PASS information

Title	A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Sweden
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Active substance	B01AF01 Antithrombotic agents, direct Factor Xa Inhibitors, Rivaroxaban
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Product reference	BAY 59-7939
Procedure number	EMEA/H/C/00944
Marketing authorization holder(s)	Bayer Pharma AG, D-13353 Berlin, Germany
Joint PASS	No
Research question and objectives	To assess patterns of drug utilization and to quantify outcomes related to safety and effectiveness in new users of rivaroxaban compared with new users of standard of care in routine clinical practice in Sweden. To provide a detailed description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed standard of care for the first time, and describe the characteristics of rivaroxaban use (including indication, dose and duration). To determine time-trends in the characteristics of first-time use of rivaroxaban. To study the occurrence of hospitalization for a) intracranial haemorrhage, (b) gastrointestinal bleeding, (c) urogenital bleeding among users of rivaroxaban (for DVT/PE treatment, SPAF and ACS) in comparison with individuals receiving current standard of care. Secondary objectives: to study the occurrence of hospitalizations for other bleeding events and to study non-

	infective liver disease (secondary safety outcome); to study outcomes related to effectiveness (ischaemic stroke or myocardial infarction); and, if numbers permit, to conduct analysis of subgroups, especially elderly and patients with comorbidities.
Country(-ies) of study	Sweden
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Marketing authorization holder

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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.

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2 List of abbreviations

ACS	Acute Coronary Syndromes
ALT	Alanine aminotransferase
ASA	Acetylsalicylic acid
AST	Asparagine aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
BMI	Body Mass Index
CrCl	Creatinine Clearance
DVT	Deep Vein Thrombosis
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicine Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance
HES	Hospital Episode Statistics
LISA	Longitudinal integration database for health insurance and labour market studies
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
PCP	Primary Care Practitioner
PE	Pulmonary Embolism
PRAC	Pharmacovigilance and risk assessment committee
REC	Research Ethics Committee
RMP	Risk Management Plan
SPAF	Stroke Prevention in Atrial Fibrillation
VTE	Venous Thromboembolism

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4 Abstract

A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Sweden

Version 1.3, 20 Jan 2015

Principal investigator: Leif Friberg, MD, PhD

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Rationale and background

Rivaroxaban is an oral, direct Factor Xa inhibitor with multiple indications, including: treatment of venous thromboembolism (VTE) and prevention of recurrent VTE; stroke prevention in atrial fibrillation; and prevention of atherothrombotic events (when combined with antiplatelet therapy) following an acute coronary syndrome. The use of anticoagulants is associated with the risk of bleeding, and monitoring of the safety profile and patterns of rivaroxaban use in routine care is required. This study in Sweden forms part of a post-authorization safety study programme in several European countries.

Research question and objectives

To provide a detailed description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed standard of care for the first time, and describe the characteristics of rivaroxaban use (including indication, dose and duration). To determine time-trends in the characteristics of first-time use of rivaroxaban. Primary safety outcomes are the occurrence of hospitalization for a) intracranial haemorrhage, (b) gastrointestinal bleeding, (c) urogenital bleeding among users of rivaroxaban in comparison with individuals receiving current standard of care.

Study design

This study has a cohort design.

Population

All patients who have filled a prescription for rivaroxaban, warfarin, aspirin, clopidogrel, ticlopidine, prasugrel or ticagrelor in any pharmacy in Sweden.

Variables

Detailed descriptive variables will be captured for the population, including co-medications and comorbidities. Primary safety outcomes are the occurrence of hospitalization for a) intracranial haemorrhage, (b) gastrointestinal bleeding, (c) urogenital bleeding and (d) other bleeding. Other outcomes of interest include non-infective liver disease and outcomes related to effectiveness.

Data sources

Swedish national health registers (The Drug, Patient and Cause of Death Registers, and additionally the LISA [Longitudinal integration database for health insurance and labour market studies] register if permission granted).

Study size

The size of the population receiving rivaroxaban will be dependent on market uptake across the indications of interest. Based on an incidence of haemorrhagic stroke in warfarin-treated patients of 5 per 1000 person-years, 12,000 rivaroxaban-treated patient-years and 48,000 warfarin-treated patient-years would be required to exclude a 50% increased risk of haemorrhagic stroke in rivaroxaban-treated patients compared with warfarin-treated patients with a power of 80%.

Data analysis

The diagnosis associated with the prescribing of the index drug will be grouped by indication. The patient populations will be described according to demographics, previous and current disease and concomitant medication at baseline both overall and stratified by indication. For descriptive purposes, annualized crude incidence rates of the specified outcome events will be calculated, accompanied by 95% confidence intervals.

For evaluation of safety and effectiveness outcome events, Cox proportional hazards regression model will be used. Propensity score matching will be done to account for confounding by indication.

Milestones

Data collection will start from December 9, 2011 (rivaroxaban received marketing authorization for DVT treatment in Sweden) and finish on December 31, 2018.

5 Amendments and updates

Table 1: Amendments

Number	Date	Section of study protocol	Amendment	Reason
2	20 Jan 2015	9.3.2.1 9.4.2 9.7 9.8 9.9 ENCePP Checklist	Addition to section on bleeding definition Addition to section on renal failure definition Addition of section to handle missing data Addition of information on patient population Addition of section on data management and quality control	Response to PRAC review from 9 Jan 2015
1	05 Nov 2014	9.3.1 9.4.2 9.7 9.8	Additional variables for patient characterisation and analyses thereof; strengthened analyses of renal impairment; additional information on Quality Control	Response to PRAC review

6 Milestones

Table 2: Milestones

Milestone	Planned date
Start of data collection (Marketing Authorization granted for DVT treatment)	December 9, 2011
Interimreport2 2 years drug utilization data and crude incidences for primary safety outcomes	Q4 2015
Interim report 2 4 years drug utilization data and crude incidences for primary safety outcomes	Q4 2017

End of data collection	Q4 2018
Final data availability	Q4 2019
Progress reports	Annual in November 2014–19
Final report of study results with full outcomes analysis	Q4 2020
Registration in the EU PAS register	Study to be registered after PRAC approval

7 Rationale and background

Rivaroxaban, a direct Factor Xa inhibitor, is licensed for multiple indications:

- The treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients (15 mg rivaroxaban twice daily [bid] for 3 weeks, then 15 mg or 20 mg once daily [od]).
- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (stroke prevention in atrial fibrillation [SPAF]) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (20 mg rivaroxaban od).
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (recommended dose: 10 mg rivaroxaban od for 35 days following hip replacement surgery and 14 days following knee replacement surgery).
- Co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (recommended dose 2.5 mg bid).

As is the case with other anticoagulants, rivaroxaban may also cause haemorrhage (Lassen, Ageno et al. 2008; Turpie, Lassen et al. 2009). It is therefore important the assess frequency of bleedings with rivaroxaban, in comparison with standard of care, as a safety outcome. A post-authorization safety study programme is therefore planned for several European countries.

This document summarizes the design of a population-based study in Sweden aiming to characterize new users of rivaroxaban, assess patterns of drug utilization, including adherence to label recommendations, and to assess the risk of bleeding and death associated with rivaroxaban treatment compared with the standard of care in routine clinical practice in Sweden, for SPAF, DVT/PE treatment and ACS. For SPAF and DVT/PE treatment, standard of care is treatment with the most widely used vitamin K antagonist, warfarin, and for the secondary prevention of ACS, standard of care is antiplatelet drug(s) such as low-dose acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor. The standard of care treatments for ACS will require at least dual antiplatelet therapy, and be analysed as combination treatment, irrespective of the individual drug combinations used.

8 Research questions and objectives

This post-authorization study was designed to assess patterns of drug utilization and to quantify outcomes related to safety and effectiveness in new users of rivaroxaban compared with new users of standard of care.

8.1 Primary objective

8.1.1 Patient characteristics and drug utilization

- To provide a detailed description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed standard of care for the first time, and describe the characteristics of rivaroxaban use (including indication, dose and duration).
- To determine time-trends in the characteristics of first-time use of rivaroxaban.

8.1.2 Safety and effectiveness outcomes

- To study the occurrence of hospitalization for a) intracranial haemorrhage, (b) gastrointestinal bleeding, (c) urogenital bleeding among users of rivaroxaban (for DVT/PE treatment, SPAF and ACS) in comparison with individuals receiving current standard of care.

8.2 Secondary objectives

- To study the occurrence of hospitalization for bleeding events not specified as primary safety outcomes ("other bleeding", secondary safety outcome) in individuals receiving rivaroxaban, in comparison with those receiving current standard of care.
- To study the occurrence of non-infective liver disease (secondary safety outcome) in individuals receiving rivaroxaban in comparison with those receiving current standard of care.
- To study outcomes related to effectiveness (ischaemic stroke or myocardial infarction) in individuals receiving rivaroxaban in comparison with those receiving current standard of care. Other studies in the PASS programme will consider DVT/PE as an outcome related to effectiveness. However, the Swedish registries are not suitable for detection of recurrent VTE while on treatment with anticoagulants because the original VTE diagnosis is often used at follow up visits.
- To study all-cause mortality as well as cause-specific mortality.
- If numbers permit, to conduct analysis of subgroups of safety and effectiveness outcomes, especially elderly and patients with comorbidities.

9 Research methods

9.1 Study design

This study has a cohort design, see Section 9.2 for details.

9.2 Setting

The study population will be identified in three steps using data from the Swedish national health registers that are maintained by the national Board of Health and Welfare. In order to get access to data from these registers, approval from the local ethical review board is mandatory. Before data can be handed over, the legal department at the Board of Health of Welfare will also make an independent assessment of whether there are any possible violations against personal integrity according to the Swedish law on the handling of computerized personal information (in Swedish: Personuppgiftslagen SFS 1998:204).

Step 1:

All male and female patients who have filled a prescription for rivaroxaban, warfarin, aspirin, clopidogrel, ticlopidine, prasugrel and ticagrelor in any pharmacy in Sweden, between December 9, 2011 (when rivaroxaban was granted marketing authorization for DVT in Sweden) and December 31, 2018 will be identified. The date of the first purchase within this period will be used as index date.

Step 2:

Information about the patients who were identified in Step 1 will be obtained from the Patient register. Diagnoses of AF, DVT/PE or ACS in the Patient register will be used to group patients according to the presumed reason for treatment (Figure 1).

A diagnosis of AF or atrial flutter given within a month before or on the date of the first drug purchase during the study period will assign the patient to the AF indication. Users of rivaroxaban will be compared with users of warfarin.

A diagnosis of DVT or PE given within a month before or on the date of the first drug purchase during the study period will assign the patient to the DVT/PE treatment indication. Users of rivaroxaban will be compared with users of warfarin.

A procedure code for elective hip or knee replacement surgery within a month before or on the date of the first drug purchase during the study period will assign the patient to the VTE-prevention indication. This indication will only be captured in the drug utilization part of the study and not included in the safety and effectiveness evaluation part.

A diagnosis of myocardial infarction or unstable angina pectoris given within a month before or on the date of the first drug purchase during the study period will assign the patient to the ACS indication. Users of rivaroxaban alone or in combination with platelet-active drugs will be compared with users of aspirin and/or other antiplatelet drugs (standard care). The comparison drugs will consist of at least dual antiplatelet and be analysed in combination, irrespective of the individual drugs used.

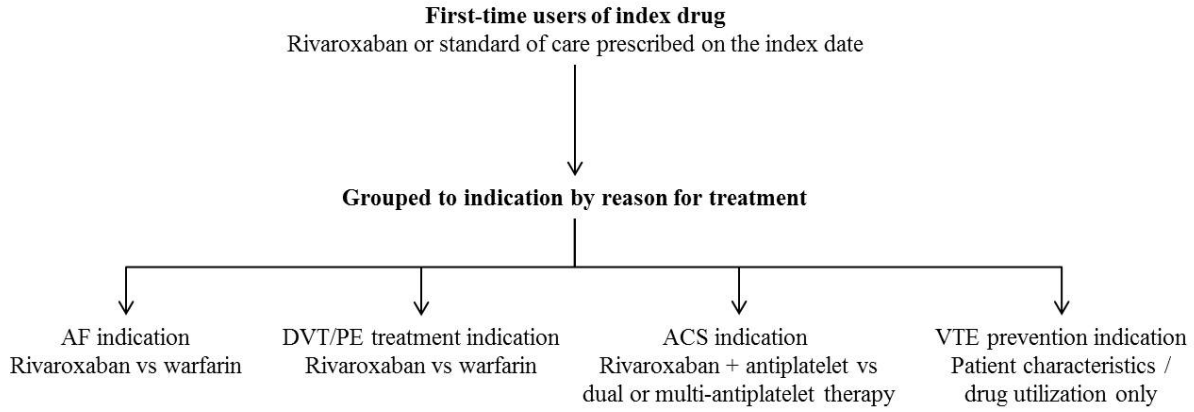

Figure 1. Subdivision of study cohorts in the main analysis.

Patients who qualify for participation in more than one indication may do so. Patients without at least one of these diagnoses within the qualification period will be excluded from safety analyses, but drug utilization information will be collected.

Step 3

The Drug Register will be used to discriminate patients who have previously been using anticoagulant or antithrombotic medication from patients who have been newly initiated on treatment.

For the AF and DVT/PE treatment indications, patients who have filled a prescription for warfarin or another oral anticoagulant at any time after July 1, 2005 (the date when the Prescribed Drug Register became operational nationally) will be excluded.

For the ACS indication, patients who have been using one or more platelet inhibitors will be allowed to remain in this study arm, albeit this treatment is a comparator in this part of the study. This is to ensure patient selection remains representative: many patients with ACS have a prehistory of ischaemic heart disease for which platelet inhibition is standard treatment and thus exclusion of patients with prior use of platelet inhibitors risk excluding a majority of typical ACS patients.

Patients who switch from rivaroxaban to any other anticoagulant will be censored at the time of the first purchase of the new drug. Patients who switch from warfarin to rivaroxaban will be studied separately. This group is defined as patients with a filled prescription of warfarin within 6 months of the first filled prescription of rivaroxaban.

Data collected for comparison of cohorts is described in section 9.3. The characteristics of the two study cohorts in the first year and subsequent years of the enrolment period will be compared.

The same cohort used for description of drug utilization will be used in the analysis of outcomes related to safety and effectiveness (see Section 9.3.2). For patients receiving treatment for the prevention of VTE following elective hip or knee replacement surgery (i.e. those in the VTE-prevention indication), only descriptive information regarding baseline conditions will be collected; information on bleeding events during treatment will not be studied (outcomes with long-term use are of interest in this study).

Strengths of the study pertaining to the research question include:

- The study captures the whole Swedish population, ensuring representativeness. Moreover, the Prescribed Drug Register is-almost complete. It keeps track of every single pill that is dispensed, in any pharmacy throughout the country, and this information is linked to the individual who received it. The quality of the Swedish health registers is well known all over the world and they provide a unique source of information for real-world, post-marketing studies of drug use (Ludvigsson, Andersson et al. 2011).
- It uses observational data from routine clinical practice with no selection and no possibility to influence prescribing behaviour.
- The Swedish health registers are a well-validated resource for pharmacoepidemiology research (Ludvigsson, Andersson et al. 2011).

The enrolment period will start on the day of the first approval of rivaroxaban in Sweden for DVT (December 9, 2011). Enrolment will end on December 31, 2018. Minimum follow-up will be 12 months, thus censoring will be made on 31 December 2018.

Days at risk will be counted from index date.

Due to delayed reporting to the Patient Register and the Cause of Death Register, complete data for 2018 will not be available for analysis until August/September 2019.

9.3 Variables

9.3.1 Patient characteristics and drug utilization

The following data will be collected for comparison between the two cohorts:

- age and sex distribution at index date
- dose of rivaroxaban at index date, no dose specifications for comparators
- diagnosis associated with the prescribing of the index drug
- use of specific prescribed medications both in the year before the index date and following the index date, confirming ACS indication: antiplatelet drugs (low-dose acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor);
- use of other prescribed medications both in the year before the index date and following the index date: anticoagulants (including dabigatran etexilate and apixaban), antiarrhythmic drugs, antihypertensive drugs, statins, antidiabetic agents, non-steroidal anti-inflammatory drugs, oral steroids, acid-suppressive drugs, disease-modifying anti-rheumatic drugs, antidepressants, antipsychotic drugs, oral contraceptives, hormone-replacement therapy, strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein (e.g. the systemic azole antimycotics ketoconazole, itraconazole, voriconazole and posaconazole and the HIV-protease inhibitor ritonavir), strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine or phenobarbital) and fluconazole
- comorbidity based on diagnoses before the index date (back as far as 1997) as specified in Table 4
- Renal impairment: in addition to the codes in Table 4, the following will be determined:
  - time since first diagnosis of chronic kidney disease (CKD). CKD is a progressive disease with a well-known natural history. The time since first diagnosis may therefore potentially be used as a marker of disease severity.
  - Use or non-use of medication used by patients with advanced renal disease, such as phosphate binding drugs (ATC codes A12AA or A12AX), sodium bicarbonate (ATC code A02AH) or erythropoietin and similar anti-anaemia drugs (B03XA).
  - Presence or absence of a code for dialysis.
- healthcare utilization in the year prior to the index date (e.g. outpatient visits and hospital admissions).

9.3.2 Safety and effectiveness outcomes

For each outcome, potential cases will be identified using ICD-10 and procedure codes **(Annex 3, Table 4)**.

For the purpose of this study, clinically relevant bleedings will be defined as bleedings leading to hospital admission. This restriction is needed to minimize differential misclassification caused by the variability in patients' behavior in seeking care for less severe bleedings. Similarly, the physicians' attitude to recording these events may differ between new drugs and standard of care. The consequence of restricting to bleedings identified through hospitalization is that bleedings leading to death before hospital admission will be ignored. It is assumed that the number of bleeding events missed due to this restriction is small. Nevertheless, the magnitude and impact of this restriction will be assessed in separate analyses by examining patients' records identified in the Cause-of-Death Register, who do not have a corresponding record in the Patient Register.

Furthermore, a validation study of this scheme is under consideration, in which the full medical records from a sample of patients will be scrutinized and where bleeding events will be classified according to the standard ISTH criteria and the correspondence between the registry based classification and the ISTH classification will be assessed. To estimate the severity of bleedings from registry data, patients will also be categorized as follows:

0. No bleeding diagnosis
1. Bleedings recorded in open care only, i.e. not requiring a hospitalization.
2. Bleedings with hospitalization, but without blood transfusion
3. Bleedings with hospitalization, with blood transfusion
4. A diagnosis of bleeding as the underlying cause of death.

9.3.2.1 Primary safety outcome; Occurrence of intracranial haemorrhage, gastrointestinal bleeding and urogenital bleeding

Definitions of bleeding events by ICD codes are listed in Annex 3, Table 4. As a sensitivity analysis, endpoint events will be stratified with regard to the placement of the bleeding diagnosis at discharge: as principal diagnosis, position among secondary diagnoses (first, second or lower). This procedure is motivated by the suspicion that a serious diagnosis with a very low ranking in the order of diagnoses at discharge may in fact represent an erroneous use of a code for an acute event, when in fact it was used to describe a past event. For example, the code for acute intracerebral haemorrhage (I63) placed a secondary diagnosis in the seventh position is unlikely to represent a life-threatening event.

The definition above is restricted to events identified through hospitalizations. This restriction is needed to minimize differential misclassification caused by the variability in patients' behavior in seeking care for less severe bleedings. Similarly, the physicians' attitude to recording these events may differ between new drugs and standard of care. The consequence of restricting to bleedings identified through hospitalization is that bleedings leading to death before hospital admission will be ignored. It is assumed that the number of bleeding events missed due to this restriction is small. Nevertheless, the magnitude and impact of this restriction will be assessed in separate analyses by examining patients' records identified in the Cause-of-Death Register, who do not have a corresponding record in the Patient Register (see below).

Furthermore, a validation study of this scheme is under consideration, in which the full medical records from a sample of patients will be scrutinized and where bleeding events will be classified according to the standard ISTH criteria and the correspondence between the registry based classification and the ISTH classification will be assessed. To estimate the severity of bleedings from registry data, patients will also be categorized as follows:

0. No bleeding diagnosis
1. Bleedings recorded in open care only, i.e. not requiring a hospitalization.
2. Bleedings with hospitalization, but without blood transfusion
3. Bleedings with hospitalization, with blood transfusion
4. A diagnosis of bleeding as the underlying cause of death.

9.3.2.2 Secondary safety outcomes: definition

Other bleeding leading to hospitalization: any diagnosis of "other bleeding" codes (Table 4).

Non-infective liver disease: any diagnosis of liver disease (codes K70-77) during follow-up.

9.3.2.3 Secondary outcomes related to effectiveness

- *Ischaemic stroke*: using the strict definition (ICD-10 code: I63), not counting unspecified stroke (ICD-10 code: I64) which may also represent some cases with intracerebral bleedings. This group is generally very small and represents approximately 3% of all stroke events in the national Swedish stroke register.
- *Myocardial infarction*: Any diagnosis of myocardial infarction (ICD-10 code: I21) after index date.

9.3.2.4 Deaths

Crude all-cause mortality as well as cause-specific mortality will be analysed and presented in relation to treatment arm.

9.4 Data sources

The data source for this study will be the national Swedish Drug Register, the national Swedish Patient Register and the national Cause of Death Register. If access is granted, we will also use the Swedish LISA (Longitudinal integration database for health insurance and labour market studies) database containing information about socioeconomic conditions.

Data from these registers will be cross-matched with the use of the unique 10 digit civic registration numbers which are used in all contacts with the healthcare system and in contacts with authorities in Sweden. Such numbers are given to all residents in Sweden, irrespective of citizenship.

The registers are maintained by a governmental agency, the National Board of Health and Welfare. After cross-matching, this agency substitutes the civic registration numbers for anonymous numbers before data are made available to researchers in order protect the personal integrity of patient data.

Nevertheless, this anonymized information is considered as sensitive and the handling of such data is strictly regulated by Swedish law. Access to data requires permission by the regional Ethics committee.

9.4.1 The Drug register

The Drug register stores details about every prescription dispensed, in all pharmacies in Sweden since July 1, 2005. The Drug Register is almost complete, because all pharmacies in the country are required to participate by law, and information is transferred electronically whenever a drug is dispensed.

The register does not contain information about prescriptions that have been issued but not dispensed, and about drugs used by patients during hospital stay. Patient in long-term care are included in the register, the limitation only concerns acute hospitalizations. The register does not include information on non-prescribed (over-the-counter) drugs. Drugs used by patients in long-term care and in community care are included in the Drug Register.

9.4.2 The Patient Register

The Swedish Patient Register carries detailed information about all hospitalizations and outpatient visits to hospital-affiliated open clinics all over Sweden since 1987 (for Stockholm and some regions back to 1964). While the Swedish Patient Register is a hospital based register, it is not limited to hospitalization, and there are more registrations for open clinic visits than for hospitalizations. For example, in a new dataset including all patients with a clinical diagnosis of atrial fibrillation in Sweden (2005–2013) there were approximately 420,000 unique individuals with 3.2 million hospitalisations and 11.3 million outpatient visits providing diagnostic codes. The indications for treatments of patients managed exclusively in primary care may not be identified. However, two recent studies of AF prevalence in Sweden, one only using hospital data and the other using hospital data and primary care data for a region where primary care data is available, showed that it was only approximately 10% of the AF population that had been exclusively managed in primary care during a mean follow up of 2.5 years and thus not been detected through search of hospital registers. ((Bjorck, Palaszewski et al. 2013; Friberg and Bergfeldt 2013))

Thus, the Swedish registers are well suited to capture both minor and major bleeding events provided that the condition is serious enough to render a diagnostic code. The number of missed clinically relevant bleedings is likely to be small.

Variables in the register include date of admission and discharge, principal and secondary diagnoses and codes for surgical and other interventions.

Information about hospital contacts given before the individual index date will be used for the description of previous and current disease at baseline, and as covariates in multivariable analyses. We propose that the search for previous diagnoses is limited to those given after 1997 when the current version of the International Classification of Diseases (ICD-10) was introduced in Sweden. This eliminates the problem with translation of diagnostic codes. Moreover, diagnoses given more than 15 years ago, which have not caused any further hospital contacts, are not likely to be relevant today, or affect current risk estimates. The specific codes we propose to use as definitions are listed in Table 4.

Information about previous diagnoses in the Patient Register will be used to calculate individual risk scores for AF related stroke and bleedings. The CHA_2DS_2-VASc scheme (Lip, Nieuwlaat et al. 2010)

is a widely used point based scoring system, for estimation of stroke risk in patients with AF. Points are given for age, previous ischaemic stroke or TIA/systemic embolism, heart failure, hypertension, diabetes, vascular disease and female sex. HAS-BLED (Pisters, Lane et al. 2010) is a similar point-based scheme for assessment of bleeding risk. Points are given for age, hypertension, renal, disease, liver disease, stroke history, previous bleeds, medication, alcohol use and "labile INR" (i.e. poorly controlled anticoagulant treatment). Since information about individual INR values will not be available, a "modified HAS-BLED" score excluding the INR component will be calculated.

The Patient Register will also be used for detection of events during follow up; most importantly for detection of bleeding event but also for stroke, thromboembolism and acute coronary events.

9.4.3 The Cause of Death Register

The primary mortality endpoint will be death from any cause. For determination of cause-specific mortality, the Cause of Death Register will be used. Information from this register will also provide information about dates of deaths needed for determination of individual time-at-risk during follow-up.

9.4.4 The LISA register

The LISA register is a longitudinal database for studies of health insurance utilization and labour market conditions. It contains detailed information about educational level, economic conditions, periods of unemployment, type of work etc. This information, which has recently become available for medical research, will provide additional information about socioeconomic conditions at baseline that may have impact on health and thus on outcome.

9.5 Study Size

The size of the population receiving rivaroxaban will be dependent on market uptake across the indications of interest (DVT/PE treatment, ACS and SPAF).

According to a preliminary sample size calculation, based on an incidence of haemorrhagic stroke in warfarin-treated patients of 5 per 1000 person-years, 12,000 rivaroxaban-treated patient-years and 48,000 warfarin-treated patient-years would be required to exclude a 50% increased risk of haemorrhagic stroke in rivaroxaban-treated patients compared with warfarin-treated patients with a power of 80%.

9.6 Data management

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

The National Board of Health and Welfare maintains the registers and will make excerpts in accordance with our 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 and substituted by anonymized numbers. The files will be delivered as encrypted SAS-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.

9.7 Data analysis

The following analyses will be performed.

The diagnosis associated with the prescribing of the index drug will be grouped into the following indications:

- prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- treatment of DVT or PE, and prevention of recurrent DVT and PE
- prevention of VTE in adult patients undergoing elective hip or knee replacement surgery (drug utilization only)
- secondary prevention after ACS with or without myocardial infarction and with or without angioplasty

The patient populations will be described according to demographics, previous and current disease and concomitant medication at baseline both overall and stratified by indication. Descriptive statistics and age- and sex-adjusted odds-ratios with 95% confidence intervals will be presented.

A gross categorization of patients according to degree of renal disease will be created based on the markers described in section 9.3.1; for example:

End-stage renal disease

- a code for dialysis (DR016 or DR024) given within one year before index date.

Advanced renal disease

- a diagnosis of chronic renal failure (N18) given 3 years or more before index date or
- any diagnosis of renal disease (N17-19) before index in combination with use of phosphate binding drugs, sodium bicarbonate or erythropoetic drugs within one year before index date.
- not being categorized as end stage renal disease (see above)

Mild renal disease

- any diagnosis of renal disease (N17–19) before index
- not being categorized as end stage or advanced renal disease (see above).

No renal disease

- none of the above

This is a crude classification of the severity of renal disease. Misclassification of patients' renal status will most likely occur in those with mild renal disease whereas severe renal disease will be more accurately classified. To validate and adjust this grading of severity of renal disease, a separate validation study will be carried out. The classification described above based on information on clinical diagnoses in combination with the use of specific drugs will be compared with information on creatinine measurements for a subset of patients captured by a laboratory test database covering about 600000 inhabitants in Stockholm with more than 2 creatinine results and diagnostic codes. Information on stage of renal failure, if available on these patients, will also be extracted from The Swedish Renal Register.

Crude annualized incidence rates of the specified endpoint events will be presented accompanied by 95% confidence intervals based on the exact method when the observed number of events is 20 or less and based on a normal approximation of the Poisson distribution if the number of events is greater than 20.

Event-free survival will be presented graphically with the Kaplan–Meier method, and analysed using univariable and several multivariable Cox regressions. In the multivariable models cofactors with previously verified association with bleeding, stroke, myocardial infarction or VTE will be introduced in the analyses according to the specific endpoint being analysed. The analyses will be performed in a manual stepwise manner, showing the impact of addition of new cofactors on the point estimate. Censoring will be done at the specific endpoint, death or end of follow-up whichever occurred first.

Propensity score matching regarding the likelihood of receiving rivaroxaban or standard of care will be performed in order to reduce differences between groups due to confounding by indication.

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 such as exposure to rivaroxaban or standard of care and hospitalizations for bleedings or any other outcome event; otherwise this individual is not eligible to be a member of the study population. However, missing values may occur for potential confounder or effect modifying variables. In this case, individuals with missing values will be kept in the analysis and a separate category will be created for missing values of that variable. In sub-analyses to evaluate confounding or effect modification by variables with a large proportion of missing values, the evaluation will be considered to be conducted on the subset with complete data for the variable of interest.

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 (Ingelsson, Arnlov et al. 2005; Smith, Platonov et al. 2010; Ludvigsson, Andersson et al. 2011). The review by Ludvigsson et al (2011) 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 can be omitted if there are 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. A second data analyst will review data preparation steps and analysis programs as well as the strategy for the statistical analysis. 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 log 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. Log 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 of the research methods

Limitations of this study include:

- 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. Propensity score matching and multivariate analyses will not be able to eliminate this effect completely, since all relevant information about comorbidities will not be recorded in the registries.
- 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 obesity, smoking and alcoholism. Thus, risk scores according to CHA2DS2-VASc and HAS-BLED are likely to represent underestimates of the true score.
- Information on prescriptions dispensed but not used, and about drugs used by patients during hospital stay, are not captured.

- The dose of warfarin will be based on assumptions that may be approximately correct on group level but may not be correct for each individual, this implies a potential for misclassification (Skeppholm and Friberg 2014).
- Inadequate data concerning medication compliance or persistence on-medication.
- The broad classification of renal failure used in this study will likely result in lower sensitivity to detect mild renal failure than for more severe forms of renal failure where the sensitivity is expected to be higher.

9.10 Other aspects

None applicable.

10 Protection of human subjects

This study protocol will be approved by a Research Ethics Committee (REC), and the study will be conducted in accordance with Good Pharmacoepidemiology Practices (European Medicines Agency 2012) (ISPE 2007).

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, reporting of individual adverse reactions is not required. In case adverse events/reactions will be identified, they will be reported in aggregated form in the final 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 as outlined in Section 6.
- 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.

13 List of references

Bjorck, S., B. Palaszewski, et al. (2013). "Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study." Stroke **44**(11): 3103-3108.

European Medicines Agency (2012) "Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products."

Friberg, L. and L. Bergfeldt (2013). "Atrial fibrillation prevalence revisited." J Intern Med **274**(5): 461-468.

Ingelsson, E., J. Arnlov, et al. (2005). "The validity of a diagnosis of heart failure in a hospital discharge register." Eur J Heart Fail **7**(5): 787-791.

ISPE. (2007). "Guidelines for good pharmacoepidemiology practices (second revision)." Retrieved 10 Oct, 2010, from http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

Lassen, M. R., W. Ageno, et al. (2008). "Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty." N Engl J Med **358**(26): 2776-2786.

Lip, G. Y., R. Nieuwlaat, et al. (2010). "Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation." Chest **137**(2): 263-272.

Ludvigsson, J. F., E. Andersson, et al. (2011). "External review and validation of the Swedish national inpatient register." BMC Public Health **11**: 450.

Pisters, R., D. A. Lane, et al. (2010). "A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey." Chest **138**(5): 1093-1100.

Skeppholm, M. and L. Friberg (2014). "Adherence to warfarin treatment among patients with atrial fibrillation." In preparation.

Smith, J. G., P. G. Platonov, et al. (2010). "Atrial fibrillation in the Malmo Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity." Eur J Epidemiol **25**(2): 95-102.

Turpie, A. G., M. R. Lassen, et al. (2009). "Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial." Lancet **373**(9676): 1673-1680.

Annex 1. List of stand-alone documents

Table 3: 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:
A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice 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]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

To be added to EU PAS register one PRAC approval is granted.

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)	☒	☐	☐	7-8
2.1.2 The objective(s) of the study?	☒	☐	☐	7-8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7-8
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☒	☐	☐	7-8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**

[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 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)	☒	☐	☐	9-17
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9-17
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)	☒	☐	☐	9-17

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	9-12
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9-12
4.2.2 Age and sex?	☒	☐	☐	9-12
4.2.3 Country of origin?	☒	☐	☐	9-12
4.2.4 Disease/indication?	☒	☐	☐	9-12
4.2.5 Co-morbidity?	☒	☐	☐	9-12
4.2.6 Seasonality?	☐	☒	☐	9-12
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9-12

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)	☒	☐	☐	9
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)	☒	☐	☐	8, 14, 17
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	10-11
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?	☒	☐	☐	13
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)	☒	☐	☐	14-17

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)	☒	☐	☐	17

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.)	☒	☐	☐	9-10
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.)	☒	☐	☐	13
8.1.3 Covariates?	☒	☐	☐	12, 26
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)	☒	☐	☐	9-10
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	13
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	12, 26
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	9, 12, 26
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	12-13
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical	☒	☐	☐	9,13

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
Therapeutic Chemical (ATC)Classification System)				
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	13-15,

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:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	13
10.2 Is the choice of statistical techniques described?	☒	☐	☐	16
10.3 Are descriptive analyses included?	☒	☐	☐	16
10.4 Are stratified analyses included?	☒	☐	☐	13
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	16
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?	☒	☐	☐	19
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	15-16
11.3 Are methods of quality assurance described?	☒	☐	☐	11 and 15
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	13-15, 17
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	19-20

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**

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
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	15
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?	☒	☐	☐	9
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9, 16

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?	☐	☒	☐	

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?	☐	☒	☐	

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Annex 3. Additional information: ICD-10 codes

Table 4. ICD-10 codes used to define disease conditions

Condition	**ICD-10 or Swedish procedure code beginning with**
Intracranial bleeding	I60-62, S064, S065, S066
Gastrointestinal bleeding	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 bleeding	N02, R319, N95
Other bleeding	H431, R04, R58, D629, procedure code DR029
Anaemia	D50-64
Coagulation or platelet defect	D65-69
Ischaemic stroke	I63
Unspecified stroke	I64
TIA	G45
Peripheral systemic emboli	I74
Thromboembolism (composite)	I63-64, G45, I74
Pulmonary embolism	I26
Deep venous thrombosis	I801-802
Venous thromboembolism (composite)	I26, I801-802
Myocardial infarction	I21,I252
Ischaemic heart disease	I20-25
PCI-procedure	Procedure code FNG
CABG-procedure	Procedure codes FNA,FNB,FNC,FND,FNE,FNE,FNH
Peripheral arterial disease	I70-73
Vascular disease (as in CHA_2DS_2-VASc)	I21, I252, I70-73
Heart failure	I50
Valvular disease	I34-39, I050, I052, Q232, Z952, Z953 procedure codes FG,FJE, FJF,FK,FM
Prosthetic heart valve (biological)	Z953
Prosthetic heart valve (mechanic)	Z952
Pacemaker or ICD	Z950, Z450, procedure code FPE
Hypertension	I10-15
Diabetes	E10-14
Renal failure	N17-19, procedure codes DR016, DR024, KAS00, KAS10, KAS20
Liver disease	K70-77, procedure codes JJB, JJC
Thyroid disease	E00-07
Chronic obstructive pulmonary disease	J43-44
Cancer	Diagnosis in chapter C within previous 3 years
Alcohol (Swedish alcohol index)	E244,F10,G312,G621,G721,I426,K292, K70, K860,O354,P043, Q860,T51,Y90-91,Z502,Z714
Frequent faller	W00-19 (2 or more hospitalizations with diagnosis)
Dementia	F00-03

Annex 4. Signature pages