NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Apixaban drug utilization study in Stroke prevention in atrial fibrillation (SPAF)
Protocol number	B0661076
AEMPS Code	PFI-API-2016-01
Protocol version identifier	4.0
Date of last version of protocol	15-Feb-2016
Active substance	Apixaban B01AF02
Medicinal product	Eliquis®
Research question and objectives	Evaluate the apixaban utilization according to the approved SPAF indication and recommendations by EMA. The study objectives are: Objective 1: To characterise patients using apixaban according to demographics, comorbidity, risk of thromboembolic events ($CHADS_2$ and CHA_2DS_2-Vasc scores), risk of bleeding events (HAS-BLED score), comedications and compare it with the profile of patients treated with VKA, dabigatran and rivaroxaban. Objective 2: Describe the level of appropriate usage according to the posology recommended in the apixaban SmPC. Objective 3: Describe the potential interactions with other drugs prescribed concomitantly according with the SmPC recommendations. Objective 4: Estimate the level of apixaban adherence by the medication possession ratio (MPR) and discontinuation rates and compare it with VKA, dabigatran and

	rivaroxaban cohort. Objective 5: To analyze INR (International Normalized Ratio) values during the last 12 months and to obtain TTR (Time in Therapeutic Range) values in patients previously treated with VKA and, during the whole study period for those in the cohort treated with VKA
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ATC	Anatomical Therapeutic Chemical classification system
AF	atrial fibrillation
BMI	body mass index
DDD	defined daily dose
DOAC	direct oral anticoagulant
DUS	drug utilization study
DVT	deep vein thrombosis
EMA	European Medicine Agency
FDA	Food and Drug Administration
HR	hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICS	Institut Català de la Salut
INR	International normalized ratio
ISPE	International Society for Pharmacoepidemiology
MPR	medication possession ratio
NSAIDs	nonsteroidal anti-inflammatory drugs
NVAF	non-valvular atrial fibrillation
PASS	Post-Authorisation Safety Study
PE	pulmonary embolism
P-gp	P-glycoprotein
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SPAF	Stroke prevention in atrial fibrillation
TIA	transient ischemic attack
TTT	Time in a therapeutic range
VKA	vitamin K antagonists
VTE	venous thromboembolic events

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Title

Apixaban drug utilization study for Stroke prevention in atrial fibrillation (SPAF).

Rationale and background

Apixaban is a direct oral anticoagulant, which inhibits the factor Xa. Its clinical efficiency in prevention of stroke and systemic embolism in adult patients with NVAF (non-valvular atrial fibrillation) was demonstrated as well as has shown better safety profile compared with warfarin. A Drug Utilization study will evaluate whether this drug has been used in accordance with the approved indication and recommendations described in the summary of product characteristics (SmPC) and estimate possible misuse or overuse apixaban.

Research question and objectives

The primary research question is to evaluate the apixaban utilization according to the approved SPAF indication and recommendations by EMA.

In addition a comparison with a cohort of NVAF patients treated with VKA, dabigatran and rivaroxaban for the SPAF indication will also be performed.

Objective 1: To characterize patients using apixaban according to demographics, comorbidity, risk of thromboembolic events ($CHADS_2$ and CHA_2DS_2-Vasc scores), risk of bleeding events (HAS-BLED score), comedications and compare it with the profile of patients treated with VKA, dabigatran and rivaroxaban.

Objective 2: Describe the level of appropriate usage according to the posology recommended in the apixaban SmPC.

Objective 3: Describe the potential interactions with other drugs prescribed concomintatly according with the SmPC recommendations.

Objective 4: Estimate the level of apixaban adherence by the medication possession ratio (MPR) and discontinuation rates and compare it with VKA, dabigatran and rivaroxaban cohort.

Objective 5: To analyze INR (International Normalized Ratio) values during the last 12 months and to obtain TTR (Time in Therapeutic Range) values in patients previously treated with VKA, and during the whole study period for those in the cohort treated with VKA.

Study design

Retrospective cohort study using data from the SIDIAP database (Sistema d´informació pel desenvolupament de la investigació en atenció primària-information system for advancement of research in primary health care) in Catalonia, Spain. The observational study period will be from August 2013 until December 2015.

Population

The study population for this cohort include all eligible subjects from the source population with a first –recorded prescription of apixaban, VKA, dabigatran or rivaroxaban registered in SIDIAP database and prior diagnosis of NVAF for study period.

Variables:

Sociodemographic characterization of the patients in both groups of drugs will be assessed for each variable (age, sex, toxic habits, MEDEA index, BMI).

Comorbidity: Apixaban, VKA, dabigatran and rivaroxaban users will be characterized according to presence of comorbidity at the baseline period (12 months prior to the initial prescription) before the start date. Comorbidity will be assessed for each disease/condition detailed.

Concomitant treatments at the index date will be identified. Concurrent use of potentially interacting medications will be assessed for the months during follow-up period of the study.

Apixaban dose will be assessed during the study period for each patient at two different doses 2.5mg BID and 5mg BID.

Thromboembolic risk characterization in patients with NVAF and bleeding risk will be assessed at the start date for each risk score CHADS2, CHA2DS2Vasc and HAS-BLED.

INR and TTR estimations would be done for current apixaban users which previously have been treated with VKA drugs and for current VKA users and its measurement would be done by data of prothrombin time.

Apixaban, VKA, dabigatran and rivaroxaban adherence will be measured by MPR (medication possession ratio) and by discontinuation rates, identified from pharmacy invoice data prescriptions during the study period.

Data sources

The data source is SIDIAP database, which contains anonymized clinical information that originates from different data sources: 1) eCAP™ (electronic medical records in Primary Care of the Institut Català de la Salut [ICS]); which includes information since 2006 on sociodemographic characteristics, health conditions registered as ICD10 codes, General

Practitioners' prescriptions, clinical parameters and toxic habits. 2) Laboratory data. 3) Prescriptions and their corresponding pharmacy invoice data; available since 2005: information on all pharmaceutical products dispensed by community pharmacies with Catalan Health System prescriptions, by ATC codes.

Study size

The sample size is driven by the prescription of apixaban in source population of database. According to previous data, we estimate that we would have approx. 2000 patients treated with apixaban, 14000 with VKA (warfarina 2000, acenocumarol 12000), 4000 with dabigatran and 500 with rivaroxaban.

Data analysis

The analysis will be performed using SAS software, version 9.4 (SAS Institute). The use and patterns of use of Apixaban and VKA will be summarised by the total number of users, prescriptions, and number of defined daily doses (DDDs), and by the number of users according to daily dose and duration of use. Characteristics of users, comorbidity, comedications, use of interacting drugs will be described as number and percentage of patients with each condition. The number and percentage of all variables will be calculated by apixaban VKA, dabigatran and rivaroxaban group. In general, frequencies will be used to describe the study sample characteristics and characteristics of each category group. Chi-square tests and ANOVA will be utilized to compare categorical and continuous variables, respectively, across the category groups.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason

5. MILESTONES

Milestone	Planned date
Drafting of the Protocol, AEMPS classification, Research Ethics Committee evaluation	November 2015-January 2016
Start of data collection, study variables operational definition	April 2016
End of data collection (data management and extraction)	June 2016
Statistical analysis	July-September 2016
Interim report	November 2016
Final study report.	December 2016

6. RATIONALE AND BACKGROUND

We present a non-interventional post authorization study on the use of apixaban in Catalonia –Spain public health care population.

Apixaban was authorized in 2011 by European Medicines Agency (EMA) for prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, and treatment and prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE).[1]

The apixaban SPAF indication was commercialized in Spain for the first time in August 2013 as Eliquis, 5 mg BID film-coated tablets.[1]

Apixaban is a direct oral anticoagulant (DOAC), which inhibits factor Xa. Its clinical efficiency in prevention of stroke and systemic embolism in adult patients with NVAF was demonstrated by clinical trial: CV185030 (ARISTOTLE), where it demonstrated superior efficacy compared to warfarin in the primary composite endpoint of stroke or systemic embolism: 1.27 % / year with apixaban vs. 1.60% / year with warfarin (hazard ratio [HR], 0.79; 95 % confidence interval [CI], 0.66 to 0.95). While in the primary endpoint for safety it showed better safety profile compared with warfarin in severe bleeding: 2.13 % / year apixaban vs 3.09 % / year warfarin (HR, 0.69; 95 %, CI: 0.60 to 0.80).[2]

Until now, most of the observational studies for apixaban were about cost-effectiveness, which is explained due to the relatively high price of this new drug. According to the study "Patterns of initiation of oral anticoagulants in patients with atrial fibrillation (AF) - quality and cost implications" the patients were characterized by prescription and comparing apixaban with other DOAC in the treatment of NVAF and the authors found that DOACs are being incorporated quickly into clinical practice, especially among patients with low values of $CHADS_2$ score and HAS-BLED score.[3]

It is a relatively new drug, recently launched on the Spanish market and according to the detailed bibliographic review and database of registered clinical trials, www.clinicaltrialsregister.eu; there are no drug utilization studies (DUS) of apixaban in Spanish population. EMA recommends additional monitoring for this drug and pharmacovigilance plan which includes performing drug utilization and post marketing studies.

This DUS protocol will evaluate whether this drug has been used properly and in accordance with the approved indications and recommendations described in the summary of product characteristics (SmPC) and estimate possible misuse or overuse of apixaban.

7. RESEARCH QUESTION AND OBJECTIVES

The primary research question is to evaluate the apixaban utilization according to the approved SPAF indication and recommendations by EMA.

In addition a comparison with a cohort of NVAF patients treated with VKA, dabigatran and rivaroraban for the SPAF indication will also be performed.

Objective 1: To characterise patients using apixaban according to demographics, comorbidity, risk of thromboembolic events ($CHADS_2$ and CHA_2DS_2-Vasc scores) [4], risk of bleeding events (HAS-BLED score) [5], comedications and compare it with the profile of patients treated with VKA, dabigatran and rivaroxaban.

Objective 2: Describe the level of appropriate usage according to the posology recommended in the apixaban SmPC.

Objective 3: Describe the potential interactions with other drugs prescribed concomitantly according with the SmPC recommendations.

Objective 4: Estimate the level of apixaban adherence by the medication possession ratio (MPR) and discontinuation rates and compare it with the VKA, dabigatran and rivaroxaban cohort.

Objective 5: To analyze INR (International Normalized Ratio) values during the last 12 months and to obtain TTR (Time in Therapeutic Range) values in patients previously treated with VKA, and during the whole study period for those in the cohort treated with VKA.

8. RESEARCH METHODS

8.1. Study design

This DUS is a retrospective, observational and cohort study. The users of apixaban are patients identified in the primary health care database SIDIAP (Sistema d´informació pel desenvolupament de la investigació en atenció primària- information system for advancement of research in primary health care) in Catalonia, Spain.

Study cohort

The study cohort includes all individuals diagnosed with NVAF from source population who had a new prescription for apixaban, VKA (warfarin or acenocoumarol), dabigatran or rivaroraban from August 2013 until December 2015 and a previously recorded diagnostic of NVAF. All the patients enrolled in the cohort will be subdivided in four main groups.

Group 1: Patients who are on treatment with apixaban, this group will have two subgroups,

1a: patients who have initiated with apixaban as treatment naïve (no prior prescription of VKA previous to the 12 months before index date),

1b: patients who previously have been treated with VKA in the 12 months before index date.

Group 2: Patients who are on treatment with VKA, this group will have two subgroups,

2a: patients who have initiated with VKA as treatment naïve (no prior prescription of VKA previous to the 12 months before index date),

2b: patients who previously have been treated with VKA in the 12 months before index date.

Group 3: Patients who are on treatment with dabigatran, this group will have two subgroups,

3a: patients who have initiated with dabigatran as treatment naïve (no prior prescription of VKA previous to the 12 months before index date),

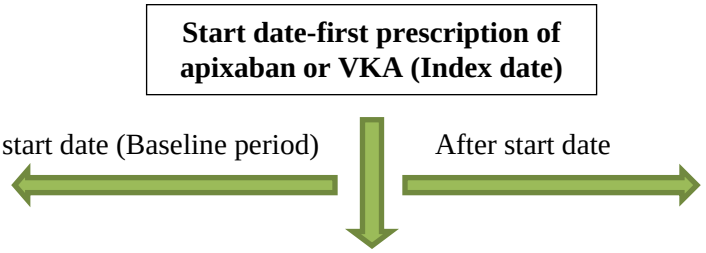
3b: patients who previously have been treated with VKA in the 12 months before index date.

Group 4: Patients who are on treatment with rivaroxaban, this group will have two subgroups,

4a: patients who have initiated with rivaroxaban as treatment naïve (no prior prescription of VKA previous to the 12 months before index date),

4b: patients who previously have been treated with VKA in the 12 months before index date.

Figure 1. Overview of Study Design



	12 months	Follow -up	
		1 month	>1 month
Comorbidity			
Co-medication			
Medicine adherence			
INR for VKA			

VKA: vitamin K antagonists

8.2. Setting

SIDIAP currently collects information from 274 primary health care centers, including more than 5.8 million patients, about 80 % of the Catalonia population, or more than 10 % of the Spanish population covered by the Catalan Institute of Health.

The study population for these cohorts includes all eligible subjects from the source population with a first –recorded prescription of apixaban VKA, dabigatran or rivaroxaban for the SPAF indication, registered in SIDIAP database and diagnosis of NVAF for study period.

The study period is defined as the time between the dates when apixaban became commercialized for the SPAF indication, which in Spain was since August 2013 until latest date of interest for our study which is December 2015.

8.2.1. Inclusion criteria

1. Patients more than 18 years-old

2. Patients diagnosed with NVAF registered in primary care according to ICD-10.

3. Patients initiating apixaban (naïve or VKA experienced), VKA (naïve or VKA experienced), dabigatran or rivaroxaban for the SPAF indication

4. Continuous enrolment in the 12 months pre-index.

8.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients with valvular heart disease (ICD 10: I05.0-I05.09, I08.0-I08.9) including patients with mitral prosthetic valves.

2. Lost to follow-up (e.g. transfer to primary care center non-ICS)

8.3. Variables

Sociodemographic: age, sex, socioeconomic index,[6] toxic habits (alcohol and smoking), and BMI (see Table below).

Table 1. Sociodemographic characteristics

Variable	Role	Data source	Operational definition
Age	Baseline characteristics	SIDIAP	birth date (month/year)
Sex	Baseline characteristics	SIDIAP	male or female
Socioeconomic index	Baseline characteristics	SIDIAP	MEDEA index
Smoking habits	Baseline characteristics	SIDIAP	smoker, non-smoker and ex-smoker
Alcoholic habits	Baseline characteristics	SIDIAP	No intake, moderate intake, risk consumption
Body mass index	Baseline characteristics	SIDIAP	Kg/m^2 (two prior year)

SIDIAP: Sistema d´informació pel desenvolupament de la investigació en atenció primària

Comorbidity: heart failure, peripheral artery disease, ischemic heart disease, myocardial infraction, hypertension, diabetes mellitus, DVT, PE, liver disease, renal disease, cerebrovascular disease, cancer and chronic obstructive pulmonary disease. Diagnoses will be identified for the ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10^{th} Revision) codes.[7] Serum creatinine (to estimate glomerular filtration rate [GFR] using the Modification of Diet in Renal Disease [MDRD] formula) (see table below). These variables are obtained from the 12 months prior to enrollment in the study and 12 months of inclusion.

Table 2. Comorbidity

Variable	Role	Data source(s)	Operational definition**
Heart failure	Comorbidity	SIDIAP	I50
Peripheral artery disease	Comorbidity	SIDIAP	I73.8, I73.9
Ischemic heart disease	Comorbidity	SIDIAP	I20*-I25*
Acute myocardial infarction	Comorbidity	SIDIAP	I21*
Hypertension	Comorbidity	SIDIAP	I10*-I15*
Diabetes mellitus	Comorbidity	SIDIAP	E10*-E14*, R73*
Deep Vein Thrombosis and Pulmonary Embolism	Comorbidity	SIDIAP	I26*, I74*
Liver disease	Comorbidity	SIDIAP	K70*-K77*
Renal disease	Comorbidity	SIDIAP	N17*-N19*
Cerebrovascular disease	Comorbidity	SIDIAP	I60*-I69*
Cancer	Comorbidity	SIDIAP	C00*-D48*
Chronic obstructive pulmonary disease	Comorbidity	SIDIAP	J40-J45*
Creatinine clearance	Comorbidity	SIDIAP LAB	ml/min/1.73m^2 (MDRD)

**ICD-10: International Classification of Diseases 10th Revision; SIDIAP: Sistema d´informació pel desenvolupament de la investigació en atenció primària, MDRD: Modification of Diet in Renal Disease

Medication

The drug dispensing will be identified from the invoicing database of CatSalut. ATC code[8] will be used to identify the medication (see table 3). The patients will be followed up to the prescription other anticoagulant

Two groups of doses will be established according to the apixaban SmPC; 5mg/BID or 2.5 mg/BID in the SPAF indication.

The co-medications will be identified from prescription data at the index date and collected from the inclusion in the study and up to one month after.

For each user of apixaban, there will be search for concurrent use of other drugs as follows:

Concurrent use at the start date:

- patients who have at least one prescription for potentially interacting medication recorded at the start date,

- patients who have at least one prescription for potentially interacting medication recorded during the time of current use of apixaban.

Table 3.Medication

ATC	Drugs description
A02BC	Proton pump inhibitors
A10	Drugs used in diabetes
A10A	Insulins
A10B, A10X	Blood glucose lowering drugs
B01	Antithrombotic agents
B01AC	Platelet aggregation inhibitors
B01AC04	Clopidogrel
B01AC06, B01AC30, B01AC56	Acetylsalicylic acid
B01AC01-B01AC03, B01AC05, B01AC07-B01AC22, B01AC24	Other platelet aggregation inhibitors
B01AA	Vitamin K antagonists
B01AB	Heparins
B01AD, B01AE, B01AF01, B01AX	Other antithrombotic agents
B01AF02	Apixaban
B03A	Iron preparations
C	Cardiovascular medications
C01A	Cardiac glycosides
C01B	Antiarrhythmics, Class I and III
C01C	Cardiac stimulants excluding cardiac glycosides
C01D	Vasodilators used in cardiac diseases
C01E	Other cardiac preparations
C03	Diuretics
C04	Peripheral vasodilators
C04AD03	Pentoxifylline
C07	Beta blocking agents
C08	Calcium channel blockers
C02	Antihypertensives
C09	Agents acting on the renin-angiotensin system
C09A, C09B	Angiotensin-converting-enzyme inhibitors
C09C, C09D	Angiotensin II receptor antagonists
C09X	Renin-inhibitors
C10	Lipid-modifying agents
C10AA	Statins
C10AB, C10AC, C10AD, C10AX, C10BA	Other lipid-modifying agents
G03C, G03D, G03F	Hormone replacement therapy
H02	Systemic corticosteroids
L04	Immunosuppressants
M01A, N02BA, M01B, M01C	Drugs for musculoskeletal system
M01A	Non-steroidal anti-inflammatory drugs
N02BA	Acetylsalicylic acid (other analgesics and antipyretics)
M01B-M01C	Other antirheumatic agents
N06A	Antidepressants
N06AB	Selective serotonin reuptake inhibitors
R03	Drugs for obstructive airway diseases

ATC: Anatomical therapeutic chemical

The co-medications may interact with apixaban.

Apixaban is metabolized mainly via cytochrome P450 3A4/5 (CYP3A4/5) with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Apixaban is a substrate of transport proteins, P-glycoprotein (P-gp) and breast cancer resistance protein. Medications potentially interacting with apixaban are listed in the risk management plan and in the SmPC and include (see table 4):

- Interaction with strong inhibitors of both CYP450 3A4 and P-gp such as azole-antimycotics (e.g., ketoconazole).

- Interaction with strong inducers of both CYP3A4 and P-gp such as rifampicin, phenytoin, carbamazepine, phenobarbital or may lead to a ~50% reduction in apixaban exposure.

Table 4. Medications potentially interacting with apixaban

Medication	Substrates P-gp/CYP3A4	Inhibitors CYP3A4	Inducers CYP3A4
Calcium channel blockers			
Diltiazem	X	X	
Statins			
Simvastatin	X		
Antimycotics			
Itraconazole		X	
Antimycobacterials			
Rifampin			X
Antipsychotics			
Pimozide	X		
Macrolide antibiotics			
Clarithromycin	X	X	
Erythromycin	X	X	
Antiepileptics			
Phenytoin			X
Carbamazepine			X

P-gp: P-glycoprotein; CYP3A4: cytochrome P450 3A4.

Potential pharmacodynamics interactions due to an increased bleeding risk by concomitant use any other anticoagulants, platelet aggregation inhibitors and NSAIDs.

Coagulation variables

The INR will be collected from SIDIAP database for each patient.

The TTR of INR is the time in which INR is maintained between 2 and 3. The values will be calculated by INR (Roosendaal algorithm) for patients previously treated with VKA or who are currently on treatment with VKA. (see data analysis)

This variable will be obtained from the 12 months prior to enrollment in the study and 12 months of inclusion.

Thomboemblolic risk and bleeding risk assessment:

- **$CHADS_2$:** this score helps to estimate the risk of stroke in patients with NVAF and to determine which antithrombotic treatment is most appropriate. Its values will be calculated with SIDIAP data, which include presence of congestive heart failure history, hypertension history, age ≥ 75, diabetes mellitus history, stroke or TIA for each patient enrolled in the study.

- **CHA_2DS_2Vasc:** this is another type of score to estimate, in a relatively simple way the risk of cerebrovascular accident in the case of patients with AF. The values of this variable would be calculated with SIDIAP data, which include presence of congestive heart failure history, hypertension history, age ≥ 75, diabetes mellitus history, stroke or TIA, vascular disease and gender for each patient enrolled in the study.

- **HAS-BLED:** this rating score measures the risk of occurrence of major hemorrhage in a year, it includes several factors such as hypertension (systolic blood pressure > 160 mmHg), impaired renal function, impaired liver function; prior stroke; prior major bleeding; Labile INR (less than 60% of the time in therapeutic range); over 65 years of age, medication usage predisposing to bleeding (antiplatelet agents, NSAIDs) and, moderate use and overuse of alcohol. Values of this variable will be calculated by SIDIAP patient data.

Medication adherence outcome

Definition of the therapeutic adherence: medication possession ratio (MPR), defined daily dose (DDD), TTR and accumulative discontinuation rate.

The therapeutic adherence will be assessed through pharmacy invoice data (drug dispensing) from the pharmacies for patients who initiate treatment between August 2013 and 2014. For each patient with prescription of apixaban, VKA, dabigatran and rivaroxaban we will determine two dates. First invoice date (index date - when the patient took the drug for the first time), and date of the last invoicing. MPR will be calculated using variable medication possession ration calculation (VMPR), DDD and TTR. The calculations will be performed as follows:

$$\text{VMPR} = \frac{\text{All days supply}}{\text{Elapsed days (inclusive of last prescription)}}$$

"All days' supply"=sum of days' supply between the index date and last prescription dispensed (inclusive of the last prescription) and "elapsed days"=number of days between the index date and the last prescription dispensed (inclusive of days' supply) during the 12-month observation period (last date of service minus first date of service plus 1). Any prescription days' supply that spanned the 12-month end date was truncated at 12 months.[9]

MPR will be evaluated for patients receiving medication for at least 12 months during the period between the first and the last prescription. There will be two categories of adherence,

good adherence with at least 80% of MPR and poor therapeutic adherence with less than 80% MPR.

Additionally, we will use the WHO defined daily dose (DDD) methodology to evaluate drug utilization,8 in order to calculate utilization of VKA anticoagulants medications using invoicing data. The DDD values will be obtained from the WHO ATC/DDD index to derive DDDs for each medication. DDD is a measure that represents that average daily maintenance dose for the main indication of a drug. We will use to aggregate data on different doses and formulations to enable comparisons of utilization across different VKA . For NOACs use the package size to derive days of supply (Rivaroxaban once daily, Dabigatran and Apixaban twice daily) as the WHO DDD does not separate between standard and low dose.

The adherence to VKA is evaluated by TTR of INR, which is the time in which INR is maintained between 2 and 3. The primary health care centers covered by ICS accounting 70% of the Catalonia population treated with VKA.

In addition, accumulative discontinuation rates will be analyzed. Discontinuation rates will be defined by lack of subsequent prescription of the index drugs within 2 months after last supply day of the last prescription and will be analyzed by calculating the accumulative discontinuation (treatment withdrawal or switch) rate.

8.4. Data sources

To investigate the use of apixaban, this DUS requires an efficient means to identify sufficient number of patient taking this drug. At present, the largest and most readily accessible drug utilization data come from automated databases that record prescriptions, diagnoses, and procedures on an individual-patient basis. Such databases accumulate records longitudinally so that patient experience can be observed before and after prescription of a drug of interest.

The data source is SIDIAP database, which contains anonymized clinical information that originates from different data sources: 1) eCAP™ (electronic medical records in Primary Care of the Institut Català de la Salut [ICS]); which includes information since 2006 on sociodemographic characteristics, health conditions registered as ICD10 codes, General Practitioners' prescriptions, clinical parameters and toxic habits. 2) Laboratory data. 3) Prescriptions and their corresponding pharmacy invoice data; available since 2005: information on all pharmaceutical products dispensed by community pharmacies with Catalan Health System prescriptions, by ATC codes.

8.5. Study size

There will be no calculation of sample size. The sample size is driven by the prescription of apixaban in source population of database. According to previous data, we estimate that we would have approx. 2000 patients treated with apixaban, 14000 with VKA (warfarina 2000, acenocumarol 12000), 4000 with dabigatran and 500 with rivaroxaban.

8.6. Data Management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. SIDIAP database will maintain any patient-identifying information securely on site according to internal standard operating procedures.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with periodic backup of files to tape. Standard procedures will be in place at each research Centre to restore files in the event of a hardware or software failure.

8.7. Data analysis

This section provides an overview about the statistical methods that will be applied in order to answer each research questions. The core statistical elements (analysis populations, definition and measurement of endpoints and other key variables and statistical methodology) are adequately detailed.

Sociodemographic characteristics for the four groups (apixaban, dabigatran, rivaroxaban and VKA) at the start date will be provided: (1) for all variables, number and percentage of missing data; (2) for categorical variables (sex, toxic habits and MEDEA index), number and percentage for each category; (3) for continuous variables (age, BMI), mean, standard deviation, median, interquartile range, minimum and maximum.

Comorbidities at the start date will be identified by codes in table 2. The total number of patients with at least one disease and the number and percentage of patients with each specific condition will be provided for all groups (apixaban, dabigatran, rivaroxaban and VKA).

Concurrent use of medications listed in table 3 at the start date for apixaban will be quantified by the number and percentage of users.

Risk of stroke and major hemorrhage event will be assessed at the start date with $CHADS_2$, CHA_2DS_2Vasc and HAS-BLED. For each scale, number and percentage of each category for four groups (apixaban, dabigatran and rivaroxaban, VKA) will be provided.

Appropriate use of apixaban during the study period will be assessed for two groups of patients depending on the recommended daily dose: 5 or 2.5 mg twice daily. Mean, standard deviation, median, interquartile range, minimum and maximum of the estimated daily dose will be calculated in each group. Lower dose of apixaban (2.5 mg twice daily) is recommended in these situations:

- Patients with at least two of the following characteristics: (1) serum creatinine $\geq$ 1.5 mg/dL (133 micromole/L) (2) age $\geq$ 80 years and (3) body weight $\leq$ 60 kg.

- Patients with severe renal impairment (creatinine clearance below 30 mL/min)

Number of patients receiving an inappropriate dose will be provided: those taking high dose that met these criteria and patients taking lower dose outside these criteria.

Potential pharmacokinetic and pharmacodynamic interactions with apixaban will be assessed according to comedications at the start date. Number and percentage of each interaction listed in table 4 will be reported.

Apixaban, VKA, dabigatran and rivaroxaban user adherences will be assessed during the study period through the MPR. The number of days of supply will be estimated based on the number and the size of the packages between the index date and last prescription dispensed. Values above 80% will be considered as good adherence. For each group, number and percentage of users with good adherence and summary statistics as mean, standard deviation, median, interquartile range, minimum and maximum for MPR will be provided. In addition, monthly discontinuation rates for all groups during the first year of treatment will be calculated. Median and interquartile range for the time to discontinuation and a graph representing the accumulative discontinuation rates over time will be provided.

Additionally, in order to compare drug utilization DDD will be used in the VKA and package size in NOACs. We calculate mean, standard deviation, median, interquartile range, minimum and maximum in terms of DDD for each drug.

For VKA users, INR registered during at least one year (i.e, only applicable to patients with first prescription prior to January 2015) will be collected. INR will be categorized according to the risk level: risk for coagulation (INR<2); optimal range (2<INR<3); and risk of hemorrhages (INR>3). Median and interquartile range for INR and number of percentage for each category of the categorized INR will be provided.

TTR well be calculated according to F.R. Roosendaal's algorithm with linear interpolation.[10] Between two INR determinations, TTR was estimated as the number of days that the patient remains into the optimal range assuming that the changes in INR occurs in a linear way. For each patient, the total TTR is defined as the sum of estimated TTRs between each couple of INR determinations. Median and standard deviation of total TTR for VKA will be provided.

For categorical variables, comparisons between groups will be performed with a chi-square test or a Fisher test as appropriate. P-values resulting from those tests will be reported. Odds ratios for each group relative to apixaban will be estimated with their 95% confidence interval.

For numerical variables, comparisons between groups will be carried out through a one-way anova or a Kruskal-Wallis test as appropriate. P-values resulting from those tests will be reported. Mean differences relatives to apixaban will be estimated with their 95% confidence intervals.

Analysis will be performed using SAS software, version 9.4 (SAS Institute).

In addition, detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8. Quality control

IDIAP Jordi Gol will be in charge of implementing their standard operating procedures to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. All programming written by one study analyst will be reviewed independently by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

8.9. Limitations of the research methods

DUS conducted in automated health databases allow identification of patients who are prescribed or dispensed the drugs of interest and characterization of these patients according to prior medical history, use of medications, and patterns of use of medications. Health care databases have become a useful tool for conducting research to study the safety of drugs as information on diagnoses and treatments is recorded on an ongoing basis.

However, the use of automated health databases for research has some limitations, mainly related to the type and completeness of the recorded information. Regarding prescription data, databases provide detailed information on prescribed and/or dispensed medications but not on the actual use of the medications by patients. Overall, this can result in misclassification of drug exposure. Another limitation on the assessment of medication use in databases is that over-the-counter medications are usually not recorded. Therefore, we are not able to ascertain the concomitant use of apixaban and non-prescribed NSAIDs. The use of external data (e.g., health surveys), when available, might help to quantify the use of over-the-counter medications.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

In this study the data records of patients who are totally anonymous will be used. In accordance with national law, it is not necessary to ask participants for their informed consent. Confidentiality rules provided by law 15/1999 (Ley Orgánica de Protección de Datos) will be respected.

9.2. Patient withdrawal

Not Applicable.

9.3. 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 informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, 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.

9.4. Ethical Conduct of the Study

The protocol is presented to the Comitè Ètic d'Investigació Clínica de l'IDIAP Jordi Gol for approval.

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 described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice guidelines issued by the International Epidemiological Association, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research, International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences, EMA, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guide on Methodological Standards in Pharmacoepidemiology, and FDA (Food and Drug Administration) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes 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) are not available and adverse events (AE) are not reportable as individual AE reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware.

The results of this study will be comprehensively summarized in a final report. It is furthermore planned to publish the findings in a peer-reviewed journal.

The IDIAP may independently prepare publications based on the study results irrespective of data ownership and publish the results accordance with the principles of scientific independence and transparency and respecting the criteria established in the Code of Conduct ENCePP. The marketing authorisation holder will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication (EMA, 2012, Section VIII.B.7; module VIII).

12. REFERENCES

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable