NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

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Marketing Authorisation Holder (MAH)	Bristol-Myers Squibb/Pfizer EEIG
Joint PASS	No
Research question and objectives	This is a descriptive study using retrospectively collected data from electronic health record databases. The study describes the utilization pattern of apixaban in the Netherlands (01 Dec 2011 through 31 Dec 2014). The study aimed 1) to estimate the proportions of apixaban users who receive the drug for the approved indications at the time of the first apixaban dispensing and 2) to describe the characteristics of the patients who were prescribed apixaban for

	on-label and off-label indications.
Country(-ies) of study	The Netherlands
Author	[redacted]

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	Bristol-Myers Squibb/Pfizer EEIG
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Annex 1. List of stand-alone documents

Protocol Amendment 3

1. ABSTRACT (STAND-ALONE DOCUMENT)

Title: POST-APPROVAL SAFETY STUDY (PASS) OF THE UTILIZATION PATTERN OF APIXABAN IN THE NETHERLANDS

Date: 20 May 2016

Name and affiliation of the main author:
[redacted]

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 is a concerning aspect of apixaban (ELIQUIS®) utilization in real-world clinical practice, but the frequency of off-label apixaban use is not known.

Research question and objectives: The objective of this study is to estimate the proportions of apixaban users who receive the drug for the approved indications at the time of the first apixaban dispensing, and describe the characteristics of the patients who were prescribed apixaban for on-label and off-label indications.

Study design: This is a descriptive study using retrospectively collected data from linked electronic healthcare databases in the PHARMO Database Network in the Netherlands.

Setting: The study included individuals with an apixaban dispensing between 1 December 2011 and 31 December 2014 who were included in the PHARMO In-patient or Out-patient Pharmacy Databases. For a subset of these individuals, primary care records were available from the PHARMO General Practitioner (GP) Database. The PHARMO Database Network includes electronic healthcare data for over 4 million people in the Netherlands.

Subjects and study size: This is a descriptive study assessing the utilization pattern of apixaban in real-world in-patient and out-patient settings. All apixaban users identified in the In-Patient or Out-patient Pharmacy Databases between 01 December 2011 and 31 December 2014 were included in this study. There were no study exclusion criteria.

Variables and data sources: Apixaban dispensing was identified in the In-patient and Out-patient Pharmacy databases. Records from the GP database and the Hospitalisation Database were linked to provide information about the indication and comorbidities for which apixaban was used. Comedications were identified in the Out-patient Pharmacy Database.

Data were collected on the users' age, gender, and the length of time they contributed data to the database. Data on the users' dispensings and their recent clinical history including potential reasons for apixaban use were also ascertained. Users were classified as on-label if they had records of Total Knee Arthroplasty or Total Hip Arthroplasty (TKA/THA) within

30 days prior to the date of first apixaban dispensing, or nonvalvular atrial fibrillation (NVAF), deep venous thrombosis (DVT) or pulmonary embolism (PE) any time prior to the first apixaban dispensing.

Apixaban dispensations that were not classified as on-label were classified as off-label if the corresponding patient's medical records included evidence of a pre-defined off-label use. If neither on-label nor off-label use could be identified the patient's indication was considered unknown.

Results: In total, 896 apixaban users were identified in the PHARMO Database Network. For all of these users hospital admission data was available up to 2013. Among users who started apixaban in 2014, 20% had hospital admission data available up to the first dispensing. For 137 (15%) apixaban users, primary care information from the GP Database was available.

Apixaban users tended to be more often male (57%) than female (43%) and the mean age at the first dispensing of apixaban was 70 years. The initial prescriber of apixaban was most often a cardiologist (60%). The most common apixaban dose (85%) was 10 mg per day taken as 5 mg twice a day, which was consistent with the dosing guidance for the NVAF indication.

Among 896 apixaban users identified in the PHARMO Database Network, 307 users (34%; CI 95 31-37%) were assigned an on-label indication, mostly NVAF (33%; CI 95 30-37%, N = 300), and 40 users (4%; CI 95 3-6%) were assigned an off-label indication. No indication could be assigned to the majority of apixaban users (61%; CI 95 58-64%, N = 549). The estimated 34% of on-label use of apixaban was likely to be lower than the true proportion of on-label use due to incomplete linkages between in-patient, out-patient, hospital and GP databases. Only 15% (137/896) of apixaban users had both hospital and GP data, which was critical to capturing diagnoses that were suggestive of an apixaban indication. In this sub-cohort of 137 apixaban users with both GP and hospital data, 92 users (67%; CI 95 59-75) had on on-label indications, 2 (1%; CI 95 0-3%) had off-label indications and 43 (31% CI 95 24-39%) patients could not be classified as on-label or off-label. The majority of patients in the subcohort (64%; CI 95 56-72%) were assigned to the NVAF indication but small numbers of patients with THA/TKA (2%, N = 3) and DVT/PE (1%, N = 1) were identified.

Restricting the study cohort to those with an assigned indication leads to an estimated on-label proportion of 88% (307 of 347; CI 95 85-92%) overall and 98% (92 of 94; CI 95 95-100%) in the subset of apixaban users with both hospital and GP data.

A history of chronic kidney disease and liver disorders were observed among about 1% of apixaban users.

Discussion: In order to retrospectively distinguish off-label from on-label apixaban use with healthcare databases, records of the prescribed indication must be available. The data sources used to infer indication of use in this study were the GP Database and the Hospitalisation

Database. NVAF with no concerning symptoms may not require hospital admission and therefore the GP data is crucial for the assignment of indications.

NVAF may be the main indication for apixaban use in the Netherlands. Although for many users the indication of use remained unknown, the available data do not suggest extensive off-label use.

Marketing Authorisation Holder(s):

Bristol-Myers Squibb/Pfizer EEIG

Names and affiliations of principal investigators:

[redacted]

2. LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition
AF	Atrial Fibrillation
ATC	Anatomical Therapeutic Chemical classification system
CI 95	95% Confidence Interval
CVV	Classificatie van Verrichtingen (Classification of procedures)
DVT	Deep Vein Thrombosis
GP	General Practitioner
ICD-9	International Statistical Classification of Diseases and Related Health Problems - Ninth Revision
ICD-10	International Statistical Classification of Diseases and Related Health Problems - Tenth Revision
ICPC	International Classification of Primary Care
IQR	Inter-Quartile Range
NVAF	Non-Valvular Atrial Fibrillation
NYHA	New York Heart Association

Abbreviation/Acronym	Definition
PE	Pulmonary Embolism
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Systemic Embolism
SmPC	Summary of Product Characteristics
THA	Total Hip Arthroplasty
TIA	Transient Ischaemic Attack
TKA	Total Knee Arthroplasty
VTE	Venous ThromboEmbolism

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Name, degree(s)	**Title**	**Affiliation**
[redacted]	[redacted]	[redacted]
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[redacted]		[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	Q4 2014	05 November 2014	None
End of data collection	Q4 2015	Q1 2016	
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 PHARMO was delayed and with agreement from the

Milestone	Planned date	Actual date	Comments
			Agency, the interim report was delivered at a later date. (B0661018 Protocol)
Final report of study results	31 May 2016	20 May 2016	Amended date as agreed on with the Agency. (B0661018 Protocol)

6. RATIONALE AND BACKGROUND

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 labelled indications, or use in patients who do not meet age requirements, or other criteria as outlined in the SmPC.

Apixaban is an orally administered anticoagulant that inhibits coagulation factor Xa. It is currently approved in the European Union for the prevention of venous thromboembolism (VTE) in adults undergoing elective total hip arthroplasty (THA) or elective total knee arthroplasty (TKA), for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) and one or more risk factors, and for the treatment and subsequent prevention of deep venous thrombosis (DVT) and pulmonary embolism (PE); these indications, referred to as THA/TKA, NVAF, and treatment of DVT/PE, along with the date of approval are shown in Table 6.1. Use of apixaban outside of the approved indications is a regulatory and safety concern.

To address this concern, the Sponsor conducted this study describing the apixaban utilization pattern in the Netherlands with the PHARMO Database Network. The PHARMO Database Network includes in-patient and out-patient dispensing data (both secondary and primary care). Diagnostic information is available from hospitalised in-patients and primary care, but not from outpatient specialist visits or in-hospital treatment for less than 24 hours (or not requiring a bed). Apixaban tablets may be first administered to hospitalized in-patients who have undergone elective TKA/THA and then continue to be prescribed in the out-patient setting following discharge from the hospital. In this case, the PHARMO Database Network will capture the indication and the patient will be classified as on-label or off-label. Alternatively, a specialist, such as a cardiologist, may diagnose a patient with NVAF in the out-patient setting. In this case, the specialist diagnosis will not be captured, but the General Practitioner (GP), who acts as a gatekeeper for health services in the Netherlands, will record the diagnosis.

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

Table 6.1. Indications for apixaban and dates of authorisation

	Abbreviated Indication	Indication	Date of EMA Authorization
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 >= 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class >= II).	19 November 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
TKA/THA: total knee or hip arthroplasty
VTE: Venous thromboembolic events

7. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this study was to describe the utilization patterns of apixaban in the Netherlands.

Specifically, the study aimed to:

1. Estimate the proportions of apixaban users who receive the drug for the approved indications at the time of the first apixaban dispensing,
2. Describe the characteristics of the patients who were 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
2*	22 January 2013	Substantial	6.2-6.3, 7.2	Addition of NVAF indication	EMA authorised NVAF indication
			7.1, 9	More details on sample size were presented.	Clarify sample size was made
			1.1, 3	Writing clarification	Clarifications were made to the writing to more accurately describe study
3	19 May 2015	Substantial	1.1	Addition of DVT/PE treatment added.	EMA authorised DVT/PE indication
			6.3, 7.2	A longer timeframe 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 the Netherlands	Sample size was updated to reflect current projections
			1.1, 6.1 – 6.4, 7.1-7.3, 9, 10.2	Updated AE language, and data sources for sensitivity analysis, and other language	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

9. RESEARCH METHODS

9.1. Study design

This is a descriptive study using retrospectively collected data from electronic healthcare databases. The study describes the utilization pattern of apixaban users with data available through the PHARMO Database Network in the Netherlands.

9.2. Setting

Apixaban dispensing was identified in the Out-patient and In-patient Pharmacy Databases. Relevant clinical histories for the apixaban users were obtained from the Hospitalisation Database. A subcohort was used to augment the data from the Hospitalisation Database with diagnoses from the GP Database. Indications for apixaban use were inferred from applicable hospital discharge diagnoses and procedure codes and from GP diagnoses. More information on the databases is found in Section 9.5.

The study period was 01 December 2011 through 31 December 2014.

9.3. Subjects

All users identified in the Out-patient Pharmacy Database or In-patient Pharmacy Database who received an apixaban dispensing during the study period were included in this study.

The date of the first apixaban dispensing observed in the database was considered the index date. On-label and off-label use was classified during time windows relative to this index date.

This is a descriptive study assessing the utilization pattern of apixaban in real-world in-patient and out-patient settings. There were no study exclusion criteria and no mandated dosing or duration requirement.

9.4. Variables

9.4.1. Descriptive data

The following patient demographics and characteristics were reported:

- Gender: Male, Female,
- Age at first apixaban dispensing date: <18 years, 18-44 years, 45-64 years, 65-84 years, 85+ years, mean and standard deviation (SD), median and interquartile range (IQR),
- Database history before the first apixaban dispensing: <1 year, 1-4 years, 5-9 years, 10+ years, mean and standard deviation (SD), median and interquartile range (IQR),
- Database follow-up after the first apixaban dispensing: <6 months, 6-11 months, 12+ months, mean and standard deviation (SD), median and interquartile range (IQR),
- Specialty of first prescriber: GP, internal medicine, cardiology, surgery, other.

9.4.2. Outcome data

9.4.2.1. Indication of use

The main endpoint of interest for the study was indication for apixaban use, which was categorized as on-label or off-label.

For the purpose of this study, on-label use of apixaban was defined as a dispensing of the drug to:

1) An adult (i.e., 18 years of age or older) and,
2) A patient whose hospital records include:
    a) An elective THA/TKA within 30 days before the apixaban prescription, or,
    b) An apixaban prescription after 19 November 2012 and a diagnosis of NVAF any time before the apixaban prescription, or,
    c) An apixaban prescription after 28 July 2014 and a diagnosis of DVT or PE any time before the apixaban prescription.

All treatment indications approved during the study were classified and are reported as on-label only following the date of approval of this indication and are reported as off-label on the date of approval and prior to that date. See also Table 6.1.

Identification of TKA / THA and other surgeries

THA, TKA, and other orthopaedic surgeries were identified via appropriate procedure codes and ICD-9-CM and ICD-10 codes from linked hospital discharge diagnoses, and by ICPC codes and free text search in the linked GP data.

The following algorithm was used to identify the apixaban users who have undergone elective THA/TKA surgery.

- First, procedure codes were used to identify all apixaban users who had undergone THA/TKA surgery within 30 days before apixaban dispensing including total and partial replacement procedures (i.e., elective surgeries on the day of the dispensing and up to 29 days prior to the day of dispensing are on label). These procedure codes are provided in Table 15.1.

- Second, hospital discharge diagnoses (both primary and secondary) were used to see if these included hip or knee fracture diagnostic codes within 30 days before apixaban dispensing (i.e., on the day of the dispensing and up to 29 days prior to the day of dispensing). These procedure codes are provided in Table 15.2.

    - If the primary or secondary discharge diagnoses included hip or knee fracture, then surgery was considered non-elective and apixaban dispensing was classified as off-label.

    - If the primary or secondary discharge diagnoses did not include hip or knee fracture, then surgery was considered elective and apixaban dispensing was classified as on-label.

- Third, for the subgroup with GP data available, GP diagnosis codes and structured text fields were mined to identify THA/TKA surgery and fractures within 30 days

before apixaban dispensing (i.e., on the day of the dispensing and up to 29 days prior to the day of dispensing).

Identification of NVAF and other conditions

Apixaban users with an on-label NVAF indication were those with an atrial fibrillation (AF) diagnosis code and no record of either mitral stenosis or an implanted mechanical prosthetic heart value. The European Heart Rhythm Association defines NVAF as, "AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis (usually of rheumatic origin)"[1]. However, the severity of the mitral stenosis cannot be ascertained from the PHARMO records, so any evidence of mitral stenosis regardless of the severity as well as any evidence of a prosthetic heart valve including a fully artificial heart excludes the patient from an on-label NVAF classification. NVAF can be a chronic condition, and therefore a diagnosis of AF any time before the apixaban dispensing was interpreted as evidence of an on-label or off-label indication. Similarly, mitral stenosis or the implantation of a mechanical heart valve any time prior to the apixaban diagnosis excluded the patient from an on-label NVAF classification. Primary and secondary hospital discharge codes were examined first followed by GP diagnostic codes. ICD-9-CM and ICD-10-CM codes for AF are provided in Table 15.3 and ICD-9-CM and ICD-10-CM codes that define a mechanical heart valve and mitral stenosis are in Table 15.4.

Indication for the treatment of DVT/PE

Apixaban users with an on-label DVT/PE indication were those with a primary or secondary discharge code for DVT or PE or those with a GP record of DVT or PE any time before the apixaban dispensing. Primary and secondary hospital discharge codes were examined and GP diagnostic codes and free text were assessed where available. Diagnosis codes are provided in Table 15.5.

Off-label and unknown indications

Apixaban users who did not have evidence of on-label indications were examined for off-label indications. Specific diagnoses and surgeries other than THA/TKA from the hospital discharge records and the GP data at the time of or within 30 days prior to the first apixaban dispensing of off-label use were considered as the possible indications for the off-label use. If discharge records during this period did not provide possible indications, information from hospital discharges or GP consultations up to 365 days before the first apixaban dispensing were also examined. Table 15.6 shows more detail on off-label diagnosis codes. If on-label or off-label indications could not be identified, then the patient was classified as having an unknown indication.

9.4.2.2. Apixaban dose and duration

Apixaban treatment was assessed by selecting all dispensings from the Out-patient and In-patient Pharmacy Database between 01 December 2011 and 31 December 2014. The dispensings were converted into treatment episodes of uninterrupted use.

The duration of use was determined for these dispensings to construct episodes of continuous use. The duration of use was calculated by dividing the number of units dispensed by the number of units used per day. Use of the drug class was considered uninterrupted if the duration of a gap between dispensings was less than half the period of the given dispensing or less than 7 days[2]. Otherwise, apixaban use was considered interrupted and the treatment episode ended. As patients are likely to refill medication before the end of the previous dispensing, the start of the duration of a dispensing within an episode of use was shifted to the end of the duration of the previous dispensing. The end date of an episode was set at half the duration of the final dispensing within that episode. Apixaban users could contribute multiple treatment episodes to the analysis.

The following was assessed:

- Treatment duration: < 10 days, 10-14 days, 15-31 days, 32-38 days, >38 days
- Treatment dose: 5 mg, 10 mg, 20 mg.

Treatment duration was based on the first episode of continuous use. Treatment dose was the daily dose on the date of the first apixaban dispensing (and during the first apixaban dispensing).

9.4.2.3. Concomitant medication and co-morbidity

Concomitant medication use was defined as use within 30 days before and after/including the date of first apixaban dispensing. Dispensings of selected drug groups were assessed:

Antithrombotic agents
- Vitamin K antagonists
- Heparins
- Platelet aggregation inhibitors excluding heparin
- Enzymes
- Direct thrombin inhibitors
- Other antithrombotic agents

Anti-inflammatory and anti-rheumatic products, non-steroids

CYP3A4 and P-gp inhibitors
- Antimycotics for systemic use
- Protease inhibitors
- Selective serotonin reuptake inhibitors
- Phenylalkylamine derivatives
- Antiarrhythmics, class Ia
- Selective beta blocking agents
- Benzothiazepine derivatives
- HMG CoA reductase inhibitors
- Eryithromycin
- Clarithromycin

- Selective immunosuppressants

CYP3A4 and P-gp inducers

- Carboxamide derivatives
- Thiazolidinediones
- Glucocorticoids
- Short-acting sulfonamides
- Macrolides (excl erythromycin and clarithromycin)
- Antibiotics for tuberculosis
- Non-nucleoside reverse transcriptase inhibitors
- Preparations increasing uric acid excretion
- Barbiturates and derivatives
- Hydantoin derivatives
- Succinimide derivatives
- Piperidinedione derivatives
- St. John's Wart

ATC codes are provided in Table 15.7. Besides this list of specified drugs, common medication used within 6 months before the date of the first apixaban dispensing was listed as an indication of comorbidity.

Co-morbidity was defined as a diagnosis within 365 days before the first apixaban dispensing. Hospital discharge and GP diagnoses of selected diagnoses were assessed:

- Chronic kidney disease (CKD)
- Acute and subacute necrosis of liver
- Chronic liver disease and cirrhosis
- Liver abscess and sequelae of chronic liver disease
- Other disorders of liver
- Coagulation defects
- Subarachnoid haemorrhage
- Intracerebral haemorrhage
- Other and unspecified intracranial haemorrhage
- Gastric ulcer
- Duodenal ulcer
- Peptic ulcer, site unspecified
- Acute and subacute bacterial endocarditis
- Oesophageal varices with bleeding
- Oesophageal varices without mention of bleeding
- Oesophageal varices in diseases classified elsewhere
- Primary thrombocytopenia
- Secondary thrombocytopenia
- Thrombocytopenia, unspecified
- Incision and excision of skull, brain and meninges

- Operations on spinal cord and spinal canal structures

ICD-9, ICD-10 and ICPC codes are provided in Table 15.8.

9.5. Data sources and measurement

Data for the study were obtained from the PHARMO Database Network in the Netherlands [3,4]. The longitudinal nature of the PHARMO Database Network system enables follow-up on more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of ten years. Data collection period, catchment area and overlap between data sources differ. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Other information available is dependent on the data source.

To address the objectives of the present study the following PHARMO databases were used:

- Out-patient Pharmacy Database
- In-patient Pharmacy Database
- GP Database
- Hospitalisation Database

A detailed description of these databases is given below. Details relating to the measurement of variables are described in Section 9.4.

9.5.1. Out-patient Pharmacy Database

The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensings are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System (WHO Anatomical Therapeutic Chemical Classification System [www.whocc.no]). Out-patient pharmacy data cover a catchment area representing 3.8 million residents.

9.5.2. In-patient Pharmacy Database

The In-patient Pharmacy Database comprises drug dispensings from the hospital pharmacy given during a hospitalization. The dispensing records include information on type of drug, start and end date of use, strength, dosage regimen and route of administration. Drug dispensings are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System (WHO Anatomical Therapeutic Chemical Classification System [www.whocc.no]). In-patient pharmacy data cover a catchment area representing 2.0 million residents.

9.5.3. General Practitioner Database

The GP Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System (WHO Anatomical Therapeutic Chemical Classification System [www.whocc.no]). Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) (International Classification of Primary Care [www.nhg.org]), which can be mapped to ICD codes, but can also be entered as free text. GP data cover a catchment area representing 2.5 million residents.

9.5.4. Hospitalisation Database

The Hospitalisation Database comprises hospital admissions from the Dutch Hospital Data Foundation (Dutch Hospital Data Foundation [www.dutchhospitaldata.nl]) for more than 24 hours and admissions for less than 24 hours for which a bed is required. The records include information on discharge diagnoses, procedures, and hospital admission and discharge dates. Diagnoses are coded according to the International Classification of Diseases (WHO International Classification of Diseases [www.who.int]) and procedures are coded according to the Dutch Hospital Data Foundation owned registration system for procedures [www.dutchhospitaldata.nl] which links to the Dutch Healthcare Authority (NZa) declaration codes [www.nza.nl] and the Dutch Classification of Procedures (Dutch Classification of Procedures [class.who-fic.nl]).

For 2014, due to a change in governance, central permission for use of the hospitalization data was not granted by the Dutch Hospital Data Foundation but permission needed to be obtained from each individual hospital.

For this study, hospitalization data were thus available up to 31 December 2013 for all apixaban users, but limited data were available for 2014. Further implications are discussed in section 11.2.

9.6. Bias

The assignment of indication of apixaban use depends on the recording of the condition in the database, as further discussed in section 11.2. There may be misclassification of indication for apixaban use. In the overall cohort, there is higher sensitivity for hospital-based indications (orthopaedic procedures, PE) than for conditions that may not need hospital admission (NVAF, DVT) as only a subset is also covered by the GP Database.

Incomplete linkages between in-patient, out-patient, hospital and GP databases or insufficient record retrieval in any one of these databases could result in misclassification of indication. This in particular applies to apixaban users who started in 2014, because for only few of

them hospitalization data was available up to the date of first apixaban dispensing (most had data up to 31 December 2013, see section 9.5.4).

9.7. Study Size

This is a descriptive study of drug usage without any pre-defined hypothesis to be tested. Therefore, no power calculations for hypothesis testing were relevant. All individuals identified to have received apixaban in the database in the study period were included in the study without any sampling procedure.

The Sponsor's initial sample size projection suggested that approximately 600 patients would be included in the study. Based on preliminary data, it was suggested that data from 500 apixaban patients would provide sufficiently precise estimates of on-label and off-label use as per B0661018 Protocol Amendment 3 (Table 9.1).

Table 9.1. Precision Around the Off Label Use Proportion Estimates Assuming a Total Sample Size of 500 Apixaban users

Off label use (%)	Width of 95% CI for off label use (%)
5	4.0
15	6.5
25	7.8
35	8.5
45	8.9

9.8. Data transformation

Section 9.3 describes how dispensing information was used to identify apixaban users. Section 9.4.2.1 describes how diagnosis codes from the databases were used to infer indication of apixaban use.

Further details are described in the statistical analysis plan (SAP), which is dated, filed and maintained by the Sponsor.

9.9. Statistical methods

9.9.1. Main summary measures

Inferred indications of apixaban use and patient characteristics are reported descriptively. Proportions of on- and off-label use are reported with 95% confidence intervals (CI 95). Categorical data including duration of apixaban use are presented as counts (n) and percentages (%). Continuous data (except duration of apixaban use) are presented as means with standard deviation (SD) and as medians with interquartile range (IQR). Results are presented for the overall cohort and for the sub-group with GP data available, and by indication, given sufficient sample size across strata ($N \geq 5$, see section 9.11).

All data were analysed using SAS programs organized within SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, USA) using SAS version 9.4 under Windows.

9.9.2. Main statistical methods

All the statistical methods were descriptive and described above (section 9.9.1).

9.9.3. Missing values

No missing values were imputed. All missing values were treated as missing completely at random.

9.9.4. Sensitivity analyses

A post-hoc sensitivity analysis was performed by only including apixaban users from 2013, to account for the limited hospital information from 2014 (see section 9.5.4).

9.9.5. Amendments to the statistical analysis plan

In the list of codes to identify NVAF, separate codes were listed for “paroxysmal atrial fibrillation”, “persistent atrial fibrillation” and “chronic atrial fibrillation”. However, upon extraction of the data only the higher-level ICD-10 code I48 “Atrial fibrillation/flutter” was observed. The code list was updated accordingly (see Table 15.3).

An extensive list of procedure codes to identify “Incision and excision of skull, brain and meninges” or “Operations on spinal cord and spinal canal structures” was added to the code list. These additional codes (N = 1109) are available upon request.

9.10. Quality control

Data collection, extraction and post-processing for research purposes were conducted following quality control standard operating procedures. SAS program development was performed following the PHARMO work instructions. SAS QC did not include formal double programming but did include a review of the programs, ensuring a traceable, written record organized within SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, USA) using SAS version 9.4 under Windows. Deliverable review was performed by the Senior Research Quality Manager.

9.11. Protection of human subjects

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 Epidemiology Practices (ISPE 2007). Ethics Committee approval was not required because all data sources used are anonymous and are linked through probabilistic linkage using demographic variables of the apixaban users. All other identifying information was deleted after the linkage of the various databases. This approach is approved by the

Dutch Data Protection Authority ('College Bescherming Persoonsgegevens'). Confidentiality of patient records was maintained at all times. All analyses of electronic records were performed using appropriately de-identified data without access to personal identifying information. In addition, PHARMO has the policy not to report patient characteristics on patient groups with less than 5 individuals.

10. RESULTS

10.1. Participants

All 896 individuals in the PHARMO Out-patient and In-patient Pharmacy Databases who were dispensed apixaban between 01 December 2011 and 31 December 2014 were included in the analysis. The first apixaban dispensings in the database were observed in June 2013 (N = 7). In subsequent months the number increased to almost 700 dispensings in the final month (Figure 10.1).

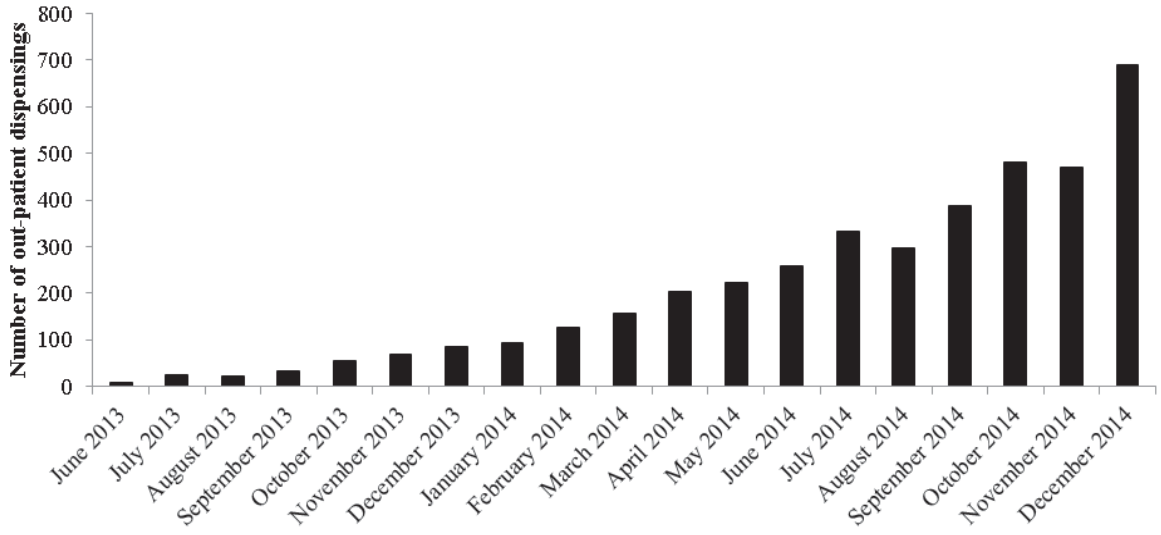

Figure 10.1. Dispensing of apixaban in the PHARMO Database Network until 31 December 2014, per month

For 7 of 896 (0.8%) apixaban users, the first apixaban dispensing was observed in the In-patient Pharmacy Database. For 5 users, subsequent apixaban dispensing was observed in the Out-patient Pharmacy Database.

Hospital discharge diagnoses and procedures from the Hospitalisation Database were available up to end of 2013 for all apixaban users represented in the In- and Out-patient Pharmacy Databases. Among users who started apixaban in 2014, 20% had hospital admission data available up to the first dispensing.

A sub-cohort of apixaban users for whom out-patient pharmacy dispensings and hospital discharge diagnoses as well as GP records were available was created. From among 896 apixaban users, 137 (15%) were also in the GP Database (Figure 10.2).

Apixaban users were assigned to an indication group by the algorithms described in section 9.4.2.1. A hierarchy was applied in the assignment of indication, as presented in Figure 10.2. The distribution of indications is further described in section 10.3.1.

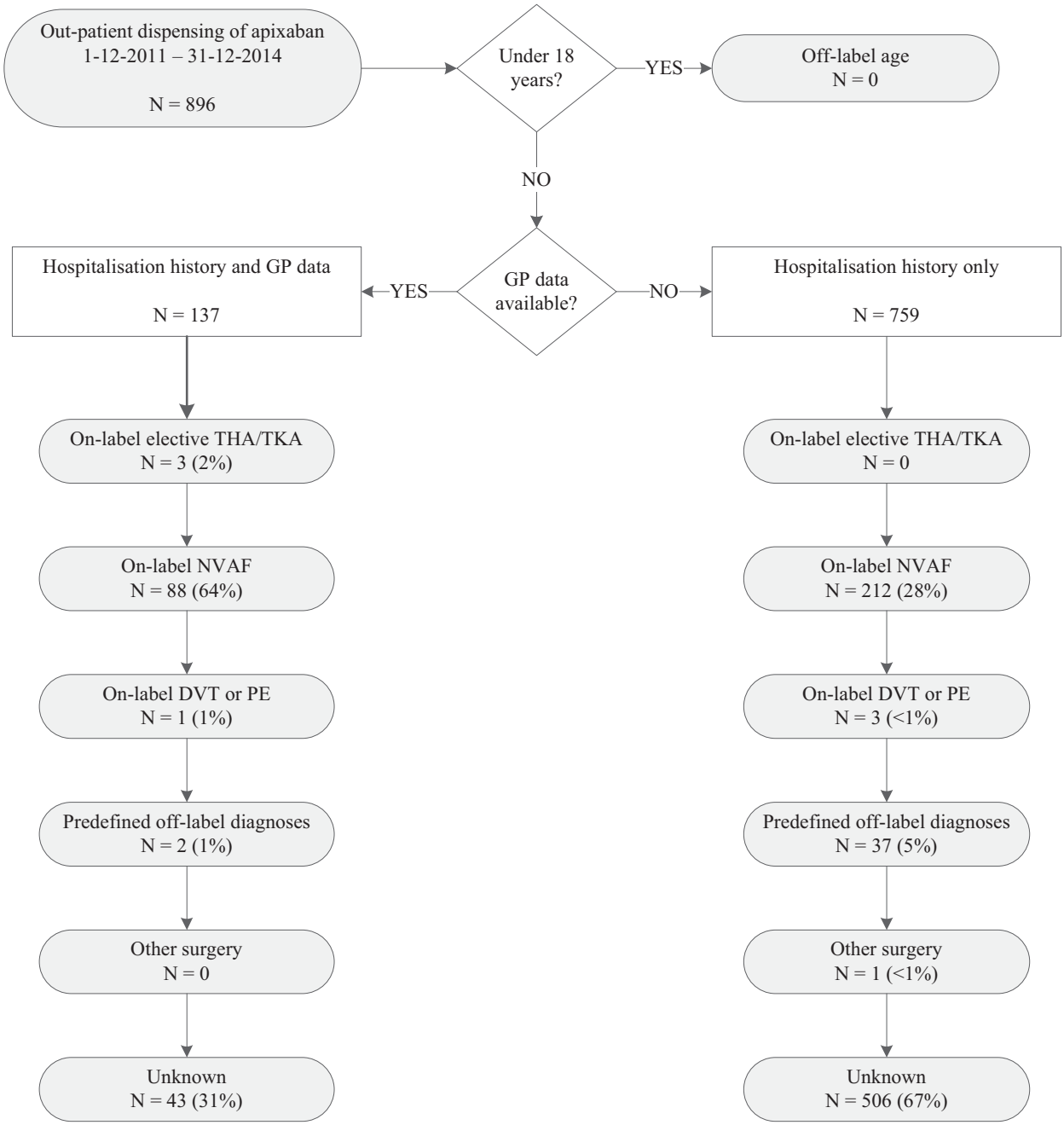

Figure 10.2. Flow chart of indication assignment among apixaban users from the PHARMO Database Network

10.2. Descriptive data

Descriptive data are presented overall (N = 896) and for the following indications: NVAF (N = 300), off-label (N = 40) or unknown (N =549). The data were sparse in the THA/TKA and DVT/PE cohorts which prevented presentation of patient characteristics.

Among apixaban users, 57% was male and the mean age at the first dispensing of apixaban was 70 (SD = 10) years (Table 10.1). The mean length of the database histories before date of first apixaban dispensing was 11 (SD = 5) years. Database follow-up was, for most users, limited by the end of the study period (31 December 2014).

Gender and age distributions as well as database history and follow-up were similar between the indication cohorts.

The initial prescriber of apixaban was most often a cardiologist: 60% in the overall cohort and ranging from 58% to 68% in the indication cohorts.

The sub-cohort with GP data available included relatively more men than the sub-cohort without GP data (65% vs 56%) (Table 10.2). The age and prescriber distributions were similar.

Table 10.1. General characteristics of apixaban users from the PHARMO Database Network, by indication

	All apixaban users	On-Label			Off-Label**	Unknown
	N = 896 n (%)	THA/TKA N = 3 n (%)	NVAF N = 300 n (%)	DVT/PE N = 4 n (%)	N = 40 n (%)	N = 549 n (%)
Gender						
Male	515 (57)	*	174 (58)	*	22 (55)	316 (58)
Female	381 (43)	*	126 (42)	*	18 (45)	233 (42)
Age at first apixaban dispensing (years)						
18-44	11 (1)	*	2 (1)	*	2 (5)	7 (1)
45-64	201 (22)	*	69 (23)	*	7 (18)	124 (23)
65-84	619 (69)	*	210 (70)	*	30 (75)	373 (68)
85+	65 (7)	*	19 (6)	*	1 (3)	45 (8)
Mean ± SD	70 ± 10	*	70 ± 9	*	69 ± 12	70 ± 11
Median (IQR)	70 (65-77)	*	70 (65-76)	*	72 (65-76)	70 (65-77)
Database history before first apixaban dispensing						
<1 year	6 (1)	*	2 (1)	*	0 (0)	4 (1)
1-4 years	99 (11)	*	28 (9)	*	2 (5)	67 (12)
5-9 years	238 (27)	*	86 (29)	*	12 (30)	137 (25)
10+ years	553 (62)	*	184 (61)	*	26 (65)	341 (62)
Mean ± SD	11 ± 5	*	11 ± 5	*	13 ± 5	11 ± 5
Median (IQR)	11 (8-16)	*	10 (8-16)	*	16 (9-17)	11 (8-16)
Database follow-up after first apixaban dispensing						
<6 months	14 (2)	*	5 (2)	*	0 (0)	9 (2)
6-11 months	384 (43)	*	134 (45)	*	14 (35)	231 (42)
12+ months	498 (56)	*	161 (54)	*	26 (65)	309 (56)
Mean ± SD	13 ± 5	*	13 ± 5	*	14 ± 6	13 ± 5
Median (IQR)	12 (10-16)	*	12 (9-16)	*	14 (10-16)	12 (10-17)
Specialty of first prescriber						
GP	112 (13)	*	34 (11)	*	5 (13)	73 (13)
Internal medicine	19 (2)	*	4 (1)	*	1 (3)	14 (3)
Cardiology	535 (60)	*	184 (61)	*	27 (68)	319 (58)
Surgery	1 (<0.5)	*	1 (<0.5)	*	0 (0)	0 (0)
Other	229 (26)	*	77 (26)	*	7 (18)	143 (26)

*No patient characteristics are reported on patient groups with less than 5 individuals.
** Off-label indications included AF with evidence of a mechanical prosthetic heart valves or mitral stenosis (N=26), recent non-THA/TKA surgery (N=1), DVT/PE history and apixaban use before the DVT/PE approval date (N=2) or specified 'other' diagnoses as presented in Table 10.4 (N=11)

Table 10.2. General characteristics of apixaban users from the PHARMO Database Network, by GP data availability

	All patients N = 896 n (%)	GP data available N = 137 n (%)	GP data not available N = 759 n (%)
Gender			
Male	515 (57)	89 (65)	426 (56)
Female	381 (43)	48 (35)	333 (44)
Age at first apixaban dispensing (years)			
18-44	11 (1)	0 (0)	11 (1)
45-64	201 (22)	36 (26)	165 (22)
65-84	619 (69)	91 (66)	528 (70)
85+	65 (7)	10 (7)	55 (7)
Mean ± SD	70 ± 10	70 ± 10	70 ± 10
Median (IQR)	70 (65-77)	70 (64-76)	70 (65-77)
Database history before first apixaban dispensing			
<1 year	6 (1)	4 (3)	2 (<0.5)
1-4 years	99 (11)	35 (26)	64 (8)
5-9 years	238 (27)	71 (52)	167 (22)
10+ years	553 (62)	27 (20)	526 (69)
Mean ± SD	11 ± 5	7 ± 3	12 ± 5
Median (IQR)	11 (8-16)	8 (4-9)	12 (9-16)
Database follow-up after first apixaban dispensing			
<6 months	14 (2)	2 (1)	12 (2)
6-11 months	384 (43)	71 (52)	313 (41)
12+ months	498 (56)	64 (47)	434 (57)
Mean ± SD	13 ± 5	12 ± 4	14 ± 5
Median (IQR)	12 (10-16)	11 (9-15)	12 (10-17)
Specialty of first prescriber			
GP	112 (13)	18 (13)	94 (12)
Internal medicine	19 (2)	0 (0)	19 (3)
Cardiology	535 (60)	90 (66)	445 (59)
Surgery	1 (<0.5)	0 (0)	1 (<0.5)
Other	229 (26)	29 (21)	200 (26)

10.3. Outcome data

10.3.1. Indication of use

Table 10.3 presents the distribution of on-label, off-label and unknown indications overall and by availability of GP data.

An on-label indication could be assigned to 307 (34% (CI 95 31-37%) of 896 apixaban users, and the majority of the on-label users (98%, 300 of 307) had a record of NVAF. Few apixaban users (N = 40; 4% (CI 95 3-6%)) were assigned to an off-label indication; for most users the indication remained unknown (N = 549; 61% (CI 95 58-64%)).

Because the indication for majority of classifiable apixaban users was NVAF which in itself does not lead to hospital admission, the sub-cohort with GP data available provided more information about the diagnoses that were potential indications of use. In this sub-cohort, the majority of users (88 of 137; 64% (CI 95 56-72%)) had a history of NVAF; in total 67% (CI 95 59-75%) could be assigned to an on-label indication. Off-label indications were observed for 2 users (1% (CI 95 0-3%)) and for 43 users the indication remained unknown (31% (CI 95 24-39%)).

A post-hoc sensitivity analysis was performed by only including apixaban users from 2013, to account for the limited hospital information from 2014. In this sub-cohort (N = 107), no patients were identified with THA/TKA or DVT/PE. In the dataset limited to apixaban users who also had GP data, 4 of 5 users (80% (CI 95 45-100%)) were assigned to the NVAF cohort.

When assuming that the missing information about indications was at random, we can restrict the study cohort to those with an assigned indication. This leads to on-label proportions of 88% (307 of 347; CI 95 85-92%) overall and 98% (92 of 94; CI 95 95-100%) in the GP subset.

Table 10.3. On- and off-label indications for apixaban use by data sources

Indication	All apixaban users N = 896 n (%)	GP data available N = 137 n (%)	No GP data available N = 759 n (%)
On-label indications			
THA/TKA	3 (<0.5)	3 (2)	0 (0)
NVAF	300 (33)	88 (64)	212 (28)
DVT/PE	4 (<0.5)	1 (1)	3 (<0.5)
Off-label indications*			
<18 years of age	0 (0)	0 (0)	0 (0)
Other surgery	1 (<0.5)	0 (0)	1 (<0.5)
Other conditions	11 (1)	2 (1)	9 (1)
AF with mechanical prosthetic heart valves or mitral stenosis	26 (3)	0 (0)	26 (3)
DVT/PE before 28 July 2014	2 (<0.5)	0 (0)	2 (<0.5)
Unknown	549 (61)	43 (31)	506 (67)

* Apixaban users with multiple off-label conditions were classified first by age and then by the event that occurred most closely in time to the apixaban dispensing.

Most off-label users (N = 26 of 40; 65%) had a discharge diagnosis of AF but also had a diagnostic code that could potentially indicate the presence of a mechanical prosthetic heart valve or mitral stenosis. Patients with a record that was specifically suggestive of a prosthetic heart valve included 4 patients with a record of the “presence of a mechanical prosthetic heart valve” (ICD 9 code V43.3), 3 patients with a record of the “presence of a prosthetic heart valve” (ICD 9 code Z95.2), and 1 patients with a record of the “presence of other heart-

valve replacement (ICD 9 code Z95.4). The specific diagnosis codes are listed in Table 10.5. One user had cholecystectomy but also pacemaker lead replacement (this was the user with 'other surgery') and 2 users had a history of DVT/PE but started apixaban before the approval date of the DVT/PE indication. The observed 'other' diagnoses (11 users; 28%) are presented in Table 10.4. Most of these users had a recent diagnosis of 'other forms of chronic ischemic heart disease'.

Table 10.4. Off-label apixaban users from the PHARMO Database Network with discharge diagnoses other than on-label THA/TKA, NVAF or DVT/PE

Description	All apixaban users N = 40 n (%)	GP data available N = 2 n (%)	No GP data available N = 38 n (%)
Valvular AF: AF with mechanical prosthetic heart valves or mitral stenosis	26 (65)	*	26 (68)
Other surgery**	1 (3)	*	1 (3)
VTE and first dispensing before 28 July 2014	2 (5)	*	2 (5)
Angina pectoris	1 (3)	*	1 (3)
Other forms of chronic ischemic heart disease	6 (15)	*	5 (13)
Occlusion and stenosis of precerebral arteries	1 (3)	*	1 (3)
Occlusion and stenosis of cerebral arteries	2 (5)	*	2 (5)
Arterial embolism and thrombosis	1 (3)	*	0 (0)

*No patient characteristics are reported on patient groups with less than 5 individuals.
** cholecystectomy and pacemaker lead replacement within 30 days prior to the first apixaban dispensing

Table 10.5. Off-label apixaban users from the PHARMO Database Network with AF and potential mechanical prosthetic heart valves or mitral stenosis*

Description	All apixaban users N = 26 n (%)
Complications of cardiac and vascular prosthetic devices, implants and grafts	7 (27)
Endocarditis, valve unspecified	1 (4)
Non-rheumatic mitral valve disorders	1 (4)
Other congenital malformations of heart	5 (19)
Presence of cardiac and vascular implants and grafts	10 (38)
Rheumatic mitral valve disease	9 (35)

*Patients could have more than one diagnosis

10.3.2. Apixaban dose and duration

Table 10.6 lists the categorized duration of the first period of continuous use of apixaban. Most users (N = 836; 93%) had one treatment episode during the study period. Most users (N = 661; 74%) were treated with apixaban for more than 38 days. The daily dose of the first apixaban dispensing was 10 mg for most users (N = 759; 85%).

Most users took 2 doses per day: 2 times 5 mg (98% of 10 mg users) or 2 times 2.5 mg (95% of 5 mg users) (not shown in table).

Table 10.6. Treatment dose and duration among apixaban users from the PHARMO Database Network, by indication

	All apixaban users N = 896 n (%)	On-Label			Off-Label** N = 40 n (%)	Unknown N = 549 n (%)
		THA/TKA N = 3 n (%)	NVAF N = 300 n (%)	DVT/PE N = 4 n (%)		
Treatment duration						
< 10 days	75 (8)	*	25 (8)	*	4 (10)	46 (8)
10-14 days	58 (6)	*	19 (6)	*	1 (2)	38 (7)
15-31 days	84 (9)	*	34 (11)	*	3 (7)	44 (8)
32-38 days	18 (2)	*	5 (2)	*	2 (5)	11 (2)
>38 days	661 (74)	*	217 (72)	*	30 (75)	410 (75)
Daily dose* **						
5 mg	134 (15)	*	41 (14)	*	9 (22)	82 (15)
10 mg	759 (85)	*	256 (86)	*	31 (78)	467 (85)
20 mg	0 (0)	*	0 (0)	*	0 (0)	0 (0)

*No patient characteristics are reported on patient groups with less than 5 individuals.
** Off-label indications included AF with documented potential mechanical prosthetic heart valves or mitral stenosis (N=26), recent non-THA/TKA surgery (N=1), DVT/PE history and apixaban use before the DVT/PE approval date (N=2) or specified 'other' diagnoses as presented in Table 10.4 (N=11).
*** for 3 users with NVAF the daily dose was unknown

10.3.3. Concomitant medication and co-morbidity

Table 10.7 lists the observed dispensing of selected drugs during the 30 days prior to and the 30 days after the first apixaban dispensing. The numbers reflect the number of users per drug, not the number of dispensings.

Antithrombotic agents were already used by a minority of apixaban users: 14% used platelet aggregation inhibitors, 12% used vitamin K antagonists, 3% used direct thrombin inhibitors and 1% used heparin just before the first apixaban dispensing. The proportion of previous antithrombotic drug use appeared highest in the off-label group; however note that the estimate was based on small numbers. Some antithrombotic drug dispensings were observed after the apixaban dispensing; the end date of apixaban use was not taken into account.

The most frequently observed drugs from the list were selective beta blocking agents. Dispensings were observed just before the first apixaban dispensing (N = 183; 20%) as well as just after the first apixaban dispensing (N = 302; 34%). Observed dispensings were metoprolol (C07AB02, N = 132 before and N = 214 after), atenolol (C07AB03, N = 5 before and N = 20 after), bisoprolol (C07AB07, N = 42 before and N = 69 after) and nebivolol (C07AB12, N = 5 before and N = 4 after).

HMG CoA reductase inhibitors were used by 144 (16%) individuals just before and by 186 (21%) individuals just after the first apixaban dispensing. Observed dispensings before the first apixaban dispensing were simvastatin (C10AA01, N = 78 before and N = 101 after), pravastatin (C10AA03, N = 12 before and N = 20 after), fluvastatin (C10AA04, N = 3 before and N = 6 after), atorvastatin (C10AA05, N = 31 before and N = 41 after) and rosuvastatin (C10AA07, N = 20 before and N = 20 after).

Platelet aggregation inhibitors were used by 127 (14%) individuals just before the first apixaban dispensing and 46 (5%) used them after the first apixaban dispensing. The use of vitamin K antagonists was similar: 106 (12%) users before the first apixaban dispensing and 18 (2%) after the first apixaban dispensing.

Table 10.8 lists the most frequently dispensed drugs, other than those in the selected list of Table 10.7, among apixaban users in the 6 months preceding the first apixaban dispensing. Most frequently used were the proton pump inhibitors omeprazole and pantoprazole, each used by respectively 20% and 14%, of apixaban users.

Table 10.9 lists the observed diagnoses of selected conditions during the 365 days prior to the first apixaban dispensing. Few of these diagnoses were observed. Chronic kidney disease (CKD) was observed among 7 (1%) users. Six (1%) users had a record of liver disease or coagulation defects.

Table 10.7. Selected concomitant medication (other dispensings within 30 days before and after/including the date of the first apixaban dispensing)

	All apixaban users N = 896		On-Label THA/TKA N = 3		On-Label NVAF N = 300		On-Label DVT/PE N = 4		Off-Label** N = 40		Unknown N = 549	
	30 days before n (%)	30 days after n (%)	30 days before n (%)	30 days after n (%)	30 days before n (%)	30 days after n (%)	30 days before n (%)	30 days after n (%)	30 days before n (%)	30 days after n (%)	30 days before n (%)	30 days after n (%)
Antithrombotic agents												
Vitamin K antagonists	106 (12)	18 (2)	*	*	46 (15)	6 (2)	*	*	9 (22)	2 (5)	50 (9)	10 (2)
Heparins	9 (1)	3 (<0.5)	*	*	2 (1)	2 (1)	*	*	1 (2)	0 (0)	6 (1)	1 (<0.5)
Platelet aggregation inhibitors excluding heparin	127 (14)	46 (5)	*	*	31 (10)	15 (5)	*	*	5 (12)	8 (20)	90 (16)	23 (4)
Enzymes	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Direct thrombin inhibitors	26 (3)	4 (<0.5)	*	*	11 (4)	2 (1)	*	*	1 (2)	0 (0)	14 (3)	2 (<0.5)
Other antithrombotic agents	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Anti-inflammatory and anti-rheumatic products												
Anti-inflammatory and anti-rheumatic products, non-steroids	28 (3)	21 (2)	*	*	9 (3)	8 (3)	*	*	1 (2)	0 (0)	18 (3)	12 (2)
CYP3A4 and P-gp inhibitors												
Antimycotics for systemic use	1 (<0.5)	1 (<0.5)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	1 (<0.5)	1 (<0.5)
Protease inhibitors	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Selective serotonin reuptake inhibitors	16 (2)	18 (2)	*	*	5 (2)	3 (1)	*	*	2 (5)	3 (7)	9 (2)	12 (2)
Phenylalkylamine derivatives	22 (2)	44 (5)	*	*	10 (3)	13 (4)	*	*	2 (5)	5 (12)	9 (2)	25 (5)
Antiarrhythmics, class Ia	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Selective beta blocking agents	183 (20)	302 (34)	*	*	69 (23)	96 (32)	*	*	7 (17)	15 (37)	105 (19)	189 (34)
Benzothiazepine derivatives	5 (1)	6 (1)	*	*	1 (<0.5)	0 (0)	*	*	0 (0)	1 (2)	4 (1)	5 (1)
HMG CoA reductase inhibitors	144 (16)	186 (21)	*	*	32 (11)	60 (20)	*	*	10 (24)	13 (32)	100 (18)	111 (20)
Eryithromycin	0 (0)	1 (<0.5)	*	*	0 (0)	1 (<0.5)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Clarithromycin	2 (<0.5)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	2 (<0.5)	0 (0)
Selective immunosuppressants	2 (<0.5)	3 (<0.5)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	2 (<0.5)	3 (1)
CYP3A4 and P-gp inducers												
Carboxamide derivatives	1 (<0.5)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	1 (<0.5)	0 (0)

	All apixaban users N = 896		On-Label THA/TKA N = 3		On-Label NVAF N = 300		On-Label DVT/PE N = 4		Off-Label** N = 40		Unknown N = 549	
	30 days before n (%)	30 days after n (%)	30 days before n (%)	30 days after n (%)	30 days before n (%)	30 days after n (%)	30 days before n (%)	30 days after n (%)	30 days before n (%)	30 days after n (%)	30 days before n (%)	30 days after n (%)
Thiazolidinediones	1 (<0.5)	2 (<0.5)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	1 (<0.5)	2 (<0.5)
Glucocorticoids	23 (3)	23 (3)	*	*	10 (3)	6 (2)	*	*	3 (7)	1 (2)	9 (2)	15 (3)
Short-acting sulphonamides	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Macrolides (excl erythromycin and clarithromycin)	2 (<0.5)	1 (<0.5)	*	*	0 (0)	1 (<0.5)	*	*	0 (0)	0 (0)	2 (<0.5)	0 (0)
Antibiotics for tuberculosis	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Non-nucleoside reverse transcriptase inhibitors	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Preparations increasing uric acid excretion	1 (<0.5)	1 (<0.5)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	1 (<0.5)	1 (<0.5)
Barbiturates and derivatives	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Hydantoin derivatives	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Succinimide derivatives	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
Piperidinedione derivatives	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)
St. John's Wart	0 (0)	0 (0)	*	*	0 (0)	0 (0)	*	*	0 (0)	0 (0)	0 (0)	0 (0)

*No patient characteristics are reported on patient groups with less than 5 individuals.
** Off-label indications included AF with documented mechanical prosthetic heart valves or mitral stenosis (N=26), recent non-THA/TKA surgery (N=1), DVT/PE history and apixaban use before the DVT/PE approval date (N=2) or specified 'other' diagnoses as presented in Table 10.4 (N=11).
Patients could have more than one dispensation

Table 10.8. Common medication used within 6 months before the date of the first apixaban dispensing

	All apixaban users N = 896 n (%)	On-Label			Off-Label** N = 40 n (%)	Unknown N = 549 n (%)
		THA/TKA N = 3 n (%)	NVAF N = 300 n (%)	DVT/PE N = 4 n (%)		
Omeprazole (proton pump inhibitor)	182 (20)	*	57 (19)	*	10 (24)	113 (21)
Pantoprazole (proton pump inhibitor)	129 (14)	*	49 (16)	*	12 (29)	65 (12)
Metformin (biguanide)	94 (10)	*	35 (12)	*	3 (7)	55 (10)
Colecalciferol (vitamin D analogue)	55 (6)	*	20 (7)	*	4 (10)	29 (5)
Calcium in combination	57 (6)	*	22 (7)	*	2 (5)	32 (6)
Hydrochlorothiazide (thiazide)	100 (11)	*	29 (10)	*	7 (17)	64 (12)
Furosemide (sulfonamide)	111 (12)	*	38 (13)	*	8 (20)	65 (12)
Sotalol (beta blocking agent)	114 (13)	*	50 (17)	*	5 (12)	59 (11)
Amlodipine (dihydropyridine derivative)	84 (9)	*	28 (9)	*	4 (10)	51 (9)
Perindopril (ace inhibitor)	80 (9)	*	28 (9)	*	10 (24)	42 (8)

*No patient characteristics are reported on patient groups with less than 5 individuals.
** Off-label indications included AF with documented mechanical prosthetic heart valves or mitral stenosis (N=26), recent non-THA/TKA surgery (N=1), DVT/PE history and apixaban use before the DVT/PE approval date (N=2) or specified 'other' diagnoses as presented in Table 10.4 (N=11).
Patients could have dispensation of more than one drug

Table 10.9. Selected co-morbidity within 365 days preceding and including the date of the first apixaban dispensing

Condition	All apixaban users N = 896 n (%)	On-Label			Off-Label** N = 40 n (%)	Unknown N = 549 n (%)
		THA/TKA N = 3 n (%)	NVAF N = 300 n (%)	DVT/PE N = 4 n (%)		
Chronic kidney disease (CKD)	7 (1)	*	5 (2)	*	0 (0)	1 (<5)
Acute and subacute necrosis of liver	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Chronic liver disease and cirrhosis	1 (<0.5)	*	1 (<0.5)	*	0 (0)	0 (0)
Liver abscess and sequelae of chronic liver disease	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Other disorders of liver	2 (<0.5)	*	2 (1)	*	0 (0)	0 (0)
Coagulation defects	3 (<0.5)	*	1 (<0.5)	*	1 (3)	0 (0)
Subarachnoid haemorrhage	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Intracerebral haemorrhage	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Other and unspecified intracranial haemorrhage	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Gastric ulcer	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Duodenal ulcer	1 (<0.5)	*	0 (0)	*	0 (0)	0 (0)
Peptic ulcer, site unspecified	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Acute and subacute bacterial endocarditis	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Oesophageal varices with bleeding	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Oesophageal varices without mention of bleeding	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Oesophageal varices in diseases classified elsewhere	0 (0)	*	0 (0)	*	0 (0)	0 (0)
Primary thrombocytopenia	1 (<0.5)	*	1 (<0.5)	*	0 (0)	0 (0)
Secondary thrombocytopenia	1 (<0.5)	*	0 (0)	*	1 (3)	0 (0)
Thrombocytopenia, unspecified	1 (<0.5)	*	0 (0)	*	0 (0)	0 (0)
Incision and excision of skull, brain and meninges	2 (<0.5)	*	2 (1)	*	0 (0)	0 (0)
Operations on spinal cord and spinal canal structures	0 (0)	*	0 (0)	*	0 (0)	0 (0)

*No patient characteristics are reported on patient groups with less than 5 individuals.
** Off-label indications included AF with documented mechanical prosthetic heart valves or mitral stenosis (N=26), recent non-THA/TKA surgery (N=1), DVT/PE history and apixaban use before the DVT/PE approval date (N=2) or specified 'other' diagnoses as presented in Table 10.4 (N=11) Patients could have more than one diagnosis

10.4. Main results

Main results were presented in the previous sections.

10.5. Other analyses

Not applicable.

10.6. Adverse events / adverse reactions

This study includes unstructured data (e.g., narrative fields in the database) that were converted to structured (i.e., 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 (i.e. identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) were not available and adverse events were not reportable as individual AE reports.

11. DISCUSSION

11.1. Key results

Among 896 apixaban users identified in the PHARMO Database Network, 307 (34%) were assigned an on-label indication, mostly NVAF (33%), 40 (4%) were assigned an off-label indication. For the majority of users (61%), no indication could be assigned. The estimated 34% of on-label use of apixaban was likely to be lower than the true proportion of on-label use due to incomplete linkages between in-patient, out-patient, hospital and GP databases. Only 15% (137/896) of apixaban users had both hospital and GP data, which was critical in capturing diagnoses that suggestive of apixaban indications.

In a sub-cohort of apixaban users with both GP data and hospitalization data, more diagnostic information was available in particular about NVAF which in itself does not lead to hospitalization. In this subcohort the majority (64%) were assigned to the NVAF indication. The group with unknown indication was 31% of the sub-cohort with GP data. Therefore, we conclude that the GP data are crucial for the assignment of indication of apixaban use and the proportion of on- and off-label use can be better estimated from this sub-cohort.

The proportions of apixaban users with a recent THA/TKA procedure or a history of DVT/PE were low. NVAF thus seems to be the main indication of apixaban.

Apixaban users tended to be more often male (57%) than female (43%) and the mean age at the first dispensing of apixaban was 70 years. The initial prescriber of apixaban was most often a cardiologist (60%). The dosing of apixaban, for on-label NVAF patients and

unassigned patients, was mostly 10 mg per day taken as 5 mg twice a day and for more than 38 days, which is consistent with the NVAF indication.

Concomitant dispensing of selective beta blocking agents was observed for 34% of apixaban users and in addition, HMG CoA reductase inhibitors were used by 21% of apixaban users. Other drugs were used by 5% or less of apixaban users. In the assessment of selected co-morbidities, a history of chronic kidney disease and liver disorders were observed among about 1% of apixaban users.

11.2. Limitations

The assignment of indication of apixaban use depends on the recording of the condition in the database. The availability of data on apixaban use were however limited. The data sources used for this study were the Hospitalisation Database and the General Practitioner Database. Orthopaedic procedures occur in the hospital; however these procedures may also take place in private clinics not covered by the Hospitalisation Database. NVAF in itself does not lead to hospital admission. For these reasons, the GP data is crucial for the assignment of indications. However, only 15% of apixaban users were linked to both hospital and GP data.

Even more crucial were the GP data in the 2014 analysis, because hospitalization data were not available up to the date of the first apixaban dispensing for most users (80%) who started in 2014 (see section 9.5.4). The limited data from 2014 affected the identification of THA/TKA procedures because these were identified in the 30 days before the first apixaban dispensing and earlier data could not fill the role of the missing data. With the dataset limited to 2013 to account for the missing hospital data in 2014, no THA/TKA procedures were identified at all, so even if the 2014 would be available few additional apixaban users with THA/TKA are expected. For DVT/PE, which was an approved indication only starting in 2014, we also do not expect many users as the starting dose of 20 mg was not observed.

Instead of drawing definite conclusions about on- and off-label use, the results should be interpreted in terms of sensitivity and assumptions about the users with unknown indications.

11.3. Interpretation

The interpretation of the results was limited by the completeness of the the diagnostic information retrieved from the GP and Hospitalisation Databases. However, the available data suggested that NVAF is the most common on-label indication among the study population. The actual proportion of on-label apixaban users may be estimated up to over 90% when assuming that the missing information was at random [(307 of 347 (88%) users (with known diagnosis) in the overall set and 92 of 94 (98%) users in the GP subset were on-label)]. In addition, for users assigned to the off-label cohorts we may actually have missed the labelled condition as well.

The second objective was to describe the characteristics of the patients who were prescribed apixaban for on-label and off-label indications. Gender, age, prescriber and treatment dose and duration distributions were similar among apixaban users with NVAF and those with

unknown indication. This supports the assumption that most users fitted the NVAF indication.

11.4. Generalisability

The PHARMO Out-patient Pharmacy Database and the GP Database are representative for the Netherlands in terms of gender and age distribution. All individuals in the Netherlands should be registered with a GP, as this is a requirement of the mandatory health insurance in the Netherlands. We therefore do not expect any selection bias to occur. Generalisability may however be limited in smaller sub-groups.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

NVAF may be the main indication for apixaban use in the Netherlands. Although for many users the indication of use remained unknown, the data do not suggest extensive off-label use as the users with unknown indication did not differ from those with NVAF.

14. REFERENCES

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15. LIST OF SOURCE TABLES AND FIGURES

15.1. Definition of Primary Endpoints: THA/TKA replacement codes

Table 15.1. Procedure codes for ON-LABEL hip and knee replacement surgery in the Netherlands

variable	system	code	Description
Total Hip Replacement	CVV	5815	Total hip prosthesis
Total Hip Replacement	CVV	58150	Implantation of total hip prosthesis
Total Hip Replacement	CVV	58151	Removal of total hip prosthesis
Total Hip Replacement	CVV	581510	Removal of total hip prosthesis, of unspecified site
Total Hip Replacement	CVV	581511	Removal of acetabulum component
Total Hip Replacement	CVV	581512	Removal of femur component, of unspecified site
Total Hip Replacement	CVV	581513	Removal of acetabulum component with (part) femur component
Total Hip Replacement	CVV	581514	Removal of femur component, head
Total Hip Replacement	CVV	581515	Removal of femur component, steel head
Total Hip Replacement	CVV	58152	Replacement of total hip prosthesis
Total Hip Replacement	CVV	581520	Replacement of total hip prosthesis, of unspecified site
Total Hip Replacement	CVV	581521	Replacement of acetabulum component
Total Hip Replacement	CVV	581522	Replacement of femur component, of unspecified site
Total Hip Replacement	CVV	581523	Replacement of acetabulum component with (part) femur component
Total Hip Replacement	CVV	581524	Replacement of femur component, head
Total Hip Replacement	CVV	581525	Replacement of femur component, steel head
Total Hip Replacement	CVV	58153	Exploration of total hip prosthesis
Total Hip Replacement	ZA	3856	HIP-THIGH - prosthesis FEMUR HEAD AND ACETABULUM
Total Hip Replacement	ZA	038540	HIP – ARTHROTOMY
Other Hip Replacement	CVV	5816	Other arthroplasty of hip
Other Hip Replacement	CVV	58160	Implantation of head arthroplasty
Other Hip Replacement	CVV	58161	Implantation of hip arthroplasty
Other Hip Replacement	CVV	58162	Implantation of double hip arthroplasty
Other Hip Replacement	CVV	58163	Arthroplasty of hip without osteotomy
Other Hip Replacement	CVV	58164	Arthroplasty of hip with osteotomy
Other Hip Replacement	CVV	58165	Removal or replacement of head prosthesis of hip and conversion of head prosthesis to total hip prosthesis
Other Hip Replacement	CVV	581650	Removal of head prosthesis of hip
Other Hip Replacement	CVV	581651	Replacement of head prosthesis of hip
Other Hip Replacement	CVV	581652	Conversion of head prosthesis to total hip prosthesis
Other Hip Replacement	CVV	58166	Resection-arthroplasty of hip
Other Hip Replacement	CVV	58167	Exploration of remaining arthroplasty of hip
Other Hip Replacement	CVV	58168	Remaining specific arthroplasty of hip
Other Hip Replacement	CVV	58169	Arthroplasty of hip, not specified
Hip complaints	ICPC	L13	Hip symptom/complaint
Hip complaints	ICPC	L89	Coxarthrosis
Knee replacement	CBV	3864	Knee - total or partial meniscectomy
Knee replacement	CBV	3866	Knee - implantation of knee prosthesis

variable	system	code	Description
Knee replacement	CBV	3869	Lower leg amputation
Knee replacement	CBV	19030	Knee prosthesis
Knee replacement	CVV	58145	Implantation of knee prosthesis
Knee replacement	CVV	581450	Implantation of knee prosthesis, of unspecified site
Knee replacement	CVV	581451	Prosthesis hemiarthroplasty, of unspecified site
Knee replacement	CVV	581452	Prosthesis medial hemiarthroplasty, of unspecified site
Knee replacement	CVV	581453	Prosthesis lateral hemiarthroplasty, of unspecified site
Knee replacement	CVV	581454	Total prosthesis arthroplasty
Knee replacement	CVV	58146	Removal of knee prosthesis
Knee replacement	CVV	581460	Removal of knee prosthesis, of unspecified site
Knee replacement	CVV	581461	Removal of femur component
Knee replacement	CVV	581462	Removal of tibia component
Knee replacement	CVV	581463	Removal of all components
Knee replacement	CVV	581464	Removal of patella component
Knee replacement	CVV	581469	Removal of knee prosthesis
Knee replacement	CVV	58147	Replacement of knee prosthesis and conversion of partial knee prosthesis to total knee prosthesis
Knee replacement	CVV	581470	Replacement of knee prosthesis, of unspecified site
Knee replacement	CVV	581471	Replacement of femur component
Knee replacement	CVV	581472	Replacement of tibia component
Knee replacement	CVV	581473	Replacement of all components
Knee replacement	CVV	581474	Replacement of patella component
Knee replacement	CVV	581475	Conversion of partial knee prosthesis to total knee prosthesis
Knee replacement	CVV	581479	Replacement of knee prosthesis
Knee replacement	CVV	58148	Exploration of knee prosthesis
Knee replacement	CVV	58149	Not specific arthroplasty of knee
Knee replacement	ZA	3866	Knee - removal knee joint prosthesis
Knee complaints	ICPC	L15	Knee symptom/complaint
Knee complaints	ICPC	L78	Sprain/strain of knee
Knee complaints	ICPC	L90	Gonarthrosis
Knee complaints	ICPC	L96	Acute internal damage knee
Knee complaints	ICPC	L97	Chronic internal damage knee

Hospital diagnoses are coded according to the WHO International Classification of Diseases (ICD-9 until 2013 and ICE-10 from 2013) and procedures are coded according to the Dutch Hospital Data Foundation owned registration system for procedures [www.dutchhospitaldata.nl] which links to the Dutch Healthcare Authority (NZa) declaration codes [www.nza.nl](CBV and ZA, from 2013) and the Dutch Classification of Procedures (Dutch Classification of Procedures [class.who-fic.nl]) (CVV, until 2013). GP diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [www.nhg.org].

Table 15.2. Diagnostic codes for hip or knee fractures that EXCLUDE on-label use

variable	system	code	Description
Hip fracture	ICD9	820	Fracture of neck of femur
Hip fracture	ICD9	821	Fracture of other and unspecified parts of femur
Hip fracture	ICD10	M8005	Postmenopausal osteoporosis with pathological fracture, pelvic region and thigh
Hip fracture	ICD10	M8015	Postoophorectomy osteoporosis with pathological fracture, pelvic region and thigh
Hip fracture	ICD10	M8025	Osteoporosis of disuse with pathological fracture, pelvic region and thigh
Hip fracture	ICD10	M8035	Postsurgical malabsorption osteoporosis with pathological fracture, pelvic region and thigh

variable	system	code	Description
Hip fracture	ICD10	M8045	Drug-induced osteoporosis with pathological fracture, pelvic region and thigh
Hip fracture	ICD10	M8055	Idiopathic osteoporosis with pathological fracture, pelvic region and thigh
Hip fracture	ICD10	M8085	Other osteoporosis with pathological fracture, pelvic region and thigh
Hip fracture	ICD10	M8095	Unspecified osteoporosis with pathological fracture, pelvic region and thigh
Hip fracture	ICD10	M9075	Fracture of bone in neoplastic disease, pelvic region and thigh
Hip fracture	ICD10	S72	Fracture of femur
Hip fracture	ICPC	L75	Fracture: femur
Knee fracture	ICD9	822	Fracture of patella
Knee fracture	ICD10	M9076	Fracture of bone in neoplastic disease, lower leg
Knee fracture	ICD10	M8006	Postmenopausal osteoporosis with pathological fracture, lower leg
Knee fracture	ICD10	M8016	Postoophorectomy osteoporosis with pathological fracture, lower leg
Knee fracture	ICD10	M8026	Osteoporosis of disuse with pathological fracture, lower leg
Knee fracture	ICD10	M8036	Postsurgical malabsorption osteoporosis with pathological fracture, lower leg
Knee fracture	ICD10	M8046	Drug-induced osteoporosis with pathological fracture, lower leg
Knee fracture	ICD10	M8056	Idiopathic osteoporosis with pathological fracture, lower leg
Knee fracture	ICD10	M8086	Other osteoporosis with pathological fracture, lower leg
Knee fracture	ICD10	M8096	Unspecified osteoporosis with pathological fracture, lower leg
Knee fracture	ICD10	S82	Fracture of lower leg, including ankle
Knee fracture	ICPC	L73	Fracture: tibia/fibula
Other fracture	ICD9	827	Other multiple and ill-defined fractures of lower limb
Other fracture	ICD9	828	Multiple fractures involving both lower limbs lower with upper limb and lower limb(s) with rib(s) and sternum
Other fracture	ICD9	829	Fracture of unspecified bones
Other fracture	ICD9	E887	Fracture, cause unspecified
Other fracture	ICD10	M9070	Fracture of bone in neoplastic disease, multiple sites
Other fracture	ICD10	M8000	Postmenopausal osteoporosis with pathological fracture, multiple sites
Other fracture	ICD10	M8010	Postoophorectomy osteoporosis with pathological fracture, multiple sites
Other fracture	ICD10	M8020	Osteoporosis of disuse with pathological fracture, multiple sites
Other fracture	ICD10	M8030	Postsurgical malabsorption osteoporosis with pathological fracture, multiple sites
Other fracture	ICD10	M8040	Drug-induced osteoporosis with pathological fracture, multiple sites
Other fracture	ICD10	M8050	Idiopathic osteoporosis with pathological fracture, multiple sites
Other fracture	ICD10	M8080	Other osteoporosis with pathological fracture, multiple sites
Other fracture	ICD10	M8090	Unspecified osteoporosis with pathological fracture, multiple sites
Other fracture	ICD10	M843	Stress fracture, not elsewhere classified

Hospital diagnoses are coded according to the WHO International Classification of Diseases (ICD-9 until 2013 and ICE-10 from 2013). GP diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [www.nhg.org].

15.2. Definition of Primary Endpoints: NVAF Indication

Table 15.3. Diagnostic ICD-9, ICD-10 AND ICPC Codes for ON-LABEL NVAF use

variable	system	code	Description
Atrial fibrillation	ICD10	I48	Atrial fibrillation/flutter
Atrial fibrillation	ICD9	42731	Atrial fibrillation
Atrial fibrillation	ICPC	K78	Atrial fibrillation/flutter

Hospital diagnoses are coded according to the WHO International Classification of Diseases (ICD-9 until 2013 and ICE-10 from 2013). GP diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [www.nhg.org].

Table 15.4. Definition of Endpoints: ICD-9, ICD-10 AND ICPC for the exclusions for on-label NVAF

variable	system	code	Description
Rheumatic mitral valve disease	ICD9	3941	Rheumatic mitral insufficiency
Rheumatic mitral valve disease	ICD9	3949	Other and unspecified mitral valve diseases
Rheumatic mitral valve disease	ICD9	4240	Mitral valve disorders
Rheumatic mitral valve disease	ICD10	I050	Mitral stenosis
Rheumatic mitral valve disease	ICD10	I051	Rheumatic mitral stenosis
Rheumatic mitral valve disease	ICD10	I052	Rheumatic mitral stenosis with insufficiency
Rheumatic mitral valve disease	ICD10	I058	Other rheumatic mitral valve diseases
Rheumatic mitral valve disease	ICD10	I059	Rheumatic mitral valve disease, unspecified
Multiple valve diseases	ICD9	3960	Mitral valve stenosis and aortic valve stenosis
Multiple valve diseases	ICD9	3961	Mitral valve stenosis and aortic valve insufficiency
Multiple valve diseases	ICD9	3962	Mitral valve insufficiency and aortic valve stenosis
Multiple valve diseases	ICD9	3963	Mitral valve insufficiency and aortic valve insufficiency
Multiple valve diseases	ICD9	3968	Multiple involvement of mitral and aortic valves
Multiple valve diseases	ICD9	3969	Mitral and aortic valve diseases unspecified
Multiple valve diseases	ICD10	I080	Rheumatic disorders of both mitral and aortic valves
Multiple valve diseases	ICD10	I081	Rheumatic disorders of both mitral and tricuspid valves
Multiple valve diseases	ICD10	I083	Combined rheumatic disorders of mitral, aortic and tricuspid valves
Multiple valve diseases	ICD10	I088	Other rheumatic multiple valve diseases
Multiple valve diseases	ICD10	I089	Rheumatic multiple valve disease, unspecified
Other rheumatic heart diseases	ICD9	391	Rheumatic fever with heart involvement
Other rheumatic heart diseases	ICD10	I091	Rheumatic diseases of endocardium, valve unspecified
Other rheumatic heart diseases	ICD10	I098	Other specified rheumatic heart disease
Other rheumatic heart diseases	ICD10	I099	Rheumatic heart disease, unspecified
Other rheumatic heart diseases	ICPC	K71	Rheumatic fever/heart disease
Non-rheumatic mitral valve disorders	ICD9	3940	Mitral stenosis
Non-rheumatic mitral valve disorders	ICD9	3942	Mitral stenosis with insufficiency

variable	system	code	Description
Rheumatic mitral valve disease	ICD10	I340	Mitral (valve) insufficiency
Rheumatic mitral valve disease	ICD10	I341	Mitral (valve) prolapse
Non-rheumatic mitral valve disorders	ICD10	I342	Non-rheumatic mitral (valve) stenosis
Non-rheumatic mitral valve disorders	ICD10	I348	Other non-rheumatic mitral valve disorders
Non-rheumatic mitral valve disorders	ICD10	I349	Non-rheumatic mitral valve disorder, unspecified
Non-rheumatic mitral valve disorders	ICPC	K83	Heart valve disease NOS
Endocarditis, valve unspecified	ICD9	421	Acute and subacute endocarditis
Endocarditis, valve unspecified	ICD9	4249	Endocarditis valve unspecified
Endocarditis, valve unspecified	ICD10	I38	Endocarditis, valve unspecified
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD9	03642	Meningococcal endocarditis
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD9	07422	Coxsackie endocarditis
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD9	0932	Syphilitic endocarditis
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD9	09884	Gonococcal endocarditis
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD9	11281	Candidal endocarditis
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD9	11504	Histoplasma capsulatum endocarditis
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD9	11514	Histoplasma duboisii endocarditis
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD9	11594	Histoplasmosis endocarditis
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD10	I390	Mitral valve disorders in diseases classified elsewhere
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD10	I394	Multiple valve disorders in diseases classified elsewhere
Endocarditis and heart valve disorders in diseases classified elsewhere	ICD10	I398	Endocarditis, valve unspecified, in diseases classified elsewhere
Complications of cardiac and vascular prosthetic devices, implants and grafts	ICD9	9960	Mechanical complication of cardiac device implant and graft
Complications of cardiac and vascular prosthetic devices, implants and grafts	ICD9	9961	Mechanical complication of other vascular device, implant, and graft
Complications of cardiac and vascular prosthetic devices, implants and grafts	ICD10	T820	Mechanical complication of heart valve prosthesis
Complications of cardiac and vascular prosthetic devices, implants and grafts	ICD10	T825	Mechanical complication of other cardiac and vascular devices and implants
Complications of cardiac and vascular prosthetic devices, implants and grafts	ICD10	T826	Infection and inflammatory reaction due to cardiac valve prosthesis
Complications of cardiac and vascular prosthetic devices, implants and grafts	ICD10	T827	Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts
Complications of cardiac and vascular prosthetic devices, implants and grafts	ICD10	T828	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts
Complications of cardiac and vascular prosthetic devices, implants and grafts	ICD10	T829	Unspecified complication of cardiac and vascular prosthetic device, implant and graft
Presence of cardiac and vascular implants and grafts	ICD9	V432	Heart replaced by other means
Presence of cardiac and vascular implants and grafts	ICD9	V433	Heart valve replaced by other means

variable	system	code	Description
Presence of cardiac and vascular implants and grafts	ICD9	V434	Blood vessel replaced by other means
Presence of cardiac and vascular implants and grafts	ICD10	Z952	Presence of prosthetic heart valve
Presence of cardiac and vascular implants and grafts	ICD10	Z954	Presence of other heart-valve replacement
Presence of cardiac and vascular implants and grafts	ICD10	Z958	Presence of other cardiac and vascular implants and grafts
Presence of cardiac and vascular implants and grafts	ICD10	Z959	Presence of cardiac and vascular implant and graft, unspecified
Congenital malformations of aortic and mitral valves	ICD9	7463	Congenital stenosis of aortic valve
Congenital malformations of aortic and mitral valves	ICD9	7465	Congenital mitral stenosis
Congenital malformations of aortic and mitral valves	ICD10	Q232	Congenital mitral stenosis
Other congenital malformations of heart	ICD9	745	Bulbus cordis anomalies and anomalies of cardiac septal closure
Other congenital malformations of heart	ICD9	7460	Anomalies of pulmonary valve congenital
Other congenital malformations of heart	ICD9	7461	Tricuspid atresia and stenosis congenital
Other congenital malformations of heart	ICD9	7462	Ebstein's anomaly
Other congenital malformations of heart	ICD9	7464	Congenital insufficiency of aortic valve
Other congenital malformations of heart	ICD9	7466	Congenital mitral insufficiency
Other congenital malformations of heart	ICD9	7467	Hypoplastic left heart syndrome
Other congenital malformations of heart	ICD9	7468	Other specified congenital anomalies of heart
Other congenital malformations of heart	ICD9	7469	Unspecified congenital anomaly of heart
Other congenital malformations of heart	ICD10	Q232	Congenital mitral stenosis
Other congenital malformations of heart	ICD10	Q238	Other congenital malformations of aortic and mitral valves
Other congenital malformations of heart	ICD10	Q239	Congenital malformation of aortic and mitral valves, unspecified
Other congenital malformations of heart	ICD10	Q248	Other specified congenital malformations of heart
Other congenital malformations of heart	ICD10	Q249	Congenital malformation of heart, unspecified
Other congenital malformations of heart	ICPC	K73	Congenital anomaly cardiovascular
Prosthetic replacement of mitral valve	CVV	53501	Closed valvulotomy of mitral valve
Prosthetic replacement of mitral valve	CVV	53511	Open valvulotomy of mitral valve
Prosthetic replacement of mitral valve	CVV	53521	Replacement of mitral valve
Prosthetic replacement of mitral valve	CBV	333081	Heart - implantation of mitral valve prosthesis
Prosthetic replacement of mitral valve	CBV	333081B	Heart - replacement of mitral valve prosthesis using VATS

variable	system	code	Description
Prosthetic replacement of mitral valve	CBV	333081C	Heart - MAZE-procedure and mitral valve replacement
Prosthetic replacement of mitral valve	CBV	333081D	Heart - venal pulmonary isolation and mitral valve replacement
Prosthetic replacement of mitral valve	CBV	333086B	Heart - aortic valve replacement and mitral valve replacement
Prosthetic replacement of mitral valve	CBV	333086N	Heart - aortic root and mitral valve replacement
Prosthetic replacement of mitral valve	CBV	333086P	Heart - aortic valve replacement - mitral valve replacement - tricuspid valve replacement
Prosthetic replacement of mitral valve	CBV	333087B	Heart - mitral valve replacement using thorascopy
Prosthetic replacement of mitral valve	CBV	333110C	Heart - left ventricle - mitral valve replacement
Prosthetic replacement of mitral valve	CBV	683013	Heart valve - bjork-shiley mitral valve
Prosthetic replacement of mitral valve	CBV	683014	Heart valve - bjork-shiley mitral valve
Prosthetic replacement of mitral valve	CBV	683018	Heart valve - ionesco-shiley mitral valve
Prosthetic replacement of mitral valve	CBV	683022	Heart valve - mitroflow mitral valve
Prosthetic replacement of mitral valve	CBV	683036	Heart valve - transcatheter mitral valve prosthesis
Prosthetic replacement of mitral valve	CBV	683091	Duromedic - aorta - mitral valve
Prosthetic replacement of mitral valve	CBV	683099	Aortic valve - mitral valve prosthesis
Prosthetic replacement of mitral valve	CBV	683099M	Mitral valve prosthesis
Prosthetic replacement of mitral valve	CBV	190292	Mitral valve prosthesis
Prosthetic replacement of mitral valve	CBV	190308	Aortic valve prosthesis - mitral valve prosthesis
Prosthetic replacement of mitral valve	ZA	190292	Mitral valve prosthesis
Prosthetic replacement of mitral valve	ZA	190308	Aortic valve prosthesis - mitral valve prosthesis
Prosthetic replacement of mitral valve	CBV	333086D	Heart - aortic valve replacement - mitral valve replacement - tricuspid valve repair
Prosthetic replacement of mitral valve	CBV	333086F	Heart - mitral valve replacement and tricuspid valve repair
Prosthetic replacement of mitral valve	CBV	333086J	Heart - MAZE-procedure - mitral valve replacement - tricuspid valve repair
Repair of mitral valve for stenosis	CVV	53531	Valvulopasty of mitral valve
Repair of mitral valve for stenosis	CBV	333080B	Heart - mitral valve repair
Repair of mitral valve for stenosis	CBV	333080Q	Heart - mitral valve repair using thorascopy
Repair of mitral valve for stenosis	CBV	333080U	Heart - MAZE-procedure and mitral valve repair
Repair of mitral valve for stenosis	CBV	333080W	Heart - venal pulmonary isolation and mitral valve repair
Repair of mitral valve for stenosis	CBV	333080X	Heart - aortic root and mitral valve repair
Repair of mitral valve for stenosis	CBV	333086A	Heart - aortic valve replacement and mitral valve repair
Repair of mitral valve for stenosis	CBV	333086H	Heart - mitral valve repair using VATS
Repair of mitral valve for stenosis	CBV	333209D	Heart - mitral valve repair using balloon catheter
Repair of mitral valve for stenosis	CBV	333086E	Heart - mitral valve repair and tricuspid valve repair
Repair of mitral valve for stenosis	CBV	333086K	Heart - MAZE-procedure - mitral valve repair - tricuspid valve repair
Prosthetic replacement of tricuspid valve	CVV	53513	Open valvulotomy of tricuspid valve
Prosthetic replacement of tricuspid valve	CVV	53523	Replacement of tricuspid valve
Prosthetic replacement of tricuspid	CBV	333035B	Heart - ebstein procedure with tricuspid valve

variable	system	code	Description
valve			replacement
Prosthetic replacement of tricuspid valve	CBV	333087D	Heart - replacement of tricuspid valve using thorascopy
Prosthetic replacement of tricuspid valve	CBV	333093	Heart - implantation of tricuspid valve prosthesis
Prosthetic replacement of tricuspid valve	CBV	683038	Heart valve - transcatheter tricuspid valve prosthesis
Prosthetic replacement of tricuspid valve	CBV	683099T	Tricuspid valve prosthesis
Prosthetic replacement of tricuspid valve	CBV	190294	Tricuspid valve prosthesis

Hospital diagnoses are coded according to the WHO International Classification of Diseases (ICD-9 until 2013 and ICE-10 from 2013) and procedures are coded according to the Dutch Hospital Data Foundation owned registration system for procedures [www.dutchhospitaldata.nl] which links to the Dutch Healthcare Authority (NZa) declaration codes [www.nza.nl](CBV and ZA, from 2013) and the Dutch Classification of Procedures (Dutch Classification of Procedures [class.who-fic.nl]) (CVV, until 2013). GP diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [www.nhg.org].

15.3. Definition of Primary Endpoints: DVT/PE Indication

Table 15.5. Diagnostic ICD-9, ICD-10 AND ICPC Codes for ON-LABEL DVT/PE

variable	system	code	Description
Deep venous thrombosis	ICD9	45111	Phlebitis and thrombophlebitis of femoral vein (deep) (superficial)
Deep venous thrombosis	ICD9	45119	Phlebitis and thrombophlebitis of deep veins of lower extremities, other
Deep venous thrombosis	ICD9	4532	Other venous embolism and thrombosis of inferior vena cava
Deep venous thrombosis	ICD10	I801	Phlebitis and thrombophlebitis of femoral vein
Deep venous thrombosis	ICD10	I802	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
Deep venous thrombosis	ICD10	I822	Embolism and thrombosis of vena cava
Deep venous thrombosis	ICD10	I828	Embolism and thrombosis of other specified veins
Deep venous thrombosis	ICD10	I829	Embolism and thrombosis of unspecified vein
Deep venous thrombosis	ICPC	K94	Phlebitis/thrombophlebitis
Pulmonary embolism	ICD9	4151	Pulmonary embolism and infarction
Pulmonary embolism	ICD10	I26	Pulmonary embolism
Pulmonary embolism	ICPC	K93	Pulmonary embolism

*No specific codes for acute venous embolism and thrombosis of deep vessels are available in the Netherlands.
Hospital diagnoses are coded according to the WHO International Classification of Diseases (ICD-9 until 2013 and ICE-10 from 2013). GP diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [www.nhg.org].

15.4. Definition of Primary Endpoints: Off-label Indication

Note: All surgeries other than TKA/THA were be off-label

Table 15.6. OFF-LABEL diagnoses

Variable	System	Code	Description
Angina pectoris	ICD9	413	Angina pectoris
Angina pectoris	ICD10	I20	Angina pectoris
Angina pectoris	ICPC	K74	Angina pectoris
Acute myocardial infarction	ICD9	410	Acute myocardial infarction
Acute myocardial infarction	ICD10	I21	Acute myocardial infarction
Acute myocardial infarction	ICPC	K75	Acute myocardial infarction
Other acute and subacute forms of ischemic heart disease	ICD9	411	Other acute and subacute forms of ischemic heart disease
Other acute and subacute forms of ischemic heart disease	ICD10	I22	Subsequent myocardial infarction
Other acute and subacute forms of ischemic heart disease	ICD10	I23	Certain current complications following acute myocardial infarction
Old myocardial infarction	ICD9	412	Old myocardial infarction
Old myocardial infarction	ICD10	I252	Old myocardial infarction
Other forms of chronic ischemic heart disease	ICD9	414	Other forms of chronic ischemic heart disease
Other forms of chronic ischemic heart disease	ICD10	I24	Other acute ischaemic heart diseases
Other forms of chronic ischemic heart disease	ICD10	I25	Chronic ischaemic heart disease
Other forms of chronic ischemic heart disease	ICPC	K76	Ischaemic heart disease w/o angina
Atrial flutter	ICD9	42732	Atrial flutter
Atrial flutter	ICD10	I483	Typical atrial flutter
Atrial flutter	ICD10	I484	Atypical atrial flutter
Atrial flutter	ICD10	I489	Atrial fibrillation and atrial flutter, unspecified
Occlusion and stenosis of precerebral arteries	ICD9	4330	Occlusion and stenosis of basilar artery
Occlusion and stenosis of precerebral arteries	ICD9	4331	Occlusion and stenosis of carotid artery
Occlusion and stenosis of precerebral arteries	ICD9	4332	Occlusion and stenosis of vertebral artery
Occlusion and stenosis of precerebral arteries	ICD9	4333	Occlusion and stenosis of precerebral arteries, multiple and bilateral
Occlusion and stenosis of precerebral arteries	ICD9	4338	Occlusion and stenosis of other specified precerebral arteries
Occlusion and stenosis of precerebral arteries	ICD9	4339	Occlusion and stenosis of unspecified precerebral arteries
Occlusion and stenosis of precerebral arteries	ICD10	I630	Cerebral infarction due to thrombosis of precerebral arteries
Occlusion and stenosis of precerebral arteries	ICD10	I631	Cerebral infarction due to embolism of precerebral arteries
Occlusion and stenosis of precerebral arteries	ICD10	I632	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries

Variable	System	Code	Description
Occlusion and stenosis of precerebral arteries	ICD10	I633	Cerebral infarction due to thrombosis of cerebral arteries
Occlusion of cerebral arteries	ICD10	I634	Cerebral infarction due to embolism of cerebral arteries
Occlusion of cerebral arteries	ICD10	I635	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
Occlusion of cerebral arteries	ICD10	I636	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
Occlusion of cerebral arteries	ICD10	I638	Other cerebral infarction
Occlusion of cerebral arteries	ICD10	I639	Cerebral infarction, unspecified
Occlusion of cerebral arteries	ICD10	I693	Sequelae of cerebral infarction
Occlusion of cerebral arteries	ICD9	4340	Cerebral thrombosis
Occlusion of cerebral arteries	ICD9	4341	Cerebral embolism
Occlusion of cerebral arteries	ICD9	4349	Occlusion of cerebral artery, unspecified
Occlusion of cerebral arteries	ICPC	K89	Transient cerebral ischaemia
Occlusion of cerebral arteries	ICPC	K90	Stroke/cerebrovascular accident
Occlusion of cerebral arteries	ICD10	I64	Stroke, not specified as haemorrhage or infarction
Arterial embolism and thrombosis	ICD9	444	Arterial embolism and thrombosis
Arterial embolism and thrombosis	ICD10	I74	Arterial embolism and thrombosis
Arterial embolism and thrombosis	ICPC	K92	Other peripheral arterial diseases
Phlebitis and thrombophlebitis	ICD9	4510	Phlebitis and thrombophlebitis of superficial vessels of lower extremities
Phlebitis and thrombophlebitis	ICD9	4512	Phlebitis and thrombophlebitis of lower extremities, unspecified
Phlebitis and thrombophlebitis	ICD9	4518	Phlebitis and thrombophlebitis of other sites
Phlebitis and thrombophlebitis	ICD9	45181	Phlebitis and thrombophlebitis of iliac vein
Phlebitis and thrombophlebitis	ICD9	45189	Phlebitis and thrombophlebitis of other sites, other
Phlebitis and thrombophlebitis	ICD9	4519	Phlebitis and thrombophlebitis of unspecified site
Phlebitis and thrombophlebitis	ICD10	I800	Phlebitis and thrombophlebitis of superficial vessels of lower extremities
Phlebitis and thrombophlebitis	ICD10	I803	Phlebitis and thrombophlebitis of lower extremities, unspecified
Phlebitis and thrombophlebitis	ICD10	I808	Phlebitis and thrombophlebitis of other sites
Phlebitis and thrombophlebitis	ICD10	I809	Phlebitis and thrombophlebitis of unspecified site
Portal vein thrombosis	ICD9	452	Portal vein thrombosis
Portal vein thrombosis	ICD10	I81	Portal vein thrombosis
Portal vein thrombosis	ICPC		
Other venous embolism and thrombosis	ICD9	4530	Budd-Chiari syndrome
Other venous embolism and thrombosis	ICD9	4531	Thrombophlebitis migrans
Other venous embolism and thrombosis	ICD9	4533	Venous embolism and thrombosis of renal vein
Other venous embolism and thrombosis	ICD9	4538	Venous embolism and thrombosis of other specified veins
Other venous embolism and thrombosis	ICD9	4539	Venous embolism and thrombosis of unspecified site
Other venous embolism and thrombosis	ICD9	6715	Other phlebitis and thrombosis in pregnancy and the puerperium
Other venous embolism and thrombosis	ICD9	6732	Obstetrical blood-clot embolism

Variable	System	Code	Description
Other venous embolism and thrombosis	ICD9	67130	Deep phlebothrombosis, antepartum, unspecified as to episode of care or not applicable
Other venous embolism and thrombosis	ICD9	67131	Deep phlebothrombosis, antepartum, delivered, with or without mention of antepartum condition
Other venous embolism and thrombosis	ICD9	67132	Deep phlebothrombosis, antepartum, delivered, with mention of postpartum complication
Other venous embolism and thrombosis	ICD9	67133	Deep phlebothrombosis, antepartum, antepartum condition or complication
Other venous embolism and thrombosis	ICD9	67134	Deep phlebothrombosis, antepartum, postpartum condition or complication
Other venous embolism and thrombosis	ICD9	67140	Deep phlebothrombosis, postpartum, unspecified as to episode of care or not applicable
Other venous embolism and thrombosis	ICD9	67141	Deep phlebothrombosis, postpartum, delivered, with or without mention of antepartum condition
Other venous embolism and thrombosis	ICD9	67142	Deep phlebothrombosis, postpartum, delivered, with mention of postpartum complication
Other venous embolism and thrombosis	ICD9	67143	Deep phlebothrombosis, postpartum, antepartum condition or complication
Other venous embolism and thrombosis	ICD10	67144	Deep phlebothrombosis, postpartum, postpartum condition or complication
Other venous embolism and thrombosis	ICD10	I820	Budd-Chiari syndrome
Other venous embolism and thrombosis	ICD10	I821	Thrombophlebitis migrans
Other venous embolism and thrombosis	ICD10	I823	Embolism and thrombosis of renal vein
Other venous embolism and thrombosis	ICD10	O225	Cerebral venous thrombosis in pregnancy
Other venous embolism and thrombosis	ICD10	K645	Perianal venous thrombosis
Other venous embolism and thrombosis	ICD10	O882	Obstetric thromboembolism
Other venous embolism and thrombosis	ICD9	V125	Personal history of diseases of circulatory system
Acute pulmonary heart disease	ICD9	4150	Acute cor pulmonale
Acute pulmonary heart disease	ICPC	K82	Cor pulmonale

* When no ICPC code is given, no specific code was available.
Hospital diagnoses are coded according to the WHO International Classification of Diseases (ICD-9 until 2013 and ICE-10 from 2013). GP diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [www.nhg.org].

15.5. Definition of Variables: ATC codes for co-dispensed medications

Table 15.7. ATC codes for co-dispensed medications

Antithrombotic agents	
B01AA	Vitamin K antagonists
B01AB	Heparins
B01AC	Platelet aggregation inhibitors excluding heparin
B01AD	Enzymes
B01AE	Direct thrombin inhibitors
B01AX	Other antithrombotic agents
Anti-inflammatory and anti-rheumatic products	
M01A	Anti-inflammatory and anti-rheumatic products, non-steroids
CYP3A4 and P-gp inhibitors	
J02A	Antimycotics for systemic use
J05AE	Protease inhibitors
N06AB	Selective serotonin reuptake inhibitors
C08DA	Phenylalkylamine derivatives
C01BA	Antiarrhythmics, class Ia
C07AB	Selective beta blocking agents
C08DB	Benzothiazepine derivatives
C10AA	HMG CoA reductase inhibitors
J01FA01	Eryithromycin
J01FA09	Clarithromycin
L04AA	Selective immunosuppressants
CYP3A4 and P-gp inducers	
N03AF	Carboxamide derivatives
A10BG	Thiazolidinediones
H02AB	Glucocorticoids
J01EB	Short-acting sulfonamides
J01FA	Macrolides (excl erythromycin and clarithromycin)
J04AB	Antibiotics for tuberculosis
J05AG	Non-nucleoside reverse transcriptase inhibitors
M04AB	Preparations increasing uric acid excretion
N03AA	Barbiturates and derivatives
N03AB	Hydantoin derivatives
N03AD	Succinimide derivatives
N05CE	Piperidinedione derivatives
No ATC code	St. John's Wart

15.6. Definition of Variables: ICD and ICPC codes for co-morbidity

Table 15.8. ICD-9, ICD-10 and ICPC codes for co-morbidity

variable	system	code	Description
Chronic kidney disease (CKD)	ICD9	585	Chronic kidney disease (CKD)
Chronic kidney disease (CKD)	ICD10	N18	Chronic kidney disease
Chronic kidney disease (CKD)	ICPC	U99.01	Renal insufficiency
Acute and subacute necrosis of liver	ICD9	570	Acute and subacute necrosis of liver
Acute and subacute necrosis of liver	ICD10	K720	Acute and subacute hepatic failure
Chronic liver disease and cirrhosis	ICD9	571	Chronic liver disease and cirrhosis
Chronic liver disease and cirrhosis	ICD10	K70	Alcoholic liver disease
Chronic liver disease and cirrhosis	ICD10	K73	Chronic hepatitis, not elsewhere classified
Chronic liver disease and cirrhosis	ICD10	K74	Fibrosis and cirrhosis of liver
Chronic liver disease and cirrhosis	ICD10	K740	Hepatic fibrosis
Chronic liver disease and cirrhosis	ICD10	K741	Hepatic sclerosis
Chronic liver disease and cirrhosis	ICD10	K742	Hepatic fibrosis with hepatic sclerosis
Chronic liver disease and cirrhosis	ICD10	K743	Primary biliary cirrhosis
Chronic liver disease and cirrhosis	ICD10	K744	Secondary biliary cirrhosis
Chronic liver disease and cirrhosis	ICD10	K745	Biliary cirrhosis, unspecified
Chronic liver disease and cirrhosis	ICD10	K746	Other and unspecified cirrhosis of liver
Chronic liver disease and cirrhosis	ICD10	K760	Fatty (change of) liver, not elsewhere classified
Chronic liver disease and cirrhosis	ICD10	R160	Hepatomegaly, not elsewhere classified
Chronic liver disease and cirrhosis	ICD10	R162	Hepatomegaly with splenomegaly, not elsewhere classified
Chronic liver disease and cirrhosis	ICPC	D96	Hepatomegaly
Chronic liver disease and cirrhosis	ICPC	D97	Cirrhosis/other liver disease
Liver abscess and sequelae of chronic liver disease	ICD9	572	Liver abscess and sequelae of chronic liver disease
Liver abscess and sequelae of chronic liver disease	ICD10	K750	Abscess of liver
Liver abscess and sequelae of chronic liver disease	ICD10	K751	Phlebitis of portal vein
Liver abscess and sequelae of chronic liver disease	ICD10	K766	Portal hypertension
Liver abscess and sequelae of chronic liver disease	ICD10	K767	Hepatorenal syndrome
Liver abscess and sequelae of chronic liver disease	ICD10	K729	Hepatic failure, unspecified
Other disorders of liver	ICD9	573	Chronic passive congestion of liver
Other disorders of liver	ICD10	K71	Toxic liver disease
Other disorders of liver	ICD10	K752	Nonspecific reactive hepatitis
Other disorders of liver	ICD10	K753	Granulomatous hepatitis, not elsewhere classified
Other disorders of liver	ICD10	K754	Autoimmune hepatitis
Other disorders of liver	ICD10	K758	Other specified inflammatory liver diseases
Other disorders of liver	ICD10	K759	Inflammatory liver disease, unspecified
Other disorders of liver	ICD10	K761	Chronic passive congestion of liver
Other disorders of liver	ICD10	K762	Central haemorrhagic necrosis of liver

variable	system	code	Description
Other disorders of liver	ICD10	K763	Infarction of liver
Other disorders of liver	ICD10	K764	Peliosis hepatis
Other disorders of liver	ICD10	K765	Hepatic veno-occlusive disease
Other disorders of liver	ICD10	K768	Other specified diseases of liver
Other disorders of liver	ICD10	K769	Liver disease, unspecified
Other disorders of liver	ICD10	K77	Liver disorders in diseases classified elsewhere
Other disorders of liver	ICPC	D72	Viral hepatitis
Coagulation defects	ICD9	286	Coagulation defects
Coagulation defects	ICD10	D65	Disseminated intravascular coagulation [defibrination syndrome]
Coagulation defects	ICD10	D66	Hereditary factor VIII deficiency
Coagulation defects	ICD10	D67	Hereditary factor IX deficiency
Coagulation defects	ICD10	D68	Other coagulation defects
Coagulation defects	ICPC	B83	Purpura/coagulation defects/thrombocytopenia
Subarachnoid haemorrhage	ICD9	430	Subarachnoid haemorrhage
Subarachnoid haemorrhage	ICD10	I60	Subarachnoid haemorrhage
Intracerebral haemorrhage	ICD9	431	Intracerebral haemorrhage
Intracerebral haemorrhage	ICD10	I61	Intracerebral haemorrhage
Other and unspecified intracranial haemorrhage	ICD9	432	Other and unspecified intracranial haemorrhage
Other and unspecified intracranial haemorrhage	ICD10	I62	Other nontraumatic intracranial haemorrhage
Gastric ulcer	ICD9	531	Gastric ulcer
Gastric ulcer	ICD10	K25	Gastric ulcer
Gastric ulcer	ICPC	D86	Gastric ulcer
Duodenal ulcer	ICD9	532	Duodenal ulcer
Duodenal ulcer	ICD10	K26	Duodenal ulcer
Duodenal ulcer	ICPC	D85	Duodenal ulcer
Peptic ulcer, site unspecified	ICD9	533	Peptic ulcer, site unspecified, acute with haemorrhage
Peptic ulcer, site unspecified	ICD10	K27	Peptic ulcer, site unspecified
Peptic ulcer, site unspecified	ICPC	D86	Peptic ulcer other
Acute and subacute bacterial endocarditis	ICD9	421	Acute and subacute endocarditis
Acute and subacute bacterial endocarditis	ICD10	I33	Acute and subacute endocarditis
Acute and subacute bacterial endocarditis	ICD10	I38	Endocarditis, valve unspecified
Acute and subacute bacterial endocarditis	ICD10	I398	Endocarditis, valve unspecified, in diseases classified elsewhere
Oesophageal varices with bleeding	ICD9	4560	Oesophageal varices with bleeding
Oesophageal varices with bleeding	ICD10	I850	Oesophageal varices with bleeding
Oesophageal varices without mention of bleeding	ICD9	4561	Oesophageal varices without mention of bleeding
Oesophageal varices without mention of bleeding	ICD10	I859	Oesophageal varices without mention of bleeding
Oesophageal varices in diseases classified elsewhere	ICD9	4562	Oesophageal varices in diseases classified elsewhere
Oesophageal varices in diseases	ICD10	I982	Oesophageal varices in diseases classified

variable	system	code	Description
classified elsewhere			elsewhere
Oesophageal varices in diseases classified elsewhere	ICD10	I983	Oesophageal varices with bleeding in diseases classified elsewhere
Primary thrombocytopenia	ICD9	2873	Primary thrombocytopenia
Primary thrombocytopenia	ICD10	D693	Idiopathic primary thrombocytopenia
Primary thrombocytopenia	ICD10	D694	Other primary thrombocytopenia
Secondary thrombocytopenia	ICD9	2874	Secondary thrombocytopenia
Secondary thrombocytopenia	ICD10	D695	Secondary thrombocytopenia
Thrombocytopenia, unspecified	ICD9	2875	Thrombocytopenia, unspecified
Thrombocytopenia, unspecified	ICD10	D696	Thrombocytopenia, unspecified
Thrombocytopenia, unspecified	ICD10	D820	Wiskott-Aldrich syndrome
Thrombocytopenia, unspecified	ICPC	B83	Purpura/coagulation defect
Incision and excision of skull, brain and meninges	CVV	501	incision and excision of skull, brain and meninges
Other operations on skull, brain and meninges	CVV	502	other operations on skull, brain and meninges
Operations on spinal cord and spinal canal structures	CVV	503	operations on spinal cord and spinal canal structures

Hospital diagnoses are coded according to the WHO International Classification of Diseases (ICD-9 until 2013 and ICE-10 from 2013) and procedures are coded according to the Dutch Hospital Data Foundation owned registration system for procedures [www.dutchhospitaldata.nl] which links to the Dutch Healthcare Authority (NZa) declaration codes [www.nza.nl](CBV and ZA, from 2013) and the Dutch Classification of Procedures (Dutch Classification of Procedures [class.who-fic.nl]) (CVV, until 2013). GP diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [www.nhg.org].

[redacted]

NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

POST-APPROVAL SAFETY STUDY (PASS) OF THE UTILIZATION PATTERN OF APIXABAN IN THE NETHERLANDS

Compound Number:	BMS-562247-01
Compound Name:	Apixaban
Study Number:	B0661018
Version and Date:	Protocol Amendment 3 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 the Netherlands, as described herein, and a second study of apixaban drug utilization in Sweden, which is described in a separate protocol.

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

Table 1. Indications and Dates of EMA Authorisation

	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 >= 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class >= 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 patterns of apixaban in the Netherlands.

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 the Netherlands (01 Dec 2011 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 Dec 2011 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 an 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

The data source for this study will be the PHARMO medical record linkage system, a population-based, patient-centric data tracking system that includes high-quality and complete information on patient demographics, mortality, drugs dispensed by outpatient pharmacies and a subset of hospital pharmacies, hospital morbidity, clinical laboratory and

pathology findings, and general practitioner (GP) information. Specifically, four databases will be used: the Inpatient Pharmacy Database, Outpatient Pharmacy Database, the Hospitalisation Database, and the GP Database. Information will be captured on apixaban dispensed to hospitalized patients and to patients receiving apixaban from outpatient pharmacies. These prescriptions will be linked to diagnoses and surgeries from inpatient and GP records.

The PHARMO databases cover 3.2 million community-dwelling inhabitants of 65 municipal areas in the Netherlands and are linked via probabilistic linkage methods to form a database network on a patient level. Dispensed drugs are coded using the Anatomical Therapeutic Chemical (ATC) classification system, and medical diagnoses are coded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. The database has been used in previous studies of anticoagulant use and bleeding risk (Penning-van Beest, Erkens et al. 2005; Penning-van Beest, Koerselman et al. 2007; Penning-van Beest, Koerselman et al. 2008).[1, 2, 3]

6.2. Data Compilation Procedure

Patients who received an outpatient pharmacy dispensing of apixaban (prescriptions of GPs and specialist physicians) will be identified as well as patients who were prescribed apixaban in-hospital during an admission.

Hip and knee replacement and other surgeries will be identified via appropriate procedure and ICD-9 codes from linked hospital discharge diagnoses, and by International Classification of Primary Care (ICPC) codes or free text indication field in the linked GP data. 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 using a similar approach**.**

6.3. Decision Rules 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 NVAF and 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:

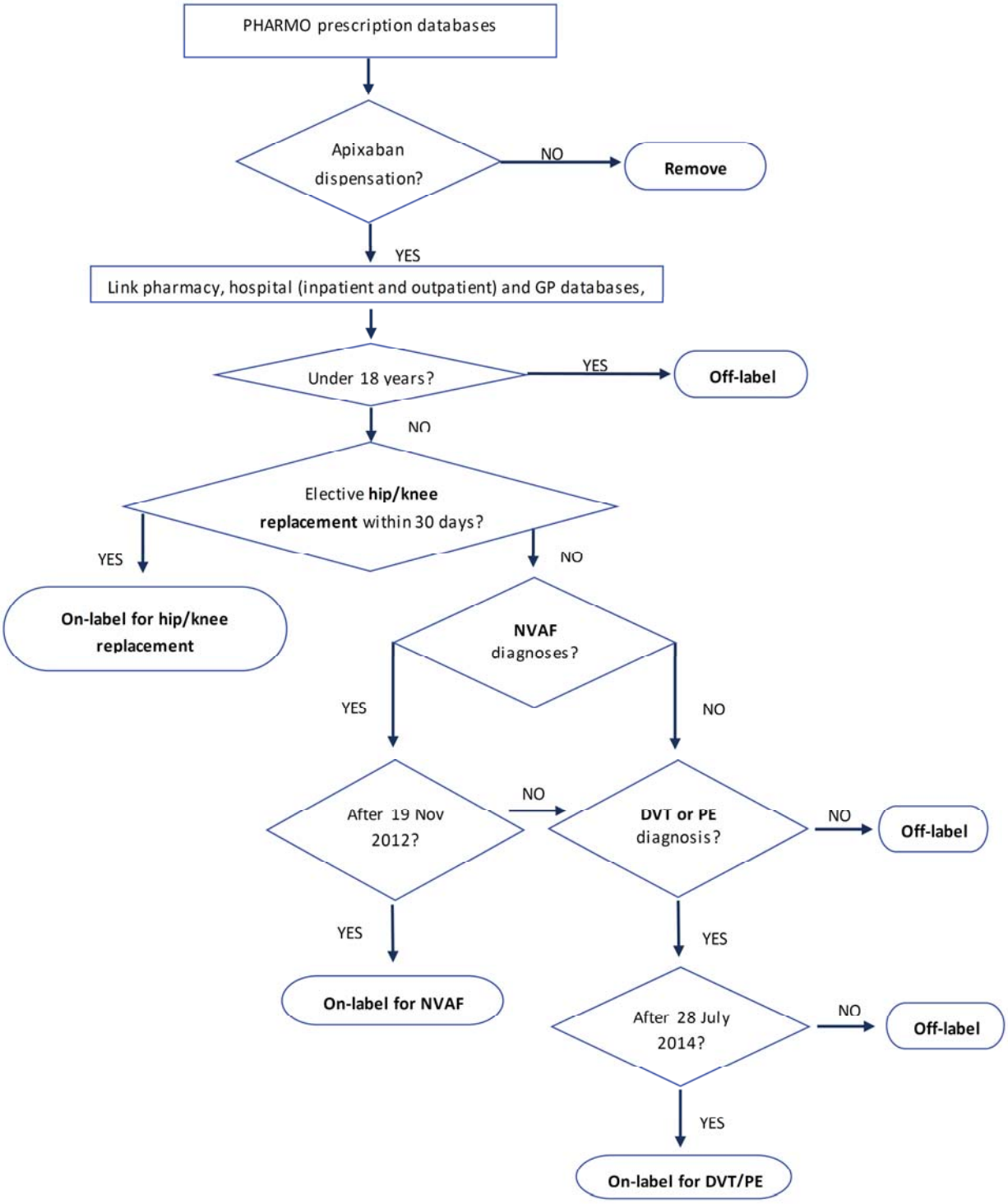
    a) An elective hip or knee replacement within 30 days before the apixaban prescription, or

    b) An apixaban prescription after 19 November 2012 and a diagnosis of NVAF before the apixaban prescription, or,

    c) An apixaban prescription after 28 July 2014 and a diagnosis of DVT or PE before the apixaban prescription (Figure 1).

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

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



6.4. Data Elements

- Patient demographics: Age and Gender.
- Information on dispensing of apixaban: dispensing date, dose, amount dispensed, duration of use based on amount of drug prescribed.
- Hospital admission information: dates of hospital admission and discharges, ICD-9 discharge diagnoses, surgical procedure codes.
- GP information: ICPC diagnosis codes, and a short free text field in the database with information on the indication.
- 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 for a hypothesis test is relevant. 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.

As shown in the table below, 500 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 7.8 percent (Table 2).

Table 2. Precision Around the Off Label Use Proportion Estimates Assuming a Total Sample Size of 500 Patients

Off label use (%)	Width of 95% CI for off label use (%)
5	4.0
15	6.5
25	7.8
35	8.5
45	8.9

The actual numbers will depend on the uptake of the drug following launch.

7.2. Data Analysis

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, ie, the index date. 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 (eg, 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 treatments 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 PHARMO 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 hypercoaguable states in which apixaban could be used off-label.

5. Patients with 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.

Data on diagnoses and surgeries made in the out-patient setting are only available through the GP data. As a consequence, information on diagnoses and surgeries made in the out-patient setting is only available for apixaban users with GP available data and unknown for apixaban users without GP data available.

A sensitivity analysis will therefore calculate the percentage of on-label or off-label apixaban users in the subgroup with GP data. This assumes that the availability of GP data is not related to the ratio of on-label or off-label use.

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 (other than hip or knee replacement surgery) and diagnoses (other than NVAF and treatment of DVT/PE) 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.

In addition to the stratified analyses by indication described above, stratified analysis according to the inpatient and outpatient subgroups will be presented in the PHARMO study reports.

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 network that collects the variables required to fulfill the objectives. There are strong linkage systems that use different patient characteristics to probabilistically link different data sources. This database network has been used for multiple pharmacoepidemiologic studies, including those of anticoagulant use and bleeding risk (Penning-van Beest, Erkens et al. 2005; Penning-van Beest, Koerselman et al. 2007; Penning-van Beest, Koerselman et al. 2008).[1, 2, 3]

- The database has coverage of all age groups.

- Hospital admission data as well as general practitioner records can be used to obtain information on the indication.

- 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:

- Although in principle all admissions are captured in the hospital admission database, small gaps in data collection have been observed and might also occur during the study period. In addition, surgical procedures conducted outside the Netherlands will not be captured. General practitioner records will also be used to obtain information on the indication, however, GP data will not be available for all patients.

- Validation of the data in the database by reviewing individual patients' original medical records will not be possible.

- If the uptake of apixaban use following launch is slow, the study will have relatively small number of patients in the analysis.

- This study is based on healthcare records data being collected by the PHARMO Institute in the Netherlands and then accessed by the investigators for analyses. As a result, any unforeseen delay in the collection and compilation of data is beyond the control of the Sponsor and may affect the study timeline.

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.

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, Institution 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

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