NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Beyond Pooled –Part of the BEYOND study program (BEnefit of NOACs studY of nOn-valvular AF patieNts in NorDic countries)
Protocol number	B0661103
Protocol version identifier	1
Date of last version of protocol	28 SEPTEMBER 2017
EU Post Authorisation Study (PAS) register number	Study not registered
Active substance	B01AA03 – warfarin B01AE07 – dabigatran B01AF01 – rivaroxaban B01AF02 – apixaban
Medicinal product	Warfarin Pradaxa® - dabigatran Xarelto® - rivaroxaban Eliquis® - apixaban
Product reference	EU/1/11/691/001-015
Procedure number	EMEA/H/C/002148
Marketing Authorisation Holder (MAH)	Bristol-Myers Squibb/Pfizer European Economic Interest Group (EEIG)
Joint PASS	No

Research question and objectives	The overall aim of this study is to evaluate effectiveness and safety of each NOAC compared with warfarin in treatment-naïve initiators of anticoagulants with NVAF in routine clinical practice in Denmark, Norway and Sweden. The study will use pooled data from nationwide registries in Denmark, Norway and Sweden.
Country(-ies) of study	Sweden Denmark Norway
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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial fibrillation
ACE	Angiotensin converting enzyme
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BEYOND	**BE**nefit of NOACs stud**Y** of n**O**n-valvular AF patie**N**ts in Nor**D**ics
CAD	Coronary artery disease
CDM	Common data model
$CHADS_2$	Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke [double weight]
CHA_2DS_2VASc	Congestive heart failure/LV dysfunction, Hypertension, Age≥75 y, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 y, Sex category
CHF	Congestive heart failure
CI	Confidence interval
CPE	Centre for Pharmacoepidemiology
DK	Denmark
DVT	Deep vein thrombosis
EMA	European Medicines Agency
GI	Gastrointestinal
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practice
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol
HR	Hazard ratio
ICD-10	International Classification of Diseases, Tenth Revision
ID	Identification
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
NO	Norway
NI	Non-interventional
NOAC	Non-vitamin K oral anticoagulants
NOMESCO	Nordic Medico-Statistical Committee
NSAID	Non-steroidal antiinflammatory drug
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
PAD	Peripheral arterial disease
PAS	Post-Authorisation Study
PE	Pulmonary embolism

RCT	Randomised controlled trial
RR	Relative risk
SAP	Statistical Analysis Plan
SE	Sweden
SSRI	Selective serotonin reuptake inhibitor
TIA	Transient ischaemic attack
US	United States
VKA	Vitamin K antagonist

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Title: Beyond Pooled – Part of the BEYOND study program (BEnefit of NOACs studY of nOn-valvular AF patieNts in NorDic countries)

Rationale and background: Atrial fibrillation (AF) is the most common cardiac rhythm disorder, and constitutes a significant healthcare burden across Europe. Most AF patients require treatment with oral anticoagulants (OACs), for which vitamin K antagonists (VKAs) have been the standard care. Challenges of treatment with VKAs include the need for close monitoring; dietary restrictions; and concerns about drug interactions. Bleeding, especially intracranial bleeding, is the main safety concern associated with VKAs use. Non-vitamin K oral anticoagulants (NOACs) represent an alternative treatment option for patients with non-valvular AF (NVAF), since they allow for a more convenient anti-coagulant regimen than VKAs, with comparable efficacy and safety. There is a need for data on comparative effectiveness and safety of OACs in routine clinical practice. *Research question and objectives*: This study aims to assess effectiveness and safety of apixaban, rivaroxaban, dabigatran, and warfarin among adults with NVAF; and to describe characteristics and health care utilization among their users. *Study design:* These aims will be examined in a cohort study based on data from national population-based administrative registries in Denmark, Norway, and Sweden. *Population:* In this cohort study, the study population will be comprised of treatment-naïve adult NVAF patients initiating apixaban, rivaroxaban, dabigatran, or warfarin in 2013-2016 in Denmark (DK), Norway (NO), and in 2013-2015 in Sweden (SE). *Data sources:* Information will be drawn from Danish national registries (National Patient Registry, National Health Services Prescription Database, Civil Registration System and Statistics Denmark) Norwegian national registries (Patient Registry, Prescription Database, Population Register of Norway, Statistics Norway) and Swedish national registries (Total Population Register, National Patient Register, Prescribed Drug Register and Statistics Sweden). *Variables*: The primary endpoints are stroke/systemic embolism and major bleeding. The secondary endpoints are ischaemic stroke, haemorrhagic stroke, major intracranial bleeding, major gastrointestinal bleeding, acute myocardial infarction, or death of any cause; any hospitalized bleeding, and composite outcome of ischemic stroke, systemic embolism, myocardial infarction, or all-cause mortality. Demographic, clinical and socioeconomic characteristics will be assessed descriptively. Health care utilisation associated with the primary endpoints will be assessed descriptively. Selected analyses will be stratified in subgroups defined by country; age; sex; CHA_2DS_2VASc (Congestive heart failure/LV dysfunction, Hypertension, Age≥75 y, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 y, Sex category) score; $CHADS_2$ (Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke [double weight]) score; HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol) score; initial dose; chronic renal impairment; congestive heart failure, coronary artery disease, diabetes, prior stroke and peripheral arterial disease. The primary analyses will be conducted using standard NOAC doses. Sensitivity analyses for selected contrasts will include those of reduced OAC doses depending on sample size, and intention-to-treat-like analyses. *Study Size*: The study will include at least 11,000 patients who were dispensed apixaban for the first time during the study period. *Data analyses*: Data from the three countries will be combined on the individual level. Crude and adjusted hazard ratios will be computed, using pairwise contrasts

of each NOAC against warfarin. Adjusted estimates will be obtained using pairwise propensity-score matched samples. This study will provide real world evidence about safety and effectiveness of the NOACs in patients with NVAF overall and in selected patient subgroups. *Milestones:* The data collection is anticipated to start on 1st October, 2017 and the Final Study Report will be submitted approximately end of June, 2018.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Start of data collection	06 October 2017
End of data collection	01 March 2018
Registration in the EU PAS register	06 October 2017
Final study report	01 June 2018

6. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is the most common cardiac rhythm disorder, which constitutes a significant healthcare burden across Europe. Prevalence of AF has been increasing in the last decade owing to diagnostic advances (1). In Scandinavian countries, AF prevalence in adults is 2%-3% (2). Risk of AF increases with age, and it is more frequent in men than in women (1). AF is associated with, on average, a five-fold increase in the risk of stroke and a doubling of risk of death (2). Most AF patients require treatment with oral anticoagulants (OACs), for which the standard care have been vitamin K antagonists (VKAs) (3). VKAs are very effective in stroke prevention when optimally dosed. Challenges of treatment with VKAs include the need for close monitoring (via the international normalized ratio [INR] measures) to maintain the optimal anticoagulation level; dietary restrictions to allow for constant dosing; and concerns about drug interactions. Bleeding, especially intracranial bleeding, is the main safety concern associated with VKAs use (4).

Non-vitamin K oral anticoagulants (NOACs) represent an alternative treatment option for patients with non-valvular AF (NVAF), since they allow for a more convenient anti-coagulant regimen than VKAs (primarily warfarin), with comparable efficacy and safety (3). In randomised controlled trials (RCTs) of NOACs vs. warfarin among patients with NVAF (the ARISTOTLE trial [apixaban] (5); the RE-LY trial [dabigatran] (6); and the ROCKET-AF trial [rivaroxaban] (7)), apixaban was the only NOAC with lower rate of discontinuation or major bleeding compared with warfarin (5-7). In two network meta-analyses of the three trials' data (adjusted indirect comparisons of each NOAC against warfarin), apixaban was more efficacious (8) and safer as measured by discontinuation and bleeding outcomes (9) compared with rivaroxaban or dabigatran. A subsequent meta-analysis included four additional RCTs, evaluating edoxaban and ximelagatran in addition to apixaban, dabigatran and rivaroxaban. It showed no evidence for superiority of any NOAC drug class of once vs. twice daily regimen (10).

NOACs are recommended as first-line treatment strategy for stroke prevention in patients with AF by both United States (US) (11) and European (12) guidelines. However, national and sub-national payers in Europe are requiring data on comparative effectiveness and safety of OACs in routine clinical practice since the efficacy and safety achieved in the idealized clinical trial settings may not necessarily translate to routine practice because of the differences in the patient populations, the intensity of follow-up, and the variations in care that patients receive. The increasing interest in post-trial use of approved therapies and improved access to information on health care derived from multiple sources outside typical clinical research settings, including electronic health records, claims and billing data, product and disease registries, has led to a rapid growth in the field of real world evidence, including real world evidence on OACs. Key to understanding the usefulness of real-world evidence is an appreciation of its potential for complementing the knowledge gained from traditional clinical trials.

A number of observational studies have examined the safety and effectiveness of NOACs in real world settings, including both European and US studies. In three recent Danish cohort studies, NOACs and warfarin were associated with similar risks of ischemic stroke, but apixaban and dabigatran conferred lower risks of death (13) and bleeding (13-15). In a

Norwegian study, apixaban and dabigatran were associated with a lower risk of major or clinically relevant non-major bleeding than warfarin, with the exception of gastrointestinal bleeding, which was higher with dabigatran and rivaroxaban (16). Similar findings have been reported from the US, i.e., dabigatran, rivaroxaban, and apixaban were found to have similar effectiveness, but apixaban may be associated with a lower bleeding risk and rivaroxaban may be associated with an elevated bleeding risk (17). A Danish study of outcomes among patients treated with reduced-dose OACs found generally comparable rates of thromboembolic and bleeding events in all groups, noting a trend towards a higher rate of thromboembolic events associated with reduced dose of apixaban (18).

OAC treatment should, in principle, be life-long or at least long-term and without unnecessary interruptions, if the full benefit of the therapy is to be obtained. Knowledge about real-world OAC treatment patterns and adherence to treatment is therefore essential as it may be particularly challenging to extrapolate findings on adherence from trials on OACs to general practice since OACs are long-term preventive medications that address no ongoing symptoms. Furthermore, appropriate dosing may be hard to achieve in clinical practice because of the complexity of real-world settings. Existing data on adherence with NOACs provide somewhat conflicting results. A recent nationwide Danish study, which included NOACs initiators between August 2011 and February 2016, showed that 10% of NOAC initiators switched to a VKA within one year of initiation. The one year-risks of switching were 12% for initiators of dabigatran, 8% among initiators of rivaroxaban, and 6% among initiators of apixaban (19). Another Danish study reported high adherence to dabigatran, where approximately 75% of the patients were > 80% adherent to medication regimes during the first year (20). In Sweden, an overall high adherence to OACs has also been reported, with higher persistence for warfarin and apixaban than for dabigatran and rivaroxaban in routine clinical care (21). In contrast, in the US, the estimated discontinuation rate was 47% with a mean follow-up time of 416 days regardless of OAC used (22).

Although the first generation of real-world evidence on NOACs is reassuring and nicely complements the phase III RCTs, more insights and data are clearly still needed. Among the limitations affecting many of the existing studies are the relatively short average duration of follow-up, concerns about residual confounding, and only moderate statistical precision due to sample size. The limitations are of a particular concern regarding apixaban as the observation period for apixaban has been shortest and study populations the smallest of the studied NOACs, because apixaban was launched later than the other agents. Thus, evidence is needed on long-term safety and effectiveness of apixaban from large-scale population-based studies. The uptake of NOACs in the Scandinavian countries has been high (23, 24). That, in combination with nearly 100% completeness of out of hospital dispensations, person-level linkage to data from other high-quality registries with national coverage, and complete follow-up, make Scandinavian countries an optimal setting to address comparative effectiveness of NOACs in routine clinical practice. Other advantages of the Scandinavian countries for pharmacoepidemiologic research include universal access to health care, similar clinical practice, as well as uniform recording practices, comparable patterns of hospitalization and referral to specialist care, and high overall quality of care, including high quality of warfarin therapy (25-33).

This study aims to assess effectiveness and safety of apixaban, rivaroxaban, dabigatran, and warfarin among patients with NVAF and to describe characteristics and health care utilization level among their users. The specific study objectives will be addressed using routinely collected data pooled from national health and administrative registries in the three Scandinavian countries – Denmark, Norway, and Sweden.

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

7. RESEARCH QUESTION AND OBJECTIVES

The overall aim of this study is to evaluate effectiveness and safety of each NOAC compared with warfarin in treatment-naïve adult initiators of anticoagulants with NVAF in routine clinical practice in Denmark, Norway and Sweden. The specific objectives as applied to the study population are listed below.

7.1. Primary objectives

- To compare risks of stroke or systemic embolism among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin.

- To compare risks of major bleeding among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin.

7.2. Secondary objectives

- To compare risks of ischemic stroke among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of haemorrhagic stroke among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of major intracranial bleeding among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of major gastrointestinal bleeding among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of acute myocardial infarction among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare all-cause mortality among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of the composite outcome of ischemic stroke, systemic embolism, acute myocardial infarction, or all-cause mortality among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of any hospitalized bleeding among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To describe demographic, clinical, and socioeconomic [to the extent possible] characteristics for OAC treatment naïve patients with NVAF who initiate apixaban, dabigatran, rivaroxaban, or warfarin.

7.3. Exploratory objective

To describe bleeding- and stroke-related acute care hospital care resource utilization among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin, specifically, the number of hospitalizations and bed days and to assess associated costs to the extent possible.

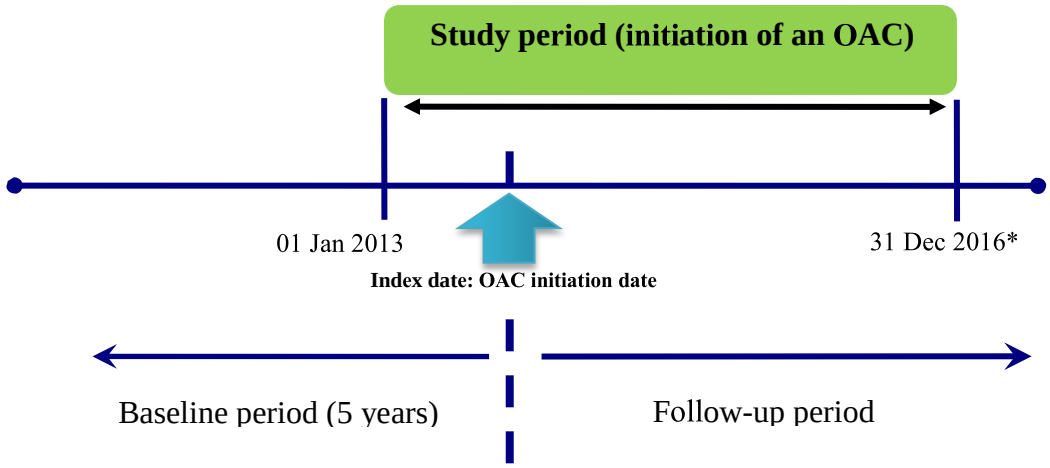
8. RESEARCH METHODS

8.1. Study design

This study will be a cohort study based on data from national routine population-based administrative health registries and databases in Denmark, Norway, and Sweden. The period for identifying the study population will be from 01 January 2013 to 31 December 2016 in Denmark and Norway and from 01 January 2013 to 31 December 2015 in Sweden, to reflect dates of apixaban availability and the years of available data. For each patient included in the study, the date of dispensation of the first OAC during the above period will be the index date (Figure 1).

This study will utilize the ‘active comparator new user’ design (34-36). Restriction of the study population to OAC treatment initiators (new users) emulates the principle of RCTs of aligning the start of follow-up with the start of treatment. This design reduces the risk of selection bias, such as healthy initiator bias, whereby prevalent users of medications may represent a selected group of all users, in that they are depleted of patients who discontinued treatment after experiencing an adverse event (AE) shortly after initiation (‘depletion of susceptibles’) (37). Depletion of susceptibles is avoided by the new user design. Propensity-score matched contrasts will be estimated for each NOAC vs. warfarin, to allow comparison of results with those from RCTs.

Figure 1. Study design schema



Abbreviation: OAC oral anticoagulant
*31 Dec 2015 in Sweden

8.2. Setting

This study will be set in the three Scandinavian countries, each of which has tax-supported universal health care; routine recording of prescription dispensations, hospital diagnoses, migrations and deaths, and individual-level data linkage, thus enabling nearly complete follow-up of the entire populations and virtually no selection bias in epidemiologic studies.

The source population of this study will be persons who are alive and residents of each Scandinavian country on 01 January 2013. In 2013, the adult population was 4,412, 327 persons in Denmark (www.statistikbanken.dk, figure for first quarter 2013); 3,928,378 persons in Norway (https://www.ssb.no/en/befolkning) and 7,627,772 persons in Sweden (http://www.scb.se/, figure for 31 December 2012).

8.3. Study population

The study population will be identified as adults (age 18 years or older on the index date) in the source population who have been diagnosed with non-valvular atrial fibrillation and initiated apixaban, rivaroxaban or dabigatran ('the NOACs') or warfarin between 01 January 2013 and 31 December 2016 (31 December 2015 for Sweden). Warfarin accounts for >98% of the vitamin K antagonists dispensed in the Scandinavian countries (Table 2). In the main analyses, patients will be followed from the index date until a given endpoint, death, OAC switching or discontinuation, emigration, or 31 December 2016, whichever comes first. In the sensitivity analyses of selected contrasts (an intention-to-treat like analysis), patients will be followed from the index date until a given endpoint, death, emigration, or 31 December 2016 (31 December 2015 for Sweden), whichever comes first.

8.3.1. Inclusion criteria

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

1. Age 18 years or older on the date of initiation of a NOAC or warfarin

2. Initiation of apixaban, dabigatran, rivaroxaban, or warfarin between 01 January 2013 and 31 December 2016 (31 December 2015 for Sweden) (inclusive); the date of the first dispensation of any of the above agents during the study period will be the index date

3. Diagnosis of AF recorded, using International Classification of Diseases, Tenth Revision (ICD-10) codes, in each country's national patient registry up to 5 years before or up to 60 days after the index date, inclusive

8.3.2. Exclusion criteria

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

1. Diagnosis of mitral stenosis AND/OR record of presence of mechanical heart valves identified by ICD-10 or procedure codes at any time before the index date, to rule out non-NVAF indication of OAC use

2. A diagnosis of pulmonary embolism (PE) or deep vein thrombosis (DVT) recorded up to 6 months before and including the index date, to rule out non-NVAF indication of OAC use

3. A record of knee arthroplasty or hip arthroplasty 6 weeks before and including the index date, to rule out non-NVAF indication of OAC use

4. A dispensation, within the 12 months of the index date (the washout period), of any VKAs Anatomical Therapeutic Chemical (ATC) codes B01AA), direct thrombin inhibitors (ATC codes B01AE), or direct factor Xa inhibitors (ATC codes B01AF)

5. Dispensation of more than one different OACs on the index date

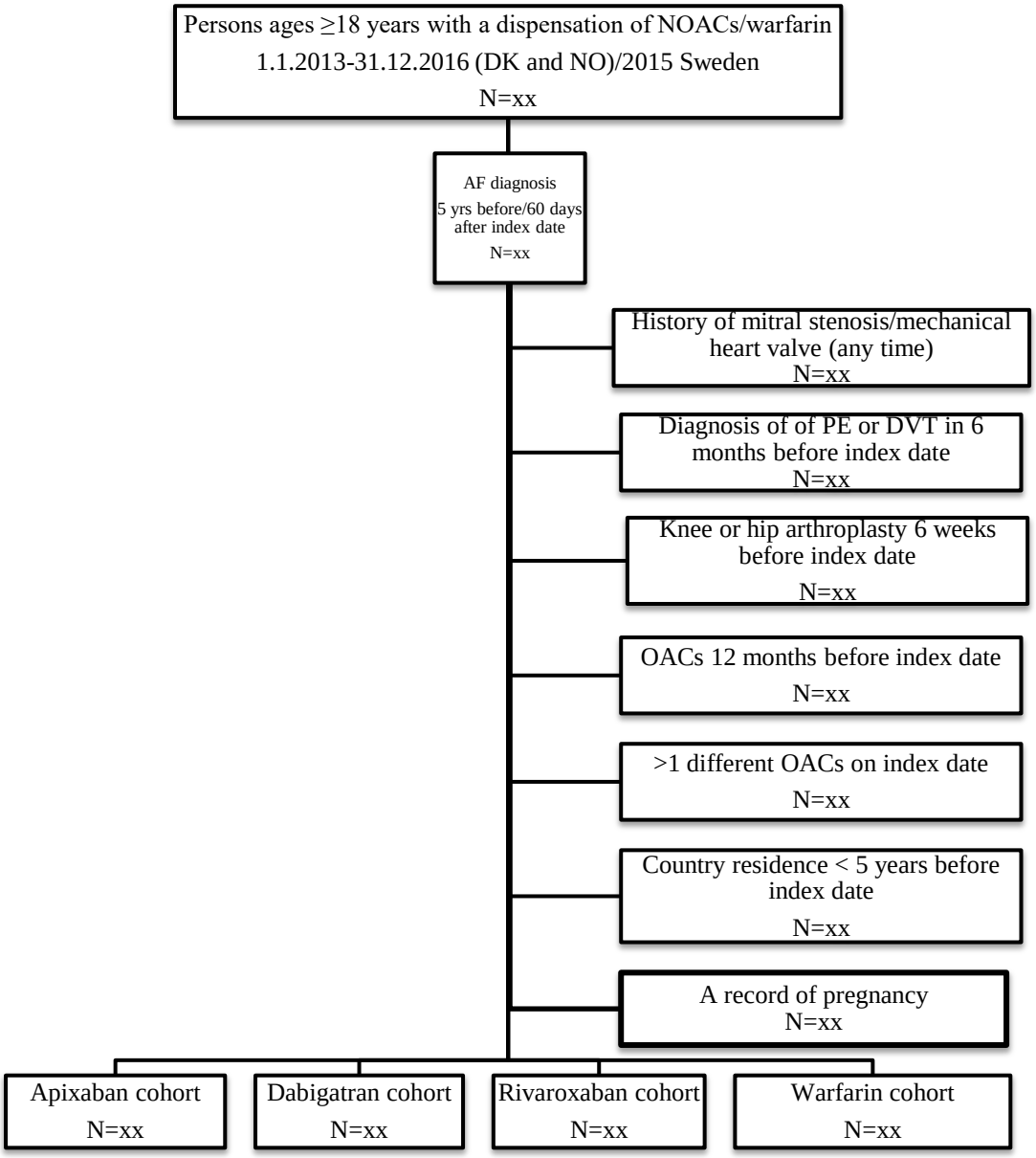
6. Residence in a given country for less than 5 years before the index date

7. A record of pregnancy in a national patient registry

After applying the inclusion and exclusion criteria, eligible patients will be assigned to the following exposure cohorts based on the newly initiated OAC, with index date being the date of initiation (Figure 2):

- **Apixaban cohort:** NVAF patients who initiated apixaban on the index date
- **Dabigatran cohort:** NVAF patients who initiated dabigatran on the index date
- **Rivaroxaban cohort:** NVAF patients who initiated rivaroxaban on the index date
- **Warfarin cohort:** NVAF patients who initiated warfarin on the index date

Figure 2. Flow diagram of identification of the study population



Abbreviations: AF atrial fibrillation, DVT deep vein thrombosis, NOAC non-vitamin K oral anticoagulant, OAC oral anticoagulant, PE pulmonary embolism

8.4. Variables

8.4.1. Exposure

Initiation of an OAC in each cohort will be measured using outpatient dispensations recorded in the nationwide prescription registries of the three Scandinavian countries (see Table 1 in the section Data sources).

8.4.2. Endpoints

The following primary and secondary endpoints will be defined.

8.4.2.1. Primary endpoints

- Stroke or systemic embolism
- Major bleeding (intracranial; gastrointestinal [GI]; other) at an acute hospitalization

8.4.2.2. Secondary endpoints

- Ischemic stroke at an acute hospitalization
- Haemorrhagic stroke at an acute hospitalization
- Major intracranial bleeding at an acute hospitalization
- Major gastrointestinal bleeding at an acute hospitalization
- Acute myocardial infarction at an acute hospitalization
- Death from any cause
- Composite endpoint of ischemic stroke, systemic embolism, acute myocardial infarction, or death from any cause
- Any bleeding at an acute hospitalization

8.4.2.3. Exploratory endpoints

- Distributions of bleeding- and stroke-related health care resource utilization indicators, including annual distributions of the number of hospitalizations with major bleeding and stroke (and bed days); annual number of ER/unplanned visits with major bleeding and stroke; annual number of outpatient specialist visits (with major bleeding and stroke), and annual costs.

8.4.3. Covariates

Baseline characteristics of the study cohorts will be ascertained during the 5-year baseline before and including the index date (38): age at index date (in groups and as a continuous variable), sex, comorbidity (using the Charlson Comorbidity Index (39, 40)), the CHA_2DS_2VASc score, $CHADS_2$ score, the HAS-BLED score, major bleeding, ischemic stroke, transient ischemic attack (TIA), history of CHF, cancer, diabetes, hypertension, renal failure, liver failure, myocardial infarction, alcohol abuse, peripheral arterial disease (PAD), coronary artery disease (CAD). Baseline concomitant medication use will be assessed as history of dispensations for angiotensin converting enzyme (ACE) inhibitors, amiodarone, dronedarone, beta-blockers, H2-receptor antagonists, proton pump inhibitors, antidiabetics, anti-platelets, statins, aspirin, selective serotonin reuptake inhibitors (SSRIs), and non-steroidal anti-inflammatory drugs (NSAIDs). Socioeconomic characteristics will include

income, education, and employment. Data on socioeconomic characteristics will be available in Denmark and Sweden.

8.4.4. Subgroups

Consistency for the primary endpoints and of the composite secondary endpoint will be evaluated among patients according to the following clinical or demographic characteristics:

- In each country (Denmark, Norway, Sweden)
- By age at OAC initiation (<65; 65-<75 years, ≥75-<85 years; and in patients ≥85 years if sample size permits)
- By sex (men and women)
- According to CHA_2DS_2VASc score category in the baseline
- According to $CHADS_2$ score category in the baseline
- According to HAS-BLED score category in the baseline
- According to dosage in the baseline (standard dose and reduced dose)
- In patients with/without chronic renal impairment in the baseline
- In patients with/ without congestive heart failure (CHF) in the baseline
- In patients with/ without coronary artery disease (CAD) in the baseline
- In patients with/ without peripheral arterial disease (PAD) in the baseline
- In patients with/ without stroke in the baseline
- In patients with/without diabetes in the baseline

Depending on sample size, subgroup analyses for the primary and the composite endpoint may be repeated in some of the above subgroups with appropriate re-matching.

8.5. Data sources

Data for this study will originate from selected national registries in Denmark, Norway and Sweden. Table 1 summarizes definition of exposures, outcomes along with the data sources that will be used to identify variables for this study. In each country, data from all registries are individually linkable via a unique personal identifier. An important advantage is similar data structure, and coding systems used in all three Scandinavian countries.

Table 1. National registries in Denmark, Norway and Sweden and type of data available from each

Variable	Role	Data source(s)	Operational definition
AF and inclusion/exclusion criteria based on hospital diagnoses and procedures	Definition of the study population	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	Diagnostic and procedure codes during hospital encounters, see Annex 3
Initiation of an OAC (apixaban, dabigatran, rivaroxaban, warfarin)	Exposure	Danish National Health Services Prescription Database (33, 43), Norwegian Prescription Database (33), Swedish Prescribed Drug Register (33)	An outpatient dispensation with a relevant ATC code, see Annex 3
Stroke/systemic embolism	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	Diagnoses during hospital encounters, see Annex 3
Ischaemic stroke	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	Diagnoses during hospital encounters, see Annex 3
Haemorrhagic stroke	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	Diagnoses during hospital encounters, see Annex 3
Major bleeding	Endpoint	Danish National Patient Registry(30), Norwegian Patient Registry(41), Swedish National Patient Register (32, 42)	Diagnoses during hospital encounters, see Annex 3
Intracranial bleeding	Endpoint	Danish National Patient Registry(30), Norwegian Patient Registry(41), Swedish National Patient Register (32, 42)	Diagnoses during hospital encounters, see Annex 3
Gastrointestinal bleeding	Endpoint	Danish National Patient Registry(30), Norwegian Patient Register(41), Swedish National Patient Register (32, 42)	Diagnoses during hospital encounters, see Annex 3
Other bleeding	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	Diagnoses during hospital encounters, see Annex 3
Acute myocardial infarction	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	Diagnoses during hospital encounters, see Annex 3
Death of all causes	Endpoint	Danish Civil Registration System (31), National Population Register of Norway, Swedish Total Population Register (29), National Registry (Norway) (44), Swedish Population Register (29)	As recorded
Any hospitalized bleeding	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	Diagnoses during hospital encounters, see Annex 3
Emigration	Censoring variable	Danish Civil Registration System (31), National Population Register of Norway, Swedish Total Population Register (29), National Registry (Norway) (44), Swedish Population Register (29)	As recorded
Sex	Covariate	Danish Civil Registration System (31), National Population Register of Norway, Swedish Total Population Register (29), National Registry (Norway) (44), Swedish Population Register (29)	As recorded
Age, years	Covariate/subgroup variable	Danish Civil Registration System (31), National Population Register of Norway, Swedish Total Population Register (29), National Registry(Norway) (44), Swedish Population Register (29)	As recorded

Variable	Role	Data source(s)	Operational definition
Renal impairment	Covariate/subgroup variable	Danish Civil Registration System (31), National Population Register of Norway, Swedish Total Population Register (29), National Registry (Norway) (44), Swedish Population Register (29)	Diagnoses and procedures during hospital encounters, see Annex 3
CHA_2DS_2VASc score (45, 46)	Covariate/subgroup variable	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42) Danish National Health Services Prescription Database (33, 43), Norwegian Prescription Database (33), Swedish Prescribed Drug Register (33)	Derived, See Annex 3
$CHADS_2$ score	Covariate/subgroup variable	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42) Danish National Health Services Prescription Database (33, 43), Norwegian Prescription Database (33), Swedish Prescribed Drug Register (33)	Derived, See Annex 3
HAS-BLED, score (45, 46)	Covariate/subgroup variable	Danish National Patient Registry (29), Norwegian Patient Registry (41), Swedish National Patient Register (31, 42) Danish National Health Services Prescription Database (33, 43), Norwegian Prescription Database (33), Swedish Prescribed Drug Register (33)	Derived, See Annex 3
Concomitant medication	Covariate	Danish National Health Services Prescription Database (33, 43), Norwegian Prescription Database (33), Swedish Prescribed Drug Register (33)	An outpatient dispensation with a relevant ATC code, see Annex 3
Comorbidities	Covariates	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	Diagnoses and procedures during hospital encounters, see Annex 3
Health care utilisation	Descriptive characteristics	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	Types and dates of inpatient (planned and unplanned), outpatient (planned and unplanned), visits
Household income	Covariate	Statistics Denmark, Statistics Norway [not for pooled analysis], Statistics Sweden	Household income during 3 full calendar years preceding the index date, Euro
Education	Covariate	Statistics Denmark, Statistics Norway [not for pooled analysis], Statistics Sweden	Highest attained education, categorised into high/medium/low
Employment	Covariate	Statistics Denmark, Statistics Norway [not for pooled analysis], Statistics Sweden	Employment status in the calendar year preceding index date (employed/unemployed/retired)
Health care cost	Endpoint	Published data on health care costs for specific types of visit	Per year, Euro

8.6. Study size

Table 2 shows the number of users of NOACs in Denmark, Norway and Sweden in 2013-2015. Population risk of major bleeding in the study population is 2-3% per year (47). The number of eligible OAC users with NVAF will be smaller. A recent Danish comparative effectiveness study of OACs in new users with NVAF based on OACs use data between 2012 and 2015 enrolled approximately 35,000 initiators of warfarin, 12,000 initiators of dabigatran (150 mg); 7,000 initiators of rivaroxaban (20 mg), and 6,000 initiators of apixaban (5 mg) (13). In the apixaban group there were 90 cases of major bleeding after 1 year of follow-up and 109 cases after 2.5 years of follow-up (13). Another Danish study included more than 50,000 NOAC initiators with NVAF in August 2011-February 2016, of whom 70% were VKA naïve; the study included more than 12,000 initiators each of apixaban and rivaroxaban and more than 25,000 initiators of dabigatran. The study also demonstrated that about half of the NOAC initiators use these medication for the AF indication (19). In Norway, a study of anticoagulant-naïve NVAF patients initiating warfarin or NOACs in 2013-mid 2015, there were more than 6,000 initiators each of apixaban and rivaroxaban and nearly 8,000 initiators of dabigatran (16). Conservatively assuming the size of the apixaban cohort to be 24,000 patients in 2015, the expected number of major bleeding events in the apixaban group (the smallest) is 300 – 400 in the first year of follow-up.

Table 2. Persons ages 20 years or older with a dispensation of NOACs and VKAs for <u>any</u> indication in Denmark, Norway and Sweden, 2013-2015*

ATC code (active substance)	Denmark			Norway			Sweden		
	2013	2014	2015	2013	2014	2015	2013	2014	2015
B01AE07 (Dabigatran etexilate)	21,617	23,465	21,212	13,873	15,351	13,835	10,658	13,627	14,013
B01AF01 (Rivaroxaban)	10,877	16,023	22,500	13,394	20,759	25,439	9,652	21,140	33,868
B01AF02 (Apixaban)	1,772	8,023	17,926	2,258	8,636	21,498	2,072	17,132	46,926
B01AA(VKAs)**	91,202	89,783	87,851	87,900	77,681	69,212	202,729	202,729	188,966

*Unique in each calendar year; age categories as reported by the sources listed below
**Nearly all warfarin, e.g., in 2015 Denmark 98.2%, Norway 99.9%;Sweden 99.8%
Sources:
Denmark www.medstat.dk;
Norway www.norpd.no;
Sweden http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel%

Table 3, Table 4, Figure 3 and Figure 4 show the per-group size needed to detect a given increase/reduction of 1-year bleeding risk for alpha = 0.025 and alpha = 0.05 (calculations performed using PROC POWER in SAS 9.4). The 1-year background risk of bleeding was set to 2% in Table 3, and 3% in Table 4. The estimations show that the study should be able to identify a relative risk (RR) of 0.8 with a power of 90% and an alpha of 0.05 in a population with a background yearly bleeding risk of 2% if there are included at least 17,307 apixaban users (the smallest group) (Table 3). The estimations furthermore show that the study should be able to identify a relative risk of 0.8 with a power of 90% and an alpha of 0.05 in a population with a background yearly bleeding risk of 3% if there are at least 11,433 apixaban users (the smallest group) (Table 4). Similar computations apply to the other primary endpoint of stroke/systemic embolism.

Table 3. Group size for pairwise estimation of RR for a NOAC vs. warfarin 0.8 to 1.5. Assumptions: alpha=0.025 or 0.05. 1-year background risk of bleeding = 0.02

Computed N per Group					
Index	**Alpha**	**Relative Risk**	**Nominal Power**	**Actual Power**	**N per Group**
1	0.025	0.8	0.8	0.800	20959
2	0.025	0.8	0.9	0.900	27367
3	0.025	0.9	0.8	0.800	88543
4	0.025	0.9	0.9	0.900	115614
5	0.025	1.1	0.8	0.800	97671
6	0.025	1.1	0.9	0.900	127534
7	0.025	1.2	0.8	0.800	25530
8	0.025	1.2	0.9	0.900	33335
9	0.025	1.3	0.8	0.800	11833
10	0.025	1.3	0.9	0.900	15451
11	0.025	1.4	0.8	0.800	6927
12	0.025	1.4	0.9	0.900	9044
13	0.025	1.5	0.8	0.800	4604
14	0.025	1.5	0.9	0.900	6011
15	0.050	0.8	0.8	0.800	17307
16	0.050	0.8	0.9	0.900	23170
17	0.050	0.9	0.8	0.800	73115
18	0.050	0.9	0.9	0.900	97880
19	0.050	1.1	0.8	0.800	80653
20	0.050	1.1	0.9	0.900	107972
21	0.050	1.2	0.8	0.800	21082
22	0.050	1.2	0.9	0.900	28222
23	0.050	1.3	0.8	0.800	9772
24	0.050	1.3	0.9	0.900	13081
25	0.050	1.4	0.8	0.800	5720
26	0.050	1.4	0.9	0.900	7657
27	0.050	1.5	0.8	0.800	3802
28	0.050	1.5	0.9	0.900	5089

Figure 3. Group size for pairwise estimation of RR for a NOAC vs. warfarin 0.8 to 1.5. Assumptions: alpha=0.025 or 0.05. 1-year background risk of bleeding = 0.02

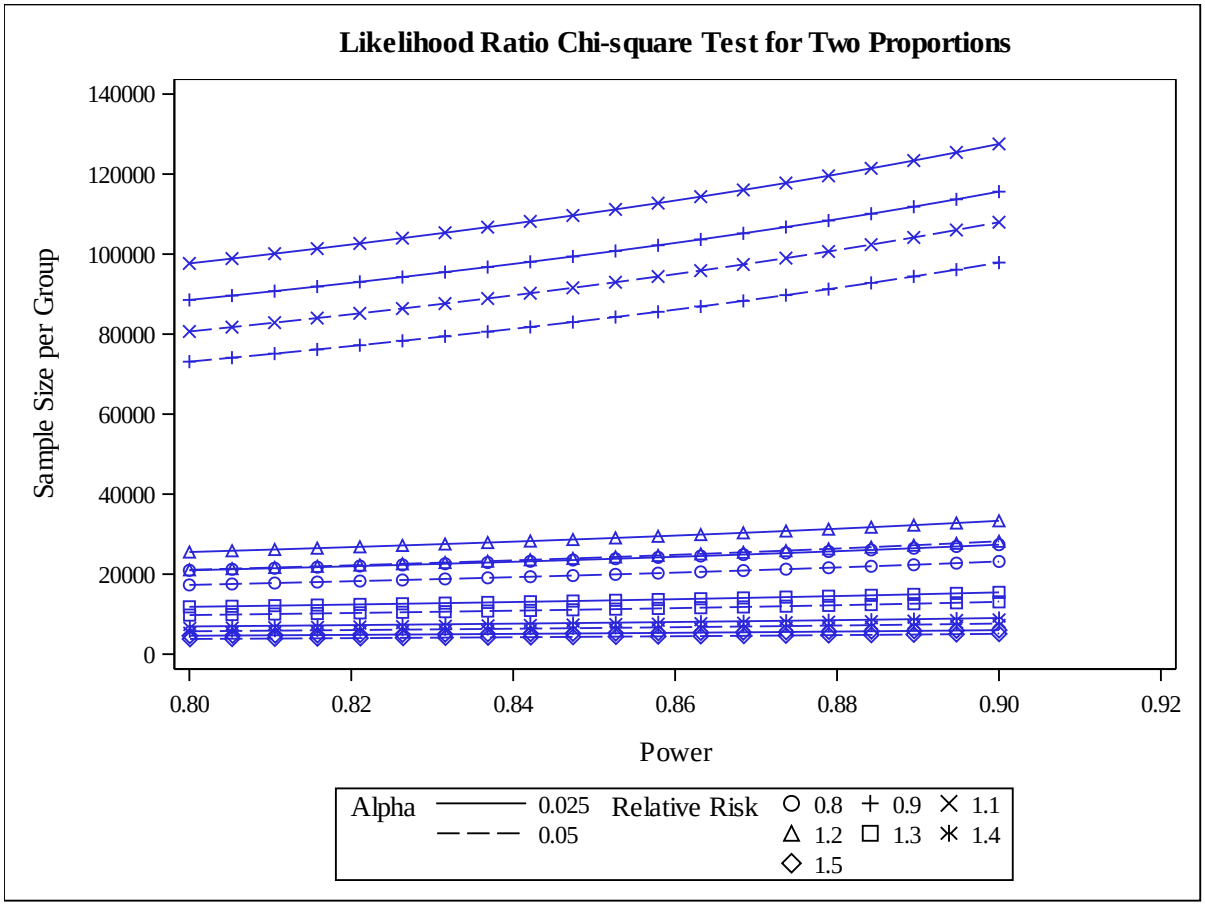
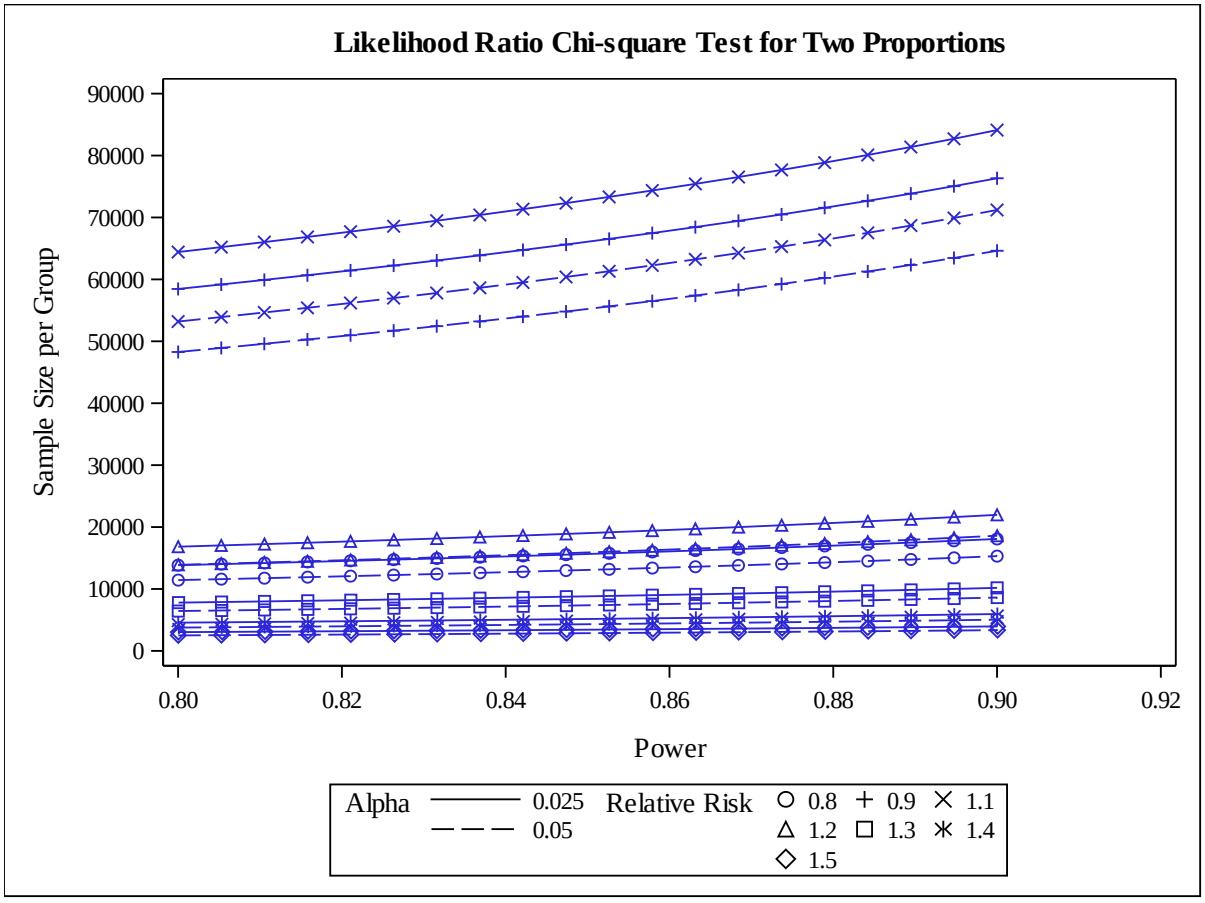


Table 4. . Group size for pairwise estimation of RR for a NOAC vs. warfarin 0.8 to 1.5. Assumptions: alpha=0.025 or 0.05. 1-year background risk of bleeding = 0.03

Computed N per Group					
Index	**Alpha**	**Relative Risk**	**Nominal Power**	**Actual Power**	**N per Group**
1	0.025	0.8	0.8	0.800	13845
2	0.025	0.8	0.9	0.900	18078
3	0.025	0.9	0.8	0.800	58457
4	0.025	0.9	0.9	0.900	76330
5	0.025	1.1	0.8	0.800	64416
6	0.025	1.1	0.9	0.900	84111
7	0.025	1.2	0.8	0.800	16829
8	0.025	1.2	0.9	0.900	21974
9	0.025	1.3	0.8	0.800	7797
10	0.025	1.3	0.9	0.900	10180
11	0.025	1.4	0.8	0.800	4561
12	0.025	1.4	0.9	0.900	5956
13	0.025	1.5	0.8	0.800	3030
14	0.025	1.5	0.9	0.900	3957
15	0.050	0.8	0.8	0.800	11433
16	0.050	0.8	0.9	0.900	15305
17	0.050	0.9	0.8	0.800	48272
18	0.050	0.9	0.9	0.900	64622
19	0.050	1.1	0.8	0.800	53192
20	0.050	1.1	0.9	0.900	71209
21	0.050	1.2	0.8	0.800	13897
22	0.050	1.2	0.9	0.900	18604
23	0.050	1.3	0.8	0.800	6438
24	0.050	1.3	0.9	0.900	8619
25	0.050	1.4	0.8	0.800	3767
26	0.050	1.4	0.9	0.900	5042
27	0.050	1.5	0.8	0.800	2502
28	0.050	1.5	0.9	0.900	3350

Figure 4. Group size for pairwise estimation of RR for a NOAC vs. warfarin 0.8 to 1.5. Assumptions: alpha=0.025 or 0.05. 1-year background risk of bleeding = 0.03



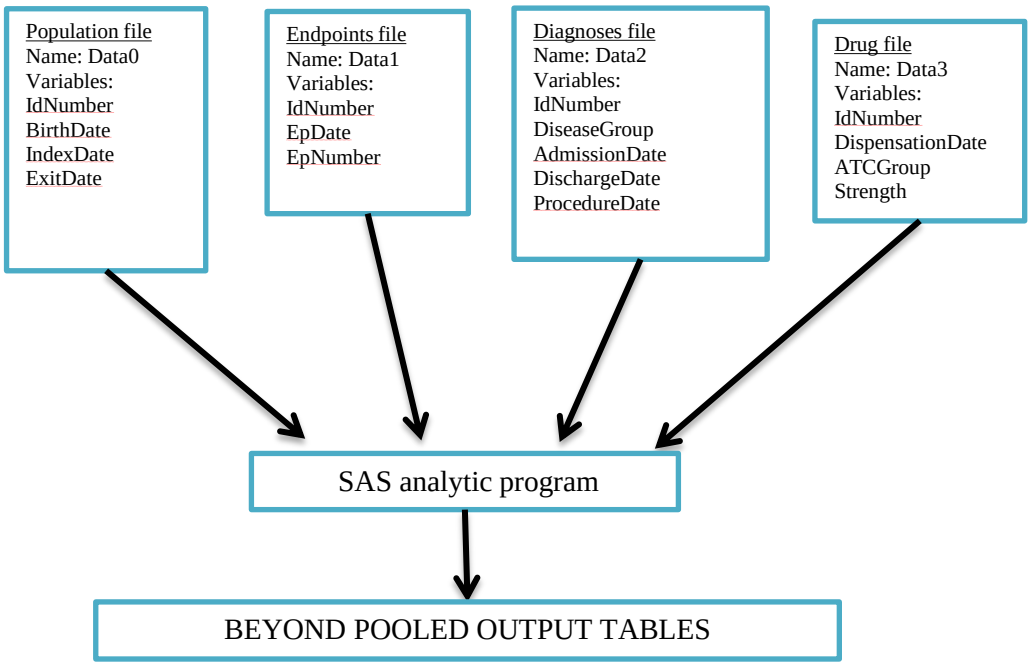
8.7. Data management

The planned analyses will be conducted, by a statistician at the Department of Clinical Epidemiology Aarhus University Hospital, on combined individual-level datasets from all three countries, prepared according to a common data model (CDM) (48). A CDM is a set of uniform datasets, whereby specified parameters include the names and the number of the datasets, full list of variables in each dataset (including all candidate variables for inclusion in estimation of propensity score), and attributes of each variable (including name, type, length, format). The CDM for this study will be developed by the Department of Clinical Epidemiology, Aarhus University Hospital and will consist, at a minimum, of a population file, a diagnosis file (covariates), an endpoint file, and a drug file (exposures and covariates); additional files containing socioeconomic variables may be created.

Each research partner will complete all data management (cleaning, coding, plausibility checks etc.) required to convert the raw data into the pre-specified CDM. Within each country, the CDM input data files will be linkable on individual level via a unique study

identifier. This identifier will replace the true personal identifier for the purpose of analysis. The completed input dataset will be transferred for analysis to a secure server at Statistics Denmark, where all data will be kept in accordance to the rules and regulations governing protection of personal data. Figure 5 shows an example of a CDM.

Figure 5. An example of the files prepared in each country according to a common data model.



The CDM will be detailed in the final SAP. Data will be managed and analysed using SAS software version 9.2 or higher (Cary, NC, USA). Investigators in Norway and Sweden will obtain all approvals required for data transfer to Denmark for analysis. All investigators have experience conducting multinational studies using CDM, both in Scandinavian (49, 50) and in other European studies (51).

8.8. Data analysis

All analyses will be conducted on the combined patient-level dataset and on patient-level dataset stratified by country. In the analysis combined across the three countries, country will be used as a cluster variable to account for within-country correlation in the multivariate models.

A statistician at the Department of Clinical Epidemiology, Aarhus University Hospital, will write the analytic code and will conduct all analyses within the scope of this protocol, including propensity score estimation, pooled analyses and analyses stratified by country.

Full operational definition for each variable, the CDM, and the analytic strategy, including variables for inclusion in the propensity score models, will be provided in the SAP.

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

8.8.1. Descriptive analysis

First, baseline characteristics (demographics, comorbidities, concomitant medications, risk factors, socioeconomic characteristics) of all patients included in the analysis will be described overall and by exposure cohort. Continuous variables (e.g., age, income) will be summarized using categories and/or means/medians as appropriate; categorical variables will be summarized using frequencies and proportions. Baseline characteristics both before and after propensity score matching (described below) will be presented.

For the primary and secondary endpoints, incidence rates and cumulative incidences (risks) at 1, 3, 6, and 12 months will be estimated in the four exposure cohorts.

8.8.2. Main analysis

To compare risks of the endpoints across the study cohorts, time to event analysis will be undertaken, using Cox proportional-hazards regression, with death as competing risk for endpoints not including death. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CI) will be estimated for initiators of each NOAC. Follow-up will end on the date of a given endpoint, date of death (for non-death endpoints), date of discontinuation of or switch from the index OAC, date of emigration, or 31 December 2016, whichever comes first. A patient will be considered on-treatment from the date of initiation of the on-study OAC and for the subsequent number of days corresponding to the number of tablets in a package for rivaroxaban (used once daily) or half the number of tablets in a package for dabigatran and apixaban (used twice daily). A 30-day grace period will be added to account for minor non-compliance and irregular prescription refills. The on-treatment time for patients treated with warfarin will be estimated based on a recently published Danish estimation algorithm using on maximum likelihood estimation of a parametric two-component mixture model for the waiting time distribution (52). The algorithm found that 80% of current warfarin users will have presented themselves again for a refill after 91 days.

To control confounding, propensity-score matched analysis will be used. Each study NOAC will be compared against warfarin, using pairwise propensity-score matched samples. For each contrast, propensity score will be computed as the probability of receiving a given NOAC vs. a given comparator.

8.8.3. Sensitivity analysis

- Selected analyses will be repeated with full re-matching among patients with standard NOAC dose. Depending on sample size, these analyses can be performed on the lower NOAC dosage. For the dose-based sensitivity analysis, initiators of the NOACs will be classified according to the pill strength in the index dispensation to standard-dose regimen (5 mg for apixaban, 150 mg for dabigatran; 20 mg for rivaroxaban) or reduced-dose regimen (2.5 mg for apixaban, ≤110 mg for dabigatran, ≤15 mg for rivaroxaban) (18).

- Intention-to-treat-like analysis of the primary endpoints. Patients in the study population will be considered as treated with a given OAC from the day of the first dispensation during the study period until a given endpoint, death, emigration, or 31 December 2016, whichever comes first.

- Analyses of the bleeding endpoints defined by primary unplanned hospitalized diagnoses.

8.9. Quality control

Data management and analyses will be conducted according to each institution's standard procedures. At a minimum, all study documents (protocol, report, publications) will be reviewed by the entire research team, and a senior epidemiologist in each institution will review the report before submission to the sponsor. Clinical expertise is available for appropriate interpretation of results. At the start of the project, a kick-off meeting will establish a regular communication plan (via e-mail and regular teleconferences); and establish internal timelines to be completed in time to allow review and quality control before submitting each deliverable.

Each institution will follow its internal quality control procedures and will ensure the necessary compliance with local data protection, storage and archiving, and patient privacy laws and regulations and will obtain all permission necessary to conduct this study.

8.10. Strengths and limitations of the research methods

All Scandinavian countries have tax-supported universal health care; routine recording of prescription dispensations, hospital diagnoses, migrations and deaths, and the possibility for individual-level data linkage of all data, thus enabling nearly complete follow-up of the entire populations and virtually no selection bias in epidemiologic studies.

Data in Scandinavian national registries have been validated and the validity has in general been found to be high in all countries (53-61). For example, the positive predictive value of the combined diagnosis of AF and/or atrial/flutter and other cardiovascular diagnoses in the Danish National Patient registry typically exceeds 95% (62-64), and similar findings have been reported from Norway (51) and in Sweden (65). Other hospital diagnoses have also been validated, including the Charlson Comorbidity Index (39, 42). For drugs used

chronically, there is also high level of agreement between general practitioner and dispensation records (66). Furthermore, the CHA_2DS_2VASc, $CHADS_2$ and the HAS-BLED scores can be constructed based on registry data (the HAS-BLED version does not include data on labile INR) (67, 68).

Limitations of the methods include misclassification of treatment presence and timing by relying on dispensing information, and potential confounding by indication, whereby an OAC choice is guided by patients' characteristics that predict bleeding outcomes. Using 12 months OAC-free pre-index date period to identify new users may include patients with previous exposure to OACs; thus not all OAC initiators in this study will be truly treatment naive. Furthermore, the definition of the endpoint 'major bleeding' in this study that relies on routinely collected data, will be inherently different from the definition of the 'major bleeding' endpoint used in RCTs. There is a risk of under-ascertainment of absolute risks of bleeding outcomes if not all of them are reflected/correctly recorded by hospital diagnoses. At the same time, specificity of recording is high and relative estimates are therefore expected to be unbiased. Finally, routinely collected data contain no information on the quality of warfarin treatment control or dose. Nor can severity of most comorbidities be established.

8.11. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information and consent

All parties will ensure protection of patient personal data and will not include patient names on any MAH forms, reports, publications, or in any other disclosures, except where required by laws. No data transfer to MAH will take place in this study.

Registry-based studies in the Scandinavian countries do not require patient consent but they need to be approved by each country's relevant authority (Data Protection Agency and/or Ethics Committee). Investigators in each of the three countries will be responsible for obtaining all required approvals and compliance with all relevant local laws. In all analytic datasets, personal identifiers will be replaced with a study ID to protect patient identity. No data or analyses which imply a risk of identifying individual patients will be reported.

9.2. Patient withdrawal

Not applicable.

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with

the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to the MAH.

9.4. Ethical conduct of the study

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

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes unstructured data (e.g., narrative fields in the database) that will be converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and AEs are not reportable as individual AE reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

At the end of this study a single report based on analysis of combined data from the three countries (and country-specific results) will be prepared and submitted to the MAH. The investigators maintain the rights to present results from this study at scientific conferences and to publish the results in peer-reviewed journals.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately. In addition, the investigator will inform Pfizer immediately of any serious breaches of this non-interventional study protocol that the investigator becomes aware of.

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: BEYOND Pooled –
Part of the BEYOND study program (BEnefit of NOACs studY of nOn-valvular AF patieNts in NorDic countries)

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Milestones are contingent on data delivery from the data custodians

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	6
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1 and 8.4
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	8.8.1
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	8.8.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	10

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	8.2
	4.2.2 Age and sex?	☒	☐	☐	8.3
	4.2.3 Country of origin?	☒	☐	☐	8.2
	4.2.4 Disease/indication?	☒	☐	☐	8.3
	4.2.5 Duration of follow-up?	☒	☐	☐	8.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.3

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.4.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	8.10
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 drug?	☒	☐	☐	8.8.2

Comments:

Re 5.3: On-treatment and overall risks will be estimated

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.4.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.4.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	8.10
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	8.4.2.3

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	8.7
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	8.7
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	8.10
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.10
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	8.10

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.4.4

Comments:

Re 8.1: subgroup analyses are planned

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.5
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.5
9.1.3 Covariates?	☒	☐	☐	8.5
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.5
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.5
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.5 Annex 3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.5 Annex 3
9.3.3 Covariates?	☒	☐	☐	8.5 Annex 3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.5

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	8.8
10.2 Are descriptive analyses included?	☒	☐	☐	8.8
10.3 Are stratified analyses included?	☒	☐	☐	8.8
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	8.8
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	8.6

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.7

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.2 Are methods of quality assurance described?	☒	☐	☐	8.9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	11

Comments:

Re 11.3: There is an independent Steering Committee + publication plan

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.10
12.1.2 Information bias?	☒	☐	☐	8.10
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	8.10
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.6

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
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?	☒	☐	☐	5

Comments:

Re 15.1: not a regulator-mandated PASS

Name of the main authors of the protocol: Vera Ehrenstein, MPH, DSc
Søren Paaske Johnsen, MD, PhD

Date: 27/September/2017

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

INITIAL ALGORITHMS USED TO DEFINE STUDY VARIABLES

Panel 1. Drugs (ATC-code)

Warfarin	B01AA03
Apixaban	B01AF02
Dabigatran	B01AE07
Rivaroxaban	B01AF01
Vitamin K inhibitors (exclusion criterion)	B01AA
Direct thrombin inhibitors (exclusion criterion)	B01AE
Direct factor Xa inhibitors (exclusion criterion)	B01AF
Platelet inhibitors	B01AC
Low-dose aspirin	B01AC06, B01AC30
ADP-receptor blockers	B01AC04, B01AC22, B01AC24
Angiotensin-converting enzyme inhibitors	C01A, C01B
Amiodarone	C01BD01
Dronedarone	C01BD07
Beta-blockers	C07
H2-receptor antagonists	A02BA
Statins	C10AA
Non-steroidal anti-inflammatory drugs	M01A, ÷M01AX05, N02BA01
Antidiabetic agents	A10
Proton pump inhibitors	A02BC
Selective serotonin reuptake inhibitors (SSRIs)	N06AB

Panel 2. Diseases (ICD-10*, procedure, or ATC-codes)

Condition	Codes	Clarification
Endpoints		
Stroke	Haemorrhagic stroke I61 Intracerebral haemorrhage	Diagnoses in any position (primary, secondary) from **acute/unplanned** inpatient hospitalizations
	Ischaemic stroke I63 Cerebral infarction I64 Stroke, not specified as haemorrhage or infarction	Diagnoses in any position (primary, secondary) from **acute/unplanned** inpatient hospitalizations
Systemic embolism	I74 Arterial embolism and thrombosis	Diagnoses in any position (primary, secondary) from **acute/unplanned** inpatient hospitalizations
Acute myocardial infarction	I21 Acute myocardial infarction	Diagnoses in any position (primary, secondary) from **acute/unplanned** inpatient hospitalizations
Major bleeding		
Intracranial bleeding	I60 Subarachnoid haemorrhage I61 Intracerebral haemorrhage I620 Subdural haemorrhage (acute)(nontraumatic) I621 Nontraumatic extradural haemorrhage I629 Intracranial haemorrhage (nontraumatic), unspecified	Diagnoses in any position (primary, secondary) from **acute/unplanned** inpatient hospitalizations
Gastrointestinal bleeding	K250 Gastric ulcer : acute with haemorrhage K252 Gastric ulcer : acute with both haemorrhage and perforation K254 Gastric ulcer : chronic or unspecified with haemorrhage K256 Gastric ulcer : chronic or unspecified with both haemorrhage and perforation K260 Duodenal ulcer : acute with haemorrhage K262 Duodenal ulcer : acute with both haemorrhage and perforation K264 Duodenal ulcer : chronic or unspecified with haemorrhage K266 Duodenal ulcer : chronic or unspecified with both haemorrhage and perforation I850 Oesophageal varices with bleeding I983 Oesophageal varices with bleeding in diseases classified elsewhere K270 Peptic ulcer, site unspecified : acute with haemorrhage K272 Peptic ulcer, site unspecified : acute with both haemorrhage and perforation K274 Peptic ulcer, site unspecified : chronic or unspecified with haemorrhage K276 Peptic ulcer, site unspecified : chronic or	Diagnoses in any position (primary, secondary) from **acute/unplanned** inpatient hospitalizations

Panel 2. Diseases (ICD-10*, procedure, or ATC-codes)

Condition	Codes	Clarification
	unspecified with both haemorrhage and perforation K280 Gastrojejunal ulcer : acute with haemorrhage K282 Gastrojejunal ulcer : acute with both haemorrhage and perforation K284 Gastrojejunal ulcer : chronic or unspecified with haemorrhage K286 Gastrojejunal ulcer : chronic or unspecified with both haemorrhage and perforation K290 Acute haemorrhagic gastritis K298A Acute haemorrhagic duodenitis (Denmark (DK) only) K638C Bleeding from GI tract, unspecified (DK only) K661 Haemoperitoneum (excl. traumatic) K920 Haematemesis K921 Melaena K922 Gastrointestinal haemorrhage, unspecified	
Other bleeding	H448B Hemophalmos (DK only) H356 Retinal haemorrhage H313 Choroidal haemorrhage and rupture (NOS, expulsive) H210 Hyphaema H113 Conjunctival haemorrhage H470B Haemorrhage in optic nerve sheaths (DK only) H431 Vitreous haemorrhage I312 Haemopericardium, not elsewhere classified N02 Recurrent and persistent haematuria R31 Unspecified haematuria N421 Congestion and haemorrhage of prostate N831 Corpus luteum cyst, Haemorrhagic corpus luteum cyst N857 Haematometra N920 Excessive and frequent menstruation with regular cycle N921 Excessive and frequent menstruation with irregular cycle N923 Ovulation bleeding M250 Haemarthrosis R233 Spontaneous ecchymoses R040 Epistaxis R041 Haemorrhage from throat	Diagnoses in any position (primary, secondary) from **acute/unplanned** inpatient hospitalizations

Panel 2. Diseases (ICD-10*, procedure, or ATC-codes)

Condition	Codes	Clarification
	R042 Haemoptysis R048 Haemorrhage from other sites in respiratory passages R049 Haemorrhage from respiratory passages, unspecified T810 Haemorrhage and haematoma complicating a procedure, not elsewhere classified	
Any major bleeding	Union of all codes of intracranial, gastrointestinal and other bleeding	Diagnoses in any position (primary, secondary) from **acute/unplanned** inpatient visits
Any bleeding	To be defined in the SAP	Diagnoses in primary or secondary position from **acute/unplanned** inpatient visits
Inclusion/exclusion criteria		
Atrial fibrillation	I48 atrial fibrillation or flutter	Diagnoses in any position (primary, secondary) from all inpatient and outpatient visits
Cardioversion##¤	BFFA0 external Direct Current cardioversion BFFA01 synchronized Direct Current cardioversion BFFA04 synchronized Direct Current atrial defibrillation	Hospital based Direct Current cardioversion for atrial fibrillation
Venous thromboembolism (deep venous thrombosis and pulmonary embolism)	I26 Pulmonary embolism I801 Phlebitis and thrombophlebitis of femoral vein I802 Phlebitis and thrombophlebitis of other deep vessels of lower extremities I803 Phlebitis and thrombophlebitis of lower extremities, unspecified I808 Phlebitis and thrombophlebitis of other sites I809 Phlebitis and thrombophlebitis of unspecified site	Diagnoses in any position (primary, secondary) from all inpatient hospitalizations and outpatient visits
Valve operations	Nordic Medico-Statistical Committee (NOMESCO) Procedure codes: KFGE00 Mechanical prosthesis for the tricuspid valve KFJF00 Mechanical prosthesis for the pulmonary valve	

Panel 2. Diseases (ICD-10*, procedure, or ATC-codes)

Condition	Codes	Clarification
	KFKD00 Mechanical prosthesis for the mitral valve KFMD00 Mechanical prosthesis for the aortic valve	
Valvular disorders	ICD-10: I050 Rheumatic mitral stenosis I052 Rheumatic mitral stenosis with insufficiency I059 Rheumatic mitral valve disease, unspecified I080 Rheumatic disorders of both mitral and aortic valves I081 Rheumatic disorders of both mitral and tricuspid valves I083 Combined rheumatic disorders of mitral, aortic and tricuspid valves I342 Non-rheumatic mitral (valve) stenosis	Diagnoses in any position (primary, secondary) from **all** inpatient hospitalizations and outpatient visits
Knee or hip arthroplasty	NOMESCO: NFB: Primary prosthetic replacement of hip joint NFC: Secondary prosthetic replacement of hip joint NGB: Primary prosthetic replacement of knee joint NGC Secondary prosthetic replacement of knee joint NFG Excision, reconstruction and fusion of hip joint NGG Excision, reconstruction and fusion of knee joint	
Pregnancy	O00-O99	
Comorbidities/subgroups		
Bleeding#	See codes above for any bleeding	Diagnoses in any position (primary, secondary) from **all** inpatient hospitalizations and outpatient visits
Ischemic stroke#	See codes above for ischemic stroke	Diagnoses in **any** position (primary, secondary) from all inpatient and outpatient visits
Transient ischemic attack (TIA)	ICD-10: G458 Other transient cerebral ischaemic attacks and related syndromes G459 Transient cerebral ischaemic attack, unspecified	Diagnoses in **any** position (primary, secondary) from all inpatient hospitalizations and outpatient visits
Congestive heart failure	ICD-10: I50: Heart failure I11.0: Hypertensive heart disease with (congestive) heart failure I13.0: Hypertensive heart disease and renal disease with (congestive) heart failure	Diagnoses in **any** position (primary, secondary) from all inpatient hospitalizations and outpatient visits

Panel 2. Diseases (ICD-10*, procedure, or ATC-codes)

Condition	Codes	Clarification
	I13.2: Hypertensive heart and renal disease with both (congestive) heart failure and renal failure I51.7: Cardiomegaly I25.5: Ischemic cardiomyopathy I42: Cardiomyopathy I43: Cardiomyopathy in diseases classified elsewhere	
Cancer (except non-melanoma skin cancer)	ICD-10: C00-C97 Malignant neoplasms (÷C44 Other malignant neoplasms of skin)	Diagnoses in **any** position (primary, secondary) from all inpatient hospitalizations and outpatient visits
Diabetes	ICD-10: E10 Type 1 diabetes mellitus E11 Type 2 diabetes mellitus E12 Malnutrition-related diabetes mellitus E13 Other specified diabetes mellitus E14 Unspecified diabetes mellitus E891 Postprocedural hypoinsulinaemia E891A Postpancreatectomy hyperglycaemia (DK) G590 Diabetic mononeuropathy G632 Diabetic polyneuropathy G730 Myasthenic syndromes in endocrine diseases (use in NO&SE) G730A Myasthenic syndromes in diabetes (use in DK; code in use until 2011; after 2011 same as NO&SE) G990 Autonomic neuropathy in endocrine and metabolic diseases (use in NO&SE) G990C Autonomic neuropathy in diabetes (use in DK; code in use until 2011; after 2011 same as NO&SE) H280 Diabetic cataract H360 Diabetic retinopathy I792 Peripheral angiopathy in diseases classified elsewhere (use in NO&SE) I792A Diabetic peripheral angiopathy (use in DK; code in use until 2011; after 2011 same as NO&SE) M142 Diabetic arthropathy N083 Glomerular disorders in diabetes mellitus ATC: A10 Drugs used in diabetes	Diagnoses in **any** position (primary, secondary) from all inpatient hospitalizations and outpatient visits
Hypertension	ICD-10: I10 Essential (primary) hypertension I11 Hypertensive heart disease I12 Hypertensive renal disease I13 Hypertensive heart and renal disease I15 Secondary hypertension Treatment with at least two of the following classes of antihypertensive drugs:	Diagnoses in **any** position (primary, secondary) from all inpatient hospitalizations and outpatient visits Defined from diagnosis AND/OR treatment with **at least two classes** of antihypertensive drugs (both

Panel 2. Diseases (ICD-10*, procedure, or ATC-codes)

Condition	Codes	Clarification
	I· Alpha adrenergic blockers (C02A, C02B, C02C) II· Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52) III· Vasodilators (C02DB, C02DD, C02DG, C04, C05) IV· Beta blockers (C07) V· Calcium channel blockers (C07F, C08, C09BB, C09DB) VI· Renin-angiotensin system inhibitors (C09) Or at least one antihypertensive combination drug (C09BB04, C09DA, C09DB, C09DX01, C09DX04, C07B)	drugs prescribed within one year before the AF diagnosis) (18)
Coronary artery disease (CAD)#	ICD-10: I20 Angina pectoris I21 Acute myocardial infarction I22 Subsequent myocardial infarction I23 Certain current complications following acute myocardial infarction I249 Acute ischaemic heart disease, unspecified I25 Chronic ischaemic heart disease	Diagnoses in **any** position (primary, secondary) from all inpatient hospitalizations and outpatient visits
Liver failure	ICD-10: D684C Acquired coagulation defect caused by liver disease I850 Oesophageal varices with bleeding I859 Oesophageal varices without bleeding I982B Oesophageal varices without bleeding in diseases classified elsewhere (DK only) K70 Alcoholic liver disease K72 Hepatic failure, not elsewhere classified K74 Fibrosis and cirrhosis of liver K767 Hepatorenal syndrome	Diagnoses in **any** position (primary, secondary) from all inpatient hospitalizations and outpatient visits
Peripheral arterial disease (PAD)	ICD-10: I700 Atherosclerosis of aorta I701 Atherosclerosis of renal artery I702 Atherosclerosis of arteries of extremities I708 Atherosclerosis of other arteries I709 Generalized and unspecified atherosclerosis	Diagnoses in **any** position (primary, secondary) from all inpatient hospitalizations and outpatient visits
Renal failure, chronic	ICD-10: E102 Type 1 diabetes mellitus with renal complications E112 Type 2 diabetes mellitus with renal complications E122 Malnutrition-related diabetes mellitus with renal complications E132 Other specified diabetes mellitus with renal complications E142 Unspecified diabetes mellitus with renal complications	Diagnoses in **any** position (primary, secondary) from all inpatient hospitalizations and outpatient visits

Panel 2. Diseases (ICD-10*, procedure, or ATC-codes)

Condition	Codes	Clarification
	I12 Hypertensive renal disease (excluding excludingI129 Hypertensive renal disease without renal failure) N01 Rapidly progressive nephritic syndrome N03 Rapidly progressive nephritic syndrome N083 Glomerular disorders in diabetes mellitus N085 Glomerular disorders in systemic connective tissue disorders N118C Chronic interstitial nephritis N14 Drug- and heavy-metal-induced tubulo-interstitial and tubular conditions N150 Balkan nephropathy N16 Renal tubulo-interstitial disorders in diseases classified elsewhere (÷N160 Renal tubulo-interstitial disorders in infectious and parasitic diseases classified elsewhere) N18 Chronic kidney disease (÷N181 Chronic kidney disease, stage 1) N19 Unspecified kidney failure N26 Unspecified contracted kidney P960 Congenital renal failure Q601 Renal agenesis, bilateral Q602 Renal agenesis, unspecified Z992 2 Dependence on renal dialysis Z49 Care involving dialysis (code not Used in Denmark) Renal dialysis procedure codes DK: BJFD2 (treatment [‘OPR’] codes) NO: KAGD, JAGD SE: DR016, DR024 (NOMESCO) PBL, PBU (KVÅ-code)	
Alcoholism	ICD-10: E244 Alcohol-induced pseudo-Cushing syndrome E529A Alcoholic pellagra (DK only) F10 Mental and behavioural disorders due to use of alcohol G312 Degeneration of nervous system due to alcohol G405B Special epileptic syndromes (incl. seizures related to alcohol) G621 Alcoholic polyneuropathy G721 Alcoholic myopathy I426 Alcoholic cardiomyopathy K292 Alcoholic gastritis K70 Alcoholic liver disease K860 Alcohol-induced chronic pancreatitis T510 Toxic effects of ethanol T519 Toxic effects of alcohol, unspecified	Diagnoses in **any** position (primary, secondary) from all inpatient hospitalizations and outpatient visits

Panel 2. Diseases (ICD-10*, procedure, or ATC-codes)

Condition	Codes	Clarification
	Z502 Alcohol rehabilitation Z714 Alcohol abuse counselling and surveillance Z721 Problems related to lifestyle (alcohol use) ATC: N07BB Drugs used in alcohol dependence	
Cardioversion##¤	BFFA0 external Direct Current cardioversion BFFA01 synchronized Direct Current cardioversion BFFA04 synchronized Direct Current atrial defibrillation	Hospital based Direct Current cardioversion for atrial fibrillation

Abbreviations: ICD-10, International Classification of Diseases, Tenth Revision; ATC, Anatomical Therapeutic Chemical; NOMESCO Nordic Medico-Statistical Committee
*Letters at the end of ICD-10 codes are specific to the Danish version of the ICD-10
#Considered covariate (not endpoint) if occurring at the same date as start of OAC therapy.
¤##Danish treatment codes.

Panel 3. Definitions of risk scores

CHA_2DS_2VASc score		
Risk factor	**Score**	**Definition**
Congestive heart failure	1	See Panel 2
Hypertension	1	See Panel 2
Age	2	≥ 75 years
Diabetes	1	See Panel 2
Stroke/TIA/arterial embolism	2	See Panel 2 (stroke = "ischemic stroke")
Vascular disease (ischemic heart disease, peripheral arterial disease)	1	See Panel 2
Age	1	65-74 years
Sex **C**ategory	1	Female sex. Only counted when other risk factors are present.
$CHADS_2$ score		
Risk factor		
Congestive **h**eart failure history	1	See Panel 2
Hypertension	1	See Panel 2
Age	1	≥ 75 years
Stroke or TIA	2	See Panel 2 (stroke = "ischemic stroke")
HAS-BLED score		
Risk factor	**Score**	**Definition**
Hypertension	1	See Panel 2
Abnormal renal or liver function	-	
Abnormal renal function	1	See "renal failure, chronic" in Panel 2
Abnormal liver function	1	See "liver failure" in Panel 2
Stroke	1	See "ischemic stroke" in Panel 2
Bleeding	1	See "bleeding, any" in Panel 2
Labile INR	1	Not included
Elderly	1	> 65 years
Drugs or alcohol	-	
Drugs	1	See "platelet-inhibitors" and "non-steroidal anti-inflammatory drugs" in Panel 2
Alcoholism	1	See Panel 2

Abbreviations: ICD-10, International Classification of Diseases, Tenth Revision; ATC, Anatomical Therapeutic Chemical; TIA, transient ischemic attack; INR, international normalized ratio

Panel 4. Charlson Comorbidity Index (Romano modification)

Disease category	Condition	ICD- 10 code and translation¤
1	Myocardial infarction	I21: Acute myocardial infarction I22: Subsequent myocardial infarction I23 Complications of AMI I25: Old myocardial infarction
2	Congestive heart failure	I50: Heart failure I11.0: Hypertensive heart disease with (congestive) heart failure I13.0: Hypertensive heart disease and renal disease with (congestive) heart failure I13.2: Hypertensive heart and renal disease with both (congestive) heart failure and renal failure I51.7: Cardiomegaly I25.5: Ischemic cardiomyopathy I42: Cardiomyopathy I43: Cardiomyopathy in diseases classified elsewhere
3	Peripheral vascular disease	I71 Aortic aneurysm and dissection I73.1: Thromboangiitis obliterans [Buerger] I73.8: Other specified peripheral vascular diseases I73.9: Peripheral vascular disease, unspecified I79.2: Peripheral angiopathy in diseases classified elsewhere I70: Atherosclerosis I79.0:Aneurysm of aorta in diseases classified elsewhere I77.1: Stricture of artery
4	Cerebrovascular disease	I60: Subarachnoid haemorrhage I61 Intracerebral haemorrhage I62 Other nontraumatic intracranial haemorrhage I63: Cerebral infarction I64:Stroke, not specified as haemorrhage or infarction I65: Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction I66: Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction G45: Transient cerebral ischemic attacks and related syndromes G46: Vascular syndromes of brain in cerebrovascular diseases I68: Cerebrovascular disorders in diseases classified elsewhere I67: Other cerebrovascular diseases I69: Sequelae of cerebrovascular disease H34.0 Transient retinal artery occlusion R47.0B (DK)
5	Dementia	F00: Dementia in Alzheimer's Disease F01: Vascular dementia F02: Dementia in other diseases classified elsewhere F03: Unspecified dementia F05.1: Delirium superimposed on dementia G30: Alzheimer's disease

Panel 4. Charlson Comorbidity Index (Romano modification)

Disease category	Condition	ICD- 10 code and translation¤
6	Chronic pulmonary disease	J40-J47: Chronic lower respiratory J60 Coalworker pneumoconiosis J61 Pneumoconiosis due to asbestos and other mineral fibres J62 Pneumoconiosis due to dust containing silica J63 Pneumoconiosis due to other inorganic dusts J64 Unspecified pneumoconiosis J65 Pneumoconiosis associated with tuberculosis J66 Airway disease due to specific organic dust J67 Hypersensitivity pneumonitis due to organic dust J68.4 Chronic respiratory conditions due to chemicals, gases, fumes and vapours J70.1 Chronic and other pulmonary manifestations due to radiation J70.3: Lung diseases due to external agents (Chronic): J84.1: Other interstitial pulmonary diseases with fibrosis J96.1: Chronic respiratory failure J98.2 Interstitial emphysema J98.3 Compensatory emphysema I26.0 Pulmonary embolism with mention of acute cor pulmonale I27.0: Primary pulmonary hypertension I27.2: Other secondary pulmonary hypertension I27.8: Other specified pulmonary heart diseases I27.9:: Pulmonary heart disease, unspecified
7	Connective tissue disease	M32: Systemic lupus erythematosus M34 Systemic sclerosis M33: Dermatopolymyositis M05: Seropositive rheumatoid arthritis M06: other rheumatoid arthritis M35.3: polymyalgia rheumatic M31.5: Giant cell arteritis with polymyalgia rheumatica
8	Ulcer disease	K25: Gastric ulcer K26: Duodenal ulcer K27: Peptic ulcer, site unspecified K28: Gastrojejunal ulcer
9	Mild liver disease	K70.3: Alcoholic cirrhosis of liver K74: Fibrosis and cirrhosis of liver (including biliary cirrhosis) ("*Nonalcoholic/toxic")* K71.7: Toxic liver disease with fibrosis and cirrhosis of liver K76.9:Liver disease unspecified *("nonalcoholic/nontoxic*") K76.0: Fatty (change of) liver, not elsewhere classified (*nonalcoholic/ nontoxic*)
10	Diabetes	E10.0: Insulin-dependent diabetes mellitus with coma E10.1: Insulin-dependent diabetes mellitus with ketoacidosis E10.9: Insulin-dependent diabetes mellitus without complications E11.0: Non-insulin-dependent diabetes mellitus with coma E11.1: Non-insulin-dependent diabetes mellitus with

Panel 4. Charlson Comorbidity Index (Romano modification)

Disease category	Condition	ICD- 10 code and translation¤
		ketoacidosis E11.9: Non-insulin-dependent diabetes mellitus without complications
11	Diabetes with end organ damage	E10.2: Insulin-dependent diabetes mellitus with renal complications E10.3: Insulin-dependent diabetes mellitus with ophthalmic complication E10.4: Insulin-dependent diabetes mellitus with neurological complications E10.5: Insulin-dependent diabetes mellitus circulatory complication E10.6: Insulin-dependent diabetes mellitus with other specified complications. E10.7: Insulin-dependent diabetes mellitus with multiple complications E10.8: Insulin-dependent diabetes mellitus with other specified complications E11.2: Non-insulin-dependent diabetes mellitus with renal complications E11.3: Non-insulin-dependent diabetes mellitus with ophthalmic complication E11.4: Non-insulin-dependent diabetes mellitus with neurological complications E11.5: Non-insulin-dependent diabetes mellitus circulatory complication E11.6: Non-insulin-dependent diabetes mellitus with other specified complications. E11.7: Non-insulin-dependent diabetes mellitus with multiple complications E11.8: Non-insulin-dependent diabetes mellitus with other specified complications
12	Hemiplegia	G81: Hemiplegia G82: Paraplegia and tetraplegia G83: Other paralytic syndromes
13	Moderate or severe renal disease	N18: Chronic renal failure N19: Unspecified renal failure N25.0 Renal osteodystrophy Z94.0: Kidney transplant status Z99.2 :Dependence on renal dialysis Z49: Care involving dialysis (S and N)
14	Any tumour / Leukaemia / Lymphoma	C00-C76: Any tumour C91-C95: Leukaemia C81-85; C88; C90; C96: Lymphoma D89.0: Polyclonal hypergammaglobulinaemia

Panel 4. Charlson Comorbidity Index (Romano modification)

Disease category	Condition	ICD- 10 code and translation¤
15	Moderate or severe liver disease	K72: Hepatic failure, not elsewhere classified K70.4 Alcoholic hepatic failure K71.1: Toxic liver disease with hepatic necrosis K76.6: Portal hypertension K76.7: Hepatorenal syndrome E85.0: Oesophageal varices with bleeding E85.9: Oesophageal varices without bleeding I98.2: Oesophageal varices in diseases classified elsewhere I86.4: Gastric varices
16	Metastatic solid tumour	C77: Secondary and unspecified malignant neoplasm of lymph nodes C78: Secondary malignant neoplasm of respiratory and digestive organs C79: Secondary malignant neoplasm of other sites C80: Malignant neoplasm without specification of site