

**PASS information**

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|--|---|
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| <b>Research question and objectives</b>                  | <p><i>The objectives of the study are to:</i></p> <ol style="list-style-type: none"> <li><i>1. Estimate the proportions of apixaban users in the out-patient setting who receive the drug for the approved indications at the time of the study,</i></li> <li><i>2. Describe the characteristics of the patients who are prescribed apixaban in the out-patient setting for on-label and off-label indications.</i></li> </ol>  |
| <b>Country(-ies) of study</b>                            | <i>Sweden</i>   |
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## 1. ABSTRACT

### Title

POST-APPROVAL SAFETY STUDY (PASS) OF THE UTILIZATION PATTERN OF APIX-  
ABAN IN SWEDEN

20 May 2016

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[REDACTED]

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### Keywords

Apixaban, Drug utilization, on-label, off-label, Novel Oral Anticoagulant

### Rationale and background

Off-label use of a medicinal product occurs when that product is intentionally used for a medical purpose that is not in accordance with the authorised product information. Off-label use of a medicinal product can be of concern, and the frequency of off-label apixaban (ELIQUIS®) use is not known.

In the European Union (EU), apixaban is approved for three indications: (1) prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, (2) prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age  $\geq 75$  years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class  $\geq$  II), (3) treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

### Research question and objectives

The objectives of this study were (1) to estimate the proportion of apixaban users who received the drug on-label, and (2) describe the characteristics of patients using the drug on-label and off-label.

### Study design

This non-interventional descriptive study used retrospectively collected data from the national health registers in Sweden.

## Setting

The Swedish national registers include information on the entire population of Sweden.

## Subjects and study size, including dropouts

This Final Study Report includes all the patients who received at least one apixaban dispensing in a Swedish community pharmacy in first three years after the drug became available (1 January 2012 through 31 December 2014).

*A-priori* the Sponsor projected that 600 patients would receive apixaban after THA/TKA from 2012 to 2014 and that data from those patients would provide sufficient precision around the apixaban utilization estimates. The projected sample size was revised to 19,000 patients in the Protocol B0661017 Amendment 3 based on preliminary data.

## Variables and data sources

The Prescribed Drug Register (PDR) holds data from all community pharmacy dispensing and the National Patient Register (NPR) holds data from all hospital inpatient and outpatient encounters were used for analysis. Apixaban users were identified from PDR.

The main variable was indication for apixaban use. The specific indication as intended by the prescriber was not recorded in the PDR, so a proxy for the indication was assigned from the diagnostic and surgical codes in the NPR. The assigned proxy indications were classified as on-label or off-label based on a predefined criteria of hospital diagnostic and surgical codes. If an apixaban user did not have a record from the pre-defined criteria prior to the apixaban dispensation, then that user remained unclassified.

Data were also collected on patients' age, gender, length of follow-up in the database, other concomitant prescriptions (including other antithrombotics and commonly used medications), and their clinical history (including comorbidities such as renal or hepatic disease).

We anticipated that some diagnoses, particularly NVAF, may be under ascertained from the hospital records, so a regional primary care database from *Västra Götaland* County (VEGA) was added as a sensitivity analysis.

## Results

### Main analysis

**Objective 1:** A total of 17 592 apixaban users were included in the study of which 86.4% (95% Confidence Interval [CI]: 85.9%-86.9%, n=15 204) were assigned on-label indications, 7.7% (CI: 7.3%-8.1%, n=1 358) were assigned off-label indications, and 5.9% (CI: 5.5%-6.2%, n=1 030) were unclassified. Among 16 562 patients assigned to a predefined indication, 91.8% (CI: 91.4%-92.2%) had an indication that was on-label and 8.2% (CI: 7.8%-8.6%) had an off-label indication.

The on-label indications included an elective THA/TKA for 17.3% (n = 2 636) of all on-label patients, a diagnosis of NVAf for 79.9% (n=12 151) of on-label patients and a diagnosis of DVT/PE for 2.7% (n=417) of on-label patients. Among the off-label users, off-label conditions accounted for 42.3% (n=575) of off-label use, non-elective THA/TKA accounted for 0.7% (n=10), off-label AF for 31.5% (n=428), other VTE or DVT/PE before approval for 8.0% (n=108), and off-label surgeries represented 17.3% (n=235) of off-label indications; 2 patients were under 18 years of age when they received apixaban.

**Objective 2:** Among apixaban users, 52.4% were men and 47.6% were women. The mean age of on-label users (73.6 years) was similar to the mean ages for off-label (74.2 years) and unclassified (73.7 years) apixaban users. Common co-medications that were dispensed within 30 days of the apixaban dispensation included other antithrombotics, CYP3A4 and P-gp inhibitors, selective beta blocking agents, HMG CoA reductase inhibitors, osmotically acting laxatives, natural opium alkaloids and anilides. Apixaban for NVAf was associated with longest duration of use (median = 175 days) compared to patients receiving apixaban for THA/TKA (median = 30 days), DVT/PE (median = 84 days). The strength of 5 mg, corresponding to a daily dose of 10 mg, was most commonly prescribed dosage. A history of renal disease occurred in 3.3% (n=561) of patients and liver disorders occurred in 0.4% (n=66) of patients.

### Sensitivity analysis with primary care data

Using data from both the VEGA primary care database and the national hospital registers (n = 5 157), 88.7% (n = 4 572) of patients had on-label indications, 8.9% (n = 457) had off-label indications, and only 2.5% (n=128) could not be classified as on- or off-label users. Of the 97.5% of users with an assigned indication, 90.9% (n=4 572) had an on-label indication and 9.1% (n=457) had an off-label indication.

### Discussion

The majority of apixaban users, 86%, received the drug for an on-label indication. We were not able to infer an indication for 6% of patients who may have received apixaban in the primary care setting. The inclusion of primary care data for a subset of patients did not change the distribution of on-label and off-label indications substantially. When excluding those with an unclassified indication, 92% of all use was for on-label indications. Comorbidities and co-medications, such as opioids following surgery, reflected the age of apixaban users and the indications for use.

### Marketing Authorisation Holder(s)

Bristol-Myers Squibb/Pfizer EEIG, United Kingdom

### Names and affiliations of principal investigators

[REDACTED]

## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition  |
|--------------|---|
| AF           | Atrial Fibrillation   |
| ATC          | Anatomical Therapeutic Chemical classification system   |
| CI           | Confidence Interval   |
| CPE          | Centre for Pharmacoepidemiology   |
| DVT          | Deep Vein Thrombosis  |
| EU           | European Union  |
| GP           | General Practitioner  |
| ICD-10       | International Statistical Classification of Diseases and Related Health Problems - Tenth Revision |
| IQR          | Inter-Quartile Range  |
| NPR          | National Patient Register   |
| NVAF         | Non-Valvular Atrial Fibrillation  |
| NYHA         | New York Heart Association  |
| PDR          | Prescribed Drug Register  |
| PE           | Pulmonary Embolism  |
| SAP          | Statistical Analysis Plan   |
| SE           | Systemic Embolism   |
| SmPC         | Summary of Product Characteristics  |
| THA          | Total Hip Arthroplasty  |
| TIA          | Transient Ischaemic Attack  |
| TKA          | Total Knee Arthroplasty   |
| VAf          | Valvular Atrial Fibrillation  |
| VEGA         | <i>Västra Götaland</i> County Database  |
| VTE          | Venous Thromboembolism  |

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### 3. INVESTIGATORS

#### Principal Investigator(s) of the Protocol

| Name, degree(s) | Title | Affiliation |
|-----------------|-------|-------------|
|                 |       |             |
|                 |       |             |
|                 |       |             |

### 4. OTHER RESPONSIBLE PARTIES

#### 5. MILESTONES

| Milestone                           | Planned date     | Actual date      | Comments  |
|-------------------------------------|------------------|------------------|---|
| Start of data collection            | Q4 2014          | 05 November 2014 | None  |
| End of data collection              | Q4 2015          | Q4 2015          |   |
| Registration in the EU PAS register | Q4 2013          | 20 November 2013 | None  |
| Interim report 1                    | 31 December 2013 | 9 December 2013  | Due to low number of apixaban dispensing, a study progress report was provided.   |
| Interim report 2                    | 31 December 2014 | 19 May 2015      | The delivery of the data to the Karolinska Institute was delayed, and with agreement from the Agency, the interim report was delivered at a later date. (B0661017 Protocol) |
| Final report of study results       | 31 May 2016      | 20 May 2016      | Amended date as agreed on with the Agency. (B0661017 Protocol)  |

## 6. RATIONALE AND BACKGROUND

Off-label drug use occurs when a healthcare provider chooses to prescribe a drug in a manner that is inconsistent with the approved prescribing information. For medicinal products approved by the European Commission, the conditions for use are identified in the Summary of Product Characteristics (SmPC). Examples of off-label prescribing may include, but are not limited to the administration of the drug in doses, routes of administration or for reasons outside of the approved indications, or use in patients who do not meet age requirements, or other criteria as outlined in the SmPC.

The prescribing of apixaban (ELIQUIS®) outside of the indicated uses is a regulatory and potentially a safety concern. Apixaban is an orally administered anticoagulant that inhibits coagulation factor Xa. It is currently approved for (Table 1):

1. Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.
2. Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAf), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age  $\geq 75$  years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class  $\geq$  II).
3. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Table 1. Indications for apixaban and dates of authorization

|    | <b>Abbreviated Indication</b> | <b>Indication</b>   | <b>Date of EMA Authorization</b> |
|----|-------------------------------|---|----------------------------------|
| 1. | THA/TKA                       | Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery   | 18 May 2011                      |
| 2. | NVAf                          | Prevention of stroke and systemic embolism in adult patients with NVAf, with one or more risk factors, such as prior stroke or TIA; age $\geq 75$ years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class $\geq$ II). | 19 November 2012                 |
| 3. | DVT/PE                        | Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.  | 28 July 2014                     |

DVT: Deep vein thrombosis

NVAf: Non-valvular atrial fibrillation

NYHA: New York Heart Association

PE: Pulmonary Embolism

SE: Systemic Embolism

TIA: Transient Ischaemic Attack

THA/TKA: Total Hip Arthroplasty / Total Knee Arthroplasty

VTE: Venous Thromboembolic Events

The data for this Final Study Report include apixaban dispensing that occurred from 1 January 2012 through 31 December 2014. Apixaban dispensations are classified as on-label only if the apixaban is dispensed after receiving regulatory approval for the applicable indications. If the dispensation date is on or before the date of the approval of the associated indication, then this use is classified as off-label.

This non-interventional study was designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the European Medicines Agency (EMA).

## 7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to describe the utilization patterns of apixaban in Sweden.

Specifically, the study objectives are to:

1. Estimate the proportions of apixaban users in the out-patient setting who receive the drug for the approved indications at the time of the study,
2. Describe the characteristics of the patients who are prescribed apixaban in the out-patient setting for on-label and off-label indications.

## 8. AMENDMENTS AND UPDATES

| Number | Date            | Section of study protocol | Amendment or update   | Reason  |
|--------|-----------------|---------------------------|---|---|
| 2*     | 22 January 2013 | 6.2-6.3, 7.2              | Addition of NVAF indication   | EMA authorised NVAF indication  |
|        |                 | 7.1                       | More details on sample size were presented.   | Clarification of sample size was made   |
|        |                 | 1.1, 3                    | Writing clarification   | Clarifications were made to the writing to more accurately describe study                         |
| 3      | 19 May 2015     | 1.1                       | Addition of DVT/PE treatment added.   | EMA authorised DVT/PE indication  |
|        |                 | 6.1                       | Removed Stockholm County primary care data  | Stockholm County primary care data was not available so it was removed from the protocol          |
|        |                 | 6.3, 7.2                  | Extension of the timeframe that was used to identify NVAF diagnoses and diagnoses that exclude the NVAF indication. | Results from the interim report suggested patients had NVAF diagnoses early in the patient record |
|        |                 | 7.1, 7.2                  | Updated final sample size in Sweden   | Sample size was updated to reflect current projections  |

| Number | Date | Section of study protocol        | Amendment or update   | Reason  |
|--------|------|----------------------------------|-----------------------|---|
|        |      | 1.1, 6.1 – 6.3, 7.1-7.3, 9, 10.2 | Writing clarification | Clarifications were made to the writing to more accurately describe study |

\* The final version of the protocol was labelled as Final Amended and the next version was labelled Amendment 2; the final version was amendment 3

## 9. RESEARCH METHODS

### 9.1. Study design

This is a descriptive, non-interventional study using retrospectively collected electronic data from the Swedish national health registers. The registers cover the entire population of Sweden (9.7 million people in 2014). The major strength of the study is the size of the cohort, the complete nationwide coverage, and the high quality of the data from the Swedish national health registers.

### 9.2. Setting

The study included all patients identified in the National Prescribed Drug Register (PDR) who had received at least one apixaban dispensing from a community pharmacy during the study period. The PDR contains information on the patient, the prescribed drugs coded according to the Anatomic Therapeutic Chemical (ATC) classification system, the date of the dispensation, and the specialty of the prescribing physician. Prescriptions from primary care physicians and specialists, such as cardiologists, who treat patients in the outpatient setting would typically be filled in community pharmacies and be recorded in the PDR. However, drugs dispensed to hospitalised inpatients are not recorded in the PDR.

The main analysis considered only in- and outpatient hospital diagnoses from January 1997 until the first apixaban dispensing and procedures within 30 days of the first apixaban dispensing. Diagnoses and procedures performed by surgeons, cardiologists and other specialists during in- and outpatient hospital contacts were collected from the Swedish National Patient Register (NPR). However, the NPR lacks information on General Practitioner (GP) visits.

To address the possibility that the hospital based data sources missed information from GP records, a sensitivity analysis was performed where the national hospital based records were supplemented with GP records from a regional database in the Gothenburg area (VEGA). Data from GP visits outside the Gothenburg area were not available. As with the national data, drug dispensations from the Gothenburg area were collected from outpatient pharmacies through the PDR.

### 9.3. Subjects

The study included residents of Sweden with at least one recorded apixaban dispensing over the first 3 years that the drug was available (January 1, 2012 to December 31, 2014). Patients with less than 6 months of database history (i.e. recent immigrants) were excluded, as were patients

with a date of death before the apixaban index date. There were not any study mandated dosing or duration of use requirements.

#### 9.4. Variables

The index date is defined as the first apixaban dispensation date observed in PDR during the study period for each individual. The operational definitions and coding scheme of the variables are described below.

- Patient demographics and characteristics:
  - Age at index date (categorical: <18, 18-44, 45-64, 65-84, 85+, median and inter-quartile range, IQR)
  - Gender (categorical: male, female)
- Information on dispensing of apixaban:
  - Dispensing date, estimated daily dose (categorical: 5 mg, 10 mg corresponding to twice daily use of the recorded tablet strength), amount dispensed, duration of use based on amount of drug prescribed (categorical: <10 days, 10-14 days, 15-31 days, 32-38 days, >38 days), refill date, repeat dispensing
  - Department specialty (categorical: orthopaedic, surgery, GP, internal medicine, cardiology, other)
- Hospital admission information:
  - Dates of hospital admission and discharges
  - ICD-10 discharge diagnoses (primary and secondary)
  - Surgical procedure codes
- Outpatient hospital office visit information:
  - Date of visit
  - ICD-10 diagnosis codes
  - Department type.
- Primary care records for VEGA:
  - Date of contact
  - Contact type (visit, telephone)
  - ICD-10 diagnosis codes
- Other concomitantly dispensed drugs:
  - ATC code, dispensing date, dose, quantity dispensed

##### 9.4.1. Endpoints

The main endpoint of interest for the study was the indication for apixaban use. The condition that the prescriber intended to treat with apixaban is not directly recorded in the PDR, so we used diagnosis and procedure codes in the NPR from before the apixaban dispensation date as proxies for the indication. The proxy indications, based on appropriate Nordic procedure and ICD-10 codes from linked hospital discharge diagnoses, were categorized as on-label or off-label based on predefined diagnosis and procedure codes ([Appendix 2](#)). If a pre-defined code could not be identified in the patient's records, then the user was designated as having an unclassified indication. The patients were assigned an on-label and off-label status based on the first apixaban dispensation only, and the date of the first apixaban dispensation was defined as the index date.

#### 9.4.2. Definition of THA/TKA

Apixaban users who were assigned on-label THA/TKA indications had a record of a THA/TKA procedure (including total and partial replacement procedures) within 30 days of the apixaban dispensation, and did not have a diagnosis of hip or knee fracture. A record of hip or knee fracture within 30 days of apixaban dispensation suggested that the THA/TKA procedure was not elective, and thus inconsistent with the on-label THA/TKA indication.

#### 9.4.3. Definition of NVAf

NVAf is defined as 'AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis', according to the European Heart Rhythm Association (5). The register coding systems do not record the severity of the mitral stenosis so any evidence of mitral stenosis or any evidence of a mechanical prosthetic heart valve was defined as off-label usage among AF patients. The diagnostic and procedure codes for identifying cardiac disorders are shown in [Appendix 2](#).

#### 9.4.4. Identification of DVT/PE

DVT patients were defined as patients with a DVT diagnostic code before the apixaban dispensation including:

1. Embolism and thrombosis of vena cava and other thoracic veins,
2. Embolism and thrombosis of other specified veins,
3. Embolism and thrombosis of unspecified vein,
4. Phlebitis and thrombophlebitis of deep vessels of lower extremities.

PE patients were defined as patients with a PE diagnostic code before the apixaban dispensation. Patients with other diagnoses of venous thromboembolism, e.g. involving superficial vessels or other specific sites, are categorised as off-label users (other VTE).

#### 9.4.5. Decision Rules for On- and Off-Label Classification

Apixaban dispensations made for a specific indication were classified as on-label after the day that the indication received regulatory approval. Apixaban was approved for the prevention of VTE in patients with elective THA/TKA prior to the start of this study so that all dispensations for elective THA/TKA during the study period were classified as on-label regardless of the date of dispensing. Apixaban was approved for the prevention of stroke and SE in NVAf patients on 19 November 2012, and dispensations for this indication were classified as off-label on or before 19 November 2012; they were classified as on-label after 19 November 2012. Approval for the treatment of DVT and PE occurred on 28 July 2014 and dispensation for this indication were classified as off-label on or before 28 July 2014; they were classified as on-label after 28 July 2014.

The classification for each individual was made in a hierarchical and sequential fashion ([Figure 1](#)) based on the dispensation at the index date with ordering:

- 1) any use less than 18 years of age,
- 2) on-label THA/TKA,
- 3) on-label NVAf,
- 4) on-label DVT/PE,

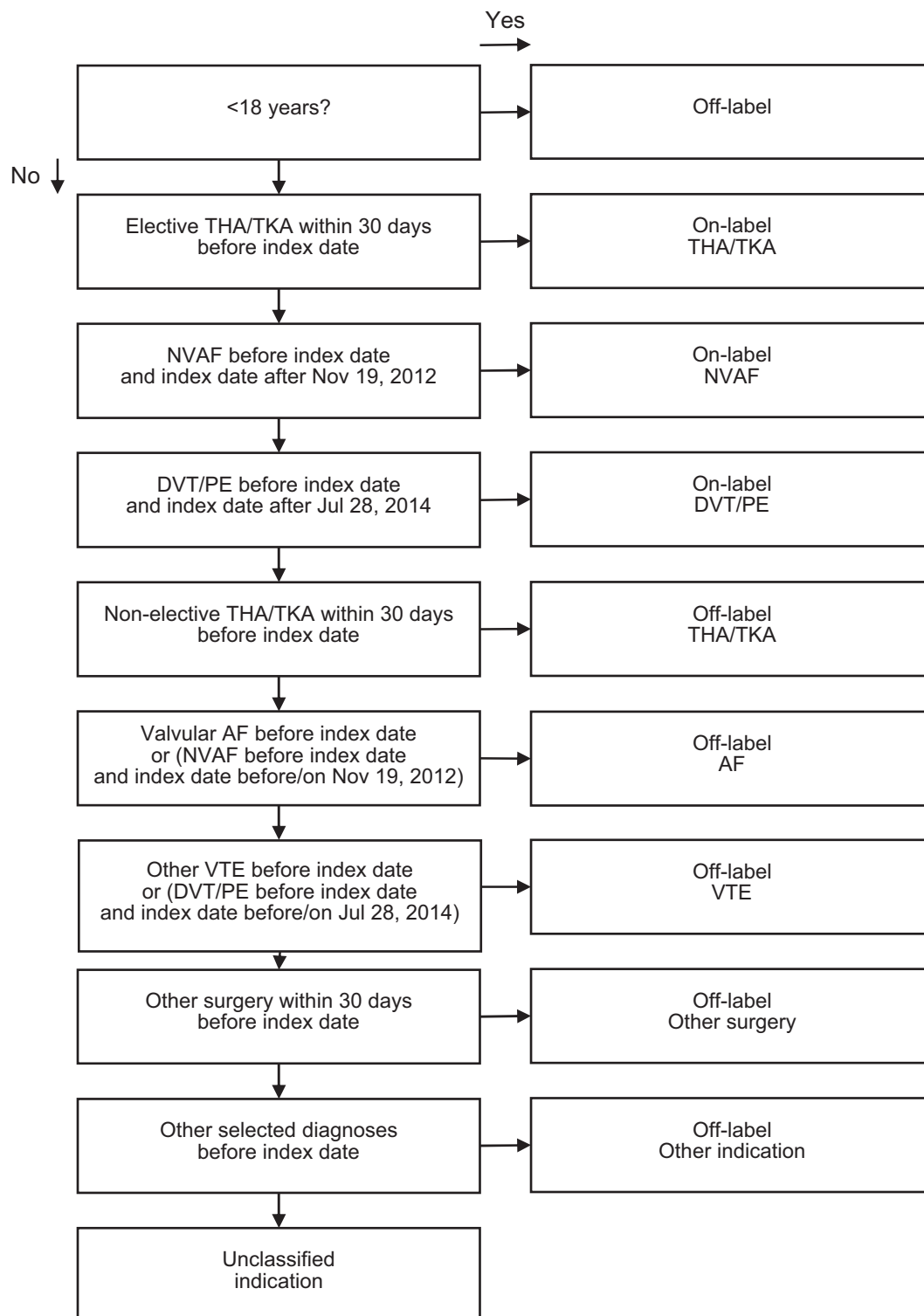
- 5) off-label THA/TKA (non-elective),
- 6) off-label AF (AF with valvular disorder or NVAF before approval),
- 7) off-label VTE (other and non-specific VTE or DVT/PE before approval),
- 8) other off-label surgeries,
- 9) other specified off-label diagnoses,
- 10) unclassified indication.

The patient's age at the time of the first apixaban dispensing was used to identify use in children.

The procedure codes related to other surgeries are provided using the NOMESCO classification in [Appendix 2](#).

Other diagnoses listed as potential off-label indications for apixaban are given in [Table 2](#), and in Appendix 2.

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**Figure 1. Decision process for identifying on- vs. off-label use**

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| <b>Table 2: Other specified off-label diagnoses</b> |   |
|---|---|
| <b>ICD 10</b>                                       | <b>Text</b>   |
| <b>I20</b>  | Angina pectoris   |
| <b>I21</b>  | Acute myocardial infarction   |
| <b>I22</b>  | Subsequent myocardial infarction                                    |
| <b>I23</b>  | Certain current complications following acute myocardial infarction |
| <b>I24</b>  | Other acute ischemic heart diseases                                 |
| <b>I25</b>  | Chronic ischemic heart disease                                      |
| <b>I63</b>  | Cerebral infarction   |
| <b>I64</b>  | Stroke not specified as haemorrhage or infarction                   |
| <b>I74</b>  | Arterial embolism and thrombosis                                    |

### 9.5. Data sources and measurement

Patients in the PDR who had used apixaban were linked to NPR by the personal identification number (PIN) unique to all Swedish citizens. Relevant clinical history for the apixaban users identified from the PDR was obtained from the NPR. The NPR contains data from all hospital admissions in Sweden ICD-10 coded from 1997 to present. At each discharge, information is collected about the patient's demographics, primary and secondary diagnoses, procedure codes, hospitals and wards of admission, and dates of admission and discharge.

Primary care records for apixaban users were retrieved for the population of VEGA database (Gothenburg area 1.6 million inhabitants, available from 2004). These records are based on patient contacts to primary care centres and collected in the health administrative databases of *Västra Götaland* county.

The final protocol was approved by an Ethics Committee. The study is being conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follows generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

### 9.6. Bias

This is a descriptive drug utilization study where no formal statistical analyses have been performed and thus there are no effect estimates that could be biased. There is a potential of misclassification between on- and off-label use.

The absence of primary care diagnoses outside the Gothenburg area could introduce bias in the classification of off- and on-label use if certain diagnoses are more common among GP's than in

hospitals and vice versa. This may especially pertain to NVAF, since PE is a medical emergency that requires hospitalization and TKA/THA is performed in the hospital. DVT could be diagnosed by a GP alone, but it would usually involve some consultation with a specialist. Therefore we believe that NVAF is the most likely diagnosis to be absent from the specialist/hospital records.

In addition, administrations of apixaban to hospital admitted in-patients were not captured. If the in-hospital use is not followed by the use of apixaban outside hospital, then this would lead to missing data. Moreover these missing data could introduce a bias in the estimate of the proportions of off- and on-label users if the in-hospital indications differ from the out-patient indications. No adjustments for biases were performed in this report.

## 9.7. Study Size

All the patients who had received apixaban in the database over the study period were included in the study without any sampling procedure. Power calculations for hypothesis testing were not performed because this is a descriptive study of drug usage without pre-defined hypotheses.

Based on the Sponsor's projection prior to the study, the number of patients using apixaban in 2012-2014 for prevention of VTE following elective THA/TKA was expected to be approximately 600. It was later projected that up to 19,000 patients including those with THA/TKA, NVAF, and for the DVT/PE indications could be available for analysis (Protocol B0661017 Amendment 3). This final report covers 17 592 patients who received apixaban between 1 January 2012 and 31 December 2014, which yields a 95% confidence interval width of 0.3% to 1.5%, depending on the estimated proportion.

## 9.8. Data transformation

Data were transformed into minimal informative datasets for demographics, drugs, diagnoses, person characteristics and primary care data using a beta version of the Centre for Pharmacoepidemiology (CPE) developed Nordic data model (NDM). From the NDM datasets two analysis datasets, one for all patients and one for patients with primary care data available, were created and used in the analyses.

## 9.9. Statistical methods

Only descriptive statistics such as numbers, proportions, median with interquartile range and mean with standard deviation were used in this study.

### 9.9.1. Main summary measures

A detailed methodology for data analysis is documented in the Statistical Analysis Plan (SAP), which is dated, filed and maintained by the Sponsor.

Descriptive analyses of the data were conducted. The demographic and clinical characteristics of patients identified to have received an apixaban dispensation were described. The proportions of patients receiving the drug for indications within and outside the approved label in each of the study years were calculated. For off-label users, selected comorbidities and clinical procedures (e.g., surgeries) within 30 days prior to the apixaban dispensation, constituting possible indications for off-label use, were tabulated.

The dose and duration of apixaban use as well as patient's comorbidities and concomitant medications were described.

Categorical data were presented as counts (n) and proportions (%). Continuous data were presented as means with standard deviation (SD) and as medians with interquartile range (IQR) when appropriate.

### 9.9.2. Main statistical methods

No statistical modelling was performed. For estimated proportions, 95% exact confidence intervals (CI) are given using the exact Clopper-Pearson method (1).

### 9.9.3. Missing values

Date of birth and sex cannot be missing since these are parts of the unique personal identifier used as key for data retrieval. All records from the patient register contain at least a main diagnosis and from zero to 21 secondary diagnoses. There is no information on the number of originally recorded diagnoses per person and hospital contact, i.e. missingness for diagnoses cannot be identified. The prescribed drug registers hold only filled and recorded prescriptions, i.e. there is no way to identify missing records.

### 9.9.4. Sensitivity analyses

The primary care data subset was presented separately to show the additional information from the data in the VEGA database (Gothenburg County), and to provide a sensitivity analysis assessing the effect of absence of primary care data elsewhere in the country.

### 9.9.5. Amendments to the statistical analysis plan

Diagnoses of phlebitis and thrombophlebitis of the deep veins of lower extremities (I80.1, I80.2, I80.3) were moved to the on-label indications. These diagnoses were considered DVT, as defined in several large epidemiological studies (2-4). Procedure codes for pulmonary and aortic mechanical prosthetic heart valves (FJF00, FJF96, FMD00, FMD96) were added so that all patients with mechanical valves are excluded from the NVAf category.

## 9.10. Quality control

Data collection, extraction and processing for research purposes were conducted following Center for Pharmacoepidemiology (CPE) quality control standard guidelines.

SAS program development was performed following the CPE work instructions.

SAS QC did not include formal double programming but review of the code scripts. Deliverable review was performed by a senior scientist.

## 10. RESULTS

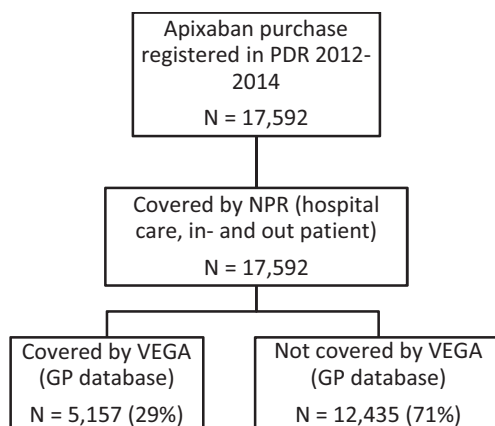
### 10.1. Participants

All individuals obtaining prescriptions for apixaban between 1 January 2012 and 31 December 2014, were included in the study. Only 3 individuals were identified in year 2012, 2 073 individuals were identified in year 2013 and 15 516 individuals were identified in year 2014. In total 17 592 unique individuals were included in the current final report (Figure 2).

Out of a total of 2 075 patients to whom apixaban was dispensed in 2013, 2 073 were included in the study with index year 2013. One patient who filled an apixaban prescription in 2013 returned the package to the pharmacy and was therefore not counted as a user. One patient used apixaban in 2012, 2013 and 2014 and was counted as a user in 2012.

Out of a total of 17 138 patients to whom apixaban was dispensed in 2014, 15 516 were included in the study with index year 2014. Nine patients who filled an apixaban prescription in 2014 returned the packages and were not counted as users. In total, 1 601 patients used apixaban in both 2013 and 2014 and were counted as users in 2013. Furthermore, eleven patients were excluded due to immigration and one patient died before the index date.

**Figure 2. Participants in the study**



## 10.2. Descriptive data

Apixaban users were more often men (n=9 226, 52.4%) than women (n=8 366, 47.6%). The mean age of on-label users (73.6 years) was similar to the mean ages for off-label users (74.2 years) and unclassified users (73.7 years). [Table 3](#) shows general characteristics for apixaban treated patient by type of use.

The database history prior to the index data was similar for all types of use with more than 99% of patients having at least 5 years of database history, but less than 10 years of database history. Follow-up time after the index date was longer for on-label users, mean 6 months as compared to 5.5 months for off-label users.

Physicians from internal medicine (n=8 251, 46.9 %), orthopaedic (n=2 707, 15.4%), GP (n=2 605, 14.8 %) or cardiology (n=2 203, 12.5%) departments were the most common apixaban prescribers. Prescriptions made by GPs more often resulted in an unclassified indication (19.3%, 503/2605) than prescriptions from orthopaedists (0.3%, 9/2707), surgeons (3.0%, 7/232) or other specialists. A higher proportion of orthopaedic surgeons had patients with on-label indications (97.3%, 2637/2707) compared to the other specialists and GPs.

| <b>Table 3. General characteristics of apixaban-treated patients (hospital data)</b> |  |   |  |                  |
|--|--|---|--|------------------|
|  | <b>Type of Apixaban use (n=17 592)</b> |   |  |                  |
|  | <b>On-label</b>                        | <b>Off-label</b>                          |  | <b>Total</b>     |
|  |  | <b>Off-label with assigned indication</b> | <b>Off-label unclassified indication</b> |                  |
|  | N (%)                                  | N (%)                                     | N (%)                                    | N (%)            |
| <b>Total</b>   | 15 204 (100.0)                         | 1 358 (100.0)                             | 1 030 (100.0)                            | 17 592 (100.0)   |
| <b>Gender</b>  |  |   |  |                  |
| Male   | 7 856 (51.7)                           | 807 (59.4)                                | 563 (54.7)                               | 9 226 (52.4)     |
| Female   | 7 348 (48.3)                           | 551 (40.6)                                | 467 (45.3)                               | 8 366 (47.6)     |
| <b>Age at index date</b>   |  |   |  |                  |
| <18  |  | 2 (0.1)                                   |  | 2 (0.0)          |
| 18-44  | 189 (1.2)                              | 37 (2.7)                                  | 27 (2.6)                                 | 253 (1.4)        |
| 45-64  | 2 787 (18.3)                           | 199 (14.7)                                | 151 (14.7)                               | 3 137 (17.8)     |
| 65-84  | 9 839 (64.7)                           | 874 (64.4)                                | 681 (66.1)                               | 11 394 (64.8)    |
| 85+  | 2 389 (15.7)                           | 246 (18.1)                                | 171 (16.6)                               | 2 806 (16.0)     |
| Mean (SD)  | 73.6 (11.1)                            | 74.2 (12.5)                               | 73.7 (11.5)                              | 73.6 (11.2)      |
| Median (IQR)   | 74.0 (66.9-81.8)                       | 76.2 (68.1-82.9)                          | 74.2 (67.5-81.8)                         | 74.2 (67.0-81.9) |
| <b>Database history before index date</b>  |  |   |  |                  |
| <1 year  | 1 (0.0)                                |   |  | 1 (0.0)          |
| [1-5] years  | 55 (0.4)                               | 4 (0.3)                                   | 2 (0.2)                                  | 61 (0.3)         |
| [5-10] years   | 15 148 (99.6)                          | 1 354 (99.7)                              | 1 028 (99.8)                             | 17 530 (99.6)    |
| ≥ 10 years   |  |   |  |                  |
| Mean (SD)  | 9.0 (0.5)                              | 9.0 (0.5)                                 | 9.0 (0.5)                                | 9.0 (0.5)        |
| Median (IQR)   | 9.0 (8.7-9.3)                          | 9.0 (8.7-9.3)                             | 9.1 (8.8-9.3)                            | 9.0 (8.7-9.3)    |
| <b>Database follow-up after index date</b>   |  |   |  |                  |
| <6 months  | 8 129 (53.5)                           | 749 (55.2)                                | 622 (60.4)                               | 9 500 (54.0)     |
| [6-12] months  | 5 393 (35.5)                           | 436 (32.1)                                | 282 (27.4)                               | 6 111 (34.7)     |
| ≥ 12 months  | 1 682 (11.1)                           | 173 (12.7)                                | 126 (12.2)                               | 1 981 (11.3)     |
| Mean (SD)  | 6.0 (4.4)                              | 6.0 (4.6)                                 | 5.6 (4.5)                                | 6.0 (4.4)        |
| Median (IQR)   | 5.4 (2.2-9.2)                          | 5.3 (2.1-9.0)                             | 4.1 (1.9-8.5)                            | 5.3 (2.2-9.1)    |
| <b>Specialty of first prescriber</b>   |  |   |  |                  |
| Orthopaedic  | 2 634 (97.3)                           | 64 (2.4)                                  | 9 (0.3)                                  | 2707 (100)       |
| Surgery  | 196 (84.5)                             | 29 (12.5)                                 | 7 (3)                                    | 232 (100)        |
| GP   | 1 804 (69.3)                           | 298 (11.4)                                | 503 (19.3)                               | 2605 (100)       |
| Internal medicine  | 7 311 (88.6)                           | 611 (7.4)                                 | 329 (4)                                  | 8251 (100)       |
| Cardiology   | 1 898 (86.2)                           | 192 (8.7)                                 | 113 (5.1)                                | 2203 (100)       |
| Other medicine   | 749 (86.8)                             | 100 (11.6)                                | 14 (1.6)                                 | 863 (100)        |
| Haematology  | 32 (88.9)                              | 3 (8.3)                                   | 1 (2.8)                                  | 36 (100)         |
| Other  | 578 (83.4)                             | 61 (8.8)                                  | 54 (7.8)                                 | 693 (100)        |

### 10.3. Outcome data

No outcome events were investigated.

### 10.4. Main results

**Objective 1:** A total of 17 592 apixaban users were included in the study of which 86.4% (95% Confidence Interval [CI]: 85.9%-86.9%, n=15204) received apixaban for an on-label indication

and 7.7% (CI: 7.3%-8.1%, n=1 358) received apixaban for an off-label indication. The remaining 5.9% (CI: 5.5%-6.2%, n=1 031) could not be assigned to a predefined on-label or off-label indication and remained unclassified. For those 16 562 assigned a predefined indication, 91.8% (CI: 91.4%-92.2%, n=15 204) had an indication that was on-label and 8.2% (95% CI: 7.8%-8.6%, n=1 358) had an off-label indication, Table 4 below and [appendix 1](#) gives the results by year and in total.

The distribution of indications among the 15 204 on-label users was elective THA/TKA for 17.3% (n=2 636) of patients, NVAf for 79.9% (n=12 151) patients and DVT/PE for 2.7% (n=417) patients. The 1 358 off-label users with assigned indications included 2 with age less than 18 years, non-elective THA/TKA for 0.7% (n=10) patients, off-label AF for 31.4% (n=428), off-label VTE (including DVT/PE before the indication's approval) for 8.0% (n=108), other surgeries for 17.3% (n=235) patients and other diagnoses for 42.4% (n=575) patients.

During 2012 there were only 3 apixaban users in Sweden with probable off-label use, two with NVAf and one with other surgery (not elective THA/TKA). The distribution of on-label, off-label, and unclassified indications was similar in 2013 and 2014. There were no patients with a record of DVT/PE identified in 2013, which was prior to the approval of the DVT/PE indication. In 2014, patients with a record of DVT/PE were found in 2014.

Among the 428 patients with off-label AF, none started apixaban for AF before or on the date of the indication's approval. All of the patients who had off-label AF indications received apixaban for AF but had a possible diagnosis of valvular disorders that excluded them from an on-label classification. Among these user with a possible diagnosis of a valvular disorder, 37 had a diagnosis of mitral stenosis and 8 had mechanical prosthetic heart valves surgeries.

Among the 108 patients with off-label VTE, 43% (n=46) were persons with a diagnosis of DVT/PE, who started apixaban before the approval of the indication. The remaining 57% (n=62) had VTE where apixaban is not indicated, e.g. diagnoses of superficial phlebitis or thrombophlebitis, or other venous thromboembolism, e.g. portal vein thrombosis.

In total 235 patients had off-label use with other surgeries within 30 days prior to the apixaban index date (Appendix 1), dominated by procedures for heart and major thoracic vessels (27.8%, n=77). Surgeries affecting 10 patients or more were: intraoperative total cardiopulmonary bypass, aorto-coronary venous bypass, connection to coronary artery from internal mammary artery, implantation or replacement of permanent trans venous cardiac pacemaker, and replacement of aortic valve. In this analysis, each person could have more than one possible off-label indication.

In total 575 patients had off-label use with other pre-specified diagnoses before the apixaban index date. The most frequent diagnoses among these possible off-label indications were chronic ischemic heart disease (48.2%, n=277), angina pectoris (43.5%, n = 250), cerebral infarction (41.2%, n=237), acute myocardial infarction (29.7%, n=171). The remaining pre-specified diagnoses all occurred in less than 5% of the apixaban user.

| Table 4. On-label and off-label apixaban utilization by year and indication |            |              |
|---|------------|--------------|
| Year  | Indication | All patients |
| 2012  | Total      | 3 (100.0%)   |



|                  |   |                 |
|------------------|---|-----------------|
|                  | No listed indication (unclassified)                 |                 |
|                  | Any indication                                      | 3 (100.0%)      |
|                  | On-label indications                                |                 |
|                  | THA/TKA   |                 |
|                  | NVAF <sup>1</sup>                                   |                 |
|                  | Off-label indications                               | 3 (100.0%)      |
|                  | <18 years of age                                    |                 |
|                  | >=18 years of age non-elective THA/TKA <sup>2</sup> |                 |
|                  | >=18 years of age off-label AF <sup>3</sup>         | 2 (66.67%)      |
|                  | >=18 years of age VTE <sup>4</sup>                  | 1 (33.33%)      |
|                  | >=18 years of age Other surgery                     |                 |
|                  | >=18 years of age Other diseases                    |                 |
| <b>2013</b>      | <b>Total</b>  | 2 073 (100.0%)  |
|                  | No listed indication (unclassified)                 | 129 (6.22%)     |
|                  | Any indication                                      | 1 944 (93.78%)  |
|                  | On-label indications                                | 1 768 (85.29%)  |
|                  | THA/TKA   | 300 (14.47%)    |
|                  | NVAF <sup>1</sup>                                   | 1 468 (70.82%)  |
|                  | Off-label indications                               | 176 (8.49%)     |
|                  | <18 years of age                                    | 2 (0.10%)       |
|                  | >=18 years of age non-elective THA/TKA <sup>1</sup> | 3 (0.14%)       |
|                  | >=18 years of age off-label AF <sup>3</sup>         | 61 (2.94%)      |
|                  | >=18 years of age off-label VTE <sup>4</sup>        | 18 (0.87%)      |
|                  | >=18 years of age Other surgery                     | 33 (1.59%)      |
|                  | >=18 years of age Other diseases                    | 59 (2.85%)      |
| <b>2014</b>      | <b>Total</b>  | 15 516 (100.0%) |
|                  | No listed indication (unclassified)                 | 901 (5.81%)     |
|                  | Any indication                                      | 14 615 (94.19%) |
|                  | On-label indications                                | 13 436 (86.59%) |
|                  | THA/TKA   | 2 336 (15.06%)  |
|                  | NVAF <sup>1</sup>                                   | 10 683 (68.85%) |
|                  | DVT/PE <sup>1</sup>                                 | 417 (2.69%)     |
|                  | Off-label indications                               | 1 179 (7.60%)   |
|                  | <18 years of age                                    |                 |
|                  | >=18 years of age non-elective THA/TKA <sup>2</sup> | 7 (0.05%)       |
|                  | >=18 years of age off-label AF <sup>3</sup>         | 365 (2.35%)     |
|                  | >=18 years of age off-label VTE <sup>4</sup>        | 89 (0.57%)      |
|                  | >=18 years of age Other surgery                     | 202 (1.30%)     |
|                  | >=18 years of age Other diseases                    | 516 (3.33%)     |
| <b>2012-2014</b> | <b>Total</b>  | 17 592 (100.0%) |
|                  | No listed indication (unclassified)                 | 1 030 (5.85%)   |
|                  | Any indication                                      | 16 562 (94.15%) |
|                  | On-label indications                                | 15 204 (86.43%) |
|                  | THA/TKA   | 2 636 (14.98%)  |
|                  | NVAF <sup>1</sup>                                   | 12 151 (69.07%) |
|                  | DVT/PE <sup>1</sup>                                 | 417 (2.37%)     |
|                  | Off-label indications                               | 1 358 (7.72%)   |
|                  | <18 years of age                                    | 2 (0.01%)       |

|  |  |             |
|--|--|-------------|
|  | $\geq 18$ years of age non-elective THA/TKA <sup>2</sup> | 10 (0.06%)  |
|  | $\geq 18$ years of age off-label AF <sup>3</sup>         | 428 (2.43%) |
|  | $\geq 18$ years of age off-label VTE <sup>4</sup>        | 108 (0.61%) |
|  | $\geq 18$ years of age Other surgery                     | 235 (1.34%) |
|  | $\geq 18$ years of age Other diseases                    | 575 (3.27%) |

1 The use in NVAf or DVT/PE patients was considered on-label after the date of approval of such indication and off-label on or prior to its approval date

2 Non-elective THA/TKA

3 NVAf before or on November 19, 2012 or AF

4 DVT/PE before or on July 28, 2014 or other or non-specific VTE

**Objective 2:** We investigated comedications dispensed to 25% or more of the apixaban users within 30 days of index date (before and/or after). Frequently prescribed drugs included anti-thrombotics, CYP3A4 and P-gp inhibitors, selective beta blocking agents, HMG CoA reductase inhibitors, osmotically acting laxatives, natural opium alkaloids and anilides ([Appendix 1](#)).

Dispensings of antithrombotics were between 9 and 25 percent more common before the index date than after the index for all groups of users except on-label elective THA/TKA, which decreased only 2 percent. All categories of apixaban users, except on-label elective THA/TKA, were dispensed more CYP3A4 and P-gp inhibitors after the index date than before, an increase of between 9 and 17 percent. All categories of apixaban users, except on-label elective THA/TKA, were dispensed more selective beta blocking agents after the index date than before, an increase between 6 and 16 percent. There were small differences in the dispensing of HMG CoA reductase inhibitors; an increase of 2 percent for on-label THA/TKA and an increase of 5 percent for on-label NVAf. Osmotically acting laxatives shows an increase of 31 percent for on-label THA/TKA, other groups show changes of between 1 percent decrease and 4 percent increase after the index date. For on-label elective THA/TKA and off-label other surgeries, dispensing of natural opium alkaloids increased by 70 and 10 percent respectively after the index date, with only small differences in the other groups (1 to 3 percent increase). For on-label elective THA/TKA and off-label other surgery dispensing of anilide analgesics increased by 62 and 13 percent respectively, but there were only small differences in other groups (1 percent decrease to 3 percent increase). In apixaban users with on-label NVAf, the dispensing of diuretics and drugs affecting the renin-angiotensin system increased by 5 and 4 percent after the index date.

Patients with unclassified indications had used apixaban for a longer duration (93% with  $>38$  days) than patients with an identified proxy for the indication (82% with  $>38$  days). The majority (86.4%) of patients with an indication of THA/TKA used apixaban for 10-14 or 15-31 days, though 13% had duration  $>38$  days. For NVAf and DVT/PE 95.5% and 92.6% of patients had duration  $>38$  days. Also patients with other diagnoses had duration  $>38$  days for about 95% of the patients. Patients with other surgeries had duration  $>38$  days for 76.2% of the patients. A treatment dose of 10 mg was used in 56.3% of the patients with any classification. For patients with on-label NVAf and DVT/PE a dose of 10 mg was more commonly used (67.7% and 67.4%) than among patients with on-label THA/TKA (0.8%) ([Table 5](#)). Prior to the apixaban dispensation, renal disease had occurred in 3.2% (n=561) of patients and liver disorders had occurred in 0.4% (n=66) of patients ([Appendix 1](#)).



Table 5 Treatment dose and duration among apixaban-treated patients, by on-label, off-label or unclassified indications

|                    |                                |                          | On-label indications |                       |                      | Off-label Indications*               |                       |                        |                           |                             |
|--------------------|--------------------------------|--------------------------|----------------------|-----------------------|----------------------|--------------------------------------|-----------------------|------------------------|---------------------------|-----------------------------|
|                    | Any classification<br>N<br>(%) | Unclassified<br>N<br>(%) | THA/TKA<br>N<br>(%)  | NVAF N<br>(%)         | DVT/PE<br>N<br>(%)   | Non-elective<br>THA/TKA*<br>N<br>(%) | AF*<br>N<br>(%)       | VTE*<br>N<br>(%)       | Other surgery<br>N<br>(%) | Other diagnosis<br>N<br>(%) |
| Total              | 16 562<br>(100.0)              | 1 030<br>(100.0)         | 2 636<br>(100.0)     | 12 151<br>(100.0)     | 417<br>(100.0)       | 10<br>(100.0)                        | 428<br>(100.0)        | 108<br>(100.0)         | 235<br>(100.0)            | 575<br>(100.0)              |
| Treatment Duration |                                |                          |                      |                       |                      |                                      |                       |                        |                           |                             |
| <10 days           | 78<br>(0.5)                    | 12<br>(1.2)              |                      | 66<br>(0.5)           | 4<br>(1.0)           |                                      |                       | 2<br>(1.9)             | 2<br>(0.9)                | 4<br>(0.7)                  |
| 10-14 days         | 1 081<br>(6.5)                 | 6<br>(0.6)               | 955<br>(36.2)        | 83<br>(0.7)           | 5<br>(1.2)           |                                      | 4<br>(0.9)            | 5<br>(4.6)             | 26<br>(11.1)              | 3<br>(0.5)                  |
| 15-31 days         | 1 771<br>(10.7)                | 44<br>(4.3)              | 1 324<br>(50.2)      | 357 (2.9)             | 20<br>(4.8)          | 9<br>(90.0)                          | 10<br>(2.3)           | 5<br>(4.6)             | 27<br>(11.5)              | 18<br>(3.1)                 |
| 32-38 days         | 30<br>(0.2)                    | 4<br>(0.4)               |                      | 26<br>(0.2)           | 1<br>(0.2)           |                                      | 2<br>(0.5)            |                        | 1<br>(0.4)                |                             |
| >38 days           | 13 583<br>(82.0)               | 963<br>(93.5)            | 357<br>(13.5)        | 11 605<br>(95.5)      | 386<br>(92.6)        | 1<br>(10.0)                          | 410<br>(95.8)         | 95<br>(88.0)           | 179<br>(76.2)             | 549<br>(95.5)               |
| Mean (SD)          | 180.6<br>(149.1)               | 202.8<br>(148.0)         | 27.0<br>(31.6)       | 214.9<br>(145.1)      | 94.0<br>(44.3)       | 31.0<br>(3.2)                        | 213.2<br>(149.7)      | 236.1<br>(155.1)       | 146.9<br>(146.5)          | 206.3<br>(134.5)            |
| Median (IQR)       | 148.0<br>(60.0-268.0)          | 168.0<br>(84.0-288.0)    | 30.0<br>(10.0-30.0)  | 175.0<br>(90.0-307.2) | 84.0<br>(67.0-112.0) | 30.0<br>(30.0-30.0)                  | 168.0<br>(84.0-300.0) | 231.0<br>(107.0-336.0) | 84.0<br>(50.0-200.0)      | 174.0<br>(84.0-288.0)       |
| Treatment dose**   |                                |                          |                      |                       |                      |                                      |                       |                        |                           |                             |
| 5 mg               | 7 233 (43.7)                   | 273 (26.5)               | 2 614<br>(99.2)      | 3 926<br>(32.3)       | 136<br>(32.6)        | 10 (100.0)                           | 167<br>(39.0)         | 48<br>(44.4)           | 114<br>(48.5)             | 216<br>(37.6)               |
| 10 mg              | 9 329 (56.3)                   | 757 (73.5)               | 22 (0.8)             | 8 225<br>(67.7)       | 281<br>(67.4)        |                                      | 261<br>(61.0)         | 60<br>(55.6)           | 121<br>(51.5)             | 359<br>(62.4)               |

\*non-elective THA/TKA; includes NVAF before November 20, 2012 or VAF; includes DVT/PE before July 28, 2014 or VTE

\*\* means daily dose, i.e. 5 mg = 2.5 mg twice daily and 10 mg = 5 mg twice daily

Two patients were < 18 years and are not shown above

## 10.5. Other analyses

Sensitivity analyses were carried out to investigate the impact of the lack of primary care data. We compared the main hospital results to the VEGA database from Gothenburg County (n = 5 157) with and without the addition of primary care data.

The addition of primary care VEGA data did not change the estimated distribution of on-label use (88.7%, 4572 / 5157), off-label (8.9%, 457 / 5157n = 4 572 with VEGA versus 87.9%, n = 4 532 without VEGA), but allowed for the identification of 129 indications who were unclassified based on the hospital data alone.

## 10.6. Adverse events / adverse reactions

This study uses de-identified patient-level electronic health related databases (e-HRD), in which it is not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Furthermore, while the identifiable patient criterion may be met, the identifiable reporter criterion (a particular individual with first-hand knowledge of the

identifiable patient) will not. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports.

## 11. DISCUSSION

### 11.1. Key results

The overall objective of this study was to describe the utilization patterns of apixaban in Sweden. The current study reports final results on 17 592 apixaban users in Sweden from January 1, 2012 to 31 December 2014, who purchased apixaban at least once at a community pharmacy. The National Board of Health and Welfare reports 3, 2 075, and 17 138 apixaban users in 2012, 2013, 2014 respectively (5).

**Objective 1:** The estimated proportion of patients using apixaban for an on-label indication was 86.4% (CI: 85.9%-86.9%). The proportion of those using apixaban for an off-label indication use was 13.6% (CI: 13.1%-14.1%) including the 5.9% (CI: 5.5% - 6.2%) of patients for whom the indication was unclassified. Among patients where an indication was assigned, we found that 91.8% (CI: 91.4%-92.2%) of the users received the drug for an on-label indication and that 8.2% (CI: 7.8% -8.6%) of the users received the drug for an off-label use.

The majority of users received apixaban on-label and NVAF was the most common indication, assigned to 79.9% (n=12 151) of users followed by THA/TKA in 17.3% (n=2 636) and finally DVT/PE in 2.7% (n=417).

Also, among the 1 358 users classified as off-label users with a recorded proxy for the indication, 31.5% (n=428) had a diagnosis of atrial fibrillation and flutter before the index date.

The addition of primary care data from the *Västra Götaland* County increased the proportion of known indications from 95.0% to 97.5% but did not alter the distribution between on- and off-label use. If the Gothenburg area sample is representative for all apixaban users the effect would be the same if we could add primary care data for the whole cohort. For Stockholm county council, Forslund et al. (5) have shown that 12% of the atrial fibrillation and flutter diagnoses are captured exclusively by primary care during the period 2006-2010, i.e. 88% of the diagnoses were captured by NPR. In our study, the use of primary care data did not change the frequency of NVAF as on-label indication for apixaban, but there was a somewhat higher capture of off-label AF.

**Objective 2:** The second aim was to describe the characteristics of the patients who are prescribed apixaban for on-label and off-label indications. Common comedications that were dispensed within 30 days of the apixaban dispensation were other antithrombotics, CYP3A4 and P-gp inhibitors, selective beta blocking agents, HMG CoA reductase inhibitors, osmotically acting laxatives, natural opium alkaloids and anilides. Apixaban for NVAF was associated with longest duration of use (median = 175 days) compared to patients receiving apixaban for THA/TKA (median = 30 days), DVT/PE (median = 84 days). A daily dose of 10 mg was most commonly prescribed. A history of renal disease and/or liver disorders occurred in less than 4% (n=616) of patients.

Studies investigating off-label use of medicines in general have often found high rates, particularly in children. Knopf et al. found an off-label drug use in children of 40% (8) with 67% for the group of cardiovascular system drugs. Using IMS data, a study performed in the US found fre-

quent 21% off-label use, 46% for cardiovascular drugs (9). The frequency of off-label use depends both on the drug group in question, the indications, the treated population and the health care system. The results of this PASS should therefore be compared to other studies focusing on off-label use of NOACs.

An Irish study from 2012 (10) investigated the use of dabigatran etexilate, at the time of the study indicated for VTE prevention after THA/TKA with a limited treatment duration. Using a prescription database it was found that 42% of patients had used it for longer than the licensed maximum duration. In a smaller cohort of 510 users, 64.5% had received the drug for more than 35 days, and 32.5% of the patients with a duration of more than 90 days also received concurrent rate/rhythm control therapy, indicating that it may have been prescribed for stroke prevention in AF. In a small cohort study from the US (n=174), where the indication for dabigatran was NVAf, it was found that 20% of users had off-label use (history of valve disease or no diagnosis of atrial fibrillation (11).

A substantial off-label use of dabigatran in the US has been reported (12) based on a decreasing percentage of atrial fibrillation visits among visits where dabigatran was recorded. These results, however, were based on diagnostic and prescribing information from a physician survey. In other studies, the frequency of off-label use has been relatively low. In a study on the prescribing of different NOACs (13), 90% of prescriptions were found to adhere to FDA-approved indications, with cardiologists significantly more likely to prescribe on label than doctors from other types of clinics (97 vs. 84%). In a German study comprising 425 rivaroxaban users identified in a health insurance database (14) a labelled indication could be identified for 82% of 440 treatment periods. However, treatment durations exceeded recommendations in 95% of episodes after knee replacement and in 56% after elective hip surgery. Another study found that only 3.6% of patients used rivaroxaban on an off-label indication (15).

The current study has shown results comparable to the more recent studies above that report on-label use of NOACs among 80%-90% of patients. However, off-label use of NOACs is of particular concern in patients with mechanical heart valves, where a higher risk of thrombotic complications has been found compared to warfarin (16). The evidence of effect of NOACs in patients with other heart valve disorders is also limited. We only identified 8 apixaban users with mechanical prosthetic heart valves, but 428 patients with AF and markers of valve disorders in general. Thus, despite the overall high percentage of on-label use, the off-label use in a small patient group with heart valve disorders should be noted.

## 11.2. Limitations

The major strength of the study is the size of the cohort, the complete nationwide coverage and the high quality of the data from the Swedish national health registers.

As we have information on drugs dispensed (purchased) at the pharmacy, misclassification of actual use is a possibility because of non-adherence. Similarly, for duration of use we do not know the date on which apixaban has actually been discontinued and have based our assessment on the amount of apixaban dispensed. Thus, duration might have been overestimated.

We did not have access to the indication stated by the prescriber, so we used the first apixaban purchase for each patient and searched for hospital diagnoses and procedures (in- and outpatient) within pre-defined time-windows prior to that purchase. This approach yields only indirect evidence on the indication for apixaban use.

On- and off-label indications were assigned to apixaban using a hierarchical and sequential algorithm. In the first part of the hierarchy, each user was only assigned one indication. This applies to on-label THA/TKA, NVAF and DVT/PE, as well as the off-label indications non-elective THA/TKA, valvular AF and off-label VTE. In the last steps of the algorithm, i.e. other surgery and other possible off-label indications one user could be assigned multiple diagnoses. The strength of the hierarchical approach is that it is transparent and reproducible. A limitation is that the classification of the indication may depend on the classification sequence for those having a proxy for more than one indication. For surgical procedures, including THA/KHA we used only those most recently recorded, within 30 days before the index date. For NVAF, DVT/PE and other pre-specified diagnoses we used a longer look-back period.

Another limitation is that the diagnoses were only retrieved from hospital care, even though it included both in- and outpatient contacts, i.e. we lack diagnoses given in primary care. For a subsample of about 29% of the patients primary care diagnoses were also available. When applying these additional data, we found only small changes in the distribution of on- and off-label indications compared to using hospital diagnoses alone.

We could also only assess apixaban use in an outpatient setting since the PDR holds only community pharmacy dispensing, meaning that patients administered apixaban only in hospital will not be captured. However, patients initiating treatment while in hospital, and continuing on medication dispensed by the community pharmacy, were included.

Two estimates of the proportions of on- and off-label use were provided. One included the apixaban users with unknown indication among off-label users, the other excluded the unclassified group before calculating the proportions. The latter is equivalent to assuming that the distribution of on- and off-label use is similar among those with an indication assigned and those with an unclassified indication. As we did not have access to individual patient's health records it was not possible to validate the register-based estimates.

In the definition of NVAF, the list of diagnoses considered as markers of valvular disorders was broader than the definition ([section 9.4.3](#)). Thus, off-label use for those with NVAF may have been overestimated. On the other hand, the severity of these disorders are not reflected in the diagnosis codes, and we cannot exclude the possibility that some patients classified as having NVAF did not exhibit the risk factors also required for the indication ([Table 1](#)). While it could be considered to search for these risk factors in the health registers, some (age  $\geq 75$  years, previous stroke or TIA) could be identified with reasonable certainty, other information (hypertension, diabetes, heart failure with NYHA classification) would not be accessible without primary care register data or detailed electronic health records. Other limitations when defining NVAF could be that diagnostic codes may not indicate "valvular AF" with sufficient precision. For example, the type of valve used in the case of a valve replacement may indicate on or off-label (e.g., prosthetic vs. bioprosthetic valve), but this level of detail was not always available.

### 11.3. Interpretation

Overall, the results of this study indicate that apixaban was mainly (86%) used for on-label indications, with the majority of patients using apixaban for NVAF. Comorbidity and comedication patterns reflected both the age of the user populations and the indications. Thus, an increase in use of analgesics (opioids and anilides) as well as laxatives were seen among the users with THA/TKA and other surgery procedures. The use of HMG CoA reductase inhibitors, beta-

blockers, diuretics and ACE inhibitors would be expected in a population with AF. There were few patients with procedure codes indicating mechanical prosthetic heart valves. A history of renal disorders were uncommon and liver disorders rare.

#### 11.4. Generalisability

We investigated apixaban use in the entire Swedish population. The results might be generalizable to other populations with similar health care systems, age distributions and prescriber behaviour. However, reimbursement rules, national or regional guidelines and recommendations may affect prescribing patterns.

#### 12. OTHER INFORMATION

None

#### 13. CONCLUSION

The majority of apixaban users (86%) received the drug for an on-label indication. We were not able to infer an indication for 6% of patients who may have received apixaban in the primary care setting. The inclusion of primary care data for a subset of patients did not change the distribution of on-label and off-label indications substantially. When excluding those with an unclassified indication, the on-label use constitutes 92%. Comorbidities and comedications reflected the age of apixaban users and the indications for use.

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## Appendices

**Appendix 1: Core tables, figures and data summaries**

**Appendix 2: Data derivation details**

**Appendix 3: Data source details**

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## **Annex 1: list of stand-alone documents**

[Protocol Amendment 3](#)

## **Annex 2: Additional information**

None

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## Appendix 1: Core tables, figures, and data summaries

### Post-Approval Safety Study (PASS) of the Utilization Pattern of Apixaban in Sweden

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# 1 LIST OF CORE TABLES, FIGURES, AND DATA SUMMARIES

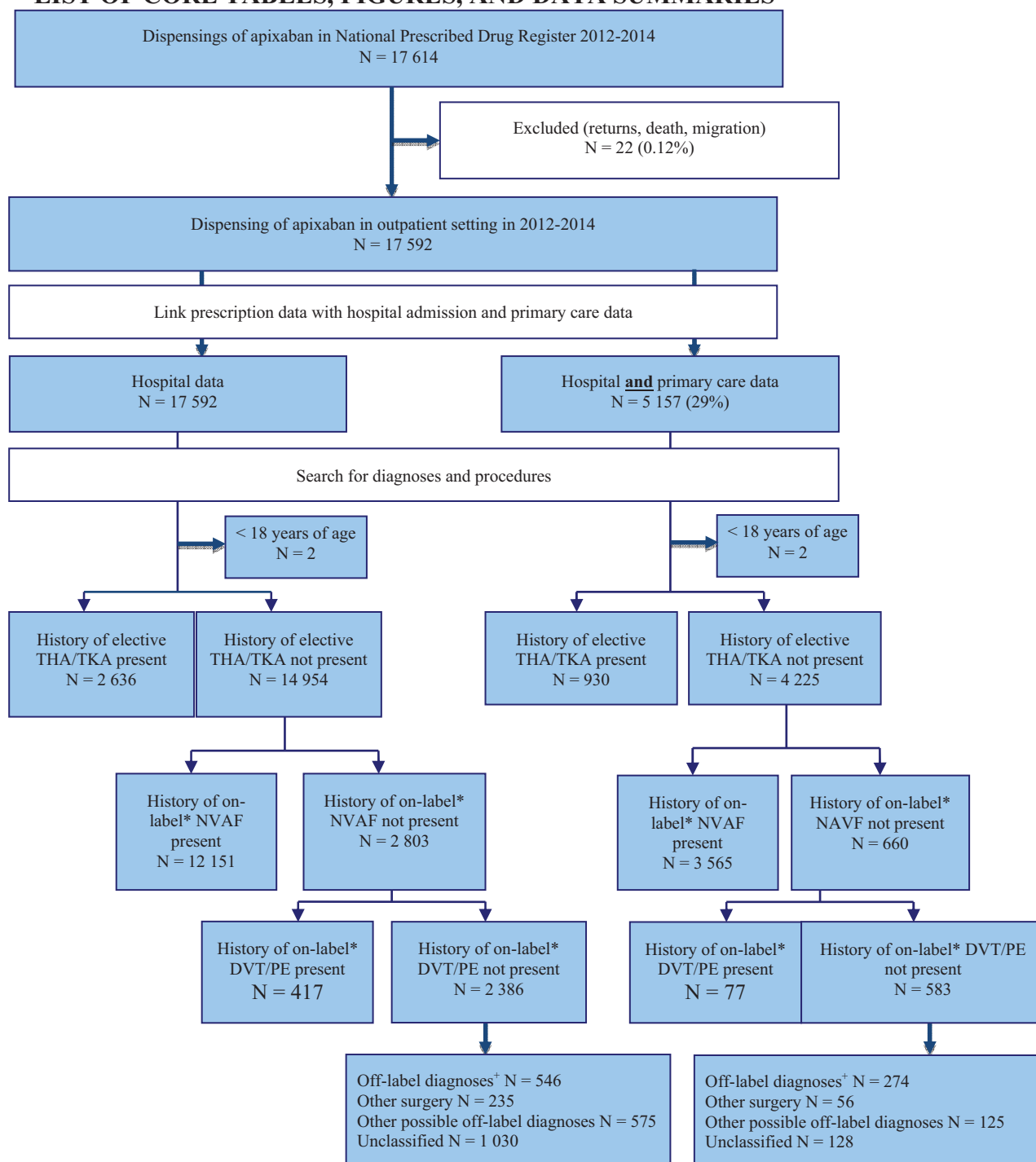


Figure 1.1 Patient selection. The date of the first observed dispensing is the study index date

\* = NVAf and DVT/PE are considered on-label starting from the day after the date of approval

+ = non-elective THA/TKA, valvular AF or NVAf before approval, other and non-specific VTE or DVT/PE before approval

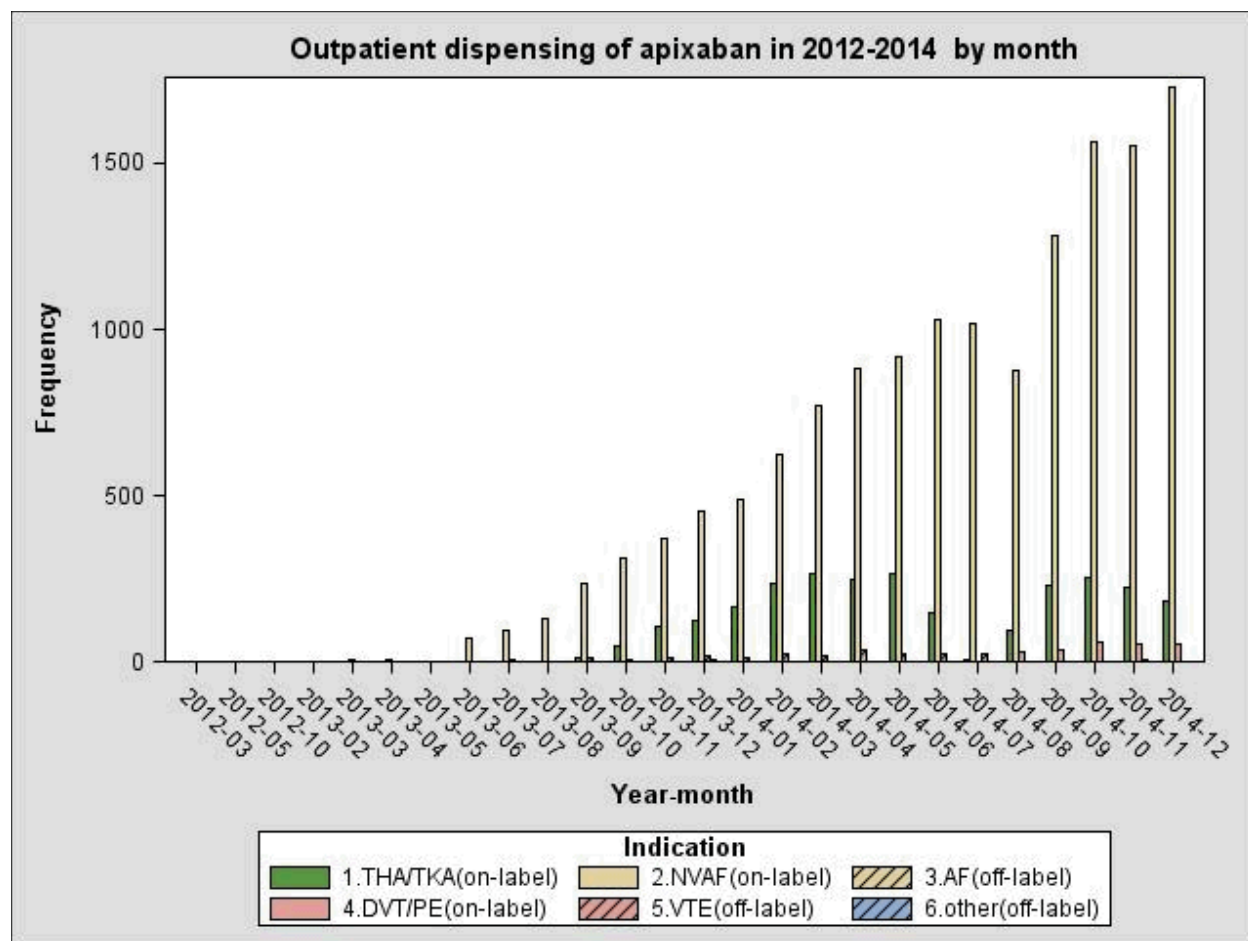


Figure 1.2 Outpatient dispensing of apixaban in 2012-2014 by month and indication

Table 1.1 Indications for apixaban use, number and proportions

| Year      | Indication  | All patients    | Sub-group with primary care data available |                    |
|-----------|---|-----------------|--|--------------------|
|           |   |                 | All data                                   | Only hospital data |
| 2012      | Total   | 3 (100.0%)      |  |                    |
|           | No listed indication (unclassified)                 |                 |  |                    |
|           | Any indication                                      | 3 (100.0%)      |  |                    |
|           | On-label indications                                |                 |  |                    |
|           | THA/TKA   |                 |  |                    |
|           | NVAF <sup>1</sup>                                   |                 |  |                    |
|           | Off-label indications                               | 3 (100.0%)      |  |                    |
|           | <18 years of age                                    |                 |  |                    |
|           | ≥18 years of age non-elective THA/TKA <sup>2</sup>  |                 |  |                    |
|           | ≥18 years of age AF or NVAF <sup>3</sup>            | 2 (66.67%)      |  |                    |
|           | ≥18 years of age VTE or DVT/PE <sup>4</sup>         | 1 (33.33%)      |  |                    |
|           | ≥18 years of age Other surgery                      |                 |  |                    |
|           | ≥18 years of age Other diseases                     |                 |  |                    |
| 2013      | Total   | 2 073 (100.0%)  | 565 (100.0%)                               | 565 (100.0%)       |
|           | No listed indication (unclassified)                 | 129 (6.22%)     | 17 (3.01%)                                 | 28 (4.96%)         |
|           | Any indication                                      | 1 944 (93.78%)  | 548 (96.99%)                               | 537 (95.04%)       |
|           | On-label indications                                | 1 768 (85.29%)  | 483 (85.49%)                               | 488 (86.37%)       |
|           | THA/TKA   | 300 (14.47%)    | 116 (20.53%)                               | 116 (20.53%)       |
|           | NVAF <sup>1</sup>                                   | 1 468 (70.82%)  | 367 (64.96%)                               | 372 (65.84%)       |
|           | Off-label indications                               | 176 (8.49%)     | 65 (11.50%)                                | 49 (8.67%)         |
|           | <18 years of age                                    | 2 (0.10%)       | 2 (0.35%)                                  | 2 (0.35%)          |
|           | ≥18 years of age non-elective THA/TKA <sup>2</sup>  | 3 (0.14%)       | 1 (0.18%)                                  | 1 (0.18%)          |
|           | ≥18 years of age AF or NVAF <sup>3</sup>            | 61 (2.94%)      | 31 (5.49%)                                 | 14 (2.48%)         |
|           | ≥18 years of age VTE or DVT/PE <sup>4</sup>         | 18 (0.87%)      | 5 (0.88%)                                  | 4 (0.71%)          |
|           | ≥18 years of age Other surgery                      | 33 (1.59%)      | 11 (1.95%)                                 | 12 (2.12%)         |
|           | ≥18 years of age Other diseases                     | 59 (2.85%)      | 15 (2.65%)                                 | 16 (2.83%)         |
|           |   |                 |  |                    |
|           |   |                 |  |                    |
| 2014      | Total   | 15 516 (100.0%) | 4 592 (100.0%)                             | 4 592 (100.0%)     |
|           | No listed indication (unclassified)                 | 901 (5.81%)     | 111 (2.42%)                                | 229 (4.99%)        |
|           | Any indication                                      | 14 615 (94.19%) | 4 481 (97.58%)                             | 4 363 (95.01%)     |
|           | On-label indications                                | 13 436 (86.59%) | 4 089 (89.05%)                             | 4 044 (88.07%)     |
|           | THA/TKA   | 2 336 (15.06%)  | 814 (17.73%)                               | 814 (17.73%)       |
|           | NVAF <sup>1</sup>                                   | 10 683 (68.85%) | 3 198 (69.64%)                             | 3 160 (68.82%)     |
|           | DVT/PE <sup>1</sup>                                 | 417 (2.69%)     | 77 (1.68%)                                 | 70 (1.52%)         |
|           | Off-label indications                               | 1 179 (7.60%)   | 392 (8.54%)                                | 319 (6.95%)        |
|           | <18 years of age                                    |                 |  |                    |
|           | ≥18 years of age non-elective THA/TKA <sup>2</sup>  | 7 (0.05%)       | 4 (0.09%)                                  | 3 (0.07%)          |
|           | ≥18 years of age AF or NVAF <sup>3</sup>            | 365 (2.35%)     | 207 (4.51%)                                | 100 (2.18%)        |
|           | ≥18 years of age VTE or DVT/PE <sup>4</sup>         | 89 (0.57%)      | 26 (0.57%)                                 | 23 (0.50%)         |
|           | ≥18 years of age Other surgery                      | 202 (1.30%)     | 45 (0.98%)                                 | 52 (1.13%)         |
|           | ≥18 years of age Other diseases                     | 516 (3.33%)     | 110 (2.40%)                                | 141 (3.07%)        |
|           |   |                 |  |                    |
| 2012-2014 | Total   | 17 592 (100.0%) | 5 157 (100.0%)                             | 5 157 (100.0%)     |
|           | No listed indication (unclassified)                 | 1 030 (5.85%)   | 128 (2.48%)                                | 257 (4.98%)        |
|           | Any indication                                      | 16 562 (94.15%) | 5 029 (97.52%)                             | 4 900 (95.02%)     |
|           | On-label indications <sup>A</sup>                   | 15 204 (86.43%) | 4 572 (88.66%)                             | 4 532 (87.88%)     |
|           | THA/TKA <sup>B</sup>                                | 2 636 (14.98%)  | 930 (18.03%)                               | 930 (18.03%)       |
|           | NVAF <sup>1B</sup>                                  | 12 151 (69.07%) | 3 565 (69.13%)                             | 3 532 (68.49%)     |
|           | DVT/PE <sup>1B</sup>                                | 417 (2.37%)     | 77 (1.49%)                                 | 70 (1.36%)         |
|           | Off-label indications <sup>A</sup>                  | 1 358 (7.72%)   | 457 (8.86%)                                | 368 (7.14%)        |
|           | <18 years of age <sup>C</sup>                       | 2 (0.01%)       | 2 (0.04%)                                  | 2 (0.04%)          |
|           | ≥18 years of age non-elective THA/TKA <sup>2C</sup> | 10 (0.06%)      | 5 (0.10%)                                  | 4 (0.08%)          |
|           | ≥18 years of age AF or NVAF <sup>3C</sup>           | 428 (2.43%)     | 238 (4.62%)                                | 114 (2.21%)        |
|           | ≥18 years of age VTE or DVT/PE <sup>4C</sup>        | 108 (0.61%)     | 31 (0.60%)                                 | 27 (0.52%)         |
|           | ≥18 years of age Other surgery <sup>C</sup>         | 235 (1.34%)     | 56 (1.09%)                                 | 64 (1.24%)         |
|           | ≥18 years of age Other diseases <sup>C</sup>        | 575 (3.27%)     | 125 (2.42%)                                | 157 (3.04%)        |

<sup>1</sup> use in NVAF or DVT/PE patients is considered on-label after the date of approval and off-label on or prior to its approval date, <sup>2</sup> Non-elective THA/TKA, <sup>3</sup> NVAF before or on November 20, 2012 or valvular AF (VAF), <sup>4</sup> DVT/PE before or on July 28, 2014 or other or non-specific VTE  
<sup>A</sup>: denominator = 'any indication', <sup>B</sup>: denominator = 'on-label indications', <sup>C</sup>: denominator = 'off-label indications',

Table 1.2 General characteristics of apixaban-treated patients, number and proportions

| Characteristic                 | Proxy for indication |                  | On-label         |                  |                  | Off-label        |                      |                  |                  |                  |                  |
|--------------------------------|----------------------|------------------|------------------|------------------|------------------|------------------|----------------------|------------------|------------------|------------------|------------------|
|                                | Any                  | Unclassified     | THA/TKA          | NVAF             | DVT/PE           | <18 years        | Non-elective THA/TKA | AF*              | VTE*             | Other surgery    | Other diagnosis  |
| <b>All patients</b>            |                      |                  |                  |                  |                  |                  |                      |                  |                  |                  |                  |
| Total                          | 16 562 (100.0)       | 1 030 (100.0)    | 2 636 (100.0)    | 12 151 (100.0)   | 417 (100.0)      | 2 (100.0)        | 10 (100.0)           | 428 (100.0)      | 108 (100.0)      | 235 (100.0)      | 575 (100.0)      |
| Gender                         |                      |                  |                  |                  |                  |                  |                      |                  |                  |                  |                  |
| Male                           | 8 663 (52.3)         | 563 (54.7)       | 1 067 (40.5)     | 6 603 (54.3)     | 186 (44.6)       | 1 (50.0)         | 2 (20.0)             | 266 (62.1)       | 47 (43.5)        | 133 (56.6)       | 358 (62.3)       |
| Female                         | 7 899 (47.7)         | 467 (45.3)       | 1 569 (59.5)     | 5 548 (45.7)     | 231 (55.4)       | 1 (50.0)         | 8 (80.0)             | 162 (37.9)       | 61 (56.5)        | 102 (43.4)       | 217 (37.7)       |
| Age at index date              |                      |                  |                  |                  |                  |                  |                      |                  |                  |                  |                  |
| <18                            | 2 (0.0)              |                  |                  |                  |                  | 2 (100.0)        |                      |                  |                  |                  |                  |
| 18-44                          | 226 (1.4)            | 27 (2.6)         | 66 (2.5)         | 84 (0.7)         | 39 (9.4)         |                  |                      | 4 (0.9)          | 6 (5.6)          | 18 (7.7)         | 9 (1.6)          |
| 45-64                          | 2 986 (18.0)         | 151 (14.7)       | 853 (32.4)       | 1 821 (15.0)     | 113 (27.1)       |                  | 3 (30.0)             | 63 (14.7)        | 20 (18.5)        | 44 (18.7)        | 69 (12.0)        |
| 65-84                          | 10 713 (64.7)        | 681 (66.1)       | 1 626 (61.7)     | 8 004 (65.9)     | 209 (50.1)       |                  | 5 (50.0)             | 298 (69.6)       | 64 (59.3)        | 143 (60.9)       | 364 (63.3)       |
| 85+                            | 2 635 (15.9)         | 171 (16.6)       | 91 (3.5)         | 2 242 (18.5)     | 56 (13.4)        |                  | 2 (20.0)             | 63 (14.7)        | 18 (16.7)        | 30 (12.8)        | 133 (23.1)       |
| Mean (SD)                      | 73.6 (11.2)          | 73.7 (11.5)      | 68.1 (10.5)      | 74.9 (10.6)      | 68.0 (16.3)      | 16.0 (0.2)       | 73.0 (13.0)          | 74.7 (10.0)      | 71.6 (15.1)      | 70.8 (15.8)      | 76.0 (11.3)      |
| Median (IQR)                   | 74.2 (67.0-81.9)     | 74.2 (67.5-81.8) | 69.0 (61.5-75.6) | 75.3 (68.2-83.0) | 71.6 (57.3-80.3) | 16.0 (15.8-16.2) | 76.3 (57.8-79.8)     | 76.0 (68.5-82.0) | 73.0 (65.4-81.9) | 74.0 (64.3-81.3) | 77.7 (70.0-84.6) |
| Database history before index  |                      |                  |                  |                  |                  |                  |                      |                  |                  |                  |                  |
| <1 year                        | 1 (0.0)              |                  |                  | 1 (0.0)          |                  |                  |                      |                  |                  |                  |                  |
| 1-4 years                      | 59 (0.4)             | 2 (0.2)          | 5 (0.2)          | 49 (0.4)         | 1 (0.2)          |                  |                      | 1 (0.2)          |                  | 1 (0.4)          | 2 (0.3)          |
| 5-9 years                      | 16 502 (99.6)        | 1 028 (99.8)     | 2 631 (99.8)     | 12 101 (99.6)    | 416 (99.8)       | 2 (100.0)        | 10 (100.0)           | 427 (99.8)       | 108 (100.0)      | 234 (99.6)       | 573 (99.7)       |
| 10+ years                      |                      |                  |                  |                  |                  |                  |                      |                  |                  |                  |                  |
| Mean (SD)                      | 9.0 (0.5)            | 9.0 (0.5)        | 8.9 (0.4)        | 9.0 (0.5)        | 9.3 (0.3)        | 8.5 (0.0)        | 8.8 (0.4)            | 8.9 (0.5)        | 8.8 (0.4)        | 8.9 (0.7)        | 9.0 (0.5)        |
| Median (IQR)                   | 9.0 (8.7-9.3)        | 9.1 (8.8-9.3)    | 8.9 (8.7-9.3)    | 9.0 (8.7-9.3)    | 9.4 (9.3-9.4)    | 8.5 (8.4-8.5)    | 8.8 (8.4-9.1)        | 9.1 (8.7-9.3)    | 8.9 (8.7-9.0)    | 9.1 (8.7-9.3)    | 9.1 (8.8-9.3)    |
| Database follow-up after index |                      |                  |                  |                  |                  |                  |                      |                  |                  |                  |                  |
| <6 months                      | 8 878 (53.6)         | 622 (60.4)       | 996 (37.8)       | 6 716 (55.3)     | 417 (100.0)      |                  | 3 (30.0)             | 245 (57.2)       | 34 (31.5)        | 137 (58.3)       | 330 (57.4)       |
| 6-11 months                    | 5 829 (35.2)         | 282 (27.4)       | 1 340 (50.8)     | 4 053 (33.4)     |                  |                  | 4 (40.0)             | 122 (28.5)       | 55 (50.9)        | 68 (28.9)        | 187 (32.5)       |
| 12+ months                     | 1 855 (11.2)         | 126 (12.2)       | 300 (11.4)       | 1 382 (11.4)     |                  | 2 (100.0)        | 3 (30.0)             | 61 (14.3)        | 19 (17.6)        | 30 (12.8)        | 58 (10.1)        |
| Mean (SD)                      | 6.0 (4.4)            | 5.6 (4.5)        | 7.0 (4.1)        | 6.0 (4.4)        | 1.7 (1.1)        | 12.4 (0.5)       | 8.3 (4.7)            | 6.1 (5.0)        | 7.7 (4.6)        | 5.8 (4.5)        | 5.7 (4.2)        |
| Median (IQR)                   | 5.4 (2.2-9.2)        | 4.1 (1.9-8.5)    | 7.6 (3.0-10.2)   | 5.3 (2.2-9.0)    | 1.6 (0.9-2.5)    | 12.4 (12.0-12.7) | 8.2 (4.3-12.8)       | 5.0 (2.1-9.0)    | 7.5 (5.3-9.6)    | 4.1 (1.8-9.4)    | 5.1 (2.1-8.5)    |

| Characteristic                                       | Proxy for indication |                     | On-label            |                     |                     | Off-label           |                      |                     |                     |                     |                     |
|--|----------------------|---------------------|---------------------|---------------------|---------------------|---------------------|----------------------|---------------------|---------------------|---------------------|---------------------|
|  | Any                  | Unclassified        | THA/TKA             | NVAF                | DVT/PE              | <18 years           | Non-elective THA/TKA | AF*                 | VTE*                | Other surgery       | Other diagnosis     |
| Department Specialty                                 |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| Orthopaedic  | 2 698 (16.3)         | 9 (0.9)             | 2 605 (98.8)        | 29 (0.2)            |                     | 2 (100.0)           | 9 (90.0)             |                     | 3 (2.8)             | 48 (20.4)           | 2 (0.3)             |
| Surgery  | 225 (1.4)            | 7 (0.7)             | 1 (0.0)             | 187 (1.5)           | 8 (1.9)             |                     |                      | 9 (2.1)             | 2 (1.9)             | 14 (6.0)            | 4 (0.7)             |
| GP   | 2 102 (12.7)         | 503 (48.8)          | 6 (0.2)             | 1 724 (14.2)        | 74 (17.7)           |                     | 1 (10.0)             | 52 (12.1)           | 32 (29.6)           | 36 (15.3)           | 177 (30.8)          |
| Internal medicine                                    | 7 922 (47.8)         | 329 (31.9)          | 12 (0.5)            | 7 074 (58.2)        | 225 (54.0)          |                     |                      | 245 (57.2)          | 46 (42.6)           | 82 (34.9)           | 238 (41.4)          |
| Cardiology   | 2 090 (12.6)         | 113 (11.0)          | 3 (0.1)             | 1 875 (15.4)        | 20 (4.8)            |                     |                      | 76 (17.8)           | 6 (5.6)             | 40 (17.0)           | 70 (12.2)           |
| Other medicine                                       | 849 (5.1)            | 14 (1.4)            | 1 (0.0)             | 727 (6.0)           | 21 (5.0)            |                     |                      | 29 (6.8)            | 6 (5.6)             | 5 (2.1)             | 60 (10.4)           |
| Haematology  | 35 (0.2)             | 1 (0.1)             |                     | 13 (0.1)            | 19 (4.6)            |                     |                      |                     | 2 (1.9)             |                     | 1 (0.2)             |
| Other  | 639 (3.9)            | 54 (5.2)            | 8 (0.3)             | 520 (4.3)           | 50 (12.0)           |                     |                      | 17 (4.0)            | 11 (10.2)           | 10 (4.3)            | 23 (4.0)            |
| Patients with primary care data available – all data |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| Total  | 5 029 (100.0)        | 128 (100.0)         | 930 (100.0)         | 3 565 (100.0)       | 77 (100.0)          | 2 (100.0)           | 5 (100.0)            | 238 (100.0)         | 31 (100.0)          | 56 (100.0)          | 125 (100.0)         |
| Gender   |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| Male   | 2 560 (50.9)         | 61 (47.7)           | 377 (40.5)          | 1 911 (53.6)        | 37 (48.1)           | 1 (50.0)            | 2 (40.0)             | 125 (52.5)          | 12 (38.7)           | 29 (51.8)           | 66 (52.8)           |
| Female   | 2 469 (49.1)         | 67 (52.3)           | 553 (59.5)          | 1 654 (46.4)        | 40 (51.9)           | 1 (50.0)            | 3 (60.0)             | 113 (47.5)          | 19 (61.3)           | 27 (48.2)           | 59 (47.2)           |
| Age at index date                                    |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| <18  | 2 (0.0)              |                     |                     |                     |                     | 2 (100.0)           |                      |                     |                     |                     |                     |
| 18-44  | 85 (1.7)             | 7 (5.5)             | 38 (4.1)            | 29 (0.8)            | 5 (6.5)             |                     |                      | 2 (0.8)             | 1 (3.2)             | 9 (16.1)            | 1 (0.8)             |
| 45-64  | 889 (17.7)           | 27 (21.1)           | 314 (33.8)          | 493 (13.8)          | 20 (26.0)           |                     | 2 (40.0)             | 26 (10.9)           | 4 (12.9)            | 12 (21.4)           | 18 (14.4)           |
| 65-84  | 3 116 (62.0)         | 77 (60.2)           | 551 (59.2)          | 2 257 (63.3)        | 36 (46.8)           |                     | 3 (60.0)             | 149 (62.6)          | 16 (51.6)           | 30 (53.6)           | 74 (59.2)           |
| 85+  | 937 (18.6)           | 17 (13.3)           | 27 (2.9)            | 786 (22.0)          | 16 (20.8)           |                     |                      | 61 (25.6)           | 10 (32.3)           | 5 (8.9)             | 32 (25.6)           |
| Mean (SD)  | 74.0 (11.8)          | 70.8 (13.5)         | 67.2 (11.1)         | 75.8 (10.9)         | 70.0 (15.9)         | 16.0 (0.2)          | 68.8 (10.7)          | 77.2 (10.3)         | 75.1 (13.7)         | 64.9 (19.8)         | 76.5 (11.6)         |
| Median (IQR)   | 74.8<br>(67.1-82.9)  | 71.4<br>(64.7-79.5) | 68.5<br>(60.4-75.2) | 76.3<br>(68.6-84.1) | 71.6<br>(59.4-82.4) | 16.0<br>(15.8-16.2) | 72.7<br>(57.8-76.9)  | 78.5<br>(69.9-85.1) | 77.0<br>(67.4-86.8) | 70.3<br>(59.1-77.7) | 78.0<br>(69.6-85.1) |
| Database history before index                        |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| <1 year  |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| 1-4 years  | 21 (0.4)             |                     | 1 (0.1)             | 19 (0.5)            |                     |                     |                      |                     |                     | 1 (1.8)             |                     |
| 5-9 years  | 5 008 (99.6)         | 128 (100.0)         | 929 (99.9)          | 3 546 (99.5)        | 77 (100.0)          | 2 (100.0)           | 5 (100.0)            | 238 (100.0)         | 31 (100.0)          | 55 (98.2)           | 125 (100.0)         |
| 10+ years  |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| Mean (SD)  | 8.9 (0.5)            | 9.0 (0.4)           | 8.9 (0.4)           | 9.0 (0.6)           | 9.3 (0.3)           | 8.5 (0.0)           | 9.0 (0.4)            | 8.9 (0.4)           | 8.8 (0.3)           | 8.7 (1.2)           | 8.9 (0.3)           |
| Median (IQR)   | 9.0<br>(8.7-9.3)     | 9.0<br>(8.7-9.3)    | 8.9<br>(8.6-9.2)    | 9.0<br>(8.8-9.3)    | 9.4<br>(9.3-9.4)    | 8.5<br>(8.4-8.5)    | 9.1<br>(8.9-9.1)     | 8.9<br>(8.7-9.2)    | 8.9<br>(8.7-9.0)    | 8.7<br>(8.5-9.2)    | 8.9<br>(8.7-9.2)    |

| Characteristic   | Proxy for indication |                     | On-label            |                     |                     | Off-label           |                      |                     |                     |                     |                     |
|--|----------------------|---------------------|---------------------|---------------------|---------------------|---------------------|----------------------|---------------------|---------------------|---------------------|---------------------|
|  | Any                  | Unclassified        | THA/TKA             | NVAF                | DVT/PE              | <18 years           | Non-elective THA/TKA | AF*                 | VTE*                | Other surgery       | Other diagnosis     |
| Database follow-up after index                                 |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| <6 months  | 2 601 (51.7)         | 68 (53.1)           | 345 (37.1)          | 1 968 (55.2)        | 77 (100.0)          |                     | 3 (60.0)             | 112 (47.1)          | 8 (25.8)            | 25 (44.6)           | 63 (50.4)           |
| 6-11 months  | 1 914 (38.1)         | 43 (33.6)           | 469 (50.4)          | 1 258 (35.3)        |                     |                     | 1 (20.0)             | 98 (41.2)           | 18 (58.1)           | 21 (37.5)           | 49 (39.2)           |
| 12+ months   | 514 (10.2)           | 17 (13.3)           | 116 (12.5)          | 339 (9.5)           |                     | 2 (100.0)           | 1 (20.0)             | 28 (11.8)           | 5 (16.1)            | 10 (17.9)           | 13 (10.4)           |
| Mean (SD)  | 6.1 (4.2)            | 6.2 (4.3)           | 7.1 (4.1)           | 5.8 (4.2)           | 1.8 (1.1)           | 12.4 (0.5)          | 6.4 (4.4)            | 6.6 (4.2)           | 7.3 (4.0)           | 7.1 (4.4)           | 6.3 (4.0)           |
| Median (IQR)   | 5.7<br>(2.3-9.2)     | 5.7<br>(2.5-9.4)    | 7.8<br>(3.0-10.4)   | 5.3<br>(2.2-8.7)    | 1.6<br>(1.0-2.9)    | 12.4<br>(12.0-12.7) | 4.4<br>(4.3-6.9)     | 6.4<br>(3.0-9.5)    | 7.3<br>(5.7-9.0)    | 7.7<br>(2.9-10.1)   | 5.9<br>(3.0-9.4)    |
| Department Specialty   |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| Orthopaedic  | 959 (19.1)           | 2 (1.6)             | 920 (98.9)          | 10 (0.3)            |                     | 2 (100.0)           | 4 (80.0)             |                     |                     | 23 (41.1)           |                     |
| Surgery  | 31 (0.6)             | 3 (2.3)             |                     | 29 (0.8)            |                     |                     |                      |                     | 1 (3.2)             | 1 (1.8)             |                     |
| GP   | 791 (15.7)           | 38 (29.7)           | 2 (0.2)             | 701 (19.7)          | 22 (28.6)           |                     |                      | 43 (18.1)           | 6 (19.4)            | 3 (5.4)             | 14 (11.2)           |
| Internal medicine  | 2 298 (45.7)         | 43 (33.6)           | 4 (0.4)             | 2 004 (56.2)        | 36 (46.8)           |                     |                      | 140 (58.8)          | 16 (51.6)           | 18 (32.1)           | 80 (64.0)           |
| Cardiology   | 564 (11.2)           | 31 (24.2)           | 1 (0.1)             | 502 (14.1)          | 3 (3.9)             |                     |                      | 33 (13.9)           | 3 (9.7)             | 9 (16.1)            | 13 (10.4)           |
| Other medicine   | 253 (5.0)            | 6 (4.7)             |                     | 214 (6.0)           | 3 (3.9)             |                     | 1 (20.0)             | 17 (7.1)            | 4 (12.9)            | 1 (1.8)             | 13 (10.4)           |
| Haematology  | 3 (0.1)              |                     |                     | 2 (0.1)             | 1 (1.3)             |                     |                      |                     |                     |                     |                     |
| Other  | 130 (2.6)            | 5 (3.9)             | 3 (0.3)             | 103 (2.9)           | 12 (15.6)           |                     |                      | 5 (2.1)             | 1 (3.2)             | 1 (1.8)             | 5 (4.0)             |
| Patients with primary care data available – only hospital data |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| Total  | 4 900 (100.0)        | 257 (100.0)         | 930 (100.0)         | 3 532 (100.0)       | 70 (100.0)          | 2 (100.0)           | 4 (100.0)            | 114 (100.0)         | 27 (100.0)          | 64 (100.0)          | 157 (100.0)         |
| Gender   |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| Male   | 2 502 (51.1)         | 119 (46.3)          | 377 (40.5)          | 1 897 (53.7)        | 35 (50.0)           | 1 (50.0)            | 1 (25.0)             | 61 (53.5)           | 11 (40.7)           | 32 (50.0)           | 87 (55.4)           |
| Female   | 2 398 (48.9)         | 138 (53.7)          | 553 (59.5)          | 1 635 (46.3)        | 35 (50.0)           | 1 (50.0)            | 3 (75.0)             | 53 (46.5)           | 16 (59.3)           | 32 (50.0)           | 70 (44.6)           |
| Age at index date  |                      |                     |                     |                     |                     |                     |                      |                     |                     |                     |                     |
| <18  | 2 (0.0)              |                     |                     |                     |                     | 2 (100.0)           |                      |                     |                     |                     |                     |
| 18-44  | 84 (1.7)             | 8 (3.1)             | 38 (4.1)            | 29 (0.8)            | 5 (7.1)             |                     |                      |                     | 1 (3.7)             | 9 (14.1)            | 2 (1.3)             |
| 45-64  | 887 (18.1)           | 29 (11.3)           | 314 (33.8)          | 495 (14.0)          | 20 (28.6)           |                     | 2 (50.0)             | 19 (16.7)           | 4 (14.8)            | 12 (18.8)           | 21 (13.4)           |
| 65-84  | 3 020 (61.6)         | 173 (67.3)          | 551 (59.2)          | 2 216 (62.7)        | 33 (47.1)           |                     | 2 (50.0)             | 78 (68.4)           | 13 (48.1)           | 36 (56.3)           | 91 (58.0)           |
| 85+  | 907 (18.5)           | 47 (18.3)           | 27 (2.9)            | 792 (22.4)          | 12 (17.1)           |                     |                      | 17 (14.9)           | 9 (33.3)            | 7 (10.9)            | 43 (27.4)           |
| Mean (SD)  | 73.9 (11.8)          | 74.5 (12.1)         | 67.2 (11.1)         | 75.8 (10.9)         | 69.0 (16.2)         | 16.0 (0.2)          | 67.9 (12.1)          | 74.3 (9.9)          | 74.9 (14.6)         | 66.6 (19.2)         | 77.0 (11.3)         |
| Median (IQR)   | 74.7<br>(67.0-82.8)  | 75.2<br>(68.2-82.6) | 68.5<br>(60.4-75.2) | 76.4<br>(68.6-84.2) | 71.0<br>(57.4-82.2) | 16.0<br>(15.8-16.2) | 67.3<br>(57.4-78.3)  | 76.1<br>(66.5-82.0) | 79.0<br>(67.2-87.1) | 71.4<br>(61.8-78.4) | 78.4<br>(71.1-85.6) |



| Characteristic                 | Proxy for indication |                  | On-label          |                  |                  | Off-label           |                      |                  |                  |                   |                  |
|--------------------------------|----------------------|------------------|-------------------|------------------|------------------|---------------------|----------------------|------------------|------------------|-------------------|------------------|
|                                | Any                  | Unclassified     | THA/TKA           | NVAF             | DVT/PE           | <18 years           | Non-elective THA/TKA | AF*              | VTE*             | Other surgery     | Other diagnosis  |
| Database history before index  |                      |                  |                   |                  |                  |                     |                      |                  |                  |                   |                  |
| <1 year                        |                      |                  |                   |                  |                  |                     |                      |                  |                  |                   |                  |
| 1-4 years                      | 21 (0.4)             |                  | 1 (0.1)           | 19 (0.5)         |                  |                     |                      |                  |                  | 1 (1.6)           |                  |
| 5-9 years                      | 4 879 (99.6)         | 257 (100.0)      | 929 (99.9)        | 3 513 (99.5)     | 70 (100.0)       | 2 (100.0)           | 4 (100.0)            | 114 (100.0)      | 27 (100.0)       | 63 (98.4)         | 157 (100.0)      |
| 10+ years                      |                      |                  |                   |                  |                  |                     |                      |                  |                  |                   |                  |
| Mean (SD)                      | 8.9 (0.6)            | 9.0 (0.4)        | 8.9 (0.4)         | 9.0 (0.6)        | 9.3 (0.1)        | 8.5 (0.0)           | 8.9 (0.4)            | 8.9 (0.4)        | 8.9 (0.3)        | 8.7 (1.1)         | 9.0 (0.3)        |
| Median (IQR)                   | 9.0<br>(8.7-9.3)     | 9.1<br>(8.8-9.3) | 8.9<br>(8.6-9.2)  | 9.0<br>(8.8-9.3) | 9.4<br>(9.3-9.4) | 8.5<br>(8.4-8.5)    | 9.0<br>(8.6-9.2)     | 8.9<br>(8.7-9.2) | 8.9<br>(8.7-9.0) | 8.8<br>(8.5-9.2)  | 9.0<br>(8.7-9.2) |
| Database follow-up after index |                      |                  |                   |                  |                  |                     |                      |                  |                  |                   |                  |
| <6 months                      | 2 519 (51.4)         | 150 (58.4)       | 345 (37.1)        | 1 927 (54.6)     | 70 (100.0)       |                     | 2 (50.0)             | 56 (49.1)        | 7 (25.9)         | 28 (43.8)         | 84 (53.5)        |
| 6-11 months                    | 1 877 (38.3)         | 80 (31.1)        | 469 (50.4)        | 1 262 (35.7)     |                  |                     | 1 (25.0)             | 46 (40.4)        | 16 (59.3)        | 25 (39.1)         | 58 (36.9)        |
| 12+ months                     | 504 (10.3)           | 27 (10.5)        | 116 (12.5)        | 343 (9.7)        |                  | 2 (100.0)           | 1 (25.0)             | 12 (10.5)        | 4 (14.8)         | 11 (17.2)         | 15 (9.6)         |
| Mean (SD)                      | 6.1 (4.2)            | 5.6 (4.1)        | 7.1 (4.1)         | 5.9 (4.2)        | 1.9 (1.1)        | 12.4 (0.5)          | 6.9 (4.9)            | 6.4 (4.2)        | 7.1 (4.0)        | 7.0 (4.4)         | 6.0 (3.9)        |
| Median (IQR)                   | 5.8<br>(2.3-9.2)     | 4.6<br>(2.2-8.7) | 7.8<br>(3.0-10.4) | 5.4<br>(2.3-8.7) | 1.7<br>(1.1-3.0) | 12.4<br>(12.0-12.7) | 5.6<br>(3.4-10.3)    | 6.3<br>(2.5-9.2) | 7.3<br>(5.4-9.0) | 7.7<br>(2.9-10.0) | 5.7<br>(2.8-8.6) |
| Department Specialty           |                      |                  |                   |                  |                  |                     |                      |                  |                  |                   |                  |
| Orthopaedic                    | 959 (19.6)           | 2 (0.8)          | 920 (98.9)        | 10 (0.3)         |                  | 2 (100.0)           | 4 (100.0)            |                  |                  | 23 (35.9)         |                  |
| Surgery                        | 31 (0.6)             | 3 (1.2)          |                   | 29 (0.8)         |                  |                     |                      |                  | 1 (3.7)          | 1 (1.6)           |                  |
| GP                             | 691 (14.1)           | 138 (53.7)       | 2 (0.2)           | 597 (16.9)       | 22 (31.4)        |                     |                      | 16 (14.0)        | 7 (25.9)         | 7 (10.9)          | 40 (25.5)        |
| Internal medicine              | 2 278 (46.5)         | 63 (24.5)        | 4 (0.4)           | 2 057 (58.2)     | 30 (42.9)        |                     |                      | 68 (59.6)        | 13 (48.1)        | 21 (32.8)         | 85 (54.1)        |
| Cardiology                     | 558 (11.4)           | 37 (14.4)        | 1 (0.1)           | 508 (14.4)       | 3 (4.3)          |                     |                      | 23 (20.2)        | 2 (7.4)          | 9 (14.1)          | 12 (7.6)         |
| Other medicine                 | 252 (5.1)            | 7 (2.7)          |                   | 226 (6.4)        | 3 (4.3)          |                     |                      | 6 (5.3)          | 2 (7.4)          | 2 (3.1)           | 13 (8.3)         |
| Haematology                    | 3 (0.1)              |                  |                   | 2 (0.1)          | 1 (1.4)          |                     |                      |                  |                  |                   |                  |
| Other                          | 128 (2.6)            | 7 (2.7)          | 3 (0.3)           | 103 (2.9)        | 11 (15.7)        |                     |                      | 1 (0.9)          | 2 (7.4)          | 1 (1.6)           | 7 (4.5)          |

\*=includes NVAF before November 20, 2012 or AF; includes DVT/PE before July 28, 2014 or VTE

Table 1.3 Off-label apixaban users classified as other surgery (select surgical procedures other than THA or TKA within 30 days of apixaban dispensing), number and proportions

| NCSP chapter | Text  |              | Sub-group with primary care data available |                    |
|--------------|---|--------------|--|--------------------|
|              |   | All Patients | All data                                   | Only hospital data |
|              |   | N=235        | N=64                                       | N=56               |
| A            | Nervous system  | 1 (0.36%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| B            | Endocrine system  | 0 (0.00%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| C            | Eye and adjacent structures   | 19 (6.86%)   | 2 (2.70%)                                  | 2 (3.08%)          |
| D            | Ear, nose and larynx  | 1 (0.36%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| E            | Teeth, jaws, mouth and pharynx  | 1 (0.36%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| F            | Heart and major thoracic vessels  | 77 (27.80%)  | 18 (24.32%)                                | 17 (26.15%)        |
| FCA          | Repair of ascending aorta   | 1 (0.27%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FFC          | Closure of isolated atrial septal defect                                      | 1 (0.27%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FGE          | Prosthetic replacement of tricuspid valve                                     | 0 (0.00%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FJA          | Biopsy of right ventricle   | 1 (0.27%)    | 1 (1.19%)                                  | 1 (1.33%)          |
| FJF          | Prosthetic replacement of pulmonary valve                                     | 0 (0.00%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FKA          | Repair of mitral valve for stenosis   | 0 (0.00%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FKB          | Annuloplasty of mitral valve for insufficiency                                | 2 (0.54%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FKC          | Repair of mitral valve for insufficiency                                      | 2 (0.54%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FKD          | Prosthetic replacement of mitral valve  | 0 (0.00%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FMD          | Replacement of aortic valve   | 10 (2.70%)   | 1 (1.19%)                                  | 1 (1.33%)          |
| FNA          | Connection to coronary artery from internal mammary artery                    | 32 (8.65%)   | 3 (3.57%)                                  | 3 (4.00%)          |
| FNC          | Aorto-coronary venous bypass  | 33 (8.92%)   | 4 (4.76%)                                  | 4 (5.33%)          |
| FNE          | Coronary bypass using free arterial graft                                     | 1 (0.27%)    | 1 (1.19%)                                  | 1 (1.33%)          |
| FNG          | Expansion and recanalization of coronary artery                               | 9 (2.43%)    | 3 (3.57%)                                  | 2 (2.67%)          |
| FPB          | Excision or ablation of aberrant pathway or focus of heart                    | 7 (1.89%)    | 3 (3.57%)                                  | 3 (4.00%)          |
| FPE          | Implantation or replacement of permanent trans venous cardiac pacemaker       | 21 (5.68%)   | 7 (8.33%)                                  | 7 (9.33%)          |
| FPG          | Implantation of permanent cardioverter-defibrillator                          | 1 (0.27%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FPH          | Removal of permanent cardiac pacemaker or cardioverter-defibrillator          | 1 (0.27%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FPJ          | Revision of pacemaker pulse generator or electrode                            | 1 (0.27%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FWC          | Reoperation for deep infection in surgery of heart and major thoracic vessels | 1 (0.27%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FXA          | Intraoperative total cardiopulmonary bypass                                   | 42 (11.35%)  | 4 (4.76%)                                  | 4 (5.33%)          |
| FXG          | Use of Intra-aortic balloon pump  | 1 (0.27%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FXH          | Removal of Intra-aortic balloon pump  | 1 (0.27%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| FXN          | Procedures using total artificial heart                                       | 0 (0.00%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| G            | Chest wall, pleura, mediastinum, diaphragm, trachea, bronchus and lung        | 4 (1.44%)    | 1 (1.35%)                                  | 1 (1.54%)          |
| H            | Mammary gland   | 0 (0.00%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| J            | Digestive system and spleen   | 9 (3.25%)    | 2 (2.70%)                                  | 2 (3.08%)          |
| K            | Urinary system, male genital organs and retroperitoneal space                 | 2 (0.72%)    | 2 (2.70%)                                  | 2 (3.08%)          |
| L            | Female genital organs   | 2 (0.72%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| M            | Obstetric procedures  | 0 (0.00%)    | 0 (0.00%)                                  | 0 (0.00%)          |
| N            | Musculoskeletal system  | 52 (18.77%)  | 24 (32.43%)                                | 23 (35.38%)        |
| NFJ,NGJ      | Knee or hip fracture surgery  | 7 (1.89%)    | 1 (1.19%)                                  | 1 (1.33%)          |

| NCSP chapter               | Text  | Sub-group with primary care data available |             |                    |
|----------------------------|---|--|-------------|--------------------|
|                            |   | All Patients                               | All data    | Only hospital data |
|                            |   | N=235                                      | N=64        | N=56               |
| N except NFJ,NGJ           | Other orthopedic surgery                        | 47 (12.70%)                                | 24 (28.57%) | 23 (30.67%)        |
| P                          | Peripheral vessels and lymphatic system         | 10 (3.61%)                                 | 4 (5.41%)   | 3 (4.62%)          |
| Q                          | Skin  | 16 (5.78%)                                 | 2 (2.70%)   | 1 (1.54%)          |
| T                          | Minor surgical procedures                       | 38 (13.72%)                                | 8 (10.81%)  | 6 (9.23%)          |
| U                          | Transluminal endoscopy                          | 26 (9.39%)                                 | 7 (9.46%)   | 4 (6.15%)          |
| X                          | Investigative procedures connected with surgery | 19 (6.86%)                                 | 4 (5.41%)   | 4 (6.15%)          |
| <b>Total other surgery</b> |   | 277 (100.0%)                               | 74 (100.0%) | 65 (100.0%)        |

\* Patients with procedures FGE00, FGE96, FKA96, FKD00, FKD96, FJF00, FJF96, FMD00 or FMD96 are off-label even if they also have a record of NVAf.

Table 1.4 a, b, c: Off-label apixaban users classified as other diagnoses, VAF and VTE:

- a) Other diagnoses (select diagnoses, ever before index date),
- b) VAF (select diagnoses, ever before index date),
- c) VTE (select diagnoses, ever before index date)

| ICD-10 code | Text   | Other diagnoses |
|-------------|--|-----------------|
| <b>A</b>    | <b>All patients, hospital data</b>                                   | <b>N=575</b>    |
| I20         | Angina pectoris  | 250 (43.48%)    |
| I21         | Acute myocardial infarction  | 171 (29.74%)    |
| I22         | Subsequent myocardial infarction                                     | 2 (0.35%)       |
| I23         | Certain current complications following acute myocardial infarction  | 2 (0.35%)       |
| I24         | Other acute ischemic heart diseases                                  | 7 (1.22%)       |
| I25         | Chronic ischemic heart disease                                       | 277 (48.17%)    |
| I63         | Cerebral infarction  | 237 (41.22%)    |
| I64         | Stroke, not specified as haemorrhage or infarction                   | 21 (3.65%)      |
| I74         | Arterial embolism and thrombosis                                     | 12 (2.09%)      |
|             | Any other, not classified above                                      | 572 (99.48%)    |
| <b>A</b>    | <b>Subgroup with primary care data available, all data</b>           | <b>N=125</b>    |
| I20         | Angina pectoris  | 38 (30.40%)     |
| I21         | Acute myocardial infarction  | 32 (25.60%)     |
| I22         | Subsequent myocardial infarction                                     |                 |
| I23         | Certain current complications following acute myocardial infarction  |                 |
| I24         | Other acute ischemic heart diseases                                  | 1 (0.80%)       |
| I25         | Chronic ischemic heart disease                                       | 60 (48.00%)     |
| I63         | Cerebral infarction  | 64 (51.20%)     |
| I64         | Stroke, not specified as haemorrhage or infarction                   | 14 (11.20%)     |
| I74         | Arterial embolism and thrombosis                                     | 2 (1.60%)       |
|             | Any other, not classified above                                      | 125 (100.0%)    |
| <b>A</b>    | <b>Subgroup with primary care data available, only hospital data</b> | <b>N=157</b>    |
| I20         | Angina pectoris  | 54 (34.39%)     |
| I21         | Acute myocardial infarction  | 38 (24.20%)     |
| I22         | Subsequent myocardial infarction                                     | 1 (0.64%)       |
| I23         | Certain current complications following acute myocardial infarction  |                 |
| I24         | Other acute ischemic heart diseases                                  | 4 (2.55%)       |

| ICD-10 code | Text   | Other diagnoses |
|-------------|--|-----------------|
| I25         | Chronic ischemic heart disease                     | 71 (45.22%)     |
| I63         | Cerebral infarction                                | 83 (52.87%)     |
| I64         | Stroke, not specified as haemorrhage or infarction | 3 (1.91%)       |
| I74         | Arterial embolism and thrombosis                   | 4 (2.55%)       |
|             | Any other, not classified above                    | 157 (100.0%)    |

| ICD-10 code | Text   | AF         |
|-------------|--|------------|
| B           | All patients, hospital data  | N=428      |
|             | NVAF before approval   |            |
| FGE00       | Replacement of tricuspid valve using mechanical prosthesis                 |            |
| FGE96       | Other prosthetic replacement of tricuspid valve                            |            |
| FJF00       | Replacement of pulmonary valve using mechanical prosthesis                 |            |
| FJF96       | Other replacement of pulmonary valve                                       |            |
| FKA96       | Other repair of mitral valve for stenosis                                  |            |
| FKD00       | Replacement of mitral valve using mechanical prosthesis                    | 1 (0.23%)  |
| FKD96       | Other replacement of mitral valve  |            |
| FMD00       | Replacement of aortic valve using mechanical prosthesis                    | 5 (1.17%)  |
| FMD96       | Other prosthetic replacement of aortic valve                               | 2 (0.47%)  |
| I050        | Rheumatic mitral stenosis  | 22 (5.14%) |
| I052        | Rheumatic mitral stenosis with insufficiency                               | 5 (1.17%)  |
| I058        | Other rheumatic mitral valve diseases                                      | 1 (0.23%)  |
| I059        | Rheumatic mitral valve disease, unspecified                                | 3 (0.70%)  |
| I080        | Rheumatic disorders of both mitral and aortic valves                       | 1 (0.23%)  |
| I081        | Rheumatic disorders of both mitral and tricuspid valves                    | 1 (0.23%)  |
| I083        | Combined rheumatic disorders of mitral, aortic and tricuspid valves        | 2 (0.47%)  |
| I088        | Other rheumatic multiple valve diseases                                    |            |
| I089        | Rheumatic multiple valve disease, unspecified                              |            |
| I091        | Rheumatic diseases of endocardium, valve unspecified                       |            |
| I098        | Other specified rheumatic heart disease                                    |            |
| I099        | Rheumatic heart disease, unspecified                                       | 1 (0.23%)  |
| I342        | Non-rheumatic mitral (valve) stenosis                                      | 18 (4.21%) |
| I348        | Other non-rheumatic mitral valve disorders                                 | 8 (1.87%)  |
| I349        | Non-rheumatic mitral valve disorder, unspecified                           | 6 (1.40%)  |
| I38         | Endocarditis, valve unspecified  | 25 (5.84%) |
| I390        | Mitral valve disorders in diseases classified elsewhere                    |            |
| I394        | Multiple valve disorders in diseases classified elsewhere                  | 1 (0.23%)  |
| I398        | Endocarditis, valve unspecified, in diseases classified elsewhere          |            |
| Q232        | Congenital mitral stenosis   | 1 (0.23%)  |
| Q238        | Other congenital malformations of aortic and mitral valves                 |            |
| Q239        | Congenital malformation of aortic and mitral valves, unspecified           |            |
| Q248        | Other specified congenital malformations of heart                          | 2 (0.47%)  |
| Q249        | Congenital malformation of heart, unspecified                              | 5 (1.17%)  |
| T820        | Mechanical complication of heart valve prosthesis                          | 1 (0.23%)  |
| T825        | Mechanical complication of other cardiac and vascular devices and implants | 12 (2.80%) |

| ICD-10 code             | Text  | AF           |
|-------------------------|---|--------------|
| T826                    | Infection and inflammatory reaction due to cardiac valve prosthesis                           | 8 (1.87%)    |
| T827                    | Infection and inflammatory reaction due to other cardiac and vascular devices, implants and   | 34 (7.94%)   |
| T828                    | Other specified complications of cardiac and vascular prosthetic devices, implants and grafts | 28 (6.54%)   |
| T829                    | Unspecified complication of cardiac and vascular prosthetic device, implant and graft         | 4 (0.93%)    |
| Z952                    | Presence of prosthetic heart valve  | 88 (20.56%)  |
| Z954                    | Presence of other heart-valve replacement   | 80 (18.69%)  |
| Z958                    | Presence of other cardiac and vascular implants and grafts                                    | 138 (32.24%) |
| Z959                    | Presence of cardiac and vascular implant and graft, unspecified                               | 44 (10.28%)  |
| I050, I052, I342, Q232  | Total mitral stenosis   | 37 (8.64%)   |
| FGE, FJF, FKA, FKD, FMD | Total mechanical prosthetic heart valves surgeries  | 8 (1.87%)    |
|                         | Any other, not classified above   | 428 (100.0%) |
| <b>B</b>                | <b>Subgroup with primary care data available, all data</b>                                    | <b>N=238</b> |
|                         | NVAF before approval  |              |
| FGE00                   | Replacement of tricuspid valve using mechanical prosthesis                                    |              |
| FGE96                   | Other prosthetic replacement of tricuspid valve   |              |
| FJF00                   | Replacement of pulmonary valve using mechanical prosthesis                                    |              |
| FJF96                   | Other replacement of pulmonary valve  |              |
| FKA96                   | Other repair of mitral valve for stenosis   |              |
| FKD00                   | Replacement of mitral valve using mechanical prosthesis                                       |              |
| FKD96                   | Other replacement of mitral valve   |              |
| FMD00                   | Replacement of aortic valve using mechanical prosthesis                                       |              |
| FMD96                   | Other prosthetic replacement of aortic valve  |              |
| I050                    | Rheumatic mitral stenosis   | 10 (4.20%)   |
| I052                    | Rheumatic mitral stenosis with insufficiency  | 2 (0.84%)    |
| I058                    | Other rheumatic mitral valve diseases   |              |
| I059                    | Rheumatic mitral valve disease, unspecified   | 5 (2.10%)    |
| I080                    | Rheumatic disorders of both mitral and aortic valves  |              |
| I081                    | Rheumatic disorders of both mitral and tricuspid valves                                       |              |
| I083                    | Combined rheumatic disorders of mitral, aortic and tricuspid valves                           | 3 (1.26%)    |
| I088                    | Other rheumatic multiple valve diseases   |              |
| I089                    | Rheumatic multiple valve disease, unspecified   | 3 (1.26%)    |
| I091                    | Rheumatic diseases of endocardium, valve unspecified  | 1 (0.42%)    |
| I098                    | Other specified rheumatic heart disease   |              |
| I099                    | Rheumatic heart disease, unspecified  | 1 (0.42%)    |
| I342                    | Non-rheumatic mitral (valve) stenosis   | 8 (3.36%)    |
| I348                    | Other non-rheumatic mitral valve disorders  | 3 (1.26%)    |
| I349                    | Non-rheumatic mitral valve disorder, unspecified  | 7 (2.94%)    |
| I38                     | Endocarditis, valve unspecified   | 149 (62.61%) |
| I390                    | Mitral valve disorders in diseases classified elsewhere                                       | 1 (0.42%)    |
| I394                    | Multiple valve disorders in diseases classified elsewhere                                     | 1 (0.42%)    |
| I398                    | Endocarditis, valve unspecified, in diseases classified elsewhere                             |              |
| Q232                    | Congenital mitral stenosis  |              |
| Q238                    | Other congenital malformations of aortic and mitral valves                                    |              |
| Q239                    | Congenital malformation of aortic and mitral valves, unspecified                              |              |

| ICD-10 code             | Text  | AF           |
|-------------------------|---|--------------|
| Q248                    | Other specified congenital malformations of heart   | 2 (0.84%)    |
| Q249                    | Congenital malformation of heart, unspecified   | 1 (0.42%)    |
| T820                    | Mechanical complication of heart valve prosthesis   |              |
| T825                    | Mechanical complication of other cardiac and vascular devices and implants                    | 2 (0.84%)    |
| T826                    | Infection and inflammatory reaction due to cardiac valve prosthesis                           | 1 (0.42%)    |
| T827                    | Infection and inflammatory reaction due to other cardiac and vascular devices, implants and   | 8 (3.36%)    |
| T828                    | Other specified complications of cardiac and vascular prosthetic devices, implants and grafts | 6 (2.52%)    |
| T829                    | Unspecified complication of cardiac and vascular prosthetic device, implant and graft         | 2 (0.84%)    |
| Z952                    | Presence of prosthetic heart valve  | 27 (11.34%)  |
| Z954                    | Presence of other heart-valve replacement   | 22 (9.24%)   |
| Z958                    | Presence of other cardiac and vascular implants and grafts                                    | 31 (13.03%)  |
| Z959                    | Presence of cardiac and vascular implant and graft, unspecified                               | 12 (5.04%)   |
| I050, I052, I342, Q232  | Total mitral stenosis   | 14 (5.88%)   |
| FGE, FJF, FKA, FKD, FMD | Total mechanical prosthetic heart valves surgeries  |              |
|                         | Any other, not classified above   | 238 (100.0%) |
| <b>B</b>                | <b>Subgroup with primary care data available, only hospital data</b>                          | <b>N=114</b> |
|                         | NVAF before approval  |              |
| FGE00                   | Replacement of tricuspid valve using mechanical prosthesis                                    |              |
| FGE96                   | Other prosthetic replacement of tricuspid valve   |              |
| FJF00                   | Replacement of pulmonary valve using mechanical prosthesis                                    |              |
| FJF96                   | Other replacement of pulmonary valve  |              |
| FKA96                   | Other repair of mitral valve for stenosis   |              |
| FKD00                   | Replacement of mitral valve using mechanical prosthesis                                       |              |
| FKD96                   | Other replacement of mitral valve   |              |
| FMD00                   | Replacement of aortic valve using mechanical prosthesis                                       |              |
| FMD96                   | Other prosthetic replacement of aortic valve  |              |
| I050                    | Rheumatic mitral stenosis   | 10 (8.77%)   |
| I052                    | Rheumatic mitral stenosis with insufficiency  | 2 (1.75%)    |
| I058                    | Other rheumatic mitral valve diseases   |              |
| I059                    | Rheumatic mitral valve disease, unspecified   | 1 (0.88%)    |
| I080                    | Rheumatic disorders of both mitral and aortic valves  |              |
| I081                    | Rheumatic disorders of both mitral and tricuspid valves                                       |              |
| I083                    | Combined rheumatic disorders of mitral, aortic and tricuspid valves                           | 1 (0.88%)    |
| I088                    | Other rheumatic multiple valve diseases   |              |
| I089                    | Rheumatic multiple valve disease, unspecified   |              |
| I091                    | Rheumatic diseases of endocardium, valve unspecified  |              |
| I098                    | Other specified rheumatic heart disease   |              |
| I099                    | Rheumatic heart disease, unspecified  | 1 (0.88%)    |
| I342                    | Non-rheumatic mitral (valve) stenosis   | 8 (7.02%)    |
| I348                    | Other non-rheumatic mitral valve disorders  | 3 (2.63%)    |
| I349                    | Non-rheumatic mitral valve disorder, unspecified  | 4 (3.51%)    |
| I38                     | Endocarditis, valve unspecified   | 7 (6.14%)    |
| I390                    | Mitral valve disorders in diseases classified elsewhere                                       |              |
| I394                    | Multiple valve disorders in diseases classified elsewhere                                     | 1 (0.88%)    |

| ICD-10 code             | Text  | AF           |
|-------------------------|---|--------------|
| I398                    | Endocarditis, valve unspecified, in diseases classified elsewhere                             |              |
| Q232                    | Congenital mitral stenosis  |              |
| Q238                    | Other congenital malformations of aortic and mitral valves                                    |              |
| Q239                    | Congenital malformation of aortic and mitral valves, unspecified                              |              |
| Q248                    | Other specified congenital malformations of heart   | 2 (1.75%)    |
| Q249                    | Congenital malformation of heart, unspecified   | 1 (0.88%)    |
| T820                    | Mechanical complication of heart valve prosthesis   |              |
| T825                    | Mechanical complication of other cardiac and vascular devices and implants                    | 2 (1.75%)    |
| T826                    | Infection and inflammatory reaction due to cardiac valve prosthesis                           | 1 (0.88%)    |
| T827                    | Infection and inflammatory reaction due to other cardiac and vascular devices, implants and   | 8 (7.02%)    |
| T828                    | Other specified complications of cardiac and vascular prosthetic devices, implants and grafts | 6 (5.26%)    |
| T829                    | Unspecified complication of cardiac and vascular prosthetic device, implant and graft         | 2 (1.75%)    |
| Z952                    | Presence of prosthetic heart valve  | 25 (21.93%)  |
| Z954                    | Presence of other heart-valve replacement   | 22 (19.30%)  |
| Z958                    | Presence of other cardiac and vascular implants and grafts                                    | 30 (26.32%)  |
| Z959                    | Presence of cardiac and vascular implant and graft, unspecified                               | 10 (8.77%)   |
| I050, I052, I342, Q232  | Total mitral stenosis   | 14 (12.28%)  |
| FGE, FJF, FKA, FKD, FMD | Total mechanical prosthetic heart valves surgeries  |              |
|                         | Any other, not classified above   | 114 (100.0%) |

| ICD-10 code | Text   | VTE          |
|-------------|--|--------------|
| C           | All patients, hospital data  | N=108        |
|             | DVT/PE before approval   | 46 (42.59%)  |
|             | Total VTE  | 62 (57.41%)  |
| I676        | Nonpyogenic thrombosis of intracranial venous system                       | 4 (3.70%)    |
| I677        | Cerebral arteritis, not elsewhere classified                               |              |
| I800        | Phlebitis and thrombophlebitis of superficial vessels of lower extremities | 16 (14.81%)  |
| I808        | Phlebitis and thrombophlebitis of other sites                              | 5 (4.63%)    |
| I809        | Phlebitis and thrombophlebitis of unspecified site                         | 10 (9.26%)   |
| I81         | Portal vein thrombosis   | 4 (3.70%)    |
| I820        | Budd-Chiari syndrome   |              |
| I821        | Thrombophlebitis migrans   | 1 (0.93%)    |
| I823        | Embolism and thrombosis of renal vein                                      |              |
| K645        | Perianal venous thrombosis   |              |
| N4881       | Thrombosis of superficial vein of penis                                    |              |
| O225        | Cerebral venous thrombosis in pregnancy                                    |              |
| O882        | Obstetric thromboembolism  |              |
| Z867A       | Personal history of pulmonary embolism                                     | 17 (15.74%)  |
| Z867B       | Personal history of deep venous thrombosis                                 | 21 (19.44%)  |
|             | Any other, not classified above  | 108 (100.0%) |
| C           | Subgroup with primary care data available, all data                        | N=31         |
|             | DVT/PE before approval   | 12 (38.71%)  |
|             | Total VTE  | 19 (61.29%)  |
| I676        | Nonpyogenic thrombosis of intracranial venous system                       | 2 (6.45%)    |



| ICD-10 code | Text   | VTE         |
|-------------|--|-------------|
| I677        | Cerebral arteritis, not elsewhere classified                               |             |
| I800        | Phlebitis and thrombophlebitis of superficial vessels of lower extremities | 7 (22.58%)  |
| I808        | Phlebitis and thrombophlebitis of other sites                              | 1 (3.23%)   |
| I809        | Phlebitis and thrombophlebitis of unspecified site                         | 8 (25.81%)  |
| I81         | Portal vein thrombosis   |             |
| I820        | Budd-Chiari syndrome   |             |
| I821        | Thrombophlebitis migrans   |             |
| I823        | Embolism and thrombosis of renal vein                                      |             |
| K645        | Perianal venous thrombosis   |             |
| N4881       | Thrombosis of superficial vein of penis                                    |             |
| O225        | Cerebral venous thrombosis in pregnancy                                    |             |
| O882        | Obstetric thromboembolism  |             |
| Z867A       | Personal history of pulmonary embolism                                     | 4 (12.90%)  |
| Z867B       | Personal history of deep venous thrombosis                                 | 6 (19.35%)  |
|             | Any other, not classified above  | 31 (100.0%) |
| <b>C</b>    | <b>Subgroup with primary care data available, only hospital data</b>       | <b>N=27</b> |
|             | DVT/PE before approval   | 13 (48.15%) |
|             | Total VTE  | 14 (51.85%) |
| I676        | Nonpyogenic thrombosis of intracranial venous system                       | 2 (7.41%)   |
| I677        | Cerebral arteritis, not elsewhere classified                               |             |
| I800        | Phlebitis and thrombophlebitis of superficial vessels of lower extremities | 2 (7.41%)   |
| I808        | Phlebitis and thrombophlebitis of other sites                              | 1 (3.70%)   |
| I809        | Phlebitis and thrombophlebitis of unspecified site                         | 3 (11.11%)  |
| I81         | Portal vein thrombosis   | 1 (3.70%)   |
| I820        | Budd-Chiari syndrome   |             |
| I821        | Thrombophlebitis migrans   |             |
| I823        | Embolism and thrombosis of renal vein                                      |             |
| K645        | Perianal venous thrombosis   |             |
| N4881       | Thrombosis of superficial vein of penis                                    |             |
| O225        | Cerebral venous thrombosis in pregnancy                                    |             |
| O882        | Obstetric thromboembolism  |             |
| Z867A       | Personal history of pulmonary embolism                                     | 4 (14.81%)  |
| Z867B       | Personal history of deep venous thrombosis                                 | 6 (22.22%)  |
|             | Any other, not classified above  | 27 (100.0%) |

Table 1.5 Treatment dose and duration among apixaban-treated patients, by classification, number and proportions

|   |                         |                       | On-label indications |                       |                      | Off-label indications |                          |                        |                        |                      |                    |
|---|-------------------------|-----------------------|----------------------|-----------------------|----------------------|-----------------------|--------------------------|------------------------|------------------------|----------------------|--------------------|
|   | Any classifica-<br>tion | Unclassified          | THA/TKA              | NVAF                  | DVT/PE               | Age <18<br>years      | Non-elective<br>THA/TKA* | AF*                    | VTE*                   | Other surgery        | Other<br>diagnosis |
| All patients  |                         |                       |                      |                       |                      |                       |                          |                        |                        |                      |                    |
| Total   | 16 562 (100.0)          | 1 030 (100.0)         | 2 636 (100.0)        | 12 151 (100.0)        | 417 (100.0)          | 2 (100.0)             | 10 (100.0)               | 428 (100.0)            | 108 (100.0)            | 235 (100.0)          | 575 (100.0)        |
| Treatment duration                                    |                         |                       |                      |                       |                      |                       |                          |                        |                        |                      |                    |
| <10 days  | 78 (0.5)                | 12 (1.2)              |                      | 66 (0.5)              | 4 (1.0)              |                       |                          |                        | 2 (1.9)                | 2 (0.9)              | 4 (0.7)            |
| 10-14<br>days   | 1 081 (6.5)             | 6 (0.6)               | 955 (36.2)           | 83 (0.7)              | 5 (1.2)              |                       |                          | 4 (0.9)                | 5 (4.6)                | 26 (11.1)            | 3 (0.5)            |
| 15-31<br>days   | 1 771 (10.7)            | 44 (4.3)              | 1 324 (50.2)         | 357 (2.9)             | 20 (4.8)             | 1 (50.0)              | 9 (90.0)                 | 10 (2.3)               | 5 (4.6)                | 27 (11.5)            | 18 (3.1)           |
| 32-38<br>days   | 30 (0.2)                | 4 (0.4)               |                      | 26 (0.2)              | 1 (0.2)              |                       |                          | 2 (0.5)                |                        | 1 (0.4)              |                    |
| >38 days  | 13 583 (82.0)           | 963 (93.5)            | 357 (13.5)           | 11 605 (95.5)         | 386 (92.6)           | 1 (50.0)              | 1 (10.0)                 | 410 (95.8)             | 95 (88.0)              | 179 (76.2)           | 549 (95.5)         |
| Mean<br>(SD)  | 180.6 (149.1)           | 202.8 (148.0)         | 27.0 (31.6)          | 214.9 (145.1)         | 94.0 (44.3)          | 50.0<br>(28.2)        | 31.0 (3.2)               | 213.2 (149.7)          | 236.1 (155.1)          | 146.9 (146.5)        | 206.3<br>(124.5)   |
| Median<br>(IQR)                                       | 148.0<br>(60.0-268.0)   | 168.0<br>(84.0-288.0) | 30.0<br>(10.0-30.0)  | 175.0<br>(90.0-307.2) | 84.0<br>(67.0-112.0) | 50.0<br>(30.0-)       | 30.0<br>(30.0-30.0)      | 168.0<br>(84.0-300.0)  | 231.0<br>(107.0-336.0) | 84.0<br>(50.0-200.0) | 174.0<br>(84.0-)   |
| Treatment dose*                                       |                         |                       |                      |                       |                      |                       |                          |                        |                        |                      |                    |
| 5 mg  | 7 233 (43.7)            | 273 (26.5)            | 2 614 (99.2)         | 3 926 (32.3)          | 136 (32.6)           | 2 (100.0)             | 10 (100.0)               | 167 (39.0)             | 48 (44.4)              | 114 (48.5)           | 216 (37.6)         |
| 10 mg   | 9 329 (56.3)            | 757 (73.5)            | 22 (0.8)             | 8 225 (67.7)          | 281 (67.4)           |                       |                          | 261 (61.0)             | 60 (55.6)              | 121 (51.5)           | 359 (62.4)         |
| Sub-group with primary care data available – all data |                         |                       |                      |                       |                      |                       |                          |                        |                        |                      |                    |
| Total   | 5 029 (100.0)           | 128 (100.0)           | 930 (100.0)          | 3 565 (100.0)         | 77 (100.0)           | 2 (100.0)             | 5 (100.0)                | 238 (100.0)            | 31 (100.0)             | 56 (100.0)           | 125 (100.0)        |
| Treatment duration                                    |                         |                       |                      |                       |                      |                       |                          |                        |                        |                      |                    |
| <10 days  | 12 (0.2)                | 1 (0.8)               |                      | 10 (0.3)              |                      |                       |                          |                        | 1 (3.2)                | 1 (1.8)              |                    |
| 10-14<br>days   | 348 (6.9)               |                       | 315 (33.9)           | 15 (0.4)              | 2 (2.6)              |                       |                          | 1 (0.4)                | 1 (3.2)                | 12 (21.4)            | 2 (1.6)            |
| 15-31<br>days   | 707 (14.1)              | 8 (6.3)               | 566 (60.9)           | 117 (3.3)             | 2 (2.6)              | 1 (50.0)              | 4 (80.0)                 | 5 (2.1)                | 1 (3.2)                | 9 (16.1)             | 2 (1.6)            |
| 32-38<br>days   | 12 (0.2)                |                       |                      | 10 (0.3)              | 1 (1.3)              |                       |                          | 1 (0.4)                |                        |                      |                    |
| >38 days  | 3 944 (78.4)            | 119 (93.0)            | 49 (5.3)             | 3 408 (95.6)          | 72 (93.5)            | 1 (50.0)              | 1 (20.0)                 | 230 (96.6)             | 28 (90.3)              | 34 (60.7)            | 121 (96.8)         |
| Mean<br>(SD)  | 176.7 (145.3)           | 223.1 (151.7)         | 26.5 (26.1)          | 212.8 (139.3)         | 97.2 (43.7)          | 50.0<br>(28.2)        | 57.6 (61.7)              | 229.1 (141.4)          | 240.9 (151.1)          | 120.7 (122.6)        | 230.2<br>(120.6)   |
| Median<br>(IQR)                                       | 144.0<br>(50.0-268.0)   | 171.0<br>(84.0-336.0) | 30.0<br>(10.0-30.0)  | 180.0<br>(90.0-302.0) | 84.0<br>(84.0-114.0) | 50.0<br>(30.0-)       | 30.0<br>(30.0-30.0)      | 201.5<br>(100.0-334.0) | 258.0<br>(92.0-318.0)  | 84.0<br>(30.0-166.0) | 241.0<br>(100.0-)  |

|   |                         |                       | On-label indications |                       |                      | Off-label indications |                          |                       |                       |                      |                    |
|---|-------------------------|-----------------------|----------------------|-----------------------|----------------------|-----------------------|--------------------------|-----------------------|-----------------------|----------------------|--------------------|
|   | Any classifica-<br>tion | Unclassified          | THA/TKA              | NVAF                  | DVT/PE               | Age <18<br>years      | Non-elective<br>THA/TKA* | AF*                   | VTE*                  | Other surgery        | Other<br>diagnosis |
| Treatment dose*   |                         |                       |                      |                       |                      |                       |                          |                       |                       |                      |                    |
| 5 mg  | 2 414 (48.0)            | 34 (26.6)             | 924 (99.4)           | 1 259 (35.3)          | 32 (41.6)            | 2 (100.0)             | 4 (80.0)                 | 102 (42.9)            | 13 (41.9)             | 30 (53.6)            | 48 (38.4)          |
| 10 mg   | 2 615 (52.0)            | 94 (73.4)             | 6 (0.6)              | 2 306 (64.7)          | 45 (58.4)            |                       | 1 (20.0)                 | 136 (57.1)            | 18 (58.1)             | 26 (46.4)            | 77 (61.6)          |
| Sub-group with primary care data available – only hospital data |                         |                       |                      |                       |                      |                       |                          |                       |                       |                      |                    |
| Total   | 4 900 (100.0)           | 257 (100.0)           | 930 (100.0)          | 3 532 (100.0)         | 70 (100.0)           | 2 (100.0)             | 4 (100.0)                | 114 (100.0)           | 27 (100.0)            | 64 (100.0)           | 157 (100.0)        |
| Treatment duration  |                         |                       |                      |                       |                      |                       |                          |                       |                       |                      |                    |
| <10 days  | 10 (0.2)                | 3 (1.2)               |                      | 7 (0.2)               |                      |                       |                          |                       | 1 (3.7)               | 1 (1.6)              | 1 (0.6)            |
| 10-14<br>days   | 347 (7.1)               | 1 (0.4)               | 315 (33.9)           | 15 (0.4)              | 2 (2.9)              |                       |                          |                       | 1 (3.7)               | 12 (18.8)            | 2 (1.3)            |
| 15-31<br>days   | 698 (14.2)              | 17 (6.6)              | 566 (60.9)           | 105 (3.0)             | 2 (2.9)              | 1 (50.0)              | 4 (100.0)                | 4 (3.5)               | 1 (3.7)               | 11 (17.2)            | 4 (2.5)            |
| 32-38<br>days   | 10 (0.2)                | 2 (0.8)               |                      | 10 (0.3)              |                      |                       |                          |                       |                       |                      |                    |
| >38 days  | 3 830 (78.2)            | 233 (90.7)            | 49 (5.3)             | 3 391 (96.0)          | 66 (94.3)            | 1 (50.0)              |                          | 109 (95.6)            | 24 (88.9)             | 40 (62.5)            | 150 (95.5)         |
| Mean<br>(SD)  | 176.5 (145.5)           | 204.2 (146.4)         | 26.5 (26.1)          | 215.1 (139.8)         | 98.1 (40.6)          | 50.0<br>(28.2)        | 30.0 (0.0)               | 217.7 (141.9)         | 223.2 (148.5)         | 131.1 (130.5)        | 217.4<br>(130.6)   |
| Median<br>(IQR)   | 144.0<br>(50.0-268.0)   | 168.0<br>(84.0-309.0) | 30.0<br>(10.0-30.0)  | 184.0<br>(91.0-302.0) | 90.5<br>(84.0-114.0) | 50.0<br>(30.0-)       | 30.0<br>(30.0-30.0)      | 199.0<br>(84.0-318.0) | 228.0<br>(60.0-318.0) | 92.0<br>(30.0-168.0) | 204.0<br>(100.0-)  |
| Treatment dose <sup>1</sup>                                     |                         |                       |                      |                       |                      |                       |                          |                       |                       |                      |                    |
| 5 mg  | 2 372 (48.4)            | 76 (29.6)             | 924 (99.4)           | 1 265 (35.8)          | 29 (41.4)            | 2 (100.0)             | 4 (100.0)                | 41 (36.0)             | 13 (48.1)             | 32 (50.0)            | 62 (39.5)          |
| 10 mg   | 2 528 (51.6)            | 181 (70.4)            | 6 (0.6)              | 2 267 (64.2)          | 41 (58.6)            |                       |                          | 73 (64.0)             | 14 (51.9)             | 32 (50.0)            | 95 (60.5)          |

\*non-elective THA/TKA; includes NVAF before November 20, 2012 or VAF; includes DVT/PE before July 28, 2014 or VTE

<sup>1</sup> means daily dose, i.e. 5 mg = 2.5 mg twice daily

Table 1.6 Selected concomitant medication (other dispensings within 30 days before and after/including index date), number and proportions

| ATC   | T<br>i<br>m<br>e<br>l | Any             | On label       |                 |              | Off label        |                             |              |              |               |                      |
|---|-----------------------|-----------------|----------------|-----------------|--------------|------------------|-----------------------------|--------------|--------------|---------------|----------------------|
|   |                       |                 | THA/TKA        | NVAF            | DVT/PE       | Age <18<br>years | Non-<br>elective<br>THA/TKA | AF*          | VTE*         | Other surgery | Other diagno-<br>sis |
| All Patients  |                       |                 |                |                 |              |                  |                             |              |              |               |                      |
| Total   |                       | 16 562 (100.0%) | 2 636 (100.0%) | 12 151 (100.0%) | 417 (100.0%) | 2 (100.0%)       | 10 (100.0%)                 | 428 (100.0%) | 108 (100.0%) | 235 (100.0%)  | 575 (100.0%)         |
| Antithrombotics   | B                     | 3 554 (21.5%)   | 188 (7.1%)     | 2 882 (23.7%)   | 136 (32.6%)  |                  | 1 (10.0%)                   | 107 (25.0%)  | 39 (36.1%)   | 47 (20.0%)    | 154 (26.8%)          |
|   | A                     | 865 (5.2%)      | 147 (5.6%)     | 574 (4.7%)      | 32 (7.7%)    |                  | 1 (10.0%)                   | 24 (5.6%)    | 8 (7.4%)     | 34 (14.5%)    | 45 (7.8%)            |
| Vitamin K Antago-<br>nists                              | B                     | 914 (5.5%)      | 1 (0.0%)       | 819 (6.7%)      | 29 (7.0%)    |                  |                             | 26 (6.1%)    | 14 (13.0%)   | 3 (1.3%)      | 22 (3.8%)            |
|   | A                     | 126 (0.8%)      | 6 (0.2%)       | 108 (0.9%)      | 3 (0.7%)     |                  |                             | 2 (0.5%)     | 1 (0.9%)     | 3 (1.3%)      | 3 (0.5%)             |
| Heparin Group   | B                     | 533 (3.2%)      | 14 (0.5%)      | 381 (3.1%)      | 78 (18.7%)   |                  |                             | 22 (5.1%)    | 11 (10.2%)   | 11 (4.7%)     | 16 (2.8%)            |
|   | A                     | 131 (0.8%)      | 27 (1.0%)      | 71 (0.6%)       | 17 (4.1%)    |                  |                             | 4 (0.9%)     | 4 (3.7%)     | 4 (1.7%)      | 4 (0.7%)             |
| Platelet Aggregation<br>Inhibitors Excl.<br>Heparin     | B                     | 1 987 (12.0%)   | 177 (6.7%)     | 1 546 (12.7%)   | 38 (9.1%)    |                  | 1 (10.0%)                   | 57 (13.3%)   | 13 (12.0%)   | 35 (14.9%)    | 120 (20.9%)          |
|   | A                     | 605 (3.7%)      | 117 (4.4%)     | 384 (3.2%)      | 14 (3.4%)    |                  | 1 (10.0%)                   | 18 (4.2%)    | 3 (2.8%)     | 29 (12.3%)    | 39 (6.8%)            |
| Enzymes   | B                     |                 |                |                 |              |                  |                             |              |              |               |                      |
|   | A                     |                 |                |                 |              |                  |                             |              |              |               |                      |
| Direct Thrombin<br>Inhibitors                           | B                     | 246 (1.5%)      | 2 (0.1%)       | 230 (1.9%)      | 1 (0.2%)     |                  |                             | 7 (1.6%)     | 1 (0.9%)     | 1 (0.4%)      | 4 (0.7%)             |
|   | A                     | 42 (0.3%)       | 1 (0.0%)       | 37 (0.3%)       | 1 (0.2%)     |                  |                             | 1 (0.2%)     |              | 2 (0.9%)      |                      |
| Other Antithrombot-<br>ic Agents                        | B                     | 3 (0.0%)        |                | 1 (0.0%)        | 1 (0.2%)     |                  |                             |              |              |               | 1 (0.2%)             |
|   | A                     | 1 (0.0%)        |                |                 |              |                  |                             | 1 (0.2%)     |              |               |                      |
| Anti-Inflammatory<br>And Antirheumatic<br>Products      | B                     | 634 (3.8%)      | 311 (11.8%)    | 274 (2.3%)      | 13 (3.1%)    | 1 (50.0%)        | 2 (20.0%)                   | 8 (1.9%)     | 1 (0.9%)     | 8 (3.4%)      | 16 (2.8%)            |
|   | A                     | 428 (2.6%)      | 210 (8.0%)     | 189 (1.6%)      | 5 (1.2%)     |                  |                             | 4 (0.9%)     | 4 (3.7%)     | 6 (2.6%)      | 10 (1.7%)            |
| Antiinflammatory<br>And Antirheumatic<br>Products, Non- | B                     | 634 (3.8%)      | 311 (11.8%)    | 274 (2.3%)      | 13 (3.1%)    | 1 (50.0%)        | 2 (20.0%)                   | 8 (1.9%)     | 1 (0.9%)     | 8 (3.4%)      | 16 (2.8%)            |
|   | A                     | 428 (2.6%)      | 210 (8.0%)     | 189 (1.6%)      | 5 (1.2%)     |                  |                             | 4 (0.9%)     | 4 (3.7%)     | 6 (2.6%)      | 10 (1.7%)            |
| CYP3A4 And P-Gp<br>Inhibitors                           | B                     | 5 227 (31.6%)   | 393 (14.9%)    | 4 299 (35.4%)   | 82 (19.7%)   |                  | 1 (10.0%)                   | 171 (40.0%)  | 30 (27.8%)   | 64 (27.2%)    | 187 (32.5%)          |
|   | A                     | 7 413 (44.8%)   | 342 (13.0%)    | 6 321 (52.0%)   | 111 (26.6%)  |                  | 1 (10.0%)                   | 210 (49.1%)  | 40 (37.0%)   | 101 (43.0%)   | 287 (49.9%)          |
| Antimycotics For<br>Systemic Use                        | B                     | 23 (0.1%)       | 3 (0.1%)       | 17 (0.1%)       |              |                  |                             | 2 (0.5%)     |              | 1 (0.4%)      |                      |
|   | A                     | 37 (0.2%)       | 3 (0.1%)       | 31 (0.3%)       | 1 (0.2%)     |                  |                             | 2 (0.5%)     |              |               |                      |
| Protease Inhibitors                                     | B                     |                 |                |                 |              |                  |                             |              |              |               |                      |
|   | A                     |                 |                |                 |              |                  |                             |              |              |               |                      |

| ATC  | T<br>i<br>m<br>e<br>l | Any           | On label   |               |            | Off label        |                             |             |            |               |                      |
|--|-----------------------|---------------|------------|---------------|------------|------------------|-----------------------------|-------------|------------|---------------|----------------------|
|  |                       |               | THA/TKA    | NVAF          | DVT/PE     | Age <18<br>years | Non-<br>elective<br>THA/TKA | AF*         | VTE*       | Other surgery | Other diagno-<br>sis |
| Selective Serotonin<br>Reuptake Inhibitors | B                     | 671 (4.1%)    | 67 (2.5%)  | 512 (4.2%)    | 27 (6.5%)  |                  |                             | 25 (5.8%)   | 9 (8.3%)   | 8 (3.4%)      | 23 (4.0%)            |
|  | A                     | 747 (4.5%)    | 64 (2.4%)  | 580 (4.8%)    | 30 (7.2%)  |                  |                             | 19 (4.4%)   | 16 (14.8%) | 8 (3.4%)      | 30 (5.2%)            |
| Phenylalkylamine<br>Derivatives            | B                     | 70 (0.4%)     |            | 65 (0.5%)     | 2 (0.5%)   |                  |                             | 2 (0.5%)    |            | 1 (0.4%)      |                      |
|  | A                     | 99 (0.6%)     | 2 (0.1%)   | 92 (0.8%)     | 1 (0.2%)   |                  |                             | 1 (0.2%)    | 1 (0.9%)   | 1 (0.4%)      | 1 (0.2%)             |
| Antiarrhythmics,<br>Class Ia               | B                     | 22 (0.1%)     |            | 20 (0.2%)     |            |                  |                             | 1 (0.2%)    |            |               | 1 (0.2%)             |
|  | A                     | 16 (0.1%)     |            | 16 (0.1%)     |            |                  |                             |             |            |               |                      |
| Beta Blocking<br>Agents, Selective         | B                     | 3 873 (23.4%) | 194 (7.4%) | 3 333 (27.4%) | 42 (10.1%) |                  |                             | 123 (28.7%) | 20 (18.5%) | 44 (18.7%)    | 117 (20.3%)          |
|  | A                     | 5 911 (35.7%) | 176 (6.7%) | 5 227 (43.0%) | 63 (15.1%) |                  | 1 (10.0%)                   | 164 (38.3%) | 23 (21.3%) | 79 (33.6%)    | 178 (31.0%)          |
| Benzothiazepine<br>Derivatives             | B                     | 38 (0.2%)     | 5 (0.2%)   | 33 (0.3%)     |            |                  |                             |             |            |               |                      |
|  | A                     | 36 (0.2%)     | 2 (0.1%)   | 32 (0.3%)     |            |                  |                             | 1 (0.2%)    |            |               | 1 (0.2%)             |
| HMG Coa Reductase<br>Inhibitors            | B                     | 2 015 (12.2%) | 198 (7.5%) | 1 557 (12.8%) | 31 (7.4%)  |                  | 1 (10.0%)                   | 72 (16.8%)  | 14 (13.0%) | 33 (14.0%)    | 109 (19.0%)          |
|  | A                     | 2 670 (16.1%) | 158 (6.0%) | 2 150 (17.7%) | 38 (9.1%)  |                  |                             | 82 (19.2%)  | 14 (13.0%) | 51 (21.7%)    | 177 (30.8%)          |
| Macrolides                                 | B                     | 12 (0.1%)     | 1 (0.0%)   | 9 (0.1%)      | 1 (0.2%)   |                  |                             | 1 (0.2%)    |            |               |                      |
|  | A                     | 15 (0.1%)     |            | 12 (0.1%)     | 1 (0.2%)   |                  |                             | 1 (0.2%)    | 1 (0.9%)   |               |                      |
| Selective<br>Immunosuppressants            | B                     | 11 (0.1%)     | 3 (0.1%)   | 7 (0.1%)      |            |                  |                             |             |            | 1 (0.4%)      |                      |
|  | A                     | 13 (0.1%)     | 2 (0.1%)   | 8 (0.1%)      |            |                  |                             | 1 (0.2%)    |            | 1 (0.4%)      | 1 (0.2%)             |
| <b>CYP3A4 And P-Gp<br/>Inducers</b>        | B                     | 620 (3.7%)    | 55 (2.1%)  | 486 (4.0%)    | 20 (4.8%)  |                  | 1 (10.0%)                   | 19 (4.4%)   | 8 (7.4%)   | 8 (3.4%)      | 23 (4.0%)            |
|  | A                     | 698 (4.2%)    | 47 (1.8%)  | 561 (4.6%)    | 23 (5.5%)  |                  | 2 (20.0%)                   | 23 (5.4%)   | 8 (7.4%)   | 9 (3.8%)      | 25 (4.3%)            |
| Carboxamide Deriv-<br>atives               | B                     | 54 (0.3%)     | 5 (0.2%)   | 43 (0.4%)     | 2 (0.5%)   |                  |                             | 1 (0.2%)    | 2 (1.9%)   |               | 1 (0.2%)             |
|  | A                     | 55 (0.3%)     | 3 (0.1%)   | 47 (0.4%)     | 1 (0.2%)   |                  |                             | 2 (0.5%)    |            |               | 2 (0.3%)             |
| Thiazolidinediones                         | B                     | 7 (0.0%)      | 1 (0.0%)   | 6 (0.0%)      |            |                  |                             |             |            |               |                      |
|  | A                     | 7 (0.0%)      |            | 7 (0.1%)      |            |                  |                             |             |            |               |                      |
| Glucocorticoids                            | B                     | 535 (3.2%)    | 46 (1.7%)  | 419 (3.4%)    | 17 (4.1%)  |                  | 1 (10.0%)                   | 16 (3.7%)   | 6 (5.6%)   | 8 (3.4%)      | 22 (3.8%)            |
|  | A                     | 596 (3.6%)    | 36 (1.4%)  | 478 (3.9%)    | 21 (5.0%)  |                  | 2 (20.0%)                   | 20 (4.7%)   | 7 (6.5%)   | 9 (3.8%)      | 23 (4.0%)            |
| Short-Acting Sul-<br>fonamides             | B                     |               |            |               |            |                  |                             |             |            |               |                      |
|  | A                     |               |            |               |            |                  |                             |             |            |               |                      |
| Macrolides                                 | B                     | 12 (0.1%)     | 1 (0.0%)   | 9 (0.1%)      | 1 (0.2%)   |                  |                             | 1 (0.2%)    |            |               |                      |
|  | A                     | 15 (0.1%)     |            | 12 (0.1%)     | 1 (0.2%)   |                  |                             | 1 (0.2%)    | 1 (0.9%)   |               |                      |

| ATC   | T<br>i<br>m<br>e<br>l | Any           | On label      |               |             | Off label        |                             |             |            |               |                      |
|---|-----------------------|---------------|---------------|---------------|-------------|------------------|-----------------------------|-------------|------------|---------------|----------------------|
|   |                       |               | THA/TKA       | NVAF          | DVT/PE      | Age <18<br>years | Non-<br>elective<br>THA/TKA | AF*         | VTE*       | Other surgery | Other diagno-<br>sis |
| Antibiotics   | B                     | 2 (0.0%)      |               | 1 (0.0%)      |             |                  |                             | 1 (0.2%)    |            |               |                      |
|   | A                     | 18 (0.1%)     | 7 (0.3%)      | 11 (0.1%)     |             |                  |                             |             |            |               |                      |
| Non-Nucleoside<br>Reverse Transcrip-<br>tase Inhibitors | B                     | 1 (0.0%)      |               | 1 (0.0%)      |             |                  |                             |             |            |               |                      |
|   | A                     |               |               |               |             |                  |                             |             |            |               |                      |
| Preparations Increasing Uric Acid Excretion             | B                     | 5 (0.0%)      |               | 5 (0.0%)      |             |                  |                             |             |            |               |                      |
|   | A                     | 4 (0.0%)      |               | 4 (0.0%)      |             |                  |                             |             |            |               |                      |
| Barbiturates And Derivatives                            | B                     | 4 (0.0%)      | 1 (0.0%)      | 3 (0.0%)      |             |                  |                             |             |            |               |                      |
|   | A                     | 4 (0.0%)      | 1 (0.0%)      | 3 (0.0%)      |             |                  |                             |             |            |               |                      |
| Hydantoin Derivatives                                   | B                     | 7 (0.0%)      | 1 (0.0%)      | 5 (0.0%)      | 1 (0.2%)    |                  |                             |             |            |               |                      |
|   | A                     | 6 (0.0%)      |               | 6 (0.0%)      |             |                  |                             |             |            |               |                      |
| Succinimide Derivatives                                 | B                     |               |               |               |             |                  |                             |             |            |               |                      |
|   | A                     |               |               |               |             |                  |                             |             |            |               |                      |
| Piperidinedione Derivatives                             | B                     |               |               |               |             |                  |                             |             |            |               |                      |
|   | A                     |               |               |               |             |                  |                             |             |            |               |                      |
| <b>Commonly Dis-<br/>pensed Drugs<sup>1</sup></b>       | B                     | 7 048 (42.6%) | 1 195 (45.3%) | 5 090 (41.9%) | 157 (37.6%) |                  | 6 (60.0%)                   | 211 (49.3%) | 51 (47.2%) | 103 (43.8%)   | 235 (40.9%)          |
|   | A                     | 9 841 (59.4%) | 2 534 (96.1%) | 6 343 (52.2%) | 191 (45.8%) | 2 (100.0%)       | 9 (90.0%)                   | 258 (60.3%) | 53 (49.1%) | 151 (64.3%)   | 300 (52.2%)          |
| Proton Pump Inhibitors                                  | B                     | 1 581 (9.5%)  | 182 (6.9%)    | 1 224 (10.1%) | 43 (10.3%)  |                  |                             | 52 (12.1%)  | 14 (13.0%) | 20 (8.5%)     | 46 (8.0%)            |
|   | A                     | 2 095 (12.6%) | 365 (13.8%)   | 1 503 (12.4%) | 48 (11.5%)  |                  | 1 (10.0%)                   | 69 (16.1%)  | 18 (16.7%) | 32 (13.6%)    | 59 (10.3%)           |
| Osmotically Acting Laxatives                            | B                     | 496 (3.0%)    | 92 (3.5%)     | 344 (2.8%)    | 19 (4.6%)   |                  |                             | 16 (3.7%)   | 3 (2.8%)   | 14 (6.0%)     | 8 (1.4%)             |
|   | A                     | 1 575 (9.5%)  | 910 (34.5%)   | 570 (4.7%)    | 26 (6.2%)   |                  | 2 (20.0%)                   | 10 (2.3%)   | 3 (2.8%)   | 22 (9.4%)     | 32 (5.6%)            |
| Sulfonamides, Plain                                     | B                     | 1 563 (9.4%)  | 61 (2.3%)     | 1 313 (10.8%) | 28 (6.7%)   |                  |                             | 69 (16.1%)  | 11 (10.2%) | 19 (8.1%)     | 62 (10.8%)           |
|   | A                     | 2 212 (13.4%) | 55 (2.1%)     | 1 892 (15.6%) | 46 (11.0%)  |                  | 1 (10.0%)                   | 96 (22.4%)  | 13 (12.0%) | 29 (12.3%)    | 80 (13.9%)           |
| Dihydropyridine Derivatives                             | B                     | 1 307 (7.9%)  | 224 (8.5%)    | 934 (7.7%)    | 26 (6.2%)   |                  |                             | 38 (8.9%)   | 8 (7.4%)   | 18 (7.7%)     | 59 (10.3%)           |
|   | A                     | 1 545 (9.3%)  | 151 (5.7%)    | 1 213 (10.0%) | 38 (9.1%)   |                  | 1 (10.0%)                   | 34 (7.9%)   | 6 (5.6%)   | 26 (11.1%)    | 76 (13.2%)           |
| ACE Inhibitors, Plain                                   | B                     | 1 517 (9.2%)  | 137 (5.2%)    | 1 214 (10.0%) | 26 (6.2%)   |                  |                             | 52 (12.1%)  | 5 (4.6%)   | 20 (8.5%)     | 63 (11.0%)           |
|   | A                     | 2 043 (12.3%) | 91 (3.5%)     | 1 721 (14.2%) | 35 (8.4%)   |                  | 1 (10.0%)                   | 66 (15.4%)  | 5 (4.6%)   | 39 (16.6%)    | 85 (14.8%)           |
| Angiotensin II Antagonists, Plain                       | B                     | 1 109 (6.7%)  | 112 (4.2%)    | 871 (7.2%)    | 17 (4.1%)   |                  |                             | 45 (10.5%)  | 10 (9.3%)  | 12 (5.1%)     | 42 (7.3%)            |
|   | A                     | 1 324 (8.0%)  | 83 (3.1%)     | 1 092 (9.0%)  | 26 (6.2%)   |                  |                             | 54 (12.6%)  | 7 (6.5%)   | 15 (6.4%)     | 47 (8.2%)            |

| ATC   | T<br>i<br>m<br>e<br>l | Any            | On label      |                |             | Off label        |                             |              |             |               |                      |
|---|-----------------------|----------------|---------------|----------------|-------------|------------------|-----------------------------|--------------|-------------|---------------|----------------------|
|   |                       |                | THA/TKA       | NVAF           | DVT/PE      | Age <18<br>years | Non-<br>elective<br>THA/TKA | AF*          | VTE*        | Other surgery | Other diagno-<br>sis |
| Natural Opium<br>Alkaloids                              | B                     | 1 003 (6.1%)   | 361 (13.7%)   | 529 (4.4%)     | 28 (6.7%)   |                  | 2 (20.0%)                   | 30 (7.0%)    | 4 (3.7%)    | 31 (13.2%)    | 18 (3.1%)            |
|   | A                     | 3 033 (18.3%)  | 2 212 (83.9%) | 647 (5.3%)     | 39 (9.4%)   | 2 (100.0%)       | 7 (70.0%)                   | 37 (8.6%)    | 7 (6.5%)    | 56 (23.8%)    | 26 (4.5%)            |
| Anilides  | B                     | 2 356 (14.2%)  | 692 (26.3%)   | 1 418 (11.7%)  | 57 (13.7%)  |                  | 3 (30.0%)                   | 63 (14.7%)   | 19 (17.6%)  | 44 (18.7%)    | 60 (10.4%)           |
|   | A                     | 4 438 (26.8%)  | 2 325 (88.2%) | 1 800 (14.8%)  | 62 (14.9%)  | 2 (100.0%)       | 8 (80.0%)                   | 77 (18.0%)   | 11 (10.2%)  | 80 (34.0%)    | 73 (12.7%)           |
| Benzodiazepine<br>Related Drugs                         | B                     | 1 417 (8.6%)   | 184 (7.0%)    | 1 063 (8.7%)   | 41 (9.8%)   |                  | 1 (10.0%)                   | 44 (10.3%)   | 13 (12.0%)  | 24 (10.2%)    | 47 (8.2%)            |
|   | A                     | 1 801 (10.9%)  | 269 (10.2%)   | 1 328 (10.9%)  | 49 (11.8%)  |                  | 3 (30.0%)                   | 56 (13.1%)   | 15 (13.9%)  | 22 (9.4%)     | 59 (10.3%)           |
| Sub-Group With Primary Care Data Available – All Data   |                       |                |               |                |             |                  |                             |              |             |               |                      |
| Total   |                       | 5 029 (100.0%) | 930 (100.0%)  | 3 565 (100.0%) | 77 (100.0%) | 2 (100.0%)       | 5 (100.0%)                  | 238 (100.0%) | 31 (100.0%) | 56 (100.0%)   | 125 (100.0%)         |
| Antithrombotics   | B                     | 1 117 (22.2%)  | 65 (7.0%)     | 911 (25.6%)    | 20 (26.0%)  |                  |                             | 70 (29.4%)   | 8 (25.8%)   | 12 (21.4%)    | 31 (24.8%)           |
|   | A                     | 300 (6.0%)     | 57 (6.1%)     | 194 (5.4%)     | 4 (5.2%)    |                  | 1 (20.0%)                   | 21 (8.8%)    | 2 (6.5%)    | 7 (12.5%)     | 14 (11.2%)           |
| Vitamin K Antago-<br>nists                              | B                     | 296 (5.9%)     |               | 262 (7.3%)     | 6 (7.8%)    |                  |                             | 19 (8.0%)    | 3 (9.7%)    | 2 (3.6%)      | 4 (3.2%)             |
|   | A                     | 34 (0.7%)      | 5 (0.5%)      | 27 (0.8%)      |             |                  |                             | 1 (0.4%)     |             | 1 (1.8%)      |                      |
| Heparin Group   | B                     | 152 (3.0%)     | 3 (0.3%)      | 120 (3.4%)     | 10 (13.0%)  |                  |                             | 11 (4.6%)    | 1 (3.2%)    | 4 (7.1%)      | 3 (2.4%)             |
|   | A                     | 48 (1.0%)      | 10 (1.1%)     | 29 (0.8%)      | 3 (3.9%)    |                  |                             | 2 (0.8%)     | 1 (3.2%)    | 1 (1.8%)      | 2 (1.6%)             |
| Platelet Aggregation<br>Inhibitors Excl.<br>Heparin     | B                     | 656 (13.0%)    | 61 (6.6%)     | 519 (14.6%)    | 4 (5.2%)    |                  |                             | 38 (16.0%)   | 3 (9.7%)    | 8 (14.3%)     | 23 (18.4%)           |
|   | A                     | 219 (4.4%)     | 44 (4.7%)     | 135 (3.8%)     | 1 (1.3%)    |                  | 1 (20.0%)                   | 19 (8.0%)    | 1 (3.2%)    | 5 (8.9%)      | 13 (10.4%)           |
| Enzymes   | B                     |                |               |                |             |                  |                             |              |             |               |                      |
|   | A                     |                |               |                |             |                  |                             |              |             |               |                      |
| Direct Thrombin<br>Inhibitors                           | B                     | 47 (0.9%)      | 1 (0.1%)      | 42 (1.2%)      | 1 (1.3%)    |                  |                             | 2 (0.8%)     | 1 (3.2%)    |               |                      |
|   | A                     | 11 (0.2%)      |               | 10 (0.3%)      |             |                  |                             |              |             | 1 (1.8%)      |                      |
| Other Antithrombot-<br>ic Agents                        | B                     | 2 (0.0%)       |               | 1 (0.0%)       |             |                  |                             |              |             |               | 1 (0.8%)             |
|   | A                     |                |               |                |             |                  |                             |              |             |               |                      |
| Anti-Inflammatory<br>And Antirheumatic<br>Products      | B                     | 220 (4.4%)     | 117 (12.6%)   | 84 (2.4%)      | 2 (2.6%)    | 1 (50.0%)        | 1 (20.0%)                   | 6 (2.5%)     |             | 4 (7.1%)      | 5 (4.0%)             |
|   | A                     | 156 (3.1%)     | 78 (8.4%)     | 72 (2.0%)      | 1 (1.3%)    |                  |                             | 2 (0.8%)     | 1 (3.2%)    |               | 2 (1.6%)             |
| Antiinflammatory<br>And Antirheumatic<br>Products, Non- | B                     | 220 (4.4%)     | 117 (12.6%)   | 84 (2.4%)      | 2 (2.6%)    | 1 (50.0%)        | 1 (20.0%)                   | 6 (2.5%)     |             | 4 (7.1%)      | 5 (4.0%)             |
|   | A                     | 156 (3.1%)     | 78 (8.4%)     | 72 (2.0%)      | 1 (1.3%)    |                  |                             | 2 (0.8%)     | 1 (3.2%)    |               | 2 (1.6%)             |
| CYP3A4 And P-Gp<br>Inhibitors                           | B                     | 1 584 (31.5%)  | 132 (14.2%)   | 1 266 (35.5%)  | 19 (24.7%)  |                  |                             | 106 (44.5%)  | 11 (35.5%)  | 8 (14.3%)     | 42 (33.6%)           |
|   | A                     | 2 315 (46.0%)  | 111 (11.9%)   | 1 936 (54.3%)  | 27 (35.1%)  |                  | 2 (40.0%)                   | 127 (53.4%)  | 14 (45.2%)  | 21 (37.5%)    | 77 (61.6%)           |



| ATC  | T<br>i<br>m<br>e<br>i | Any           | On label  |               |            | Off label        |                             |             |           |               |                      |
|--|-----------------------|---------------|-----------|---------------|------------|------------------|-----------------------------|-------------|-----------|---------------|----------------------|
|  |                       |               | THA/TKA   | NVAF          | DVT/PE     | Age <18<br>years | Non-<br>elective<br>THA/TKA | AF*         | VTE*      | Other surgery | Other diagno-<br>sis |
| Antimycotics For<br>Systemic Use           | B                     | 11 (0.2%)     | 1 (0.1%)  | 9 (0.3%)      |            |                  |                             |             |           | 1 (1.8%)      |                      |
|  | A                     | 15 (0.3%)     | 2 (0.2%)  | 12 (0.3%)     |            |                  |                             | 1 (0.4%)    |           |               |                      |
| Protease Inhibitors                        | B                     |               |           |               |            |                  |                             |             |           |               |                      |
|  | A                     |               |           |               |            |                  |                             |             |           |               |                      |
| Selective Serotonin<br>Reuptake Inhibitors | B                     | 266 (5.3%)    | 23 (2.5%) | 202 (5.7%)    | 6 (7.8%)   |                  |                             | 20 (8.4%)   | 4 (12.9%) | 2 (3.6%)      | 9 (7.2%)             |
|  | A                     | 296 (5.9%)    | 23 (2.5%) | 227 (6.4%)    | 10 (13.0%) |                  |                             | 16 (6.7%)   | 6 (19.4%) | 2 (3.6%)      | 12 (9.6%)            |
| Phenylalkylamine<br>Derivatives            | B                     | 20 (0.4%)     |           | 19 (0.5%)     |            |                  |                             |             |           |               | 1 (0.8%)             |
|  | A                     | 26 (0.5%)     |           | 24 (0.7%)     |            |                  |                             |             |           | 1 (1.8%)      | 1 (0.8%)             |
| Antiarrhythmics,<br>Class Ia               | B                     | 5 (0.1%)      |           | 4 (0.1%)      |            |                  |                             | 1 (0.4%)    |           |               |                      |
|  | A                     | 5 (0.1%)      |           | 5 (0.1%)      |            |                  |                             |             |           |               |                      |
| Beta Blocking<br>Agents, Selective         | B                     | 1 149 (22.8%) | 70 (7.5%) | 955 (26.8%)   | 10 (13.0%) |                  |                             | 79 (33.2%)  | 6 (19.4%) | 5 (8.9%)      | 24 (19.2%)           |
|  | A                     | 1 835 (36.5%) | 62 (6.7%) | 1 582 (44.4%) | 16 (20.8%) |                  | 1 (20.0%)                   | 105 (44.1%) | 9 (29.0%) | 12 (21.4%)    | 48 (38.4%)           |
| Benzothiazepine<br>Derivatives             | B                     | 7 (0.1%)      | 1 (0.1%)  | 6 (0.2%)      |            |                  |                             |             |           |               |                      |
|  | A                     | 9 (0.2%)      | 1 (0.1%)  | 8 (0.2%)      |            |                  |                             |             |           |               |                      |
| HMG Coa Reductase<br>Inhibitors            | B                     | 601 (12.0%)   | 70 (7.5%) | 457 (12.8%)   | 6 (7.8%)   |                  |                             | 39 (16.4%)  | 5 (16.1%) | 3 (5.4%)      | 21 (16.8%)           |
|  | A                     | 873 (17.4%)   | 50 (5.4%) | 709 (19.9%)   | 7 (9.1%)   |                  | 1 (20.0%)                   | 48 (20.2%)  | 4 (12.9%) | 11 (19.6%)    | 43 (34.4%)           |
| Macrolides                                 | B                     | 5 (0.1%)      | 1 (0.1%)  | 3 (0.1%)      |            |                  |                             | 1 (0.4%)    |           |               |                      |
|  | A                     | 5 (0.1%)      |           | 4 (0.1%)      | 1 (1.3%)   |                  |                             |             |           |               |                      |
| Selective<br>Immunosuppressants            | B                     | 6 (0.1%)      | 2 (0.2%)  | 4 (0.1%)      |            |                  |                             |             |           |               |                      |
|  | A                     | 1 (0.0%)      |           | 1 (0.0%)      |            |                  |                             |             |           |               |                      |
| <b>CYP3A4 And P-Gp<br/>Inducers</b>        | B                     | 200 (4.0%)    | 21 (2.3%) | 154 (4.3%)    | 2 (2.6%)   |                  |                             | 12 (5.0%)   | 3 (9.7%)  | 2 (3.6%)      | 6 (4.8%)             |
|  | A                     | 221 (4.4%)    | 17 (1.8%) | 174 (4.9%)    | 4 (5.2%)   |                  |                             | 18 (7.6%)   | 1 (3.2%)  | 2 (3.6%)      | 5 (4.0%)             |
| Carboxamide Deriv-<br>atives               | B                     | 27 (0.5%)     | 1 (0.1%)  | 23 (0.6%)     |            |                  |                             | 1 (0.4%)    | 1 (3.2%)  |               | 1 (0.8%)             |
|  | A                     | 28 (0.6%)     |           | 24 (0.7%)     |            |                  |                             | 3 (1.3%)    |           |               | 1 (0.8%)             |
| Thiazolidinediones                         | B                     | 4 (0.1%)      | 1 (0.1%)  | 3 (0.1%)      |            |                  |                             |             |           |               |                      |
|  | A                     | 3 (0.1%)      |           | 3 (0.1%)      |            |                  |                             |             |           |               |                      |
| Glucocorticoids                            | B                     | 159 (3.2%)    | 16 (1.7%) | 122 (3.4%)    | 2 (2.6%)   |                  |                             | 10 (4.2%)   | 2 (6.5%)  | 2 (3.6%)      | 5 (4.0%)             |
|  | A                     | 178 (3.5%)    | 15 (1.6%) | 138 (3.9%)    | 3 (3.9%)   |                  |                             | 15 (6.3%)   | 1 (3.2%)  | 2 (3.6%)      | 4 (3.2%)             |

| ATC   | T<br>i<br>m<br>e<br>i | Any           | On label    |               |            | Off label        |                             |             |            |               |                      |
|---|-----------------------|---------------|-------------|---------------|------------|------------------|-----------------------------|-------------|------------|---------------|----------------------|
|   |                       |               | THA/TKA     | NVAF          | DVT/PE     | Age <18<br>years | Non-<br>elective<br>THA/TKA | AF*         | VTE*       | Other surgery | Other diagno-<br>sis |
| Short-Acting Sul-<br>fonamides                          | B                     |               |             |               |            |                  |                             |             |            |               |                      |
|   | A                     |               |             |               |            |                  |                             |             |            |               |                      |
| Macrolides  | B                     | 5 (0.1%)      | 1 (0.1%)    | 3 (0.1%)      |            |                  |                             | 1 (0.4%)    |            |               |                      |
|   | A                     | 5 (0.1%)      |             | 4 (0.1%)      | 1 (1.3%)   |                  |                             |             |            |               |                      |
| Antibiotics   | B                     |               |             |               |            |                  |                             |             |            |               |                      |
|   | A                     | 5 (0.1%)      | 2 (0.2%)    | 3 (0.1%)      |            |                  |                             |             |            |               |                      |
| Non-Nucleoside<br>Reverse Transcrip-<br>tase Inhibitors | B                     |               |             |               |            |                  |                             |             |            |               |                      |
|   | A                     |               |             |               |            |                  |                             |             |            |               |                      |
| Preparations Increas-<br>ing Uric Acid Excre-<br>tion   | B                     | 3 (0.1%)      |             | 3 (0.1%)      |            |                  |                             |             |            |               |                      |
|   | A                     | 2 (0.0%)      |             | 2 (0.1%)      |            |                  |                             |             |            |               |                      |
| Barbiturates And<br>Derivatives                         | B                     | 2 (0.0%)      | 1 (0.1%)    | 1 (0.0%)      |            |                  |                             |             |            |               |                      |
|   | A                     | 1 (0.0%)      |             | 1 (0.0%)      |            |                  |                             |             |            |               |                      |
| Hydantoin Deriva-<br>tives                              | B                     | 2 (0.0%)      | 1 (0.1%)    | 1 (0.0%)      |            |                  |                             |             |            |               |                      |
|   | A                     | 1 (0.0%)      |             | 1 (0.0%)      |            |                  |                             |             |            |               |                      |
| Succinimide Deriva-<br>tives                            | B                     |               |             |               |            |                  |                             |             |            |               |                      |
|   | A                     |               |             |               |            |                  |                             |             |            |               |                      |
| Piperidinedione<br>Derivatives                          | B                     |               |             |               |            |                  |                             |             |            |               |                      |
|   | A                     |               |             |               |            |                  |                             |             |            |               |                      |
| <b>Commonly Dis-<br/>pensed Drugs<sup>1</sup></b>       | B                     | 2 144 (42.6%) | 411 (44.2%) | 1 479 (41.5%) | 37 (48.1%) |                  | 2 (40.0%)                   | 122 (51.3%) | 16 (51.6%) | 23 (41.1%)    | 54 (43.2%)           |
|   | A                     | 3 174 (63.1%) | 893 (96.0%) | 1 963 (55.1%) | 38 (49.4%) | 2 (100.0%)       | 5 (100.0%)                  | 147 (61.8%) | 17 (54.8%) | 37 (66.1%)    | 72 (57.6%)           |
| Proton Pump Inhibi-<br>tors                             | B                     | 489 (9.7%)    | 55 (5.9%)   | 381 (10.7%)   | 12 (15.6%) |                  |                             | 29 (12.2%)  | 2 (6.5%)   | 4 (7.1%)      | 6 (4.8%)             |
|   | A                     | 633 (12.6%)   | 73 (7.8%)   | 484 (13.6%)   | 9 (11.7%)  |                  |                             | 45 (18.9%)  | 2 (6.5%)   | 6 (10.7%)     | 14 (11.2%)           |
| Osmotically Acting<br>Laxatives                         | B                     | 162 (3.2%)    | 28 (3.0%)   | 114 (3.2%)    | 4 (5.2%)   |                  |                             | 12 (5.0%)   |            | 2 (3.6%)      | 2 (1.6%)             |
|   | A                     | 360 (7.2%)    | 137 (14.7%) | 193 (5.4%)    | 4 (5.2%)   |                  | 1 (20.0%)                   | 8 (3.4%)    | 3 (9.7%)   | 5 (8.9%)      | 9 (7.2%)             |
| Sulfonamides, Plain                                     | B                     | 484 (9.6%)    | 16 (1.7%)   | 391 (11.0%)   | 6 (7.8%)   |                  |                             | 45 (18.9%)  | 4 (12.9%)  | 3 (5.4%)      | 19 (15.2%)           |
|   | A                     | 747 (14.9%)   | 17 (1.8%)   | 617 (17.3%)   | 14 (18.2%) |                  | 1 (20.0%)                   | 61 (25.6%)  | 6 (19.4%)  | 4 (7.1%)      | 27 (21.6%)           |
| Dihydropyridine<br>Derivatives                          | B                     | 412 (8.2%)    | 81 (8.7%)   | 287 (8.1%)    | 5 (6.5%)   |                  |                             | 23 (9.7%)   | 1 (3.2%)   | 2 (3.6%)      | 13 (10.4%)           |
|   | A                     | 502 (10.0%)   | 43 (4.6%)   | 397 (11.1%)   | 12 (15.6%) |                  | 1 (20.0%)                   | 25 (10.5%)  |            | 4 (7.1%)      | 20 (16.0%)           |

| ATC   | T<br>i<br>m<br>e<br>l | Any            | On label     |                |             | Off label        |                             |              |             |               |                      |
|---|-----------------------|----------------|--------------|----------------|-------------|------------------|-----------------------------|--------------|-------------|---------------|----------------------|
|   |                       |                | THA/TKA      | NVAF           | DVT/PE      | Age <18<br>years | Non-<br>elective<br>THA/TKA | AF*          | VTE*        | Other surgery | Other diagno-<br>sis |
| ACE Inhibitors,<br>Plain  | B                     | 459 (9.1%)     | 56 (6.0%)    | 351 (9.8%)     | 6 (7.8%)    |                  |                             | 30 (12.6%)   | 2 (6.5%)    | 2 (3.6%)      | 12 (9.6%)            |
|   | A                     | 613 (12.2%)    | 30 (3.2%)    | 507 (14.2%)    | 6 (7.8%)    |                  | 1 (20.0%)                   | 38 (16.0%)   | 4 (12.9%)   | 9 (16.1%)     | 18 (14.4%)           |
| Angiotensin II<br>Antagonists, Plain                            | B                     | 309 (6.1%)     | 37 (4.0%)    | 239 (6.7%)     | 3 (3.9%)    |                  |                             | 18 (7.6%)    | 2 (6.5%)    | 3 (5.4%)      | 7 (5.6%)             |
|   | A                     | 410 (8.2%)     | 40 (4.3%)    | 334 (9.4%)     | 3 (3.9%)    |                  |                             | 21 (8.8%)    | 1 (3.2%)    | 2 (3.6%)      | 9 (7.2%)             |
| Natural Opium<br>Alkaloids                                      | B                     | 362 (7.2%)     | 136 (14.6%)  | 190 (5.3%)     | 7 (9.1%)    |                  | 1 (20.0%)                   | 11 (4.6%)    | 2 (6.5%)    | 8 (14.3%)     | 7 (5.6%)             |
|   | A                     | 1 087 (21.6%)  | 790 (84.9%)  | 230 (6.5%)     | 8 (10.4%)   | 2 (100.0%)       | 5 (100.0%)                  | 21 (8.8%)    | 4 (12.9%)   | 19 (33.9%)    | 8 (6.4%)             |
| Anilides  | B                     | 753 (15.0%)    | 237 (25.5%)  | 428 (12.0%)    | 13 (16.9%)  |                  | 1 (20.0%)                   | 38 (16.0%)   | 6 (19.4%)   | 10 (17.9%)    | 20 (16.0%)           |
|   | A                     | 1 524 (30.3%)  | 824 (88.6%)  | 585 (16.4%)    | 13 (16.9%)  | 2 (100.0%)       | 5 (100.0%)                  | 42 (17.6%)   | 7 (22.6%)   | 24 (42.9%)    | 22 (17.6%)           |
| Benzodiazepine<br>Related Drugs                                 | B                     | 470 (9.3%)     | 80 (8.6%)    | 326 (9.1%)     | 14 (18.2%)  |                  |                             | 25 (10.5%)   | 3 (9.7%)    | 7 (12.5%)     | 15 (12.0%)           |
|   | A                     | 634 (12.6%)    | 118 (12.7%)  | 456 (12.8%)    | 10 (13.0%)  |                  | 1 (20.0%)                   | 25 (10.5%)   | 5 (16.1%)   | 4 (7.1%)      | 15 (12.0%)           |
| Sub-Group With Primary Care Data Available – Only Hospital Data |                       |                |              |                |             |                  |                             |              |             |               |                      |
| Total   |                       | 4 900 (100.0%) | 930 (100.0%) | 3 532 (100.0%) | 70 (100.0%) | 2 (100.0%)       | 4 (100.0%)                  | 114 (100.0%) | 27 (100.0%) | 64 (100.0%)   | 157 (100.0%)         |
| Antithrombotics   | B                     | 1 089 (22.2%)  | 65 (7.0%)    | 916 (25.9%)    | 18 (25.7%)  |                  |                             | 27 (23.7%)   | 6 (22.2%)   | 15 (23.4%)    | 42 (26.8%)           |
|   | A                     | 296 (6.0%)     | 57 (6.1%)    | 196 (5.5%)     | 4 (5.7%)    |                  | 1 (25.0%)                   | 10 (8.8%)    | 2 (7.4%)    | 8 (12.5%)     | 18 (11.5%)           |
| Vitamin K Antago-<br>nists                                      | B                     | 282 (5.8%)     |              | 255 (7.2%)     | 5 (7.1%)    |                  |                             | 12 (10.5%)   | 3 (11.1%)   | 2 (3.1%)      | 5 (3.2%)             |
|   | A                     | 33 (0.7%)      | 5 (0.5%)     | 26 (0.7%)      |             |                  |                             |              |             | 1 (1.6%)      | 1 (0.6%)             |
| Heparin Group   | B                     | 152 (3.1%)     | 3 (0.3%)     | 123 (3.5%)     | 10 (14.3%)  |                  |                             | 6 (5.3%)     | 1 (3.7%)    | 4 (6.3%)      | 5 (3.2%)             |
|   | A                     | 48 (1.0%)      | 10 (1.1%)    | 30 (0.8%)      | 3 (4.3%)    |                  |                             | 1 (0.9%)     | 1 (3.7%)    | 1 (1.6%)      | 2 (1.3%)             |
| Platelet Aggregation<br>Inhibitors Excl.<br>Heparin             | B                     | 642 (13.1%)    | 61 (6.6%)    | 525 (14.9%)    | 4 (5.7%)    |                  |                             | 8 (7.0%)     | 1 (3.7%)    | 11 (17.2%)    | 32 (20.4%)           |
|   | A                     | 217 (4.4%)     | 44 (4.7%)    | 139 (3.9%)     | 1 (1.4%)    |                  | 1 (25.0%)                   | 9 (7.9%)     | 1 (3.7%)    | 6 (9.4%)      | 16 (10.2%)           |
| Enzymes   | B                     |                |              |                |             |                  |                             |              |             |               |                      |
|   | A                     |                |              |                |             |                  |                             |              |             |               |                      |
| Direct Thrombin<br>Inhibitors                                   | B                     | 47 (1.0%)      | 1 (0.1%)     | 42 (1.2%)      | 1 (1.4%)    |                  |                             | 1 (0.9%)     | 1 (3.7%)    |               | 1 (0.6%)             |
|   | A                     | 10 (0.2%)      |              | 9 (0.3%)       |             |                  |                             |              |             | 1 (1.6%)      |                      |
| Other Antithrombot-<br>ic Agents                                | B                     | 2 (0.0%)       |              | 1 (0.0%)       |             |                  |                             |              |             |               | 1 (0.6%)             |
|   | A                     |                |              |                |             |                  |                             |              |             |               |                      |
| Anti-Inflammatory<br>And Antirheumatic<br>Products              | B                     | 219 (4.5%)     | 117 (12.6%)  | 85 (2.4%)      | 2 (2.9%)    | 1 (50.0%)        | 1 (25.0%)                   | 3 (2.6%)     |             | 5 (7.8%)      | 5 (3.2%)             |
|   | A                     | 155 (3.2%)     | 78 (8.4%)    | 71 (2.0%)      | 1 (1.4%)    |                  |                             |              |             | 1 (1.6%)      | 4 (2.5%)             |

| ATC   | T<br>i<br>m<br>e<br>l | Any           | On label    |               |            | Off label        |                             |            |           |               |                      |
|---|-----------------------|---------------|-------------|---------------|------------|------------------|-----------------------------|------------|-----------|---------------|----------------------|
|   |                       |               | THA/TKA     | NVAF          | DVT/PE     | Age <18<br>years | Non-<br>elective<br>THA/TKA | AF*        | VTE*      | Other surgery | Other diagno-<br>sis |
| Antiinflammatory<br>And Antirheumatic<br>Products, Non- | B                     | 219 (4.5%)    | 117 (12.6%) | 85 (2.4%)     | 2 (2.9%)   | 1 (50.0%)        | 1 (25.0%)                   | 3 (2.6%)   |           | 5 (7.8%)      | 5 (3.2%)             |
|   | A                     | 155 (3.2%)    | 78 (8.4%)   | 71 (2.0%)     | 1 (1.4%)   |                  |                             |            |           | 1 (1.6%)      | 4 (2.5%)             |
| <b>CYP3A4 And P-Gp<br/>Inhibitors</b>                   | B                     | 1 539 (31.4%) | 132 (14.2%) | 1 266 (35.8%) | 19 (27.1%) |                  |                             | 52 (45.6%) | 8 (29.6%) | 11 (17.2%)    | 51 (32.5%)           |
|   | A                     | 2 253 (46.0%) | 111 (11.9%) | 1 935 (54.8%) | 25 (35.7%) |                  | 1 (25.0%)                   | 57 (50.0%) | 9 (33.3%) | 24 (37.5%)    | 91 (58.0%)           |
| Antimycotics For<br>Systemic Use                        | B                     | 11 (0.2%)     | 1 (0.1%)    | 9 (0.3%)      |            |                  |                             |            |           | 1 (1.6%)      |                      |
|   | A                     | 15 (0.3%)     | 2 (0.2%)    | 12 (0.3%)     |            |                  |                             | 1 (0.9%)   |           |               |                      |
| Protease Inhibitors                                     | B                     |               |             |               |            |                  |                             |            |           |               |                      |
|   | A                     |               |             |               |            |                  |                             |            |           |               |                      |
| Selective Serotonin<br>Reuptake Inhibitors              | B                     | 258 (5.3%)    | 23 (2.5%)   | 197 (5.6%)    | 7 (10.0%)  |                  |                             | 13 (11.4%) | 3 (11.1%) | 3 (4.7%)      | 12 (7.6%)            |
|   | A                     | 289 (5.9%)    | 23 (2.5%)   | 228 (6.5%)    | 9 (12.9%)  |                  |                             | 7 (6.1%)   | 5 (18.5%) | 3 (4.7%)      | 14 (8.9%)            |
| Phenylalkylamine<br>Derivatives                         | B                     | 18 (0.4%)     |             | 18 (0.5%)     |            |                  |                             |            |           |               |                      |
|   | A                     | 25 (0.5%)     |             | 23 (0.7%)     |            |                  |                             |            |           | 1 (1.6%)      | 1 (0.6%)             |
| Antiarrhythmics,<br>Class Ia                            | B                     | 5 (0.1%)      |             | 5 (0.1%)      |            |                  |                             |            |           |               |                      |
|   | A                     | 5 (0.1%)      |             | 5 (0.1%)      |            |                  |                             |            |           |               |                      |
| Beta Blocking<br>Agents, Selective                      | B                     | 1 115 (22.8%) | 70 (7.5%)   | 960 (27.2%)   | 8 (11.4%)  |                  |                             | 34 (29.8%) | 4 (14.8%) | 6 (9.4%)      | 33 (21.0%)           |
|   | A                     | 1 789 (36.5%) | 62 (6.7%)   | 1 591 (45.0%) | 13 (18.6%) |                  | 1 (25.0%)                   | 45 (39.5%) | 5 (18.5%) | 15 (23.4%)    | 57 (36.3%)           |
| Benzothiazepine<br>Derivatives                          | B                     | 7 (0.1%)      | 1 (0.1%)    | 6 (0.2%)      |            |                  |                             |            |           |               |                      |
|   | A                     | 9 (0.2%)      | 1 (0.1%)    | 8 (0.2%)      |            |                  |                             |            |           |               |                      |
| HMG Coa Reductase<br>Inhibitors                         | B                     | 591 (12.1%)   | 70 (7.5%)   | 462 (13.1%)   | 6 (8.6%)   |                  |                             | 18 (15.8%) | 3 (11.1%) | 5 (7.8%)      | 27 (17.2%)           |
|   | A                     | 850 (17.3%)   | 50 (5.4%)   | 705 (20.0%)   | 6 (8.6%)   |                  |                             | 20 (17.5%) | 3 (11.1%) | 12 (18.8%)    | 54 (34.4%)           |
| Macrolides  | B                     | 5 (0.1%)      | 1 (0.1%)    | 3 (0.1%)      |            |                  |                             | 1 (0.9%)   |           |               |                      |
|   | A                     | 5 (0.1%)      |             | 4 (0.1%)      | 1 (1.4%)   |                  |                             |            |           |               |                      |
| Selective<br>Immunosuppressants                         | B                     | 6 (0.1%)      | 2 (0.2%)    | 4 (0.1%)      |            |                  |                             |            |           |               |                      |
|   | A                     | 1 (0.0%)      |             | 1 (0.0%)      |            |                  |                             |            |           |               |                      |
| <b>CYP3A4 And P-Gp<br/>Inducers</b>                     | B                     | 194 (4.0%)    | 21 (2.3%)   | 154 (4.4%)    | 1 (1.4%)   |                  |                             | 6 (5.3%)   | 2 (7.4%)  | 3 (4.7%)      | 7 (4.5%)             |
|   | A                     | 216 (4.4%)    | 17 (1.8%)   | 175 (5.0%)    | 4 (5.7%)   |                  |                             | 9 (7.9%)   |           | 3 (4.7%)      | 8 (5.1%)             |
| Carboxamide Deriv-<br>atives                            | B                     | 26 (0.5%)     | 1 (0.1%)    | 23 (0.7%)     |            |                  |                             |            | 1 (3.7%)  |               | 1 (0.6%)             |
|   | A                     | 27 (0.6%)     |             | 25 (0.7%)     |            |                  |                             | 1 (0.9%)   |           |               | 1 (0.6%)             |

| ATC   | T<br>i<br>m<br>e<br>l | Any           | On label    |               |            | Off label        |                             |            |            |               |                      |
|---|-----------------------|---------------|-------------|---------------|------------|------------------|-----------------------------|------------|------------|---------------|----------------------|
|   |                       |               | THA/TKA     | NVAF          | DVT/PE     | Age <18<br>years | Non-<br>elective<br>THA/TKA | AF*        | VTE*       | Other surgery | Other diagno-<br>sis |
| Thiazolidinediones                                      | B                     | 4 (0.1%)      | 1 (0.1%)    | 3 (0.1%)      |            |                  |                             |            |            |               |                      |
|   | A                     | 3 (0.1%)      |             | 3 (0.1%)      |            |                  |                             |            |            |               |                      |
| Glucocorticoids   | B                     | 154 (3.1%)    | 16 (1.7%)   | 122 (3.5%)    | 1 (1.4%)   |                  |                             | 5 (4.4%)   | 1 (3.7%)   | 3 (4.7%)      | 6 (3.8%)             |
|   | A                     | 174 (3.6%)    | 15 (1.6%)   | 138 (3.9%)    | 3 (4.3%)   |                  |                             | 8 (7.0%)   |            | 3 (4.7%)      | 7 (4.5%)             |
| Short-Acting Sul-<br>fonamides                          | B                     |               |             |               |            |                  |                             |            |            |               |                      |
|   | A                     |               |             |               |            |                  |                             |            |            |               |                      |
| Macrolides  | B                     | 5 (0.1%)      | 1 (0.1%)    | 3 (0.1%)      |            |                  |                             | 1 (0.9%)   |            |               |                      |
|   | A                     | 5 (0.1%)      |             | 4 (0.1%)      | 1 (1.4%)   |                  |                             |            |            |               |                      |
| Antibiotics   | B                     |               |             |               |            |                  |                             |            |            |               |                      |
|   | A                     | 5 (0.1%)      | 2 (0.2%)    | 3 (0.1%)      |            |                  |                             |            |            |               |                      |
| Non-Nucleoside<br>Reverse Transcrip-<br>tase Inhibitors | B                     |               |             |               |            |                  |                             |            |            |               |                      |
|   | A                     |               |             |               |            |                  |                             |            |            |               |                      |
| Preparations Increas-<br>ing Uric Acid Excre-<br>tion   | B                     | 3 (0.1%)      |             | 3 (0.1%)      |            |                  |                             |            |            |               |                      |
|   | A                     | 2 (0.0%)      |             | 2 (0.1%)      |            |                  |                             |            |            |               |                      |
| Barbiturates And<br>Derivatives                         | B                     | 2 (0.0%)      | 1 (0.1%)    | 1 (0.0%)      |            |                  |                             |            |            |               |                      |
|   | A                     | 1 (0.0%)      |             | 1 (0.0%)      |            |                  |                             |            |            |               |                      |
| Hydantoin Deriva-<br>tives                              | B                     | 2 (0.0%)      | 1 (0.1%)    | 1 (0.0%)      |            |                  |                             |            |            |               |                      |
|   | A                     | 1 (0.0%)      |             | 1 (0.0%)      |            |                  |                             |            |            |               |                      |
| Succinimide Deriva-<br>tives                            | B                     |               |             |               |            |                  |                             |            |            |               |                      |
|   | A                     |               |             |               |            |                  |                             |            |            |               |                      |
| Piperidinedione<br>Derivatives                          | B                     |               |             |               |            |                  |                             |            |            |               |                      |
|   | A                     |               |             |               |            |                  |                             |            |            |               |                      |
| <b>Commonly Dis-<br/>pensed Drugs<sup>†</sup></b>       | B                     | 2 101 (42.9%) | 411 (44.2%) | 1 478 (41.8%) | 32 (45.7%) |                  | 2 (50.0%)                   | 66 (57.9%) | 14 (51.9%) | 29 (45.3%)    | 69 (43.9%)           |
|   | A                     | 3 121 (63.7%) | 893 (96.0%) | 1 971 (55.8%) | 33 (47.1%) | 2 (100.0%)       | 4 (100.0%)                  | 75 (65.8%) | 14 (51.9%) | 39 (60.9%)    | 90 (57.3%)           |
| Proton Pump Inhibi-<br>tors                             | B                     | 479 (9.8%)    | 55 (5.9%)   | 377 (10.7%)   | 9 (12.9%)  |                  |                             | 20 (17.5%) | 2 (7.4%)   | 6 (9.4%)      | 10 (6.4%)            |
|   | A                     | 625 (12.8%)   | 73 (7.8%)   | 492 (13.9%)   | 7 (10.0%)  |                  |                             | 24 (21.1%) | 2 (7.4%)   | 7 (10.9%)     | 20 (12.7%)           |
| Osmotically Acting<br>Laxatives                         | B                     | 160 (3.3%)    | 28 (3.0%)   | 116 (3.3%)    | 4 (5.7%)   |                  |                             | 6 (5.3%)   |            | 3 (4.7%)      | 3 (1.9%)             |
|   | A                     | 358 (7.3%)    | 137 (14.7%) | 192 (5.4%)    | 4 (5.7%)   |                  | 1 (25.0%)                   | 5 (4.4%)   | 1 (3.7%)   | 6 (9.4%)      | 12 (7.6%)            |

| ATC                                  | T<br>i<br>m<br>e<br>l | Any           | On label    |             |            | Off label        |                             |            |           |               |                      |
|--------------------------------------|-----------------------|---------------|-------------|-------------|------------|------------------|-----------------------------|------------|-----------|---------------|----------------------|
|                                      |                       |               | THA/TKA     | NVAF        | DVT/PE     | Age <18<br>years | Non-<br>elective<br>THA/TKA | AF*        | VTE*      | Other surgery | Other diagno-<br>sis |
| Sulfonamides, Plain                  | B                     | 476 (9.7%)    | 16 (1.7%)   | 402 (11.4%) | 5 (7.1%)   |                  |                             | 23 (20.2%) | 4 (14.8%) | 4 (6.3%)      | 22 (14.0%)           |
|                                      | A                     | 736 (15.0%)   | 17 (1.8%)   | 639 (18.1%) | 11 (15.7%) |                  |                             | 30 (26.3%) | 5 (18.5%) | 6 (9.4%)      | 28 (17.8%)           |
| Dihydropyridine<br>Derivatives       | B                     | 393 (8.0%)    | 81 (8.7%)   | 277 (7.8%)  | 4 (5.7%)   |                  |                             | 12 (10.5%) | 1 (3.7%)  | 4 (6.3%)      | 14 (8.9%)            |
|                                      | A                     | 485 (9.9%)    | 43 (4.6%)   | 391 (11.1%) | 9 (12.9%)  |                  | 1 (25.0%)                   | 12 (10.5%) |           | 5 (7.8%)      | 24 (15.3%)           |
| ACE Inhibitors,<br>Plain             | B                     | 451 (9.2%)    | 56 (6.0%)   | 356 (10.1%) | 5 (7.1%)   |                  |                             | 15 (13.2%) | 2 (7.4%)  | 2 (3.1%)      | 15 (9.6%)            |
|                                      | A                     | 602 (12.3%)   | 30 (3.2%)   | 512 (14.5%) | 4 (5.7%)   |                  | 1 (25.0%)                   | 19 (16.7%) | 3 (11.1%) | 9 (14.1%)     | 24 (15.3%)           |
| Angiotensin II<br>Antagonists, Plain | B                     | 301 (6.1%)    | 37 (4.0%)   | 235 (6.7%)  | 2 (2.9%)   |                  |                             | 11 (9.6%)  | 2 (7.4%)  | 5 (7.8%)      | 9 (5.7%)             |
|                                      | A                     | 402 (8.2%)    | 40 (4.3%)   | 333 (9.4%)  | 2 (2.9%)   |                  |                             | 12 (10.5%) | 1 (3.7%)  | 2 (3.1%)      | 12 (7.6%)            |
| Natural Opium<br>Alkaloids           | B                     | 358 (7.3%)    | 136 (14.6%) | 191 (5.4%)  | 7 (10.0%)  |                  | 1 (25.0%)                   | 8 (7.0%)   | 1 (3.7%)  | 9 (14.1%)     | 5 (3.2%)             |
|                                      | A                     | 1 081 (22.1%) | 790 (84.9%) | 231 (6.5%)  | 8 (11.4%)  | 2 (100.0%)       | 4 (100.0%)                  | 16 (14.0%) | 3 (11.1%) | 20 (31.3%)    | 7 (4.5%)             |
| Anilides                             | B                     | 741 (15.1%)   | 237 (25.5%) | 434 (12.3%) | 12 (17.1%) |                  | 1 (25.0%)                   | 16 (14.0%) | 6 (22.2%) | 12 (18.8%)    | 23 (14.6%)           |
|                                      | A                     | 1 509 (30.8%) | 824 (88.6%) | 591 (16.7%) | 11 (15.7%) | 2 (100.0%)       | 4 (100.0%)                  | 21 (18.4%) | 6 (22.2%) | 26 (40.6%)    | 24 (15.3%)           |
| Benzodiazepine<br>Related Drugs      | B                     | 462 (9.4%)    | 80 (8.6%)   | 330 (9.3%)  | 11 (15.7%) |                  |                             | 13 (11.4%) | 2 (7.4%)  | 7 (10.9%)     | 19 (12.1%)           |
|                                      | A                     | 621 (12.7%)   | 118 (12.7%) | 449 (12.7%) | 8 (11.4%)  |                  | 1 (25.0%)                   | 13 (11.4%) | 3 (11.1%) | 5 (7.8%)      | 24 (15.3%)           |

1: Time: B=within 30 days before apixaban index date, A=within 30 days after apixaban index date

\*includes NVAF before November 20, 2012; includes DVT/PE before July 28, 2014

Table 1.7 Selected diagnoses and co-morbidity, number and proportions - within 1 year prior to index date

| Co-morbidity   | Proxy for indication |                | On label       |                 |              | Off label     |                      |              |              |               |                 |
|--|----------------------|----------------|----------------|-----------------|--------------|---------------|----------------------|--------------|--------------|---------------|-----------------|
|  | Any indication       | Unclassified   | THA/TKA        | NVAF            | DVT/PE       | Age <18 years | Non-elective THA/TKA | VAF*         | VTE*         | Other surgery | Other diagnosis |
| All patients   |                      |                |                |                 |              |               |                      |              |              |               |                 |
| Total  | 16 562 (100.0%)      | 1 030 (100.0%) | 2 636 (100.0%) | 12 151 (100.0%) | 417 (100.0%) | 2 (100.0%)    | 10 (100.0%)          | 428 (100.0%) | 108 (100.0%) | 235 (100.0%)  | 575 (100.0%)    |
| Renal disease (Acute kidney                                | 544 (3.28%)          | 11 (1.07%)     | 16 (0.61%)     | 441 (3.63%)     | 20 (4.80%)   |               |                      | 37 (8.64%)   | 8 (7.41%)    | 7 (2.98%)     | 15 (2.61%)      |
| End stage renal disease                                    | 10 (0.06%)           |                |                | 7 (0.06%)       |              |               |                      | 1 (0.23%)    |              | 2 (0.85%)     |                 |
| <b>Total renal disease</b>                                 | 550 (3.32%)          | 11 (1.07%)     | 16 (0.61%)     | 444 (3.65%)     | 20 (4.80%)   |               |                      | 38 (8.88%)   | 8 (7.41%)    | 9 (3.83%)     | 15 (2.61%)      |
| Liver disorders  | 66 (0.40%)           |                | 9 (0.34%)      | 48 (0.40%)      | 2 (0.48%)    |               |                      | 1 (0.23%)    | 3 (2.78%)    |               | 3 (0.52%)       |
| <b>Renal and/or liver disease</b>                          | 605 (3.65%)          | 11 (1.07%)     | 24 (0.91%)     | 483 (3.97%)     | 22 (5.28%)   |               |                      | 38 (8.88%)   | 11 (10.19%)  | 9 (3.83%)     | 18 (3.13%)      |
| Coagulation defects  | 186 (1.12%)          | 3 (0.29%)      | 5 (0.19%)      | 150 (1.23%)     | 19 (4.56%)   |               |                      | 3 (0.70%)    | 2 (1.85%)    | 1 (0.43%)     | 6 (1.04%)       |
| Intracranial haemorrhage                                   | 130 (0.78%)          | 1 (0.10%)      | 1 (0.04%)      | 113 (0.93%)     | 4 (0.96%)    |               |                      | 5 (1.17%)    | 2 (1.85%)    |               | 5 (0.87%)       |
| Gastric, duodenal ulcer and peptic ulcer, site unspecified | 146 (0.88%)          | 2 (0.19%)      | 5 (0.19%)      | 121 (1.00%)     | 4 (0.96%)    |               |                      | 7 (1.64%)    |              | 5 (2.13%)     | 4 (0.70%)       |
| Acute and sub-acute bacterial endocarditis                 | 30 (0.18%)           | 1 (0.10%)      | 1 (0.04%)      | 10 (0.08%)      | 3 (0.72%)    |               |                      | 13 (3.04%)   |              |               | 3 (0.52%)       |
| Esophageal varices   | 6 (0.04%)            |                | 3 (0.11%)      | 1 (0.01%)       |              |               |                      | 2 (0.47%)    |              |               |                 |
| Thrombocytopenia   | 32 (0.19%)           | 1 (0.10%)      | 4 (0.15%)      | 22 (0.18%)      | 2 (0.48%)    |               |                      | 1 (0.23%)    | 1 (0.93%)    |               | 2 (0.35%)       |
| Recent brain or spinal surgery                             | 129 (0.78%)          |                | 18 (0.68%)     | 93 (0.77%)      | 9 (2.16%)    |               |                      | 4 (0.93%)    | 1 (0.93%)    |               | 4 (0.70%)       |



| Co-morbidity  | Proxy for indication |              | On label     |                |             | Off label     |                      |              |             |               |                 |
|---|----------------------|--------------|--------------|----------------|-------------|---------------|----------------------|--------------|-------------|---------------|-----------------|
|   | Any indication       | Unclassified | THA/TKA      | NVAF           | DVT/PE      | Age <18 years | Non-elective THA/TKA | VAF*         | VTE*        | Other surgery | Other diagnosis |
| <b>Subgroup with primary care data available – all data</b>           |                      |              |              |                |             |               |                      |              |             |               |                 |
| Total   | 5 029 (100.0%)       | 128 (100.0%) | 930 (100.0%) | 3 565 (100.0%) | 77 (100.0%) | 2 (100.0%)    | 5 (100.0%)           | 238 (100.0%) | 31 (100.0%) | 56 (100.0%)   | 125 (100.0%)    |
| Renal disease (Acute kidney failure, Chronic kidney disease)          | 186 (3.70%)          | 2 (1.56%)    | 7 (0.75%)    | 153 (4.29%)    | 5 (6.49%)   |               |                      | 14 (5.88%)   | 3 (9.68%)   | 1 (1.79%)     | 3 (2.40%)       |
| End stage renal disease   | 2 (0.04%)            |              |              | 2 (0.06%)      |             |               |                      |              |             |               |                 |
| <b>Total renal disease</b>  | 186 (3.70%)          | 2 (1.56%)    | 7 (0.75%)    | 153 (4.29%)    | 5 (6.49%)   |               |                      | 14 (5.88%)   | 3 (9.68%)   | 1 (1.79%)     | 3 (2.40%)       |
| Liver disorders   | 29 (0.58%)           |              | 5 (0.54%)    | 19 (0.53%)     | 1 (1.30%)   |               |                      | 1 (0.42%)    |             |               | 3 (2.40%)       |
| <b>Renal and/or liver disease</b>                                     | 211 (4.20%)          | 2 (1.56%)    | 12 (1.29%)   | 169 (4.74%)    | 6 (7.79%)   |               |                      | 14 (5.88%)   | 3 (9.68%)   | 1 (1.79%)     | 6 (4.80%)       |
| Coagulation defects   | 45 (0.89%)           |              | 3 (0.32%)    | 34 (0.95%)     | 8 (10.39%)  |               |                      |              |             |               |                 |
| Intracranial haemorrhage  | 52 (1.03%)           |              |              | 45 (1.26%)     | 2 (2.60%)   |               |                      | 4 (1.68%)    | 1 (3.23%)   |               |                 |
| Gastric, duodenal ulcer and peptic ulcer, site unspecified            | 52 (1.03%)           | 1 (0.78%)    | 1 (0.11%)    | 41 (1.15%)     | 2 (2.60%)   |               |                      | 6 (2.52%)    |             |               | 2 (1.60%)       |
| Acute and sub-acute bacterial endocarditis                            | 22 (0.44%)           |              | 2 (0.22%)    | 2 (0.06%)      | 3 (3.90%)   |               |                      | 15 (6.30%)   |             |               |                 |
| Esophageal varices  | 2 (0.04%)            |              | 1 (0.11%)    | 1 (0.03%)      |             |               |                      |              |             |               |                 |
| Thrombocytopenia  | 9 (0.18%)            |              | 2 (0.22%)    | 4 (0.11%)      | 1 (1.30%)   |               |                      | 2 (0.84%)    |             |               |                 |
| Recent brain or spinal surgery  | 38 (0.76%)           |              | 5 (0.54%)    | 29 (0.81%)     | 2 (2.60%)   |               |                      | 2 (0.84%)    |             |               |                 |
| <b>Subgroup with primary care data available – only hospital data</b> |                      |              |              |                |             |               |                      |              |             |               |                 |
| Total   | 4 900 (100.0%)       | 257 (100.0%) | 930 (100.0%) | 3 532 (100.0%) | 70 (100.0%) | 2 (100.0%)    | 4 (100.0%)           | 114 (100.0%) | 27 (100.0%) | 64 (100.0%)   | 157 (100.0%)    |
| Renal disease (Acute kidney   | 120 (2.45%)          | 2 (0.78%)    | 5 (0.54%)    | 103 (2.92%)    | 3 (4.29%)   |               |                      | 6 (5.26%)    | 2 (7.41%)   | 1 (1.56%)     |                 |

| Co-morbidity   | Proxy for indication |              | On label  |             |           | Off label     |                      |           |           |               |                 |
|--|----------------------|--------------|-----------|-------------|-----------|---------------|----------------------|-----------|-----------|---------------|-----------------|
|  | Any indication       | Unclassified | THA/TKA   | NVAF        | DVT/PE    | Age <18 years | Non-elective THA/TKA | VAF*      | VTE*      | Other surgery | Other diagnosis |
| End stage renal disease                                    | 2 (0.04%)            |              |           | 2 (0.06%)   |           |               |                      |           |           |               |                 |
| <b>Total renal disease</b>                                 | 121 (2.47%)          | 2 (0.78%)    | 5 (0.54%) | 104 (2.94%) | 3 (4.29%) |               |                      | 6 (5.26%) | 2 (7.41%) | 1 (1.56%)     |                 |
| Liver disorders  | 23 (0.47%)           |              | 3 (0.32%) | 17 (0.48%)  |           |               |                      | 1 (0.88%) |           |               | 2 (1.27%)       |
| <b>Renal and/or liver disease</b>                          | 140 (2.86%)          | 2 (0.78%)    | 8 (0.86%) | 118 (3.34%) | 3 (4.29%) |               |                      | 6 (5.26%) | 2 (7.41%) | 1 (1.56%)     | 2 (1.27%)       |
| Coagulation defects  | 41 (0.84%)           |              | 3 (0.32%) | 32 (0.91%)  | 5 (7.14%) |               |                      |           |           |               | 1 (0.64%)       |
| Intracranial haemorrhage                                   | 45 (0.92%)           |              |           | 40 (1.13%)  | 1 (1.43%) |               |                      | 3 (2.63%) | 1 (3.70%) |               |                 |
| Gastric, duodenal ulcer and peptic ulcer, site unspecified | 46 (0.94%)           | 1 (0.39%)    |           | 37 (1.05%)  | 2 (2.86%) |               |                      | 3 (2.63%) |           | 2 (3.13%)     | 2 (1.27%)       |
| Acute and sub-acute bacterial endocarditis                 | 8 (0.16%)            |              | 1 (0.11%) | 3 (0.08%)   | 1 (1.43%) |               |                      | 3 (2.63%) |           |               |                 |
| Esophageal varices   | 1 (0.02%)            |              | 1 (0.11%) |             |           |               |                      |           |           |               |                 |
| Thrombocytopenia   | 6 (0.12%)            |              | 2 (0.22%) | 2 (0.06%)   | 1 (1.43%) |               |                      | 1 (0.88%) |           |               |                 |
| Recent brain or spinal surgery                             | 38 (0.78%)           |              | 5 (0.54%) | 28 (0.79%)  | 2 (2.86%) |               |                      | 2 (1.75%) |           |               | 1 (0.64%)       |

\*includes NVAF before November 20, 2012; includes DVT/PE before July 28, 2014

Table 1.8 Number and proportions of patients with likely off-label indication and/or warfarin switchers

| All                               |              | Warfarin switcher |              |               |
|-----------------------------------|--------------|-------------------|--------------|---------------|
|                                   |              | yes               | no           | total         |
| Off-label indication              | yes          | 184 (14%)         | 1 174 (86%)  | 1 358 (8%)    |
|                                   | no           | 2 440 (16%)       | 12 764 (84%) | 15 204 (86%)  |
|                                   | unclassified | 85 (8%)           | 945 (92%)    | 1 030 (6%)    |
|                                   | total        | 2 709 (15%)       | 14 883 (85%) | 17 592 (100%) |
| Primary care – all data           |              | Warfarin switcher |              |               |
|                                   |              | yes               | no           | total         |
| Off-label indication              | yes          | 82 (18%)          | 375 (82%)    | 457 (9%)      |
|                                   | no           | 713 (16%)         | 3 859 (84%)  | 4 572 (89%)   |
|                                   | unclassified | 8 (6%)            | 120 (94%)    | 128 (2%)      |
|                                   | total        | 803 (16%)         | 4 354 (84%)  | 5 157 (100%)  |
| Primary care – only hospital data |              | Warfarin switcher |              |               |
|                                   |              | yes               | no           | total         |
| Off-label indication              | yes          | 65 (18%)          | 303 (82%)    | 368 (7%)      |
|                                   | no           | 706 (16%)         | 3 826 (84%)  | 4 532 (88%)   |
|                                   | unclassified | 32 (12%)          | 225 (88%)    | 257 (5%)      |
|                                   | total        | 803 (16%)         | 4 354 (84%)  | 5 157 (100%)  |

Table 1.9 Estimated proportions of users with 95% confidence interval

| Year | Subgroup                     | Binary classification                    | Indication   | Frequency | Proportion | 95% exact confidence interval |
|------|------------------------------|--|--------------|-----------|------------|-------------------------------|
| 2012 | All users                    | 2 classes, any/none                      | Any          | 3         | 100.0      | 29.2 - 100.0                  |
|      |                              |  | None         | 0         | 0.000      |                               |
|      |                              | 3 classes                                | On-label     | 0         | 0.000      |                               |
|      |                              |  | Off-label    | 3         | 100.0      | 29.2 - 100.0                  |
|      |                              |  | Unclassified | 0         | 0.000      |                               |
|      |                              | 2 classes with unclassified as off-label | On-label     | 0         | 0.000      |                               |
|      |                              |  | Off-label    | 3         | 100.0      | 29.2 - 100.0                  |
|      |                              | 2 classes excluding unclassified         | On-label     | 0         | 0.000      |                               |
|      |                              |  | Off-label    | 3         | 100.0      | 29.2 - 100.0                  |
|      | Primary care – all data      | 2 classes, any/none                      | Any          |           |            |                               |
|      |                              |  | None         |           |            |                               |
|      |                              | 3 classes                                | On-label     |           |            |                               |
|      |                              |  | Off-label    |           |            |                               |
|      |                              |  | Unclassified |           |            |                               |
|      |                              | 2 classes with unclassified as off-label | On-label     |           |            |                               |
|      |                              |  | Off-label    |           |            |                               |
|      |                              | 2 classes excluding unclassified         | On-label     |           |            |                               |
|      |                              |  | Off-label    |           |            |                               |
|      | Primary care – hospital data | 2 classes, any/none                      | Any          |           |            |                               |
|      |                              |  | None         |           |            |                               |
|      |                              | 3 classes                                | On-label     |           |            |                               |

| Year | Subgroup                     | Binary classification                    | Indication   | Frequency | Proportion | 95% exact confidence interval |
|------|------------------------------|--|--------------|-----------|------------|-------------------------------|
|      |                              |  | Off-label    |           |            |                               |
|      |                              |  | Unclassified |           |            |                               |
|      |                              | 2 classes with unclassified as off-label | On-label     |           |            |                               |
|      |                              |  | Off-label    |           |            |                               |
|      |                              | 2 classes excluding unclassified         | On-label     |           |            |                               |
|      |                              |  | Off-label    |           |            |                               |
| 2013 | All users                    | 2 classes, any/none                      | Any          | 1 944     | 93.8       | 92.6 - 94.8                   |
|      |                              |  | None         | 129       | 6.22       | 5.22 - 7.35                   |
|      |                              | 3 classes                                | On-label     | 1 768     | 85.3       | 83.7 - 86.8                   |
|      |                              |  | Off-label    | 176       | 8.49       | 7.33 - 9.77                   |
|      |                              |  | Unclassified | 129       | 6.22       | 5.22 - 7.35                   |
|      |                              | 2 classes with unclassified as off-label | On-label     | 1 768     | 85.3       | 83.7 - 86.8                   |
|      |                              |  | Off-label    | 305       | 14.7       | 13.2 - 16.3                   |
|      |                              | 2 classes excluding unclassified         | On-label     | 1 768     | 90.9       | 89.6 - 92.2                   |
|      |                              |  | Off-label    | 176       | 9.05       | 7.81 - 10.4                   |
|      | Primary care – all data      | 2 classes, any/none                      | Any          | 548       | 97.0       | 95.2 - 98.2                   |
|      |                              |  | None         | 17        | 3.01       | 1.76 - 4.77                   |
|      |                              | 3 classes                                | On-label     | 483       | 85.5       | 82.3 - 88.3                   |
|      |                              |  | Off-label    | 65        | 11.5       | 8.99 - 14.4                   |
|      |                              |  | Unclassified | 17        | 3.01       | 1.76 - 4.77                   |
|      |                              | 2 classes with unclassified as off-label | On-label     | 483       | 85.5       | 82.3 - 88.3                   |
|      |                              |  | Off-label    | 82        | 14.5       | 11.7 - 17.7                   |
|      |                              | 2 classes excluding unclassified         | On-label     | 483       | 88.1       | 85.1 - 90.7                   |
|      |                              |  | Off-label    | 65        | 11.9       | 9.27 - 14.9                   |
|      | Primary care – hospital data | 2 classes, any/none                      | Any          | 537       | 95.0       | 92.9 - 96.7                   |
|      |                              |  | None         | 28        | 4.96       | 3.32 - 7.08                   |
|      |                              | 3 classes                                | On-label     | 488       | 86.4       | 83.3 - 89.1                   |
|      |                              |  | Off-label    | 49        | 8.67       | 6.48 - 11.3                   |
|      |                              |  | Unclassified | 28        | 4.96       | 3.32 - 7.08                   |
|      |                              | 2 classes with unclassified as off-label | On-label     | 488       | 86.4       | 83.3 - 89.1                   |
|      |                              |  | Off-label    | 77        | 13.6       | 10.9 - 16.7                   |
|      |                              | 2 classes excluding unclassified         | On-label     | 488       | 90.9       | 88.1 - 93.2                   |
|      |                              |  | Off-label    | 49        | 9.12       | 6.83 - 11.9                   |
| 2014 | All users                    | 2 classes, any/none                      | Any          | 14615     | 94.2       | 93.8 - 94.6                   |
|      |                              |  | None         | 901       | 5.81       | 5.44 - 6.19                   |
|      |                              | 3 classes                                | On-label     | 13436     | 86.6       | 86.0 - 87.1                   |
|      |                              |  | Off-label    | 1 179     | 7.60       | 7.19 - 8.03                   |
|      |                              |  | Unclassified | 901       | 5.81       | 5.44 - 6.19                   |
|      |                              | 2 classes with unclassified as off-label | On-label     | 13436     | 86.6       | 86.0 - 87.1                   |
|      |                              |  | Off-label    | 2 080     | 13.4       | 12.9 - 14.0                   |
|      |                              | 2 classes excluding unclassified         | On-label     | 13436     | 91.9       | 91.5 - 92.4                   |
|      |                              |  | Off-label    | 1 179     | 8.07       | 7.63 - 8.52                   |
|      | Primary care –               | 2 classes, any/none                      | Any          | 4 481     | 97.6       | 97.1 - 98.0                   |

| Year      | Subgroup                     | Binary classification                    | Indication   | Frequency | Proportion | 95% exact confidence interval |
|-----------|------------------------------|--|--------------|-----------|------------|-------------------------------|
|           | all data                     | 3 classes                                | None         | 111       | 2.42       | 1.99 - 2.90                   |
|           |                              |  | On-label     | 4 089     | 89.0       | 88.1 - 89.9                   |
|           |                              |  | Off-label    | 392       | 8.54       | 7.74 - 9.38                   |
|           |                              | 2 classes with unclassified as off-label | Unclassified | 111       | 2.42       | 1.99 - 2.90                   |
|           |                              |  | On-label     | 4 089     | 89.0       | 88.1 - 89.9                   |
|           |                              | 2 classes excluding unclassified         | Off-label    | 503       | 11.0       | 10.1 - 11.9                   |
|           |                              |  | On-label     | 4 089     | 91.3       | 90.4 - 92.1                   |
|           |                              |  | Off-label    | 392       | 8.75       | 7.94 - 9.61                   |
|           | Primary care – hospital data | 2 classes, any/none                      | Any          | 4 363     | 95.0       | 94.3 - 95.6                   |
|           |                              |  | None         | 229       | 4.99       | 4.38 - 5.66                   |
|           |                              | 3 classes                                | On-label     | 4 044     | 88.1       | 87.1 - 89.0                   |
|           |                              |  | Off-label    | 319       | 6.95       | 6.23 - 7.72                   |
|           |                              |  | Unclassified | 229       | 4.99       | 4.38 - 5.66                   |
|           |                              | 2 classes with unclassified as off-label | On-label     | 4 044     | 88.1       | 87.1 - 89.0                   |
|           |                              |  | Off-label    | 548       | 11.9       | 11.0 - 12.9                   |
|           |                              | 2 classes excluding unclassified         | On-label     | 4 044     | 92.7       | 91.9 - 93.4                   |
|           |                              |  | Off-label    | 319       | 7.31       | 6.56 - 8.12                   |
| 2012-2014 | All users                    | 2 classes, any/none                      | Any          | 16562     | 94.1       | 93.8 - 94.5                   |
|           |                              |  | None         | 1 030     | 5.85       | 5.51 - 6.21                   |
|           |                              | 3 classes                                | On-label     | 15204     | 86.4       | 85.9 - 86.9                   |
|           |                              |  | Off-label    | 1 358     | 7.72       | 7.33 - 8.12                   |
|           |                              |  | Unclassified | 1 030     | 5.85       | 5.51 - 6.21                   |
|           |                              | 2 classes with unclassified as off-label | On-label     | 15204     | 86.4       | 85.9 - 86.9                   |
|           |                              |  | Off-label    | 2 388     | 13.6       | 13.1 - 14.1                   |
|           |                              | 2 classes excluding unclassified         | On-label     | 15204     | 91.8       | 91.4 - 92.2                   |
|           |                              |  | Off-label    | 1 358     | 8.20       | 7.79 - 8.63                   |
|           | Primary care – all data      | 2 classes, any/none                      | Any          | 5 029     | 97.5       | 97.1 - 97.9                   |
|           |                              |  | None         | 128       | 2.48       | 2.07 - 2.94                   |
|           |                              | 3 classes                                | On-label     | 4 572     | 88.7       | 87.8 - 89.5                   |
|           |                              |  | Off-label    | 457       | 8.86       | 8.10 - 9.67                   |
|           |                              |  | Unclassified | 128       | 2.48       | 2.07 - 2.94                   |
|           |                              | 2 classes with unclassified as off-label | On-label     | 4 572     | 88.7       | 87.8 - 89.5                   |
|           |                              |  | Off-label    | 585       | 11.3       | 10.5 - 12.2                   |
|           |                              | 2 classes excluding unclassified         | On-label     | 4 572     | 90.9       | 90.1 - 91.7                   |
|           |                              |  | Off-label    | 457       | 9.09       | 8.31 - 9.92                   |
|           | Primary care – hospital data | 2 classes, any/none                      | Any          | 4 900     | 95.0       | 94.4 - 95.6                   |
|           |                              |  | None         | 257       | 4.98       | 4.41 - 5.61                   |
|           |                              | 3 classes                                | On-label     | 4 532     | 87.9       | 87.0 - 88.8                   |
|           |                              |  | Off-label    | 368       | 7.14       | 6.45 - 7.87                   |
|           |                              |  | Unclassified | 257       | 4.98       | 4.41 - 5.61                   |
|           |                              | 2 classes with unclassified as off-label | On-label     | 4 532     | 87.9       | 87.0 - 88.8                   |
|           |                              |  | Off-label    | 625       | 12.1       | 11.2 - 13.0                   |
|           |                              | 2 classes excluding unclassified         | On-label     | 4 532     | 92.5       | 91.7 - 93.2                   |

| Year | Subgroup | Binary classification | Indication | Frequency | Proportion | 95% exact confidence interval |
|------|----------|-----------------------|------------|-----------|------------|-------------------------------|
|      |          |                       | Off-label  | 368       | 7.51       | 6.79 - 8.28                   |

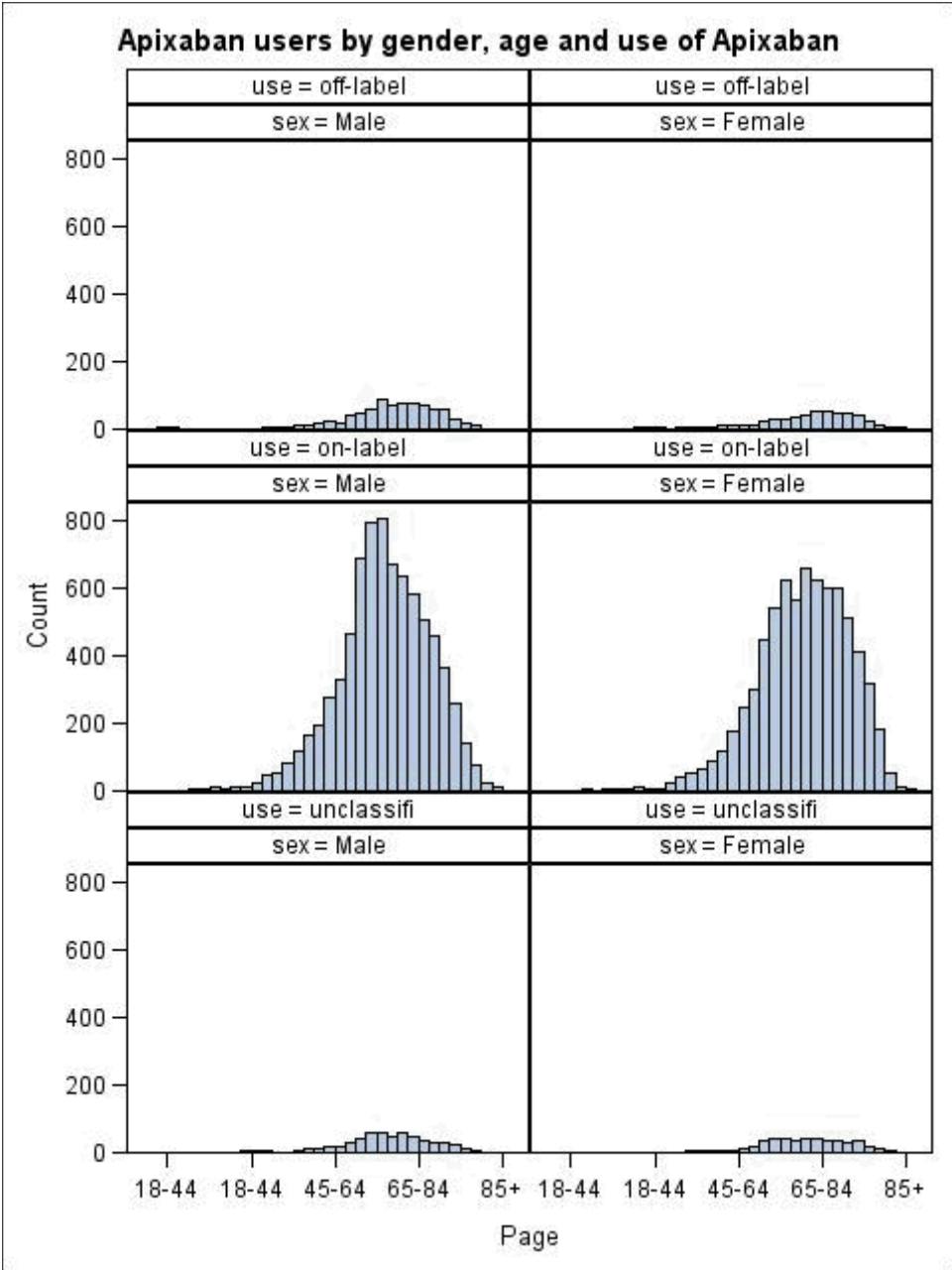


Figure 1.3 Distribution of on-, off-label and unclassified Apixaban users by gender and age



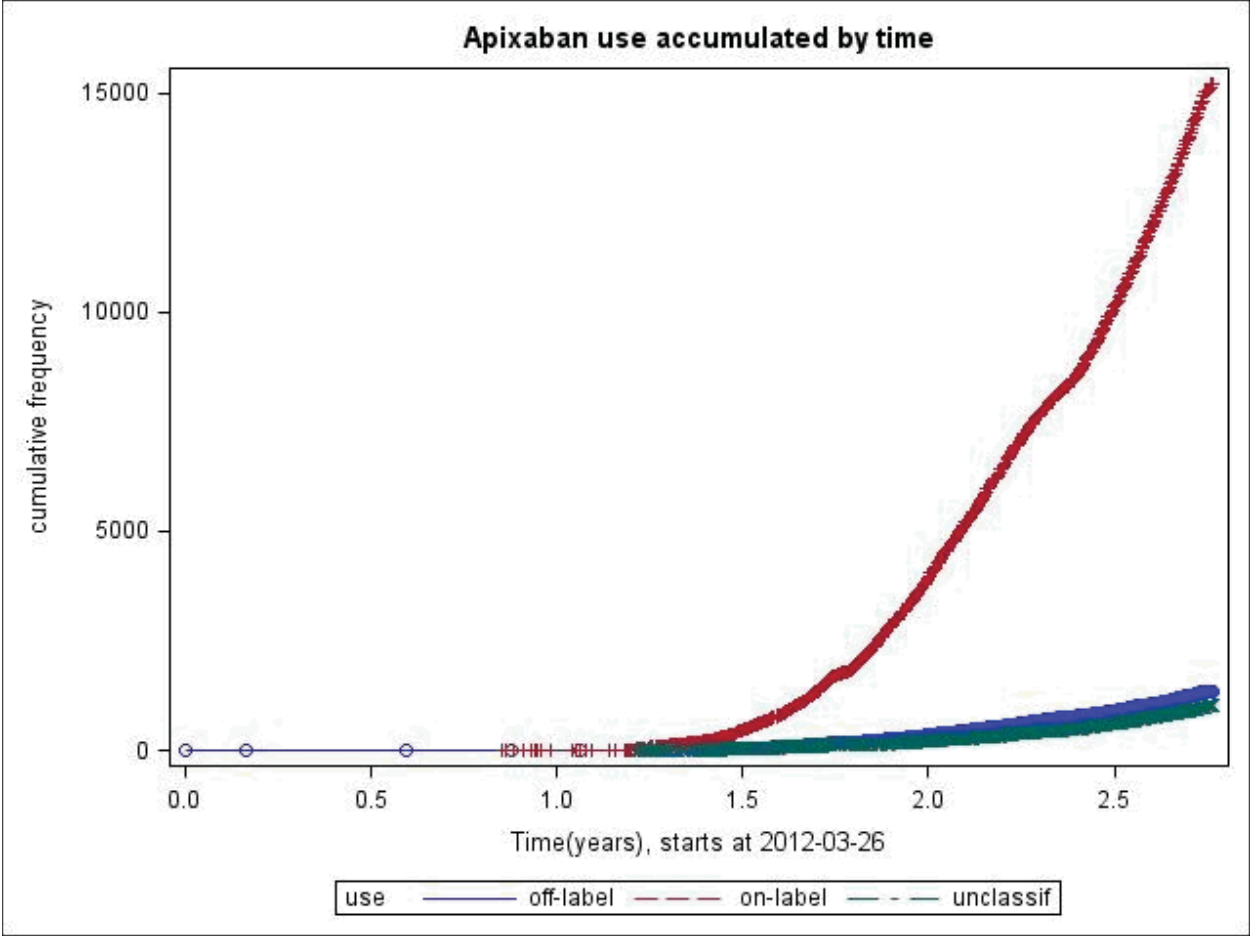


Figure 1.4. Apixaban use accumulated by time

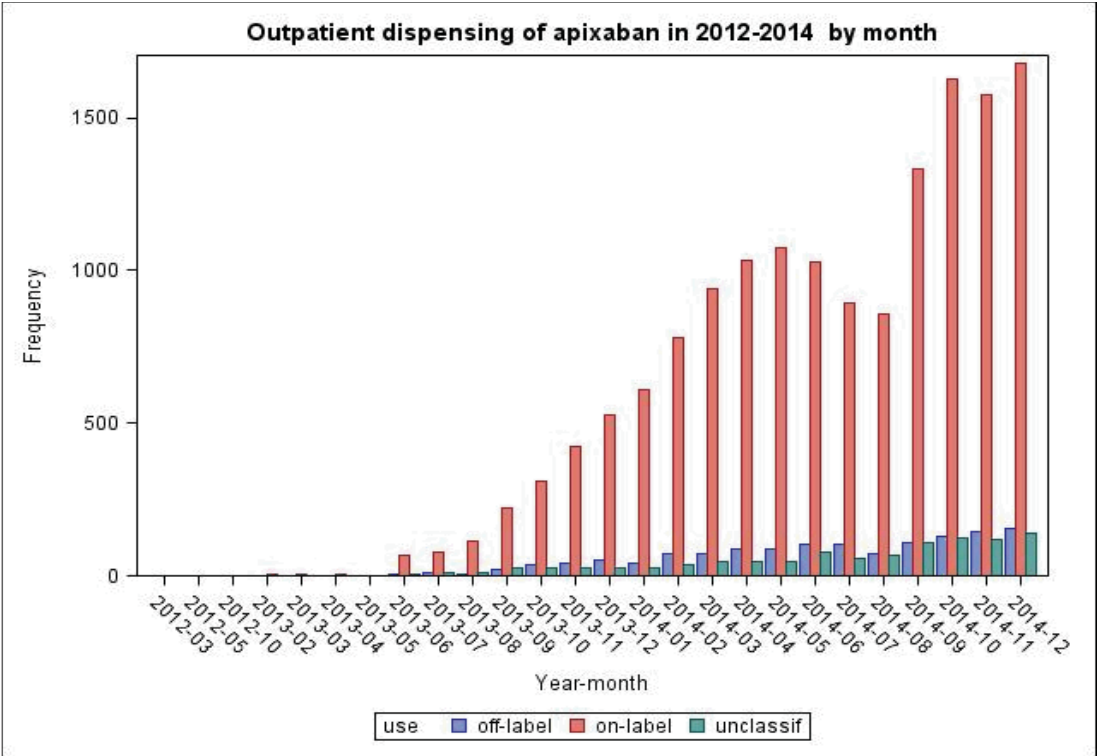


Figure 1.5 Outpatient dispensing of Apixaban in 2012- December 2014 by month and on-label, off-label and unclassified indications

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## APPENDIX 2: DATA DERIVATION DETAILS

### A1 Definition of Primary Endpoints: THA/TKA indication (NOMESCO classification of surgical procedures)

| A1.1 Definition of Endpoints: On Label Knee / Hip Replacement Codes   |  |        |
|---|--|--------|
| Category  | Specific Description   | Code   |
| <b>NFB: Primary prosthetic replacement of hip joint</b><br><br>Includes: Primary replacement after previous fracture treatment or other operation on joint  | Primary partial prosthetic replacement of hip joint not using cement   | NFB 0y |
|   | Primary partial prosthetic replacement of hip joint using cement   | NFB 1y |
|   | Primary total prosthetic replacement of hip joint not using cement   | NFB 20 |
|   | Primary total prosthetic replacement of hip joint using hybrid technique   | NFB 30 |
|   | Primary total prosthetic replacement of hip joint using cement   | NFB 40 |
|   | Primary prosthetic interposition arthroplasty of hip joint   | NFB 59 |
|   | Other primary prosthetic replacement of hip joint  | NFB 99 |
| <b>NFC: Secondary prosthetic replacement of hip joint</b><br><br>Second or later implantation of prosthesis or part of prosthesis                           | Secondary implantation of partial prosthesis in hip joint not using cement <i>Excludes: Of component of total prosthesis</i>     | NFC 0y |
|   | Secondary implantation of partial prosthesis in hip joint using cement<br><i>Excludes: Of component of total prosthesis</i>      | NFC 1y |
|   | Secondary implantation of total prosthesis in hip joint not using cement<br><i>Includes: Of component of total prosthesis</i>    | NFC 2y |
|   | Secondary implantation of total prosthesis in hip joint using hybrid technique <i>Includes: Of component of total prosthesis</i> | NFC 3y |
|   | Secondary implantation of total prosthesis in hip joint using cement   | NFC 4y |
|   | Secondary implantation of interposition prosthesis in hip joint  | NFC 59 |
|   | Other secondary prosthetic replacement in hip joint  | NFC 99 |
| <b>NGB: Primary prosthetic replacement of knee joint</b><br><br>Includes: Primary replacement after previous fracture treatment or other operation on joint | Primary partial prosthetic replacement of knee joint not using cement  | NGB 0y |
|   | Primary partial prosthetic replacement of knee joint using cement  | NGB 1y |
|   | Primary total prosthetic replacement of knee joint not using cement  | NGB 20 |
|   | Primary total prosthetic replacement of knee joint using hybrid technique  | NGB 30 |
|   | Primary total prosthetic replacement of knee joint using cement  | NGB 40 |
|   | Primary prosthetic interposition arthroplasty of knee joint  | NGB 59 |
|   | Other primary prosthetic replacement of knee joint   | NGB 99 |
| <b>NGC Secondary prosthetic replacement of knee joint</b><br><br>Second or later implantation of prosthesis or part of                                      | Secondary implantation of partial prosthesis in knee joint not using cement <i>Excludes: Of component of total prosthesis</i>    | NGC 0y |
|   | Secondary implantation of partial prosthesis in knee joint using cement<br><i>Excludes: Of component of total prosthesis</i>     | NGC 1y |
|   | Secondary implantation of total prosthesis in knee joint not using ce-   | NGC 2y |

| <b>A1.1 Definition of Endpoints: On Label Knee / Hip Replacement Codes</b> |   |             |
|--|---|-------------|
| <b>Category</b>  | <b>Specific Description</b>   | <b>Code</b> |
| prosthesis   | ment <i>Includes: Of component of total prosthesis</i>  |             |
|  | Secondary implantation of total prosthesis in knee joint using hybrid technique <i>Includes: Of component of total prosthesis</i> | NGC 3y      |
|  | Secondary implantation of total prosthesis in knee joint using cement   | NGC 4y      |
|  | Secondary implantation of interposition prosthesis in knee joint  | NGC 59      |
|  | Other secondary prosthetic replacement in knee joint  | NGC 99      |

| <b>A1.2 Definition of Endpoints: ICD-10 for the Exclusions for On-Label THA/TKA</b> |  |             |
|---|--|-------------|
| <b>Category</b>   | <b>Specific Description</b>                                    | <b>Code</b> |
| <b>Fracture of lower leg, including ankle (whole S82)</b>                           | Fracture of patella  | S82.0       |
|   | Fracture of upper end of tibia                                 | S82.1       |
|   | Fracture of shaft of tibia                                     | S82.2       |
|   | Fracture of lower end of tibia                                 | S82.3       |
|   | Fracture of fibula alone                                       | S82.4       |
|   | Fracture of medial malleolus                                   | S82.5       |
|   | Fracture of lateral malleolus                                  | S82.6       |
|   | Multiple fractures of lower leg                                | S82.7       |
|   | Fractures of other parts of lower leg                          | S82.8       |
|   | Fracture of lower leg, part unspecified                        | S82.9       |
|   | Postmenopausal osteoporosis with pathological fracture, G=knee | M80.0G      |
|   | Stress fracture, not elsewhere classified, G=knee              | M84.3G      |
|   | Fracture of bone in neoplastic disease, G=knee                 | M90.7G      |
| <b>Fracture of femur (whole S72)</b>  | Fracture of neck of femur                                      | S72.0       |
|   | Pertrochanteric fracture                                       | S72.1       |
|   | Subtrochanteric fracture                                       | S72.2       |
|   | Fracture of shaft of femur                                     | S72.3       |
|   | Fracture of lower end of femur                                 | S72.4       |
|   | Multiple fractures of femur                                    | S72.7       |
|   | Fractures of other parts of femur                              | S72.8       |
|   | Fracture of femur, part unspecified                            | S72.9       |
|   | Postmenopausal osteoporosis with pathological fracture, F=hip  | M80.0F      |
|   | Stress fracture, not elsewhere classified, F=hip               | M84.3F      |
|   | Fracture of bone in neoplastic disease, F=hip                  | M90.7F      |

## A2 Definition of Primary Endpoints: NVAf Indication

| <b>A2.1 Definition of Endpoints: ICD-10 Codes for On-Label Use</b> |   |     |
|--|---|-----|
| Atrial Fibrillation and flutter (no subcodes)                      | Atrial Fibrillation and flutter (no subcodes) | I48 |

| <b>A2.2 Definition of Endpoints: ICD-10 for the Exclusions for On-Label NVAf</b> |  |             |
|--|--|-------------|
| <b>Category</b>  | <b>Specific Description</b>                  | <b>Code</b> |
| Rheumatic mitral valve diseases (I05 excluding I05.1)                            | Rheumatic mitral stenosis                    | I05.0       |
|  | Rheumatic mitral stenosis with insufficiency | I05.2       |
|  | Other rheumatic mitral valve diseases        | I05.8       |
|  | Rheumatic mitral valve disease, unspecified  | I05.9       |

| <b>A2.2 Definition of Endpoints: ICD-10 for the Exclusions for On-Label NVAf</b>                               |   |             |
|--|---|-------------|
| <b>Category</b>  | <b>Specific Description</b>   | <b>Code</b> |
| Multiple valve diseases (I08 excluding I08.2)  | Rheumatic disorders of both mitral and aortic valves                                  | I08.0       |
|  | Rheumatic disorders of both mitral and tricuspid valves                               | I08.1       |
|  | Combined rheumatic disorders of mitral, aortic and tricuspid valves                   | I08.3       |
|  | Other rheumatic multiple valve diseases   | I08.8       |
|  | Rheumatic multiple valve disease, unspecified   | I08.9       |
| Other rheumatic heart diseases (I09 excluding I09.0 and I09.2)   | Rheumatic diseases of endocardium, valve unspecified                                  | I09.1       |
|  | Other specified rheumatic heart disease   | I09.8       |
|  | Rheumatic heart disease, unspecified  | I09.9       |
| Non-rheumatic mitral valve disorders (I34 excluding I34.0 and I34.1)   | Non-rheumatic mitral (valve) stenosis   | I34.2       |
|  | Other non-rheumatic mitral valve disorders  | I34.8       |
|  | Non-rheumatic mitral valve disorder, unspecified                                      | I34.9       |
| Endocarditis, valve unspecified  | Endocarditis, valve unspecified   | I38         |
| Endocarditis and heart valve disorders in diseases classified elsewhere (I39 excluding I39.1, I39.2 and I39.3) | Mitral valve disorders in diseases classified elsewhere                               | I39.0       |
|  | Multiple valve disorders in diseases classified elsewhere                             | I39.4       |
|  | Endocarditis, valve unspecified, in diseases classified elsewhere                     | I39.8       |
| Prosthetic replacement of tricuspid valve  | Replacement of tricuspid valve using mechanical prosthesis                            | FGE 00      |
|  | Other prosthetic replacement of tricuspid valve                                       | FGE 96      |
| Repair of mitral valve for stenosis  | Other repair of mitral valve for stenosis   | FKA 96      |
| Prosthetic replacement of mitral valve   | Replacement of mitral valve using mechanical prosthesis                               | FKD 00      |
|  | Other replacement of mitral valve   | FKD 96      |
| Prosthetic replacement of pulmonary valve  | Replacement of pulmonary valve using mechanical prosthesis                            | FJF 00      |
|  | Other replacement of pulmonary valve  | FJF 96      |
| Prosthetic replacement of aortic valve   | Replacement of aortic valve using mechanical prosthesis                               | FMD 00      |
|  | Other prosthetic replacement of aortic valve  | FMD 96      |
| Mechanical complication of heart valve prosthesis  | Mechanical complication of heart valve prosthesis                                     | T82.0       |
|  | Breakdown (mechanical) of heart valve prosthesis                                      | T82.01      |
|  | Displacement of heart valve prosthesis  | T82.02      |
|  | Leakage of heart valve prosthesis   | T82.03      |
|  | Other mechanical complication of heart valve prosthesis                               | T82.09      |
| T82.5<br><br>Mechanical complication of other cardiac and vascular devices and implants                        | Breakdown (mechanical) of artificial heart  | T82.512     |
|  | Breakdown (mechanical) of other cardiac and vascular devices and implants             | T82.518     |
|  | Breakdown (mechanical) of unspecified cardiac and vascular devices and implants       | T82.519     |
|  | Displacement of other cardiac and vascular devices and implants                       | T82.52      |
|  | unspecified complication of cardiac and vascular prosthetic device, implant and graft | T82.520     |
|  | Displacement of artificial heart  | T82.522     |
|  | Displacement of other cardiac and vascular devices and implants                       | T82.528     |
|  | Displacement of unspecified cardiac and vascular devices and implants                 | T82.529     |
|  | Leakage of other cardiac and vascular devices and implants                            | T82.53      |
|  | Leakage of artificial heart   | T82.532     |
|  | Leakage of other cardiac and vascular devices and implants                            | T82.538     |

| <b>A2.2 Definition of Endpoints: ICD-10 for the Exclusions for On-Label NVAf</b>                    |  |             |
|---|--|-------------|
| <b>Category</b>   | <b>Specific Description</b>  | <b>Code</b> |
|   | Leakage of unspecified cardiac and vascular devices and implants                                   | T82.539     |
|   | Other mechanical complication of other cardiac and vascular devices and implants                   | T82.59      |
|   | Other mechanical complication of artificial heart  | T82.592     |
|   | Other mechanical complication of other cardiac and vascular devices and implants                   | T82.598     |
|   | Other mechanical complication of unspecified cardiac and vascular devices and implants             | T82.599     |
| Infection and inflammatory reaction due to cardiac valve prosthesis                                 | Infection and inflammatory reaction due to cardiac valve prosthesis                                | T82.6       |
| Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts  | Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts | T82.7       |
| T82.8 Other specified complications of cardiac and vascular prosthetic devices, implants and grafts | Other specified complications of cardiac and vascular prosthetic devices, implants and grafts      | T82.8       |
|   | Embolism of cardiac and vascular prosthetic devices, implants and grafts                           | T82.81      |
|   | Embolism of cardiac prosthetic devices, implants and grafts  | T82.817     |
|   | Fibrosis of cardiac and vascular prosthetic devices, implants and grafts                           | T82.82      |
|   | Fibrosis of cardiac prosthetic devices, implants and grafts  | T82.827     |
|   | Haemorrhage of cardiac and vascular prosthetic devices, implants and grafts                        | T82.83      |
|   | Haemorrhage of cardiac prosthetic devices, implants and grafts                                     | T82.837     |
|   | Pain from cardiac and vascular prosthetic devices, implants and grafts                             | T82.84      |
|   | Pain from cardiac prosthetic devices, implants and grafts  | T82.847     |
|   | Stenosis of cardiac and vascular prosthetic devices, implants and grafts                           | T82.85      |
|   | Stenosis of cardiac prosthetic devices, implants and grafts  | T82.857     |
|   | Thrombosis of cardiac and vascular prosthetic devices, implants and grafts                         | T82.86      |
|   | Thrombosis of cardiac prosthetic devices, implants and grafts                                      | T82.867     |
|   | Other specified complication of cardiac and vascular prosthetic devices, implants and grafts       | T82.89      |
|   | Other specified complication of cardiac prosthetic devices, implants and grafts                    | T82.897     |
|   | Unspecified complication of cardiac and vascular prosthetic device, implant and graft              | T82.9       |
| Presence of cardiac and vascular implants and grafts  | Presence of prosthetic heart valve   | Z95.2       |
|   | Presence of other heart-valve replacement  | Z95.4       |
|   | Presence of other cardiac and vascular implants and grafts   | Z95.8       |
|   | Presence of other cardiac implants and grafts  | Z95.81      |
|   | Presence of heart assist device  | Z95.811     |
|   | Presence of fully implantable artificial heart   | Z95.812     |
|   | Presence of other cardiac implants and grafts  | Z95.818     |
|   | Presence of cardiac and vascular implant and graft, unspecified                                    | Z95.9       |
| Congenital malformations of   | Congenital mitral stenosis   | Q23.2       |



| <b>A2.2 Definition of Endpoints: ICD-10 for the Exclusions for On-Label NVAf</b> |  |             |
|--|--|-------------|
| <b>Category</b>  | <b>Specific Description</b>                                      | <b>Code</b> |
| aortic and mitral valves   | Other congenital malformations of aortic and mitral valves       | Q23.8       |
|  | Congenital malformation of aortic and mitral valves, unspecified | Q23.9       |
| Other congenital malformations of heart  | Other specified congenital malformations of heart                | Q24.8       |
|  | Congenital malformation of heart, unspecified                    | Q24.9       |

### A3 Definition of Primary Endpoints: DVT/PE Indication

| <b>A3.1 Definition of Primary Endpoints: ICD-10 Codes for On-Label DVT/PE</b> |   |             |
|---|---|-------------|
| <b>Category</b>   | <b>Specific Description</b>   | <b>Code</b> |
| Phlebitis and thrombophlebitis  | Phlebitis and thrombophlebitis of femoral vein                            | I80.1       |
|   | Phlebitis and thrombophlebitis of other deep vessels of lower extremities | I80.2       |
|   | Phlebitis and thrombophlebitis of lower extremities, unspecified          | I80.3       |
| Deep Venous Thrombosis  | Embolism and thrombosis of vena cava                                      | I82.2       |
|   | Embolism and thrombosis of other specified veins                          | I82.8       |
|   | Embolism and thrombosis of unspecified vein                               | I82.9       |
| Pulmonary embolism  | Pulmonary embolism with mention of acute cor pulmonale                    | I26.0       |
|   | Pulmonary embolism without mention of acute cor pulmonale                 | I26.9       |

| <b>A3.2 Definition of Primary Endpoints: ICD-10 Codes for Off-Label DVT/PE</b> |  |             |
|--|--|-------------|
| <b>Category</b>  | <b>Specific Description</b>  | <b>Code</b> |
| Other cerebrovascular disease  | Nonpyogenic thrombosis of intracranial venous system                       | I67.6       |
|  | Cerebral arteritis, not elsewhere classified                               | I67.7       |
| Phlebitis and thrombophlebitis   | Phlebitis and thrombophlebitis of superficial vessels of lower extremities | I80.0       |
|  | Phlebitis and thrombophlebitis of other sites                              | I80.8       |
|  | Phlebitis and thrombophlebitis of unspecified site                         | I80.9       |
| Portal vein thrombosis   | Portal vein thrombosis   | I81         |
| Other venous embolism and thrombosis   | Budd-Chiari syndrome   | I82.0       |
|  | Thrombophlebitis migrans   | I82.1       |
|  | Embolism and thrombosis of renal vein                                      | I82.3       |
|  | Cerebral venous thrombosis in pregnancy                                    | O22.5       |
|  | Perianal venous thrombosis   | K64.5       |
|  | Thrombosis of superficial vein of penis                                    | N48.81      |
|  | Obstetric thromboembolism  | O882        |
|  | Personal history of pulmonary embolism                                     | Z867A       |
|  | Personal history of deep venous thrombosis                                 | Z867B       |

### A4 Definition of Primary Endpoints: Off-Label Indication

| <b>A4.1 Off-Label Surgeries</b> |                     |
|---------------------------------|---------------------|
| <b>Surgery Category</b>         | <b>NCSP Chapter</b> |
| Nervous system                  | A                   |
| Endocrine system                | B                   |



| <b>A4.1 Off-Label Surgeries</b>  |                     |
|--|---------------------|
| <b>Surgery Category</b>  | <b>NCSP Chapter</b> |
| Eye and adjacent structures  | C                   |
| Ear, nose and larynx   | D                   |
| Teeth, jaws, mouth and pharynx   | E                   |
| Heart and major thoracic vessels                                       | F                   |
| Chest wall, pleura, mediastinum, diaphragm, trachea, bronchus and lung | G                   |
| Mammary gland  | H                   |
| Digestive system and spleen  | J                   |
| Urinary system, male genital organs and retroperitoneal space          | K                   |
| Female genital organs  | L                   |
| Obstetric procedures   | M                   |
| Musculoskeletal system   | N                   |
| Peripheral vessels and lymphatic system                                | P                   |
| Skin   | Q                   |
| Minor surgical procedures  | T                   |
| Transluminal endoscopy   | U                   |
| Investigative procedures connected with surgery                        | X                   |

| <b>A4.2 Definition of Primary Endpoints: ICD-10 Codes for Other Diagnoses</b> |   |             |
|---|---|-------------|
| <b>Category</b>   | <b>Specific Description</b>   | <b>Code</b> |
| Angina pectoris   | Unstable angina   | I20.0       |
|   | Angina pectoris with documented spasm   | I20.1       |
|   | Other forms of angina pectoris  | I20.8       |
|   | Angina pectoris, unspecified  | I20.9       |
| Acute myocardial infarction   | Acute transmural myocardial infarction of anterior wall   | I21.0       |
|   | Acute transmural myocardial infarction of inferior wall   | I21.1       |
|   | Acute transmural myocardial infarction of other sites   | I21.2       |
|   | Acute transmural myocardial infarction of unspecified site  | I21.3       |
|   | Acute subendocardial myocardial infarction  | I21.4       |
|   | Acute myocardial infarction, unspecified  | I21.9       |
| Subsequent myocardial infarction  | Subsequent myocardial infarction of anterior wall   | I22.0       |
|   | Subsequent myocardial infarction of inferior wall   | I22.1       |
|   | Subsequent myocardial infarction of other sites   | I22.8       |
|   | Subsequent myocardial infarction of unspecified site  | I22.9       |
| Certain current complications following acute myocardial infarction           | Haemopericardium as current complication following acute myocardial infarction (MI)                                     | I23.0       |
|   | Atrial septal defect as current complication following acute MI   | I23.1       |
|   | Ventricular septal defect as current complication following acute MI  | I23.2       |
|   | Rupture of cardiac wall without haemopericardium as current complication following acute MI                             | I23.3       |
|   | Rupture of chordae tendineae as current complication following acute myocardial infarction                              | I23.4       |
|   | Rupture of papillary muscle as current complication following acute myocardial infarction                               | I23.5       |
|   | Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction | I23.6       |
|   | Other current complications following acute myocardial infarction   | I23.8       |
| Other acute   | Coronary thrombosis not resulting in myocardial infarction  | I24.0       |

| <b>A4.2 Definition of Primary Endpoints: ICD-10 Codes for Other Diagnoses</b> |  |             |
|---|--|-------------|
| <b>Category</b>   | <b>Specific Description</b>  | <b>Code</b> |
| ischaemic heart diseases  | Dressler's syndrome  | I24.1       |
|   | Other forms of acute ischaemic heart disease   | I24.8       |
|   | Acute ischaemic heart disease, unspecified   | I24.9       |
| Chronic ischaemic heart disease   | Atherosclerotic cardiovascular disease, so described                                 | I25.0       |
|   | Atherosclerotic heart disease  | I25.1       |
|   | Old myocardial infarction  | I25.2       |
|   | Aneurysm of heart  | I25.3       |
|   | Coronary artery aneurysm   | I25.4       |
|   | Ischaemic cardiomyopathy   | I25.5       |
|   | Silent myocardial ischaemia  | I25.6       |
|   | Other forms of chronic ischaemic heart disease                                       | I25.8       |
|   | Chronic ischaemic heart disease, unspecified   | I25.9       |
| Cerebral infarction   | Cerebral infarction due to thrombosis of precerebral arteries                        | I63.0       |
|   | Cerebral infarction due to embolism of precerebral arteries                          | I63.1       |
|   | Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries | I63.2       |
|   | Cerebral infarction due to thrombosis of cerebral arteries                           | I63.3       |
|   | Cerebral infarction due to embolism of cerebral arteries                             | I63.4       |
|   | Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries    | I63.5       |
|   | Cerebral infarction due to cerebral venous thrombosis, nonpyogenic                   | I63.6       |
|   | Other cerebral infarction  | I63.8       |
|   | Cerebral infarction, unspecified   | I63.9       |
| Stroke, not specified as haemorrhage or infarction                            | <i>No subclass</i>   | I64         |
| Arterial embolism and thrombosis  | Embolism and thrombosis of abdominal aorta   | I74.0       |
|   | Embolism and thrombosis of other and unspecified parts of aorta                      | I74.1       |
|   | Embolism and thrombosis of arteries of upper extremities                             | I74.2       |
|   | Embolism and thrombosis of arteries of lower extremities                             | I74.3       |
|   | Embolism and thrombosis of arteries of extremities, unspecified                      | I74.4       |
|   | Embolism and thrombosis of iliac artery  | I74.5       |
|   | Embolism and thrombosis of other arteries  | I74.8       |
|   | Embolism and thrombosis of unspecified artery  | I74.9       |

| <b>A5 Definition of Covariates: ATC Codes for Co-Prescribed Medications</b> |                             |             |
|---|-----------------------------|-------------|
| <b>Category</b>   | <b>Specific Description</b> | <b>Code</b> |
| Vitamin K antagonists   | Dicoumarol                  | B01AA01     |
|   | Phenindione                 | B01AA02     |
|   | Warfarin                    | B01AA03     |
|   | Phenprocoumon               | B01AA04     |
|   | Acenocoumarol               | B01AA07     |
|   | Ethyl biscoumacetate        | B01AA08     |
|   | Clorindione                 | B01AA09     |
|   | Diphenadione                | B01AA10     |
|   | Tioclomarol                 | B01AA11     |
|   | Fluindione                  | B01AA12     |
|   |                             |             |
| Heparin group   | Heparin                     | B01AB01     |
|   | Antithrombin III            | B01AB02     |
|   | Dalteparin                  | B01AB04     |

|   |                                       |         |
|---|---------------------------------------|---------|
|   | Enoxaparin                            | B01AB05 |
|   | Nadroparin                            | B01AB06 |
|   | Parnaparin                            | B01AB07 |
|   | Reviparin                             | B01AB08 |
|   | Danaparoid                            | B01AB09 |
|   | Tinzaparin                            | B01AB10 |
|   | Sulodexide                            | B01AB11 |
|   | Bemiparin                             | B01AB12 |
|   | Heparin, combinations                 | B01AB51 |
|   |                                       |         |
| Platelet aggregation inhibitors excluding heparin | Ditazole                              | B01AC01 |
|   | Cloricromen                           | B01AC02 |
|   | Picotamide                            | B01AC03 |
|   | Clopidogrel                           | B01AC04 |
|   | Ticlopidine                           | B01AC05 |
|   | Acetylsalicylic acid                  | B01AC06 |
|   | Dipyridamole                          | B01AC07 |
|   | Carbasalate calcium                   | B01AC08 |
|   | Epoprostenol                          | B01AC09 |
|   | Indobufen                             | B01AC10 |
|   | Iloprost                              | B01AC11 |
|   | Abciximab                             | B01AC13 |
|   | Aloxiprin                             | B01AC15 |
|   | Eptifibatide                          | B01AC16 |
|   | Tirofiban                             | B01AC17 |
|   | Triflusal                             | B01AC18 |
|   | Beraprost                             | B01AC19 |
|   | Treprostinil                          | B01AC21 |
|   | Prasugrel                             | B01AC22 |
|   | Cilostazol                            | B01AC23 |
|   | Ticagrelor                            | B01AC24 |
|   | Combinations                          | B01AC30 |
|   | Acetylsalicylic acid and esomeprazole | B01AC56 |
| Enzymes   | Streptokinase                         | B01AD01 |
|   | Alteplase                             | B01AD02 |
|   | Anistreplase                          | B01AD03 |
|   | Urokinase                             | B01AD04 |
|   | Fibrinolysin                          | B01AD05 |
|   | Brinase                               | B01AD06 |
|   | Retepase                              | B01AD07 |
|   | Saruplase                             | B01AD08 |
|   | Ancrod                                | B01AD09 |
|   | Drotrecogin alfa (activated)          | B01AD10 |
|   | Tenecteplase                          | B01AD11 |
|   | Protein C                             | B01AD12 |
| Direct thrombin inhibitors                        | Desirudin                             | B01AE01 |
|   | Lepirudin                             | B01AE02 |
|   | Argatroban                            | B01AE03 |
|   | Melagatran                            | B01AE04 |
|   | Ximelagatran                          | B01AE05 |
|   | Bivalirudin                           | B01AE06 |
|   | Dabigatran etexilate                  | B01AE07 |
| Other antithrombotic agents                       | Defibrotide                           | B01AX01 |

|   |   |         |
|---|---|---------|
|   | Dermatan sulfate                        | B01AX04 |
|   | Fondaparinux                            | B01AX05 |
|   | Rivaroxaban                             | B01AX06 |
| Anti-inflammatory and antirheumatic products, nonsteroids | All products under M01A                 | M01A    |
| CYP3A4 and P-gp inhibitors                                | Antimycotics for systemic use           | J02A    |
|   | Protease inhibitors                     | J05AE   |
|   | Selective serotonin reuptake inhibitors | N06AB   |
|   | Verapamil                               | C08DA   |
|   | Quinidine                               | C01BA   |
|   | Talinolol                               | C07AB   |
|   | Diltiazem                               | C08DB   |
|   | Atorvastatin                            | C10AA   |
|   | Erythromycine + Clarithromycine         | J01FA   |
|   | Cyclosporin                             | L04AA   |
| CYP3A4 and P-gp inducers                                  | Carbamazepine                           | N03AF   |
|   | Troglitazone                            | A10BG   |
|   | Dexamethasone                           | H02AB   |
|   | Sulfadimidine                           | J01EB   |
|   | Troleandomycin                          | J01FA   |
|   | Rifampicin + Rifabutin                  | J04AB   |
|   | Nevirapine                              | J05AG   |
|   | Sulfinpyrazone                          | M04AB   |
|   | Phenobarbital + Primidone               | N03AA   |
|   | Phenytoin                               | N03AB   |
|   | Ethosuximide                            | N03AD   |
|   | Glutethimide                            | N05CE   |
| Commonly prescribed drugs                                 | Proton pump inhibitors                  | A02BC   |
|   | Osmotically acting laxatives            | A06AD   |
|   | Sulfonamides, plain                     | C03CA   |
|   | Dihydropyridine derivatives             | C08CA   |
|   | ACE inhibitors, plain                   | C09AA   |
|   | Angiotensin II antagonists, plain       | C09CA   |
|   | Natural opium alkaloids                 | N02AA   |
|   | Anilides                                | N02BE   |
|   | Benzodiazepine related drugs            | N05CF   |

| A6.1 Definition of Comorbidities (ICD 10 codes) |  |      |
|---|--|------|
| Category  | Specific Description                             | Code |
| Renal disease                                   | Acute kidney failure                             | N17  |
|   | Chronic kidney disease                           | N18  |
|   | Unspecified kidney failure                       | N19  |
| Liver disorder                                  | Alcoholic liver disease                          | K70  |
|   | Toxic liver disease                              | K71  |
|   | Hepatic failure, not elsewhere classified        | K72  |
|   | Chronic hepatitis, not elsewhere classified      | K73  |
|   | Fibrosis and cirrhosis of liver                  | K74  |
|   | Other inflammatory liver diseases                | K75  |
|   | Other diseases of liver                          | K76  |
|   | Liver disorders in diseases classified elsewhere | K77  |

| <b>A6.1 Definition of Comorbidities (ICD 10 codes)</b>     |   |             |
|--|---|-------------|
| <b>Category</b>  | <b>Specific Description</b>   | <b>Code</b> |
|  | Hepatomegaly, not elsewhere classified                                | R16.0       |
|  | Hepatomegaly with splenomegaly, not elsewhere classified              | R16.2       |
| Coagulation defects  | Disseminated intravascular coagulation [defibrination syndrome]       | D65         |
|  | Hereditary factor VIII deficiency                                     | D66         |
|  | Hereditary factor IX deficiency                                       | D67         |
|  | Other coagulation defects   | D68         |
|  |   |             |
| Intracranial haemorrhage                                   | Nontraumatic subarachnoid hemorrhage                                  | I60         |
|  | Nontraumatic intracerebral hemorrhage                                 | I61         |
|  | Other and unspecified nontraumatic intracranial hemorrhage            | I62         |
| Gastric, duodenal ulcer and peptic ulcer, site unspecified | Gastric ulcer   | K25         |
|  | Duodenal ulcer  | K26         |
|  | Peptic ulcer, site unspecified  | K27         |
| Acute and subacute bacterial endocarditis                  | Acute and subacute endocarditis                                       | I33         |
|  | Acute and subacute infective endocarditis                             | I38.9       |
|  | Acute and subacute endocarditis, unspecified                          | I39.8       |
| Esophageal varices   | Esophageal varices  | I85         |
|  | Oesophageal varices without bleeding in diseases classified elsewhere | I98.2       |
|  | Oesophageal varices with bleeding in diseases classified elsewhere    | I98.3       |
| Thrombocytopenia   | Immune thrombocytopenic purpura                                       | D69.3       |
|  | Thrombocytopenia, unspecified   | D69.6       |
|  | Wiskott-Aldrich syndrome  | D82.0       |

| <b>A6.2 Definition of Comorbidities (NOMSECO Codes)</b>   |  |             |
|---|--|-------------|
| <b>Category</b>   | <b>Specific Description</b>  | <b>Code</b> |
| Diagnostic intracranial procedures; Therapeutic implantation of stimulation or injection devices, see: AAW; Stereotactic procedures, see: AAG; Removal of intracranial electrodes, see: AEA | Exploratory craniotomy   | AAA 00      |
|   | Biopsy through craniotomyStereotactic intracranial biopsy, see: AAG 00 | AAA 10      |
|   | Insertion of intraventricular pressure monitoring device               | AAA 20      |
|   | Insertion of epidural pressure monitoring device                       | AAA 25      |
|   | Insertion of intracerebral pressure monitoring device                  | AAA 27      |
|   | Insertion of epidural electrodes                                       | AAA 30      |
|   | Insertion of subdural electrodes                                       | AAA 35      |
|   | Insertion of intracerebral electrodes                                  | AAA 40      |
|   | Intracranial endoscopy   | AAA 50      |
|   | Other diagnostic intracranial procedures                               | AAA 99      |
| Excision and destruction of intracranial lesion; Includes: Transcranial operation on pituitary gland. Operations by cranial base approach, see: AAE   | Extirpation of intracranial lesion                                     | AAB 00      |
|   | Partial excision of intracranial lesion                                | AAB 10      |
|   | Destruction of intracranial lesion                                     | AAB 20      |
|   | Evacuation of spontaneous intracranial haematoma                       | AAB 30      |
|   | Other excision or destruction of intracranial lesion                   | AAB 99      |

| <b>A6.2 Definition of Comorbidities (NOMSECO Codes)</b>   |  |             |
|---|--|-------------|
| <b>Category</b>   | <b>Specific Description</b>  | <b>Code</b> |
| Operations for intracranial aneurysm and other vascular lesions Endovascular procedures, see: AAL | Ligature of intracranial aneurysm Using clips and similar devices                                      | AAC 00      |
|   | Ligature of feeding artery of intracranial aneurysm  | AAC 05      |
|   | Reinforcement of intracranial aneurysm wall  | AAC 10      |
|   | Trapping of intracranial aneurysm  | AAC 15      |
|   | Anastomosis to intracranial vessel   | AAC 20      |
|   | Intracranial occlusion of vascular fistula   | AAC 30      |
|   | Extirpation of intracranial arterio-venous malformation  | AAC 40      |
|   | Other operation for aneurysm or other intracranial vascular lesion                                     | AAC 99      |
| Operations for head injuries Partial excision of skull cap, see: AAK 80                           | Evacuation of epidural haematoma   | AAD 00      |
|   | Evacuation of acute subdural haematoma   | AAD 05      |
|   | Evacuation of chronic subdural haematoma   | AAD 10      |
|   | Evacuation of traumatic intracerebral haematoma  | AAD 15      |
|   | Revision of penetrating or perforating injury of skull; Includes: Removal of intracranial foreign body | AAD 30      |
|   | Revision of fracture of skull; Includes: Of depressed fracture   | AAD 40      |
|   | Other operation for head injury  | AAD 99      |
| Operations by cranial base approach; Includes: Operations on pituitary gland                      | Transsphenoidal exploration  | AAE 00      |
|   | Transsphenoidal total or partial excision of intracranial lesion                                       | AAE 10      |
|   | Transoral total or partial excision of intracranial lesion   | AAE 20      |
|   | Transcervical total or partial excision of intracranial lesion   | AAE 25      |
|   | Translabirinthine total or partial excision of intracranial lesion                                     | AAE 30      |
|   | Transtemporal total or partial excision of intracranial lesion   | AAE 40      |
|   | Zygomaticotemporal total or partial excision of intracranial lesion                                    | AAE 50      |
|   | Other operation by cranial base approach   | AAE 99      |
| Shunt operations on ventricles of brain and intracranial cysts                                    | Ventriculostomy; External drainage of ventricle of brain   | AAF 00      |
|   | Ventriculoperitoneal shunt   | AAF 05      |
|   | Lumboperitoneal shunt  | AAF 10      |
|   | Ventriculoatrial shunt   | AAF 15      |
|   | Revision of shunt of ventricle of brain; Intraabdominal revision, see: JAL 50-51                       | AAF 20      |
|   | Removal of shunt of ventricle of brain   | AAF 25      |
|   | Implantation of intraventricular injection device  | AAF 30      |
|   | Implantation of reservoir for intraventricular therapy   | AAF 35      |
|   | Shunt of intracranial cyst to peritoneum   | AAF 40      |
|   | Fenestration of intracranial cyst  | AAF 45      |
|   | Other shunt operation on ventricle of brain or intracranial cyst                                       | AAF 99      |
| Stereotactic intracranial operations  | Stereotactic intracranial biopsy   | AAG 00      |
|   | Stereotactic intracranial destruction of nucleus or nerve  | AAG 10      |

| <b>A6.2 Definition of Comorbidities (NOMSECO Codes)</b>  |   |             |
|--|---|-------------|
| <b>Category</b>  | <b>Specific Description</b>   | <b>Code</b> |
|  | tract   |             |
|  | Stereotactic intracranial implantation of electrodes; Includes: Of intracerebral stimulation device (deep brain stimulator); Replacement of impulse generator and removal of device, see: AEA | AAG 20      |
|  | Stereotactic intracranial implantation of radioactive agent   | AAG 30      |
|  | Stereotactic intracranial implantation of fetal tissue  | AAG 40      |
|  | Stereotactic intracranial radiotherapy  | AAG 50      |
|  | Other stereotactic intracranial operation   | AAG 99      |
| Operations on cranial nerves Implantation of intracranial stimulation or injection device, see: AAW 01-02; Reconstructive operations for facial palsy, see AAP | Rhizotomy of cranial nerve  | AAH 10      |
|  | Decompression of cranial nerve  | AAH 20      |
|  | Thermal destruction of cranial nerve  | AAH 30      |
|  | Injection into cranial nerve  | AAH 40      |
|  | Cranial nerve anastomosis   | AAH 50      |
|  | Microvascular decompression of cranial nerve  | AAH 60      |
|  | Other operation on cranial nerve  | AAH 99      |
| Operations for epilepsy; Implantation of vagus nerve stimulating device, see: ADB 00   | Hemispherectomy   | AAJ 00      |
|  | Lobectomy for epilepsy  | AAJ 10      |
|  | Hippocampectomy   | AAJ 15      |
|  | Excision of epileptic focus   | AAJ 20      |
|  | Transcision of nerve tracts for epilepsy  | AAJ 25      |
|  | Callosotomy for epilepsy  | AAJ 30      |
|  | Hemidecortication for epilepsy  | AAJ 35      |
|  | Other operation for epilepsy  | AAJ 99      |
| Operations on skull and dura; For injury, see: AAD 40; Additional code for specification of grafts and flaps, see: ZZ  | Cranioplasty  | AAK 00      |
|  | Repair of dura  | AAK 10      |
|  | Operations for craniostomosis   | AAK 20      |
|  | Craniofacial reconstruction in congenital malformations   | AAK 30      |
|  | Closure of cerebrospinal fluid fistula  | AAK 40      |
|  | Biopsy of skull   | AAK 70      |
|  | Excision of lesion of skull   | AAK 75      |
|  | Partial excision of skull cap; For relief of acute cerebral edema   | AAK 80      |
|  | Replantation of previously excised part of skull cap  | AAK 85      |
|  | Other operation on skull or dura  | AAK 99      |
| Intracranial endovascular procedures; Open operations for intracranial aneurysms and vascular malformations, see: AAC  | Endovascular occlusion of intracranial aneurysm   | AAL 00      |
|  | Intracranial endovascular thrombolysis  | AAL 10      |
|  | Endovascular occlusion of intracranial arterio-venous malformation  | AAL 20      |
|  | Endovascular occlusion of intracranial fistula  | AAL 30      |
|  | Endovascular occlusion of feeding arteries of intracranial tumour   | AAL 40      |
|  | Other intracranial endovascular procedure   | AAL 99      |
| Operations for intracranial infection;   | Puncture and evacuation of intracerebral abscess  | AAM 00      |



| <b>A6.2 Definition of Comorbidities (NOMSECO Codes)</b>  |   |             |
|--|---|-------------|
| <b>Category</b>  | <b>Specific Description</b>   | <b>Code</b> |
| Drainage and reservoir operations on ventricles or intracranial cysts, see: AAF  | Excision of intracerebral abscess   | AAM 10      |
|  | Evacuation of epidural or subdural empyema  | AAM 30      |
|  | Other operation for intracranial infection  | AAM 99      |
| Operations for intracranial congenital malformations   | Excision and repair of encephalocele  | AAN 00      |
|  | Other operation for intracranial congenital malformation  | AAN 99      |
| Reconstructive operations for facial palsy; Operation for ptosis of eye-brow only, see: CBJ 50   | Lacal transposition of muscle for facial palsy  | AAP 00      |
|  | Cross-facial transplantation of nerve for facial palsy  | AAP 10      |
|  | Microvascular transposition of muscle for facial palsy  | AAP 20      |
|  | Other reconstructive operation for facial palsy   | AAP 99      |
| Removal of implants and external fixation devices from skull   |   | AAU         |
| Removal of implant or external fixation device from skull; From teeth, mandible and maxilla, see: EBU-EHU                                |   | AAU 00      |
| Other operations on skull and intracranial structures; Replacement and removal of intracranial stimulation or injection device, see: AEA | Implantation of intracranial stimulation device   | AAW 01      |
|  | Implantation of intracranial injection device   | AAW 02      |
|  | Other operation on skull or intracranial structure  | AAW 99      |
| Spinal cord and nerve roots; Additional code for extraspinal procedures on nerve roots by laparoscopic approach, see: ZXC 90             |   | AB          |
| Diagnostic operations on spinal cord and nerve roots   | Exploratory laminectomy   | ABA 00      |
|  | Biopsy of lesion of spinal canal  | ABA 10      |
|  | Intrathecal endoscopy   | ABA 20      |
|  | Epiduroscopy  | ABA 30      |
|  | Other diagnostic operation on spinal cord or nerve root   | ABA 99      |
| Operations for lesions of spinal cord and nerve roots; Additional code for tissue destructive physical or chemical agent, see: ZXC       | Excision of lesion of spinal canal; Includes: Removal of foreign body   | ABB 00      |
|  | Excision of lesion of nerve root; Includes: Total or partial excision of nerve root   | ABB 02      |
|  | Desctruction of lesion of nerve root  | ABB 04      |
|  | Percutaneous destruction of lesion of nerve root; Additional code for imaging technique, see: ZXM; Additional code for laparoscopic access, see: ZXC 90 | ABB 06      |
|  | Resection of lesion of spinal canal   | ABB 10      |
|  | Drainage of intra- or extramedullary cyst of spinal canal   | ABB 20      |
|  | Destruction of lesion of spinal canal   | ABB 30      |
|  | Evacuation of spontaneous haematoma of spinal canal   | ABB 40      |
|  | Other operation for lesion of spinal canal  | ABB 99      |
| Decompression of spinal cord and nerve roots; Excision of bone, see: NAK, NAR. Other operations on soft tissue, see: NAM                 | Percutaneous endoscopic discectomy for cervical intervertebral disc displacement  | ABC 01      |
|  | Percutaneous endoscopic discectomy for thoracic intervertebral disc displacement  | ABC 04      |
|  | Percutaneous endoscopic discectomy for lumbar intervertebral disc displacement  | ABC 07      |
|  | Microsurgical excision of cervical intervertebral disc displacement   | ABC 10      |
|  | Microsurgical excision of thoracic intervertebral disc displacement   | ABC 13      |



| <b>A6.2 Definition of Comorbidities (NOMSECO Codes)</b>  |  |             |
|--|--|-------------|
| <b>Category</b>  | <b>Specific Description</b>  | <b>Code</b> |
|  | placement  |             |
|  | Microsurgical excision of lumbar intervertebral disc displacement  | ABC 16      |
|  | Open discectomy of cervical spine  | ABC 20      |
|  | Anterior decompression of cervical spine with insertion of interbody fixating implant;"Cage" operation without intended osseous fusion. Interbody fusion, see: NAG | ABC 21      |
|  | Open discectomy of thoracic spine  | ABC 23      |
|  | Open discectomy of lumbar spine  | ABC 26      |
|  | Insertion of expanding implant between spinous processes; As alternative to laminectomy in spinal stenosis   | ABC 28      |
|  | Decompression of cervical nerve roots  | ABC 30      |
|  | Decompression of thoracic nerve roots  | ABC 33      |
|  | Decompression of lumbar nerve roots  | ABC 36      |
|  | Decompression of cauda equina  | ABC 40      |
|  | Decompression of cervical spinal canal and nerve roots   | ABC 50      |
|  | Decompression of thoracic spinal canal and nerve roots   | ABC 53      |
|  | Decompression of lumbar spinal canal and nerve roots   | ABC 56      |
|  | Decompression of cervical spinal cord  | ABC 60      |
|  | Decompression of thoracic spinal cord  | ABC 63      |
|  | Decompression of lumbar spinal cord  | ABC 66      |
|  | Other decompressive operation on spinal cord or nerve root   | ABC 99      |
| Operations on spinal cord and nerve roots for pain or impaired function; Replacement and removal of spinal stimulation or injection device, see: AEA | Open cordotomy   | ABD 10      |
|  | Percutaneous cordotomy; Additional code for technique, see: ZXC  | ABD 15      |
|  | Myelotomy  | ABD 20      |
|  | Implantation of spinal stimulation device  | ABD 30      |
|  | Implantation of spinal injection device  | ABD 40      |
|  | Transection of spinal nerve root for pain or impaired function; For lesion of dorsal root entry zone   | ABD 50      |
|  | Implantation of spinal nerve electrode; Includes percutaneous nerve evaluation PNE 1   | ABD 60      |
|  | Implantation of spinal nerve stimulation device; Includes percutaneous nerve evaluation PNE 2  | ABD 65      |
|  | Other operation on spinal cord or nerve for pain or impaired function  | ABD 99      |
| Operations for congenital malformations of spine   | Excision and repair of myelocoele or meningocele   | ABE 10      |
|  | Mobilisation of tethered cord or diastematomyelia  | ABE 20      |
|  | Excision of dermal sinus   | ABE 30      |
|  | Operation for hydromyelia  | ABE 40      |
|  | Occipitocervical decompression   | ABE 50      |
|  | Other operation for spinal malformation  | ABE 99      |
| Other operation on spinal cord or nerve root   |  | ABW 99      |

### APPENDIX 3: DATA SOURCE DETAILS

The national board of health and welfare maintain the registries. To obtain access to the data, an application is submitted to the national board of health and welfare, including permission from the Ethics Council at the Karolinska institute and a technical description used for extraction of data. Only a subset of these variables is needed to fulfil the aims of the protocol.

#### A1 The Prescribed Drug Register and the Patient Register

| Register                                  | Contents  |
|---|---|
| Swedish National Prescribed Drug Register | Information on all prescribed drugs in Sweden since 1 July 2005.  |
| Swedish National Patient Register         | Information on all completed public inpatient visits since 1987.<br><br>Information on visits with surgical intervention since 1997.<br><br>Data on ambulatory care visits since 2001.<br><br>Data on private health care providers since 2001. |

## A2 Contents of Prescribed Drug Register

Information available in PDR is listed below. Each record in PDR corresponds to one dispensing. Only a subset of these variables is needed to fulfil the aims of the protocol.

1. Pharmacy data
  - a. County
2. Patient data
  - a. personal registration number (YYYYMMDD-nnnn)
  - b. Sex (M/F)
  - c. Age
  - d. County, municipality
3. Prescriber data
  - a. Occupation
  - b. Education code
  - c. Residency code
4. Workplace data
  - a. County
  - b. Workplace code
  - c. Ownership
  - d. Form of care
  - e. Business focus
5. Prescription data
  - a. Date of dispensing
  - b. Date of prescription
  - c. Prescription type
  - d. Type of benefit
  - e. Issue category
  - f. Start package (Y/N)
  - g. Change allowed (Y/N)
  - h. Change code (generic/parallel import)
  - i. Product identity
  - j. Product type
  - k. Number of whole packages
  - l. Prescription text
6. Cost data
  - a. Price
  - b. Total cost
  - c. Patient cost
  - d. Country council cost

- e. Value-added tax (VAT)
- f. Additional cost (difference between prescribed and generic drug cost)
- 7. Product data
  - a. ATC code
  - b. Defined daily dose per package
  - c. Package size
  - d. Drug name
  - e. Brand name (e.g. Panadol)
  - f. Brand Identity
  - g. Prescription required (Y/N)
  - h. Medical products agency's registration number
  - i. Speciality identity
  - j. Nordic product number

Unfortunately no description of PDR is available in English from the National Board of Health and Welfare. The above list has been translated from Swedish.

### A3 Contents of Patients Register

Information available in NPR is listed below. Each record in NPR corresponds to one care visit. Only a subset of these variables is needed to fulfil the aims of the protocol.

1. Patient data
  - a. personal registration number (YYYYMMDD-nnnn)
  - b. Sex (M/F)
  - c. Age (in years at discharge)
  - d. place of residence (county, municipality)
2. Geographical data
  - a. county council
  - b. hospital/ clinic
  - c. Department
3. Administrative data
  - a. date of admission
  - b. date of discharge
  - c. length of stay
  - d. acute/planned admission (Y/N)
  - e. admitted from (hospital/special housing/home)
  - f. discharged to (hospital/special housing/home/deceased)
4. Medical data
  - a. main diagnosis (1 diagnosis per visit)
  - b. secondary diagnosis (0-21 diagnoses per visit)
  - c. external cause of injury and poisoning (0-7 causes per visit)
  - d. procedures (0-30 procedures per visit)

For further description of PAR, see

<http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish>.

#### **A4 Data That Will Be Used for Analysis From Prescribed Drug Register**

The following variables will be included in the application to the national board of health and welfare:

1. Patient data
  - a. Anonymous PIN (serial number)
  - b. Gender (M/F)
  - c. Age
  - d. County
2. Prescription data
  - a. Date of dispensing
  - b. Date of prescription
  - c. Number of whole packages
3. Product data
  - a. ATC code
  - b. Defined daily dose per package

## **A5 Data That Will Be Used for Analysis From Patient Register**

The following variables will be included in the application to the national board of health and welfare.

1. Patient data
  - a. Anonymous PIN (serial number)
  - b. Gender (M/F)
  - c. Age
  - d. County
2. Administrative data
  - a. Date of admission
  - b. Date of discharge
3. Medical data
  - a. Main diagnosis (1 diagnosis per visit)
  - b. Secondary diagnosis (0-21 diagnoses per visit)
  - c. Procedures (0-30 procedures per visit)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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**NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL**  
**POST-APPROVAL SAFETY STUDY (PASS) OF THE UTILIZATION PATTERN OF**  
**APIXABAN IN SWEDEN**

|                          |                                     |
|--------------------------|-------------------------------------|
| <b>Compound Number:</b>  | BMS-562247-01                       |
| <b>Compound Name:</b>    | Apixaban                            |
| <b>Study Number:</b>     | B0661017                            |
| <b>Version and Date:</b> | Protocol Amendment 3<br>19 May 2015 |

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## 1. INTRODUCTION

Off-label prescription occurs when a practitioner chooses to prescribe a drug in a manner that is inconsistent with the prescribing information approved by the governing regulatory authority. For medicinal products approved by the European Commission, the licensed indications are documented in the Summary of Product Characteristics (SmPC). Examples of off-label prescribing may include, but are not limited to the administration of the drug in doses, routes of administration or for reasons outside of labeled indications, or use in patients who do not meet age requirements, or other criteria as outlined in the label.

### 1.1. Background and Rationale

Apixaban is an orally administered anticoagulant that inhibits coagulation factor Xa. It is currently approved for:

- 1) Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery,
- 2) Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAf) with one or more risk factors,
- 3) Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

These indications, referred to as knee and hip replacement, NVAf, and treatment of DVT/PE, along with the date of approval are shown in Table 1. Use of apixaban outside these indications is a regulatory and safety concern.

To address this concern, the Sponsor proposes two studies describing the utilization of the product in two countries of the European Union (EU): a drug utilization study focusing on off-label use of apixaban in Sweden, as described herein, and a second study of apixaban drug utilization in the Netherlands, which is described in a separate protocol.

The approved SmPC in Sweden will be used as the single reference safety document for this study.

**Table 1. Indications and Dates of EMA Authorisations**

|    | Abbreviated Indication | Indication   | Date of EMA Authorisation |
|----|------------------------|--|---------------------------|
| 1. | THA/TKA                | Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery  | 18 May 2011               |
| 2. | NVAf                   | Prevention of stroke and SE in adult patients with NVAf, with one or more risk factors, such as prior stroke or TIA; age $\geq$ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class $\geq$ II). | 19 Nov 2012               |
| 3. | Treatment of DVT/PE    | Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.   | 28 July 2014              |

DVT: Deep vein thrombosis

NVAF: Non-valvular atrial fibrillation

NYHA: New York Heart Association

PE: Pulmonary Embolism

SE: Systemic Embolism

TIA: Transient Ischaemic Attack

VTE: Venous Thromboembolic Events

## 2. STUDY OBJECTIVES AND ENDPOINTS

The overall objective of this study is to describe the utilization pattern of apixaban in Sweden.

Specifically, the study seeks to:

1. **Estimate** the proportion of apixaban users in the outpatient settings who receive the drug for the approved indications at the time of the study,
2. **Describe** the characteristics of the patients who are prescribed apixaban for on-label and off-label indications.

## 3. STUDY DESIGN

This will be a descriptive study using retrospectively collected data from electronic health record databases. The study will describe the utilization pattern of apixaban during the first three years after launch for the VTE prevention indication in Sweden (01 Jan 2012 through 31 Dec 2014).

## 4. STUDY POPULATION

### 4.1. Inclusion Criteria

All patients identified in the database who have received an apixaban dispensation during the study period (01 Jan 2012 through 31 Dec 2014) will be included in this study.

### 4.2. Exclusion Criteria

There is no exclusion criterion. All patients identified in the database who have received at least one apixaban dispensation during the study period will be included.

## 5. STUDY TREATMENT AND DURATION

This is a descriptive study assessing the utilization pattern of apixaban in real-world outpatient settings. There is no study mandated dosing or duration requirement.

## 6. STUDY PROCEDURES

### 6.1. Data Source

Patients using apixaban will be identified from the National Prescribed Drug Register (PDR) which contains information on all drugs prescribed in Sweden that are dispensed to patients outside hospitals, including information about patients, drugs by ATC codes, dates, settings of the dispensing, and the specialty of the prescribing physician.

Relevant clinical history for the apixaban users identified from the PDR will be obtained from the National Patient Register (NPR). Patients in the PDR who have used apixaban will be linked to the NPR by a personal identification number (PIN) unique to all Swedish citizens. The NPR contains data from all hospital admissions in Sweden from 1987 to present. At each discharge, information is collected about the patient's demographics, primary and secondary diagnoses, procedure codes, hospitals and wards of admission, and dates of admission and discharge. Patients who have undergone knee or hip replacement surgery will be identified by applicable procedure codes and relevant ICD-10 diagnostic codes. The ICD-10 classification system was used from 1997 and onwards so data on diagnoses and procedures may extend back to 1997.

Since 2001, it is also possible to collect the same information from visits to hospital outpatient offices. Information about other diagnoses (eg, atrial fibrillation) in patients admitted to the hospitals without knee or hip replacement or visiting hospital outpatient offices will also be retrieved. The register is updated annually and data from the previous year is usually available for analyses in November each year after completion of data quality checks.

The databases cover the whole Swedish population of 9.3 million inhabitants. In 2008, about 14,500 knee and hip replacement surgeries and 4,600 hemi-hip arthroplasties were performed; 78% of the procedures were performed for primary arthrosis. The number of primary TKA was 10,600 in 2008. In addition, re-operations and revisions were also performed. Following an average hospital stay of 4 days, 25% of the patients are discharged to rehabilitation centers or nursing homes and 75% of the patients are discharged to home. The total number of hip arthroplasties increased by 10% from 2008 to 2010.

Inpatient and outpatient hospital data are available through the NPR, but the register does not include information from primary care visits. To address the missing primary care data, a sensitivity analysis will examine primary care records for apixaban users in Västra Götaland County (1.6 million, available from 2006). These regional data will supplement the nationwide data with greater detail for patients in Västra Götaland County, as well as provide an insight into the effect of missing primary care data. At this time, Västra Götaland is the only region in Sweden where primary care data are available. These records are based on patient contacts to primary care centers and collected in the health administrative databases.

The total number of persons diagnosed with atrial fibrillation and flutter in inpatient settings in 2010 was 25,672 (0.3%) according to national Swedish health statistics. The overall prevalence of atrial fibrillation has been studied in a geographically well-defined area of northern Sweden using data from a quality register of anticoagulant treatment and was found to be 2.5% in 2010 (Andersson, Londahl et al. 2012).<sup>1</sup>

## 6.2. Data Compilation Procedure

Patients who received a dispensation for apixaban (identified by ambulatory prescriptions by general practitioner or specialist physician) will be identified. The personal identification numbers of these patients will be used to link to their hospital records.

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Hip and knee replacement and other surgeries will be identified via appropriate procedure codes and ICD-10 codes from hospital discharge diagnoses. The following algorithm will be used to identify the patients who have undergone the elective hip or knee replacement surgery:

- First, procedure codes will be used to identify all patients who have undergone hip or knee replacement surgery within 30 days before apixaban prescription (including total and partial replacement procedures).
- Second, hospital discharge diagnoses (both primary and secondary) will be used to see if these included hip or knee fracture diagnostic codes.
  - If yes, then the hip or knee replacement surgery will be considered non-elective and apixaban prescription off-label.

If the primary or secondary discharge diagnoses do not include hip or knee fracture, then surgery will be considered elective and apixaban prescription on-label.

NVAF and treatment of DVT/PE will be identified by ICD-10 diagnosis codes in the main or secondary discharge diagnoses as well as in hospital outpatient visits and, where available, the primary care diagnoses.

### **6.3. Decision Rule for Defining On- and Off-label Use**

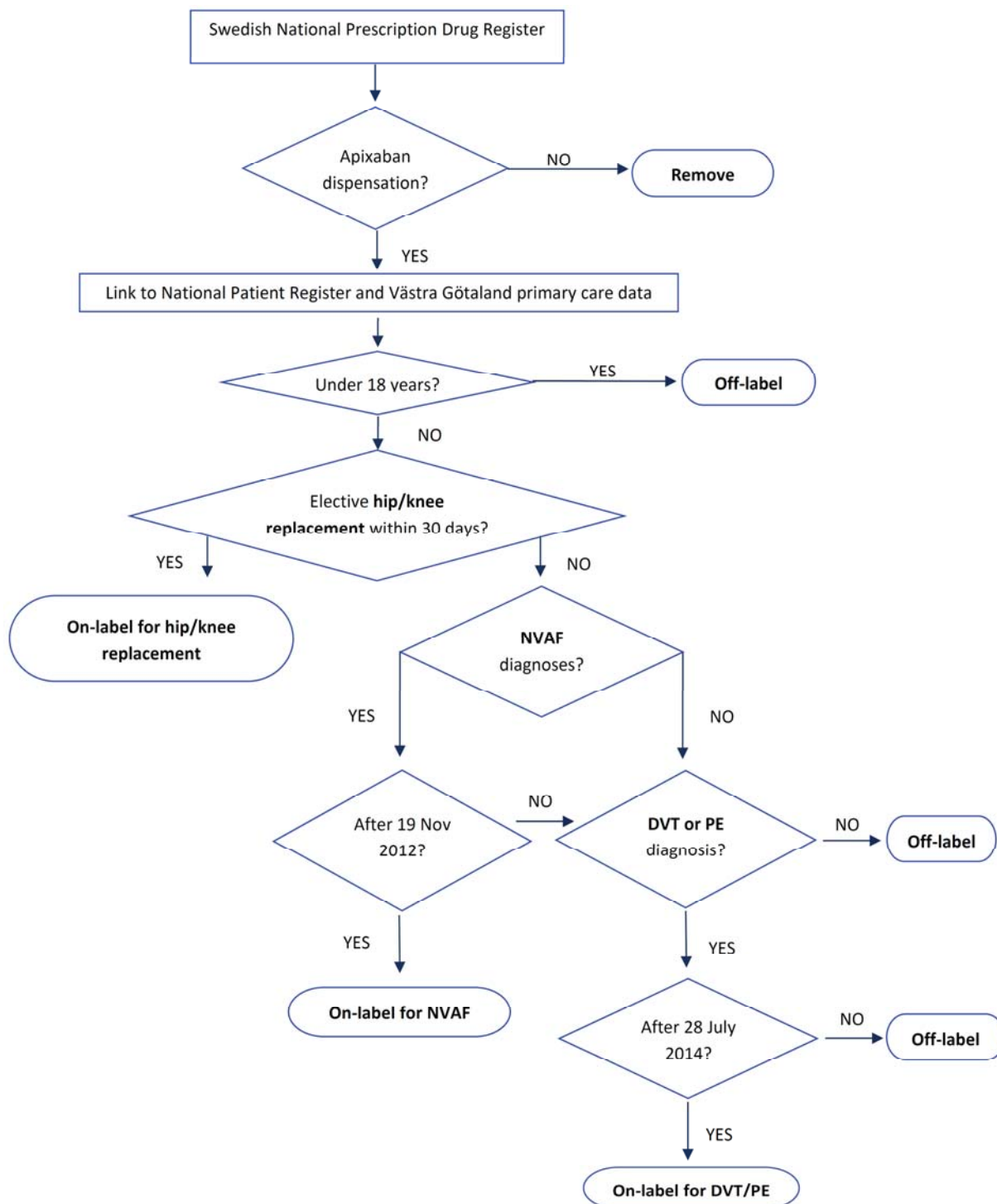
For the purpose of this study, apixaban prescriptions for the NVAF and treatment of DVT/PE indications will be considered off-label up to and including the date that apixaban received approval for those uses in the EU. Apixaban prescriptions for the NVAF and the treatment of DVT/PE indications will be classified as on-label starting on the day after regulatory approval and continuing through the end of the study.

On-label use of apixaban will be defined as a dispensation of the drug to:

1. An adult (ie, 18 years of age or older) and
2. A patient whose hospital records include:
  - a) An elective hip or knee replacement within 30 days before the apixaban prescription, or,
  - b) An apixaban prescription after 19 November 2012 and a diagnosis of NVAF before that apixaban prescription, or,
  - c) An apixaban prescription after 28 July 2014 and a diagnosis of DVT or PE before the apixaban prescription (Figure 1).



**Figure 1: Flow Chart for Record linkage and On and Off-label Classification.**



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If during the study apixaban receives approval for any other condition in Sweden, the new indication will be considered on-label use following the date of approval.

#### 6.4. Data Elements

- Patient demographics: Age and Gender.
- Information on prescription for apixaban: dispensing date, dose, amount dispensed, duration of use based on amount of drug prescribed, refill date, and repeat prescription.
- Hospital admission information: dates of hospital admission and discharges, ICD-10 diagnosis codes in discharge diagnoses, surgical procedure codes.
- Outpatient hospital office visit information: date of visit, ICD-10 diagnosis codes, department type.
- Primary care records in Västra Götaland County (see above): date of contact, contact type (visit, telephone), ICD-10 diagnosis codes.
- Other recently dispensed drugs: ATC code, dispensing date, dose, amount dispensed, use at the time of apixaban dispensing based on amount of drug prescribed.

The operational definitions and coding scheme of the variables will be described in the statistical analysis plan.

### 7. DATA ANALYSIS/STATISTICAL METHODS

The variables to be collected in this study will be documented in a Statistical Analysis Plan. This document may modify the plans outlined in the protocol; however, any major modifications will be reflected in a protocol amendment.

#### 7.1. Sample Size Calculation

This is a descriptive study of drug usage without any pre-defined hypothesis to be tested. Therefore, no power calculation was performed. All individual patients identified to have received apixaban in the database in the study period will be included in the study without any sampling procedure.

Based on the Sponsor's projection of the number of patients using apixaban in 2012-2014 for prevention of VTE following a hip or knee replacement it is expected that approximately 600 patients will be included in the study. It is projected that up to 13,000 patients with atrial fibrillation (AF) may be included in the study.

As shown in the table below, 19,000 apixaban patients with any indication will provide sufficiently precise estimates of on-label use. For instance, if 25% of patients use apixaban off label, the width of the 95% CI for the off-label use percent will be 1.2 percent ([Table 2](#)).

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**Table 2: Precision Around the Off Label Use Proportion Estimates Assuming a Total Sample Size of 19,000 Patients**

| Off label use (%) | Width of 95% CI for off label use (%) |
|-------------------|---------------------------------------|
| 5                 | 0.6                                   |
| 15                | 1.0                                   |
| 25                | 1.2                                   |
| 35                | 1.4                                   |
| 45                | 1.4                                   |

## 7.2. Data Analyses

Descriptive analyses of patient level data will be conducted. Patients will be classified as on-label or off-label apixaban users based on their first prescription for apixaban. The demographic and clinical characteristics of patients identified to have received an apixaban dispensation will be described. The proportion of patients receiving the drug for indications within and outside the approved label in each of the study years will be estimated and any trend over time will be described. From the hospital discharge records, the comorbidities and clinical procedures (e.g., surgeries) at the time of or within 30 days prior to the off-label use will be tabulated as the possible indications for the off-label use. If discharge records during this period do not provide possible indications, information from previous discharges will also be tabulated according to the most recent diagnosis. Furthermore, possible switching from other antithrombotic treatment will be investigated based on dispensed prescriptions during the past year. The dose and duration of prescriptions will be summarized where available.

Stratified descriptive analyses by indication will be performed as described below. As the first step, the study will estimate the proportions of all patients in Swedish databases over the 3-years post-launch period who received apixaban for:

1. VTE prevention following elective hip and knee replacement surgery (on-label indication).
2. NVAf (off-label indication before the approval, and on-label following the approval).
3. Treatment of DVT/PE (off-label indication before the approval, and on-label following the approval).
4. Any other conditions from a list of pre-defined off-label indications, including other types of surgery and history of other diseases (off-label indications). These may include but will not be limited to hip fracture surgeries, general surgeries, gynaecologic and abdominal surgeries, and diagnoses such as cancer, myocardial infarctions, other cardiac conditions, and other hypercoagulable states in which apixaban could be used off-label.

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5. Patients who have no evidence of the conditions for on-label use and who cannot be assigned to the list of pre-defined off-label uses will be classified as off-label and unknown.

The only available primary data is from patients in Västra Götaland County. Primary care data may contain information on the conditions that are used to classify on-label or off-label apixaban use. A sensitivity analysis will compare the proportion of on-label users based on both primary care and hospital data to the proportion of on-label use when only the hospital data is used among those in Västra Götaland County. This assumes that the availability of GP data is not related to the ratio of on-label or off-label use and that Västra Götaland County is representative of all of Sweden.

Second, descriptive analyses will be performed in each of the indication strata to summarize:

1. Demographic characteristics of patients and prescriber specialty.
2. Estimated duration of apixaban treatment and dosages used.
3. Concomitant medication use, with the focus on contra-indicated medications.
4. History of treatment with other anticoagulants.
5. Select co-morbid conditions/medical history, such as renal impairment, severe hepatic impairment, congenital or acquired bleeding disorders.

For off-label indication strata, distribution of surgical procedures and diagnoses that patients had prior to receiving apixaban to infer possible indications that apixaban was used for. For instance, counts and proportions of patients who had other orthopaedic surgery (eg, hip fracture), within 30 days of apixaban prescription will be reported.

### 7.3. Interim Analysis

The analysis will be conducted annually for three years. Interim reports will include all data available at the time of the analysis and may not include all the analyses that will be conducted in the final report.

## 8. DATA COLLECTION AND DATA MANAGEMENT

The details of data collection procedures have been described in [Section 6](#).

### 8.1. Access to Data

The Sponsor will not have access to health register records at the level of the individual patient but only to tables with aggregated data. In case of an audit from a regulatory authority or Pfizer, the investigator will be able to document the data processing and statistical analysis and thus verify the reported results.

### 8.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## 9. ADVERSE EVENT REPORTING AND SERIOUS ADVERSE EVENT REPORTING

This study includes unstructured data (eg, narrative fields in the database) that will be converted to structured (ie, coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports.

## 10. STRENGTHS AND LIMITATIONS

### 10.1. Strengths:

- The study will use an established database that routinely collects information on the variables required to fulfill the objectives. There are strong linkage systems that utilize the unique national identifier of the patients to link different data sources. This database has been used for many pharmacoepidemiologic studies, including those looking at atrial fibrillation and orthopedic surgery populations (Weiss, Stark et al. 2006; Andersson, Londahl et al. 2012).<sup>2,1</sup>

- The database has coverage of all age groups.
- The database has coverage of all hospital admission and discharge diagnoses.
- By repeating the annual analysis over a three-year period after launch of apixaban, the study will provide data on changing trends, if any.

#### **10.2. Limitations:**

- The study is based on outpatient prescriptions. Therefore patients who receive apixaban only during hospital stay (either for the approved indication or for any off-label indication) and do not refill following discharge will not be included. This limitation will be addressed by the Netherlands study where inpatient medication use data are available from the inpatient pharmacy database covering a population of over 1 million patients from a representative sample of hospital pharmacies.
- Diagnoses are retrieved from hospital discharge records (nationwide), outpatient clinic contacts (nationwide) and primary care records (available for one county only, see above). Therefore, information on possible indications may in some cases be missing.
- Validation of the data in the database by reviewing individual patients' original medical records will not be possible.
- This study is based on medical records data being collected by the relevant government agencies and county health administrations in Sweden and then accessed by the investigators for analyses. As a result, any unforeseen delay in the collection and compilation of data by one or more of the agencies is beyond the control of the Sponsor and may affect the study timeline.

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## **11. QUALITY CONTROL AND QUALITY ASSURANCE**

Investigators are responsible for following their standard institutional procedures to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data.

## **12. ETHICS**

### **12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and other relevant documents from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

### **12.2. Ethical Conduct of the Study**

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), EMA ENCePP Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

### **12.3. Subject Information and Consent**

This is a retrospective study of de-identified data from existing databases without any direct enrollment of subjects. Therefore, no informed consent is applicable.

## **13. COMMUNICATION AND PUBLICATION OF STUDY RESULTS**

### **13.1. Publications by Investigators**

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

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Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

For all publications relating to the Study, Investigator will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

#### 14. REFERENCES

1. Andersson, P., M. Londaal, et al. (2012). "The prevalence of atrial fibrillation in a geographically well-defined population in Northern Sweden: implications for anticoagulation prophylaxis." J Intern Med.
2. Weiss, R. J., A. Stark, et al. (2006). "Orthopaedic surgery of the lower limbs in 49,802 rheumatoid arthritis patients: results from the Swedish National Inpatient Registry during 1987 to 2001." Ann Rheum Dis **65**(3): 335-341.

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