NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A retrospective nationwide register study to characterize and compare non-valvular atrial fibrillation (NVAF) patients in Norway treated with novel oral anticoagulants (NOACs) and warfarin on drug utilization patterns, discontinuation and bleeding complication rates
Protocol acronym	*Beyond* Study Norway – Part of the BEYOND study program (**BE**nefit of NOACs stud**Y** of n**O**n-valvular AF patie**N**ts in nor**D**ic countries)
Protocol number	B0661052
Protocol version identifier	1
Date of last version of protocol	Final version 12 December 2014
EU Post Authorization Study (PAS) register number	Study not registered
Active substance	B01A A03 – warfarin B01A E07 – dabigatran B01A F01 – rivaroxaban B01A F02 – apixaban
Medicinal product	Warfarin Pradaxa® - dabigatran Xarelto® - rivaroxaban Eliquis® - apixaban
Research question and objectives	The study aims to describe the drug utilization patterns and characteristics of patients on oral anticoagulant therapy (OAC) and to describe and compare the discontinuation rates and the risk of bleeding complications between different OAC therapies. The study will be undertaken on nation-wide registries in Norway during the early post-marketing period of the novel oral anticoagulants

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	Acute Coronary Syndrome
AE	Adverse Events
AF	Atrial Fibrillation
ATC	Anatomical Therapeutic Chemical Classification System
BMS	Bristol-Myers Squibb
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
Crl	Credibility limit
DDD	Defined Daily Dose
DVT	Deep Venous Thrombosis
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HAS-BLED	Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol
ICD10	10th revision of the International Classification of Diseases System
ICPC	International Classification of Primary Care
INR	International Normalized Ratio
ISTH	International Society of Thrombosis and Hemostasis
NCMP	Norwegian Classification of Medical Procedures
NCSP	The Nordic Medical Statistics Committees Classification of Surgical Procedures
NOAC	Novel Oral Anticoagulants, also called Non-vitamin K antagonist Oral Anticoagulants
NorPD	Norwegian Prescription Database
NPR	The Norwegian Patient Register
NR	Norwegian Computing Center
NSAID	Nonsteroidal Anti-inflammatory Drugs
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulants
PASS	Post-Authorization Safety Study
PE	Pulmonary Embolism
SAP	Statistical Analysis Plan
SMS	Short Message Service
VKA	Vitamin K Antagonists

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Beyond study Norway - BEnefit of NOACs studY of nOn-valvular AF patieNts in norDic countries

Title:

A retrospective nationwide register study to characterize and compare non-valvular atrial fibrillation (NVAF) patients in Norway treated with novel oral anticoagulants (NOACs) and warfarin on drug utilization patterns, discontinuation and bleeding complication rates

Final version dated 12 December 2014,
Author: Christian Jonasson, Lifandis AS

Rationale and background

Patients with NVAF are at increased risk for stroke (1). Warfarin and other vitamin K antagonists are effective treatments, reducing the risk of stroke by about two thirds, but their use is limited by a narrow therapeutic range, drug and food interactions, required monitoring, and risk of bleeding (2). In recent years three novel oral anticoagulant (NOACs) drugs (apixaban, dabigatran and rivaroxaban), recently referred to drug class non-vitamin K antagonist oral anticoagulants, have been introduced as new therapeutic alternatives to warfarin for NVAF patients (3-5). A fourth NOAC, edoxaban, is currently being assessed by the European Medicines Agency (EMA) and will not be within the scope of this research. The uptake of the NOACs in the early post-marketing authorization period and the types and characteristics of patients being treatment is of interest. In particular, there is interest in whether those outcomes observed in clinical trials, especially the rates of bleeding events and discontinuation, are being seen in clinical practice and, furthermore, whether there are differences regarding these rates between the NOACs, which have not been compared in a clinical trial. The clinical trial data in NVAF patients for NOACs have shown that apixaban is the only NOAC to show a combined statistically significant lower rate of stroke/systemic embolisms, discontinuation and major bleeding compared with warfarin (3-5). Moreover, indirect comparisons of NOACs using warfarin as a common comparator show that discontinuation rates and some bleeding outcomes are also significantly lower for apixaban compared with either rivaroxaban or dabigatran (only dabigatran 150 mg for the bleeding comparison) (6).

Whilst there is a keen interest in actual drug usage data from clinical practice, there are a number of limitations with this kind of observational research, especially where it is undertaken shortly after a medicine is launched and available for use within a particular country. A potential channeling bias may be present in observational studies if clinicians initially use the new medicine in patients with comorbidities and other factors predisposing them to the outcome. If this is the case then outcomes such as discontinuation and bleeding rates can be systematically different from those patients on other

therapies, and therefore, bias the analysis. It is, therefore, vital to first describe patients on the therapies being investigated to assess how their characteristics vary, before then going on to examine initial experience with outcomes.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer/Bristol-Myers Squibb (BMS).

Research question & objectives

The research questions to be addressed are:
- What are the characteristics of NVAF patients treated with different oral anticoagulants (OACs), do these differ between OACs, and how do these change over time?
- What is the rate of discontinuation of NVAF patients to each OAC and does this differ between OACs?
- What is the risk of bleeding in NVAF patients during treatment with OAC and does this risk differ between OACs?

Study objectives are:
1. Primary objective is to describe and compare the clinical and patient characteristics such as CHADS2, CHA2DS2-VASc and HAS-BLED (Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol) score, previous OAC use, bleeding history, concomitant medications and co-morbidities of all NVAF patients who initiated an OAC in the study period, overall and separately by each OAC (apixaban, dabigatran, rivaroxaban, warfarin), by OAC-switch status and previous OAC use (naïve versus experienced).
2. To determine predictive factors of patients initiating each OAC as monotherapy (without a switch from a different OAC) in terms of the $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED score, previous OAC use, concomitant medications, co-morbidities and the estimated probability of initiating OAC therapy (pooled over the full study period and also estimated within consecutive 3-month periods over the study period). To identify predictive factors of switching.
3. To measure and compare discontinuation rates of NVAF patients treated with each OAC therapy (NOACs and warfarin) in Norway unadjusted and adjusted for differences in measured baseline patient characteristics. To identify predictive factors of discontinuation
4. To compare clinically relevant bleedings and major bleeding rates for NVAF patients treated with OAC therapy (NOACs and warfarin) in Norway unadjusted and adjusted for differences in measured baseline patient characteristics

Study design

This retrospective cohort study will make use of an individual patient level linked dataset combining data from the National Patient Register (NPR) and the Norwegian Prescription Database (NorPD). Using these linked datasets, NVAF patients initiated on a new anticoagulant between 01 January 2013

and end of September 2014 (or later depending on data available from the registries), will be identified and followed until the end of the study period or death.

We define new users (with or without prior OAC experience) as patients redeeming their first prescription of a new OAC in the study period, i.e. no previous prescription for the same OAC in the previous 180 days. The focus will be on the following user groups:

1. New warfarin users
2. New apixaban users
3. New rivaroxaban users
4. New dabigatran users

Population

The study will be undertaken in Norway and will include all adult patients with NVAF and a prescription dispensed on either a NOAC or warfarin in the study period (01 January 2013 to end of September 2014 depending on data availability). The NVAF study population is defined in accordance with the updated American Heart Association (AHA)/American College of Cardiology (ACC) 2014 guidelines which defines NVAF as atrial fibrillation in the absence rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair. Patients with valvular atrial fibrillation, deep venous thrombosis and pulmonary embolism during the last 6 months and those who have undergone knee or hip replacement surgery in the last 5 weeks before starting OACs or use of OAC for any other indication will be excluded. Individual level data will be analyzed from NPR and NorPD from 01 January 2008 for as long as data retrieval is possible in 2014.

Variables

Patient characteristics/Co-variates
Co-variates will include the established risk score for bleeding, the HAS-BLED, and the risk scores for stroke, the CHADS2 and CHA2DS2VASc. These risk scores will be constructed based on information present in the registries. Some of the baseline characteristics present in the risk scores will also be included alone, such as bleeding history and previous stroke and ischemic heart disease. In addition to the variables that is included in the above-mentioned risk scores other co-variates known as potential risk factors or confounders will also be included, such as other co-morbidities (e.g. dementia, chronic obstructive pulmonary disease (COPD), cancer), co-medications (e.g. acid-suppressive drugs), prescriber specialty, time since NVAF diagnosis (if available) and prior use of OAC in the baseline period.

Endpoints

Discontinuation:
- The date of discontinuation of OAC treatment will be defined by the date of the last redeemed prescription plus the estimated length of that prescription (length of OAC supply estimated from

the redeemed pack-size and strength), plus a 30-day grace period to take into account incomplete adherence to treatment and dose modifications.

Bleeding:
- The main bleeding endpoint is all clinically relevant bleeding episodes, which is defined as all bleeding episodes recorded in NPR between the index date (start of OAC treatment) and the end of study period
- A major bleeding endpoint is defined as any bleeding event which occurs in a critical area or organ **or** blood transfusion ≤10 days after hospital admission date
- Individual bleeding endpoints of interest such as intracranial hemorrhage and gastrointestinal bleeding will be described separately

OAC exposure
OAC exposure is defined as a single or series of redemptions of a new OAC starting in the period from 01 January 2013 to end of study period. The strength (and the associated dosing as displayed in Table 4) together with the pack size of each redemption will be used to calculate the length of the OAC exposure. Gaps must be within 30 days from the end of OAC supply to next redemption to be counted as continuous treatment or else the patient is considered to have discontinued their therapy. The end of OAC supply will be estimated from the last redemption.

Data sources

Two data sources will form the basis for the analyses, the Norwegian Prescription Database (NorPD) (7) and the Norwegian Patient Register (NPR) (8). The NorPD is a register covering all prescriptions redeemed at pharmacies nationwide and data is available from 1st January 2004. NorPD does not include information on drugs administered during hospital stays (e.g. chemotherapy, intravenous antibiotics) or drugs used at nursing homes. The NPR was established for research purposes in 2008 and contains all hospital admissions or appointments (both hospitalizations and outpatient consultations), length of stay and procedures (surgical and medical) from all hospitals in Norway. ICD10 (10th revision of the International Classification of Diseases System) of codes are used for all diagnoses and NCMP (Norwegian Classification of Medical Procedures) and NCSP (The Nordic Medical Statistics Committees Classification of Surgical Procedures) for medical and surgical procedures. Both registries are nation-wide and provision of the information is mandatory, which eliminates the risk of both selection and re-call bias. The large and detailed dataset also makes it possible for us to adjust for risk factors and analyze in depth the different sources of bias and confounding so important for studies of this kind.

Study size

Approximately 2,000 patients had redeemed a prescription for apixaban in the NorPD registry up until the end of 2013, and with 3-4 additional quarters of data available from the registries, we anticipate a total of 5,000 patients on apixaban will be available. This includes both NVAF patients

registered in NPR and NVAF patients prescribed OAC in NorPD. A proportion will have apixaban prescribed in primary care on reimbursement code for NVAF, but without any hospital contact for NVAF during the study period. Regarding the other OACs 10,000 patients are assumed to be on rivaroxaban in the same period, 10,000 on dabigatran (with 50% assumed to be on 150 mg and 50% on 110 mg for the purposes of power calculation) and 50,000 on warfarin.

Assuming different sample size scenarios for the apixaban group, power calculations were made around the unadjusted odds ratios for each comparison at one year on the primary endpoint (comparison of patient characteristics), discontinuation rate, and clinically relevant bleeding.

For the primary objective related to patient characteristics the study is sufficiently powered, with the expected sample sizes, to detect small differences in the $CHADS_2$ score (<0.5 point difference at 80% power) and in the HAS-BLED risk score (<0.3 point difference at 80% power).

Power calculations were performed on the apixaban discontinuation rate reported in ARISTOTLE (3) and adjusted using a published indirect comparison (6) to derive the rates for the other OACs. Annual discontinuation rates of 16.2% for apixaban, 17.9% for warfarin, 19.2% for rivaroxaban, 23.5% for dabigatran 110 mg and 24.5% for dabigatran 150 mg are assumed. With 2,000 apixaban patients and assumed sample sizes for the other OACs, the comparison between apixaban and warfarin will be under-powered while the remaining comparisons (apixaban versus rivaroxaban and both dabigatran doses) will be sufficiently powered.

Power calculations on the main bleeding endpoint assumed that the combination of clinically relevant non-major and major bleeding from the ARISTOTLE trial (4.1% per year) would represent the clinically relevant bleeding rate to be observed in the Norwegian registries. Annual clinically relevant bleeding rates for the other OACs were derived using the published indirect comparison. The annual bleeding rates used in these calculations were: 4.1% for apixaban, 5.8% for warfarin, 5.9% for rivaroxaban, 5.3% for dabigatran 150 mg and 4.7% for dabigatran 110 mg. These calculations indicate that with a sample size of approximately 1,500 apixaban patients with a minimum of one year of follow up, there would be acceptable levels of power (70-80%) in the comparisons with warfarin and rivaroxaban respectively. The comparison of apixaban with dabigatran will, however, be under-powered. As a result of these calculations, the comparative bleeding analysis will only be undertaken if a preliminary analysis of the data indicates that the comparisons of apixaban with warfarin and rivaroxaban (separately) will be sufficiently powered. Bleeding rates will be described using descriptive and summary statistics regardless of the number of patients available.

Data analysis

Throughout all the analyses continuous variables will be described by the mean, standard deviation, median, first and third quartiles, and minimum and maximum. Categorical variables will be described by the number and percentage of patients in each category. Follow-up time will be described as a continuous variable for each patient, and also be reported as the total number of patient-months for each OAC.

Regression analysis will be the primary analytical approach with both unadjusted and adjusted models to be estimated and patient (clinical and demographic) characteristics, OAC group, previous OAC use, co-morbidities, concomitant medications measured at baseline as candidate independent variables. For binary independent variables, logistic regression models will be considered with the final model selected by backwards stepwise selection. Predictive performance of the final models will be assessed by the c-statistic. For time to event analyses our primary approach will be Cox proportional hazard regression analysis with the same candidate independent variables as above. A propensity score matching approach will also be considered as an analysis option. The stroke events and deaths during the study period will be counted and analyzed descriptively.

Primary objective 1: describe and compare clinical and patient characteristics of all NVAF patients initiated with OAC

All NVAF patients initiated with an OAC will be described by patients' characteristics such as age, gender, $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED score, previous OAC use, concomitant medications, co-morbidities, time since NVAF diagnosis and specialty of prescriber. As well as the OAC specific user groups, a description of all users (without distinguishing between OACs) will be undertaken. Within OAC user groups, switchers and non-switchers will be described as separate groups, as well as naïve versus experienced OAC use.

A summary of frequencies of switches between the OACs will be given. A switch is defined as dispensing another OAC within 30 days of the end of the supply for the previous OAC Switches to be examined are:

1. Switching from a first OAC to a second OAC
2. Switching from a NOAC to warfarin (first time switch)
3. Switching from warfarin to a NOAC (first time switch)
4. Switching from a NOAC to another NOAC (first time switch)

Whether OAC was used as monotherapy or together with anti-thrombotic treatment for each group will be further explored, i.e. aspirin or anti-platelet treatments in ATC (Anatomical Therapeutic Chemical Classification System) group B01AC.

A comparison of the characteristics of patients initiating each OAC will be undertaken considering differences in means with 95% CIs and by unpaired t-tests or Mann-Whitney U tests (if normality assumptions seem unreasonable). Comparisons between the user groups given categorical background variables could be done by considering differences in proportions with 95% CIs and by chi-squared tests or Fisher's exact test (if required).

Objective 2: predicting factors associated with initiating each OAC as monotherapy & switching

To examine which of the above patient characteristics predict which OAC treatment patients are on, a multinomial logistic regression model (NOACs as a group versus warfarin and each NOAC separately versus warfarin) will be performed. Odds ratios with 95% uncertainty intervals will be

reported from the regression analyses. Predictive factors associated with the abovementioned switch patterns will also be analyzed using a logistic regression model.

Objective 3: describe and compare discontinuation rates associated with each OAC

The rate of discontinuation in each OAC group by switch status will be estimated. A summary of the cumulative incidence, defined both as the number who discontinue divided by 1) the number of patients and 2) the number of 100 patient years, with 95% confidence intervals at different time periods (3, 6, 9 months and 3 month intervals up to a possible 24 months if data allows) and at end of study period, will be given.

As the patients might have different exposure times a survival analysis will be conducted for the time to discontinuation from the onset of OAC use using the Cox proportional hazard modelling approach. Predictive factors of discontinuation based on the relevant background variables will be assessed from the cox proportional hazard model. Kaplan-Meier plots for relevant background variables will be presented. After examining the number of deaths in our study population competing risk methods will be considered. Univariate Cox proportional hazard models will be specified, and thereafter a backward stepwise approach to obtain a final model. Finally time-dependent variables can be considered. Initially, there will be a check for the statistical reasonability of a linear functional form in the regression term for continuous background variables, for example age, and also for possible interaction terms, for example between age and gender. Separate models will be estimated on non-switch and all patients for comparisons of apixaban with warfarin and other NOACs, respectively, to account for the potential bias that warfarin patients are more likely to switch to NOACs, than NOAC patients on to warfarin. The number of deaths in the study population will be assessed using a competing risk modelling approach. Alternatively, and as an option, a marginal structural modelling approach might be undertaken.

Objective 4: describe and compare clinically relevant and major bleeding rates across OAC groups

Incidence bleeding rates at 1, 3, 6 and 9 months (and in 3 months intervals up to a possible maximum of 24 months if data allows) for clinically relevant and major bleeding will be described separately, expressed as 1) rate per patient and 2) per 100 patient years with associated confidence intervals.

As some patients might experience bleeding more than once throughout the study period, it is important to differ between the patients experiencing bleeding just once and those having several bleeding episodes. The time to a first bleeding episode for each patient will first be considered. Kaplan-Meier plots displaying risks for various patient groups will be helpful in understanding differences in bleeding risk. Cox proportional hazard regression models with relevant patient characteristics as explanatory variables (such as age, gender, co-medication, co-morbidities, HAS-BLED score) will be defined. Separate models will be estimated on non-switch and all patients for comparisons of apixaban with warfarin and other NOACs, respectively, to account for the potential bias that warfarin patients are more likely to switch to NOACs, than NOAC patients on to warfarin. The number of deaths in the study population will be assessed using a competing risk modelling

approach. Alternatively, and as an option, a marginal structural modelling approach might be undertaken.

We expect the proportion of patients with multiple bleeding episodes during the study period to be low and only sufficient for descriptive analyses.

Separate analyses (descriptive analysis and a cox-modelling approach for first bleeding episode) will be performed on comparing rates of intracranial bleeding or gastrointestinal bleedings across OAC groups.

Milestones

The study protocol will be finalized in December 2014. Data will be extracted from registries during first half of 2015. A preliminary report will be generated in October 2015 and a final study report will be produced at the end of November 2015.

4. MILESTONES

Milestone	Planned date
Final study protocol	12 December 2014
Application to Independent Ethics Committee	19 December 2014
Application sent to register holders (NPR, NorPD) and Norwegian Data Protection Authority notification	23 December 2014
Registration in the EU PAS register	30 January 2015
Start of data collection	01 May 2015
End of data collection	01 July 2015
Preliminary assessment of bleeding rates to assess analytical approach	01 September 2015
Preliminary report	15 October 2015
Final study report	30 November 2015

5. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is the most common cardiac rhythm disorder and represents a significant healthcare burden across Europe. Many AF patients will require anticoagulation treatment, for which the standard of care has been vitamin K antagonists (VKAs) (1). The only VKA on the Norwegian market is warfarin. The main challenges of treatment with warfarin is close monitoring of the anticoagulant effect (international normalized ratio (INR) measures) to maintain the right anticoagulation level, dietary restrictions to allow for a constant dosing and several drug to drug interactions (2). Although warfarin is effective in stroke prevention when optimally dosed, the management challenges present a significant unmet need for other treatment options. Novel Oral Anticoagulants or NOACs (dabigatran, rivaroxaban and apixaban), also referenced as non-vitamin K antagonist oral anticoagulants, represent a new treatment option for NVAF patients, and provide a more convenient anticoagulant regime whilst offering similar or better efficacy and safety (3-5). As the uptake of NOACs increases in Europe, there is a need for data on how they are used in clinical practice. In particular, there is interest in whether those outcomes, especially the rates of bleeding events and discontinuation, observed in clinical trials, are being seen in clinical practice, and whether there are any differences between the NOACs. The clinical trial data in NVAF patients for NOACs shows that apixaban is the only NOAC to demonstrate a combined statistically significant lower rate of stroke/systemic embolisms, discontinuation and major bleeding compared with warfarin (3-5). Moreover, indirect comparisons of NOACs using warfarin as a common comparator show that discontinuation rates and some bleeding outcomes are also significantly lower for apixaban compared with either rivaroxaban or dabigatran (only dabigatran 150 mg for the bleeding comparison) (6).

Whilst there is a keen interest in actual drug usage data from clinical practice, there are a number of limitations with this kind of observational research, especially where it is undertaken shortly after a medicine is launched and available for use within a particular country. A potential channeling bias may be present in observational studies if clinicians initially use the new medicine in patients with comorbidities and other factors predisposing them to the outcome. If this is the case then outcomes

such as discontinuation and bleeding rates can be systematically different from those patients on other therapies, and therefore, bias the analysis. It is, therefore, vital to first describe NVAF patients on the therapies being investigated and to assess how their characteristics may vary, before then going on to examine initial experience with outcomes.

This study will initially focus on describing the patients on each type of oral anticoagulant (OAC) of interest (dabigatran, apixaban, rivaroxaban and warfarin) and then on describing and comparing discontinuation and bleeding outcomes. Assessing the impact of different OACs on stroke / systemic embolism is out of the scope of this research because a longer follow up period would be required to adequately examine this endpoint and ensure sufficient power. A fourth NOAC, edoxaban, is currently being assessed by the EMA and therefore not within the scope of this research.

This study is part of the BEYOND study program with similar designed studies being undertaken in Denmark and Sweden.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer/BMS.

6. RESEARCH QUESTIONS AND OBJECTIVES

Research questions:

- What are the characteristics of NVAF patients treated with different OACs, do these differ between OACs, and how do these change over time?

- What is the rate of discontinuation of NVAF patients to each OAC and does this differ between OACs?

- What is the risk of bleeding in NVAF patients during treatment with OAC and does this risk differ between OACs?

Objectives

1. Primary objective is to describe and compare the clinical and patient characteristics such as $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED score, previous OAC use, bleeding history, concomitant medications and co-morbidities of all NVAF patients who initiated an OAC in the study period, overall and separately by each OAC (apixaban, dabigatran, rivaroxaban, warfarin), by OAC-switch status and previous OAC use (naïve versus experienced).

2. To determine predictive factors of patients initiating each OAC as monotherapy (without a switch from a different OAC) in terms of the $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED score, previous OAC use, concomitant medications, co-morbidities and the estimated probability of initiating OAC therapy (pooled over the full study period and also estimated within consecutive 3-month periods over the study period). To identify predictive factors of switching.

3. To measure and compare discontinuation rates of NVAF patients treated with each OAC therapy (NOACs and warfarin) in Norway unadjusted and adjusted for differences in measured baseline patient characteristics. To identify predictive factors of discontinuation.

4. To compare clinically relevant bleedings and major bleeding rates for NVAF patients treated with OAC therapy (NOACs and warfarin) in Norway unadjusted and adjusted for differences in measured baseline patient characteristics

Except where otherwise stated, objectives will be addressed separately among patients who switch and who do not switch from another OAC (as defined in the Variable Section). Comparisons involving warfarin and each NOAC will be done amongst OAC-non-switch patients only; comparisons involving each NOAC (i.e., excluding warfarin) will be done on both OAC-non-switch and OAC-switch patients. For objectives 3 and 4, the main analysis will compare apixaban with other OACs, and sensitivity analyses will make the remaining comparisons between the OACs.

7. RESEARCH METHODS

7.1. Study design

This study will be a retrospective cohort study based on data extracted from register databases in Norway and the design is summarized in Figure 1. The study population will comprise all adult NVAF patients in Norway redeeming a prescription for a new OAC (NOAC or warfarin) in the study period, defined as from 01 January 2013 to the end of September 2014 (or later depending on availability of data) and followed until the end of the study period or death. This initiation of a new OAC is the index event and requires that there is no previous prescription redeemed for the same OAC in the preceding 180 days (from end date of OAC supply to date of new OAC redemption). Patients will be included with or without prior OAC experience. The focus in this study will be on four main groups:

1. New warfarin users
2. New apixaban users
3. New rivaroxaban users
4. New dabigatran users

Figure 1: Study Design
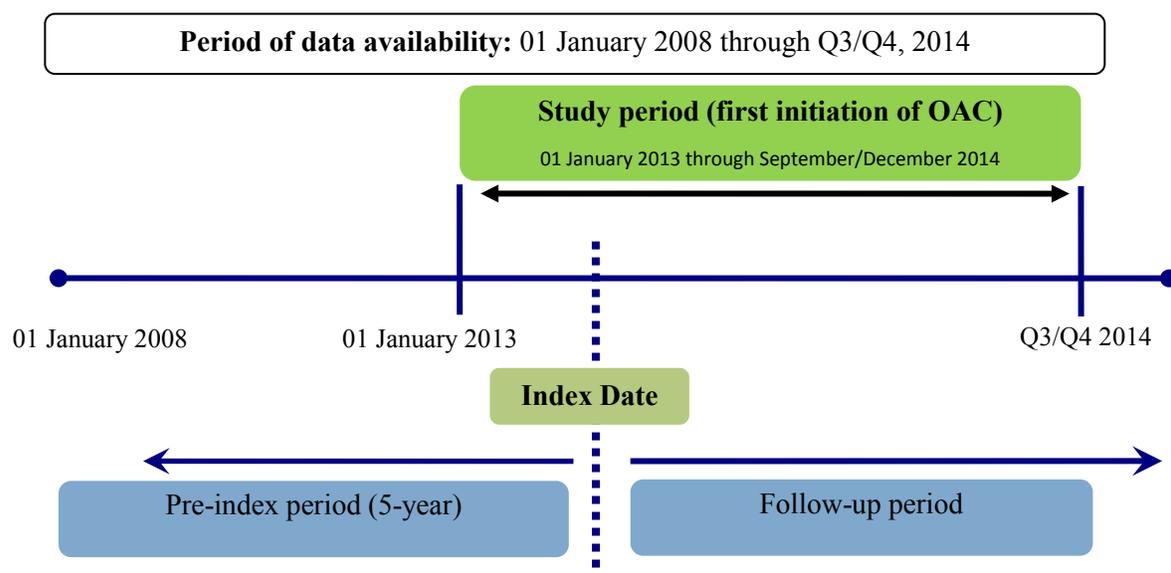
Warfarin has been the traditional treatment in Norway for many years, while dabigatran was marketed for NVAF patients from 01 July 2008, apixaban from 15 February 2013 and rivaroxaban from 01 February 2012. The three NOACs were granted Norwegian general reimbursement in 01 January 2013 (dabigatran and rivaroxaban) and 15 July 2013 (apixaban). The study period (i.e. from 01 January 2013) was defined to incorporate all use of the NOACs once they had been reimbursed.

Table 1: OAC marketing authorization dates and reimbursement dates for NVAF indication[1]

ATC code	Drug	Marketed	NVAF Reimbursement
B01AA03	warfarin	04/October/1962	Early
B01AF02	apixaban	15/February/2013	15/July/2013
B01AF01	rivaroxaban	01/February/2012	01/January/2013
B01AE07	dabigatran	01/July/2008	01/January/2013

Patients with valvular atrial fibrillation, deep venous thrombosis and pulmonary embolism during the last 6 months and those who have undergone knee or hip replacement surgery in the last 5 weeks before starting OACs will be excluded.

The period for data retrieval will be from 01 January 2008 to 30 September 2014 (the end of the study period might be extended according to data availability). Data on outcomes and endpoints will be

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[1] Source: http/www.legemiddelverket.no

retrieved from 01 January 2013 to the end of the study period, whereas for baseline characteristics it will be from the time of index date and the previous time period as detailed in Table 2.

As a consequence of how we define new users there is a chance for patients to be part of more than one user group (hence be counted twice or even more). Patients may switch among OACs during the study period, so a person-time based analysis will be used to account for the time varying nature of OAC exposure. A patient will contribute person-time to the exposure category for a specific OAC while that patient is receiving that drug. If the patient is switched to another OAC, she/he will contribute person-time to the new drug for the time that patient is on the new drug. Any outcome event will be applied to the drug that the patient was receiving during the event.

7.1.1. Definition of Endpoints

Patient characteristics

Section 7.3 defines the list of patient characteristics to be assessed.

Definition of discontinuation

The date of discontinuation of OAC treatment will be defined by the date of the last redeemed prescription plus the estimated length of that prescription (length of OAC supply estimated from the redeemed pack-size and strength), plus a 30-day grace period to take into account incomplete adherence to treatment and dose modifications.

Definition of bleeding

The main bleeding endpoint is all clinically relevant bleeding episodes, which is defined as all bleeding episodes recorded in NPR (with the relevant ICD10 codes listed below) between the index date (start of OAC treatment) and the end of study period. This endpoint will include the following types of bleeding:

Gastrointestinal bleedings:
K920   Hematemesis*
K921   Melena*
K922   Unspecified GI bleeding
K25, K26, K27, K28 with fourth position being 0, 2, 4 or 6 indicating gastroduodenal and gastrojejunal ulcers with bleeding
K625   Hemorrhage from anus and rectum
K228   Hemorrhage or the oesophagus
K221   Ulcer of esophagus with bleeding
K291   Acute gastritis with bleeding
K535   Eosinophilic gastritis with bleeding
K625   Hemorrhage of anus and rectum
I850   Esophageal varices with bleeding

Intracranial hemorrhage:

I60x	Subarachnoid haemorrhage*
I61x	Intracerebral haemorrhage*
I62x	Other non-traumatic intracranial haemorrhage*
I690	Sequelae of subarachnoid hemorrhage*
I691	Sequelae of intracerebral hemorrhage*
I692	Sequelae of other non-traumatic intracranial hemorrhage*

Other organ bleedings:

Heart:

I230	Haemopericardium as complication of MI*
I312	Haemopericardium, not elsewhere classified*

Joints:

M250	Hemathrosis*

Eye:

H431	Vitreous hemorrhage*
H356	Retinal haemorrhage*
H113	Conjunctival haemorrhage
H313	Choroidal hemorrhage and rupture*
H450	Vitreous hemorrhage in diseases classified elsewhere*
H448	Other disorders of the globe, hemophtlamos*

Airways:

R04x	Haemorrage from respiratory passages
J942	Haemothorax*

Genitourinary system:

N02x	Recurrent and persistent haematuria
R31x	Unspecified haematuria
N836	Hematosalpinx
N837	Hematoma of the broad ligament
N92x	Excessive, frequent and irregular menstruation
N93x	Other abnormal uterine and vaginal bleeding

Other bleedings:

A985	Haemorrhagic fever with renal symptomsN421 Congestion and haemorrhage of prostate
N857	Hematometra
N921	Excessive and frequent menstruation
O721	Other immediate postpartum haemorrhage
K661	Hemoperitoneum*
R58x	Bleeding, not elsewhere classified
S064	Epidural hemorrhage
S065	Traumatic subdural hemorrhage

S066   Traumatic subarachnoid hemorrhage

S068   Other intracranial injuries, traumatic haemorrhage

T14x   Superficial injury of unspecified region, hematoma

D62x   Acute posthaemorrhagic anemia

D683   Haemorrhagic disorder due to circulating anticoagulants

D698   Other specified haemorrhagic conditions,

D699   Haemorrhagic condition, unspecified

A separate analysis will differentiate all clinically relevant bleeding to major bleedings. Major bleeding will be defined by an adapted version of the ISTH (International Society of Thrombosis and Hemostasis definition) (9) based on the information available from the Norwegian registries:

- Any bleeding event which occurs in a critical area or organ (marked with an asterix above) **or**
- Blood transfusion ≤10 days after hospital admission date

Definition of Blood transfusion (procedure codes):

REGG00   Transfusion of allogeneic erythrocytes

RXGG02   Transfusion with full blood, allogeneic

NPR is lacking information on laboratory measurements. Hence, we cannot use the ISTH definition of a major bleeding episode defined by a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more. Neither can we assess fatal bleeding events as per ISTH definition. The Norwegian Cause of Death registry releases data on an annual basis only (each November), i.e. November 2014 release of 2013 data. With this lag time it was not considered meaningful to link NorPD and NPR data with the Norwegian Cause of Death registry.

Individual bleeding endpoints of interest such as intracranial hemorrhage and gastrointestinal bleeding will be analyzed separately.

Patients to be included in the bleeding analysis should have a supply of OAC covering the bleeding episode event, plus a 7 days grace period for those patients discontinuing their therapy. Any bleeding event happening after the date of discontinuation plus 7 days or after a switch in OAC therapy will not be included. Illustration: a patient being dispensed a 100 tablet size package of 5 mg apixaban 01 October 2013 (5 mg x 2 = 50 days' supply) with a bleeding event reported 15 October 2013 has a supply covering the bleeding episode, while another patient being dispensed a 100 tablets package prescription of 2.5 mg warfarin (2.5 mg x 3 taken once daily = 33 days' supply) on 01 October 2013 and with a bleeding event on 23 February 2014 does not have OAC supply covering the bleeding event.

7.2. Setting

The study will be undertaken in Norway and will comprise all adult patients with NVAF and an initiated treatment with either a NOAC or warfarin during the study period between 01 January 2013 and end of September 2014 (or later depending on availability of data). Death and end of study period mark the end of the study.

The NVAF study population is defined in accordance with the American Heart Association (AHA)/American College of Cardiology (ACC) updated 2014 guidelines which define NVAF as atrial fibrillation in the absence rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

The study will be undertaken using national registries which capture the entire study population and as no sampling will be used, the results will be entirely generalizable.

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

7.2.1. Inclusion criteria

1. Age ≥18 at the date of first OAC redemption date (index date)

2. Diagnosed with atrial fibrillation or flutter. Defined as ICD10 codes; I480 (paroxysmal AF), I481 (persisting AF), I482 (chronic AF), I483 (typical AF), I484 (atypical AF) or I489 (unspecified atrial fibrillation or flutter) as given by from NPR **or** a OAC redemption from NorPD using reimbursement code for AF

3. Redemption of a prescription for a new OAC (warfarin, dabigatran, rivaroxaban or apixaban) during the study period. This initiation of a new OAC is the index event and requires that there is no previous prescription for the same OAC in the preceding 180 days (counted from end of OAC supply to date of new OAC redeemed).

7.2.2. Exclusion criteria

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

1. Valvular atrial fibrillation defined as presence of ICD10 codes; I05 (Rheumatic valve diseases), I06 (Rheumatic aortic valve diseases), I07 (Rheumatic tricuspid valve disease), I08 (multiple valve disease), I342 (non-rheumatic mitral valve stenosis), Z952 (presence of prosthetic heart valve) and procedure codes FKD (prosthetic replacement of mitral valve), FKA (Repair of mitral valve for stenosis), FKB (Annuloplasty of mitral valve for insufficiency), FKC (Repair of mitral valve for insufficiency), FKW (Other operations on mitral valve) and FMD (replacement of aortic valve)

2. Deep Venous Thrombosis (DVT) as defined by ICD10 codes I80 (Phlebitis and thrombophlebitis), Pulmonary Embolism (PE) as defined by ICD10 code I26 or I82 (other venous

embolism and thrombosis), Other venous embolism and thrombosis within last 6 months before index date

3. Knee and/or hip replacement surgery (NCSP procedure codes; NGB, NGC, NFB or NFC) 5 weeks before index date

7.3. Variables and OAC exposure

Table 2 provides an overview of the relevant baseline patient characteristics and how these are defined based on information from the registries. The most recent information from the registries will be used for a particular characteristic.

Table 2: Definition of baseline characteristics for NVAF patients

Variable	Data source(s)	Operational definition	Relevance	Period prior to index
Alcoholism	NPR	ICD10: E244, E52, G621, G721, I426, K70, K860, O345, T51, Z714, Z721	Co-variate and included in HAS-BLED	From 1st January 2008
Age	NorPD	Age (year/month)	Co-variate and included in HAS-BLED, CHADS$_2$ and CHA$_2$DS$_2$VASc	At the time of index visit
Chronic kidney disease (CKD)	NPR	ICD10 codes: E102, E112, E132, E142, I120, N085, N02-N08, N11-N12, N14, N168, N18, N19, N26, Q612, Q613, Q615, Q619	Co-variate and included in HAS-BLED	From 1st January 2008
Congestive Heart Failure	NorPD and NPR	Either NorPD: Reimbursement codes I50 **or** NPR: ICD10 code I50	Co-variate in CHADS$_2$ and CHA$_2$DS$_2$VASc score	From 1st January 2008
Dementia	NPR	ICD10 codes: F00-F04, G30	Co-variate	From 1st January 2008
Diabetes	NorPD (medication as proxy for diagnosis)	ATC codes:A10 A and A10 B	Co-variate in CHADS$_2$ and CHA$_2$DS$_2$VASc score	From 1st January 2008
Gender	NPR and NorPD	Gender (man/women)	Co-variate and included CHA$_2$DS$_2$VASc score	
History of stroke or TIA	NPR	ICD10 codes: I63, I64, G45	Co-variate and included in HAS-BLED, CHADS$_2$ and CHA$_2$DS$_2$VAS score	From 1st January 2008
Peripheral Artery Disease	NPR	ICD10 codes: I739 and I702	Co-variate and included CHA$_2$DS$_2$VASc score	From 1st January 2008
Hypertension	NorPD (medication as proxy for diagnosis)	NorPD: Reimbursement codes I10-I13, I15	Co-variate and included in HAS-BLED, CHADS$_2$ and CHA$_2$DS$_2$VAS score	From 1st January 2008
Aspirin as antithrombotic treatment	NorPD	ATC codes: B01 A C06	Co-variate and included in HAS-BLED	1 year prior to the index date
Prescriber specialty	NorPD	Cardiologist, hematologist, primary care	Co-variate	Specialty at the time of index date
Ischemic heart disease	NPR	ICD10 codes: I20 (angina), I21to I23 (myocardial infarction) I24 (acute ischemic heart disease and I25 (chronic ischemic heart disease)	Co-variate	From 1st January 2008
Previous bleeding episode	NPR	As defined by ICD10 codes in section 8.1.1 during 01 January 2008 to 31 December 2012	Co-variate and included in HAS-BLED	From 1st January 2008

Variable	Data source(s)	Operational definition	Relevance	Period prior to index
Prior OAC use in baseline period	NorPD	- Proportion previous OAC users - Time interval between exhaustion of last redemption and initiation of OAC in study period ATC codes B01 AA03 (warfarin), B01AF02 (apixaban), B01AF01 (rivaroxaban) and B01AE07 during 01 January 2008 to 31 December 2012	Co-variate	From 1st January 2008
Time since NVAF diagnosis	NPR and NorPD	Either first NorPD redemption of OAC (reimbursement code ICD10 I48 or ICPC K78) from 1.1.2004 or first time NPR ICD10 code I48 from 01 January 2008	Co-variate	1 January 2004 for OAC use (NorPD) and 1 January 2008 for NVAF diagnosis
COPD	NorPD and NPR	Reimbursement code for COPD in NorPD (ICD10 J44, ICPC R95 or COPD reported in NPR (ICD10 J44)	Co-variate	1 year prior to the index date
Liver disease	NPR	ICD10 codes: K70-K75	Co-variate an included in the HAS-BLED score	
Death	NorPD	Time of death (month/year)	To assess follow-up and censoring	From 1st January 2008
Active cancer	NPR	ICD10 codes: C00-C97 during the previous 12 months	Co-variate	1 year prior to the index date
Prior thrombocytopenia	NPR	ICD10 codes D692 to D696	Co-variate	1 year prior to the index date
Prior anemia	NPR	ICD10 codes D50 to D68	Co-variate	1 year prior to the index date
Modified HAS-BLED score	NPR and NorPD	– Hypertension (as defined above in table) during last year prior to index date – Renal impairment as defined by either hemodialysis (procedure code KAGD40) or kidney transplantation (procedure code KAS) or CKD stage 3 and 4 (ICD10 code N183 and N184) – Liver impairment (ICD10 K71-K74) – Stroke (as defined above) during the last year prior to index visit – Prior major bleeding (critical organ) last year before index date (as defined in 8.1.1) – Age ≥ 65 years – Therapy with either Nonsteroidal Anti-inflammatory Drugs (NSAID M01A) or anti-platelets (B01AC) in the previous year before index date – Alcoholism (as defined above in table) Total HAS-BLED score from 0 to 8	Co-variate	HAS bled score estimated at the time of index date
CHADS$_2$	NPR, NorPD	- CHF (as defined above) - Hypertension (as defined above) - Age ≥75 years - Diabetes (as defined above) - Previous stroke (ICD10 I63-I64), TIA (ICD10 I69) or thromboembolism (ICD10 G45)	Co-variate	Score to be calculate at the time of index visit
CHA$_2$DS$_2$VASc	NPR, NorPD	In addition to CHADS$_2$ - Peripheral artery disease (ICD10; I739) - Age 64-74 years - Sex	Co-variate	Score too be calculate at the time of index visit

The summary of product characteristics of OACs for NVAF patients gives a standard dose for most patients and a reduced dose for certain sub-groups of patients, as displayed in Table 3.

Table 3: Recommended strengths and dosing of OACs according to the label for NVAF patients

Drug	Daily frequency	Tablet size options	Standard dose as per labelling	Reduced dose as per labelling
Apixaban	two times daily	5 mg 2.5 mg	5 mg x2	2,5 mg x 2 for eGFR 15-29ml/min or 2 of the following; Age ≥80y, ≤60kg, S-creatinine ≥133µmol/L
Dabigatran	two times daily	150 mg 110 mg	150 mg x 2	110 mg x 2 for age ≥75-80y, co-med with verapamil
Rivaroxaban	once daily	20 mg 15 mg	20 mg x 1	15mg x1 for eGFR 15-49 ml/min'
Warfarin	individualised	2.5 mg	Individualized and should be based on INR 2.5 (2.0-3.0)	

Warfarin is dosed based on the patients' regular INR measurements. Consequently, there will be a greater variation in the daily intake of warfarin compared with the NOACs (which are fixed dosed). There is no information available on INR values or dosing instructions (only strength and pack size) in NorPD and therefore a standard daily dose for warfarin in the study will be set as 7.5 mg (three tablets 2.5 mg taken once daily). A reduced standard daily dose of 5 mg (two tablets 2.5 mg taken once daily) will be applied in the study for subjects with chronic kidney disease (CKD) stage 3 and 4 and if over the age of 80 years the reduced standard daily dose will be 2.5 mg (one tablet 2.5 mg taken once daily). In Norway warfarin is only available as 2.5 mg tablets. The NOACs are fixed dosed and a different approach needs to be applied. Subjects with OAC use for other indications (DVT, PE, orthopedic surgery (and acute coronary syndrome (ACS) for 2.5 mg rivaroxaban)) will be excluded, so all use should be for the treatment of NVAF. Since NorPD does not give the dosing schedule (once or twice daily etc) or weight, the strength (mg) of the redemption of the three dispensed NOACs will define a standard daily dose for each patient.

Table 4: Standard daily doses of OAC to be used in study will be defined by the strength of the redeemed prescription.

Drug	Standard daily dose in study (main)	Standard daily dose in study (reduced)
Apixaban	5 mg x 2	2.5 mg x 2
Dabigatran	150 mg x 2	110 x 2
Rivaroxaban	20 mg x 1	15 mg x 1
Warfarin	7.5 mg	5 mg for CKD 3-4) 2.5 mg for ≥80 years

OAC exposure

OAC exposure is defined as a single or series of redemptions of a new OAC starting in the period from 01 January 2013 to end of study period. The strength (and the associated dosing as displayed in Table 4) together with the pack size of each redemption will be used to calculate the length of the OAC exposure. Gaps must be within 30 days from the end of OAC supply to next redemption to be counted as continuous treatment or else the patient is considered to have discontinued their therapy. The end of OAC supply will be estimated from the last redemption.

Figure 2: Illustration of definition of OAC supply:

Redemption #1	Redemption #2	Redemption #3	Redemption #4	Redemption #5
15Feb2013	20Apr2013	01Jul2013	08Sep2013	12May2014
Apixaban 5 mg	Apixaban 5 mg	Apixaban 5 mg	Apixaban 5 mg	Apixaban 5 mg
2 x 100 tbl	2 x 100 tbl	2 x 100 tbl	2 x 100 tbl	2 x 100 tbl
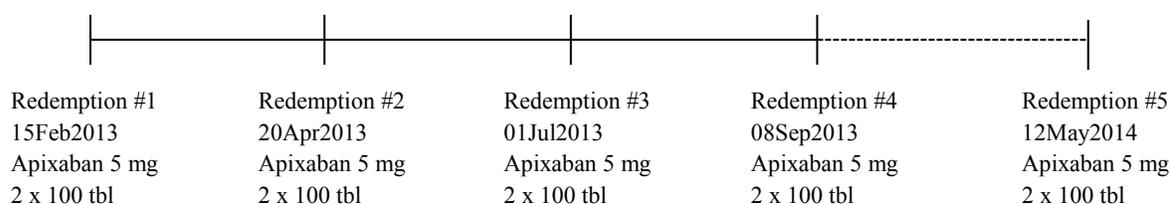
In figure 2 the start of apixaban was 15 February 2013. There is no gap without coverage being over >30 days for periods between redemptions 1 and 2, 2 and 3, and 3 and 4. End of therapy in this example is defined as the date of the last redemption (08 September 2013) plus 100 days (the total days of supply from two 100 tablet pack, i.e. 5 mg two times daily as per Table 4) which gives 17 December 2013. 30 days from 17 December 2013 gives 16 January 2014 which is a gap period that is longer than 30 days before the next redemption starting 12 May 2014. The OAC exposure end date is 17 December 2013. In this example the same patient re-institute apixaban after a period without OAC supply lasting 146 days (from December 2013 to 12 May 2014).

Definition of OAC switch is if a prescription for a different OAC is redeemed within 30 days from the end of OAC supply for the first OAC.

All patients with relevant prescription redemptions in NorPD will be considered, both those with and without registrations in NPR. Throughout the analysis it will be assumed that the amount dispensed was consumed.

7.4. Data sources

Two data sources will form the basis for the analyses, the Norwegian Prescription Database (NorPD) (7) and the Norwegian Patient Register (NPR) (8). The NorPD is a register covering all prescriptions redeemed at pharmacies nationwide and data is available from 01 January 2004. Each medication is coded according to the Anatomical Therapeutic Chemical (ATC) system. The prescription registry also includes information about date of redemption, quantity dispensed, the defined daily dose (DDD) of the dispensed drug and strength. NorPD does not cover drug administered during hospital stays, drugs used at nursing home or over-the-counter drugs. From March 2007 the NorPD includes the

reimbursement code using either the ICD10, ICPC and occasionally reimbursement codes defined by Norwegian Medicines Authority. Annex 3 Table 4 lists the type of variables present in NorPD.

The NPR was established for research purposes in 2008 and contains all hospital visits (emergency visits, hospitalizations and outpatient consultations), length of stay and procedures (surgical and medical) from all hospitals in Norway. ICD10 codes are used for all diagnoses and NCMP and NCSP for medical and surgical procedures. Annex 3 Table 5 lists the type of variables present in NPR.

The registries are nation-wide and provision of the information is mandatory, which eliminates the risk of both selection and re-call bias. The large and detailed dataset also makes it possible for us to adjust for risk factors and analyze in depth the different sources of bias and confounding so important for studies of this kind.

Data from the registries will be linked using the unique 11-digit national identification number. NorPD is a pseudonymized register and the registry holder will according to national guidelines handle the linkage and release the dataset in a coded form so that all participants remain de-identified.

7.5. Study size

Approximately 2,000 patients had redeemed a prescription for apixaban in the NorPD registry up until the end of 2013, and with 3-4 additional quarters of data available from the registries, a total of 5,000 patients on apixaban is anticipated to be available. This includes both NVAF patients registered in NPR and NVAF patients prescribed OAC in NorPD. A proportion will have apixaban prescribed in primary care on a reimbursement code for NVAF, but without any hospital contact for NVAF during the study period. Regarding the other OACs 10,000 patients are assumed to be on rivaroxaban in the same period, 10,000 on dabigatran (with 50% assumed to be on 150 mg and 50% on 110 mg for the purposes of power calculation) and 50,000 on warfarin.

Table 5: Number of patients having at least one redemption of an OAC prescription in the period 2008 to end of 2013 as given by NorPD. The table gives the total OAC use for all indications.

ATC code and drug	Number of users (year)					
	2008	2009	2010	2011	2012	2013
warfarin	84,152	86,318	88,630	92,131	94,709	87,994
apixaban	0	0	0	0	335	2,260
rivaroxaban	0	45	191	898	1,332	13,423
dabigatran	<5	9	187	1,168	4,102	13,879

Power calculations were performed on the unadjusted odds ratios for each comparison at one year on the primary endpoint (comparison of patient characteristics), discontinuation and clinically relevant bleeding rate. One year rates were chosen as the basis for the power calculations to avoid making assumptions about the incidence of discontinuation and bleeding over shorter time points. Power calculations were performed using EAST version 6.

For the primary objective related to patient characteristics the study is sufficiently powered, with the expected sample sizes, to detect small differences between OAC groups in the $CHADS_2$ score (<0.5

point difference at 80% power) and in the HAS-BLED risk score (<0.3 point difference at 80% power).

Power calculations were performed on the discontinuation rate for apixaban in the ARISTOTLE trial (3) and adjusted to calculate the rates for the other OACs using the results of the published indirect comparison (6). Annual discontinuation rates used were 16.2% for apixaban, 17.9% for warfarin, 19.2% for rivaroxaban, 23.5% for dabigatran 110 mg and 24.5% for dabigatran 150 mg is assumed. Using the assumed sample sizes for the other OACs, the number of apixaban patients required for 80% power in each comparison would be 4,600 for apixaban versus warfarin, whereas the remaining comparisons required far fewer apixaban patients (1,745 versus rivaroxaban and below 300 for comparisons against each dabigatran dose).

Power calculations on the main bleeding endpoint assumed that the combination of clinically relevant non-major and major bleeding from the ARISTOTLE trial (4.1% per year) would represent the clinically relevant bleeding rate to be observed in the Norwegian registries. Annual clinically relevant bleeding rates for the other OACs were derived using the indirect comparison results. The annual bleeding rates used in these calculations were: 4.1% on apixaban, 5.9% on rivaroxaban, 5.3% on dabigatran 150 mg and 4.7% on dabigatran 110 mg. These calculations indicate that with sample sizes of approximately 1,600 apixaban patients, there would be acceptable levels of power (70-80%) in the comparisons with warfarin and rivaroxaban. The comparison of apixaban with dabigatran will, however, be under-powered. As a result of these calculations, the comparative bleeding analysis will only be undertaken if a preliminary analysis of the data indicates that the comparisons of apixaban with warfarin and rivaroxaban (separately) will be sufficiently powered. Bleeding rates will be described using descriptive and summary statistics regardless of the number of patients available.

7.6. Data management

The data will be analyzed with R (10). R is a language and environment for statistical computing and graphics. R provides a wide variety of statistical (linear and nonlinear modelling, classical statistical tests, time-series analysis, classification, clustering and so on) and graphical techniques. R is open source.

As stated in part 8.4, the data preparation of the two datasets will be done by NorPD as they are authorized to do so. All data will be completely patient de-identified for this study.

The data from NorPD and NPR are considered high quality register data, however, some quality checking and data cleaning will be done to check for reasonability and consistency of data.

7.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. 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.

Missing data is not expected to be significant, as NorPD and NPD are both high quality national registers. But if there are any missing values, typically registered as NA (not applicable) in the data files, these will be reported for all variables. If missing values should occur, then imputation (if possible) will be carried out.

Throughout the analyses continuous variables will be described by the mean, standard deviation, median, first and third quartiles, and minimum and maximum. Categorical variables will be described by the number and percentage of patients in each category. Follow-up time will be described as a continuous variable for each patient, and also be reported as the total number of patient-months for each OAC.

Regression analysis will be the primary analytical approach with both unadjusted and adjusted models to be estimated and patient (clinical and demographic) characteristics, OAC group, previous OAC use, co-morbidities, concomitant medications measured at baseline as candidate independent variables. For binary independent variables, logistic regression models will be considered with the final model selected by backwards stepwise selection, using minimization of the Akaike Information Criterion (AIC) as the measure of model fit. Time-dependent exposure variables, such as the number of different OACs dispensed, prescriber specialty and hospitalizations throughout the observation period can be included. However, by including time-dependent variables (some of) the previous significant background variables might become insignificant. Time-dependent variables measures steps on the way to an event. Hence, they describe the process, and should not be interpreted in the same way as the other background variables. Predictive performance of the final models will be assessed by the c-statistic. For time to event analyses our primary approach will be Cox proportional hazard regression analysis with the same candidate independent variables as above. The proportional hazards assumption will be checked using Schoenfeld residuals. If proportional hazards are not met, models will be stratified on the appropriate covariable or time-interaction terms will be introduced as required.

A propensity score matching approach will also be considered as an analysis option using initiation of warfarin or apixaban as the dependent variable and all characteristics, including comorbidities, the CHA_2DS_2VASc, the HAS-BLED score, and previous OAC as candidate independent variables.

It is still in the early post-marketing period of NOACs use in NVAF. Consequently, there will not be enough statistical power to conduct comparative statistical testing of the efficacy of the different OACs on stroke outcomes. Incident stroke episodes among the four OAC user groups during the study period will be counted and subject to a descriptive analysis only. Stroke is defined as an episode recorded in NPR between the index date and the end of the study period with ICD10 codes; I60 (subarachnoid hemorrhage), I61 (intracerebral hemorrhage), I62 (Other non-traumatic intracranial haemorrhage), I63 (cerebral infarction), I64 (stroke, not specified as hemorrhage or infarction) or G45 (transient cerebral ischemic attacks and related syndromes).

Death rates will also be counted in the four user OAC groups using the NorPD data variable on date of death.

7.7.1. Primary objective 1: describe and compare clinical and patient characteristics of all NVAF patients initiated with OAC

All NVAF patients meeting the inclusion criteria will be described by patients' characteristics such as age, gender, $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED score, previous OAC use, concomitant medications, co-morbidities, time since NVAF diagnosis and specialty of prescriber. As well as the OAC specific user groups, a description of all users (without distinguishing between OACs) will be undertaken. Within OAC user groups, switchers and non-switchers will be described as separate groups, as well as naïve versus experienced OAC use.

Switching patterns for the patients in each of the four groups will be mapped out as suggested in figure 3. A summary of frequencies of switches between the OACs will be given. A switch is defined as dispensing another OAC within the 30 days between the end date of OAC supply and the date of redemption for a different OAC. As already stated, patients with a new prescription fulfillment for OAC 180 days or more between the end of OAC supply and the date of new OAC redemption will be denoted a new OAC user.

A summary of frequencies of switches between the OACs will be given. Switches to be examined are:
1. Switching from a first OAC to a second OAC
2. Switching from a NOAC to warfarin (first time switch)
3. Switching from warfarin to a NOAC (first time switch)
4. Switching from a NOAC to another NOAC (first time switch)

Whether OAC was used as monotherapy or together with anti-thrombotic treatment for each group will be further explored (aspirin or anti-platelet treatment, ATC group B01AC).

Figure 3: Two flow charts illustrating switch paths to be explored for the OACs warfarin (W), apixaban (A), rivaroxaban (R) and dabigatran (D).
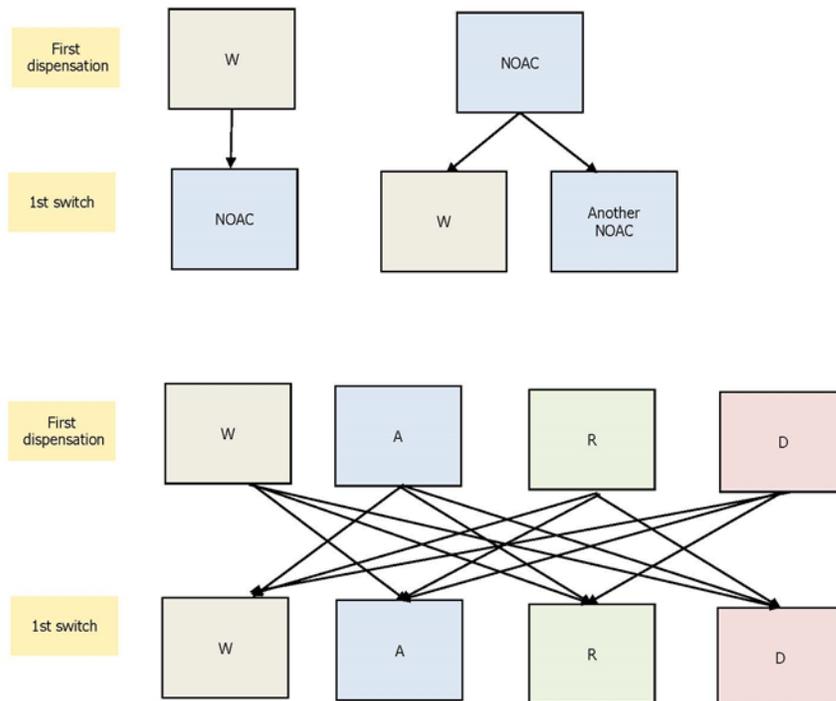
A comparison of the characteristics of patients initiating each OAC will be undertaken through other statistical tests. Comparisons between the user groups given continuous background variables could be done by considering differences in means with 95% confidence intervals (CIs) and by unpaired t-tests or Mann-Whitney U tests (if normality assumptions seem unreasonable). Comparisons between the user groups given categorical background variables could be done by considering differences in proportions with 95% CIs and by chi-squared tests or Fisher's exact test (if required).

7.7.2. Objective 2: determine predictive factors for initiating each OAC as monotherapy & switching

To examine which of the above patient characteristics predict which OAC treatment patients are on, multinomial logistic regression models (NOACs as a group versus warfarin and each NOAC separately versus warfarin) will be performed. Odds ratios with 95% uncertainty intervals will be reported from the regression analyses. Predictive factors associated with the abovementioned switch patterns will also be analyzed using a logistic regression model.

7.7.3. Objective 3: describe and compare discontinuation rates associated with each OAC

Discontinuation is defined as last date of the estimated OAC supply plus a 30 day grace period, with the actual date of discontinuation being the last date of OAC supply (as defined in 8.3). The discontinuation analysis will focus on apixaban comparison versus warfarin, dabigatran and rivaroxaban. The rate of discontinuation in each OAC group by switch status will be estimated. A

summary of the cumulative incidence, defined both as the number who discontinue divided by 1) the number of patients and 2) the number of 100 patient years, with 95% confidence intervals at different time periods (3, 6, 9 months and in 3 month intervals up to a possible 24 months if data allows) and at end of study period, will be given.

As patients might have different exposure times, a survival analysis will be conducted for the time to discontinuation from the onset of OAC use using the Cox proportional hazard modelling approach. Predictive factors of discontinuation based on the relevant background variables will be assessed from the cox proportional hazard model. Kaplan-Meier plots for relevant background variables will be presented. After examining the number of deaths in our study population competing risk methods will be considered. Univariate Cox proportional hazard models will be specified, and thereafter a backward stepwise approach to obtain a final model. Finally time-dependent variables can be considered. Initially, there will be a check for the statistical reasonability of a linear functional form in the regression term for continuous background variables, for example age, (by applying the pspline-function in R), and also for possible interaction terms, for example between age and gender. A dummy variable will be incorporated in the model to contrast the naïve OAC group (no previous OAC use in the previous 180 days) from the experienced OAC group (different OAC used during the previous 180 days).

Separate models will be estimated on non-switch and all patients for comparisons of apixaban with warfarin and other NOACs, respectively, to account for the potential bias that warfarin patients are more likely to switch to NOACs, than NOAC patients on to warfarin. The number of deaths in the study population will be assessed using a competing risk modelling approach. Alternatively, and as an option, a marginal structural modelling approach might be undertaken.

A propensity score matching (adjustment) approach might be considered in an additional analysis.

7.7.4. Objective 4: describe and compare clinically relevant and major bleeding rates across OAC groups

The risk of bleeding will be estimated in all four user groups:

1. New warfarin users
2. New apixaban users
3. New rivaroxaban users
4. New dabigatran users

The bleeding analysis will focus on apixaban comparison versus warfarin, dabigatran and rivaroxaban.

Incidence bleeding rates at 1, 3, 6 and 9 months (and in 3 months intervals up to a possible maximum of 24 months if data allows) for clinically relevant and major bleeding will be described separately, expressed as 1) rate per patient and 2) per 100 patient years with associated confidence intervals.

Patients to be included in the bleeding analysis should have a supply of OAC covering the bleeding episode event. Any bleeding event occurring after the end date of OAC supply plus 7 days will not be included. Any bleeding events occurring after a patient switches OAC will not be counted against that therapy.

The time to a first bleeding episode for each patient will first be considered. Kaplan-Meier plots displaying risks for various patient groups will be helpful in understanding differences in bleeding risk. Cox proportional hazard regression models with relevant patient characteristics as explanatory variables (as age, gender, co-medication, co-morbidities, HAS-BLED score) will be defined. A dummy variable will be incorporated in the model to contrast the naïve OAC group (no previous OAC use in the previous 180 days) from the experienced OAC group (different OAC used during the previous 180 days). Separate models will be estimated on non-switch and all patients for comparisons of apixaban with warfarin and other NOACs, respectively, to account for the potential bias that warfarin patients are more likely to switch to NOACs, than NOAC patients on to warfarin. The number of deaths in the study population will be assessed using a competing risk modelling approach. Alternatively, and as an option, a marginal structural modelling approach might be undertaken.

Some patients might also experience bleeding more than once throughout the observation period. When considering bleeding rates it is therefore important to differentiate between the patients experiencing bleeding just once and those having multiple bleeding episodes. The proportion of patients with multiple bleeding episodes during the study period will be low and only sufficient for descriptive analysis.

Separate analyses (descriptive analysis and a cox-modelling approach for first bleeding episode) will be performed on comparing rates of intracranial bleeding and gastrointestinal bleedings across OAC groups.

7.7.5. Sensitivity analyses

The following sensitivity analyses will be undertaken to test the robustness of findings to assumptions main in the above analyses:

1. Varying the time window for definition of OAC switch from the standard 30 days to 0 days
2. Varying the gap period for capturing discontinuation events from 30 days (the base case) to 45 days and 15 days
3. Varying the gap period (discontinuers) for capturing bleeding events from 7 days (the base case) to 15 days and 30 days
4. Varying the gap period (switchers) for capturing bleeding events from 0 days (the base case) to 7 days
5. Analyzing dabigatran 110 mg twice a day and dabigatran 150 mg twice a day as separate OACs for discontinuation and bleeding endpoints

6. Excluding OAC patients not having NVAF diagnosis present in NPR, i.e. exclude those with NVAF related reimbursement codes in NorPD only, for the bleeding and discontinuation endpoints

7. Analyze the following comparisons separately: dabigatran versus rivaroxaban, dabigatran versus warfarin and rivaroxaban versus warfarin, for the bleeding and discontinuation endpoints

8. Estimate the end of OAC supply from the total OAC supply for a series of OAC redemptions instead of using only the last OAC redemption

9. Analyze the bleeding and discontinuation endpoints on a fully naïve OAC users population defined as no previous OAC redeemed in 180 days prior to index date

7.8. Quality control

The data will be delivered by NorPD on a computer disc with an access code on SMS (Short Message Service) or in an email to the research group representatives at Lifandis and the statistician at NR who will conduct the analysis. A Pfizer statistician will also have access to the data file for quality control purposes, and will also secure safe and proper storage of data. The data will be stored in a central database at Lifandis (accessible to Hilde Kjeldstad Berg and Christian Jonasson) and the Norwegian Computing Center (accessible to Ingunn F. Tvete) and not on a single computer/laptop. The Norwegian Computing Center has a support team of four highly qualified system consultants/ IT managers who ensure good data management and security. As previously stated, the data are public data available on request to all interested and they are completely de-identified.

7.9. Strengths and limitations of the research methods

The NOACs are relatively new drugs on the market, and so it is not clear whether the observation period in this study is sufficiently long nor if the sample sizes are sufficiently large enough to obtain representative bleeding and discontinuation rates. We will compare our findings with the ones in the ARISTOTLE (apixaban) (3), RE-LY (dabigatran) (4) and ROCKET-AF (rivaroxaban) (5) trials and other relevant reference bleeding rates.

There might be a bias in the data as newer drugs could have been given to poor responding or more fragile patients compared to established drugs (channeling bias or confounding by indication).

As with all prescription register research one does not know whether the amount dispensed was actually consumed, which may bias the event rates upwards if sub-optimal doses are being used. There is also no information on drugs purchased over the counter (OTC), like NSAID/aspirin or antacids. However, most drugs purchased as OTC are used short-term and with lower strengths than those prescribed. Overall, we expect no major influence from OTC consumed drugs.

NOACs are fixed dosed, but dose-adjusted for subgroups with higher age or renal decline. Warfarin, on the other hand, is prescribed based on repeated INR measures which gives a large intra-individual variation. Since we have no information on labile INR this can lead to misclassification bias.

A further limitation lies in the comorbidities assessed in the study as the NPR only contains information on hospital-based patient contacts, and consequently, typical diagnoses handled in

primary care are underrepresented. However, redemption of typical primary care drugs together with the reimbursement code will be used as a proxy for an underlying diagnosis.

Patient characteristics such height/weight, smoking, laboratory measures like hemoglobin and blood pressure cannot be captured. Information on INR values cannot be retrieved from the databases. Neither is there information on the cause of death for those who died during the study period.

The study will collect a nation-wide and complete dataset from mandatory registries in Norway and thereby eliminate selection and re-call bias. The large dataset also makes it possible for us to adjust for risk factors and analyze in depth the different sources of bias commonly seen in pharmacoepidemiological research.

7.10. Other aspects

Not applicable

8. PROTECTION OF HUMAN SUBJECTS

The Norwegian Institute of Public Health will perform the merging of data from the NPR and NorPD. No identification of patients is made elsewhere and data delivered are completely de-identified. The data will be stored by Lifandis and NR and analyzed by an independent statistical company (NR). Lifandis and NR will store the data file in a central database and not on a single computer/laptop. The Norwegian Computing Center has a support team of 4 highly qualified system consultants who ensure good data management and security. A Pfizer statistician will also have access to data file in order for quality controls to be performed. Pfizer will also secure safe and proper storage of data. Other members of the study team (chapter 2) will only have access to processed and aggregated data.

The data file will be deleted 30 June 2017 when the main manuscript(s) has been accepted in a scientific peer-reviewed journal and no further analysis is being requested or anticipated.

8.1. Patient Information and Consent

Patient informed consent is not applicable to the data sources used in this study since the health care registries utilized for the study are mandatory information collected on all resident Norwegians admitted to hospital (NPR) or having a prescription drug redeemed at pharmacy (NorPD).

8.2. Patient withdrawal

Not applicable

8.3. Independent Ethics Committee (IEC)

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

8.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

9. 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 adverse events are not reportable as individual adverse events (AE) reports.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

* A Study Report will be completed comprising a full statistical report and a slide deck

* A primary manuscript will be prepared, in accordance with Pfizer/BMS Publication policy in cooperation between Pfizer, BMS, Lifandis and Norwegian clinicians. Abstracts to scientific meetings will be submitted to first proper scientific meetings

* The author group will discuss and decide on whether one, two or more manuscript(s) will be written based on the results generated. The same goes for abstracts submitted to scientific meetings

* Prior to commencing any publication activities, written agreements between Lifandis, Pfizer/BMS, NR and each participating author need to be signed.

Development and preparation of study reports and publications will be a joint cooperation between Lifandis, NR, involved clinicians and Pfizer/BMS. Lifandis representatives will initiate and lead the study report and dissemination work.

In accordance with the Declaration of Helsinki, both authors and publishers have ethical obligations. In the publication of the results of the study, the authors are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise made publicly available. Lifandis and Pfizer/BMS endeavor to publish the results of the study and are committed to ensure that the data are reported in a responsible and coherent manner.

Lifandis and Pfizer/BMS seek to ensure that publications in biomedical journals follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals.

Lifandis and Pfizer/BMS are committed to ensuring that authorship for all publications should comply with the criteria defined by the ICMJE. These state that: "Each author should have participated sufficiently in the work to take public responsibility for the content."

Each manuscript, abstract, oral or poster presentations are subject to internal Pfizer/BMS Publication team review and approval.

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12. LIST OF TABLES

13. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Annex 3 Table 1: Co-medication drugs to be retrieved from NorPD using ATC codes

ATC code and drug class	ATC code	Drug sub-class
A02 Drugs for acid-related disorders	A02A	Antacids
	A02B A	Histamine-2-antagonists
	A02B B	Prostaglandins
	A02B C	Proton Pump Inhibitors
A10 Drugs used in diabetes	A10 A	Insulin and analogues
	A10 B	Glucose-lowering drug, non-insulin
B01 Antithrombotic agents	B01A B	Heparin derivates
	B01A C	Antithrombotic treatments (e.g.acetylsalicylic acid, prasugrel, ticagrelor, clopidogrel)
	B01A D	Enzymes (e.g. alteplase, streptokinase)
C01 Cardiac therapy	C01 A	Cardiac glycosides
	C01 B	Anti-arrhythmics, class I and III (e.g.amiodarone)
	C01 C	Cardiac stimulants, excl. cardiac glycosides
	C01 D	Vasodilators used in cardiac disease
C03 Diuretics	C03 A	Low-ceiling diuretics (e.g. thiazides)
	C03 C	High-ceiling diuretics (e.g.furosemide)
	C03 D	Potassium-sparing agents (e.g. spironolactone)
	C03 E	Diuretics and potassium-sparing agents in combination
	C03 X	Other diuretics
C07 Beta-blockers	C07 A	Beta-blocking agents (e.g. metoprolol and atenolol)
	C07 B	Beta-blocking agents and thiazides

C08 Calcium channel blockers	C08 C	Selective calcium channel blockers with mainly vascular effects (e.g. amlodipine, felodipine)
	C08 D	Selective calcium channel blockers with direct cardiac effects (e.g. verapamil)
C09 Agents acting on the renin-angiotensin system	C09 A	ACE inhibitors, plain (e.g. enalapril)
	C09 B	ACE inhibitors and diuretics (e.g. enalapril and thiazides)
	C09 C	Angiotensin II antagonists, plain (e.g. losartan)
	C09 D	Angiotensin II antagonists combinations (e.g. losartan and amlodipine)
	C09 X	Other agents acting on the renin-angiotensin system (e.g. aliskiren)
C10 Drugs for dyslipidemia	C10 A	Lipid modifying agents, plain (e.g. fibrates, statins, omega-3 and ezetimib)
	C10 B	Lipid modifying agents, combinations (e.g. simvastatin and exetimib)
M01A Anti-inflammatory and anti-rheumatic drugs, non-steroids	M01 A B	Acetic acid derivates (e.g. diclofenac, indomethacin)
	M01 A C	Oxicams (e.g. piroxicam)
	M01 A E	Propionic acid derivates (e.g. naproxen)
	M01 A F	Fenamates (e.g tolfenamic acid)
	M01 A H	Coxibs (e.g. celecoxib)
	M01 A X	Other anti-inflammatory and anti-rheumatic drugs, non-steroids
N06 Psychoanaleptics	N06 A B	Serotonine reuptake inhibitors (e.g.citalopram)
	N06 D	Anti-dementia drugs (e.g.donepezil)
R03 Drugs for respiratory system	R03 A	Adrenergics, inhalants (short-acting beta-2)
	R03 B	Other drugs for obstructive airways disease (inhaled glucocorticosteroids, anticholinergics)

Annex 3 Table 2: Co-morbidities to be retrieved from NPR using ICD10 codes

ICD10	Diagnosis
A985	Haemorrhagic fever with renal symptoms
B15-19	Viral hepatitis
C00-C97	Malignant neoplasms
D50-D68	Anaemias
D65-D69	Coagulation defects abnormalities, incl. thrombocytopenia
E05	Hyperthyroidism
E06	Thyroiditis
E10	Insulin-dependent diabetes mellitus
E11	Non-insulin-dependent diabetes mellitus
E12	Malnutrition-related diabetes mellitus
E13	Other specified diabetes mellitus
E14	Unspecified diabetes mellitus
E244	Alcohol induced pseudo Cushing syndrome
E52	Pellagra
F00-04	Dementia
G30	Alzheimer's disease
G312	Degeneration of nervous system due to alcohol
G45	Transient cerebral ischemic attacks and related syndromes
G621	Alcoholic polynephropathy
G721	Alcoholic myopathy
H113	Conjunctival haemorrhage
H356	Retinal haemorrhage
H431	Vitreous hemorrhage
H313	Choroidal hemorrhage and rupture
H448	Other disorders of the globe, hemophtlamos
H450	Vitreous hemorrhage in diseases classified elsewhere
I05	Rheumatic mitral valve diseases
I06	Rheumatic aortic valve diseases
I07	Rheumatic tricuspid valve diseases
I08	Multiple valve diseases
I09	Other rheumatic heart diseases
I10	Primary hypertension
I11	Hypertensive heart disease
I12	Hypertensive kidney disease
I13	Hypertensive heart- and kidney disease
I15	Secondary hypertension
I20	Angina
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I25	Chronic ischaemic heart disease

I26	Pulmonary embolism
I312	Haemopericardium, not elsewhere classified
I34	Non-rheumatic mitral valve diseases
I35	Non-rheumatic aortic valve diseases
I36	Nonrheumatic tricuspid valve disorders
I37	Pulmonary valve disorders
I38	Endocarditis, valve unspecified
I39	Endocarditis and heart valve disorders in diseases classified elsewhere
I48	Atrial fibrillation
I42	Cardiomyopathy
I426	Alcoholic cardiomyopathy
I48	Atrial fibrillation and flutter (disease under study)
I49	Arrhythmia
I50	Heart failure
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other non-traumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
I69	Sequelae of cerebrovascular disease
I70	Atherosclerosis
I739	Peripheral vascular disease, unspecified
I74	Arterial embolism and thrombosis
I80	Phlebitis and thrombophlebitis
I81	Portal vein thrombosis
I82	Other venous embolism and thrombosis
I850	Esophageal varices with bleeding
J44	COPD
J81	Pulmonary oedema
J942	Haemothorax
K221	Ulcer of esophagus with bleeding
K228	Hemorrhage or the oesophagus
K25	Gastric ulcer
K26	Duodenal ulcer
K27	Peptic ulcer, unspecified
K28	Gastrojejunal ulcer
K29	Gastritis and duodenitis
K535	Eosinophilic gastritis with bleeding
K552	Angiodysplasia of colon
K57	Diverticulitis
K625	Hemorrhage from anus and rectum
K661	Hemoperitoneum
K70	Alcoholic liver disease
K71	Toxic liver disease

K72	Hepatic liver disease, not elsewhere classified
K73	Chronic hepatitis, not elsewhere classified
K74	Fibrosis and cirrhosis of liver
K75	Other inflammatory liver diseases
K76	Other diseases of the liver
K860	Alcohol induced chronic pancreatitis
K92	Other diseases of digestive system, hematemesis, melena, GI haemorrhage
M250	Hemathrosis
N00-08	Glomerular diseases
N10-12	Acute and chronic tubulo interstitial nephritis
N14	Drug and heavy metal induced nephropathy
N15-N16	Other renal tubulo interstitial diseases
N17	Acute renal failure
N18	Chronic kidney disease
N19	Unspecified kidney failure
N26	Unspecified contracted kidney
N421	Congestion and haemorrhage of prostate
N836	Hematosalpinx
N837	Hematoma of the broad ligament
N857	Hematometra
N92	Excessive, frequent and irregular menstruation
N93	Other abnormal uterine and vaginal bleeding
O354	Maternal care for (suspected) damage to fetus from alcohol
O721	Other immediate postpartum haemorrhage
Q20-26	Congenital malformation of the heart
Q61	Cystic kidney disease
R04	Haemorrhage from respiratory passages
R31	Unspecified haematuria
R58	Bleeding, not elsewhere classified
S064	Epidural haemorrhage
S065	Traumatic subdural haemorrhage
S066	Traumatic subarachnoid haemorrhage
S068	Other intracranial injuries, traumatic haemorrhage
T14	Superficial injury of unspecified region, hematoma
T51	Toxic effect of alcohol
Z714	Alcohol abuse counselling and surveillance
Z721	Problems related to life-style, alcohol abuse
Z952	Presence of prosthetic heart valve

Also fourth character subdivisions of ICD10 will be retrieved from NPR, e.g. K25 (gastric ulcer) will be divided into;

K250 Gastric ulcer acute with hemorrhage

K251 Gastric ulcer acute with perforation

K252 Gastric ulcer acute with both hemorrhage and perforation

K253 Gastric ulcer acute without hemorrhage or perforation

K254 Gastric ulcer chronic or unspecified with hemorrhage

K255 Gastric ulcer chronic or unspecified with perforation

K256 Gastric ulcer chronic or unspecified with both hemorrhage and perforation

K257 Gastric ulcer chronic without hemorrhage or perforation

K259 Gastric ulcer unspecified as acute or chronic, without hemorrhage or perforation

Annex 3 Table 3: Procedure to be retrieved from NPR using NCSP and NCMP codes

NCSP or NCMP codes	Procedure
FGA	Repair of tricuspid valve for stenosis
FGB	Repair of Ebstein's anomaly
FGC	Annuloplasty of tricuspid valve for insufficiency
FGD	Repair of tricuspid valve for insufficiency
FGE	Prosthetic replacement of tricuspid valve
FGW	Other operations on tricuspid valve
FKA	Repair of mitral valve for stenosis
FKB	Annuloplasty of mitral valve for insufficiency
FKC	Repair of mitral valve for insufficiency
FKD	Prosthetic replacement of mitral valve
FKW	Other operations on mitral valve
FMD	Replacement or aortic valve
NFB	Primary prosthetic replacement of hip joint
NFC	Primary prosthetic replacement of hip joint
NGB	Primary prosthetic replacement of knee joint
NGC	Primary prosthetic replacement of knee joint
REGG00	Transfusion of allogeneic erythrocytes
REGG05	Transfusion of autologous erythrocytes
RTGG00	Transfusion of allogeneic thrombocytes
RTGG05	Transfusion of autologous thrombocytes
RXGG02	Transfusion with full blood, allogeneic
RXGG03	Transfusion with full blood, autologous

All subdivisions on the relevant will be retrieved from NPR

Annex 3 Table 4: Data variable categories to be retrieved from NorPD

- Prescriber's specialty
- Patient's serial ID
- Patient's sex
- Patient's age
- Date of death
- Prescription number
- Dispensing number
- Dispensing date
- Number of packs
- Number of DDDs
- Type of prescription/requisition
- Reimbursement code
- Drug's product number
- Drug's description
- Size of package
- Packaging unit
- Strength of drug
- ATC-code
- DDD
- DDD unit

Annex 3 Table 5: Data variable categories to be retrieved from NPR

- Age
- Gender
- Primary and secondary diagnoses using ICD10 codes
- Date of admission
- Date of discharge
- Days in hospital
- Type of hospital
- Diagnosis-related group (DRG)
- Medical and surgical procedures (NCMP and NCSP codes)