EU PE&PV 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 3.0
1 June 2018
EU PAS Register No: 16014

TABLE OF CONTENTS

1 Title

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 3.0 – 1 June 2018, EU PAS Register No: 16014.

2 Marketing authorization holder

Not applicable

3 Responsible parties

Name	Role
Dr. Helga Gardarsdottir[1,2]	Principal Investigator, Mondriaan Database lead
Dr. Patrick Souverein[1]	Study Objective 1 co-lead, CPRD Database lead
Dr. Rianne van den Ham[1]	Study Objective 1 co-lead , CPRD Database co-lead
Dr. Rolf Groenwold[1,2]	CPRD&Mondriaan co-investigator
Dr. Christiane Gasse[3]	AU Danish National Registers co-investigator
Marietta Rottenkolber[4]	Study Objective 3 co-lead, Bavarian Claims Database lead
Dr. Consuelo Huerta[5]	BIFAP Database lead
Dr. Elisa Martín Merino[5]	BIFAP Database co-lead
Dr. Dolores Montero[5]	BIFAP Database co-investigator
Dr. Luz M León-Muñoz[5]	BIFAP Database co-investigator
Dr. Luisa Ibanez[6]	Study Objective 2 Lead, SIDIAP Database lead
Elena Ballarín[6]	SIDIAP Database co-investigator
Dr. Mónica Sabaté[6]	SIDIAP Database co-lead
Dr. Xavier Vidal[6]	SIDIAP Database co-lead
Prof. Dr. Nicholas Moore[7]	French Claims Database lead
Dr. Cecile Droz[7]	French Claims Database co-investigator
Mr. Régis Lassalle[7]	French Claims Database co-investigator
Dr. Morten Andersen[8]	CU Danish National Registers lead
Prof. Marieke De Bruin[8]	CU Danish Natonal Registries co-investigator
Dr. Sven Schmiedl[9]	Study Objective 3 co-lead, AOK NORDWEST lead
Prof. Dr. Katrin Janhsen[9]	AOK NORDWEST co-lead
Prof. Dr. Olaf Klungel[1,2]	PI/coordinator of EU PE&PV Research Network
Ms. Satu J Siiskonen[1]	Project manager of EU PE&PV Research Network

1. Universiteit Utrecht, David de Wiedgebouw, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands (UU)
2. University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands (UMCU)
3. Aarhus University, Nordre Ringgade 1, 8000 Aarhus C, Denmark (AU)
4. Klinikum der Universität München, Campus Großhadern, Marchioninistraße 15, 81377 München, Germany (KUM)
5. Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS), Calle Campezo, 1, 28022 Madrid, Spain
6. Fundació Institut Català de Farmacologia (FICF), Hospital Universitari Vall d'Hebron, Hospital Vall d'Hebron, Passeig de la Vall d'Hebron, 119 - 129, 08035 Barcelona, Spain.
7. Bordeaux Pharmacoepi, Université de Bordeaux, 3 Ter Place de la Victoire, 33000 Bordeaux CEDEX, France (UB)
8. University of Copenhagen (UC), Pharmacoepidemiology Research Collaboration (PRC), Copenhagen, Denmark
9. Witten/Herdecke University, Alfred-Herrhausen-Straße 50, 58448 Witten, Germany (UW/H)

Contact principal investigator Dr. Helga Gardarsdottir: h.gardarsdottir@uu.nl

4 Abstract

Title: 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 3.0– 1 June 2018, EU PAS Register No: 16014. Main author: Dr. H. Gardarsdottir, Universiteit Utrecht, Utrecht, The Netherlands and University Medical Center Utrecht, The Netherlands

Rationale and background: The protocol 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 protocol 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.

Research question and objectives:

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.

Objective 2. The utilization of DOACs in the EU for treatment of NVAF, including the characterization of new DOAC users in NVAF patients.

Objective 3. Prescribers' compliance with recommendations included in sections 4.1, 4.3, 4.4, and 4.5 of the SmPC of each DOAC.

Study design: Three studies will be conducted to answer the research questions listed in our aim: one retrospective cohort study (objective 1) and two descriptive studies (objectives 2 & 3).

Population: The study on prescriber compliance with recommendations (objective 3) includes all DOAC users. The study cohort for objective 1 and 2 consists of new users (≥18 years) of DOACs with non-valvular atrial fibrillation (objective 1 only) from the respective data sources.

Variables:

Objective 1: Major bleeding (haemorrhagic stroke/intracranial bleeding, gastrointestinal bleeding, or other extracranial or unclassified bleeding), DOAC exposure, effect modifiers (age, renal function, BMI) and potential confounders (risk factors for bleeding).

Objective 2**:** Patient characteristics, prevalence of DOAC use, co-morbidities, co-medication use, switching, dose adjustments and treatment duration.

Objective 3: Variables 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.

Data sources: These studies will be performed in the following databases: Mondriaan, Danish Registries, Bavarian Claims database, AOK NORDWEST, BIFAP, SIDIAP, CPRD, and EGB.

Study size: This is a large database study.

Data analysis:

Objective 1: 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.

Objective 2: The analysis will be descriptive and will be conducted stratified by database, individual DOACs, age group, gender, and calendar year.

Objective 3: The analysis will be descriptive and using information on the index date.

Milestones: Final study report and manuscripts will be available 12 months after the signature date (estimated Q4/2017, actual Q2/2018).

5 Amendments and updates

Date	Amendment	Justification	Protocol section
17 March 2017	Dr. Luz M León-Muñoz′ Co-investigator BIFAP Database Mr. Régis Lassalle, Co-investigator/French Claims Database added to the research group Elena Ballarin, Co-investigator, SIDIAP	There are changes in the composition of the research group	3 Responsible parties
02 May 2017	Several sections have been clarified.	Clarification was requested by the researchers.	Several small adjustments have been made. See highlighted changes.
02 May 2017	Version 1.2 was replaced with version 1.3	Version 1.2 (date 17 March 2017) was a working document for the research group during the first steps of the analysis. There are no substantial changes between these two versions.	
09 June 2017	Version 1.4 and 1.5	Both versions were working documents, during the analysis several small inconsistensies were corrected. No substantial changes were made.	Several small adjustments have been made.
16 June 2017 20 June 2017 28 June 2017 7 July 2017 8 February 2018	Version 2.0 Version 2.1 Version 2.2 Version 2.3 Version 2.4	All identified inconsistencies were corrected so that the analyses could be finalized.	Several small adjustments have been made. Timelines were corrected on page 8. Composition of the research group was updated.
1 June 2018	Version 3.0	Remaining inconsistencies were corrected and a final version was prepared. Additional sensitivity analysis objective 1 added, as requested by EMA. Reference to Annex IV was removed (Annex IV not present).	Several small adjustments have been made. Timelines were corrected on page 8.

6 Milestones

Milestone	Planned date
1. Preliminary study plan	Date+1 Months
2. Study protocol	Date+3 Months
3. Study report	Date+12 Months
4. Manuscripts	Date+13 Months
5. Final report	Date+13 Months

Deadlines are based on signature date = 1 September 2016.
Deadlines of milestones were corrected due to the additional time spent on EMA review process and delays due to unforeseen circumstances regarding data and resources availability.

Final deadlines are:

09/02/2018: Interim report (excluding Danish data)
15/06/2018: Final study report (including Danish data)
15/06/2018: Manuscript (European study)
15/06/2018: Manuscript (CNODES collaboration meta-analyses obj 1, not described in this protocol)

7 Rationale and background

The protocol 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 protocol 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.

8 Research question and 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 prevalence of use, 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 Annex I & Annex II).

9 Research methods

Three studies will be conducted to answer the research questions listed in our aim: two descriptive drug utilization studies (objectives 2 & 3) and a retrospective cohort study will be conducted among NVAF patients to assess the risk of major bleeding associated with the use of DOACs and VKAs (objective 1). These studies will be conducted in at least 4 data sources (Table 9.1.). 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 9.1., for database description see section 9.4).

Table 9.1. 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)

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

9.1a Study design

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

9.2a Setting

The study cohort consists of new users (≥18 years) of DOACs (e.g. can have prior use of OACs) with non-valvular atrial fibrillation (NVAF) from the respective data sources (see section 9.4).
To make sure that only patients are selected that receive DOACs for the indication of NVAF, the following methodologies was applied in a hierarchical manner. The method selected for each database is dependent on the availability of data in the data sources.
Order of approach:

1. A linked diagnosis of NVAF to the first prescriptions of the DOAC (BIFAP). If not possible, then:
2. A medical code for NVAF ±3 months around the index date (date of first DOAC prescription/dispensing) in one of the following files;
    a. GP-record (CPRD, BIFAP, SIDIAP, Mondriaan)
    b. Claims-record (AOK Nordwest, Bavarian)
3. A medical code for NVAF prior to index date + 3 months after the index date in case of Hospital-record (DK, EGB)

New users are defined as patients initiating DOACs during the study period (2008-2015) without any use of DOACs for at least 12 months (365 days) prior to the index date. Patients registered in the database less than one year (365 days) before the index date (date of first DOAC prescription) will be excluded. Patients with a history of valvular atrial fibrillation on index date or prior to initiating DOACs will be excluded (see Annex IV for codes). For DOAC and disease codes see Annex I and Annex IV.

9.3a Variables

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

The study population is divided into three mutually exclusive treatment pattern groups: users that continue the initial DOAC until the end of follow-up, users that switch therapy to other D(OAC), and users that discontinue therapy. Follow up of each patient is until switch of therapy, discontinuation or end of study.

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

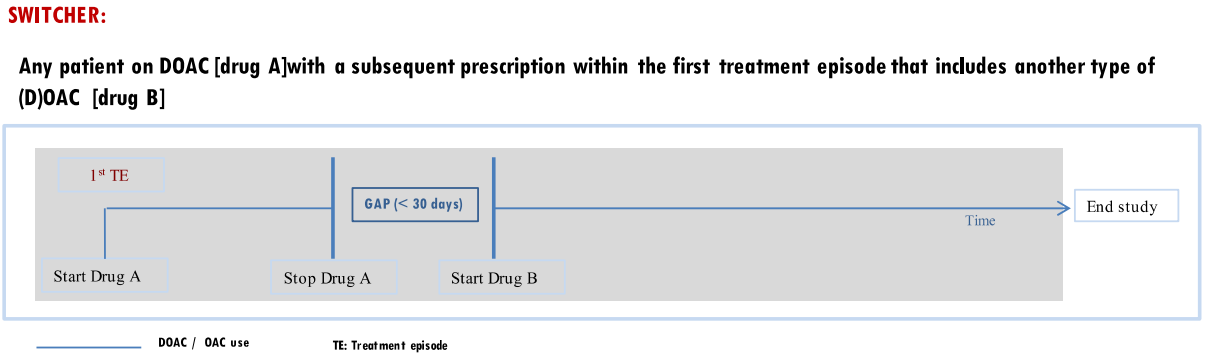
- number of patients,
- patient characteristics (age, gender, low or high body weight [<50kg, 50-100 kg, >100kg] and BMI [<20kgm2, 20-24.9 kg/m2, 25-29.9 kg/m2, 30-34.9 kg/m2, ≥35 kg/m2]
- co-morbidities (chronic kidney disease, hepatic impairment, previous haemorrhagic episodes, and previous cardiovascular events [for codes see table A3.2 [Annex III]) and table A4.2 [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 prescription date of the drug is during the DOAC first treatment episode (see 9.3c Variables, Treatment episodes) (see 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).

Information about the following measurements - weight, BMI and kidney function - will be assessed during the 12 months prior to index date. In case of multiple measurements, the one closest to the index date will be selected.

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 any patient with a subsequent prescription within the

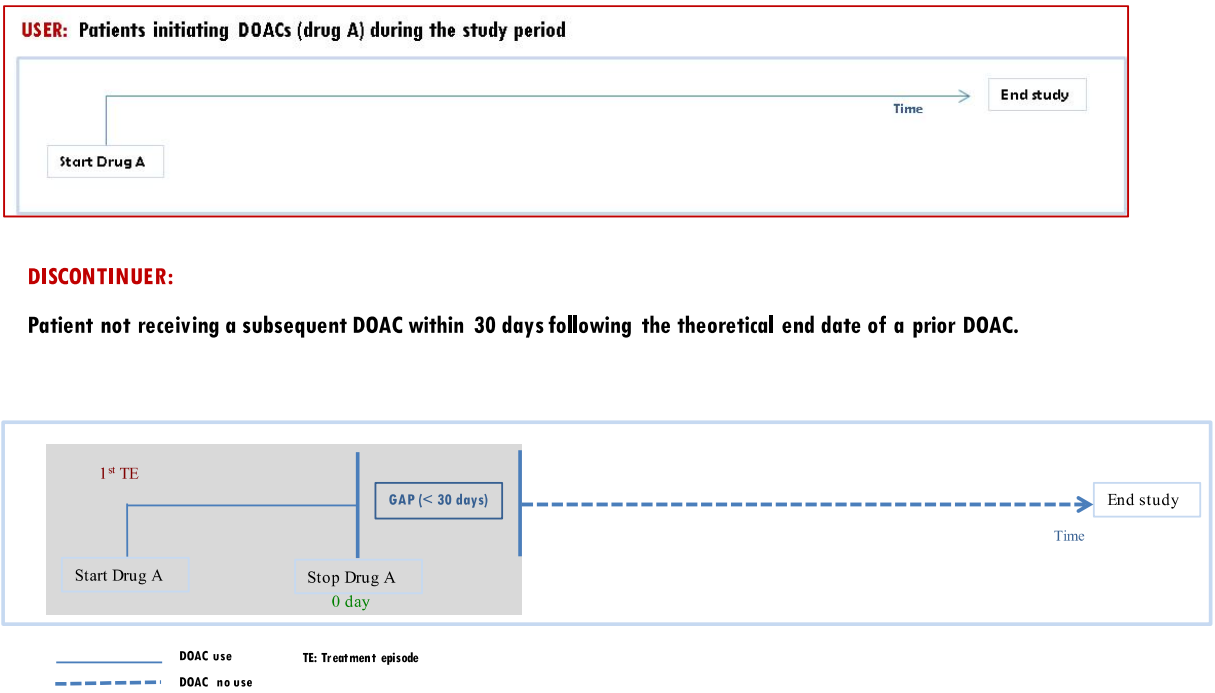
first treatment episode including the permissible gap of 30 days (see 9.3c Variables, Treatment episodes) that includes another type of (D)OAC (at least one prescription of antithrombotic drug (B01AA [VKA], B01AE [direct thrombin inhibitors], or B01AF [direct factor Xa inhibitors] (see Figure 9.1.). Only those that discontinue the use of the initial DOAC while receiving a different type of (D)OACs are considered switchers e.g. these do not receive a second prescription of the initial DOAC (drug A figure 9.1) after start date of the new (D)OAC (drug B, figure 9.1).

Figure 9.1. Switching to another antithrombotic agent



c) *Discontinuation*. Patients will be considered to have discontinued therapy if they do not receive a subsequent DOAC within 30 days following the theoretical end date of a prior DOAC.

Figure 9.2. DOAC usage patterns; users, and discontinuers



d) *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 9.3c Variables, Treatment episodes), or switch of therapy. 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 will be used as a surrogate [15,16]. The date of the last dispensing/prescription plus the estimated duration of the dispensing/prescription plus days remaining from picking up to early 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. Patients not receiving any other prescription or filling of DOAC within 30 days after the theoretical end date of a prior prescription will be considered to have discontinued therapy.).
The gap length is set to 30 days (see 9.3c Variables, Treatment episodes) and a sensitivity analyses will be performed taking into account a gap of 60 days.

d) *Dose adjustments*. Number of users for the different active principles contained in each DOAC tablet (e.g. Eliquis 2.5 mg vs Eliquis 5 mg) will be provided by renal impairment categories (when possible), age and sex categories A dose adjustment is defined as a change from one active principle's strength contained in each tablet to another strength of the same active principle. Information about the laboratory value indicating renal impairment category will be assessed at baseline as well as +/-6 months around the date of dose adjustment. In case of multiple measurements, the measurement closest to the date of dose adjustment will be selected.

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

9.1b Study design

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

9.2b Setting

The study cohort consists of new users (≥18 years) of DOACs from the respective data sources (see Table 9.4.). New users are defined as patients initiating DOACs during the study period (2008-2015) without any use of DOACs for at least 12 months (365 days) prior to the index date. Patients registered in the database less than one year (365 days) before the index date (date of first DOAC prescription) will be excluded.

9.3b Variables

The following outcomes will be reported:
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 Annex III).

We will use the documented ICD/READ/ICPC-coded diagnosis in the databases as a proxy of the indication (see Annex IV). Indications described in the SmPC section 4.1 will be checked according to the following order of approach:

1. A linked indication to the first prescriptions of the DOAC. If not possible, then:
2. A medical code for the indication ±3 months around the index date in one of the following files;
    c. GP-record (CPRD, Bifap, SIDIAP, Mondriaan)
    d. Claims-record (Bavarian)
3. A medical code for the indication prior to index date + 3 months after the index date in case of Hospital-record (DK)

A sensitivity analysis will be performed where indications will be defined as registered any time prior until 3 months after index date (approach step 2). 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 indications (OL).

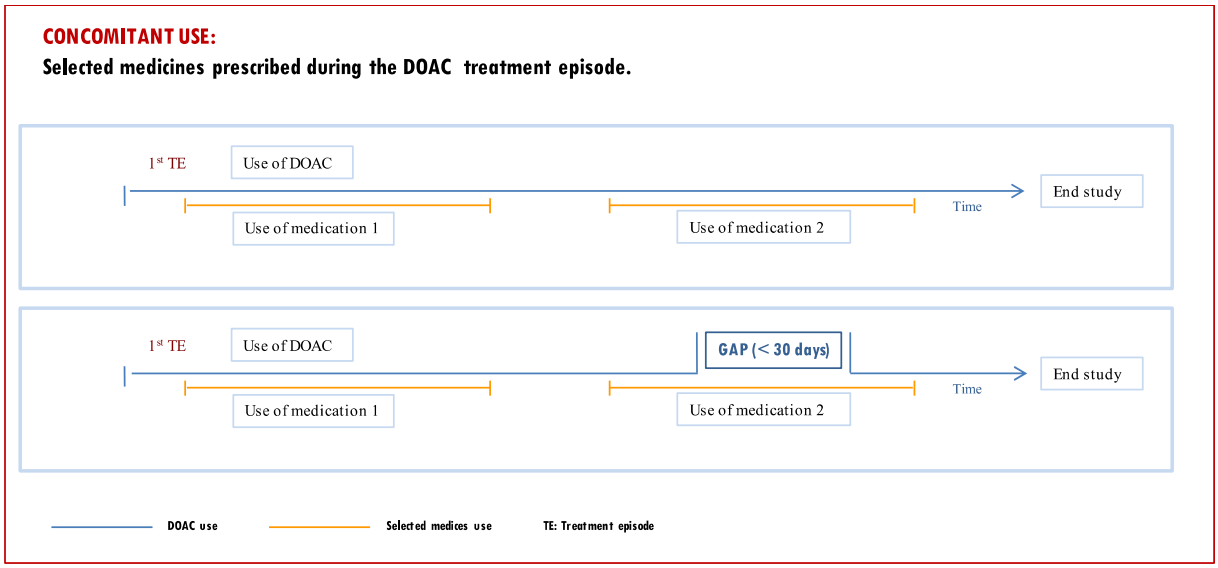
Table 9.2. Indication for use of DOACs (mutually exclusive)

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 /Unknown/Missing (OL)	All indications other than those indicated above, or when there is no indication available

Co-morbidities listed in the SmPC section 4.3 and 4.4 i.e. contraindications, and special warnings and precautions, will be assessed during various time periods prior to the index date, depending on the type of co-morbidity. In addition, we will also assess the registered co-morbidities according to the approach indicated to identify indication for use above ±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 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 Annex III). Use of the medicines listed in the SmPC sections 4.3, 4.4. and 4.5. (see Figure 9.3) will be considered concomitant when date of prescribing is during the DOAC first treatment episode and at baseline. Concomitant use of potential interacting drugs during the DOAC treatment episode will be determined for each individual DOAC.

Figure 9.3. Concomitant use of DOACs and medication listed in SmPC sections 4.3, 4.4 and 4.5



Cohort study (objective 1)

9.1c Study design

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

9.2c Setting

The study population consists of all new (D)OAC users aged ≥18 years and at least one year (365 days) register in the database with a recorded diagnosis of NVAF. To make sure that only patients are selected that receive (D)OACs for the indication of NVAF, the following methodologies will be applied in a hierarchical manner. The method selected for each database is dependent on the availability of data in the data sources.

Order of approach:

1. A linked diagnosis of NVAF to the first prescriptions of the (D)OAC. If not possible, then:
2. A medical code for NVAF ±3 months around the index date in one of the following files.
    a. GP-record (CPRD, Bifap)
    b. Claims-record (AOK Nordwest)
3. A medical code for NVAF prior to index date + 3 months after the index date in case of Hospital-record (DK)

We identified new users of antithrombotic drugs (D)OACs (DOACs and VKAs, see Annex I) with NVAF during 2008-2015. New users were defined as patients initiating DOACs during the study period (2008-2015) without any use of (D)OACs for at least 12 months (365 days) prior to first use during the study period. Patients with a history of valvular atrial fibrillation on or before date of initiating (D)OAC during the study period will be excluded (see 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. When the outcome occurs on the index date, these will be excluded.

9.3c Variables

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 [17].

This includes haemorrhagic stroke/intracranial bleeding, gastrointestinal bleeding, or other extracranial or unclassified bleeding and traumatic intracranial bleeding (see Table A3.1 for codes). Some of these bleeding events will also be assessed individually, such as gastrointestinal bleeding and intracranial haemorrhage. For the purpose of comparison, these outcomes are in line with a recent observational study done in the Danish database [18]. The validity of outcomes has also been assessed and fond reliable in the other data sources [19-27]. The UK Read code system, ICD-9, ICD-10, ICD-10-GM, and ICPC-2 codes will be used to define outcomes (see Annex III for codes).

For the main analysis we will use all available bleeding events (irrespective of hospital admission).

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

Several sensitivity analyses are planned. In CPRD, an additional analysis will be conducted that includes hospital admission events only, rather than all primary care outcome events. In BIFAP, both GI bleeding events and stroke events will be validated.

Post-hoc sensitivity analyses will performed where the outcome definition will be adjusted to exclude outcome events that are unlikely to be genuinely major bleeding events, such as nose bleeds and hematuria (see Annex III Table A3.1.1 for included and excluded codes). Furthermore, an post-hoc analysis will be performed excluding TIAs from the initial definition of our secondary outcome of stroke.

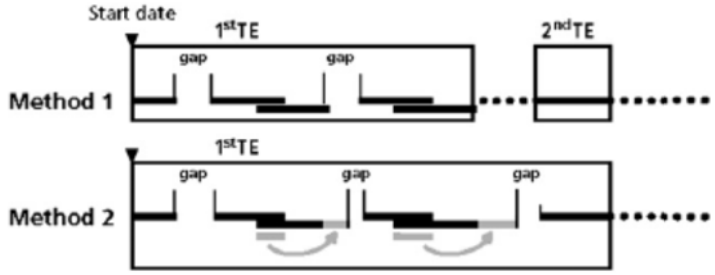
Exposure definition

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.

Assessment of the length of individual (D)OAC prescriptions
We will use a step-wise uniform approach in all databases when assessing exposure duration. The preferred method for calculating the individual prescription duration is by using information on the prescribed number of tablets and the dosage. When information on the prescribed number of tablets and or the dosage is not available we will apply the same method for assessing treatment duration to ensure consistency. A method explored earlier within the Danish database will be used. This method defines duration of use for a single prescription as the median time between prescriptions (individual based and on ATC code) [15,16]. When only 1-3 prescriptions are available for an individual patient or when estimated duration-DDD*number of packages>100, the method of median time between prescriptions cannot be applied. In these cases, the duration will be based on the most frequently occurring estimated prescription duration for the specific drug in the study population (see item 9.3a Variables, c).

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. [28]. 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 9.4., 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 9.4., method 1). In order to facilitate exposure classification, a new row will be created in case a patient switches from one type of (D)OAC to another within a treatment episode (Figure 9.5.). Long periods of current/past use will be cut into periods of 6 months in order to assess time-dependent co-variates.
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 9.4. Constructing drug treatment episodes based on estimated duration of a dispensed prescription and gaps of a defined length



TE: treatment episode

Figure 9.5. 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

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). For the primary analysis, we further stratified according to the strength of the DOAC used.

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; thrombocytopenia, hypertension, history of stroke/TIA, history of major bleeding event, presence of malignancy, concomitant use of medicines that increase bleeding risk (NSAIDs, corticosteroids, SSRI's and antiplatelet drugs), history of pulmonary embolism (PE) or deep venous thrombosis (DVT) and peptic ulcer diseases. Important risk factors considered for ischaemic stroke are: prior stroke/TIA, PE/DVT, hypertension, diabetes mellitus, congestive heart failure and other (cardio)vascular disease (angina, myocardial infarction, coronary heart disease, aortic plaque and peripheral arterial 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 Annex 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 [29]. 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 (various time intervals prior to index date), 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.

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 and BIFAP, 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. Also, in some databases kidney function measurements are not always registered as an absolute value but more indicating if the GFR is larger than a specific value, e.g. above 60 ml/min. In these cases the patient will be defined according to the category closest to the value give, which in case of above 60ml/min would be as normal to mildly reduced.

9.4 Data sources

9.4.1 Database characteristics

Table 9.3. Database Characteristics

	Mondriaan	National Registries Denmark	Bavarian Claims	AOK NORDWEST[3]	BIFAP	SIDIAP	CPRD	EGB
Source population	0.4m	5.5m	10.5m	2.7m	7.5m	7.0m	12.5m	0.7m
Year(s) covered for this study	2012-2015	2008-2015	2008-2015	2008-2015	2008-2015	2009-2015	2008-2015	2013-2015
Type of database	GP prescribing data and pharmacy dispensing data	Dispensing data	Claims database including data for dispensed and reimbursed drugs	Claims database including data for dispensed and reimbursed drugs	General practice prescribing data	General practice prescribing data linked to reimbursed drugs	General practice prescribing data	Claims database including dispensing data
Data available since	1991	1994	2008	2007	2001	2006	1987	2004
Demographic variables available								
Date of registration	Yes	Yes	Yes (first consultation)	Yes	Yes	Yes	Yes	Yes
Date of transferring out	Yes	Yes	Yes (last consultation)	Yes	Yes	Yes	Yes	Yes
Date of birth	DD-MM-YY	MM-YY	MM-YY	MM-YY	MM-YY	MM-YY	MM-YY	MM-YY
Gender	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Drug information available								
Active international coding	ATC	ATC	ATC	ATC	ATC	ATC	BNF	ATC
Product coding	HPK	Varenr	PZN	PZN	CNF	Yes[1]	Product code	CIP-13
Date of prescribing/dispensing	Yes	Yes	Yes (for each prescription the quarter is documented)	Primary care sector: Yes Secondary care sector: Yes (only for a few selected (expensive) compounds, but no (D)OACs prescriptions)	Yes	Yes[3]	Yes	Yes
Quantity prescribed/dispensed	Yes	Yes	Yes (package size)	Yes (package size)	Yes	Yes[4]	Yes	Yes

Table 9.3. Database Characteristics, continued	**Mondriaan**	**National Registries Denmark**	**Bavarian Claims**	**AOK NORDWEST**[3]	**BIFAP**	**SIDIAP**	**CPRD**	**EGB**
Dosing regimen	No	No	No	No	Yes	Yes[2]	Yes	No
Outcome information								
Outpatient primary care diagnosis	ICPC	Yes	ICD-10-GM (for each diagnosis the quarter is documented)	ICD-10-GM (quarterly base)	ICPC-2, ICD-9	ICD-10	ICD-9, ICD-10	ICD-10
Hospital discharge diagnosis	No	ICD-8, ICD-9, ICD-10	No	ICD-10-GM	No	No[5]	ICD-9, ICD-10	No
Laboratory tests	Yes	No	No	No	Yes	Yes	Yes	No
Mortality	Yes	Yes	No	No (incompletely recorded, e.g. no follow-up for patients leaving the AOK)	Yes (no cause of death)	Yes (no cause of death)	Yes	Yes

1 Is registered but not available for research due to confidentiality reasons
2 Only in prescribing data
3 For dispensing: MM/YY
4 Number of reimbursed packages
5 Available for 28% of included population

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.

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).

Bavarian claims database
The Bavarian statutory health insurance physicians' association (KVB) database is based on accounting information of the Bavarian physicians. The KVB processes claims data for all statutorily licensed ambulatory physicians in Bavaria, Germany. This includes ~9000 GPs, 13 000 specialists and 4000 psychotherapists (including both psychological and medical psychotherapists). The database exists since 2001 and covers 84% of the Bavarian population excluding those with private health insurance. It compiles, based on accounting information of Bavarian physicians, data on diagnoses, performed medical services, and drug utilisation of all outpatients on statutory health insurance, which amounts to 10.5 million people. All diagnoses of general practitioners and specialists are documented. In addition, the database contains the age and sex of all patients. All diagnoses and patient characteristics are documented on an individual basis. The database is subdivided quarterly, i.e. for each diagnosis or prescription the quarter is documented, but not the exact date. A patient is documented only in the database if he has a consultation. The patient identifier has been changed in 2008. Therefore, the database allow for tracking of patients for the time period 2008-2015,
Data to evaluate pharmacotherapy were obtained from the corresponding pharmacy claims data. A prescription is recorded in the database only if it is prescribed and filled at the pharmacy. A unique identifier exists in both databases enabling a linkage of data between prescribed drugs and indications. Nevertheless, the linkage is only possible for a particular consultation. If more than one drug has been prescribed and more than one indication were documented at a particular consultation, linkage between drugs and indications has to be assessed manually taken into account indication areas of the prescribed drugs.
The International Statistical Classification of Diseases and Related Health Problems (ICD-10) was used for coding diagnoses and the Anatomical Therapeutic Chemical classification system (ATC) was used for coding drugs.

AOK NORDWEST
The AOK ('Allgemeine Ortskrankenkasse') consisting of several regional AOK units, is the largest provider of a nationwide statutory healthcare insurance in Germany. In the AOK databases, claims data of the primary care sector

(general practitioners and specialists) 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 and drug dispensing data for reimbursed drugs are documented on a daily base 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. In this study, databases of the AOK NORDWEST representing 2.7 million inhabitants in a Western (Westfalen/Lippe) and a Northern part (Schleswig-Holstein) of Germany will be used. For the two German regions covered by the AOK NORDWEST, a population coverage of approximately 24% is reached.

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.

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 7.0 million patients (80% of the Catalan population). SIDIAP has available, for each of the 7.0 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 prescriptions and medications dispensed by the pharmacy offices: since 2005. In this study, dispensing data will be used to assess exposure to drug use.

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 of 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.

Clinical Practice Research Datalink (CPRD 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.

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].

9.4.2 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.

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.

Danish National Registries
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.

Bavarian claims database
The left censoring date is the earliest event that is recorded for an individual patient (prescription or diagnosis) after January 1, 2008.
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.

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.

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.

9.5 Study size

Table 9.4. 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	7.0m	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		1,583
Warfarin (B01AA03)	With NVAF		9,289			920		82,892	475
	All	1,998	1,892	252,247	64,864		0		
Phenprocoumon (B01AA04)	With NVAF			158,916	40,864				
	All	7,909				190,192	85,560		894
Acenocoumarol (B01AA07)	With NVAF					87,530			268
	All								9,208
Fluindione (B01AA12)	With NVAF								2,762
	All	438	23,466	20,319	5,225	4,648	4,126		1447
Dabigatran (B01AE07)	With NVAF		4,978	12,801	3,292	1,627		1,633	434
	All	474	16,085	70,804	18,207	5,854	3,741		2201
Rivaroxaban (B01AF01)	With NVAF			44,606	11,470	1,695		4,896	660
	All	110	8,024	5,738	1,475	1,309	2,065		
Apixaban (B01AF02)	With NVAF			3,615	930	498		2,684	
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) ¥as requested by primary care practitioner

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/Apixaban 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 9.1). 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/incident users.

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

9.6 Data management

9.6.1 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

9.6.2 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 results 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

9.7 Data analysis

9.7a Descriptive study investigating the utilization of DOACs in NVAF patients (Objective 2)

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: <75, 75-79 and ≥80 years [EMA tender technical specifications]), sex (absolute numbers and percentage), co-morbidities (chronic kidney disease by diagnosis codes , see table A3.2, and/or by lab values when available: Normal >80 ml/min, mildly reduced 50-80 ml/min, moderately reduced (CrCl 30-49 ml/min), severely reduced (CrCl 15-29 ml/min), very severely reduced (CrCl <15 ml/min) [definition might slightly differ between databases based on availability], hepatic impairment associated with coagulopathy and clinically relevant (for codes see Table A3.2), previous major hemorrhagic episodes (haemorrhagic stroke, intracranial bleeding, extracranial or unclassified major bleeding, gastrointestinal bleeding, traumatic intracranial bleeding), and previous cardiovascular events (myocardial infarction, angina, coronary heart disease, congestive heart failure, stroke/transient ischemic attack, aortic plaque, peripheral arterial disease, deep vein thrombosis/pulmonary embolism [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). Additionally the use of concomitant medication is analysed during the follow-up in the first treatment episode. The list of relevant PIMP is presented in section Annex III. The number and percentage of users with comorbidity or concomitant medication at baseline will be calculated by sex and age group.

Information about the following measurements - weight, BMI and kidney function - will be assessed during the 12 months prior to index date. In case of multiple measurements, the one closest to the index date will be selected. Co-morbidities will be assessed during various time periods prior to the index date, depending on the type of co-morbidity (see Annex IV).

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 for 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. The analysis will be stratified by sex and age group.
- The *percentage of discontinuation* will be reported. For each individual DOAC a Kaplan-Meier curve for the time until discontinuation will be estimated. Log rank tests will be applied for differences among the individual DOACs and specific subgroups (chronic kidney disease by diagnosis codes, see Table A3.2 age and sex).
- Dose adjustment will be expressed as the *percentage of patients with adjusted dosage as defined in section 9.3a d* (see Table A1.5) for each individual DOACs. The analysis will be stratified by sex and age group and chronic kidney disease by diagnosis codes, see Table A3.2 and LAB values when available: Normal >80 ml/min, mildly reduced 50-80 ml/min, moderately reduced (CrCl 30-49 ml/min), severely reduced (CrCl 15-29 ml/min), very severely reduced (CrCl <15 ml/min) [definition might slightly differ between databases based on availability].
- *Percentage of new DOACs users with any concomitant PIMP* during treatment episodes (see 9.3c Variables, 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 Annex III. This data will be stratified by the number of concomitant interacting drugs prescribed during a treatment episode (Table A3.3. and A3.5.), 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 Annex V).
As the (D)OACs can be prescribed for other indications than NVAF, a sensitivity analysis will be performed where patients with multiple (D)OAC indications will be excluded from the study population. For this analysis all patients with other (D)OAC indications than NVAF in a +/- 3 month period around the first (D)OAC will be excluded.

9.7b Descriptive study investigating prescriber compliance with SmPC recommendations (Objective 3)
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 (SmPC 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).

The analysis will be conducted stratified by:

- database: Mondrian, Danish, Bavarian, BIFAP, SIDIAP and CPRD.
- individual DOACs: dabigatran, rivaroxaban and apixaban.
- age group: <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 [definition might slightly differ between databases based on availability].

Information about the following measurements - weight, BMI and kidney function - will be assessed during the 12 months prior to index date. In case of multiple measurements, the one closest to the index date will be selected. Co-morbidities will be assessed during various time periods prior to the index date, depending on the type of co-morbidity (see Annex IV).

9.7c Cohort study (Objective 1)

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.
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.
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 and past use). Analyses will be stratified by sex, age and the possible effect modifiers (see 9.3c, Effect modifiers (subgroups)).
As the (D)OACs can be prescribed for other indications than NVAF, a sensitivity analysis will be performed where patients with multiple (D)OAC indications will be excluded from the study population. For this analysis all patients with other (D)OAC indications than NVAF in a +/- 3 month period around the first (D)OAC will be excluded.

9.8 Quality control

9.8.1 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.

9.8.2 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 Data management Practice as well national and international guidelines and legislation concerning data-handling and privacy issues.

9.9 Limitations of the research methods

9.9.1 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 9.4.). 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 (See Table 9.3.). 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.

9.9.2 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 channelling 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 9.9.3 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 [19-27]. 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, 30-32].

9.9.3 Methodological study on exposure misclassification

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.

Study 1. Primary non-adherence

Population
The study cohort consists of patients (≥18 years) of (D)OACs from SIDIAP 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.

Study 2. Exposure misclassification based on type of prescriber

Population
The study cohort consists of patients (>18 years) of (D)OACs from 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

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

10 Protection of human subjects
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 contact the principal investigator.

11 Management and reporting of adverse events/adverse reactions
Not applicable, only secondary data will be used.

12 Plans for disseminating and communicating study results
The study results will be disseminated and communicated in accordance with the EMA tender specifications (EMA/2015/27/PH).

13 References

1. Pedersen CB. The Danish Civil Registration System. Scan J Public Health 2011;39:22-25.
2. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scan J Public Health 2011;39:54-57.
3. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scan J Public Health2011;39:30-33.
4. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39:38-41.
5. WHO Collaborating Centre for Drugs Statistics Methodology, Guidelines for ATCclassification and DDD assignment 2015. Oslo, 2015.
6. Jensen VM, Rasmussen AW. Danish Education Registers. Scand J Public Health 2011;39:91-94.
7. Janhsen K. [Public health research with statutory health insurance drug data]. [Article in German] Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2004;47:521-5.
8. Blin P et al. A population database study of outcomes associated with vitamin K antagonists in atrial fibrillation before DOAC.Br J ClinPharmacol 2016; 81: 569-78.
9. Larsen TB et al.Efficacy and safety of dabigatranetexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am CollCardiol. 2013 Jun 4;61(22):2264-73.
10. Larsen TB, Gorst-Rasmussen A,Rasmussen LH, Skjøth F, Rosenzweig M, Lip GY.Bleeding events among new starters and switchers to dabigatran compared with warfarin in atrial fibrillation. Am J Med. 2014 Jul;127(7):650-656.e5.
11. Eikelboom JW et al. Risk of bleeding with 2 doses of Dabiatran compared with warfarin in older and younger patients with atrial fibrillation: An analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123;2363-2372.
12. van den Ham HA et al. The patterns of anticoagulation control and the risk of stroke, bleeding and mortality in patients with non-valvular atrial fibrillation. J ThrombHaeomst 2013;11:107-15.
13. Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009;361 (12):1139-5.
14. Patel MR et al. Rivaroxaban versus warfarin in patients with atrial fibrillatioin. NEJM2011;365(10):883-91.
15. Wimberley T, Støvring H, Sørensen HJ, Horsdal HT, MacCabe JH, Gasse C. Predictors of treatment resistance in patients with schizophrenia: a population-based cohort study. Lancet Psychiatry. 2016 Apr;3(4):358-66. doi: 10.1016/S2215-0366(15)00575-1. Erratum in: Lancet Psychiatry. 2016 Apr;3(4):320. PubMed PMID: 26922475.
16. Schuerch M, Gasse C, Robinson NJ, Alvarez Y, Walls R, Mors O, Christensen J,Hesse U, de Groot M, Schlienger R, Reynolds R, Klungel O, de Vries F. Impact of varying outcomes and definitions of suicidality on the associations of antiepileptic drugs and suicidality: comparisons from UK Clinical Practice Research Datalink (CPRD) and Danish national registries (DNR). Pharmacoepidemiol Drug Saf. 2016 Mar;25 Suppl 1:142-55. doi: 10.1002/pds.3928. PubMed PMID: 27038360.
17. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of thrombosis and haemostasis. 2005;3(4):692-694
18. Larsen TB, Skjoth F, Nielsen PB, Kjaeldgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: Propensity weighted nationwide cohort study. *BMJ*. 2016;353:i3189. doi: 10.1136/bmj.i3189 [doi].
19. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ.Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 2010;69:4-14.
20. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. The British Journal of General Practice 2010;60:e128.

21. Herrett E, Gallagher A, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827-36.
22. Hartmann J, Weidmann C, Biehle R. [Validation of SHI Claims Data Exemplified by Gender-specific Diagnoses]. [Article in German] Gesundheitswesen. 2016;78:e53-e58.
23. Schmedt N, Gil M, Martin E, Requena G, Bezemer I, De Berardis G, et al. Harmonization of Outcome Extraction for Ischemic and Hemorrhagic Stroke Across Data Sources in the SAFEGUARD Project.
24. Pharmacoepidemiology and Drug Safety, 2013; 22: (Suppl. 1): 1–521 DOI: 10.1002/pds.3512 http://www.safeguard-diabetes.org/?q=system/files/private/Harmonization_Ischemic_Hemorrhagic_Stroke_ICPE-2013_Poster.pdf
25. Patricia García-Poza, PharmD; Francisco J de Abajo, MD, PhD, MPH; Miguel J. Gil, MD, PhD, MPH ; Ana Chacón, MD, PhD, Verónica Bryant, NP; Luis A. García-Rodríguez MD, MSc. Risk of nonfatal ischemic stroke associated with non-steroidal antiinflammatory drugs and acetaminophem: a nested case-control study. J Thromb Haemost. 2015;13(5):708-18.
26. Ruigomez A et al. Ascertainment of acute liver injury in two European primary care databases. Eur J ClinPharmacol2014 Oct;70(10):1227-35.
27. Schmidt M et al. The Danish National Patient Registry: a review of content, data quality, and research potential. ClinEpidemiol 2015;7:449-490.
28. Gardarsdottir H, Souverein PC, Egberts ACG, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap. J ClinEpidemiol 2010;63(4):422-7.
29. Ude R, Maitland-van der Zee AH, Egberts TC, den Breeijen JH, Leufkens HG, van Solinge WW, De Bruin ML. Validity of diagnostic codes and laboratory measurements to identify patients with idiopathic acute liver injury in a hospital database. Pharmacoepidemiol Drug Saf. 2016 Mar;25 Suppl 1:21-8
30. Gasse C et al. Drug interactions and risk of acute bleeding leading to hospitalisation or death in patients with chronic atrial fibrillation treated with warfarin. ThrombHaemost. 2005 Sep;94(3):537-43.
31. Schmiedl S, Rottenkolber M, et al. Bleeding complications and liver injuries during phenprocoumon treatment: a multicentre prospective observational study in internal medicine departments. DtschArztebl Int. 2013 Apr;110(14):244-52.
32. Schmiedl S, Rottenkolber M et al. Self-medication with over-the-counter and prescribed drugs causing adverse-drug-reaction-related hospital admissions: results of a prospective, long-term multi-centre study. Drug Saf. 2014 Apr;37(4):225-35.

Annexes

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

Table A1.1. 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
	Fluindione	**B01AA12**	
DOAC	*Direct factor Xa inhibitors*	***B01AF***	
	Rivaroxaban	**B01AF01**	20 mg
	Apixaban	**B01AF02**	10 mg
	Direct thrombin inhibitors	***B01AE***	
	Dabigatran	**B01AE07**	300 mg

Table A1.2. 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 A1.3. 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 A1.4. 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	Time window for identification
Myocardial Infarction /Angina (MI-A)	I20, I21, I22, I23, I25.2	410–410.99	410.x, 412.x, 413.x, 429.7	I20, I21, I22, I23, I25.2	K74, K75, K76	As described in section 9.2a (p10), 9.3b (p12) and 9.2c (p14)
Prevention after Hip/Knee replacement (PHK)	Z96.64, Z96.65		V43.64, V43.65 Procedure codes (OPS): 81.51, 81.52, 81.53, 81.54, 81.55	Z96.64, Z96.65, 5-820[iv] 5-821 5-822 5-823	L54.25, A89.3	As described in section 9.2a (p10), 9.3b (p12) and 9.2c (p14)
Non-valvular atrial fibrillation (NVAF) *	I48	427.93, 427.94	427.3x	I48 (including atrial flutter)	K78 (including atrial flutter)	As described in section 9.2a (p10), 9.3b (p12) and 9.2c (p14)
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults[iii]	I80.1, I80.2, I82.4, I82.5, I26	DVT: 451 PE: 450.9	415.1., 451.x, 451.81, 453.4, 453.5,	I80.1, I80.2, I82.4, I82.5, PE: I26	ICPC codes extension in BIFAP[i] K94.01, K94.15 K93 K93.1 K93.2 K93.3 K93.4 – K93.6	As described in section 9.2a (p10), 9.3b (p12) and 9.2c (p14)
Other/unknown/missing indications (OL)						As described in section 9.2a (p10), 9.3b (p12) and 9.2c (p14)

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. iv) OPS codes * Excluding patients with valvular atrial fibrillation (see table 4.1 for codes).

Table A1.5. 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

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

Table A2.1. 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. o presence of current or recent gastrointestinal ulceration o malignant neoplasms at high risk of bleeding, o recent brain or spinal injury, o ophthalmic surgery, o recent intracranial haemorrhage, o known or suspected oesophageal varices, o arteriovenous malformations, o 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 ketoconazole, cyclosporine, itraconazole and dronedarone • Prosthetic heart valves requiring anticoagulant treatment
APIXABAN		
RIBAROXABAN		• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. • Concomitant treatment of Acute Coronary Syndrome

		(ACS) with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) (see section 4.4).

Table A2.2. 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) exceptions
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 enzymes > 2 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 mL/min) 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 or total bilirubin ≥ 1.5 x ULN were excluded in clinical trials. Use of thrombolytic agents for the treatment of acute ischemic stroke Patients with prosthetic heart valves Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary Embolectomy
RIBAROXABAN	Surgery and invasive procedures (to stop therapy) Interaction with other medicinal products affecting	Severe renal creatinine clearance 15 - 29 ml/min with caution Moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations with caution

	haemostasis and other pharmacodynamic interactions (see 4.5)	Contraindicated for the treatment of ACS in patients with a prior stroke or TIA

Table A2.3. 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	**Transporter interaction: P-gp** **strong P-gp inhibitor co-medication CONTRAINDICATED** 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

	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)	

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 A3.1. ICD and ICPC codes for major bleeding.

Outcome	ICD-10	ICD-8	ICD-9-CM	ICD-10-GM	ICPC	Time window for identification
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	I60 I61 I62	K90.5- K90.8 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	Cohort study: = During follow up as outcome Descriptive studies: = 6 months prior to index date
Extracranial or unclassified major bleeding	D62, J94.2, H11.3, H31.3, H35.6, H43.1, N95.0, R04, R31, R58, M25.0		285.1, 511.1, 511.89, 372.72, 363.6, 362.81, 379.23, 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, N95.0, R04, R31, R58, M25.0	A10.1 (bleeding) F75.4, F75.9, F75.12, L99.14, R06.1, R06.2, R06.3, R24.1, U06.1, U06.3, X12.1, X12.3, X12.4	Cohort study: = During follow up as outcome Descriptive studies: = 6 months prior to index date
Gastrointestinal bleeding[ii]	I85, K22.6, K22.8, 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, K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K.29.71, K29.81, K29.91, K31.8 (not in DK), K62.5, K66.01, K92.0, K92.1, K92.2, K66.1 K57.01, K57.11, K57.03, K57.13, K57.21, K57.31,	##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;	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, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9,	I85, K22.6, K22.8, 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, K31.82 K55.22, K57.01, K57.11, K57.03, K57.13, K57.21, K57.31, K57.23, K57.33, K57.41, K57.51, K57.43, K57.53, K57.81, K57.91, K57.83, K57.93, K62.5, K92.0, K92.1, K92.2, K66.1	No specific code for GI bleeding D14 (haematemesis) D15 (melaena) D16 (rectal bleeding) D84, D85	Cohort study: = During follow up as outcome Descriptive studies: = 6 months prior to index date

	K57.23, K57.33, K55.2, K57.41, K57.51, K57.43, K57.53, K57.81, K57.91, K57.83, K57.93					
Traumatic intracranial bleeding	S06.3, S06.4, S06.5, S06.6, S06.8	S06.3, S06.4, S06.5, S06.6	852.0, 852.1, 852.2, 852.3, 852.4, 852.5, 853.0, 853.1800.1-8, 801.1-8,	S06.33, S06.34, S06.38, S06.4, S06.5, S06.6, S06.8	K90.22. K90.23, K90.25, K990.26, K90.27	Cohort study: = During follow up as outcome Descriptive studies: = 6 months prior to index date
Secondary outcome						
Cerebral infarction[iii]	I63	430-434; 436	433.x1, 434.01, 434.11, 434.91	I63	ICPC codes extension in BIFAP[i] K90.3-EMBOLISMO (ARTERIAL) CEREBRAL (ICTUS) K90.9 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	Cohort study: = During follow up as outcome Descriptive studies: = 6 months prior to index date
Stroke (not specified as haemorrhage or infarction) and TIA	I64, G45		430. 431, 432, 433, 434, 435	I64, G45	ICPC codes extension in BIFAP[i] K90.1-ACCIDENTE CEREBROVASCULAR NC K90.2-CONVULSIONES	Cohort study: = During follow up as outcome Descriptive studies: = 6 months prior to

					POR APOLEJIA K90.19-ACCIDENTE CEREBROVASCULAR/ICTUS/ACV (EXC. AIT) K91.8-SECUELA/S DE ICTUS/ACV K89	index date

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 A3.1.1 Posthoc sensitivity analysis of ICD and ICPC codes for major bleeding, excluding probable non-major bleeding codes.

Extracranial or unclassified major bleeding

ICD10		**ICD9**		**ICD-10 GM**	**ICPC_BIFAP**
D62	**Acute posthemorrhagic anemia**	**285.1**	**Acute posthemorrhagic anemia**	**D62**	
J94.2	**Hemothorax**	511.1	With effusion, with mention of a bacterial cause other than tuberculosis	**J94.2**	A10.1
		511.89	Other specified forms of effusion, except tuberculous		F75.4
H11.3	Conjunctival hemorrhage	372.72	Conjunctival hemorrhage	H11.3	F75.9
H31.3	**Choroidal hemorrhage and rupture**	**363.6**	**Choroidal hemorrhage and rupture**	**H31.3**	**F75.12**
H35.6	**Retinal hemorrhage**	**362.81**	**Retinal hemorrhage**	**H35.6**	**L99.14**
H43.1	**Vitreous hemorrhage**	**379.23**	**Vitreous hemorrhage**	**H43.1**	R06.1
N95.0	Postmenopausal bleeding	627.1	Postmenopausal bleeding	N95.0	R06.2
R04	Hemorrhage form respiratory passages	784.7	Epistaxis	R04	R06.3
		784.8	Hemorrhage from throat		R24.1
		786.3	Hemoptysis		U06.1
R31	Hematuria	599.7	Hematuria	R31	U06.3
R58	Hemorrhage, not elsewhere classified	459.0	Hemorrhage, unspecified	R58	X12.1
		596.7	Hemorrhage into bladder wall		X12.3
M25.0	**Hemarthrosis**	**719.1**	**Hemarthrosis**	**M25.0**	X12.4

Codes in bold are retained, other codes are excluded as outcome event codes

Table A3.2. Codes for Contraindications according to the SmPC section 4.3.- Clinical conditions

Contraindications	ICD-10	ICD-8	ICD-9-CM	ICD-10-GM	ICPC	Time window for identification	Comment
Active clinically significant bleeding	See table A3.1					Active=within 6 weeks prior to index prescription	
	Risk factors for major bleeding						
Gastrointestinal ulceration	K22; K25-K28	530.91; 530.98; 531-534;	530.2, 531.x–534.x	K22.1, K25-K28	D85 D86	= 6 months prior to index date	
Malignant neoplasms	C00-C97 excluding C43, C44	140-194; Excluding: 172, 173 195-199 200-207	140.x–209.x, Excluding: 172, 173	C00-C97 excluding C43, C44	T71, D76, Y77, U77, U76, U75, R84, D75, D74, A79, Y78, T73, N74, B74, B74, S77, R85, D77, L71, U79, K72, H75, F74, B72, B73, D78, K99, W72, X76, X77	= 6 months prior to index date	
Brain or spinal injury	S06.x, S14, S24, S34, T09.3, T09.4	N850, N851, N852, N853, N854, N950-N959	850, 851, 852, 853, 854, 800.1-8, 801.1-8, 952	S06.x, S14, S24, S34, T09.3, T09.4	N79, N80. N81	Recent= 6 months prior to index date	.
Esophagitis, gastritis of gartoesophageal reflux	K20, K21, K29		530.1, 530.81, 535		D84.02, D84.03, D87.1	Known or suspected = ever before index date	
Oesophageal varices	I85	456.0	456.0, 456.1, 456.2	I85	K99.18	Known or suspected = ever before index date	
Arteriovenous malformations	Q20-Q28	747, 747.1, 747.2, 747.3, 747.4, 747.5, 747.6,747.8 , 747.9	745, 746, 747	Q20-Q28		= ever before index date	
vascular aneurysms	I25.4, I28.1,	437, 441, 442,	414.11, 417.1, 437.3,	I25.4, I28.1, I67.1, I71,		= ever before	

Contraindications	ICD-10	ICD-8	ICD-9-CM	ICD-10-GM	ICPC	Time window for identification	Comment
or major intraspinal or intracerebral vascular abnormalities	I67.1, I71, I72, I79.0		441, 442	I72, I79.0		index date	
Prosthetic hearth valves	Z95.2, Z95.3 Z95.4	Y30	V42.2, V43.3	Z95.2, Z95.3 Z95.4		= ever before index date	
Hepatic impairment associated with coagulopathy and clinically relevant bleeding risk (moderate/severe impairment) [ii]	B15.0, B16.0, B16.2, B19.0, I85, K70.4, K72, K76.6	571, 563 571; 573.01; 573.04 070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00; 456.10	070.0, 070.01, 070.20, 070.21, 070.30, 070.31, 070.6, 456.0, 456.1, 456.21, 570, 572.2, 572.3, 572.8	B15.0, B16.0, B16.2, B19.0, I85, K70.4, K72, K76.6	D97.3, D97.5, D97.12, K99.19, K99.19	= ever before index date	
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, N18.9 N19, Q61, Z94.0	(Charlson Index) 403; 404; 580-584; 590.09	403.01 403.11 403.91 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 580.8, 581, 582, 585.3, 584, 585.5, 585.5, 585.6, 585.9, 586, 588, 590.1, 590.20, 590.8, 753.1 V42.0	I12 I13 N00 N01 N03 N04 N05 N07 N08, N10, N11, N12, N14, N17, N18.4, N18.5, N18.9 N19, Q61, Z94.0	U99.01 ICPC codes extension in BIFAP[i] U99.10-INSUFICIENCIA RENAL CRONICA U99.9-INSUFICIENCIA RENAL AGUDA	= 12 months prior to index date	

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) Reference Thygesen S et al. *BMC Medical Research Methodology 2011* **DOI:** 10.1186/1471-2288-11-83

Table A3.3. 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	

ATC	Drug	Comment
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	
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 A3.4. 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	ICD-10-GM	ICPC	Time window for identification
Chronic and acute kidney disease	See Table A3.2 (ever before index date)					
Hepatic impairment (mild)[ii]	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0		070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.59, 571.0-6, 571.8, 571.9, 573.3	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0	D72.11, D72.12, D97	= ever before index date
Stroke/TIA	I63, I64, G45	430-438	433.xx 434.xx 436.xx V12.54, 435.xx	I63, I64, G45	K90, K89	= ever before index date
DVT, PE	I80.1, I80.2, I82.4, I82.5 I26	DVT: 451 PE: 450.9	451.1x, 451.81, 415.1x, 453.4, 453.5	I80.1, I80.2, I80.4, I82.4, I82.5 I26	K94.01, K94.14, K93	= 6 months prior to index date
Alcohol	E52, F10, G31.2, G62.1, G72.1 I42.6, K29.2, K70, K86.0, L278A (only in DK), O35.4, T51 Z71.4 Z72.1	303	265, 303.00, 303.01, 303.02, 303.90, 303.91, 303.92, 305.00, 305.01, 305.02, 357.5, 425.5, 535.3, 571.1, 571.2, 571.3, 655.4, 980	E52.9, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, T51	P15, P16,	= ever before index date
Any malignancy, including lymphoma and leukaemia and metastatic solid tumour, except non-melanoma carcinoma of the skin	See Table A3.2. (6 months prior to index date)					
Gastrointestinal Ulceration	See Table A3.2. (6 months prior to index date)					
Thrombocytopenia	D69.1, D69.3, D69.4, D69.41, D69.42, D69.49, D69.5, D69.51, D69.59, D69.6 D82.0	287.0, 287.1,287.3, 287.9	287 ,287.1,287.3, 287.30, 287.31 , 287.32,287.33, 287.39, 287.4, 287.41, 287.49, 287.5, 279.12	D69.1, D69.3, D69.4, D69.5, D69.6 D82.0	B83, K99	= 6 months prior to index date
Congenital or	D65-D69		286.x	D65-69		= ever before index

acquired coagulation disorders						date
Major trauma [iii)]	S02.0, S02.1, S02.7, S04.0, S06.0, S06.3-S06.9, S07, S11.0 S11.2, S12, S12.8, S14, S15, S17, S22.2, S22.4, S22.5, S24, S25, S26, S27.3, S27.4, S27.9, S28, S32, S34, S35, S36, S37.0, S38, S42.21, S42.31, S42.41, S48, S57, S58, S67, S68, S72, S75.0, S75.1, S75.2, S77, S78, S82.11, S82.8, S82.84, S82.85, S85, S88, S98, S27.0, S27.1, S27.3, S70-72	E800-E807, E810-E819 E820-E823 E825-E827 E830-E838 E840-E845 N850-N854 N860-N869 N870-N879 N900-N907	800.x, 801.x, 803.x, 804.x, 805.x, 806.x, 807.03-807.08, 807.13-807.18, 807.2, 807.3, 807.4, 807.5, 807.6, 808.x, 812.1x, 812.3x, 812.5x, 813.1x, 813.3x, 813.5x, 813.9x, 820.x, 821.x, 823.1x, 823.3x, 824.5, 824.7, 850.2, 850.3, 850.4, 851.x, 852.x, 853.x, 854.x, 860.x, 861.x, 862.8, 862.9, 863.x, 864.x, 865.x, 866.x, 874.1x, 874.5, 877.x, 896.x, 897.x, 900.x, 901.x, 902.x, 904.0, 904.1, 904.2, 904.3, 904.4x, 904.5x, 925.x, 926.x, 927.x, 928.x, 929.x, 950.3, 952.x	S02.0, S02.1, S02.7, S04.0, S06.0, S06.3-S06.9, S07, S11.0 S11.2, S12, S12.8, S14, S15, S17, S22.2, S22.4, S22.5, S24, S25, S26, S27.3, S27.4, S27.9, S28, S32, S34, S35, S36, S37.0, S38, S42.21, S42.31, S42.41, S48, S57, S58, S67, S68, S72, S75.0, S75.1, S75.2, S77, S78, S82.11, S82.8, S82.84, S82.85, S85, S88, S98, S27.0, S27.1, S27.3, S70-72	L72, L75, L73, N79, A80, A81, F79, N81	= 6 months prior to index date
vascular retinopathy	H35.0	377.0	362.1	H35.0	F83	= 6 months prior to index date
Bacterial endocarditis	I33.0	421.0	421.0	I33.0	K70, K71 ICPC codes extension in BIFAP[i] K70.1-AGUDO Y SUBAGUDO ENDOCARDITIS	= 6 months prior to index date

					K70.4-ENDOCARD. (AGUD.) (SUBA.) NO REUMATICA K71.5- ENDOCARD. (AGUD.) (SUBA.) REUMATICA (CRON./AG.)	
Bronchiectasis or history of pulmonary bleeding	J47 Q33.4 R04.2 R04.8	518 783.1	494 748.61 786.3 786.30 786.39	J47 Q33.4 R04.2 R04.8	R24	= ever before index date
prosthetic heart valves	See Table A3.2. (ever before index date)					
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	= 6 months prior to index date

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) Reference Thygesent S et al. *BMC Medical Research Methodology 2011* **DOI:** 10.1186/1471-2288-11-83. Iii) Reference Sears J et al. J Occup Rehabil 2015;25:742-751.

Table A3.5. 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	
J05AX66	dasabuvir, ombitasvir, paritaprevir and ritonavir	
J01FA09	clarithromycin	
Anticoagulants and antiplatelet aggregation medicinal products which may increase the risk of bleeding		

ATC	Drug	Comment
when used concomitantly		
See Table A3.3.		
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	

Annex IV: Information about codes for the Cohort study

Table A4.1. ICD and ICPC codes used to identify the study population.

Study population	ICD-10-DK	ICD-8- DK	ICD-9-CM	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	I05.0, I05.1, I05.2, I05.8, I05.9, I06, I08, I34, I35 Z95.2, Z95.3, Z95.4,	424.0, 424.1, 424.1, 394, 395, 396 494.0, 424.1	394.0, 394.1, 394.2, 394.9, 395, 396, 424, V42.2, V43.3	I05.0, I05.1, I05.2, I05.8, I05.9, Z95.2, Z95.3, Z95.4, I06, I08, I34, I35	K71, K83	

Table A4.2. 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	Time window for identification
Conditions						
Major Bleeding	See table A3.1 (ever before index date)					
Hypertension	See below (risk factors for ischaemic stroke)					
Stroke/TIA	See Table A3.4.(ever before index date)					
DVT, PE	See Table A3.4.(ever before index date)					
Alcohol	See Table A3.4.(ever before index date)					
Any malignancy, including lymphoma and leukaemia and metastatic solid tumour, except malignant neoplasm of the skin	See Table A3.2.(six months before index date)					
Gastrointestinal ulcer	See Table A3.2. (ever before index date)					
Thrombocytopenia	See Table A3.4. (6 months before index date)					
Hepatic impairment	See table A3.2 for moderate/severe impairment and A3.4 for mild impairment.					

Risk factors for ischaemic stroke	ICD-10-DK	ICD-8- DK	ICD-9-CM (2)	ICD-10-GM	ICPC	Time window for identification
Conditions						= ever before index date
Stroke/TIA	See table A3.4 (ever before index date)					
DVT, PE	See table A3.4 (ever before index date)					
Hypertension	I10, I11, I12, I13, I15	400-404	401-405	I10, I11, I12, I13, I15	K86, K87	= 6 months prior to index date
Congestive heart failure	I11.0; I13.0; I13.2; I42.0; I50 ATC: C03C	782.49	402.01, 402.11, 402.91, 428.x, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93	I11.0, I13.0, I13.2, I42.0, I50	K77, K87	= ever before index date
Diabetes*	E10-E14	249, 250	250, 357.2, 362.0,	E10- E14	F83, F92, L17, S97, T89, T90	= ever before index date

Risk factors for ischaemic stroke	ICD-10-DK	ICD-8- DK	ICD-9-CM (2)	ICD-10-GM	ICPC	Time window for identification
	ATC: A10					
Other cardiovascular disease - Coronary heart disease (MI/Angina), atherosclerosisþaortic plaque, peripheral vascular disease	I20, I21, I22, I23, I24, I25, I65, I66, I70.0, I70.2, I73.9	413, 410–410.99, 420-429 (Other heart diseases) 40.0 Arteriosclerosis of aorta; 440.2 Arteriosclerosis of t	410, 411, 413, 414, 429.7 433, 434, 440.0, 440.2 443.9	I20, I21, I22, I23, I24, I25, I65, I66, I70.0, I70.2, I73.9	K76, K75, K74,	= ever before index date

* besides a clinical diagnoses for diabetes a patient is also able to get marked as somebody with the disease when they have a prescription for antidiabetic drugs in the 6 months before index date. Codes for the prescriptions can be found in A4.3.

Table A4.3. ATC codes for risk factors - Medication

ATC	Drug	Comment
M01A	NSAIDs	
N06AB	SSRIs	
H02	Corticosteroids	
B01AC	Antiplatelet drugs	
A10	Antidiabetic drugs	
COMBINED GROUP	ANTIHYPERTENSIVES	
C02AC05	Moxonidin	
C02CA04	Doxazosin	
C03	Diuretics	
C07	Beta blocking agents	
C08	Calcium channel blockers	
C09A	ACE inhibitors	
C09C	Angiotensin II antagonists	

* Reference: Treatment of hypertension in DK:https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/hjerte-kar/tilstande-og-sygdomme/oevrige-sygdomme/hypertension/

Annex V: Output/Results tables

Output sheets (template) are available on request. Please contact the principal investigator.