NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Post-Authorization Safety Study (PASS): Investigating the occurrence of major bleedings in real life, in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone compared against patients on warfarin and dronedarone.
Protocol number	B0661075
Protocol version identifier	1
Date of last version of protocol	06 April 2016
European Union (EU) Post Authorisation Study (PAS) register number	Study not registered
Active substance	B01AA03 - warfarin B01AF02 - apixaban C01BD07 - dronedarone
Medicinal product	Warfarin, Eliquis, Multaq
Product reference	EU/1/11/691/001-015

Procedure number	European Medicines Agency(EMEA)/H/C/002148
Marketing Authorisation Holder (MAH)	Bristol-Myers Squibb/Pfizer EEIG
Joint PASS	No
Research question and objectives	*Research question:* What is the occurrence of bleedings and mortality in real life, in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone compared against patients on warfarin and dronedarone? *Primary objective:* To compare the occurrence of major bleedings in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.
Country(-ies) of study	Sweden
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
AF	Atrial Fibrillation
ATC	Anatomical Therapeutic Chemical Classification System
BMS	Bristol-Myers Squibb
CHADS2	Congestive heart failure, Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication), Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism
CHA2DS2VASc	Congestive heart failure, Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication), Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism, Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque), Age 65–74 years, Sex category (i.e. female sex)
COPD	Chronic Obstructive Pulmonary Disease
eGFR	Estimated Glomerular Filtration Rate
EMEA	European Medicines Agency
EU	European Union
GPP	Good Pharmacoepidemiology Practices
HAS-BLED	Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol
ICD-10	10th revision of the International Classification of Diseases System
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
MPR	Medication Possession Ratio
NOAC	Novel Oral Anticoagulant
NI	Non-Interventional
PAS	Post Authorisation Study
PASS	Post-Authorisation Safety Study
SAP	Statistical Analysis Plan
SPC	Summary of Product Characteristics

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
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Leif Friberg, MD PhD	Associate professor, senior consultant cardiologist	Karolinska Institutet	Friberg Research AB Storskogsvägen 5, 16765 Bromma, Sweden

Country Coordinating Investigators

Not applicable.

3. ABSTRACT

Title: Investigation of the occurrence of major bleedings in real life, in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone compared against patients on warfarin and dronedarone.

Final version dated: 06 April 2016

Authors

Angelo Modica, Senior Medical Advisor CV/Meta, Medical GIP and Health & Value, Pfizer AB

Leif Friberg, Associate Professor, Senior Consultant, Karolinska Institutet

Rationale and background

Swedish patients with paroxysmal AF are frequently treated with dronedarone as a way to prevent the occurrence of attacks of AF. Dabigatran and rivaroxaban are not recommended in combination with dronedarone, according to their respective Summary of Product Characteristics (SPC), as a result of their pharmacokinetic profile. Dronedarone is a strong P-glycoprotein
(P-gp) inhibitor with a potential to increase the bioavailability of dabigatran and rivaroxaban. The SPC of apixaban does not give any recommendation against combinatory treatment with dronedarone. Although the interaction with dronedarone has not been tested, from a theoretical point of view there is no contraindication to combine apixaban with dronedarone since dronedarone only inhibits CYP3A4 moderately. Nevertheless, there are hospitals in Sweden using the combination of apixaban and dronedarone in patients while others have decided to continue using warfarin in combination with dronedarone until there are some re-assuring data with apixaban in combination with dronedarone. We aim to investigate the occurrence of major bleeding among patients treated with dronedarone in combination with warfarin or apixaban in a real-life setting.

This is a real-world outcomes data study that will contribute to an increased knowledge about the appropriate use of apixaban in combination with dronedarone in patients with paroxysmal AF.

Research question and objectives

Research question

What is the occurrence of bleedings and mortality in real life, in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone compared against patients on warfarin and dronedarone?

Objectives

Primary objective: To compare the occurrence of major bleedings in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Secondary objective: To compare the occurrence of intracranial haemorrhage in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Secondary objective: To compare the occurrence of major gastrointestinal bleedings in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Secondary objective: To compare the occurrence of all-cause mortality in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Exploratory objective: To compare the occurrence of bleeding-related mortality in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Study design and data sources

A retrospective cohort study using national register linkage data. Data from the following registers will be extracted and linked:

- Dispensed Drug register: [1] Dispensing date and dosing for prescribed drugs. Data will be extracted for the time-period from the start of the register July 01, 2005 until June 30, 2016.

- Patient register: [2] Information on patient demographics, comorbidity and previous and incident events (e.g. major bleedings). Data will be extracted from 1997 until the end of 2015. The reason for choosing 1997 as the starting point is that the current version of the International Classification of Diseases (ICD-10) was introduced in Sweden in that year. Diagnoses given earlier than 1997, which has not generated new contacts since then, is not likely to be clinically relevant. Besides starting 1997 makes translation of diagnostic codes between ICD-9 and ICD-10 unnecessary. The reason for terminating harvesting of data at the end of 2015 is due to the current practice at the Board of Health and Welfare to only make data from the Patient register available on a full calendar year basis. It has been decided that data in the future should be made available continuously but it is not probable that this has been implemented in

time to be of benefit for this study. Use will be made of the most recent complete data at the time of data harvest.

- Cause of death register: [3] Information on date and cause of death up to the end of 2015, with additional information of vital status from the national population register for the first six months of 2016.

Population

The study population will be identified through the following steps:

1) Identification of all individuals with a diagnosis of atrial fibrillation (ICD-10 code I48 with or without subcodes) in the Patient Register between July 01, 2005 and December 31, 2015 (or later if more recent data has been made available by the Board of Health and Welfare at the time data harvest in Q3 2016).
2) Among these, all individuals with at least one filled prescription of dronedarone between May 29, 2013, and December 31, 2015 will be identified from the Swedish Drug register.
3) The date for the first filled prescription of dronedarone defines the preliminary index date.
4) Among patients with a filled prescription of dronedarone, all individuals with a filled prescription of apixaban or warfarin made
    a. within 90 days *before* the preliminary index date will be identified. The preliminary index date will be renamed index date since that date identifies the date when combination treatment started.
    b. within 90 days *after* the preliminary index date will be identified. The preliminary index date will be replaced by the date of purchase of apixaban or warfarin because this will be the date when combination therapy started.
5) Patients with valvular AF defined as patients with mechanical heart valves (Z952) implanted before index, or with a diagnosis of mitral stenosis before index (I342, I050, I052, Q232) will be excluded
6) Two study groups will be formed, one consisting of patients on apixaban + dronedarone, the other consisting of patients on warfarin + dronedarone.

Study size

The cumulative number of patients exposed to the apixaban-dronedarone combination is estimated to be approximately 1000 patients by the end of 2015. The number of patients exposed to the combination of warfarin-dronedarone during the same period can be estimated to be over 2000.

Variables – include exposures, outcomes, and key co-variates

Bleeding
The main bleeding endpoint is "major bleeding" defined as:

- Any intracranial bleeding, or
- Hospitalization with a bleeding diagnosis
- Fatal bleed defined by a diagnosis in the Cause of Death register (underlying cause of death or first contributory cause of death), or a hospital discharge code of "4" indicating death during hospital stay in conjunction with a bleeding diagnosis as principal or first secondary diagnosis.

Secondary endpoints are:

- Any hospitalization with a diagnosis of:
    - Intracranial bleed
    - Gastrointestinal bleed
    - Urogenital bleed
    - Other bleed
    - Contacts without overnight stay a bleeding diagnosis in principal or first secondary position.

Data analysis

For the assessment of bleeding events during follow up, uni and multivariable Cox regression will be used. Introduction of covariates will be done stepwise starting with only adjustment for age and gender, then for all cofactors that were significantly associated with the outcome after adjustment for age and sex alone and finally with addition of medication at baseline.

Propensity score matching will be used. Binary logistic regression will be used to generate individual propensity scores for the likelihood of getting treatment with apixaban rather than warfarin. Matching will then be made in a 1:1 fashion without replacement and with a calliper of 0.01. Matched cohorts will thereafter be compared with regard to bleeding events, without further adjustments, and after multivariable Cox regression.

In secondary analyses, different risk time variables will be used for each endpoint. It will thus be possible to assess more than the first bleeding event for each patient, as long as they are of different types. In this way a patient with e.g. a gastrointestinal bleed after six months and an intracranial bleed one month later will have both events counted, and not just the first one. This limits some of the problems with competing diagnoses.

All tests will be two-sided. Confidence intervals are 95% and p-values <0.05 will be considered as significant.

Milestones

The study protocol will be finalized and approved by Pfizer in April 2016.

Application for Ethical Approval and for data access will be filed in April 2016.
Provided that all necessary permissions are granted, data from the Patient register and the Drug register will be obtained from the Board of Health and Welfare when complete data for 2015 become available which is expected to be in September 2016.
A preliminary report will be generated in November 2016 and a final study report will be produced at the end of February 2017.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Final study protocol	*06 April 2016*
Application to Independent Ethics Committee	*30 April 2016*
Application sent to register holders (National Board of Health and Welfare)	*01 July 2016*
Registration in the EU PAS register	*01 August 2016*
Start of data collection	*01 September 2016*
End of data collection	*31 October 2016*
Preliminary study report	*30 November 2016*
Final study report	*28 February 2017*

6. RATIONALE AND BACKGROUND

Swedish patients with paroxysmal AF are frequently treated with dronedarone as a way to prevent the occurrence of attacks of AF. Dabigatran and rivaroxaban are not recommended in combination with dronedarone, according to their respective SPC, as a result of their pharmacokinetic profile. Dronedarone is a strong P-glycoprotein (P-gp) inhibitor with a potential to increase the bioavailability of dabigatran and rivaroxaban. The SPC of apixaban does not give any recommendation against combinatory treatment with dronedarone. Although the interaction with dronedarone has not been tested, from a theoretical point of view there is no contraindication to combine apixaban with dronedarone since dronedarone only inhibits CYP3A4 moderately. Nevertheless, there are hospitals in Sweden using the combination of apixaban and dronedarone in patients while others have decided to continue using warfarin in combination with dronedarone until there are some re-assuring data with apixaban in combination with dronedarone. We aim to investigate the occurrence of major bleeding among patients treated with dronedarone in combination with warfarin or apixaban in a real-life setting.

This is a real-world outcomes data study that will contribute to an increased knowledge about the appropriate use of apixaban in combination with dronedarone in patients with paroxysmal AF.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What is the occurrence of bleedings and mortality in real life, in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone compared against patients on warfarin and dronedarone?

Primary objective: To compare the occurrence of major bleedings in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Secondary objective: To compare the occurrence of intracranial hemorrhage in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Secondary objective: To compare the occurrence of major gastrointestinal bleedings in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Secondary objective: To compare the occurrence of all-cause mortality in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Exploratory objective: To compare the occurrence of bleeding-related mortality in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

8. RESEARCH METHODS

Methodology for the statistical analyses will be detailed in a statistical analysis plan (SAP).

8.1. Study design

Retrospective cohort study using national register linkage data. The occurrence of bleeding events between patients with AF treated with the combination of apixaban and dronedarone will be compared against patients on the combination of warfarin and dronedarone. All individuals with a hospital diagnosis of AF will be identified through the national Swedish Patient register. For all these patients, information will be obtained on dronedarone, apixaban and warfarin prescriptions through the national all-inclusive Prescribed Drug register.

Data from the following registers will be extracted and linked:

- Dispensed Drug register: [1] Dispensing date and dosing for prescribed drugs. Data will be extracted for the time-period from the start of the register July 01, 2005 until June 30, 2016.
- Patient register: [2] Information on patient demographics, comorbidity and previous and incident events (e.g. major bleedings). Data will be extracted from 1997 until the end of 2015. The reason for choosing 1997 as the starting point is that the current version of the International Classification of Diseases (ICD-10) was introduced in Sweden in that year. Diagnoses given earlier than 1997, which has not generated new contacts since then, is not likely to be clinically relevant. Besides starting 1997 makes translation of diagnostic codes between ICD-9 and ICD-10 unnecessary. The reason for terminating harvesting of data at the end of 2015 is due to the current practice at the Board of Health and Welfare to only make data from the Patient register available on a full calendar year basis. It has been decided that data in the future should be made available continuously but it is not probable that this has been implemented in time to be of benefit for this study. Use will be made of the most recent complete data at the time of data harvest.
- Cause of death register:[3] Information on date and cause of death up to the end of 2015, with additional information of vital status from the national population register for the first six months of 2016.

8.2. Setting

Subject Identification

All individuals with a hospital diagnosis of AF will be identified through the national Swedish Patient register. For all these patients, information will be obtained on dronedarone, apixaban and warfarin prescriptions through the national all-inclusive Prescribed Drug register for the entire study period (from May 29, 2013 to June 30, 2016).

The study population will be identified through the following steps:

1) Identification of all individuals with a diagnosis of atrial fibrillation (ICD-10 code I48 with or without subcodes) in the Patient Register between July 01, 2005 and December 31, 2015 (or later if more recent data has been made available by the Board of Health and Welfare at the time data harvest in Q3 2016).
2) Among these, all individuals with at least one filled prescription of dronedarone between May 29, 2013, and December 31, 2015 will be identified from the Swedish Drug register.
3) The date for the first filled prescription of dronedarone defines the preliminary index date.
4) Among patients with a filled prescription of dronedarone, all individuals with a filled prescription of apixaban or warfarin made:

a. within 90 days *before* the preliminary index date will be identified. The preliminary index date will be renamed index date since that date identifies the date when combination treatment started.

b. within 90 days *after* the preliminary index date will be identified. The preliminary index date will be replaced by the date of purchase of apixaban or warfarin because this will be the date when combination therapy started.

5) Patients with valvular AF defined as patients with mechanical heart valves (Z952) implanted before index, or with a diagnosis of mitral stenosis before index (I342, I050, I052, Q232) will be excluded

6) Two study groups will be formed, one consisting of patients on apixaban + dronedarone, the other consisting of patients on warfarin + dronedarone.

8.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Patients that have ≥1 AF diagnosis registered in the Patient register
- Patients ≥18 years
- Patients who had a filled prescription for apixaban or warfarin during the identification period

8.2.2. Exclusion criteria

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

- Patients with valvular AF (defined as mechanical heart valve or mitral stenosis)

8.3. Variables

A list of covariates with definitions according to the ICD-10 coding system has been included in the appendix. Covariates are defined by diagnoses, medication or other conditions observed or documented before or on index date.

Co-variates will include the established risk score for bleeding, the HAS-BLED, and the risk scores for stroke, the CHADS2 and CHA2DS2VASc. These risk scores will be constructed based on information present in the registries. In addition to the variables that is included in the above-mentioned risk scores other co-variates known as potential risk factors or confounders will also be included, such as other co-morbidities (e.g. dementia, chronic obstructive pulmonary disease (COPD), cancer), co-medications (e.g. acid-suppressive drugs), time since first diagnosis of atrial fibrillation and prior use of oral anticoagulants.

Endpoint events are events that occurred after index date.

Identification of bleeding events in a retrospective registry study cannot be done in the same way as in a supervised prospective randomized trial where the severity of bleeding events can be assessed individually with access to medical records, lab tests and patient reporting.

Administrative registers have low sensitivity for detection of minor bleeding events not leading to hospitalization, but reported by patients in response to questionnaires in studies. Therefore, only major bleeds will be assessed in the present study.

According to the International Society on Thrombosis and Haemostasis a major bleed is bleed which is fatal, occurs in a critical area or organ, leading to hospitalization and/or prolonged hospital stay and a fall of Hemoglobin count of 20 g/L or transfusion of ≥units of blood.

Swedish registry data can identify fatal bleeds from either a diagnosis in the Cause of Death register (underlying cause of death or fist contributory cause of death), or a hospital discharge code of "4" indicating death during hospital stay in conjunction with a bleeding diagnosis as principal or first secondary diagnosis.

The definition of what exactly constitutes a bleeding in a critical organ, apart from intracranial bleeds, is associated with problems of differentiating between trival and serious bleeds from codes alone.

The placing of a code for bleeding may be seen as an indicator of the severity of the bleed. A bleeding diagnosis placed after 7 or 8 other diagnoses are less likely to be serious than one placed as first diagnosis. In order to detect major bleeds, it therefore seems reasonable to use only diagnoses given as principal or first secondary diagnosis and associated with hospitalization (defined as at least one night in hospital).

Information about drop of hemoglobin count is not available from the Swedish registers, but codes for blood transfusion are. The codes do not tell how many units of blood that were given, but according to Swedish clinical practice transfusion of single units of blood are never given to adult patients.

The main bleeding endpoint is “major bleeding” defined as:

- Any intracranial bleeding, or
- Hospitalization with a bleeding diagnosis
- Fatal bleed defined by a diagnosis in the Cause of Death register (underlying cause of death or first contributory cause of death), or a hospital discharge code of "4" indicating death during hospital stay in conjunction with a bleeding diagnosis as principal or first secondary diagnosis.

Secondary endpoints are:

- Any hospitalization with a diagnosis of:
    - Intracranial bleed

- Gastrointestinal bleed
- Urogenital bleed
- Other bleed
- Contacts without overnight stay a bleeding diagnosis in principal or first secondary position.

The above criteria for detection of bleeds has been set up according to the findings in a just concluded validation study in which the local medical records of 761 patients with bleedings according to the Patient Register were subjected to manual scrutiny. The study is completed but the manuscript has not yet been submitted to a journal for publication.

The bleeding endpoint will include the following types of bleeding:

Intracranial:
I60 Subarachnoid haemorrhage
I61 Intracerebral haemorrhage
I62 Other non-traumatic intracranial haemorrhage
S064 Epidural haemorrhage (traumatic)
S065 Traumatic subdural haemorrhage
S066 Traumatic subarachnoid haemorrhage

Gastrointestinal:
I850 Esophageal varices with bleeding
I983 Esophageal varices with bleeding in diseases specified elsewhere
K228 Haemorrhage or the oesophagus
K25, K26, K27, K28 with fourth position being 0, 2, 4 or 6 indicating gastroduodenal and gastrojejunal ulcers with bleeding
K290 Acute haemorrhagic gastritis
K625 Haemorrhage from anus and rectum
K661 Haemoperitoneum
K920 Haematemesis
K921 Melena
K922 Unspecified gastrointestinal bleeding
K926 Gastro-oesophageal laceration-haemorrhage syndrome

Urogenital
N02 Recurrent and persistent haematuria
N421 Congestion and haemorrhage of prostate
N836 Haematosalpinx
N837 Haematoma of the broad ligament
N857 Haematometra
N939 Abnormal uterine and vaginal bleeding, unspecified
R319 Unspecified haematuria

Other:

H113 Conjunctival haemorrhage
H313 Choroidal haemorrhage and rupture
H356 Retinal haemorrhage
H431 Vitreous haemorrhage
H450 Vitreous haemorrhage in diseases classified elsewhere
I312 Haemopericardium
J942 Haemothorax
M250 Haemathrosis
R04 Haemorrhage from respiratory passages
R58 Bleeding, not elsewhere classified
D629 Acute posthaemorrhagic anaemia
D683 Haemorrhagic disorder due to circulating anticoagulants
D698 Other specified haemorrhagic conditions,
D699 Haemorrhagic condition, unspecified

Definition of Blood transfusion (procedure codes):
DR029 Transfusion of allogeneic erythrocytes
DR033 Transfusion with full blood, allogeneic

8.4. Data sources

This study will use data from national registers where data from the different registers are linked through personal identity numbers. Similar data, but for earlier time periods, have been used in several studies before.[5-9] Data will be extracted from national registers and linked through the use of personal id numbers. The linkage will be done by the National Board of Health and Welfare (Socialstyrelsen) and unidentified data will be provided to the investigator.

Data from the following registers will be extracted and linked:

The dispensed drug register:	Dispensing date and dosing for prescribed drugs. Data is available from 01 July 2005. Data will be extracted for the period 01 July 2005 until 30 June 2016.
Patient register:	Information on patient demographics, events and co-morbidity. Data will be extracted for the period 1997 until 31 December 2015 (or later if available).
Cause of death register:	Information on date and cause of death. Data will be extracted until 31 December 2015.

8.5. Study size

Approximately 9,500 patients with atrial fibrillation filled a prescription of apixaban up to the end of 2014. Considering the accelerating uptake of apixaban in the AF population,

another year of data from the registries, is likely to generate a total of 20,000 patients on apixaban available for the study.

A small number of patients could have had apixaban prescribed in primary care without ever having received a hospital diagnosis of atrial fibrillation. Depending on the criteria for selection of the study population (i.e. a diagnosis of atrial fibrillation) these individuals will not be included in the study

From another data set we know that 310 patients were treated with the combination of dronedarone and apixaban at baseline during 2013 and 2014. More patients could have been exposed to the combination during follow up, although this information is presently unavailable. The number of patients with the combination dronedarone and warfarin was higher. The proposed study will include another full year. The cumulative number of patients with the apixaban-dronedarone combination could be estimated to be approximately 1000 patients considering the accelerated uptake of apixaban and a growing acceptance among clinicians for combining dronedarone and apixaban. The number of patients exposed to the combination of warfarin-dronedarone during the same period can be estimated to be over 2000.

We hypothesize that the annual rate of major bleeds in the warfarin-dronedarone cohort is 3% and that the apixaban-dronedarone increase bleeds by 33%. Then the needed number of patients needed to test this hypothesis would be approximately 5,512 on each drug combination with a two sided 95% significance level and 80% power. The study will therefore not have sufficient statistical power to confirm or reject the hypothesis, but it may still be informative since no systematic studies regarding the outcomes of patients with the apixaban-dronedarone combination have been done.

8.6. Data management

All analysis will be performed in Stata.

This study will be performed by associate professor Leif Friberg, Karolinska Institutet, a researcher/ cardiologist who is very experienced with registry research and that is well known and respected in the scientific community in Sweden and worldwide.

The data preparation of the two datasets will be done by the National Board of Health and Welfare (Socialstyrelsen) as they are authorized to do so. All data will be completely patient de-identified for this study.

Data management and analyses will be done exclusively through syntax files which will be saved and will provide a safeguard for traceability of all results, and will also facilitate minor changes of criteria if needed. The sponsor (Pfizer) will store data provided by the National Board of Health and Welfare (Socialstyrelsen) for a period of 10 years after termination of the study, along with syntax files developed for data management and analysis.

8.7. Data analysis

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

For descriptive analyses describing the two cohorts at baseline, Chi2 and t-tests will be used.

For time dependent analyses, made in analogy with the intention to treat principle, censoring will be made at the event, death and end of observation period

For time dependent analyses made in analogy with the on treatment principle, additional censoring will be done when a patient no longer is on combination treatment. It is, however, not possible to determine exactly when combination treatment stops from registry data alone. Therefore the following approximation is suggested:

Treatment with a drug can be assumed to continue as long as there is sufficient drug supply and there is no purchase of an incompatible drug (for instance if a patient in the apixaban cohort makes a purchase of warfarin or another Novel Oral Anticoagulant (NOAC), it is reasonable to assume that treatment with apixaban stopped the day when the new drug was purchased).

If the dispensed quantity and the prescribed dose of a drug is known, it is possible to determine how long this quantity will last if it is taken as prescribed and it is possible to determine a certain date when treatment stopped.

In real life, patients may forget to take their medication now and then, which will make supplies last longer and postpone the true discontinuation date. On the other hand, patients may stop taking a drug they´ve already purchased in which case the true discontinuation date will be earlier than the one which could be estimated from purchases. It is therefore important to recognize these limitations inherent in on treatment analyses based on prescription data.

Medication possession ratio (MPR) is a method for estimation of patient compliance/endurance. The MPR is defined as the number of days of medication supplied within the refill interval divided by the number of days in the refill interval. In this case, we assess the *cumulative* number of days of medication supplied during time at risk.

Warfarin, which does not have a known dosage, poses a special problem. However, the number of days between refills can be used to estimate whether a certain patient is on or off treatment at a certain point of time.

Generally, drugs in Sweden cannot be prescribed in larger quantities than what is expected to last 3 months. This is, however, not a strict rule, and available sizes of packages influence

prescriptions. For instance, a patient with a maintenance dose of 1,5 tablets a day needs approximately 140 tablets during a three-month period, but will most likely receive a prescription for 200 tablets, because warfarin only comes in packages of 100 tablets.

The mean dose for AF patients in Sweden is 1.8 tablets per day for male and 1.5 tablets for females according to a study of more than 1 million dosing instructions with corresponding International Normalized Ratio (INR) values and information about the achieved time within therapeutic range.[4] Hence, a typical warfarin patient is expected to come for refill every 4.5 month.

With the refill method, it is assumed that:

- All days between two filled prescriptions are treatment days, i.e. full adherence for that period.
- Treatment is considered to have stopped 3 months after the preceding purchase if there is no refill within 6 months.
- Patients who only made one purchase are considered to have stopped after 3 months.

The refill method has been validated in the study referred to above.

When comparing compliance/adherence between patients on apixaban and warfarin it is necessary to use the refill method in the same way for both cohorts. The more exact pill count based method for apixaban patients can therefore only be used for the purpose of sensitivity analysis.

The MPR measure of compliance/endurance during follow up is unsuitable for use as a covariate in intention to treat analyses, partly because the future compliance/endurance was not known at baseline and partly because bleeds and other events during follow up may influence decisions about treatment. MPR during follow up can however be used in stratified intention to treat analyses, and in on treatment analyses.

Assessment of MPR in the year before inclusion for other drugs commonly used in the cohort, e.g. betablockers, can be used as a covariate for general drug compliance.

For the assessment of bleeding events during follow up, uni and multivariable Cox regression will be used. Introduction of covariates will be done stepwise starting with only adjustment for age and gender, then for all cofactors that were significantly associated with the outcome after adjustment for age and sex alone and finally with addition of medication at baseline.

Propensity score matching will be used. Binary logistic regression will be used to generate individual propensity scores for the likelihood of getting treatment with apixaban rather than warfarin. Matching will then be made in a 1:1 fashion without replacement and with a calliper of 0.01. Matched cohorts will thereafter be compared with regard to bleeding events, without further adjustments, and after multivariable Cox regression.

In secondary analyses, different risk time variables will be used for each endpoint. It will thus be possible to assess more than the first bleeding event for each patient, as long as they are of different types. In this way a patient with e.g. a gastrointestinal bleed after six months and an intracranial bleed one month later will have both events counted, and not just the first one. This limits some of the problems with competing diagnoses.

All tests will be two-sided. Confidence intervals are 95% and p-values <0.05 will be considered as significant.

8.8. Quality control

All data will be completely patient de-identified for this study. This study will use data from national registers where data from the different registers are linked through personal identity numbers. Similar data, but for earlier time periods, have been used in several studies before.[5-9] Data will be extracted from national registers and linked through the use of personal id numbers. The linkage will be done by the National Board of Health and Welfare (Socialstyrelsen) and unidentified data will be provided to the investigator.

8.9. Limitations of the research methods

This observational study will be the first to describe and compare bleeding events upon concomitant treatment with dronedarone and apixaban or warfarin, respectively, in the real-world setting in Sweden. Among the strengths of this study, the linkage of Swedish databases in the study will provide high quality representative data of prescriptions of dronedarone, apixaban and warfarin at the national level. In addition, the prescription data will identify all patients, even those who are rarely selected for participation in studies due to cognitive impairment and poor general health (expected to have poor adherence); and will include all patients regardless of physicians' characteristics, minimizing selection bias.

Since registry data by definition only give positive information when a condition is present, never the opposite, there will be no problems with missing data to handle.

However, given the retrospective observational study design, and the use of electronic medical records as data source, there are a number of limitations resulting from this type of the study. Despite the quality of the data, it is possible that some measures may be incorrect and/or missing. Therefore, some measures and clinical outcomes might be underestimated.

A major limitation for non-randomized registry studies is vulnerability to confounding by indication. More specifically; the choice between warfarin or apixaban is influenced by the prescribers´appreciation of what is most suitable for the specific patient. These factors might not be apparent from registry data and therefore not possible to adjust for. In order to minimize this effect, matching for the likelihood of either treatment based on available information will be used in order to construct two cohorts with similar background characteristics (propensity score matching).

The assessment of drug exposure during follow up will not be as exact as in prospective randomized studies were pill counts are used. Purchase of a drug does not prove that it was actually ingested.

Although starting dates for treatment can be assessed by purchase dates, dates of termination of treatment can rarely be exactly defined. Patients may stop taking a drug while still having more of it in supply. Drug exposure will be assessed by a combination of counting medicine possession ratios and intervals between purchases. This will render better reliability if the observation period is longer, than if it is shorter. The observation period for the proposed study is relatively short. As a sensitivity analysis, patients will therefore be analysed both according to the drug combination at baseline (in analogy with intention to treat) and with censoring when combination treatment is assumed to have stopped (in analogy with on treatment or per protocol analyses).

Individual doses of warfarin are not known and the methods that will be used to assess it comprise limitations.

No individual adjudication of bleeding events by scrutiny of local medical records is possible in an anonymized registry study. The validity of Swedish registry data for detection of bleeding is presumed to be of high quality but has not been studied with relation to positive and negative predictive values related to the position of bleeding codes as principal or secondary diagnoses. However, a manual scrutiny of local medical records for a random sample 1000 patients with bleeds of various degrees of severity according to the Patient- and the Cause of Death registries has been performed and a manuscript is under preparation. Preliminary data shows that hospitalization with a bleeding diagnosis as principal or first secondary diagnosis, alternatively a bleeding diagnosis as underlying or first contributory cause of death, has the best combination of sensitivity and specificity for detection of incident bleeding events.

Registry data are typically of binary nature which may not be much of a problem for discrete event like bleeds, stroke or myocardial infarction, but is more problematic for conditions like hypertension, diabetes and renal disease were the degree of disease, and thus the prognostic impact may vary considerably. For renal disease, a special semiquantitative scheme has been adopted, but for most other ongoing conditions, this is a limitation to consider. Whether this imprecision affects the cohorts differentially is unknown.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

Not applicable.

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

This study does not require informed consent but review and approval from the local ethics committees is needed.

Patient informed consent is not applicable to the data sources used in this study since the health care registries utilized for the study are mandatory information collected on all resident Swedes admitted to hospital or having a prescription drug redeemed at pharmacy.

9.2. Patient withdrawal

Not Applicable.

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

This study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements.

The investigator must ensure that the required approvals from Ethics Committees, Independent Review Committees, Regulatory Authorities, and/or other local governance bodies are obtained before study initiation. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and other relevant documents, if applicable, from the IRB/IEC. All correspondence should be retained in the Investigator File. Copies of approvals should be forwarded to Pfizer.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes unstructured data (e.g., narrative fields in the database) that will be converted to structured (i.e., coded) data solely by a computer using automated/algorithmic

methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse events (AE) reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be reported and discussed in a study report. The final study report will be submitted to Medicinal Product Agency according to the regulations.

COMMUNICATION OF ISSUES

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

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

12. REFERENCES

1. http://www.socialstyrelsen.se/register/halsodataregister/lakemedelsregistret (Accessed 03 December 2015.)

2. https://www.socialstyrelsen.se/register/halsodataregister/patientregistret (Accessed 03 December 2015.)

3. http://www.socialstyrelsen.se/register/dodsorsaksregistret (Accessed 03 December 2015.)

4. Skeppholm, Friberg. Adherence to warfarin treatment among patients with atrial fibrillation. Clin Res Cardiol 2014;103:998-1005.

5. Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. BMJ. 2012;344:e3522.

6. Friberg L, Rosenqvist M, Lip GY. Net Clinical Benefit of Warfarin in Patients with Atrial Fibrillation: A Report from the Swedish Atrial Fibrillation Cohort Study. Circulation. 2012 Apr 18;125:2298-307.

7. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012 Jun;33(12):1500-10.

8. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. J Intern Med. 2013 Jul 23;274(5):461-8.

9. Sjalander S, Sjalander A, Svensson PJ, Friberg L. Atrial fibrillation patients do not benefit from acetylsalicylic acid. Europace. 2014 May;16(5):631-8.

13. LIST OF TABLES

14. LIST OF FIGURES

Not Applicable.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ean Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
PASS Study: Investigating of the occurrence of major bleedings in real life, in patients with atrial fibrillation (AF) treated with the combination of apixaban and droneadarone compared against patients on warfarin and dronedarone.

Study reference number:
B0661075

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	12,13,15
1.1.2 End of data collection[2]	☒	☐	☐	15
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	13
1.1.6 Final report of study results.	☒	☐	☐	13

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

A complete dataset is expected from the National Board of Health and Welfare sept 2016. Registration in the EU PAS register will be done when the final approved protocol is ready.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	13
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	14-16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	13-14
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	14
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	17-18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	20

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	19
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	19
4.2.2 Age and sex?	☒	☐	☐	15-16
4.2.3 Country of origin?	☒	☐	☐	15
4.2.4 Disease/indication?	☒	☐	☐	15
4.2.5 Co-morbidity?	☒	☐	☐	16
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	18

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and	☒	☐	☐	15-16

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
categorising exposure)				
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	21
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	15-16
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	13
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	17-19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	17,24

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	16-17
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	16

Comments:

Appendix table 2 (covariates), 3 (effect modifiers)

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	17
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	16-17
8.1.3 Covariates?	☒	☐	☐	16
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	15-16,19
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	17-19

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	16-18, 22
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	16-17
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	16-17
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	16
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	19

Comments:

Appendix table 1 (endpoints), 2 (co-variates) and 3 (co-variates)

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	20

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	21-23
10.3 Are descriptive analyses included?	☒	☐	☐	21
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	16,21-23
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	16, 21-23

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	20
11.3 Are methods of quality assurance described?	☒	☐	☐	23
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	23
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

11.5 The study will probably be peer reviewed by journal

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒ ☐	☐ ☒	☐ ☐	23
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	20
12.3 Does the protocol address other limitations?	☒	☐	☐	23

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	25
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	20

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	25

Comments:

8.7

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	26
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	26

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Appendix table 1

Definitions of previous events by ICD-10 codes, Swedish surgical procedural codes or medication.

Covariate	ICD-10 or procedure code beginning with
Intracerebral bleeding	Hospitalization with I61 as principal or first secondary diagnosis
Intracranial bleeding	Hospitalization with I60-62, S064- 066, I690-962 as principal or first secondary diagnosis
Gastrointestinal bleeding	I850, I983, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922, K926
Urogenital bleeding	N02, N421, N836, N837, N857, N939, N95, R319,
Other bleeding	H113, H313, H356, H431, H450, I312, J942, R04, R58, D629, D683, D698, D699 procedure
Transfusion	procedure codes DR029 and DR033
Any bleeding	Any of intracranial, gastrointestinal, urogenital or other bleeding
Ischaemic stroke	Hospitalization with I63 as principal or first secondary diagnosis
Unspecified stroke	Hospitalization with I64 as principal or first secondary diagnosis
TIA	G45
Systemic embolism	Hospitalization with I74 as principal or first secondary diagnosis
Thromboemboli incl TIA	Hospitalization with I63, I64 or I74 as principal or first secondary diagnosis, and any G45 diagnosis
Thromboemboli no TIA	Hospitalization with I63, I64 or I74 as principal or first secondary diagnosis
Any stroke (HASBLED)	Hospitalization with I61, I63 or I64 as principal or first secondary diagnosis
Myocardial infarction	Hospitalization with I21 or I22 as principal or first secondary diagnosis
PCI	procedure code FNG
CABG	procedure codes FNA, FNB, FNC, FND, FNE, FNF, FNH, FNJ, FNK, FNW
Pulmonary embolism	I26
Deep venous thrombosis	I801-802
Cardiovascular death	Diagnosis i ICD series "I", as underlying or first contributory cause of death

Appendix table 2

Definitions of comorbidity.

Covariate	ICD-10 or procedure code beginning with
Heart failure	I50,I110,I130,I132,I255,K761,I42-43
Hypertension	I10-15
Diabetes	E10-14 or use of antidiabetic drug (ATC codes beginning with A10)
Ischaemic heart disease without infarction	I20, I240, I248, I249, I25 except I252
Peripheral arterial	I70-73

disease	
Vascular disease	I21, I22, I252, I70-73 (as in CHA2DS2-VASc)
Mitral stenosis	I342, I050, I052, Q232
Mechanical heart valve	Z952
Other valvular disease	I34-39, I05-08, Q22-23 except valvular AF
Pacemaker or ICD	Z950, Z450, procedure code FPE
Renal failure	N18-19, procedure codes DR016, DR024, KAS00, KAS10, KAS20
Liver disease	K70-77, procedure codes JJB, JJC
Hypothyroidism	E00-03 , E890
Thyrotoxicosis	E05 within preceding year
COPD	J43-44
Asthma	J45-46
Anaemia	D50-64
Coagulation or platelet defect	D65-69
Cancer	Chapter C except C44 (basalioma) within preceding 3 years
Alcohol abuse ('alcohol index')	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Dementia	F00-03, F051, G300-301, G308-309
Frequent faller	≥2 hospitalizations with diagnosis W00-19 or R296

Appendix table3

Definition of risk scores.

Risk scores composed of diagnoses defined above	
CHADS2,	1 point each for : heart failure, hypertension , age ≥75 years, diabetes. 2 points for thromboembolism
CHA2DS2-VASc	1 point each for : heart failure, hypertension, age 65-74 years, diabetes, vascular disease, female sex 2 points each for 75 years, thromboembolism
HAS-BLED (modified)	1 point each for hypertension, renal failure, liver disease, thromboembolism, any bleeding, age ≥65 years, prescription of antiplatelet agent or NSAID, alcohol abuse

Appendix table 4

The Stockholm Renal Staging Scheme.

Stage	**Definition by code**	**Definition by drug** (ATC code)
End stage	a code for end stage renal disease (N185) during the preceding year or	
	a code for dialysis (DR016 or DR024) given ≥2 times during the preceding year	
Advanced	a code for chronic renal failure stage 3 or 4 (N183-4) during the preceding year or	
	a code for chronic renal failure (N18) within the preceding year and at least once ≥ 3 years ago or	
	a code for renal failure (N17-19) during the preceding year and purchase of any of the following drugs	phosphate binding drugs (A12AA, V03AE02 - 05) or
		resonium (V03AE01) or
		active vit D (A11CC03-4) or
		sodium bicarbonate (A02AH) or
		erytropoetic drugs (B03XA)
	not categorized as stage 3	
Mild	any diagnosis of renal failure (N17-19) within the preceding year and	
	not belonging to stage 2-3	
No failure	not belonging to any of the stages above	