EU PV & PE Research Network under the
Framework service contract (nr. EMA/2015/27/PH)

Study Protocol

"Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: non-interventional study of patients taking Direct Oral Anticoagulants in the EU"

Version: 01 November 2016

For EMA review

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Any amendments to and/or deviations from this protocol will be documented by the PI/coordinator of EU PV & PE Research Network.

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1 Context of the proposal

The proposal described has been developed under the Framework service contract (nr. EMA/2015/27/PH) with regard to the re-opening of competition no.3. The objective of this proposal is to describe a pharmacoepidemiological study using longitudinal data collected in 8 electronic health care databases from 6 EU countries to characterize the risk of major bleeding in Direct Oral Anticoagulant (DOAC) users in a real-world setting to help establish the effectiveness of existing and future risk minimization measures. The research undertaken will focus on targeted clinical and demographic subgroups for which variations in plasma concentrations might affect the safety of the products.

2 Objectives

The objectives of this proposal are to measure:

Objective 1. The risk of major bleeding, such as gastrointestinal bleeding, intracranial bleeding and haemorrhagic stroke, associated with use of DOACs when compared to other oral anticoagulants (OACs), i.e. vitamin K antagonists (VKAs), in patients with non-valvular atrial fibrillation (NVAF) overall and in relevant clinical and demographical subgroups in a real-life setting. These include patients with chronic kidney disease, with hepatic impairment, the elderly (>=75 years), patients with low or high body weight (<50kg or >100kg) and patients treated with contraindicated or potentially hazardous co-medications as listed in sections 4.3, 4.4, and 4.5 of the SmPC of each product. Risk estimates will be provided for all DOACs as a group, as well as for each DOAC separately and in comparison to VKA.

Objective 2. The utilization of DOACs in the EU for treatment of NVAF, including the characterization of new DOAC users in NVAF patients. This includes assessing the degree of switching between different DOACs, other OACs, time on therapy, the degree of dose adjustment, prevalence of concomitant exposure to potentially interacting drugs and the rate of permanent discontinuation.

Objective 3. Prescribers' compliance with recommendations included in sections 4.1, 4.3, 4.4, and 4.5 of the SmPC of each DOAC (see 8.1 Annex I & 8.2 Annex II).

3 Methods

3.1 Data sources

3.1.1 Mondriaan

The Dutch Mondriaan project is a private-public collaboration funded by the Dutch TOP Institute Pharma. Under the umbrella of Mondriaan, the participating databases currently include: The Almere Health Care Group (AHC) database, The General Practitioners of Utrecht(JHN) database and the Leidse Rijn Julius Gezondheidscentra (LRJG). The cumulative number of persons having data in Mondriaan reached around 1.4 million comprising mainly of general practitioner (GP) data complemented by pharmacy dispensing data and linkages to survey data. The three databases within Mondriaan have different starting dates and scope of data. The Mondriaan-AHC is a GP and pharmacy database. The JHN is a GP database set up in 1995 and includes data dating till the end of 2005. The LRJG is a GP database with a linkage to additional survey records. Survey information is periodically up-dated through follow-up, including information on a wide range of health and lifestyle related variables.

3.1.2 Danish National Registries

Denmark has a tax-funded health care system ensuring easy and equal access to health care for all its citizens, and all contacts with the system are recorded in administrative and medical registers. The records carry a unique personal identification number, called the CPR-number, assigned to every Danish citizen. Linkage between registers at an individual level is possible because this CPR-number is used in all Danish registers [1]. All registers have a nationwide coverage and an almost 100% capture of contacts covering information on currently 5.6 million inhabitants plus historical information. For the purpose of the study we will obtain information from the following registries. Contacts to somatic hospitals have been recorded in the Danish National Patient Register (NPR) since 1977 also including outpatient and emergency contacts since 1995. All diagnoses are classified according to the World Health Organization's (WHO) International Classification of Diseases (ICD). From 1969 to 1993 the 8th revision (ICD-8) was used, until the 10th revision (ICD-10) was implemented in 1994 [2,3]. The Danish National Prescription Registry (DNPR) includes data on all drugs dispensed from Danish pharmacies from 1995 and onwards, including dispensing date, Anatomical Therapeutic Chemical (ATC) code and amount [4]. The ATC classification system, as controlled by the WHO, is widely used in drug utilization studies [5]. Sociodemographic data is available from the Danish Civil Registration System, such as gender, date of birth, migration, vital status and civil status recorded since 1968 [1]. Information on education status is recorded in the Danish education registers, providing information on the highest completed education level [6]. The Danish registries have been extensively used previously for studying OACs/NOACs (e.g. Reference 9).

3.1.3 Bavarian claims database

The Bavarian statutory health insurance physicians' association database is based on accounting information of the Bavarian physicians. This German database includes a population-based outpatient data on diagnoses, medical services performed and drug utilization, covering 10.5 million people. It is a pharmacy (claims) database linked to outpatient treatment data through general practitioners and specialists. All diagnoses from general practitioners and specialists are recorded quarterly (i.e. the quarter but not the precise date is documented for each diagnosis or prescription). A patient is documented in the database only when consulting a physician. Pharmaceuticals are recorded only if they were prescribed and filled at the pharmacy. The database exists since 2001 and covers 84% of the Bavarian population excluding those with private insurance. The German modification of the International Statistical Classification of Diseases and Related Health Problems (ICD-10-GM) is used for coding diagnoses and the Anatomical Therapeutic Chemical (ATC) classification system is used for coding drugs.

3.1.4 AOK NORDWEST

The AOK NORDWEST is a large statutory healthcare database representing 2.7 million inhabitants in a Western (Westfalen/Lippe) and a Northern part (Schleswig-Holstein) of Germany. In this database, claims data of the primary and the secondary care sector are stored separately but data linkage is possible [7]. For the primary care sector, diagnoses are ICD-coded and documented on a quarterly base. For the primary care sector, drug prescription data for reimbursed drugs are documented on a daily base (prescribing date) using a unique nationwide standardized identification number for drugs (PZN: Pharma-Zentral-Nummer) allowing a linkage to ATC codes and dose considerations. For the secondary care sector, suspected diagnosis leading to hospital admission and diagnoses at hospital discharge are available on a daily base. For the secondary care sector, drug utilization data are only available for a very few selected, expensive compounds directly reimbursed by the health insuring companies. For the two German regions covered by the AOK NORDWEST, a population coverage of approximately 24% is reached.

3.1.5 BIFAP

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria), a computerized database of medical records of primary care (www.bifap.aemps.es) is a non-profit research project funded by the Spanish Agency for Medicines and Medical Devices (AEMPS). The project started in 2001 and currently includes clinical information of 5,714 physicians (4,871 General Practitioners (GPs) and 843 paediatricians). Nine participating Autonomous Region send their data to BIFAP every year. BIFAP database includes anonymized clinical and prescription/dispensing data from around 7.5 million patients covering around 16.4% of the Spanish population. Diagnoses are classified according to the International Classification of Primary Care (ICPC)-2 and ICD-9 code system.

3.1.6 System for the Development of Research in Primary Care (SIDIAP)

The Information System for the Development of Research in Primary Care (SIDIAP database) was created in 2010 under the auspices of the Catalan Institute of Health and the IDIAP Jordi Gol Research Institute. Its main aim is to promote the development of research based on data from primary care electronic health records and other complementary databases. SIDIAP's main objective is, therefore, to generate reliable research data from the computerized medical records, used in the Primary Health Care setting within the Catalan Institute of Health and other complementary databases.

Currently the SIDIAP database stores information of 274 Primary Care Practices in Catalonia, with a total population of 5.8 million patients (80% of the Catalan population). SIDIAP has available, for each of the 5.8 million citizens assigned to the Catalan Institute of Health primary care patients, the following information connected to a unique and anonymous personal identifier:

- Information from the ECAP medical records software: all information registered since the start-up of the program is available, varying from 1998 to 2005. The following data can be obtained for each individual: Demographic data, Socio-demographic status, Visits to Primary Care, Health problems (ICD-10 Code), Clinical variables, Immunization, Referrals, Prescriptions.
- Information on laboratory results: from 2006. Validation and homogenization protocols ensure the quality of these data.
- Information on medication dispensed by the pharmacy offices: since 2005.

In addition, SIDIAP has been linked to other databases in Catalonia, by individual users Ids, using trusted third-party cross-linkage. Some of these databases are:

- CMBD-AH (CatSalut): Hospital discharge database, with information an diagnoses and therapeutic procedures occurring during admission to any of the hospitals in Catalonia.
- Deaths (Health Department): Dates and causes of death in all deceases of Catalonia residents.
- Others: Cancer registries, The Catalan Registry of Arthroplasties (RACat), etc.

3.1.7 Clinical Practice Research Datalink (UK)

The Clinical Practice Research Datalink (CPRD, formerly known as the General Practice Research Database [GPRD]), comprises computerized medical records of general practitioners (GPs) from 1987 onwards. The database contains data from over 600 practices based throughout the United Kingdom, providing information on 12.5 million patients, of which 5 million are currently active. The data covers 8% of the population. GPs play a gatekeeper role in the UK health care system, as they are responsible for primary health care and specialist referrals. Patients are affiliated to a practice, which centralizes the medical information from the GPs, specialist referrals, hospitalizations and tests. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, laboratory results, hospital admissions and death. Many practices are entirely paperless and have included key historical events prior to 1987 in a patient's record. The validity of a wide range of drug exposure data is routinely tested. Practices that want to contribute data to CPRD are carefully selected and trained in the software used to record medical data. Only those practices that meet quality standards are then used for research (about 10% of the practices that send data to CPRD do not meet the quality standards). Furthermore, validation studies are conducted regularly by comparing CPRD data to written notes of general practitioners. Recent additions to the database include external record linkage to other National Health Services (NHS) datasets, such as the national Hospital Episode Statistics (with extended data on all hospitalizations) and Death Certificates, increased availability of free text information via new automated system, the possibility of genetic linkage studies, prospective data collections such as questionnaires, copies of patient–based correspondence, the conduct of multi-country studies, and performing randomization studies within the database.

3.1.8 French Claims database: EGB

The database used in this study is the EGB. The "*Echantillon Généraliste de Bénéficiaires*"(EGB), a permanent 1/97 representative sample of SNIIRAM (N=700,000). SNIIRAM is the nationwide healthcare insurance database linked to the national hospital-discharge summary database and the national death registry. SNIIRAM includes 66 million persons, over 97% of the French population from birth (or immigration) to death (or emigration). Subjects remain followed even if a subject changes health insurance, occupation, or retires. It

contains anonymized data on demographic characteristics (gender, year of birth, month and year of death), long-term diseases (ALD) resulting in full insurance coverage; reimbursed outpatient healthcare expenditures (visits, medical procedures, lab tests, dispensed drugs, medical devices), as well as all hospital procedures and discharge summaries (ICD10). EGB can be accessed within one month. EGB has been used to study outcomes with Vitamin K antagonists in NVAF [8].

3.2 Period of valid data collection

Each data source has a period of valid data collection, from the left censoring date, up to the right censoring date.

For the proposed studies, we will consider the study period from 2008 to 2015 for all the databases where possible.

3.2.1 CPRD/Mondriaan/BIFAP/SIDIAP

The left censoring date is the latest of the following: the date that a practice was enrolled into the database and became up to research standard or the date that a patient enrolled into a practice.

The right censoring date is the earliest of the following: the date a patient died, the date a patient was transferred out of the practice, the end of the database data collection, the date that the practice left the database or the latest recorded event date (Mondriaan, BIFAP, SIDIAP). As deaths may not always be well recorded in Mondriaan and BIFAP, we will right censor patients in these databases on patient's latest recorded event date.

3.2.2 Danish registers

The left censoring date is the latest of the following: the date that register started, the date of birth or immigration of an individual living in Denmark.

The right censoring date is the earliest of the following: the date an individual died or emigrated or the end of the database data collection.

3.2.3 Bavarian claims

The left censoring date is the earliest event that is recorded for an individual patient (prescription or diagnosis) after January 1, 2004.

The right censoring date is the latest event that is recorded for an individual patient (prescription or diagnosis) before December 31, 2015. Death is not well recorded in the Bavarian claims data.

3.2.4 AOK NORDWEST

The left censoring date is the entry date to the AOK NORDWEST.

The right censoring date is the latest event that is recorded for an individual patient (prescription, diagnosis). Death is incompletely recorded in the AOK NORDWEST.

3.2.5 EGB

The left censoring date is the entry date to the EGB.

The right censoring date is the latest event that is recorded for an individual patient. Death is recorded in the EGB.

3.3 Ethical issues

Each data source has their own ethical guidelines and data protection procedure in place. For more information about the data sharing regarding this study, please see 8.6 Annex VI.

4 Feasibility

Table 4.1. Number of users of (D)OACs in the different databases

		Mondriaan[1]	National Registries Denmark[2]	Bavarian Claims[3]	AOK NORDWEST[3]	BIFAP	SIDIAP	CPRD[6]	EGB
Total population		0.4m	5.5m	10.5m	2.7m	7.5m	5.8m	12.5m	0.7m
Year(s) of measurement		2014	2014	2013	2013	2005-2014	2014	2011-2014	2013
Oral anticoagulant users									
	All	0	88,158	n.c.	n.c.	2,123	8,075		
Warfarin (B01AA03)	With NVAF		9,289			920		129,279	
	All	1,998	1,892	252,247	64,864		0	NA	
Phenprocoumon (B01AA04)	With NVAF			158,916	40,864				
	All	7,909				190,192	85,560	NA	
Acenocoumarol (B01AA07)	With NVAF					87,530			
	All	438	23,466	20,319	5,225	4,648	4,126		
Dabigatran (B01AE07)	With NVAF		4,978	12,801	3,292	1,627		3,544	3300
	All	474	16,085	70,804	18,207	5,854	3,741		
Rivaroxaban (B01AF01)	With NVAF			44,606	11,470	1,695		5,345	6700
	All	110	8,024	5,738	1,475	1,309	2,065		
Apixaban (B01AF02)	With NVAF			3,615	930	498		1,462	
Information needed for subgroup analysis[4]									
Renal failure/Kidney disease		D	D	D	D	V, D	V, D	V, D	D
Liver disease		D	D	D	D	V, D	V, D	V, D	D
Body mass index/low & high body weight				D	D	V, D		V	
Estimated number of major bleeding events[5]									
	OACs	NA	663[6]		1,798	3,891	NA	3,412	NA
	DOACs	NA	234[6]		628	152	NA	527	NA

1. Not including Mondriaan-NPCRD

2. Number of people “With AF” and (D)OAC use between August 1, 2011 and June 30, 2012 based on Larsen TB et al [9]. Co-morbidities are based on hospital admissions with respective diagnoses.

3. In Germany, Phenprocoumon represents approximately 99% of all Vitamin-K-antagonists DDD’s (Warfarin: 1%). User data is for year 2013, all indications, based on Glaeske BARMER GEK Arzneimittelreport 2014.

4. Availability of (lab) values (V) and or diagnostic codes (D)

5. Estimation for the primary outcome i.e. number of major bleeding events.
Studies investigating the association between oral anticoagulant drugs and major bleeding have reported that major bleeding occurs in 2.8-5.9% of patients using OACs [8-15] and 2.1-5.9% of Dabigatran/Rivaroxaban/apibaxan users (DOACs) [9-15]. The number of expected major bleed events are presented for the databases, which will perform the association study (objective 1, see table 5.1). These estimations are based on the mean values for OACs (4.4%) and the DOACs (4.0%), based on results from observational studies and clinical trials. For those databases where the number of patients with NVAF is not known, a 60% prevalence of NVAF is assumed.

6. Numbers are for new users. Based on: Larsen TB et al. [10].

7. The majority of OAC users in the UK use warfarin

5 Study Designs

Three studies will be conducted to answer the research questions listed in our aim: one cohort study (objective 1) and two descriptive studies (objectives 2 & 3). These studies will be conducted in at least 4 data sources (Table 5.1.)

Table 5.1. List of study designs to be conducted in each data source.

	Cohort (objective 1)	Descriptive (objective 2)	Descriptive (objective 3)
Mondriaan		X	X
Danish Registries	X	X	X*
Bavarian		X**	X**
AOK NORDWEST	X	X	
BIFAP	X	X	X
SIDIAP		X	X
CPRD	X	X	X
EGB		X	

*DK: Indications for (D)OAC treatment assessable based on registered hospital contacts as in- or outpatient or at emergency rooms related to indications according to respective SmPCs
** Indications, diagnoses and prescriptions are available on a quarterly base (outpatient care)

5.1 Descriptive studies

5.1.1 Data Sources

Two descriptive drug utilization studies will be performed to assess objective 2 and 3. These studies will be performed in the following databases: Mondriaan, Danish Registries, Bavarian Claims database, AOK NORDWEST, BIFAP, SIDIAP, CPRD, EGB (for list of study designs conducted in each data source see Table 5.1., for database description see section 3.1).

5.1.2 Descriptive study investigating the utilization of DOACs in NVAF patients (objective 2)

5.1.2.1 Study design

An observational cohort study of new users of DOACs of interest (Dabigatran, Rivaroxaban, Apixaban – see 8.1 Annex I) with the indication non-valvular atrial fibrillation will be performed.

Population

The study cohort consists of new users (≥18 years) of DOACs with incident non-valvular atrial fibrillation from the respective data sources (see section 3.1). New users will be defined as patients initiating DOACs during the study period (2008-2015) without any use of DOACs for at least 12 months prior to the index date. Patients registered in the database less than one year before the index date (date of first DOAC prescription) will be excluded. For DOAC and disease codes see 8.1 Annex I. and 8.4 Annex IV

5.1.2.2 Outcomes

Outcomes will be presented including descriptive analysis of patient characteristics of new DOAC users, the number of patients switching to another antithrombotic agent, and treatment duration.

a) *Description of new DOAC users* will be presented according to pre-specified parameters including

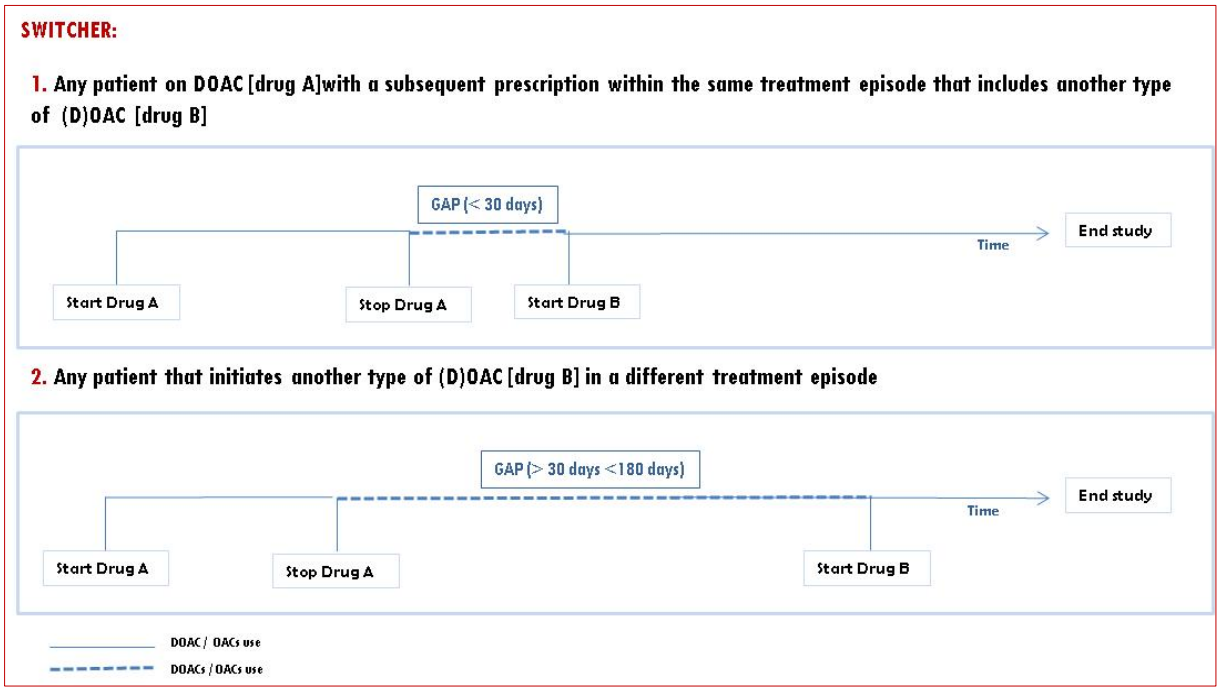
- number of patients,
- patient characteristics (age, gender, low or high body weight (<50kg or >100kg)
- co-morbidities (chronic kidney disease, hepatic impairment, previous hemorrhagic episodes, and previous cardiovascular events [for codes see table 8.3.2 [8.3. Annex III]) and table 8.4.2 [8.4. Annex IV]).
- concomitant exposures to potential interacting medicine products drug (PIMP) as listed in section 4.5 of the DOAC SmPCs (only available for prescription drugs). Concomitant exposures will be defined as

prescribing of the aforementioned products during a period of DOAC use, i.e., if the treatment episodes (see 5.2.3.2. Treatment episodes) of PIMP and DOAC overlap (see 8.2 Annex II).

- number of DOAC prescriptions prescribed/dispensed per calendar year (dispensing databases: Danish registries, Bavarian, AOK Nordwest, SNIIRAM/EGB; prescribing database: CPRD; prescribing/dispensing database: BIFAP, Mondriaan, SIDIAP)
- type of prescriber (GP or specialist).

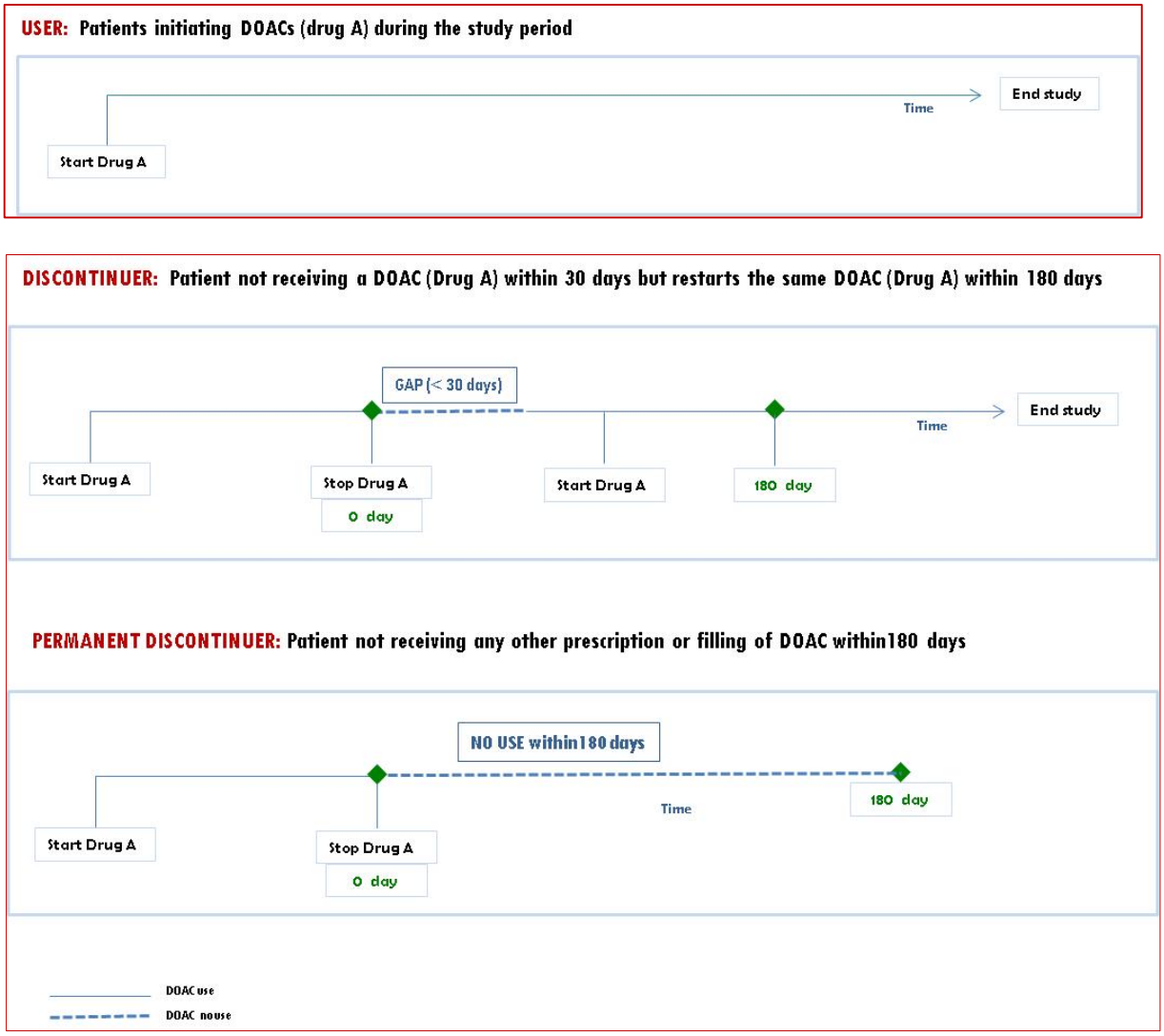
b) *Switching to another antithrombotic agent* and time on therapy before switching are of particular interest and, hence, will be evaluated descriptively. A switcher is defined as: 1) any patient with a subsequent prescription within the same treatment episode (see 5.2.3.2 Treatment episodes) that includes another type of (D)OAC (at least one prescription of antithrombotic drug (B01AA [VKA], B01AC [antiplatelets], B01AE [direct thrombin inhibitors], or B01AF [direct factor Xa inhibitors] and 2) any patient that re-initiates use of (D)OAC (at least one prescription of antithrombotic drug (B01AA [VKA], B01AC [antiplatelets], B01AE [direct thrombin inhibitors] or B01AF [direct factor Xa inhibitors]) between day 30 and 180 from discontinuation (see figure 5.1.).

Figure 5.1. Switching to another antithrombotic agent



c) *Treatment duration*, defined as the time on therapy, will be calculated as the number of days on therapy between receiving the initial DOAC and the discontinuation of therapy (see 5.2.3.2 Treatment episodes). The expected duration of each prescription will be estimated using the prescribed quantity based on package sizes and the prescribed daily dose. In case of missing data (e.g., daily dose or package size is missing), the database-specific median treatment duration or a typical period for prescribing medicines for chronic diseases in the country (e.g., 90 days) will be used as a surrogate. The date of the last dispensing/prescription plus the estimated duration of the dispensing/prescription is considered the date of drug discontinuation. A limit on the number of days allowed between refills or prescriptions will be defined to consider permissible gaps taking into account the pharmacological properties of the considered drugs. The gap length is set to 30 days (see 5.2.3.2 Treatment episodes) and a sensitivity analyses will be performed taking into account a gap of 60 days.
Patients not receiving any other prescription or filling of DOAC within 180 days after the calculated date of drug discontinuation will be considered as DOAC permanent discontinuers (See figure 5.2.).

Figure 5.2. DOAC usage patterns; users, discontinuers and permanent discontinuers



d) *The mean daily start dose* will be calculated for the first prescription of new DOACs users in the databases in which it is available. The mean daily start dose will be defined as number of defined daily doses (DDD) and stratified by EMA renal impairment categories (when possible). Dose adjustments during follow-up will be evaluated as appropriate based on renal function and the recommended dose in the SmPC for the indication "non-valvular atrial fibrillation".

5.1.2.3 Analysis

The analysis will be descriptive and will be conducted stratified by database, individual DOACs, age group, gender, and calendar year.

Analyses of the baseline characteristics of DOACs users

The baseline characteristics of users of DOACs will be presented as a table. The characteristics of interest are age (mean, standard deviation, age groups: 18-<30, 30-<40, 40-<50, 50-<60, 60-<70, 70-<80, 80-<90, ≥90, as well as, <75, 75-79 and ≥80 years [EMA tender technical specifications]), sex (absolute numbers and percentage), co-morbidities (chronic kidney disease, hepatic impairment, previous hemorrhagic episodes, and previous cardiovascular events (myocardial infarction, angina, coronary heart disease, congestive heart failure, stroke/transient ischemic attack, peripheral arterial disease [absolute numbers and percentage]) and concomitant medication (potential interacting medicine products (PIMP), as listed in section 4.5 of the DOAC SmPCs (only available on prescription drugs). The list of relevant PIMP is presented in section 8.3 Annex III. The

number and percentage of users with comorbidity or concomitant medication at baseline will be calculated by sex and age group.

Drug utilization analysis

- *Annual period prevalences (APP)* will be estimated and defined as the number of new users during the year of interest divided by the total number of patients in the database at midyear (1st July). For all APP, direct standardisation by age and sex will be performed based upon the European standard population. The APP will be stratified by sex and age group.
- For each year the *number of DOAC users and number of DOAC prescriptions* will be calculated (absolute numbers, percentages, mean and standard deviation). The analysis will be stratified by year of DOAC type, sex, age group and prescriber type (GP or specialist).
- The *absolute number and percentage of switchers* related to the total number of new DOACs users will be estimated in the total period and for each calendar year. The analysis will be stratified by sex and age group.
- The *percentage of permanent discontinuation* will be reported. For each individual DOAC a Kaplan-Meier curve for the time until permanent discontinuation will be estimated. Log rank tests will be applied for differences among the individual DOACs and subgroups of interest (e.g. chronic kidney disease, hepatic impairment, age, sex).
- Dose adjustment will be expressed as the *percentage of patients with appropriate dosage* (see Table 8.5.1) for each individual DOACs as recommended in the SmPC for patients with nonvalvular atrial fibrillation. The analysis will be stratified by sex and age group.
- The number of DDDs prescribed at the baseline will be calculated using the documented information on package size and the days of supply of the first prescription for DOACs. The number of DDDs prescribed at the start date will be stratified by individual DOAC, sex and age group.
- *Percentage of new DOACs users with any concomitant PIMP* during treatment episodes (see 5.2.3.2 Treatment episodes) will be expressed as the absolute numbers of patients as well as percentage over the total number of users per year and for the whole study period. The list of relevant PIMP is presented in 8.3 Annex III. This data will be stratified by the number of concomitant interacting drugs, inappropriate drug classes (Table 8.3.3. and 8.3.5), age group, and sex.

All results will be displayed in a tabular format for each database. Table shells of the analysis tables are provided in a separate Excel file (see 8.5 Annex V).

5.1.3 Descriptive study investigating prescriber compliance with SmPC recommendations (objective 3)

5.1.3.1 Study design

An observational cohort study of new users of DOACs of interest (Dabigatran, Rivaroxaban, Apixaban – (see 8.1 Annex I) will be performed.

Population

The study cohort consists of new users (≥18 years) of DOACs from the respective data sources (see Table 4.1). New users were defined as patients initiating DOACs during the study period (2008-2015) without any use of DOACs for at least 12 months prior to the index date. Patients registered in the database less than one year before the index date (date of first DOAC prescription) will be excluded.

5.1.3.2 Outcomes

Prescriber compliance with recommendations included in SmPC section 4.1 (Therapeutic indications), 4.3 (Contraindications), 4.4 (Special Warnings and precautions for use), and 4.5 (Interaction with other medicinal products and other forms of interaction) of each individual DOAC (see 8.3 Annex III).

We will use the documented ICD/READ/ICPC-coded diagnosis in the databases as a proxy of the indication (see 8.4 Annex IV. Indications described in the SmPc section 4.1 will be checked in the period ±3 months around the index date. A sensitivity analysis will be performed where indications will be defined as registered any time prior until 3 months after index date. The number of patients without any approved diagnosis will be calculated. Indications will be defined in the following mutually exclusive groups as: Myocardial infarction/Angina (MI-A), prevention after Hip/Knee replacement (PHK), prevention of stroke and systemic

embolism in adult patients with non-valvular atrial fibrillation (NVAF), treatment of deep vein thrombosis and pulmonary embolism including prevention of recurrent DVT and PE in adults (DVT-PE), and other (off-label) indications (OOL).

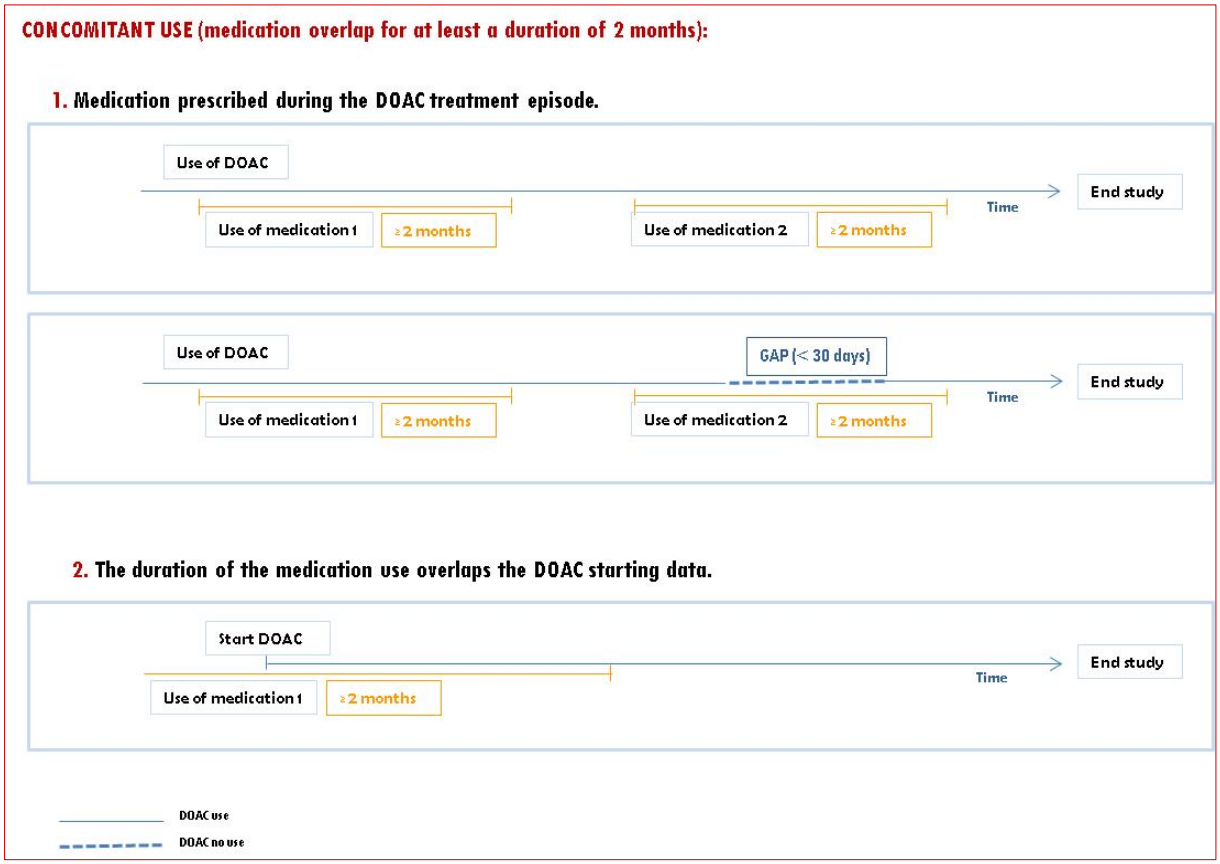
Table 5.2. Indication for use of DOACs

Indication	Description
Myocardial Infarction /Angina (MI-A)	Prevention of atherothrombotic events after an acute coronary syndrome (ACS)
Prevention after Hip/Knee replacement (PHK)	Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery
Non-valvular atrial fibrillation (NVAF)	Prevention of stroke and systemic embolism in adult patients with NVAF Atrial Fibrillation, with one or more risk factors, such as prior stroke or transient ischemic attack; age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus, hypertension registered only
Treatment of deep vein thrombosis and pulmonary embolism including prevention of recurrent DVT and PE in adults (DVT-PE)	Treatment of deep vein thrombosis and pulmonary embolism including prevention of recurrent DVT and PE in adults (DVT-PE)
Combination groups	Combination of above mentioned indications: - MI-A + PHK - MI-A + NVAF - MI-A + DVT-PE - PHK + NVAF - PHK + DVT-PE - NVAF + DVT-PE
Other (OOL)	All indications other than those indicated above

Co-morbidities listed in the SmPC section 4.3 and 4.4 will be assessed in the period ±3 months around the index date. Potential comorbidities listed in SmPC sections 4.3 and 4.4 will be identified through their READ, ICPC, or ICD code (see 8.3 Annex III).

Concomitant use of other (potentially interacting) medication listed in the sections 4.3, 4.4 and 4.5 will be assessed and will be identified through their Anatomical Therapeutic Classification (ATC) code (see 8.3. Annex III). Use of these medications will be considered concomitant when prescribed during the DOAC treatment episode or when the duration of the medication use overlaps the DOAC starting date (see Figure 5.3.). Use will be considered concomitant when the medicines listed in the SmPC sections 4.3, 4.4. and 4.5. overlap for at least a duration of 2 months. A sensitivity analysis will be provided using a criterion of at least 1 month concomitant use. Concomitant use of potential interacting drugs during the DOAC treatment episode will be determined for each individual DOAC.

Figure 5.3. Concomitant use of DOACs and medication listen in SmPC sections 4.3, 4.4 and 4.5



5.1.3.3 Analysis

The analysis will be descriptive and using information on the index date.

- Number and percentage of new DOACs users who meet the approved therapeutic indications (section 4.1.) and without any contraindication (SmPC section 4.3.) and without any diagnostic or medicinal product specified in the Special warning section (SmPC section 4.4), and without any potential interaction product specified in the section 4.5.
- Number and percentage of new DOACs users who meet the approved therapeutic indications (SmPC section 4.1.).
- Number and percentage of new DOACs users with any contraindication (SmPC section 4.3.). Description and stratification in categories (1,2 and ≥3).
- Number and percentage of new DOACs with any diagnostic or medicinal product specified in the Special warning section (SmPC section 4.4). Description and stratification in categories (1,2 and ≥3).
- Number and percentage of new DOACs users with any potential interaction product specified in the SmPC section 4.5. Description and stratification in categories (1,2 and ≥3).
- Number and percentage of new DOACs users with any off-label indications. In case that more than one diagnoses code meets the criteria, all diagnoses will be described. The diagnoses not matching the approved indications will be classified in “other off-label” category.

The analysis will be conducted stratified by:

- database: Mondrian, Danish, Bavarian, BIFAP, SIDIAP and CPRD.
- individual DOACs: dabigatran, rivaroxaban and apixaban.
- age group: 18-<30, 30-<40, 40-<50, 50-<60, 60-<70, 70-<80, 80-<90, ≥90, as well as, <75, 75-79 and ≥80 years [EMA tender technical specifications].
- gender: male, female.

- study period 2008-2015
- calendar year: 2008, 2009, 2010, 2011, 2012, 2013, 2014 and 2015.
- Indication: approved (each one), and non-approved as unique category.
- Renal function: normal >80 ml/min, mild impairment (creatinine clearance 50 - 80 ml/min), moderate impairment (creatinine clearance 30 - 49 ml/min), severe impairment (creatinine clearance 15 - 29 ml/min) and very severe < 15 ml/min.

5.2 Cohort study

A retrospective cohort study will be conducted among incident NVAF patients to assess the risk of major bleeding associated with the use of DOACs and VKAs (objective 1).

5.2.1 Population and study period

The study population consists of all patients aged ≥18 years with a first-ever recorded diagnosis of NVAF during a patient's period of valid data collection. Within this cohort of NVAF patients, we identified new users of antithrombotic drugs (D)OACs (DOACs and VKAs, see 8.1 Annex I), initiating a (D)OAC on the date of or after NVAF diagnosis during 2008-2015. New users were defined as patients initiating DOACs during the study period (2008-2015) without any use of DOACs for at least 12 months prior to the index date. Patients with a history of valvular atrial fibrillation (mitral stenosis or mechanical heart valves) will be excluded (see 8.4. Annex IV for codes).

The date of the first prescription of (D)OAC (index date) will define the start of follow-up. Each patient will then be followed until a major bleeding (outcome) occurs or until the end of valid data collection, move or death, whichever comes first.

5.2.2 Outcome

The primary outcome of interest is any major bleeding which is defined as symptomatic bleeding in a critical area or organ, as agreed by the International Society on Thrombosis and Haemostasis [15].

This includes haemorrhagic stroke/intracranial bleeding, gastrointestinal bleeding, or other extracranial or unclassified bleeding. Some of these bleeding events will also be assessed individually, such as gastrointestinal bleeding and intracranial hemorrhage. For the purpose of comparison, these outcomes are in line with a recent observational study done in the Danish database [16]. The UK Read code system, ICD-9, ICD-10, ICD-10-GM, and ICPC-2 codes will be used to define outcomes (see 8.3 Annex III for codes).

For the main analysis we will use all available bleeding events (irrespective of hospital admission). As a sensitivity analysis we will define major bleeding as bleeding that lead to a hospital admission in databases that have a linkage to hospital data.

Secondary outcomes include stroke, including ischaemic stroke and haemorrhagic stroke, and all-cause mortality.

The analysis will be corrected for patients with a history of any of these events.

5.2.3 Exposure definition

Within a cohort of patients with a diagnosis of NVAF, we will identify all (D)OAC prescriptions for new users of (D)OACs. Total follow-up time of patients will be divided into periods of current and past use with patients switching between these periods according to their pattern of use.

5.2.3.1 Assessment of the length of individual (D)OAC prescriptions

In each data source, options for assessing prescription duration for individual prescriptions are different. In CPRD, a fixed duration of 28 days will be applied, as this is the regular prescribing practice in the UK and has been used in earlier studies on OACs [17]. In the Dutch Mondriaan database, OAC prescription length is difficult to assess as the dose regimen is based on INR values, usually a fixed duration of 180 days is applied. In the Spanish BIFAP, OAC prescription length will be calculated based on prescribed daily dose recorded by GP and number of pills prescribed. In the AOK Nordwest, OAC prescription length will be estimated based on the package size and DDD. If variables are not available, a fixed duration of 90 days will be applied. In the Danish

registries, OAC prescription duration length will be based on the median time between prescriptions (see item 5.1.2.2c).

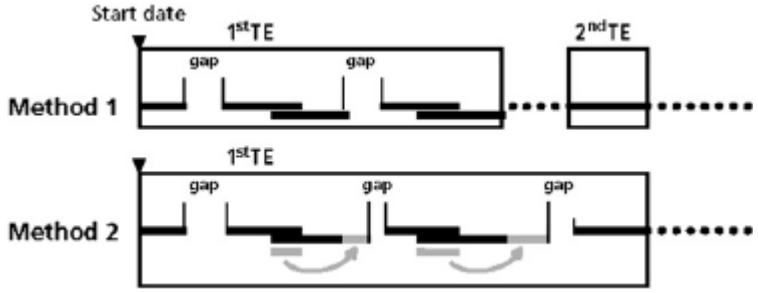
5.2.3.2 Treatment episodes

To assess period of **current use**, treatment episodes of (D)OACs will be constructed allowing for a 30 day permissible gap between the theoretical end date of a prescription and the subsequent prescription. Treatment episodes will be defined as a series of subsequent prescriptions for (D)OAC, independent of dose changes and constructed according to the method of Gardarsdottir et al. [18]. In case a subsequent prescription for the same drug is collected before the theoretical end date of a previous prescription, the number of overlapping days is added to the theoretical end date of the subsequent prescription (see Figure 1, method 2). As estimation of prescription length is difficult in some databases, the number of overlapping days will be maximized at 90 days.

If the subsequent prescription is within the same treatment episode included another type of (D)OAC, the patient is considered to have switched therapy and the remaining tablet days from the prior prescription are disregarded (see figure 1, method 1). In order to facilitate exposure classification, a new row will be created in case a patients switches from one type of (D)OAC to another within a treatment episode (Figure 2). Sensitivity analyses will be conducted to assess the impact of the permissible gap length (0 days, 60, days, 90 days) on the association with the outcome (HR described below).

Past use is defined as the period of time after following end of treatment episode, until a subsequent treatment episode is initiated, death, outcome or end of follow up.

Figure 1. Constructing drug treatment episodes based on estimated duration of a dispensed prescription and gaps of a defined length



TE: treatment episode

Figure 2. Handling of product switches within treatment episodes

x---drug A----| **(90 days)**
x----drug A---| **(90 days)**
x ---drug B----| **(90 days)**

t=0 t=30 t=60 → time

This example translates into a treatment episode as below:

Start	Stop	Drug
0	60	drug A
60	90	drug B

5.2.3.3 Exposure characteristics

For each current use row in the resultant data matrix, we will further classify exposure according to the type of drug (VKAs vs. DOAC, as well by individual product). The last prescribed daily dose (categorized low/medium/high in DDD-equivalent doses –cut-off to be decided) within each exposure row. The cumulative number of DDDs used will be treated both continuously, as well as categorical (cumulative DDD of less than 180, ≥180 and <365 and ≥365 DDD).

5.2.4 Potential confounders

Potential confounders considered in this study are based on literature review (i.e., risk factors for major bleeding and ischaemic stroke reported in the literature). No data-driven methods (e.g., change in effect estimate) will be applied to select confounders. The presence of a confounding variable will be assessed by reviewing the computerised medical records prior to initiation of (D)OAC treatment. Important risk factors considered for major bleeding are; chronic kidney disease, hepatic impairment, anaemia, thrombocytopenia, (uncontrolled) hypertension, history of cerebrovascular disease, history of major bleeding event, presence of malignancy, concomitant use of medicines that increase bleeding risk (NSAIDs, corticosteroids, SSRI's), excessive fall risk (i.e. benzodiazepine, antidepressant use), history of pulmonary embolism. Important risk factors considered for ischaemic stroke are: prior stroke/TIA, hypertension, diabetes mellitus, congestive heart failure, vascular disease, proteinuria, and chronic kidney disease. The UK Read code system, ICD-9, ICD-10, ICD-10-GM, and ICPC-2 codes will be used to define these risk factors (see 8.4 Appendix IV). Additionally we will use, where possible, lab-values on eGFR for chronic kidney disease and clinical parameters and lab-values that indicate hepatic impairment (Child Pugh Score) if appropriate. Hepatic impairment will also be assessed (where possible) using an algorithm which combines liver disease related diagnostic code with a referral and liver test abnormality [19]. Sex, weight (<50, 50-100, >100 kg), body mass index (BMI), smoking status and alcohol status will be considered at baseline (i.e., OAC initiation) and considered constant throughout follow-up. Age, comorbidities (ever before), and co-medication (6 months before) use will be considered as time dependent confounders and their status will be updated whenever the exposure status changes, or when exposure state exceeds 6 months at the start of each 6-month interval.

To assess the impact of missing values for BMI, smoking and alcohol we will apply multiple imputations in CPRD and extend the findings in a qualitative manner to the other databases.

5.2.5 Effect modifiers (subgroups)

Subgroups considered for stratified analysis of DOACs and major bleeding include:
chronic kidney disease, hepatic impairment, age >=75 years, low/high bodyweight (<50 kg or >100 kg), treatment with contra-indicated or hazardous co-medications as listed in sections 4.3, 4.4 and 4.5 of the SmPC of each product. Renal function will be defined as "normal-mildly reduced" (CrCl 50-80 mL/min), "moderately reduced (CrCl 30-49 mL/min)", "severely reduced (CrCl 15-29 mL/min)", and "very severely reduced (CrCl<15 mL/min)" or haemodialysis. In CPRD, some stages of chronic kidney disease are defined slightly differently from EMA tender technical specification, with CrCl 30-60 ml/min as moderately reduced and CrCl 60-90 ml/min as normal to mildly reduced.

5.2.6 Analysis

Baseline characteristics will be summarized as means and standard deviations or proportions where appropriate. Crude incidence rates of outcomes per 1,000 person years will be estimated, stratified by sex and age groups. Cox proportional hazard regression analysis will be applied to estimate effects (adjusted hazard ratios, HR) of (D)OAC treatment using STATA13 or the SAS 9.2/3/4 PHREG procedure.
Different analysis strategies will be applied to assess the outcomes where major bleeding will be defined as all bleedings registered in the GP medical file, as well as only including major bleedings leading to hospitalization. In addition, we will assess the risk (HR) of stroke and all-cause mortality.
In separate analyses, (D)OAC use will be included as time-fixed (i.e. estimating the effect of initiating treatment with a particular (D)OAC) and time-varying exposures. In case of time-fixed exposure confounders are only considered at baseline. In analyses of time-varying exposures, potential confounders will be included as time-varying covariates. Given the time-varying nature of the analysis (where treatment switching is not at a limited number of fixed time points) and the large size of the databases, PS analysis (e.g., PS matching) is considered not superior to conventional regression analysis based adjustment for confounding. Current use of VKAs will serve as the reference group and will be used to compare to the other exposure groups (current use of DOAC only, mixed use and past use). Analyses will be stratified by sex, age and the possible effect modifiers (see 5.2.5).

6 Limitations

6.1 Limitations related to the data source.

A major limitation is related to data availability and completeness within each data source. Information on important factors such as socioeconomic status is not always recorded in most databases. Moreover missing data on glomerular filtration rate (GFR), hepatic values, weight, height, alcohol and smoking might be an issue in some of the databases (See table 4.1). To assess the impact of missing values for BMI, smoking and alcohol we will apply multiple imputations in CPRD and extend the findings in a qualitative manner to the other databases. Information on hospitalization is available to a different extent in the different databases. This information is recorded in the databases by adding the specialist reports or through linkage to hospital data. Information on the indication motivating the drug prescription might also be incomplete.

6.2 Limitations related to methodology.

Potential limitations of this observational pharmacoepidemiological study arise due to (i) possible misclassification of the exposure status, e.g., unknown exposure status during hospitalization and incorrect calculation of the treatment duration; (ii) unmeasured confounding; and (iii) missing data. Confounding might occur when the disease that prompted the decision to treat may itself increase the risk of the outcome of interest, or the perceived risk of the outcome may influence the selection of the drug (indication or channeling bias), which may particularly occur during the introduction phase of a newly marketed drug.

Misclassification of the exposure is a potential concern in pharmacoepidemiological studies using databases since we mainly use prescription data and do not have complete information on dispensing or the actual drug intake. In addition, drugs prescribed by physicians other than GPs could be missed when using prescribing databases as these are commonly general practice databases. However, the exposure misclassification is expected to be non-differential and therefore we may expect a distortion of the risk towards the null value. To support the assumption that misclassification is non-differential, we will use a subset of data from the Dutch Mondriaan database (i.e. ZGA) and BIFAP that contains information on both prescriptions and dispensings (see 6.3. Methodological study on exposure misclassification). The concordance between the two will be quantified and the impact of disconcordance on the effects of (D)OACs on major bleedings will be assessed through sensitivity analyses.

Despite the fact that all (D)OACs are prescription drugs, over the counter (OTC) medication could influence (D)OAC exposure to some extent. For example, using (OTC) low-dose ASA or NSAIDs may lower the risk for receiving a (D)OAC due to an ASA- or NSAID-related increased bleeding risk. On the other hand, the bleeding risk will be increased in (D)OAC users receiving ASA and NSAIDS. Taken together, the exposure as well as the outcome might be influenced by OTC not documented in the databases.

Regarding the outcome, cases of major bleeding will only be identified by detection of specific recorded codes or texts for major bleeding in the databases. No additional criteria will be required, as the diagnosis is straightforward and no major errors are expected. Studies on the validity of diagnosis have been performed in some of the databases showing high validity [21-27]. In addition, major bleeding has been widely studied in primary and secondary health care databases and data are likely to be complete. The researchers involved in the consortium have already performed numerous studies on bleedings [8,12, 25-27].

6.3 Methodological study on exposure misclassification.

6.3.1 Study design

To assess misclassification of exposure we will perform two observational cohort studies. A study on primary non-adherence will be performed in patients who initiate (D)OACs and a study on exposure misclassification will be assessed in a population that gets a (D)OAC dispensed during the study period.

6.3.1.1 Primary non-adherence

Population

The study cohort consists of patients (≥18 years) of (D)OACs from Mondriaan and BIFAP that get their first (D)OAC dispensed during the study period. Only those patients using (D)OACs will be included where information about prescribing and dispensing is available.

New users were defined as patients without any use of (D)OACs in for at least 12 months. Patients registered in the database less than one year before the index date (date of first DOAC prescription) will be excluded.

Outcomes
Primary non-adherence (PNA) defined as all patients who receive a first (D)OAC(index date) prescribe which do not get their first prescribed (D)OAC dispensed during 12 months following index date.

Analysis
The proportion of PNA patients will be compared for each (D)OAC to assess if there are significant differences.

6.3.1.2 Exposure misclassification based on type of prescriber

Population
The study cohort consists of patients (>18 years) of (D)OACs from Mondriaan and Danish registries who get their first (D)OAC dispensed during the study period.
New users will be defined as patients without any use of (D)OACs in for at least 12 months. Patients registered in the database less than one year before the index date (date of first DOAC prescription) will be excluded.

Outcomes
Prescription durations per prescription and type of prescriber will be identified during follow up and defined as GP prescribed (D)OAC days or specialist prescribed (D)OAC days

6.3.2 Analysis
GP/Specialist ratio (D)OAC days will be assessed and compared for each (D)OAC.

7 References

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8 Annexes

8.1 Annex I: Information about the study drugs, dosing and indication.

Table 8.1.1. Oral anticoagulants, ATC codes and DDD

Medication class	Name	ATC	DDD
OAC	*Vitamin K antagonists*	***B01AA***	
	Warfarin	**B01AA03**	7.5 mg
	Phenprocoumon	**B01AA04**	3 mg
	Acenocoumarol	**B01AA07**	5 mg
DOAC	*Direct factor Xainhibitors*	***B01AF***	
	Rivaroxaban	**B01AF01**	20 mg
	Apixaban	**B01AF02**	10 mg
	Direct thrombininhibitors	***B01AE***	
	Dabigatran	**B01AE07**	300 mg

Table 8.1.2. CPRD product codes

prodcode	productname
4446	Acenocoumarol 1mg tablets
15376	Acenocoumarol 4mg tablets
55577	Sinthrome 1mg tablets (Lexon (UK) Ltd)
5305	Sinthrome 1mg tablets (Merus Labs LuxcoS.a R.L.)
15006	Sinthrome 4mg Tablet (Alliance Pharmaceuticals Ltd)
47566	Apixaban 2.5mg tablets
54066	Apixaban 5mg tablets
53740	Eliquis 2.5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
58594	Eliquis 5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
39444	Dabigatranetexilate 110mg capsules
46632	Dabigatranetexilate 150mg capsules
39503	Dabigatranetexilate 75mg capsules
39755	Pradaxa 110mg capsules (BoehringerIngelheim Ltd)
46678	Pradaxa 150mg capsules (BoehringerIngelheim Ltd)
42474	Pradaxa 75mg capsules (BoehringerIngelheim Ltd)
65876	Edoxaban 15mg tablets
65247	Edoxaban 30mg tablets
66529	Lixiana 30mg tablets (Daiichi Sankyo UK Ltd)
65850	Lixiana 60mg tablets (Daiichi Sankyo UK Ltd)
13502	Dindevan 10mg Tablet (Goldshield Pharmaceuticals Ltd)
13644	Dindevan 25mg Tablet (Goldshield Pharmaceuticals Ltd)
13501	Dindevan 50mg Tablet (Goldshield Pharmaceuticals Ltd)
13505	Phenindione 10mg tablets
46924	Phenindione 10mg tablets (AMCo)
13504	Phenindione 25mg tablets

13503	Phenindione 50mg tablets
39119	Rivaroxaban 10mg tablets
47353	Rivaroxaban 15mg tablets
62150	Rivaroxaban 2.5mg tablets
47207	Rivaroxaban 20mg tablets
39639	Xarelto 10mg tablets (Bayer Plc)
64500	Xarelto 2.5mg tablets (Bayer Plc)
8466	Marevan 1mg tablets (AMCo)
8467	Marevan 3mg tablets (AMCo)
17965	Marevan 500microgram tablets (AMCo)
13348	Marevan 5mg tablets (AMCo)
34087	Warfarin 1mg Tablet (Celltech Pharma Europe Ltd)
34576	Warfarin 1mg Tablet (Lagap)
23078	Warfarin 1mg Tablet (WB Pharmaceuticals Ltd)
45	Warfarin 1mg tablets
43408	Warfarin 1mg tablets (A A H Pharmaceuticals Ltd)
47944	Warfarin 1mg tablets (Actavis UK Ltd)
53752	Warfarin 1mg tablets (Alliance Healthcare (Distribution) Ltd)
39866	Warfarin 1mg tablets (Almus Pharmaceuticals Ltd)
51509	Warfarin 1mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)
51484	Warfarin 1mg tablets (Bristol Laboratories Ltd)
65285	Warfarin 1mg tablets (Crescent Pharma Ltd)
58519	Warfarin 1mg tablets (DE Pharmaceuticals)
34019	Warfarin 1mg tablets (IVAX Pharmaceuticals UK Ltd)
34416	Warfarin 1mg tablets (Kent Pharmaceuticals Ltd)
34517	Warfarin 1mg tablets (Mylan Ltd)
51496	Warfarin 1mg tablets (Phoenix Healthcare Distribution Ltd)
34299	Warfarin 1mg tablets (Teva UK Ltd)
66570	Warfarin 1mg tablets (Waymade Healthcare Plc)
36099	Warfarin 1mg/5ml oral suspension
50000	Warfarin 1mg/ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
34086	Warfarin 3mg Tablet (Celltech Pharma Europe Ltd)
31511	Warfarin 3mg Tablet (WB Pharmaceuticals Ltd)
61	Warfarin 3mg tablets
43407	Warfarin 3mg tablets (A A H Pharmaceuticals Ltd)
54946	Warfarin 3mg tablets (Actavis UK Ltd)
53745	Warfarin 3mg tablets (Bristol Laboratories Ltd)
58962	Warfarin 3mg tablets (DE Pharmaceuticals)
34758	Warfarin 3mg tablets (IVAX Pharmaceuticals UK Ltd)
56314	Warfarin 3mg tablets (Kent Pharmaceuticals Ltd)
34526	Warfarin 3mg tablets (Mylan Ltd)
59578	Warfarin 3mg tablets (Phoenix Healthcare Distribution Ltd)
34417	Warfarin 3mg tablets (Teva UK Ltd)

833	Warfarin 3mg/5ml oral solution
55316	Warfarin 3mg/5ml oral suspension
63071	Warfarin 4mg tablets
6262	Warfarin 500microgram tablets
40143	Warfarin 500microgram tablets (A A H Pharmaceuticals Ltd)
60589	Warfarin 500microgram tablets (Actavis UK Ltd)
62310	Warfarin 500microgram tablets (AMCo)
65746	Warfarin 500microgram tablets (DE Pharmaceuticals)
62309	Warfarin 500microgram tablets (Kent PharmaceuticalsLtd)
65496	Warfarin 500microgram tablets (Phoenix Healthcare Distribution Ltd)
59400	Warfarin 500microgram tablets (Sigma Pharmaceuticals Plc)
34088	Warfarin 5mg Tablet (Celltech Pharma Europe Ltd)
34691	Warfarin 5mg Tablet (Regent Laboratories Ltd)
33711	Warfarin 5mg Tablet (WB Pharmaceuticals Ltd)
1781	Warfarin 5mg tablets
43409	Warfarin 5mg tablets (A A H Pharmaceuticals Ltd)
34918	Warfarin 5mg tablets (Actavis UK Ltd)
58787	Warfarin 5mg tablets (Alliance Healthcare (Distribution) Ltd)
34864	Warfarin 5mg tablets (IVAX Pharmaceuticals UK Ltd)
34418	Warfarin 5mg tablets (Mylan Ltd)
31937	Warfarin 5mg tablets (Teva UK Ltd)
38044	Warfarin 5mg/5ml oral solution
60949	Warfarin 5mg/5ml oral suspension
44866	Warfarin sodium 1mg/ml oral supension SF
38041	Warfarin sodium 5mg/ml oral suspension
43655	Warfarin sodium oral solution
48070	Warfarin sodium tablets
30202	Warfarin wbp 1mg Tablet (BoehringerIngelheim Ltd)
30203	Warfarin wbp 3mg Tablet (BoehringerIngelheim Ltd)
34095	Warfarin wbp 5mg Tablet (BoehringerIngelheim Ltd)
64678	Edoxaban 60mg tablets
48966	Rivaroxaban 15mg tablets
54451	Rivaroxaban 20mg tablets
20754	WARFARIN
10560	WARFARIN 10 MG TAB
48869	Warfarin 1mg/ml oral suspension sugar free
54892	Warfarin 1mg/ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
57032	Warfarin 1mg/ml oral suspension sugar free (Rosemont Pharmaceuticals Ltd)
66286	Warfarin 2.5mg/5ml oral solution
56640	Xarelto 15mg tablets (Bayer Plc)
56289	Xarelto 20mg tablets (Bayer Plc)

Table 8.1.3. Indications and product recommended dose according to SmPCs for dabigatran, rivaroxaban and apixaban (SmPC item 4.1)

Indication	Rivaroxavan	Dabigatran			Apixaban	
Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine	**Xarelto™ 2.5 mg**					
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery	**Xarelto™ 10 mg**	**Pradaxa™ 75 mg**	**Pradaxa™ 110 mg**		**Eliquis™ 2.5 mg**	
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.	**Xarelto™ 15 mg** **Xarelto™ 20 mg**			**Pradaxa™ 150 mg**		**Eliquis™ 5 mg**
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults						

Table 8.1.4. Codes for indication according to the SmPC section 4.1.

Therapeutic indications SmPC section 4.3	ICD-10	ICD-8	ICD-9-CM (2)	ICD-10-GM	ICPC	Comment
Myocardial Infarction /Angina (MI-A)	I20, I21,I22,I23	410–410.99	(3) 410, (2) 412.x	I20, I21, I22, I23	K75	
Prevention after Hip/Knee replacement (PHK)	Nordic Classification of Surgery Procedures (NCSP)[ii]: KNFB, KNFC, KNGB, KNGC (Staerk L. et al 2016)		81.51, 81.52, 81.53, 81.54, 81.55		Z96.64 and Z96.65 (artificial hip/knee joint)	
Non-valvular atrial fibrillation (NVAF)	I48	427.93, 427.94	427.31 427.32	I48 (including atrial flutter)	K78 (including atrial flutter)	
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults[iii]	I80.1, I80.2 PE: I26	DVT: 451 PE: 450.9		I80.1, I80.2 PE: I26	ICPC codes extension in BIFAP[i] K93.4 -TROMBOEMBOLISMO PULMONAR K94.6 -TVP (TROMB. VENOSA PROFUNDA) K94.15 -TROMBOSIS VENOSA PROFUNDA EEII K93.1- EMBOLISMO (ARTERIAL) PULMONAR K93.2 -INFARTO PULMONAR (EMBOLISM.) K93.3-TROMBOSIS PULMONAR (EMBOLIA)	For defining DVT, the specific codes I80.1, I80.2 are used. However, I80.3, I80.8, I80.9 might be worth including too.
Other known off-label indications (OOL)						Off-label indications will be defined data driven.

i) BIFAP includes diagnostic data based on International Classification of Primary Care (ICPC). ICPC is a classification of the most frequent health problems in primary care with limited granularity (~700 codes). The software allows the primary care practitioner to add (write) new descriptors of diagnosis when the existing list of diagnosis descriptors is lacking for a particular diagnosis. Then, the most common descriptors of each ICPC are indexed in BIFAP by adding a fourth digit to the ICPC code of reference (1,2,...n). This is the index utilized for events information extraction for research.

ii) Staerk L et al. *BMJ* 2015;351:h5876

iii) Mellemkjaer L, Sørensen HT, Dreyer L, Olsen J, Olsen JH. Admission for and mortality from primary venous thromboembolism in women of fertile age in Denmark, 1977-95. BMJ. 1999 Sep 25;319(7213):820-1.

Table 8.1.5. Posology and method of administration (SmPC item 4.2)

	Rivaroxaban	Dabigatran	Apixaban
Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the	**2.5 mg twice daily** daily dose of 75 - 100 mg ASA or a daily dose of 75 - 100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine. Extension beyond 12 months(24 maximum) Started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.		
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery	**10 mg once daily.** The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established. Major hip surgery, a treatment duration of 5 weeks is recommended. Major knee surgery, a treatment duration of 2 weeks is recommended	**220 mg once daily** (2 of 110 mg)*. (initiated within 1-4 hours of completed surgery with a single of 110 mg capsule and continuing with 2 capsules once daily thereafter) 10 days knee replacement surgery 28-35 days hip replacement surgery **150 mg once daily** (2 capsules of 75 mg) - Patients with moderate renal impairment (creatinine clearance, CrCL 30-50 mL/min) - Patients who receive concomitant verapamil, amiodarone, quinidine [see Concomitant use of Pradaxa with mild to moderate P-glycoprotein (P-gp) inhibitors, i.e. amidarone, quinidine or verapamil (pVTEporthopaedic surgery)] - Patients aged 75 or above [see Elderly (pVTEporthopaedic surgery)]	**2.5 mg twice daily** (initiated within 12-14 hours of completed surgery - 10 to 14 days knee replacement surgery - 32 to 38 days hip replacement surgery

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.	**20 mg once daily**, (recommended maximum dose). **Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE*** -Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and -- longer durations should be based on permanent risk factors or idiopathic DVT or PE. In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance15 - 29 ml/min) renal impairment the following dosage recommendations apply: - prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation,: 15 mg once daily - treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting	**300 mg** as one 150 mg capsule twice daily. Therapy should be continued long term.	**5 mg taken twice daily**. Therapy should be continued long term. 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: -age ≥ 80 years, -body weight ≤ 60 kg, or -serum creatinine ≥ 1.5 mg/dL (133 micromole/L). **Prevention of stroke and systemic embolism in patients with NVAF**, patients with severe renal impairment (creatinine clearance 15-29 mL/min), and patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of **apixaban 2.5 mg twice daily**
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults		**300 mg** as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. *(Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, imobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.)* <u>Exceptions to indication 2 and 3:</u> 220 mg taken as one 110 mg capsule twice daily: -Patients aged 80 years or above -Patients who receive concomitant verapamil 300 or 220 based on individual assessment of the thromboembolic risk and the risk of bleeding: - Patients between 75-80 years - Patients with moderate renal impairment (CrCL 30-50 mL/min) - Patients with gastritis, esophagitis or gastroesophageal reflux -Other patients at increased risk of bleeding	**Treatment of DTV and PE:** **10 mg taken orally twice daily** for the first 7 days followed by 5 mg taken orally twice daily. (*Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, imobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE*.) **Treatment for prevention of recurrentDTV and PE**:**

*

	Dosing schedule	Maximum daily dose
Day 1 – 21	15 mg twice daily	30 mg
Day 22 and onwards	20 mg once daily	20 mg

**

Table 1:

	Dosing schedule	Maximum daily dose
Treatment of DVT or PE	10 mg twice daily for the first 7 days	20 mg
	followed by 5 mg twice daily	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE	2.5 mg twice daily	5 mg

8.2 Annex II: Information about contraindications (SmPC item 4.3), special warnings and precautions (SmPC item 4.4) and interactions (SmPC item 4.5).

Table 8.2.1. Registered contraindications (SmPC item 4.3)

	Contraindications (SmPC item 4.3) all	Contraindications (SmPC item 4.3) exceptions

DABIGATRAN	**Clinical conditions or diseases**
	• Active clinically significant bleeding
	• Risk factor for major bleeding.
	  ○ presence of current or recent gastrointestinal ulceration
	  ○ malignant neoplasms at high risk of bleeding,
	  ○ recent brain or spinal injury,
	  ○ ophthalmic surgery,
	  ○ recent intracranial haemorrhage,
	  ○ known or suspected oesophageal varices,
	  ○ arteriovenous malformations,
	  ○ vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
	• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
	
	Drugs
	• Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparinetc), heparin derivatives (fondaparinuxetc),
	• Oral anticoagulants (warfarin, rivaroxaban, apixaban, dabigatranetc)
	except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
		• severe renal impairment (CrCL< 30 mL/min)
		• Concomitant treatment with systemic ketocona cyclosporine, itraconazole and dronedarone
		• Prosthetic heart valves requiring anticoagulant treatment

APIXABAN		
RIBAROXABAN		• Hepatic disease associated with coagulopathy a clinically relevant bleeding risk including cirrhot patients with Child Pugh B and C. • Concomitant treatment of Acute Coronary Synd (ACS) with antiplatelet therapy in patients with a stroke or a transient ischaemic attack (TIA) (see 4.4).

Table 8.2.2. Special warnings and precautions for use (SmPC item 4.4)

	Special warnings and precautions for use (4.4) all	Special warnings and precautions for use (4.4) except
DABIGATRAN	**Other conditions, disease and procedures with haemorrhage risk** age ≥ 75 years low body weight < 50 kg/60 kg	Moderate renal impairment (CrCL 30-50 mL/min), Hepatic impairment Patients with elevated liver enzyr ULN not recomended
APIXABAN	Congenital or acquired coagulation disorders Thrombocytopenia or functional platelet defects Recent biopsy, major trauma Bacterial endocarditis Esophagitis, gastritis or gastroesophageal reflux Uncontrolled severe arterial hypertension vascular retinopathy Bronchiectasis or history of pulmonary bleeding In hip fracture surgery it is not recommended Spinal/epidural anaesthesia or puncture is not recommended Dosing recommendations before and after invasive procedures and surgical intervention (to stop therapy)	Severe renal impairment (creatinine clearance 15-29 n which may lead to an increased bleeding risk It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A orB) Patients with elevated liver enzymes ALT/AST >2 x ULN bilirubin ≥ 1.5 x ULN were excluded in clinical trials. Use of thrombolytic agents for the treatment of acute stroke Patients with prosthetic heart valves Haemodynamically unstable PE patients or patients wl require thrombolysis or pulmonary Embolectomy
RIBAROXABAN	Surgery and invasive procedures (to stop therapy) Interaction with other medicinal products affecting haemostasis and other pharmacodynamic interactions (see 4.5)	Severe renal creatinine clearance 15 - 29 ml/min with Moderate renal impairment (creatinine clearance 30 - ml/min) concomitantly receiving other medicinal prod which increase rivaroxaban plasma concentrationswitl Contraindicated for the treatment of ACS in patients w prior stroke or TIA

Table 8.2.3. Interaction with other medicinal products and other forms of interaction (SmPC item 4.5)

	Interaction with other medicinal products and other forms of interaction (SmPC item 4.5) all	Interaction with other medicinal products and other forms of interaction (SmPC item 4.5) exceptions
DABIGATRAN	**1. Transporter interactions:** **1.1. CYP3A4 and/or P-gp inhibitors (Increased dabigatran plasma levels which may result in an increased risk of bleeding)** 1.1.1. **strong CYP3A4 and/or P-gp inhibitor co-medication** systemic ketoconazole, cyclosporine, itraconazole dronedarone tacrolimus 1.1.2. **not strong CYP3A4 and/or P-gp inhibitors** amiodarona, posaconzole, quinidine, verapamil ticragrelor **1.2. CYP3A4 and/or P-gp inducers(decreased concentrations)** Rifampicin, carbamazepine, or phenytoin, Hypericumperforatum **1.3. Other affecting P-gp** Ritornavir **2. Anticoagulants and antiplatelet aggregation medicinal products which may increase the risk of bleeding when used concomitantly** - platelet aggregation medicinal products such as, GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, dextran, and sulfinpyrazone - acetylsalicylic acid (ASA), - clopidogrel or - non steroidal antiinflammatory drug (NSAID)	**Transporter interaction: P-gp** **strong P-gp inhibitor co-medication CONTRAINDICAT** sistemic ketoconazole, cyclosporine, itraconazole dronedarone **not strong P-gp inhibitor** clarithromycin **Other** SSRIs and SNRIs,
APIXABAN		**Transporter interaction: CYP3A4 and/or P-gp** voriconazole naproxen,
RIBAROXABAN		**Transporter interaction: CYP3A4 and/or P-gp** voriconazole erythromycin fluconazole

8.3 Annex III: Coding for major bleeding, contraindications (SmPC item 4.3), special warnings and precautions (SmPC item 4.4) and interactions (SmPC item 4.5).

Table 8.3.1. ICD and ICPC codes for major bleeding.

Outcome	ICD-10	ICD-8	ICD-9-CM	ICD-10-GM	ICPC	Comments
Primary outcome						
Major bleeding						
Haemorrhagic stroke/ intracranial Bleeding	I60 I61 I62	431.00, 431.08 to 431.90, 431.98, 431.99	430, 431, 432 852.0, 852.2, 852.4, 853.0	I60 I61 I62	ICPC codes extension in BIFAP[i] K90.5-HEMORRA., SANGR. NC CEREBRAL/ICTUS K90.7-HEMORRA., SANGR. NC MENINGEA K90.6-HEMORRA., SANGR. NC INTRACRANEAL K90.8-HEMORRA., SANGR. NC SUBARACNOIDEA K90.12-RUPTURA INTRACRANEAL (VASO) K90.13-RUPTURA VASO SANGUIN., CEREB. K90.15-AVC HEMORRAGIC K90.18-CEREBRAL, HEMORRAGIA K90.25-HEMORRA., SANGR. NC SUBARACNOIDEA POR LESION	
Extracranial or unclassified major bleeding	D62, J942, H113, H313, H356, H431 N02 N95 R04 R31 R58		459.0,596.7,599.7, 627.1,719.1,784.7, 784.8,786.3	D62, J94.2, H11.3, H31.3, H35.6, H43.1, N02, N95, R04, R31, R58	A10 (bleeding)	
Gastrointestinal bleeding[ii]	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5 K92.0, K92.1, K92.2	##Gastric, duodenal, or gastrojejunal ulcer; hematemesis; or melena 530.98, 531.90, 531.92, 531.95, 532.90, 533.90, 534.90, 535.01, 784.59, 785.79;	Upper GI: 456.0, 530.7, 530.82;531.0, 531.2, 531.4, 531.6;532.0, 532.2, 532.4, 532.6;533.0, 533.2, 533.4, 533.6; 534.0, 534.2, 534.4, 534.6;535.01, 535.21, 535.31, 535.41,535.51, 535.61;537.83 **Lower GI: 562.02, 562.03, 562.12, 562.13; 568.81, 569.3, 569.85, 578	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0 K62.5, K92.0, K92.1, K92.2	No specific code for GI bleeding D14 (haematemesis) D15 (melaena) D16 (rectal bleeding)	

Traumatic intracranial bleeding	S063C S064 S065 S066	S063C S064 S065 S066		S06.33, S06.34, S06.38, S06.4, S06.5, S06.6	A80 A81	
Secondary outcome						
Cerebral infarction[iii]	I63	Stroke: 430-434; 436	***433.x1, 434.x (except subcode: x0), 436 (2) 433.xx 434.xx 436.xx	I63	ICPC codes extension in BIFAP[i] K90.3-EMBOLISMO (ARTERIAL) CEREBRAL (ICTUS) K90.10-INFARTO CEREBRAL K90.11-OCLUSION (ARTERIAL) CEREBRAL (ICTUS) K90.14-TROMBOSIS CEREBRAL (ICTUS) K90.16-AVC ISQUEMIC K90.17-AVC TROMBOTIC K90.20-INFARTO CEREBRAL LACUNAR K90.21-INFARTO CEREBELOSO	
Stroke, not specified as haemorrhage or infarction	I64			I64	ICPC codes extension in BIFAP[i] K90.1-ACCIDENTE CEREBROVASCULAR NC K90.2-CONVULSIONES POR APOLEJIA K90.19-ACCIDENTE CEREBROVASCULAR/ICTUS/ACV (EXC. AIT) K91.8-SECUELA/S DE ICTUS/ACV	

i) BIFAP includes diagnostic data based on International Classification of Primary Care (ICPC). ICPC is a classification of the most frequent health problems in primary care with limited granularity (~700 codes). The software allows the primary care practitioner to add (write) new descriptors of diagnosis when the existing list of diagnosis descriptors is lacking for a particular diagnosis. Then, the most common descriptors of each ICPC are indexed in BIFAP by adding a fourth digit to the ICPC code of reference (1,2,...n). This is the index utilized for events information extraction for research.

ii)Gamst J et al. BMJ Open. 2014 Nov 14;4(11):e006486

iii) Giner-Soraino et al. BMJ Open. 2016 Jan 28;6(1):e010144

Table 8.3.2. Codes for Contraindications according to the SmPC section 4.3.- Clinical conditions

Contraindications	ICD-10	ICD-8	ICD-9-CM	ICD-10-GM	ICPC	Comment
Active clinically significant bleeding	See table 8.3.1.					
Risk factors for major bleeding						
Gastrointestinal ulceration	K22.1; K25-K28	530.91; 530.98; 531-534;	** 531.x–534.x	K22.1, K25-K28	D85 D86	Based on Charlson Index: (ICD-8 and 10)
Malignant neoplasms	C00-C96 excluding C43, C44	140-194 195-199 204-207 200-203 204-207 Add missing codes! Excluding: 172, 173	** 140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6 196.x–199.x	C00-C96 excluding C43, C44	T71, D76, Y77, U77, U76, U75, R84, D75, D74, A79, Y78, T73, N74, B74, B74.01,S77, R85, D77, L71.01, S80, N76, U79, K72.01, H75.01, F74.01, B72.01, B72.02, B73	Based on Charlson Index: (ICD-8)
Brain or spinal injury	S06, S06.2, S06.3, S06.4, S06.5, S06.6, S06.8, S06.9, S14, S24, S34, T09.3, T09.4	N850-N854, N852, N853, N854, N950-N959	854.00, 959.01, 952, 952.0, 952.1 , 952.2, 952.3, 952.4, 952.8, 952.9	S06, S06.2, S06.3, S06.4, S06.5, S06.6, S06.8, S06.9, S14, S24, S34, T09.3, T09.4		Text search for description of diagnosis in ICPC code system in BIFAP will be assessed for event identification. List of diagnosis description will be provided.
Haemorrhagic stroke/intracranial bleeding	I60 I61 I62	431.00, 431.08 to 431.90, 431.98, 431.99	(2), (3): 430, 431, 432 (3): 852.0, 852.2, 852.4, 853.0	I60 I61 I62	K90.01, K90.02 ICPC codes extension in BIFAP[i] K90.5-HEMORRA., SANGR. NC CEREBRAL/ICTUS K90.7-HEMORRA., SANGR. NC MENINGEA K90.6-HEMORRA., SANGR. NC INTRACRANEAL K90.8-HEMORRA., SANGR. NC SUBARACNOIDEA K90.12-RUPTURA INTRACRANEAL (VASO) K90.13-RUPTURA VASO SANGUIN., CEREB. K90.15-AVC HEMORRAGIC	

Contraindications	ICD-10	ICD-8	ICD-9-CM	ICD-10-GM	ICPC	Comment
					K90.18-CEREBRAL, HEMORRAGIA K90.25-HEMORRA., SANGR. NC SUBARACNOIDEA POR LESION	
Oesophageal varices	I85	456.0	456.0, 456.1	I85		*Text search for description of diagnosis in ICPC code system in BIFAP will be assessed for event identification. List of diagnosis description will be provided.
Arteriovenous malformations	Q20-Q28	747, 747.1, 747.2, 747.3, 747.4, 747.5, 747.6,747.8 , 747.9	747, 747.1, 747.2, 747.3, 747.4, 747.5, 747.6,747.8 , 747.9	Q20-Q28		*Text search for description of diagnosis in ICPC code system in BIFAP will be assessed for event identification. List of diagnosis description will be provided.
vascular aneurysms or major intraspinal or intracerebral vascular abnormalities	I25.4, I28.1, I67.1, I71, I72, I79.0	441, 441.0, 441.1, 441.2, 441.9,442	437.3, 441, 441.1, 441.2,441.3 , 441.4, 441.5, 441.6 , 441.7, 441.9, 442	I25.4, I28.1, I67.1, I71, I72, I79.0		
Prosthetic hearth valves	Z95.2	Y30	V43.3	Z95.2		
Hepatic impairment associated with coagulopathy and clinically relevant	B15.0, B16.0, B16.2, B19.0, I85, K70.3, K70.4, K71, K72, R17	Cirrhosis: 571, 563 571; 573.01; 573.04 (Charlson Index) 070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00; 456.10	**456.0-456.2 570 572.2-5.72.8 573.4-573.5 V42.7	B15.0, B16.0, B16.2, B19.0, I85, K70.3, K70.4, K71, K72, R17	D97.04 (Cirrhosis) ICPC codes extension in BIFAP[i] D97.14-Cirrosis biliar primaria D97.2-Cirrosis hepatica D97.9-Cirrosis biliar	Additional, less specific codes might be worth including too: B18, B94.2, E83.0, E83.1, , K70.1, K70.2,

Contraindications	ICD-10	ICD-8	ICD-9-CM	ICD-10-GM	ICPC	Comment
bleeding risk						K70.9, K73, K74, K76.0, K76.6
Severe renal impairment/Chronic and acute kidney disease	I12, I13, N00, N01, N03, N04, N05, N07, N08, N10, N11, N12, N14, N17, N18.4, N18.5, N18.8, N18.9 N19, Q61	(Charlson Index) 403; 404; 580-584; 590.09	(2) 403.01 403.11 403.91 404.02 404.03 404.12 404.12 404.13 404.92 404.93 585.3-585.9 586 V42.0 V45.1 V56.x	I12 I13 N00 N01 N03 N04 N05 N07 N08, N10, N11, N12, N14, N17, N18.4, N18.5, N18.8, N18.9 N19, Q61	U99.01 ICPC codes extension in BIFAP[i] U99.10-INSUFICIENCIA RENAL CRONICA U99.9-INSUFICIENCIA RENAL AGUDA	

i) BIFAP includes diagnostic data based on International Classification of Primary Care (ICPC). ICPC is a classification of the most frequent health problems in primary care with limited granularity (~700 codes). The software allows the primary care practitioner to add (write) new descriptors of diagnosis when the existing list of diagnosis descriptors is lacking for a particular diagnosis. Then, the most common descriptors of each ICPC are indexed in BIFAP by adding a fourth digit to the ICPC code of reference (1,2,...n). This is the index utilized for events information extraction for research.

Table 8.3.3. Codes for Contraindications according to the SmPC section 4.3 and section 4.4. - Medication

ATC	Drug	Comment
B01AA	**Vitamin K antagonists**	
B01AA01	dicoumarol	
B01AA02	phenindione	
B01AA03	warfarin	
B01AA04	phenprocoumon	
B01AA07	acenocoumarol	
B01AA08	ethylbiscoumacetate	
B01AA09	clorindione	
B01AA10	diphenadione	
B01AA11	tioclomarol	
B01AA12	fluindione	
B01AB	**Heparin group**	
B01AB01	heparin	
B01AB02	antithrombin III	
B01AB04	dalteparin	
B01AB05	enoxaparin	
B01AB06	nadroparin	
B01AB07	parnaparin	
B01AB08	reviparin	
B01AB09	danaparoid	
B01AB10	tinzaparin	
B01AB11	sulodexide	
B01AB12	bemiparin	
B01AB51	heparin, combinations	
B01AC	**Platelet aggregation inhibitors excl. heparin**	
B01AC01	ditazole	
B01AC02	cloricromen	
B01AC03	picotamide	
B01AC04	clopidogrel	
B01AC05	ticlopidine	
B01AC06	acetylsalicylic acid	
B01AC07	dipyridamole	
B01AC08	carbasalate calcium	
B01AC09	epoprostenol	
B01AC10	indobufen	
B01AC11	iloprost	
B01AC13	abciximab	
B01AC15	aloxiprin	
B01AC16	eptifibatide	
B01AC17	tirofiban	
B01AC18	triflusal	
B01AC19	beraprost	
B01AC21	treprostinil	
B01AC22	prasugrel	
B01AC23	cilostazol	
B01AC24	ticagrelor	
B01AC25	cangrelor	
B01AC26	vorapaxar	
B01AC27	selexipag	
B01AC30	combinations	
B01AC56	acetylsalicylic acid, combinations with proton pump inhibitors	
B01AE	**Direct thrombin inhibitors**	
B01AE01	desirudin	
B01AE02	lepirudin	
B01AE03	argatroban	
B01AE04	melagatran	
B01AE05	ximelagatran	

ATC	Drug	Comment
B01AE06	bivalirudin	
B01AE07	dabigatranetexilate	
B01AF	**Direct factor Xa inhibitors**	
B01AF01	rivaroxaban	
B01AF02	apixaban	
B01AX	**Other antithrombotic agents**	
B01AX01	defibrotide	
B01AX04	dermatansulfate	
B01AX05	fondaparinux	
Strong P-gp inhibitor co-medication		
D01AC08	Ketoconazole	
J02AC02	Itraconazole	
L04AD01	Cyclosporine	
C01BD07	Dronedarone	

Table 8.3.4. Codes for Special warnings and precautions for use according to the SmPCitem 4.4. - Clinical conditions

	ICD-10-DK	ICD-8- DK	ICD-9-CM (2)	ICD-10-GM	ICPC	Comment
Chronic and acute kidney disease	See Table 8.3.2					
Hepatic impairment	See Table 8.3.2					
Stroke/TIA	I63, I64, G45	430-438	433.xx 434.xx 436.xx V12.54, 435.xx	I63, I64, G45	K90, K89	
DVT, PE	I80.1, I80.2 I26			I80.1, I80.2 I26	K94.01, K93	For defining DVT, the specific codes I80.1, I80.2 are used. However, I80.3, I80.8, I80.9 might be worth including too.
Alcohol	E529A F10, G312 G621 G721 I426 K292 K70 K860 L278A O354 T51 Z714 Z721	303	** 291 303.00, 303.01, 303.02, 303.90, 303.91, 303.92, 305.00, 305.01, 305.02, 357.5, 425.5, 535.3	E52.9, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, T51	P15, P16,	
Any malignancy, including lymphoma and leukaemia and metastatic solid tumour, except malignant neoplasm of the skin	See Table 8.3.2.					
Peptic ulcer disease	See Table 8.3.2.					
Thrombocytopenia	D69.1, D69.3, D69.4, D69.5, D69.6 D82.0	287,287.1,287.3, 287.9	287 ,287.1,287.3, 287.30, 287.31 , 287.32,287.33, 287.39	D69.1, D69.3, D69.4, D69.5, D69.6 D82.0	B83	
Congenital or acquired coagulation disorders	D65-D69			D65-69		
Major trauma	S00-S09, S10-S19, S20-S29, S30-S39	E800-E807, E810-E819	959,959.0,959.01	S00-S09, S10-S19, S20-S29, S30-S39	A80	

	S40-S49, S50-S59, S60-S69, S70-S79, S80-S89, S90-S99, T00-T07, T08-T14 V00-V09, V10-V19, V20-V29, V30-V39 V40-V49, V50-V59 V60-V69, V70-V79 V80-V89, V90-V94 V95-V97, V98-V99 W00-W19	E820-E823 E825-E827 E830-E838 E840-E845 N850-N854 N860-N869 N870-N879 N900-N907	959.09,959.1 959.11,959.12 959.13,959.14 959.19,959.2 959.3,959.4 959.6,959.7 959.8,959.9 E800-E807 E810-E819 E820-E825 E826-E829 E830-E838 E840-E845 E846-E849	S40-S49, S50-S59, S60-S69, S70-S79, S80-S89, S90-S99, T00-T07, T08-T14 V00-V09, V10-V19, V20-V29, V30-V39 V40-V49, V50-V59 V60-V69, V70-V79 V80-V89, V90-V94 V95-V97, V98-V99 W00-W19	A81 A82	
vascular retinopathy	H35.0	377.0	362.1	H35.0	F83	
Bacterial endocarditis	I33.0	421.0	421.0	I33.0	K70, K71 ICPC codes extension in BIFAP[i] K70.1-AGUDO Y SUBAGUDO ENDOCARDITIS K70.4-ENDOCARD. (AGUD.) (SUBA.) NO REUMATICA K71.5-ENDOCARD. (AGUD.) (SUBA.) REUMATICA (CRON./AG.)	
Bronchiectasis or history of pulmonary bleeding	J47 Q33.4	518 783.1	494 748.61	J47 Q33.4	R24	

	R04.2 R04.8		786.3 786.30 786.39	R04.2 R04.8		
prosthetic heart valves	Z95.2	Y30	V43.3	Z95.2		
Hip Fracture	S72.0 S72.1 S72.2	N820 N821	820 820.0 820.1 820.2 820.3 820.8 820.9 V43.64	S72.0 S72.1 S72.2	L75 L75.01 ICPC codes extension in BIFAP[i] L75.1-Fractura de cadera L75.2- Fratura del cuello de femur	

i) BIFAP includes diagnostic data based on International Classification of Primary Care (ICPC). ICPC is a classification of the most frequent health problems in primary care with limited granularity (~700 codes). The software allows the primary care practitioner to add (write) new descriptors of diagnosis when the existing list of diagnosis descriptors is lacking for a particular diagnosis. Then, the most common descriptors of each ICPC are indexed in BIFAP by adding a fourth digit to the ICPC code of reference (1,2,...n). This is the index utilized for events information extraction for research.

Table 8.3.5. Codes for interaction with other medicinal products and other forms of interaction according to the SmPC item 4.5.

ATC	Drug	Comment
Strong CYP3A4 and/or P-gp inhibitor co-medication		
G01AF11	ketoconazole	
J02AB02	ketoconazole	
L04AD01	cyclosporin	
J02AC02	itraconazole	
C01BD07	dronedarone	
L04AD02	tacrolimus	
J02AC03	voriconazol	
J01FA01	erythromycine	
J02AC01	fluconazol	
not strong CYP3A4 and/or P-gp inhibitors		
C01BD01	amiodarone	
J02AC04	posaconazole	
C01BA01	quinidine	
C01BA51	quinidine, combinations excl. psycholeptics	
C01BA71	quinidine, combinations with psycholeptics	
C08DA01	verapamil	
C08DA51	verapamil, combinations	
B01AC24	ticagrelor	
CYP3A4 and/or P-gpinducers(decreased concentrations)		
J04AB02	rifampicin	
J04AM02	rifampicin and isoniazid	
J04AM05	rifampicin, pyrazinamide and isoniazid	
J04AM06	rifampicin, pyrazinamide, ethambutol and isoniazid	
N03AF01	carbamazepine	
N03AB02	phenytoin	
N03AB52	phenytoin, combinations	
N06AX25	Hypericiherba	
Other affecting P-gp		
J05AE03	ritonavir	
J05AR10	lopinavir and ritonavir	
J05AX67	ombitasvir, paritaprevir and ritonavir	
05AX66	dasabuvir, ombitasvir, paritaprevir and ritonavir	
Anticoagulants and antiplatelet aggregation medicinal products which may increase the risk of bleeding when used concomitantly		
See table 8.4.3.		

ATC	Drug	Comment
B05AA05	Dextran	
M04AB02	Sulfinpyrazon	
Non steroidal antiinflammatory drug (NSAID)		
M01	Antiinflammatory and antirheumatic products, Non-steroids	
Other		
N06AB	Selective serotonin re-uptake inhibitors	
N06AX16	Venlafaxine	
N06AX21	Duloxetine	
N06AX23	Desvenlafaxine	

8.4 Annex IV: Information about codes for the Cohort study

Table 8.4.1. ICD and ICPC codes used to identify the study population.

Study population	ICD-10-DK	ICD-8- DK	ICD-9-CM (2)	ICD-10-GM	ICPC	Comment
Diagnosis						
(Hospital contact with) atrial fibrillation	I48	427.93, 427.94	427.31 427.32	I48 (including atrial flutter)	K78 (including atrial flutter)	
Exclusion?*						
Valvular atrial fibrillation (mitral stenosis or mechanical heart valves)	I05 Z952 Z953 Z954	424.0 (chronic, non-rheumatic disease of mitral) 424.1 (aortic)		I05 Z95.2 Z95.3 Z95.4	K83.02	

Table 8.4.2. ICD and ICPC codes of co-morbidities and risk factors

Risk factors for bleeding	ICD-10	ICD-8	ICD-9-CM	ICD-10-GM	ICPC	Comment
Conditions	See Table 8.3.4					
Hypertension	See Table 8.3.4					
Stroke/TIA	See Table 8.3.4					
DVT, PE	See Table 8.3.4					
Alcohol	See Table 8.3.4					
Any malignancy, including lymphoma and leukaemia and metastatic solid tumour, except malignant neoplasm of the skin	See Table 8.3.2.					
Peptic ulcer disease	See Table 8.3.2.					
Thrombocytopenia	See Table 8.3.4.					

Risk factors for ischaemic stroke	ICD-10-DK	ICD-8- DK	ICD-9-CM (2)	ICD-10-GM	ICPC	Comment
Conditions						
Stroke/TIA			See Table 8.3.4			
DVT, PE			See Table 8.3.4			
Hypertension	I10, I11, I12, I14, I15 At least two of the following: I: C02A, C02B, C02C II: C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09XA52 III: C02DB, C02DD, C02DG, C04, C05 IV: C07F, C08, C09BB, C09DB V: C09	400-404	Hypertension	I10, I11, I12, I14, I15	I10, I11, I12, I14, I15 At least two of the following: I: C02A, C02B, C02C II: C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09XA52 III: C02DB, C02DD, C02DG, C04, C05 IV: C07F, C08, C09BB, C09DB V: C09	
Congestive heart	I11.0; I13.0; I13.2;	782.49	398.91, 402.01,	I11.0, I13.0, I13.2,	K77	

Risk factors for ischaemic stroke	ICD-10-DK	ICD-8- DK	ICD-9-CM (2)	ICD-10-GM	ICPC	Comment
failure	I42.0; I50 ATC: C03C		402.11, 402.91, 428.x, 518.4; 404.01, 404.03, 404.11, 404.13, 404.91, 404.93	I42.0, I50		
Diabetes	E10-E14 ATC: A10	249, 250	250, 253.5, 271.4, 275.0, 357.2, 362.0, 588.1, 648.0, 790.2, 790.6	E10, E11, E12, E13, E14	T90	
Other cardiovascular disease (Angina, MI, Coronary heart disease, Aortic plaque, PAD)	I20, I21, I22, I23, I24, I25, I65, I66, I70.0, I70.2, I73.9	413, 410–410.99, 420-429 (Other heart diseases)	410, (2) 412.x	I20, I21, I22, I23, I24, I25, I65, I66, I70.0, I70.2, I73.9	K91, K76, K75, K74, K92, K99.01	

Other risk factors	ICD-10-DK	ICD-8- DK	ICD-9-CM (2)	ICD-10-GM	ICPC	Comment
Dementia	F00-F03; F05.1; G30, G31.0, G31.1, G31.82, G31.9 + antidementia drugs	Charlson: 290.09, 290.20, 293.09, Dementia study: 290.10; 290.11, 290.09-19, 293.09-19,	** 290.x, 294.1, 331.2	F00-F03, F05.1, G30, G31.0, G31.1, G31.82, G31.9	P70	
Chronic pulmonary disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	490-493; 515-518;	** 416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	R91, R95, R96	Based on Charlson Index (ICD-8 and 10)
Rheumatic disease	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	712, 716; 734; 446, 135.99	** 446.5, 710.0– 710.4, 714.0– 714.2, 714.8, 725.x	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	L88, K71, R83.02	Based on Charlson Index: Connective tissue disease (ICD-8 and 10)
Peptic ulcer disease (also included as risk factor for bleeding)	K22.1; K25-K28	530.91; 530.98; 531-534;	** 531.x–534.x	K22.1, K25, K26, K27, K28	D85 D86	Based on Charlson Index: (ICD-8 and 10)
Hemiplegia or paraplegia	G81; G82	344	** 334.1, 342.x, 343.x, 344.0–344.6,	G81, G82	N18	Based on Charlson Index: (ICD-8 and 10)

Other risk factors	ICD-10-DK	ICD-8- DK	ICD-9-CM (2)	ICD-10-GM	ICPC	Comment
			344.9			
Any malignacy, including lymphoma and leukaemia and metastatic solid tumour, except malignant neoplasm of the skin (also included as risk factor for bleeding)	C00-C96 excluding C43, C44	140-194 (any tumour) 195-199 (metastatic solid tumour) 204-207 (leukemia) 200-203, 275.59 (lymphoma) codes!	** 140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6 196.x–199.x	C00-C96 excluding C43, C44	T71, D76, Y77, U77, U76, U75, R84, D75, D74, A79, Y78, T73, N74, B74, S77, R85, D77, L71.01, S80, N76, U79, K72.01, H75.01, F74.01	Based on Charlson Index: (ICD-8)
AIDS/HIV	B20, B21-B24, O98.7, Z21	079.83	042.x–044.x	B20, B21, B22, B23, B24, O98.7, Z21	B90	Based on Charlson Index: (ICD-8 and 10)

* Charlson index: predicts 1-year motality risk of a patient. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one.

Table 8.4.3. ATC codes for risk factors - Medication

ATC	Drug	Comment
M01A	NSAIDs	
N06AB	SSRIs	
H02	Corticosteroids	
B01AC	Antiplatelet drugs	
A10	Antidiabetic drugs	
C10	Lipid lowering drugs	
At least two of the following: I: C02A, C02B, C02C II: C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09XA52 III: C02DB, C02DD, C02DG, C04, C05 IV: C07F, C08, C09BB,	Anti-hypertensives	

ATC	Drug	Comment
C09DB V: C09		

8.5 Annex V: Output/Results tables

Output sheets are included in attached xls.files

8.6 Annex VI: Quality control, data storage and sharing

Quality control

The members of the consortium have similar local quality assurance systems in place. In addition, several quality assurance measures are taken that will be maintained in the proposed consortium across the centres, such as adherence to the ENCePP code of conduct and apply for ENCePP Seal, development of protocols according the ENCePP guidance, registration of protocols at the ENCePP registry of studies, sharing and comparison of program codes across centres, documentation of harmonization of coding systems across multiple datasets (exposure, outcome, confounder definitions), blinded conduct of studies. Study protocols are peer-reviewed by an advisor (at least one member of the consortium that is not leading nor actively participating in the study). Regarding conflict of interest, a declaration of conflict of interest by the candidate partners that will be in a position to be principal investigator or co-investigator should be presented to the Steering Committee.

Quality management system of coordinator of consortium (Universiteit Utrecht).

The Division of Pharmacoepidemiology & Clinical Pharmacology is working according to a quality management system based on ISO 9001 principles, at the moment in development towards certification. The quality management system is system and process oriented and based on continuous improvement. All primary and secondary processes within the division are included in the quality system, from creating research proposals, through managing PhD projects to data management, reporting and archival. The system is based upon standard operating procedures implemented throughout the division with regular internal audits as well as external audits that lead to certification. The quality management system is based on national and international external quality requirements where available and pertinent, including the guidelines for Good Pharmacoepidemiological Practices, ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Good Clinical Practice, and Good Clinical Datamanagement Practice as well national and international guidelines and legislation concerning data-handling and privacy issues.

Data storage

All data generated in the study will be recorded in a way that allows verification of the published results whilst respecting data protection legislation. The following will be shared between consortium members and stored locally at Utrecht University for archiving:

- All codes for structuring data used for analysis
- All codes for statistical analysis
- All analysis outputs

Data access and sharing

Due to data protection legislation the data from each consortium member cannot be stored locally at Utrecht University. However, the consortium members will apply with the “ENCePP Code of Conduct – Implementation Guidelines for Sharing of ENCePP Study Data” and allow access to their data in the following circumstances:

- With the aim to corroborate the study resultas in the interest of Public Health.
- To confirm compliance with the ENCePP Code of Conduct, e.g. to demonstrate that the audit trail established in line with the Code’s requirements does allow corroboration of results, or
- In the context of an audit by a competent authority

Access to data can be provided as stated in Chapter IV: *1 Approaches for replying to data access requests* of the above mentioned Code of Conduct, item 4. On-site access

8.7 Annex VII: Study timelines and deliverables

Deliverable	**Date**
1. Preliminary study plan	Date+1 Months
2. Study protocol	Date+3 Months
3. Study report	Date+11 Months
4. Manuscripts	Date+12 Months
5. Final report	Date+12 Months

Deadlines are based on signature date = 1 September 2016