

Study Report
Post Authorisation Safety Study (PASS) of the Utilisation Patterns of Apixaban in Denmark

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NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

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Joint PASS	No
Research question and objectives	<p>The study objectives are:</p> <ol style="list-style-type: none">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.
Country of study	Denmark

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Marketing Authorisation Holder(s)

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Apixaban

B0661073 NON-INTERVENTIONAL STUDY REPORT

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial fibrillation
ATC	Anatomical Therapeutic Chemical classification system
CIOMS	Council for International Organizations of Medical Sciences
CI	Confidence interval
CRS	Civil Registration System
DPA	Data Protection Agency
DDD	Defined Daily Dose
DNHSPD	Danish National Health Services Prescription Database
DNPR	Danish National Patient Registry
DVT	Deep vein thrombosis
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EEIG	European Economic Interest Grouping
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HA	Hip arthroplasty
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ICD-10	International Statistical Classification of Diseases and Related Health Problems - Tenth Revision
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
KA	Knee arthroplasty
MAH	Marketing Authorisation Holder
MAI	Medication Appropriateness Index
NI	Non-interventional
NOAC	Non-vitamin K oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
NVAF	Non-valvular atrial fibrillation
NYHA	New York Heart Association
PASS	Post-Authorisation Safety Study
PE	Pulmonary embolism
PRAC	Pharmacovigilance Risk Assessment Committee
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Systemic embolism
SmPC	Summary of Product Characteristics
TIA	Transient ischaemic attack

US	United States
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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Stephen Schachterle, PhD, MPH	Associate Director	Epidemiology Worldwide Safety and Regulatory Pfizer Inc.
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4. OTHER RESPONSIBLE PARTIES

Name, degree(s)	Role
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Morten Madsen, MSc Statistician Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark	Statistical analysis, data management

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	31 August 2016	31 August 2016	
End of data collection	30 November 2016	30 November 2016	
Registration in the EU PAS register	26 August 2016	17 August 2016	ENCePP database Reference: EUPAS147 86
Final report of study results	31 August 2017	31 July 2017	

6. RATIONALE AND BACKGROUND

Apixaban (ELIQUIS[®]) is a non-vitamin K oral anticoagulant (NOAC) that inhibits the coagulation factor Xa. NOACs, which became available in 2008,¹ provide an alternative to vitamin K antagonists (VKAs), which have been the mainstay of oral anticoagulation therapy for over a half century.² Patients and providers may choose NOACs because, compared with VKAs, NOACs have fewer food and drug interactions, a lower risk of bleeding for a similar anticoagulation benefit, and a more predictable effect that allows patients to maintain an optimal therapeutic dose without frequent dose monitoring.^{3,4}

On 18 May 2011, apixaban was approved in the European Union (EU) for the prevention of venous thromboembolism (VTE) in adults who have undergone elective hip arthroplasty (HA) or knee arthroplasty (KA). Following the initial approval, apixaban received an approval, on 19 November 2012, for the prevention of stroke and systemic embolism (SE) in adults with nonvalvular atrial fibrillation (NVAf), with one or more risk factors such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; or symptomatic heart failure (New York Heart Association [NYHA] Class \geq II). Subsequently, on 28 July 2014, apixaban was approved for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for prevention of recurrent DVT and PE in adults. In Denmark, apixaban has been commercially available since late 2012.⁵

Previous investigations into utilisation of NOACs applied differing definitions of on-label use, and reported varying proportions of on-label and off-label use. For instance, in Denmark, national health registry data from 1,612 dabigatran users were examined for off-label use between 22 August and 31 December 2011. Depending on a patient's risk factors for bleeding, dabigatran was indicated for NVAf at a high dose (150 mg) or low dose (110 mg). Dabigatran 150 mg was prescribed off-label in 44.5% of patients and dabigatran 110 mg was prescribed off-label in 9.7% patients.⁶ In France, about 23% of dabigatran patients were classified as off-label.⁷ In Belgium, 53.8% of dabigatran and rivaroxaban use were reported as off-label because the prescriptions had at least 1 inappropriate rating in a 10-category appropriate-use scale. Inappropriate dosing, particularly failure to adapt NOAC dosing to the patient's renal function, was cited as a common type of off-label use.⁸⁻¹¹ In the United States (US), dabigatran was prescribed off-label to 20% of all patients receiving the drug, including 10.9% of patients with valvular atrial fibrillation (AF) and 8.6% of patients with no identified AF diagnosis.¹² Another US study evaluated dabigatran utilisation with nationwide IMS Health data, and reported that 8% of dabigatran prescriptions were off-label in Quarter 4, 2010, increasing to 37% by Quarter 4, 2011.¹³

The Marketing Authorisation Holder (MAH) undertook a Post-Authorisation Safety Study (PASS) to examine utilisation of apixaban in Sweden according to the drug's approved indications as part of a commitment to the European Medicines Agency (EMA). In that study (n = 17,592), 86.4% of apixaban users were assigned to an on-label indication, 7.7% were assigned to an off-label indication, and 5.9% of users could not be assigned to an on-label or off-label indication with the available data.¹⁴

To understand the patterns of post-authorisation apixaban use, the MAH initiated a study to evaluate the utilisation of apixaban in Denmark.

This non-interventional (NI) study is designated as a PASS and is a commitment to the EMA.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study was to describe utilisation patterns of apixaban in Denmark with regard to on-label and off-label use.

Specifically, the study aimed 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.

8. AMENDMENTS AND UPDATES

Table 8.1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	14 March 2016	Administrative	Abstract (3) Milestones (5) Variables (8.3) Data Sources (8.4) Data Management (8.6) Institutional Review Board (IRB) / Independent Ethics Committee (IEC) (9.3)	Dates of the milestones were amended. Updates and clarifications to names of Danish registries. Clarification of SAS version. Clarification on retaining correspondences and approvals from the Danish Data Protection Agency (DPA)	Dates were amended to align to EMA/ Pharmacovigilance Risk Assessment Committee (PRAC) review procedure. To clarify changes to current names of registries. To update to versions of statistical software. To clarify procedures for retaining information from the Danish DPA

9. RESEARCH METHODS

This study has been conducted in accordance with Amendment 1 of the final study protocol, dated 14 March 2016 (Appendix 2). The protocol stated that the study period would include data from 18 May 2011 through 31 December 2014. However, because data were available from 18 May 2011 through 31 December 2015, the study period was extended through 2015.

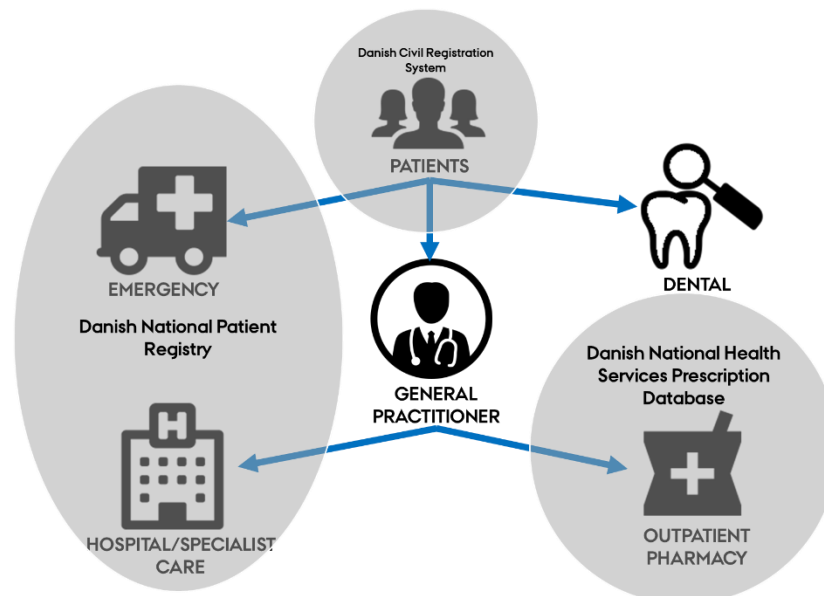
9.1. Study design

This was a descriptive, retrospective study based on electronic data routinely and prospectively collected from the Danish national registries (Section 9.5). Apixaban users were identified through dispensation records, and medical histories were assembled from registrations of hospital encounters and medication use. Indication for apixaban treatment was assigned by examining a patient's medical history at the time of the first recorded dispensation of apixaban.

9.2. Setting

The study was conducted in Denmark (population 5.6 million). Denmark is a welfare state with universal tax-funded access to health care, including access to secondary care triaged by general practitioners (Figure 9.1).

Figure 9.1 Patients' access to health care in Denmark and linked data sources



9.3. Subjects

The source population was comprised of persons who were alive and residents of Denmark between 18 May 2011 and 31 December 2015 (inclusive). The eligible study population consisted of all patients with at least one outpatient dispensation for apixaban during the study period. There were no exclusion criteria.

9.4. Variables

The main endpoint of interest for the study was the indication for apixaban use, classified as on-

label, off-label, or unknown, based on medical histories (diagnoses, procedures, or medication use) identifiable around the time of the first outpatient dispensation of apixaban. The date of the first outpatient dispensation of apixaban during the study period was defined as the index date. All patients' apixaban use was classified as on-label, off-label, or unknown according to their dispensation at the index date regardless of later dispensations. The on-label, off-label, and unknown classifications were made based on the indication(s) that were authorised as of the index date. [Table 9.1](#) shows indications for apixaban use and dates of authorisation for each indication.

Table 9.1. Indications for apixaban and dates of authorisation in the European Union

Abbreviated Indication	Indication	Date of EMA Authorisation
HA/KA	Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery	18 May 2011
NVAF	Prevention of stroke and SE in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age 75 years or older; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class \geq II).	19 November 2012
Treatment of DVT/PE	Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.	28 July 2014
Abbreviations: DVT: Deep vein thrombosis, HA: Hip arthroplasty, KA: Knee arthroplasty NVAF: Non-valvular atrial fibrillation, NYHA: New York Heart Association, PE: Pulmonary embolism, SE: Systemic embolism, TIA: Transient ischaemic attack, VTE: Venous thromboembolism		

Accordingly, on-label use of apixaban was defined as a dispensation of the drug to:

1. An adult (patients 18 years of age or older) and
2. A patient whose hospital records (diagnoses and procedures recorded at inpatient stays or outpatient specialist visits) were indicative of any of the following:
 - a. After 18 May 2011: an elective HA or KA within 30 days before the first apixaban dispensation,
 - b. After 19 November 2012: a diagnosis of NVAF recorded, since 1994, before or up to 60 days after the first apixaban dispensation. Diagnoses that followed the first-recorded dispensation were used to accommodate NVAF diagnosis made in general practice prior to prompting a record in the hospital setting,^{4,5}
 - c. After 28 July 2014: a diagnosis of DVT or PE recorded, since 1994, before the first apixaban dispensation.

On-label use of apixaban for NVAF was further classified into 'pure on-label use' and 'potential on-label use'. Pure on-label use was defined as NVAF in the presence of one or more of the following risk factors on or before the apixaban initiation date, including age 75 years or older; any history of hypertension; any history of diabetes mellitus; any history of stroke or TIA, any history of symptomatic heart failure (NYHA Class \geq II). All other on-label apixaban use for NVAF was classified as 'potential on-label use'.

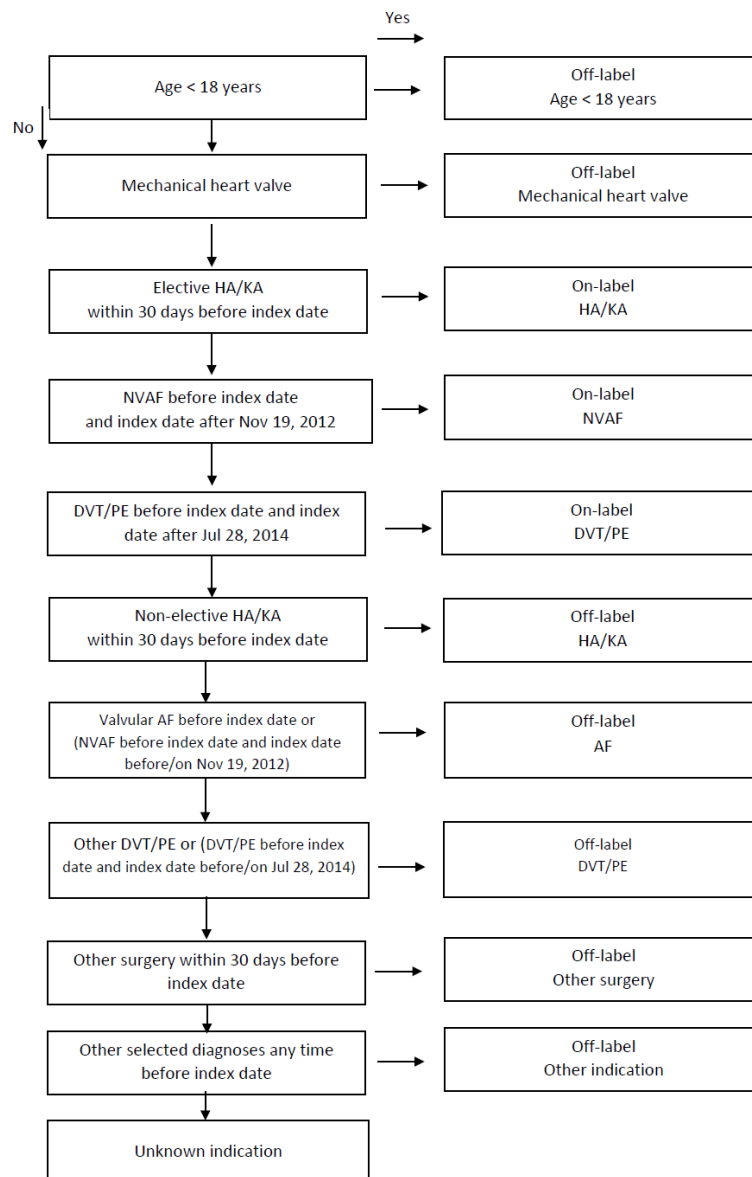
Off-label indications were predefined based on approved indications from the Summary of Product Characteristics (SmPC) and included (but were not limited to) non-elective KA and HA, other orthopaedic surgeries, general surgeries, and gynaecologic and abdominal surgeries,

as well as diagnoses such as cancer, myocardial infarction, other cardiac conditions, and other hypercoagulable states. If multiple indications were identified for the same patient initiating apixaban, patients were classified according to the hierarchy shown in [Figure 9.2](#). If an on-label or off-label indication could not be identified in a patient's medical history, then that patient was classified as having an unknown apixaban indication.

Patient data included sex, age at first dispensation, prior and concomitant use of selected medications including anticoagulation agents, hospital-based diagnoses and procedures, and morbidities such as cardiovascular, renal or hepatic disease. Additional data on the specialty of the prescriber and the treatment dose and duration were included.

Prior use of a medication was defined by 1 or more dispensation of that medication from 2004 and up to 31 days before the index date (inclusive); concomitant use was defined as 1 or more dispensation dated within 30 days before/after the index date (inclusive). Daily dose (mg) (median, interquartile range [IQR], range) was estimated by dividing the total amount of apixaban in the first dispensation (pill strength \times number of pills per package \times number of packages) by the number of days between the first and the second apixaban dispensation. For patients with 1 dispensation during the study period and for patients with days between the first two dispensations resulting in apparent daily dose of >100 mg ($n=175$, days between dispensation ranged between 1 and 16), daily dose was assumed to be 5 mg for dispensations with 2.5-mg pill strength and 10 mg for dispensations with 5-mg pill strength. This assumptions was made based on the most prevalent indication of NVAF and the dosing recommendations in the SmPC. Patients contributed to the estimates of treatment duration and cumulative dose as long as they had evidence of an apixaban supply based on dispensation data, while remaining in the study population.

Figure 9.2 Patient identification and on-label/off-label/unknown indication



9.5. Data sources and measurement

The registries and databases used in this study are linkable by a unique personal identifier (which encodes date of birth and sex) and include the Danish Civil Registration System (CRS),¹⁵ the Danish National Patient Registry (DNPR),¹⁶ and the Danish National Health Services Prescription Database (DNHSPD).¹⁷ Dispensations of apixaban were identified in the DNHSPD. Data on diagnoses and procedures from inpatient and outpatient hospital encounters were obtained by linking the dispensation records to the records of these patients in the DNPR.

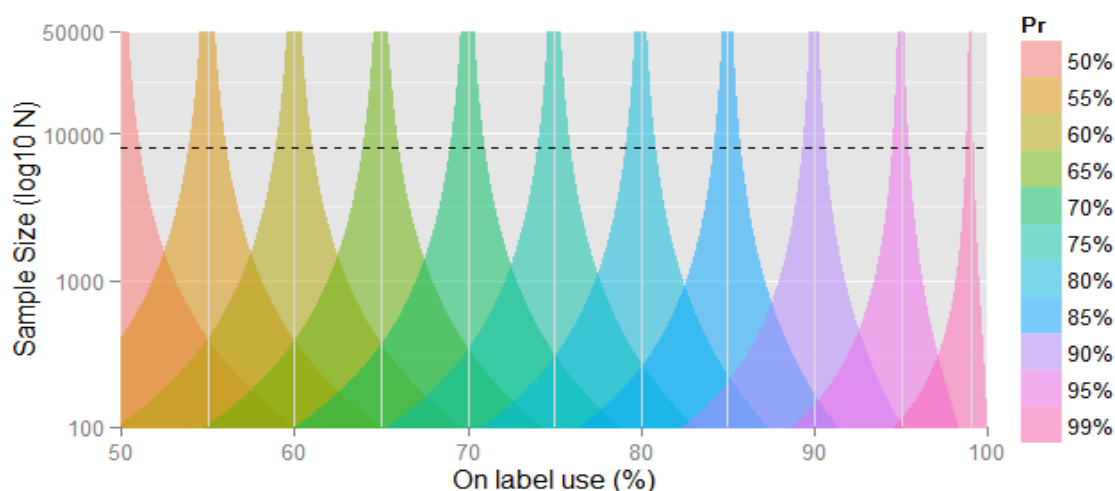
9.6. Bias

The main potential source of bias in the study is from a lack of directly recorded data on indication for apixaban use. In the absence of such data, classifying apixaban use into on-label and off-label must rely on records of hospital inpatient and specialist clinic outpatient diagnoses and procedures, or on prior use of medications. Diagnoses made in general practice that are not subsequently recorded in hospital settings do not generate records in routine national registries and therefore could not be used to define indication for apixaban use. Lack of information about diagnoses from general practice may be particularly relevant for the NVAF indication because NVAF is treated by general practice physicians. Thus, patients without evidence of an NVAF diagnosis could be misclassified into the off-label or unknown indication category. This misclassification would result in an overestimation of the proportion of apixaban used off-label or for an unknown indication, and an underestimation of apixaban used on-label for NVAF.

9.7. Study size

This descriptive study did not include any *a priori* hypothesis about the differences between patient groups; therefore, a formal sample size calculation to detect pre-defined effects is not applicable. The projected sample size was 8,000 patients with a dispensation of apixaban from May 2011 through December 2014. At this sample size, proportions that are separated by 5% (e.g., 75%, 80%, %, etc., [Figure 9.3](#)) would be distinguishable with exact binomial confidence intervals. All patients with an outpatient reimbursed dispensation of apixaban during the study period were included in this study. The expected study size was estimated based on publically available dispensation data (www.medstat.dk). The actual study included an additional year of data (through December 2015) and was more than twice as large as was initially projected.

Figure 9.3. Precision around proportions of on-label use



9.8. Data transformation

Detailed methodology for data management from the raw registry variables is documented in the Statistical Analysis Plan (SAP), which was dated, filed and maintained by the sponsor.

9.9. Statistical methods

9.9.1. Main summary measures

Categorical variables were summarised using frequencies and proportions; continuous variables were summarised using mean with standard deviation (SDs) and/or median with interquartile IQR, maximum, and minimum, as appropriate. Age was reported as a continuous variable and in clinically relevant categories, to identify paediatric use (off-label, younger than 18 years) and use among elderly patients (85 years or older). Cumulative treatment duration was classified using 60-day categories.

9.9.2. Main statistical methods

The proportions of patients with an on-label, off-label, or unknown apixaban indication among all patients were estimated with exact Clopper-Pearson 95% confidence intervals (CIs). The classification of on-label, off-label, and unknown indications followed a prespecified hierarchy and the drug approval schedule. The NVAF indication was stratified into purely on-label NVAF indication and potential on-label NVAF indication as described above. Additionally, the proportion of on-label and off-label apixaban initiators among all apixaban initiators who could be assigned to an indication was reported [e.g. on-label/(on-label + off-label)]; patients with unknown indication did not contribute to this calculation. On-label, off-label and unknown indications were reported cumulatively, by the 3 approved indications, and by the approval schedule.

The time on the study for each patient began on the date of first apixaban dispensation and ended on earliest of the date of death, emigration, or the study end, on 31 December 2015. Patients were followed forward to estimate daily dose, cumulative duration of use, and the number of apixaban dispensations during the study period.

Age, sex, calendar period, prescriber specialty at the index date, and distribution of the time from the index date until death, emigration or study end for all patients with an apixaban dispensation were tabulated, overall and by indication. Comorbidities and comedications, including those that are contraindicated for use with apixaban, were tabulated overall and by indication.

For the off-label indication categories, the distribution of surgical procedures recorded 30 days before and including the index date, and diagnoses recorded any time before the index date were tabulated to infer possible specific off-label indications for apixaban. For surgeries, non-elective KA/HA and mechanical valves were reported specifically; other surgeries were reported in broad chapters. All definitions of the study variables are detailed in Appendix 3.

9.9.3. Missing values

For each variable, missing values were reported as a separate category, whenever applicable.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the Statistical Analysis Plan

None.

9.10. Quality control

Aarhus University and Aarhus University's Department of Clinical Epidemiology standard procedures were followed to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, description of available data, and extent of validation of endpoints.

9.11. Protection of human subjects

9.11.1. Patient Information and Consent

All parties ensured protection of patient personal data and did not include patient names on any MAH forms, reports, publications, or in any other disclosures, except where required by laws. No data transfer to MAH has taken place in this study.

An informed consent or an approval of an Institutional Review Board (IRB) or an Independent Ethics Committee (IEC) was not required for this study, as it was based on routinely collected routine administrative data. This study received a required approval from the Danish Data Protection Agency (DPA) according to standard procedures (record number KEA-2015-17). All registry-based research conforms to the Danish Act on Processing of Personal Data (www.datatilsynet.dk).

9.11.2. Patient Withdrawal

Not applicable. The retrospective nature of these data makes patient withdrawal not applicable.

9.11.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

An application to conduct the study was filed with the Danish Data Protection Agency (DPA) according to standard procedures. The study commenced after the DPA's permission was granted. All correspondence with the DPA has been retained in the Investigator File and copies of DPA approvals will be forwarded to MAH.

9.11.4. Ethical Conduct of the Study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in 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, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, Food and Drug Administration (FDA) Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

10. RESULTS

10.1. Participants

Between 18 May 2011 and 31 December 2015, there were 19,709 patients with an outpatient dispensation of apixaban in Denmark. No dispensation of apixaban was identified in the first authorisation period, 18 May 2011 – 19 November 2012, when only the HA/KA indication was approved. Thus, the remainder of the report describes utilisation of apixaban in the remaining two authorisation periods. During the second authorisation period (20 November 2012 – 28 July 2014), the NVAF indication was added, and 22.6% (4,449/19,709) of patients had their first apixaban dispensation. During the third authorisation period (29 July 2014 – 31 December 2015), the VTE indication was added, and 77.4% (15,260/19,709) of the patients had their first apixaban dispensation during that period ([Table 15.1](#)).

10.2. Descriptive data

Men comprised 51.6% (10,172/19,709) of the study population. For all patients, the median age was 76 years (IQR, 68 – 83 years), and 21.9% (4,307/19,709) of patients were 85 years of age or older on the index date. Median follow-up time from the first apixaban dispensation to death/emigration/study end was 9.5 months (IQR, 4.2 – 15.5 months). Apixaban was primarily prescribed by healthcare providers from departments of internal medicine (28.0%, n=5,520), cardiology (24.7%, n=4,873), or in general practice (24.0%, n=4,738) ([Table 15.2](#)).

10.3. Outcome data

Not applicable.

10.4. Main results

10.4.1. On-label indications, off-label indications, unknown indications

Of the 19,709 patients with a first-time dispensation of apixaban during the study period, any on-label indication could be assigned to 82.6% (95% CI: 82.1% - 83.1%) of all patients. A record of an on-label NVAF indication was identified for 76.1% (95% CI: 75.5% - 76.7%) of all patients. Pure on-label NVAF indication, which was defined as a record of NVAF with at least one of the risk factors for the NVAF, accounted 68.7% (95% CI: 68.1% - 69.4%) of all patients. Among the 15,002 patients with on-label NVAF indication, pure NVAF accounted for 90.3% (95% CI: 89.8% - 90.8%) of the patients, while a potential on-label NVAF indication accounted for 9.7% (95% CI: 9.2% - 10.2%) of the patients. An on-label DVT/PE classification was assigned to 6.3% (95% CI: 5.9% - 6.6%) of all 19,709 patients, and an on-label HA/KA indication was assigned to 0.2% (95% CI: 0.2% - 0.3%) of all patients. Among all patients, 17.4% (95% CI: 16.9% - 17.9%) could not be assigned to an on-label indication, including 6.7% (95% CI: 6.3% - 7.0%) of patients with an unknown indication and 10.8% (95% CI: 10.3% - 11.2%) with an assigned off-label indication. In total, an indication for apixaban use could be assigned to 93.3% (18,398/19,709) of all patients. Among the patients with an assigned indication, 88.5% (95% CI: 88.0% - 88.9%) were assigned to an on-label indication and 11.5% (95% CI: 11.1% - 12.0%) were assigned to an off-label indication ([Table 15.1](#)).

In the second authorisation period, during which both elective HA/KA and NVAF were the approved indications, 4,449 patients had their first outpatient dispensation of apixaban. Among

them, 81.3% (95% CI: 80.1% - 82.4%) were assigned to an on-label indication, 11.9% (95% CI: 10.9% - 12.9%) were assigned to an off-label indication, and 6.9% (95% CI: 6.2% - 7.7%) had an unknown indication ([Table 15.1](#)).

In the final authorisation period, during which elective HA/KA, NVAf, and DVT/PE were the approved indications, 15,260 patients had their first outpatient dispensation of apixaban. Among them, 83.0% (95% CI: 82.4% - 83.6%) were assigned to an on-label indication, 10.4% (95% CI: 10.0% - 10.9%) were assigned to an off-label indication, and 6.6% (95% CI: 6.2 - 7.0) was assigned to an unknown indication ([Table 15.1](#), [Figure 15.1](#)). Distributions of apixaban indications according to calendar time are shown in [Figure 15.1](#), [Figure 15.2](#), [Figure 15.3](#), and [Figure 15.4](#).

10.4.2. Characteristics of apixaban use

Among all 19,709 patients with a dispensation of apixaban, 15.6% (n=3,081) had a single dispensation during the study period, and 54.4% (n=10,720) of patients had estimated cumulative duration of longer than 180 days. Overall, 60.4% (n=11,898) of the apixaban initiators received a pill strength of 5 mg in the first dispensation and 39.6% (n=7,811) received a pill strength of 2.5 mg in the first dispensation. Estimated median daily doses were lower for the off-label indications ([Table 15.3](#)). The overall proportion of patients with a cumulative duration over 180 days was greater for patients with an on-label NVAf indication (56.7%, 8,503/15,002) than for the patients with on-label HA/KA (39.5%, 17/43) or on-label DVT/PE (31.3%, 386/1,233) indications. For patients with off-label and unknown indications, the proportion of those with greater than 180 days estimated cumulative duration of use ranged from 42.1% (127/302) for surgery other than KA/HA to 58.6% (542/928) for diseases other than NVAf or DVT/PE ([Table 15.3](#)).

10.4.3. Characteristics of apixaban users

Among the 19,709 apixaban initiators, 63.0% (n=12,408) had a history of cardiovascular disease, 15.6% (n=3,068) had a history of diabetes, and 2.2% (n=433) had a history of liver disorders. Patients who received apixaban also had histories of coagulation defects (1.9%, n=372), intracranial haemorrhage (2.2%, n=429), gastrointestinal ulcer (7.5%, n=1,483), and oesophageal varices (0.2%, n=31). The prevalence of renal disease as measured by diagnostic codes was 5.7% overall (1,117/19,709), but higher among patients with potential mechanical heart valve (14.2%, 87/611) or with off-label NVAf (12.4%, 14/113). Prevalence of end-stage renal disease, as measured by diagnostic codes without laboratory data, did not exceed 0.1% in any category of off-label, on-label, or unknown indications ([Table 15.4](#)).

Prevalence of prior use of any antithrombotic agents was 73.0% (n=14,293), including prevalence of prior warfarin use of 30.5% (n=5,981). Concomitant treatment with any heparin group agent was 0.8% (n=150); prevalence of concomitant use of dalteparin was 0.5% (n=90), fewer than 5 patients had a record of concomitant use of enoxaparin, and there was no concomitant use of fondaparinux. Concomitant use of dabigatran was recorded for 3.8% (n=745) of the apixaban initiators, and concomitant use of rivaroxaban was 2.2% (n=425) of apixaban users. Prevalence of prior use of atorvastatin was 14.6% (n=2,852); 2.4% (n=474) of patients had prior use of diltiazem, and 8.3% (n=1,631) had prior use of verapamil ([Table 15.5](#)).

Among the 155 patients classified as receiving apixaban for off-label DVT/PE during the study period, 36.8% (n=57) had diagnoses of phlebitis and thrombophlebitis other than phlebitis and

thrombophlebitis of the deep veins of lower extremities, and 36.1% (n=56) of the patients had diagnoses of phlebitis and thrombophlebitis of the deep veins of lower extremities. Among 42 patients with pulmonary embolism, 28.6% (n=12) were in May 2014; fewer than 5 were in June 2014; and 16.7% (n=7) were in July 2014 but prior to the addition of the VTE indication. Among the 22 patients with off label DVT dispensation, there were fewer than 5 patients in each month and year preceding the approval date of the DVT/PE indication ([Table 15.6](#)).

Among the 302 patients classified as 'off-label other surgery', 29.1% (n=88) had transluminal endoscopy, 15.2% (n=46) had a minor surgical procedure, 14.2% (n=43) had surgery of musculoskeletal system other than KA/HA, 12.6% (n=38) had operations on digestive system and spleen, and 11.9% (n=36) had operations of heart and major thoracic vessels other than valve implantations ([Table 15.7](#)).

Among the 937 patients with for whom protocol-prespecified diagnoses indicative of a known off-label indication could be identified, the most common diagnosis was angina pectoris (47.7%, n=447) followed by chronic ischaemic heart disease (42.0%, n=394) and cerebral infarction (39.0%, n=365) ([Table 15.8](#)). All diagnoses stemmed from inpatient or outpatient hospital encounters.

Among the 611 patients with a potential mechanical heart valve, 18 had definite mechanical heart valve (defined by procedure codes for *implantation of a total artificial heart; replacement of tricuspid valve using mechanical prosthesis; replacement of pulmonary valve using mechanical prosthesis; replacement of mitral valve using mechanical prosthesis; replacement of mitral valve using mechanical prosthesis*; or diagnostic code for *breakdown [mechanical] of artificial heart*). The distribution of the indications among the 593 patients with potential mechanical valves (but without a record of mechanical valves) are shown in [Table 15.9](#) and the frequencies of all category-defining diagnostic and procedure code of all 611 patients with potential mechanical heart valves are listed in [Table 15.10](#).

10.5. Other analyses

None.

10.6. Adverse events / adverse reactions

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 adverse event (AE) reports.

11. DISCUSSION

11.1. Key results

Among 19,709 patients with an outpatient dispensation of apixaban between 18 May 2011 and 31 December 2015 in Denmark, the period prevalence of any on-label indication was 82.6%, the period prevalence of any off-label indication was 10.8%, and the period prevalence of unknown

indication was 6.7%. Prevalence of on-label use among patients with an identifiable indication assigned was 88.5%.

The period prevalence of on-label-NVAF indication was 76.1% among all patients. Prevalence of pure on-label NVAF was 69.2% overall. Pure on-label NVAF indication accounted for 90.3% of NVAF indications while potential on-label NVAF accounted for 9.7% of all patients with an on-label NVAF indication. The prevalence of the on-label DVT/PE indication was 7.0%, and the prevalence of on-label elective HA/KA indication was 0.2%. Overall, 17.4% of the 19,709 apixaban initiators were not classified as on-label users based on the initial outpatient dispensation. Of those, 38.2% had an unknown indication. The distribution of on-label, off-label and unknown indications based on the initial apixaban dispensation was similar in the two authorisation periods for which the data were available.

More than 60% of apixaban initiators had cardiovascular disease and nearly 16% had diabetes; more than 30% had used warfarin before initiating apixaban. Based on diagnostic codes alone, prevalence of renal disease was 5.7%, and prevalence of end-stage renal disease did not exceed 0.1%. The apparent concomitant use of other anticoagulants (including other NOACs) by initiators of apixaban is likely an artefact of defining concomitant use as any dispensation for another coagulant in the 30 days before or after the first apixaban dispensation, and may represent medication switches, since the date of discontinuation is not recorded. Our observation of concomitant use of apixaban with dabigatran (3.8%) or rivaroxaban (2.2%) are consistent with a Danish study of NOACs utilisation (based on the same data sources), which reported that within 1 year of initiation, 10% of NOAC users switched to a VKA, and 4.8% switched to another NOAC.⁵

The overall prevalence of off-label indications (10.8%, not excluding unknown indications) in this study is substantially lower than that reported in several studies in the US, which evaluated prescribing using differing definitions of off-label use including: the Medication Appropriateness Index (MAI) criteria for appropriate indication, choice, dosage, modalities and practicability of administration, drug-drug interactions, drug-disease interactions, duplication, and duration. In one study of 148 oral anticoagulant users with NVAF (not including apixaban), the prevalence of at least one inappropriate use indicator was 28% of among users of rivaroxaban, and 47% among users of dabigatran.¹⁸ In another US study of 120 adult NOAC users in primary care, prevalence of any type of inappropriate use was 60% overall, and the most prevalent inappropriate use was inappropriate dosing (33%). Only 10% of the patients included in that study used apixaban.¹⁰ Furthermore, definitions used in the above studies are different from those applied in this study.

In Sweden, with health care and data collection system similar to that of Denmark, the overall prevalence of on-label use was 86%, and prevalence of on-label use in patients with known indications was 92%.¹⁴ These results are in agreement with the present study.

11.2. Strengths and limitations

This population-based study was conducted using data from Denmark, a welfare state with uniform access to high-quality medical care. Because apixaban is dispensed primarily by outpatient pharmacies, the completeness of the outpatient apixaban outpatient dispensation data is assumed to be nearly 100%; in 2015, only 2% of the total defined daily doses (DDDs) for apixaban were dispensed in hospitals (www.medstat.dk).

Data in the Danish national registries have been validated for many algorithms identifying medical events. The positive predictive value of the combined diagnosis of AF and/or atrial flutter in the DNPR is more than 90% independent of sex.¹⁹ The positive predictive value of thromboembolism diagnosis is 90%.²⁰ Positive predictive values for valve surgeries range between 98% and 100%.²¹ For drugs used chronically, there is high level of agreement between general practitioner and dispensation records.¹⁷ Completeness and validity of surgical procedures in the DNPR is close to 100%.¹⁶ Other hospital diagnoses have also been validated.^{22,23} Mortality and migration status data are updated daily and are 100% complete.¹⁵ Furthermore, owing to a large size of the study population, most of the results were estimated with high precision.

The main limitation of this analysis is the absence of direct data on indication, necessitating reliance on indirect information to assign indication of apixaban use. Owing to the lack of data on diagnoses from general practice, not all diagnostic history of apixaban initiators could be ascertained. This may explain why nearly 40% of patients not classified to an on-label indication could not be classified according to a prespecified indication. Use of hospital diagnoses of NVAf that were recorded both before and after the date of the first apixaban dispensation was aimed at capturing patients who receive the NVAf diagnosis and the initial apixaban dispensation outside hospital. For such patients, a hospital diagnosis of NVAf could succeed the first dispensation of apixaban for this indication. This approach has been used in other studies based on the Danish data.^{5,24} Overall, this limitation is likely to cause overestimation of the prevalence of off-label use of apixaban.

Furthermore, dispensation of apixaban during hospital stays is not reflected in the available data sources. For patients who received the first dose of apixaban in a hospital and a subsequent dose via an outpatient dispensation, indication would be based on the first-recorded outpatient dispensation, which could be later than the initiation date. Thus, this study did not capture patients receiving apixaban dispensations only in the hospital (for example, in relation to HA/KA, since they stay in hospitals for 2-3 days) and never thereafter during the study period. In Denmark, contrary to the dosing specified in the SmPC, for the HA/KA indication, a short-term oral coagulation therapy is used; in most cases, the medication is dispensed during the hospitalisation for HA/KA, and patient is not subsequently treated. Because hospital dispensations to inpatients do not generate records in the DNHSPD, a potentially substantial proportion of patients treated for the HA/KA indication were not captured in the analysis.

For the indication DVT/PE, whenever a specific diagnosis of phlebitis was recorded, the use was classified as off-label. However, diagnostic codes for both phlebitis and thrombophlebitis of the deep veins of the lower extremities were classified as on-label. It cannot be ruled out that, for a proportion of patients with phlebitis alone, higher-level diagnostic codes, not distinguishing phlebitis from thrombophlebitis, were used to record diagnoses. This could potentially cause underestimation of the prevalence of off-label DVT/PE use by the available data. Finally, because lack of sales, apixaban utilisation could not be assessed during the first authorisation period, 18 May 2011 - 19 November 2012.

11.3. Interpretation

In this population-based nationwide study that included all initiators of apixaban in Denmark identifiable from outpatient dispensations, 82.6% of the patients initiating apixaban were

assigned an identifiable on-label indication. Because NVAF was the predominant on-label indication, and because not all NVAF diagnosed outside hospitals could be captured by the available data, the observed proportion of on-label use of apixaban is likely to be a conservative estimate. The observation, in Sweden, that inclusion of primary care diagnoses increased the prevalence of on-label use corroborates this conjecture. A very low number (N=18) of patients were identified with confirmed mechanical valves based on recorded procedure codes. Prevalences of liver and renal diseases were low as measured by diagnostic codes, but are likely underascertained in the absence of laboratory data on the nationwide sample.

11.4. Generalisability

The results of this study are likely to be generalisable to future populations of Danish patients and to other populations with similar underlying health care systems. The results of this study were similar to those reported in Sweden, despite differences in the primary health care systems in the two countries: in contrast to Denmark, in Sweden, general practitioners do not have gatekeeping function to specialist care.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

The majority (83%) of apixaban initiators in Denmark received the drug for an on-label indication; nearly 11% of patients had evidence of an off-label indication, and nearly 7% of patients could not be assigned to a known indication. Owing to absence of diagnoses from general practice in this study and given that NVAF is the most common on-label indication, diagnosed in general practice, the true extent of on-label NVAF use is likely greater and the true extent of off-label use is likely lower than suggested by the results.

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15. RESULTS TABLES AND FIGURES

Figure 15.1. Bar chart of each on-label indication, each off-label indication and any unknown indication, by month and year of study period (2011-2015)

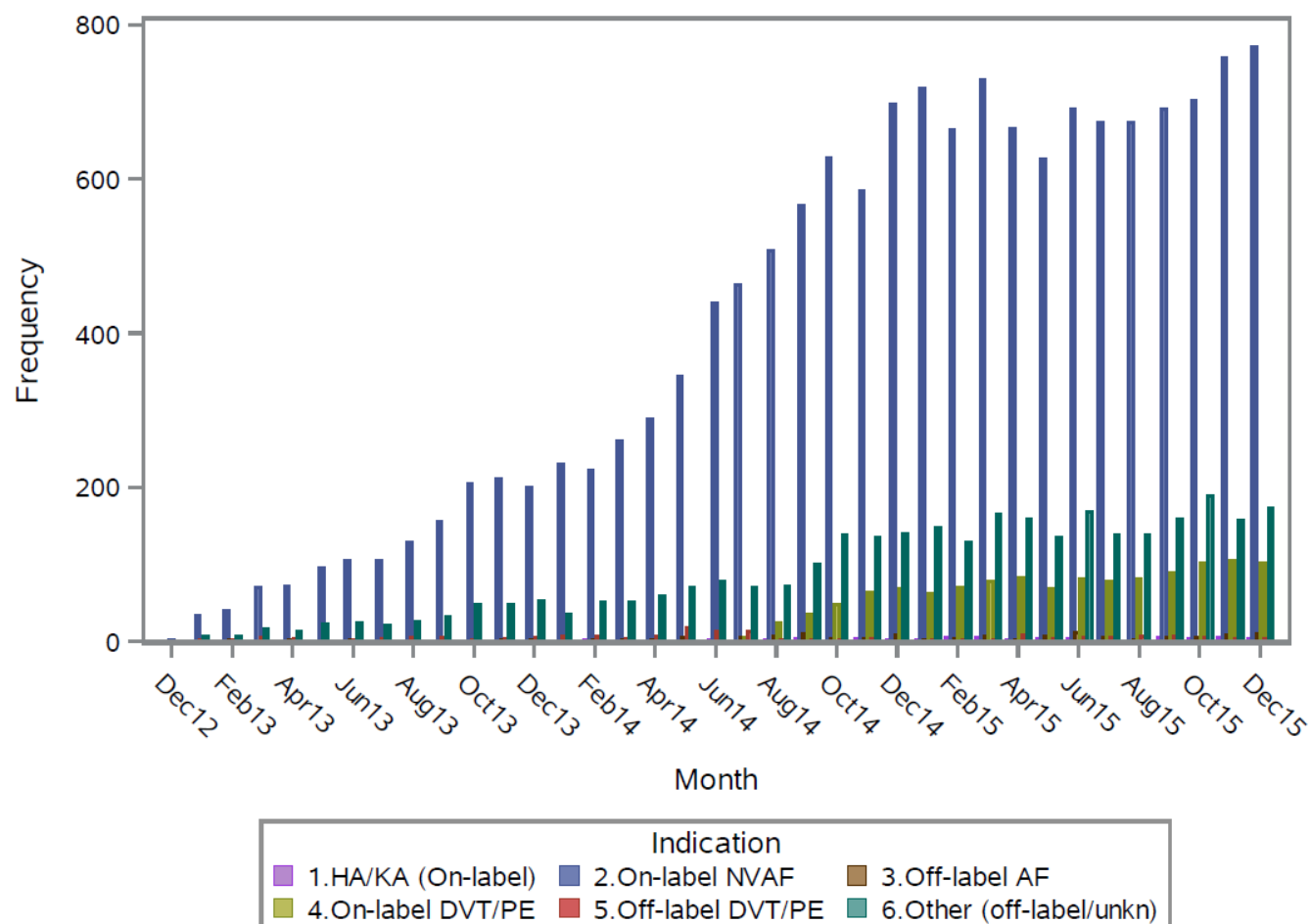


Figure 15.2. Bar chart of each on-label indication, each off-label indication and any unknown indication, by approval period (2011-2015)

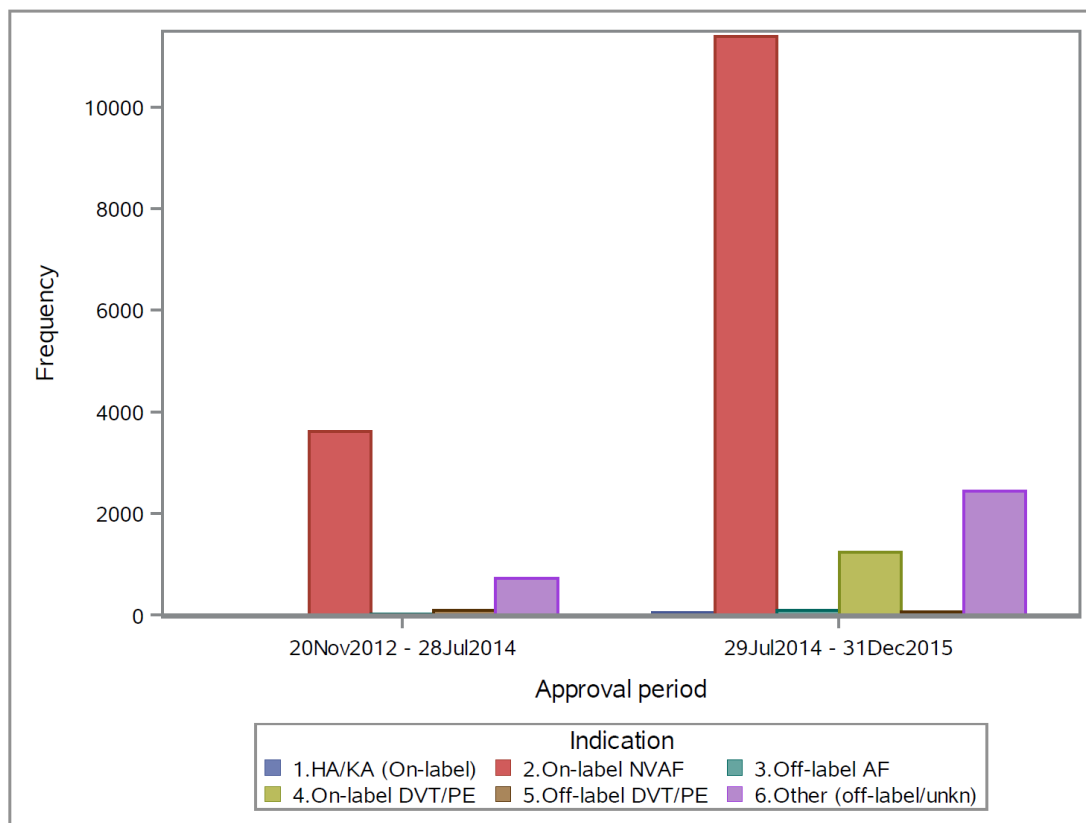


Figure 15.3. Bar chart of any on-label, any off-label and any unknown indication, by month and year of the study period (2011-2015)

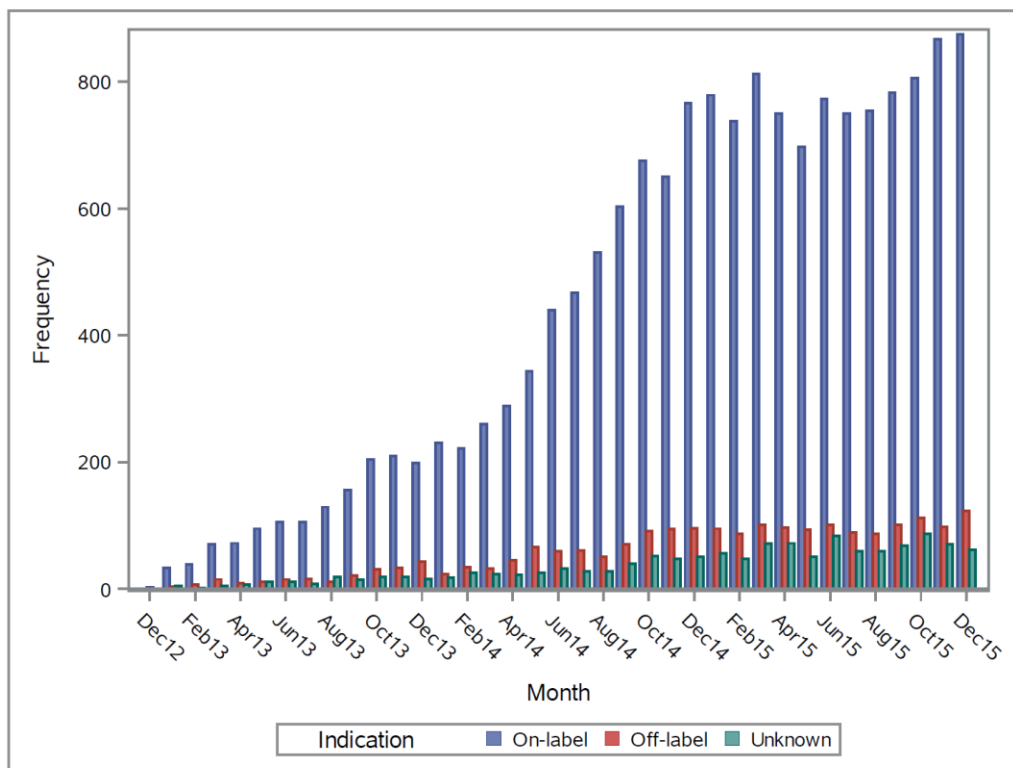


Figure 15.4. Bar chart of any on-label and any off-label indication for patients with an assigned indication, by month and year of the study period (2011-2015)

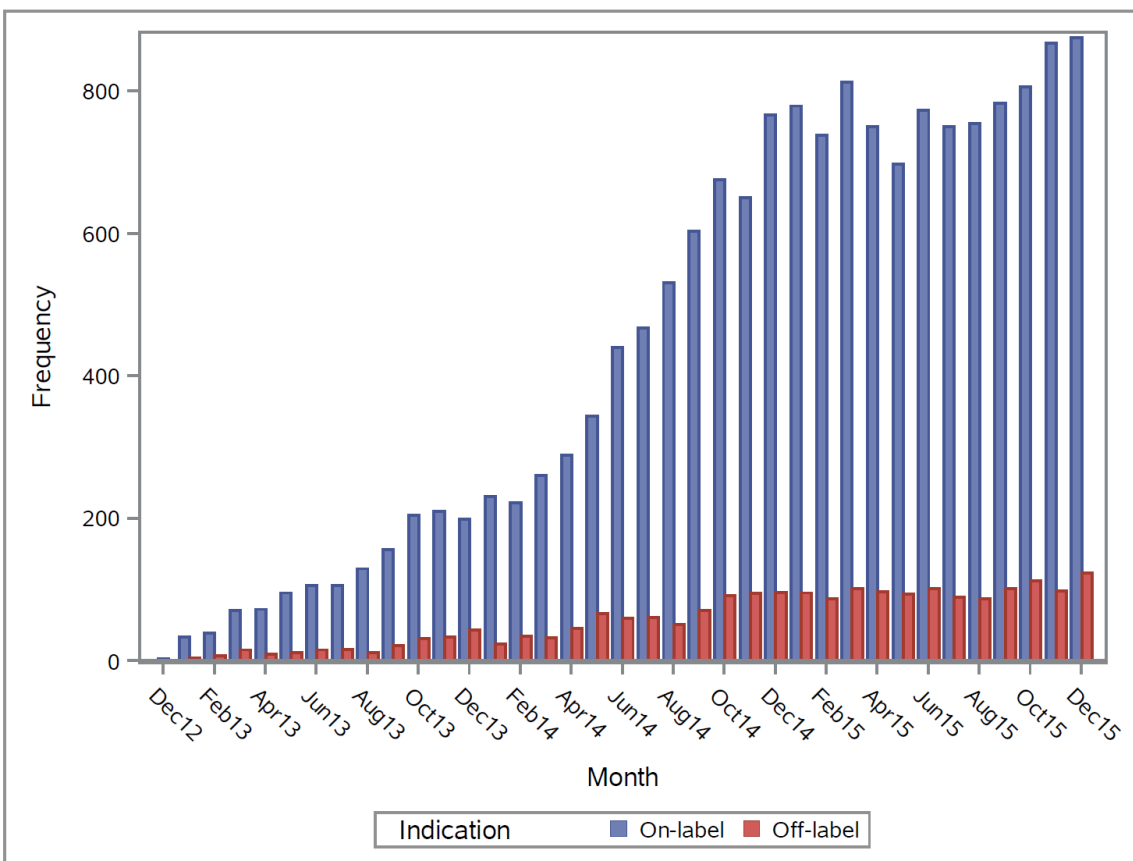


Table 15.1 Indications for apixaban use in Denmark, overall and by approval period (2011-2015)

Approval period (on-label indications)	Category	N	Percent (95% CI**)
Overall	All patients with first apixaban dispensation during the study*	19,709	
	On-label indication	16,278	82.6 (82.1 - 83.1)
	Elective HA/KA	43	0.2 (0.2 - 0.3)
	NVAF	15,002	76.1 (75.5 - 76.7)
	Pure on-label NVAF	13,547	68.7 (68.1 - 69.4)
	Potential on-label NVAF	1,455	7.4 (7.0 - 7.8)
	DVT/PE	1,233	6.3 (5.9 - 6.6)
	Off-label indication	2,120	10.8 (10.3 - 11.2)
	< 18 years of age	<5	NR
	Mechanical heart valve***	611	3.1 (2.9 - 3.4)
	Non-elective HA/KA	9	0.0 (0.0 - 0.1)
	Off-label NVAF/valvular AF	113	0.6 (0.5 - 0.7)
	Off-label DVT/PE	155	0.8 (0.7 - 0.9)
	Other surgery within 30 days before index date	302	1.5 (1.4 - 1.7)
	Other diagnoses any time before index date	928	4.7 (4.4 - 5.0)
	Unknown indication	1,311	6.7 (6.3 - 7.0)
	Known indication*	18,398	
	Any on-label indication among known indications	16,278	88.5 (88.0 - 88.9)
	Any off-label indication among known indications	2,120	11.5 (11.1 - 12.0)
18 May 2011 – 19 November 2012 (Elective HA/KA)	No dispensation of in Denmark observed during this period.		
20 November 2012 – 28 July 2014 (Elective HA/KA, NVAF)	All patients with first apixaban dispensation during the period*	4,449	
	On-label indication	3,615	81.3 (80.1 - 82.4)
	Elective HA/KA	<5	NR
	NVAF	3,613	81.2 (80.0 - 82.3)
	Pure on-label NVAF	3,346	75.2 (73.9 - 76.5)
	Potential on-label NVAF	267	6.0 (5.3 - 6.7)
	Off-label indication	528	11.9 (10.9 - 12.9)
	< 18 years of age	-	-
	Mechanical heart valve	135	3.0 (2.6 - 3.6)
	Non-elective HA/KA	<5	NR
	Off-label NVAF/valvular AF	18	0.4 (0.2 - 0.6)
	Off-label DVT/PE	96	2.2 (1.8 - 2.6)
	Other surgery within 30 days before index date	52	1.2 (0.9 - 1.5)
	Other diagnoses any time before index date	224	5.0 (4.4 - 5.7)
	Unknown indication	306	6.9 (6.2 - 7.7)
	Known indication*	4,143	
	Any on-label indication among known indications	3,615	87.3 (86.2 - 88.3)
	Any off-label indication among known indications	528	12.7 (11.7 - 13.8)
29 July 2014 – 31 December 2015 (Elective HA/KA, NVAF, DVT/PE)	All patients with first apixaban dispensation during the period*	15,260	
	On-label indication	12,663	83.0 (82.4 - 83.6)
	Elective HA/KA	41	0.3 (0.2 - 0.4)
	NVAF	11,389	74.6 (73.9 - 75.3)
	Pure on-label NVAF	10,201	66.8 (66.1 - 67.6)
	Potential on-label NVAF	1,188	7.8 (7.4 - 8.2)
	DVT/PE	1,233	8.1 (7.7 - 8.5)
	Off-label indication	1,592	10.4 (10.0 - 10.9)
	< 18 years of age	<5	NR
	Mechanical heart valve	476	3.1 (2.8 - 3.4)
	Non-elective HA/KA	6	0.0 (0.0 - 0.1)
	Off-label NVAF/valvular AF	95	0.6 (0.5 - 0.8)
	Off-label DVT/PE****	59	0.4 (0.3 - 0.5)
	Other surgery within 30 days before index date	250	1.6 (1.4 - 1.9)

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	Other diagnoses any time before index date	704	4.6 (4.3 - 5.0)
	Unknown indication	1,005	6.6 (6.2 - 7.0)
	Known indication*	14,255	
	Any on-label indication among known indications	12,663	88.8 (88.3 - 89.3)
	Any off-label indication among known indications	1,592	11.2 (10.7 - 11.7)

*The values is used as the denominator for proportions shown below.

**CI is calculated using the exact Clopper-Pearson method. Values of confidence limits may equal to values of point estimates due to rounding.

***Includes 18 patients with definite mechanical valves (defined by procedure codes FXN Implantation of a total artificial heart; FGE00 Replacement of tricuspid valve using mechanical prosthesis; FJF00 Replacement of pulmonary valve using mechanical prosthesis; FKD00 Replacement of mitral valve using mechanical prosthesis; FMD00 Replacement of mitral valve using mechanical prosthesis; or ICD-10 code T82.5 Breakdown [mechanical] of artificial heart).

****Off-label DVT/PE indications after the approval of the DVT/PE indication include thromboses and embolisms that are not included in the approved DVT/PE indication definition.

Abbreviations: AF atrial fibrillation; DVT deep vein thrombosis; HA hip arthroplasty; KA knee arthroplasty; NVAf non-valvular atrial fibrillation; PE pulmonary embolism.

NR: non-reportable to avoid identification of individuals.

<5 indicates a count between 1 and 4.

Table 15.2. Characteristics of patients initiating apixaban in Denmark by pre-defined indication status (2011-2015)

Characteristic	All	On-label indication			Off-label indication							Unknown indication
		Elective HA/KA	NVAF/AF	On-label DVT/PE	Age<18 years	Mechanical heart valve	Non-elective HA/KA	NVAF	Off-label DVT/PE	Surgery other than KA/HA	Disease other than NVAF or DVT/PE	
Total	19,709	43	15,002	1,233	<5	611	9	113	155	302	928	1,311
Sex, n (%)												
Male	10,172 (51.6)	17 (39.5)	7,735 (51.6)	582 (47.2)	<5	367 (60.1)	<5	53 (46.9)	82 (52.9)	149 (49.3)	529 (57.0)	654 (49.9)
Female	9,537 (48.4)	26 (60.5)	7,267 (48.4)	651 (52.8)	<5	244 (39.9)	6 (66.7)	60 (53.1)	73 (47.1)	153 (50.7)	399 (43.0)	657 (50.1)
Age at index date, years, n (%)												
<18	<5	-	-	-	<5	-	-	-	-	-	-	-
18-<45	299 (1.5)	-	100 (0.7)	130 (10.5)	-	<5	-	<5	16 (10.3)	10 (3.3)	6 (0.6)	31 (2.4)
45-<65	2,747 (13.9)	<5	2,044 (13.6)	318 (25.8)	-	36 (5.9)	-	12 (10.6)	49 (31.6)	40 (13.2)	88 (9.5)	158 (12.1)
65-<85	12,354 (62.7)	37 (86.0)	9,500 (63.3)	609 (49.4)	-	417 (68.2)	<5	77 (68.1)	62 (40.0)	181 (59.9)	625 (67.3)	842 (64.2)
85+	4,307 (21.9)	<5	3,358 (22.4)	176 (14.3)	-	154 (25.2)	5 (55.6)	22 (19.5)	28 (18.1)	71 (23.5)	209 (22.5)	280 (21.4)
Age at index date												
Mean (SD)	75 (11.5)	76 (7.4)	76 (10.8)	67 (16.7)	17 (0.7)	77 (9.2)	83 (9.2)	75 (11.0)	68 (16.2)	74 (13.3)	76 (10.1)	75 (11.7)
Median (IQR)	76 (68 - 83)	76 (72 - 82)	76 (68 - 84)	70 (58 - 80)	17 (16 - 17)	79 (72 - 85)	85 (75 - 89)	76 (69 - 84)	69 (58 - 81)	76 (68 - 84)	77 (70 - 84)	76 (69 - 83)
Time from initiation of apixaban until death, emigration or study end, months, median (IQR)	9.5 (4.2 - 15.5)	8.2 (2.8 - 11.3)	9.9 (4.4 - 16.0)	6.4 (2.6 - 10.8)	7.0 (6.4 - 7.6)	9.2 (3.9 - 14.6)	12.1 (4.2 - 16.1)	8.4 (3.1 - 14.8)	17.4 (5.9 - 20.2)	7.9 (3.2 - 13.6)	10.5 (4.6 - 16.3)	9.2 (4.1 - 15.7)
Prescriber specialty, n (%)												
General practice	4,738 (24.0)	5 (11.6)	3,435 (22.9)	208 (16.9)	-	118 (19.3)	<5	20 (17.7)	59 (38.1)	55 (18.2)	279 (30.1)	557 (42.5)
Cardiology	4,873 (24.7)	9 (20.9)	3,760 (25.1)	305 (24.7)	<5	194 (31.8)	-	45 (39.8)	39 (25.2)	56 (18.5)	215 (23.2)	248 (18.9)
Neurology	1,395 (7.1)	<5	1,099 (7.3)	30 (2.4)	-	45 (7.4)	-	11 (9.7)	10 (6.5)	15 (5.0)	149 (16.1)	35 (2.7)
Orthopaedic surgery	182 (0.9)	9 (20.9)	120 (0.8)	18 (1.5)	-	<5	<5	-	<5	20 (6.6)	<5	5 (0.4)

Internal medicine	5,520 (28.0)	15 (34.9)	4,322 (28.8)	474 (38.4)	-	159 (26.0)	<5	24 (21.2)	27 (17.4)	83 (27.5)	139 (15.0)	276 (21.1)
Thoracic and vascular surgery	90 (0.5)	-	51 (0.3)	-	-	7 (1.1)	-	<5	5 (3.2)	22 (7.3)	<5	<5
All other	405 (2.1)	-	302 (2.0)	38 (3.1)	-	12 (2.0)	-	<5	5 (3.2)	21 (7.0)	11 (1.2)	14 (1.1)
Specialty not identified	2,506 (12.7)	<5	1,913 (12.8)	160 (13.0)	-	74 (12.1)	<5	10 (8.8)	9 (5.8)	30 (9.9)	128 (13.8)	175 (13.3)

Abbreviations: AF atrial fibrillation; DVT deep vein thrombosis; HA hip arthroplasty; IQR interquartile range; KA knee arthroplasty; NVAf non-valvular atrial fibrillation; PE pulmonary embolism; SD standard deviation.

'-' indicates zero observations

<5 indicates a count between 1 and 4.

Table 15.3. Characteristics of apixaban treatment in Denmark, overall and by indication (2011-2015)

Characteristic	All	On-label indication			Off-label indication							Unknown indication
		Elective HA/KA	NVAF/AF	On-label DVT/PE	Age<18 years	Mechanical heart valve	Non-elective HA/KA	NVAF	Off-label DVT/PE	Surgery other than KA/HA	Disease other than NVAF or DVT/PE	
Total	19,709	43	15,002	1,233	<5	611	9	113	155	302	928	1,311
Calendar period of first dispensation, n (%)												
18 May 2011-19 November 2012	-	-	-	-	-	-	-	-	-	-	-	-
20 November 2012 – 28 July 2014	4,449 (22.6)	<5	3,613 (24.1)	-	-	135 (22.1)	<5	18 (15.9)	96 (61.9)	52 (17.2)	224 (24.1)	306 (23.3)
29 July 2014 – 31 December 2015**	15,260 (77.4)	41 (95.3)	11,389 (75.9)	1,233 (100)	<5	476 (77.9)	6 (66.7)	95 (84.1)	59 (38.1)	250 (82.8)	704 (75.9)	1,005 (76.7)
Pill strength at first dispensation, n (%)												
2.5 mg	7,811 (39.6)	14 (32.6)	5,927 (39.5)	407 (33.0)	<5	303 (49.6)	8 (88.9)	52 (46.0)	67 (43.2)	144 (47.7)	393 (42.3)	495 (37.8)
5.0 mg	11,898 (60.4)	29 (67.4)	9,075 (60.5)	826 (67.0)	<5	308 (50.4)	<5	61 (54.0)	88 (56.8)	158 (52.3)	535 (57.7)	816 (62.2)
Estimated cumulative duration of use, n (%)*												
<60 days	3,394 (17.2)	10 (23.3)	2,486 (16.6)	282 (22.9)	-	96 (15.7)	<5	21 (18.6)	39 (25.2)	61 (20.2)	153 (16.5)	243 (18.5)
60-120 days	3,704 (18.8)	14 (32.6)	2,610 (17.4)	395 (32.0)	<5	142 (23.2)	<5	30 (26.5)	25 (16.1)	83 (27.5)	147 (15.8)	256 (19.5)
121-180 days	1,891 (9.6)	<5	1,403 (9.4)	170 (13.8)	-	63 (10.3)	-	7 (6.2)	15 (9.7)	31 (10.3)	86 (9.3)	114 (8.7)
>180 days	10,720 (54.4)	17 (39.5)	8,503 (56.7)	386 (31.3)	<5	310 (50.7)	5 (55.6)	55 (48.7)	76 (49.0)	127 (42.1)	542 (58.4)	698 (53.2)
Estimated daily dose, mg*												
Median (IQR)	9.4 (5.2 - 10.0)	10.0 (5.0 - 10.0)	9.4 (5.2 - 10.0)	10.0 (5.4 - 10.0)	7.5 (5.0 - 10.0)	7.5 (5.0 - 10.0)	6.0 (5.0 - 7.4)	7.1 (5.0 - 10.0)	7.8 (5.0 - 10.0)	8.7 (5.2 - 10.0)	9.4 (5.1 - 10.0)	9.6 (5.1 - 10.0)
Minimum, maximum	0.0, 10.0	3.6, 10.0	0.1, 10.0	0.8, 10.0	5.0, 10.0	0.2, 10.0	5.0, 10.0	1.3, 10.0	0.2, 10.0	1.1, 10.0	0.4, 10.0	0.0, 10.0
Total number of dispensations during the study period, median (IQR)	5 (2 - 9)	3 (1 - 5)	5 (2 - 9)	3 (2 - 5)	4 (1 - 7)	4 (2 - 8)	3 (2 - 9)	4 (2 - 7)	4 (2 - 9)	4 (2 - 6)	5 (2 - 10)	4 (2 - 9)

Abbreviations: AF atrial fibrillation; DVT deep vein thrombosis; HA hip arthroplasty; IQR interquartile range; KA knee arthroplasty; NVAF non-valvular atrial fibrillation; PE pulmonary embolism.

*- indicates zero observations, <5 indicates a count between 1 and 4.

*Defined for patients with 2 or more dispensations of apixaban during the study period by dividing the amount dispensed by the number of days between the first and the second dispensations. For patients with only 1 dispensation or for patients with days between the dispensations resulting in apparent daily dose of >100 mg (N=175, days between dispensation ranged between 1 and 16), daily dose is assumed to be 5 mg for dispensations with 2.5-mg pill strength and 10 mg for dispensations with 5-mg pill strength.

**Off-label DVT/PE indications after the approval of the DVT/PE indication include thromboses and embolisms that are not included in the approved DVT/PE indication.

Table 15.4. Hospital-recorded comorbidity, among persons initiating apixaban in Denmark overall and by indication (2011-2015)

Comorbidity, n (%)*	All	On-label indication					Off-label indication					Unknown indication
		Elective HA/KA	NVAF/AF	On-label DVT/PE	Age<18 years	Mechanical heart valve	Non-elective HA/KA	NVAF	Off-label DVT/PE	Surgery other than KA/HA	Disease other than NVAF or DVT/PE	
Total	19,709	43	15,002	1,233	<5	611	9	113	155	302	928	1,311
Diabetes	3,068 (15.6)	<5	2,402 (16.0)	136 (11.0)	-	137 (22.4)	-	20 (17.7)	22 (14.2)	48 (15.9)	152 (16.4)	147 (11.2)
Cardiovascular disease	12,408 (63.0)	23 (53.5)	9,785 (65.2)	543 (44.0)	-	536 (87.7)	<5	85 (75.2)	72 (46.5)	173 (57.3)	775 (83.5)	414 (31.6)
Renal disease	1,117 (5.7)	<5	835 (5.6)	56 (4.5)	<5	87 (14.2)	<5	14 (12.4)	9 (5.8)	11 (3.6)	50 (5.4)	49 (3.7)
End-stage renal disease	14 (0.1)	-	8 (0.1)	<5	-	<5	-	<5	-	-	<5	<5
Liver disorders	433 (2.2)	<5	308 (2.1)	39 (3.2)	-	21 (3.4)	-	<5	7 (4.5)	10 (3.3)	17 (1.8)	27 (2.1)
Coagulation defects	372 (1.9)	<5	232 (1.5)	88 (7.1)	-	15 (2.5)	-	-	17 (11.0)	<5	11 (1.2)	<5
Intracranial haemorrhage	429 (2.2)	-	324 (2.2)	26 (2.1)	-	22 (3.6)	-	<5	7 (4.5)	5 (1.7)	30 (3.2)	13 (1.0)
Gastric, duodenal ulcer and peptic ulcer	1,483 (7.5)	<5	1,139 (7.6)	95 (7.7)	-	77 (12.6)	<5	11 (9.7)	5 (3.2)	22 (7.3)	61 (6.6)	70 (5.3)
Acute and subacute bacterial endocarditis	111 (0.6)	<5	28 (0.2)	8 (0.6)	-	46 (7.5)	-	22 (19.5)	-	<5	<5	<5
Oesophageal varices	31 (0.2)	-	26 (0.2)	<5	-	-	-	-	<5	-	<5	<5
Thrombocytopenia	81 (0.4)	-	55 (0.4)	6 (0.5)	-	6 (1.0)	-	-	<5	<5	<5	5 (0.4)
Recent brain or spinal surgery (within 30 days of apixaban dispensation)	83 (0.4)	-	66 (0.4)	<5	-	5 (0.8)	-	-	<5	10 (3.3)	-	-

Abbreviations: AF atrial fibrillation; DVT deep vein thrombosis; HA hip arthroplasty; IQR interquartile range; KA knee arthroplasty; NVAF non-valvular atrial fibrillation; PE pulmonary embolism.

'-' indicates zero observations

<5 indicates a count between 1 and 4.

*Lookback period from 1 January 1994 and up to and including the index date

Table 15.5. Concomitant and previous medication use (at least one dispensation) among persons initiating apixaban in Denmark, overall and by indication (2011-2015)

Medication	Type of use*	All n (%)	On-label indication					Off-label indication					Unknown indication
			Elective HA/KA	NVAF/AF	On-label DVT/PE	Age<18 years	Mechanical heart valve	Non-elective HA/KA	NVAF	Off-label DVT/PE	Surgery other than KA/HA	Disease other than NVAF or DVT/PE	
Antithrombotic agents, any	Prior	14,293 (73.0)	32 (74.4)	11,022 (73.9)	822 (67.2)	<5	579 (94.8)	<5	100 (89.3)	123 (79.4)	172 (57.0)	795 (85.9)	643 (49.7)
	Concomitant	5,108 (26.1)	6 (14.0)	3,907 (26.2)	289 (23.6)	-	214 (35.0)	<5	34 (30.4)	46 (29.7)	77 (25.5)	317 (34.3)	215 (16.6)
Vitamin K antagonists	Prior	6,021 (30.7)	8 (18.6)	4,840 (32.5)	420 (34.3)	<5	378 (61.9)	<5	60 (53.6)	84 (54.2)	21 (7.0)	94 (10.2)	114 (8.8)
	Concomitant	1,309 (6.7)	<5	1,023 (6.9)	96 (7.8)	-	64 (10.5)	-	11 (9.8)	21 (13.5)	13 (4.3)	36 (3.9)	44 (3.4)
Warfarin	Prior	5,981 (30.5)	8 (18.6)	4,808 (32.2)	416 (34.0)	<5	376 (61.5)	<5	60 (53.6)	84 (54.2)	21 (7.0)	92 (9.9)	114 (8.8)
	Concomitant	1,303 (6.7)	<5	1,019 (6.8)	96 (7.8)	-	64 (10.5)	-	11 (9.8)	20 (12.9)	13 (4.3)	35 (3.8)	44 (3.4)
Phenprocoumon	Prior	126 (0.6)	-	91 (0.6)	11 (0.9)	-	15 (2.5)	-	<5	<5	-	<5	-
	Concomitant	6 (0.0)	-	<5	-	-	-	-	-	<5	-	<5	-
Heparin group, any	Prior	612 (3.1)	<5	394 (2.6)	122 (10.0)	-	43 (7.0)	-	<5	17 (11.0)	<5	16 (1.7)	14 (1.1)
	Concomitant	150 (0.8)	-	98 (0.7)	24 (2.0)	-	5 (0.8)	-	-	8 (5.2)	<5	7 (0.8)	5 (0.4)
Heparin	Prior	<5	-	<5	-	-	<5	-	-	-	-	-	-
	Concomitant	<5	-	-	-	-	<5	-	-	-	-	-	-
Dalteparin	Prior	378 (1.9)	<5	256 (1.7)	60 (4.9)	-	31 (5.1)	-	<5	10 (6.5)	<5	11 (1.2)	7 (0.5)
	Concomitant	90 (0.5)	-	60 (0.4)	12 (1.0)	-	<5	-	-	<5	<5	5 (0.5)	<5
Enoxaparin	Prior	46 (0.2)	-	35 (0.2)	6 (0.5)	-	<5	-	-	-	-	-	<5
	Concomitant	<5	-	<5	-	-	-	-	-	-	-	-	-
Tinzaparin	Prior	210 (1.1)	-	114 (0.8)	60 (4.9)	-	14 (2.3)	-	-	10 (6.5)	<5	5 (0.5)	<5
	Concomitant	58 (0.3)	-	37 (0.2)	12 (1.0)	-	-	-	-	5 (3.2)	<5	<5	<5
Platelet aggregation inhibitors excl. heparin, any	Prior	11,436 (58.4)	27 (62.8)	8,817 (59.1)	479 (39.2)	-	514 (84.1)	<5	75 (67.0)	68 (43.9)	152 (50.3)	771 (83.4)	531 (41.1)
	Concomitant	2,821 (14.4)	<5	2,115 (14.2)	108 (8.8)	-	131 (21.4)	<5	14 (12.5)	12 (7.7)	57 (18.9)	257 (27.8)	122 (9.4)
Clopidogrel	Prior	3,426 (17.5)	<5	2,527 (16.9)	138 (11.3)	-	196 (32.1)	<5	25 (22.3)	28 (18.1)	48 (15.9)	381 (41.2)	79 (6.1)
	Concomitant	942 (4.8)	-	675 (4.5)	43 (3.5)	-	45 (7.4)	<5	<5	<5	24 (7.9)	117 (12.6)	32 (2.5)
Acetylsalicylic acid	Prior	10,524 (53.7)	25 (58.1)	8,169 (54.8)	434 (35.5)	-	487 (79.7)	<5	71 (63.4)	63 (40.6)	135 (44.7)	651 (70.4)	488 (37.7)
	Concomitant	1,845 (9.4)	<5	1,430 (9.6)	56 (4.6)	-	92 (15.1)	-	10 (8.9)	9 (5.8)	31 (10.3)	131 (14.2)	84 (6.5)
Dipyridamole	Prior	1,102 (5.6)	<5	842 (5.6)	55 (4.5)	-	46 (7.5)	<5	6 (5.4)	5 (3.2)	20 (6.6)	105 (11.4)	20 (1.5)
	Concomitant	202 (1.0)	<5	150 (1.0)	12 (1.0)	-	5 (0.8)	-	<5	<5	5 (1.7)	21 (2.3)	<5
Prasugrel	Prior	32 (0.2)	-	24 (0.2)	<5	-	<5	-	-	-	-	<5	-
	Concomitant	7 (0.0)	-	6 (0.0)	-	-	-	-	-	-	-	-	<5

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Medication	Type of use*	All n (%)	On-label indication					Off-label indication					Unknown indication
			Elective HA/KA	NVAF/A F	On-label DVT/PE	Age<18 years	Mechanical heart valve	Non-elective HA/KA	NVAF	Off-label DVT/PE	Surgery other than KA/HA	Disease other than NVAF or DVT/PE	
Ticagrelor	Prior	285 (1.5)	-	210 (1.4)	14 (1.1)	-	24 (3.9)	-	<5	-	7 (2.3)	27 (2.9)	-
	Concomitant	48 (0.2)	-	41 (0.3)	-	-	<5	-	-	-	<5	<5	-
Combinations	Prior	433 (2.2)	<5	315 (2.1)	22 (1.8)	-	20 (3.3)	-	<5	5 (3.2)	10 (3.3)	48 (5.2)	10 (0.8)
	Concomitant	37 (0.2)	<5	27 (0.2)	<5	-	-	-	-	-	<5	<5	<5
Direct thrombin inhibitors, any	Prior	2,301 (11.7)	6 (14.0)	2,016 (13.5)	33 (2.7)	-	86 (14.1)	<5	21 (18.8)	6 (3.9)	15 (5.0)	40 (4.3)	77 (6.0)
	Concomitant	745 (3.8)	<5	655 (4.4)	9 (0.7)	-	18 (2.9)	<5	6 (5.4)	<5	7 (2.3)	16 (1.7)	30 (2.3)
Dabigatran etexilate	Prior	2,301 (11.7)	6 (14.0)	2,016 (13.5)	33 (2.7)	-	86 (14.1)	<5	21 (18.8)	6 (3.9)	15 (5.0)	40 (4.3)	77 (6.0)
	Concomitant	745 (3.8)	<5	655 (4.4)	9 (0.7)	-	18 (2.9)	<5	6 (5.4)	<5	7 (2.3)	16 (1.7)	30 (2.3)
Direct factor Xa inhibitors, any	Prior	961 (4.9)	<5	651 (4.4)	178 (14.6)	-	34 (5.6)	-	6 (5.4)	18 (11.6)	10 (3.3)	24 (2.6)	38 (2.9)
	Concomitant	425 (2.2)	-	289 (1.9)	69 (5.6)	-	13 (2.1)	-	<5	13 (8.4)	<5	15 (1.6)	21 (1.6)
Rivaroxaban	Prior	961 (4.9)	<5	651 (4.4)	178 (14.6)	-	34 (5.6)	-	6 (5.4)	18 (11.6)	10 (3.3)	24 (2.6)	38 (2.9)
	Concomitant	425 (2.2)	-	289 (1.9)	69 (5.6)	-	13 (2.1)	-	<5	13 (8.4)	<5	15 (1.6)	21 (1.6)
Other antithrombotic agents, any	Prior	<5	-	-	-	-	<5	-	-	-	-	-	-
	Concomitant	-	-	-	-	-	-	-	-	-	-	-	-
Fondaparinux	Prior	<5	-	-	-	-	<5	-	-	-	-	-	-
	Concomitant	-	-	-	-	-	-	-	-	-	-	-	-
CYP3A4 and P-gp inhibitors	Prior	10,380 (53.0)	19 (44.2)	7,895 (52.9)	686 (56.1)	-	392 (64.2)	<5	66 (58.9)	76 (49.0)	149 (49.3)	522 (56.4)	574 (44.4)
	Concomitant	3,845 (19.6)	<5	3,003 (20.1)	190 (15.5)	-	144 (23.6)	<5	27 (24.1)	18 (11.6)	75 (24.8)	206 (22.3)	177 (13.7)
Antimycotics for systemic use	Prior	2,596 (13.3)	<5	1,935 (13.0)	216 (17.7)	-	85 (13.9)	-	15 (13.4)	23 (14.8)	36 (11.9)	121 (13.1)	161 (12.5)
	Concomitant	325 (1.7)	<5	251 (1.7)	25 (2.0)	-	11 (1.8)	<5	<5	<5	13 (4.3)	6 (0.6)	14 (1.1)
Selective serotonin reuptake inhibitors	Prior	4,045 (20.6)	<5	3,040 (20.4)	314 (25.7)	-	140 (22.9)	-	28 (25.0)	29 (18.7)	57 (18.9)	224 (24.2)	210 (16.2)
	Concomitant	1,413 (7.2)	<5	1,102 (7.4)	86 (7.0)	-	51 (8.3)	-	13 (11.6)	6 (3.9)	26 (8.6)	75 (8.1)	53 (4.1)
Verapamil	Prior	1,631 (8.3)	<5	1,413 (9.5)	42 (3.4)	-	72 (11.8)	-	12 (10.7)	<5	8 (2.6)	41 (4.4)	37 (2.9)
	Concomitant	612 (3.1)	-	535 (3.6)	13 (1.1)	-	13 (2.1)	-	<5	-	<5	16 (1.7)	28 (2.2)
Quinidine	Prior	<5	-	<5	-	-	-	-	-	-	-	<5	-
	Concomitant	-	-	-	-	-	-	-	-	-	-	-	-
Diltiazem	Prior	474 (2.4)	<5	376 (2.5)	25 (2.0)	-	18 (2.9)	-	<5	<5	6 (2.0)	30 (3.2)	13 (1.0)
	Concomitant	100 (0.5)	-	74 (0.5)	5 (0.4)	-	<5	-	<5	<5	<5	9 (1.0)	5 (0.4)
Atorvastatin	Prior	2,852 (14.6)	6 (14.0)	2,139 (14.3)	137 (11.2)	-	163 (26.7)	<5	21 (18.8)	14 (9.0)	46 (15.2)	199 (21.5)	126 (9.7)
	Concomitant	1,607 (8.2)	<5	1,227 (8.2)	67 (5.5)	-	71 (11.6)	-	7 (6.3)	10 (6.5)	39 (12.9)	107 (11.6)	77 (6.0)
Erythromycin or Clarithromycin	Prior	3,512 (17.9)	9 (20.9)	2,649 (17.8)	256 (20.9)	-	126 (20.6)	-	29 (25.9)	29 (18.7)	48 (15.9)	152 (16.4)	214 (16.6)

Apixaban
B0661073 NON-INTERVENTIONAL STUDY REPORT

Medication	Type of use*	All n (%)	On-label indication					Off-label indication					Unknown indication
			Elective HA/KA	NVAF/A F	On-label DVT/PE	Age<18 years	Mechanical heart valve	Non-elective HA/KA	NVAF	Off-label DVT/PE	Surgery other than KA/HA	Disease other than NVAF or DVT/PE	
	Concomitant	112 (0.6)	-	91 (0.6)	7 (0.6)	-	6 (1.0)	<5	<5	-	<5	<5	<5
Cyclosporin	Prior	11 (0.1)	-	9 (0.1)	<5	-	-	-	-	-	-	-	<5
	Concomitant	<5	-	-	-	-	-	-	-	-	-	-	<5
CYP3A4 and P-gp inducers	Prior	389 (2.0)	<5	306 (2.1)	34 (2.8)	-	7 (1.1)	-	<5	<5	5 (1.7)	16 (1.7)	14 (1.1)
	Concomitant	68 (0.3)	-	51 (0.3)	8 (0.7)	-	-	-	<5	<5	<5	<5	<5
Carbamazepine	Prior	233 (1.2)	<5	180 (1.2)	21 (1.7)	-	<5	-	<5	<5	<5	9 (1.0)	11 (0.9)
	Concomitant	42 (0.2)	-	33 (0.2)	<5	-	-	-	-	<5	<5	<5	<5
Dexamethasone	Prior	-	-	-	-	-	-	-	-	-	-	-	-
	Concomitant	<5	-	<5	-	-	-	-	-	-	-	-	-
Rifampicin or Rifabutin	Prior	48 (0.2)	-	39 (0.3)	6 (0.5)	-	<5	-	-	-	<5	<5	-
	Concomitant	5 (0.0)	-	<5	<5	-	-	-	-	-	-	-	-
Phenobarbital or primidone	Prior	97 (0.5)	-	78 (0.5)	6 (0.5)	-	<5	-	<5	-	<5	7 (0.8)	<5
	Concomitant	11 (0.1)	-	9 (0.1)	-	-	-	-	<5	-	-	<5	-
Phenytoin	Prior	25 (0.1)	-	19 (0.1)	<5	-	-	-	-	-	-	-	<5
	Concomitant	10 (0.1)	-	6 (0.0)	<5	-	-	-	-	<5	-	-	<5
Ethosuximide	Prior	<5	-	<5	-	-	-	-	-	-	-	-	-
	Concomitant	-	-	-	-	-	-	-	-	-	-	-	-
Commonly prescribed drugs**													
Proton pump inhibitors	Prior	9,871 (50.4)	23 (53.5)	7,430 (49.8)	676 (55.3)	<5	402 (65.8)	<5	75 (67.0)	79 (51.0)	146 (48.3)	486 (52.5)	551 (42.6)
	Concomitant	4,354 (22.2)	14 (32.6)	3,318 (22.2)	303 (24.8)	-	188 (30.8)	<5	28 (25.0)	36 (23.2)	83 (27.5)	202 (21.8)	178 (13.8)
Analgesics	Prior	13,853 (70.7)	39 (90.7)	10,561 (70.8)	863 (70.6)	<5	513 (84.0)	5 (55.6)	90 (80.4)	112 (72.3)	206 (68.2)	674 (72.9)	789 (61.0)
	Concomitant	5,901 (30.1)	35 (81.4)	4,457 (29.9)	427 (34.9)	<5	210 (34.4)	7 (77.8)	35 (31.3)	47 (30.3)	134 (44.4)	250 (27.0)	298 (23.0)
Anti-inflammatory and antirheumatic products, non-steroids (NSAIDs)	Prior	14,659 (74.8)	40 (93.0)	11,148 (74.7)	947 (77.4)	<5	454 (74.3)	6 (66.7)	83 (74.1)	120 (77.4)	222 (73.5)	702 (75.9)	936 (72.4)
	Concomitant	1,027 (5.2)	13 (30.2)	740 (5.0)	76 (6.2)	-	26 (4.3)	<5	6 (5.4)	7 (4.5)	22 (7.3)	40 (4.3)	96 (7.4)
Benzodiazepine derivatives***	Prior	236 (1.2)	-	177 (1.2)	16 (1.3)	-	9 (1.5)	-	<5	<5	<5	19 (2.1)	7 (0.5)
	Concomitant	55 (0.3)	-	46 (0.3)	<5	-	-	-	-	-	<5	<5	<5
Systemic anti-infectives	Prior	18,261 (93.2)	39 (90.7)	13,917 (93.3)	1,159 (94.8)	<5	589 (96.4)	7 (77.8)	107 (95.5)	141 (91.0)	267 (88.4)	857 (92.6)	1,177 (91.0)
	Concomitant	4,815 (24.6)	10 (23.3)	3,712 (24.9)	330 (27.0)	<5	166 (27.2)	<5	25 (22.3)	33 (21.3)	107 (35.4)	204 (22.1)	224 (17.3)

Abbreviations: AF atrial fibrillation; DVT deep vein thrombosis; HA hip arthroplasty; KA knee arthroplasty; NVAF non-valvular atrial fibrillation; PE pulmonary embolism.
‘-’ indicates zero observations

Medication	Type of use*	All n (%)	On-label indication					Off-label indication					Unknown indication
			Elective HA/KA	NVAF/AF	On-label DVT/PE	Age<18 years	Mechanical heart valve	Non-elective HA/KA	NVAF	Off-label DVT/PE	Surgery other than KA/HA	Disease other than NVAF or DVT/PE	

<5 indicates a count between 1 and 4.

Prior use defined by 1 or more dispensation dated from 2004 to 31 days before the date of the first dispensation of apixaban.

Concomitant use defined as 1 or more dispensation dated 30 days before/after the date of the first dispensation of apixaban

* Maximum period from 1 January 2004

**Not mutually exclusive with any other reported drugs

*** Not routinely reimbursed, may be under-recorded

Table 15.6. Distribution of other DVT/PE among 155 patients classified as ‘off-label DVT/PE’

Diagnosis*	Total =155, n (%)
Deep venous thrombosis	22 (14.2)**
Pulmonary embolism	42 (27.1)***
Phlebitis and thrombophlebitis of the deep veins of lower extremities	56 (36.1)
Other cerebrovascular disease	6 (3.9)
Phlebitis and thrombophlebitis other than phlebitis and thrombophlebitis of the deep veins of lower extremities	57 (36.8)
Portal vein thrombosis	6 (3.9)
Other venous embolism and thrombosis	12 (7.7)

*Categories are not mutually exclusive

**For these 22 dispensations there were <5 patients in each month and year preceding the approval date.

***Distribution of month and year of these 42 dispensations are as follows: Jan 2013: <5; Mar 2013: <5; Apr 2013: <5; Jul 2013: <5; Sep 2013: <5; Oct 2013: <5; Nov 2013: <5; Jan 2014: <5; Feb 2014: <5; Mar 2014: <5; Apr 2014: <5; May 2014: 12 (28.6%); Jun 2014: <5 (9.5%); Jul 2014: 7 (16.7%).

Table 15.7. Distribution of surgical procedures among 302 apixaban initiators classified as ‘off-label other surgery’ in Denmark (2011-2015)

Procedure*	Total=302, n (%)
Nervous system	10 (3.3)
Endocrine system	<5 (NR)
Eye and adjacent structures	17 (5.6)
Ear, nose and larynx	<5 (NR)
Teeth, jaws, mouth and pharynx	<5 (NR)
Heart and major thoracic vessels (other than implantation of a mechanical prosthetic heart valve or implantation of a total artificial heart)	36 (11.9)
Chest wall, pleura, mediastinum, diaphragm, trachea, bronchus and lung	29 (9.6)
Mammary gland	<5 (NR)
Digestive system and spleen	38 (12.6)
Urinary system, male genital organs and retroperitoneal space	13 (4.3)
Female genital organs	5 (1.7)
Obstetric procedures	<5 (NR)
Musculoskeletal system (other than KA/HA)	43 (14.2)
Knee or hip fracture surgery	18 (6.0)
Other orthopaedic surgery	26 (8.6)
Peripheral vessels and lymphatic system	31 (10.3)
Skin	24 (7.9)
Minor surgical procedures	46 (15.2)
Transluminal endoscopy	88 (29.1)
Investigative procedures connected with surgery	<5 (NR)

*Categories are not mutually exclusive

NR non-reportable to avoid identification of individuals

<5 indicates a count between 1 and 4

Table 15.8. Distribution of prespecified hospital diagnoses among 937 apixaban initiators classified as ‘other selected diagnoses before index date’ in Denmark (2011-2015)

Diagnosis*	Total =937, n (%)
Angina pectoris	447 (47.7)
Acute myocardial infarction	222 (23.7)
Subsequent myocardial infarction	5 (0.5)
Certain current complications following acute myocardial infarction	<5 (NR)
Other acute ischaemic heart diseases	16 (1.7)
Chronic ischaemic heart disease	394 (42.0)
Cerebral infarction	365 (39.0)
Stroke, not specified as haemorrhage or infarction	188 (20.1)
Arterial embolism and thrombosis	21 (2.2)

*Categories are not mutually exclusive

NR non-reportable to avoid identification of individuals

<5 indicates a count between 1 and 4

Table 15.9. Distribution of indications among 593 patients with potential mechanical valves and without a record of a mechanical valve

Indication category	Total=593, n (%)
On-label Elective HA/KA	<5 (NR)
On-label NVAf	444 (74.9)
On-label DVT/PE	16 (2.7)
Off-label HA/KA	<5 (NR)
Off-label AF	58 (9.8)
Off-label Other surgery	13 (2.2)
Off-label Other indication	44 (7.4)
Unknown indication	16 (2.7)

NR non-reportable to avoid identification of individuals

<5 indicates a count between 1 and 4

Table 15.10. Distribution of diagnostic and procedure codes classifying patients to the ‘potential mechanical valve’ off-label indication among 611 patients with potential mechanical valves and without a record of a mechanical valve

ICD-10 code	Code description	Number of records*
T820A	Mechanical complication of heart valve prosthesis (insufficiency)	<5
T820C	Mechanical complication of heart valve prosthesis (displacement)	<5
T826	Infection and inflammatory reaction due to cardiac valve prosthesis	<5
T828	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	26
T828P	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts (specification: functional problems with pacemaker treatment)	7
T828PM	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts (specification: pacemaker-induced tachycardia)	<5
T829	Unspecified complication of cardiac and vascular prosthetic device, implant and graft	7
Z952	Presence of prosthetic heart valve	1,031
Z954	Presence of other heart-valve replacement	82
Z959	Presence of cardiac and vascular implant and graft, unspecified	158
Procedure code	Code description	
FJF10	Replacement of pulmonary valve using biological prosthesis	<5
FJF20	Replacement of pulmonary valve using homograft	<5
FKA00	Commissurotomy of mitral valve	<5
FKD00	Replacement of mitral valve using mechanical prosthesis	<5
FKD10	Replacement of mitral valve using biological prosthesis	39
FMD00	Replacement of aortic valve using mechanical prosthesis	21
FMD10	Replacement of aortic valve using biological prosthesis	410
FMD11	Transapical replacement of aortic valve using biological prosthesis	13
FMD12A	Transaortic transcatheter aortic valve implantation (TAVI)	<5
FMD14	Percutaneous replacement of aortic valve using biological prosthesis	54
FMD20	Replacement of aortic valve using homograft	5
FMD30	Replacement of aortic root using homograft and reimplantation of coronary arteries	6
FMD96	Other prosthetic replacement of aortic valve	<5

*Multiple records possible for the same patient

NR non-reportable to avoid identification of individuals

<5 indicates a count between 1 and 4