Observational Study Information

Title	Treatment and outcomes among patients with atrial fibrillation and acute coronary syndrome in Sweden.
Protocol version identifier	1.0
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IMPACT study number	19562
Study type/Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☐ NO
EU PAS register number	EUPAS23407
Active substance	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Medicinal product	Not applicable
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen Please note that, effective 1st January 2017, Bayer Pharma AG transfers its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Research question and objectives	**Primary Objective** • To describe the variety of antithrombotic treatment regimens administered in patients with atrial fibrillation and acute coronary syndrome and to identify the most common ones; the duration of the most common treatment regimes will be estimated. • To assess the incidence of clinicaly relevant bleeding events associated with hospitalization and effectiveness outcomes including death:

	overall and among subgroups of patients.
Country(-ies) of study	Sweden
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Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
MAH contact person	Dr. Gunnar Brobert

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of Contents

2. List of abbreviations

AF Atrial fibrillation
ACS Acute Coronary Syndrom
AMI Acute Myocardial Infarction
CI Confidence Interval
EMA European Medicine Agency
ENCePP European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
GCP Good Clinical Practice
HR Hazard Ratio
NOACs non-vit K oral anticoagulants
NVAF Non valvular Atrial Fibrillation
PCI Percutaneous Coronary Intervention
PAS Post-Authorization Study
PASS Post-Authorization Safety Study
STROBE Strengthening the Reporting of Observational Studies in Epidemiology
VKAs Vitamin K antagonists

3. Responsible parties

Contact details of the responsible parties at Bayer AG are available upon request.

Collaborators / Committees

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4. Abstract

Title

Treatment and outcomes among patients with atrial fibrillation and acute coronary syndrome in Sweden.

v 1.0, 21 June 2017

Dr Leif Friberg,

Friberg Research AB, Stockholm, Sweden

Rationale and background

Patients with a history of acute coronary syndrome (ACS) and atrial fibrillation (AF) are at high risk for major adverse cardiovascular events, therefore they are placed on a combination therapy containing an anticoagulant and one or several antiplatelet agents, in particular if a percutaneous coronary intervention (PCI) was conducted. Such drug combinations are associated with increased risk of bleeding complications. During recent years several new non-vitamin K anticoagulants (NOACs) and antiplatelet drugs have been introduced; however, although all of them were extensively studied individualy, most of the combined regimes have not been subjected to randomised trials regarding safety and efficacy.

The recently completed PIONEER AF-PCI trial demonstrated a good safety profile of a regimen containing rivaroxaban (1); however the study was not designed to assess the regimen's efficacy. Therefore it is important to understand how patients with AF and ACS (including those undergoing PCI procedure) are treated in real-life settings and what are their outcomes.

Research question and objectives

This population-based study will describe prescription patterns of antithrombotic drugs in real life among patients with atrial fibrillation and acute coronary syndrome in Sweden, and will study safety and effectiveness endpoints related to the most commonly administered treatment regimens.

Primary Objective

- To describe the variety of antithrombotic treatment regimens administered in patients with AF and ACS and to identify the most common ones; the duration of the most common treatment regimes will be estimated.
- To assess the incidence of clinicaly relevant bleeding events associated with hospitalization and effectiveness outcomes including death: overall and among subgroups of patients including those undergoing PCI.

Study design

This is a retrospective cohort study which will utilize non-randomized unselected data from nationwide mandatory health registers in Sweden.

Population

Extensive health registers that capture life-long data on the entire population and are linked via a unique personal identification number exist in Sweden and offer an excellent opportunity to study routine clinical practice and associated outcomes.

The study will include patients with AF and ACS: (1) who did not undergo PCI; (2) who underwent PCI without stent implantation; (3) who underwent PCI with stent implantation.

The inclusion period will start 1st December 2011 (the date when NOACs became available for Stroke Prevention in AF, SPAF) and will include patients up to 1st October 2016. The observation period will also start on 1st December 2011 but will continue another three months until 31st December 2016 in order to give a minimum follow-up period of 3 months. The lookback period for the medical history and concomitant diseases will start in 1997 when ICD-10 was implemented in Sweden.

Index date is defined as the date of discharge of patients with AF after an ACS event. Time at risk will be counted from index plus seven days to allow time for patients to collect prescribed drugs.

Variables

Detailed descriptive variables incuding baseline characteristics will be captured for the population, including co-medications and comorbidities. CHA_2DS_2Vasc scores will be calculated. Antithrombotic drug combinations, drug strength, treatment duration and most commonly prescribed regimens will be identified. Exposure of a certain drug or a drug combination during follow up will be estimated as the number of days the dispensed drug supply would be expected to last if drug adherence was 90%, thus allowing for occasional dropped doses. The assumed dosages would be the standard dose for the particular strenght of the drug. Patients on non-standard dosing will be classified as receiving "other treatment". For warfarin, where a standard dosing does not exist, an approach based on assessment of refill intervals will be employed.

To measure safety and effectiveness outcomes the variables indicating the following events will be analysed: hospitalization or death with a diagnosis of bleeding; hospitalization for recurrent ACS; revascularization procedure; ischaemic stroke or systemic embolism; death from any cause.

Data sources

<u>The Patient register</u>

The Patient register started 1964 and contains data on hosptializations, specialized open care and day surgery in Sweden (including dates of admission and discharge, primary and secondary diagnoses, surgical procedures etc).

The Dispensed Drug register

This register started on July 1, 2005 and contains information on all dispensed prescription drugs.

The Cause of Death register

The Cause of Death contains information on causes and dates of deaths since 1961.

The LISA (Longitudinal integration database for health insurance and labour market studies) register

The LISA holds detailed information about individual´s socioeconomic variables.

Study size

This is a population-based study. The entire source population of Sweden is about 10 million inhabitants. Annually there are about 50,000 ACS hospitalizations in Sweden, and about half of them have an myocardial infarction; among those 10-15% have AF. In total an estimated sample size will be 30,000 patients.

Data analysis

The analysis will be based on descriptive statistics. Use of study medications: dose at first prescription, duration of treatment and duration of the most common combination regimens will be defined. Unadjusted event rates according to a regimen and an outcome will be presented in table format as well as displayed as Kaplan Meier graphs. Multivariable Cox regression with adjustments for cofactors will be made pairwise for the major treatment pathways using rivaroxaban-containing regimen as a reference, to determing the risk factors associated with effectiveness and safety outcomes. The analysis will be conducted for subgroups of patients: (1) no PCI; (2) PCI without stent; and (3) PCI with stent.

Milestones

The project is planned to begin in July 2017 and will end in March 2018.

5. Amendments and updates

None

6. Milestones

This study will be conducted between January 2017 and April 2018

Milestone	Project timeline

Protocol development and submission for review and comment	May - June 2017
Ethics Submission & Approval	July-August 2017
Data Extraction	October 2017
Data Analysis and reporting	January - March 2018

7. Rationale and Background

Patients with a history of acute coronary syndrome (ACS), i.e. acute myocardial infarction (AMI) or unstable angina pectoris, and atrial fibrillation (AF) are at high risk for major adverse cardiovascular events (2-4). These patients need both an anticoagulant and one or several antiplatelet agents (5) in particular if a percutaneous coronary intervention (PCI) was conducted. Such drug combinations are associated with increased risk of bleeding complications: more aggressive combinations with higher bleeding risk are generally used in the first months when the risk of stent thrombosis and reinfarction is higher, with subsequent switch to less intense treatment later on according to perceived individual thrombotic and haemorrhagic risk. During recent years several new non-vitamin K anticoagulants (NOACs) and antiplatelet drugs have been introduced; however, although all of them were extensively studied individualy, most of the combined regimes have not been subjected to randomised trials regarding safety and efficacy.

The recently completed PIONEER AF-PCI trial demonstrated a good safety profile of a regimen containing rivaroxaban (1); however the study was not designed to assess the regimen's efficacy. Therefore it is important to understand how patients with AF and ACS (including those undergoing PCI procedure) are treated in real-life settings and what are their outcomes.

Extensive health registers that capture life-long data on the entire population and are linked via a unique personal identification number exist in Sweden and offer an excellent opportunity to study routine clinical practice and associated outcomes.

8. Research question and objectives

This population-based study will describe prescription patterns of antithrombotic drugs in real life among patients with atrial fibrillation and acute coronary syndrome in Sweden, and will study safety and effectiveness endpoints related to the most commonly administered treatment regimens.

8.1 Primary Objective

- To describe the variety of antithrombotic treatment regimens administered in patients with AF and ACS and to identify the most common ones; the duration of the most common treatment regimes will be estimated.
- To assess the incidence of clinicaly relevant bleeding events associated with hospitalization and effectiveness outcomes including death: overall and among subgroups of patients including those undergoing PCI.

8.2 Secondary Objective

Not applicable

9. Research methods

9.1 Study design

- This is a retrospective cohort study which will utilize non-randomized unselected data from nationwide mandatory health registers in Sweden.
- The study will include patients with AF and ACS.
- Patients will be grouped according to anticoagulant treatment regimen at baseline. The baseline period will be defined by a prescription of an NOAC or antiplatelet agent within 90 days before and up to 7 days after an index date (defined as a hospital discharge after an ACS event). Due to the wide variation in dose requirements for warfarin and in order to capture all individuals with ongoing treatment, the baseline period for warfarin is defined as 183 days before, up to 7 days after an index date. We assume that most of patients collect their prescription within the 7- day period after their hospital discharge.
- Patients on anticoagulant treatment will be followed from the index date up to the specified outcomes, death, or end of follow-up. Incidence of the events will be calculated for the total follow-up period and additionally for the 7-day overlap period after the index date (to allow patients the time to collect their medicines from a pharmacy before the start of calculating exposure time) to identify any events that might have occurred (although this number ought to be very small).
- Treatment history data will be defined by a filled prescription before (excluding) the index date.
- Censoring:

  Days at risk will be counted from index date plus seven days to allow time for patients to collect prescribed drugs.

  During follow up censoring will be made:

  - when there is a switch to another oral anticoagulant;
  - when available drug supply is assumed to be exhausted indicating treatment cessation (estimated according to the refill method described under section 9.3.2.)
  - at the occurence of a specified endpoint event;
  - at emigration;
  - at death;
  - at end of follow up on December 31, 2016.

- Linkage of data will be done by personal identification numbers given to all permanent residents in Sweden irrespective of citizenship. These numbers never change and are used in all contacts with authorities and health services thus making it possible to follow individual patients over a lifetime, with emigration as an only exception. There is no opting out from these registers. For data protection reasons data is anonymized before they are made available for research purposes and an access to data is strictly regulated. The Patient Register, Dispensed Drug- and the Cause of Death register are maintained by the national Board of Health and Welfare, while the LISA register is maintained by Statistics Sweden.

9.1.1 Primary end-points

- Composition and frequency of treatment regimens (that include combinations of a vitamin K antagonist, antiplatelet therapy, a P2Y12 inhibitor without or with rivaroxaban) in patients with both AF and ACS including those who underwent the PCI with or without a stent placing.
- Prescribed strength and treatment duration of the most common regimens.
- Safety outcomes: hospitalization or death with a diagnosis of bleeding ("clinicaly relevant bleedings").
- Effectiveness outcomes: hospitalization for recurrent ACS, revascularization procedure (percutaneous coronary procedure or coronary bypass grafting), ischaemic stroke or systemic embolism; death from any cause.

9.1.2 Secondary end-point

Not applicable

9.2 Setting

In Sweden all registered OACs (warfarin, dabigatran, rivaroxaban, and apixaban, with a recent addition of edoxaban) are used in clinical practice. Phenprocoumon can be prescribed under a special licence in case of intolerance to other oral anticoagulants, but only 310 patients in Sweden used it for any indication in 2015. Oral antiplatelet drugs used are acetacetylic acid, clopidogrel, ticagrelor, prasugrel and dipyridamol. Ticlodipin was deregistered in 2006, but was still used under a special licence by 41 patients in 2015.

9.2.1 Study time-frame

- The study period will start from 1st December 2011 (the date when NOACs became available for Stroke Prevention in AF, SPAF) and will include patients up to 31st December 2016.
- The lookback period for the medical history and concomitant diseases will start in 1997 when ICD-10 was implemented in Sweden.
- A minimum follow-up time is 3 months.

- Index date is defined as the date of discharge of patients with AF after an ACS event.

9.2.2 Selection criteria

Inclusion criteria:

- Diagnosis of ACS defined by a hospital discharge (ICD-10 code of I21 for myocardial infarction or I20.0 for unstable angina pectoris (with or without sub-codes) during the study period and a diagnosis of AF (ICD-10 code I48 with or without sub-codes) in the Patient Register before or on the same day as the patient was discharged for ACS.

Exclusion criteria:

- No exclusions will be made as the registries capture the entire life-time of entire population of Sweden.

9.2.3 Study population

- The study will include patients with AF and ACS:
  - who did not undergo PCI,
  - who underwent PCI without stent implantation (NOMESCO code FNG00-96 except FNG05),
  - who underwent PCI with stent implantation (NOMESCO code FNG05).
- The sources of data are nationwide mandatory health registers in Sweden: (a) The Patient register; (b) The Dispensed Drug register; (c) The Cause of Death register; and (d) The LISA (Longitudinal integration database for health insurance and labour market studies) register.
- As no exclusions will be made, the study sample will be representative of the country's population.

9.3 Variables

The following variables will be collected:

9.3.1 Baseline characteristics

- demographic (age, sex, marital status, immigrant status) and socioeconomic status (educational level, disposable income after taxes and transferations);
- medical history and concomitant disease (see Table 1 for the list of diagnoses);
- CHA_2DS_2Vasc scores will be calculated based on the presence/ history of congestive heart failure, hypertension, age, diabetes mellitus, vascular disease, female sex and prior thromboembolitic event;
- medical treatment history (not including ancoagulantsand antithrombotic drugs) prior to the diagnosis of ACS (dispensed 4 months before the index date and within 7 days from the

index date): beta blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocker, statins, verapamil, diltiazem, digoxin, diuretics, dihydropyridine calcium blockers, class 1 and class 3 antiarrhythmic drugs, nonsteroidal anti-inflammatory drugs, proton pump inhibitors;

- composition and frequency of every anticoagulant and antithrombotic treatment regimen at baseline (purchased 4 months before and within 7 days after the index date): this information will be obtained from the national Dispensed Drug register. In case of dispensations for more than one antithrombotic drug at baseline the following rules will apply:
    - in case of recorded dispensation of more than one NOAC or NOAC plus warfarin (at index date), the latest drug will define a treatment group as combinations of different OACs should not be possible;
    - in case of recorded dispensation of more than one NOAC or NOAC plus warfarin at the index date, this patients will be excluded from the outcome analysis;
    - other combinations of antithrombotic drugs will be analyzed as separate groups in subgroups of sufficient size to make analyses meaningful.

9.3.2 Drug exposure

Time at risk will be counted from index date plus seven days to allow time for patients to collect prescribed drugs.

Duration of most commonly prescribed regimens will be calculated in the following way:

Exposure of a certain drug or a drug combination during follow up will be estimated as the number of days the dispensed drug supply would be expected to last if drug adherence was 90%, thus allowing for occasional dropped doses.

The assumed dosages would be the standard dose for the particular strenght of the drug, namely:

- Rivaroxaban 2.5 mg twice daily, 15 and 20 mg once daily
- Dabigatran 110 and 150 mg twice daily
- Apixaban 2.5 and 5 mg twice daily

Patients on non-standard dosing (rivaroxaban 10 mg or dabigatran 75 mg) will be classified as receiving “other treatment”; in these cases drug exposure during follow up will not be estimated.

For acetylsalicylic acid, clopidogrel and prasugrel, once daily dosing will be assumed. For ticagrelor and dipyridamol twice a day dosing will be assumed.

For warfarin, where a standard dosing does not exist, an approach based on assessment of refill intervals will be employed. All days between subsequent refills will be considered to be days on treatment as long as the refill interval does not exceed 6 months in which case treatment is assumed to have stopped 3 months after the preceding dispensation. The last dispensation is assumed to have lasted 3 months. This is a modification of a method which previously been evaluted in a study of

25,000 patients with known dosages, and International Normalised Ratio values (6). The method aims to estimate the total exposure time rather than a dose of warfarin.

9.3.3 Outcomes of interest

- Antithrombotic combination treatment regimens in patients with AF and ACS including those who underwent the PCI with or without a stent placing.
- Safety outcomes: hospitalization or death with a diagnosis of bleeding ("clinicaly relevant bleedings").
- Effectiveness outcomes:
    - hospitalization for recurrent ACS;
    - revascularization procedure (percutaneous stenting procedure or coronary bypass grafting);
    - ischaemic stroke or systemic embolism;
    - death from any cause.

ICD-10 codes (see Table 2) will be used to identify outcome events of interest.

9.4 Data sources

The Patient register

The Patient register started 1964 as a register of hosptializations in Sweden and reached national coverage in 1987. In 2001, specialized open care and day surgery was added to the register. It does not carry information from primary care or nursing homes. The register hold information about dates of admission and discharge, primary and secondary diagnoses, surgical procedures and much more. The register has frequently been used for research purposes and the data quality is generally of very high standard.

The Dispensed Drug register

This register started on July 1, 2005 in its present form. Details about all dispensed prescription drugs are are registered automatically in all pharmacies all over the country. All pharmacies are requiered to participate by law thus there are practically no missing data regarding prescription drugs. However, over the counter drugs are not available in the register, nor medication given during acute hospitalization. Drugs used in old people´s homes and nursery homes are included.

The Cause of Death register

The Cause of Death register lists dates, underlying and up to 48 contributary causes of death as well as information about accidental and violent death since 1961.

The LISA (Longitudinal integration database for health insurance and labour market studies) register

The LISA holds detailed information about each individual´s education, income, line of work, family and hundreds of other socioeconomic variables. The LISA register, which is maintained by Statistics Sweden is updated every year. For the purpose of this study we intend to obtain information about emigration, immigration, immigrant status (Swedish origin yes/no), marital status, cohabition (yes/no), educational level, disposable income afer taxes and transferations.

9.5 Study size

This is a population-based study. The entire source population of Sweden is about 10 million inhabitants. Annually there are about 50,000 ACS hospitalizations in Sweden, and about half of them have an myocardial infarction; among those 10-15% have AF. In total an estimated sample size will be 30,000 patients.

9.6 Data Management

Stata software will be used for data management and preparation of files for statistical analyses which will be performed in Stata and R.

The National Board of Health and Welfare maintains the registers and will make excerpts in accordance with investigator's demands if these have been approved by the local ethics committee and by the legal department at the National Board of Health and Welfare.

After linking has been done, personal identifiers will be removed by the National Board of Health and Welfare and substituted by anonymized numbers. The files will be delivered to the investigator as encrypted csv-files. The delivered data volume is estimated to be over 50 Gigabyte, divided into smaller files for technical reasons. From these files, one or more working files will be prepared that can be used for statistical analyses.

Data will be protected by encryption on computers with limited access and under PIN code protection as requested by the Board of Health and Welfare.

This study is based on routinely collected clinical data (secondary data) and does not involve any primary data collection.

Strategy for handling missing data

According to the nature of the Swedish registers missing data is not possible. Either there is information, or there is not. However, in very rare instances there may appear miscoded or incomprehensible information, e.g. patients with impossible high age, patients without gender, missing date for a contact. If the correction of such erroneous data can not be made, exclusion of that contact or patient will be done. The number of such exclusions will be reported.

As a general strategy, no data imputation strategies will be applied to supplement missing data. The requirement for inclusion is complete data for critical variables; otherwise this individual is not eligible to be a member of the study population.

9.7 Data analysis

The analysis will be of explorative and descriptive nature and will be conducted for subgroups of patients: (1) those who did not undergo PCI ("no PCI"); (2) who underwent PCI without stent implantation ("PCI without stent"); and (3) who underwent PCI with stent implantation ("PCI with stent").

The following descriptive statistics will be calculated: frequencies and percentages will be calculated to the variables of interests, continuous and count variables will be described using mean (±standard deviation), proportions, median (quartiles) and minimum and maximum values. 95% confidence intercals will be computed for descriptive varaibles.

The following outcomes will be assessed:

- Use of study medications: dose at first prescription, duration of treatment (time on index medication) and discontinuation defined by the surrogate methods described above or switch to another study drug.
- All types of treatment regimes will be identified, and duration of the most common ones will be described.

The main analyses will be made similarly to the intention to treatment principle where patients are grouped according to treatment at baseline not accounting for changes during follow up. The longer the follow up period, the more crossover. Therefore the analyses will be made in two separate time-periods frames at 3 months, and from 3 months after index date to the end of the follow up with updating of baseline variables and restart of the counting of days at risk each time.

Unadjusted event rates according to a regimen and an outcome will be presented in table format as well as displayed as Kaplan Meier graphs. Multivariable Cox regression with adjustments for cofactors will be made pairwise for the major treatment pathways using rivaroxaban-containing regimen as a reference to determing the risk factors associated with effectiveness and safety outcomes. The analysis of risk factors will be conducted within each subgroup ((1) no PCI; (2) PCI without stent; and (3) PCI with stent) for the most common treatment regimens.

Differences in the incidence of bleedings and ischemic events in subgroups per PCI and per treatment will be further analyzed and attempts will be made to explain these differences. The study does not intend to "control/adjust" for the reasons behind differences in incidence rates of bleeding and ischemic events, which would not be possible.

9.8 Quality control

The Swedish Board of Health and Welfare, which maintains the national health registries, continually control quality and integrity of data. More than 99% of non-psychiatric hospitalizations have technically correct entries in the Patient Register (see 8.1.2). Information is also available online at the Board of Health and Welfare There are several studies that have assessed the validity of diagnoses in the Swedish patient register, both regarding sensitivity and specificity (7-9). The review by Ludvigsson et al, 2011 (8) provides an excellent overview of a number of validation

studies, confirming that validity of diagnoses differs in the registers. Diagnoses signifying discrete events are mostly correct (e.g. stroke, myocardial infarction), whereas diagnoses related to continuous conditions may sometimes be omitted in patients with several other competing diagnoses of higher importance. Regarding missing diagnoses in the Patient Register, some degree of validation can be obtained by cross-linking data with quality registers for some diseases that have such specific registers (e.g. stroke, heart failure, ischaemic heart disease, diabetes). In previous studies where the investigators performed such cross-linking, more patients were generally found in the Patient Register than in the quality registers, indicating good sensitivity to identify such events.

A quality assurance procedure will be employed to ensure that all data management steps as well as the statistical analyses are carried out appropriately. Data management and all data analyses will performed through syntax files which will be recorded and made available for scrutiny by Bayer.

Plausibility checks will confirm that the data extraction and record linkage from the various national registers has been accurately performed by the data provider (Swedish National Board of Health and Welfare). Various internal plausibility checks will be done, e.g. to identify variable values out of expected range. File preparation and statistical analytical procedures will be recorded in syntax files which will make it possible to trace all figures back to the original source files obtained from the data provider. This will also allow tracing and correcting any subsequent errors in derived variables. Syntax files will also facilitate independent external scrutiny of data quality. Back-ups of data files will be performed daily and kept in a secure location. The originals and the final analysis file will be archived.

9.9 Limitations

The possibility for unmeasured confounders for bleeding affecting the data, e.g. inadequate or missing recording of ethnicity, alcohol intake or over-the-counter use of some medications.

Confounding by indication is probable e.g. patients with renal failure are more likely to receive warfarin than other oral anticoagulants.

Some unmeasured confounding due to missing or imprecisely reported and recorded information, i.e. on alcohol consumption, smoking or drug abuse, might occur, however as the study has a descriptive nature capture of these data is not relevant for addresing the research questions.

Data in the registries are mostly binary, while risk is a continuum. For example, a diagnosis of hypertension will cover both patients with borderline hypertension and malignant hypertension, although the impact on the prognosis is very different.

In patients with poor health, in whom many different diagnoses could be used at discharge, competition between diagnoses is likely to lead to omission of less severe or acute diagnoses that would have been listed in patients with fewer concomitant diseases.

Over-reporting of disease is uncommon, whereas under-reporting is very common, especially for life style related conditions like obesityor alcoholism. Thus, risk scores according to CHA_2DS_2-VASc are likely to represent underestimates of the true scores.

Information on prescriptions dispensed but not used, and about drugs used by patients during hospital stay, are not captured.

The information about the exposure to warfarin will be inexact due to the highly varying dosages of warfarin. There is no standard dose from which the time time the dispensed drug quantity can be

calculated. The interval between refill purchases is only a surrogate for this, which will be less exact in patients with few refills and short follow up than in patients with many refills and long follow up.

Therefore interpretation of differences in outcomes related to analysed treatment regimes involving warfarin should be made with caution considering that the exposure to warfarin will be determined in another way than to the other antithrombotic drugs.

The study findings may not be representative for other countries as this study is based on Swedish data only; however it might be applicable to other Scandinavian settings with similar health systems. The findings could also be extrapolated to at least several other European settings with similar population structure and treatment approaches. Besides, the study is representative for Sweden as it captures entire popuation.

9.10 Other aspects

None

10. Protection of human subjects

This study protocol has been approved by a Research Ethics Committee (REC), and the study will be conducted in accordance with Good Pharmacoepidemiology Practices (10, 11).

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. Reports of adverse events/reactions will be summarized in the study report (European Medicines Agency 2012).

12. Plans for disseminating and communicating study results

The study will be registered on clinicaltrials.gov and on the ENCePP website.

Reports will be shared with the authorities.

Routine updates will be provided annually in the PBRER.

The principal investigator intends to present and/or publish data from this study in internationally recognised forums following Good Publication Practice.

Study results will be published following guidelines of the International Committee of Medical Journal Editors (ICMJE, 2013), and communication in appropriate scientific venues will be considered.

When reporting results of this study, the appropriate STROBE checklist (STROBE, 2007) will be followed.

13. List of references

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Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009

Study title: Treatment and outcomes among patients with atrial fibrillation and acute coronary syndrome in Sweden.

Study reference number:

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]	☒	☐	☐	9
1.1.2 End of data collection[2]	☒	☐	☐	9
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	9

Comments:

The study is not yet registered in the EU PAS register however will be registered soon.

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)	☒	☐	☐	9

[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.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.2 The objective(s) of the study?	☒	☐	☐	10
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	10,12
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☐	☐	☒	
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)	☒	☐	☐	10
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☒	11
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)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	12
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12
4.2.2 Age and sex?	☒	☐	☐	12
4.2.3 Country of origin?	☒	☐	☐	12
4.2.4 Disease/indication?	☒	☐	☐	10,12
4.2.5 Co-morbidity?	☐	☐	☒	
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)	☒	☐	☐	12

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 categorising exposure)	☒	☐	☐	13-14
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)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the product?	☐	☐	☒	
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?	☒	☐	☐	11
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)	☐	☒	☐	

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)	☒	☐	☐	17
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

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.)	☒	☐	☐	14-15
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.)	☒	☐	☐	14-15
8.1.3 Covariates?	☒	☐	☐	14-15
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, product quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	14-15
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	14-15
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	12
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	12
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	12,14-15
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	11, 15

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	15

Comments:

This is a population-based study.

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?	☒	☐	☐	16
10.3 Are descriptive analyses included?	☒	☐	☐	16
10.4 Are stratified analyses included?	☒	☐	☐	16
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

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?	☒	☐	☐	15-16
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	16
11.3 Are methods of quality assurance described?	☒	☐	☐	16
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	16
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	17
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)	☒	☐	☐	17

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
12.3 Does the protocol address other limitations?	☒	☐	☐	17

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?	☒	☐	☐	18
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	18

Comments:

The application to the ethics approval is still pending

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?	☒	☐	☐	9

Comments:

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)?	☐	☐	☒	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	18

Comments:

Name of the main author of the protocol: Gunnar Brobert

Date: 21/06/2017

Signature: _____

Annex 3. Additional information

Table 1. Definitions of medical history: events of interest and concomitant diseases

Covariate	ICD-10 or procedure code beginning with
Intracranial bleed	I60-62, S064-066 , I690-692
Gastrointestinal bleed	I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922
Urogenital bleed	N02, R319, N95
Other bleed	H431, R04, R58, D629, procedure code DR029
Ischaemic stroke	I63, I693
Unspecified stroke	I64, I694
Systemic emboli	I74
TIA	G45
Thromboembolism	I63-64, I693-694, I74, G45
Anaemia	D50-64
Coagulation or platelet defect	D65-69
Renal failure	N18-19, procedure codes DR016, DR024, KAS00, KAS10, KAS20
Liver disease	K70-77, procedure codes JJB, JJC
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)
Vascular disease	I21, I22, I252, I70-73 (as in CHA_2DS_2-VASc)
Mitral stenosis	I342, I050, I052, Q232
Mechanical heart valve	Z952
Other valvular disease	I34-39, I05-08, Q22-23 except valvular atrial fibrillation
Pacemaker or ICD	Z950, Z450, procedure code FPE
Hypothyroidism	E00-03 , E890
Thyrotoxicosis	E05 within preceding year
COPD	J43-44
Asthma	J45-46
Cancer	Chapter C except C44 (basalioma) within preceding 3 years

Alcohol index[a]	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 hospitalisations with diagnosis W00-19 or R296
CHA_2DS_2-VASc score	1 point each for: heart failure, hypertension, age 65-74 years, diabetes, vascular disease, female sex and 2 points each for age ≥75 years and thromboembolism

[a]A set of codes used by the Swedish Board of Health and Welfare for annual reporting alcohol related mortality in the population.
TIA, transient ischemic attack; ICD, implantable cardioverter defibrillator; COPD, chronic obstructive pulmonary disease

Table 2. ICD-10 codes used to identify outcome events

Code	Meaning			
I60	Subarachnoid haemorrhage	Haemorrhagic stroke	Intracranial bleeding	Major bleeding
I61	Intracerebral haemorrhage			
I62	Sub- and epidural haemorrhages			
S064	Traumatic epidural haemorrhages			
S065	Traumatic subdural haemorrhages			
S066	Traumatic subarachnoid haemorrhages			
K226	Gastro-oesophageal laceration-haemorrhage syndrome (Boerhave)		Gastrointestinal bleeding	
K25	Bleeding gastric ulcer (subcodes 0,2,4,6 only)			
K26	Bleeding duodenal ulcer (subcodes 0,2,4,6 only)			
K27	Bleeding peptic ulcer unspecified (subcodes 0,2,4,6 only)			
K28	Bleeding gastrojejunal ulcer (subcodes 0,2,4,6 only)			
K290	Acute haemorrhagic gastritis			
K625	Haemorrhage of anus and rectum			
K661	Haemoperitoneum			
K920-K922	Haematemesis, melena and unspecified GI bleeding			
I850 I983	Oesophageal varices with bleeding			
N02	Haematuria		Other bleeding	
R319	Haematuria, unspecified			
N939	Abnormal uterine and vaginal bleeding			
N950	Postmenopausal bleed			
N501A	Haemorrhage in male genital organ			
H113	Conjunctival haemorrhage			
H313	Choroidal haemorrhage			
H356	Retinal haemorrhage			
H431	Vitreous haemorrhage			
H450	Vitreous haemorrhage in diseases classified elsewhere			
H922	Ear bleeding			
I312	Haemopericardium			
J942	Haemothorax			
M250	Haemarthrosis			
R04	Nosebleed			
R58	Haemorrhage not elsewhere classified			
T810	Haemorrhage and haematoma complicating a procedure not elsewhere classified			
D500	Iron deficiency anaemia secondary to blood loss (chronic)			

D629	Anaemia after acute major bleeding		
DR029 DR033 Z513	Procedure codes for transfusion		
I63	Ischaemic stroke		
I64	Unspecified stroke		
I74	Systemic embolism		
I60-61 I63-64 I74	All-cause stroke or systemic embolism		
I21-22	Myocardial infarction		