NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	*Major bleeding in patients with atrial fibrillation treated with apixaban versus warfarin in combination with amiodarone: the APIXAMIO study*
Protocol number	B0661167
Protocol version identifier	1
Date	*<DD Month YYYY> This is the date on which the protocol content is considered final. This date must match the date in the header.*
EU Post Authorization Study (PAS) register number	Study not registered
Active substance	Apixaban-B01AF02 Warfarin-B01AA03 Amiodarone-C01BD01
Medicinal product	Eliquis, Waran, Waran orion, Cordarone
Product reference	EU/1/11/691/001-015
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Marketing Authorization Holder(s) (MAH)	Bristol-Myers Squibb/Pfizer EEIG
Joint PASS	No
Research question and objectives	What are the clinical characteristics of patients co-treated with amiodarone and apixaban or warfarin in Sweden. Is there a difference in safety outcomes between those treated with amiodarone in combination with either apixaban or warfarin. Primary objective: To describe the clinical characteristics in patients with AF treated with amiodarone in combination with apixaban or warfarin. To compare the occurrence of major bleedings in patients with atrial fibrillation treated with the combination of apixaban + amiodarone versus the combination of warfarin + amiodarone.
Country(-ies) of study	Sweden
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

In the table below, list all abbreviations and their definitions. Rows should be added as needed. To be finalized

Abbreviation	Definition
AF	Atrial Fibrillation
CYP	Cytochrome P450
INR	International Normalized Ratio
NOAC	Non-vitamin K antagonist Oral Anticoagulant
OAC	Oral Anticoagulant
P-gp	Plasma glycoprotein
RCT	Randomized Controlled Trials
SAP	Statistical Analysis Plan
TTR	Time in Therapeutic Range
UCR	Uppsala Clinical Research Center

3. RESPONSIBLE PARTIES

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For PASS involving sites/investigators in EU countries:

Not applicable

4. ABSTRACT

Title: Major bleeding in patients with atrial fibrillation treated with apixaban versus warfarin in combination with amiodarone: the APIXAMIO study.

Rationale and background

In comparison with warfarin, apixaban was both more effective in preventing strokes and safer in terms of major bleedings as well as intracranial bleedings, irrespective of age and the use of amiodarone in the ARISTOTLE trial.

In a subanalysis of the ARISTOTLE trial, amiodarone use was associated with increased risk of stroke and systemic embolism and lower TTR when used with warfarin. Furthermore, apixaban consistently reduced the rate of stroke and systemic embolism, death and major bleeding compared with warfarin in patients treated with or without amiodarone. However, randomized controlled trials (RCT), are in general considered to involve a more selected patient-population than is usually seen in real life, meaning that frail patients are frequently excluded in RCTs. We decided therefore to investigate whether or not we could replicate the relative safety-relations in terms of major bleeding, between apixaban and warfarin in combination with amiodarone, in real life reflecting a broader unselected patient population.

The present real-world study will describe the patient characteristics in patients treated with amiodarone in combination with either apixaban or warfarin, and if deemed possible after feasibility assessment, compare safety outcomes in these two patient cohorts.

Research question and objectives

Research question:

What are the clinical characteristics of patients co-treated with amiodarone and apixaban or warfarin in Sweden. Is there a difference in major bleeding between those treated with amiodarone in combination with either apixaban or warfarin.

Objectives:

Step 1:

Primary objective:

- To describe the clinical characteristics in patients with AF treated with amiodarone in combination with either apixaban or warfarin.

- Utilizing the descriptive data to assess feasibility of moving forward with a comparative effectiveness study between apixaban and warfarin (step 2).

Step 2:

- To compare the occurrence of major bleedings in patients with atrial fibrillation treated with the combination of apixaban and amiodarone versus the combination of warfarin and amiodarone.

Secondary objective: To compare apixaban versus warfarin in patients treated with amiodarone regarding occurrence of:

- Intracranial bleeding
- Gastrointestinal bleeding
- Urogenital bleeding
- All-cause mortality (exploratory)
- Cardiovascular mortality (exploratory)
- Stroke or systemic embolism (exploratory)

Study design

A retrospective registry-based observational study using merged data from various Swedish national registries.

Population

All new patients with AF, treated with amiodarone in combination with apixaban or warfarin between 2013-06-01 and 2018-12-31, identified through Swedish national registries, excluding patients with mechanical valves and mitral stenosis.

Commented [IB1]: What numbers of patients do you expect to get in this 2.5 year period? Why cut-off at 2018 is it because of teh delay in data being available on the system?

Commented [MA2R1]: It is because we re-use a database that is already set from a previous RWD study, we have looked into the numbers and believe the data size will be enough. If not after step one, we can consider creating a completely new database.

Commented [GB3R1]: The data for inclusion spans over 4.5 years.

Variables

Exposure: Treatment with amiodarone in combination with apixaban or warfarin.

Key covariates: See appendix.

Outcomes:

Primary: Major bleeding.

Secondary: Intracranial bleeding, Gastrointestinal bleeding, Urogenital bleeding

Exploratory: All-cause mortality, Cardiovascular mortality, Stroke or systemic embolism.

Data sources

Data from the following registries will be extracted and linked:

- The National Patient Register: Information about patient demographics, comorbidities and previous and incident events will be extracted. Data will be extracted from 2007-01-01 – 2018-12-31.
- The National Cause of Death Register: Data about mortality, including cause of mortality will be obtained from the register. Data will be extracted from 2013-06-01 – 2018-12-31.
- The Swedish Prescribed Drug Registry: Dispensing data and dosing for prescribed drugs will be extracted from the register. Data will be extracted for the time-period 2012-12-01 – 2018-12-31.

Study size

All patients with AF treated concomitantly with amiodarone and oral anticoagulation (apixaban or warfarin) and registered in the National Patient Register, during the time period above, will be included in the study.

Data analysis

Described in detail in the statistical analysis plan (SAP).

Milestones

- The study protocol will be finalized and approved by Pfizer Q3 2021
- Ethical application will be submitted Q3 2021, approval will be obtained Q3 2021.
- Start and end of data collection Q4 2021 (Swedish administrative health databases)
- Completion of feasibility assessment Q4 2021
- Preliminary study report Q1-2 2022
- Final study report Q2-3 2022

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	Q4 2021
Start of data collection	Q4 2021
End of data collection	Q4 2021
Registration in the EU PAS register	Q4 2021
Final study report	Q3 2022

7. RATIONALE AND BACKGROUND

Patients with atrial fibrillation (AF) have a five-fold increased risk for stroke in comparison with the general population. The more risk factors for stroke the patient has, according to specific risk-scores, the higher risk for stroke and in addition higher risk for bleeding.[1] To decrease the risk for stroke, patients are recommended treatment with oral anticoagulant drugs (OAC).[2,3] Of the OACs, non-vitamin K Antagonist Oral Anticoagulants (NOACs) are preferred over warfarin due to a more favourable safety profile.[2,3]

However, concerns have been raised that the safety profile of NOACs can be impacted by drugs interacting with the metabolism of the anticoagulant, especially in a situation where concomitant treatment leads to inhibition of both CYP3A4 and P-glykoprotein (P-gp). A previous example of that concern was with apixaban when combining with dronedarone, which is a moderate inhibitor of CYP3A4 and a strong inhibitor of P-gp. There was no pharmacokinetic data published and therefore, Pfizer and BMS funded a retrospective registry-based study evaluating clinical data from Swedish national registers.[4] The results showed that the incidence of bleeding was numerically lower in the group treated with

apixaban than in the group with warfarin, but the overall bleeding rates were low, reflecting a selected healthier patient population, which is generally the case when prescribing dronedarone. However, amiodarone, a class III antiarrhytmic drug is more often prescribed among older patients with structural heart disease. Amiodarone inhibits both CYP3A4 and P-gp and theoretically this might increase the concentration of apixaban if combined, especially in patients with renal impairment.[5,6]

Amiodarone is mainly recommended for patients with paroxysmal AF as a rhythm control strategy to prevent relapses of AF. Also, amiodarone is recommended for patients with persistent AF as a last resort when rate control cannot be achieved with combination therapy in patients who do not qualify for non-pharmacological rate control, i.e. atrioventricular node ablation and pacing.[2]

In a recently published observational study from Sweden, patients with AF treatment with antiarrythmic drugs were younger and healthier than those not prescribed antiarrythmic drugs.[7] However, the prevalence of heart failure was most frequent in the patient group prescribed amiodarone (43%). In comparison, the prevalence of heart failure in the group not prescribed antiarrythmic drugs was 30%, and the occurence among patients prescribed other antiarrythmic drugs were: sotalol (13%), dronedarone (12%), disopyramide (10%) and flecainide (5%), respectively. Also, the patient group prescribed amiodarone had the second highest unadjusted mortality rate, with the highest rate of mortality observed among patients not receiving any antiarrythmic drugs.

In a sub-analysis of the ARISTOTLE trial, the usage of amiodarone versus no treatment with amiodarone in combination with warfarin was associated with increased risk of stroke and systemic embolism, and lower time in the therapeutic ranges.[8] Furthermore, apixaban versus warfarin, combined with amiodarone was associated with lower rates of stroke and systemic embolism, death and major bleeding.[8] However, randomized controlled trials (RCTs) are in general considered to involve a more selected patient-population than is usually observed in real-life settings, meaning that the frail patients are frequently not included in the RCTs.[9]

Therefore, we aim to investigate the occurrence of major bleeding among patients treated with amiodarone in combination with apixaban or warfarin in a real-life setting among unselected patient with AF.

The present real-world study will describe the patient characteristics in patients treated with amiodarone in combination with either apixaban or warfarin, and if deemed possible after feasibility assessment, compare safety outcomes in these two patient groups.

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

Commented [JA4]: Was the decision from the BMS EU QPPV? I ask as our VICTORIE study was changed to a non-PASS - BMS seem to have changed the criteria for a PASS. It's possible you may find this study is not classified with a PASS if you haven't had this checked. Ignore if this has been confirmed by the BMS EU QPPV though.

Commented [MA5R4]: I have not asked, I just thought so due to the eventual comparative part in step 2. But I will ask BMS EU QPPV. Thanks!

8. RESEARCH QUESTION AND OBJECTIVES

Research question

The main scope of this study is descriptive and also to compare safety outcomes in patients treated with apixaban versus warfarin in combination with amiodarone. However, before the comparative effectiveness analysis can take place a feasibility assessment will be performed (step one) to understand if the data is suffient to be able to conduct a comparison with high validity. If it is determined in step 1 that a comparative analyses cannot be performed in a robust manner, the project will not proceed into step 2.

Commented [JA6]: You should probably add that if it is determined that comparative analyses cannot be performed in a robust manner, the study will remain descriptive.

Commented [GB7R6]: Added

Objectives

Step 1
Primary objective:

- To describe the clinical characteristics in patients with AF treated with amiodarone in combination with either apixaban or warfarin.
- Utilizing descriptive data, assess whether it is feasible to perform a comparative effectiveness study between apixaban and warfarin in regard to the primary objective in step 2.

Commented [DA8]: would suggest to mention which specific outcomes will be measured in the Step 1.

Commented [GB9R8]: No clinical outcomes in step 1. Only descriptive statistics.

Step 2
Primary objective:

- To compare the occurrence of major bleeding in patients treated with amiodarone in combination with apixaban versus warfarin.

Secondary objectives: To compare patients treated with amiodarone in combination with apixaban versus warfarin regarding occurrence of:

- Intracranial bleeding
- Gastrointestinal bleeding
- ~~Urogenital bleeding~~
- Other bleedings leading to hospitalization/transfusion of blood

Commented [JA10]: Usually we break this down into:
ICH
GI bleeding
Other major bleeding

Is it worth adding other major bleeds to the list to comprehensively break down the major bleeds and cover those that aren't in your three current categories?

Commented [MA11R10]: Added! @Gorav will we include transfusion in other bleeding?

Commented [GB12R10]: Will also include urogenital bleeding into other

Exploratory objectives: To compare patients treated with amiodarone in combination with apixaban versus warfarin regarding occurrence of:

- All-cause mortality
- Cardiovascular mortality
- Ischemic stroke or systemic embolism

9. RESEARCH METHODS

Methodology for the statistical analyses will be detailed in a statistical analysis plan (SAP).

9.1. Study design

The analysis presented in the statistical analysis plan (SAP) will be performed in two steps. In the first step a feasibility assessment will be performed to conclude that there is enough power to perform the proposed analysis comparing apixaban with warfarin in patients treated with amiodarone. If feasible, the second step will in primary analyses compare the occurrence of major bleeding in patients treated with amiodarone in combination with apixaban or warfarin.

This study will be a retrospective observational registry study based on data from mandatory national patient registries in Sweden. Data for this study will originate from selected national registries in Sweden which are linkable using the unique 10-digit personal number available to all Swedish citizens. Patients with AF will be identified in the National Patient Register between 2007-01-01 – 2018-12-31. However, the study period will be between 2013-06-01 – 2018-12-31, to reflect dates of apixaban availability for AF in Sweden according to the Swedish Medical Products Agency and the years of available data. See figure 1 for a schematic presentation of timelines and registries included in the proposed study. All individuals with a hospital diagnosis of AF will be identified through the National Patient Register. For all included patients, information about amiodarone, apixaban and warfarin filled prescriptions will be obtained from the Swedish Prescribed Drug Registry.

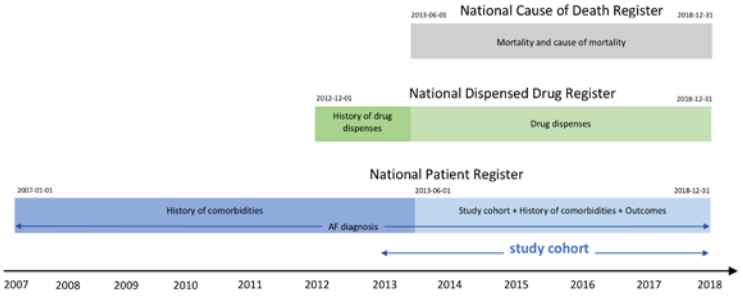

Figure 1. Schematic presentation of the timelines and registries included in the study.

9.2. Setting

Study size

All individuals with a hospital diagnosis of AF will be identified through the national Swedish Patient register. For all these patients, information will be obtained on amiodarone, apixaban and warfarin prescriptions through the Swedish Prescribed Drug Registry for the entire study period (from 2013-06-01 to 2018-12-31).

The study population will be identified through the following steps:

1. All individuals ≥18 years of age with a diagnosis of atrial fibrillation (ICD-10 code I48 with or without subcodes) in the National Patient Register between 2007-01-01 and 2018-12-31. All individuals with valvular AF defined as patients with mechanical heart valves (Z952) or a diagnosis of mitral stenosis (I342, I050, I052, Q232) will be excluded. Patients with an acute venous thromboembolism 6 months period before and including the index date (I26, I801, I802, I803, I808, I809, I822, I823, I828, I829, O223, O871, O882) will be excluded. Patients with diagnosis or procedure-code for hip/knee replacement surgery within 6 weeks before and including index date (NFB, NFC, NGB, NGC, NFG, NGG) will be excluded. Patients with a diagnosis code indicating pregnancy 9 months before and including index date (A34, O00-O99, Z33, Z34, Z35, Z36, Z37, Z39, Z640, Z641) will be excluded. Patients dispensing simultaneously more than one OAC (ATC code B01AA03, B01AE07, B01AF01, B01AF02, B01AF03) during the identification period will be excluded.
2. All individuals with at least one filled prescription of amiodarone between 2013-06-01 (approval date for apixaban for AF in Sweden according to the Swedish Medical Products Agency) and 2018-12-31 from the Swedish Prescribed Drug Registry. The date for the first filled prescription of amiodarone defines the preliminary index date.
3. All individuals with a filled prescription of apixaban or warfarin after the preliminary index date (start date of amiodarone). For patients with a filled prescription of apixaban or warfarin after the preliminary index date, the preliminary index date will be substituted by the start date of the oral anticoagulant and set as the index date

Commented [IB13]: Is this normally sufficient for comaprisions to have at least oen filled prescription?

Commented [GB14R13]: In this population some patients might only have one dispense while others might have serval. However, patients will be cencored if they stop or switch treatment strategy. This concept is often used.

Commented [JA15]: Are you going to specify how long after amiodarone initiation patients can receive apixaban? How will you determine the patient is still on amiodarone when they start apixaban?

Commented [GB16R15]: Yes. Amiodarone dosage can vary between individual patients and over time. Thus, the pill consumption method cannot be utilized. Generally, drugs in Sweden cannot be prescribed in larger quantities than what is expected to last 3 months. An interruption gap of 30 days will be set to identify detectable gaps in dispensing data. If the patients does not have any additional amiodarone dispense during this period the patient will not be part of the analsysis. See the exposure section for details.

because this was when co-treatment with both amiodarone and either one of the oral anticoagulants began.

OR

For patients already on oral anticoagulant treatment (apixaban or warfarin) when amiodarone was initiated, the preliminary index date will be set as index date because this will be when co-treatment begins). Ongoing anticoagulant treatment will be defined by a filled prescription of apixaban or warfarin ~~within~~ which is still ongoing when treatment with amiodarone began, see the exposure section for details about how treatment duration is calculated. ~~6 months before the amiodarone starting date.~~

Commented [JA17]: How will you determine if the amiodarone patient is still on apixaban if they have an apixaban prescription 5 months before starting amiodarone? The 180 days duration seems excessive for apixaban prescriptions when you can make more accurate assessments based on pack size/dose.

Commented [GB18R17]: Agree, the 180 days duration might be too long. We have changed the strategy for how exposure over time is calculated, see the exposure section for details.

9.2.1. Inclusion criteria

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

1. Patients that have one or more AF (ICD-10 I48) diagnosis registered in the National Patient Register
2. Patients ≥ 18 years
3. Patients who had a filled prescription for amiodarone and apixaban or warfarin during the identification period

Commented [JA19]: Are these patients who are using these drugs as their first ever OAC or could some one who was on rivaroxaban and then switched to apixaban be included?

Commented [GB20R19]: Yes, prior switch is allowed.

9.2.2. Exclusion criteria

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

1. Patients with valvular AF (defined as patients with mechanical heart valves (Z952) implanted before index, or with a diagnosis of mitral stenosis before and including index date (I342, I050, I052, Q232).
2. Patients with an acute venous thromboembolism 6 months period before and including the index date (I26, I801, I802, I803, I808, I809, I822, I823, I828, I829, O223, O871, O882).
3. Patients with diagnosis or procedure-code for hip/knee replacement surgery within 6 weeks before and including index date (NFB, NFC, NGB, NGC, NFG, NGG).
4. Diagnosis codes indicating pregnancy 9 months before and including index date (A34, O00-O99, Z33, Z34, Z35, Z36, Z37, Z39, Z640, Z641).

Commented [JA21]: Suggest you also exclude any patients with more than one OAC prescription at the same time. (eg apix + warfarin, apix + riva etc). Rare but should be excluded.

Also: pregnancy should be excluded.

Commented [GB22R21]: Added

~~3.~~5. Patients dispensing simultaneously more than one OAC (ATC code B01AA03, B01AE07, B01AF01, B01AF02, B01AF03) during the identification period.

9.3. Variables

A list of covariates with definitions according to the ICD-10/ATC coding system has been included in the appendix. Covariates are defined by diagnoses, medication or other conditions observed or documented before or on index date. Covariates known as potential risk factors or confounders will also be included, e.g. previous stroke.

Information about the prescribed oral anticoagulant and amiodarone at baseline and during follow-up will be obtained from the Swedish Prescribed Drug Registry.

Outcomes are events that occurred after the index date. See Table 1 below for details on variable definitions.

A list of other covariates is available in the appendix.

Table 1. Variable definitions.

Variable	Definition	Source
Treatment with apixaban	ATC code: B01AF02	Swedish Prescribed Drug Registry
Apixaban dosage	Variable in the register	Swedish Prescribed Drug Registry
Treatment with warfarin	ATC code: B01AA03	Swedish Prescribed Drug Registry
Treatment with amiodarone	ATC code: C01BD01	Swedish Prescribed Drug Registry

Exposure

After applying the inclusion and exclusion criteria, eligible patients will be assigned to the following exposure cohorts:

1. Amiodarone + apixaban
2. Amiodarone + warfarin

Commented [JA23]: Are the any clinical reasons to think that patients who are on amiodarone for a while and then get prescribed apixaban are different from patients who are prescribed apixaban for a while and then get prescribed amiodarone?

Commented [IB24R23]: They could have been on another antiarrythmic before amiodarone. How is this accounted for?

Commented [GB25R23]: They could be different but this is very difficult to account for in an observational study which to some extent has to be pragmatic. We could exclude patients on prior antiarrthmic drugs but I think that would result in several patients being excluded.

Exposure will be defined at index date (see section about inclusion and exclusion criteria). Patients who switch treatment during the follow-up (e.g. from warfarin to apixaban) will remain in their original treatment arm but will be censored at the date of switch. In case both apixaban and warfarin has been dispensed on the same day, that patient will be censored. Similarly, patients who stop any treatment during follow-up (e.g. drug discontinuation of warfarin during follow-up) will be censored at the date of drug discontinuation.

Based on drug dispense information, including date of dispense and ATC codes, drug treatment at any given time can be estimated. For patients treated with apixaban, a method based of pill consumption (number of pills dispensed/number of pills consumed daily [two for apixaban]) can be utilized. A 30-day grace period will be added to identify detectable gaps in dispensing data. The grace period ~~was~~will be introduced to allow for some degree of non-compliance and for irregular dispensing due to stockpiling.

-However, for warfarin and amiodarone, the dosage can vary between individual patients and over time. Thus, the pill consumption method cannot be easily utilized. Generally, drugs in Sweden cannot be prescribed in larger quantities than what is expected to last 3 months. This is, however, not a strict rule, and available sizes of packages influence prescriptions. For instance, a patient with a maintenance dose of warfarin of 1.5 tablets a day needs approximately 140 tablets during a three-month period but will most likely receive a prescription for 200 tablets, because warfarin only comes in packages of 100 tablets. The mean dose of warfarin for patients with AF in Sweden is 1.8 tablets per day for male and 1.5 tablets for females according to a study of more than 1 million dosing instructions with corresponding International Normalized Ratio (INR) values and information about the achieved time within therapeutic range.[10] Hence, a typical warfarin patient is expected to come for refill every 4.5 month. With this background and since the daily dosage of warfarin ~~and amiodarone~~ varies between individual patients and over time, ~~each dispense will be estimated to~~a mean dosage of warfarin/week for patients, based on age and sex from the Swedish oral anticoagulant registry (AuriculA) will be utilized, see table below. As above, an interruption gap of 30 days will be set to identify detectable gaps in dispensing data.

Mean dosage of warfarin (mg/week) based on age and sex (1 warfarin tablet = 2.5 mg)								
Age/ Sex	≤29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80-89 years	≥90 years
Male	45.4	50.4	44.5	42.5	36.9	32.0	27.4	24.3
Female	46.7	48.3	44.5	39.4	34.3	28.5	23.7	20.6

For amiodarone, the dosage can vary between individual patients and over time. As drugs in Sweden cannot be prescribed in larger quantities than what is expected to last 3 months, each dispense of amiodarone will be estimated to last 3 months. In addition, a 30-day grace period will be added to identify detectable gaps in dispensing data. ~~(last 3 months (90 days)).~~ ~~An~~

Commented [DA26]: please confirm if the patients will be censored if they stop apixaban, warfarin OR amiodarone treatment? and for each cohort, patients would be required to be on concurrent treatment for the entire follow-up?

Commented [GB27R26]: As mentioned, patients will be censored if they stop or switch any of the studied treatment combinations.

Commented [DA28]: agree, the 90-day gap might be considered too long. Perhaps, a sensitivity analysis with a 30-day gap might be useful. In Alliance-sponsored studies we usually allow a 30-day gap.

Commented [JA29]: Suggestion: You might consider stratifying the calculated duration of warfarin and amiodarone based on age rather than using an average for the whole population? We took this approach in BEYOND pooled. The 90 days grace period is quite a long period compared to many other Alliances studies which typically use 30 days (though not unheard of in the literature).

~~interruption gap of 90 days will be set to identify detectable gaps in dispensing data.~~ ~~The grace period was introduced to allow for some degree of non-compliance and for irregular dispensing due to stockpiling.~~ ~~I.e. a dispense of warfarin and amiodarone is considered to last 180 days and if no other dispensation takes place after that the patient is considered to be unexposed after 180 days.~~

~~When comparing apixaban and warfarin it is necessary to use the same method to account for adherence. Thus, the above proposed refill method will be implemented for warfarin, apixaban and amiodarone.~~

Commented [JA30]: Do you? Even if the treatment duration can be more accurately estimated for apixaban by using the pack size and dose? We didn't use the same approach for each in BEYOND pooled for warfarin vs apixaban as it is more accurate to estimate treatment duration for the NOACs based on pack size and dose. I don't think assuming a prescripton duration of 180 days for apixaban is realisatic and runs the risk that you will be attributing outcomes to apixaban when the patient was no longer taking the drug.

Outcomes

A list of outcomes with definitions according to the ICD-10 coding system has been included in the appendix. Outcomes are events that occur after index date. The main study outcome is major bleeding. Identification of bleeding events in a retrospective registry study cannot be performed in the same way as in a prospective randomized trial where the severity of bleeding events can be assessed individually with access to medical records, biomarker tests and patient reporting. Administrative registers have low sensitivity for detection of minor bleeding events not resulting in hospitalization. Therefore, only major bleeding events (fatal bleeding, intracranial bleedings and other major bleeding events associated with a hospitalization) will be assessed in the present study. According to the International Society on Thrombosis and Haemostasis, major bleeding is defined as a bleeding events which are fatal, occurs in critical areas or organs, results in hospitalization and/or prolonged hospital stay and a fall in hemoglobin level of ≥20 g/L or transfusion of ≥2 units of blood. The definition of what exactly constitutes a bleeding in a critical organ, apart from intracranial bleeding, is difficult to assess from ICD-10 codes alone. Moreover, information about hemoglobin drop is not available in the National Patient Register, but codes about blood transfusions are available.

Commented [IB31]: Aaron, per your earlier comment, here the study talks about evaluating other major bleeding events.

- Intracranial bleeding
- ~~Gastrointestinal bleeding~~
- ~~Urogenital bleeding~~
- Other bleeding/transfusion of blood

Commented [JA32]: This was missing from the study objectives? As per previous comment, I would recommend other bleeding is incouded to cover all the bleeds that do not fall into the other categories.

Commented [GB33R32]: Added it to the study objectives. Also, urogenital bleeding will be combined into other bleeding as per suggestion.

These outcomes based on ICD-10 codes have previously been validated in a Swedish study including patients with AF.[11] Additional to bleeding events, the exploratory objectives includes the following outcomes as detailed in the appendix: all-cause mortality, cardiovascular mortality and stroke/systemic embolism in patients treated with amiodarone in combination with apixaban versus warfarin.

9.4. Data sources

The study will use data from Swedish administrative health databases using the unique personal identification number available to all Swedish citizens. The linkage between different health databases will be performed by the National Board of Health and Welfare (Socialstyrelsen) and a de-identified data base will be provided to the investigators. More details about the registries are provided below

National Patient Register: For this study, the patient cohort will be identified in the National Patient Register. Moreover, data about comorbidities and outcome (e.g. major bleeding) will be obtained from the same registry. The National Patient Register is a mandatory nationwide registry that includes discharge diagnosis for all patients admitted to Swedish hospitals since 1987. Previous studies have shown that the registry has high validity for several diagnoses, including major bleeding.[11,12] Data will be extracted from 2007-01-01 until 2018-12-31. The reason for choosing 2007-01-01 as the starting point for data collection is to allow collection about prior comorbidities before the index date.

Swedish Prescribed Drug Register: The Swedish Prescribed Drug Register includes dispensing date and dosing for prescribed drugs data (including anatomical therapeutic chemical [ATC] codes). The Swedish Prescribed Drug Register has captured data about all prescribed drugs dispensed at Swedish pharmacies since 2005 and has been shown useful in pharmacoepidemiological studies.[13] Data will be extracted between 2012-12-01 until 2018-12-31. The reason for choosing 2012-12-01 as the starting point for data collection is to define medications dispensed within 6 months before index date.

National Cause of Death Register: The National Cause of Death Register is a Mandatory nationwide registry that has collected vital status of all Swedish citizens since 1961. The register includes data about mortality (including cause of death and date) in Sweden. Data will be extracted from 2013-06-01 until 2018-12-31.

9.5. Study size

All patients with AF between 2013-06-01 (dates of apixaban availability for AF in Sweden according to the Swedish Medical Products Agency) to 2018-12-31 (end of available data) will be included in the study. In prior reports from the National Patient Register with data available between December 2011 and December 2014, excluding patients with mitral stenosis and mechanical valve prosthesis, a total of 49,418 new warfarin and 18,638 new NOAC (6,547 apixaban) patients were included.[14] Considering the accelerating uptake of apixaban in the Swedish AF population (market share of apixaban for AF in Sweden, among

OAC treated, is currently approximately 60%), and four years of additional data from the National Patient Registry, the dataset is likely to generate a total of 20,000 patients on apixaban available for the study.

From another study comparing apixaban versus warfarin in patients treated with concomitant dronedarone between May 2013 and December 2016, 2,890 patients had a combination of apixaban + dronedarone.[4] In the same study, 5,419 patients had a combination of warfarin + dronedarone.[4] In another Swedish study using data from the National Patient Register between 2010 and 2015, 10,541 patients with AF were treated with amiodarone and 8,254 patients were treated with dronedarone.[7] Given that amiodarone is frequently used among patients with AF, we estimate that a similar number of patients will be treated with apixaban + amiodarone or warfarin + amiodarone as in the dronedarone referred above. As the proposed study includes two additional years of data, and considering the accelerated uptake of apixaban in Sweden, we estimate that the number of patients treated with apixaban + amiodarone or apixaban + warfarin will be higher.

Commented [IB34]: This addresses my earlier comment, thank you.

Prior to the start of step 2 in this project, a feasibility assessment, by analyzing the descriptive data, will be conducted to determine whether or not it is possible to move on with the comparative part of this study.

9.6. Data management

This study will be performed by researcher Gorav Batra, Associate Professor Christina Christersson and Professor Claes Held, all at Uppsala University.

All data management and statistical analysis will be performed using either R statistics, SAS or SPSS.

The linkage of registers will be performed by the National Board of Health and Welfare (Socialstyrelsen).

Data management and statistical analysis will be performed by statisticians at Uppsala Clinical Research Center (UCR).

All data will be completely patient de-identified for this study. Data management and analyses will be done exclusively through syntax files which will be saved and will provide a safeguard for traceability of all results and will also facilitate minor changes of criteria if needed.

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, UCR agrees to keep all study-related records. The records should be retained by UCR according to local regulations or as specified in the research agreement, whichever is longer. UCR must ensure that the records continue to be stored securely for so long as they are retained.

If for any reason UCR becomes unable to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless UCR has expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

UCR must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. 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.

A statistician at Uppsala Clinical Research Center, Uppsala University, Sweden will write the analytic code and will conduct all analyses within the scope of this protocol. Full operational definition for each variable, and the analytic strategy, including variables for inclusion in the analyses are described in the SAP.

In step 1 the descriptive statistics will be performed such as patient characteristics, risk-scores for stroke, concomitant medications and so on. If feasibility assessment permits moving forward with the comparative part a propensity score matching analysis will be conducted. Individual propensity scores for the likelihood of receiving apixaban + amiodarone rather than warfarin + amiodarone will be obtained by logistic regression.

Commented [JA35]: You might consider IPTW instead to avoid losing patients during matching, particularly if you are only just making about 5000 apix+amiodarone prior to PSM.

In step 2 Kaplan-Meier estimates with accompanying at risk tables for the on-treatment ~~intention-to-treat~~ analysis will be plotted to illustrate all outcomes with regard to apixaban + amiodarone versus warfarin + amiodarone. This will be performed for all patients before the propensity score matching and for selected patients after the propensity score matching.

Commented [JA36]: As you are censoring patients at discontinuation, switch etc this is not ITT, it is an ontreatment analysis.

~~Matched cohorts~~ will be compared with regard to outcome using Cox regression analysis. Time at risk will be counted from index date + 1 day. The observation period will end at 2018-12-31. However, censoring will be performed at the time of outcome, death, end of follow-up or drug discontinuation, whichever comes first. Patients who switch treatment during the follow-up (e.g. from warfarin to apixaban) will remain in their original treatment arm but will be censored at the date of switch. In case both apixaban and warfarin have been dispensed on the same day, that patient will be censored.

Supplementary analyses

In a first supplementary analyses, only OAC and amiodarone naïve patients will be included (i.e., patients with dispense of NOAC [apixaban, dabigatran, rivaroxaban and edoxaban], ~~or~~ warfarin or amiodarone) within 12 months before index date will be excluded (washout period). This approach reduces some of the problems associated with confounding by indication.

In a second supplementary analyses, different risk time variables will be used for each endpoint included in the composite endpoint of major bleeding. It will thus be possible to assess more than the first bleeding event for each patient, as long as they are of different types. In this way a patient with e.g. a gastrointestinal bleed after six months and an intracranial bleed three month later will have both events counted, and not just the first one. This approach reduces some of the problems associated with competing diagnoses.

All tests will be two-sided. Confidence intervals are 95% and p-values <0.05 will be considered as significant.

Commented [JA37]: ?

Commented [GB38R37]: Naïve to any OAC as per ealier suggestions from Pfizer

Commented [JA39]: How does this translate for the patients on amiodarone who receive apixaban vs patents on apixaban who receive amiodarone? Shouldn't patients also be naïve to amiodarone as well? Why only naïve to OAC?

Commented [GB40R39]: Added naïve to amiodarone

9.8. Quality control

All data will be completely patient de-identified for this study. This study will utilize data from Swedish administrative health databases. The Swedish administrative health databases, including the National Patient Register has been shown to have high validity.[12] Similarly, the National Dispensed Drug Registry has previously been used in several studies to capture data about all prescribed drugs dispensed at Swedish pharmacies since 2005.[13] Similar data, but for earlier time periods, have been used in several studies before.[1,4,7] Quality control will be continuously performed during the data management and statistical analysis.

9.9. Strengths and limitations of the research methods

This real-world observational descriptive registry study in Sweden is of high interest among physicians as it will contribute to an increased understanding about the safety profile of apixaban versus warfarin in patients treated with concomitant amiodarone. Moreover, the unique possibility of linkage of Swedish administrative health databases will provide high quality representative data of treatment with NOAC and warfarin at a national level. In addition, the prescription data will identify all patients, even those who are rarely selected for participation in studies due to poor general health (expected to have poor adherence); and will include all patients regardless of physicians' characteristics, minimizing selection bias.

However, there are some limitations that merit consideration. Given the retrospective observational study design, and the use of administrative health databases as data source, there are some limitations resulting from this type of study. First and despite the quality of

the data, it is possible that some measures may be incorrect and/or missing. Therefore, some measures and clinical outcomes might be underestimated.

Second, information about comorbidities will be limited to the diseases that are registered in the National Patient Register. A major limitation for non-randomized registry studies is vulnerability to confounding by indication. More specifically; the choice between warfarin or apixaban is influenced by the prescribers´ appreciation of what is most suitable for the specific patient. These factors might not be apparent from registry data and therefore not possible to adjust for. In order to minimize this effect, matching for the likelihood of either treatment based on available information will be used in order to construct two cohorts with similar background characteristics (propensity score matching).

Third, assessment of drug exposure during follow-up will not be as exact as in randomized clinical trials were pill counts are used. Filled prescription of a drug does not prove that it was actually ingested. Although starting dates for treatment can be assessed by purchase dates, dates of termination of treatment can rarely be exactly defined. Therefore, intervals between drug purchases, with its limitations, will be assessed to derive drug exposure.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information. The linkage of registers will be performed by the National Board of Health and Welfare (Socialstyrelsen). All data will be completely patient de-identified for this study.

10.2. Patient consent

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

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must

be forwarded to Pfizer.

10.4. Ethical conduct of the study

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

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and 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 (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results will be presented at international conferences and submitted for publication in peer-reviewed journals.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

For PASS protocols submitted in the EU, a copy of the ENCePP Checklist for Study protocols (available at http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml*) should be completed and signed by the main author of the study protocol, and included in Annex 2.*

For all other NI studies (i.e., PASS protocols not submitted in the EU and non-PASS protocols), this annex is not required.

ANNEX 3. ADDITIONAL INFORMATION

Additional annexes may be included if necessary. If not needed, enter "Not applicable".