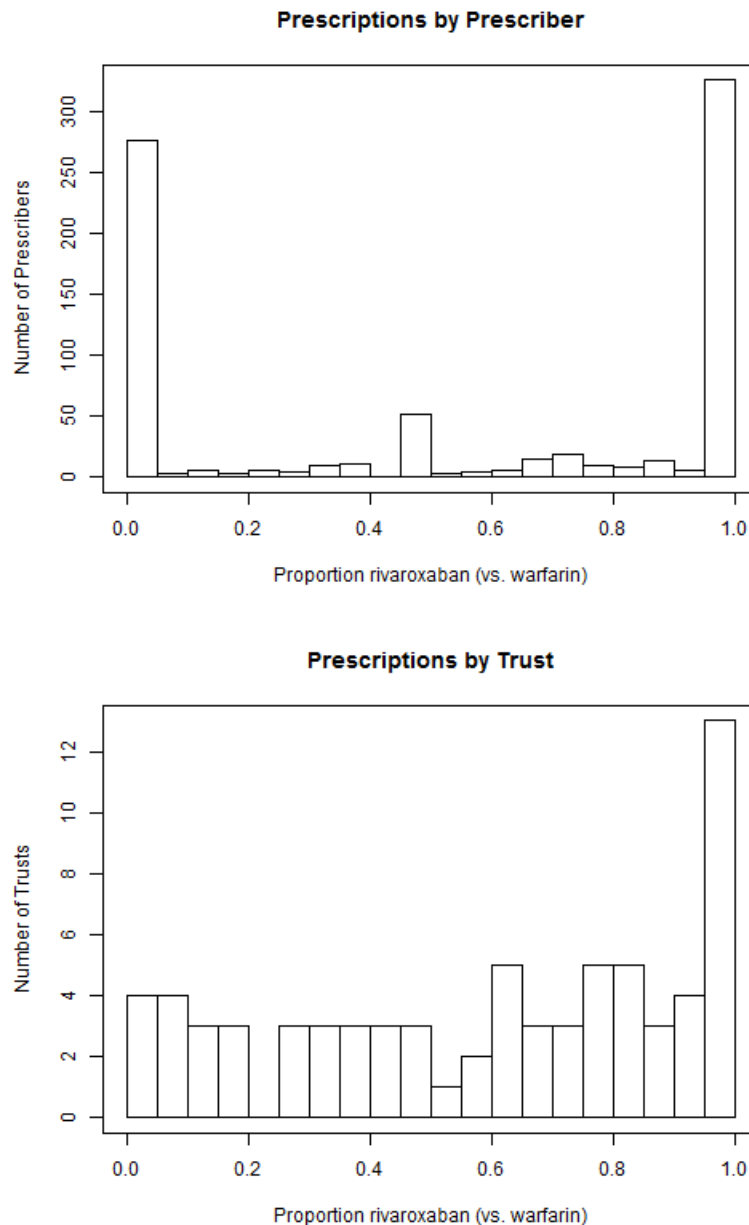
The results of this exploratory analysis, based on the final ROSE study data are summarised below.

Following the data processing described above, the data available for analysis included 3,574 patients, 1,468 (41.1%) of whom were prescribed warfarin and 2,106 (58.9%) rivaroxaban. These patients were associated with 780 different prescribers, with between 1-115 patients within a prescriber (mean of 4.6). There were 73 trusts, with between 1-47 prescribers within a trust (mean of 11). The proportion of patients with rivaroxaban vs. warfarin prescriptions reported by prescriber and trust is visualised in Figure 1.



### Appendix 3. Multilevel Modelling of Prescribing Variability Report

**Figure 1: Histograms of the proportion of patients prescribed with rivaroxaban (vs. warfarin) by prescriber and trust.**



Of the 3,574 patients with complete data available for analysis, the majority had a clinical indication of DVT/PE (2,014/3,574; 56.4%), closely followed by NVAf/AF (1,474/3,574; 41.2%), with a small proportion of patients having indications of mixed (i.e., AF & DVT/PE composite: 41/3,574; 1.1%) and other (i.e., off-label: 45/3,574; 1.3%).

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

Summaries of the numbers of patients per prescriber, and patients and prescribers per trust, by indication, are provided in Table 1.

**Table 1: Summaries of the numbers of patients, prescribers and trusts, by clinical indication.**

Indication	Summary	Mean	Median (Range)
<b>Overall</b>	Patients by Trust (n=73)	49	35 (1-254)
	Prescribers (n=780) by Trust	11	7 (1-47)
	Patients (n=3574) by Prescriber	4.6	1 (1-115)
<b>DVT/PE</b>	Patients by Trust (n=64)	31.5	22 (1-150)
	Prescribers (n=569) by Trust	9.1	5.5 (1-35)
	Patients (n=2014) by Prescriber	3.5	1 (1-76)
<b>Mixed</b>	Patients by Trust (n=26)	1.6	1 (1-3)
	Prescribers (n=37) by Trust	1.4	1 (1-3)
	Patients (n=41) by Prescriber	1.1	1 (1-3)
<b>NVAF/AF</b>	Patients by Trust (n=62)	23.8	15 (1-148)
	Prescribers (n=336) by Trust	5.5	3 (1-21)
	Patients (n=1474) by Prescriber	4.4	1 (1-79)
<b>Other</b>	Patients by Trust (n=23)	2	2 (1-6)
	Prescribers (n=36) by Trust	1.6	1 (1-5)
	Patients (n=45) by Prescriber	1.2	1 (1-4)

The observed prescription rates of rivaroxaban versus warfarin (per patient), by indication group, are given in Table 2.

## Appendix 3. Multilevel Modelling of Prescribing Variability Report

**Table 2: Prescription rates (rivaroxaban versus warfarin) by patient clinical indication.**

		Prescription		
		warfarin	rivaroxaban	Total
<b>Indication</b>	<b>DVT/PE</b>	800 (39.7%)	1214 (60.3%)	2014 (100%)
	<b>Mixed</b>	22 (53.7%)	19 (46.3%)	41 (100%)
	<b>NVAF/AF</b>	618 (41.9%)	856 (58.1%)	1474 (100%)
	<b>Other</b>	28 (62.2%)	17 (37.8%)	45 (100%)
	<b>Overall</b>	1468 (41.1%)	2106 (58.9%)	3574 (100%)

### Univariate Analyses

The univariate analyses may provide some interesting initial results on the potential associations observed between individual patient characteristics, for example, and the odds of a prescription of rivaroxaban vs. warfarin. They also offer a convenient way of summarising the characteristics of the study population and provide a complete list of the candidate characteristics considered in the multiple variable modelling. For the patient-level variables, we have presented the mean, standard deviation [SD], median and range for each continuous variable (presented in the format: "mean (SD); median (range)"), and the number (%) of patients for each binary/categorical variable, split by the patients that were prescribed warfarin and those that were prescribed rivaroxaban (with an overall "Total" column also given). For the prescriber and trust-level variables, the summaries are split by prescribers or trusts where all patients were prescribed warfarin, all rivaroxaban or where a mixture of warfarin/rivaroxaban prescriptions were made. It should be noted that, the results of the univariate analyses do not account for the effects of the other variables and therefore could be subject to confounding – this would be evident if variables that were significant in the univariate analyses subsequently dropped out of the multiple variable modelling.

Note: In general, the prescriber and trust-level characteristics were constant within a prescriber and trust, respectively. For example, a male prescriber always had a prescriber gender of male, across all of their patients. However, for the prescriber professional years registered (experience), this variable varied slightly between patients within a prescriber, depending on the time in the study that the prescriber saw that patient. Therefore, this variable is considered in the patient univariate analyses, despite experience being a prescriber characteristic.

## **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

### ***All Indications***

The univariate analysis results can be found in the Appendix towards the end of this report. In particular, the overall univariate results (across all indications) are shown in Table 6, Table 7 and Table 8 for the patient, prescriber and trust-level characteristics, respectively. Some discussion of these results is given below. Note: Effects that were significant at the 5% level and comparisons between categorical variable groupings where the CI does not contain 1 are highlighted in particular.

For the patient-level characteristics, the univariate analyses across all indications provide some evidence of patients with prior/at baseline history of congestive heart failure, hypertension (CHADS2VASC) and bleeding predisposition, and a CHADS2VASC score group of moderate or high compared with low risk being associated with a lower odds of being prescribed rivaroxaban. A patient with a clinical indication of other (off-label) is also estimated to have a lower odds of being prescribed rivaroxaban compared with DVT/PE. Whereas, patients with prior substance misuse, and a patient-specific prescriber reason for prescribing of lifestyle choice, non-adherence with prior anticoagulant, side-effects with prior anticoagulant, patient preference, and poor control, are estimated to have a higher odds of being prescribed rivaroxaban.

For the prescriber-level characteristics, the univariate analyses across all indications provide some evidence of prescribers with a clinical specialism of care of elderly, endocrinology, gastroenterology, other and respiratory being associated with a lower odds of prescribing rivaroxaban than a haematology specialism (which was the most common clinical specialism observed). Prescribers with a higher percentage of patients with a reason for prescribing of expert guidelines and potential ease of reversibility were also estimated to have a lower odds of prescribing rivaroxaban.

At the trust level, across all indications, there was no evidence (at the 5% level) that any of the characteristics considered were individually associated with the odds of prescribing rivaroxaban.

### ***DVT/PE***

The univariate results for the DVT/PE clinical indication are given in Table 9, Table 10 and Table 11 for the patient, prescriber and trust-level characteristics, respectively.

For the patient-level characteristics, the univariate analyses for DVT/PE provide some evidence of patients with prior/at baseline history of congestive heart failure, vascular disease and hypertension (CHADS2VASC), and a higher CHADS2VASC score, or CHADS2VASC score group

### **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

of high compared with low risk, being associated with a lower odds of being prescribed rivaroxaban. Whereas, patients with a patient-specific prescriber reason for prescribing of lifestyle choice, side-effects with prior anticoagulant, patient preference, and poor control, are estimated to have a higher odds of being prescribed rivaroxaban.

For the prescriber-level characteristics, the univariate analyses for DVT/PE provide some evidence of prescribers with a clinical specialism of care of elderly, endocrinology, gastroenterology, general medicine, other and respiratory being associated with a lower odds of prescribing rivaroxaban than a haematology specialism (which was the most common observed). Prescribers with a higher percentage of patients with a reason for prescribing of clinical judgement and potential ease of reversibility were also estimated to have a lower odds of prescribing rivaroxaban. Whereas, prescribers with specialist status, and prescribers with a higher percentage of patients with a reason for prescribing of patient group direction were estimated to have a higher odds of prescribing rivaroxaban.

At the trust level, for DVT/PE, trusts that had a higher percentage of hospitals that are other hospitals (i.e., not general or teaching hospitals) were estimated to have a higher odds of prescribing rivaroxaban.

#### ***NVAF/AF***

The univariate results for the NVAF/AF clinical indication are given in Table 12, Table 13 and Table 14 for the patient, prescriber and trust-level characteristics, respectively.

For the patient-level characteristics, the univariate analyses for NVAF/AF provide some evidence of patients with a prior/at baseline history of CVA and a patient-specific prescriber reason for prescribing of lifestyle choice, non-adherence with prior anticoagulant, side-effects with prior anticoagulant, patient preference, and poor control, having a higher odds of being prescribed rivaroxaban.

For the prescriber-level characteristics, the univariate analyses for NVAF/AF provide some evidence of prescribers with a clinical specialism of anticoagulation being associated with a lower odds of prescribing rivaroxaban than a haematology specialism (which was the most common observed) and similarly for prescribers with nurse as their professional qualification rather than medic. Prescribers with a higher percentage of patients with a reason for prescribing of NICE recommendations, expert guidelines, hospital formulary and potential ease of reversibility, and prescribers with a higher number of professional years registered were also estimated to have a lower odds of prescribing rivaroxaban. Prescribers with a higher percentage of patients with a reason for prescribing of clinical judgement and prescribers with

### **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

a specialism of stroke compared with haematology were estimated to have a higher odds of prescribing rivaroxaban.

At the trust level, for NVAF/AF, there was no evidence (at the 5% level) that any of the characteristics considered were individually associated with the odds of prescribing rivaroxaban.

#### **Multiple Variable Analyses**

The main, multiple variable analysis results can be found in the following Tables section of this report. A brief discussion of these results is also given below.

#### ***All Indications***

A summary of the results of the multiple variable multilevel logistic regression modelling across all indications is given in Table 3, including the intercept coefficient, ORs for the fixed effects (patient, prescriber and trust characteristics), variance components, MORs, etc. for the model fitted in each step.

Looking at the proportional change in the variance between models, it appears that accounting for possible differences in the patient characteristics has limited impact on the variance explained by differences in prescribing practice between prescribers and between trusts. However, the addition of the prescriber effects is estimated to reduce the prescriber and trust variance components, and the addition of the trust effects is estimated to further reduce the trust variance component.

These data suggest that variability in prescribing is dominated by the variability at the trust level compared with the prescriber level – in each model the between-trust variance is estimated to be greater than the between-prescriber variance (final model variance: 1.68 and 2.74, between-prescriber and between-trust respectively). Though the MOR for the trust variance component (final model MOR: 4.85) is large relative to a number of the fixed patient, prescriber and trust effects, we see a larger effect on the odds of prescribing rivaroxaban for patients with a patient-specific prescriber reason for prescribing of non-adherence with prior anticoagulant, lifestyle choice, poor control and side-effects with prior anticoagulant (final model OR: 22.75, 50.78, 72.62 and 43.45, respectively, in favour of rivaroxaban), having controlled for the other characteristics available. Note: To contrast the magnitude of the estimated effects for those in favour of warfarin compared with those in favour of rivaroxaban, or vice-versa, the reciprocal of the OR can be taken to put these on a comparable scale.

### **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

Other variables that are estimated to have a relatively large, independent effect on the odds of prescribing rivaroxaban vs. warfarin are the patient characteristic prior/at baseline history of congestive heart failure (final model OR: 0.675, in favour of warfarin) and an indication of other (off-label) rather than DVT/PE (0.318, in favour of warfarin); and the trust characteristic type of trust (2.97 for foundation vs. acute).

#### ***DVT/PE***

A summary of the results of the multiple variable multilevel logistic regression modelling for the DVT/PE clinical indication is given in Table 4, including the intercept coefficient, ORs for the fixed effects (patient, prescriber and trust characteristics), variance components, MORs, etc. for the model fitted in each step.

Looking at the proportional change in the variance between models, it appears that accounting for possible differences in the patient characteristics has limited impact on the variance explained by differences in prescribing practice between prescribers and between trusts. However, the addition of the prescriber effects is estimated to reduce the prescriber variance component, and the addition of the trust effects is estimated to reduce the trust variance component.

These data suggest that variability in prescribing is dominated by the variability at the trust level compared with the prescriber level – in each model the between-trust variance is estimated to be greater than the between-prescriber variance (final model variance: 1.01 and 2.81, between-prescriber and between-trust respectively). Though, the MOR for the trust variance component (final model MOR: 4.94) is large relative to many of the fixed patient, prescriber and trust effects, we see a larger effect on the odds of prescribing rivaroxaban for patients with a patient-specific prescriber reason for prescribing of lifestyle choice, poor control and side-effects with prior anticoagulant (final model OR: 82.55, 27.92 and 45.78, respectively, in favour of rivaroxaban), having controlled for the other characteristics available. Other variables that are estimated to have a relatively large, independent effect on the odds of prescribing rivaroxaban vs. warfarin are the patient characteristic prior/at baseline history of congestive heart failure (final model OR: 0.313, in favour of warfarin), a patient-specific prescriber reason for prescribing of patient preference (3.68, in favour of rivaroxaban); and the trust characteristic type of trust (3.95 for foundation vs. acute).

#### ***NVAF/AF***

A summary of the results of the multiple variable multilevel logistic regression modelling for the NVAF/AF clinical indication is given in Table 5 (see Step 1 to Step 4 columns), including

### **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

the intercept coefficient, ORs for the fixed effects (patient, prescriber and trust characteristics), variance components, MORs, etc. for the model fitted in each step.

Looking at the proportional change in the variance between models, it appears that accounting for possible differences in the patient characteristics has limited impact on the variance explained by differences in prescribing practice between prescribers and between trusts. However, the addition of the prescriber effects is estimated to reduce the prescriber and trust variance components, and the addition of the trust effects is estimated to further reduce the trust variance component (though, the prescriber variance component estimate increases in this step).

For the final model, having accounted for the trust effects, variability in prescribing is estimated to be dominated by the variability at the prescriber level compared with the trust level (final model variance: 2.40 and 1.70, between-prescriber and between-trust respectively). Though, the MORs for the prescriber and trust variance components (final model MOR: 4.38 and 3.47, respectively) are smaller than many of the fixed patient, prescriber and trust effects. For example, we see a larger, independent effect on the odds of prescribing rivaroxaban for patients with a patient-specific prescriber reason for prescribing of non-adherence with prior anticoagulant, lifestyle choice, poor control, patient preference and side-effects with prior anticoagulant (final model OR: 46.06, 20.06, 27.30, 11.72 and 25.12, respectively, in favour of rivaroxaban); the prescriber characteristic nurse rather than medic as a professional qualification (0.118, in favour of warfarin); and the trust characteristic region being London versus East of England (0.098, in favour of warfarin).

#### **Sensitivity Analyses**

##### ***Interactions with Indication***

In each modelling step, for the overall model (across all indications), interactions with the fixed effects retained in the model were considered as additional candidate variables in the modelling.

The results of this sensitivity analysis, in terms of the estimated variance components, were very similar to those from the main, overall model (final model variance: 1.70 and 2.75 at the prescriber and trust levels for the sensitivity analysis, compared with 1.68 and 2.74 for the main model, respectively).

Furthermore, the interpretation of the fixed effects, in terms of whether there was evidence of these being associated with higher rivaroxaban or warfarin prescription rates, were broadly



### **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

consistent with the results obtained in the main analysis (summarised in Table 3, Table 4 and Table 5).

All of those variables retained in the overall model (across all indications) from the main analysis (see Table 3) were also present in the model including interactions with indication, with the same direction of effect (i.e., in favour of rivaroxaban or warfarin), except for patient prior/at baseline history of hypertension which was dropped.

Where interactions with indication were retained in the sensitivity analysis, these were also evident when comparing the main overall results with those stratified by indication. For example, a patient-specific prescriber reason for prescribing of lifestyle choice was estimated to be associated with an increase in the odds of a rivaroxaban prescription, but with a smaller effect for NVAf/AF than for DVT/PE. This is also evident from the corresponding odds ratios for lifestyle choice for the NVAf/AF (final model OR: 20.056, 95% CI = 9.189, 35.808) and DVT/PE (82.55, 95% CI = 37.671, 149.575) stratified model results.

Given the consistency of the outputs for this sensitivity analysis with those of the main analysis, tables of these results are not presented.

#### ***Disease Scores***

A further sensitivity analysis, for each set of modelling results, was also undertaken considering the inclusion of the patient HAS-BLED and CHADS<sub>2</sub>VASC disease scores. In this case, the disease scores were considered as the combined, grouped variables (no bleed risk/moderate bleed risk/high bleed risk, and no stroke risk/moderate stroke risk/high stroke risk, respectively) and also discrete, count variables, rather than just the individual patient factors that contribute to these scores, which were included in the main analysis (such as prior/at baseline history of hypertension which features in both scores).

Exploring the inclusion of these scores for each of the final models from the main analysis, only the discrete HAS-BLED score was retained and only for the stratified model for the NVAf/AF clinical indication. The model estimates for this extended model are given in Table 5 (see Step 5 column). A one point increase in the HAS-BLED score was estimated to be associated with a 19.6% decrease in the odds of a patient being prescribed rivaroxaban (OR: 0.804, 95% CI = 0.656, 0.998). However, it should be noted that the model also includes the individual prior/at baseline history of hypertension variable that contributes directly to the HAS-BLED score, which has the opposite effect – presence of hypertension is estimated to be associated with an increase in the odds of a rivaroxaban prescription (OR: 2.08, 95% CI =

### **Appendix 3. Multilevel Modelling of Prescribing Variability Report**

1.277, 3.238). Given the relationship between these two variables, these effects need to be considered together, which makes their interpretation somewhat difficult.

## Appendix 3. Multilevel Modelling of Prescribing Variability Report

### Tables

**Table 3: Summary of the results of the multiple variable multilevel logistic regression analysis for all indications.**

Explanatory Variables		Step 1: Empty Model	Step 2: + Patient Characteristics	Step 3: + Prescriber Characteristics	Step 4: + Trust Characteristics
<b>Fixed Effects</b>					
Intercept (SE); 95% CI		0.555 (0.255); (0.061, 1.085)	-0.221 (0.283); (-0.721, 0.352)	-0.322 (0.271); (-0.821, 0.218)	-1.023 (0.406); (-1.782, -0.256)
<u>Patient Characteristics; OR (95% CI)</u>					
<i>Patient-specific prescriber reason for prescribing: non-adherence with prior anticoagulant</i>	No		Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p<0.0001
	Yes		20.287 (4.027, 70.708)	22.602 (5.173, 74.696)	22.75 (4.65, 81.803)
<i>Prior/at baseline history of congestive heart failure</i>	No		Reference; LRT p=0.0405	Reference; LRT p=0.0411	Reference; LRT p=0.0472
	Yes		0.669 (0.444, 1.004)	0.67 (0.463, 0.976)	0.675 (0.466, 0.976)
<i>Prior/at baseline history of CVA</i>	No		Reference; LRT p=0.0415	<dropped>	
	Yes		1.431 (1.026, 1.921)		
<i>Prior/at baseline history of hypertension</i>	No		Reference; LRT p=0.0276	Reference; LRT p=0.0243	Reference; LRT p=0.0256
	CHADS2VASC		0.745 (0.58, 0.973)	0.754 (0.575, 0.968)	0.754 (0.554, 0.965)
<i>Indication</i>	CHADS2VASC & HAS-BLED		1.106 (0.821, 1.436)	1.137 (0.889, 1.47)	1.133 (0.849, 1.482)
	DVT/PE		Reference; LRT p=0.0165	Reference; LRT p=0.0171	Reference; LRT p=0.0178
	Mixed		0.353 (0.151, 1.098)	0.35 (0.157, 1.103)	0.35 (0.15, 1.008)
	NVAF/AF		0.933 (0.688, 1.28)	0.949 (0.718, 1.262)	0.95 (0.731, 1.29)
	Other		0.311 (0.137, 0.722)	0.314 (0.125, 0.779)	0.318 (0.131, 0.807)

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<i>Patient-specific prescriber reason for prescribing: lifestyle choice</i>	No	Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p<0.0001
	Yes	49.198 (28.372, 73.431)	50.411 (29.179, 76.27)	50.775 (29.428, 77.595)
<i>Patient-specific prescriber reason for prescribing: poor control</i>	No	Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p<0.0001
	Yes	65.209 (9.244, 171.211)	68.258 (9.713, 157.39)	72.617 (12.206, 169.685)
<i>Patient-specific prescriber reason for prescribing: patient preference</i>	No	Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p<0.0001
	Yes	3.954 (2.13, 7.244)	4.633 (2.515, 8.11)	4.727 (2.551, 7.866)
<i>Patient-specific prescriber reason for prescribing: side-effects with prior anticoagulant</i>	No	Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p<0.0001
	Yes	34.453 (10.078, 80.484)	41.605 (13.087, 104.842)	43.452 (13.911, 109.688)
<b>Prescriber Characteristics</b>				
Percentage of patients with reason for prescribing: expert guidelines			Reference; LRT p=0.0076 0.982 (0.971, 0.995)	Reference; LRT p=0.004 0.981 (0.969, 0.994)
Percentage of patients with reason for prescribing: potential ease of reversibility			Reference; LRT p<0.0001 0.947 (0.927, 0.962)	Reference; LRT p<0.0001 0.946 (0.929, 0.962)
<b>Trust Characteristics</b>				
Type of Trust	Acute			Reference; LRT p=0.0173
	Foundation			2.971 (1.163, 7.268)
	Integrated			0.115 (0.032, 2.912)
<b>Variance Components</b>				
Between-prescriber variance (SE)		1.837 (0.108)	1.802 (0.121)	1.644 (0.118)
SD; 95% CI		1.355 (0.964, 1.383)	1.342 (0.955, 1.433)	1.282 (0.907, 1.369)
				1.683 (0.119)
				1.297 (0.928, 1.398)

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MOR	3.643	3.598	3.397	3.447
PCV	-	-1.9%	-8.8%	2.4%
Between-Trust variance (SE)	3.69 (0.223)	3.862 (0.243)	3.371 (0.23)	2.741 (0.22)
SD; 95% CI	1.921 (1.432, 2.25)	1.965 (1.469, 2.367)	1.836 (1.368, 2.188)	1.656 (1.206, 1.921)
MOR	6.248	6.518	5.762	4.851
PCV	-	4.7%	-12.7%	-18.7%

*CI = Confidence Interval (Parametric Bootstrap); SE = Standard Error (Wald); MOR = Median Odds Ratio; PCV = Proportional Change in the Variance;*

*LRT = Likelihood Ratio Test;*

*Bayesian logistic mixed-effect models using weakly informative Normal priors for the fixed effects to regularise the estimates.*

*The variance at the lowest (patient) level is not determined because the outcome is dichotomous.*

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**Table 4: Summary of the results of the multiple variable multilevel logistic regression analysis for DVT/PE.**

Explanatory Variables		Step 1: Empty Model	Step 2: + Patient Characteristics	Step 3: + Prescriber Characteristics	Step 4: + Trust Characteristics
<b>Fixed Effects</b>					
Intercept (SE); 95% CI		0.576 (0.289); (0.004, 1.142)	-0.203 (0.302); (-0.774, 0.424)	-0.665 (0.344); (-1.33, -0.024)	-1.249 (0.442); (-1.994, -0.441)
<u>Patient Characteristics; OR (95% CI)</u>					
<i>Prior/at baseline history of congestive heart failure</i>	No		Reference; LRT p=0.0003	Reference; LRT p=0.0003	Reference; LRT p=0.0003
	Yes		0.306 (0.163, 0.646)	0.307 (0.149, 0.628)	0.313 (0.156, 0.601)
<i>Patient-specific prescriber reason for prescribing: lifestyle choice</i>	No		Reference; LRT p<0.0001 71.075 (32.818, 114.701)	Reference; LRT p<0.0001	Reference; LRT p<0.0001
	Yes			82.799 (38.524, 141.57)	82.55 (37.671, 149.575)
<i>Patient-specific prescriber reason for prescribing: poor control</i>	No		Reference; LRT p=0.0005	<i>Reference; LRT p=0.0007</i>	Reference; LRT p=0.0009
	Yes		29.882 (2.674, 70.438)		27.917 (2.2, 48.702)
<i>Patient-specific prescriber reason for prescribing: patient preference</i>	No		Reference; LRT p=0.0007	Reference; LRT p=0.0001	Reference; LRT p<0.0001
	Yes		2.994 (1.53, 5.434)	3.533 (1.83, 6.588)	3.678 (1.824, 7.289)
<i>Patient-specific prescriber reason for prescribing: side-effects with prior anticoagulant</i>	No		Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p<0.0001
	Yes		31.803 (6.436, 87.651)	42.49 (6.889, 134.869)	45.78 (8.689, 103.052)
<u>Prescriber Characteristics</u>					
Percentage of patients with reason for prescribing: clinical judgement				Reference; LRT p=0.0201 0.988 (0.979, 0.998)	Reference; LRT p=0.0188 0.988 (0.979, 0.997)

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

Percentage of patients with reason for prescribing: potential ease of reversibility

Specialist status

No

Yes

Reference; LRT  
p<0.0001

0.955 (0.936, 0.971)

Reference; LRT p=0.029

1.675 (1.05, 2.64)

Reference; LRT  
p<0.0001

0.953 (0.935, 0.968)

<dropped>

#### Trust Characteristics

Percentage of hospitals within Trust that are other hospitals

Type of Trust

Acute

Foundation

Integrated

Reference; LRT  
p=0.0031

1.025 (1.009, 1.041)

Reference; LRT  
p=0.0186

3.95 (1.448, 9.917)

0.271 (0.054, 6.197)

#### Variance Components

Between-prescriber variance (SE)

1.116 (0.127)

1.159 (0.158)

0.98 (0.152)

1.014 (0.154)

SD; 95% CI

1.057 (0.557,  
1.144)

1.077 (0.54, 1.223)

0.99 (0.526, 1.115)

1.007 (0.539, 1.14)

MOR

2.74

2.792

2.571

2.613

PCV

-

3.8%

-15.4%

3.4%

Between-Trust variance (SE)

4.17 (0.256)

4.143 (0.287)

4.022 (0.282)

2.806 (0.249)

SD; 95% CI

2.042 (1.487,  
2.464)

2.035 (1.43, 2.428)

2.006 (1.433, 2.403)

1.675 (1.119, 1.968)

MOR

7.013

6.969

6.773

4.942

PCV

-

-0.6%

-2.9%

-30.2%

CI = Confidence Interval (Parametric Bootstrap); SE = Standard Error (Wald); MOR = Median Odds Ratio; PCV = Proportional Change in the Variance;

LRT = Likelihood Ratio Test;

Bayesian logistic mixed-effect models using weakly informative Normal priors for the fixed effects to regularise the estimates.

The variance at the lowest (patient) level is not determined because the outcome is dichotomous.

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

**Table 5: Summary of the results of the multiple variable multilevel logistic regression analysis for NVAf/AF.**

Explanatory Variables		Step 1: Empty Model	Step 2: + Patient Characteristics	Step 3: + Prescriber Characteristics	Step 4: + Trust Characteristics	Step 5: + Disease Scores (Sensitivity Analysis)
<b>Fixed Effects</b>						
Intercept (SE); 95% CI		0.478 (0.311); (-0.197, 1.078)	-0.812 (0.358); (-1.568, -0.188)	-0.622 (0.351); (-1.286, 0.084)	-0.144 (0.663); (-1.321, 0.723)	0.152 (0.674); (-1.113, 1.244)
<u>Patient Characteristics; OR (95% CI)</u>						
Patient-specific prescriber reason for prescribing: non-adherence with prior anticoagulant	No		Reference; LRT p=0.0001	Reference; LRT p=0.0002	Reference; LRT p=0.0002	Reference; LRT p=0.0002
	Yes		47.874 (4.106, 98.891)	40.941 (3.077, 71.695)	46.064 (3.991, 55.561)	48.179 (4.434, 70.617)
Prior/at baseline history of CVA	No		Reference; LRT p=0.0028	Reference; LRT p=0.0051	Reference; LRT p=0.0133	Reference; LRT p=0.0023
	Yes		2.228 (1.362, 3.498)	2.116 (1.365, 3.178)	1.965 (1.299, 2.967)	2.423 (1.572, 3.813)
Prior/at baseline history of hypertension (HAS-BLED)	No		Reference; LRT p=0.0452	Reference; LRT p=0.0315	Reference; LRT p=0.0288	Reference; LRT p=0.0035
	Yes		1.524 (1.058, 2.255)	1.578 (1.075, 2.237)	1.586 (1.052, 2.323)	2.08 (1.277, 3.238)
HAS-BLED score			-	-	-	Reference; LRT p=0.0473 0.804 (0.656, 0.998)
Patient-specific prescriber reason for prescribing: lifestyle choice	No		Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p<0.0001
	Yes		20.931 (9.788, 37.247)	19.168 (9.055, 34.009)	20.056 (9.189, 35.808)	20.097 (9.608, 36.363)
Patient-specific prescriber reason for prescribing: poor control	No		Reference; LRT p=0.0007	Reference; LRT p=0.001	Reference; LRT p=0.001	Reference; LRT p=0.0012
	Yes		30.533 (2.948, 64.119)	28.707 (3.323, 59.197)	27.3 (2.945, 71.642)	25.852 (2.827, 56.505)
Patient-specific prescriber reason for prescribing: patient preference	No		Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p=0.0001	Reference; LRT p=0.0001
	Yes		11.711 (3.005, 38.39)	12.38 (2.839, 34.673)	11.715 (2.698, 40.282)	11.606 (3.044, 39.867)



### Appendix 3. Multilevel Modelling of Prescribing Variability Report

<i>Patient-specific prescriber reason for prescribing: side-effects with prior anticoagulant</i>		Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p<0.0001	Reference; LRT p<0.0001
	No				
	Yes	30.212 (5.522, 91.238)	25.324 (4.991, 77.919)	25.123 (4.594, 70.271)	26.98 (5.553, 81.191)
<u>Prescriber Characteristics</u>					
Professional years registered			Reference; LRT p=0.0203 0.964 (0.934, 0.996)	<dropped>	<dropped>
Percentage of patients with reason for prescribing: NICE recommendations			Reference; LRT p=0.0013 0.984 (0.973, 0.994)	Reference; LRT p=0.0003 0.982 (0.972, 0.992)	Reference; LRT p=0.0003 0.982 (0.973, 0.991)
Percentage of patients with reason for prescribing: potential ease of reversibility			Reference; LRT p=0.0026 0.95 (0.908, 0.982)	Reference; LRT p=0.0018 0.946 (0.9, 0.977)	Reference; LRT p=0.0023 0.948 (0.903, 0.978)
Professional qualification	Medic		Reference; LRT p=0.0068	Reference; LRT p=0.0007	Reference; LRT p=0.0005
	Nurse		0.173 (0.054, 0.707)	0.118 (0.04, 0.493)	0.112 (0.039, 0.389)
<u>Trust Characteristics</u>					
Geographic region	East of England			Reference; LRT p=0.0152 0.098 (0.033, 0.515)	Reference; LRT p=0.0114 0.098 (0.032, 0.561)
	London				
	North			0.636 (0.18, 3.131)	0.651 (0.183, 3.475)
	West				
	South			1.638 (0.385, 8.06)	1.663 (0.398, 7.873)
	East				
	South			2.703 (0.784, 10.411)	2.894 (0.693, 12.324)
	West			0.508 (0.144, 2.775)	0.499 (0.133, 3.346)
West Midlands				0.646 (0.157, 3.571)	0.676 (0.146, 3.543)
Yorkshire and Humber					
<b>Variance Components</b>					

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

Between-prescriber variance (SE)	2.213 (0.202)	2.329 (0.226)	2.064 (0.229)	2.4 (0.235)	2.369 (0.232)
SD; 95% CI	1.488 (0.932, 1.678)	1.526 (0.898, 1.726)	1.437 (0.835, 1.641)	1.549 (0.94, 1.783)	1.539 (0.947, 1.791)
MOR	4.133	4.288	3.937	4.383	4.342
PCV	-	5.20%	-11.40%	16.30%	-1.30%
Between-Trust variance (SE)	4.032 (0.294)	3.822 (0.306)	3.214 (0.291)	1.699 (0.266)	1.623 (0.265)
SD; 95% CI	2.008 (1.391, 2.402)	1.955 (1.277, 2.376)	1.793 (1.105, 2.276)	1.303 (0.521, 1.563)	1.274 (0.197, 1.524)
MOR	6.789	6.455	5.53	3.467	3.371
PCV	-	-5.20%	-15.90%	-47.20%	-4.40%

*CI = Confidence Interval (Parametric Bootstrap); SE = Standard Error (Wald); MOR = Median Odds Ratio; PCV = Proportional Change in the Variance;*

*LRT = Likelihood Ratio Test;*

*Bayesian logistic mixed-effect models using weakly informative Normal priors for the fixed effects to regularise the estimates.*

*The variance at the lowest (patient) level is not determined because the outcome is dichotomous.*

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

#### References

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## Appendix 3. Multilevel Modelling of Prescribing Variability Report

### Appendix

#### Univariate Analysis Tables

##### *All Indications*

**Table 6: Summary of the patient-level results of the univariate multilevel logistic regression analyses for all indications.**

Patient Characteristic	Group	Warfarin (n=1468)	Rivaroxaban (n=2106)	Total (n=3574)	OR (95% CI)
Age at index group	Less than 65	570 (41.2%)	815 (58.8%)	1385 (100%)	Reference; LRT p=0.3661 0.847 (0.658, 1.104) 0.886 (0.701, 1.114)
	65 to 74	390 (42.5%)	527 (57.5%)	917 (100%)	
	75+	508 (39.9%)	764 (60.1%)	1272 (100%)	
Gender	Male	812 (41.2%)	1157 (58.8%)	1969 (100%)	Reference; LRT p=0.706 0.964 (0.778, 1.148)
	Female	656 (40.9%)	949 (59.1%)	1605 (100%)	
Marital status	Married	715 (39.4%)	1100 (60.6%)	1815 (100%)	Reference; LRT p=0.4762 0.869 (0.541, 1.406) 0.985 (0.667, 1.439) 1.134 (0.676, 1.767) 0.964 (0.428, 2.126) 1.388 (0.976, 1.968) 1.169 (0.884, 1.575)
	Co-habiting	66 (40%)	99 (60%)	165 (100%)	
	Divorced	90 (39.8%)	136 (60.2%)	226 (100%)	
	Other/ Unknown	205 (56%)	161 (44%)	366 (100%)	
	Separated	23 (43.4%)	30 (56.6%)	53 (100%)	
	Single	134 (38.8%)	211 (61.2%)	345 (100%)	
	Widowed	235 (38.9%)	369 (61.1%)	604 (100%)	
Self-reported employment status	Full time	235 (37.7%)	388 (62.3%)	623 (100%)	Reference; LRT p=0.0647 1.786 (0.592, 5.684) 1.305 (0.383, 3.868) 0.644 (0.355, 1.152) 0.727 (0.457, 1.198) 0.781 (0.599, 1.02) 0.697 (0.423, 1.169) 1.445 (0.902, 2.384) 0.73 (0.484, 1.064)
	Carer/ Other/ Volunteer/ Student	9 (31%)	20 (69%)	29 (100%)	
	Disabled/ Sick leave	5 (20.8%)	19 (79.2%)	24 (100%)	
	House husband/wife/ Mother/ maternity leave	44 (37.6%)	73 (62.4%)	117 (100%)	
	Part time	69 (41.6%)	97 (58.4%)	166 (100%)	
	Pensioner/ Retired	723 (40%)	1084 (60%)	1807 (100%)	
	Self-employed	56 (43.1%)	74 (56.9%)	130 (100%)	
	Unemployed	61 (33%)	124 (67%)	185 (100%)	
	Unknown	266 (54%)	227 (46%)	493 (100%)	

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Ethnicity	White	1202 (39%)	1880 (61%)	3082 (100%)	Reference; LRT p=0.4645 1.073 (0.563, 2.129)  1.076 (0.52, 2.222) 3.078 (0.893, 10.256) 0.936 (0.585, 1.494)
	Asian	42 (56%)	33 (44%)	75 (100%)	
	Black/ African/ Caribbean	22 (35.5%)	40 (64.5%)	62 (100%)	
	Other	8 (32%)	17 (68%)	25 (100%)	
	Unknown	194 (58.8%)	136 (41.2%)	330 (100%)	
Prior/at baseline history of DVT/PE	No	846 (40.2%)	1256 (59.8%)	2102 (100%)	Reference; LRT p=0.9327 0.991 (0.792, 1.227)
	Yes	622 (42.3%)	850 (57.7%)	1472 (100%)	
Prior/at baseline history of CVA (HAS- BLED narrow def.)	No	1271 (41.7%)	1778 (58.3%)	3049 (100%)	Reference; LRT p=0.3313 1.173 (0.846, 1.644)
	Yes	197 (37.5%)	328 (62.5%)	525 (100%)	
Prior/at baseline history of CVA (CHADS2VASC)	No	1157 (41.9%)	1606 (58.1%)	2763 (100%)	Reference; LRT p=0.0958 1.283 (0.929, 1.687)
	Yes	311 (38.3%)	500 (61.7%)	811 (100%)	
Prior/at baseline history of abnormal liver function	No	1441 (41%)	2071 (59%)	3512 (100%)	Reference; LRT p=0.5686 0.826 (0.405, 1.711)
	Yes	27 (43.5%)	35 (56.5%)	62 (100%)	
Prior/at baseline history of renal disease	No	1433 (40.9%)	2070 (59.1%)	3503 (100%)	Reference; LRT p=0.1035 0.598 (0.307, 1.146)
	Yes	35 (49.3%)	36 (50.7%)	71 (100%)	
Prior/at baseline history of diabetes mellitus	No	1226 (40.2%)	1821 (59.8%)	3047 (100%)	Reference; LRT p=0.4073 0.895 (0.673, 1.158)
	Yes	242 (45.9%)	285 (54.1%)	527 (100%)	
Prior/at baseline history of congestive heart failure	No	1307 (40.3%)	1938 (59.7%)	3245 (100%)	Reference; LRT p=0.0268 0.692 (0.522, 0.959)
	Yes	161 (48.9%)	168 (51.1%)	329 (100%)	
Prior/at baseline history of vascular disease	No	1233 (40.8%)	1790 (59.2%)	3023 (100%)	Reference; LRT p=0.1121 0.799 (0.601, 1.033)
	Yes	235 (42.6%)	316 (57.4%)	551 (100%)	
Prior/at baseline history of hypertension (CHADS2VASC)	No	568 (36.3%)	996 (63.7%)	1564 (100%)	Reference; LRT p=0.0468 0.813 (0.665, 0.995)
	Yes	900 (44.8%)	1110 (55.2%)	2010 (100%)	

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Prior/at baseline history of hypertension (HAS-BLED)	No	988 (39%)	1546 (61%)	2534 (100%)	Reference; LRT p=0.283 1.134 (0.888, 1.456)
	Yes	480 (46.2%)	560 (53.8%)	1040 (100%)	
Prior/at baseline history of hypertension	No	568 (36.3%)	996 (63.7%)	1564 (100%)	Reference; LRT p=0.006 0.691 (0.547, 0.894) 0.976 (0.777, 1.23)
	CHADS2VASC	420 (43.3%)	550 (56.7%)	970 (100%)	
	CHADS2VASC & HAS-BLED	480 (46.2%)	560 (53.8%)	1040 (100%)	
Prior/at baseline history of bleeding predisposition	No	1089 (39%)	1703 (61%)	2792 (100%)	Reference; LRT p=0.0206 0.763 (0.611, 0.958)
	Yes	379 (48.5%)	403 (51.5%)	782 (100%)	
Prior/at baseline history of medications predisposing to bleeds	No	884 (39.5%)	1354 (60.5%)	2238 (100%)	Reference; LRT p=0.7143 0.96 (0.771, 1.223)
	Yes	584 (43.7%)	752 (56.3%)	1336 (100%)	
Prior/at baseline history of excessive alcohol consumption/alcohol misuse	No	1383 (40.8%)	2007 (59.2%)	3390 (100%)	Reference; LRT p=0.4755 1.167 (0.774, 1.867)
	Yes	85 (46.2%)	99 (53.8%)	184 (100%)	
Prior smoking	No	1056 (40.4%)	1556 (59.6%)	2612 (100%)	Reference; LRT p=0.5495 1.071 (0.866, 1.325)
	Yes	412 (42.8%)	550 (57.2%)	962 (100%)	
Prior substance misuse	No	1454 (41.2%)	2075 (58.8%)	3529 (100%)	Reference; LRT p=0.0448 2.313 (0.917, 5.693)
	Yes	14 (31.1%)	31 (68.9%)	45 (100%)	
HAS-BLED score group	Low	660 (37.4%)	1103 (62.6%)	1763 (100%)	Reference; LRT p=0.4832 0.866 (0.678, 1.111) 0.9 (0.719, 1.177)
	Moderate	341 (43.3%)	446 (56.7%)	787 (100%)	
	High	467 (45.6%)	557 (54.4%)	1024 (100%)	
CHADS2VASC score group	Low	171 (35.2%)	315 (64.8%)	486 (100%)	Reference; LRT p=0.0221 0.68 (0.497, 0.955) 0.669 (0.504, 0.917)
	Moderate	281 (42.4%)	381 (57.6%)	662 (100%)	
	High	1016 (41.9%)	1410 (58.1%)	2426 (100%)	
Patient-specific prescriber reason for prescribing: lifestyle choice	No	1411 (50.2%)	1398 (49.8%)	2809 (100%)	Reference; LRT p<0.0001 44.745 (25.689, 65.779)
	Yes	57 (7.5%)	708 (92.5%)	765 (100%)	

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Patient-specific prescriber reason for prescribing: non-adherence with prior anticoagulant		No	1467 (41.4%)	2076 (58.6%)	3543 (100%)	Reference; LRT p<0.0001
		Yes	1 (3.2%)	30 (96.8%)	31 (100%)	17.368 (4.561, 57.631)
Patient-specific prescriber reason for prescribing: side-effects with prior anticoagulant		No	1464 (41.8%)	2036 (58.2%)	3500 (100%)	Reference; LRT p<0.0001
		Yes	4 (5.4%)	70 (94.6%)	74 (100%)	22.182 (7.977, 52.893)
Patient-specific prescriber reason for prescribing: patient preference		No	1428 (42.6%)	1928 (57.4%)	3356 (100%)	Reference; LRT p<0.0001
		Yes	40 (18.3%)	178 (81.7%)	218 (100%)	2.835 (1.699, 4.75)
Patient-specific prescriber reason for prescribing: poor control		No	1468 (41.4%)	2075 (58.6%)	3543 (100%)	Reference; LRT p<0.0001
		Yes	0 (0%)	31 (100%)	31 (100%)	53.013 (9.331, 118.258)
Age at index			66.1 (15.9); 68.5 (18-95)	66.2 (16.3); 69 (18-101)	66.2 (16.2); 69 (18-101)	0.996 (0.989, 1.002); LRT p=0.1621
Index of multiple deprivation rank decile			5.5 (2.8); 6 (1-10)	5.7 (2.7); 6 (1-10)	5.7 (2.7); 6 (1-10)	0.998 (0.963, 1.035); LRT p=0.9186
Index of multiple deprivation rank			16563.9 (9074.2); 16432 (21-32798)	17181.1 (9034); 17189.5 (21-32838)	16927.6 (9054.3); 16857.5 (21-32838)	1 (1, 1); LRT p=0.907
HAS-BLED score			1.8 (1.3); 2 (0-6)	1.7 (1.3); 1 (0-7)	1.7 (1.3); 2 (0-7)	0.959 (0.884, 1.038); LRT p=0.3077
CHADS2VASC score			2.9 (2); 3 (0-9)	2.8 (2.1); 3 (0-9)	2.8 (2); 3 (0-9)	0.963 (0.909, 1.012); LRT p=0.1765
Indication	DVT/PE		800 (39.7%)	1214 (60.3%)	2014 (100%)	Reference; LRT p=0.0152
	Mixed		22 (53.7%)	19 (46.3%)	41 (100%)	0.505 (0.219, 1.271)
	NVA/AF		618 (41.9%)	856 (58.1%)	1474 (100%)	0.832 (0.637, 1.078)
	Other		28 (62.2%)	17 (37.8%)	45 (100%)	0.333 (0.148, 0.836)
*Professional years registered (prescriber characteristic)			23.9 (11.2); 22.8 (0.578-63.811)	21.7 (9.4); 20.6 (0.611-56.186)	22.6 (10.3); 21.4 (0.578-63.811)	0.996 (0.978, 1.012); LRT p=0.614

Categorical variable summaries show the number (%) of patients per group. Continuous variable summaries show the mean (standard deviation); median (range). CI = Confidence Interval (Parametric Bootstrap); LRT = Likelihood Ratio Test; OR = Odds Ratio. \*Prescriber characteristic that varies between patients.

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**Table 7: Summary of the prescriber-level results of the univariate multilevel logistic regression analyses for all indications.**

Prescriber Characteristic	Group	Warfarin (n=275)	Warfarin/ Rivaroxaban (n=181)	Rivaroxaban (n=324)	Total (n=780)	OR (95% CI)
Gender	Male	188 (36.8%)	120 (23.5%)	203 (39.7%)	511 (100%)	Reference; LRT p=0.5373
	Female	87 (32.3%)	61 (22.7%)	121 (45%)	269 (100%)	1.124 (0.779, 1.707)
Professional qualification	Medic	259 (36%)	155 (21.6%)	305 (42.4%)	719 (100%)	Reference; LRT p=0.8112
	Nurse	16 (26.2%)	26 (42.6%)	19 (31.1%)	61 (100%)	0.924 (0.477, 1.832)
Career level	Junior	51 (40.2%)	13 (10.2%)	63 (49.6%)	127 (100%)	Reference; LRT p=0.6218
	Mid-level	45 (29%)	36 (23.2%)	74 (47.7%)	155 (100%)	1.324 (0.71, 2.56)
	Senior level	179 (35.9%)	132 (26.5%)	187 (37.6%)	498 (100%)	1.314 (0.68, 2.31)
Specialist status	No	95 (36%)	40 (15.2%)	129 (48.9%)	264 (100%)	Reference; LRT p=0.2261
	Yes	180 (34.9%)	141 (27.3%)	195 (37.8%)	516 (100%)	1.29 (0.835, 1.948)
Clinical specialism	Haematology	12 (19.4%)	16 (25.8%)	34 (54.8%)	62 (100%)	Reference; LRT p<0.0001
	A&E	4 (23.5%)	3 (17.6%)	10 (58.8%)	17 (100%)	1.026 (0.288, 3.926)
	Acute Medicine	35 (41.7%)	20 (23.8%)	29 (34.5%)	84 (100%)	0.485 (0.267, 1.085)
	Anticoagulation	7 (19.4%)	16 (44.4%)	13 (36.1%)	36 (100%)	1.266 (0.558, 3.682)
	Cardiology	51 (39.8%)	28 (21.9%)	49 (38.3%)	128 (100%)	0.488 (0.281, 1.125)
	Care of Elderly	26 (53.1%)	6 (12.2%)	17 (34.7%)	49 (100%)	0.297 (0.136, 0.822)
	Endocrinology	7 (46.7%)	4 (26.7%)	4 (26.7%)	15 (100%)	0.187 (0.063, 0.825)
	Gastroenterology	10 (58.8%)	2 (11.8%)	5 (29.4%)	17 (100%)	0.152 (0.044, 0.772)
	General Medicine	43 (34.1%)	17 (13.5%)	66 (52.4%)	126 (100%)	0.485 (0.267, 1.169)
	Neurology	4 (23.5%)	3 (17.6%)	10 (58.8%)	17 (100%)	2.785 (0.541, 15.845)
	Other	22 (55%)	5 (12.5%)	13 (32.5%)	40 (100%)	0.266 (0.105, 0.851)
	Research	1 (20%)	2 (40%)	2 (40%)	5 (100%)	0.325 (0.057, 3.833)
	Respiratory	27 (36.5%)	21 (28.4%)	26 (35.1%)	74 (100%)	0.349 (0.188, 0.896)
	Stroke	26 (23.6%)	38 (34.5%)	46 (41.8%)	110 (100%)	1.394 (0.744, 3.172)



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Percentage of patients with reason for prescribing: clinical judgement	87.3 (32.5); 100 (0-100)	86.7 (23.5); 100 (0-100)	85.4 (32.2); 100 (0-100)	86.3 (30.5); 100 (0-100)	0.996 (0.988, 1.004); LRT p=0.2974
Percentage of patients with reason for prescribing: NICE recommendations	37.9 (46.9); 0 (0-100)	38.4 (37.9); 33.3 (0-100)	36.7 (45.6); 0 (0-100)	37.5 (44.4); 0 (0-100)	0.994 (0.988, 1.001); LRT p=0.0589
Percentage of patients with reason for prescribing: expert guidelines	8.3 (26.3); 0 (0-100)	7.4 (20.7); 0 (0-100)	3.1 (15.6); 0 (0-100)	6 (21.2); 0 (0-100)	0.983 (0.97, 0.996); LRT p=0.0066
Percentage of patients with reason for prescribing: hospital formulary	12.8 (32.2); 0 (0-100)	15.6 (27.9); 0 (0-100)	20.3 (38.2); 0 (0-100)	16.6 (34.1); 0 (0-100)	0.998 (0.991, 1.007); LRT p=0.7089
Percentage of patients with reason for prescribing: patient group direction	2.7 (15.5); 0 (0-100)	5.9 (17.9); 0 (0-95.238)	5.9 (22.5); 0 (0-100)	4.8 (19.2); 0 (0-100)	1.006 (0.995, 1.017); LRT p=0.3735
Percentage of patients with reason for prescribing: potential ease of reversibility	7.8 (25.5); 0 (0-100)	6 (13.3); 0 (0-50)	0.4 (5.8); 0 (0-100)	4.3 (17.2); 0 (0-100)	0.955 (0.937, 0.97); LRT p<0.0001

Categorical variable summaries show the number (%) of patients per group. Continuous variable summaries show the mean (standard deviation); median (range). CI = Confidence Interval (Parametric Bootstrap); LRT = Likelihood Ratio Test; OR = Odds Ratio.

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

**Table 8: Summary of the trust-level results of the univariate multilevel logistic regression analyses for all indications.**

Trust Characteristic	Group	Warfarin (n=3)	Warfarin/Rivaroxaban (n=60)	Rivaroxaban (n=10)	Total (n=73)	OR (95% CI)
Geographic region	East of England	0 (0%)	6 (85.7%)	1 (14.3%)	7 (100%)	Reference; LRT p=0.4477
	London	1 (10%)	9 (90%)	0 (0%)	10 (100%)	0.361 (0.079, 1.696)
	North West	1 (7.1%)	11 (78.6%)	2 (14.3%)	14 (100%)	0.942 (0.224, 4.04)
	South East	1 (12.5%)	4 (50%)	3 (37.5%)	8 (100%)	1.245 (0.174, 6.086)
	South West	0 (0%)	12 (80%)	3 (20%)	15 (100%)	2.579 (0.615, 9.347)
	West Midlands	0 (0%)	9 (100%)	0 (0%)	9 (100%)	1.28 (0.272, 6.019)
	Yorkshire and Humber	0 (0%)	9 (90%)	1 (10%)	10 (100%)	0.992 (0.21, 5.31)
Type of Trust	Acute	1 (4%)	20 (80%)	4 (16%)	25 (100%)	Reference; LRT p=0.1072
	Foundation	2 (4.3%)	39 (83%)	6 (12.8%)	47 (100%)	2.156 (0.797, 4.925)
	Integrated	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0.147 (0.044, 4.011)
Number of hospitals within Trust participating in ROSE study	1	3 (5.1%)	48 (81.4%)	8 (13.6%)	59 (100%)	Reference; LRT p=0.52
	2	0 (0%)	8 (80%)	2 (20%)	10 (100%)	1.146 (0.293, 4.685)
	3	0 (0%)	4 (100%)	0 (0%)	4 (100%)	0.36 (0.054, 2.897)
Catchment population served		459570 (351064.7); 296702 (219520-862488)	421253.1 (199290.6); 358060 (96605-1070599)	354572 (98148.9); 367536.5 (162215-469793)	413693.4 (194407.1); 357445 (96605-1070599)	1 (1, 1); LRT p=0.8143
Catchment population served group		5 (3.5); 3 (3-9)	4.7 (2); 4 (1-10)	4 (1.1); 4 (2-5)	4.6 (1.9); 4 (1-10)	1.022 (0.792, 1.331); LRT p=0.8692
Socioeconomic status of Trust population served - index of multiple deprivation rank decile		3.7 (2.1); 3 (2-6)	5.3 (2.6); 5 (1-10)	5.4 (2.1); 5.5 (3-8)	5.3 (2.5); 5 (1-10)	1.12 (0.927, 1.372); LRT p=0.253
Socioeconomic status of Trust population served - index of multiple deprivation rank		9952.7 (6860.2); 6674 (5347-17837)	15865.6 (8580.4); 15578 (918-32664)	15747.7 (6526.1); 15452.5 (7751-24840)	15606.5 (8267.5); 15234 (918-32664)	1 (1, 1); LRT p=0.243

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Number of hospitals within Trust	6 (1); 6 (5-7)	6 (3.5); 5.5 (1-14)	5.9 (4); 5 (1-11)	6 (3.5); 6 (1-14)	1.021 (0.895, 1.164); LRT p=0.7814
Percentage of hospitals within Trust that are teaching hospitals	0 (0); 0 (0-0)	11.9 (30.9); 0 (0-100)	5 (15.8); 0 (0-50)	10.5 (28.7); 0 (0-100)	0.995 (0.977, 1.013); LRT p=0.562
Percentage of hospitals within Trust that are general hospitals	33.3 (57.7); 0 (0-100)	78.6 (38.3); 100 (0-100)	65 (47.4); 100 (0-100)	74.9 (40.9); 100 (0-100)	0.997 (0.985, 1.01); LRT p=0.6855
Percentage of hospitals within Trust that are other hospitals	66.7 (57.7); 100 (0-100)	9.4 (27.3); 0 (0-100)	30 (48.3); 0 (0-100)	14.6 (34.1); 0 (0-100)	1.009 (0.993, 1.023); LRT p=0.2887
Proportion of hospitals within Trust participating in ROSE study	0.2 (0); 0.2 (0.143-0.2)	0.3 (0.3); 0.2 (0.071-2)	0.3 (0.3); 0.2 (0.1-1)	0.3 (0.3); 0.2 (0.071-2)	0.715 (0.208, 3.435); LRT p=0.6555

Categorical variable summaries show the number (%) of patients per group. Continuous variable summaries show the mean (standard deviation); median (range). CI = Confidence Interval (Parametric Bootstrap); LRT = Likelihood Ratio Test; OR = Odds Ratio.

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#### DVT/PE

**Table 9: Summary of the patient-level results of the univariate multilevel logistic regression analyses for DVT/PE.**

Patient Characteristic	Group	Warfarin (n=800)	Rivaroxaban (n=1214)	Total (n=2014)	OR (95% CI)
Age at index group	Less than 65	430 (39.1%)	669 (60.9%)	1099 (100%)	Reference; LRT p=0.3646 0.802 (0.583, 1.081) 0.9 (0.663, 1.254)
	65 to 74	195 (39.9%)	294 (60.1%)	489 (100%)	
	75+	175 (41.1%)	251 (58.9%)	426 (100%)	
Gender	Male	436 (39.1%)	678 (60.9%)	1114 (100%)	Reference; LRT p=0.8709 1.021 (0.782, 1.308)
	Female	364 (40.4%)	536 (59.6%)	900 (100%)	
Marital status	Married	378 (38.4%)	607 (61.6%)	985 (100%)	Reference; LRT p=0.1354 0.87 (0.524, 1.44) 1.13 (0.693, 1.953) 1.269 (0.706, 2.264) 0.807 (0.315, 2.14) 1.789 (1.162, 2.548) 1.088 (0.689, 1.662)
	Co-habiting	50 (36.5%)	87 (63.5%)	137 (100%)	
	Divorced	50 (37.6%)	83 (62.4%)	133 (100%)	
	Other/ Unknown	114 (51.1%)	109 (48.9%)	223 (100%)	
	Separated	15 (42.9%)	20 (57.1%)	35 (100%)	
	Single	93 (35.4%)	170 (64.6%)	263 (100%)	
	Widowed	100 (42%)	138 (58%)	238 (100%)	
Self-reported employment status	Full time	178 (36.2%)	314 (63.8%)	492 (100%)	Reference; LRT p=0.0864 1.355 (0.496, 4.162) 0.972 (0.287, 3.77) 0.471 (0.239, 1.027) 0.716 (0.394, 1.301) 0.741 (0.522, 1.014) 0.766 (0.434, 1.44) 1.518 (0.834, 2.567) 0.655 (0.392, 1.068)
	Carer/ Other/ Volunteer/ Student	9 (36%)	16 (64%)	25 (100%)	
	Disabled/ Sick leave	5 (25%)	15 (75%)	20 (100%)	
	House husband/wife/ Mother/ maternity leave	31 (44.3%)	39 (55.7%)	70 (100%)	
	Part time	48 (40%)	72 (60%)	120 (100%)	
	Pensioner/ Retired	304 (39.9%)	457 (60.1%)	761 (100%)	
	Self-employed	37 (37.8%)	61 (62.2%)	98 (100%)	
	Unemployed	40 (29.9%)	94 (70.1%)	134 (100%)	
	Unknown	148 (50.3%)	146 (49.7%)	294 (100%)	
Ethnicity	White	653 (38.4%)	1049 (61.6%)	1702 (100%)	Reference; LRT p=0.6268 1.434 (0.608, 3.531) 1.112 (0.476, 2.273)
	Asian	22 (47.8%)	24 (52.2%)	46 (100%)	
	Black/ African/ Caribbean	15 (30%)	35 (70%)	50 (100%)	

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	Other	4 (25%)	12 (75%)	16 (100%)	2.802 (0.683, 13.671)
	Unknown	106 (53%)	94 (47%)	200 (100%)	1.049 (0.571, 1.934)
Prior/at baseline history of DVT/PE	No	222 (35.2%)	409 (64.8%)	631 (100%)	Reference; LRT p=0.238
	Yes	578 (41.8%)	805 (58.2%)	1383 (100%)	0.83 (0.625, 1.136)
Prior/at baseline history of CVA (HAS-BLED narrow def.)	No	753 (39.4%)	1159 (60.6%)	1912 (100%)	Reference; LRT p=0.441
	Yes	47 (46.1%)	55 (53.9%)	102 (100%)	0.805 (0.443, 1.376)
Prior/at baseline history of CVA (CHADS2VASC)	No	721 (38.9%)	1133 (61.1%)	1854 (100%)	Reference; LRT p=0.2222
	Yes	79 (49.4%)	81 (50.6%)	160 (100%)	0.754 (0.454, 1.277)
Prior/at baseline history of abnormal liver function	No	784 (39.8%)	1187 (60.2%)	1971 (100%)	Reference; LRT p=0.8282
	Yes	16 (37.2%)	27 (62.8%)	43 (100%)	0.91 (0.37, 2.284)
Prior/at baseline history of renal disease	No	785 (39.7%)	1193 (60.3%)	1978 (100%)	Reference; LRT p=0.7502
	Yes	15 (41.7%)	21 (58.3%)	36 (100%)	0.867 (0.361, 2.135)
Prior/at baseline history of diabetes mellitus	No	697 (38.9%)	1095 (61.1%)	1792 (100%)	Reference; LRT p=0.094
	Yes	103 (46.4%)	119 (53.6%)	222 (100%)	0.723 (0.493, 1.108)
Prior/at baseline history of congestive heart failure	No	750 (39%)	1175 (61%)	1925 (100%)	Reference; LRT p=0.0003
	Yes	50 (56.2%)	39 (43.8%)	89 (100%)	0.345 (0.184, 0.669)
Prior/at baseline history of vascular disease	No	718 (38.7%)	1139 (61.3%)	1857 (100%)	Reference; LRT p=0.0053
	Yes	82 (52.2%)	75 (47.8%)	157 (100%)	0.526 (0.338, 0.821)
Prior/at baseline history of hypertension (CHADS2VASC)	No	448 (37.7%)	739 (62.3%)	1187 (100%)	Reference; LRT p=0.05
	Yes	352 (42.6%)	475 (57.4%)	827 (100%)	0.772 (0.612, 1.003)
Prior/at baseline history of hypertension (HAS-BLED)	No	637 (39.3%)	984 (60.7%)	1621 (100%)	Reference; LRT p=0.5541
	Yes	163 (41.5%)	230 (58.5%)	393 (100%)	0.907 (0.669, 1.284)
Prior/at baseline history of hypertension	No	448 (37.7%)	739 (62.3%)	1187 (100%)	Reference; LRT p=0.115

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	CHADS2VASC	189 (43.5%)	245 (56.5%)	434 (100%)	0.723 (0.529, 1.005)
	CHADS2VASC & HAS-BLED	163 (41.5%)	230 (58.5%)	393 (100%)	0.833 (0.58, 1.204)
Prior/at baseline history of bleeding predisposition	No	575 (37.4%)	964 (62.6%)	1539 (100%)	Reference; LRT p=0.0581 0.752 (0.557, 1.021)
	Yes	225 (47.4%)	250 (52.6%)	475 (100%)	
Prior/at baseline history of medications predisposing to bleeds	No	620 (40.3%)	918 (59.7%)	1538 (100%)	Reference; LRT p=0.4969 1.112 (0.805, 1.439)
	Yes	180 (37.8%)	296 (62.2%)	476 (100%)	
Prior/at baseline history of excessive alcohol consumption/alcohol misuse	No	751 (39.5%)	1149 (60.5%)	1900 (100%)	Reference; LRT p=0.8229 0.938 (0.57, 1.73)
	Yes	49 (43%)	65 (57%)	114 (100%)	
Prior smoking	No	589 (41.3%)	837 (58.7%)	1426 (100%)	Reference; LRT p=0.7021 1.059 (0.777, 1.419)
	Yes	211 (35.9%)	377 (64.1%)	588 (100%)	
Prior substance misuse	No	787 (39.9%)	1187 (60.1%)	1974 (100%)	Reference; LRT p=0.1262 2.07 (0.773, 4.719)
	Yes	13 (32.5%)	27 (67.5%)	40 (100%)	
HAS-BLED score group	Low	496 (38.6%)	789 (61.4%)	1285 (100%)	Reference; LRT p=0.5746 0.898 (0.654, 1.215) 0.839 (0.569, 1.232)
	Moderate	167 (40.2%)	248 (59.8%)	415 (100%)	
	High	137 (43.6%)	177 (56.4%)	314 (100%)	
CHADS2VASC score group	Low	157 (34.1%)	304 (65.9%)	461 (100%)	Reference; LRT p=0.0376 0.719 (0.514, 1.034) 0.653 (0.469, 0.903)
	Moderate	231 (42.1%)	318 (57.9%)	549 (100%)	
	High	412 (41%)	592 (59%)	1004 (100%)	
Patient-specific prescriber reason for prescribing: lifestyle choice	No	781 (51.7%)	730 (48.3%)	1511 (100%)	Reference; LRT p<0.0001 62.349 (29.488, 102.734)
	Yes	19 (3.8%)	484 (96.2%)	503 (100%)	
Patient-specific prescriber reason for prescribing: non-adherence with prior anticoagulant	No	799 (39.9%)	1202 (60.1%)	2001 (100%)	Reference; LRT p=0.0711 4.649 (0.934, 22.822)
	Yes	1 (7.7%)	12 (92.3%)	13 (100%)	

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Patient-specific prescriber reason for prescribing: side-effects with prior anticoagulant	No	798 (40.4%)	1179 (59.6%)	1977 (100%)	Reference; LRT p<0.0001 17.189 (4.217, 63.941)
	Yes	2 (5.4%)	35 (94.6%)	37 (100%)	
Patient-specific prescriber reason for prescribing: patient preference	No	765 (41.1%)	1096 (58.9%)	1861 (100%)	Reference; LRT p=0.0067 2.132 (1.175, 3.781)
	Yes	35 (22.9%)	118 (77.1%)	153 (100%)	
Patient-specific prescriber reason for prescribing: poor control	No	800 (40%)	1202 (60%)	2002 (100%)	Reference; LRT p=0.0007 25 (2.681, 64.71)
	Yes	0 (0%)	12 (100%)	12 (100%)	
Age at index		60.6 (16.7); 63 (18-95)	59.9 (16.6); 62 (18-97)	60.2 (16.7); 62.5 (18-97)	0.994 (0.986, 1.002); LRT p=0.1011
Index of multiple deprivation rank decile		5.6 (2.7); 6 (1-10)	5.5 (2.7); 5 (1-10)	5.5 (2.7); 5 (1-10)	0.961 (0.916, 1.008); LRT p=0.1123
Index of multiple deprivation rank		16603 (9061.8); 16636 (21-32798)	16431.8 (8999.3); 16178 (21-32817)	16499.8 (9022.3); 16347 (21-32817)	1 (1, 1); LRT p=0.105
HAS-BLED score		1.3 (1.2); 1 (0-6)	1.2 (1.2); 1 (0-6)	1.3 (1.2); 1 (0-6)	0.922 (0.837, 1.036); LRT p=0.1434
CHADS2VASC score		2.1 (1.8); 2 (0-8)	1.8 (1.6); 1 (0-8)	1.9 (1.7); 1 (0-8)	0.906 (0.845, 0.974); LRT p=0.0095
*Professional years registered ( <b>prescriber characteristic</b> )		21.8 (11.4); 20.7 (0.592-50.622)	20.9 (9.1); 20 (0.611-56.186)	21.3 (10); 20.2 (0.592-56.186)	1.008 (0.989, 1.028); LRT p=0.3835

Categorical variable summaries show the number (%) of patients per group. Continuous variable summaries show the mean (standard deviation); median (range). CI = Confidence Interval (Parametric Bootstrap); LRT = Likelihood Ratio Test; OR = Odds Ratio. \*Prescriber characteristic that varies between patients.

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

**Table 10: Summary of the prescriber-level results of the univariate multilevel logistic regression analyses for DVT/PE.**

Prescriber Characteristic	Group	Warfarin (n=205)	Warfarin/Rivaroxaban (n=119)	Rivaroxaban (n=245)	Total (n=569)	OR (95% CI)
Gender	Male	135 (38.7%)	72 (20.6%)	142 (40.7%)	349 (100%)	Reference; LRT p=0.0814
	Female	70 (31.8%)	47 (21.4%)	103 (46.8%)	220 (100%)	1.433 (0.962, 2.111)
Professional qualification	Medic	192 (37.4%)	98 (19.1%)	223 (43.5%)	513 (100%)	Reference; LRT p=0.3073
	Nurse	13 (23.2%)	21 (37.5%)	22 (39.3%)	56 (100%)	1.427 (0.749, 2.798)
Career level	Junior	44 (44.9%)	10 (10.2%)	44 (44.9%)	98 (100%)	Reference; LRT p=0.6494
	Mid-level	36 (29.5%)	30 (24.6%)	56 (45.9%)	122 (100%)	1.29 (0.658, 2.627)
	Senior level	125 (35.8%)	79 (22.6%)	145 (41.5%)	349 (100%)	1.325 (0.746, 2.437)
Specialist status	No	88 (42.3%)	29 (13.9%)	91 (43.8%)	208 (100%)	Reference; LRT p=0.0142
	Yes	117 (32.4%)	90 (24.9%)	154 (42.7%)	361 (100%)	1.7 (1.081, 2.734)
Clinical specialism	Haematology	12 (20%)	13 (21.7%)	35 (58.3%)	60 (100%)	Reference; LRT p=0.0002
	A&E	4 (23.5%)	3 (17.6%)	10 (58.8%)	17 (100%)	0.62 (0.223, 2.408)
	Acute Medicine	33 (42.3%)	18 (23.1%)	27 (34.6%)	78 (100%)	0.434 (0.24, 1.166)
	Anticoagulation	4 (12.1%)	14 (42.4%)	15 (45.5%)	33 (100%)	1.066 (0.5, 3.535)
	Cardiology	25 (41.7%)	10 (16.7%)	25 (41.7%)	60 (100%)	0.433 (0.227, 1.222)
	Care of Elderly	19 (55.9%)	3 (8.8%)	12 (35.3%)	34 (100%)	0.169 (0.075, 0.642)
	Endocrinology	7 (50%)	3 (21.4%)	4 (28.6%)	14 (100%)	0.09 (0.031, 0.547)
	Gastroenterology	8 (57.1%)	2 (14.3%)	4 (28.6%)	14 (100%)	0.121 (0.038, 0.768)
	General Medicine	35 (35.7%)	14 (14.3%)	49 (50%)	98 (100%)	0.305 (0.183, 0.886)
	Neurology	0 (0%)	0 (0%)	5 (100%)	5 (100%)	5.673 (0.429, 20.436)
	Other	20 (60.6%)	2 (6.1%)	11 (33.3%)	33 (100%)	0.116 (0.045, 0.494)



### Appendix 3. Multilevel Modelling of Prescribing Variability Report

Research	1 (20%)	2 (40%)	2 (40%)	5 (100%)	0.313 (0.054, 2.324) 0.247 (0.135, 0.667) 0.373 (0.198, 1.142)
Respiratory	26 (36.1%)	21 (29.2%)	25 (34.7%)	72 (100%)	
Stroke	11 (23.9%)	14 (30.4%)	21 (45.7%)	46 (100%)	
Percentage of patients with reason for prescribing: clinical judgement	88.5 (30.5); 100 (0-100)	88.1 (21.1); 100 (0-100)	82.8 (33.7); 100 (0-100)	85.9 (30.4); 100 (0-100)	0.984 (0.975, 0.993); LRT p=0.0005
Percentage of patients with reason for prescribing: NICE recommendations	34.9 (45.3); 0 (0-100)	36.4 (38.3); 25 (0-100)	39.8 (45.6); 0 (0-100)	37.3 (44.1); 0 (0-100)	0.999 (0.993, 1.006); LRT p=0.8006
Percentage of patients with reason for prescribing: expert guidelines	7.7 (25.3); 0 (0-100)	9.3 (23.1); 0 (0-100)	4.1 (16.8); 0 (0-100)	6.5 (21.6); 0 (0-100)	0.988 (0.973, 1.003); LRT p=0.0751
Percentage of patients with reason for prescribing: hospital formulary	12.4 (30.9); 0 (0-100)	16.1 (28.1); 0 (0-100)	26.5 (41.1); 0 (0-100)	19.3 (35.7); 0 (0-100)	1.002 (0.994, 1.01); LRT p=0.652
Percentage of patients with reason for prescribing: patient group direction	2.1 (13.1); 0 (0-100)	7.2 (19.5); 0 (0-95.238)	7.7 (25.4); 0 (0-100)	5.6 (20.6); 0 (0-100)	1.016 (1.005, 1.03); LRT p=0.0178
Percentage of patients with reason for prescribing: potential ease of reversibility	8.1 (25.5); 0 (0-100)	6.9 (13.5); 0 (0-50)	1.1 (8.1); 0 (0-100)	4.8 (17.6); 0 (0-100)	0.965 (0.948, 0.978); LRT p<0.0001

Categorical variable summaries show the number (%) of patients per group. Continuous variable summaries show the mean (standard deviation); median (range). CI = Confidence Interval (Parametric Bootstrap); LRT = Likelihood Ratio Test; OR = Odds Ratio.

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

**Table 11: Summary of the trust-level results of the univariate multilevel logistic regression analyses for DVT/PE.**

Trust Characteristic	Group	Warfarin (n=5)	Warfarin/Rivaroxaban (n=48)	Rivaroxaban (n=11)	Total (n=64)	OR (95% CI)
Geographic region	East of England	1 (16.7%)	5 (83.3%)	0 (0%)	6 (100%)	Reference; LRT p=0.5274
	London	1 (12.5%)	5 (62.5%)	2 (25%)	8 (100%)	1.189 (0.149, 4.305)
	North West	1 (7.1%)	10 (71.4%)	3 (21.4%)	14 (100%)	1.86 (0.301, 6.619)
	South East	0 (0%)	4 (80%)	1 (20%)	5 (100%)	1.948 (0.28, 8.461)
	South West	0 (0%)	12 (85.7%)	2 (14.3%)	14 (100%)	4.573 (0.739, 13.189)
	West Midlands and Yorkshire	1 (11.1%)	7 (77.8%)	1 (11.1%)	9 (100%)	1.99 (0.256, 6.732)
	Humber	1 (12.5%)	5 (62.5%)	2 (25%)	8 (100%)	3.974 (0.461, 15.305)
Type of Trust	Acute	2 (10%)	15 (75%)	3 (15%)	20 (100%)	Reference; LRT p=0.0825
	Foundation	3 (7%)	32 (74.4%)	8 (18.6%)	43 (100%)	3.161 (1.111, 8.308)
	Integrated	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0.325 (0.073, 10.119)
Number of hospitals within Trust participating in ROSE study	1	5 (9.4%)	38 (71.7%)	10 (18.9%)	53 (100%)	Reference; LRT p=0.8971
	2	0 (0%)	8 (88.9%)	1 (11.1%)	9 (100%)	0.8 (0.157, 3.474)
	3	0 (0%)	2 (100%)	0 (0%)	2 (100%)	0.654 (0.076, 9.505)
Catchment population served		399939.4 (273975.9); 243996 (219520-862488)	406086.3 (194308.8); 352252 (96605-1070599)	386537.7 (159736); 332748 (162215-687879)	402246.2 (192452.1); 346223.5 (96605-1070599)	1 (1, 1); LRT p=0.5403
Catchment population served group		4.6 (2.6); 3 (3-9)	4.5 (1.9); 4 (1-10)	4.4 (1.7); 4 (2-7)	4.5 (1.9); 4 (1-10)	1.087 (0.788, 1.462); LRT p=0.5868

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

Socioeconomic status of Trust population served - index of multiple deprivation rank decile	4.8 (2.4); 5 (2-8)	5.6 (2.6); 5 (1-10)	4.2 (1.9); 4 (1-8)	5.3 (2.6); 5 (1-10)	1.043 (0.843, 1.314); LRT p=0.7131
Socioeconomic status of Trust population served - index of multiple deprivation rank	13688.8 (7666.8); 14744 (5347-23384)	16941.6 (8746); 16344.5 (2136-32664)	12018.5 (6036.1); 10143 (2905-24840)	15841.3 (8391.8); 14989 (2136-32664)	1 (1, 1); LRT p=0.6376
Number of hospitals within Trust	3.8 (2.2); 3 (2-7)	6.2 (3.6); 6 (1-14)	5.5 (3.2); 5 (1-11)	5.9 (3.5); 5.5 (1-14)	1.038 (0.891, 1.239); LRT p=0.6576
Percentage of hospitals within Trust that are teaching hospitals	0 (0); 0 (0-0)	12.2 (31.5); 0 (0-100)	9.1 (30.2); 0 (0-100)	10.7 (29.9); 0 (0-100)	0.998 (0.979, 1.017); LRT p=0.7992
Percentage of hospitals within Trust that are general hospitals	80 (44.7); 100 (0-100)	78.1 (38.6); 100 (0-100)	54.5 (52.2); 100 (0-100)	74.2 (41.9); 100 (0-100)	0.989 (0.977, 1.002); LRT p=0.1242
Percentage of hospitals within Trust that are other hospitals	20 (44.7); 0 (0-100)	9.7 (27.3); 0 (0-100)	36.4 (50.5); 0 (0-100)	15.1 (34.5); 0 (0-100)	1.02 (1.004, 1.038); LRT p=0.025
Proportion of hospitals within Trust participating in ROSE study	0.3 (0.2); 0.3 (0.143-0.5)	0.3 (0.3); 0.2 (0.071-2)	0.3 (0.3); 0.2 (0.1-1)	0.3 (0.3); 0.2 (0.071-2)	0.739 (0.182, 3.497); LRT p=0.7033

Categorical variable summaries show the number (%) of patients per group. Continuous variable summaries show the mean (standard deviation); median (range). CI = Confidence Interval (Parametric Bootstrap); LRT = Likelihood Ratio Test; OR = Odds Ratio.

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

#### *NVAF/AF*

**Table 12: Summary of the patient-level results of the univariate multilevel logistic regression analyses for NVAF/AF.**

Patient Characteristic	Group	Warfarin (n=618)	Rivaroxaban (n=856)	Total (n=1474)	OR (95% CI)
Age at index group	Less than 65	119 (47.2%)	133 (52.8%)	252 (100%)	Reference; LRT p=0.9529 1.047 (0.631, 1.651) 0.984 (0.642, 1.479)
	65 to 74	182 (44.9%)	223 (55.1%)	405 (100%)	
	75+	317 (38.8%)	500 (61.2%)	817 (100%)	
Gender	Male	346 (43.1%)	457 (56.9%)	803 (100%)	Reference; LRT p=0.8801 0.975 (0.701, 1.387)
	Female	272 (40.5%)	399 (59.5%)	671 (100%)	
Marital status	Married	309 (39.4%)	476 (60.6%)	785 (100%)	Reference; LRT p=0.7315 0.614 (0.196, 1.988) 0.806 (0.404, 1.526) 0.806 (0.375, 1.664) 1.01 (0.243, 4.034) 0.922 (0.471, 1.817) 1.288 (0.871, 1.918)
	Co-habiting	14 (58.3%)	10 (41.7%)	24 (100%)	
	Divorced	35 (41.7%)	49 (58.3%)	84 (100%)	
	Other/ Unknown	86 (64.2%)	48 (35.8%)	134 (100%)	
	Separated	8 (47.1%)	9 (52.9%)	17 (100%)	
	Single	36 (48.6%)	38 (51.4%)	74 (100%)	
	Widowed	130 (36.5%)	226 (63.5%)	356 (100%)	
Self-reported employment status	Full time	49 (43%)	65 (57%)	114 (100%)	Reference; LRT p=0.3463 9.519 (0.375, 23.265) 2.42 (0.182, 13.248) 1.595 (0.588, 4.29) 0.69 (0.279, 1.771) 1.139 (0.638, 1.967) 0.525 (0.175, 1.723) 0.891 (0.342, 2.267) 0.788 (0.367, 1.722)
	Carer/ Other/ Volunteer/ Student	0 (0%)	3 (100%)	3 (100%)	
	Disabled/ Sick leave	0 (0%)	3 (100%)	3 (100%)	
	House husband/wife/ Mother/ maternity leave	11 (25%)	33 (75%)	44 (100%)	
	Part time	19 (44.2%)	24 (55.8%)	43 (100%)	
	Pensioner/ Retired	390 (38.8%)	614 (61.2%)	1004 (100%)	
	Self-employed	18 (60%)	12 (40%)	30 (100%)	
	Unemployed	19 (42.2%)	26 (57.8%)	45 (100%)	
	Unknown	112 (59.6%)	76 (40.4%)	188 (100%)	
Ethnicity	White	508 (38.9%)	799 (61.1%)	1307 (100%)	Reference; LRT p=0.8318 0.573 (0.203, 1.919)
	Asian	19 (67.9%)	9 (32.1%)	28 (100%)	

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

	Black/ African/ Caribbean	6 (54.5%)	5 (45.5%)	11 (100%)	0.813 (0.201, 4.892)
	Other	3 (42.9%)	4 (57.1%)	7 (100%)	1.595 (0.218, 11.486)
	Unknown	82 (67.8%)	39 (32.2%)	121 (100%)	0.742 (0.343, 1.661)
Prior/at baseline history of DVT/PE	No	595 (41.8%)	830 (58.2%)	1425 (100%)	Reference; LRT p=0.95
	Yes	23 (46.9%)	26 (53.1%)	49 (100%)	1.03 (0.453, 2.454)
Prior/at baseline history of CVA (HAS- BLED narrow def.)	No	480 (44.8%)	591 (55.2%)	1071 (100%)	Reference; LRT p=0.0289
	Yes	138 (34.2%)	265 (65.8%)	403 (100%)	1.66 (1.057, 2.471)
Prior/at baseline history of CVA (CHADS2VASC)	No	403 (47.4%)	448 (52.6%)	851 (100%)	Reference; LRT p=0.0012
	Yes	215 (34.5%)	408 (65.5%)	623 (100%)	2.136 (1.336, 3.338)
Prior/at baseline history of abnormal liver function	No	608 (41.7%)	849 (58.3%)	1457 (100%)	Reference; LRT p=0.1662
	Yes	10 (58.8%)	7 (41.2%)	17 (100%)	0.404 (0.096, 1.578)
Prior/at baseline history of renal disease	No	600 (41.6%)	843 (58.4%)	1443 (100%)	Reference; LRT p=0.3836
	Yes	18 (58.1%)	13 (41.9%)	31 (100%)	0.64 (0.218, 1.723)
Prior/at baseline history of diabetes mellitus	No	488 (41.3%)	695 (58.7%)	1183 (100%)	Reference; LRT p=0.468
	Yes	130 (44.7%)	161 (55.3%)	291 (100%)	1.162 (0.779, 1.684)
Prior/at baseline history of congestive heart failure	No	516 (41.3%)	732 (58.7%)	1248 (100%)	Reference; LRT p=0.8386
	Yes	102 (45.1%)	124 (54.9%)	226 (100%)	1.05 (0.685, 1.672)
Prior/at baseline history of vascular disease	No	479 (43.3%)	626 (56.7%)	1105 (100%)	Reference; LRT p=0.9905
	Yes	139 (37.7%)	230 (62.3%)	369 (100%)	0.997 (0.697, 1.432)
Prior/at baseline history of hypertension (CHADS2VASC)	No	104 (29.9%)	244 (70.1%)	348 (100%)	Reference; LRT p=0.4451
	Yes	514 (45.6%)	612 (54.4%)	1126 (100%)	1.197 (0.796, 1.768)
Prior/at baseline history of hypertension (HAS- BLED)	No	316 (37.1%)	535 (62.9%)	851 (100%)	Reference; LRT p=0.0678
	Yes	302 (48.5%)	321 (51.5%)	623 (100%)	1.422 (0.972, 2.049)

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

Prior/at baseline history of hypertension	No	104 (29.9%)	244 (70.1%)	348 (100%)	Reference; LRT p=0.1887 1 (0.672, 1.558) 1.422 (0.912, 2.322)
	CHADS2VASC	212 (42.1%)	291 (57.9%)	503 (100%)	
	CHADS2VASC & HAS-BLED	302 (48.5%)	321 (51.5%)	623 (100%)	
Prior/at baseline history of bleeding predisposition	No	476 (40%)	713 (60%)	1189 (100%)	Reference; LRT p=0.2292 0.778 (0.527, 1.161)
	Yes	142 (49.8%)	143 (50.2%)	285 (100%)	
Prior/at baseline history of medications predisposing to bleeds	No	240 (36.6%)	416 (63.4%)	656 (100%)	Reference; LRT p=0.7257 0.933 (0.633, 1.375)
	Yes	378 (46.2%)	440 (53.8%)	818 (100%)	
Prior/at baseline history of excessive alcohol consumption/alcohol misuse	No	584 (41.4%)	825 (58.6%)	1409 (100%)	Reference; LRT p=0.7489 1.128 (0.507, 2.371)
	Yes	34 (52.3%)	31 (47.7%)	65 (100%)	
Prior smoking	No	426 (38%)	696 (62%)	1122 (100%)	Reference; LRT p=0.9025 0.976 (0.677, 1.394)
	Yes	192 (54.5%)	160 (45.5%)	352 (100%)	
Prior substance misuse	No	617 (41.9%)	854 (58.1%)	1471 (100%)	Reference; LRT p=0.2969 3.088 (0.224, 16.966)
	Yes	1 (33.3%)	2 (66.7%)	3 (100%)	
HAS-BLED score group	Low	144 (32.4%)	300 (67.6%)	444 (100%)	Reference; LRT p=0.9618 0.933 (0.591, 1.467) 0.976 (0.624, 1.561)
	Moderate	162 (45.8%)	192 (54.2%)	354 (100%)	
	High	312 (46.2%)	364 (53.8%)	676 (100%)	
CHADS2VASC score group	Low	9 (52.9%)	8 (47.1%)	17 (100%)	Reference; LRT p=0.1829 1.625 (0.422, 5.238) 2.667 (0.661, 8.142)
	Moderate	45 (44.1%)	57 (55.9%)	102 (100%)	
	High	564 (41.6%)	791 (58.4%)	1355 (100%)	
Patient-specific prescriber reason for prescribing: lifestyle choice	No	581 (47.4%)	644 (52.6%)	1225 (100%)	Reference; LRT p<0.0001 17.051 (8.505, 29.306)
	Yes	37 (14.9%)	212 (85.1%)	249 (100%)	

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

Patient-specific prescriber reason for prescribing: non-adherence with prior anticoagulant	No	618 (42.4%)	840 (57.6%)	1458 (100%)	Reference; LRT p<0.0001 35.959 (4.767, 81.189)
	Yes	0 (0%)	16 (100%)	16 (100%)	
Patient-specific prescriber reason for prescribing: side-effects with prior anticoagulant	No	616 (42.7%)	825 (57.3%)	1441 (100%)	Reference; LRT p<0.0001 16.813 (3.933, 54.336)
	Yes	2 (6.1%)	31 (93.9%)	33 (100%)	
Patient-specific prescriber reason for prescribing: patient preference	No	613 (43.4%)	800 (56.6%)	1413 (100%)	Reference; LRT p=0.0003 7.288 (2.343, 17.054)
	Yes	5 (8.2%)	56 (91.8%)	61 (100%)	
Patient-specific prescriber reason for prescribing: poor control	No	618 (42.4%)	841 (57.6%)	1459 (100%)	Reference; LRT p=0.0002 34.191 (3.637, 89.622)
	Yes	0 (0%)	15 (100%)	15 (100%)	
Age at index		73.3 (11.4); 75 (24-95)	75.1 (10.8); 76 (28-101)	74.4 (11.1); 76 (24-101)	1.001 (0.988, 1.016); LRT p=0.8654
Index of multiple deprivation rank decile		5.5 (2.8); 5 (1-10)	6 (2.7); 6 (1-10)	5.8 (2.7); 6 (1-10)	1.065 (1.005, 1.128); LRT p=0.0652
Index of multiple deprivation rank		16552.8 (9073); 16128.5 (38-32753)	18262.7 (9008.6); 18799.5 (117-32838)	17545.8 (9071.9); 17437 (38-32838)	1 (1, 1); LRT p=0.0624
HAS-BLED score		2.5 (1.2); 3 (0-6)	2.3 (1.3); 2 (0-7)	2.4 (1.3); 2 (0-7)	1.054 (0.909, 1.222); LRT p=0.5013
CHADS2VASC score		3.9 (1.7); 4 (0-9)	4.2 (1.8); 4 (0-9)	4 (1.8); 4 (0-9)	1.106 (0.999, 1.222); LRT p=0.0707
*Professional years registered ( <b>prescriber characteristic</b> )		26.5 (10.4); 26.9 (0.578-63.811)	22.8 (9.8); 21.3 (0.619-50.622)	24.3 (10.2); 22.9 (0.578-63.811)	0.968 (0.94, 0.998); LRT p=0.0273

Categorical variable summaries show the number (%) of patients per group. Continuous variable summaries show the mean (standard deviation); median (range). CI = Confidence Interval (Parametric Bootstrap); LRT = Likelihood Ratio Test; OR = Odds Ratio. \*Prescriber characteristic that varies between patients.

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

**Table 13: Summary of the prescriber-level results of the univariate multilevel logistic regression analyses for NVAf/AF.**

Prescriber Characteristic	Group	Warfarin (n=118)	Warfarin/Rivaroxaban (n=68)	Rivaroxaban (n=150)	Total (n=336)	OR (95% CI)
Gender	Male	83 (34%)	52 (21.3%)	109 (44.7%)	244 (100%)	Reference; LRT p=0.2644 0.685 (0.391, 1.354)
	Female	35 (38%)	16 (17.4%)	41 (44.6%)	92 (100%)	
Professional qualification	Medic	104 (33.3%)	61 (19.6%)	147 (47.1%)	312 (100%)	Reference; LRT p=0.0002 0.099 (0.033, 0.394)
	Nurse	14 (58.3%)	7 (29.2%)	3 (12.5%)	24 (100%)	
Career level	Junior	8 (24.2%)	1 (3%)	24 (72.7%)	33 (100%)	Reference; LRT p=0.4941 0.529 (0.153, 1.819) 0.825 (0.245, 2.718)
	Mid-level	20 (35.1%)	11 (19.3%)	26 (45.6%)	57 (100%)	
	Senior level	90 (36.6%)	56 (22.8%)	100 (40.7%)	246 (100%)	
Specialist status	No	18 (23.1%)	8 (10.3%)	52 (66.7%)	78 (100%)	Reference; LRT p=0.1768 0.576 (0.264, 1.325)
	Yes	100 (38.8%)	60 (23.3%)	98 (38%)	258 (100%)	
Clinical specialism	Haematology	5 (19.2%)	9 (34.6%)	12 (46.2%)	26 (100%)	Reference; LRT p=0.0018 0.258 (0.118, 5.15) 1.382 (0.292, 6.425) 0.084 (0.022, 0.585) 0.711 (0.235, 1.967) 0.583 (0.165, 1.94) 4.639 (0.253, 18.224) 0.684 (0.068, 9.24) 0.99 (0.274, 3.525) 6.499 (0.931, 30.661)
	A&E	1 (100%)	0 (0%)	0 (0%)	1 (100%)	
	Acute Medicine	6 (37.5%)	4 (25%)	6 (37.5%)	16 (100%)	
	Anticoagulation	7 (58.3%)	5 (41.7%)	0 (0%)	12 (100%)	
	Cardiology	34 (39.1%)	19 (21.8%)	34 (39.1%)	87 (100%)	
	Care of Elderly	13 (61.9%)	0 (0%)	8 (38.1%)	21 (100%)	
	Endocrinology	2 (50%)	0 (0%)	2 (50%)	4 (100%)	
	Gastroenterology	1 (50%)	0 (0%)	1 (50%)	2 (100%)	
	General Medicine	12 (30%)	2 (5%)	26 (65%)	40 (100%)	
	Neurology	3 (25%)	2 (16.7%)	7 (58.3%)	12 (100%)	



### Appendix 3. Multilevel Modelling of Prescribing Variability Report

Other	3 (37.5%)	1 (12.5%)	4 (50%)	8 (100%)	1.825 (0.268, 14.615)
Research	1 (100%)	0 (0%)	0 (0%)	1 (100%)	0.252 (0.19, 4.269)
Respiratory	3 (42.9%)	0 (0%)	4 (57.1%)	7 (100%)	1.082 (0.108, 7.38)
Stroke	27 (27.3%)	26 (26.3%)	46 (46.5%)	99 (100%)	3.202 (1.153, 7.823)
Percentage of patients with reason for prescribing: clinical judgement	83.2 (33.6); 100 (0-100)	86.3 (25.4); 100 (0-100)	90.4 (25.5); 100 (0-100)	87 (28.7); 100 (0-100)	1.015 (1.001, 1.029); LRT p=0.0289
Percentage of patients with reason for prescribing: NICE recommendations	46.2 (45.6); 50 (0-100)	40.6 (38.5); 42.9 (0-100)	29 (41.5); 0 (0-100)	37.4 (43); 4.3 (0-100)	0.98 (0.97, 0.989); LRT p<0.0001
Percentage of patients with reason for prescribing: expert guidelines	9.2 (25.1); 0 (0-100)	9.6 (26); 0 (0-100)	2.2 (12.6); 0 (0-100)	6.2 (20.9); 0 (0-100)	0.978 (0.959, 0.999); LRT p=0.0244
Percentage of patients with reason for prescribing: hospital formulary	18.1 (35.6); 0 (0-100)	20 (32.7); 0 (0-100)	6.5 (20.7); 0 (0-100)	13.3 (29.8); 0 (0-100)	0.979 (0.964, 0.994); LRT p=0.0029
Percentage of patients with reason for prescribing: patient group direction	3.4 (16.7); 0 (0-100)	7.9 (23.4); 0 (0-95.238)	3 (13); 0 (0-100)	4.1 (16.9); 0 (0-100)	0.979 (0.953, 1.005); LRT p=0.0741
Percentage of patients with reason for prescribing: potential ease of reversibility	5.8 (20.3); 0 (0-100)	4.6 (10.7); 0 (0-50)	1.2 (5.6); 0 (0-33.333)	3.5 (13.6); 0 (0-100)	0.934 (0.891, 0.966); LRT p<0.0001

Categorical variable summaries show the number (%) of patients per group. Continuous variable summaries show the mean (standard deviation); median (range). CI = Confidence Interval (Parametric Bootstrap); LRT = Likelihood Ratio Test; OR = Odds Ratio.

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

**Table 14: Summary of the trust-level results of the univariate multilevel logistic regression analyses for NVAF/AF.**

Trust Characteristic	Group	Warfarin (n=9)	Warfarin/Rivaroxaban (n=41)	Rivaroxaban (n=12)	Total (n=62)	OR (95% CI)
Geographic region	East of England	0 (0%)	4 (66.7%)	2 (33.3%)	6 (100%)	Reference; LRT p=0.2771
	London	1 (11.1%)	7 (77.8%)	1 (11.1%)	9 (100%)	0.147 (0.034, 0.874)
	North West	3 (30%)	6 (60%)	1 (10%)	10 (100%)	0.62 (0.157, 3.678)
	South East	2 (25%)	3 (37.5%)	3 (37.5%)	8 (100%)	1.28 (0.276, 7.896)
	South West	1 (7.7%)	8 (61.5%)	4 (30.8%)	13 (100%)	1.315 (0.301, 6.599)
	West Midlands	0 (0%)	8 (100%)	0 (0%)	8 (100%)	0.975 (0.209, 7)
	Yorkshire and Humber	2 (25%)	5 (62.5%)	1 (12.5%)	8 (100%)	0.417 (0.081, 3.4)
Type of Trust	Acute	1 (4.5%)	16 (72.7%)	5 (22.7%)	22 (100%)	Reference; LRT p=0.265
	Foundation	7 (17.9%)	25 (64.1%)	7 (17.9%)	39 (100%)	1.022 (0.31, 3.422)
	Integrated	1 (100%)	0 (0%)	0 (0%)	1 (100%)	0.081 (0.058, 6.885)
Number of hospitals within Trust participating in ROSE study	1	9 (18%)	30 (60%)	11 (22%)	50 (100%)	Reference; LRT p=0.6804
	2	0 (0%)	7 (87.5%)	1 (12.5%)	8 (100%)	1.308 (0.25, 5.197)
	3	0 (0%)	4 (100%)	0 (0%)	4 (100%)	0.466 (0.077, 3.253)
Catchment population served		321735 (118971.9); 296702 (171059-503498)	425797.2 (219374.7); 354972 (96605-1070599)	423898.3 (130630.3); 409460.5 (265240-687879)	410323.9 (194540.7); 356208.5 (96605-1070599)	1 (1, 1); LRT p=0.5316
Catchment population served group		3.7 (1.2); 3 (2-6)	4.8 (2.2); 4 (1-10)	4.6 (1.3); 4.5 (3-7)	4.6 (1.9); 4 (1-10)	1.094 (0.781, 1.473); LRT p=0.5634
Socioeconomic status of Trust population served - index of multiple deprivation rank decile		4.8 (2); 5 (2-8)	5.1 (2.5); 5 (1-10)	5.8 (2.7); 5 (3-10)	5.2 (2.5); 5 (1-10)	1.081 (0.824, 1.371); LRT p=0.5298
Socioeconomic status of Trust population served - index of multiple deprivation rank		14027.4 (6565.3); 16416 (4031-23863)	15322.1 (8371.1); 14744 (918-32664)	17250.2 (8942.3); 15062 (6572-31931)	15507.4 (8183.4); 14989 (918-32664)	1 (1, 1); LRT p=0.5413

### Appendix 3. Multilevel Modelling of Prescribing Variability Report

Number of hospitals within Trust	5.3 (3.4); 5 (1-11)	6 (3.7); 5 (1-14)	6 (2.9); 5.5 (2-11)	5.9 (3.4); 5 (1-14)	0.982 (0.813, 1.169); LRT p=0.8406
Percentage of hospitals within Trust that are teaching hospitals	0 (0); 0 (0-0)	10.2 (27.6); 0 (0-100)	12.5 (31.1); 0 (0-100)	9.1 (26.3); 0 (0-100)	1.011 (0.987, 1.036); LRT p=0.355
Percentage of hospitals within Trust that are general hospitals	88.9 (33.3); 100 (0-100)	84.6 (32.4); 100 (0-100)	54.2 (49.8); 75 (0-100)	79.3 (37.9); 100 (0-100)	0.991 (0.976, 1.008); LRT p=0.2743
Percentage of hospitals within Trust that are other hospitals	11.1 (33.3); 0 (0-100)	5.3 (19.9); 0 (0-100)	33.3 (49.2); 0 (0-100)	11.6 (31); 0 (0-100)	1.006 (0.983, 1.028); LRT p=0.5886
Proportion of hospitals within Trust participating in ROSE study	0.3 (0.3); 0.2 (0.091-1)	0.3 (0.3); 0.2 (0.071-2)	0.2 (0.1); 0.2 (0.1-0.5)	0.3 (0.3); 0.2 (0.071-2)	0.509 (0.1, 3.534); LRT p=0.4287

Categorical variable summaries show the number (%) of patients per group. Continuous variable summaries show the mean (standard deviation); median (range). CI = Confidence Interval (Parametric Bootstrap); LRT = Likelihood Ratio Test; OR = Odds Ratio.

#### Appendix 4. Other Treatments for the Contextual cohort

	N	%
<b>Oral anticoagulant</b>		
Dalteparin	10	83.33
Enoxaparin	2	16.67
<b>Age at index (years)</b>		
18-24	0	0.00
25-29	0	0.00
30-34	0	0.00
35-39	0	0.00
40-44	0	0.00
45-49	0	0.00
50-54	0	0.00
55-59	3	25.00
60-64	1	8.33
65-69	5	41.67
70-74	2	16.67
75-79	1	8.33
80-84	0	0.00
85-89	0	0.00
90-94	0	0.00
>94	0	0.00
Median (IQR)	61.5 (61.5, 70)	
Mean (SD)	65.92 (5.63)	
<b>Gender</b>		
Male	3	25.00
Female	9	75.00
<b>Indication</b>		
AF	0	0.00
DVT/PE	12	100.00
<i>Treatment of DVT</i>	7	58.33
<i>Treatment of DVT/PE</i>	0	0.00
<i>Prevention of recurrent DVT/PE</i>	0	0.00
<i>Other DVT/PE</i>	5	41.67
Mixed	0	0.00
Other	0	0.00
<b>Haemorrhage events</b>		
Intracranial	0	0.00
Gastrointestinal	2	16.67
Urogenital	0	0.00
Intraocular	0	0.00
Spinal cord	0	0.00
Pericardial	0	0.00
Intraarticular	0	0.00
Intramuscular with compartment syndrome	0	0.00
Retroperitoneal	0	0.00
<b>Haemorrhage-related events</b>		
Decreased haemoglobin ( $\geq 2\text{g/dL}$ )	3	25.00
Bleeding requiring transfusion	3	25.00
A fatal outcome	0	0.00
<b>Recurrent thromboembolic events</b>		

#### Appendix 4. Other Treatments for the Contextual cohort

	N	%
CVA	0	0.00
DVT	0	0.00
PE	0	0.00
<b>Incident thromboembolic events</b>		
CVA	0	0.00
DVT	0	0.00
PE	0	0.00
<b>Other events</b>		
Hepatic Failure	0	0.00
Abnormal LFTs 3x ULN	0	0.00

## Appendix 5. Other Indications for Treatment

### Rivaroxaban treated patients

First Indication (PT)	Second Indication (PT)	Frequency
Intracardiac thrombus		3
Thrombophlebitis		3
Thrombophlebitis superficial		3
Atrial flutter		2
Antiphospholipid antibodies		1
Carotid artery thrombosis		1
Cerebellar infarction		1
Cerebrovascular accident		1
Embolic stroke		1
Left ventricular dysfunction	Ejection fraction decreased	1
Portal vein thrombosis		1
Subclavian vein thrombosis		1
Superior sagittal sinus thrombosis	Transverse sinus thrombosis	1
Thrombosis prophylaxis		1
Unevaluable event		1

### Warfarin treated patients

First Indication (PT)	Second Indication (PT)	Frequency
Atrial flutter		6
Intracardiac thrombus		4
Embolism		2
Heart valve replacement		2
Intracranial venous sinus thrombosis		2
Thromboembolectomy		2
Cerebral thrombosis		1
Cerebrovascular accident		1
Embolism venous		1
Implantable defibrillator insertion		1
Jugular vein thrombosis		1
Left ventricular dysfunction		1
Missing		1
Mitral valve prolapse		1
Peripheral artery thrombosis		1
Peripheral ischaemia		1
Portal vein thrombosis	Embolism venous	1
Thrombolysis		1
Thrombosis		1
Thrombosis mesenteric vessel		1
Unevaluable event		1
Vertebral artery occlusion	Cerebrovascular accident	1

## Appendix 6. Other Supporting Reasons for Prescribing

System Organ Class	Preferred Term	Ret	Treatment group	AF/NVAF		DVT/PE		Mixed		Other	
				N	%	N	%	N	%	N	%
Injury, poisoning and procedural complications	Contusion	Bruising	rivaroxaban	0	0.00	1	0.07	0	0.00	0	0.00
Injury, poisoning and procedural complications	Contusion	Bruising	warfarin	0	0.00	0	0.00	0	0.00	0	0.00
Investigations	Electrocardiogram	ECG test	rivaroxaban	1	0.10	0	0.00	0	0.00	0	0.00
Investigations	Electrocardiogram	ECG test	warfarin	0	0.00	0	0.00	0	0.00	0	0.00
Metabolism and nutrition disorders	Gout	GOUT	rivaroxaban	0	0.00	1	0.07	0	0.00	0	0.00
Metabolism and nutrition disorders	Gout	GOUT	warfarin	0	0.00	0	0.00	0	0.00	0	0.00
Psychiatric disorders	Depression	DEPRESSION	rivaroxaban	0	0.00	1	0.07	0	0.00	0	0.00
Psychiatric disorders	Depression	DEPRESSION	warfarin	0	0.00	0	0.00	0	0.00	0	0.00
Skin and subcutaneous tissue disorders	Alopecia	HAIR LOSS	rivaroxaban	0	0.00	1	0.07	0	0.00	0	0.00
Skin and subcutaneous tissue disorders	Alopecia	HAIR LOSS	warfarin	0	0.00	0	0.00	0	0.00	0	0.00
Surgical and medical procedures	Anticoagulant therapy	Anticoagulant therapy	rivaroxaban	1	0.10	0	0.00	0	0.00	0	0.00
Surgical and medical procedures	Anticoagulant therapy	Anticoagulant therapy	warfarin	0	0.00	0	0.00	0	0.00	0	0.00

## Appendix 7a. Other Medical History Prior to Starting

	AF			DVT/PE			Mixed (AF and DVT/PE)			Other indication			Total
	Rivaroxaban	Warfarin	Total	Rivaroxaban	Warfarin	Total	Rivaroxaban	Warfarin	Total	Rivaroxaban	Warfarin	Total	N=101
	N=15	N=17	N=32	N=31	N=32	N=63	N=5	N=0	N=5	N=0	N=1	N=1	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Other bleeding events in main tables:													
Epistaxis	7 (36.84)	7 (38.89)	14 (37.84)	7 (17.95)	14 (37.84)	21 (27.63)	4 (66.67)	0	4 (66.67)	0	1 (100.00)	1 (100.00)	40 (33.33)
Fall	2 (10.53)	6 (33.33)	8 (21.62)	15 (38.46)	8 (21.62)	23 (30.26)	1 (16.67)	0	1 (16.67)	0	0	0	32 (26.67)
Haemoptysis	3 (15.79)	1 (5.56)	4 (10.81)	10 (25.64)	9 (24.32)	19 (25.00)	1 (16.67)	0	1 (16.67)	0	0	0	24 (20.00)
Haematoma	2 (10.53)	0	2 (5.41)	3 (7.69)	0	3 (3.95)	0	0	0	0	0	0	5 (4.17)
Contusion	3 (15.79)	0	3 (8.11)	1 (2.56)	0	1 (1.32)	0	0	0	0	0	0	4 (3.33)
Blood blister	0	0	0	0	2 (5.41)	2 (2.63)	0	0	0	0	0	0	2 (1.67)
Conjunctival haemorrhage	0	1 (5.56)	1 (2.70)	0	1 (2.70)	1 (1.32)	0	0	0	0	0	0	2 (1.67)
Haematospermia	1 (5.26)	1 (5.56)	2 (5.41)	0	0	0	0	0	0	0	0	0	2 (1.67)
Haemothorax	0	0	0	2 (5.13)	0	2 (2.63)	0	0	0	0	0	0	2 (1.67)
Arterial haemorrhage	0	1 (5.56)	1 (2.70)	0	0	0	0	0	0	0	0	0	1 (0.83)
Catheter site haemorrhage	0	1 (5.56)	1 (2.70)	0	0	0	0	0	0	0	0	0	1 (0.83)
Haematoma evacuation	0	0	0	1 (2.56)	0	1 (1.32)	0	0	0	0	0	0	1 (0.83)
Haemorrhage in pregnancy	0	0	0	0	1 (2.70)	1 (1.32)	0	0	0	0	0	0	1 (0.83)
Injection site haematoma	1 (5.26)	0	1 (2.70)	0	0	0	0	0	0	0	0	0	1 (0.83)
Skin haemorrhage	0	0	0	0	1 (2.70)	1 (1.32)	0	0	0	0	0	0	1 (0.83)
Subchorionic haematoma	0	0	0	0	1 (2.70)	1 (1.32)	0	0	0	0	0	0	1 (0.83)



## Appendix 7b(i). Other Medical History Prior to Starting rivaroxaban - NVAf/AF

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	NVAf/AF	Osteoarthritis	44	11.67
rivaroxaban	NVAf/AF	Unevaluable event	26	6.90
rivaroxaban	NVAf/AF	Asthma	24	6.37
rivaroxaban	NVAf/AF	Myocardial ischaemia	19	5.04
rivaroxaban	NVAf/AF	Hypothyroidism	18	4.77
rivaroxaban	NVAf/AF	Gout	18	4.77
rivaroxaban	NVAf/AF	Lower respiratory tract infection	13	3.45
rivaroxaban	NVAf/AF	Glaucoma	12	3.18
rivaroxaban	NVAf/AF	Arthritis	12	3.18
rivaroxaban	NVAf/AF	Hiatus hernia	11	2.92
rivaroxaban	NVAf/AF	Urinary tract infection	11	2.92
rivaroxaban	NVAf/AF	Depression	11	2.92
rivaroxaban	NVAf/AF	Hypertension	11	2.92
rivaroxaban	NVAf/AF	Benign prostatic hyperplasia	11	2.92
rivaroxaban	NVAf/AF	Hyperthyroidism	11	2.92
rivaroxaban	NVAf/AF	Pneumonia	10	2.65
rivaroxaban	NVAf/AF	Angina pectoris	10	2.65
rivaroxaban	NVAf/AF	Cardiac pacemaker insertion	10	2.65
rivaroxaban	NVAf/AF	Cataract operation	9	2.39
rivaroxaban	NVAf/AF	Gastrooesophageal reflux disease	9	2.39
rivaroxaban	NVAf/AF	Cholecystectomy	9	2.39
rivaroxaban	NVAf/AF	Knee arthroplasty	8	2.12
rivaroxaban	NVAf/AF	Sleep apnoea syndrome	8	2.12
rivaroxaban	NVAf/AF	Osteoporosis	8	2.12
rivaroxaban	NVAf/AF	Cataract	8	2.12
rivaroxaban	NVAf/AF	Convulsion	7	1.86
rivaroxaban	NVAf/AF	Cholelithiasis	7	1.86
rivaroxaban	NVAf/AF	Diverticulum	7	1.86
rivaroxaban	NVAf/AF	Diverticulitis	7	1.86
rivaroxaban	NVAf/AF	Aortic aneurysm	6	1.59
rivaroxaban	NVAf/AF	Polymyalgia rheumatica	6	1.59
rivaroxaban	NVAf/AF	Herpes zoster	6	1.59
rivaroxaban	NVAf/AF	Aortic stenosis	6	1.59
rivaroxaban	NVAf/AF	Chest pain	6	1.59
rivaroxaban	NVAf/AF	Cellulitis	6	1.59
rivaroxaban	NVAf/AF	Migraine	6	1.59
rivaroxaban	NVAf/AF	Skin ulcer	6	1.59
rivaroxaban	NVAf/AF	Appendicectomy	5	1.33
rivaroxaban	NVAf/AF	Rheumatoid arthritis	5	1.33
rivaroxaban	NVAf/AF	Dyspnoea	5	1.33
rivaroxaban	NVAf/AF	Macular degeneration	5	1.33
rivaroxaban	NVAf/AF	Epilepsy	5	1.33
rivaroxaban	NVAf/AF	Mitral valve incompetence	5	1.33
rivaroxaban	NVAf/AF	Spinal column stenosis	4	1.06
rivaroxaban	NVAf/AF	Psoriasis	4	1.06
rivaroxaban	NVAf/AF	Anxiety	4	1.06
rivaroxaban	NVAf/AF	Radiotherapy	4	1.06
rivaroxaban	NVAf/AF	Transurethral prostatectomy	4	1.06
rivaroxaban	NVAf/AF	Anaemia	4	1.06

## Appendix 7b(i). Other Medical History Prior to Starting rivaroxaban - NVAf/AF

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	NVAf/AF	Bronchiectasis	4	1.06
rivaroxaban	NVAf/AF	Obesity	4	1.06
rivaroxaban	NVAf/AF	Toe amputation	3	0.80
rivaroxaban	NVAf/AF	Age-related macular degeneration	3	0.80
rivaroxaban	NVAf/AF	Angiopathy	3	0.80
rivaroxaban	NVAf/AF	Meningioma	3	0.80
rivaroxaban	NVAf/AF	Gastritis	3	0.80
rivaroxaban	NVAf/AF	Duodenal ulcer	3	0.80
rivaroxaban	NVAf/AF	Constipation	3	0.80
rivaroxaban	NVAf/AF	Ventricular septal defect	3	0.80
rivaroxaban	NVAf/AF	Spinal osteoarthritis	3	0.80
rivaroxaban	NVAf/AF	Stent placement	3	0.80
rivaroxaban	NVAf/AF	Pulmonary tuberculosis	3	0.80
rivaroxaban	NVAf/AF	Colitis	3	0.80
rivaroxaban	NVAf/AF	Bradycardia	3	0.80
rivaroxaban	NVAf/AF	Back pain	3	0.80
rivaroxaban	NVAf/AF	Haemorrhoids	3	0.80
rivaroxaban	NVAf/AF	Vertigo	3	0.80
rivaroxaban	NVAf/AF	Palpitations	3	0.80
rivaroxaban	NVAf/AF	Sciatica	3	0.80
rivaroxaban	NVAf/AF	Asbestosis	3	0.80
rivaroxaban	NVAf/AF	Microcytic anaemia	3	0.80
rivaroxaban	NVAf/AF	Headache	3	0.80
rivaroxaban	NVAf/AF	Orthostatic hypotension	2	0.53
rivaroxaban	NVAf/AF	Trigeminal neuralgia	2	0.53
rivaroxaban	NVAf/AF	Device malfunction	2	0.53
rivaroxaban	NVAf/AF	Ultrasound scan	2	0.53
rivaroxaban	NVAf/AF	Dizziness	2	0.53
rivaroxaban	NVAf/AF	Rhinitis	2	0.53
rivaroxaban	NVAf/AF	Myelodysplastic syndrome	2	0.53
rivaroxaban	NVAf/AF	Skin neoplasm excision	2	0.53
rivaroxaban	NVAf/AF	Blepharitis	2	0.53
rivaroxaban	NVAf/AF	Rotator cuff syndrome	2	0.53
rivaroxaban	NVAf/AF	Rheumatic fever	2	0.53
rivaroxaban	NVAf/AF	Coeliac disease	2	0.53
rivaroxaban	NVAf/AF	Thrombolysis	2	0.53
rivaroxaban	NVAf/AF	Congenital cystic kidney disease	2	0.53
rivaroxaban	NVAf/AF	Hernia	2	0.53
rivaroxaban	NVAf/AF	Ankle fracture	2	0.53
rivaroxaban	NVAf/AF	Retinal detachment	2	0.53
rivaroxaban	NVAf/AF	Vitamin B12 deficiency	2	0.53
rivaroxaban	NVAf/AF	Osteitis deformans	2	0.53
rivaroxaban	NVAf/AF	Femur fracture	2	0.53
rivaroxaban	NVAf/AF	Temporal arteritis	2	0.53
rivaroxaban	NVAf/AF	Laser therapy	2	0.53
rivaroxaban	NVAf/AF	Eczema	2	0.53
rivaroxaban	NVAf/AF	Prostatic disorder	2	0.53
rivaroxaban	NVAf/AF	Dyslipidaemia	2	0.53
rivaroxaban	NVAf/AF	Uterine cancer	2	0.53

## Appendix 7b(i). Other Medical History Prior to Starting rivaroxaban - NVAF/AF

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	NVAF/AF	Inguinal hernia	2	0.53
rivaroxaban	NVAF/AF	Crohn's disease	2	0.53
rivaroxaban	NVAF/AF	Surgery	2	0.53
rivaroxaban	NVAF/AF	Clostridial infection	2	0.53
rivaroxaban	NVAF/AF	International normalised ratio increased	2	0.53
rivaroxaban	NVAF/AF	Peripheral vascular disorder	2	0.53
rivaroxaban	NVAF/AF	Left ventricular hypertrophy	2	0.53
rivaroxaban	NVAF/AF	Raynaud's phenomenon	2	0.53
rivaroxaban	NVAF/AF	Erectile dysfunction	2	0.53
rivaroxaban	NVAF/AF	Oesophagitis	2	0.53
rivaroxaban	NVAF/AF	Vaginal prolapse	2	0.53
rivaroxaban	NVAF/AF	Prostatomegaly	2	0.53
rivaroxaban	NVAF/AF	Hyponatraemia	2	0.53
rivaroxaban	NVAF/AF	Oedema peripheral	2	0.53
rivaroxaban	NVAF/AF	Psoriatic arthropathy	2	0.53
rivaroxaban	NVAF/AF	Presyncope	2	0.53
rivaroxaban	NVAF/AF	Tuberculosis	2	0.53
rivaroxaban	NVAF/AF	Rash	2	0.53
rivaroxaban	NVAF/AF	Spondylitis	2	0.53
rivaroxaban	NVAF/AF	Prostate cancer	2	0.53
rivaroxaban	NVAF/AF	Haemorrhoid operation	2	0.53
rivaroxaban	NVAF/AF	Urosepsis	2	0.53
rivaroxaban	NVAF/AF	Investigation	2	0.53
rivaroxaban	NVAF/AF	Intraocular lens implant	2	0.53
rivaroxaban	NVAF/AF	Joint arthroplasty	2	0.53
rivaroxaban	NVAF/AF	Biopsy prostate	2	0.53
rivaroxaban	NVAF/AF	Amaurosis fugax	2	0.53
rivaroxaban	NVAF/AF	Renal mass	2	0.53
rivaroxaban	NVAF/AF	Pleural effusion	2	0.53
rivaroxaban	NVAF/AF	Iron deficiency anaemia	2	0.53
rivaroxaban	NVAF/AF	Spondylolisthesis	2	0.53
rivaroxaban	NVAF/AF	Abdominal pain	2	0.53
rivaroxaban	NVAF/AF	Meniere's disease	2	0.53
rivaroxaban	NVAF/AF	Femoral neck fracture	2	0.53
rivaroxaban	NVAF/AF	Duodenitis	2	0.53
rivaroxaban	NVAF/AF	Gastrostomy tube insertion	2	0.53
rivaroxaban	NVAF/AF	Tachycardia	2	0.53
rivaroxaban	NVAF/AF	Dyspepsia	2	0.53
rivaroxaban	NVAF/AF	Agoraphobia	1	0.27
rivaroxaban	NVAF/AF	Electrocardiogram ambulatory	1	0.27
rivaroxaban	NVAF/AF	Normochromic normocytic anaemia	1	0.27
rivaroxaban	NVAF/AF	Ulcerative keratitis	1	0.27
rivaroxaban	NVAF/AF	Urinary retention	1	0.27
rivaroxaban	NVAF/AF	Computerised tomogram	1	0.27
rivaroxaban	NVAF/AF	Retinal tear	1	0.27
rivaroxaban	NVAF/AF	Haemolytic anaemia	1	0.27
rivaroxaban	NVAF/AF	Seborrhoeic dermatitis	1	0.27
rivaroxaban	NVAF/AF	Prostatic specific antigen increased	1	0.27
rivaroxaban	NVAF/AF	Sinus rhythm	1	0.27

## Appendix 7b(i). Other Medical History Prior to Starting rivaroxaban - NVAf/AF

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	NVAf/AF	Sepsis	1	0.27
rivaroxaban	NVAf/AF	Schizophrenia	1	0.27
rivaroxaban	NVAf/AF	Ventricular hypertrophy	1	0.27
rivaroxaban	NVAf/AF	Fibrosis	1	0.27
rivaroxaban	NVAf/AF	Venous insufficiency	1	0.27
rivaroxaban	NVAf/AF	Otosclerosis	1	0.27
rivaroxaban	NVAf/AF	Renal failure	1	0.27
rivaroxaban	NVAf/AF	Deafness	1	0.27
rivaroxaban	NVAf/AF	Pneumothorax	1	0.27
rivaroxaban	NVAf/AF	Ear infection	1	0.27
rivaroxaban	NVAf/AF	Bipolar disorder	1	0.27
rivaroxaban	NVAf/AF	Interstitial lung disease	1	0.27
rivaroxaban	NVAf/AF	Anaemia macrocytic	1	0.27
rivaroxaban	NVAf/AF	Renal failure acute	1	0.27
rivaroxaban	NVAf/AF	Basedow's disease	1	0.27
rivaroxaban	NVAf/AF	Mastoidectomy	1	0.27
rivaroxaban	NVAf/AF	Tooth extraction	1	0.27
rivaroxaban	NVAf/AF	Seasonal allergy	1	0.27
rivaroxaban	NVAf/AF	Femoral artery occlusion	1	0.27
rivaroxaban	NVAf/AF	Colitis ulcerative	1	0.27
rivaroxaban	NVAf/AF	Musculoskeletal pain	1	0.27
rivaroxaban	NVAf/AF	Colonoscopy	1	0.27
rivaroxaban	NVAf/AF	Porphyria non-acute	1	0.27
rivaroxaban	NVAf/AF	Pleurisy	1	0.27
rivaroxaban	NVAf/AF	Bronchitis	1	0.27
rivaroxaban	NVAf/AF	Carotid arteriosclerosis	1	0.27
rivaroxaban	NVAf/AF	Uterine polyp	1	0.27
rivaroxaban	NVAf/AF	Wrist fracture	1	0.27
rivaroxaban	NVAf/AF	Adrenal adenoma	1	0.27
rivaroxaban	NVAf/AF	Removal of internal fixation	1	0.27
rivaroxaban	NVAf/AF	Peritonitis	1	0.27
rivaroxaban	NVAf/AF	Splenic infarction	1	0.27
rivaroxaban	NVAf/AF	Pulmonary fibrosis	1	0.27
rivaroxaban	NVAf/AF	Oral candidiasis	1	0.27
rivaroxaban	NVAf/AF	Aspergillosis	1	0.27
rivaroxaban	NVAf/AF	Migraine with aura	1	0.27
rivaroxaban	NVAf/AF	Sigmoidoscopy	1	0.27
rivaroxaban	NVAf/AF	Carotid artery stenosis	1	0.27
rivaroxaban	NVAf/AF	Aortic valve incompetence	1	0.27
rivaroxaban	NVAf/AF	Open angle glaucoma	1	0.27
rivaroxaban	NVAf/AF	Bronchiolitis	1	0.27
rivaroxaban	NVAf/AF	Abdominal hernia	1	0.27
rivaroxaban	NVAf/AF	Cognitive disorder	1	0.27
rivaroxaban	NVAf/AF	Rheumatic heart disease	1	0.27
rivaroxaban	NVAf/AF	Lichen sclerosus	1	0.27
rivaroxaban	NVAf/AF	Eyelid ptosis	1	0.27
rivaroxaban	NVAf/AF	Endoscopic retrograde cholangiopancreatography	1	0.27
rivaroxaban	NVAf/AF	Lumbar spinal stenosis	1	0.27
rivaroxaban	NVAf/AF	Periarthritis	1	0.27

## Appendix 7b(i). Other Medical History Prior to Starting rivaroxaban - NVAf/AF

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	NVAf/AF	Urethral stenosis	1	0.27
rivaroxaban	NVAf/AF	Retinal artery embolism	1	0.27
rivaroxaban	NVAf/AF	Prostatic specific antigen	1	0.27
rivaroxaban	NVAf/AF	Photophobia	1	0.27
rivaroxaban	NVAf/AF	Depressed mood	1	0.27
rivaroxaban	NVAf/AF	Syncope	1	0.27
rivaroxaban	NVAf/AF	Renal stone removal	1	0.27
rivaroxaban	NVAf/AF	Angina unstable	1	0.27
rivaroxaban	NVAf/AF	Cardiac myxoma	1	0.27
rivaroxaban	NVAf/AF	Coronary artery disease	1	0.27
rivaroxaban	NVAf/AF	Parotid gland enlargement	1	0.27
rivaroxaban	NVAf/AF	Chemotherapy	1	0.27
rivaroxaban	NVAf/AF	Congestive cardiomyopathy	1	0.27
rivaroxaban	NVAf/AF	Cholecystitis	1	0.27
rivaroxaban	NVAf/AF	Dermatitis	1	0.27
rivaroxaban	NVAf/AF	Folate deficiency	1	0.27
rivaroxaban	NVAf/AF	Irritable bowel syndrome	1	0.27
rivaroxaban	NVAf/AF	Rehabilitation therapy	1	0.27
rivaroxaban	NVAf/AF	Dry eye	1	0.27
rivaroxaban	NVAf/AF	Embolism	1	0.27
rivaroxaban	NVAf/AF	Lesion excision	1	0.27
rivaroxaban	NVAf/AF	Bacterial disease carrier	1	0.27
rivaroxaban	NVAf/AF	Biopsy	1	0.27
rivaroxaban	NVAf/AF	Acidosis	1	0.27
rivaroxaban	NVAf/AF	Diabetic retinopathy	1	0.27
rivaroxaban	NVAf/AF	Carotid artery occlusion	1	0.27
rivaroxaban	NVAf/AF	Ileostomy closure	1	0.27
rivaroxaban	NVAf/AF	Uterine leiomyoma	1	0.27
rivaroxaban	NVAf/AF	Cranial nerve injury	1	0.27
rivaroxaban	NVAf/AF	Blood albumin increased	1	0.27
rivaroxaban	NVAf/AF	Head titubation	1	0.27
rivaroxaban	NVAf/AF	Abdominal pain upper	1	0.27
rivaroxaban	NVAf/AF	Vision blurred	1	0.27
rivaroxaban	NVAf/AF	Aplastic anaemia	1	0.27
rivaroxaban	NVAf/AF	Confusional state	1	0.27
rivaroxaban	NVAf/AF	Erosive duodenitis	1	0.27
rivaroxaban	NVAf/AF	Neuropathy peripheral	1	0.27
rivaroxaban	NVAf/AF	Lipoma	1	0.27
rivaroxaban	NVAf/AF	Multiple sclerosis	1	0.27
rivaroxaban	NVAf/AF	Hypotension	1	0.27
rivaroxaban	NVAf/AF	Pulmonary hypertension	1	0.27
rivaroxaban	NVAf/AF	Amnesic disorder	1	0.27
rivaroxaban	NVAf/AF	Scoliosis	1	0.27
rivaroxaban	NVAf/AF	Metabolic acidosis	1	0.27
rivaroxaban	NVAf/AF	Joint injury	1	0.27
rivaroxaban	NVAf/AF	Respiratory failure	1	0.27
rivaroxaban	NVAf/AF	Spinal fracture	1	0.27
rivaroxaban	NVAf/AF	Mitral valve prolapse	1	0.27
rivaroxaban	NVAf/AF	Female sterilisation	1	0.27

## Appendix 7b(i). Other Medical History Prior to Starting rivaroxaban - NVAf/AF

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	NVAf/AF	Neutrophilia	1	0.27
rivaroxaban	NVAf/AF	Muscular dystrophy	1	0.27
rivaroxaban	NVAf/AF	Bone graft	1	0.27
rivaroxaban	NVAf/AF	Synovitis	1	0.27
rivaroxaban	NVAf/AF	Colporrhaphy	1	0.27
rivaroxaban	NVAf/AF	Debridement	1	0.27
rivaroxaban	NVAf/AF	Retinal vein occlusion	1	0.27
rivaroxaban	NVAf/AF	Endoscopy upper gastrointestinal tract	1	0.27
rivaroxaban	NVAf/AF	Computerised tomogram head	1	0.27
rivaroxaban	NVAf/AF	Personality disorder	1	0.27
rivaroxaban	NVAf/AF	Pancreatitis	1	0.27
rivaroxaban	NVAf/AF	Vascular dementia	1	0.27
rivaroxaban	NVAf/AF	Shoulder operation	1	0.27
rivaroxaban	NVAf/AF	Cerebrovascular disorder	1	0.27
rivaroxaban	NVAf/AF	Carpal tunnel decompression	1	0.27
rivaroxaban	NVAf/AF	Pleural fibrosis	1	0.27
rivaroxaban	NVAf/AF	Bladder neoplasm	1	0.27
rivaroxaban	NVAf/AF	Clavicle fracture	1	0.27
rivaroxaban	NVAf/AF	Heart valve incompetence	1	0.27
rivaroxaban	NVAf/AF	Anaemia haemolytic autoimmune	1	0.27
rivaroxaban	NVAf/AF	Fracture malunion	1	0.27
rivaroxaban	NVAf/AF	Arteriosclerosis coronary artery	1	0.27
rivaroxaban	NVAf/AF	Cutaneous lupus erythematosus	1	0.27
rivaroxaban	NVAf/AF	Vitreous detachment	1	0.27
rivaroxaban	NVAf/AF	Body mass index increased	1	0.27
rivaroxaban	NVAf/AF	Insomnia	1	0.27
rivaroxaban	NVAf/AF	Vitamin B complex deficiency	1	0.27
rivaroxaban	NVAf/AF	Cyst	1	0.27
rivaroxaban	NVAf/AF	Anal fissure	1	0.27
rivaroxaban	NVAf/AF	Cardiomegaly	1	0.27
rivaroxaban	NVAf/AF	Ear, nose and throat examination	1	0.27
rivaroxaban	NVAf/AF	Retinal degeneration	1	0.27
rivaroxaban	NVAf/AF	Renal infarct	1	0.27
rivaroxaban	NVAf/AF	Bowen's disease	1	0.27
rivaroxaban	NVAf/AF	Alopecia	1	0.27
rivaroxaban	NVAf/AF	Pemphigoid	1	0.27
rivaroxaban	NVAf/AF	Blood pressure	1	0.27
rivaroxaban	NVAf/AF	Breast operation	1	0.27
rivaroxaban	NVAf/AF	Gouty arthritis	1	0.27
rivaroxaban	NVAf/AF	Costochondritis	1	0.27
rivaroxaban	NVAf/AF	Dementia Alzheimer's type	1	0.27
rivaroxaban	NVAf/AF	Pituitary tumour benign	1	0.27
rivaroxaban	NVAf/AF	Otitis externa	1	0.27
rivaroxaban	NVAf/AF	Periodic limb movement disorder	1	0.27
rivaroxaban	NVAf/AF	Endoscopy	1	0.27
rivaroxaban	NVAf/AF	Tendon rupture	1	0.27
rivaroxaban	NVAf/AF	Emergency care	1	0.27
rivaroxaban	NVAf/AF	Intestinal obstruction	1	0.27
rivaroxaban	NVAf/AF	Biopsy bladder	1	0.27

## Appendix 7b(i). Other Medical History Prior to Starting rivaroxaban - NVAf/AF

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	NVAf/AF	Change of bowel habit	1	0.27
rivaroxaban	NVAf/AF	Angiogram	1	0.27
rivaroxaban	NVAf/AF	Iodine allergy	1	0.27
rivaroxaban	NVAf/AF	Retinopathy	1	0.27
rivaroxaban	NVAf/AF	Gastroenteritis	1	0.27
rivaroxaban	NVAf/AF	Barrett's oesophagus	1	0.27
rivaroxaban	NVAf/AF	Thalassaemia beta	1	0.27
rivaroxaban	NVAf/AF	Diarrhoea	1	0.27
rivaroxaban	NVAf/AF	Parotitis	1	0.27
rivaroxaban	NVAf/AF	Dilatation atrial	1	0.27
rivaroxaban	NVAf/AF	Gastrointestinal endoscopic therapy	1	0.27
rivaroxaban	NVAf/AF	Peripheral coldness	1	0.27
rivaroxaban	NVAf/AF	Synovial rupture	1	0.27
rivaroxaban	NVAf/AF	Humerus fracture	1	0.27
rivaroxaban	NVAf/AF	Prostatism	1	0.27
rivaroxaban	NVAf/AF	Fibula fracture	1	0.27
rivaroxaban	NVAf/AF	Tendonitis	1	0.27
rivaroxaban	NVAf/AF	Selective IgA immunodeficiency	1	0.27
rivaroxaban	NVAf/AF	Essential tremor	1	0.27
rivaroxaban	NVAf/AF	Arterial stenosis	1	0.27
rivaroxaban	NVAf/AF	Glucose tolerance impaired	1	0.27
rivaroxaban	NVAf/AF	Cardiomyopathy	1	0.27
rivaroxaban	NVAf/AF	Diplopia	1	0.27
rivaroxaban	NVAf/AF	Inguinal hernia repair	1	0.27
rivaroxaban	NVAf/AF	Urinary incontinence	1	0.27
rivaroxaban	NVAf/AF	Cautery to nose	1	0.27
rivaroxaban	NVAf/AF	Drug eruption	1	0.27
rivaroxaban	NVAf/AF	Sinusitis	1	0.27
rivaroxaban	NVAf/AF	Blister	1	0.27
rivaroxaban	NVAf/AF	Nocturia	1	0.27
rivaroxaban	NVAf/AF	Vitamin D deficiency	1	0.27
rivaroxaban	NVAf/AF	Circulatory collapse	1	0.27
rivaroxaban	NVAf/AF	Arthritis infective	1	0.27
rivaroxaban	NVAf/AF	Osteotomy	1	0.27
rivaroxaban	NVAf/AF	Hyperparathyroidism	1	0.27
rivaroxaban	NVAf/AF	Vitamin B12 decreased	1	0.27
rivaroxaban	NVAf/AF	Behcet's syndrome	1	0.27
rivaroxaban	NVAf/AF	Rib fracture	1	0.27
rivaroxaban	NVAf/AF	Internal fixation of fracture	1	0.27
rivaroxaban	NVAf/AF	Intervertebral disc protrusion	1	0.27
rivaroxaban	NVAf/AF	Conjunctivitis	1	0.27
rivaroxaban	NVAf/AF	Pyelonephritis	1	0.27
rivaroxaban	NVAf/AF	Skin lesion	1	0.27
rivaroxaban	NVAf/AF	Substance-induced psychotic disorder	1	0.27
rivaroxaban	NVAf/AF	Gastric ulcer	1	0.27
rivaroxaban	NVAf/AF	Fibromyalgia	1	0.27
rivaroxaban	NVAf/AF	Ultrasound pelvis	1	0.27
rivaroxaban	NVAf/AF	Ectropion	1	0.27
rivaroxaban	NVAf/AF	Intervertebral disc disorder	1	0.27

# Appendix 7b(i). Other Medical History Prior to Starting rivaroxaban - NVAF/AF

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	NVAF/AF	Cough	1	0.27
rivaroxaban	NVAF/AF	Gastroenteritis Escherichia coli	1	0.27
rivaroxaban	NVAF/AF	Nephrolithiasis	1	0.27
rivaroxaban	NVAF/AF	Renal failure chronic	1	0.27
rivaroxaban	NVAF/AF	Lentigo	1	0.27
rivaroxaban	NVAF/AF	Tenosynovitis	1	0.27
rivaroxaban	NVAF/AF	Synovial cyst	1	0.27
rivaroxaban	NVAF/AF	Tongue disorder	1	0.27
rivaroxaban	NVAF/AF	Infection	1	0.27
rivaroxaban	NVAF/AF	Nerve injury	1	0.27
rivaroxaban	NVAF/AF	Hyperkalaemia	1	0.27
rivaroxaban	NVAF/AF	Iridocyclitis	1	0.27
rivaroxaban	NVAF/AF	Foot deformity	1	0.27
rivaroxaban	NVAF/AF	Systemic lupus erythematosus	1	0.27
rivaroxaban	NVAF/AF	Endometrial hypertrophy	1	0.27
rivaroxaban	NVAF/AF	Actinic keratosis	1	0.27
rivaroxaban	NVAF/AF	Ankylosing spondylitis	1	0.27
rivaroxaban	NVAF/AF	Hernia repair	1	0.27
rivaroxaban	NVAF/AF	Hidradenitis	1	0.27
rivaroxaban	NVAF/AF	Stomach mass	1	0.27
rivaroxaban	NVAF/AF	Breast lump removal	1	0.27
rivaroxaban	NVAF/AF	Goitre	1	0.27
rivaroxaban	NVAF/AF	Parkinson's disease	1	0.27
rivaroxaban	NVAF/AF	Tibia fracture	1	0.27
		<b>TOTAL</b>	<b>377</b>	



## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Asthma	109	12.69
rivaroxaban	DVT/PE	Osteoarthritis	70	8.15
rivaroxaban	DVT/PE	Depression	59	6.87
rivaroxaban	DVT/PE	Unevaluable event	57	6.64
rivaroxaban	DVT/PE	Hypothyroidism	41	4.77
rivaroxaban	DVT/PE	Pneumonia	38	4.42
rivaroxaban	DVT/PE	Gout	35	4.07
rivaroxaban	DVT/PE	Knee arthroplasty	34	3.96
rivaroxaban	DVT/PE	Hiatus hernia	31	3.61
rivaroxaban	DVT/PE	Gastrooesophageal reflux disease	31	3.61
rivaroxaban	DVT/PE	Osteoporosis	30	3.49
rivaroxaban	DVT/PE	Anxiety	30	3.49
rivaroxaban	DVT/PE	Arthritis	27	3.14
rivaroxaban	DVT/PE	Rheumatoid arthritis	21	2.44
rivaroxaban	DVT/PE	Angina pectoris	20	2.33
rivaroxaban	DVT/PE	Irritable bowel syndrome	18	2.10
rivaroxaban	DVT/PE	Lower respiratory tract infection	18	2.10
rivaroxaban	DVT/PE	Sleep apnoea syndrome	17	1.98
rivaroxaban	DVT/PE	Cellulitis	17	1.98
rivaroxaban	DVT/PE	Diverticulum	17	1.98
rivaroxaban	DVT/PE	Surgery	16	1.86
rivaroxaban	DVT/PE	Urinary tract infection	16	1.86
rivaroxaban	DVT/PE	Varicose vein	16	1.86
rivaroxaban	DVT/PE	Polymyalgia rheumatica	16	1.86
rivaroxaban	DVT/PE	Cholecystectomy	16	1.86
rivaroxaban	DVT/PE	Myocardial ischaemia	15	1.75
rivaroxaban	DVT/PE	Back pain	15	1.75
rivaroxaban	DVT/PE	Benign prostatic hyperplasia	14	1.63
rivaroxaban	DVT/PE	Chest pain	14	1.63
rivaroxaban	DVT/PE	Arthralgia	14	1.63
rivaroxaban	DVT/PE	Eczema	14	1.63
rivaroxaban	DVT/PE	Crohn's disease	13	1.51
rivaroxaban	DVT/PE	Anaemia	13	1.51
rivaroxaban	DVT/PE	Arthroscopy	13	1.51
rivaroxaban	DVT/PE	Obesity	13	1.51
rivaroxaban	DVT/PE	Hernia repair	12	1.40
rivaroxaban	DVT/PE	Skin ulcer	11	1.28
rivaroxaban	DVT/PE	Migraine	11	1.28
rivaroxaban	DVT/PE	Sciatica	11	1.28
rivaroxaban	DVT/PE	Hypertension	11	1.28
rivaroxaban	DVT/PE	Glaucoma	11	1.28
rivaroxaban	DVT/PE	Barrett's oesophagus	10	1.16
rivaroxaban	DVT/PE	Bronchiectasis	10	1.16
rivaroxaban	DVT/PE	Appendicectomy	9	1.05
rivaroxaban	DVT/PE	Colitis ulcerative	9	1.05
rivaroxaban	DVT/PE	Fibromyalgia	9	1.05
rivaroxaban	DVT/PE	Haemorrhoids	9	1.05
rivaroxaban	DVT/PE	Ankle fracture	9	1.05
rivaroxaban	DVT/PE	Drug abuser	9	1.05

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Oesophagitis	9	1.05
rivaroxaban	DVT/PE	Nephrolithiasis	8	0.93
rivaroxaban	DVT/PE	Tendon rupture	7	0.81
rivaroxaban	DVT/PE	Emergency care	7	0.81
rivaroxaban	DVT/PE	Thrombophlebitis	7	0.81
rivaroxaban	DVT/PE	Hyperthyroidism	7	0.81
rivaroxaban	DVT/PE	Psoriasis	7	0.81
rivaroxaban	DVT/PE	Multiple sclerosis	7	0.81
rivaroxaban	DVT/PE	Prostatomegaly	7	0.81
rivaroxaban	DVT/PE	Ovarian cyst	7	0.81
rivaroxaban	DVT/PE	Spinal osteoarthritis	7	0.81
rivaroxaban	DVT/PE	Parkinson's disease	7	0.81
rivaroxaban	DVT/PE	Varicose vein operation	6	0.70
rivaroxaban	DVT/PE	Cataract operation	6	0.70
rivaroxaban	DVT/PE	Investigation	6	0.70
rivaroxaban	DVT/PE	Chemotherapy	6	0.70
rivaroxaban	DVT/PE	Cataract	6	0.70
rivaroxaban	DVT/PE	Erectile dysfunction	6	0.70
rivaroxaban	DVT/PE	Fibula fracture	6	0.70
rivaroxaban	DVT/PE	Foot fracture	6	0.70
rivaroxaban	DVT/PE	Femur fracture	6	0.70
rivaroxaban	DVT/PE	Femoral neck fracture	6	0.70
rivaroxaban	DVT/PE	Depressed mood	6	0.70
rivaroxaban	DVT/PE	Diverticulitis	6	0.70
rivaroxaban	DVT/PE	Renal cyst	6	0.70
rivaroxaban	DVT/PE	Pain in extremity	5	0.58
rivaroxaban	DVT/PE	Humerus fracture	5	0.58
rivaroxaban	DVT/PE	Dyspnoea	5	0.58
rivaroxaban	DVT/PE	Macular degeneration	5	0.58
rivaroxaban	DVT/PE	Alcohol abuse	5	0.58
rivaroxaban	DVT/PE	Abdominal pain	5	0.58
rivaroxaban	DVT/PE	Biopsy	5	0.58
rivaroxaban	DVT/PE	Uterine leiomyoma	5	0.58
rivaroxaban	DVT/PE	Dyspepsia	5	0.58
rivaroxaban	DVT/PE	Cholecystitis	5	0.58
rivaroxaban	DVT/PE	Oedema peripheral	5	0.58
rivaroxaban	DVT/PE	Intervertebral disc protrusion	5	0.58
rivaroxaban	DVT/PE	Gastric ulcer	5	0.58
rivaroxaban	DVT/PE	Psoriatic arthropathy	5	0.58
rivaroxaban	DVT/PE	Laparoscopic surgery	5	0.58
rivaroxaban	DVT/PE	Iron deficiency anaemia	5	0.58
rivaroxaban	DVT/PE	Vitamin B12 deficiency	5	0.58
rivaroxaban	DVT/PE	Pulmonary fibrosis	5	0.58
rivaroxaban	DVT/PE	Pleural effusion	5	0.58
rivaroxaban	DVT/PE	Colitis	4	0.47
rivaroxaban	DVT/PE	Neuropathy peripheral	4	0.47
rivaroxaban	DVT/PE	Bladder neoplasm	4	0.47
rivaroxaban	DVT/PE	Tuberculosis	4	0.47
rivaroxaban	DVT/PE	Phlebitis	4	0.47

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Limb injury	4	0.47
rivaroxaban	DVT/PE	Ligament injury	4	0.47
rivaroxaban	DVT/PE	Seasonal allergy	4	0.47
rivaroxaban	DVT/PE	Upper limb fracture	4	0.47
rivaroxaban	DVT/PE	Vitamin D deficiency	4	0.47
rivaroxaban	DVT/PE	Cholelithiasis	4	0.47
rivaroxaban	DVT/PE	Osteotomy	4	0.47
rivaroxaban	DVT/PE	Respiratory failure	4	0.47
rivaroxaban	DVT/PE	Spinal cord injury	4	0.47
rivaroxaban	DVT/PE	Endocarditis	4	0.47
rivaroxaban	DVT/PE	Prostate cancer	4	0.47
rivaroxaban	DVT/PE	Joint dislocation	4	0.47
rivaroxaban	DVT/PE	Osteopenia	4	0.47
rivaroxaban	DVT/PE	Hip fracture	4	0.47
rivaroxaban	DVT/PE	Renal colic	4	0.47
rivaroxaban	DVT/PE	Dementia	4	0.47
rivaroxaban	DVT/PE	Vomiting	4	0.47
rivaroxaban	DVT/PE	Fall	4	0.47
rivaroxaban	DVT/PE	Renal failure acute	4	0.47
rivaroxaban	DVT/PE	Alcoholism	4	0.47
rivaroxaban	DVT/PE	Foot deformity	4	0.47
rivaroxaban	DVT/PE	Transurethral prostatectomy	4	0.47
rivaroxaban	DVT/PE	Polycystic ovaries	4	0.47
rivaroxaban	DVT/PE	Lymphoedema	3	0.35
rivaroxaban	DVT/PE	Hernia	3	0.35
rivaroxaban	DVT/PE	Polypectomy	3	0.35
rivaroxaban	DVT/PE	Laparoscopy	3	0.35
rivaroxaban	DVT/PE	Abdomen scan	3	0.35
rivaroxaban	DVT/PE	Urinary retention	3	0.35
rivaroxaban	DVT/PE	Tendonitis	3	0.35
rivaroxaban	DVT/PE	Deafness	3	0.35
rivaroxaban	DVT/PE	Mental disorder	3	0.35
rivaroxaban	DVT/PE	Aortic aneurysm	3	0.35
rivaroxaban	DVT/PE	Duodenal ulcer	3	0.35
rivaroxaban	DVT/PE	Coronary artery disease	3	0.35
rivaroxaban	DVT/PE	Cough	3	0.35
rivaroxaban	DVT/PE	Headache	3	0.35
rivaroxaban	DVT/PE	Head injury	3	0.35
rivaroxaban	DVT/PE	Endometriosis	3	0.35
rivaroxaban	DVT/PE	Tinnitus	3	0.35
rivaroxaban	DVT/PE	Tibia fracture	3	0.35
rivaroxaban	DVT/PE	Gastroenteritis	3	0.35
rivaroxaban	DVT/PE	Ankle operation	3	0.35
rivaroxaban	DVT/PE	Orthostatic hypotension	3	0.35
rivaroxaban	DVT/PE	Clavicle fracture	3	0.35
rivaroxaban	DVT/PE	Microcytic anaemia	3	0.35
rivaroxaban	DVT/PE	Ultrasound scan	3	0.35
rivaroxaban	DVT/PE	Cardiac pacemaker insertion	3	0.35
rivaroxaban	DVT/PE	Vertigo	3	0.35

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Essential hypertension	3	0.35
rivaroxaban	DVT/PE	Circulatory collapse	3	0.35
rivaroxaban	DVT/PE	Oral candidiasis	3	0.35
rivaroxaban	DVT/PE	Asbestosis	3	0.35
rivaroxaban	DVT/PE	Venous insufficiency	3	0.35
rivaroxaban	DVT/PE	Uterine dilation and curettage	3	0.35
rivaroxaban	DVT/PE	Breast lump removal	3	0.35
rivaroxaban	DVT/PE	Raynaud's phenomenon	3	0.35
rivaroxaban	DVT/PE	Rectal polyp	3	0.35
rivaroxaban	DVT/PE	Neuralgia	3	0.35
rivaroxaban	DVT/PE	Radius fracture	3	0.35
rivaroxaban	DVT/PE	Rotator cuff syndrome	3	0.35
rivaroxaban	DVT/PE	Synovial cyst	3	0.35
rivaroxaban	DVT/PE	Pulmonary hypertension	3	0.35
rivaroxaban	DVT/PE	Vasectomy	3	0.35
rivaroxaban	DVT/PE	Schizophrenia	3	0.35
rivaroxaban	DVT/PE	Knee operation	3	0.35
rivaroxaban	DVT/PE	Myalgia	3	0.35
rivaroxaban	DVT/PE	Skin neoplasm excision	3	0.35
rivaroxaban	DVT/PE	Visual impairment	3	0.35
rivaroxaban	DVT/PE	Epilepsy	3	0.35
rivaroxaban	DVT/PE	Diarrhoea	3	0.35
rivaroxaban	DVT/PE	Volvulus	3	0.35
rivaroxaban	DVT/PE	Drug abuse	3	0.35
rivaroxaban	DVT/PE	Carpal tunnel syndrome	3	0.35
rivaroxaban	DVT/PE	Rectal prolapse	3	0.35
rivaroxaban	DVT/PE	Pelvic inflammatory disease	3	0.35
rivaroxaban	DVT/PE	Pelvic fracture	3	0.35
rivaroxaban	DVT/PE	Duodenitis	3	0.35
rivaroxaban	DVT/PE	Colonoscopy	3	0.35
rivaroxaban	DVT/PE	Carpal tunnel decompression	3	0.35
rivaroxaban	DVT/PE	Ligament operation	3	0.35
rivaroxaban	DVT/PE	Wrist fracture	3	0.35
rivaroxaban	DVT/PE	Pneumothorax	3	0.35
rivaroxaban	DVT/PE	Pancreatitis	3	0.35
rivaroxaban	DVT/PE	Lipoma	3	0.35
rivaroxaban	DVT/PE	Neoplasm	3	0.35
rivaroxaban	DVT/PE	Body mass index increased	3	0.35
rivaroxaban	DVT/PE	Radiotherapy	3	0.35
rivaroxaban	DVT/PE	Umbilical hernia	2	0.23
rivaroxaban	DVT/PE	Corneal transplant	2	0.23
rivaroxaban	DVT/PE	Hypertonic bladder	2	0.23
rivaroxaban	DVT/PE	Cerebrovascular disorder	2	0.23
rivaroxaban	DVT/PE	Hypertensive heart disease	2	0.23
rivaroxaban	DVT/PE	Trigeminal neuralgia	2	0.23
rivaroxaban	DVT/PE	Lung lobectomy	2	0.23
rivaroxaban	DVT/PE	Sepsis	2	0.23
rivaroxaban	DVT/PE	Gastritis	2	0.23
rivaroxaban	DVT/PE	Road traffic accident	2	0.23

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Renal failure chronic	2	0.23
rivaroxaban	DVT/PE	Pickwickian syndrome	2	0.23
rivaroxaban	DVT/PE	Thrombophlebitis superficial	2	0.23
rivaroxaban	DVT/PE	Echocardiogram	2	0.23
rivaroxaban	DVT/PE	HIV test positive	2	0.23
rivaroxaban	DVT/PE	Dermal cyst	2	0.23
rivaroxaban	DVT/PE	Rosacea	2	0.23
rivaroxaban	DVT/PE	Benign familial pemphigus	2	0.23
rivaroxaban	DVT/PE	Hypochromic anaemia	2	0.23
rivaroxaban	DVT/PE	Ischaemia	2	0.23
rivaroxaban	DVT/PE	Pulmonary valve stenosis	2	0.23
rivaroxaban	DVT/PE	Seronegative arthritis	2	0.23
rivaroxaban	DVT/PE	Arthritis bacterial	2	0.23
rivaroxaban	DVT/PE	Tremor	2	0.23
rivaroxaban	DVT/PE	Vitamin B complex deficiency	2	0.23
rivaroxaban	DVT/PE	Dementia Alzheimer's type	2	0.23
rivaroxaban	DVT/PE	Oesophageal stenosis	2	0.23
rivaroxaban	DVT/PE	Intestinal obstruction	2	0.23
rivaroxaban	DVT/PE	Inguinal hernia	2	0.23
rivaroxaban	DVT/PE	Cyst	2	0.23
rivaroxaban	DVT/PE	Incisional hernia	2	0.23
rivaroxaban	DVT/PE	Mallory-Weiss syndrome	2	0.23
rivaroxaban	DVT/PE	Temporal arteritis	2	0.23
rivaroxaban	DVT/PE	Adrenal mass	2	0.23
rivaroxaban	DVT/PE	Urinary tract disorder	2	0.23
rivaroxaban	DVT/PE	Peripheral vascular disorder	2	0.23
rivaroxaban	DVT/PE	Orchitis	2	0.23
rivaroxaban	DVT/PE	Aortic valve incompetence	2	0.23
rivaroxaban	DVT/PE	Joint swelling	2	0.23
rivaroxaban	DVT/PE	Chondrocalcinosis pyrophosphate	2	0.23
rivaroxaban	DVT/PE	Dermatologic examination	2	0.23
rivaroxaban	DVT/PE	Alcohol problem	2	0.23
rivaroxaban	DVT/PE	Decubitus ulcer	2	0.23
rivaroxaban	DVT/PE	Lung abscess	2	0.23
rivaroxaban	DVT/PE	Herpes zoster	2	0.23
rivaroxaban	DVT/PE	Pleurisy	2	0.23
rivaroxaban	DVT/PE	Transurethral bladder resection	2	0.23
rivaroxaban	DVT/PE	Nasal polyps	2	0.23
rivaroxaban	DVT/PE	Arthropathy	2	0.23
rivaroxaban	DVT/PE	Oral lichen planus	2	0.23
rivaroxaban	DVT/PE	Arthrodesis	2	0.23
rivaroxaban	DVT/PE	Spinal cord compression	2	0.23
rivaroxaban	DVT/PE	Eye laser surgery	2	0.23
rivaroxaban	DVT/PE	Bipolar disorder	2	0.23
rivaroxaban	DVT/PE	Familial risk factor	2	0.23
rivaroxaban	DVT/PE	Localised infection	2	0.23
rivaroxaban	DVT/PE	Fibrous histiocytoma	2	0.23
rivaroxaban	DVT/PE	Rectal polypectomy	2	0.23
rivaroxaban	DVT/PE	Patella fracture	2	0.23

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Intraocular lens implant	2	0.23
rivaroxaban	DVT/PE	Panic attack	2	0.23
rivaroxaban	DVT/PE	Pernicious anaemia	2	0.23
rivaroxaban	DVT/PE	Ligament sprain	2	0.23
rivaroxaban	DVT/PE	Cystocele	2	0.23
rivaroxaban	DVT/PE	Abscess limb	2	0.23
rivaroxaban	DVT/PE	Pyeloplasty	2	0.23
rivaroxaban	DVT/PE	Computerised tomogram	2	0.23
rivaroxaban	DVT/PE	Inflammatory bowel disease	2	0.23
rivaroxaban	DVT/PE	Menopausal symptoms	2	0.23
rivaroxaban	DVT/PE	Breast mass	2	0.23
rivaroxaban	DVT/PE	Cast application	2	0.23
rivaroxaban	DVT/PE	Drug dependence	2	0.23
rivaroxaban	DVT/PE	Palpitations	2	0.23
rivaroxaban	DVT/PE	Prostatic specific antigen increased	2	0.23
rivaroxaban	DVT/PE	Cervical dysplasia	2	0.23
rivaroxaban	DVT/PE	Mitral valve incompetence	2	0.23
rivaroxaban	DVT/PE	Hyponatraemia	2	0.23
rivaroxaban	DVT/PE	Angina unstable	2	0.23
rivaroxaban	DVT/PE	Abdominoplasty	2	0.23
rivaroxaban	DVT/PE	Bursitis	2	0.23
rivaroxaban	DVT/PE	Tricuspid valve incompetence	2	0.23
rivaroxaban	DVT/PE	Hand fracture	2	0.23
rivaroxaban	DVT/PE	Tendon operation	2	0.23
rivaroxaban	DVT/PE	Polyarteritis nodosa	2	0.23
rivaroxaban	DVT/PE	Periarthritis	2	0.23
rivaroxaban	DVT/PE	Morton's neuroma	2	0.23
rivaroxaban	DVT/PE	Impaired fasting glucose	2	0.23
rivaroxaban	DVT/PE	Orthopaedic procedure	2	0.23
rivaroxaban	DVT/PE	Ankylosing spondylitis	2	0.23
rivaroxaban	DVT/PE	Polyp	2	0.23
rivaroxaban	DVT/PE	Toe operation	2	0.23
rivaroxaban	DVT/PE	Vaginal operation	2	0.23
rivaroxaban	DVT/PE	Myocarditis	2	0.23
rivaroxaban	DVT/PE	Immunisation	2	0.23
rivaroxaban	DVT/PE	Adenoma benign	2	0.23
rivaroxaban	DVT/PE	Goitre	2	0.23
rivaroxaban	DVT/PE	Plantar fasciitis	2	0.23
rivaroxaban	DVT/PE	Mobility decreased	2	0.23
rivaroxaban	DVT/PE	Vascular dementia	2	0.23
rivaroxaban	DVT/PE	Biliary colic	2	0.23
rivaroxaban	DVT/PE	Atrial septal defect	2	0.23
rivaroxaban	DVT/PE	Thoracic outlet syndrome	2	0.23
rivaroxaban	DVT/PE	Polyarthritis	2	0.23
rivaroxaban	DVT/PE	Gastric banding	2	0.23
rivaroxaban	DVT/PE	Endoscopy	2	0.23
rivaroxaban	DVT/PE	Uterine polyp	2	0.23
rivaroxaban	DVT/PE	Haemangioblastoma	2	0.23
rivaroxaban	DVT/PE	Osteomyelitis	2	0.23

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Myasthenia gravis	2	0.23
rivaroxaban	DVT/PE	Congenital cystic kidney disease	2	0.23
rivaroxaban	DVT/PE	Parkinsonism	2	0.23
rivaroxaban	DVT/PE	Renal failure	2	0.23
rivaroxaban	DVT/PE	Pharyngeal pouch	2	0.23
rivaroxaban	DVT/PE	Spondylitis	2	0.23
rivaroxaban	DVT/PE	Varicella	2	0.23
rivaroxaban	DVT/PE	Coeliac disease	2	0.23
rivaroxaban	DVT/PE	Neutropenia	2	0.23
rivaroxaban	DVT/PE	Rhabdomyolysis	2	0.23
rivaroxaban	DVT/PE	Pleuritic pain	2	0.23
rivaroxaban	DVT/PE	Cardiac murmur	2	0.23
rivaroxaban	DVT/PE	Poisoning deliberate	1	0.12
rivaroxaban	DVT/PE	Lipoma excision	1	0.12
rivaroxaban	DVT/PE	Alcohol use	1	0.12
rivaroxaban	DVT/PE	Loop electrosurgical excision procedure	1	0.12
rivaroxaban	DVT/PE	Biopsy prostate	1	0.12
rivaroxaban	DVT/PE	Campylobacter infection	1	0.12
rivaroxaban	DVT/PE	Fracture treatment	1	0.12
rivaroxaban	DVT/PE	Prurigo	1	0.12
rivaroxaban	DVT/PE	Tooth extraction	1	0.12
rivaroxaban	DVT/PE	Nephrotic syndrome	1	0.12
rivaroxaban	DVT/PE	Anal fistula	1	0.12
rivaroxaban	DVT/PE	Aortic arteriosclerosis	1	0.12
rivaroxaban	DVT/PE	Rhinitis allergic	1	0.12
rivaroxaban	DVT/PE	Labyrinthitis	1	0.12
rivaroxaban	DVT/PE	Ocular pemphigoid	1	0.12
rivaroxaban	DVT/PE	Compression fracture	1	0.12
rivaroxaban	DVT/PE	Addison's disease	1	0.12
rivaroxaban	DVT/PE	Hyperkalaemia	1	0.12
rivaroxaban	DVT/PE	Lipoedema	1	0.12
rivaroxaban	DVT/PE	Hemiparesis	1	0.12
rivaroxaban	DVT/PE	Prostatitis	1	0.12
rivaroxaban	DVT/PE	Meniscus lesion	1	0.12
rivaroxaban	DVT/PE	Meningioma	1	0.12
rivaroxaban	DVT/PE	Small intestinal obstruction	1	0.12
rivaroxaban	DVT/PE	Dysmenorrhoea	1	0.12
rivaroxaban	DVT/PE	Haemolytic anaemia	1	0.12
rivaroxaban	DVT/PE	Prostatism	1	0.12
rivaroxaban	DVT/PE	Blood magnesium decreased	1	0.12
rivaroxaban	DVT/PE	Retinitis pigmentosa	1	0.12
rivaroxaban	DVT/PE	Dupuytren's contracture	1	0.12
rivaroxaban	DVT/PE	Ultrasound kidney	1	0.12
rivaroxaban	DVT/PE	Eyelid ptosis	1	0.12
rivaroxaban	DVT/PE	Inflammatory marker increased	1	0.12
rivaroxaban	DVT/PE	Fracture displacement	1	0.12
rivaroxaban	DVT/PE	Proteinuria	1	0.12
rivaroxaban	DVT/PE	Fatigue	1	0.12
rivaroxaban	DVT/PE	Gastrostomy tube insertion	1	0.12

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Anogenital dysplasia	1	0.12
rivaroxaban	DVT/PE	Thrombosis prophylaxis	1	0.12
rivaroxaban	DVT/PE	Polycythaemia vera	1	0.12
rivaroxaban	DVT/PE	Injection	1	0.12
rivaroxaban	DVT/PE	Retinal vein occlusion	1	0.12
rivaroxaban	DVT/PE	Spigelian hernia	1	0.12
rivaroxaban	DVT/PE	Systemic lupus erythematosus	1	0.12
rivaroxaban	DVT/PE	Renal disorder	1	0.12
rivaroxaban	DVT/PE	Urticaria	1	0.12
rivaroxaban	DVT/PE	Pericarditis	1	0.12
rivaroxaban	DVT/PE	Acquired claw toe	1	0.12
rivaroxaban	DVT/PE	Spinal disorder	1	0.12
rivaroxaban	DVT/PE	Bladder operation	1	0.12
rivaroxaban	DVT/PE	Exposure to chemical pollution	1	0.12
rivaroxaban	DVT/PE	Spinal fusion surgery	1	0.12
rivaroxaban	DVT/PE	Rectal examination	1	0.12
rivaroxaban	DVT/PE	Faeces discoloured	1	0.12
rivaroxaban	DVT/PE	Synovial rupture	1	0.12
rivaroxaban	DVT/PE	Abdominal hernia	1	0.12
rivaroxaban	DVT/PE	Nephrogenic anaemia	1	0.12
rivaroxaban	DVT/PE	Urethral stenosis	1	0.12
rivaroxaban	DVT/PE	Renal mass	1	0.12
rivaroxaban	DVT/PE	Cervical laser therapy	1	0.12
rivaroxaban	DVT/PE	Blood creatine phosphokinase	1	0.12
rivaroxaban	DVT/PE	Ventricular hypertrophy	1	0.12
rivaroxaban	DVT/PE	Palliative care	1	0.12
rivaroxaban	DVT/PE	Ureteric obstruction	1	0.12
rivaroxaban	DVT/PE	Dermatitis	1	0.12
rivaroxaban	DVT/PE	Joint dislocation postoperative	1	0.12
rivaroxaban	DVT/PE	Neuropathic arthropathy	1	0.12
rivaroxaban	DVT/PE	Cauda equina syndrome	1	0.12
rivaroxaban	DVT/PE	Vagotomy	1	0.12
rivaroxaban	DVT/PE	Beckwith-Wiedemann syndrome	1	0.12
rivaroxaban	DVT/PE	Impaired gastric emptying	1	0.12
rivaroxaban	DVT/PE	Gouty arthritis	1	0.12
rivaroxaban	DVT/PE	Suicidal ideation	1	0.12
rivaroxaban	DVT/PE	Cystoscopy	1	0.12
rivaroxaban	DVT/PE	Microalbuminuria	1	0.12
rivaroxaban	DVT/PE	Cardiac disorder	1	0.12
rivaroxaban	DVT/PE	Peritonitis	1	0.12
rivaroxaban	DVT/PE	Nausea	1	0.12
rivaroxaban	DVT/PE	Vena cava thrombosis	1	0.12
rivaroxaban	DVT/PE	Hypoventilation	1	0.12
rivaroxaban	DVT/PE	Blood alcohol increased	1	0.12
rivaroxaban	DVT/PE	Dry eye	1	0.12
rivaroxaban	DVT/PE	Pericardial effusion	1	0.12
rivaroxaban	DVT/PE	General physical health deterioration	1	0.12
rivaroxaban	DVT/PE	Electrocardiogram ST-T segment abnormal	1	0.12
rivaroxaban	DVT/PE	Blindness unilateral	1	0.12



## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Corneal abrasion	1	0.12
rivaroxaban	DVT/PE	Folate deficiency	1	0.12
rivaroxaban	DVT/PE	Adrenal adenoma	1	0.12
rivaroxaban	DVT/PE	Multiple fractures	1	0.12
rivaroxaban	DVT/PE	Bowen's disease	1	0.12
rivaroxaban	DVT/PE	Biliary dilatation	1	0.12
rivaroxaban	DVT/PE	Elective surgery	1	0.12
rivaroxaban	DVT/PE	Ureteric stenosis	1	0.12
rivaroxaban	DVT/PE	Gastroenterostomy	1	0.12
rivaroxaban	DVT/PE	Vaginal prolapse	1	0.12
rivaroxaban	DVT/PE	Fibrocystic breast disease	1	0.12
rivaroxaban	DVT/PE	Central venous catheterisation	1	0.12
rivaroxaban	DVT/PE	Neurodermatitis	1	0.12
rivaroxaban	DVT/PE	Idiopathic pulmonary fibrosis	1	0.12
rivaroxaban	DVT/PE	Blood testosterone decreased	1	0.12
rivaroxaban	DVT/PE	Urge incontinence	1	0.12
rivaroxaban	DVT/PE	May-Thurner syndrome	1	0.12
rivaroxaban	DVT/PE	Drug hypersensitivity	1	0.12
rivaroxaban	DVT/PE	Musculoskeletal chest pain	1	0.12
rivaroxaban	DVT/PE	Inguinal hernia repair	1	0.12
rivaroxaban	DVT/PE	Ultrasound pelvis	1	0.12
rivaroxaban	DVT/PE	Uveitis	1	0.12
rivaroxaban	DVT/PE	Gastrointestinal tract adenoma	1	0.12
rivaroxaban	DVT/PE	Constipation	1	0.12
rivaroxaban	DVT/PE	Endotracheal intubation	1	0.12
rivaroxaban	DVT/PE	Central nervous system infection	1	0.12
rivaroxaban	DVT/PE	Cervical cord compression	1	0.12
rivaroxaban	DVT/PE	Syncope	1	0.12
rivaroxaban	DVT/PE	Post-traumatic stress disorder	1	0.12
rivaroxaban	DVT/PE	Change of bowel habit	1	0.12
rivaroxaban	DVT/PE	Venous stent insertion	1	0.12
rivaroxaban	DVT/PE	Radial nerve palsy	1	0.12
rivaroxaban	DVT/PE	Stent placement	1	0.12
rivaroxaban	DVT/PE	Complex partial seizures	1	0.12
rivaroxaban	DVT/PE	Peyronie's disease	1	0.12
rivaroxaban	DVT/PE	Dissociative identity disorder	1	0.12
rivaroxaban	DVT/PE	Appendicitis	1	0.12
rivaroxaban	DVT/PE	Benign breast neoplasm	1	0.12
rivaroxaban	DVT/PE	Peptic ulcer	1	0.12
rivaroxaban	DVT/PE	Colporrhaphy	1	0.12
rivaroxaban	DVT/PE	Skin lesion excision	1	0.12
rivaroxaban	DVT/PE	Sjogren's syndrome	1	0.12
rivaroxaban	DVT/PE	Female sterilisation	1	0.12
rivaroxaban	DVT/PE	Nephritis	1	0.12
rivaroxaban	DVT/PE	Henoch-Schonlein purpura	1	0.12
rivaroxaban	DVT/PE	Laceration	1	0.12
rivaroxaban	DVT/PE	IgA nephropathy	1	0.12
rivaroxaban	DVT/PE	Muscle strain	1	0.12
rivaroxaban	DVT/PE	Metatarsal excision	1	0.12

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Toe amputation	1	0.12
rivaroxaban	DVT/PE	Gastroenteritis viral	1	0.12
rivaroxaban	DVT/PE	Open angle glaucoma	1	0.12
rivaroxaban	DVT/PE	Pneumonia aspiration	1	0.12
rivaroxaban	DVT/PE	Iron deficiency	1	0.12
rivaroxaban	DVT/PE	Pneumonia klebsiella	1	0.12
rivaroxaban	DVT/PE	Bladder irritation	1	0.12
rivaroxaban	DVT/PE	Vasculitis cerebral	1	0.12
rivaroxaban	DVT/PE	Presyncope	1	0.12
rivaroxaban	DVT/PE	Computerised tomogram abnormal	1	0.12
rivaroxaban	DVT/PE	Oesophagogastroduodenoscopy	1	0.12
rivaroxaban	DVT/PE	Iritis	1	0.12
rivaroxaban	DVT/PE	Myelitis transverse	1	0.12
rivaroxaban	DVT/PE	Spina bifida	1	0.12
rivaroxaban	DVT/PE	Wound	1	0.12
rivaroxaban	DVT/PE	Electrocardiogram	1	0.12
rivaroxaban	DVT/PE	Thyroid cyst	1	0.12
rivaroxaban	DVT/PE	Needle issue	1	0.12
rivaroxaban	DVT/PE	Foreign travel	1	0.12
rivaroxaban	DVT/PE	Postural orthostatic tachycardia syndrome	1	0.12
rivaroxaban	DVT/PE	Colonic polyp	1	0.12
rivaroxaban	DVT/PE	Intestinal mass	1	0.12
rivaroxaban	DVT/PE	Thalassaemia beta	1	0.12
rivaroxaban	DVT/PE	Meniscus operation	1	0.12
rivaroxaban	DVT/PE	Stress urinary incontinence	1	0.12
rivaroxaban	DVT/PE	Non-cardiac chest pain	1	0.12
rivaroxaban	DVT/PE	Joint injection	1	0.12
rivaroxaban	DVT/PE	Acute myocardial infarction	1	0.12
rivaroxaban	DVT/PE	Blood immunoglobulin G decreased	1	0.12
rivaroxaban	DVT/PE	Bladder neck operation	1	0.12
rivaroxaban	DVT/PE	Lesion excision	1	0.12
rivaroxaban	DVT/PE	Atelectasis	1	0.12
rivaroxaban	DVT/PE	Acne	1	0.12
rivaroxaban	DVT/PE	Cervical spinal stenosis	1	0.12
rivaroxaban	DVT/PE	Localised oedema	1	0.12
rivaroxaban	DVT/PE	Nerve block	1	0.12
rivaroxaban	DVT/PE	Lens extraction	1	0.12
rivaroxaban	DVT/PE	Auricular perichondritis	1	0.12
rivaroxaban	DVT/PE	Oesophageal achalasia	1	0.12
rivaroxaban	DVT/PE	Neck pain	1	0.12
rivaroxaban	DVT/PE	Diverticular perforation	1	0.12
rivaroxaban	DVT/PE	Endometrial ablation	1	0.12
rivaroxaban	DVT/PE	Dementia with Lewy bodies	1	0.12
rivaroxaban	DVT/PE	Myelopathy	1	0.12
rivaroxaban	DVT/PE	Wound complication	1	0.12
rivaroxaban	DVT/PE	Haemorrhoid operation	1	0.12
rivaroxaban	DVT/PE	Pituitary tumour benign	1	0.12
rivaroxaban	DVT/PE	Influenza	1	0.12
rivaroxaban	DVT/PE	Stress fracture	1	0.12

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Drain placement	1	0.12
rivaroxaban	DVT/PE	Intracranial pressure increased	1	0.12
rivaroxaban	DVT/PE	Victim of spousal abuse	1	0.12
rivaroxaban	DVT/PE	Nasal septum deviation	1	0.12
rivaroxaban	DVT/PE	Thrombosis	1	0.12
rivaroxaban	DVT/PE	Dysphagia	1	0.12
rivaroxaban	DVT/PE	C-reactive protein increased	1	0.12
rivaroxaban	DVT/PE	Retinopathy	1	0.12
rivaroxaban	DVT/PE	Lumbar vertebral fracture	1	0.12
rivaroxaban	DVT/PE	Stem cell transplant	1	0.12
rivaroxaban	DVT/PE	Myomectomy	1	0.12
rivaroxaban	DVT/PE	Temporal lobe epilepsy	1	0.12
rivaroxaban	DVT/PE	Cardiac monitoring	1	0.12
rivaroxaban	DVT/PE	Lichen planus	1	0.12
rivaroxaban	DVT/PE	Breast prosthesis removal	1	0.12
rivaroxaban	DVT/PE	Monarthrititis	1	0.12
rivaroxaban	DVT/PE	Kidney infection	1	0.12
rivaroxaban	DVT/PE	Lymphocytosis	1	0.12
rivaroxaban	DVT/PE	Pneumonia legionella	1	0.12
rivaroxaban	DVT/PE	Costochondritis	1	0.12
rivaroxaban	DVT/PE	Corneal erosion	1	0.12
rivaroxaban	DVT/PE	Abdominal mass	1	0.12
rivaroxaban	DVT/PE	Brugada syndrome	1	0.12
rivaroxaban	DVT/PE	Oesophageal disorder	1	0.12
rivaroxaban	DVT/PE	Platelet count decreased	1	0.12
rivaroxaban	DVT/PE	High frequency ablation	1	0.12
rivaroxaban	DVT/PE	Rheumatoid factor increased	1	0.12
rivaroxaban	DVT/PE	Intestinal perforation	1	0.12
rivaroxaban	DVT/PE	Corneal dystrophy	1	0.12
rivaroxaban	DVT/PE	Pyelonephritis	1	0.12
rivaroxaban	DVT/PE	Mixed connective tissue disease	1	0.12
rivaroxaban	DVT/PE	Brain oedema	1	0.12
rivaroxaban	DVT/PE	Cardiomyopathy	1	0.12
rivaroxaban	DVT/PE	Orthostatic hypertension	1	0.12
rivaroxaban	DVT/PE	Chlamydial infection	1	0.12
rivaroxaban	DVT/PE	Iridocyclitis	1	0.12
rivaroxaban	DVT/PE	Schizophrenia, paranoid type	1	0.12
rivaroxaban	DVT/PE	Removal of internal fixation	1	0.12
rivaroxaban	DVT/PE	Urosepsis	1	0.12
rivaroxaban	DVT/PE	Neurofibromatosis	1	0.12
rivaroxaban	DVT/PE	Prostatic disorder	1	0.12
rivaroxaban	DVT/PE	Salpingitis	1	0.12
rivaroxaban	DVT/PE	Rib fracture	1	0.12
rivaroxaban	DVT/PE	Cardiovascular evaluation	1	0.12
rivaroxaban	DVT/PE	Wrist surgery	1	0.12
rivaroxaban	DVT/PE	Gynaecomastia	1	0.12
rivaroxaban	DVT/PE	Proctitis ulcerative	1	0.12
rivaroxaban	DVT/PE	Pain	1	0.12
rivaroxaban	DVT/PE	Colostomy	1	0.12

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Staphylococcal infection	1	0.12
rivaroxaban	DVT/PE	Interstitial lung disease	1	0.12
rivaroxaban	DVT/PE	Infected skin ulcer	1	0.12
rivaroxaban	DVT/PE	Attention deficit/hyperactivity disorder	1	0.12
rivaroxaban	DVT/PE	Abdominal distension	1	0.12
rivaroxaban	DVT/PE	Groin abscess	1	0.12
rivaroxaban	DVT/PE	Parathyroid gland enlargement	1	0.12
rivaroxaban	DVT/PE	Continuous positive airway pressure	1	0.12
rivaroxaban	DVT/PE	Shoulder operation	1	0.12
rivaroxaban	DVT/PE	Compression stockings application	1	0.12
rivaroxaban	DVT/PE	Ear infection	1	0.12
rivaroxaban	DVT/PE	Vlth nerve paralysis	1	0.12
rivaroxaban	DVT/PE	Vitrectomy	1	0.12
rivaroxaban	DVT/PE	Cardiomegaly	1	0.12
rivaroxaban	DVT/PE	Mass excision	1	0.12
rivaroxaban	DVT/PE	Ileostomy closure	1	0.12
rivaroxaban	DVT/PE	Anal fissure	1	0.12
rivaroxaban	DVT/PE	Bronchogenic cyst	1	0.12
rivaroxaban	DVT/PE	Lacrimal duct procedure	1	0.12
rivaroxaban	DVT/PE	Bunion operation	1	0.12
rivaroxaban	DVT/PE	Dyskinesia oesophageal	1	0.12
rivaroxaban	DVT/PE	Alopecia	1	0.12
rivaroxaban	DVT/PE	Body mass index decreased	1	0.12
rivaroxaban	DVT/PE	Haematocrit increased	1	0.12
rivaroxaban	DVT/PE	Pelvic mass	1	0.12
rivaroxaban	DVT/PE	Biopsy lymph gland	1	0.12
rivaroxaban	DVT/PE	Multiple system atrophy	1	0.12
rivaroxaban	DVT/PE	Ultrasound Doppler normal	1	0.12
rivaroxaban	DVT/PE	Eye operation	1	0.12
rivaroxaban	DVT/PE	Turner's syndrome	1	0.12
rivaroxaban	DVT/PE	Post viral fatigue syndrome	1	0.12
rivaroxaban	DVT/PE	Cystitis	1	0.12
rivaroxaban	DVT/PE	Skin graft	1	0.12
rivaroxaban	DVT/PE	Anaemia macrocytic	1	0.12
rivaroxaban	DVT/PE	Thrombolysis	1	0.12
rivaroxaban	DVT/PE	Poland's syndrome	1	0.12
rivaroxaban	DVT/PE	Insomnia	1	0.12
rivaroxaban	DVT/PE	Ovarian mass	1	0.12
rivaroxaban	DVT/PE	Pancreatitis acute	1	0.12
rivaroxaban	DVT/PE	Dizziness	1	0.12
rivaroxaban	DVT/PE	Glucose tolerance impaired	1	0.12
rivaroxaban	DVT/PE	Carotid artery aneurysm	1	0.12
rivaroxaban	DVT/PE	Viral infection	1	0.12
rivaroxaban	DVT/PE	Actinic keratosis	1	0.12
rivaroxaban	DVT/PE	Foreign body	1	0.12
rivaroxaban	DVT/PE	Renal ischaemia	1	0.12
rivaroxaban	DVT/PE	Post procedural pulmonary embolism	1	0.12
rivaroxaban	DVT/PE	Serum ferritin decreased	1	0.12
rivaroxaban	DVT/PE	Cerebral sarcoidosis	1	0.12

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Skin infection	1	0.12
rivaroxaban	DVT/PE	Klippel-Trenaunay syndrome	1	0.12
rivaroxaban	DVT/PE	Cerebral palsy	1	0.12
rivaroxaban	DVT/PE	Liposuction	1	0.12
rivaroxaban	DVT/PE	Poliomyelitis	1	0.12
rivaroxaban	DVT/PE	Intervertebral disc operation	1	0.12
rivaroxaban	DVT/PE	Varicocele	1	0.12
rivaroxaban	DVT/PE	Clostridial infection	1	0.12
rivaroxaban	DVT/PE	Angiogram	1	0.12
rivaroxaban	DVT/PE	Open fracture	1	0.12
rivaroxaban	DVT/PE	Granulomatosis with polyangiitis	1	0.12
rivaroxaban	DVT/PE	Gastric pH decreased	1	0.12
rivaroxaban	DVT/PE	Normochromic normocytic anaemia	1	0.12
rivaroxaban	DVT/PE	Candidiasis	1	0.12
rivaroxaban	DVT/PE	Computerised tomogram thorax abnormal	1	0.12
rivaroxaban	DVT/PE	Polyglandular disorder	1	0.12
rivaroxaban	DVT/PE	Pancreatic duct dilatation	1	0.12
rivaroxaban	DVT/PE	Hip surgery	1	0.12
rivaroxaban	DVT/PE	Bacterial disease carrier	1	0.12
rivaroxaban	DVT/PE	Sigmoidoscopy	1	0.12
rivaroxaban	DVT/PE	Trisomy 21	1	0.12
rivaroxaban	DVT/PE	Respiratory tract infection	1	0.12
rivaroxaban	DVT/PE	Oesophagoscopy	1	0.12
rivaroxaban	DVT/PE	Skin lesion	1	0.12
rivaroxaban	DVT/PE	Chondrodystrophy	1	0.12
rivaroxaban	DVT/PE	Wound treatment	1	0.12
rivaroxaban	DVT/PE	Oesophageal polyp	1	0.12
rivaroxaban	DVT/PE	Duodenal ulcer haemorrhage	1	0.12
rivaroxaban	DVT/PE	Wisdom teeth removal	1	0.12
rivaroxaban	DVT/PE	Keloid scar	1	0.12
rivaroxaban	DVT/PE	Spinal decompression	1	0.12
rivaroxaban	DVT/PE	Thoracic vertebral fracture	1	0.12
rivaroxaban	DVT/PE	Cerebral ischaemia	1	0.12
rivaroxaban	DVT/PE	Meniere's disease	1	0.12
rivaroxaban	DVT/PE	Eosinophilia	1	0.12
rivaroxaban	DVT/PE	Motor neurone disease	1	0.12
rivaroxaban	DVT/PE	Vitamin B12 decreased	1	0.12
rivaroxaban	DVT/PE	Nodule	1	0.12
rivaroxaban	DVT/PE	Haemoglobin decreased	1	0.12
rivaroxaban	DVT/PE	Psychiatric symptom	1	0.12
rivaroxaban	DVT/PE	Foot operation	1	0.12
rivaroxaban	DVT/PE	Sinus congestion	1	0.12
rivaroxaban	DVT/PE	Fracture	1	0.12
rivaroxaban	DVT/PE	Biopsy brain	1	0.12
rivaroxaban	DVT/PE	Mean platelet volume normal	1	0.12
rivaroxaban	DVT/PE	Salivary gland neoplasm	1	0.12
rivaroxaban	DVT/PE	Congestive cardiomyopathy	1	0.12
rivaroxaban	DVT/PE	Open reduction of fracture	1	0.12
rivaroxaban	DVT/PE	Hypertrophic cardiomyopathy	1	0.12

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Testicular pain	1	0.12
rivaroxaban	DVT/PE	Dermatitis atopic	1	0.12
rivaroxaban	DVT/PE	Dehydration	1	0.12
rivaroxaban	DVT/PE	Muscle spasms	1	0.12
rivaroxaban	DVT/PE	Paranasal sinus hypersecretion	1	0.12
rivaroxaban	DVT/PE	Hearing impaired	1	0.12
rivaroxaban	DVT/PE	Osteitis deformans	1	0.12
rivaroxaban	DVT/PE	Endoscopy small intestine	1	0.12
rivaroxaban	DVT/PE	Left ventricular hypertrophy	1	0.12
rivaroxaban	DVT/PE	Intervertebral discitis	1	0.12
rivaroxaban	DVT/PE	Pituitary cyst	1	0.12
rivaroxaban	DVT/PE	Bradycardia	1	0.12
rivaroxaban	DVT/PE	Ophthalmoplegia	1	0.12
rivaroxaban	DVT/PE	Internal fixation of fracture	1	0.12
rivaroxaban	DVT/PE	Hernia hiatus repair	1	0.12
rivaroxaban	DVT/PE	Vasculitis	1	0.12
rivaroxaban	DVT/PE	Respiratory disorder	1	0.12
rivaroxaban	DVT/PE	Arthritis infective	1	0.12
rivaroxaban	DVT/PE	Peripheral sensorimotor neuropathy	1	0.12
rivaroxaban	DVT/PE	Enterovesical fistula	1	0.12
rivaroxaban	DVT/PE	Ventricular extrasystoles	1	0.12
rivaroxaban	DVT/PE	Endoscopy upper gastrointestinal tract	1	0.12
rivaroxaban	DVT/PE	Neurilemmoma	1	0.12
rivaroxaban	DVT/PE	Tachycardia	1	0.12
rivaroxaban	DVT/PE	Encephalopathy	1	0.12
rivaroxaban	DVT/PE	Melanocytic naevus	1	0.12
rivaroxaban	DVT/PE	Sarcopenia	1	0.12
rivaroxaban	DVT/PE	Convulsion	1	0.12
rivaroxaban	DVT/PE	Post herpetic neuralgia	1	0.12
rivaroxaban	DVT/PE	Spinal column stenosis	1	0.12
rivaroxaban	DVT/PE	Bronchitis	1	0.12
rivaroxaban	DVT/PE	Renal infarct	1	0.12
rivaroxaban	DVT/PE	Cast removal	1	0.12
rivaroxaban	DVT/PE	Diplopia	1	0.12
rivaroxaban	DVT/PE	Contusion	1	0.12
rivaroxaban	DVT/PE	Aortic stenosis	1	0.12
rivaroxaban	DVT/PE	Pancytopenia	1	0.12
rivaroxaban	DVT/PE	Transfusion	1	0.12
rivaroxaban	DVT/PE	Anal lesion excision	1	0.12
rivaroxaban	DVT/PE	Tendon disorder	1	0.12
rivaroxaban	DVT/PE	Myotonic dystrophy	1	0.12
rivaroxaban	DVT/PE	Vaginitis bacterial	1	0.12
rivaroxaban	DVT/PE	Uterine cyst	1	0.12
rivaroxaban	DVT/PE	Rheumatic fever	1	0.12
rivaroxaban	DVT/PE	Suture insertion	1	0.12
rivaroxaban	DVT/PE	Confusional state	1	0.12
rivaroxaban	DVT/PE	Aneurysm repair	1	0.12
rivaroxaban	DVT/PE	Benign neoplasm of thyroid gland	1	0.12
rivaroxaban	DVT/PE	Premature menopause	1	0.12

## Appendix 7b(ii). Other Medical History Prior to Starting rivaroxaban - DVT/PE

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	DVT/PE	Overdose	1	0.12
rivaroxaban	DVT/PE	Osteolysis	1	0.12
rivaroxaban	DVT/PE	Sickle cell anaemia	1	0.12
rivaroxaban	DVT/PE	Transient psychosis	1	0.12
rivaroxaban	DVT/PE	Thermal burn	1	0.12
rivaroxaban	DVT/PE	Infarction	1	0.12
rivaroxaban	DVT/PE	Perineurial cyst	1	0.12
rivaroxaban	DVT/PE	Tendon injury	1	0.12
rivaroxaban	DVT/PE	Pancreatic cyst	1	0.12
rivaroxaban	DVT/PE	Post thrombotic syndrome	1	0.12
rivaroxaban	DVT/PE	Biopsy bladder	1	0.12
rivaroxaban	DVT/PE	Empyema	1	0.12
rivaroxaban	DVT/PE	Leukopenia	1	0.12
rivaroxaban	DVT/PE	Compartment syndrome	1	0.12
rivaroxaban	DVT/PE	Bullous lung disease	1	0.12
rivaroxaban	DVT/PE	Papilloma excision	1	0.12
rivaroxaban	DVT/PE	Blepharitis	1	0.12
rivaroxaban	DVT/PE	Rotator cuff repair	1	0.12
rivaroxaban	DVT/PE	Lung neoplasm	1	0.12
rivaroxaban	DVT/PE	Hydrocele operation	1	0.12
rivaroxaban	DVT/PE	Secondary progressive multiple sclerosis	1	0.12
rivaroxaban	DVT/PE	Parotidectomy	1	0.12
		<b>TOTAL</b>	<b>859</b>	

### Appendix 7b(iii). Other Medical History Prior to Starting rivaroxaban - Mixed

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	Mixed	Asthma	2	11.11
rivaroxaban	Mixed	Palpitations	2	11.11
rivaroxaban	Mixed	Acute pulmonary oedema	1	5.56
rivaroxaban	Mixed	Arthritis	1	5.56
rivaroxaban	Mixed	Acquired oesophageal web	1	5.56
rivaroxaban	Mixed	Oesophagitis	1	5.56
rivaroxaban	Mixed	Gastrooesophageal reflux disease	1	5.56
rivaroxaban	Mixed	Osteoarthritis	1	5.56
rivaroxaban	Mixed	Cataract	1	5.56
rivaroxaban	Mixed	Peripheral vascular disorder	1	5.56
rivaroxaban	Mixed	Aortic aneurysm rupture	1	5.56
rivaroxaban	Mixed	Exostosis	1	5.56
rivaroxaban	Mixed	Cholecystectomy	1	5.56
rivaroxaban	Mixed	Weight decreased	1	5.56
rivaroxaban	Mixed	Skin ulcer	1	5.56
rivaroxaban	Mixed	Hernia repair	1	5.56
rivaroxaban	Mixed	Hypersensitivity	1	5.56
rivaroxaban	Mixed	Anaemia	1	5.56
rivaroxaban	Mixed	Cholecystitis	1	5.56
rivaroxaban	Mixed	Infection	1	5.56
rivaroxaban	Mixed	Hypothyroidism	1	5.56
rivaroxaban	Mixed	Vitamin B12 deficiency	1	5.56
rivaroxaban	Mixed	Convulsion	1	5.56
rivaroxaban	Mixed	Humerus fracture	1	5.56
rivaroxaban	Mixed	Age-related macular degeneration	1	5.56
rivaroxaban	Mixed	Sleep apnoea syndrome	1	5.56
rivaroxaban	Mixed	Anxiety	1	5.56
rivaroxaban	Mixed	Paraesthesia	1	5.56
rivaroxaban	Mixed	Sepsis	1	5.56
rivaroxaban	Mixed	Neuropathy peripheral	1	5.56
rivaroxaban	Mixed	Hip fracture	1	5.56
		<b>TOTAL</b>	<b>18</b>	



# Appendix 7b(iv). Other Medical History Prior to Starting rivaroxaban - Other

Treatment group	Indication	Preferred term	Number	%
rivaroxaban	Other	Asthma	2	18.18
rivaroxaban	Other	Intra-abdominal haemorrhage	1	9.09
rivaroxaban	Other	Small intestinal obstruction	1	9.09
rivaroxaban	Other	Cutaneous lupus erythematosus	1	9.09
rivaroxaban	Other	Drug abuse	1	9.09
rivaroxaban	Other	Duodenitis	1	9.09
rivaroxaban	Other	Unevaluable event	1	9.09
rivaroxaban	Other	Angiogram	1	9.09
rivaroxaban	Other	Epilepsy	1	9.09
rivaroxaban	Other	Post procedural drainage	1	9.09
rivaroxaban	Other	Bronchiectasis	1	9.09
rivaroxaban	Other	Hypoaesthesia	1	9.09
rivaroxaban	Other	Knee arthroplasty	1	9.09
rivaroxaban	Other	Glaucoma	1	9.09
rivaroxaban	Other	Myeloproliferative disorder	1	9.09
rivaroxaban	Other	Bipolar disorder	1	9.09
rivaroxaban	Other	Hypothyroidism	1	9.09
rivaroxaban	Other	Gastritis	1	9.09
rivaroxaban	Other	Coeliac disease	1	9.09
rivaroxaban	Other	Hernia repair	1	9.09
rivaroxaban	Other	Antiphospholipid syndrome	1	9.09
rivaroxaban	Other	Alcohol abuse	1	9.09
rivaroxaban	Other	Herpes zoster	1	9.09
		<b>TOTAL</b>	<b>11</b>	

## Appendix 7c(i). Other Medical History Prior to Starting warfarin - NVAF/AF

Treatment group	Indication	Preferred term	Number	%
warfarin	NVAF/AF	Osteoarthritis	39	10.08
warfarin	NVAF/AF	Asthma	27	6.98
warfarin	NVAF/AF	Unevaluable event	24	6.20
warfarin	NVAF/AF	Depression	20	5.17
warfarin	NVAF/AF	Hypertension	18	4.65
warfarin	NVAF/AF	Cardiac pacemaker insertion	18	4.65
warfarin	NVAF/AF	Gout	16	4.13
warfarin	NVAF/AF	Hiatus hernia	15	3.88
warfarin	NVAF/AF	Arthritis	15	3.88
warfarin	NVAF/AF	Hypothyroidism	15	3.88
warfarin	NVAF/AF	Myocardial ischaemia	14	3.62
warfarin	NVAF/AF	Knee arthroplasty	13	3.36
warfarin	NVAF/AF	Gastrooesophageal reflux disease	13	3.36
warfarin	NVAF/AF	Angina pectoris	13	3.36
warfarin	NVAF/AF	Benign prostatic hyperplasia	12	3.10
warfarin	NVAF/AF	Rheumatoid arthritis	12	3.10
warfarin	NVAF/AF	Glaucoma	11	2.84
warfarin	NVAF/AF	Diverticulum	11	2.84
warfarin	NVAF/AF	Lower respiratory tract infection	11	2.84
warfarin	NVAF/AF	Cholecystectomy	11	2.84
warfarin	NVAF/AF	Osteoporosis	11	2.84
warfarin	NVAF/AF	Cataract	10	2.58
warfarin	NVAF/AF	Polymyalgia rheumatica	9	2.33
warfarin	NVAF/AF	Sleep apnoea syndrome	8	2.07
warfarin	NVAF/AF	Obesity	8	2.07
warfarin	NVAF/AF	Hernia repair	7	1.81
warfarin	NVAF/AF	Aortic aneurysm	7	1.81
warfarin	NVAF/AF	Pneumonia	7	1.81
warfarin	NVAF/AF	Back pain	7	1.81
warfarin	NVAF/AF	Epilepsy	7	1.81
warfarin	NVAF/AF	Stent placement	6	1.55
warfarin	NVAF/AF	Appendicectomy	6	1.55
warfarin	NVAF/AF	Anaemia	6	1.55
warfarin	NVAF/AF	Mitral valve incompetence	6	1.55
warfarin	NVAF/AF	Cholelithiasis	6	1.55
warfarin	NVAF/AF	Varicose vein	5	1.29
warfarin	NVAF/AF	Anxiety	5	1.29
warfarin	NVAF/AF	Barrett's oesophagus	5	1.29
warfarin	NVAF/AF	Psoriasis	5	1.29
warfarin	NVAF/AF	Gastritis	5	1.29
warfarin	NVAF/AF	Dyspnoea	5	1.29
warfarin	NVAF/AF	Aortic stenosis	5	1.29
warfarin	NVAF/AF	Parkinson's disease	5	1.29
warfarin	NVAF/AF	Asbestosis	5	1.29
warfarin	NVAF/AF	Iron deficiency anaemia	5	1.29
warfarin	NVAF/AF	Irritable bowel syndrome	5	1.29
warfarin	NVAF/AF	Palpitations	5	1.29
warfarin	NVAF/AF	Migraine	5	1.29
warfarin	NVAF/AF	Coeliac disease	4	1.03

## Appendix 7c(i). Other Medical History Prior to Starting warfarin - NVAF/AF

Treatment group	Indication	Preferred term	Number	%
warfarin	NVAF/AF	Bronchiectasis	4	1.03
warfarin	NVAF/AF	Cataract operation	4	1.03
warfarin	NVAF/AF	Carpal tunnel decompression	4	1.03
warfarin	NVAF/AF	Oedema peripheral	4	1.03
warfarin	NVAF/AF	Sciatica	4	1.03
warfarin	NVAF/AF	Spinal osteoarthritis	4	1.03
warfarin	NVAF/AF	Microcytic anaemia	4	1.03
warfarin	NVAF/AF	Temporal arteritis	4	1.03
warfarin	NVAF/AF	Pulmonary hypertension	4	1.03
warfarin	NVAF/AF	Erectile dysfunction	4	1.03
warfarin	NVAF/AF	Transurethral prostatectomy	4	1.03
warfarin	NVAF/AF	Urinary tract infection	4	1.03
warfarin	NVAF/AF	Carpal tunnel syndrome	3	0.78
warfarin	NVAF/AF	Pyloric stenosis	3	0.78
warfarin	NVAF/AF	Age-related macular degeneration	3	0.78
warfarin	NVAF/AF	Alcohol abuse	3	0.78
warfarin	NVAF/AF	Inguinal hernia repair	3	0.78
warfarin	NVAF/AF	Macular degeneration	3	0.78
warfarin	NVAF/AF	Renal impairment	3	0.78
warfarin	NVAF/AF	Renal failure acute	3	0.78
warfarin	NVAF/AF	Dermatitis	3	0.78
warfarin	NVAF/AF	Pleural effusion	3	0.78
warfarin	NVAF/AF	Hyperthyroidism	3	0.78
warfarin	NVAF/AF	Biliary colic	3	0.78
warfarin	NVAF/AF	Hyponatraemia	3	0.78
warfarin	NVAF/AF	Sepsis	3	0.78
warfarin	NVAF/AF	Cardiomegaly	3	0.78
warfarin	NVAF/AF	Pancreatitis	3	0.78
warfarin	NVAF/AF	Actinic keratosis	3	0.78
warfarin	NVAF/AF	Helicobacter infection	3	0.78
warfarin	NVAF/AF	Atrial septal defect	3	0.78
warfarin	NVAF/AF	Nephrolithiasis	3	0.78
warfarin	NVAF/AF	Colitis ulcerative	3	0.78
warfarin	NVAF/AF	Duodenal ulcer	3	0.78
warfarin	NVAF/AF	Aortic valve incompetence	3	0.78
warfarin	NVAF/AF	Inguinal hernia	3	0.78
warfarin	NVAF/AF	Bipolar I disorder	2	0.52
warfarin	NVAF/AF	Gastric ulcer	2	0.52
warfarin	NVAF/AF	Retinal detachment	2	0.52
warfarin	NVAF/AF	Cardiomyopathy	2	0.52
warfarin	NVAF/AF	Myasthenia gravis	2	0.52
warfarin	NVAF/AF	Prostatism	2	0.52
warfarin	NVAF/AF	Intervertebral disc degeneration	2	0.52
warfarin	NVAF/AF	Congenital cystic kidney disease	2	0.52
warfarin	NVAF/AF	Diverticulitis	2	0.52
warfarin	NVAF/AF	Raynaud's phenomenon	2	0.52
warfarin	NVAF/AF	Sinusitis	2	0.52
warfarin	NVAF/AF	Scoliosis	2	0.52
warfarin	NVAF/AF	Meningioma	2	0.52

## Appendix 7c(i). Other Medical History Prior to Starting warfarin - NVAF/AF

Treatment group	Indication	Preferred term	Number	%
warfarin	NVAF/AF	Crohn's disease	2	0.52
warfarin	NVAF/AF	Colitis	2	0.52
warfarin	NVAF/AF	Lipoma	2	0.52
warfarin	NVAF/AF	Lymphoedema	2	0.52
warfarin	NVAF/AF	Cystoscopy	2	0.52
warfarin	NVAF/AF	Tuberculosis	2	0.52
warfarin	NVAF/AF	Renal failure chronic	2	0.52
warfarin	NVAF/AF	Lumbar spinal stenosis	2	0.52
warfarin	NVAF/AF	Joint injury	2	0.52
warfarin	NVAF/AF	Pyrexia	2	0.52
warfarin	NVAF/AF	Vitamin B12 deficiency	2	0.52
warfarin	NVAF/AF	Oesophagitis	2	0.52
warfarin	NVAF/AF	Essential hypertension	2	0.52
warfarin	NVAF/AF	Pernicious anaemia	2	0.52
warfarin	NVAF/AF	Transfusion	2	0.52
warfarin	NVAF/AF	Fibula fracture	2	0.52
warfarin	NVAF/AF	Infection	2	0.52
warfarin	NVAF/AF	Haemorrhoids	2	0.52
warfarin	NVAF/AF	Glucose tolerance impaired	2	0.52
warfarin	NVAF/AF	Mitral valve prolapse	2	0.52
warfarin	NVAF/AF	Vertigo	2	0.52
warfarin	NVAF/AF	Dupuytren's contracture	2	0.52
warfarin	NVAF/AF	Colonic polyp	2	0.52
warfarin	NVAF/AF	Staphylococcal infection	2	0.52
warfarin	NVAF/AF	Appendicitis	2	0.52
warfarin	NVAF/AF	Aortic dilatation	2	0.52
warfarin	NVAF/AF	Duodenitis	2	0.52
warfarin	NVAF/AF	Ankylosing spondylitis	2	0.52
warfarin	NVAF/AF	Circulatory collapse	2	0.52
warfarin	NVAF/AF	Cellulitis	2	0.52
warfarin	NVAF/AF	Seasonal allergy	2	0.52
warfarin	NVAF/AF	Endoscopic retrograde cholangiopancreatography	2	0.52
warfarin	NVAF/AF	Skin neoplasm excision	2	0.52
warfarin	NVAF/AF	Dermal cyst	2	0.52
warfarin	NVAF/AF	Transurethral bladder resection	2	0.52
warfarin	NVAF/AF	VIIIth nerve paralysis	2	0.52
warfarin	NVAF/AF	Panic attack	1	0.26
warfarin	NVAF/AF	Proctalgia	1	0.26
warfarin	NVAF/AF	Rheumatic fever	1	0.26
warfarin	NVAF/AF	Arthralgia	1	0.26
warfarin	NVAF/AF	Gastrostomy tube insertion	1	0.26
warfarin	NVAF/AF	Urinary retention	1	0.26
warfarin	NVAF/AF	Wrist fracture	1	0.26
warfarin	NVAF/AF	Fungal infection	1	0.26
warfarin	NVAF/AF	Hernia hiatus repair	1	0.26
warfarin	NVAF/AF	Pemphigoid	1	0.26
warfarin	NVAF/AF	Macular hole	1	0.26
warfarin	NVAF/AF	Weight decreased	1	0.26
warfarin	NVAF/AF	Pancreatic neoplasm	1	0.26

## Appendix 7c(i). Other Medical History Prior to Starting warfarin - NVAF/AF

Treatment group	Indication	Preferred term	Number	%
warfarin	NVAF/AF	Lactic acidosis	1	0.26
warfarin	NVAF/AF	Acute coronary syndrome	1	0.26
warfarin	NVAF/AF	Interstitial lung disease	1	0.26
warfarin	NVAF/AF	Vertigo positional	1	0.26
warfarin	NVAF/AF	Blepharitis	1	0.26
warfarin	NVAF/AF	Skin ulcer	1	0.26
warfarin	NVAF/AF	Trabeculectomy	1	0.26
warfarin	NVAF/AF	Post procedural haemorrhage	1	0.26
warfarin	NVAF/AF	Cervical polypectomy	1	0.26
warfarin	NVAF/AF	Urinary incontinence	1	0.26
warfarin	NVAF/AF	Thrombolysis	1	0.26
warfarin	NVAF/AF	Pericardial effusion	1	0.26
warfarin	NVAF/AF	Eczema	1	0.26
warfarin	NVAF/AF	Tendon sheath lesion excision	1	0.26
warfarin	NVAF/AF	Gastritis erosive	1	0.26
warfarin	NVAF/AF	Meniscus removal	1	0.26
warfarin	NVAF/AF	Pruritus	1	0.26
warfarin	NVAF/AF	Swelling	1	0.26
warfarin	NVAF/AF	Drug abuse	1	0.26
warfarin	NVAF/AF	Microangiopathy	1	0.26
warfarin	NVAF/AF	Respiratory failure	1	0.26
warfarin	NVAF/AF	Hip surgery	1	0.26
warfarin	NVAF/AF	Lymphadenopathy	1	0.26
warfarin	NVAF/AF	Pulmonary fibrosis	1	0.26
warfarin	NVAF/AF	Mastoidectomy	1	0.26
warfarin	NVAF/AF	Head injury	1	0.26
warfarin	NVAF/AF	Anaemia megaloblastic	1	0.26
warfarin	NVAF/AF	Alcoholism	1	0.26
warfarin	NVAF/AF	Vertebral foraminal stenosis	1	0.26
warfarin	NVAF/AF	Heart valve incompetence	1	0.26
warfarin	NVAF/AF	Volvulus	1	0.26
warfarin	NVAF/AF	Serratia infection	1	0.26
warfarin	NVAF/AF	Guillain-Barre syndrome	1	0.26
warfarin	NVAF/AF	Loss of consciousness	1	0.26
warfarin	NVAF/AF	Vascular dementia	1	0.26
warfarin	NVAF/AF	Cervical laser therapy	1	0.26
warfarin	NVAF/AF	Prolactinoma	1	0.26
warfarin	NVAF/AF	Ovarian cyst	1	0.26
warfarin	NVAF/AF	Cardiac monitoring	1	0.26
warfarin	NVAF/AF	Sarcoidosis	1	0.26
warfarin	NVAF/AF	Cholelithotomy	1	0.26
warfarin	NVAF/AF	Tricuspid valve incompetence	1	0.26
warfarin	NVAF/AF	Essential tremor	1	0.26
warfarin	NVAF/AF	Immunisation	1	0.26
warfarin	NVAF/AF	Dilatation atrial	1	0.26
warfarin	NVAF/AF	Parkinsonism	1	0.26
warfarin	NVAF/AF	Acquired oesophageal web	1	0.26
warfarin	NVAF/AF	Chorioretinopathy	1	0.26
warfarin	NVAF/AF	Intestinal angina	1	0.26

## Appendix 7c(i). Other Medical History Prior to Starting warfarin - NVAF/AF

Treatment group	Indication	Preferred term	Number	%
warfarin	NVAF/AF	Urinary tract disorder	1	0.26
warfarin	NVAF/AF	Bursitis	1	0.26
warfarin	NVAF/AF	Thrombophlebitis	1	0.26
warfarin	NVAF/AF	Fibroma	1	0.26
warfarin	NVAF/AF	Lobar pneumonia	1	0.26
warfarin	NVAF/AF	Lymphocytosis	1	0.26
warfarin	NVAF/AF	Goitre	1	0.26
warfarin	NVAF/AF	Bladder catheterisation	1	0.26
warfarin	NVAF/AF	Dyspepsia	1	0.26
warfarin	NVAF/AF	Spinal column stenosis	1	0.26
warfarin	NVAF/AF	Tendonitis	1	0.26
warfarin	NVAF/AF	Endoscopy	1	0.26
warfarin	NVAF/AF	Ischaemic cardiomyopathy	1	0.26
warfarin	NVAF/AF	Femoral hernia repair	1	0.26
warfarin	NVAF/AF	Hypoacusis	1	0.26
warfarin	NVAF/AF	Arthropathy	1	0.26
warfarin	NVAF/AF	Syncope	1	0.26
warfarin	NVAF/AF	Echocardiogram	1	0.26
warfarin	NVAF/AF	Peripheral vascular disorder	1	0.26
warfarin	NVAF/AF	Electrocardiogram ambulatory	1	0.26
warfarin	NVAF/AF	Renal infarct	1	0.26
warfarin	NVAF/AF	Biopsy endometrium	1	0.26
warfarin	NVAF/AF	Dupuytren's contracture operation	1	0.26
warfarin	NVAF/AF	Cautery to nose	1	0.26
warfarin	NVAF/AF	Radius fracture	1	0.26
warfarin	NVAF/AF	Peritonitis	1	0.26
warfarin	NVAF/AF	Meniere's disease	1	0.26
warfarin	NVAF/AF	Device failure	1	0.26
warfarin	NVAF/AF	Liver injury	1	0.26
warfarin	NVAF/AF	Hyperparathyroidism primary	1	0.26
warfarin	NVAF/AF	Peripheral ischaemia	1	0.26
warfarin	NVAF/AF	Ligament sprain	1	0.26
warfarin	NVAF/AF	Pulmonary tuberculosis	1	0.26
warfarin	NVAF/AF	Orthostatic hypotension	1	0.26
warfarin	NVAF/AF	Ventricular septal defect	1	0.26
warfarin	NVAF/AF	Basedow's disease	1	0.26
warfarin	NVAF/AF	Ankle fracture	1	0.26
warfarin	NVAF/AF	Intra-ocular injection	1	0.26
warfarin	NVAF/AF	Calculus bladder	1	0.26
warfarin	NVAF/AF	Intervertebral disc operation	1	0.26
warfarin	NVAF/AF	Uterine dilation and curettage	1	0.26
warfarin	NVAF/AF	Kyphoscoliosis	1	0.26
warfarin	NVAF/AF	Cerebral atrophy	1	0.26
warfarin	NVAF/AF	Pleural fibrosis	1	0.26
warfarin	NVAF/AF	Rosacea	1	0.26
warfarin	NVAF/AF	Acromegaly	1	0.26
warfarin	NVAF/AF	Vitamin B complex deficiency	1	0.26
warfarin	NVAF/AF	Presyncope	1	0.26
warfarin	NVAF/AF	Cardiovascular evaluation	1	0.26

## Appendix 7c(i). Other Medical History Prior to Starting warfarin - NVAF/AF

Treatment group	Indication	Preferred term	Number	%
warfarin	NVAF/AF	Parathyroidectomy	1	0.26
warfarin	NVAF/AF	Ventricular extrasystoles	1	0.26
warfarin	NVAF/AF	Arthroscopy	1	0.26
warfarin	NVAF/AF	Normochromic normocytic anaemia	1	0.26
warfarin	NVAF/AF	Cat scratch disease	1	0.26
warfarin	NVAF/AF	Thalassaemia trait	1	0.26
warfarin	NVAF/AF	Periarthritis	1	0.26
warfarin	NVAF/AF	Viral upper respiratory tract infection	1	0.26
warfarin	NVAF/AF	Tendon operation	1	0.26
warfarin	NVAF/AF	Malaise	1	0.26
warfarin	NVAF/AF	Polyarteritis nodosa	1	0.26
warfarin	NVAF/AF	Cervicobrachial syndrome	1	0.26
warfarin	NVAF/AF	Muscle spasms	1	0.26
warfarin	NVAF/AF	Generalised anxiety disorder	1	0.26
warfarin	NVAF/AF	Vomiting	1	0.26
warfarin	NVAF/AF	Sigmoidoscopy	1	0.26
warfarin	NVAF/AF	Deep vein thrombosis postoperative	1	0.26
warfarin	NVAF/AF	Hypolipidaemia	1	0.26
warfarin	NVAF/AF	Elbow operation	1	0.26
warfarin	NVAF/AF	Urinary hesitation	1	0.26
warfarin	NVAF/AF	Renal cyst	1	0.26
warfarin	NVAF/AF	Transient global amnesia	1	0.26
warfarin	NVAF/AF	Chest pain	1	0.26
warfarin	NVAF/AF	Bowen's disease	1	0.26
warfarin	NVAF/AF	Hypochondriasis	1	0.26
warfarin	NVAF/AF	Hypertonic bladder	1	0.26
warfarin	NVAF/AF	Pituitary tumour	1	0.26
warfarin	NVAF/AF	Right ventricular dysfunction	1	0.26
warfarin	NVAF/AF	Drug dependence	1	0.26
warfarin	NVAF/AF	Proteinuria	1	0.26
warfarin	NVAF/AF	Foot deformity	1	0.26
warfarin	NVAF/AF	Headache	1	0.26
warfarin	NVAF/AF	Dysphagia	1	0.26
warfarin	NVAF/AF	Left ventricular hypertrophy	1	0.26
warfarin	NVAF/AF	Coronary artery disease	1	0.26
warfarin	NVAF/AF	Mitral valve stenosis	1	0.26
warfarin	NVAF/AF	Injection	1	0.26
warfarin	NVAF/AF	Myelopathy	1	0.26
warfarin	NVAF/AF	Otitis externa	1	0.26
warfarin	NVAF/AF	Hydrocephalus	1	0.26
warfarin	NVAF/AF	Hypergonadism	1	0.26
warfarin	NVAF/AF	Hamartoma	1	0.26
warfarin	NVAF/AF	Folate deficiency	1	0.26
warfarin	NVAF/AF	Adverse reaction	1	0.26
warfarin	NVAF/AF	Attention deficit/hyperactivity disorder	1	0.26
warfarin	NVAF/AF	Pneumonia aspiration	1	0.26
warfarin	NVAF/AF	Oesophageal candidiasis	1	0.26
warfarin	NVAF/AF	Calculus prostatic	1	0.26
warfarin	NVAF/AF	Tinnitus	1	0.26

## Appendix 7c(i). Other Medical History Prior to Starting warfarin - NVAF/AF

Treatment group	Indication	Preferred term	Number	%
warfarin	NVAF/AF	Colonoscopy	1	0.26
warfarin	NVAF/AF	Haemorrhoid operation	1	0.26
warfarin	NVAF/AF	Ulna fracture	1	0.26
warfarin	NVAF/AF	Diarrhoea	1	0.26
warfarin	NVAF/AF	Pancreatic insufficiency	1	0.26
warfarin	NVAF/AF	Intraocular lens implant	1	0.26
warfarin	NVAF/AF	Aphasia	1	0.26
warfarin	NVAF/AF	Drop attacks	1	0.26
warfarin	NVAF/AF	Palindromic rheumatism	1	0.26
warfarin	NVAF/AF	Incisional hernia	1	0.26
warfarin	NVAF/AF	Polycystic ovaries	1	0.26
warfarin	NVAF/AF	Addison's disease	1	0.26
warfarin	NVAF/AF	Hidradenitis	1	0.26
warfarin	NVAF/AF	Corneal neovascularisation	1	0.26
warfarin	NVAF/AF	Vasculitis	1	0.26
warfarin	NVAF/AF	Migraine with aura	1	0.26
warfarin	NVAF/AF	Tendon rupture	1	0.26
warfarin	NVAF/AF	Angina unstable	1	0.26
warfarin	NVAF/AF	Ureteric obstruction	1	0.26
warfarin	NVAF/AF	Rectal abscess	1	0.26
warfarin	NVAF/AF	Intermittent claudication	1	0.26
warfarin	NVAF/AF	Cystocele	1	0.26
warfarin	NVAF/AF	Radiotherapy to skin	1	0.26
warfarin	NVAF/AF	Proctitis	1	0.26
warfarin	NVAF/AF	Abdominal pain upper	1	0.26
warfarin	NVAF/AF	Lung neoplasm	1	0.26
warfarin	NVAF/AF	Neutropenic sepsis	1	0.26
warfarin	NVAF/AF	Laparoscopy	1	0.26
warfarin	NVAF/AF	Seborrhoeic dermatitis	1	0.26
warfarin	NVAF/AF	Menopausal symptoms	1	0.26
warfarin	NVAF/AF	Glomerulonephritis	1	0.26
warfarin	NVAF/AF	Sickle cell anaemia	1	0.26
warfarin	NVAF/AF	Prostatic specific antigen increased	1	0.26
warfarin	NVAF/AF	Colposcopy	1	0.26
warfarin	NVAF/AF	Intervertebral disc disorder	1	0.26
warfarin	NVAF/AF	Chondrocalcinosis pyrophosphate	1	0.26
warfarin	NVAF/AF	Laparoscopic surgery	1	0.26
warfarin	NVAF/AF	Ventricular hypokinesia	1	0.26
warfarin	NVAF/AF	Rectal prolapse	1	0.26
warfarin	NVAF/AF	Lesion excision	1	0.26
warfarin	NVAF/AF	Intestinal obstruction	1	0.26
warfarin	NVAF/AF	Gynaecomastia	1	0.26
warfarin	NVAF/AF	Gastric lavage	1	0.26
warfarin	NVAF/AF	Dysmenorrhoea	1	0.26
warfarin	NVAF/AF	Cerebellar ischaemia	1	0.26
warfarin	NVAF/AF	Intestinal ischaemia	1	0.26
warfarin	NVAF/AF	Intervertebral disc protrusion	1	0.26
warfarin	NVAF/AF	Prostatic disorder	1	0.26
warfarin	NVAF/AF	International normalised ratio increased	1	0.26



## Appendix 7c(i). Other Medical History Prior to Starting warfarin - NVAF/AF

Treatment group	Indication	Preferred term	Number	%
warfarin	NVAF/AF	Tremor	1	0.26
warfarin	NVAF/AF	Phaeochromocytoma	1	0.26
warfarin	NVAF/AF	Lipoma excision	1	0.26
warfarin	NVAF/AF	Amnesia	1	0.26
warfarin	NVAF/AF	Myocardial infarction	1	0.26
warfarin	NVAF/AF	Uterine prolapse	1	0.26
warfarin	NVAF/AF	Sternal fracture	1	0.26
warfarin	NVAF/AF	Hair follicle tumour benign	1	0.26
warfarin	NVAF/AF	Spinal compression fracture	1	0.26
warfarin	NVAF/AF	Rhinitis	1	0.26
warfarin	NVAF/AF	Gastroenteritis	1	0.26
warfarin	NVAF/AF	Cerebrovascular disorder	1	0.26
warfarin	NVAF/AF	Lichen planus	1	0.26
warfarin	NVAF/AF	Pericarditis	1	0.26
warfarin	NVAF/AF	Joint dislocation	1	0.26
warfarin	NVAF/AF	Herpes zoster	1	0.26
warfarin	NVAF/AF	Prostate cancer	1	0.26
warfarin	NVAF/AF	Oophorectomy	1	0.26
warfarin	NVAF/AF	Umbilical hernia	1	0.26
warfarin	NVAF/AF	Carotid artery stenosis	1	0.26
warfarin	NVAF/AF	Amblyopia	1	0.26
warfarin	NVAF/AF	Acute myocardial infarction	1	0.26
warfarin	NVAF/AF	Emergency care	1	0.26
warfarin	NVAF/AF	Marfan's syndrome	1	0.26
warfarin	NVAF/AF	Neurofibromatosis	1	0.26
warfarin	NVAF/AF	Investigation	1	0.26
warfarin	NVAF/AF	Gastrointestinal infection	1	0.26
warfarin	NVAF/AF	Sjogren's syndrome	1	0.26
warfarin	NVAF/AF	Angiogram	1	0.26
warfarin	NVAF/AF	Macrocytosis	1	0.26
warfarin	NVAF/AF	Labyrinthitis	1	0.26
warfarin	NVAF/AF	Laceration	1	0.26
		<b>TOTAL</b>	<b>387</b>	

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Asthma	85	11.52
warfarin	DVT/PE	Osteoarthritis	56	7.59
warfarin	DVT/PE	Depression	55	7.45
warfarin	DVT/PE	Unevaluable event	49	6.64
warfarin	DVT/PE	Hypothyroidism	44	5.96
warfarin	DVT/PE	Hiatus hernia	36	4.88
warfarin	DVT/PE	Gastrooesophageal reflux disease	33	4.47
warfarin	DVT/PE	Pneumonia	29	3.93
warfarin	DVT/PE	Arthritis	24	3.25
warfarin	DVT/PE	Diverticulum	21	2.85
warfarin	DVT/PE	Knee arthroplasty	21	2.85
warfarin	DVT/PE	Gout	20	2.71
warfarin	DVT/PE	Epilepsy	20	2.71
warfarin	DVT/PE	Osteoporosis	20	2.71
warfarin	DVT/PE	Back pain	18	2.44
warfarin	DVT/PE	Angina pectoris	18	2.44
warfarin	DVT/PE	Cellulitis	17	2.30
warfarin	DVT/PE	Rheumatoid arthritis	17	2.30
warfarin	DVT/PE	Migraine	16	2.17
warfarin	DVT/PE	Varicose vein	16	2.17
warfarin	DVT/PE	Irritable bowel syndrome	15	2.03
warfarin	DVT/PE	Spinal osteoarthritis	15	2.03
warfarin	DVT/PE	Ankle fracture	15	2.03
warfarin	DVT/PE	Anxiety	14	1.90
warfarin	DVT/PE	Myocardial ischaemia	14	1.90
warfarin	DVT/PE	Sleep apnoea syndrome	14	1.90
warfarin	DVT/PE	Nephrolithiasis	13	1.76
warfarin	DVT/PE	Polymyalgia rheumatica	13	1.76
warfarin	DVT/PE	Gastritis	12	1.63
warfarin	DVT/PE	Hypertension	11	1.49
warfarin	DVT/PE	Lower respiratory tract infection	11	1.49
warfarin	DVT/PE	Sciatica	11	1.49
warfarin	DVT/PE	Glaucoma	11	1.49
warfarin	DVT/PE	Urinary tract infection	11	1.49
warfarin	DVT/PE	Cholecystectomy	11	1.49
warfarin	DVT/PE	Skin ulcer	10	1.36
warfarin	DVT/PE	Colitis ulcerative	10	1.36
warfarin	DVT/PE	Bronchiectasis	10	1.36
warfarin	DVT/PE	Eczema	10	1.36
warfarin	DVT/PE	Arthroscopy	9	1.22
warfarin	DVT/PE	Haemorrhoids	9	1.22
warfarin	DVT/PE	Haemoglobin increased	9	1.22
warfarin	DVT/PE	Obesity	9	1.22
warfarin	DVT/PE	Diverticulitis	9	1.22
warfarin	DVT/PE	Macular degeneration	9	1.22
warfarin	DVT/PE	Arthralgia	8	1.08
warfarin	DVT/PE	Fibromyalgia	8	1.08
warfarin	DVT/PE	Cholelithiasis	8	1.08
warfarin	DVT/PE	Crohn's disease	8	1.08

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Iron deficiency anaemia	8	1.08
warfarin	DVT/PE	Renal failure acute	8	1.08
warfarin	DVT/PE	Surgery	8	1.08
warfarin	DVT/PE	Chest pain	7	0.95
warfarin	DVT/PE	Musculoskeletal pain	7	0.95
warfarin	DVT/PE	Benign prostatic hyperplasia	7	0.95
warfarin	DVT/PE	Investigation	7	0.95
warfarin	DVT/PE	Dyspepsia	7	0.95
warfarin	DVT/PE	Varicose vein operation	7	0.95
warfarin	DVT/PE	Parkinson's disease	7	0.95
warfarin	DVT/PE	Inguinal hernia repair	6	0.81
warfarin	DVT/PE	Psoriasis	6	0.81
warfarin	DVT/PE	Appendicectomy	6	0.81
warfarin	DVT/PE	Spondylitis	6	0.81
warfarin	DVT/PE	Cardiac pacemaker insertion	6	0.81
warfarin	DVT/PE	Pleural effusion	5	0.68
warfarin	DVT/PE	Joint injury	5	0.68
warfarin	DVT/PE	Cataract	5	0.68
warfarin	DVT/PE	Otitis externa	5	0.68
warfarin	DVT/PE	Thrombophlebitis	5	0.68
warfarin	DVT/PE	Urosepsis	5	0.68
warfarin	DVT/PE	Hernia	5	0.68
warfarin	DVT/PE	Anaemia	5	0.68
warfarin	DVT/PE	Oedema peripheral	5	0.68
warfarin	DVT/PE	Femoral neck fracture	5	0.68
warfarin	DVT/PE	Carpal tunnel syndrome	5	0.68
warfarin	DVT/PE	Road traffic accident	5	0.68
warfarin	DVT/PE	Joint dislocation	5	0.68
warfarin	DVT/PE	Cataract operation	5	0.68
warfarin	DVT/PE	Deafness	5	0.68
warfarin	DVT/PE	Debridement	5	0.68
warfarin	DVT/PE	Sjogren's syndrome	5	0.68
warfarin	DVT/PE	Aortic aneurysm	5	0.68
warfarin	DVT/PE	Hyperparathyroidism	4	0.54
warfarin	DVT/PE	Lymphoedema	4	0.54
warfarin	DVT/PE	Lower limb fracture	4	0.54
warfarin	DVT/PE	Glucose tolerance impaired	4	0.54
warfarin	DVT/PE	Hyperthyroidism	4	0.54
warfarin	DVT/PE	Sinusitis	4	0.54
warfarin	DVT/PE	Diarrhoea	4	0.54
warfarin	DVT/PE	Pneumothorax	4	0.54
warfarin	DVT/PE	Knee operation	4	0.54
warfarin	DVT/PE	Hyponatraemia	4	0.54
warfarin	DVT/PE	Limb injury	4	0.54
warfarin	DVT/PE	Lung neoplasm	4	0.54
warfarin	DVT/PE	Seasonal allergy	4	0.54
warfarin	DVT/PE	Vitamin B12 deficiency	4	0.54
warfarin	DVT/PE	Oesophagitis	4	0.54
warfarin	DVT/PE	Raynaud's phenomenon	4	0.54

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Alcohol abuse	4	0.54
warfarin	DVT/PE	Hernia repair	4	0.54
warfarin	DVT/PE	Sarcoidosis	4	0.54
warfarin	DVT/PE	Rib fracture	4	0.54
warfarin	DVT/PE	Phlebitis	4	0.54
warfarin	DVT/PE	Cholecystitis	4	0.54
warfarin	DVT/PE	Osteotomy	4	0.54
warfarin	DVT/PE	Computerised tomogram	4	0.54
warfarin	DVT/PE	Uterine leiomyoma	4	0.54
warfarin	DVT/PE	Abscess drainage	4	0.54
warfarin	DVT/PE	Osteopenia	4	0.54
warfarin	DVT/PE	Duodenal ulcer	4	0.54
warfarin	DVT/PE	Inguinal hernia	4	0.54
warfarin	DVT/PE	Laparoscopic surgery	4	0.54
warfarin	DVT/PE	Myalgia	3	0.41
warfarin	DVT/PE	Vitamin D deficiency	3	0.41
warfarin	DVT/PE	Coronary artery disease	3	0.41
warfarin	DVT/PE	Umbilical hernia repair	3	0.41
warfarin	DVT/PE	Radius fracture	3	0.41
warfarin	DVT/PE	Dyspnoea	3	0.41
warfarin	DVT/PE	Meniere's disease	3	0.41
warfarin	DVT/PE	Intervertebral disc protrusion	3	0.41
warfarin	DVT/PE	Umbilical hernia	3	0.41
warfarin	DVT/PE	Pilonidal sinus repair	3	0.41
warfarin	DVT/PE	Colonoscopy	3	0.41
warfarin	DVT/PE	Facial bones fracture	3	0.41
warfarin	DVT/PE	Musculoskeletal disorder	3	0.41
warfarin	DVT/PE	Scoliosis	3	0.41
warfarin	DVT/PE	Spondylolisthesis	3	0.41
warfarin	DVT/PE	Tibia fracture	3	0.41
warfarin	DVT/PE	Dizziness	3	0.41
warfarin	DVT/PE	Stem cell transplant	3	0.41
warfarin	DVT/PE	Abdominal pain	3	0.41
warfarin	DVT/PE	Emergency care	3	0.41
warfarin	DVT/PE	Retinal vein occlusion	3	0.41
warfarin	DVT/PE	Endometriosis	3	0.41
warfarin	DVT/PE	Essential hypertension	3	0.41
warfarin	DVT/PE	Infection	3	0.41
warfarin	DVT/PE	Intermittent claudication	3	0.41
warfarin	DVT/PE	Colitis	3	0.41
warfarin	DVT/PE	Sepsis	3	0.41
warfarin	DVT/PE	Aortic stenosis	3	0.41
warfarin	DVT/PE	Appendicitis	3	0.41
warfarin	DVT/PE	Ankle operation	3	0.41
warfarin	DVT/PE	Intervertebral disc degeneration	3	0.41
warfarin	DVT/PE	Small intestinal obstruction	3	0.41
warfarin	DVT/PE	Asbestosis	3	0.41
warfarin	DVT/PE	Tonsillectomy	3	0.41
warfarin	DVT/PE	VIIth nerve paralysis	3	0.41

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Overdose	3	0.41
warfarin	DVT/PE	Rosacea	3	0.41
warfarin	DVT/PE	Pulmonary fibrosis	3	0.41
warfarin	DVT/PE	Wrist fracture	3	0.41
warfarin	DVT/PE	Labyrinthitis	3	0.41
warfarin	DVT/PE	Polycystic ovaries	3	0.41
warfarin	DVT/PE	Gastric ulcer	3	0.41
warfarin	DVT/PE	Urinary incontinence	2	0.27
warfarin	DVT/PE	Dyslipidaemia	2	0.27
warfarin	DVT/PE	Polyarthritits	2	0.27
warfarin	DVT/PE	Arthrodesis	2	0.27
warfarin	DVT/PE	Prostatic specific antigen increased	2	0.27
warfarin	DVT/PE	Sickle cell trait	2	0.27
warfarin	DVT/PE	Neuropathy peripheral	2	0.27
warfarin	DVT/PE	Synovial cyst	2	0.27
warfarin	DVT/PE	Maculopathy	2	0.27
warfarin	DVT/PE	Memory impairment	2	0.27
warfarin	DVT/PE	Learning disorder	2	0.27
warfarin	DVT/PE	Schizophrenia	2	0.27
warfarin	DVT/PE	Nasal polyps	2	0.27
warfarin	DVT/PE	Vomiting	2	0.27
warfarin	DVT/PE	Benign breast neoplasm	2	0.27
warfarin	DVT/PE	Weight decreased	2	0.27
warfarin	DVT/PE	Femur fracture	2	0.27
warfarin	DVT/PE	Meniscus lesion	2	0.27
warfarin	DVT/PE	Laceration	2	0.27
warfarin	DVT/PE	Hand fracture	2	0.27
warfarin	DVT/PE	Asperger's disorder	2	0.27
warfarin	DVT/PE	Psychotic disorder	2	0.27
warfarin	DVT/PE	Depressed mood	2	0.27
warfarin	DVT/PE	Transurethral prostatectomy	2	0.27
warfarin	DVT/PE	Psoriatic arthropathy	2	0.27
warfarin	DVT/PE	Pleurisy	2	0.27
warfarin	DVT/PE	Hypercalcaemia	2	0.27
warfarin	DVT/PE	Tinnitus	2	0.27
warfarin	DVT/PE	Dysphagia	2	0.27
warfarin	DVT/PE	Monoclonal gammopathy	2	0.27
warfarin	DVT/PE	Upper limb fracture	2	0.27
warfarin	DVT/PE	Gastric polyps	2	0.27
warfarin	DVT/PE	Calculus bladder	2	0.27
warfarin	DVT/PE	Cognitive disorder	2	0.27
warfarin	DVT/PE	Breast cyst	2	0.27
warfarin	DVT/PE	Spinal column stenosis	2	0.27
warfarin	DVT/PE	Wound	2	0.27
warfarin	DVT/PE	Staphylococcal infection	2	0.27
warfarin	DVT/PE	Aspiration joint	2	0.27
warfarin	DVT/PE	Ulna fracture	2	0.27
warfarin	DVT/PE	Abdominal pain lower	2	0.27
warfarin	DVT/PE	Cutaneous lupus erythematosus	2	0.27

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Angina unstable	2	0.27
warfarin	DVT/PE	Pilonidal cyst	2	0.27
warfarin	DVT/PE	Echocardiogram	2	0.27
warfarin	DVT/PE	Colitis ischaemic	2	0.27
warfarin	DVT/PE	Stent placement	2	0.27
warfarin	DVT/PE	Renal colic	2	0.27
warfarin	DVT/PE	Spinal fusion surgery	2	0.27
warfarin	DVT/PE	Thrombophlebitis superficial	2	0.27
warfarin	DVT/PE	Tooth extraction	2	0.27
warfarin	DVT/PE	Cyst	2	0.27
warfarin	DVT/PE	Schizophrenia, paranoid type	2	0.27
warfarin	DVT/PE	Pancreatitis	2	0.27
warfarin	DVT/PE	Parathyroidectomy	2	0.27
warfarin	DVT/PE	Respiratory failure	2	0.27
warfarin	DVT/PE	Gastroenteritis	2	0.27
warfarin	DVT/PE	Interstitial lung disease	2	0.27
warfarin	DVT/PE	Stasis dermatitis	2	0.27
warfarin	DVT/PE	Myelitis	2	0.27
warfarin	DVT/PE	Chemotherapy	2	0.27
warfarin	DVT/PE	Carpal tunnel decompression	2	0.27
warfarin	DVT/PE	Ovarian cyst	2	0.27
warfarin	DVT/PE	Cyst removal	2	0.27
warfarin	DVT/PE	Dyspnoea exertional	2	0.27
warfarin	DVT/PE	Peyronie's disease	2	0.27
warfarin	DVT/PE	Barrett's oesophagus	2	0.27
warfarin	DVT/PE	Head injury	2	0.27
warfarin	DVT/PE	Vascular parkinsonism	2	0.27
warfarin	DVT/PE	Vertigo	2	0.27
warfarin	DVT/PE	Arteritis	2	0.27
warfarin	DVT/PE	Trigeminal neuralgia	2	0.27
warfarin	DVT/PE	Gastric banding	2	0.27
warfarin	DVT/PE	Papilloma	2	0.27
warfarin	DVT/PE	Cast application	2	0.27
warfarin	DVT/PE	Aortic valve incompetence	2	0.27
warfarin	DVT/PE	Rheumatic fever	2	0.27
warfarin	DVT/PE	Prostate cancer	2	0.27
warfarin	DVT/PE	Fasciotomy	2	0.27
warfarin	DVT/PE	Skin lesion	2	0.27
warfarin	DVT/PE	Peripheral artery stenosis	2	0.27
warfarin	DVT/PE	Periarthritis	2	0.27
warfarin	DVT/PE	Skin neoplasm excision	2	0.27
warfarin	DVT/PE	Duodenitis	2	0.27
warfarin	DVT/PE	Hyperkeratosis	2	0.27
warfarin	DVT/PE	Nephrotic syndrome	2	0.27
warfarin	DVT/PE	Urinary retention	2	0.27
warfarin	DVT/PE	Postoperative wound infection	2	0.27
warfarin	DVT/PE	Wound infection	2	0.27
warfarin	DVT/PE	Radiotherapy	2	0.27
warfarin	DVT/PE	Cardiac valve disease	2	0.27

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Musculoskeletal chest pain	2	0.27
warfarin	DVT/PE	Oesophageal stenosis	2	0.27
warfarin	DVT/PE	Fall	2	0.27
warfarin	DVT/PE	Impaired fasting glucose	2	0.27
warfarin	DVT/PE	Tuberculosis	2	0.27
warfarin	DVT/PE	Breast lump removal	2	0.27
warfarin	DVT/PE	Aortic dilatation	2	0.27
warfarin	DVT/PE	Myasthenia gravis	2	0.27
warfarin	DVT/PE	Tympanic membrane perforation	2	0.27
warfarin	DVT/PE	Pulmonary hypertension	2	0.27
warfarin	DVT/PE	Essential tremor	2	0.27
warfarin	DVT/PE	Rotator cuff repair	2	0.27
warfarin	DVT/PE	Oesophagogastroduodenoscopy	2	0.27
warfarin	DVT/PE	Platelet count decreased	2	0.27
warfarin	DVT/PE	Left ventricular hypertrophy	2	0.27
warfarin	DVT/PE	Cast removal	2	0.27
warfarin	DVT/PE	Sebaceous cyst excision	2	0.27
warfarin	DVT/PE	Body mass index increased	2	0.27
warfarin	DVT/PE	Peripheral ischaemia	1	0.14
warfarin	DVT/PE	Post viral fatigue syndrome	1	0.14
warfarin	DVT/PE	Mitral valve incompetence	1	0.14
warfarin	DVT/PE	Peripheral nerve operation	1	0.14
warfarin	DVT/PE	Alcoholism	1	0.14
warfarin	DVT/PE	Bladder neck resection	1	0.14
warfarin	DVT/PE	Viral infection	1	0.14
warfarin	DVT/PE	Syncope	1	0.14
warfarin	DVT/PE	Behcet's syndrome	1	0.14
warfarin	DVT/PE	Hypertensive crisis	1	0.14
warfarin	DVT/PE	Bronchopneumonia	1	0.14
warfarin	DVT/PE	Normochromic normocytic anaemia	1	0.14
warfarin	DVT/PE	Right ventricular dysfunction	1	0.14
warfarin	DVT/PE	Ulcerative keratitis	1	0.14
warfarin	DVT/PE	Erythema	1	0.14
warfarin	DVT/PE	Ligament injury	1	0.14
warfarin	DVT/PE	Hyperglycaemia	1	0.14
warfarin	DVT/PE	Dysuria	1	0.14
warfarin	DVT/PE	Choroidal neovascularisation	1	0.14
warfarin	DVT/PE	Biopsy small intestine	1	0.14
warfarin	DVT/PE	Microcytosis	1	0.14
warfarin	DVT/PE	Bacteraemia	1	0.14
warfarin	DVT/PE	Pneumonitis	1	0.14
warfarin	DVT/PE	Adrenal mass	1	0.14
warfarin	DVT/PE	Uterine dilation and curettage	1	0.14
warfarin	DVT/PE	Benign neoplasm of skin	1	0.14
warfarin	DVT/PE	Medical diet	1	0.14
warfarin	DVT/PE	Muscular dystrophy	1	0.14
warfarin	DVT/PE	Tongue ulceration	1	0.14
warfarin	DVT/PE	Carotid artery dissection	1	0.14
warfarin	DVT/PE	Microangiopathy	1	0.14

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Goitre	1	0.14
warfarin	DVT/PE	Ear infection	1	0.14
warfarin	DVT/PE	Gastric volvulus	1	0.14
warfarin	DVT/PE	Joint dislocation postoperative	1	0.14
warfarin	DVT/PE	Blood ethanol increased	1	0.14
warfarin	DVT/PE	Female genital tract fistula	1	0.14
warfarin	DVT/PE	Jejunal perforation	1	0.14
warfarin	DVT/PE	Mean cell haemoglobin decreased	1	0.14
warfarin	DVT/PE	Transfusion	1	0.14
warfarin	DVT/PE	Salivary gland operation	1	0.14
warfarin	DVT/PE	Urethral dilatation	1	0.14
warfarin	DVT/PE	Gangrene	1	0.14
warfarin	DVT/PE	Varices oesophageal	1	0.14
warfarin	DVT/PE	Confusional state	1	0.14
warfarin	DVT/PE	Perinephric collection	1	0.14
warfarin	DVT/PE	Joint injection	1	0.14
warfarin	DVT/PE	Blood immunoglobulin A decreased	1	0.14
warfarin	DVT/PE	Thrombosis prophylaxis	1	0.14
warfarin	DVT/PE	Myositis	1	0.14
warfarin	DVT/PE	Colonic polyp	1	0.14
warfarin	DVT/PE	Bradycardia	1	0.14
warfarin	DVT/PE	Laryngeal leukoplakia	1	0.14
warfarin	DVT/PE	Pancreatitis acute	1	0.14
warfarin	DVT/PE	Tooth injury	1	0.14
warfarin	DVT/PE	Herpes virus infection	1	0.14
warfarin	DVT/PE	Neurological symptom	1	0.14
warfarin	DVT/PE	Cardiac disorder	1	0.14
warfarin	DVT/PE	Cough	1	0.14
warfarin	DVT/PE	Hysteroscopy	1	0.14
warfarin	DVT/PE	Constipation	1	0.14
warfarin	DVT/PE	Pelvic fracture	1	0.14
warfarin	DVT/PE	Smear cervix abnormal	1	0.14
warfarin	DVT/PE	Pulseless electrical activity	1	0.14
warfarin	DVT/PE	Adenomyosis	1	0.14
warfarin	DVT/PE	Wound treatment	1	0.14
warfarin	DVT/PE	Hypokalaemia	1	0.14
warfarin	DVT/PE	Dysmenorrhoea	1	0.14
warfarin	DVT/PE	Pyrexia	1	0.14
warfarin	DVT/PE	Disseminated tuberculosis	1	0.14
warfarin	DVT/PE	Therapeutic embolisation	1	0.14
warfarin	DVT/PE	Drug abuse	1	0.14
warfarin	DVT/PE	Injection	1	0.14
warfarin	DVT/PE	Accident	1	0.14
warfarin	DVT/PE	Injury	1	0.14
warfarin	DVT/PE	Cystocele	1	0.14
warfarin	DVT/PE	Petechiae	1	0.14
warfarin	DVT/PE	Latent tuberculosis	1	0.14
warfarin	DVT/PE	Aspergillosis	1	0.14
warfarin	DVT/PE	Hypersplenism	1	0.14



## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Loss of consciousness	1	0.14
warfarin	DVT/PE	Breast mass	1	0.14
warfarin	DVT/PE	Benign endocrine neoplasm	1	0.14
warfarin	DVT/PE	Myelopathy	1	0.14
warfarin	DVT/PE	Papilloma excision	1	0.14
warfarin	DVT/PE	Urticaria	1	0.14
warfarin	DVT/PE	Acrochordon	1	0.14
warfarin	DVT/PE	Renal failure chronic	1	0.14
warfarin	DVT/PE	Intracardiac thrombus	1	0.14
warfarin	DVT/PE	Vasculitis	1	0.14
warfarin	DVT/PE	Anti-cyclic citrullinated peptide antibody positive	1	0.14
warfarin	DVT/PE	Change of bowel habit	1	0.14
warfarin	DVT/PE	Polyp	1	0.14
warfarin	DVT/PE	Bladder neck obstruction	1	0.14
warfarin	DVT/PE	Mobility decreased	1	0.14
warfarin	DVT/PE	Thoracic outlet syndrome	1	0.14
warfarin	DVT/PE	Hyperplastic cholecystopathy	1	0.14
warfarin	DVT/PE	Gene mutation	1	0.14
warfarin	DVT/PE	Polypectomy	1	0.14
warfarin	DVT/PE	Vena cava filter insertion	1	0.14
warfarin	DVT/PE	Plantar fasciitis	1	0.14
warfarin	DVT/PE	Oral lichen planus	1	0.14
warfarin	DVT/PE	Aneurysm	1	0.14
warfarin	DVT/PE	Calculus ureteric	1	0.14
warfarin	DVT/PE	Cerebral palsy	1	0.14
warfarin	DVT/PE	Affective disorder	1	0.14
warfarin	DVT/PE	Muscle twitching	1	0.14
warfarin	DVT/PE	Osteochondrosis	1	0.14
warfarin	DVT/PE	Tremor	1	0.14
warfarin	DVT/PE	Osteogenesis imperfecta	1	0.14
warfarin	DVT/PE	Liver abscess	1	0.14
warfarin	DVT/PE	Ileal stenosis	1	0.14
warfarin	DVT/PE	Humerus fracture	1	0.14
warfarin	DVT/PE	Vocal cord paresis	1	0.14
warfarin	DVT/PE	Bronchopulmonary aspergillosis	1	0.14
warfarin	DVT/PE	Wheezing	1	0.14
warfarin	DVT/PE	Malaise	1	0.14
warfarin	DVT/PE	Thyroid neoplasm	1	0.14
warfarin	DVT/PE	Carotid artery disease	1	0.14
warfarin	DVT/PE	Cystoscopy	1	0.14
warfarin	DVT/PE	Palpitations	1	0.14
warfarin	DVT/PE	Ocular hypertension	1	0.14
warfarin	DVT/PE	Pancreatitis chronic	1	0.14
warfarin	DVT/PE	Serum ferritin decreased	1	0.14
warfarin	DVT/PE	Brain injury	1	0.14
warfarin	DVT/PE	Reflux laryngitis	1	0.14
warfarin	DVT/PE	Retinopathy	1	0.14
warfarin	DVT/PE	Diaphragmatic paralysis	1	0.14
warfarin	DVT/PE	Infected dermal cyst	1	0.14

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Sputum discoloured	1	0.14
warfarin	DVT/PE	Biopsy skin	1	0.14
warfarin	DVT/PE	Cervical spinal stenosis	1	0.14
warfarin	DVT/PE	Mass excision	1	0.14
warfarin	DVT/PE	Mechanical ventilation	1	0.14
warfarin	DVT/PE	Parotidectomy	1	0.14
warfarin	DVT/PE	High frequency ablation	1	0.14
warfarin	DVT/PE	Biopsy	1	0.14
warfarin	DVT/PE	Respiratory disorder	1	0.14
warfarin	DVT/PE	Colonic obstruction	1	0.14
warfarin	DVT/PE	Joint instability	1	0.14
warfarin	DVT/PE	Pituitary tumour	1	0.14
warfarin	DVT/PE	Wisdom teeth removal	1	0.14
warfarin	DVT/PE	Abdominal hernia	1	0.14
warfarin	DVT/PE	Colonic stenosis	1	0.14
warfarin	DVT/PE	Social problem	1	0.14
warfarin	DVT/PE	Cerebral sarcoidosis	1	0.14
warfarin	DVT/PE	Prostatism	1	0.14
warfarin	DVT/PE	Cervical dysplasia	1	0.14
warfarin	DVT/PE	Gastroenteritis Escherichia coli	1	0.14
warfarin	DVT/PE	Necrosis	1	0.14
warfarin	DVT/PE	Vascular test normal	1	0.14
warfarin	DVT/PE	Nodal osteoarthritis	1	0.14
warfarin	DVT/PE	Phlebitis infective	1	0.14
warfarin	DVT/PE	Lactose intolerance	1	0.14
warfarin	DVT/PE	Hormone replacement therapy	1	0.14
warfarin	DVT/PE	Tricuspid valve incompetence	1	0.14
warfarin	DVT/PE	Stapedectomy	1	0.14
warfarin	DVT/PE	Myelitis transverse	1	0.14
warfarin	DVT/PE	Lobar pneumonia	1	0.14
warfarin	DVT/PE	Pain	1	0.14
warfarin	DVT/PE	Incisional hernia repair	1	0.14
warfarin	DVT/PE	Ulcer	1	0.14
warfarin	DVT/PE	Cardiac complication associated with device	1	0.14
warfarin	DVT/PE	Myocarditis	1	0.14
warfarin	DVT/PE	Sebaceous hyperplasia	1	0.14
warfarin	DVT/PE	Haemorrhage	1	0.14
warfarin	DVT/PE	Bipolar I disorder	1	0.14
warfarin	DVT/PE	Anal skin tags	1	0.14
warfarin	DVT/PE	Hydronephrosis	1	0.14
warfarin	DVT/PE	Anaesthesia	1	0.14
warfarin	DVT/PE	Decreased appetite	1	0.14
warfarin	DVT/PE	Rehabilitation therapy	1	0.14
warfarin	DVT/PE	Bronchopulmonary aspergillosis allergic	1	0.14
warfarin	DVT/PE	Bunion operation	1	0.14
warfarin	DVT/PE	Bulimia nervosa	1	0.14
warfarin	DVT/PE	Dialysis	1	0.14
warfarin	DVT/PE	Acrochordon excision	1	0.14
warfarin	DVT/PE	Pernicious anaemia	1	0.14

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Hypomagnesaemia	1	0.14
warfarin	DVT/PE	Oophorectomy	1	0.14
warfarin	DVT/PE	Phaeochromocytoma	1	0.14
warfarin	DVT/PE	Neuralgia	1	0.14
warfarin	DVT/PE	Oesophagogastric fundoplasty	1	0.14
warfarin	DVT/PE	Intervertebral disc operation	1	0.14
warfarin	DVT/PE	Septic shock	1	0.14
warfarin	DVT/PE	Epicondylitis	1	0.14
warfarin	DVT/PE	Pyelonephritis	1	0.14
warfarin	DVT/PE	Orthostatic hypotension	1	0.14
warfarin	DVT/PE	Tooth abscess	1	0.14
warfarin	DVT/PE	Bullous lung disease	1	0.14
warfarin	DVT/PE	Coeliac disease	1	0.14
warfarin	DVT/PE	Restless legs syndrome	1	0.14
warfarin	DVT/PE	Haemangioblastoma	1	0.14
warfarin	DVT/PE	Dyspareunia	1	0.14
warfarin	DVT/PE	Ultrasound Doppler abnormal	1	0.14
warfarin	DVT/PE	Somnolence	1	0.14
warfarin	DVT/PE	Atrial septal defect	1	0.14
warfarin	DVT/PE	Visual field defect	1	0.14
warfarin	DVT/PE	Arteriosclerosis	1	0.14
warfarin	DVT/PE	Fungal infection	1	0.14
warfarin	DVT/PE	Seasonal affective disorder	1	0.14
warfarin	DVT/PE	Foot fracture	1	0.14
warfarin	DVT/PE	Drug intolerance	1	0.14
warfarin	DVT/PE	Colectomy	1	0.14
warfarin	DVT/PE	Hypertonia	1	0.14
warfarin	DVT/PE	Ingrowing nail	1	0.14
warfarin	DVT/PE	Defaecation urgency	1	0.14
warfarin	DVT/PE	Congenital renal cyst	1	0.14
warfarin	DVT/PE	Joint arthroplasty	1	0.14
warfarin	DVT/PE	Pemphigoid	1	0.14
warfarin	DVT/PE	Thrombectomy	1	0.14
warfarin	DVT/PE	Scar excision	1	0.14
warfarin	DVT/PE	Stress fracture	1	0.14
warfarin	DVT/PE	Epidural anaesthesia	1	0.14
warfarin	DVT/PE	Mastoidectomy	1	0.14
warfarin	DVT/PE	Connective tissue disorder	1	0.14
warfarin	DVT/PE	Claustrophobia	1	0.14
warfarin	DVT/PE	Drug dependence	1	0.14
warfarin	DVT/PE	Ventricular hypertrophy	1	0.14
warfarin	DVT/PE	Inflammation	1	0.14
warfarin	DVT/PE	Dehydration	1	0.14
warfarin	DVT/PE	Renal artery stenosis	1	0.14
warfarin	DVT/PE	Testicular swelling	1	0.14
warfarin	DVT/PE	Shoulder operation	1	0.14
warfarin	DVT/PE	Uterovaginal prolapse	1	0.14
warfarin	DVT/PE	Psychiatric evaluation	1	0.14
warfarin	DVT/PE	Lithotripsy	1	0.14

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Temporal lobe epilepsy	1	0.14
warfarin	DVT/PE	Anal abscess	1	0.14
warfarin	DVT/PE	Testicular cyst	1	0.14
warfarin	DVT/PE	Angiogram pulmonary	1	0.14
warfarin	DVT/PE	Lichen planus	1	0.14
warfarin	DVT/PE	Gastroenteritis viral	1	0.14
warfarin	DVT/PE	Groin pain	1	0.14
warfarin	DVT/PE	Dementia	1	0.14
warfarin	DVT/PE	Deafness neurosensory	1	0.14
warfarin	DVT/PE	Incontinence	1	0.14
warfarin	DVT/PE	Necrolytic migratory erythema	1	0.14
warfarin	DVT/PE	Orchitis	1	0.14
warfarin	DVT/PE	Lymphadenopathy mediastinal	1	0.14
warfarin	DVT/PE	Abdomen scan	1	0.14
warfarin	DVT/PE	Endoscopy upper gastrointestinal tract	1	0.14
warfarin	DVT/PE	Haemodialysis	1	0.14
warfarin	DVT/PE	Micturition urgency	1	0.14
warfarin	DVT/PE	Stress urinary incontinence	1	0.14
warfarin	DVT/PE	Vertigo positional	1	0.14
warfarin	DVT/PE	Vitiligo	1	0.14
warfarin	DVT/PE	Ventricular septal defect	1	0.14
warfarin	DVT/PE	Paranoia	1	0.14
warfarin	DVT/PE	Fibroadenoma of breast	1	0.14
warfarin	DVT/PE	Myxoedema coma	1	0.14
warfarin	DVT/PE	Eyelid ptosis	1	0.14
warfarin	DVT/PE	Rectal examination normal	1	0.14
warfarin	DVT/PE	Mastoid operation	1	0.14
warfarin	DVT/PE	Ultrasound testes	1	0.14
warfarin	DVT/PE	Pneumoconiosis	1	0.14
warfarin	DVT/PE	General anaesthesia	1	0.14
warfarin	DVT/PE	Enterostomy	1	0.14
warfarin	DVT/PE	Pleurectomy	1	0.14
warfarin	DVT/PE	Polyarteritis nodosa	1	0.14
warfarin	DVT/PE	Stress	1	0.14
warfarin	DVT/PE	Orthopaedic examination	1	0.14
warfarin	DVT/PE	Blepharospasm	1	0.14
warfarin	DVT/PE	Rhinitis	1	0.14
warfarin	DVT/PE	Motor neurone disease	1	0.14
warfarin	DVT/PE	Nasopharyngitis	1	0.14
warfarin	DVT/PE	Anaemia haemolytic autoimmune	1	0.14
warfarin	DVT/PE	Hypertrophic cardiomyopathy	1	0.14
warfarin	DVT/PE	Neoplasm	1	0.14
warfarin	DVT/PE	Bronchospasm	1	0.14
warfarin	DVT/PE	Endoscopic retrograde cholangiopancreatography	1	0.14
warfarin	DVT/PE	Haemangioma removal	1	0.14
warfarin	DVT/PE	Dermatitis	1	0.14
warfarin	DVT/PE	Vulvectomy	1	0.14
warfarin	DVT/PE	Pyoderma gangrenosum	1	0.14
warfarin	DVT/PE	Physical assault	1	0.14

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Mole excision	1	0.14
warfarin	DVT/PE	Myxoedema	1	0.14
warfarin	DVT/PE	Klippel-Trenaunay syndrome	1	0.14
warfarin	DVT/PE	Visual acuity reduced	1	0.14
warfarin	DVT/PE	Synovitis	1	0.14
warfarin	DVT/PE	Pubis fracture	1	0.14
warfarin	DVT/PE	Prostatitis	1	0.14
warfarin	DVT/PE	Electrocardiogram ST-T segment abnormal	1	0.14
warfarin	DVT/PE	Compression fracture	1	0.14
warfarin	DVT/PE	Toe operation	1	0.14
warfarin	DVT/PE	Colposcopy	1	0.14
warfarin	DVT/PE	Joint swelling	1	0.14
warfarin	DVT/PE	Bladder repair	1	0.14
warfarin	DVT/PE	Dementia Alzheimer's type	1	0.14
warfarin	DVT/PE	Congenital tricuspid valve atresia	1	0.14
warfarin	DVT/PE	Macrocytosis	1	0.14
warfarin	DVT/PE	Limb crushing injury	1	0.14
warfarin	DVT/PE	Joint effusion	1	0.14
warfarin	DVT/PE	Gastrointestinal hypomotility	1	0.14
warfarin	DVT/PE	Hyperhidrosis	1	0.14
warfarin	DVT/PE	Apicectomy	1	0.14
warfarin	DVT/PE	Soft tissue mass	1	0.14
warfarin	DVT/PE	Lung lobectomy	1	0.14
warfarin	DVT/PE	Congestive cardiomyopathy	1	0.14
warfarin	DVT/PE	Congenital cystic kidney disease	1	0.14
warfarin	DVT/PE	Ankylosing spondylitis	1	0.14
warfarin	DVT/PE	Diaphragmatic disorder	1	0.14
warfarin	DVT/PE	Rotator cuff syndrome	1	0.14
warfarin	DVT/PE	Upper respiratory tract infection	1	0.14
warfarin	DVT/PE	Abscess intestinal	1	0.14
warfarin	DVT/PE	Cataract cortical	1	0.14
warfarin	DVT/PE	Microvascular coronary artery disease	1	0.14
warfarin	DVT/PE	Electrocardiogram normal	1	0.14
warfarin	DVT/PE	Urogenital fistula	1	0.14
warfarin	DVT/PE	Body tinea	1	0.14
warfarin	DVT/PE	Peripheral artery thrombosis	1	0.14
warfarin	DVT/PE	Neurogenic bladder	1	0.14
warfarin	DVT/PE	Renal tubular acidosis	1	0.14
warfarin	DVT/PE	Budd-Chiari syndrome	1	0.14
warfarin	DVT/PE	Nuclear magnetic resonance imaging	1	0.14
warfarin	DVT/PE	Device related sepsis	1	0.14
warfarin	DVT/PE	Venous stent insertion	1	0.14
warfarin	DVT/PE	Dermal cyst	1	0.14
warfarin	DVT/PE	Retro-orbital neoplasm	1	0.14
warfarin	DVT/PE	Skeletal dysplasia	1	0.14
warfarin	DVT/PE	Renal impairment	1	0.14
warfarin	DVT/PE	Acute respiratory distress syndrome	1	0.14
warfarin	DVT/PE	Administration site infection	1	0.14
warfarin	DVT/PE	Circulatory collapse	1	0.14

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Arterial disorder	1	0.14
warfarin	DVT/PE	Leukocytoclastic vasculitis	1	0.14
warfarin	DVT/PE	Vascular dementia	1	0.14
warfarin	DVT/PE	Facet joint block	1	0.14
warfarin	DVT/PE	Diverticulum intestinal	1	0.14
warfarin	DVT/PE	Impaired healing	1	0.14
warfarin	DVT/PE	Endodontic procedure	1	0.14
warfarin	DVT/PE	Epididymitis	1	0.14
warfarin	DVT/PE	Perineal laceration	1	0.14
warfarin	DVT/PE	Epiphyseal surgery	1	0.14
warfarin	DVT/PE	Adenoidectomy	1	0.14
warfarin	DVT/PE	Partial seizures	1	0.14
warfarin	DVT/PE	Iritis	1	0.14
warfarin	DVT/PE	Bipolar disorder	1	0.14
warfarin	DVT/PE	Ischaemia	1	0.14
warfarin	DVT/PE	Oral neoplasm	1	0.14
warfarin	DVT/PE	Cholesteatoma	1	0.14
warfarin	DVT/PE	Onychomycosis	1	0.14
warfarin	DVT/PE	Cervical polypectomy	1	0.14
warfarin	DVT/PE	Tympanoplasty	1	0.14
warfarin	DVT/PE	Gastrointestinal disorder	1	0.14
warfarin	DVT/PE	Atrophic vulvovaginitis	1	0.14
warfarin	DVT/PE	Micturition disorder	1	0.14
warfarin	DVT/PE	Fibula fracture	1	0.14
warfarin	DVT/PE	Pickwickian syndrome	1	0.14
warfarin	DVT/PE	Mean cell volume normal	1	0.14
warfarin	DVT/PE	Seronegative arthritis	1	0.14
warfarin	DVT/PE	Actinic keratosis	1	0.14
warfarin	DVT/PE	Drug detoxification	1	0.14
warfarin	DVT/PE	Haemangioma of skin	1	0.14
warfarin	DVT/PE	Ultrasound antenatal screen	1	0.14
warfarin	DVT/PE	Ovarian mass	1	0.14
warfarin	DVT/PE	X-ray limb	1	0.14
warfarin	DVT/PE	Hypoxia	1	0.14
warfarin	DVT/PE	Coccydynia	1	0.14
warfarin	DVT/PE	Oesophageal disorder	1	0.14
warfarin	DVT/PE	Arteriovenous malformation	1	0.14
warfarin	DVT/PE	Headache	1	0.14
warfarin	DVT/PE	Melanocytic naevus	1	0.14
warfarin	DVT/PE	Open angle glaucoma	1	0.14
warfarin	DVT/PE	Neutropenia	1	0.14
warfarin	DVT/PE	Attention deficit/hyperactivity disorder	1	0.14
warfarin	DVT/PE	Oedema	1	0.14
warfarin	DVT/PE	Pleural fibrosis	1	0.14
warfarin	DVT/PE	Rectal tenesmus	1	0.14
warfarin	DVT/PE	Trigger finger	1	0.14
warfarin	DVT/PE	Demyelination	1	0.14
warfarin	DVT/PE	Nausea	1	0.14
warfarin	DVT/PE	Intentional self-injury	1	0.14

## Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE

Treatment group	Indication	Preferred term	Number	%
warfarin	DVT/PE	Palindromic rheumatism	1	0.14
warfarin	DVT/PE	Bladder catheter removal	1	0.14
warfarin	DVT/PE	Glomerulonephritis	1	0.14
warfarin	DVT/PE	Basedow's disease	1	0.14
warfarin	DVT/PE	Tonsillitis	1	0.14
warfarin	DVT/PE	Musculoskeletal deformity	1	0.14
warfarin	DVT/PE	Kidney duplex	1	0.14
warfarin	DVT/PE	Meningitis	1	0.14
warfarin	DVT/PE	Pre-existing condition improved	1	0.14
warfarin	DVT/PE	Cataract subcapsular	1	0.14
warfarin	DVT/PE	Otitis media	1	0.14
warfarin	DVT/PE	Neck pain	1	0.14
warfarin	DVT/PE	Major depression	1	0.14
warfarin	DVT/PE	Empty sella syndrome	1	0.14
warfarin	DVT/PE	Glomus jugulare tumour	1	0.14
warfarin	DVT/PE	Eustachian tube dysfunction	1	0.14
warfarin	DVT/PE	Influenza like illness	1	0.14
warfarin	DVT/PE	Lumbar spinal stenosis	1	0.14
warfarin	DVT/PE	Substance-induced psychotic disorder	1	0.14
warfarin	DVT/PE	Mental disorder	1	0.14
warfarin	DVT/PE	Renal cyst	1	0.14
warfarin	DVT/PE	Immunisation	1	0.14
warfarin	DVT/PE	Biopsy lymph gland	1	0.14
warfarin	DVT/PE	Fatigue	1	0.14
warfarin	DVT/PE	Abnormal behaviour	1	0.14
warfarin	DVT/PE	Skull fracture	1	0.14
warfarin	DVT/PE	Post herpetic neuralgia	1	0.14
warfarin	DVT/PE	Acquired oesophageal web	1	0.14
warfarin	DVT/PE	Muir-Torre syndrome	1	0.14
warfarin	DVT/PE	Endoscopy	1	0.14
warfarin	DVT/PE	Suicide attempt	1	0.14
warfarin	DVT/PE	Breast reconstruction	1	0.14
warfarin	DVT/PE	Localised infection	1	0.14
warfarin	DVT/PE	Mammoplasty	1	0.14
warfarin	DVT/PE	Peptic ulcer	1	0.14
warfarin	DVT/PE	Drug abuser	1	0.14
warfarin	DVT/PE	Systemic lupus erythematosus	1	0.14
warfarin	DVT/PE	Uveitis	1	0.14
warfarin	DVT/PE	Inflammatory bowel disease	1	0.14
warfarin	DVT/PE	Tendonitis	1	0.14
warfarin	DVT/PE	Tenosynovitis stenosans	1	0.14
warfarin	DVT/PE	Impaired self-care	1	0.14
warfarin	DVT/PE	Amnesia	1	0.14
warfarin	DVT/PE	Vasectomy	1	0.14
warfarin	DVT/PE	Idiopathic pulmonary fibrosis	1	0.14
warfarin	DVT/PE	Acute myocardial infarction	1	0.14
warfarin	DVT/PE	Cardiac septal defect	1	0.14
warfarin	DVT/PE	Dilatation ventricular	1	0.14
warfarin	DVT/PE	Mesenteric lymphadenopathy	1	0.14

**Appendix 7c(ii). Other Medical History Prior to Starting warfarin - DVT/PE**

<b>Treatment group</b>	<b>Indication</b>	<b>Preferred term</b>	<b>Number</b>	<b>%</b>
warfarin	DVT/PE	Cystitis	1	0.14
warfarin	DVT/PE	Nerve injury	1	0.14
warfarin	DVT/PE	Lymphadenopathy	1	0.14
warfarin	DVT/PE	Bone deformity	1	0.14
		<b>TOTAL</b>	<b>738</b>	



### Appendix 7c(iii). Other Medical History Prior to Starting warfarin - Mixed

Treatment group	Indication	Preferred term	Number	%
warfarin	Mixed	Diverticulum	2	11.76
warfarin	Mixed	Asthma	2	11.76
warfarin	Mixed	Gout	2	11.76
warfarin	Mixed	Osteoporosis	2	11.76
warfarin	Mixed	Renal failure acute	1	5.88
warfarin	Mixed	Haemorrhoids	1	5.88
warfarin	Mixed	Prostatomegaly	1	5.88
warfarin	Mixed	Neurofibromatosis	1	5.88
warfarin	Mixed	Intestinal obstruction	1	5.88
warfarin	Mixed	Staphylococcus test positive	1	5.88
warfarin	Mixed	Malaria	1	5.88
warfarin	Mixed	Gastrooesophageal reflux disease	1	5.88
warfarin	Mixed	Dehydration	1	5.88
warfarin	Mixed	Gastritis	1	5.88
warfarin	Mixed	Polypectomy	1	5.88
warfarin	Mixed	Laparoscopy	1	5.88
warfarin	Mixed	Dysphonia	1	5.88
warfarin	Mixed	Skin ulcer	1	5.88
warfarin	Mixed	Mitral valve incompetence	1	5.88
warfarin	Mixed	Angina pectoris	1	5.88
warfarin	Mixed	Ear, nose and throat examination normal	1	5.88
warfarin	Mixed	Uterine polyp	1	5.88
warfarin	Mixed	Lower respiratory tract infection	1	5.88
warfarin	Mixed	Back pain	1	5.88
warfarin	Mixed	Parkinson's disease	1	5.88
warfarin	Mixed	Vena cava filter insertion	1	5.88
warfarin	Mixed	Coeliac disease	1	5.88
warfarin	Mixed	Cellulitis	1	5.88
warfarin	Mixed	Varicose vein	1	5.88
warfarin	Mixed	Aortic stenosis	1	5.88
warfarin	Mixed	Carpal tunnel syndrome	1	5.88
warfarin	Mixed	Colitis ulcerative	1	5.88
warfarin	Mixed	Cholelithiasis	1	5.88
warfarin	Mixed	Cholecystectomy	1	5.88
warfarin	Mixed	Spinal osteoarthritis	1	5.88
warfarin	Mixed	Arterial stent insertion	1	5.88
warfarin	Mixed	Rheumatoid arthritis	1	5.88
warfarin	Mixed	Arthritis	1	5.88
warfarin	Mixed	Bronchiectasis	1	5.88
warfarin	Mixed	Spondylitis	1	5.88
warfarin	Mixed	Road traffic accident	1	5.88
		<b>TOTAL</b>	<b>17</b>	

#### Appendix 7c(iv). Other Medical History Prior to Starting warfarin - Other

Treatment group	Indication	Preferred term	Number	%
warfarin	Other	Asthma	2	15.38
warfarin	Other	Hypothyroidism	2	15.38
warfarin	Other	Osteopetrosis	1	7.69
warfarin	Other	Arthralgia	1	7.69
warfarin	Other	Gouty arthritis	1	7.69
warfarin	Other	Cholelithiasis	1	7.69
warfarin	Other	Rheumatoid arthritis	1	7.69
warfarin	Other	Respiratory failure	1	7.69
warfarin	Other	Knee arthroplasty	1	7.69
warfarin	Other	Ureterectomy	1	7.69
warfarin	Other	Pain in extremity	1	7.69
warfarin	Other	Gastroenteritis	1	7.69
warfarin	Other	Bronchiectasis	1	7.69
warfarin	Other	Carotid artery dissection	1	7.69
warfarin	Other	Lip injury	1	7.69
warfarin	Other	Phlebitis	1	7.69
warfarin	Other	Migraine	1	7.69
warfarin	Other	Aortic bruit	1	7.69
warfarin	Other	Cardiac pacemaker insertion	1	7.69
warfarin	Other	Anaemia	1	7.69
warfarin	Other	Convulsion	1	7.69
warfarin	Other	Angiodysplasia	1	7.69
warfarin	Other	Spinal column stenosis	1	7.69
warfarin	Other	Streptococcal abscess	1	7.69
warfarin	Other	Carotid sinus syndrome	1	7.69
warfarin	Other	Unevaluable event	1	7.69
warfarin	Other	Facet joint block	1	7.69
warfarin	Other	Angina pectoris	1	7.69
		<b>TOTAL</b>	<b>13</b>	

## Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban

### Appendix 8a(i). Reasons for Switch from Oral Anticoagulant to rivaroxaban for NVAF/AF group (N=144)

System Organ Class	Reason for Switch to Rivaroxaban	n	%
Cardiac disorders	Atrial fibrillation	4	2.8
	Cardiac failure	1	0.7
	Mitral valve incompetence	1	0.7
	Tricuspid valve incompetence	1	0.7
Congenital, familial and genetic disorders	Factor VII deficiency	1	0.7
Gastrointestinal disorders	Abdominal discomfort	2	1.4
	Diarrhoea	3	2.1
	Dyspepsia	1	0.7
General disorders and administration site conditions	Adverse drug reaction	2	1.4
	Doctor decision	33	22.9
	Dr Preference	14	9.7
	Drug intolerance	3	2.1
	Drug not effective	1	0.7
	Fatigue	1	0.7
	Lifestyle issues	11	7.6
	NICE guidelines	2	1.4
	Prescribing guidelines	1	0.7
	Reason not provided	9	6.3
	Secondary care advice, formulary or guidelines	2	1.4
	Stroke risk	2	1.4
Injury, poisoning and procedural complications	Perirenal haematoma	1	0.7
Investigations	Anticoagulation drug level below therapeutic	5	3.5
	International normalised ratio	3	2.1
	International normalised ratio decreased	2	1.4
	International normalised ratio fluctuation	9	6.3
	International normalised ratio increased	1	0.7
	Prothrombin level increased	1	0.7
Nervous system disorders	Cerebrovascular accident	9	6.3
	Headache	2	1.4
	Lacunar infarction	1	0.7
	Lethargy	2	1.4
	Transient ischaemic attack	1	0.7
Respiratory, thoracic and mediastinal disorders	Epistaxis	1	0.7
Skin and subcutaneous tissue disorders	Alopecia	2	1.4
	Increased tendency to bruise	1	0.7
	Pruritus	2	1.4
	Rash	2	1.4

**Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban**

<b>System Organ Class</b>	<b>Reason for Switch to Rivaroxaban</b>	<b>n</b>	<b>%</b>
Social circumstances	Skin disorder	1	0.7
	Elderly	2	1.4
	Refusal of treatment by patient	24	16.7
	Treatment noncompliance	8	5.6
Surgical and medical procedures	Cardioversion	1	0.7
	Drug therapy changed	3	2.1
	Hospitalisation	3	2.1
Vascular disorders	Haemorrhage	1	0.7
	Ischaemia	1	0.7
	Peripheral coldness	1	0.7

## Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban

### Appendix 8a(ii). Reasons for Switch from Oral Anticoagulant to rivaroxaban for DVT/PE group (N=86)

System Organ Class	Reason for Switch to Rivaroxaban	n	%
Blood and lymphatic system disorders	Polycythaemia	1	1.2
Gastrointestinal disorders	Diarrhoea	1	1.2
	Dyspepsia	1	1.2
	Malabsorption	1	1.2
General disorders and administration site conditions	Adverse drug reaction	2	2.3
	Doctor decision	15	17.4
	Dr Preference	3	3.5
	Drug intolerance	1	1.2
	Intolerance to drug	1	1.2
	Lifestyle issues	19	22.1
	Local protocol	1	1.2
	Pharmacist decision	1	1.2
	Potentiating drug interaction	1	1.2
	Practice advice, formulary or guidelines	1	1.2
	Reason not provided	4	4.7
	Secondary care advice, formulary or guidelines	3	3.5
	Seen in haematology	1	1.2
	Cellulitis	1	1.2
Investigations	Anticoagulation drug level below therapeutic	2	2.3
	Fibrin D dimer	1	1.2
	International normalised ratio	3	3.5
	International normalised ratio fluctuation	12	14
	International normalised ratio increased	1	1.2
Nervous system disorders	Headache	2	2.3
	Memory impairment	1	1.2
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1	1.2
Skin and subcutaneous tissue disorders	Alopecia	1	1.2
	Rash pruritic	1	1.2
	Rash vesicular	1	1.2
	Skin irritation	1	1.2
Social circumstances	Refusal of treatment by patient	9	10.5
	Treatment noncompliance	5	5.8
Surgical and medical procedures	Anticoagulant therapy	1	1.2
	Chemotherapy	1	1.2
	Drug therapy changed	4	4.7
Vascular disorders	Deep vein thrombosis	5	5.8

**Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban**

<b>System Organ Class</b>	<b>Reason for Switch to Rivaroxaban</b>	<b>n</b>	<b>%</b>
	Poor venous access	1	1.2

**Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban**

**Appendix 8a(iii). Reasons for Switch from Oral Anticoagulant to rivaroxaban for Mixed group (N=8)**

<b>System Organ Class</b>	<b>Reason for Switch to Rivaroxaban</b>	<b>n</b>	<b>%</b>
Gastrointestinal disorders	Gingival bleeding	1	13.0
General disorders and administration site conditions	Doctor decision	1	13.0
	Lifestyle issues	2	25.0
	Prescribing guidelines	1	13.0
	Reason not provided	1	13.0
	International normalised ratio fluctuation	1	13.0
	Cerebrovascular accident	1	13.0
	Epistaxis	1	13.0
	Alopecia	1	13.0

## **Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban**

### **Appendix 8a(iv). Reasons for Switch from Oral Anticoagulant to rivaroxaban for Other group (N=7)**

<b>System Organ Class</b>	<b>Reason for Switch to Rivaroxaban</b>	<b>n</b>	<b>%</b>
General disorders and administration site conditions	Doctor decision	1	14.3
	Drug ineffective	1	14.3
	End of course	1	14.3
	Lifestyle issues	1	14.3
Investigations	International normalised ratio fluctuation	2	28.6
Skin and subcutaneous tissue disorders	Alopecia	1	14.3
Surgical and medical procedures	Drug therapy changed	1	14.3
Vascular disorders	Poor venous access	1	14.3



## Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban

### Appendix 8a(v). Reasons for Switch from Parenteral Anticoagulant to rivaroxaban for NVAF/AF group (N=99)

System Organ Class	Reason for Switch to Rivaroxaban	n	%
Cardiac disorders	Atrial fibrillation	17	17.2
General disorders and administration site conditions	Doctor decision	25	25.3
	Dr Preference	6	6.1
	Lifestyle issues	4	4.0
	Planned duration R for stopping	1	1.0
	Practice advice, formulary or guidelines	1	1.0
	Pre-existing condition improved	1	1.0
	Prescribing guidelines	1	1.0
	Reason not provided	23	23.2
	Secondary care advice, formulary or guidelines	3	3.0
	Stroke risk	6	6.1
	Cardiovascular evaluation	1	1.0
Investigations	International normalised ratio	1	1.0
Nervous system disorders	Cerebrovascular accident	1	1.0
	Transient ischaemic attack	1	1.0
Renal and urinary disorders	Renal impairment	1	1.0
Social circumstances	Refusal of treatment by patient	5	5.1
Surgical and medical procedures	Anticoagulant therapy	6	6.1
	Drug therapy changed	3	3.0
	Prophylaxis	1	1.0
	Thrombosis prophylaxis	1	1.0
Vascular disorders	Deep vein thrombosis	1	1.0

## Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban

### Appendix 8a(vi). Reasons for Switch from Parenteral Anticoagulant to rivaroxaban for DVT/PE group (N=721)

System Organ Class	Reason for Switch to Rivaroxaban	n	%
Blood and lymphatic system disorders	Anaemia	1	0.1
Cardiac disorders	Acute myocardial infarction	2	0.3
	Atrial fibrillation	1	0.1
Gastrointestinal disorders	Abdominal tenderness	1	0.1
	Crohn's disease	1	0.1
	Gastrointestinal haemorrhage	1	0.1
General disorders and administration site conditions	Adverse drug reaction	1	0.1
	Anticoagulant clinic	3	0.4
	Diagnosis revised	2	0.3
	Doctor decision	69	9.6
	Dr Preference	2	0.3
	Drug intolerance	1	0.1
	Drug trial protocol	1	0.1
	Fracture risk	1	0.1
	Hospital advised	5	0.7
	Hospital changed medication	4	0.6
	Hospital decision	1	0.1
	Injection site discomfort	2	0.3
	Injection site haematoma	2	0.3
	Injection site mass	1	0.1
	Injection site pain	5	0.7
	Lifestyle issues	56	7.8
	Local prescribing policy	15	2.1
	Local protocol	26	3.6
	NICE guidelines	2	0.3
	Oedema peripheral	1	0.1
	Only one prescription	1	0.1
	Osteoporosis risk	1	0.1
	Pharmacist decision	2	0.3
	Planned duration R for stopping	5	0.7
	Practice advice, formulary or guidelines	14	1.9
	Practice protocol	2	0.3
	Pre-existing condition improved	1	0.1
	Prescribing advisor advice	3	0.4
	Prescribing guidelines	58	8.0
	Reason not provided	115	16.0
	Referred to specialist	3	0.4
	Secondary care advice, formulary or guidelines	29	4.0
Injury, poisoning and procedural complications	Contusion	1	0.1
	Post procedural pulmonary embolism	1	0.1
Investigations	Angiogram pulmonary	1	0.1

## Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban

System Organ Class	Reason for Switch to Rivaroxaban	n	%
	Angiogram pulmonary normal	1	0.1
	Anticoagulation drug level above therapeutic	1	0.1
	Cardiovascular evaluation	1	0.1
	Computerised tomogram	1	0.1
	Haemoglobin decreased	1	0.1
	International normalised ratio	2	0.3
	International normalised ratio fluctuation	3	0.4
	Investigation	2	0.3
	Oesophagogastroduodenoscopy	1	0.1
	Ultrasound Doppler	4	0.6
	Ultrasound Doppler abnormal	5	0.7
	Ultrasound scan	3	0.4
	Ultrasound testes	1	0.1
Musculoskeletal and connective tissue disorders	Mobility decreased	1	0.1
	Osteoporosis	1	0.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	3	0.4
	Neoplasm malignant	1	0.1
	Ovarian cancer	1	0.1
	Prostate cancer	1	0.1
	Waldenstrom's macroglobulinaemia	1	0.1
Psychiatric disorders	Phobia	1	0.1
Renal and urinary disorders	Renal impairment	1	0.1
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	49	6.8
Social circumstances	Drug diversion	1	0.1
	Foreign travel	1	0.1
	Refusal of treatment by patient	29	4.0
Surgical and medical procedures	Anticoagulant therapy	83	11.5
	Drug therapy changed	82	11.4
	Hospitalisation	1	0.1
	Knee arthroplasty	1	0.1
	Prophylaxis	4	0.6
	Therapy regimen changed	17	2.4
	Thrombolysis	2	0.3
	Thrombosis prophylaxis	2	0.3
	Venous stent insertion	1	0.1
Vascular disorders	Aortic aneurysm	1	0.1
	Deep vein thrombosis	54	7.5
	Embolism venous	1	0.1
	Poor venous access	2	0.3
	Thrombophlebitis	1	0.1
	Thrombophlebitis superficial	2	0.3

**Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban**

**Appendix 8a(vii). Reasons for Switch from Parenteral Anticoagulant to rivaroxaban for Mixed group (N=6)**

<b>System Organ Class</b>	<b>Reason for Switch to Rivaroxaban</b>	<b>n</b>	<b>%</b>
General disorders and administration site conditions	Doctor decision	1	16.7
	Lifestyle issues	1	16.7
	Reason not provided	1	16.7
Social circumstances	Refusal of treatment by patient	2	33.3
Surgical and medical procedures	Drug therapy changed	2	33.3

**Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban**

**Appendix 8a(viii). Reasons for Switch from Parenteral Anticoagulant to rivaroxaban for Other group (N=3)**

<b>System Organ Class</b>	<b>Reason for Switch to Rivaroxaban</b>	<b>n</b>	<b>%</b>
General disorders and administration site conditions	Reason not provided	1	33.3
Social circumstances	Refusal of treatment by patient	1	33.3
Surgical and medical procedures	Drug therapy changed	1	33.3

## Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban

### Appendix 8a(ix). Reasons for Switch from Antiplatelet to rivaroxaban for NVAF/AF group (N=359)

System Organ Class	Reason for Switch to Rivaroxaban	n	%
Cardiac disorders	Atrial fibrillation	146	40.7
	Atrial flutter	1	0.3
	Myocardial infarction	1	0.3
Gastrointestinal disorders	Vomiting	1	0.3
General disorders and administration site conditions	Doctor decision	84	23.4
	Dr Preference	23	6.4
	Drug ineffective	1	0.3
	Drug intolerance	1	0.3
	Drug regimen changed	1	0.3
	Hospital decision	1	0.3
	Lifestyle issues	3	0.8
	Malaise	1	0.3
	NICE guidelines	7	1.9
	Pain	1	0.3
	Planned duration R for stopping	3	0.8
	Practice advice, formulary or guidelines	6	1.7
	Practice policy	1	0.3
	Pre-existing condition improved	6	1.7
	Prescribing guidelines	12	3.3
	Reason not provided	30	8.4
	Secondary care advice, formulary or guidelines	5	1.4
	Stopped by specialist	1	0.3
	Stroke risk	14	3.9
Injury, poisoning and procedural complications	Contusion	1	0.3
Investigations	Cardiac monitoring	1	0.3
	Cardiovascular evaluation	2	0.6
	Computerised tomogram	1	0.3
	Echocardiogram	1	0.3
	Electrocardiogram	1	0.3
	Electrocardiogram abnormal	1	0.3
	Electrocardiogram ambulatory	2	0.6
	Electrocardiogram ambulatory abnormal	1	0.3
	Heart rate increased	1	0.3
	Transient ischaemic attack	11	3.1
Nervous system disorders	Cerebellar infarction	1	0.3
	Cerebral infarction	1	0.3
	Cerebrovascular accident	21	5.8
	Embolic cerebral infarction	1	0.3
	Ischaemic stroke	2	0.6
	Transient ischaemic attack	11	3.1

**Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban**

<b>System Organ Class</b>	<b>Reason for Switch to Rivaroxaban</b>	<b>n</b>	<b>%</b>
Skin and subcutaneous tissue disorders	Rash	1	0.3
Social circumstances	Refusal of treatment by patient	4	1.1
Surgical and medical procedures	Anticoagulant therapy	21	5.8
	Carotid endarterectomy	1	0.3
	Drug therapy changed	11	3.1
	Prophylaxis	3	0.8
	Therapy regimen changed	2	0.6

## Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban

### Appendix 8a(x). Reasons for Switch from Antiplatelet to rivaroxaban for DVT/PE group (N=78)

System Organ Class	Reason for Switch to Rivaroxaban	n	%
Cardiac disorders	Acute myocardial infarction	2	2.6
	Bradycardia	1	1.3
General disorders and administration site conditions	Doctor decision	8	10.3
	Hospital advised	1	1.3
	Lifestyle issues	1	1.3
	Practice advice, formulary or guidelines	3	3.8
	Prescribing guidelines	3	3.8
	Reason not provided	14	17.9
	Secondary care advice, formulary or guidelines	3	3.8
	Stroke risk	1	1.3
Investigations	Anticoagulation drug level above therapeutic	1	1.3
	Cardiovascular evaluation	1	1.3
	Ultrasound Doppler abnormal	1	1.3
	Vascular test normal	1	1.3
Nervous system disorders	Cerebrovascular accident	1	1.3
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	11	14.1
Surgical and medical procedures	Anticoagulant therapy	7	9.0
	Antiplatelet therapy	1	1.3
	Drug therapy changed	12	15.4
	Haemorrhage prophylaxis	1	1.3
	Knee arthroplasty	1	1.3
	Thrombosis prophylaxis	1	1.3
Vascular disorders	Deep vein thrombosis	10	12.8
	Embolism venous	1	1.3



**Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban**

**Appendix 8a(xi). Reasons for Switch from Antiplatelet to rivaroxaban for Mixed group (N=7)**

<b>System Organ Class</b>	<b>Reason for Switch to Rivaroxaban</b>	<b>n</b>	<b>%</b>
Cardiac disorders	Atrial fibrillation	2	28.6
General disorders and administration site conditions	Doctor decision	2	28.6
	Reason not provided	2	28.6
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	3	42.9
Surgical and medical procedures	Drug therapy changed	1	14.3

**Appendix 8a. Reasons for Switching Medications Prior to Starting rivaroxaban**

**Appendix 8a(xii). Reasons for Switch from Antiplatelet to rivaroxaban for Other group (N=3)**

<b>System Organ Class</b>	<b>Reason for Switch to Rivaroxaban</b>	<b>n</b>	<b>%</b>
General disorders and administration site conditions	Doctor decision	2	33.3
	Reason not provided	3	50.0
Nervous system disorders	Carotid artery thrombosis	1	16.7
	Embolic stroke	1	16.7

## Appendix 8b. Reasons for Switching Medications Prior to Starting warfarin

### Appendix 8b(i). Reasons for Switch from Parenteral Anticoagulant to warfarin for NVAF/AF group (N=95)

System Organ Class	Reason for Switch to Warfarin	n	%
Cardiac disorders	Atrial fibrillation	8	8.4
General disorders and administration site conditions	Clinical trial	1	1.1
	Doctor decision	11	11.6
	Dr Preference	4	4.2
	Lifestyle issues	13	13.7
	Planned duration R for stopping	1	1.1
	Practice advice, formulary or guidelines	4	4.2
	Pre-existing condition improved	1	1.1
	Reason not provided	14	14.7
	Secondary care advice, formulary or guidelines	1	1.1
Investigations	Anticoagulation drug level above therapeutic	8	8.4
	Cardiovascular evaluation	1	1.1
	International normalised ratio	11	11.6
Social circumstances	Refusal of treatment by patient	1	1.1
Surgical and medical procedures	Anticoagulant therapy	19	20
	Drug therapy changed	2	2.1
	Prophylaxis	1	1.1
	Therapy regimen changed	2	2.1

## Appendix 8b. Reasons for Switching Medications Prior to Starting warfarin

### Appendix 8b(ii). Reasons for Switch from Parenteral Anticoagulant to warfarin for DVT/PE group (N=528)

System Organ Class	Reason for Switch to Warfarin	n	%
Blood and lymphatic system disorders	Heparin-induced thrombocytopenia	1	0.2
Cardiac disorders	Atrial fibrillation	1	0.2
Gastrointestinal disorders	Duodenal ulcer	1	0.2
General disorders and administration site conditions	Anticoagulant clinic	1	0.2
	Dispensing policy	1	0.2
	Doctor decision	44	8.3
	Dr Preference	7	1.3
	End of course	2	0.4
	Hospital advised	6	1.1
	Hospital decision	4	0.8
	Hospital stopped it	1	0.2
	Injection site haematoma	2	0.4
	Lifestyle issues	25	4.7
	Local protocol	5	0.9
	NICE guidelines	6	1.1
	No longer pregnant	2	0.4
	Planned duration	1	0.2
	Planned duration R for stopping	4	0.8
	Practice advice, formulary or guidelines	2	0.4
	Pre-existing condition improved	1	0.2
	Prescribing guidelines	20	3.8
	Reason not provided	55	10.4
	Secondary care advice, formulary or guidelines	50	9.5
	Short course only	1	0.2
Injury, poisoning and procedural complications	Fracture	1	0.2
Investigations	Angiogram pulmonary	1	0.2
	Anticoagulation drug level above therapeutic	28	5.3
	Colonoscopy	1	0.2
	Computerised tomogram	1	0.2
	Drug level	4	0.8
	Endoscopy	1	0.2
	Haemoglobin decreased	1	0.2
	International normalised ratio	30	5.7
	International normalised ratio increased	2	0.4
	Investigation	1	0.2
	Liver function test abnormal	1	0.2
	Oesophagogastroduodenoscopy	1	0.2
	Renal function test	1	0.2
	Ultrasound Doppler	1	0.2

## Appendix 8b. Reasons for Switching Medications Prior to Starting warfarin

System Organ Class	Reason for Switch to Warfarin	n	%
	Ultrasound scan	1	0.2
Musculoskeletal and connective tissue disorders	Pain in extremity	1	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1	0.2
Psychiatric disorders	Depression	1	0.2
Renal and urinary disorders	Renal failure	1	0.2
Respiratory, thoracic and mediastinal disorders	Haemoptysis	1	0.2
	Pulmonary embolism	46	8.7
Social circumstances	Refusal of treatment by patient	11	2.1
	Treatment noncompliance	2	0.4
Surgical and medical procedures	Angioplasty	1	0.2
	Anticoagulant therapy	132	25
	Chemotherapy	1	0.2
	Drug therapy changed	23	4.4
	Emergency care	1	0.2
	Hospitalisation	1	0.2
	Prophylaxis	2	0.4
	Surgery	2	0.4
	Therapy regimen changed	4	0.8
	Venous stent insertion	1	0.2
Vascular disorders	Deep vein thrombosis	38	7.2
	Thrombophlebitis superficial	1	0.2
	Thrombosis	1	0.2

## Appendix 8b. Reasons for Switching Medications Prior to Starting warfarin

### Appendix 8b(iii). Reasons for Switch from Parenteral Anticoagulant to warfarin for Mixed group (N=12)

System Organ Class	Reason for Switch to Warfarin	n	%
Cardiac disorders	Atrial fibrillation	1	8.3
General disorders and administration site conditions	Doctor decision	1	8.3
	Dr Preference	1	8.3
	Drug effect satisfactory	1	8.3
	Lifestyle issues	2	16.7
	Reason not provided	1	8.3
Investigations	Anticoagulation drug level above therapeutic	1	8.3
	International normalised ratio	1	8.3
Surgical and medical procedures	Anticoagulant therapy	4	33.3
Vascular disorders	Deep vein thrombosis	1	8.3
	Post thrombotic syndrome	1	8.3

## **Appendix 8b. Reasons for Switching Medications Prior to Starting warfarin**

### **Appendix 8b(iv). Reasons for Switch from Parenteral Anticoagulant to warfarin for Other group (N=11)**

<b>System Organ Class</b>	<b>Reason for Switch to Warfarin</b>	<b>n</b>	<b>%</b>
General disorders and administration site conditions	Doctor decision	1	9.1
	Dr Preference	1	9.1
	Reason not provided	2	18.2
	Secondary care advice, formulary or guidelines	3	27.3
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1	9.1
Surgical and medical procedures	Anticoagulant therapy	1	9.1
	Therapy regimen changed	2	18.2
	Thromboembolectomy	1	9.1
Vascular disorders	Aortic thrombosis	1	9.1

## Appendix 8b. Reasons for Switching Medications Prior to Starting warfarin

### Appendix 8b(v). Reasons for Switch from Antiplatelet to warfarin for NVAf/AF group (N=235)

System Organ Class	Reason for Switch to Warfarin	n	%
Cardiac disorders	Atrial fibrillation	92	39.1
	Cardiac failure congestive	1	0.4
General disorders and administration site conditions	Cardiac assessment	1	0.4
	Diagnosis revised	2	0.9
	Doctor decision	29	12.3
	Dr Preference	11	4.7
	Drug ineffective	1	0.4
	Government advice or guidelines	1	0.4
	Hospital advised	1	0.4
	Lifestyle issues	6	2.6
	Local protocol	1	0.4
	NICE guidelines	6	2.6
	Planned duration R for stopping	2	0.9
	Practice advice, formulary or guidelines	6	2.6
	Pre-existing condition improved	1	0.4
	Prescribing advisor advice	1	0.4
	Prescribing guidelines	17	7.2
	Reason not provided	21	8.9
	Secondary care advice	1	0.4
	Secondary care advice, formulary or guidelines	7	3.0
	Stroke risk	4	1.7
Investigations	Anticoagulation drug level above therapeutic	9	3.8
	Anticoagulation drug level below therapeutic	1	0.4
	Cardiovascular evaluation	1	0.4
	Electrocardiogram	1	0.4
	Electrocardiogram ambulatory	1	0.4
	International normalised ratio	11	4.7
	International normalised ratio increased	1	0.4
	International normalised ratio normal	1	0.4
	Stroke risk	4	1.7
Nervous system disorders	Cerebrovascular accident	15	6.4
	Ischaemic stroke	1	0.4
	Transient ischaemic attack	3	1.3
Social circumstances	Elderly	1	0.4
	Treatment noncompliance	1	0.4
Surgical and medical procedures	Anticoagulant therapy	22	9.4
	Cardioversion	3	1.3
	Drug therapy changed	4	1.7
	Hospitalisation	1	0.4
	Prophylaxis	1	0.4
	Therapy regimen changed	4	1.7



## Appendix 8b. Reasons for Switching Medications Prior to Starting warfarin

System Organ Class	Reason for Switch to Warfarin	n	%
Vascular disorders	Thrombosis prophylaxis	1	0.4
	Deep vein thrombosis	1	0.4
	Embolism	1	0.4

## Appendix 8b. Reasons for Switching Medications Prior to Starting warfarin

### Appendix 8b(vi). Reasons for Switch from Antiplatelet to warfarin for DVT/PE group (N=48)

System Organ Class	Reason for Switch to Warfarin	n	%
General disorders and administration site conditions	Doctor decision	3	6.3
	Dr Preference	1	2.1
	Drug trial protocol	1	2.1
	Lifestyle issues	1	2.1
	Planned duration R for stopping	1	2.1
	Pre-existing condition improved	2	4.2
	Prescribing guidelines	1	2.1
	Reason not provided	11	22.9
	Secondary care advice, formulary or guidelines	4	8.3
	Short course only	1	2.1
Investigations	Anticoagulation drug level above therapeutic	1	2.1
	Drug level	1	2.1
	International normalised ratio	2	4.2
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	4	8.3
Surgical and medical procedures	Anticoagulant therapy	4	8.3
	Coronary artery bypass	1	2.1
	Drug therapy changed	5	10.4
Vascular disorders	Deep vein thrombosis	8	16.7

## Appendix 8b. Reasons for Switching Medications Prior to Starting warfarin

### Appendix 8b(vii). Reasons for Switch from Antiplatelet to warfarin for Mixed group (N=8)

System Organ Class	Reason for Switch to Warfarin	n	%
General disorders and administration site conditions	NICE guidelines	1	12.5
	Reason not provided	1	12.5
Investigations	Anticoagulation drug level above therapeutic	1	12.5
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1	12.5
Surgical and medical procedures	Anticoagulant therapy	2	25.0
	Drug therapy changed	1	12.5
Vascular disorders	Deep vein thrombosis	1	12.5
	Post thrombotic syndrome	1	12.5

## **Appendix 8b. Reasons for Switching Medications Prior to Starting warfarin**

### **Appendix 8b(viii). Reasons for Switch from Antiplatelet to warfarin for Other group (N=8)**

<b>System Organ Class</b>	<b>Reason for Switch to Warfarin</b>	<b>n</b>	<b>%</b>
Cardiac disorders	Atrial fibrillation	2	25.0
	Atrial flutter	2	25.0
General disorders and administration site conditions	Dr Preference	1	12.5
	Lifestyle issues	1	12.5
	Prescribing guidelines	1	12.5
Investigations	International normalised ratio	1	12.5
Nervous system disorders	Cerebrovascular accident	1	12.5
Vascular disorders	Arterial thrombosis	1	12.5

## Appendix 9a. Other Medication History - AF

Drug (drug class)	Rivaroxaban								Warfarin							
	Any use		Prior		During		Period Unknown		Any use		Prior		During		Period Unknown	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<b>Analgesics and Anti-inflammatory Agents</b>																
Paracetamol	267	27.7	217	22.5	206	21.3	0	0.0	225	28.3	184	23.2	175	22.0	4	0.5
Aspirin (>300mg)	161	16.7	145	15.0	37	3.8	9	0.9	183	23.0	161	20.3	65	8.2	12	1.5
<b>NSAID</b>																
Celecoxib	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Chondroitin	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1
Diclofenac	2	0.2	1	0.1	0	0.0	1	0.1	4	0.5	2	0.3	0	0.0	2	0.3
Etoricoxib	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Glucosamine	2	0.2	0	0.0	0	0.0	2	0.2	5	0.6	0	0.0	0	0.0	5	0.6
Glucosamine/Chondroitin	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Ibuprofen	13	1.3	6	0.6	5	0.5	4	0.4	10	1.3	5	0.6	5	0.6	3	0.4
Indomethacin	1	0.1	0	0.0	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1
Ketorolac Trometamol	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1
Meloxicam	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Naproxen	14	1.5	8	0.8	5	0.5	6	0.6	12	1.5	7	0.9	3	0.4	5	0.6
Nsaids	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Piroxicam	3	0.3	0	0.0	0	0.0	3	0.3	1	0.1	0	0.0	0	0.0	1	0.1
Topical Nsaids	10	1.0	1	0.1	3	0.3	6	0.6	3	0.4	0	0.0	1	0.1	2	0.3
Drug Not Specified	18	1.9	15	1.6	9	0.9	0	0.0	14	1.8	12	1.5	8	1.0	0	0.0
<b>Total</b>	<b>68</b>	<b>7.0</b>	<b>32</b>	<b>3.3</b>	<b>23</b>	<b>2.4</b>	<b>27</b>	<b>2.8</b>	<b>48</b>	<b>6.0</b>	<b>26</b>	<b>3.3</b>	<b>17</b>	<b>2.1</b>	<b>20</b>	<b>2.5</b>
<b>Other Analgesics/Antiinflammatories</b>																
Analgesics	163	16.9	105	10.9	98	10.2	32	3.3	129	16.2	82	10.3	90	11.3	19	2.4
Anesthetics	4	0.4	1	0.1	1	0.1	3	0.3	3	0.4	1	0.1	0	0.0	2	0.3
Antidiarrheals, Intestinal Antiinflammatories	5	0.5	1	0.1	0	0.0	4	0.4	8	1.0	1	0.1	1	0.1	7	0.9
Antigout Preparations	6	0.6	1	0.1	2	0.2	4	0.4	3	0.4	0	0.0	0	0.0	3	0.4
Antipirotozoals	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0
Corticosteroids For Systemic Use	57	5.9	9	0.9	11	1.1	43	4.5	52	6.5	8	1.0	9	1.1	41	5.2
Corticosteroids, Dermatological Preparations	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Drugs For Obstructive Airway Diseases	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Immunosuppressive Agents	11	1.1	1	0.1	1	0.1	10	1.0	7	0.9	1	0.1	0	0.0	6	0.8
Nasal Preparation	0	0.0	0	0.0	0	0.0	0	0.0	2	0.3	0	0.0	0	0.0	2	0.3
Topical Products For Joint And Muscular Pain	1	0.1	1	0.1	1	0.1	0	0.0	6	0.8	1	0.1	2	0.3	4	0.5
Drug Not Specified	24	2.5	19	2.0	16	1.7	0	0.0	22	2.8	18	2.3	14	1.8	0	0.0
<b>Total</b>	<b>226</b>	<b>23.4</b>	<b>133</b>	<b>13.8</b>	<b>124</b>	<b>12.8</b>	<b>88</b>	<b>9.1</b>	<b>193</b>	<b>24.3</b>	<b>111</b>	<b>14.0</b>	<b>114</b>	<b>14.4</b>	<b>70</b>	<b>8.8</b>

# Appendix 9a. Other Medication History - AF

Drug (drug class)	Rivaroxaban								Warfarin							
<b>Anticonvulsants</b>																
Phenytoin	2	0.2	2	0.2	1	0.1	0	0.0	2	0.3	2	0.3	1	0.1	0	0.0
Phenobarbitone	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0
Carbamazepine	7	0.7	7	0.7	6	0.6	0	0.0	4	0.5	3	0.4	2	0.3	1	0.1
Primidone	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<b>Other anticonvulsants</b>																
Gabapentin	9	0.9	0	0.0	0	0.0	9	0.9	12	1.5	2	0.3	1	0.1	10	1.3
Lamotrigine	5	0.5	4	0.4	3	0.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Levetiracetam	6	0.6	3	0.3	4	0.4	2	0.2	4	0.5	3	0.4	2	0.3	1	0.1
Oxcarbazepine	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Pregabalin	12	1.2	3	0.3	4	0.4	8	0.8	6	0.8	2	0.3	1	0.1	4	0.5
Sodium Valproate	4	0.4	3	0.3	4	0.4	0	0.0	5	0.6	5	0.6	4	0.5	0	0.0
Topiramate	2	0.2	2	0.2	2	0.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Valproate Semisodium	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Drug Not Specified	1	0.1	1	0.1	1	0.1	0	0.0	2	0.3	2	0.3	2	0.3	0	0.0
<b>Total</b>	<b>39</b>	<b>4.0</b>	<b>17</b>	<b>1.8</b>	<b>19</b>	<b>2.0</b>	<b>20</b>	<b>2.1</b>	<b>27</b>	<b>3.4</b>	<b>13</b>	<b>1.6</b>	<b>9</b>	<b>1.1</b>	<b>15</b>	<b>1.9</b>
<b>Anti-infectives</b>																
Ketoconazole	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Itraconazole	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Posaconazole	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ritonavir	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1
Clarithromycin	34	3.5	17	1.8	20	2.1	1	0.1	29	3.7	18	2.3	18	2.3	0	0.0
Erythromycin	5	0.5	2	0.2	3	0.3	0	0.0	2	0.3	1	0.1	1	0.1	0	0.0
Rifampicin	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sulfamethoxazole	3	0.3	1	0.1	0	0.0	2	0.2	3	0.4	0	0.0	0	0.0	3	0.4
Metronidazole	12	1.2	4	0.4	8	0.8	2	0.2	10	1.3	2	0.3	9	1.1	0	0.0
Griseofulvin	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<b>Other antiinfectives</b>																
Antibacterials For Systemic Use	160	16.6	90	9.3	105	10.9	18	1.9	129	16.2	63	7.9	79	9.9	19	2.4
Antidiarrheals, Intestinal Antiinflammatories	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Antimycobacterials	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Antimycotics For Systemic Use	5	0.5	3	0.3	3	0.3	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Antivirals For Systemic Use	4	0.4	3	0.3	1	0.1	1	0.1	2	0.3	1	0.1	1	0.1	1	0.1
Unspecified Anti-Infectives	3	0.3	2	0.2	1	0.1	0	0.0	4	0.5	3	0.4	1	0.1	1	0.1
Drug Not Specified	7	0.7	4	0.4	3	0.3	0	0.0	3	0.4	2	0.3	3	0.4	0	0.0
<b>Total</b>	<b>173</b>	<b>17.9</b>	<b>98</b>	<b>10.2</b>	<b>111</b>	<b>11.5</b>	<b>20</b>	<b>2.1</b>	<b>136</b>	<b>17.1</b>	<b>68</b>	<b>8.6</b>	<b>83</b>	<b>10.5</b>	<b>21</b>	<b>2.6</b>

# Appendix 9a. Other Medication History - AF

Drug (drug class)	Rivaroxaban								Warfarin							
<b>Antidepressants</b>																
<b>Tricyclics</b>																
Amitriptyline	13	1.3	7	0.7	6	0.6	5	0.5	17	2.1	7	0.9	8	1.0	9	1.1
Clomipramine	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Dothiepin	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Impramine	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0
Drug Not Specified	19	2.0	17	1.8	13	1.3	0	0.0	22	2.8	19	2.4	15	1.9	0	0.0
<b>Total</b>	<b>33</b>	<b>3.4</b>	<b>25</b>	<b>2.6</b>	<b>20</b>	<b>2.1</b>	<b>6</b>	<b>0.6</b>	<b>39</b>	<b>4.9</b>	<b>27</b>	<b>3.4</b>	<b>24</b>	<b>3.0</b>	<b>9</b>	<b>1.1</b>
<b>MAOI (drug not specified)</b>	<b>2</b>	<b>0.2</b>	<b>1</b>	<b>0.1</b>	<b>2</b>	<b>0.2</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>
<b>SSRI</b>																
Citalopram	29	3.0	11	1.1	11	1.1	14	1.5	17	2.1	7	0.9	8	1.0	9	1.1
Escitalopram	3	0.3	1	0.1	1	0.1	2	0.2	1	0.1	0	0.0	1	0.1	0	0.0
Fluoxetine	5	0.5	3	0.3	3	0.3	2	0.2	14	1.8	3	0.4	3	0.4	11	1.4
Fluvoxamine	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0
Paroxetine	3	0.3	2	0.2	1	0.1	1	0.1	4	0.5	1	0.1	0	0.0	3	0.4
Sertraline	9	0.9	3	0.3	2	0.2	5	0.5	11	1.4	5	0.6	6	0.8	5	0.6
Drug Not Specified	24	2.5	20	2.1	17	1.8	0	0.0	21	2.6	19	2.4	14	1.8	0	0.0
<b>Total</b>	<b>69</b>	<b>7.2</b>	<b>39</b>	<b>4.0</b>	<b>35</b>	<b>3.6</b>	<b>24</b>	<b>2.5</b>	<b>64</b>	<b>8.1</b>	<b>36</b>	<b>4.5</b>	<b>33</b>	<b>4.2</b>	<b>28</b>	<b>3.5</b>
<b>St John's Wort</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>1</b>	<b>0.1</b>	<b>0</b>	<b>0.0</b>	<b>1</b>	<b>0.1</b>	<b>0</b>	<b>0.0</b>
<b>Other antidepressants</b>																
Duloxetine	2	0.2	2	0.2	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0
Mirtazapine	16	1.7	7	0.7	12	1.2	3	0.3	8	1.0	5	0.6	3	0.4	2	0.3
Trazodone	0	0.0	0	0.0	0	0.0	0	0.0	3	0.4	1	0.1	1	0.1	2	0.3
Venlafaxine	5	0.5	1	0.1	1	0.1	4	0.4	2	0.3	2	0.3	2	0.3	0	0.0
Drug Not Specified	19	2.0	14	1.5	14	1.5	0	0.0	17	2.1	16	2.0	11	1.4	0	0.0
<b>Total</b>	<b>40</b>	<b>4.1</b>	<b>24</b>	<b>2.5</b>	<b>26</b>	<b>2.7</b>	<b>7</b>	<b>0.7</b>	<b>30</b>	<b>3.8</b>	<b>25</b>	<b>3.1</b>	<b>18</b>	<b>2.3</b>	<b>4</b>	<b>0.5</b>
<b>Female hormone products</b>																
<b>Oestrogen and/or progestogen</b>	<b>6</b>	<b>0.6</b>	<b>4</b>	<b>0.4</b>	<b>4</b>	<b>0.4</b>	<b>2</b>	<b>0.2</b>	<b>4</b>	<b>0.5</b>	<b>3</b>	<b>0.4</b>	<b>1</b>	<b>0.1</b>	<b>1</b>	<b>0.1</b>
<b>HRT</b>	<b>3</b>	<b>0.3</b>	<b>3</b>	<b>0.3</b>	<b>1</b>	<b>0.1</b>	<b>0</b>	<b>0.0</b>	<b>7</b>	<b>0.9</b>	<b>6</b>	<b>0.8</b>	<b>4</b>	<b>0.5</b>	<b>1</b>	<b>0.1</b>
<b>Other female hormones</b>	<b>5</b>	<b>0.5</b>	<b>5</b>	<b>0.5</b>	<b>5</b>	<b>0.5</b>	<b>0</b>	<b>0.0</b>	<b>6</b>	<b>0.8</b>	<b>3</b>	<b>0.4</b>	<b>3</b>	<b>0.4</b>	<b>2</b>	<b>0.3</b>

**Appendix 9b. Other Medication History - DVT/PE**

Drug (drug class)	Rivaroxaban								Warfarin							
	Any use		Prior		During		Period Unknown		Any use		Prior		During		Period Unknown	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<b>Analgesics and Anti-inflammatory Agents</b>																
Paracetamol	632	41.3	519	33.9	515	33.6	2	0.1	532	43.9	415	34.2	469	38.7	2	0.2
Aspirin (>300mg)	77	5.0	58	3.8	39	2.5	4	0.3	65	5.4	56	4.6	21	1.7	4	0.3
NSAID																
Celecoxib	1	0.1	0	0.0	0	0.0	1	0.1	3	0.2	1	0.1	1	0.1	1	0.1
Chondroitin	2	0.1	0	0.0	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Dexketoprofen	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Diclofenac	18	1.2	12	0.8	9	0.6	5	0.3	22	1.8	13	1.1	7	0.6	77	6.4
Etodolac	2	0.1	2	0.1	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Etoricoxib	1	0.1	1	0.1	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1
Glucosamine	14	0.9	0	0.0	0	0.0	14	0.9	5	0.4	0	0.0	0	0.0	5	0.4
Ibuprofen	85	5.5	58	3.8	45	2.9	13	0.8	78	6.4	50	4.1	35	2.9	14	1.2
Indomethacin	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ketoprofen	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0
Ketorolac Trometamol	2	0.1	0	0.0	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Mefenamic Acid	0	0.0	0	0.0	0	0.0	0	0.0	2	0.2	1	0.1	1	0.1	1	0.1
Meloxicam	7	0.5	1	0.1	2	0.1	5	0.3	1	0.1	1	0.1	0	0.0	0	0.0
Naproxen	37	2.4	28	1.8	19	1.2	4	0.3	33	2.7	25	2.1	14	1.2	5	0.4
Parecoxib	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1
Piroxicam	7	0.5	4	0.3	5	0.3	2	0.1	3	0.2	1	0.1	2	0.2	1	0.1
Topical Products For Joint And Muscular	14	0.9	8	0.5	6	0.4	4	0.3	10	0.8	5	0.4	3	0.2	4	0.3
Drug Not Specified	65	4.2	54	3.5	35	2.3	0	0.0	41	3.4	30	2.5	21	1.7	0	0.0
<b>Total</b>	<b>233</b>	<b>15.2</b>	<b>158</b>	<b>10.3</b>	<b>111</b>	<b>7.2</b>	<b>48</b>	<b>3.1</b>	<b>179</b>	<b>14.8</b>	<b>116</b>	<b>9.6</b>	<b>78</b>	<b>6.4</b>	<b>36</b>	<b>3.0</b>
<b>Other Analgesics/Antiinflammatories</b>																
Analgesics	455	29.7	326	21.3	313	20.4	57	3.7	421	34.7	289	23.8	313	25.8	40	3.3
Anesthetics	5	0.3	3	0.2	2	0.1	1	0.1	8	0.7	3	0.2	3	0.2	3	0.2
Antidiarrheals, Intestinal Antiinflammatories	16	1.0	1	0.1	1	0.1	15	1.0	17	1.4	5	0.4	4	0.3	11	0.9
Antigout Preparations	6	0.4	0	0.0	0	0.0	6	0.4	5	0.4	0	0.0	1	0.1	4	0.3
Antiprotozoals	8	0.5	1	0.1	0	0.0	7	0.5	4	0.3	0	0.0	0	0.0	4	0.3
Corticosteroids For Systemic Use	125	8.2	15	1.0	13	0.8	108	7.0	102	8.4	17	1.4	18	1.5	82	6.8
Corticosteroids, Dermatological Preparations	1	0.1	1	0.1	1	0.1	0	0.0	2	0.2	1	0.1	2	0.2	0	0.0
Drugs For Obstructive Airway Diseases	3	0.2	3	0.2	2	0.1	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0
Immunosuppressive Agents	25	1.6	1	0.1	1	0.1	24	1.6	24	2.0	3	0.2	3	0.2	21	1.7
Nasal Preparations	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Topical Products For Joint And Muscular Pain	2	0.1	1	0.1	1	0.1	1	0.1	3	0.2	0	0.0	0	0.0	3	0.2
Drug Not Specified	41	2.7	33	2.2	28	1.8	0	0.0	35	2.9	33	2.7	23	1.9	0	0.0



**Appendix 9b. Other Medication History - DVT/PE**

Drug (drug class)	Total	Rivaroxaban							Warfarin								
		584	38.1	373	24.3	353	23.0	194	12.7	506	41.7	335	27.6	346	28.5	143	11.8
Anticonvulsants																	
Phenytoin	3	0.2	3	0.2	3	0.2	0	0.0	12	1.0	12	1.0	11	0.9	0	0.0	
Phenobarbitone	2	0.1	2	0.1	2	0.1	0	0.0	2	0.2	0	0.0	0	0.0	2	0.2	
Carbamazepine	8	0.5	7	0.5	6	0.4	1	0.1	12	1.0	10	0.8	9	0.7	2	0.2	
Primidone	1	0.1	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1	
Other anticonvulsants																	
Clonazepam	4	0.3	2	0.1	1	0.1	2	0.1	2	0.2	2	0.2	2	0.2	0	0.0	
Gabapentin	38	2.5	7	0.5	5	0.3	31	2.0	44	3.6	10	0.8	11	0.9	33	2.7	
Lamotrigine	5	0.3	4	0.3	3	0.2	0	0.0	5	0.4	3	0.2	3	0.2	2	0.2	
Levetiracetam	5	0.3	4	0.3	3	0.2	1	0.1	7	0.6	6	0.5	4	0.3	1	0.1	
Pregabalin	37	2.4	15	1.0	13	0.8	22	1.4	24	2.0	5	0.4	3	0.2	19	1.6	
Sodium Valproate	6	0.4	4	0.3	4	0.3	1	0.1	9	0.7	8	0.7	5	0.4	1	0.1	
Topiramate	3	0.2	1	0.1	1	0.1	2	0.1	3	0.2	1	0.1	1	0.1	2	0.2	
Drug Not Specified	4	0.3	3	0.2	3	0.2	0	0.0	4	0.3	3	0.2	3	0.2	0	0.0	
Total	95	6.2	38	2.5	32	2.1	58	3.8	89	7.3	34	2.8	28	2.3	57	4.7	
Anti-infectives																	
Ketoconazole	2	0.1	1	0.1	1	0.1	0	0.0	2	0.2	0	0.0	1	0.1	1	0.1	
Itraconazole	1	0.1	1	0.1	1	0.1	0	0.0	3	0.2	1	0.1	3	0.2	0	0.0	
Posaconazole	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0	
Ritonavir	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0	
Clarithromycin	77	5.0	45	2.9	48	3.1	4	0.3	73	6.0	42	3.5	42	3.5	2	0.2	
Erythromycin	5	0.3	3	0.2	3	0.2	0	0.0	10	0.8	6	0.5	5	0.4	1	0.1	
Rifampicin	1	0.1	1	0.1	1	0.1	0	0.0	3	0.2	0	0.0	2	0.2	1	0.1	
Sulfamethoxazole	4	0.3	1	0.1	1	0.1	3	0.2	7	0.6	0	0.0	1	0.1	6	0.5	
Metronidazole	28	1.8	11	0.7	20	1.3	4	0.3	21	1.7	10	0.8	12	1.0	3	0.2	
Griseofulvin	3	0.2	1	0.1	2	0.1	0	0.0	2	0.2	1	0.1	1	0.1	0	0.0	
Other antiinfectives																	
Antibacterials For Systemic Use	385	25.1	241	15.7	259	16.9	30	2.0	340	28.1	189	15.6	215	17.7	43	3.5	
Antifungals For Dermatological Use	2	0.1	2	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
Antimycobacterials	10	0.7	0	0.0	0	0.0	0	0.0	2	0.2	1	0.1	1	0.1	1	0.1	
Antimycotics For Systemic Use	0	0.0	4	0.3	5	0.3	3	0.2	6	0.5	3	0.2	3	0.2	2	0.2	
Antiprotozoals	2	0.1	0	0.0	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	
Antivirals For Systemic Use	9	0.6	1	0.1	1	0.1	7	0.5	9	0.7	3	0.2	3	0.2	5	0.4	
Unspecified anti-infectives	7	0.5	7	0.5	3	0.2	0	0.0	2	0.2	1	0.1	1	0.1	0	0.0	
Drug Not Specified	9	0.6	7	0.5	5	0.3	0	0.0	11	0.9	5	0.4	9	0.7	0	0.0	
Total	409	26.7	255	16.6	267	17.4	41	2.7	358	29.5	199	16.4	228	18.8	50	4.1	
Antidepressants																	

**Appendix 9b. Other Medication History - DVT/PE**

Drug (drug class)	Rivaroxaban								Warfarin							
<b>Tricyclics</b>																
Amitriptyline	47	3.1	31	2.0	31	2.0	14	0.9	32	2.6	18	1.5	16	1.3	13	1.1
Clomipramine	0	0.0	0	0.0	0	0.0	0	0.0	2	0.2	1	0.1	1	0.1	1	0.1
Dothiepin	2	0.1	0	0.0	0	0.0	2	0.1	2	0.2	1	0.1	1	0.1	1	0.1
Doxepin	1	0.1	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	1	0.1	0	0.0
Imipramine Hydrochl	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Lofepramine	0	0.0	0	0.0	0	0.0	0	0.0	2	0.2	2	0.2	2	0.2	0	0.0
Nortriptyline	1	0.1	1	0.1	0	0.0	0	0.0	3	0.2	1	0.1	1	0.1	2	0.2
Trimipramine	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Drug Not Specified	46	3.0	39	2.5	35	2.3	0	0.0	30	2.5	25	2.1	28	2.3	0	0.0
<b>Total</b>	<b>96</b>	<b>6.3</b>	<b>74</b>	<b>4.8</b>	<b>68</b>	<b>4.4</b>	<b>17</b>	<b>1.1</b>	<b>69</b>	<b>5.7</b>	<b>49</b>	<b>4.0</b>	<b>50</b>	<b>4.1</b>	<b>17</b>	<b>1.4</b>
<b>MAOI (drug not specified)</b>	<b>4</b>	<b>0.3</b>	<b>4</b>	<b>0.3</b>	<b>3</b>	<b>0.2</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>
<b>SSRI</b>																
Citalopram	38	2.5	22	1.4	22	1.4	14	0.9	36	3.0	20	1.7	17	1.4	13	1.1
Escitalopran	2	0.1	2	0.1	2	0.1	0	0.0	2	0.2	1	0.1	1	0.1	1	0.1
Fluoxetine	30	2.0	21	1.4	20	1.3	8	0.5	20	1.7	10	0.8	10	0.8	9	0.7
Fluvoxamine	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Paroxetine	4	0.3	3	0.2	4	0.3	0	0.0	3	0.2	2	0.2	1	0.1	1	0.1
Sertraline	28	1.8	11	0.7	14	0.9	13	0.8	23	1.9	16	1.3	14	1.2	7	0.6
Drug Not Specified	26	1.7	25	1.6	22	1.4	0	0.0	23	1.9	22	0.0	17	0.0	0	0.0
<b>Total</b>	<b>123</b>	<b>8.0</b>	<b>83</b>	<b>5.4</b>	<b>82</b>	<b>5.4</b>	<b>36</b>	<b>2.3</b>	<b>106</b>	<b>8.7</b>	<b>71</b>	<b>5.9</b>	<b>60</b>	<b>5.0</b>	<b>30</b>	<b>2.5</b>
<b>St John's Wort</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>
<b>Other antidepressants</b>																
Duloxetine	5	0.3	2	0.1	1	0.1	3	0.2	5	0.4	2	1.7	2	0.2	3	0.2
Lithium	1	0.1	1	0.1	1	0.1	0	0.0	1	0.1	1	0.8	1	0.1	0	0.0
Mirtazapine	34	2.2	25	1.6	22	1.4	8	0.5	23	1.9	16	13.2	16	1.3	5	0.4
Trazodone	2	0.1	1	0.1	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1
Venlafaxine	11	0.7	10	0.7	8	0.5	1	0.1	9	0.7	8	6.6	8	0.7	0	0.0
Drug Not Specified	33	2.2	31	2.0	23	1.5	0	0.0	32	2.6	28	23.1	23	1.9	0	0.0
<b>Total</b>	<b>82</b>	<b>5.4</b>	<b>67</b>	<b>4.4</b>	<b>53</b>	<b>3.5</b>	<b>13</b>	<b>0.8</b>	<b>68</b>	<b>5.6</b>	<b>54</b>	<b>4.5</b>	<b>50</b>	<b>4.1</b>	<b>9</b>	<b>0.7</b>
<b>Female hormone products</b>																
<b>Oestrogen and/or progestogen</b>	<b>55</b>	<b>3.6</b>	<b>26</b>	<b>1.7</b>	<b>23</b>	<b>1.5</b>	<b>22</b>	<b>1.4</b>	<b>51</b>	<b>4.2</b>	<b>37</b>	<b>3.1</b>	<b>24</b>	<b>2.0</b>	<b>11</b>	<b>0.9</b>
<b>HRT</b>	<b>13</b>	<b>0.8</b>	<b>13</b>	<b>0.8</b>	<b>6</b>	<b>0.4</b>	<b>0</b>	<b>0.0</b>	<b>21</b>	<b>1.7</b>	<b>20</b>	<b>1.7</b>	<b>12</b>	<b>1.0</b>	<b>1</b>	<b>0.1</b>
<b>Other female hormones</b>	<b>18</b>	<b>1.2</b>	<b>15</b>	<b>1.0</b>	<b>11</b>	<b>0.7</b>	<b>1</b>	<b>0.1</b>	<b>19</b>	<b>1.6</b>	<b>11</b>	<b>0.9</b>	<b>10</b>	<b>0.8</b>	<b>7</b>	<b>0.6</b>

# Appendix 9c. Other Medication History - Mixed

Drug (drug class)	Rivaroxaban								Warfarin							
	Any use		Prior		During		Period Unknown		Any use		Prior		During		Period Unknown	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<b>Analgesics and Anti-inflammatory Agents</b>																
Paracetamol	9	39.1	8	34.8	7	30.4	0	0.0	18	66.7	14	51.9	14	51.9	0	0.0
Aspirin (>300mg)	2	8.7	2	8.7	0	0.0	0	0.0	5	18.5	5	18.5	0	0.0	0	0.0
NSAID																
Ibuprofen	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	0	0.0	0	0.0	1	3.7
Drug Not Specified	0	0.0	0	0.0	0	0.0	0	0.0	2	7.4	2	7.4	0	0.0	0	0.0
<b>Total</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>3</b>	<b>11.1</b>	<b>2</b>	<b>7.4</b>	<b>0</b>	<b>0.0</b>	<b>1</b>	<b>3.7</b>
<b>Other Analgesics/Antiinflammatories</b>																
Analgesics	4	17.4	2	8.7	2	8.7	1	4.3	9	33.3	4	14.8	5	18.5	3	11.1
Antigout Preparations	0	0.0	0	0.0	0	0.0	0	0.0	2	7.4	0	0.0	0	0.0	2	7.4
Corticosteroids For Systemic Use	2	8.7	1	4.3	1	4.3	1	4.3	2	7.4	1	3.7	1	3.7	1	3.7
Drug Not Specified	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	0	0.0	1	3.7	0	0.0
<b>Total</b>	<b>6</b>	<b>26.1</b>	<b>3</b>	<b>13.0</b>	<b>3</b>	<b>13.0</b>	<b>2</b>	<b>8.7</b>	<b>11</b>	<b>40.7</b>	<b>4</b>	<b>14.8</b>	<b>6</b>	<b>22.2</b>	<b>5</b>	<b>18.5</b>
<b>Anticonvulsants</b>																
Phenytoin	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Phenobarbitone	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Carbamazepine	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	1	3.7	1	3.7	0	0.0
Primidone	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<b>Other anticonvulsants</b>																
Gabapentin	0	0.0	0	0.0	0	0.0	0	0.0	2	7.4	0	0.0	0	0.0	2	7.4
Pregabalin	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	0	0.0	0	0.0	1	3.7
Sodium Valproate	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	0	0.0	0	0.0	1	3.7
<b>Total</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>4</b>	<b>14.8</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>4</b>	<b>14.8</b>
<b>Anti-infectives</b>																
Ketoconazole	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Itraconazole	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Posaconazole	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ritonavir	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Clarithromycin	1	4.3	1	4.3	0	0.0	0	0.0	3	11.1	1	3.7	3	11.1	0	0.0
Erythromycin	1	4.3	0	0.0	1	4.3	0	0.0	1	3.7	0	0.0	1	3.7	0	0.0
Rifampicin	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	0	0.0	1	3.7	0	0.0
Sulfamethoxazole	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	0	0.0	1	3.7	0	0.0
Metronidazole	1	4.3	0	0.0	1	4.3	0	0.0	4	14.8	1	3.7	3	11.1	0	0.0
Griseofulvin	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	0	0.0	1	3.7	0	0.0
<b>Other antiinfectives</b>																
Antibacterials For Systemic Use	4	17.4	2	8.7	2	8.7	0	0.0	11	40.7	5	18.5	8	29.6	2	7.4

**Appendix 9c. Other Medication History - Mixed**

Drug (drug class)	Rivaroxaban								Warfarin								
	Total	4	17.4	2	8.7	2	8.7	0	0.0	11	40.7	5	18.5	8	29.6	2	7.4
Antidepressants																	
Tricyclics																	
Dothiepin	0	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	1	3.7	1	3.7	0	0.0
Drug Not Specified	0	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	1	3.7	1	3.7	0	0.0
Total	0	0	0.0	0	0.0	0	0.0	0	0.0	2	7.4	2	7.4	2	7.4	0	0.0
MAOI (drug not specified)	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
SSRI																	
Citalopram	0	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	0	0.0	1	3.7	0	0.0
Escitalopran	1	4.3	1	4.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0.0
Fluoxetine	1	4.3	0	0.0	0	0.0	1	4.3	0	0.0	0	0.0	0	0.0	0	0.0	0.0
Paroxetine	0	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	0	0.0	0	0.0	1	3.7
Drug Not Specified	0	0	0.0	0	0.0	0	0.0	0	0.0	2	7.4	2	7.4	1	3.7	0	0.0
Total	2	8.7	1	4.3	0	0.0	1	4.3	4	14.8	2	7.4	2	7.4	1	3.7	3.7
St John's Wort	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other antidepressants																	
Mirtazepine	0	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	1	3.7	1	3.7	0	0.0
Drug Not Specified	1	4.3	1	4.3	1	4.3	0	0.0	1	3.7	1	3.7	1	3.7	0	0.0	0.0
Total	1	4.3	1	4.3	1	4.3	0	0.0	2	7.4	2	7.4	2	7.4	0	0.0	0.0
Female hormone products																	
Oestrogen and/or progestogen	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
HRT	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other female hormones	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

**Appendix 9d. Other Medication History - Other**

Drug (drug class)	Rivaroxaban								Warfarin							
	Any use		Prior		During		Period Unknown		Any use		Prior		During		Period Unknown	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<b>Analgesics and Anti-inflammatory Agents</b>																
Paracetamol	9	40.9	8	36.4	8	36.4	0	0.0	17	50.0	14	41.2	10	29.4	0	0.0
Aspirin (>300mg)	5	22.7	5	22.7	1	4.5	0	0.0	4	11.8	3	8.8	2	5.9	0	0.0
NSAID																
Celecoxib	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	2.9	1	2.9	0	0.0
Naproxen	1	4.5	1	4.5	1	4.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Parecoxib	1	4.5	0	0.0	0	0.0	1	4.5	0	0.0	0	0.0	0	0.0	0	0.0
Drug Not Specified	3	9.1	3	13.6	1	4.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<b>Total</b>	<b>4</b>	<b>18.2</b>	<b>4</b>	<b>18.2</b>	<b>2</b>	<b>9.1</b>	<b>1</b>	<b>4.5</b>	<b>1</b>	<b>2.9</b>	<b>1</b>	<b>2.9</b>	<b>1</b>	<b>2.9</b>	<b>0</b>	<b>0.0</b>
<b>Other Analgesics/Anti-inflammatories</b>																
Analgesics	7	31.8	5	22.7	3	13.6	2	9.1	9	26.5	7	20.6	4	11.8	1	2.9
Anesthetics	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	2.9	0	0.0	0	0.0
Antidiarrheals, Intestinal Anti-inflammatories	0	0.0	0	0.0	0	0.0	0	0.0	2	5.9	0	0.0	0	0.0	2	5.9
Antiprotozoals	1	0.0	0	0.0	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Corticosteroids For Systemic Use	2	9.1	1	4.5	1	4.5	1	4.5	2	5.9	0	0.0	0	0.0	2	5.9
Corticosteroids, Dermatological Preparations	1	4.5	1	4.5	1	4.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<b>Total</b>	<b>9</b>	<b>40.9</b>	<b>6</b>	<b>27.3</b>	<b>4</b>	<b>18.2</b>	<b>3</b>	<b>13.6</b>	<b>11</b>	<b>32.4</b>	<b>7</b>	<b>20.6</b>	<b>4</b>	<b>11.8</b>	<b>4</b>	<b>11.8</b>
<b>Anticonvulsants</b>																
Phenytoin	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Phenobarbitone	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Carbamazepine	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Primidone	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<b>Other anticonvulsants</b>																
Gabapentin	1	4.5	1	4.5	1	4.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Lamotrigine	1	4.5	1	4.5	1	4.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Levetiracetam	0	0.0	0	0.0	0	0.0	0	0.0	2	5.9	2	5.9	1	2.9	0	0.0
Sodium Valproate	1	4.5	1	4.5	1	4.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<b>Total</b>	<b>2</b>	<b>9.1</b>	<b>2</b>	<b>9.1</b>	<b>2</b>	<b>9.1</b>	<b>0</b>	<b>0.0</b>	<b>2</b>	<b>5.9</b>	<b>2</b>	<b>5.9</b>	<b>1</b>	<b>2.9</b>	<b>0</b>	<b>0.0</b>
<b>Anti-infectives</b>																
Ketoconazole	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Itraconazole	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Posaconazole	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ritonavir	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Clarithromycin	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Erythromycin	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Rifampicin	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

**Appendix 9d. Other Medication History - Other**

Drug (drug class)	Rivaroxaban								Warfarin							
	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sulfamethoxazole	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Metronidazole	0	0.0	0	0.0	0	0.0	0	0.0	2	5.9	0	0.0	0	0.0	0	0.0
Griseofulvin	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other antiinfectives																
Antibacterials For Systemic Use	5	22.7	4	18.2	2	9.1	1	4.5	8	23.5	7	20.6	6	17.6	0	0.0
Antiprotozoals	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	2.9	1	2.9	0	0.0
Drug Not Specified	1	4.5	0	0.0	1	4.5	0	0.0	1	2.9	1	2.9	0	0.0	0	0.0
<b>Total</b>	<b>6</b>	<b>27.3</b>	<b>4</b>	<b>18.2</b>	<b>3</b>	<b>13.6</b>	<b>1</b>	<b>4.5</b>	<b>9</b>	<b>26.5</b>	<b>8</b>	<b>23.5</b>	<b>6</b>	<b>17.6</b>	<b>0</b>	<b>0.0</b>
Antidepressants																
Tricyclics																
Amitriptyline	1	4.5	0	0.0	0	0.0	1	4.5	1	2.9	1	2.9	1	2.9	0	0.0
Nortriptyline	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	1	2.9
<b>Total</b>	<b>1</b>	<b>4.5</b>	<b>0</b>	<b>0.0</b>	<b>0</b>	<b>0.0</b>	<b>1</b>	<b>4.5</b>	<b>2</b>	<b>5.9</b>	<b>1</b>	<b>2.9</b>	<b>1</b>	<b>2.9</b>	<b>1</b>	<b>2.9</b>
MAOI (drug not specified)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
SSRI																
Escitalopram	1	4.5	0	0.0	0	0.0	1	4.5	0	0.0	0	0.0	0	0.0	0	0.0
Paroxetine	1	4.5	0	0.0	0	0.0	1	4.5	0	0.0	0	0.0	0	0.0	0	0.0
Sertraline	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	2.9	1	2.9	0	0.0
Drug Not Specified	2	4.5	2	9.1	1	4.5	0	0.0	1	2.9	0	0.0	1	2.9	0	0.0
<b>Total</b>	<b>3</b>	<b>13.6</b>	<b>2</b>	<b>9.1</b>	<b>1</b>	<b>4.5</b>	<b>2</b>	<b>9.1</b>	<b>2</b>	<b>5.9</b>	<b>1</b>	<b>2.9</b>	<b>2</b>	<b>5.9</b>	<b>0</b>	<b>0.0</b>
St John's Wort	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other antidepressants																
Mirtazepine	1	4.5	1	4.5	1	4.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Drug Not Specified	0	0.0	0	0.0	0	0.0	0	0.0	2	5.9	2	5.9	2	5.9	0	0.0
<b>Total</b>	<b>1</b>	<b>4.5</b>	<b>1</b>	<b>4.5</b>	<b>1</b>	<b>4.5</b>	<b>0</b>	<b>0.0</b>	<b>2</b>	<b>5.9</b>	<b>2</b>	<b>5.9</b>	<b>2</b>	<b>5.9</b>	<b>0</b>	<b>0.0</b>
Female hormone products																
Oestrogen and/or progestogen	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
HRT	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	2.9	1	2.9	0	0.0
Other female hormones	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	1	2.9	1	2.9	0	0.0

**Appendix 9e. Other Medication Use - All Indications**

Organ System	Drug Class (Period of Use Unknown)	AF				DVT/PE				Mixed				Other			
		Rivaroxaban (N=965)		Warfarin (N=794)		Rivaroxaban (N=1532)		Warfarin (N=1212)		Rivaroxaban (N=23)		Warfarin (N=27)		Rivaroxaban (N=22)		Warfarin (N=34)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Alimentary Tract And Metabolism	Alimentary system medication not otherwise specified	0	0.0	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Stomatological Preparations	1	0.1	2	0.3	0	0.0	4	0.3	0	0.0	0	0.0	0	0.0	0	0.0
	Drugs For Acid Related Disorders	246	25.5	268	33.8	429	28.0	379	31.3	10	43.5	13	48.1	10	45.5	11	32.4
	Drugs For Functional Gastrointestinal Disorders	20	2.1	25	3.1	60	3.9	48	4.0	1	4.3	2	7.4	1	4.5	2	5.9
	Antiemetics And Antinauseants	7	0.7	6	0.8	27	1.8	34	2.8	1	4.3	2	7.4	2	9.1	4	11.8
	Bile And Liver Therapy	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Laxatives	91	9.4	81	10.2	156	10.2	142	11.7	5	21.7	6	22.2	2	9.1	4	11.8
	Antidiarrheals, Intestinal Antiinflammatory/Anti-infective Agents	18	1.9	13	1.6	32	2.1	25	2.1	0	0.0	3	11.1	0	0.0	0	0.0
	Antiobesity Preparations, Excl. Diet Products	2	0.2	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
	Digestives, Incl. Enzymes	2	0.2	1	0.1	1	0.1	2	0.2	0	0.0	0	0.0	0	0.0	0	0.0
	Drugs Used In Diabetes	90	9.3	89	11.2	104	6.8	91	7.5	2	8.7	3	11.1	2	9.1	4	11.8
	Vitamins	32	3.3	41	5.2	67	4.4	63	5.2	3	13.0	2	7.4	4	18.2	2	5.9
	Mineral Supplements	102	10.6	78	9.8	133	8.7	107	8.8	2	8.7	4	14.8	0	0.0	5	14.7
Blood And Blood Forming Organs	Antithrombotic Agents	85	8.8	68	8.6	78	5.1	83	6.8	0	0.0	4	14.8	1	4.5	3	8.8
	Antihemorrhagics	4	0.4	7	0.9	6	0.4	21	1.7	0	0.0	1	3.7	0	0.0	0	0.0
	Antianemic Preparations	50	5.2	51	6.4	105	6.9	96	7.9	2	8.7	5	18.5	3	13.6	1	2.9
	Blood Substitutes And Perfusion Solutions	6	0.6	4	0.5	4	0.3	9	0.7	0	0.0	2	7.4	0	0.0	1	2.9
Cardiovascular System	Cardiac Therapy	187	19.4	198	24.9	85	5.5	73	6.0	8	34.8	8	29.6	2	9.1	6	17.6
	Antihypertensives	47	4.9	38	4.8	40	2.6	44	3.6	0	0.0	2	7.4	0	0.0	1	2.9
	Diuretics	212	22.0	245	30.9	208	13.6	176	14.5	8	34.8	12	44.4	2	9.1	9	26.5
	Peripheral Vasodilators	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
	Vasoprotectives	23	2.4	39	4.9	13	0.8	17	1.4	1	4.3	2	7.4	1	4.5	1	2.9
	Beta Blocking Agents	381	39.5	399	50.3	189	12.3	172	14.2	8	34.8	13	48.1	2	9.1	12	35.3
	Calcium Channel Blockers	180	18.7	152	19.1	174	11.4	145	12.0	4	17.4	7	25.9	4	18.2	5	14.7
	Agents Acting On The Renin-Angiotensin System	332	34.4	316	39.8	302	19.7	252	20.8	7	30.4	8	29.6	8	36.4	13	38.2
	Lipid Modifying Agents	388	40.2	348	43.8	305	19.9	276	22.8	8	34.8	11	40.7	6	27.3	13	38.2
Dermatologicals	Antifungals For Dermatological Use	12	1.2	9	1.1	11	0.7	12	1.0	0	0.0	0	0.0	0	0.0	0	0.0
	Emollients And Protectives	12	1.2	10	1.3	19	1.2	18	1.5	0	0.0	0	0.0	0	0.0	0	0.0
	Preparations For Treatment Of Wounds And Ulcers	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Antipruritics, Incl. Antihistamines, Anesthetics, Etc.	0	0.0	2	0.3	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
	Antipsoriatics	0	0.0	2	0.3	2	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
	Antibiotics And Chemotherapeutics For Dermatological Use	4	0.4	3	0.4	7	0.5	3	0.2	0	0.0	0	0.0	0	0.0	0	0.0
	Corticosteroids, Dermatological Preparations	5	0.5	10	1.3	15	1.0	19	1.6	0	0.0	1	3.7	0	0.0	1	2.9
	Antiseptics And Disinfectants	5	0.5	5	0.6	6	0.4	4	0.3	1	4.3	0	0.0	0	0.0	0	0.0
	Medicated Dressings	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Other Dermatological Preparations	3	0.3	0	0.0	3	0.2	2	0.2	0	0.0	0	0.0	0	0.0	0	0.0
Genito Urinary System And Sex Hormones	Other Gynecologicals	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
	Sex Hormones And Modulators Of The Genital System	2	0.2	1	0.1	5	0.3	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0

**Appendix 9e. Other Medication Use - All Indications**

Organ System	Drug Class (Period of Use Unknown)	AF				DVT/PE				Mixed				Other			
		Rivaroxaban (N=965)		Warfarin (N=794)		Rivaroxaban (N=1532)		Warfarin (N=1212)		Rivaroxaban (N=23)		Warfarin (N=27)		Rivaroxaban (N=22)		Warfarin (N=34)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Urologicals	70	7.3	64	8.1	100	6.5	63	5.2	1	4.3	5	18.5	3	13.6	1	2.9
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Pituitary And Hypothalamic Hormones And Analogues	0	0.0	1	0.1	3	0.2	2	0.2	0	0.0	0	0.0	0	0.0	0	0.0
	Corticosteroids For Systemic Use	0	0.0	1	0.1	7	0.5	4	0.3	0	0.0	0	0.0	0	0.0	0	0.0
	Thyroid Therapy	63	6.5	43	5.4	78	5.1	75	6.2	2	8.7	1	3.7	1	4.5	3	8.8
	Calcium Homeostasis	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0	1	3.7	0	0.0	0	0.0
Antiinfectives For Systemic Use	Antibacterials For Systemic Use	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Immune Sera And Immunoglobulins	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
	Vaccines	4	0.4	3	0.4	4	0.3	6	0.5	0	0.0	0	0.0	0	0.0	0	0.0
Antineoplastic And Immunomodulating Agents	Antineoplastic Agents	3	0.3	3	0.4	17	1.1	6	0.5	0	0.0	0	0.0	1	4.5	2	5.9
	Endocrine Therapy	14	1.5	8	1.0	29	1.9	18	1.5	1	4.3	0	0.0	0	0.0	2	5.9
	Immunostimulants	0	0.0	1	0.1	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Immunosuppressive Agents	6	0.6	4	0.5	15	1.0	23	1.9	0	0.0	2	7.4	1	4.5	0	0.0
Musculo-Skeletal System	Topical Products For Joint And Muscular Pain	0	0.0	0	0.0	0	0.0	2	0.2	0	0.0	0	0.0	0	0.0	0	0.0
	Muscle Relaxants	3	0.3	2	0.3	12	0.8	3	0.2	0	0.0	0	0.0	1	4.5	0	0.0
	Antigout Preparations	25	2.6	25	3.1	28	1.8	29	2.4	0	0.0	2	7.4	1	4.5	2	5.9
	Drugs For Treatment Of Bone Diseases	31	3.2	38	4.8	74	4.8	47	3.9	1	4.3	0	0.0	1	4.5	2	5.9
	Other Drugs For Disorders Of The Musculo-Skeletal System	16	1.7	10	1.3	28	1.8	28	2.3	0	0.0	0	0.0	0	0.0	2	5.9
Nervous System	Anesthetics	1	0.1	2	0.3	3	0.2	6	0.5	0	0.0	0	0.0	1	4.5	0	0.0
	Antiepileptics	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Anti-Parkinson Drugs	5	0.5	5	0.6	15	1.0	8	0.7	0	0.0	1	3.7	0	0.0	0	0.0
	Psycholeptics	46	4.8	53	6.7	109	7.1	88	7.3	1	4.3	3	11.1	4	18.2	2	5.9
	Psychoanaleptics	5	0.5	2	0.3	5	0.3	3	0.2	0	0.0	1	3.7	0	0.0	0	0.0
	Other Nervous System Drugs	18	1.9	12	1.5	26	1.7	21	1.7	0	0.0	0	0.0	0	0.0	1	2.9
Antiparasitic Products, Insecticides And Repellents	Antiprotozoals	0	0.0	3	0.4	1	0.1	3	0.2	0	0.0	0	0.0	0	0.0	0	0.0
	Ectoparasiticides, Incl. Scabicides, Insecticides And Repellents	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Respiratory System	Nasal Preparations	8	0.8	3	0.4	13	0.8	14	1.2	0	0.0	0	0.0	0	0.0	0	0.0
	Drugs For Obstructive Airway Diseases	100	10.4	93	11.7	232	15.1	160	13.2	6	26.1	3	11.1	2	9.1	6	17.6
	Cough And Cold Preparations	14	1.5	12	1.5	40	2.6	18	1.5	1	4.3	0	0.0	1	4.5	1	2.9
	Antihistamines For Systemic Use	42	4.4	33	4.2	99	6.5	91	7.5	3	13.0	2	7.4	1	4.5	2	5.9
Sensory Organs	Ophthalmologicals	36	3.7	29	3.7	39	2.5	26	2.1	0	0.0	1	3.7	1	4.5	1	2.9
	Otologicals	2	0.2	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Ophthalmological And Otological Preparations	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Various	All Other Therapeutic Products	9	0.9	5	0.6	20	1.3	12	1.0	0	0.0	1	3.7	0	0.0	0	0.0
	General Nutrients	21	2.2	10	1.3	33	2.2	22	1.8	2	8.7	3	11.1	1	4.5	1	2.9
	Contrast Media	0	0.0	0	0.0	2	0.1	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Herbal/Food Supplement	Herbal/Food	16	1.7	17	2.1	31	2.0	12	1.0	1	4.3	0	0.0	0	0.0	0	0.0
Juices	Juices	1	0.1	0	0.0	10	0.7	2	0.2	0	0.0	0	0.0	0	0.0	0	0.0
OTC	OTC Medication	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other	Other	2	0.2	5	0.6	3	0.2	1	0.1	0	0.0	0	0.0	1	4.5	0	0.0
Not Specified	Not Specified	11	1.1	12	1.5	16	1.0	9	0.7	0	0.0	0	0.0	1	4.5	0	0.0



## Appendix 10a. Incidence Densities for Non-Target Tickbox Events

Treatment Group	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Abnormal liver function tests	11	2	1	2	3	1	0	20	2.4	0.5	0.2	0.5	0.8	0.3	0.8
rivaroxaban	Cardiac Arrhythmias	7	4	5	0	1	3	2	22	1.5	0.9	1.2	0.0	0.3	0.8	0.9
rivaroxaban	Breastfeeding	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Coronary artery bypass graft	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Congestive heart failure	5	2	3	2	5	0	0	17	1.1	0.5	0.7	0.5	1.3	0.0	0.7
rivaroxaban	Other coagulation disorder	1	0	1	0	1	0	2	5	0.2	0.0	0.2	0.0	0.3	0.0	0.2
rivaroxaban	COPD	3	1	2	1	0	0	0	7	0.6	0.2	0.5	0.3	0.0	0.0	0.3
rivaroxaban	Diabetes mellitus (Type I or II)	1	0	0	0	2	0	0	3	0.2	0.0	0.0	0.0	0.5	0.0	0.1
rivaroxaban	Other hospitalisation	36	24	13	15	13	15	9	125	7.7	5.5	3.2	3.8	3.5	4.2	5.1
rivaroxaban	Hypercholesterolaemia	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Hypertension	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Prolonged immobility	6	1	0	1	2	2	4	16	1.3	0.2	0.0	0.3	0.5	0.6	0.7
rivaroxaban	Liver disorder	2	2	1	2	0	0	1	8	0.4	0.5	0.2	0.5	0.0	0.0	0.3
rivaroxaban	Malignancies	4	1	3	3	2	1	1	15	0.9	0.2	0.7	0.8	0.5	0.3	0.6
rivaroxaban	Menorrhagia	2	2	2	2	0	0	0	8	0.4	0.5	0.5	0.5	0.0	0.0	0.3
rivaroxaban	Myocardial infarction	1	0	1	0	0	0	0	2	0.2	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Peripheral arterial disease	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Percutaneous coronary intervention	1	0	0	1	1	0	0	3	0.2	0.0	0.0	0.3	0.3	0.0	0.1
rivaroxaban	Pregnancies (within last 12 months)	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Implanted prosthetic heart valve	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Raised blood pressure	0	0	2	0	1	1	0	4	0.0	0.0	0.5	0.0	0.3	0.3	0.2
rivaroxaban	Renal impairment (Stage 1-2 CKD)	1	1	0	0	0	2	0	4	0.2	0.2	0.0	0.0	0.0	0.6	0.2
rivaroxaban	Renal impairment (Stage 3-4 CKD)	1	0	3	0	1	0	2	7	0.2	0.0	0.7	0.0	0.3	0.0	0.3
rivaroxaban	Renal failure (Stage 5 CKD)	1	0	0	1	0	0	1	3	0.2	0.0	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Other recent major surgery	4	0	1	2	1	0	1	9	0.9	0.0	0.2	0.5	0.3	0.0	0.4
rivaroxaban	Thrombocytopenia	0	0	0	2	0	0	0	2	0.0	0.0	0.0	0.5	0.0	0.0	0.1
rivaroxaban	Thrombophilia disorders	1	1	1	1	0	1	0	5	0.2	0.2	0.2	0.3	0.0	0.3	0.2
rivaroxaban	Transient ischaemic attack	0	2	1	0	0	0	1	4	0.0	0.5	0.2	0.0	0.0	0.0	0.2
warfarin	Abnormal liver function tests	14	4	4	2	2	1	1	28	3.6	1.1	1.2	0.6	0.7	0.3	1.4
warfarin	Cardiac Arrhythmias	3	1	7	3	3	2	0	19	0.8	0.3	2.1	0.9	1.0	0.7	1.0
warfarin	Breastfeeding	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Coronary artery bypass graft	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

## Appendix 10a. Incidence Densities for Non-Target Tickbox Events

Treatment Group	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	Congestive heart failure	4	0	3	3	2	0	2	14	1.0	0.0	0.9	0.9	0.7	0.0	0.7
warfarin	Other coagulation disorder	0	1	1	0	0	0	0	2	0.0	0.3	0.3	0.0	0.0	0.0	0.1
warfarin	COPD	1	0	1	0	1	0	1	4	0.3	0.0	0.3	0.0	0.3	0.0	0.2
warfarin	Diabetes mellitus (Type I or II)	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Other hospitalisation	23	20	24	17	16	12	7	119	6.0	5.7	7.2	5.3	5.2	4.1	6.0
warfarin	Hypercholesterolaemia	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Hypertension	0	1	0	0	1	0	1	3	0.0	0.3	0.0	0.0	0.3	0.0	0.2
warfarin	Prolonged immobility	4	4	1	1	0	2	1	13	1.0	1.1	0.3	0.3	0.0	0.7	0.7
warfarin	Liver disorder	0	0	0	2	1	0	0	3	0.0	0.0	0.0	0.6	0.3	0.0	0.2
warfarin	Malignancies	3	3	3	3	3	1	0	16	0.8	0.9	0.9	0.9	1.0	0.3	0.8
warfarin	Menorrhagia	0	0	2	0	1	0	1	4	0.0	0.0	0.6	0.0	0.3	0.0	0.2
warfarin	Myocardial infarction	2	1	1	1	0	0	0	5	0.5	0.3	0.3	0.3	0.0	0.0	0.3
warfarin	Peripheral arterial disease	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Percutaneous coronary intervention	2	1	2	1	1	0	0	7	0.5	0.3	0.6	0.3	0.3	0.0	0.4
warfarin	Pregnancies (within last 12 months)	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Implanted prosthetic heart valve	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Raised blood pressure	0	0	2	0	0	0	3	5	0.0	0.0	0.6	0.0	0.0	0.0	0.3
warfarin	Renal impairment (Stage 1-2 CKD)	1	0	0	2	2	0	0	5	0.3	0.0	0.0	0.6	0.7	0.0	0.3
warfarin	Renal impairment (Stage 3-4 CKD)	2	1	1	1	0	2	0	7	0.5	0.3	0.3	0.3	0.0	0.7	0.4
warfarin	Renal failure (Stage 5 CKD)	0	0	0	1	0	0	1	2	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Other recent major surgery	2	2	0	0	2	0	0	6	0.5	0.6	0.0	0.0	0.7	0.0	0.3
warfarin	Thrombocytopenia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Thrombophilia disorders	2	0	0	0	1	0	0	3	0.5	0.0	0.0	0.0	0.3	0.0	0.2
warfarin	Transient ischaemic attack	0	0	2	0	2	1	0	5	0.0	0.0	0.6	0.0	0.7	0.3	0.3

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Blood and lymphatic system disorders	Anaemia	1	1	1	0	0	0	0	3	0.2	0.2	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Blood and lymphatic system disorders	Aplastic anaemia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Blood and lymphatic system disorders	Iron deficiency anaemia	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Blood and lymphatic system disorders	Lymphadenopathy	0	0	1	2	0	0	0	3	0.0	0.0	0.2	0.5	0.0	0.0	0.1
rivaroxaban	Blood and lymphatic system disorders	Lymphadenopathy mediastinal	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Blood and lymphatic system disorders	Retroperitoneal lymphadenopathy	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Blood and lymphatic system disorders	Thrombocytopenia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Angina pectoris	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Bradycardia	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Cardiomegaly	1	0	1	0	0	0	0	2	0.2	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Cardiac disorders	Congestive cardiomyopathy	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Coronary artery disease	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Cyanosis	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Dilatation ventricular	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Intracardiac thrombus	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Mitral valve incompetence	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Mitral valve stenosis	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Myocardial ischaemia	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Palpitations	2	5	1	0	0	0	0	8	0.4	1.1	0.2	0.0	0.0	0.0	0.3
rivaroxaban	Cardiac disorders	Pericardial effusion	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Cardiac disorders	Tricuspid valve incompetence	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Congenital, familial and genetic disorders	Syringomyelia	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Ear and labyrinth disorders	Vertigo	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Endocrine disorders	Goitre	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Endocrine disorders	Hyperthyroidism	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Endocrine disorders	Thyroid cyst	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Eye disorders	Cataract	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Eye disorders	Conjunctivitis	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Eye disorders	Eye pain	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Eye disorders	Eye pruritus	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Eye disorders	Eye swelling	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Eye disorders	Ocular hyperaemia	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Eye disorders	Photopsia	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Eye disorders	Vision blurred	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Abdominal discomfort	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Abdominal pain	2	0	0	0	1	0	0	3	0.4	0.0	0.0	0.0	0.3	0.0	0.1
rivaroxaban	Gastrointestinal disorders	Abdominal pain upper	1	0	1	0	0	0	0	2	0.2	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Gastrointestinal disorders	Abnormal faeces	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Acquired oesophageal web	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Ascites	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Colitis	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Constipation	1	1	1	2	1	0	0	6	0.2	0.2	0.2	0.5	0.3	0.0	0.2
rivaroxaban	Gastrointestinal disorders	Crohn's disease	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Gastrointestinal disorders	Diarrhoea	0	1	2	1	3	3	0	10	0.0	0.2	0.5	0.3	0.8	0.8	0.4
rivaroxaban	Gastrointestinal disorders	Diverticulum	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Dyspepsia	1	0	0	1	1	0	0	3	0.2	0.0	0.0	0.3	0.3	0.0	0.1
rivaroxaban	Gastrointestinal disorders	Dysphagia	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Epigastric discomfort	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Faecal incontinence	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Faeces discoloured	3	0	0	0	0	0	0	3	0.6	0.0	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Gastrointestinal disorders	Gastric ulcer	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Gastritis	1	0	0	1	0	0	0	2	0.2	0.0	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Gastrointestinal disorders	Gastrointestinal disorder	0	0	0	1	1	0	0	2	0.0	0.0	0.0	0.3	0.3	0.0	0.1
rivaroxaban	Gastrointestinal disorders	Gastrooesophageal reflux disease	1	0	1	0	0	0	0	2	0.2	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Gastrointestinal disorders	Haemorrhoids	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Gastrointestinal disorders	Hiatus hernia	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Ileus paralytic	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Inguinal hernia	1	0	1	0	0	0	0	2	0.2	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Gastrointestinal disorders	Intestinal ischaemia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Intestinal mass	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Mallory-Weiss syndrome	0	2	0	0	0	0	0	2	0.0	0.5	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Gastrointestinal disorders	Nausea	2	2	1	1	3	2	0	11	0.4	0.5	0.2	0.3	0.8	0.6	0.4
rivaroxaban	Gastrointestinal disorders	Oesophageal achalasia	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Oesophageal dilatation	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Oesophagitis	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Pancreatic mass	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Pancreatitis	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Pancreatitis acute	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Retching	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Gastrointestinal disorders	Vomiting	3	1	0	0	1	3	0	8	0.6	0.2	0.0	0.0	0.3	0.8	0.3
rivaroxaban	General disorders and administration site conditions	Abdominal lymphadenopathy	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Adverse drug reaction	0	4	0	0	0	0	0	4	0.0	0.9	0.0	0.0	0.0	0.0	0.2
rivaroxaban	General disorders and administration site conditions	Adverse reaction	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Anticoagulant clinic	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Antidote	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Asthenia	0	2	1	0	1	0	0	4	0.0	0.5	0.2	0.0	0.3	0.0	0.2
rivaroxaban	General disorders and administration site conditions	CATHETERISE	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	General disorders and administration site conditions	COURSE COMPLETED	1	0	1	2	1	6	1	12	0.2	0.0	0.2	0.5	0.3	1.7	0.5
rivaroxaban	General disorders and administration site conditions	Changed regime R for stopping	0	0	1	0	0	1	0	2	0.0	0.0	0.2	0.0	0.0	0.3	0.1
rivaroxaban	General disorders and administration site conditions	Chest discomfort	0	0	0	1	0	0	1	2	0.0	0.0	0.0	0.3	0.0	0.0	0.1
rivaroxaban	General disorders and administration site conditions	Chest pain	1	4	4	0	3	0	1	13	0.2	0.9	1.0	0.0	0.8	0.0	0.5
rivaroxaban	General disorders and administration site conditions	Death	0	3	2	0	2	1	0	8	0.0	0.7	0.5	0.0	0.5	0.3	0.3
rivaroxaban	General disorders and administration site conditions	Diagnosis revised	1	1	0	0	0	0	0	2	0.2	0.2	0.0	0.0	0.0	0.0	0.1
rivaroxaban	General disorders and administration site conditions	Dispensing policy	0	11	0	0	0	0	0	11	0.0	2.5	0.0	0.0	0.0	0.0	0.4
rivaroxaban	General disorders and administration site conditions	Doctor decision	11	28	8	1	2	2	4	56	2.4	6.4	1.9	0.3	0.5	0.6	2.3
rivaroxaban	General disorders and administration site conditions	Dr Preference	1	1	0	0	0	0	0	2	0.2	0.2	0.0	0.0	0.0	0.0	0.1

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	General disorders and administration site conditions	Drug difficult to obtain	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Drug ineffective	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Drug interaction	0	0	0	1	0	0	1	2	0.0	0.0	0.0	0.3	0.0	0.0	0.1
rivaroxaban	General disorders and administration site conditions	Drug intolerance	1	1	0	1	1	0	0	4	0.2	0.2	0.0	0.3	0.3	0.0	0.2
rivaroxaban	General disorders and administration site conditions	Drug no longer required	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Drug re-started	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Drug regimen changed	0	4	0	0	0	0	1	5	0.0	0.9	0.0	0.0	0.0	0.0	0.2
rivaroxaban	General disorders and administration site conditions	Drug regulator advice or guidelines	0	1	0	0	0	0	2	3	0.0	0.2	0.0	0.0	0.0	0.0	0.1
rivaroxaban	General disorders and administration site conditions	End of course	1	1	0	1	1	5	0	9	0.2	0.2	0.0	0.3	0.3	1.4	0.4
rivaroxaban	General disorders and administration site conditions	Fatigue	0	2	1	1	2	1	0	7	0.0	0.5	0.2	0.3	0.5	0.3	0.3
rivaroxaban	General disorders and administration site conditions	Feeling hot	0	2	0	0	0	0	0	2	0.0	0.5	0.0	0.0	0.0	0.0	0.1
rivaroxaban	General disorders and administration site conditions	Found on floor	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	General physical health deterioration	2	1	1	0	0	1	0	5	0.4	0.2	0.2	0.0	0.0	0.3	0.2
rivaroxaban	General disorders and administration site conditions	HOSP REF	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Hernia	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Hospital advised	1	16	0	0	1	0	2	20	0.2	3.6	0.0	0.0	0.3	0.0	0.8
rivaroxaban	General disorders and administration site conditions	Hospital changed medication	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Hospital decision	4	3	0	0	0	0	0	7	0.9	0.7	0.0	0.0	0.0	0.0	0.3
rivaroxaban	General disorders and administration site conditions	Lifestyle issues	1	9	0	0	0	1	1	12	0.2	2.1	0.0	0.0	0.0	0.3	0.5
rivaroxaban	General disorders and administration site conditions	Local prescribing policy	2	43	2	0	0	0	4	51	0.4	9.8	0.5	0.0	0.0	0.0	2.1
rivaroxaban	General disorders and administration site conditions	Local protocol	1	47	1	0	1	0	2	52	0.2	10.7	0.2	0.0	0.3	0.0	2.1
rivaroxaban	General disorders and administration site conditions	Local swelling	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Malaise	3	1	0	2	1	1	0	8	0.6	0.2	0.0	0.5	0.3	0.3	0.3
rivaroxaban	General disorders and administration site conditions	Manufacturer advice or guidelines	5	6	0	0	0	0	1	12	1.1	1.4	0.0	0.0	0.0	0.0	0.5
rivaroxaban	General disorders and administration site conditions	Multi-organ failure	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	NICE guidelines	0	17	0	0	0	0	3	20	0.0	3.9	0.0	0.0	0.0	0.0	0.8
rivaroxaban	General disorders and administration site conditions	NOT SPECIFIED.	18	40	4	7	3	5	18	95	3.8	9.1	1.0	1.8	0.8	1.4	3.9
rivaroxaban	General disorders and administration site conditions	No further prescription given	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Nodule	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Non-cardiac chest pain	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Oedema	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Oedema peripheral	3	6	2	1	2	0	1	15	0.6	1.4	0.5	0.3	0.5	0.0	0.6
rivaroxaban	General disorders and administration site conditions	Only one prescription	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Pain	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Patient concerns with drug	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	General disorders and administration site conditions	Patient muddled about medication	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Pelvic mass	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Pelvis CT	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Performance status decreased	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	General disorders and administration site conditions	Pharmacist decision	0	2	0	0	0	0	0	2	0.0	0.5	0.0	0.0	0.0	0.0	0.1
rivaroxaban	General disorders and administration site conditions	Planned duration	0	1	0	0	0	1	0	2	0.0	0.2	0.0	0.0	0.0	0.3	0.1
rivaroxaban	General disorders and administration site conditions	Planned duration R for stopping	2	6	0	0	0	0	1	9	0.4	1.4	0.0	0.0	0.0	0.0	0.4
rivaroxaban	General disorders and administration site conditions	Policy change	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	General disorders and administration site conditions	Practice advice, formulary or guidelines	1	15	0	0	0	0	0	16	0.2	3.4	0.0	0.0	0.0	0.0	0.7
rivaroxaban	General disorders and administration site conditions	Practice policy	0	2	0	0	0	0	0	2	0.0	0.5	0.0	0.0	0.0	0.0	0.1
rivaroxaban	General disorders and administration site conditions	Practice protocol	0	2	1	0	0	0	1	4	0.0	0.5	0.2	0.0	0.0	0.0	0.2
rivaroxaban	General disorders and administration site conditions	Pre-existing condition improved	1	1	1	0	1	2	1	7	0.2	0.2	0.2	0.0	0.3	0.6	0.3
rivaroxaban	General disorders and administration site conditions	Prescribing advisor advice	2	6	1	0	0	0	0	9	0.4	1.4	0.2	0.0	0.0	0.0	0.4
rivaroxaban	General disorders and administration site conditions	Prescribing guidelines	20	387	5	7	0	2	32	453	4.3	88.3	1.2	1.8	0.0	0.6	18.5
rivaroxaban	General disorders and administration site conditions	Ran out of medication	1	0	0	0	1	0	0	2	0.2	0.0	0.0	0.0	0.3	0.0	0.1
rivaroxaban	General disorders and administration site conditions	Referred to specialist	2	2	1	2	1	2	2	12	0.4	0.5	0.2	0.5	0.3	0.6	0.5
rivaroxaban	General disorders and administration site conditions	Review of diagnosis	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Routine follow up	0	1	2	0	0	0	0	3	0.0	0.2	0.5	0.0	0.0	0.0	0.1
rivaroxaban	General disorders and administration site conditions	Secondary care advice, formulary or guidelines	1	8	1	2	0	0	0	12	0.2	1.8	0.2	0.5	0.0	0.0	0.5
rivaroxaban	General disorders and administration site conditions	Seen in haematology	2	1	0	1	1	1	0	6	0.4	0.2	0.0	0.3	0.3	0.3	0.2
rivaroxaban	General disorders and administration site conditions	Short course only	0	0	2	0	0	0	0	2	0.0	0.0	0.5	0.0	0.0	0.0	0.1
rivaroxaban	General disorders and administration site conditions	Short term use only	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Stopped by consultant	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Stopped by specialist	0	0	1	1	0	0	0	2	0.0	0.0	0.2	0.3	0.0	0.0	0.1
rivaroxaban	General disorders and administration site conditions	Swelling	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	Terminal state	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	General disorders and administration site conditions	UROLOGY NOS	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Hepatobiliary disorders	Cholecystitis	1	0	0	0	0	1	0	2	0.2	0.0	0.0	0.0	0.0	0.3	0.1
rivaroxaban	Hepatobiliary disorders	Cholelithiasis	0	0	0	2	0	0	0	2	0.0	0.0	0.0	0.5	0.0	0.0	0.1
rivaroxaban	Hepatobiliary disorders	Gallbladder oedema	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Hepatobiliary disorders	Hepatic lesion	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Immune system disorders	Hypersensitivity	1	0	1	0	0	0	0	2	0.2	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Immune system disorders	Hypogammaglobulinaemia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Immune system disorders	Polyarteritis nodosa	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Appendiceal abscess	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Bronchopneumonia	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Cellulitis	1	1	1	2	3	0	0	8	0.2	0.2	0.2	0.5	0.8	0.0	0.3
rivaroxaban	Infections and infestations	Clostridial infection	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Gastroenteritis	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Gastroenteritis viral	0	0	0	1	0	1	0	2	0.0	0.0	0.0	0.3	0.0	0.3	0.1
rivaroxaban	Infections and infestations	Helicobacter infection	1	1	0	0	0	0	0	2	0.2	0.2	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Infections and infestations	Infection	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Infective exacerbation of bronchiectasis	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Infections and infestations	Kidney infection	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Klebsiella sepsis	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Infections and infestations	Lower respiratory tract infection	4	2	1	1	2	3	1	14	0.9	0.5	0.2	0.3	0.5	0.8	0.6
rivaroxaban	Infections and infestations	Neutropenic sepsis	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Oesophageal candidiasis	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Orchitis	0	1	0	0	0	0	1	2	0.0	0.2	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Infections and infestations	Osteomyelitis	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Infections and infestations	Pneumococcal infection	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Infections and infestations	Pneumonia	7	7	3	3	1	1	0	22	1.5	1.6	0.7	0.8	0.3	0.3	0.9
rivaroxaban	Infections and infestations	Pulmonary sepsis	1	0	0	1	0	0	0	2	0.2	0.0	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Infections and infestations	Respiratory tract infection	0	1	0	1	0	0	0	2	0.0	0.2	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Infections and infestations	Sepsis	2	1	1	0	0	2	0	6	0.4	0.2	0.2	0.0	0.0	0.6	0.2
rivaroxaban	Infections and infestations	Sinusitis	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Sinusitis fungal	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Skin infection	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Staphylococcal infection	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Infections and infestations	Upper respiratory tract infection	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Infections and infestations	Urinary tract infection	3	1	0	1	4	1	0	10	0.6	0.2	0.0	0.3	1.1	0.3	0.4
rivaroxaban	Infections and infestations	Urosepsis	2	0	0	0	1	0	0	3	0.4	0.0	0.0	0.0	0.3	0.0	0.1
rivaroxaban	Infections and infestations	Wound infection	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Accidental overdose	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Acetabulum fracture	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Animal bite	0	0	0	0	1	1	0	2	0.0	0.0	0.0	0.0	0.3	0.3	0.1
rivaroxaban	Injury, poisoning and procedural complications	Brain contusion	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Brain herniation	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Clavicle fracture	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Drug dose omission	2	0	0	2	0	0	0	4	0.4	0.0	0.0	0.5	0.0	0.0	0.2
rivaroxaban	Injury, poisoning and procedural complications	Fall	1	3	1	2	1	5	0	13	0.2	0.7	0.2	0.5	0.3	1.4	0.5
rivaroxaban	Injury, poisoning and procedural complications	Femoral neck fracture	2	0	0	1	0	0	0	3	0.4	0.0	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Injury, poisoning and procedural complications	Fibula fracture	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Foot fracture	0	0	1	0	0	1	0	2	0.0	0.0	0.2	0.0	0.0	0.3	0.1
rivaroxaban	Injury, poisoning and procedural complications	Head injury	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Hip fracture	2	0	0	0	0	0	0	2	0.4	0.0	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Injury, poisoning and procedural complications	Incorrect dose administered	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Injury	0	1	0	0	1	0	0	2	0.0	0.2	0.0	0.0	0.3	0.0	0.1
rivaroxaban	Injury, poisoning and procedural complications	Joint dislocation	0	2	0	1	0	0	0	3	0.0	0.5	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Injury, poisoning and procedural complications	Joint injury	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Laceration	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Injury, poisoning and procedural complications	Ligament sprain	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Lip injury	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Lumbar vertebral fracture	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Pneumothorax traumatic	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Pubis fracture	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Radius fracture	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Stress fracture	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Synovial rupture	2	1	0	0	0	0	0	3	0.4	0.2	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Injury, poisoning and procedural complications	Tibia fracture	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Toxicity to various agents	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Injury, poisoning and procedural complications	Upper limb fracture	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Investigations	Abdomen scan	2	1	4	0	0	0	0	7	0.4	0.2	1.0	0.0	0.0	0.0	0.3
rivaroxaban	Investigations	Angiogram	2	0	0	0	0	1	0	3	0.4	0.0	0.0	0.0	0.0	0.3	0.1

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Investigations	Angiogram pulmonary	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Angiogram pulmonary normal	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Anticoagulation drug level above therapeutic	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Investigations	Anticoagulation drug level therapeutic	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Antiphospholipid antibodies positive	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Arteriogram coronary	0	0	0	1	1	0	0	2	0.0	0.0	0.0	0.3	0.3	0.0	0.1
rivaroxaban	Investigations	Aspiration biopsy	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Biopsy	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Biopsy liver	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Biopsy lung	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Biopsy lymph gland	0	0	1	0	0	1	0	2	0.0	0.0	0.2	0.0	0.0	0.3	0.1
rivaroxaban	Investigations	Biopsy prostate	0	0	0	0	2	0	0	2	0.0	0.0	0.0	0.0	0.5	0.0	0.1
rivaroxaban	Investigations	Blood albumin decreased	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Blood creatine abnormal	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Blood creatinine decreased	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Investigations	Blood creatinine increased	0	1	0	1	1	0	0	3	0.0	0.2	0.0	0.3	0.3	0.0	0.1
rivaroxaban	Investigations	Blood test	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Blood urea increased	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Investigations	Body temperature increased	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Brain scan normal	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Investigations	Bronchoscopy	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Investigations	C-reactive protein increased	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Cardiovascular evaluation	1	0	0	0	0	0	1	2	0.2	0.0	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Investigations	Chest X-ray	1	0	1	0	0	1	0	3	0.2	0.0	0.2	0.0	0.0	0.3	0.1
rivaroxaban	Investigations	Chest X-ray abnormal	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Coagulation test	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Investigations	Colonoscopy	1	1	1	1	0	0	0	4	0.2	0.2	0.2	0.3	0.0	0.0	0.2
rivaroxaban	Investigations	Coma scale abnormal	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Investigations	Computerised tomogram	1	2	3	1	2	4	0	13	0.2	0.5	0.7	0.3	0.5	1.1	0.5
rivaroxaban	Investigations	Creatinine renal clearance	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Cystoscopy	0	0	1	0	0	1	0	2	0.0	0.0	0.2	0.0	0.0	0.3	0.1
rivaroxaban	Investigations	Drug level	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Ear, nose and throat examination	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Echocardiogram	2	4	0	0	1	1	0	8	0.4	0.9	0.0	0.0	0.3	0.3	0.3
rivaroxaban	Investigations	Electrocardiogram	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Electrocardiogram normal	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Endobronchial ultrasound	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Endoscopy	2	0	0	1	0	0	0	3	0.4	0.0	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Investigations	Endoscopy normal	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Endoscopy upper gastrointestinal tract	0	1	1	0	0	1	0	3	0.0	0.2	0.2	0.0	0.0	0.3	0.1
rivaroxaban	Investigations	Fibrin D dimer increased	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Globulins increased	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Glomerular filtration rate abnormal	0	0	2	0	0	0	0	2	0.0	0.0	0.5	0.0	0.0	0.0	0.1



**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Investigations	Glomerular filtration rate decreased	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Glomerular filtration rate increased	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Glycosylated haemoglobin normal	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Gynaecological examination	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Haematology test	0	0	1	0	1	0	2	4	0.0	0.0	0.2	0.0	0.3	0.0	0.2
rivaroxaban	Investigations	Haemoglobin decreased	5	2	0	0	1	0	2	10	1.1	0.5	0.0	0.0	0.3	0.0	0.4
rivaroxaban	Investigations	Heart rate decreased	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Investigations	Heart rate increased	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Hysteroscopy	1	1	0	0	0	0	0	2	0.2	0.2	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Investigations	International normalised ratio increased	0	1	0	0	0	0	2	3	0.0	0.2	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Investigations	Investigation	3	0	1	1	0	2	0	7	0.6	0.0	0.2	0.3	0.0	0.6	0.3
rivaroxaban	Investigations	Laparoscopy	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Investigations	Light chain analysis	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Mammogram	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Investigations	Nuclear magnetic resonance imaging	1	0	0	0	1	0	0	2	0.2	0.0	0.0	0.0	0.3	0.0	0.1
rivaroxaban	Investigations	Oesophagogastrroduodenoscopy	0	2	1	1	0	0	0	4	0.0	0.5	0.2	0.3	0.0	0.0	0.2
rivaroxaban	Investigations	Orthopaedic examination	0	0	0	0	2	0	0	2	0.0	0.0	0.0	0.0	0.5	0.0	0.1
rivaroxaban	Investigations	Positron emission tomogram abnormal	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Prostatic specific antigen increased	1	0	0	1	0	0	0	2	0.2	0.0	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Investigations	Scan normal	1	0	1	0	0	0	0	2	0.2	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Investigations	Sigmoidoscopy	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Investigations	Sinus rhythm	2	0	1	0	0	0	0	3	0.4	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Investigations	Stress echocardiogram	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Investigations	Ultrasound Doppler	0	0	0	0	0	2	0	2	0.0	0.0	0.0	0.0	0.0	0.6	0.1
rivaroxaban	Investigations	Ultrasound Doppler abnormal	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Investigations	Ultrasound abdomen	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Ultrasound chest	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Investigations	Ultrasound prostate	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Investigations	Ultrasound scan	1	1	1	0	1	0	0	4	0.2	0.2	0.2	0.0	0.3	0.0	0.2
rivaroxaban	Investigations	Urological examination	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Investigations	Vascular test normal	1	0	1	0	0	1	0	3	0.2	0.0	0.2	0.0	0.0	0.3	0.1
rivaroxaban	Investigations	Weight abnormal	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Investigations	Weight decreased	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Investigations	Weight increased	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Metabolism and nutrition disorders	Decreased appetite	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Metabolism and nutrition disorders	Dehydration	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Metabolism and nutrition disorders	Fluid intake reduced	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Metabolism and nutrition disorders	Fluid overload	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Metabolism and nutrition disorders	Folate deficiency	0	0	1	0	0	1	0	2	0.0	0.0	0.2	0.0	0.0	0.3	0.1
rivaroxaban	Metabolism and nutrition disorders	Hypercalcaemia	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Metabolism and nutrition disorders	Hyperglycaemia	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Metabolism and nutrition disorders	Hypoalbuminaemia	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Metabolism and nutrition disorders	Hypokalaemia	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Metabolism and nutrition disorders	Hypophagia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Metabolism and nutrition disorders	Obesity	1	0	1	0	0	0	0	2	0.2	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Metabolism and nutrition disorders	Vitamin B12 deficiency	1	0	1	0	1	0	0	3	0.2	0.0	0.2	0.0	0.3	0.0	0.1
rivaroxaban	Musculoskeletal and connective tissue disorders	Arthralgia	2	0	0	0	2	0	1	5	0.4	0.0	0.0	0.0	0.5	0.0	0.2
rivaroxaban	Musculoskeletal and connective tissue disorders	Arthritis	0	0	0	1	0	1	0	2	0.0	0.0	0.0	0.3	0.0	0.3	0.1
rivaroxaban	Musculoskeletal and connective tissue disorders	Back pain	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Musculoskeletal and connective tissue disorders	Joint swelling	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Musculoskeletal and connective tissue disorders	Limb discomfort	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Musculoskeletal and connective tissue disorders	Mobility decreased	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Musculoskeletal and connective tissue disorders	Musculoskeletal disorder	2	0	0	0	0	0	0	2	0.4	0.0	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Musculoskeletal and connective tissue disorders	Musculoskeletal pain	0	0	0	0	1	1	0	2	0.0	0.0	0.0	0.0	0.3	0.3	0.1
rivaroxaban	Musculoskeletal and connective tissue disorders	Osteoarthritis	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Musculoskeletal and connective tissue disorders	Pain in extremity	1	4	2	0	1	1	0	9	0.2	0.9	0.5	0.0	0.3	0.3	0.4
rivaroxaban	Musculoskeletal and connective tissue disorders	Rheumatoid arthritis	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Musculoskeletal and connective tissue disorders	Rotator cuff syndrome	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Musculoskeletal and connective tissue disorders	Systemic lupus erythematosus	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Musculoskeletal and connective tissue disorders	Tendonitis	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adrenal adenoma	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Haemangioma of bone	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm	3	1	2	0	0	1	0	7	0.6	0.2	0.5	0.0	0.0	0.3	0.3
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lymphoma	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Meningioma	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastatic neoplasm	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Paraneoplastic cerebellar degeneration	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Paraproteinaemia	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uterine leiomyoma	0	0	0	0	2	0	0	2	0.0	0.0	0.0	0.0	0.5	0.0	0.1
rivaroxaban	Nervous system disorders	Arachnoid cyst	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Cerebrovascular disorder	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Cognitive disorder	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Complex regional pain syndrome	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Convulsion	0	2	0	1	0	0	0	3	0.0	0.5	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Nervous system disorders	Coordination abnormal	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Nervous system disorders	Dementia	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Nervous system disorders	Dizziness	2	5	1	3	0	3	0	14	0.4	1.1	0.2	0.8	0.0	0.8	0.6
rivaroxaban	Nervous system disorders	Dysgeusia	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Headache	2	1	2	3	2	1	0	11	0.4	0.2	0.5	0.8	0.5	0.3	0.4
rivaroxaban	Nervous system disorders	Hypoaesthesia	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Lethargy	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Nervous system disorders	Loss of consciousness	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Memory impairment	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Nervous system disorders	Migraine	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Migraine with aura	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Multiple system atrophy	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Neuralgia	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Neurological symptom	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Nervous system disorders	Parkinson's disease	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Nervous system disorders	Presyncope	1	0	0	0	0	1	0	2	0.2	0.0	0.0	0.0	0.0	0.3	0.1
rivaroxaban	Nervous system disorders	Syncope	1	1	0	0	0	1	0	3	0.2	0.2	0.0	0.0	0.0	0.3	0.1
rivaroxaban	Nervous system disorders	Tremor	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Nervous system disorders	Vascular dementia	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Psychiatric disorders	Abnormal behaviour	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Psychiatric disorders	Alcoholism	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Psychiatric disorders	Anxiety	0	0	0	0	0	2	0	2	0.0	0.0	0.0	0.0	0.0	0.6	0.1
rivaroxaban	Psychiatric disorders	Confusional state	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Psychiatric disorders	Depressed mood	1	1	0	1	0	0	0	3	0.2	0.2	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Psychiatric disorders	Depression	0	0	1	0	0	1	0	2	0.0	0.0	0.2	0.0	0.0	0.3	0.1
rivaroxaban	Psychiatric disorders	Drug dependence	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Psychiatric disorders	Hallucination, auditory	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Psychiatric disorders	Insomnia	0	2	0	0	0	1	0	3	0.0	0.5	0.0	0.0	0.0	0.3	0.1
rivaroxaban	Psychiatric disorders	Sleep disorder	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Renal and urinary disorders	Anuria	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Renal and urinary disorders	Bladder dilatation	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Renal and urinary disorders	Chromaturia	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Renal and urinary disorders	Hydronephrosis	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Renal and urinary disorders	Incontinence	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Renal and urinary disorders	Nephropathy toxic	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Renal and urinary disorders	Nephrotic syndrome	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Renal and urinary disorders	Pneumaturia	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Renal and urinary disorders	Renal cyst	0	0	2	0	0	0	0	2	0.0	0.0	0.5	0.0	0.0	0.0	0.1
rivaroxaban	Renal and urinary disorders	Renal disorder	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Renal and urinary disorders	Renal failure acute	7	2	0	1	1	0	0	11	1.5	0.5	0.0	0.3	0.3	0.0	0.4
rivaroxaban	Renal and urinary disorders	Renal failure chronic	1	0	1	0	0	0	1	3	0.2	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Renal and urinary disorders	Renal impairment	3	2	0	1	2	2	0	10	0.6	0.5	0.0	0.3	0.5	0.6	0.4
rivaroxaban	Renal and urinary disorders	Renal mass	3	0	0	0	0	0	0	3	0.6	0.0	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Renal and urinary disorders	Urinary bladder polyp	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Renal and urinary disorders	Urinary retention	3	1	0	0	0	0	0	4	0.6	0.2	0.0	0.0	0.0	0.0	0.2
rivaroxaban	Reproductive system and breast disorders	Benign prostatic hyperplasia	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Reproductive system and breast disorders	Dysmenorrhoea	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Reproductive system and breast disorders	Epididymal disorder	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Reproductive system and breast disorders	Epididymitis	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Reproductive system and breast disorders	Ovarian cyst	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Reproductive system and breast disorders	Polymenorrhoea	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Reproductive system and breast disorders	Prostatomegaly	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Reproductive system and breast disorders	Scrotal oedema	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Reproductive system and breast disorders	Scrotal swelling	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Reproductive system and breast disorders	Uterine enlargement	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Reproductive system and breast disorders	Uterine polyp	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Reproductive system and breast disorders	Varicocele	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Reproductive system and breast disorders	Vulvovaginal discomfort	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Alveolitis allergic	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Alveolitis fibrosing	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Aspiration	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Asthma	1	1	0	0	0	1	0	3	0.2	0.2	0.0	0.0	0.0	0.3	0.1
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Atelectasis	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Bronchiectasis	1	1	1	0	0	1	0	4	0.2	0.2	0.2	0.0	0.0	0.3	0.2
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Cough	2	0	0	0	0	0	0	2	0.4	0.0	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Dyspnoea	6	3	4	3	2	2	1	21	1.3	0.7	1.0	0.8	0.5	0.6	0.9
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Hypoventilation	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Nasal septum disorder	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Pleural effusion	2	1	2	1	1	0	0	7	0.4	0.2	0.5	0.3	0.3	0.0	0.3
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Pleural fibrosis	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Pleuritic pain	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration	0	1	1	0	0	0	0	2	0.0	0.2	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Pneumothorax	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Pulmonary fibrosis	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Pulmonary hypertension	1	1	0	0	0	0	0	2	0.2	0.2	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Rales	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Respiratory depression	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Respiratory disorder	0	2	2	0	0	0	0	4	0.0	0.5	0.5	0.0	0.0	0.0	0.2
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Respiratory distress	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Respiratory failure	0	1	0	0	2	1	0	4	0.0	0.2	0.0	0.0	0.5	0.3	0.2
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Tracheal mass	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Respiratory, thoracic and mediastinal disorders	Wheezing	2	0	0	0	0	0	0	2	0.4	0.0	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Skin and subcutaneous tissue disorders	Blister	0	1	1	0	0	0	0	2	0.0	0.2	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Skin and subcutaneous tissue disorders	Dermatitis	0	1	0	1	0	0	0	2	0.0	0.2	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Skin and subcutaneous tissue disorders	Dermatitis allergic	1	0	0	0	0	1	0	2	0.2	0.0	0.0	0.0	0.0	0.3	0.1
rivaroxaban	Skin and subcutaneous tissue disorders	Dermatitis exfoliative	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Skin and subcutaneous tissue disorders	Dry skin	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Skin and subcutaneous tissue disorders	Hyperhidrosis	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Skin and subcutaneous tissue disorders	Pruritus	2	0	1	1	1	0	0	5	0.4	0.0	0.2	0.3	0.3	0.0	0.2
rivaroxaban	Skin and subcutaneous tissue disorders	Psoriasis	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Skin and subcutaneous tissue disorders	Rash	1	2	0	2	1	1	0	7	0.2	0.5	0.0	0.5	0.3	0.3	0.3
rivaroxaban	Skin and subcutaneous tissue disorders	Rash erythematous	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Skin and subcutaneous tissue disorders	Rash maculo-papular	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Skin and subcutaneous tissue disorders	Scab	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Skin and subcutaneous tissue disorders	Skin reaction	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Skin and subcutaneous tissue disorders	Skin ulcer	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Skin and subcutaneous tissue disorders	Subcutaneous emphysema	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Social circumstances	Bereavement	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Social circumstances	Contraindication to medical treatment	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Social circumstances	Drug abuser	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Social circumstances	Elderly	0	1	1	0	0	0	0	2	0.0	0.2	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Social circumstances	Familial risk factor	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Social circumstances	Living in residential institution	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Social circumstances	Orthosis user	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Social circumstances	Refusal of treatment by patient	3	2	0	0	4	1	1	11	0.6	0.5	0.0	0.0	1.1	0.3	0.4
rivaroxaban	Social circumstances	Treatment noncompliance	1	1	3	1	1	1	0	8	0.2	0.2	0.7	0.3	0.3	0.3	0.3
rivaroxaban	Surgical and medical procedures	Anticoagulant therapy	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Bladder catheter removal	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Bladder catheterisation	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Bladder neck operation	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Carpal tunnel decompression	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Surgical and medical procedures	Cast application	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Cataract operation	1	0	0	0	0	1	0	2	0.2	0.0	0.0	0.0	0.0	0.3	0.1
rivaroxaban	Surgical and medical procedures	Cautery to nose	1	0	1	0	0	0	0	2	0.2	0.0	0.2	0.0	0.0	0.0	0.1
rivaroxaban	Surgical and medical procedures	Cholecystectomy	0	0	0	2	0	0	0	2	0.0	0.0	0.0	0.5	0.0	0.0	0.1
rivaroxaban	Surgical and medical procedures	Compression stockings application	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Cyst drainage	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Cyst removal	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Dental care	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Surgical and medical procedures	Drain placement	1	1	0	0	0	0	0	2	0.2	0.2	0.0	0.0	0.0	0.0	0.1
rivaroxaban	Surgical and medical procedures	Drug therapy changed	2	1	0	1	0	0	1	5	0.4	0.2	0.0	0.3	0.0	0.0	0.2
rivaroxaban	Surgical and medical procedures	Emergency care	3	3	2	4	0	2	3	17	0.6	0.7	0.5	1.0	0.0	0.6	0.7
rivaroxaban	Surgical and medical procedures	Foot operation	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Gastrostomy tube insertion	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	General anaesthesia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Haemorrhage prophylaxis	1	0	0	2	0	0	0	3	0.2	0.0	0.0	0.5	0.0	0.0	0.1
rivaroxaban	Surgical and medical procedures	Haemorrhoid operation	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Surgical and medical procedures	Hernia repair	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Hydrotherapy	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Immunisation	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Incisional drainage	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Injection	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Surgical and medical procedures	Internal fixation of fracture	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Surgical and medical procedures	Joint manipulation	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.0
rivaroxaban	Surgical and medical procedures	Knee operation	1	0	0	0	0	0	0	1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Manipulation	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Medical device removal	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
rivaroxaban	Surgical and medical procedures	Nasal septal operation	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Surgical and medical procedures	Oesophageal dilation procedure	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Palliative care	0	0	2	1	0	0	0	3	0.0	0.0	0.5	0.3	0.0	0.0	0.1
rivaroxaban	Surgical and medical procedures	Physiotherapy	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Preoperative care	0	0	0	1	1	0	0	2	0.0	0.0	0.0	0.3	0.3	0.0	0.1
rivaroxaban	Surgical and medical procedures	Prophylaxis	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Rehabilitation therapy	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Retinal laser coagulation	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Surgery	3	0	1	2	0	1	0	7	0.6	0.0	0.2	0.5	0.0	0.3	0.3
rivaroxaban	Surgical and medical procedures	Therapy regimen changed	6	58	0	0	0	2	10	76	1.3	13.2	0.0	0.0	0.0	0.6	3.1
rivaroxaban	Surgical and medical procedures	Thoracic cavity drainage	0	0	0	2	0	0	0	2	0.0	0.0	0.0	0.5	0.0	0.0	0.1
rivaroxaban	Surgical and medical procedures	Thrombolysis	2	0	0	1	0	0	0	3	0.4	0.0	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Surgical and medical procedures	Tonsillectomy	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
rivaroxaban	Surgical and medical procedures	Tooth extraction	1	0	0	1	0	1	0	3	0.2	0.0	0.0	0.3	0.0	0.3	0.1
rivaroxaban	Surgical and medical procedures	Transfusion	0	2	1	1	0	0	1	5	0.0	0.5	0.2	0.3	0.0	0.0	0.2
rivaroxaban	Surgical and medical procedures	Transurethral prostatectomy	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Surgical and medical procedures	Vena cava filter insertion	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Vascular disorders	Circulatory collapse	2	1	3	1	0	0	0	7	0.4	0.2	0.7	0.3	0.0	0.0	0.3
rivaroxaban	Vascular disorders	Hypertension	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.0
rivaroxaban	Vascular disorders	Hypotension	0	0	1	0	0	0	0	1	0.0	0.0	0.2	0.0	0.0	0.0	0.0
rivaroxaban	Vascular disorders	Infarction	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Vascular disorders	Orthostatic hypotension	1	0	0	1	0	0	0	2	0.2	0.0	0.0	0.3	0.0	0.0	0.1
rivaroxaban	Vascular disorders	Poor venous access	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Vascular disorders	Post thrombotic syndrome	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Vascular disorders	Thrombophlebitis	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
rivaroxaban	Vascular disorders	Thrombophlebitis superficial	0	1	0	0	1	1	0	3	0.0	0.2	0.0	0.0	0.3	0.3	0.1
rivaroxaban	Vascular disorders	Venous insufficiency	0	1	0	0	0	0	0	1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
warfarin	Blood and lymphatic system disorders	Anaemia	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Blood and lymphatic system disorders	Lymphadenopathy	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Blood and lymphatic system disorders	Lymphadenopathy mediastinal	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Blood and lymphatic system disorders	Macrocytosis	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Blood and lymphatic system disorders	Microcytic anaemia	0	0	0	0	2	0	0	2	0.0	0.0	0.0	0.0	0.7	0.0	0.1
warfarin	Blood and lymphatic system disorders	Nephrogenic anaemia	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Blood and lymphatic system disorders	Splenic lesion	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Blood and lymphatic system disorders	Thrombocytopenia	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Cardiac disorders	Aortic valve disease mixed	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Cardiac disorders	Cardiac flutter	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Cardiac disorders	Cardiomegaly	0	0	0	1	1	0	0	2	0.0	0.0	0.0	0.3	0.3	0.0	0.1
warfarin	Cardiac disorders	Cardiomyopathy	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Cardiac disorders	Congestive cardiomyopathy	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Cardiac disorders	Left ventricular hypertrophy	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Cardiac disorders	Mitral valve incompetence	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Cardiac disorders	Palpitations	2	1	2	0	1	1	1	8	0.5	0.3	0.6	0.0	0.3	0.3	0.4

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	Cardiac disorders	Pericardial effusion	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Cardiac disorders	Sinus bradycardia	0	1	1	0	0	0	0	2	0.0	0.3	0.3	0.0	0.0	0.0	0.1
warfarin	Cardiac disorders	Tricuspid valve incompetence	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Cardiac disorders	Ventricular extrasystoles	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Congenital, familial and genetic disorders	Atrial septal defect	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Congenital, familial and genetic disorders	Gene mutation	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Congenital, familial and genetic disorders	Ventricular septal defect	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Ear and labyrinth disorders	Cerumen impaction	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Endocrine disorders	Adrenal mass	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Endocrine disorders	Goitre	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Endocrine disorders	Hyperadrenalism	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Endocrine disorders	Hyperparathyroidism	1	0	0	0	0	1	0	2	0.3	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Eye disorders	Detachment of macular retinal pigment epithelium	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Eye disorders	Episcleritis	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Gastrointestinal disorders	Abdominal discomfort	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Abdominal distension	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Abdominal mass	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Abdominal pain	2	1	0	0	1	0	1	5	0.5	0.3	0.0	0.0	0.3	0.0	0.3
warfarin	Gastrointestinal disorders	Abdominal pain lower	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Gastrointestinal disorders	Abdominal pain upper	0	1	1	0	0	1	0	3	0.0	0.3	0.3	0.0	0.0	0.3	0.2
warfarin	Gastrointestinal disorders	Ascites	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Gastrointestinal disorders	Barrett's oesophagus	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Gastrointestinal disorders	Colitis	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Constipation	0	0	0	1	0	1	0	2	0.0	0.0	0.0	0.3	0.0	0.3	0.1
warfarin	Gastrointestinal disorders	Crohn's disease	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Diarrhoea	1	1	0	1	3	0	1	7	0.3	0.3	0.0	0.3	1.0	0.0	0.4
warfarin	Gastrointestinal disorders	Diverticulum	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Gastrointestinal disorders	Duodenitis	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Dyspepsia	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Dysphagia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Enterocolonic fistula	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Gastritis	0	1	0	0	0	1	0	2	0.0	0.3	0.0	0.0	0.0	0.3	0.1
warfarin	Gastrointestinal disorders	Gastrointestinal disorder	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Gastrointestinal pain	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Gastrointestinal disorders	Gastrooesophageal reflux disease	0	0	0	1	1	2	0	4	0.0	0.0	0.0	0.3	0.3	0.7	0.2
warfarin	Gastrointestinal disorders	Hiatus hernia	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Nausea	1	2	1	1	0	1	0	6	0.3	0.6	0.3	0.3	0.0	0.3	0.3
warfarin	Gastrointestinal disorders	Oesophagitis	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Oesophagitis ulcerative	0	0	1	0	0	1	0	2	0.0	0.0	0.3	0.0	0.0	0.3	0.1
warfarin	Gastrointestinal disorders	Oral pain	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Pancreatitis	0	0	0	0	0	2	0	2	0.0	0.0	0.0	0.0	0.0	0.7	0.1
warfarin	Gastrointestinal disorders	Rectal stenosis	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Gastrointestinal disorders	Sigmoiditis	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	Gastrointestinal disorders	Vomiting	1	0	0	0	1	0	1	3	0.3	0.0	0.0	0.0	0.3	0.0	0.2
warfarin	General disorders and administration site conditions	Adverse drug reaction	3	0	1	0	0	0	1	5	0.8	0.0	0.3	0.0	0.0	0.0	0.3
warfarin	General disorders and administration site conditions	Asthenia	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	CHA2DS2-VASc annual stroke risk moderate	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	COURSE COMPLETED	0	0	0	1	0	2	0	3	0.0	0.0	0.0	0.3	0.0	0.7	0.2
warfarin	General disorders and administration site conditions	Cardiac complication associated with device	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	General disorders and administration site conditions	Chest pain	2	4	2	3	1	1	0	13	0.5	1.1	0.6	0.9	0.3	0.3	0.7
warfarin	General disorders and administration site conditions	Computerised tomogram pelvis	0	0	1	1	0	0	0	2	0.0	0.0	0.3	0.3	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	DRUG INFORMATION	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Death	1	3	3	0	2	1	1	11	0.3	0.9	0.9	0.0	0.7	0.3	0.6
warfarin	General disorders and administration site conditions	Diagnosis revised	3	0	0	1	0	0	0	4	0.8	0.0	0.0	0.3	0.0	0.0	0.2
warfarin	General disorders and administration site conditions	Difficult administration	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Doctor decision	9	2	1	2	1	1	0	16	2.3	0.6	0.3	0.6	0.3	0.3	0.8
warfarin	General disorders and administration site conditions	Dr Preference	0	1	1	1	0	1	0	4	0.0	0.3	0.3	0.3	0.0	0.3	0.2
warfarin	General disorders and administration site conditions	Drug ineffective	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Drug intolerance	2	0	0	0	0	1	0	3	0.5	0.0	0.0	0.0	0.0	0.3	0.2
warfarin	General disorders and administration site conditions	End of course	0	0	1	1	0	0	0	2	0.0	0.0	0.3	0.3	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Exercise tolerance decreased	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	General disorders and administration site conditions	Fatigue	0	0	0	1	0	1	0	2	0.0	0.0	0.0	0.3	0.0	0.3	0.1
warfarin	General disorders and administration site conditions	Feeling abnormal	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	General disorders and administration site conditions	General physical health deterioration	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Ground glass opacity in thoracic CT	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Health problems	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Hernia obstructive	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Hospital advised	1	0	0	1	0	0	0	2	0.3	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Hospital decision	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	General disorders and administration site conditions	Hospital stopped it	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Hypertrophy	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Intermittent use	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Labial reduction	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Lifestyle issues	4	1	2	1	0	0	1	9	1.0	0.3	0.6	0.3	0.0	0.0	0.5
warfarin	General disorders and administration site conditions	Local swelling	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Malaise	1	1	1	2	1	0	0	6	0.3	0.3	0.3	0.6	0.3	0.0	0.3
warfarin	General disorders and administration site conditions	Mass	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	General disorders and administration site conditions	Medical device complication	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Medical procedure	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Metaplasia	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	General disorders and administration site conditions	Multi-organ failure	1	0	0	1	0	0	0	2	0.3	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	NOT SPECIFIED.	23	1	6	2	2	4	2	40	6.0	0.3	1.8	0.6	0.7	1.4	2.0
warfarin	General disorders and administration site conditions	Nil by mouth	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Nodule	0	0	0	2	0	0	0	2	0.0	0.0	0.0	0.6	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Non-cardiac chest pain	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Not sure whether taken	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1



**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	General disorders and administration site conditions	Oedema	1	0	0	1	0	0	0	2	0.3	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Oedema peripheral	1	1	1	0	0	0	0	3	0.3	0.3	0.3	0.0	0.0	0.0	0.2
warfarin	General disorders and administration site conditions	Patient decision to not take drug	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	General disorders and administration site conditions	Patient did not attend	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	General disorders and administration site conditions	Patient muddled about medication	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Pelvis CT	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Polyp	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Practice advice, formulary or guidelines	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	General disorders and administration site conditions	Pre-existing condition improved	0	0	2	0	0	2	0	4	0.0	0.0	0.6	0.0	0.0	0.7	0.2
warfarin	General disorders and administration site conditions	Prescribing advisor advice	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Prescribing guidelines	2	0	1	0	1	0	3	7	0.5	0.0	0.3	0.0	0.3	0.0	0.4
warfarin	General disorders and administration site conditions	Ran out of medication	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Referred to specialist	1	1	1	1	0	0	1	5	0.3	0.3	0.3	0.3	0.0	0.0	0.3
warfarin	General disorders and administration site conditions	Routine follow up	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	General disorders and administration site conditions	Seen in haematology	0	0	0	1	1	0	0	2	0.0	0.0	0.0	0.3	0.3	0.0	0.1
warfarin	General disorders and administration site conditions	Specialist consultation	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	General disorders and administration site conditions	Sphincterotomy	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	General disorders and administration site conditions	Stopped by hospital physician	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Stopped by consultant	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Stopped by specialist	1	0	2	0	1	0	0	4	0.3	0.0	0.6	0.0	0.3	0.0	0.2
warfarin	General disorders and administration site conditions	Ulcer	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	General disorders and administration site conditions	Waking suddenly	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Hepatobiliary disorders	Cholangitis	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Hepatobiliary disorders	Cholelithiasis	0	0	0	1	1	1	0	3	0.0	0.0	0.0	0.3	0.3	0.3	0.2
warfarin	Infections and infestations	Anal abscess	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Infections and infestations	Bacteraemia	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Infections and infestations	Bronchopulmonary aspergillosis allergic	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Infections and infestations	Cellulitis	0	1	4	0	2	1	0	8	0.0	0.3	1.2	0.0	0.7	0.3	0.4
warfarin	Infections and infestations	Clostridial infection	2	0	0	0	0	0	0	2	0.5	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Infections and infestations	Ear infection	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Infections and infestations	Endocarditis	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Infections and infestations	Enterocolitis infectious	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Infections and infestations	Gangrene	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Infections and infestations	Gastroenteritis Escherichia coli	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Infections and infestations	Herpes zoster	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Infections and infestations	Infection	2	0	1	0	0	0	0	3	0.5	0.0	0.3	0.0	0.0	0.0	0.2
warfarin	Infections and infestations	Infective exacerbation of bronchiectasis	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Infections and infestations	Kidney infection	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Infections and infestations	Lobar pneumonia	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Infections and infestations	Lower respiratory tract infection	5	2	1	4	2	0	1	15	1.3	0.6	0.3	1.3	0.7	0.0	0.8
warfarin	Infections and infestations	Nail infection	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Infections and infestations	Orchitis	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Infections and infestations	Pneumonia	6	1	1	2	0	0	0	10	1.6	0.3	0.3	0.6	0.0	0.0	0.5

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	Infections and infestations	Pseudomonas infection	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Infections and infestations	Pyelonephritis	0	0	0	0	2	0	0	2	0.0	0.0	0.0	0.0	0.7	0.0	0.1
warfarin	Infections and infestations	Respiratory tract infection	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Infections and infestations	Rhinovirus infection	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Infections and infestations	Sepsis	3	1	1	0	1	0	0	6	0.8	0.3	0.3	0.0	0.3	0.0	0.3
warfarin	Infections and infestations	Septic shock	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Infections and infestations	Tooth abscess	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Infections and infestations	Urinary tract infection	7	1	0	0	1	1	0	10	1.8	0.3	0.0	0.0	0.3	0.3	0.5
warfarin	Infections and infestations	Urosepsis	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Infections and infestations	Wound infection	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Accidental overdose	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Drug dose omission	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Drug prescribing error	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Fall	3	1	1	4	4	2	1	16	0.8	0.3	0.3	1.3	1.3	0.7	0.8
warfarin	Injury, poisoning and procedural complications	Foot fracture	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Foreign body	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Head injury	0	1	0	0	1	1	0	3	0.0	0.3	0.0	0.0	0.3	0.3	0.2
warfarin	Injury, poisoning and procedural complications	Injury	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Injury, poisoning and procedural complications	Joint dislocation	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Joint injury	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Ligament sprain	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Limb injury	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Overdose	1	0	1	0	0	1	0	3	0.3	0.0	0.3	0.0	0.0	0.3	0.2
warfarin	Injury, poisoning and procedural complications	Post procedural complication	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Soft tissue injury	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Injury, poisoning and procedural complications	Ulnar nerve injury	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Abdomen scan	1	0	1	1	0	0	0	3	0.3	0.0	0.3	0.3	0.0	0.0	0.2
warfarin	Investigations	Angiogram	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Angiogram pulmonary	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Anticoagulation drug level above therapeutic	1	2	0	0	0	0	0	3	0.3	0.6	0.0	0.0	0.0	0.0	0.2
warfarin	Investigations	Anticoagulation drug level below therapeutic	1	1	0	0	0	1	0	3	0.3	0.3	0.0	0.0	0.0	0.3	0.2
warfarin	Investigations	Antiphospholipid antibodies positive	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Investigations	Arteriogram coronary	0	0	1	0	0	0	1	2	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Investigations	Aspiration joint	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Investigations	Aspiration pleural cavity	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Biopsy	3	0	0	1	1	0	0	5	0.8	0.0	0.0	0.3	0.3	0.0	0.3
warfarin	Investigations	Biopsy liver	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Investigations	Biopsy lung	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Investigations	Biopsy prostate	0	0	0	1	1	0	0	2	0.0	0.0	0.0	0.3	0.3	0.0	0.1
warfarin	Investigations	Biopsy vulva	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Blood albumin decreased	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Blood alcohol increased	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Investigations	Blood glucose increased	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	Investigations	Blood testosterone decreased	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Investigations	Bone densitometry	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Investigations	Brain natriuretic peptide increased	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Investigations	Brain scan normal	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Investigations	Bronchoscopy	1	1	0	0	0	1	0	3	0.3	0.3	0.0	0.0	0.0	0.3	0.2
warfarin	Investigations	Cardiovascular evaluation	2	1	0	2	0	0	0	5	0.5	0.3	0.0	0.6	0.0	0.0	0.3
warfarin	Investigations	Chest X-ray	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Investigations	Colonoscopy	1	1	1	3	1	1	0	8	0.3	0.3	0.3	0.9	0.3	0.3	0.4
warfarin	Investigations	Computerised tomogram	2	2	4	1	2	0	0	11	0.5	0.6	1.2	0.3	0.7	0.0	0.6
warfarin	Investigations	Computerised tomogram thorax abnormal	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Investigations	Cystoscopy	0	0	0	2	0	0	0	2	0.0	0.0	0.0	0.6	0.0	0.0	0.1
warfarin	Investigations	Dermatologic examination	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Echocardiogram	2	1	0	0	1	1	0	5	0.5	0.3	0.0	0.0	0.3	0.3	0.3
warfarin	Investigations	Electrocardiogram ambulatory	0	0	1	1	0	0	0	2	0.0	0.0	0.3	0.3	0.0	0.0	0.1
warfarin	Investigations	Electrocardiogram normal	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Investigations	Electromyogram	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Endoscopic retrograde cholangiopancreatography	0	0	0	1	0	1	0	2	0.0	0.0	0.0	0.3	0.0	0.3	0.1
warfarin	Investigations	Endoscopy	0	2	0	0	0	0	0	2	0.0	0.6	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Endoscopy normal	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Endoscopy upper gastrointestinal tract	0	0	0	1	1	3	0	5	0.0	0.0	0.0	0.3	0.3	1.0	0.3
warfarin	Investigations	Globulin abnormal	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Glomerular filtration rate decreased	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Haemoglobin decreased	1	1	0	0	0	0	0	2	0.3	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Haemoglobin normal	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Investigations	Heart rate irregular	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Investigations	International normalised ratio	3	2	1	2	1	0	0	9	0.8	0.6	0.3	0.6	0.3	0.0	0.5
warfarin	Investigations	International normalised ratio decreased	1	0	0	1	0	0	0	2	0.3	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Investigations	International normalised ratio fluctuation	5	3	3	0	2	0	0	13	1.3	0.9	0.9	0.0	0.7	0.0	0.7
warfarin	Investigations	International normalised ratio increased	40	10	6	3	2	4	1	66	10.4	2.8	1.8	0.9	0.7	1.4	3.3
warfarin	Investigations	Investigation	1	0	3	1	0	0	1	6	0.3	0.0	0.9	0.3	0.0	0.0	0.3
warfarin	Investigations	Laryngoscopy	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Investigations	Mean cell volume increased	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Investigations	Norovirus test positive	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Investigations	Nuclear magnetic resonance imaging	0	1	0	0	1	0	0	2	0.0	0.3	0.0	0.0	0.3	0.0	0.1
warfarin	Investigations	Oesophagogastroduodenoscopy	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Orthopaedic examination	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Investigations	Platelet count decreased	1	0	2	0	0	0	0	3	0.3	0.0	0.6	0.0	0.0	0.0	0.2
warfarin	Investigations	Protein albumin ratio decreased	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Investigations	Pulmonary function test decreased	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Investigations	Scan lymph nodes	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Investigations	Scan normal	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Investigations	Sigmoidoscopy	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Sinus rhythm	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	Investigations	Staphylococcus test positive	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Stool analysis	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Investigations	Ultrasound abdomen	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Investigations	Ultrasound pelvis	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Investigations	Ultrasound scan	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Ultrasound uterus	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Investigations	Urological examination	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Investigations	Vascular test normal	0	1	1	0	0	0	0	2	0.0	0.3	0.3	0.0	0.0	0.0	0.1
warfarin	Investigations	Vitamin K	1	0	0	0	0	0	1	2	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Weight decreased	1	1	0	0	0	0	0	2	0.3	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	Weight increased	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Investigations	X-ray	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Metabolism and nutrition disorders	Decreased appetite	2	0	0	1	0	0	0	3	0.5	0.0	0.0	0.3	0.0	0.0	0.2
warfarin	Metabolism and nutrition disorders	Fluid overload	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Metabolism and nutrition disorders	Gout	0	1	1	0	2	0	0	4	0.0	0.3	0.3	0.0	0.7	0.0	0.2
warfarin	Metabolism and nutrition disorders	Hypercalcaemia	0	2	1	0	0	0	0	3	0.0	0.6	0.3	0.0	0.0	0.0	0.2
warfarin	Metabolism and nutrition disorders	Hypocalcaemia	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Metabolism and nutrition disorders	Hypokalaemia	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Metabolism and nutrition disorders	Hypomagnesaemia	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Metabolism and nutrition disorders	Hypophosphataemia	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Metabolism and nutrition disorders	Polydipsia	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Musculoskeletal and connective tissue disorders	Arthralgia	0	1	2	2	0	0	0	5	0.0	0.3	0.6	0.6	0.0	0.0	0.3
warfarin	Musculoskeletal and connective tissue disorders	Arthritis	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Back pain	0	1	1	0	0	1	0	3	0.0	0.3	0.3	0.0	0.0	0.3	0.2
warfarin	Musculoskeletal and connective tissue disorders	Bursitis	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Groin pain	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Intervertebral disc degeneration	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Joint crepitation	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Joint swelling	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Lumbar spinal stenosis	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	0	0	1	1	1	1	0	4	0.0	0.0	0.3	0.3	0.3	0.3	0.2
warfarin	Musculoskeletal and connective tissue disorders	Musculoskeletal pain	0	1	1	0	0	0	0	2	0.0	0.3	0.3	0.0	0.0	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Osteoporosis	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Pain in extremity	1	0	1	0	0	0	0	2	0.3	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Psoriatic arthropathy	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Seronegative arthritis	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Spinal disorder	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Synovial cyst	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Musculoskeletal and connective tissue disorders	Synovitis	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenoma benign	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adrenal adenoma	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Benign neoplasm of thyroid gland	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm malignant	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Monoclonal gammopathy	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Thyroid neoplasm	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uterine cancer	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Nervous system disorders	Balance disorder	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Nervous system disorders	Carpal tunnel syndrome	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Nervous system disorders	Convulsion	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Nervous system disorders	Dizziness	2	1	2	0	2	1	0	8	0.5	0.3	0.6	0.0	0.7	0.3	0.4
warfarin	Nervous system disorders	Epilepsy	0	0	0	1	0	1	0	2	0.0	0.0	0.0	0.3	0.0	0.3	0.1
warfarin	Nervous system disorders	Headache	3	3	1	0	1	0	0	8	0.8	0.9	0.3	0.0	0.3	0.0	0.4
warfarin	Nervous system disorders	Hemianopia	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Nervous system disorders	Hypoaesthesia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Nervous system disorders	Lethargy	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Nervous system disorders	Loss of consciousness	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Nervous system disorders	Migraine	1	0	2	0	0	1	0	4	0.3	0.0	0.6	0.0	0.0	0.3	0.2
warfarin	Nervous system disorders	Multiple sclerosis	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Nervous system disorders	Myasthenia gravis	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Nervous system disorders	Sedation	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Nervous system disorders	Sensory loss	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Nervous system disorders	Somnolence	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Nervous system disorders	Syncope	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Nervous system disorders	Thoracic outlet syndrome	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Nervous system disorders	VIIth nerve paralysis	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Nervous system disorders	Vascular parkinsonism	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Psychiatric disorders	Alcohol abuse	0	0	1	1	0	0	0	2	0.0	0.0	0.3	0.3	0.0	0.0	0.1
warfarin	Psychiatric disorders	Anxiety	2	0	1	0	0	0	1	4	0.5	0.0	0.3	0.0	0.0	0.0	0.2
warfarin	Psychiatric disorders	Confusional state	0	1	0	2	0	1	0	4	0.0	0.3	0.0	0.6	0.0	0.3	0.2
warfarin	Psychiatric disorders	Delirium	0	0	0	1	1	0	0	2	0.0	0.0	0.0	0.3	0.3	0.0	0.1
warfarin	Psychiatric disorders	Depression	0	1	0	0	0	2	1	4	0.0	0.3	0.0	0.0	0.0	0.7	0.2
warfarin	Psychiatric disorders	Hallucination, auditory	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Psychiatric disorders	Psychotic disorder	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Renal and urinary disorders	Bladder mass	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Renal and urinary disorders	Bladder neck obstruction	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Renal and urinary disorders	Hydronephrosis	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Renal and urinary disorders	Nephrolithiasis	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Renal and urinary disorders	Renal cyst	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Renal and urinary disorders	Renal failure	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Renal and urinary disorders	Renal failure acute	2	1	0	1	0	0	0	4	0.5	0.3	0.0	0.3	0.0	0.0	0.2
warfarin	Renal and urinary disorders	Renal impairment	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Renal and urinary disorders	Urinary retention	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Reproductive system and breast disorders	Benign prostatic hyperplasia	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Reproductive system and breast disorders	Endometrial hyperplasia	0	1	0	1	0	0	0	2	0.0	0.3	0.0	0.3	0.0	0.0	0.1

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	Reproductive system and breast disorders	Epididymal cyst	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Reproductive system and breast disorders	Erectile dysfunction	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Reproductive system and breast disorders	Uterine polyp	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Reproductive system and breast disorders	Vulval disorder	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Respiratory, thoracic and mediastinal disorders	Aspiration	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Respiratory, thoracic and mediastinal disorders	Asthma	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Respiratory, thoracic and mediastinal disorders	Bronchiectasis	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Respiratory, thoracic and mediastinal disorders	Cough	2	1	0	0	0	0	0	3	0.5	0.3	0.0	0.0	0.0	0.0	0.2
warfarin	Respiratory, thoracic and mediastinal disorders	Dyspnoea	4	7	1	1	2	1	0	16	1.0	2.0	0.3	0.3	0.7	0.3	0.8
warfarin	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Respiratory, thoracic and mediastinal disorders	Lung consolidation	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Respiratory, thoracic and mediastinal disorders	Pleural effusion	1	1	2	0	0	0	0	4	0.3	0.3	0.6	0.0	0.0	0.0	0.2
warfarin	Respiratory, thoracic and mediastinal disorders	Pleuritic pain	1	0	1	0	0	0	1	3	0.3	0.0	0.3	0.0	0.0	0.0	0.2
warfarin	Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Respiratory, thoracic and mediastinal disorders	Pulmonary calcification	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Respiratory, thoracic and mediastinal disorders	Pulmonary fibrosis	1	0	1	0	0	0	0	2	0.3	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Respiratory, thoracic and mediastinal disorders	Pulmonary hypertension	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Respiratory, thoracic and mediastinal disorders	Respiratory disorder	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Respiratory, thoracic and mediastinal disorders	Respiratory failure	0	0	0	1	0	2	0	3	0.0	0.0	0.0	0.3	0.0	0.7	0.2
warfarin	Respiratory, thoracic and mediastinal disorders	Respiratory tract congestion	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Respiratory, thoracic and mediastinal disorders	Snoring	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Alopecia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Angioedema	0	0	0	0	0	1	0	1	0.0	0.0	0.0	0.0	0.0	0.3	0.1
warfarin	Skin and subcutaneous tissue disorders	Decubitus ulcer	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Skin and subcutaneous tissue disorders	Erythema	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Skin and subcutaneous tissue disorders	Hyperhidrosis	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Nail ridging	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Onychoclasia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Pain of skin	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Pruritus	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Pruritus generalised	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Pyoderma gangrenosum	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Rash	3	1	0	1	0	0	0	5	0.8	0.3	0.0	0.3	0.0	0.0	0.3
warfarin	Skin and subcutaneous tissue disorders	Rash maculo-papular	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Rash morbilliform	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Skin lesion	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Skin reaction	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Skin and subcutaneous tissue disorders	Skin ulcer	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Social circumstances	Bereavement	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Social circumstances	Drug abuser	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Social circumstances	Elderly	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	Social circumstances	Foreign travel	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Social circumstances	Inadequate diet	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Social circumstances	Refusal of treatment by patient	7	2	1	0	3	1	0	14	1.8	0.6	0.3	0.0	1.0	0.3	0.7
warfarin	Social circumstances	Treatment noncompliance	6	3	2	0	1	0	1	13	1.6	0.9	0.6	0.0	0.3	0.0	0.7
warfarin	Surgical and medical procedures	Antibiotic therapy	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Anticoagulant therapy	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Aortic aneurysm repair	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Breast lump removal	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Cardiac rehabilitation therapy	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Cast removal	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Cautery to nose	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Surgical and medical procedures	Chemotherapy	0	1	1	1	0	0	0	3	0.0	0.3	0.3	0.3	0.0	0.0	0.2
warfarin	Surgical and medical procedures	Cholecystectomy	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Compression stockings application	0	0	0	0	0	0	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Debridement	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Surgical and medical procedures	Diathermy	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Drug therapy changed	8	1	2	0	0	0	0	11	2.1	0.3	0.6	0.0	0.0	0.0	0.6
warfarin	Surgical and medical procedures	Emergency care	4	2	4	3	2	1	0	16	1.0	0.6	1.2	0.9	0.7	0.3	0.8
warfarin	Surgical and medical procedures	Gastrostomy tube insertion	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Hospice care	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Injection	1	0	0	0	1	0	0	2	0.3	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Surgical and medical procedures	Intra-ocular injection	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Joint injection	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Knee arthroplasty	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Nerve block	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Palliative care	0	0	2	1	0	0	0	3	0.0	0.0	0.6	0.3	0.0	0.0	0.2
warfarin	Surgical and medical procedures	Platelet transfusion	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Pleurodesis	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Polypectomy	0	1	0	1	1	0	0	3	0.0	0.3	0.0	0.3	0.3	0.0	0.2
warfarin	Surgical and medical procedures	Preoperative care	0	2	1	0	0	0	0	3	0.0	0.6	0.3	0.0	0.0	0.0	0.2
warfarin	Surgical and medical procedures	Rehabilitation therapy	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Surgical and medical procedures	Removal of foreign body	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Stent placement	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Stent removal	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Surgery	2	0	0	2	1	1	0	6	0.5	0.0	0.0	0.6	0.3	0.3	0.3
warfarin	Surgical and medical procedures	Therapy regimen changed	0	0	0	1	0	0	1	2	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Thoracic cavity drainage	0	2	0	0	0	0	0	2	0.0	0.6	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Thrombolysis	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Tooth extraction	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Tracheostomy	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Surgical and medical procedures	Transfusion	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Surgical and medical procedures	Transurethral prostatectomy	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Surgical and medical procedures	Varicose vein operation	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1

**Appendix 10b. Incidence Densities for Events Captured as Free Text**

Treatment Group	System Organ Class	Event	N1	N2	N3	N4	N5	N6	Nunk	Nall	ID1	ID2	ID3	ID4	ID5	ID6	IDA
warfarin	Surgical and medical procedures	Vascular graft	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Surgical and medical procedures	Vena cava filter insertion	1	0	0	1	2	0	0	4	0.3	0.0	0.0	0.3	0.7	0.0	0.2
warfarin	Vascular disorders	Angiodysplasia	0	0	0	1	0	0	0	1	0.0	0.0	0.0	0.3	0.0	0.0	0.1
warfarin	Vascular disorders	Aortic dilatation	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Vascular disorders	Arterial occlusive disease	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Vascular disorders	Circulatory collapse	1	1	1	1	0	0	0	4	0.3	0.3	0.3	0.3	0.0	0.0	0.2
warfarin	Vascular disorders	Hypertension	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Vascular disorders	Hypotension	0	0	0	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
warfarin	Vascular disorders	May-Thurner syndrome	1	0	0	0	0	0	0	1	0.3	0.0	0.0	0.0	0.0	0.0	0.1
warfarin	Vascular disorders	Orthostatic hypotension	0	1	0	0	0	0	0	1	0.0	0.3	0.0	0.0	0.0	0.0	0.1
warfarin	Vascular disorders	Post thrombotic syndrome	0	0	1	0	0	0	0	1	0.0	0.0	0.3	0.0	0.0	0.0	0.1
warfarin	Vascular disorders	Thrombophlebitis	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1
warfarin	Vascular disorders	Vasodilatation	0	0	0	0	1	0	0	1	0.0	0.0	0.0	0.0	0.3	0.0	0.1



## Appendix 11a. Reasons for Stopping rivaroxaban

Treatment group	Indication	System Organ Class	Reason for Stopping	n
rivaroxaban	nvaf/af	General disorders and administration site conditions	Reason not provided	11
rivaroxaban	nvaf/af	General disorders and administration site conditions	Doctor decision	7
rivaroxaban	nvaf/af	Surgical and medical procedures	Hospitalisation	7
rivaroxaban	nvaf/af	Gastrointestinal disorders	Rectal haemorrhage	5
rivaroxaban	nvaf/af	Social circumstances	Refusal of treatment by patient	5
rivaroxaban	nvaf/af	Surgical and medical procedures	Surgery	5
rivaroxaban	nvaf/af	Vascular disorders	Haemorrhage	5
rivaroxaban	nvaf/af	General disorders and administration site conditions	Malaise	4
rivaroxaban	nvaf/af	Respiratory, thoracic and mediastinal disorders	Epistaxis	4
rivaroxaban	nvaf/af	Gastrointestinal disorders	Diarrhoea	3
rivaroxaban	nvaf/af	General disorders and administration site conditions	Death	3
rivaroxaban	nvaf/af	Social circumstances	Treatment noncompliance	3
rivaroxaban	nvaf/af	Surgical and medical procedures	Cardiac pacemaker insertion	3
rivaroxaban	nvaf/af	Cardiac disorders	Atrial fibrillation	2
rivaroxaban	nvaf/af	Gastrointestinal disorders	Melaena	2
rivaroxaban	nvaf/af	General disorders and administration site conditions	Changed regime R for stopping	2
rivaroxaban	nvaf/af	General disorders and administration site conditions	Drug intolerance	2
rivaroxaban	nvaf/af	Injury, poisoning and procedural complications	Contusion	2
rivaroxaban	nvaf/af	Injury, poisoning and procedural complications	Fall	2
rivaroxaban	nvaf/af	Injury, poisoning and procedural complications	Synovial rupture	2
rivaroxaban	nvaf/af	Investigations	Arteriogram coronary	2
rivaroxaban	nvaf/af	Investigations	Biopsy prostate	2
rivaroxaban	nvaf/af	Investigations	Computerised tomogram	2
rivaroxaban	nvaf/af	Investigations	Haemoglobin decreased	2
rivaroxaban	nvaf/af	Investigations	Sinus rhythm	2
rivaroxaban	nvaf/af	Investigations	Ultrasound scan	2
rivaroxaban	nvaf/af	Nervous system disorders	Dizziness	2
rivaroxaban	nvaf/af	Nervous system disorders	Headache	2
rivaroxaban	nvaf/af	Renal and urinary disorders	Haematuria	2
rivaroxaban	nvaf/af	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	2
rivaroxaban	nvaf/af	Skin and subcutaneous tissue disorders	Dermatitis allergic	2
rivaroxaban	nvaf/af	Surgical and medical procedures	Carotid endarterectomy	2

## Appendix 11a. Reasons for Stopping rivaroxaban

Treatment group	Indication	System Organ Class	Reason for Stopping	n
rivaroxaban	nvaf/af	Surgical and medical procedures	Palliative care	2
rivaroxaban	nvaf/af	Surgical and medical procedures	Tooth extraction	2
rivaroxaban	nvaf/af	Cardiac disorders	Myocardial infarction	1
rivaroxaban	nvaf/af	Cardiac disorders	Palpitations	1
rivaroxaban	nvaf/af	Cardiac disorders	Ventricular fibrillation	1
rivaroxaban	nvaf/af	Gastrointestinal disorders	Dysphagia	1
rivaroxaban	nvaf/af	Gastrointestinal disorders	Epigastric discomfort	1
rivaroxaban	nvaf/af	Gastrointestinal disorders	Gastrointestinal haemorrhage	1
rivaroxaban	nvaf/af	Gastrointestinal disorders	Gastrooesophageal reflux disease	1
rivaroxaban	nvaf/af	Gastrointestinal disorders	Gingival bleeding	1
rivaroxaban	nvaf/af	Gastrointestinal disorders	Mallory-Weiss syndrome	1
rivaroxaban	nvaf/af	Gastrointestinal disorders	Mouth haemorrhage	1
rivaroxaban	nvaf/af	Gastrointestinal disorders	Nausea	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Adverse drug reaction	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Asthenia	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	CATHETERISE	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Chest discomfort	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Chest pain	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Drug difficult to obtain	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Drug re-started	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Fatigue	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Feeling hot	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Found on floor	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Patient concerns with drug	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Planned duration	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Planned duration R for stopping	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Review of diagnosis	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Short term use only	1
rivaroxaban	nvaf/af	General disorders and administration site conditions	Stopped by specialist	1
rivaroxaban	nvaf/af	Injury, poisoning and procedural complications	Brain contusion	1
rivaroxaban	nvaf/af	Injury, poisoning and procedural complications	Extradural haematoma	1
rivaroxaban	nvaf/af	Injury, poisoning and procedural complications	Head injury	1

## Appendix 11a. Reasons for Stopping rivaroxaban

Treatment group	Indication	System Organ Class	Reason for Stopping	n
rivaroxaban	nvaf/af	Injury, poisoning and procedural complications	Laceration	1
rivaroxaban	nvaf/af	Injury, poisoning and procedural complications	Post procedural haemorrhage	1
rivaroxaban	nvaf/af	Injury, poisoning and procedural complications	Subdural haematoma	1
rivaroxaban	nvaf/af	Investigations	Angiogram	1
rivaroxaban	nvaf/af	Investigations	Hysteroscopy	1
rivaroxaban	nvaf/af	Investigations	Ultrasound prostate	1
rivaroxaban	nvaf/af	Musculoskeletal and connective tissue disorders	Haemarthrosis	1
rivaroxaban	nvaf/af	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder cancer	1
rivaroxaban	nvaf/af	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm malignant	1
rivaroxaban	nvaf/af	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Meningioma	1
rivaroxaban	nvaf/af	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to central nervous system	1
rivaroxaban	nvaf/af	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rectal cancer	1
rivaroxaban	nvaf/af	Nervous system disorders	Cerebrovascular accident	1
rivaroxaban	nvaf/af	Nervous system disorders	Cognitive disorder	1
rivaroxaban	nvaf/af	Nervous system disorders	Dysgeusia	1
rivaroxaban	nvaf/af	Nervous system disorders	Ischaemic stroke	1
rivaroxaban	nvaf/af	Nervous system disorders	Subarachnoid haemorrhage	1
rivaroxaban	nvaf/af	Nervous system disorders	Transient ischaemic attack	1
rivaroxaban	nvaf/af	Psychiatric disorders	Alcoholism	1
rivaroxaban	nvaf/af	Psychiatric disorders	Hallucination, auditory	1
rivaroxaban	nvaf/af	Psychiatric disorders	Insomnia	1
rivaroxaban	nvaf/af	Renal and urinary disorders	Chromaturia	1
rivaroxaban	nvaf/af	Reproductive system and breast disorders	Postmenopausal haemorrhage	1
rivaroxaban	nvaf/af	Reproductive system and breast disorders	Uterine polyp	1
rivaroxaban	nvaf/af	Reproductive system and breast disorders	Vaginal haemorrhage	1
rivaroxaban	nvaf/af	Respiratory, thoracic and mediastinal disorders	Dyspnoea	1
rivaroxaban	nvaf/af	Respiratory, thoracic and mediastinal disorders	Pleural effusion	1
rivaroxaban	nvaf/af	Skin and subcutaneous tissue disorders	Pruritus	1
rivaroxaban	nvaf/af	Skin and subcutaneous tissue disorders	Rash	1
rivaroxaban	nvaf/af	Social circumstances	Contraindication to medical treatment	1
rivaroxaban	nvaf/af	Surgical and medical procedures	Aortic aneurysm repair	1
rivaroxaban	nvaf/af	Surgical and medical procedures	Aortic valve replacement	1

## Appendix 11a. Reasons for Stopping rivaroxaban

Treatment group	Indication	System Organ Class	Reason for Stopping	n
rivaroxaban	nvaf/af	Surgical and medical procedures	Bladder neck operation	1
rivaroxaban	nvaf/af	Surgical and medical procedures	Cardioversion	1
rivaroxaban	nvaf/af	Surgical and medical procedures	Drug therapy changed	1
rivaroxaban	nvaf/af	Surgical and medical procedures	Gastrostomy tube insertion	1
rivaroxaban	nvaf/af	Surgical and medical procedures	Medical device removal	1
rivaroxaban	nvaf/af	Surgical and medical procedures	Nasal septal operation	1
rivaroxaban	nvaf/af	Surgical and medical procedures	Percutaneous coronary intervention	1
rivaroxaban	nvaf/af	Surgical and medical procedures	Preoperative care	1
rivaroxaban	nvaf/af	Vascular disorders	Circulatory collapse	1
rivaroxaban	nvaf/af	Vascular disorders	Orthostatic hypotension	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	COURSE COMPLETED	23
rivaroxaban	dvt/pe	General disorders and administration site conditions	End of course	22
rivaroxaban	dvt/pe	General disorders and administration site conditions	Reason not provided	22
rivaroxaban	dvt/pe	Surgical and medical procedures	Hospitalisation	19
rivaroxaban	dvt/pe	Gastrointestinal disorders	Rectal haemorrhage	10
rivaroxaban	dvt/pe	General disorders and administration site conditions	Doctor decision	9
rivaroxaban	dvt/pe	Gastrointestinal disorders	Nausea	8
rivaroxaban	dvt/pe	Respiratory, thoracic and mediastinal disorders	Epistaxis	8
rivaroxaban	dvt/pe	Gastrointestinal disorders	Gastrointestinal haemorrhage	7
rivaroxaban	dvt/pe	Gastrointestinal disorders	Vomiting	7
rivaroxaban	dvt/pe	General disorders and administration site conditions	Pre-existing condition improved	7
rivaroxaban	dvt/pe	Nervous system disorders	Dizziness	7
rivaroxaban	dvt/pe	Social circumstances	Refusal of treatment by patient	7
rivaroxaban	dvt/pe	Social circumstances	Treatment noncompliance	7
rivaroxaban	dvt/pe	Gastrointestinal disorders	Melaena	6
rivaroxaban	dvt/pe	Investigations	Haemoglobin decreased	6
rivaroxaban	dvt/pe	Gastrointestinal disorders	Haematemesis	4
rivaroxaban	dvt/pe	General disorders and administration site conditions	Adverse drug reaction	4
rivaroxaban	dvt/pe	Injury, poisoning and procedural complications	Drug dose omission	4
rivaroxaban	dvt/pe	Nervous system disorders	Headache	4
rivaroxaban	dvt/pe	Renal and urinary disorders	Haematuria	4
rivaroxaban	dvt/pe	Skin and subcutaneous tissue disorders	Rash	4

## Appendix 11a. Reasons for Stopping rivaroxaban

Treatment group	Indication	System Organ Class	Reason for Stopping	n
rivaroxaban	dvt/pe	Surgical and medical procedures	Emergency care	4
rivaroxaban	dvt/pe	Surgical and medical procedures	Surgery	4
rivaroxaban	dvt/pe	Vascular disorders	Deep vein thrombosis	4
rivaroxaban	dvt/pe	Gastrointestinal disorders	Constipation	3
rivaroxaban	dvt/pe	General disorders and administration site conditions	Chest pain	3
rivaroxaban	dvt/pe	General disorders and administration site conditions	Oedema peripheral	3
rivaroxaban	dvt/pe	General disorders and administration site conditions	Referred to specialist	3
rivaroxaban	dvt/pe	General disorders and administration site conditions	Seen in haematology	3
rivaroxaban	dvt/pe	Injury, poisoning and procedural complications	Fall	3
rivaroxaban	dvt/pe	Investigations	Investigation	3
rivaroxaban	dvt/pe	Musculoskeletal and connective tissue disorders	Pain in extremity	3
rivaroxaban	dvt/pe	Nervous system disorders	Ischaemic stroke	3
rivaroxaban	dvt/pe	Renal and urinary disorders	Renal impairment	3
rivaroxaban	dvt/pe	Reproductive system and breast disorders	Vaginal haemorrhage	3
rivaroxaban	dvt/pe	Respiratory, thoracic and mediastinal disorders	Haemoptysis	3
rivaroxaban	dvt/pe	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	3
rivaroxaban	dvt/pe	Surgical and medical procedures	Drug therapy changed	3
rivaroxaban	dvt/pe	Cardiac disorders	Palpitations	2
rivaroxaban	dvt/pe	Gastrointestinal disorders	Dyspepsia	2
rivaroxaban	dvt/pe	Gastrointestinal disorders	Faeces discoloured	2
rivaroxaban	dvt/pe	Gastrointestinal disorders	Haematochezia	2
rivaroxaban	dvt/pe	General disorders and administration site conditions	Diagnosis revised	2
rivaroxaban	dvt/pe	General disorders and administration site conditions	Hospital advised	2
rivaroxaban	dvt/pe	General disorders and administration site conditions	Hospital decision	2
rivaroxaban	dvt/pe	General disorders and administration site conditions	Lifestyle issues	2
rivaroxaban	dvt/pe	General disorders and administration site conditions	Ran out of medication	2
rivaroxaban	dvt/pe	General disorders and administration site conditions	Secondary care advice, formulary or guidance	2
rivaroxaban	dvt/pe	General disorders and administration site conditions	Short course only	2
rivaroxaban	dvt/pe	Injury, poisoning and procedural complications	Hip fracture	2
rivaroxaban	dvt/pe	Investigations	Colonoscopy	2
rivaroxaban	dvt/pe	Investigations	International normalised ratio increased	2
rivaroxaban	dvt/pe	Investigations	Liver function test abnormal	2

## Appendix 11a. Reasons for Stopping rivaroxaban

Treatment group	Indication	System Organ Class	Reason for Stopping	n
rivaroxaban	dvt/pe	Investigations	Oesophagogastroduodenoscopy	2
rivaroxaban	dvt/pe	Respiratory, thoracic and mediastinal disorders	Dyspnoea	2
rivaroxaban	dvt/pe	Skin and subcutaneous tissue disorders	Dermatitis	2
rivaroxaban	dvt/pe	Surgical and medical procedures	Haemorrhage prophylaxis	2
rivaroxaban	dvt/pe	Surgical and medical procedures	Thrombolysis	2
rivaroxaban	dvt/pe	Surgical and medical procedures	Transfusion	2
rivaroxaban	dvt/pe	Blood and lymphatic system disorders	Anaemia	1
rivaroxaban	dvt/pe	Blood and lymphatic system disorders	Thrombocytopenia	1
rivaroxaban	dvt/pe	Cardiac disorders	Cardiac failure congestive	1
rivaroxaban	dvt/pe	Cardiac disorders	Congestive cardiomyopathy	1
rivaroxaban	dvt/pe	Cardiac disorders	Pericardial effusion	1
rivaroxaban	dvt/pe	Cardiac disorders	Ventricular fibrillation	1
rivaroxaban	dvt/pe	Eye disorders	Conjunctivitis	1
rivaroxaban	dvt/pe	Eye disorders	Eye pain	1
rivaroxaban	dvt/pe	Eye disorders	Eye pruritus	1
rivaroxaban	dvt/pe	Eye disorders	Vision blurred	1
rivaroxaban	dvt/pe	Gastrointestinal disorders	Abdominal discomfort	1
rivaroxaban	dvt/pe	Gastrointestinal disorders	Abnormal faeces	1
rivaroxaban	dvt/pe	Gastrointestinal disorders	Gastric ulcer haemorrhage	1
rivaroxaban	dvt/pe	Gastrointestinal disorders	Gastrointestinal disorder	1
rivaroxaban	dvt/pe	Gastrointestinal disorders	Ileus paralytic	1
rivaroxaban	dvt/pe	Gastrointestinal disorders	Mouth haemorrhage	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Adverse reaction	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Antidote	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Drug ineffective	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Drug interaction	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Drug intolerance	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Drug no longer required	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Drug re-started	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Fatigue	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Feeling hot	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	General physical health deterioration	1

## Appendix 11a. Reasons for Stopping rivaroxaban

Treatment group	Indication	System Organ Class	Reason for Stopping	n
rivaroxaban	dvt/pe	General disorders and administration site conditions	Hospital changed medication	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Local swelling	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Malaise	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	No further prescription given	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	No further request from patient	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Oedema	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Only one prescription	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Papillary serous endometrial carcinoma m	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Patient muddled about medication	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Planned duration	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Planned duration R for stopping	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Practice advice, formulary or guidelines	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Stopped by consultant	1
rivaroxaban	dvt/pe	General disorders and administration site conditions	Stopped by specialist	1
rivaroxaban	dvt/pe	Hepatobiliary disorders	Hepatic function abnormal	1
rivaroxaban	dvt/pe	Immune system disorders	Hypersensitivity	1
rivaroxaban	dvt/pe	Infections and infestations	Gastroenteritis	1
rivaroxaban	dvt/pe	Injury, poisoning and procedural complications	Acetabulum fracture	1
rivaroxaban	dvt/pe	Injury, poisoning and procedural complications	Contusion	1
rivaroxaban	dvt/pe	Investigations	Abdomen scan	1
rivaroxaban	dvt/pe	Investigations	Angiogram	1
rivaroxaban	dvt/pe	Investigations	Antiphospholipid antibodies positive	1
rivaroxaban	dvt/pe	Investigations	Aspiration biopsy	1
rivaroxaban	dvt/pe	Investigations	Biopsy lung	1
rivaroxaban	dvt/pe	Investigations	Biopsy lymph gland	1
rivaroxaban	dvt/pe	Investigations	Blood creatine abnormal	1
rivaroxaban	dvt/pe	Investigations	Blood test	1
rivaroxaban	dvt/pe	Investigations	Coma scale abnormal	1
rivaroxaban	dvt/pe	Investigations	Endobronchial ultrasound	1
rivaroxaban	dvt/pe	Investigations	Endoscopy	1
rivaroxaban	dvt/pe	Investigations	Endoscopy upper gastrointestinal tract	1
rivaroxaban	dvt/pe	Investigations	Glomerular filtration rate decreased	1

## Appendix 11a. Reasons for Stopping rivaroxaban

Treatment group	Indication	System Organ Class	Reason for Stopping	n
rivaroxaban	dvt/pe	Investigations	Heart rate decreased	1
rivaroxaban	dvt/pe	Investigations	Laparoscopy	1
rivaroxaban	dvt/pe	Investigations	Orthopaedic examination	1
rivaroxaban	dvt/pe	Investigations	Scan normal	1
rivaroxaban	dvt/pe	Investigations	Sigmoidoscopy	1
rivaroxaban	dvt/pe	Investigations	Ultrasound chest	1
rivaroxaban	dvt/pe	Investigations	Ultrasound scan	1
rivaroxaban	dvt/pe	Investigations	Vascular test normal	1
rivaroxaban	dvt/pe	Investigations	Weight abnormal	1
rivaroxaban	dvt/pe	Musculoskeletal and connective tissue disorders	Limb discomfort	1
rivaroxaban	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to adrenals	1
rivaroxaban	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to bone	1
rivaroxaban	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to lung	1
rivaroxaban	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastasis	1
rivaroxaban	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1
rivaroxaban	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pancreatic carcinoma metastatic	1
rivaroxaban	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Renal cancer	1
rivaroxaban	dvt/pe	Nervous system disorders	Cerebrovascular accident	1
rivaroxaban	dvt/pe	Nervous system disorders	Lethargy	1
rivaroxaban	dvt/pe	Nervous system disorders	Neurological symptom	1
rivaroxaban	dvt/pe	Psychiatric disorders	Insomnia	1
rivaroxaban	dvt/pe	Psychiatric disorders	Sleep disorder	1
rivaroxaban	dvt/pe	Renal and urinary disorders	Nephrotic syndrome	1
rivaroxaban	dvt/pe	Renal and urinary disorders	Renal mass	1
rivaroxaban	dvt/pe	Reproductive system and breast disorders	Polymenorrhoea	1
rivaroxaban	dvt/pe	Respiratory, thoracic and mediastinal disorders	Aspiration	1
rivaroxaban	dvt/pe	Respiratory, thoracic and mediastinal disorders	Cough	1
rivaroxaban	dvt/pe	Respiratory, thoracic and mediastinal disorders	Pleural effusion	1
rivaroxaban	dvt/pe	Respiratory, thoracic and mediastinal disorders	Pneumothorax	1
rivaroxaban	dvt/pe	Respiratory, thoracic and mediastinal disorders	Respiratory distress	1
rivaroxaban	dvt/pe	Respiratory, thoracic and mediastinal disorders	Wheezing	1
rivaroxaban	dvt/pe	Skin and subcutaneous tissue disorders	Dry skin	1



## Appendix 11a. Reasons for Stopping rivaroxaban

Treatment group	Indication	System Organ Class	Reason for Stopping	n
rivaroxaban	dvt/pe	Skin and subcutaneous tissue disorders	Rash erythematous	1
rivaroxaban	dvt/pe	Skin and subcutaneous tissue disorders	Rash maculo-papular	1
rivaroxaban	dvt/pe	Skin and subcutaneous tissue disorders	Scab	1
rivaroxaban	dvt/pe	Skin and subcutaneous tissue disorders	Skin reaction	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Cardiac pacemaker insertion	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Cholecystectomy	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Colon operation	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Cyst drainage	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Drain placement	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Incisional drainage	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Knee operation	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Oesophageal dilation procedure	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Palliative care	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Percutaneous coronary intervention	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Preoperative care	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Therapy regimen changed	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Thoracic cavity drainage	1
rivaroxaban	dvt/pe	Surgical and medical procedures	Vena cava filter insertion	1
rivaroxaban	dvt/pe	Vascular disorders	Circulatory collapse	1
rivaroxaban	dvt/pe	Vascular disorders	Embolism venous	1
rivaroxaban	dvt/pe	Vascular disorders	Haematoma	1
rivaroxaban	dvt/pe	Vascular disorders	Haemorrhagic infarction	1
rivaroxaban	dvt/pe	Vascular disorders	Thrombophlebitis	1
rivaroxaban	mixed	Gastrointestinal disorders	Haematemesis	1
rivaroxaban	mixed	Gastrointestinal disorders	Intestinal ischaemia	1
rivaroxaban	mixed	General disorders and administration site conditions	Reason not provided	1
rivaroxaban	mixed	Respiratory, thoracic and mediastinal disorders	Epistaxis	1
rivaroxaban	mixed	Surgical and medical procedures	Cardioversion	1
rivaroxaban	mixed	Surgical and medical procedures	Emergency care	1
rivaroxaban	mixed	Surgical and medical procedures	High frequency ablation	1
rivaroxaban	mixed	Vascular disorders	Circulatory collapse	1
rivaroxaban	other	Cardiac disorders	Intracardiac thrombus	1

## Appendix 11a. Reasons for Stopping rivaroxaban

Treatment group	Indication	System Organ Class	Reason for Stopping	n
rivaroxaban	other	Gastrointestinal disorders	Diarrhoea	1
rivaroxaban	other	Gastrointestinal disorders	Retching	1
rivaroxaban	other	General disorders and administration site conditions	End of course	1
rivaroxaban	other	General disorders and administration site conditions	Fatigue	1
rivaroxaban	other	General disorders and administration site conditions	Reason not provided	1
rivaroxaban	other	General disorders and administration site conditions	Seen in haematology	1
rivaroxaban	other	Nervous system disorders	Tremor	1
rivaroxaban	other	Vascular disorders	Thrombophlebitis superficial	1

## Appendix 11b. Reasons for Stopping warfarin

Treatment group	Indication	System Organ Class	Reason for Stopping	n
warfarin	nvaf/af	Investigations	International normalised ratio increased	31
warfarin	nvaf/af	General disorders and administration site conditions	Reason not provided	10
warfarin	nvaf/af	Social circumstances	Treatment noncompliance	7
warfarin	nvaf/af	Investigations	International normalised ratio fluctuation	6
warfarin	nvaf/af	Social circumstances	Refusal of treatment by patient	6
warfarin	nvaf/af	General disorders and administration site conditions	Doctor decision	5
warfarin	nvaf/af	Surgical and medical procedures	Hospitalisation	5
warfarin	nvaf/af	General disorders and administration site conditions	Malaise	4
warfarin	nvaf/af	Surgical and medical procedures	Drug therapy changed	4
warfarin	nvaf/af	Gastrointestinal disorders	Rectal haemorrhage	3
warfarin	nvaf/af	General disorders and administration site conditions	Death	2
warfarin	nvaf/af	Injury, poisoning and procedural complications	Fall	2
warfarin	nvaf/af	Investigations	Anticoagulation drug level above therapeutic	2
warfarin	nvaf/af	Investigations	Cardiovascular evaluation	2
warfarin	nvaf/af	Investigations	Colonoscopy	2
warfarin	nvaf/af	Surgical and medical procedures	Preoperative care	2
warfarin	nvaf/af	Surgical and medical procedures	Surgery	2
warfarin	nvaf/af	Vascular disorders	Haematoma	2
warfarin	nvaf/af	Blood and lymphatic system disorders	Microcytic anaemia	1
warfarin	nvaf/af	Cardiac disorders	Acute myocardial infarction	1
warfarin	nvaf/af	Cardiac disorders	Cardiac failure congestive	1
warfarin	nvaf/af	Cardiac disorders	Sinus bradycardia	1
warfarin	nvaf/af	Congenital, familial and genetic disorders	Atrial septal defect	1
warfarin	nvaf/af	Gastrointestinal disorders	Abdominal discomfort	1
warfarin	nvaf/af	Gastrointestinal disorders	Abdominal pain	1
warfarin	nvaf/af	Gastrointestinal disorders	Gastrointestinal haemorrhage	1
warfarin	nvaf/af	Gastrointestinal disorders	Haematochezia	1
warfarin	nvaf/af	Gastrointestinal disorders	Oral pain	1
warfarin	nvaf/af	Gastrointestinal disorders	Upper gastrointestinal haemorrhage	1
warfarin	nvaf/af	General disorders and administration site conditions	Asthenia	1
warfarin	nvaf/af	General disorders and administration site conditions	CHA2DS2-VASc annual stroke risk moderate	1
warfarin	nvaf/af	General disorders and administration site conditions	Diagnosis revised	1
warfarin	nvaf/af	General disorders and administration site conditions	Dr Preference	1
warfarin	nvaf/af	General disorders and administration site conditions	Health problems	1

## Appendix 11b. Reasons for Stopping warfarin

Treatment group	Indication	System Organ Class	Reason for Stopping	n
warfarin	nvaf/af	General disorders and administration site conditions	Hospital decision	1
warfarin	nvaf/af	General disorders and administration site conditions	Labial reduction	1
warfarin	nvaf/af	General disorders and administration site conditions	Lifestyle issues	1
warfarin	nvaf/af	General disorders and administration site conditions	Medical device complication	1
warfarin	nvaf/af	General disorders and administration site conditions	Nil by mouth	1
warfarin	nvaf/af	General disorders and administration site conditions	Not sure whether taken	1
warfarin	nvaf/af	General disorders and administration site conditions	Patient decision to not take drug	1
warfarin	nvaf/af	General disorders and administration site conditions	Patient muddled about medication	1
warfarin	nvaf/af	General disorders and administration site conditions	Practice advice, formulary or guidelines	1
warfarin	nvaf/af	General disorders and administration site conditions	Prescribing guidelines	1
warfarin	nvaf/af	General disorders and administration site conditions	Ran out of medication	1
warfarin	nvaf/af	General disorders and administration site conditions	Referred to specialist	1
warfarin	nvaf/af	General disorders and administration site conditions	Stopped by specialist	1
warfarin	nvaf/af	Injury, poisoning and procedural complications	Contusion	1
warfarin	nvaf/af	Injury, poisoning and procedural complications	Head injury	1
warfarin	nvaf/af	Investigations	Biopsy liver	1
warfarin	nvaf/af	Investigations	Biopsy lung	1
warfarin	nvaf/af	Investigations	Biopsy vulva	1
warfarin	nvaf/af	Investigations	Bronchoscopy	1
warfarin	nvaf/af	Investigations	Cystoscopy	1
warfarin	nvaf/af	Investigations	Electromyogram	1
warfarin	nvaf/af	Investigations	International normalised ratio	1
warfarin	nvaf/af	Investigations	International normalised ratio decreased	1
warfarin	nvaf/af	Investigations	Investigation	1
warfarin	nvaf/af	Investigations	Liver function test abnormal	1
warfarin	nvaf/af	Investigations	Sinus rhythm	1
warfarin	nvaf/af	Metabolism and nutrition disorders	Polydipsia	1
warfarin	nvaf/af	Musculoskeletal and connective tissue disorders	Arthralgia	1
warfarin	nvaf/af	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gastrointestinal stromal tumour	1
warfarin	nvaf/af	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastasis	1
warfarin	nvaf/af	Nervous system disorders	Carpal tunnel syndrome	1
warfarin	nvaf/af	Nervous system disorders	Epilepsy	1
warfarin	nvaf/af	Nervous system disorders	Haemorrhage intracranial	1
warfarin	nvaf/af	Nervous system disorders	Sedation	1

## Appendix 11b. Reasons for Stopping warfarin

Treatment group	Indication	System Organ Class	Reason for Stopping	n
warfarin	nvaf/af	Psychiatric disorders	Alcohol abuse	1
warfarin	nvaf/af	Psychiatric disorders	Anxiety	1
warfarin	nvaf/af	Renal and urinary disorders	Renal impairment	1
warfarin	nvaf/af	Reproductive system and breast disorders	Vulval disorder	1
warfarin	nvaf/af	Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	1
warfarin	nvaf/af	Respiratory, thoracic and mediastinal disorders	Pulmonary oedema	1
warfarin	nvaf/af	Social circumstances	Elderly	1
warfarin	nvaf/af	Surgical and medical procedures	Angioplasty	1
warfarin	nvaf/af	Surgical and medical procedures	Cardioversion	1
warfarin	nvaf/af	Surgical and medical procedures	Diathermy	1
warfarin	nvaf/af	Surgical and medical procedures	Gastrectomy	1
warfarin	nvaf/af	Surgical and medical procedures	Intensive care	1
warfarin	nvaf/af	Surgical and medical procedures	Joint injection	1
warfarin	nvaf/af	Surgical and medical procedures	Nerve block	1
warfarin	nvaf/af	Surgical and medical procedures	Palliative care	1
warfarin	nvaf/af	Surgical and medical procedures	Percutaneous coronary intervention	1
warfarin	nvaf/af	Surgical and medical procedures	Stent placement	1
warfarin	nvaf/af	Surgical and medical procedures	Therapy regimen changed	1
warfarin	nvaf/af	Surgical and medical procedures	Transurethral prostatectomy	1
warfarin	nvaf/af	Surgical and medical procedures	Vascular graft	1
warfarin	nvaf/af	Vascular disorders	Aortic dilatation	1
warfarin	dvt/pe	Investigations	International normalised ratio increased	32
warfarin	dvt/pe	General disorders and administration site conditions	Reason not provided	25
warfarin	dvt/pe	General disorders and administration site conditions	Doctor decision	12
warfarin	dvt/pe	General disorders and administration site conditions	COURSE COMPLETED	9
warfarin	dvt/pe	Social circumstances	Refusal of treatment by patient	9
warfarin	dvt/pe	Surgical and medical procedures	Drug therapy changed	9
warfarin	dvt/pe	General disorders and administration site conditions	Lifestyle issues	8
warfarin	dvt/pe	Investigations	International normalised ratio	8
warfarin	dvt/pe	Investigations	International normalised ratio fluctuation	7
warfarin	dvt/pe	General disorders and administration site conditions	Pre-existing condition improved	5
warfarin	dvt/pe	Respiratory, thoracic and mediastinal disorders	Epistaxis	5
warfarin	dvt/pe	Investigations	Colonoscopy	4
warfarin	dvt/pe	Surgical and medical procedures	Hospitalisation	4

## Appendix 11b. Reasons for Stopping warfarin

Treatment group	Indication	System Organ Class	Reason for Stopping	n
warfarin	dvt/pe	Gastrointestinal disorders	Rectal haemorrhage	3
warfarin	dvt/pe	General disorders and administration site conditions	Dr Preference	3
warfarin	dvt/pe	General disorders and administration site conditions	End of course	3
warfarin	dvt/pe	General disorders and administration site conditions	Seen in haematology	3
warfarin	dvt/pe	General disorders and administration site conditions	Stopped by specialist	3
warfarin	dvt/pe	Investigations	Bronchoscopy	3
warfarin	dvt/pe	Investigations	Liver function test abnormal	3
warfarin	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	3
warfarin	dvt/pe	Renal and urinary disorders	Haematuria	3
warfarin	dvt/pe	Social circumstances	Treatment noncompliance	3
warfarin	dvt/pe	Surgical and medical procedures	Chemotherapy	3
warfarin	dvt/pe	Gastrointestinal disorders	Abdominal pain upper	2
warfarin	dvt/pe	General disorders and administration site conditions	Diagnosis revised	2
warfarin	dvt/pe	General disorders and administration site conditions	Hospital advised	2
warfarin	dvt/pe	General disorders and administration site conditions	Prescribing guidelines	2
warfarin	dvt/pe	General disorders and administration site conditions	Referred to specialist	2
warfarin	dvt/pe	Injury, poisoning and procedural complications	Contusion	2
warfarin	dvt/pe	Investigations	Biopsy	2
warfarin	dvt/pe	Investigations	Biopsy prostate	2
warfarin	dvt/pe	Investigations	Haemoglobin decreased	2
warfarin	dvt/pe	Investigations	Platelet count decreased	2
warfarin	dvt/pe	Reproductive system and breast disorders	Vaginal haemorrhage	2
warfarin	dvt/pe	Respiratory, thoracic and mediastinal disorders	Haemoptysis	2
warfarin	dvt/pe	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	2
warfarin	dvt/pe	Surgical and medical procedures	Palliative care	2
warfarin	dvt/pe	Surgical and medical procedures	Polypectomy	2
warfarin	dvt/pe	Surgical and medical procedures	Surgery	2
warfarin	dvt/pe	Surgical and medical procedures	Thoracic cavity drainage	2
warfarin	dvt/pe	Surgical and medical procedures	Vena cava filter insertion	2
warfarin	dvt/pe	Blood and lymphatic system disorders	Thrombocytopenia	1
warfarin	dvt/pe	Cardiac disorders	Cardiac failure congestive	1
warfarin	dvt/pe	Cardiac disorders	Left ventricular dysfunction	1
warfarin	dvt/pe	Gastrointestinal disorders	Abdominal mass	1
warfarin	dvt/pe	Gastrointestinal disorders	Gastrointestinal haemorrhage	1

## Appendix 11b. Reasons for Stopping warfarin

Treatment group	Indication	System Organ Class	Reason for Stopping	n
warfarin	dvt/pe	Gastrointestinal disorders	Haematemesis	1
warfarin	dvt/pe	Gastrointestinal disorders	Melaena	1
warfarin	dvt/pe	Gastrointestinal disorders	Nausea	1
warfarin	dvt/pe	Gastrointestinal disorders	Vomiting	1
warfarin	dvt/pe	General disorders and administration site conditions	Adverse drug reaction	1
warfarin	dvt/pe	General disorders and administration site conditions	Death	1
warfarin	dvt/pe	General disorders and administration site conditions	Difficult administration	1
warfarin	dvt/pe	General disorders and administration site conditions	Drug ineffective	1
warfarin	dvt/pe	General disorders and administration site conditions	DRUG INFORMATION	1
warfarin	dvt/pe	General disorders and administration site conditions	Drug intolerance	1
warfarin	dvt/pe	General disorders and administration site conditions	General physical health deterioration	1
warfarin	dvt/pe	General disorders and administration site conditions	Hospital stopped it	1
warfarin	dvt/pe	General disorders and administration site conditions	Intermittent use	1
warfarin	dvt/pe	General disorders and administration site conditions	Malaise	1
warfarin	dvt/pe	General disorders and administration site conditions	Not sure whether taken	1
warfarin	dvt/pe	General disorders and administration site conditions	Oedema peripheral	1
warfarin	dvt/pe	General disorders and administration site conditions	Patient did not attend	1
warfarin	dvt/pe	General disorders and administration site conditions	Planned duration	1
warfarin	dvt/pe	General disorders and administration site conditions	Secondary care advice	1
warfarin	dvt/pe	General disorders and administration site conditions	Stopped by hospital physician	1
warfarin	dvt/pe	General disorders and administration site conditions	Stopped by consultant	1
warfarin	dvt/pe	Injury, poisoning and procedural complications	Accidental overdose	1
warfarin	dvt/pe	Injury, poisoning and procedural complications	Drug dose omission	1
warfarin	dvt/pe	Injury, poisoning and procedural complications	Drug prescribing error	1
warfarin	dvt/pe	Injury, poisoning and procedural complications	Foreign body	1
warfarin	dvt/pe	Injury, poisoning and procedural complications	Overdose	1
warfarin	dvt/pe	Injury, poisoning and procedural complications	Ulnar nerve injury	1
warfarin	dvt/pe	Investigations	Abdomen scan	1
warfarin	dvt/pe	Investigations	Anticoagulation drug level above therapeutic	1
warfarin	dvt/pe	Investigations	Anticoagulation drug level below therapeutic	1
warfarin	dvt/pe	Investigations	Arteriogram coronary	1
warfarin	dvt/pe	Investigations	Aspiration joint	1
warfarin	dvt/pe	Investigations	Aspiration pleural cavity	1
warfarin	dvt/pe	Investigations	Blood alcohol increased	1

## Appendix 11b. Reasons for Stopping warfarin

Treatment group	Indication	System Organ Class	Reason for Stopping	n
warfarin	dvt/pe	Investigations	Blood urine present	1
warfarin	dvt/pe	Investigations	Endoscopy	1
warfarin	dvt/pe	Investigations	Glomerular filtration rate decreased	1
warfarin	dvt/pe	Investigations	International normalised ratio decreased	1
warfarin	dvt/pe	Investigations	Investigation	1
warfarin	dvt/pe	Investigations	Orthopaedic examination	1
warfarin	dvt/pe	Investigations	Scan normal	1
warfarin	dvt/pe	Investigations	Sigmoidoscopy	1
warfarin	dvt/pe	Investigations	Vitamin K	1
warfarin	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colon cancer stage III	1
warfarin	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastasis	1
warfarin	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Multiple myeloma	1
warfarin	dvt/pe	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Oesophageal carcinoma	1
warfarin	dvt/pe	Nervous system disorders	Balance disorder	1
warfarin	dvt/pe	Nervous system disorders	Dizziness	1
warfarin	dvt/pe	Nervous system disorders	Somnolence	1
warfarin	dvt/pe	Renal and urinary disorders	Renal failure	1
warfarin	dvt/pe	Reproductive system and breast disorders	Uterine polyp	1
warfarin	dvt/pe	Respiratory, thoracic and mediastinal disorders	Aspiration	1
warfarin	dvt/pe	Respiratory, thoracic and mediastinal disorders	Pleural effusion	1
warfarin	dvt/pe	Skin and subcutaneous tissue disorders	Alopecia	1
warfarin	dvt/pe	Skin and subcutaneous tissue disorders	Pruritus	1
warfarin	dvt/pe	Skin and subcutaneous tissue disorders	Pruritus generalised	1
warfarin	dvt/pe	Skin and subcutaneous tissue disorders	Rash	1
warfarin	dvt/pe	Skin and subcutaneous tissue disorders	Skin reaction	1
warfarin	dvt/pe	Social circumstances	Bereavement	1
warfarin	dvt/pe	Social circumstances	Drug abuser	1
warfarin	dvt/pe	Social circumstances	Inadequate diet	1
warfarin	dvt/pe	Surgical and medical procedures	Cholecystectomy	1
warfarin	dvt/pe	Surgical and medical procedures	Emergency care	1
warfarin	dvt/pe	Surgical and medical procedures	Hospice care	1
warfarin	dvt/pe	Surgical and medical procedures	Injection	1
warfarin	dvt/pe	Surgical and medical procedures	Intensive care	1
warfarin	dvt/pe	Surgical and medical procedures	Pleurodesis	1



## Appendix 11b. Reasons for Stopping warfarin

Treatment group	Indication	System Organ Class	Reason for Stopping	n
warfarin	dvt/pe	Surgical and medical procedures	Preoperative care	1
warfarin	dvt/pe	Surgical and medical procedures	Removal of foreign body	1
warfarin	dvt/pe	Surgical and medical procedures	Therapy regimen changed	1
warfarin	dvt/pe	Surgical and medical procedures	Thrombolysis	1
warfarin	dvt/pe	Surgical and medical procedures	Tooth extraction	1
warfarin	dvt/pe	Surgical and medical procedures	Tracheostomy	1
warfarin	dvt/pe	Vascular disorders	Deep vein thrombosis	1
warfarin	dvt/pe	Vascular disorders	Haematoma	1
warfarin	mixed	Investigations	International normalised ratio increased	3
warfarin	mixed	Gastrointestinal disorders	Pancreatitis	1
warfarin	mixed	General disorders and administration site conditions	Medical procedure	1
warfarin	mixed	General disorders and administration site conditions	Prescribing advisor advice	1
warfarin	mixed	General disorders and administration site conditions	Prescribing guidelines	1
warfarin	mixed	General disorders and administration site conditions	Reason not provided	1
warfarin	mixed	General disorders and administration site conditions	Sphincterotomy	1
warfarin	mixed	Hepatobiliary disorders	Cholangitis	1
warfarin	mixed	Investigations	Endoscopic retrograde cholangiopancreatography	1
warfarin	mixed	Investigations	International normalised ratio	1
warfarin	mixed	Social circumstances	Treatment noncompliance	1
warfarin	mixed	Surgical and medical procedures	Hospitalisation	1
warfarin	mixed	Surgical and medical procedures	Surgery	1
warfarin	mixed	Surgical and medical procedures	Vena cava filter insertion	1
warfarin	other	Gastrointestinal disorders	Rectal haemorrhage	1
warfarin	other	General disorders and administration site conditions	Reason not provided	2
warfarin	other	Investigations	Biopsy	1
warfarin	other	Investigations	Catheterisation cardiac	1
warfarin	other	Investigations	Colonoscopy	1
warfarin	other	Vascular disorders	Angiodysplasia	1

## Appendix 12a. Causes of Death During Observation Period in rivaroxaban cohort

Cause of death	Period Weeks	1 1&2	2 3&4	3 5&6	4 7&8	5 9&10	6 11&12	Not known
<b>Cardiac disorders</b>		0	0	1	0	0	1	0
Atrial fibrillation		0	0	1	0	0	0	0
Right ventricular failure		0	0	0	0	0	0	0
Myocardial infarction		3	0	0	0	0	0	0
Cardiac failure congestive		1	0	0	0	0	0	0
Left ventricular failure		1	0	0	0	0	0	0
Myocardial ischaemia		1	0	0	0	0	0	0
Cor pulmonale		0	0	0	1	0	0	0
<i>Sub-total</i>		<i>6</i>	<i>0</i>	<i>2</i>	<i>1</i>	<i>0</i>	<i>1</i>	<i>0</i>
<b>Respiratory, thoracic and mediastinal disorders</b>								
Pulmonary embolism		3	2	2	2	0	2	0
Chronic obstructive pulmonary disease		1	1	1	2	0	0	0
Lung disorder		1	0	0	0	0	0	0
Alveolitis fibrosing		0	1	0	0	0	0	0
Respiratory failure		0	1	0	0	0	1	0
Hypoventilation		0	0	1	0	0	0	0
Pneumonia aspiration		0	0	1	0	0	0	0
Pulmonary fibrosis		0	0	1	0	0	0	0
Asthma		0	0	0	0	0	1	0
Bronchiectasis		0	0	0	0	0	1	0
<i>Sub-total</i>		<i>5</i>	<i>5</i>	<i>6</i>	<i>4</i>	<i>0</i>	<i>5</i>	<i>0</i>
<b>Infections and infestations</b>								
Pneumonia		2	2	3	1	0	1	0
Bronchopneumonia		0	0	1	0	0	1	0
Kidney infection		0	0	1	0	0	0	0
Sepsis		0	0	1	0	0	0	0
Clostridial infection		0	0	0	1	0	1	0
Orchitis		0	0	0	1	0	0	0
Pulmonary sepsis		0	0	0	1	0	0	0
Klebsiella sepsis		0	0	0	0	1	0	0
Urinary tract infection		0	0	0	0	1	0	0
Lower respiratory tract infection		0	0	0	0	0	1	0
<i>Sub-total</i>		<i>2</i>	<i>2</i>	<i>6</i>	<i>4</i>	<i>2</i>	<i>4</i>	<i>0</i>
<b>Metabolism and nutrition disorders</b>								
Diabetes mellitus		1	0	0	1	0	0	0
Obesity		0	0	1	0	0	0	0
<i>Sub-total</i>		<i>1</i>	<i>0</i>	<i>1</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>								
Pancreatic carcinoma metastatic		1	0	0	0	0	0	0
Adenocarcinoma		0	1	0	0	0	0	0
B-cell lymphoma		0	1	0	0	0	0	0
Malignant neoplasm of ampulla of Vater		0	1	0	0	0	0	0
Breast cancer metastatic		0	0	1	0	0	0	0
Ovarian cancer metastatic		0	0	1	0	0	0	0
Gastrointestinal carcinoma		0	0	0	1	0	0	0
Metastases to lung		0	0	0	1	0	0	0
Metastatic neoplasm		0	0	0	1	0	1	0
Lymphoma		0	0	0	0	1	1	0
Pancreatic carcinoma metastatic		0	0	0	0	1	0	0

**Appendix 12a. Causes of Death During Observation Period in rivaroxaban cohort**

<b>Cause of death</b>	<b>Period Weeks</b>	<b>1 1&amp;2</b>	<b>2 3&amp;4</b>	<b>3 5&amp;6</b>	<b>4 7&amp;8</b>	<b>5 9&amp;10</b>	<b>6 11&amp;12</b>	<b>Not known</b>
<i>Sub-total</i>		<i>1</i>	<i>3</i>	<i>2</i>	<i>3</i>	<i>2</i>	<i>2</i>	<i>0</i>
<b>Nervous system disorders</b>								
Cerebrovascular accident		1	1	1	0	0	1	0
Cerebrovascular disorder		0	1	1	0	0	0	0
Cerebral infarction		0	0	1	0	0	0	0
Haemorrhagic stroke		0	0	1	0	0	0	0
Ischaemic stroke		0	0	1	0	1	0	0
Parkinson's disease		0	0	0	0	0	1	0
<i>Sub-total</i>		<i>1</i>	<i>2</i>	<i>5</i>	<i>0</i>	<i>1</i>	<i>2</i>	<i>0</i>
<b>Renal and urinary disorders</b>								
Renal failure acute		1	0	0	1	0	1	0
Renal failure chronic		0	0	1	0	0	2	0
<i>Sub-total</i>		<i>1</i>	<i>0</i>	<i>1</i>	<i>1</i>	<i>0</i>	<i>3</i>	<i>0</i>
<b>Blood and lymphatic system disorders</b>								
Aplastic anaemia		0	0	0	1	0	0	0
Lymphadenopathy		0	1	0	0	0	0	0
Lymphadenopathy mediastinal		0	1	0	0	0	0	0
<i>Sub-total</i>		<i>0</i>	<i>2</i>	<i>0</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>
<b>General disorders and administration site conditions</b>								
Asthenia		0	1	1	0	0	0	0
Death		0	0	0	0	0	1	0
Abdominal lymphadenopathy		0	1	0	0	0	0	0
Multi-organ failure		0	0	1	0	0	0	0
<i>Sub-total</i>		<i>0</i>	<i>2</i>	<i>2</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>
<b>Social circumstances</b>								
Elderly		0	1	1	0	0	0	0
<i>Sub-total</i>		<i>0</i>	<i>1</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
<b>Investigations</b>								
Blood pressure increased		0	0	1	0	0	0	0
<i>Sub-total</i>		<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
<b>Musculoskeletal and connective tissue disorders</b>								
Rheumatoid arthritis		0	0	0	1	0	0	0
<i>Sub-total</i>		<i>0</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>
<b>Reproductive system and breast disorder</b>								
Epididymitis		0	0	0	1	0	0	0
<i>Sub-total</i>		<i>0</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>

## Appendix 12b. Causes of Death during Observation Period in warfarin cohort

Cause of death	Period Weeks	1 1&2	2 3&4	3 5&6	4 7&8	5 9&10	6 11&12	Not known
<b>Cardiac disorders</b>								
Atrial fibrillation		1	0	0	0	0	0	0
Cardiac arrest		1	0	1	0	0	0	0
Myocardial infarction		0	1	0	0	0	0	0
Congestive cardiomyopathy		0	0	1	0	0	0	0
Left ventricular failure		0	0	0	1	0	0	0
<i>Sub-total</i>		<i>2</i>	<i>1</i>	<i>2</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>
<b>General disorders and administration site conditions</b>								
Multi-organ failure		1	0	0	1	0	0	0
Death		0	1	1	0	0	0	1
<i>Sub-total</i>		<i>1</i>	<i>1</i>	<i>1</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>1</i>
<b>Infections and infestations</b>								
Pneumonia		1	1	0	0	1	1	0
Clostridial infection		0	1	0	0	0	0	0
Enterocolitis infectious		0	1	0	0	0	0	0
Lobar pneumonia		0	0	1	0	0	0	0
Sepsis		0	0	0	2	2	1	0
Lower respiratory tract infection		0	0	0	0	1	0	0
<i>Sub-total</i>		<i>1</i>	<i>3</i>	<i>1</i>	<i>2</i>	<i>4</i>	<i>2</i>	<i>0</i>
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>								
Lung neoplasm malignant		1	0	1	0	1	0	0
Pancreatic carcinoma		0	0	1	0	0	0	0
Oesophageal cancer metastatic		0	0	0	1	0	0	0
Metastasis		0	0	0	0	0	1	0
<i>Sub-total</i>		<i>1</i>	<i>0</i>	<i>2</i>	<i>1</i>	<i>1</i>	<i>1</i>	<i>0</i>
<b>Nervous system disorders</b>								
Cerebrovascular accident		1	0	0	0	1	0	0
<i>Sub-total</i>		<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>	<i>0</i>
<b>Vascular disorders</b>								
Hypertension		1	0	0	0	0	0	0
<i>Sub-total</i>		<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
<b>Renal and urinary disorders</b>								
Renal failure acute		0	1	0	1	0	0	0
Renal failure		0	0	0	0	1	0	0
<i>Sub-total</i>		<i>0</i>	<i>1</i>	<i>0</i>	<i>1</i>	<i>1</i>	<i>0</i>	<i>0</i>
<b>Respiratory, thoracic and mediastinal disorders</b>								
Interstitial lung disease		0	1	0	0	0	0	0
Haemoptysis		0	0	1	0	0	0	0
Pulmonary fibrosis		0	0	1	0	0	0	0
Pneumonia aspiration		0	0	0	1	0	0	0
Respiratory failure		0	0	0	1	0	1	0
Chronic obstructive pulmonary disease		0	0	0	0	0	1	0
<i>Sub-total</i>		<i>0</i>	<i>1</i>	<i>2</i>	<i>2</i>	<i>0</i>	<i>2</i>	<i>0</i>
<b>Hepatobiliary disorders</b>								
Hepatic failure		0	0	0	0	1	0	0
<i>Sub-total</i>		<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>	<i>0</i>