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	1.1
Date of last version of protocol	05 JULY 2017
EU Post Authorisation Study (PAS) register number	EUPAS21192
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
CI	Confidence interval
CKD	Chronic Kidney Disease
CMCD	Clinical and Medical Controlled Document
CPE	Centre for Pharmacoepidemiology
DK	Denmark
DVT	Deep vein thrombosis
EEIG	European Economic Interest Group
EMA	European Medicines Agency
GI	Gastrointestinal
GSOP	Global Standard Operating Procedure
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practice
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol
HF	Heart Failure
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
ITT	Intention to Treat
MAH	Marketing Authorisation Holder
N	Number
NO	Norway
NI	Non-interventional
NOAC	Non-vitamin K oral anticoagulants
NOMESCO	Nordic Medico-Statistical Committee

NSAID	Non-steroidal anti-inflammatory drug
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
PAD	Peripheral arterial disease
PASS	Post-Authorisation Safety Study
PE	Pulmonary embolism
PS	Propensity Score
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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A full list of study investigators and members of the Steering Committee can be found in Annex 1.

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. *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 any stroke/systemic embolism at an acute hospitalization with an overnight stay and any bleeding at an acute hospitalization with an overnight stay. The secondary endpoints are ischaemic stroke at an acute hospitalization with an overnight stay, haemorrhagic stroke at an acute hospitalization with an overnight stay, intracranial bleeding at an acute hospitalization with an overnight stay, gastrointestinal bleeding at an acute hospitalization with an overnight stay, acute myocardial infarction at an acute hospitalization with an overnight stay; systemic embolism at an acute hospitalization with an overnight stay; death of any cause; any bleeding at an acute or planned hospitalization with an overnight stay, any bleeding occurring at an acute hospital contact without an overnight stay, and a composite outcome of ischemic stroke at an acute hospitalization with an overnight stay, systemic embolism at an acute hospitalization with an overnight stay, acute myocardial infarction at an acute hospitalization with an overnight stay, 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 kidney disease; heart failure, coronary artery disease, diabetes, prior stroke and

peripheral arterial disease. The primary analyses will be conducted using all licensed NOAC doses. Sensitivity analyses for the primary and composite secondary endpoints will include those of reduced OAC doses, depending on sample size, intention-to-treat-like analyses, analyses using alternative covariate adjustment methods; and varying definitions of treatment variables and selected endpoints. *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 NOAC-warfarin pairwise propensity-score matched samples. This study will provide real world evidence about safety and effectiveness of each NOAC compared with warfarin 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 December, 2018.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1.1	26th June 2018	Administrative	2 (Responsible parties)	Update of names for responsible parties, and clarification of roles as principle investigators, steering committee and other responsible parties.	Change of personnel, and provision of additional clarification
		Administrative	3 (Abstract)	Abstract updated to be consistent with changes in other section of the protocol and statistical analysis plan (SAP).	Review of SAP resulted in a number of further clarifications and amendments (see entries below).
		Administrative	5 (Milestones)	End of data collection and date of final study report updated to reflect new timelines.	New timelines for availability of data from Norway has meant study timelines were required to be updated.
		Administrative	7 (Research question and objectives)	Primary objectives to clarify definition of any stroke to include ischaemic or haemorrhagic stroke. Primary and secondary endpoints updated to require acute hospitalisation with an overnight stay. Additional secondary endpoint added to provide full breakdown of composite primary endpoint. Update of description of exploratory endpoints.	Provide clarity to study objectives, and select most robust endpoint definition for analysis. Secondary endpoints added to provide full breakdown of composite endpoints, capture safety events not requiring an overnight stay in hospital . Details on exploratory endpoints added to reflect outpatient hospital visits.
		Administrative	8 (Research methods)	Updated to reflect availability of data from Sweden until 2016, so this is now in line with other countries in the study. Clarification of patient population as treatment naïve. Clarification of exclusion criteria look back periods (5 years for mitral stenosis or mechanical heart valves; 9 months for pregnancy). Definition of primary and secondary endpoints clarified to reflect updates in section 7. Additional subgroup analyses added and clarified. Additional section in 8 added for Record retention. Definition of cumulative incidence updated to incorporate data over full follow up period.	Changes made to be consistent with greater data availability in Sweden , provide clarification on definition of patients as treatment naïve and clarify exclusion criteria. Endpoints updated to reflect clarified definitions in other sections. Further subgroup analyses added after discussion with steering committee. Additional sub-sections in section 8 added as required byPfizer Clinical and Medical Controlled Document (CMCD) communication on the Global Standard Operating Procedure (GSOP) Clinical Trial 24 (CT24-GSOP) protocol and informed consent document templates 25-JUN-2018, as required by the General Data Protection Regulation.

				Definition of on treatment definition for VKA updated to reflect comments from steering committee and to be consistent with BEYOND Norway, exploratory analyses performed using alternative method based on algorithm based on Danish data. Sensitivity analyses added and clarified.	Cumulative incidence definition, calculation of VKA exposure and clarification of sensitivity analyses and addition of sensitivity analysis using regression adjustment using Cox regression were updated to reflect comments from real world data review committee and steering committees.
		Administrative	9 (Protection of human subjects)	Section 9.1 updated to reflect requirements of new protocol template: Separate section on patient information. Section 9.4 updated to accurately reflect the need for Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review in studies performed in Nordic countries.	Additional sub-sections in section 9 added as required by CMCD communication on CT24-GSOP protocol and informed consent document templates 25-JUN-2018, as required by the General Data Protection Regulation.
		Administrative	Annex 2	Section numbers updated to reflect new document structure from additional sections added in Section 8 and 9.	Consistency with rest of protocol.
		Administrative	Annex 3	Study variable definitions moved from protocol to the SAP.	Final variable definitions are now found in statistical analysis plan.

5. MILESTONES

Milestone	Planned date
Start of data collection	17 August 2018
End of data collection	22 September 2018
Registration in the EU PAS register	06 October 2017
Final study report	15 March 2019

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 dispensings, 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 ischaemic or haemorrhagic stroke (hereafter, any stroke) or systemic embolism at an acute hospitalization with an overnight stay among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin.

- To compare risks of any bleeding (i.e., intracranial, GI, other) at an acute hospitalization with an overnight stay among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin.

7.2. Secondary objectives

- To compare risks of ischaemic stroke at an acute hospitalization with an overnight stay among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of haemorrhagic stroke at an acute hospitalization with an overnight stay among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of intracranial bleeding at an acute hospitalization with an overnight stay among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of gastrointestinal bleeding at an acute hospitalization with an overnight stay among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of acute myocardial infarction at an acute hospitalization with an overnight stay among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of systemic embolism at an acute hospitalization with an overnight stay 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 endpoint of ischemic stroke at an acute hospitalization with an overnight stay, systemic embolism at an acute hospitalization with an overnight stay, acute myocardial infarction at an acute hospitalization with an overnight stay, or all-cause mortality among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of any bleeding at an acute or planned hospitalization with an overnight stay among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of any bleeding occurring at an acute hospital contact without an overnight stay among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin

- To compare risks of bleeding (intracranial, gastrointestinal, other) recorded as the primary diagnosis at an acute hospitalization with an overnight stay among the OAC-treatment naïve NVAF patients who initiate apixaban, dabigatran, rivaroxaban, or warfarin (sensitivity analysis)

- 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, number of planned and acute outpatient hospital visits, and to assess associated costs to the extent possible.

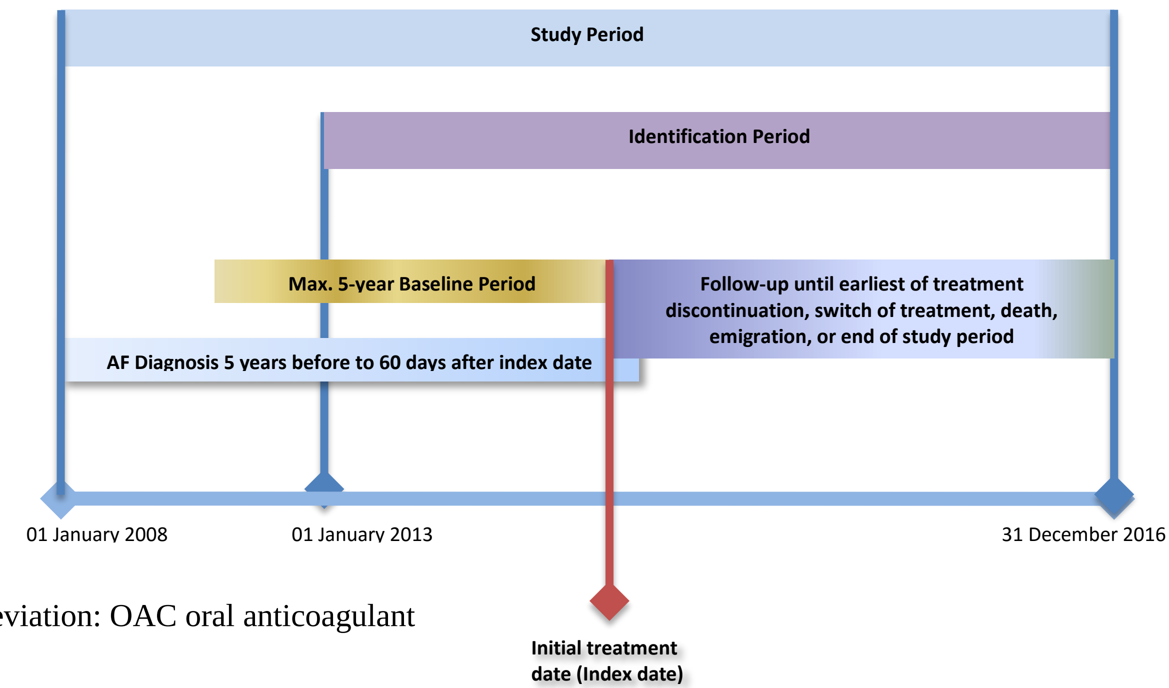
8. RESEARCH METHODS

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 (identification period) will be from 01 January 2013 to 31 December 2016, to reflect dates of apixaban availability and the years of available data. For each patient included in the study, the date of dispensing 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

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 dispensings, 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).

8.2.1. Study population

The study population will be identified as treatment-naïve adults (aged 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. 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, whichever comes first.

8.2.2. 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 (inclusive); the date of the first dispensing 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

8.2.3. Exclusion criteria

Patients meeting any of the following criteria will be excluded:

1. A diagnosis of mitral stenosis AND/OR record of presence of mechanical heart valves identified by ICD-10 or procedure codes up to 5 years 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 dispensing, 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)

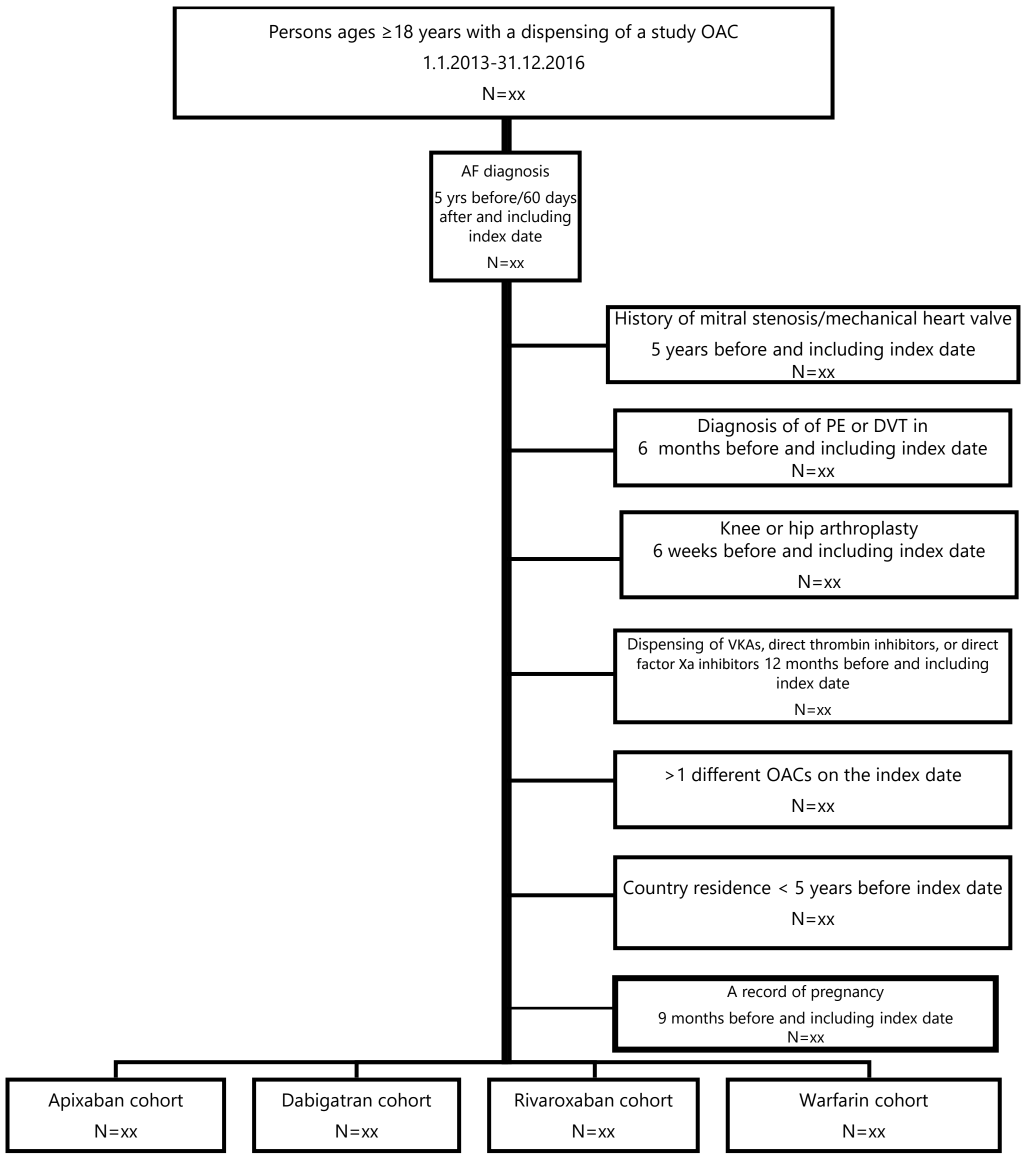
5. Dispensing of more than one different OACs on the index date

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 within 9 months before index date

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, OAC oral anticoagulant, PE pulmonary embolism, VKA vitamin K antagonist

8.3. Variables

8.3.1. Exposure

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

8.3.2. Endpoints

The following primary and secondary endpoints will be defined.

8.3.2.1. Primary endpoints

- Any stroke (i.e, ischaemic or haemorrhagic stroke) or systemic embolism
- Any bleeding (i.e., intracranial, gastrointestinal, other) at an acute hospitalization with an overnight stay

8.3.2.2. Secondary endpoints

- Ischaemic stroke at an acute hospitalization with an overnight stay
- Haemorrhagic stroke at an acute hospitalization with an overnight stay
- Intracranial bleeding at an acute hospitalization with an overnight stay
- Gastrointestinal bleeding at an acute hospitalization with an overnight stay
- Acute myocardial infarction at an acute hospitalization with an overnight stay
- Systemic embolism at an acute hospitalization with an overnight stay
- Death of all causes
- The composite endpoint of ischemic stroke at an acute hospitalization with an overnight stay, systemic embolism at an acute hospitalization with an overnight stay, acute myocardial infarction at an acute hospitalization with an overnight stay, or all-cause mortality
- Any bleeding at an acute or planned hospitalization with an overnight stay
- Any bleeding occurring at an acute hospital contact without an overnight stay

- Bleeding (intracranial, gastrointestinal, other) recorded as the primary diagnosis at an acute hospitalization with an overnight stay (sensitivity analysis)

8.3.2.3. Exploratory endpoints

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.

8.3.3. Covariates

Baseline characteristics of the study cohorts will be ascertained during the maximum of 5-year baseline before and including the index date (38): age at index date (in groups and as a continuous variable), sex, overall 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 heart failure (HF), cancer, diabetes, hypertension, chronic kidney disease, liver disease, myocardial infarction, alcohol abuse, peripheral arterial disease (PAD), coronary artery disease (CAD), dementia, cancer, and cardioversion. Baseline concomitant medication use will be assessed as history of dispensings 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.

8.3.4. 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 initial dosage in the baseline (any licensed dose for AF vs reduced dose)
- In patients with/without chronic kidney disease (CKD) in the baseline

- In patients with/ without heart failure (HF) 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 prior ischaemic stroke in the baseline
- In patients with/ without prior unspecified stroke in the baseline
- In patients with/ without prior haemorrhagic stroke in the baseline
- In patients with/ without prior TIA in the baseline
- In patients with/without prior systemic embolism at baseline
- In patients with/without prior gastrointestinal bleeding at baseline
- In patients with/without prior intracranial bleeding at 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.

8.4. 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)	See Statistical analysis plan (SAP
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)	See SAP
Any stroke/systemic embolism	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	See SAP

Variable	Role	Data source(s)	Operational definition
Ischaemic stroke	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	See SAP
Haemorrhagic stroke	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	See SAP
All bleeding outcomes	Endpoint	Danish National Patient Registry(30), Norwegian Patient Registry(41), Swedish National Patient Register (32, 42)	See SAP
Intracranial bleeding	Endpoint	Danish National Patient Registry(30), Norwegian Patient Registry(41), Swedish National Patient Register (32, 42)	See SAP
Gastrointestinal bleeding	Endpoint	Danish National Patient Registry(30), Norwegian Patient Register(41), Swedish National Patient Register (32, 42)	See SAP
Other bleeding	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	See SAP
Acute myocardial infarction	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	See SAP
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)	See SAP
Any hospitalized bleeding	Endpoint	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	See SAP
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)	See SAP
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)	See SAP
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)	See SAP
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)	See SAP
$CHADS_2$ 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)	See SAP

Variable	Role	Data source(s)	Operational definition
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)	See SAP
Concomitant medication	Covariate	Danish National Health Services Prescription Database (33, 43), Norwegian Prescription Database (33), Swedish Prescribed Drug Register (33)	See SAP
Comorbidities	Covariates	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	See SAP
Health care utilisation	Descriptive characteristics	Danish National Patient Registry (30), Norwegian Patient Registry (41), Swedish National Patient Register (32, 42)	See SAP
Household income	Covariate	Statistics Denmark, Statistics Norway [not for pooled analysis], Statistics Sweden	See SAP
Education	Covariate	Statistics Denmark, Statistics Norway [not for pooled analysis], Statistics Sweden	See SAP
Employment	Covariate	Statistics Denmark, Statistics Norway [not for pooled analysis], Statistics Sweden	See SAP
Health care cost	Endpoint	Published data on health care costs for specific types of visit	See SAP

8.5. 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 medications 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 dispensing 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 Number (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

Computed Number (N) per Group					
Index	**Alpha**	**Relative Risk**	**Nominal Power**	**Actual Power**	**N per Group**
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

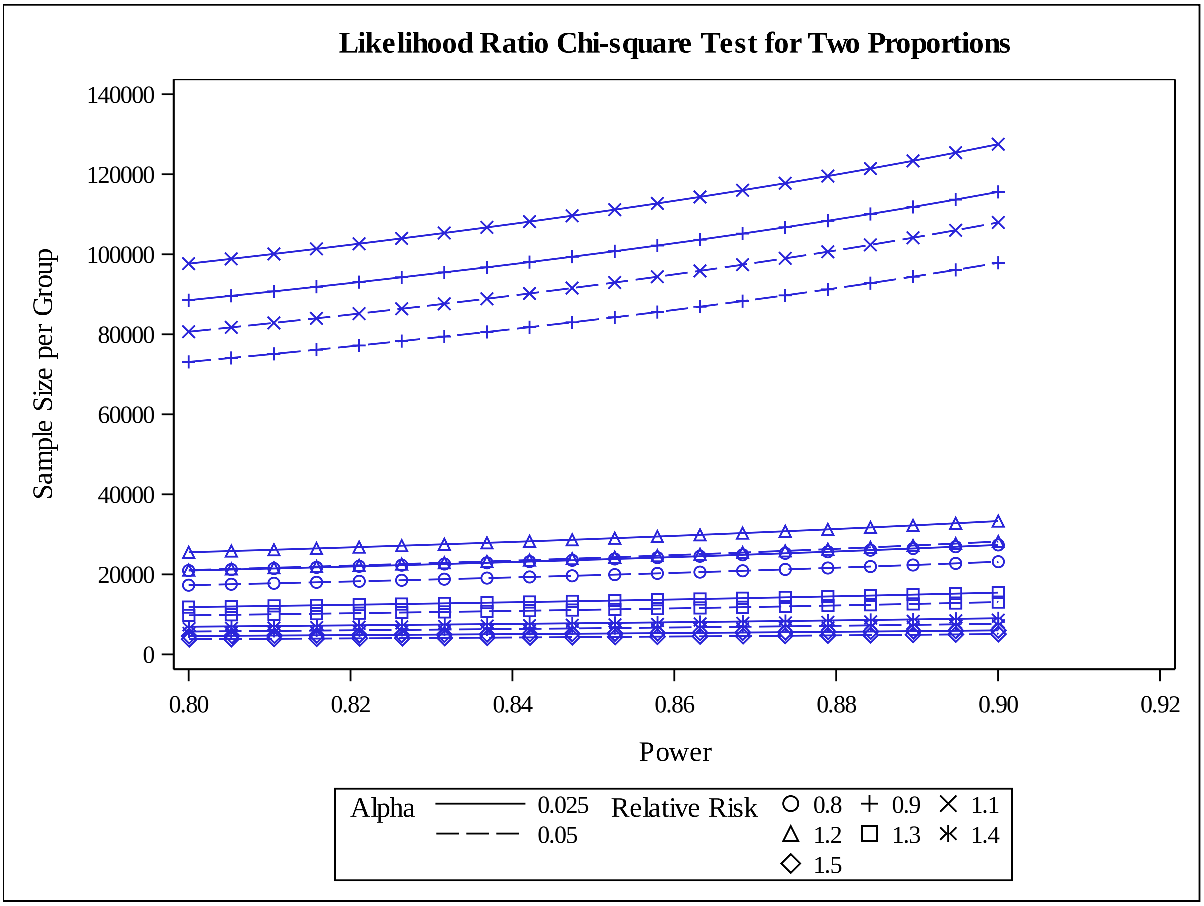
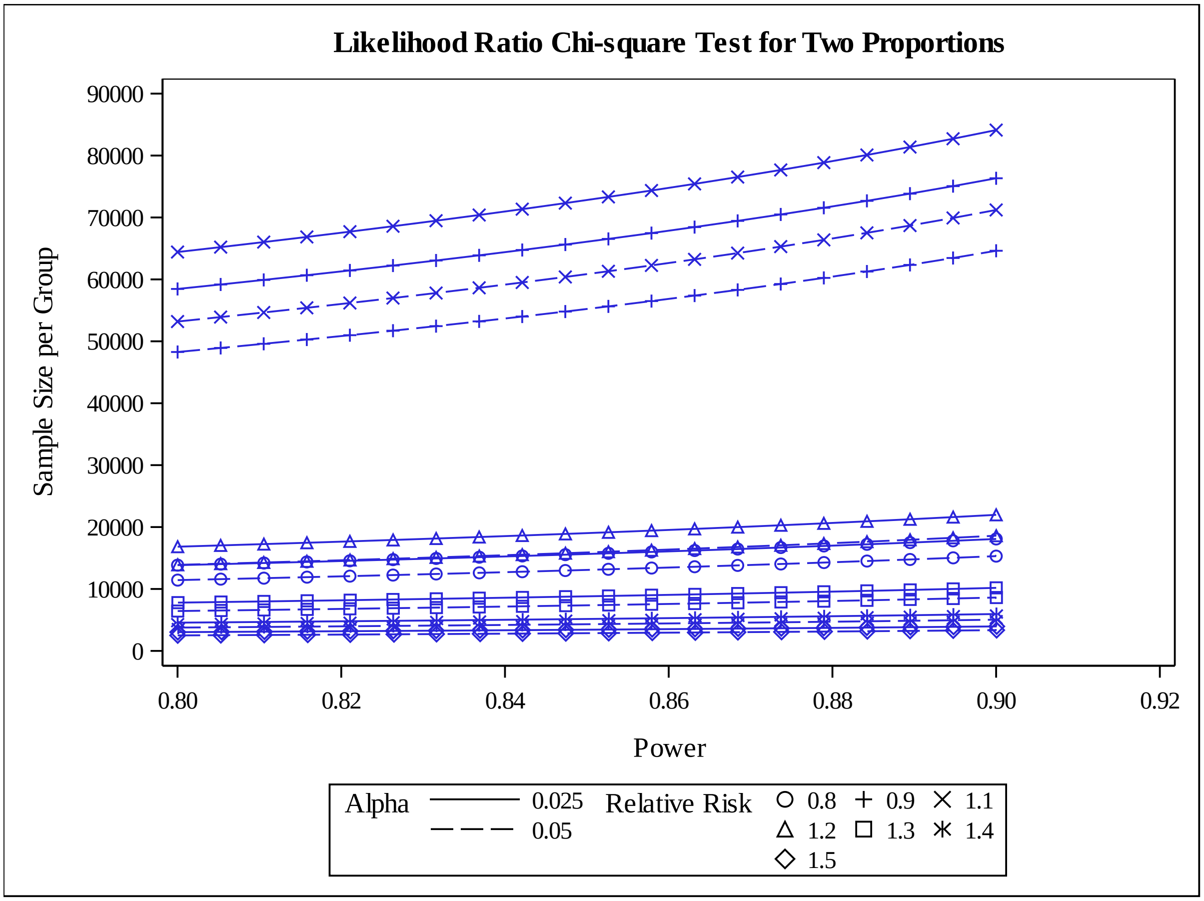


Table 4. Group size for pairwise estimation of RR for a NOAC vs. warfarin 0.8 to 1.5. Assumptions: alpha=0.025 or 0.05. 1-year background risk of bleeding = 0.03

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

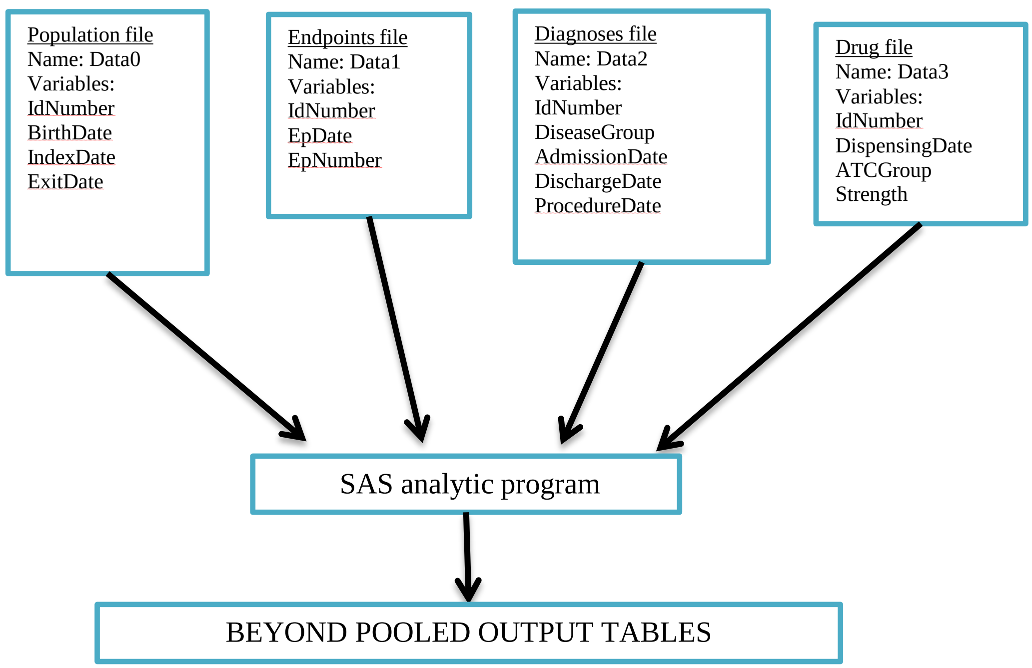


8.6. Data management

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 and quality control (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 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, North Carolina , US). 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).

8.7. 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.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a common 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.

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, and the analytic strategy, including variables for inclusion in the propensity score models, are described in the SAP.

8.7.1. 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, crude incidence rates and hazards ratios (HRs), and cumulative incidences (risks) over the follow-up period will be estimated in the four OAC cohorts.

8.7.2. 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 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 the first dispensing of the index OAC and for the subsequent number of days corresponding to the number of tablets in all dispensed packages for rivaroxaban (used once daily) or half the number of tablets in all dispensed packages for dabigatran or apixaban (used twice daily) as long as there are no more than 30 days between the expiration and the start of the two adjacent dispensings. A discontinuation will be recorded as soon as 31 days elapse after the expiration of the number of days in a given dispensing (date of dispensing + days supplied + 31 days) in the absence of the next dispensing of the same OAC.

The approach to calculate the warfarin discontinuation date will be based on the median daily dose for all warfarin patients; this median daily dose will be used to calculate an end of supply date based on the dispensing strength and number of tablets in a package for each patient. Discontinuation will be assumed if there was no warfarin prescription within 30 days of the end date of the supply.

8.7.3. Sensitivity analysis

The following sensitivity analyses will be performed overall, for the primary endpoints and the composite secondary endpoint:

1. The intention-to-treat (ITT) like analyses: the overall comparative PS-matched analyses of the primary endpoints and the composite secondary endpoint will be repeated whereby patients in each OAC cohort will be followed from the index date until a given endpoint, death, emigration, or study end (no censoring by discontinuation or switching)
2. The overall comparative analyses of the primary endpoints and the composite secondary endpoint in the propensity score (PS)-matched analysis set will be repeated whereby the on-treatment time for patients treated with warfarin will be estimated based on a recently published methods using on maximum likelihood estimation of a parametric two-component mixture model for the waiting time distribution (52, 53). The algorithm found that 80% of current warfarin users will have presented themselves again for a refill after 91 days. A 30-day grace period will be added at the end of the 91 days
3. The overall comparative analyses of the primary endpoints and the composite secondary endpoint will be repeated in the full analysis dataset using conventional adjustment instead of PS matching
4. The overall comparative analyses of the primary endpoints and the composite secondary endpoint will be repeated in the full analysis dataset using conventional adjustment instead of PS matching
5. Analysis stratified on the initial dose will be performed after PS rematching within the initial dose defined strata.

8.8. 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.

8.9. Strengths and limitations of the research methods

All Scandinavian countries have tax-supported universal health care; routine recording of prescription dispensings, 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 (54-62). 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% (63-65), and similar findings have been reported from Norway (51) and in Sweden (66). 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 dispensing records (67). 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) (68, 69).

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.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information

This analysis dataset involves data that exist in anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves anonymized structured or unstructured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Patient withdrawal

Not applicable.

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

Approval by an IRB is not required for studies based on routinely collected data. All investigators will follow appropriate local procedures to comply with all applicable local laws and regulation. All relevant documentation will be kept on file. 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

List of all investigators.

Name, degree(s)	**Title/Role**	**Affiliation**	**Address**
Pfizer Inc.			
Aaron Jenkins, PhD	Outcomes and Evidence Director, Pfizer NI study lead	Pfizer Inc.	Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS
Denmark			
Henrik Toft Sørensen, MD, PhD, DMSc	Professor Principal Investigator	Department of Clinical Epidemiology Aarhus University Hospital	Olof Palmes Allé 43-45 DK-8200 Aarhus N, Denmark, http://www.kea.au.dk/en/index.html
Vera Ehrenstein, MPH, DSc	Professor Coordinating Investigator	Same as above	Same as above
Morten Madsen, MSc	Statistician	Same as above	Same as above
Norway			
Grethe S. Tell, MPH, PhD	Professor, Principal Investigator, Norway	Department of Global Public Health and Primary Care University of Bergen	Kalfarveien 31, NO-5018 Bergen, Norway http://www.uib.no/en/globpub
Gerhard Sulo, MD, PhD	Postdoc, Clinical expert	Same as above	Same as above
Kari Juul, MSc	Project manager	Same as above	Same as above
Astrid Lunde, PhD	Statistician	Same as above	Same as above
Sweden			
Helle Kieler, MD, PhD	Professor, Principal Investigator, Sweden	Centre for Pharmacoepidemiology Karolinska Institutet	Karolinska Universitetssjukhuset Solna, Centrum för läkemedelsepidemiologi T2 171 76 Stockholm http://ki.se/en/meds/centre-for-pharmacoepidemiology
Zoltan Thinsz, BSc	Project manager	Same as above	Same as above
Marie Linder, MSc, PhD	Statistician	Same as above	Same as above
Anna Ingemarsdotter	Project administrator	Same as above	Same as above

List of Steering Committee members

Name, degree(s)	Title/Role	Affiliation	Address
Denmark			
Søren Paaske Johnsen, MD, PhD	Clinical associate professor Principal Investigator Denmark	Same as above	Same as above
Gunnar Gislason, MD, PhD	Cardiologist Member of Steering Committee*	Department of Cardiology, Gentofte University Hospital	Herlev-Gentofte Hospital - Gentofte, Kildegårdsvej 28, 2900 Hellerup
Norway			
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Mårten Rosenqvist, MD, PhD	Cardiologist Member of Steering Committee*	Same as above	Karolinska Institutet Danderyds sjukhus, 182 88 Stockholm, Sverige
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Stefan Hohnloser, MD	Cardiologist Chair of Steering Committee*	Dep. of Cardiology J. W. Goethe University	J. W. Goethe University Dep. of Cardiology Div. of Clinical Electrophysiology Building 23 c Theodor Stern Kai 7 60590 Frankfurt Germany
*Steering Committee provides advice on study design, review of study results and may act as publication authors in accordance with International Committee of Medical Journal Editors (ICMJE) criteria.			

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:
EUPAS21192

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)	☒	☐	☐	8.7.1
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)	☒	☐	☐	8.7.2
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?	☒	☐	☐	8.2
	4.2.3 Country of origin?	☒	☐	☐	8.2
	4.2.4 Disease/indication?	☒	☐	☐	8.2
	4.2.5 Duration of follow-up?	☒	☐	☐	8.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2

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)	☒	☐	☐	8.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	8.9
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?	☒	☐	☐	8.7.2

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?	☒	☐	☐	8.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
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)	☒	☐	☐	8.9
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)	☒	☐	☐	8.3.2.3

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)	☒	☐	☐	8.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	8.9

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)	☒	☐	☐	8.3.3 and 8.3.4

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:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
	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)	☒	☐	☐	8.4
	9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	SAP Appendix 1
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	SAP Appendix 1
	9.3.3 Covariates?	☒	☐	☐	SAP Appendix 1
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.4

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Is the choice of statistical techniques described?	☒	☐	☐	8.7 and SAP section 8
10.2	Are descriptive analyses included?	☒	☐	☐	8.7 and SAP section 8
10.3	Are stratified analyses included?	☒	☐	☐	8.7 and SAP section 8
10.4	Does the plan describe methods for adjusting for confounding?	☒	☐	☐	8.7 and SAP section 8
10.5	Does the plan describe methods for handling missing data?	☐	☐	☒	
10.6	Is sample size and/or statistical power estimated?	☒	☐	☐	8.5

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)	☒	☐	☐	8.6

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
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?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
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)	☒	☐	☐	8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.5

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?	☒	☐	☐	11

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: ______________________________