Post Authorization Safety Study (PASS) Information

Acronym/Title	**R**eal-world **e**vidence for non-valvular **at**rial fibrillation patients **t**reated with oral **a**nticoagulation **i**n the **N**ordics (REATTAIN)
Protocol version and date	V1.0, 19.08.2019
IMPACT study number	20030
Study type / Study phase	Observational Post marketing surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Direct thrombin inhibitor, B01AE07 dabigatran etexilate Direct factor Xa inhibitor, B01AF01 rivaroxaban Direct factor Xa inhibitor, B01AF02 apixaban
Medicinal product	See above
Product reference	N/A
Procedure number	N/A
Comparator / Reference therapy	Vitamin K antagonist, B01AA03 warfarin
Study Initiator and Funder	Bayer AG 13353 Berlin, Germany
Research question and objectives	The overall aim is to evaluate the comparative safety and effectiveness of reduced doses of NOACs vs. VKA for stroke prevention in patients with NVAF. Further, the study aims to describe the use and outcomes associated with potential under- and overdosing of each respective NOAC.
Country(-ies) of study	Denmark, Norway, Finland, Sweden
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	[redacted]

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

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

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2. List of abbreviations

AF	Atrial fibrillation
AKI	Acute kidney injury
ATC	Anatomic Therapeutic Chemical (classification system)
CCI	Charlson Comorbidity Index
CKD	Chronic Kidney Disease
CPR	Central Person Registry
DRG	Diagnosis-related group
EU	European Union
HILMO	Hoitoilmoitusjärjestelmä [Care notification system, Finland]
HR	Hazard ratio
ICD	International Classification of Diseases
ICH	Intracranial hemorrhage
IQR	Interquartile range
IS	Ischemic stroke
ITT	Intention to treat
MAH	Marketing Authorization Holder
NIHSS	National Institutes of Health stroke scale
NOAC	Non-vitamin K oral anticoagulants
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
OS	Observational study
PAS	Post-authorization study
PASS	Post-authorization safety studies
QPPV	Qualified Person responsible for Pharmacovigilance
REATTAIN	Real-world Evidence for non-valvular ATrial fibrillation patients Treated with oral Anticoagulation In the Nordics
RW	Real-world
RWE	Real-world evidence
SAP	Statistical analysis plan
SE	Systemic embolism
SQL	Structured Query Language
SSS	Scandinavian stroke scale
THL	Terveyden ja hyvinvoinnin laitos [National Institute for Health and Welfare, Finland]
TIA	Transient ischemic attack
TM	Trademark
VKA	Vitamin K antagonists
VTE	Venous thromboembolism

3. Responsible parties

3.1 Study initiator and funder

Role: OS Conduct Responsible
Name: [redacted]
E-mail:

Role: Qualified Person responsible for Pharmacovigilance (QPPV)
Name: [redacted]

Role: Outcomes Data Generation
Name: [redacted]

Role: OS Safety Lead
Name: [redacted]

Role: OS Medical Expert
Name: [redacted]

Role: OS Statistician
Name: [redacted]

Role: OS Epidemiologist
Name: [redacted]

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

3.2 Collaborator(s)/External partner(s)/Committee(s)

Contact details on the coordinating and/or principal investigators, co-investigators and steering committee members participating in the study are listed in a stand-alone document (see Table 4, Annex 1) which is available upon request.

Administrative changes of responsible persons and/or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

4. Abstract

Acronym/Title	**R**eal-world **e**vidence for non-valvular **at**rial fibrillation patients **t**reated with oral **a**nticoagulation **i**n the **N**ordics (REATTAIN)
Protocol version and date	V1.0, 19.08.2019
IMPACT study number	20030
Study type / Study phase	Observational
Rationale and background	Oral anticoagulant (OAC) treatment with either vitamin K antagonists (VKAs) or non-vitamin K antagonist oral anticoagulants (NOACs) is essential for the prevention of stroke or systemic embolism (SE) in patients with atrial fibrillation. While there are a significant number of real-world evidence (RWE) publications on the use of NOACs for stroke prevention, evidence from routine clinical practice on the use and outcomes of reduced doses of NOACs is scarce. This study aims to assess the effectiveness and safety of these regimens compared to VKA for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). The study will evaluate patients treated in routine clinical practice across the Nordic countries.
Research question and objectives	Primary objective • To describe the risk of ischemic stroke (IS)/systemic embolism (SE), and intracranial hemorrhage (ICH) in patients with NVAF initiating treatment with reduced doses of individual NOACs (rivaroxaban, apixaban, dabigatran) compared to VKA (warfarin) Secondary objectives • To describe the risk of IS/SE and ICH in patients with NVAF initiating treatment with reduced dose of individual NOACs compared to the standard dose in patients with and without renal impairment • To describe the risk of severe IS and fatal bleeding in patients with NVAF initiating treatment with reduced dose of individual NOACs compared to the standard dose in patients with and without renal impairment Further objectives • To describe treatment persistence in patients with NVAF initiating treatment with reduced doses of individual NOACs compared to VKA • To describe the risk of acute kidney injury (AKI) and kidney failure in patients with NVAF initiating treatment of reduced doses of individual NOACs compared to VKA

	• To describe the risk of severe IS and fatal bleeding in patients with NVAF initiating treatment with reduced doses of individual NOACs compared to VKA
Study design	Non-interventional cohort study over a study period of 1 January 2010 to 31 December 2018 (or latest available date in the data). The day of the first qualifying OAC dispensing (index drug) constitutes the index date.
Population	The study population comprises all patients in the Nordics (Sweden, Denmark, Finland and Norway) diagnosed with atrial fibrillation (AF) and who have been prescribed a qualifying OAC. Patients must meet the following inclusion criteria to be eligible for the study: • A qualifying OAC dispensed during the inclusion period • A primary diagnosis indicative of AF during the baseline period Patients meeting any of the following exclusion criteria will be excluded from the analysis: • Age < 18 years at index date • A diagnosis of valvular disease, pregnancy, transient cause of atrial fibrillation or venous thromboembolism in the baseline period • Hip or knee replacement surgery in the 60 days prior to or on the index date • A dispensed prescription of heparin or fondaparinux in the 60 days prior to or on the index date • A diagnosis of end-stage kidney disease or renal replacement therapy in the baseline period • More than one dispensed OAC (any dose of rivaroxaban, apixaban, dabigatran, edoxaban, or VKA) on the index date A dispensed prescription of an OAC (any dose of rivaroxaban, apixaban, dabigatran, edoxaban, or VKA) before the index date
Variables	As exposure we will assess dispensations of VKA (warfarin) or NOACs, i.e. rivaroxaban (15 mg or 20 mg once daily), apixaban (2.5 mg or 5 mg twice daily), dabigatran (150 or 110 mg twice daily). Outcomes include IS/SE, ICH, severe IS, fatal bleeding, acute kidney injury (AKI), kidney failure and treatment persistence. Covariates will include demographic and clinical characteristics.
Data sources	This study will be conducted on data from registers in Denmark, Finland, Norway and Sweden. Data will be sourced from national administrative registers, including the national patient registers, prescription registers and cause of death registers. In addition the national quality of care registers on stroke in Sweden and Denmark will be used.
Study size	Based on previous literature, the total number of NVAF patients on reduced doses of NOACs is estimated at approximately 70,000–100,000.

Data analysis	Risk of outcomes will be estimated by calculating cause-specific hazard ratios using Cox regression models. Failure curves will be used to depict how risks of events evolve over time, and cause-specific cumulative incidence functions will be used to calculate absolute risks of events taking into account the competing risk of death. To allow for a comparison across the different treatment regimens, an inverse probability of treatment weight-approach will be used to estimate treatment effect in the entire study population.
Milestones	Start of data collection: 19 August 2019 End of data collection: 15 June 2020 Registration in the EU PASS register: 30 July 2019 Final report of study results: 15 December 2020

5. Amendments

None

6. Milestones

The study milestones (see section 4) are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation, data release and analysis do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document (Table 4, Annex 1) that is available upon request.

7. Rationale and background

Oral anticoagulant (OAC) treatment with either vitamin K antagonists (VKAs) or non-vitamin K antagonist oral anticoagulants (NOACs) is essential for the prevention of stroke or systemic embolism (SE) in patients with atrial fibrillation and one or more risk factors for stroke. The pivotal clinical trials have shown a favorable risk-benefit profile of NOACs, with significant reductions in stroke, intracranial hemorrhage (ICH), and mortality, and with similar major bleeding as for VKA, but increased gastrointestinal bleeding. Subgroups analyses have also demonstrated consistent relative efficacy and safety of NOACs across a wide range of patients.

The past few years have seen a significant number of real-world evidence (RWE) publications on the use of NOACs for stroke prevention. However, evidence from routine clinical practice on the use and outcomes of reduced doses of NOACs is scarce. The use of reduced doses of NOACs has been observed in older-aged patients characterized by frailty and higher disease severity. This clinical practice reflects the need of safer while still effective treatment options in these patient populations. While insufficient for demonstrating causal relationships, RWE studies can provide valuable insights into the effectiveness and safety of anticoagulants in routine clinical practice and help clinicians make well-informed patient-tailored clinical decisions.

In light of limited evidence of the use of the reduced doses of NOACs in routine clinical practice, this study aims to assess the effectiveness and safety of these regimens compared to VKA for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). The study will evaluate patients treated in routine clinical practice across the Nordic countries (Denmark, Finland, Norway and Sweden). Subgroups of interest include patients with renal impairment and the elderly.

8. Research questions and objectives

The overall aim of the study is to evaluate the comparative safety and effectiveness of reduced doses of NOACs vs. VKA for stroke prevention in patients with NVAF. Further, the study aims to describe the use and outcomes associated with potential under- and overdosing of each respective NOAC.

All objectives are summarized in Figure 1.

8.1 Primary objective

- To describe the risk of ischemic stroke (IS)/systemic embolism (SE), and intracranial hemorrhage (ICH) in patients with NVAF initiating treatment with reduced doses of individual NOACs (rivaroxaban, apixaban, dabigatran) compared to VKA (warfarin)

8.2 Secondary objectives

The secondary objectives of the study are:

- To describe the risk of IS/SE and ICH in patients with NVAF initiating treatment with reduced dose of individual NOACs compared to the standard dose in patients with and without renal impairment
- To describe the risk of severe IS and fatal bleeding in patients with NVAF initiating treatment with reduced dose of individual NOACs compared to the standard dose in patients with and without renal impairment

8.3 Further objectives

Additional objectives are:

- To describe treatment persistence in patients with NVAF initiating treatment with reduced doses of individual NOACs compared to VKA
- To describe the risk of acute kidney injury (AKI) and kidney failure in patients with NVAF initiating treatment of reduced doses of individual NOACs compared to VKA
- To describe the risk of severe IS and fatal bleeding in patients with NVAF initiating treatment with reduced doses of individual NOACs compared to VKA

Population	Intervention	Comparator	Outcomes	Subgroups	
OAC-naïve NVAF patients	Reduced dose NOAC	VKA	IS/SE ICH	Renal impairment Elderly Diabetes Prior IS or SE Prior bleeding Frail	Primary objectives
OAC-naïve NVAF patients **with renal impairment**	Standard dose NOAC	Reduced dose NOAC	IS/SE ICH Severe IS and fatal bleeding	Elderly Prior bleeding	Secondary objectives
OAC-naïve NVAF patients **without renal impairment**	Reduced dose NOAC	Standard dose NOAC			
OAC-naïve NVAF patients	Reduced dose NOAC	VKA	Treatment persistence	Renal impairment Elderly Diabetes Prior IS or SE Prior bleeding Frail	Further objectives
			Severe IS and fatal bleeding		
			AKI and kidney failure		

Figure 1**. Overview of objectives**

9. Research methods

9.1 Study design

We will conduct a non-interventional cohort study. The study period will run from 1 January 2010 until 31 December 2018, or the latest available date in the data.

9.2 Setting

9.2.1 Study population

The population will be sourced from national administrative registers in Denmark, Finland, Norway and Sweden. The study population comprises patients with NVAF who initiate treatment with OACs (VKA or NOAC).

9.2.2 Study time frame

The study period will begin on 1 January 2010 and end on 31 December 2018, or the latest available date in the data. The day of the first qualifying OAC dispensing (index drug) will constitute the index date (the day of the first qualifying OAC dispensing). The baseline period is defined as the 12 months prior to and including the index date, and will be used to identify new users of OACs. Patients will be followed from the index date until the outcome event of interest, discontinuation of the index drug, death, end of follow-up, or the end of the study period, whichever comes first.

9.2.3 Inclusion criteria

Patients must meet all of the following inclusion criteria (see stand-alone document *Definitions and Operationalizations* for details) to be eligible for the study:

- Patients with a qualifying OAC (see Table 1) dispensed during the inclusion period
- A primary diagnosis indicative of atrial fibrillation during the baseline period

9.2.4 Exclusion criteria

Patients meeting any of the following exclusion criteria (see stand-alone document *Definitions and Operationalizations* for details) will be excluded from the analysis:

- Age < 18 years at index date
- A diagnosis of valvular disease, pregnancy, transient cause of atrial fibrillation or venous thromboembolism in the baseline period
- Hip or knee replacement surgery in the 60 days prior to or on the index date
- A dispensed prescription of heparin or fondaparinux in the 60 days prior to or on the index date
- A diagnosis of end-stage kidney disease or renal replacement therapy in the baseline period

- More than one dispensed OAC (any dose of rivaroxaban, apixaban, dabigatran, edoxaban, or VKA) on the index date

- A dispensed prescription of an OAC (any dose of rivaroxaban, apixaban, dabigatran, edoxaban, or VKA) before the index date

9.3 Variables

See the stand-alone document *Definitions and Operationalizations* for details and references.

9.3.1 Exposure definition

Table 1 provides an overview of qualifying OACs.

Table 1 - Qualifying oral anticoagulant for exposure in study

Type of OAC	ATC-code	Active substance	Standard dose	Reduced dose
VKA	B01AA03	Warfarin	-	-
NOAC	B01AE07	Dabigatran etexilat	150 mg twice daily	110 twice daily
NOAC	B01AF01	Rivaroxaban	20 mg once daily	15 mg once daily
NOAC	B01AF02	Apixaban	5 mg twice daily	2.5 twice daily

All prescriptions will be assessed based on the documented dispensation date.

Each patient will be assigned to one of the four exposure groups based on the index drug: new users of warfarin, apixaban, dabigatran or rivaroxaban. Edoxaban was not considered for the study, as it was rarely prescribed in the Nordics prior to 2016.

Exposure time will start on the index date and will be calculated as the sum of days of supply. Nonpersistence will be defined as a gap between refills that exceeds a threshold equal to the last days' supply dispensed plus a grace period of 30 days plus days of stockpiled medication [1]. The estimated date of nonpersistence (discontinuation) will be defined as the date when the days' supply, including stockpiled medications, would have been used up, at which point the patient will be censored. Patients will be considered to have switched treatments if they are dispensed another OAC before being classified as nonpersistent. The date of the first prescription of an OAC other than the index drug will be defined as the date of treatment switch, at which point the patient will be censored. For the comparison between reduced and standard doses of NOACs (secondary objectives), patients will also be censored if they switch from reduced to standard dose or vice versa.

Since NOACs are prescribed in a fixed dose, the days of supply corresponds to the number of tablets in a dispensed package for rivaroxaban (used once daily) or half the number of tablets in a package for dabigatran and apixaban (used twice daily). Days of supply for warfarin will be estimated by deriving empirical maintenance doses [2].

9.3.2 Outcomes definition

- ***IS and SE*** will be defined based on primary diagnosis codes
- ***Severe IS*** will be defined in the following ways:
    - based on severity indicators in quality of care registers, when available
    - based on diagnosis and procedure codes

- ***ICH*** will be defined based on primary diagnoses
- ***Fatal bleeding*** will be defined based on primary diagnosis in combination with subsequent death
- ***AKI*** will be defined based on primary diagnosis codes
- ***Kidney failure*** (end-stage kidney disease, kidney transplant, or initiation of long-term dialysis) will be defined based on diagnosis and procedure codes
- ***Persistence*** will be operationalized as the duration of time from initiation of treatment to discontinuation or switching as described in Section 9.3.1 (i.e. more precisely, the outcome is discontinuation/switching)

9.3.3 Covariate definition

Unless otherwise mentioned, all information on covariates will be collected during the baseline period.

Demographic characteristics

- Sex
- Age (at index date)
- Calendar year (at index date)

Clinical characteristics

- CHADS2 score
- CHA2DS2-VASc score
- HAS-BLED score
- Charlson Comorbidity Index (CCI)
- Frailty indicator

Covariates

- Alcohol abuse
- Anemia
- Aortic plaque
- Coronary heart disease:
    - Angina pectoris
    - Myocardial infarction
    - Acute ischemic heart diseases
    - Chronic ischemic heart disease
    - Coronary artery bypass graft(s)
    - Percutaneous coronary intervention
- Dementia
- Depression
- Diabetes mellitus
- Drug abuse
- Gastric or peptic ulcer disease/diseases of gastrointestinal tract

- Heart failure
- Major bleeding
- Hypertension
- Hypothyroidism
- Inflammatory bowel disease
- Other cerebrovascular disease
- Liver disease
- Hyperlipidemia
- Volume depletion
- Other metabolic disorders
- Obesity
- Peripheral artery disease
- Coronary artery disease
- Psychosis
- Pulmonary disease
- Rheumatoid arthritis/collagen vascular disease
- Renal impairment
- AKI
- Tobacco abuse
- Other vascular disease
- Malignant cancer (excl. non-melanoma skin cancer)

Comedications

- Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers
- Antiarrhythmics
- Antidepressants
- Antiplatelets
- Antiulcer drugs (except proton-pump inhibitors)
- Beta blockers
- Calcium channel blockers
- Diabetes drugs (incl. insulin)
- Diuretics
- Erythropoietin-simulating agents
- Estrogens
- Lipid modifying agents
- Non-steroidal anti-inflammatory drugs
- Proton-pump inhibitors

9.3.4 Subgroups

The following subgroups of special interest will be defined.

- Renal impairment (by stages of CKD) (and in combination with advanced age)

- Patients with renal impairment will be identified based on diagnosis and procedure codes

- Elderly (80+ years and 85+ years)
  - Age will be assessed at the index date
- Diabetes (and in combination with renal impairment)
  - Patients with diabetes will be identified based on diagnosis codes and medication use
- Frail patients
  - Frail patients will be identified based on diagnosis and procedure codes
- Prior IS or SE
  - Patients with a history of IS/SE will be identified based on diagnoses
- Prior bleeding
  - Patients with a history of bleeding will be identified based on diagnosis and procedure codes

Analyses will be conducted to test for effect modification (interaction).

9.4 Data sources

This study is to be conducted on data from registers in Sweden, Denmark, Finland and Norway. Data will be sourced from national administrative registers, including the national patient registers, the prescription registers, which contain prescribed drugs dispensed at pharmacies, and the cause of death registers. Other relevant registers include the national quality of care registers on stroke in Sweden and Denmark.

National administrative registers

The national administrative registers in the Nordic countries are summarized in Table 4.

The registers in the four countries provide near-complete coverage of the total population of over 25 million inhabitants – 5.6 million in Denmark, 5.4 million in Finland, 5.1 million in Norway and 9.6 million in Sweden. All included registers have nationwide coverage with linkage made possible using personal identification numbers.

Table 2: Relevant registers in the Nordic countries

Type of register		Specialist care	Prescription/dispensation/ reimbursement	Cause of death
Included variables relevant for this study		Diagnoses (ICD-10), procedures and admission/discharge dates	ATC-codes, strength/size, prescription, date of expedition	Date of death, cause of death
Sweden	**Holder**	*Socialstyrelsen*, the Swedish Board of Health and Welfare		
	Name of register	*Patientregistret*, National Patient Register	*Läkemedelsregistret*, Swedish Prescribed Drug Register	*Dödsorsaksregistret*, Cause of Death Register
Finland	**Holder**	*THL*, National Institute for Health and Welfare	*Kela*, the Social Insurance Institution	*Tilastokeskus*, Statistics Finland
	Name of register	*HILMO* (inpatient) and *AvoHILMO* (outpatient), Care Register for Health Care	*Kela*, Finnish Reimbursement Register	Causes of death
Norway	**Holder**	*Helsedirektoratet*, the Norwegian Institute of Health	*Folkhelseinstitutet*, Norwegian Institute of Public Health	
	Name of register	*Norsk pasientregister*, Norwegian Patient Registry	*NorPD*, Norwegian Prescription Database	*Dødsårsaksregisteret*, Norwegian Cause of Death Registry
Denmark	**Holder**	*Sundhedsdatastyrelsen*, Danish Health Data Protection Agency		*CPR-kontoret,* The CPR Office
	Name of register	*Landspatientregisteret* National Patient Register	*Lægemiddelstatistikregisteret* National Prescription Register	*Det Centrale Personregister*, The Central Person Registry

Quality of care (QoC) registers for stroke

For analyses of severity of stroke, QoC registers on stroke will be included in the countries where such registers exist.

The Swedish Stroke Register (Riks-Stroke) is a national quality register on stroke and since 1998 all Swedish hospitals admitting acute stroke patients participate. The register is one of the world's largest stroke registers and includes information on several dimensions of stroke care, including

background variables. Information on stroke severity at hospital arrival is registered, as measured by the National Institutes of Health Stroke Scale (NIHSS).

The Danish Stroke Register (Dansk Apopleksiregister) covers all patients with acute stroke from 2003 treated at a Danish hospital. The register contains data on sociodemographic, clinical, and lifestyle factors with potential prognostic impact. Reporting to the register is mandatory. Information on stroke severity at hospital arrival is registered, as measured by the Scandinavian Stroke Scale (SSS) and the NIHSS.

9.5 Study size

The literature was reviewed for relevant figures of naïve patients (new users of OACs). A targeted literature review of the number on new users of OACs with atrial fibrillation (AF) is summarized in Table 3.

Table 3: Number of naïve oral anticoagulant users per drug and country

	Denmark	**Norway**	**Sweden**
Population	5.6 million	5.1 million	9.6 million
Population covered in study (%)	100%	100%	100%
Time period	Aug 2011–Feb 2016	Jan 2013–Jun 2015	Dec 2011–Dec 2014
Users with AF by oral anticoagulant drug:			
VKA			
B01AA03 warfarin	38,893	11,427	49,418
NOACs (reduced dose)			
B01AE07 dabigatran etexilate	8,875	2,758	2,228
B01AF01 rivaroxaban	3,476	1,824	1,763
B01AF02 apixaban	4,400	1,901	2,180
Total NOAC	***16,751***	***6,483***	***6,171***
Source:	Nielsen (2017) [3]	Halvorsen 2017 [4]	Friberg (2017) [5]

Previous studies on NOAC utilization (Table 3) were used to estimate the proportion of NOAC users that have AF and reduced doses, per country. This proportion was applied to the total number of NOAC patients (sourced from national prescription statistics [6-8]) for the years included in this study to account for the longer study period.

As a result of the increasing trend of NOAC utilization (as demonstrated in Figure 2) and the longer study period, the estimated number of patients on reduced doses included in this study is 70,000. Data to approximate the number of NVAF patients on reduced doses of NOACs in Finland could not be identified, but based on the size of the total population (5.5 million), it is probable that there are 20,000–30,000 patients.

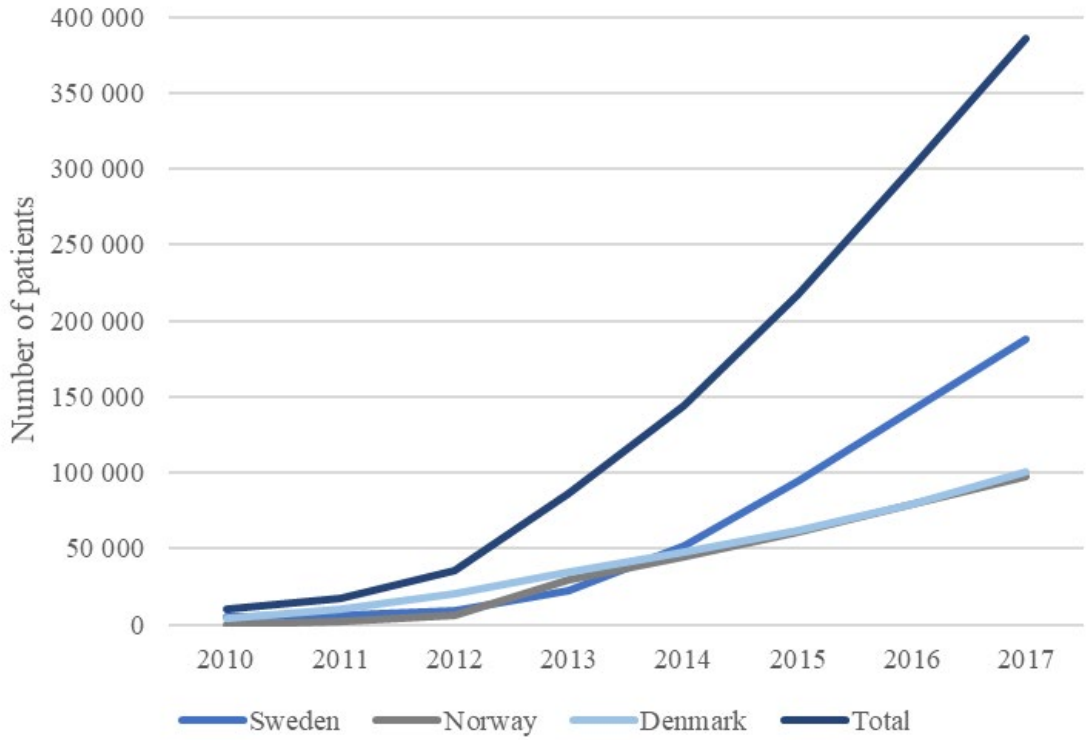

Figure 2: Patients on NOACs in the Nordics (excluding Finland)

A previous study by Nielsen et al. (2017) [3] estimated the IS/SE incidence rates in dose reduced NOACs and VKA in Denmark. In addition, the paper presents hazard rates and corresponding 95% confidence intervals for the comparison of the various NOACs with VKA for this endpoint at one year follow-up. The rates and confidence intervals were weighted for inverse propensity score. The reported hazard rates were 1.19 (95% CI: [0.95; 1.49]) for apixaban vs. VKA; 0.89 (95% CI: [0.77; 1.03]) for dabigatran vs VKA, and 0.89 (95% CI: [0.69; 1.16]) for rivaroxaban vs. VKA.

Assuming that the proportion and time patterns of IS/SE in Norway, Sweden, and Finland are the same as in Denmark, similar results are expected for each single country. The precision of the confidence intervals will slightly vary given the different population sizes.

Furthermore, with the assumption of similar and homogenous hazard ratios and variability in the four countries, the meta-analysis across the countries (if undertaken) will result in a more precise estimation of the overall hazard ratio.

9.6 Data management

Anonymized analytical datasets comprising all observations and variables required for the planned analyses will be created (variables as specified in section 9.3).

All data management and analyses will be performed centrally or, if required by national authorities, by local researchers (only applicable for Norwegian and Danish data). A comprehensive statistical analysis plan (SAP) will be developed, which in further detail will outline the definitions and statistical methods to be used. Data management and statistical analyses will be conducted with the use of SAS, SQL and/or STATA.

We will strive towards data access and storage solutions to enable pooling of the data, and if feasible, conduct the analyses on pooled data. Data harmonization could however be an extensive task as this study involves multiple data sources in several countries. The first harmonization will have to be made on the national level, making sure that the anonymized research databases (linked data) are cleaned and well-structured. Part of this work will for instance be to harmonize revisions of ICD codes and to address updated definitions of variables and their occurrences over time.

The Nordic countries have homogenous populations that are recorded in similarly structured health registers, using similar definitions and processes to record and access data. Yet, harmonizing data between countries is an extensive task with many potential hurdles. Some of these are listed below.

- Variable definitions (e.g. ICD revisions, codes expanding/contracting in scope)
- Data coverage (e.g. new clinics added)
- Data updates (e.g. outpatient data, DRG)
- Differences in reporting standards (e.g. different data formats)

All these issues may result in errors or bias if not carefully considered before setting up the database and executing the analyses. We will therefore address these challenges in detail in the SAP if pooling is determined feasible, and agreed on to be undertaken.

9.7 Data analysis

The study will initially be conducted with separate country cohorts, reporting country specific outcomes. A meta-analysis of the aggregated results may thereafter be conducted. Detailed methodology for the analyses of data collected in this study will be documented in the SAP. Any non-minor deviations from the SAP will be documented.

9.7.1 Descriptive analysis

Patients will be described at treatment initiation in terms of demographic and clinical variables. Continuous variables will be reported as number of observations, means, medians, standard deviations, interquartile range (IQR), and minimum and maximum values. For categorical variables the numbers and proportions of patients in each category will be presented in line with applicable data protection regulation (e.g. minimum of 3 patients). Person years of follow-up will be calculated from the index date to the outcome event of interest, discontinuation of the index drug, death, end of follow-up or the end of the study period, whichever comes first. Incidence rates will be calculated as the number of events over the observed person-time. Corresponding 95% confidence intervals will be computed.

9.7.2 Main analysis

This section presents an outline of the main analyses to be performed.

To determine the risk of outcomes among NOAC users compared with warfarin (reference) users, we will calculate cause-specific hazard ratios using Cox regression models (secondary objectives: standard compared to reduced dose). Failure curves will be used to depict how risks of events evolve over time. Cause-specific cumulative incidence functions will be used to calculate absolute risks of events taking into account the competing risk of death [9]. To allow for a comparison across the different treatment regimens, an inverse probability of treatment weight-approach will be used to estimate treatment effect in the entire study population [10-13]. The underlying propensity score

models will be based on the variables presented in section 9.3. Balance between treatment populations will be evaluated by standardized differences of all baseline covariates, using a threshold of 0.1 to indicate imbalance.

9.7.3 Sensitivity analysis

We will conduct pre-defined sensitivity analyses to verify the consistency of our results.

To explore the potential for bias from baseline differences and the propensity of receiving treatment with a NOAC, we will perform sensitivity analyses using ordinary crude and Cox multivariate adjusted analyses to compare the results obtained from the main analyses [14]. We will also consider sensitivity analyses to standardize the estimates to the treated population (using standardized morbidity ratio weights or matching).

Importantly, potential bias may be driven by strong treatment effect heterogeneity across the population. This will be explored in addition to the pre-planned subgroup analyses of high risk patients. For the main outcomes of interest, we will also exclude patients with a prior event during the baseline period. A longer study baseline period will be considered pending data availability.

Finally, as the introduction of each NOAC could have influenced patient selection, we will repeat the main analysis confined to time periods during which all NOACs have been available (the calendar year of treatment initiation will also be used as a covariate). Intention to treat (ITT) analyses and variable grace periods for exposure assessment (e.g. 60, 90, 180 days) and follow-up lengths (e.g. 1, 2 years, all available data) will also be considered in sensitivity analyses.

9.8 Quality control

The national and compulsory health registers included in the present study are typically governed by the national authorities in charge of public health and welfare. Reporting of information to the registers is compulsory by all health care providers and pharmacies, thus guaranteeing high completeness rates and nationwide coverage. Rigorous validation work is constantly ongoing from the health authorities in the respective countries in order to ensure that data are complete, comprehensive and of the highest quality possible. There is a large number of scientific publications based on the register data sources that will be used in this study. Data will be examined for completeness and missing data are anticipated to be minimal based on previous research and the compulsory nature of the data collection.

The analyses will be executed as stipulated in the SAP. Designated researchers will be responsible for most operational tasks such as data management, analyses, and report writing. If required by national authorities, local researchers will perform data extraction, data management and analyses. Such analyses will be supervised centrally to guarantee that the same project standards are being followed. The team will be led by a research leader with experience from similar projects.

The steps involved in data management and analyses will be recorded in maintained scripts and logs. This will simplify data updates and ensure reproducibility of results, from raw data to end results.

Data analyses are quality controlled according to an in-house protocol that includes a code review. Data cleaning and analytical steps performed will be reviewed by a second programmer. Any errors or omissions found during this review will be communicated back to the original analyst and updated accordingly.

9.9 Limitations of the research methods

9.9.1 Internal validity of study design

Due to the observational nature and absence of randomization in this study, various potential biases arise. The overall study design aims to minimize some of these biases by creating a cohort of patients newly prescribed OACs and following treatment groups over time for the outcomes of interest. Hence this (active comparator, new user) design limits the study of patients with an indication for treatment and starts follow-up for these patients at treatment initiation, ensuring correct temporality between covariate and exposure assessment.

Bias due to missing data

This study will to a large extent rely on register-based data which are known to have a high degree of completeness. Reporting of certain variables used in this study is not voluntary. For example, information on health care visits and prescriptions can be expected to be present. If information regarding dates, diagnosis codes or treatment information is absent, these records would be excluded from analysis since imputation of these types of variables would be difficult to implement and justify. In the unlikely event that a patient's health care visit or prescription would not have been captured at all by the registers, this instance of missing data would not be possible to identify.

Diagnoses of outcomes and comorbidities will be identified using diagnosis and procedure codes, which are subject to potential miscoding. The health registers included in the study do, however, cover all diagnoses and procedures in the hospital/outpatient specialist setting irrespective of where they occurred.

Misclassification bias

Given that outcomes will be defined using national and population-based health register data, there will be an inherent risk of information bias resulting from classification error.

One limitation of the study is that treatment dates are based on the date of filling the prescription at the pharmacy, but not necessarily the date of treatment administration. There is also a risk that the dispensation of the respective drug does not guarantee that the patient actually took the medication. This will always be the case in observational studies of self-administered treatments since the actual patient behavior cannot be observed. However, in case of continuous drug dispensations by the same patient, the amount of misclassification is expected to be low. Another limitation of the study is that for patients who switched between OACs, only the episode of the initial OAC will be considered in the analysis.

Furthermore, the lack of access to certain patient data in this study, e.g. laboratory values, means that proxies are instead used to identify some patient characteristics, such as level of renal impairment. The lack of some clinical data also impacts analyses of how the treatments of interest are administered in terms of populations and doses used.

In general, differential misclassification may occur if information differs between treatment groups.

Confounding

In addition to this study restricting comparisons between medications intended for patients with the same clinical indication, additional techniques used to reduce the biases inherent to observational research will be described in detail the SAP. The potential impact of confounding by indication (e.g. any drug reserved for the frailest patients will be associated with the worst outcomes) will also

indirectly be explored in the specified subgroup analyses of high risk patients. Despite efforts to correct for bias, the potential for residual confounding will still persist.

Selection bias

By choice of study design this study aims to minimize selection bias by restricting the study to new users. While the national registers used in this study have complete coverage of their respective general populations, only prescriptions filled at pharmacies are captured in the data (generally hospital-administered drugs are not captured). This is however not likely to introduce a selection bias given that the majority of OAC treatments is provided outside of the hospital setting.

9.9.2 External validity of study design

The findings of this study will reflect routine clinical practice in the Nordic region and will not be directly transferable to other countries or regions.

10. Protection of human subjects

All patient-level data are de-identified to comply with European data protection regulations. Since this study is based on anonymized data, informed consent of the patient is not required. This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy. Patient data will be linked using anonymized, unique patient identification numbers. Only the key holder in each country, usually the statistics authority or data holder, will have access to the population key. All data will be stored on encrypted and password protected servers and transfers will be managed securely, either through physical transportation or encrypted datalinks. Access to the data will be restricted to the personnel directly involved in this study.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products [Revision 1]), individual reporting of adverse reactions is not required for non-interventional study designs that are based on secondary use of data. Reports of adverse events/reactions will be summarized in the study report (European Medicines Agency 2014).

12. Plans for disseminating and communicating study results

The results of this study will be summarized in a study report. It is further planned to submit at least one publication based on the results of this study to an international peer-reviewed journal. The study will be registered in the EU PAS Register.

13. References

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Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)
Co-Investigators and Steering/Publication Committee Members	v1.0
Definitions and Operationalizations	v0.1
Statistical Analysis Plan (SAP)	–

Annex 2: Signature pages

Signature Page - OS Conduct Responsible

Title	Real-world evidence for non-valvular atrial fibrillation patients treated with oral anticoagulation in the Nordics (REATTAIN)
Protocol version and date	V1.0, 19.08.2019
IMPACT study number	20030
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Dabigatran etexilate, rivaroxaban, apixaban
Comparator / Reference therapy	Warfarin
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

[redacted]

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Title	Real-world evidence for non-valvular atrial fibrillation patients treated with oral anticoagulation in the Nordics (REATTAIN)
Protocol version and date	V1.0, 19.08.2019
IMPACT study number	20030
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
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Active substance	Dabigatran etexilate, rivaroxaban, apixaban
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The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

[redacted]

Signature Page - Outcomes Data Generation

Title	Real-world evidence for non-valvular atrial fibrillation patients treated with oral anticoagulation in the Nordics (REATTAIN)
Protocol version and date	V1.0, 19.08.2019
IMPACT study number	20030
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Dabigatran etexilate, rivaroxaban, apixaban
Comparator / Reference therapy	Warfarin
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

[redacted]

Signature Page - OS Safety Lead

Title	Real-world evidence for non-valvular atrial fibrillation patients treated with oral anticoagulation in the Nordics (REATTAIN)
Protocol version and date	V1.0, 19.08.2019
IMPACT study number	20030
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Dabigatran etexilate, rivaroxaban, apixaban
Comparator / Reference therapy	Warfarin
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

[redacted]

Signature Page - OS Medical Expert

Title	Real-world evidence for non-valvular atrial fibrillation patients treated with oral anticoagulation in the Nordics (REATTAIN)
Protocol version and date	V1.0, 19.08.2019
IMPACT study number	20030
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Dabigatran etexilate, rivaroxaban, apixaban
Comparator / Reference therapy	Warfarin
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

[redacted]

Signature Page - OS Statistician

Title	Real-world evidence for non-valvular atrial fibrillation patients treated with oral anticoagulation in the Nordics (REATTAIN)
Protocol version and date	V1.0, 19.08.2019
IMPACT study number	20030
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Dabigatran etexilate, rivaroxaban, apixaban
Comparator / Reference therapy	Warfarin
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

[redacted]

Signature Page - OS Epidemiologist

Title	Real-world evidence for non-valvular atrial fibrillation patients treated with oral anticoagulation in the Nordics (REATTAIN)
Protocol version and date	V1.0, 19.08.2019
IMPACT study number	20030
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Dabigatran etexilate, rivaroxaban, apixaban
Comparator / Reference therapy	Warfarin
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

[redacted]