NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

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
Version identifier of the final study report	1.0
Date	19 Sept 2023
EU Post Authorization Study (PAS) Register Number	EUPAS43681
Active Substance	Apixaban-B01AF02 Warfarin-B01AA03 Amiodarone-C01BD01
Medicinal Product	Eliquis, Waran, Waran Orion, Cordarone
Product Reference	EU/1/11/691/001-015
Procedure number	European Medicines Agency(EMEA)/H/C/002148
Marketing Authorization Holder(s) (MAH)	Bristol-Myers Squibb/Pfizer EEIG
Joint PASS	No
Research Question and Objectives	The main scope of this study is descriptive and, to compare safety outcomes in patients treated with apixaban versus warfarin in combination with amiodarone.

	Step 1 Primary Objective: • To describe the clinical characteristics in patients with AF treated with amiodarone in combination with either apixaban or warfarin. • To describe treatment duration during follow-up with apixaban + amiodarone or with warfarin + amiodarone. • 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. **Step 2** Primary Objective: • To compare the occurrence of major bleeding (including fatal bleeding, intracranial bleeding, gastrointestinal bleeding, other 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 • Other bleeding.
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1. ABSTRACT (STAND-ALONE DOCUMENT)

In Annex 1 as a stand-alone document.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AF	Atrial Fibrillation
ATC	Anatomical Therapeutic Chemical Classification System
CYP3A4	Cytochrome P450 3A4
EEIG	European Economic Interest Group
EMA	European Medicines Agency
EMEA	European Medicines Agency
ENCEPP	The European network of centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
ICD-10	International Classification of Disease 10th Revision
INR	International Normalized Ratio
ISPE	International Society for Pharmacoepidemiology
MAH	Market Authorization Holder
NI	Non-Interventional
NIS	Non-Interventional Study
NOAC	Non-Vitamin K Antagonist Oral Anticoagulant
OAC	Oral Anticoagulant
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study

Abbreviation	Definition
P-gp	Plasma Glycoprotein
RCT	Randomized Controlled Trials
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SPSS	Statistical Package for the Social Sciences
TTR	Time in Therapeutic Range
UCR	Uppsala Clinical Research Center

3. INVESTIGATORS

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4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned Date	Actual Date	Comments
Start of Data Collection	Q4 2021	26 November 2021	
End of Data Collection	Q4 2022	15 November 2022	
Planned Date of EUPASS Registration	Q4 2021	21 October 2021	
Final Study Report	15 October 2023	19 September 2023	

6. RATIONALE AND BACKGROUND

In a sub-analysis of the ARISTOTLE trial, amiodarone use was associated with increased risk of stroke and systemic embolism and lower TTR when used with warfarin.[1] Furthermore, apixaban consistently reduced the rate of stroke and systemic embolism, death and major bleeding compared with warfarin in patients treated with amiodarone. However, randomized controlled trials (RCTs), 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 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 AF patient population.

This real-world study describes the patient characteristics in patients treated with amiodarone in combination with either apixaban or warfarin and compared safety outcomes in these two patient cohorts if possible after feasibility assessment.

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

7. RESEARCH QUESTIONS AND OBJECTIVES

Research Question:
The main scope of this study was to compare safety outcomes in patients treated with apixaban versus warfarin in combination with amiodarone. However, before the comparative effectiveness analysis could begin, a feasibility assessment (Step 1) was performed to determine whether the data was sufficient to conduct a comparison with high validity. If it was determined in Step 1 that a robust comparative analysis could not be performed, the project would not proceed to Step 2.

7.1. Primary Objective(s)

Step 1

Primary Objective:

- To describe the clinical characteristics in patients with AF treated with amiodarone in combination with either apixaban or warfarin.
- To describe treatment duration during follow-up with apixaban + amiodarone or with warfarin + amiodarone
- 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.

Step 2

Primary Objective:

- To compare the occurrence of major bleeding (including fatal bleeding, intracranial bleeding, gastrointestinal bleeding, and other 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
- Other bleeding

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

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment Number	Date	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1	14 Mar 2022	9.7	Covariable cancer within 3 years from the index date will be included in the propensity score matching	The first descriptive analyses done showed that there was a significant difference for the occurrence of cancer in apixaban treated patients versus warfarin treated patients
2	31 Oct 2022	9.7	No adjustment for baseline characteristics during Cox regression analysis.	Earlier, it was prespecified that adjustment would be made during Cox regression analysis. But given that the matched patients sets were balanced in regard to baseline characteristics no such adjustment will be performed during cox regression analysis

9. RESEARCH METHODS

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

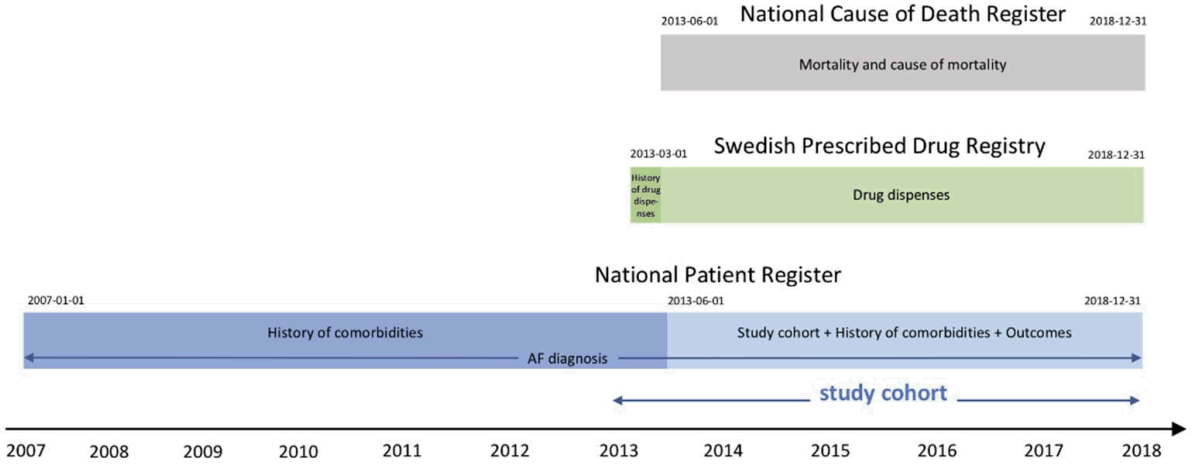
9.1. Study Design

The analysis presented in the statistical analysis plan (SAP) was performed in two steps.

In the first step, a feasibility assessment was performed to determine whether there was sufficient power to conduct the proposed analysis comparing apixaban to warfarin in patients treated with amiodarone. The second step in primary analyses, if feasible, would compare the occurrence of major bleeding in patients treated with amiodarone in combination with apixaban or warfarin.

This was a retrospective observational registry study based on data from Sweden's mandatory national patient registries. The data for this study originated from selected Swedish national registries, which were linked using the unique 10-digit personal number available to all Swedish citizens. Between 01January 2007 and 31 December 2018, patients with AF were identified in the National Patient Register. The study period, however, was from 01 June 2013 to 31 December 2018 to reflect the dates of apixaban availability for AF in Sweden as reported by the Swedish Medical Products Agency and the years of available data. Figure 1 depicts an arithmetic representation of the timelines and registries included in the proposed study. The National Patient Register was used to identify all individuals with a hospital diagnosis of AF. The Swedish Prescribed Drug Register was used to obtain information about amiodarone, apixaban, and warfarin filled prescriptions for all included patients.

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 were 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 Register for the entire study period (from 1 June 2013 – 31. December 2018 The study population was 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) before index or a diagnosis of mitral stenosis (I342, I050, I052, Q232) before and including index 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 1 June 2013 (approval date for apixaban for AF in Sweden according to the Swedish Medical Products Agency) and 31 December 2018 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, but within the exposure time of amiodarone (see section about exposure, Section 9.3), the preliminary index date was substituted by the start date of the oral anticoagulant and set as the index date 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 was set as index date because this will be when co-treatment begins). Ongoing anticoagulant treatment was defined by a filled prescription of apixaban or warfarin which is still ongoing when treatment with amiodarone began, see the exposure section for details about how treatment duration was calculated.

9.3. Subjects

9.3.1. Inclusion Criteria

To be eligible for inclusion in the study, patients must have met all of the following inclusion criteria:

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.

9.3.2. Exclusion Criteria

Patients meeting any of the following criteria were not 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).

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

9.4. Variables

Appendix 1 Variables 2021-10-05 includes a list of covariates with definitions based on the ICD-10/ATC coding system. Diagnoses, medications, or other conditions observed or documented prior to or on the index date are defined as covariates. Covariates known as potential risk factors or confounders, such as a previous stroke, were also included.

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

Outcomes are events that occurred after the index date. See Table 2 below for details on variable definitions.

A list of other covariates is available in the Appendix.

Table 2. Variable Definitions

Variable	Definition	Source
Treatment with Apixaban	ATC Code: B01AF02	Swedish Prescribed Drug Register
Apixaban Dosage	Variable in the Register	Swedish Prescribed Drug Register
Treatment with Warfarin	ATC Code: B01AA03	Swedish Prescribed Drug Register
Treatment with Amiodarone	ATC Code: C01BD01	Swedish Prescribed Drug Register

Exposure

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

1. Amiodarone + apixaban
2. Amiodarone + warfarin

Exposure was defined at index date (see Section 9.3 about inclusion and exclusion criteria). Patients who switched treatment during the follow-up (eg, from warfarin to apixaban) remained in their original treatment arm but were censored at the date of switch. In case both apixaban and warfarin had been dispensed on the same day, that patient was censored. Patients who stop any treatment during follow-up (eg, drug discontinuation of apixaban or warfarin during follow-up) were censored at the date of drug discontinuation.

Similarly, patients on amiodarone who stop treatment, or vice versa, patients on no amiodarone who starts treatment with amiodarone were censored.

Drug treatment at any given time could be estimated based on drug dispense information, such as date of dispense and ATC codes. A method based on pill consumption (number of pills dispensed/number of pills consumed daily [two for apixaban]) could be utilized by patients receiving apixaban. To identify detectable gaps in dispensing data, a 30-day grace period was added. The grace period was added to allow some degree of noncompliance as well as irregular dispensing due to stockpiling.

However, the dosage of warfarin and amiodarone may have varied between patients and over time. As a result, the pill consumption method could not be easily utilized. In general, drugs could not be prescribed in quantities greater than what was expected to last three months in Sweden. This was not a strict rule, and available package sizes influenced prescriptions. For instance, a patient on a warfarin maintenance dose of 1.5 tablets per day required approximately 140 tablets over a three-month period but most likely received a prescription for 200 tablets because warfarin is offered only in packages of 100 tablets. 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, the mean dose of warfarin for patients with AF in Sweden is 1.8 tablets per day for males and 1.5 tablets for females.10 Hence, a typical warfarin patient was expected to return for a refill every 4.5 months. With this background, and because the daily dosage of warfarin varies between patients and over time, a mean dosage of warfarin/week for patients based on age and gender from the Swedish oral anticoagulant registry (AuriculA) was utilized, as shown in the table below. As previously stated, a 30-day interruption gap was 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

Patients in Sweden cannot be prescribed greater quantities of the medicine than what is expected to last 3 months; each amiodarone dispense was estimated to last 3 months. A 30-day- grace period was also added to identify detectable gaps in dispensing data.

Outcomes

A list of outcomes with definitions according to the ICD-10 coding system is included in the appendix. Outcomes are events that occur after index date. The main study outcome was major bleeding, secondary outcomes are the individual components of major bleeding (Intracranial bleeding, gastrointestinal bleeding and other bleeding). Identification of bleeding events in a retrospective registry study could not be performed in the same way as in a prospective randomized trial where the severity of bleeding events could be assessed individually with access to medical records, biomarker tests and patient reporting.

Administrative registers had low sensitivity for detection of minor bleeding events not resulting in hospitalization. Therefore, only major bleeding events (fatal bleeding, intracranial bleedings, gastrointestinal bleeding and other major bleeding events associated with a hospitalization) were assessed in the present study. According to the International Society on Thrombosis and Haemostasias, major bleeding is defined as bleeding events which are fatal, occur 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, was difficult to assess from ICD-10 codes alone. Moreover, information about hemoglobin drop was not available in the National Patient Register, but codes about blood transfusions were available.

The outcomes based on ICD-10 codes were previously validated in a Swedish study including patients with AF.[2] In addition to bleeding events, the exploratory objectives included the following outcomes as detailed in the appendix: all-cause mortality, cardiovascular mortality, and ischemic stroke/systemic embolism in patients treated with amiodarone in combination with apixaban versus warfarin.

9.5. Data Sources

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

National Patient Register: For this study, the patient cohort was identified in the National Patient Register. Moreover, data about comorbidities and outcome (eg, major bleeding) were 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 were extracted between 01 January 2007 and 31 December 2018. The reason for selecting 01 January 2007as the starting point for data collection was to allow for the collection of prior comorbidities prior to 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 pharmacoepidemiologic studies.13 Data were extracted between 01 December 2012 until 31 December 2018. The reason for choosing 01 December 2012 as the starting point for data collection was 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 were extracted from 06 January 2013 until 31 December 2018.

9.6. 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 31 December 2018 (end of available data) were 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 generated 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 had estimated that a similar number of patients would be treated with apixaban + amiodarone or warfarin + amiodarone as in the dronedarone referred above. As the proposed study included two additional years of data, and considering the accelerated uptake of apixaban in Sweden, we had estimated that the number of patients treated with apixaban + amiodarone or apixaban + warfarin would be higher.

Prior to the start of Step 2 in this project, a feasibility assessment, by analyzing the descriptive data, was conducted to determine whether it was possible to move on with the comparative part of this study.

9.7. Data Management

This study was conducted by Associate professor Gorav Batra, Associate Professor Christina Christersson and Professor Claes Held, all at Uppsala University.

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

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

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

For this study, all patient data were completely de-identified. Data management and analysis were done exclusively through syntax files, which were saved and provided a safeguard for the traceability of all results, as well as the ability to make minor changes to criteria as necessary.

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, UCR agreed to keep all study-related records. The records will be retained by UCR according to local regulations or as specified in the research agreement, whichever is longer. UCR ensures that the records will 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 will be prospectively notified. The study records would be transferred to a designee acceptable to Pfizer.

Study records will 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 will be retained for longer than 15 years if required by applicable local regulations.

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

9.8. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study were documented in a statistical analysis plan (SAP), which is dated, filed, and maintained by the sponsor. The SAP modified the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses are reflected in a protocol amendment.

A statistician at Uppsala Clinical Research Center, Uppsala University, Sweden wrote the analytic code and conducted 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 were performed such as patient characteristics (Categorical covariates were described by frequency distribution while continuous covariates were expressed in terms of their mean and standard deviation or median and interquartile range (IQR) as appropriate.), risk scores for stroke, concomitant medications, and so on. If feasibility assessment permitted moving forward with the comparative part a propensity score matching analysis was conducted. Individual propensity scores for the likelihood of receiving apixaban + amiodarone rather than warfarin + amiodarone was obtained by logistic regression.

In the propensity score matching step, the occurrence of cancer was not specified as a comorbidity to match for. The initial descriptive analyses revealed a significant difference in the occurrence of cancer in apixaban-treated patients versus warfarin-treated patients. This difference remained regardless of whether the look-back period was within 6 months or 3 years of the index date, or at any time. Because it is well understood that the presence of active cancer is associated with an increased risk of bleeding and thrombotic events, covariable cancer within 3 years of the index date was included in the propensity score matching.

In step 2, Kaplan-Meier estimates for the on-treatment analysis would be plotted, along with at-risk tables, to illustrate all outcomes for apixaban + amiodarone versus warfarin + amiodarone. This was performed for all patients prior to propensity score matching and for selected patients after propensity score matching.

Matched cohorts were compared with regard to outcome using Cox regression analysis.

Time at risk was counted from index date + 1 day. The observation period ended at 31 December 2018. However, censoring was performed at the time of outcome, death, end of follow-up or drug discontinuation, whichever came first. Patients who switched treatment during the follow-up (eg, from warfarin to apixaban) remained in their original treatment arm but were censored at the date of switch. In case both apixaban and warfarin were dispensed on the same day, that patient would have been censored.

Supplementary Analyses

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

Different risk time variables were used in a second supplementary analysis for each endpoint included in the composite endpoint of major bleeding. As long as the bleeding events were of different types, it was possible to assess more than the first one for each patient. In this case, a patient who experienced a gastrointestinal bleed after 6 months and an intracranial bleed 3 months later would have both events counted, rather than just the first. This approach alleviated some of the issues associated with competing diagnoses.

All tests were two-sided. The confidence intervals were 95%, and p-values <0.05 were considered significant.

9.9. Quality Control

For this study, all patient data were completely de-identified. Data from Swedish administrative health databases were used in this study. Administrative health databases in Sweden, including the National Patient Register, have been shown to have high validity. (2) Similarly, since 2005, the Swedish Prescribed Drug Register has been used in several studies to collect data on all prescribed drugs dispensed at Swedish pharmacies. (7) Previously, similar data, but for earlier time periods, were used in several studies.[3-5] Throughout the data management and statistical analysis, quality control was performed on a continuous basis.

9.10. Limitations of the Research Methods

This real-world observational descriptive registry study in Sweden will gain physicians' interest because it contributed to a better understanding of the safety profile of apixaban versus warfarin in patients receiving concomitant amiodarone. Additionally, the unique possibility of linking Swedish administrative health databases provided high quality representative data of NOAC and warfarin treatment at the national level. Furthermore, the prescription data identified all patients, including those who are seldom selected for study participation due to poor general health (expected to have poor adherence); and included all patients regardless of physician characteristics, minimizing selection bias.

However, there were some limitations that merited consideration. Given the retrospective observational study design and the use of administrative health databases as a data source, this type of study had some limitations. First, despite the high quality of the data, some measures could be incorrect and/or missing. As a result, some measures and clinical outcomes may have been understated.

Second, information on comorbidities was limited to diseases registered in the National Patient Register. The vulnerability confounded by indication was a major limitation of non-randomized registry studies. More specifically, the choice between warfarin and apixaban was influenced by the prescribers' assessment of what was best for the individual patient. These factors may not have been apparent in registry data and thus could not be adjusted for. To reduce this effect, we used matching for the likelihood of either treatment based on available information to construct two cohorts with similar background characteristics (propensity score matching).

Third, the assessment of drug exposure during follow-up was not as precise as in randomized clinical trials using pill counts. A filled prescription for a drug does not prove that it was consumed. Although treatment starting dates were assessed by purchase dates, treatment termination dates were rarely exact. Therefore, intervals between drug purchases, with their limitations, were assessed to derive drug exposure.

9.11. Other Aspects

Not applicable.

9.12. Protection Of Human Subjects

9.13. Patient Information

This study involved data that was anonymized and structured and contained no patient personal information. The National Board of Health and Welfare (Socialstyrelsen) performed the register linking. For this study, all patient data were completely de-identified.

9.14. Patient Consent

As this study involved anonymized and structured data, which according to applicable legal requirements did not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer was not required.

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

Prior to the study start date, the relevant IRBs/IECs approved the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable). Any correspondence with the IRB/IEC will be retained. Copies of IRB/IEC approvals were forwarded to Pfizer.

9.16. Ethical Conduct of the Study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP).

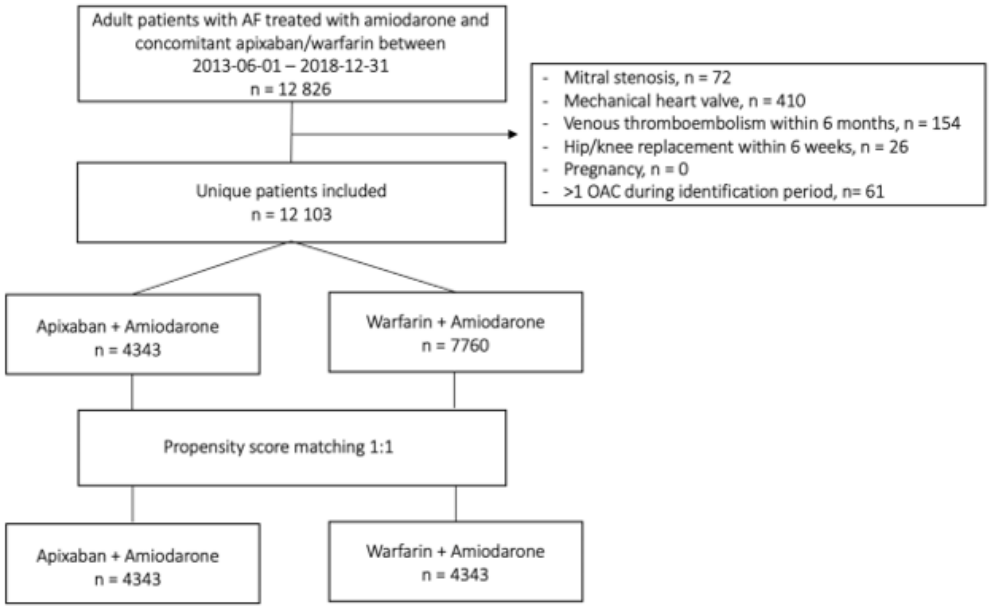
10. RESULTS

10.1. Main Results

Patient characteristics and comorbidities

After applying inclusion and exclusion criteria, 12,103 patients treated with amiodarone and concomitant warfarin or apixaban were included (4,343 [35.9%] patients treated with apixaban and 7,760 [64.1%] patients treated with warfarin) (Figure 2). Patients receiving warfarin tended to be older, more often male and with higher occurrence of heart failure, myocardial infarction and ischemic stroke than those treated with apixaban. Patients treated with apixaban had more often a history of cancer and prior intracerebral hemorrhages (Supplementary Table 4). After propensity score matching, 8,686 patients remained in the study (4,343 [50.0%] treated with apixaban and 4,343 [50.0%] treated with warfarin) (Figure 1). Balance in baseline characteristics in relation to oral anticoagulant treatment after propensity score matched cohort was achieved for most variables (Table 3).

Figure 2. Consort Diagram



Abbreviations: AF = atrial fibrillation. OAC = oral anticoagulants

Table 3. Baseline Characteristics in the Propensity Score Matched Cohort

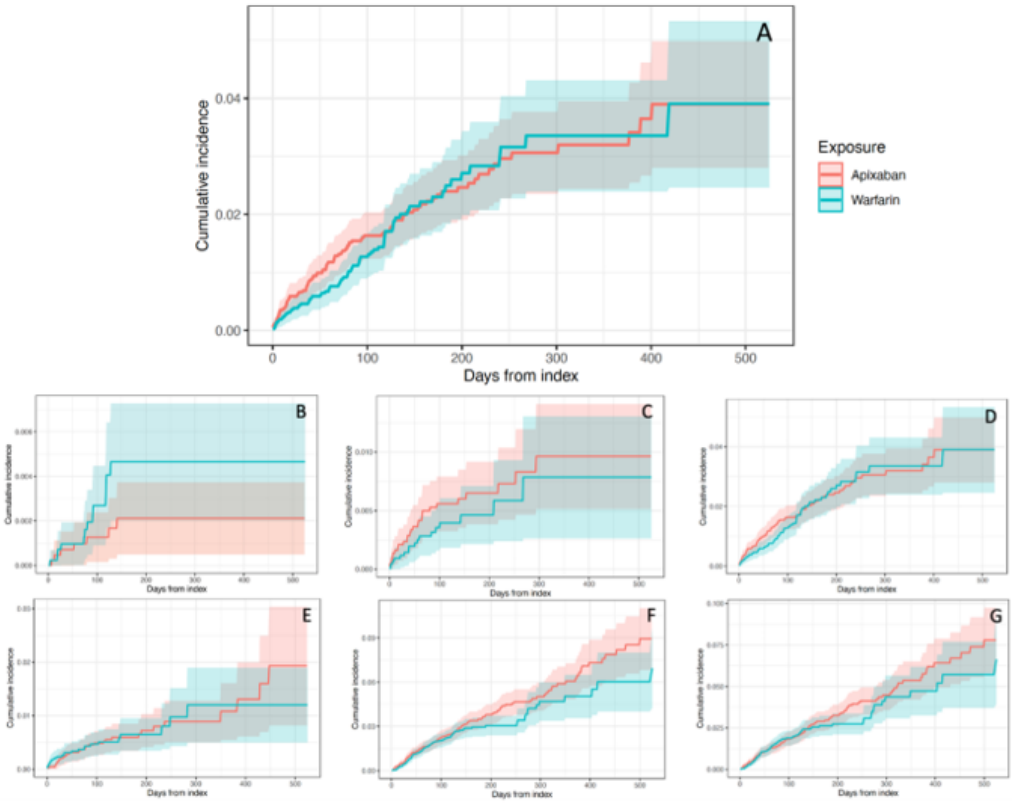
Characteristic	Apixaban (n = 4 343)	Warfarin (n = 4 343)	P-value
Demographics			
Age (years), median (IQR)	71.0 (63.5 - 77.1)	70.7 (63.3 - 77.3)	0.95
Sex, male, n (%) [missing]	2 723 (66.2%) [230]	2 844 (66.6%) [75]	0.69
Comorbidities, n (%)			
Diabetes mellitus	797 (18.4%)	797 (18.4%)	1.0
Hypertension	2 558 (58.9%)	2 587 (59.6%)	0.54
Prior stroke (any)	270 (6.2%)	261 (6.0%)	0.72
Prior ischemic stroke	243 (5.6%)	241 (5.5%)	0.96
Prior unspecified stroke	15 (0.4%)	15 (0.4%)	1.0
Prior TIA	134 (3.1%)	147 (3.4%)	0.47
COPD	333 (7.7%)	316 (7.3%)	0.51
Asthma	258 (5.9%)	252 (5.8%)	0.82
Heart failure	1 756 (40.4%)	1 787 (41.1%)	0.51
Prior myocardial infarction	888 (20.4%)	913 (21%)	0.53
Prior PCI	457 (10.5%)	487 (11.2%)	0.32
Prior CABG	451 (10.4%)	482 (11.1%)	0.30
Peripheral arterial disease	278 (6.4%)	278 (6.4%)	1.0
Prior systemic embolism	26 (0.6%)	32 (0.7%)	0.51
Prior pulmonary embolism	53 (1.2%)	78 (1.8%)	0.035
Chronic kidney disease	277 (6.4%)	348 (8.0%)	0.0037
Renal dialysis	2 (0.05%)	12 (0.3%)	0.016
Liver disease	41 (0.9%)	26 (0.6%)	0.086
Dementia	29 (0.7%)	21 (0.5%)	0.32
Prior major bleeding	429 (9.9%)	430 (9.9%)	1.0
Cancer (within last 3 years)	282 (6.5%)	284 (6.5%)	0.97
Apixaban dosage, n (%)			
5.0 mg twice daily	3 691 (85.0%)	-	-
2.5 mg twice daily	652 (15.0%)	-	-
Comedication (within last 6 months), n (%)			
Proton pump inhibitors	1 409 (32.4%)	1 372 (31.6%)	0.41
ACE inhibitors	1 677 (38.6%)	1 801 (41.5%)	0.0071
Angiotensin II antagonists	1 528 (35.2%)	1 466 (33.8%)	0.17
Beta blockers	4 049 (93.2%)	3 858 (88.8%)	<0.0001
Calcium channel antagonists	1 140 (26.2%)	1 140 (26.2%)	1.0
NSAID	267 (6.1%)	194 (4.5%)	0.00057
Statins	1 940 (44.7%)	2 068 (47.6%)	0.0063
Aspirin	1 098 (25.3%)	1 081 (24.9%)	0.69
Clopidogrel	266 (6.1%)	269 (6.2%)	0.93
Prasugrel	4 (0.1%)	4 (0.1%)	1.0
Ticagrelor	72 (1.7%)	78 (1.8%)	0.68
LMWH	91 (2.1%)	94 (2.2%)	0.88

Continuous variables are presented with medians (interquartile range [IQR]) and categorical as numbers (%). Treatment groups compared with Kruskal Wallis test and Chi square test as appropriate. Numbers within square brackets indicate number of missing values.
Abbreviations: ACE = angiotensin-converting enzyme. CABG = coronary artery bypass graft. COPD = chronic obstructive pulmonary disease. LMWH = low-molecular-weight heparin. PCI = percutaneous coronary intervention. TIA =transient ischemic attack.

Major Bleeding

The median follow-up was 4.4 months and with a total of 172 events for the primary endpoint of major bleeding. The incidence rate of major bleeding events was 4.3/100 patient years- for patients treated with apixaban + amiodarone and 4.5/100 patient years- for patients treated with warfarin + amiodarone (Figure 3-Figure 4). No statistical difference was observed for major bleeding when comparing apixaban + amiodarone versus warfarin + amiodarone (HR 1.03; 95% CI 0.76 – 1.39). Neither were there any significant differences for the secondary separate bleeding outcomes including gastrointestinal bleeding (HR 1.28; 95% CI 0.71 – 2.29), intracranial bleeding (HR 0.42; 95% CI 0.17 – 1.03) and other bleeding events (HR 1.07; 95% CI 0.74 – 1.56) (Figure 3-Figure 4).

Figure 3. Kaplan Meier Plots for (A) Major Bleeding, (B) Intracranial Bleeding, (C) Gastrointestinal Bleeding, (D) other Bleeding (eg, Pulmonary or Urogenital Bleedings), (E) Stroke or Systemic Embolism, (F) All-cause Mortality and (G) Cardiovascular Mortality



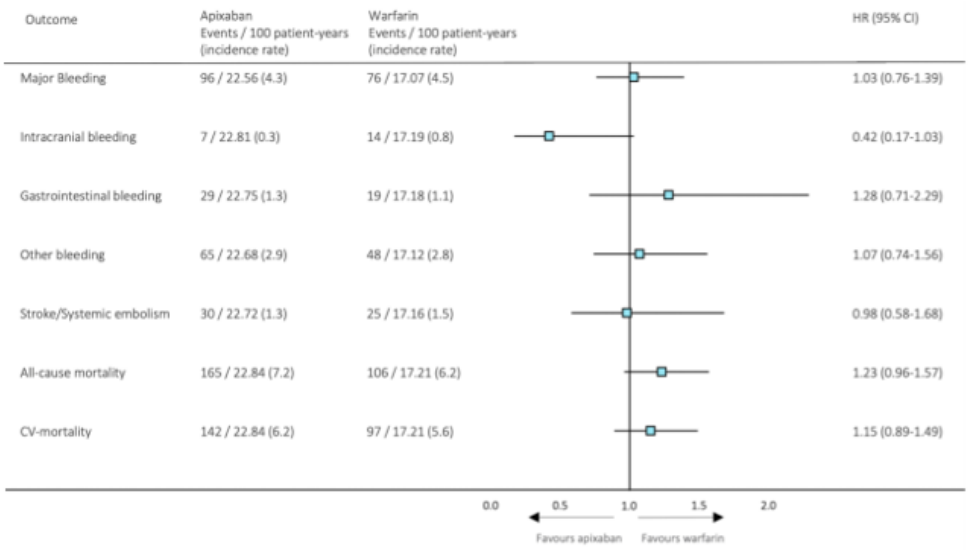
Stroke and Systemic Embolism

The exploratory outcome of stroke and systemic embolism occurred at an incidence rate of 1.3 and 1.5/100 patient-years in the apixaban + amiodarone and the warfarin + amiodarone group, respectively. No significant difference was observed when comparing the treatment strategies (HR 0.98; 95% CI 0.58-1.68).

All-cause Mortality and CV Mortality

The incidence rate of the exploratory outcome all-cause mortality was 7.2 and 6.9/100 patient-years for patients treated with apixaban + amiodarone versus warfarin + amiodarone, respectively. There was no significant difference in rates of all-cause mortality associated with apixaban + amiodarone compared to warfarin + amiodarone (HR 1.23; 95% CI 0.96 – 1.57). The exploratory outcome CV mortality occurred at an incidence rate of 6.2 and 5.6/100 patient-years in the apixaban + amiodarone and the warfarin + amiodarone group, respectively. No significant difference in CV mortality was observed when comparing apixaban + amiodarone versus warfarin + amiodarone (HR 1.15; 95% CI 0.89 – 1.49).

Figure 4. Outcomes in the Propensity Score Matched Cohort



Abbreviations: CV = cardiovascular. HR = hazard ratio. CI = confidence interval

Sensitivity analysis

In a sensitivity analysis, only matched apixaban and warfarin naïve patients were included (n = 2,066). No significant difference was observed for the primary endpoint of major bleeding in the OAC naïve propensity score matched cohort when comparing apixaban + amiodarone versus warfarin + amiodarone (HR 1.24; 95% CI 0.71 – 2.16).

11. DISCUSSION

This nationwide cohort study, including 8,686 propensity score matched patients showed no significant difference regarding major bleeding events in patients with AF treated with amiodarone in combination with apixaban versus warfarin.

Amiodarone is an antiarrhythmic drug utilized in patients with AF and is metabolized in the liver.[5,6] It is well known that amiodarone interacts with the pharmacokinetics of OACs, including apixaban and warfarin.[7,8] Thus, it is important to study the benefits and risks associated with different OAC combinations in patients treated with concomitant amiodarone. Our finding of a similar risk of major bleeding associated with apixaban versus warfarin in patients treated with amiodarone aligns with a few prior small observational studies of AAD (amiodarone, sotalol, flecainide, dronedarone, propafenone, dofetilide) and contemporary treatment with apixaban and warfarin.[9,10] The findings also align with reports from systematic reviews which included data from both observational studies and subgroup analysis of novel oral anticoagulants (NOAC) trials.[11] However, in a subgroup analysis of the ARISTOTOLE trial, specifically comparing apixaban versus warfarin in patients treated with concomitant amiodarone, apixaban was associated with lower rates of major bleeding (HR 0.61; 95% CI 0.39 – 0.96).[1] The differences in the findings from our study and the subgroup analysis from the ARISTOTLE trial might be explained by the difference in study design, remaining confounders not adjusted for, the diverse definitions of major bleeding implemented by different studies and the larger sample size and the inclusion of real-life non-selected patients in the current study.

In this study, there was a non-significant numerically lower rate of intracranial bleeding with apixaban versus warfarin in patients treated with amiodarone. Similar findings have been reported in observational studies of dronedarone with concomitant use of apixaban and warfarin.[12] Also, the ARISTOTLE trial reported that the risk for intercranial bleeding in patients on apixaban versus warfarin was statically lower with or without amiodarone.[1] In contrast to the current study, earlier studies have reported higher rate of gastrointestinal bleeding with other NOACs other than apixaban compared to warfarin.[11,13,14]

Another finding in our study was a numerically higher risk of all-cause mortality with apixaban compared with warfarin in patients treated with amiodarone. However, this has not been observed in prior subgroup analysis from NOAC trials or in systematic reviews in which apixaban compared to warfarin in amiodarone treated patients was associated with an equal or lower risk of all-cause mortality.[1] Explanations for this observation could be residual confounding and that patients treated with warfarin in the current study were, despite propensity score matching, more likely to receive concomitant treatment with cardioprotective drugs such as angiotensin-converting enzyme (ACE) inhibitors and statins, which could partially explain the slightly lower numerical rate of all-cause mortality in warfarin treated patients.[15,16]

Warfarin has multiple interactions with food and other medication, mainly due to the complete hepatic metabolization through the CYP enzymes (primarily CYP1A2, CYP2C9 and CYP3A4).[17] Known interactions between other medications are fewer with apixaban than warfarin, but still present. Apixaban is partly metabolized by the CYP3A4 enzyme but is also eliminated through the P-glycoprotein (gp) efflux transporters, enabling renal clearance combined with gastrointestinal and hepatobiliary drug excretion.[6] Amiodarone is a moderate inhibitor of the CYP2C9 and CYP3A4 enzymes and the P-gp transporter with the ability to increase the plasma concentration of both apixaban and warfarin.[5,17,18] In the ARISTOTLE trial, apixaban was superior to warfarin in preventing stroke or systemic embolism and caused less bleeding.[19] A more extensive interaction between apixaban and amiodarone may partially explain the findings in the present study, in which apixaban versus warfarin when combined with amiodarone was associated with a similar risk of major bleeding. Still, the findings in the present study suggests that apixaban is a safe oral anticoagulant in AF patients treated with amiodarone.

The recommendations from the US FDA and the European EMA include dose reduction recommendations for warfarin in patients that require concomitant amiodarone.[5,6] While our study confirms the safety of apixaban in patients treated with amiodarone, future studies could explore plasma levels of apixaban in patients treated with amiodarone to fill some knowledge gaps. In clinical practice, the duration and dosage of amiodarone should be kept as short or low as possible to decrease the risk of amiodarone-associated side-effects and potential interactions with apixaban.

The main strength of the current study was the large sample size representing real-world patients nationwide with no loss to follow-up. The Swedish national registries also provide unique opportunities to collect data and to combine registries, minimizing missing data. For estimating medical therapy over time, the National Prescribed Drug Register was utilized. However, adherence to prescribed and collected medication cannot be ascertained. Due to the observational design of the study no evidence of causation could be established, and the definition of major bleeding was based on ICD-10 codes not defined by the International Society of Thrombosis and Hemostasis (ISTH). Although the definition of major bleeding used in this study has been validated, no clinical event adjudication was made.[14] Another limitation of the study was the short follow-up. Due to the extracardiac toxicity of amiodarone, the treatment duration is often kept short, resulting in most patients only receiving short amiodarone prescriptions. Further limitations include confounding factors and a potential selection bias despite propensity score matching. Lastly, the primary outcome was a composite endpoint where patients were censored at the time of an event leaving room for competing risk.

11.1. KEY RESULTS

Not applicable.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involved data that existed as structured data at the time the study started.

In these data sources, individual patient data were not retrieved or validated, and it was not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) could not be met.

13. CONCLUSIONS

In real-life patients with AF treated with apixaban versus warfarin and with concomitant use of amiodarone, there were no significant differences in risk of major bleeding. Thus, apixaban appears to be at least as safe as warfarin in terms of major bleeding in patients with AF concomitantly treated with amiodarone. Also, the absolute rate of intracranial bleeding was lower among patients treated with apixaban versus warfarin, although not reaching statistical significance.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results were submitted for publication in peer reviewed- journals.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant was aware of any new information which might have influenced the evaluation of the benefits and risks of a Pfizer product, Pfizer would have been informed immediately.

COMMUNICATION OF ISSUES

No event of any prohibition or restriction was imposed (eg, clinical hold) by any applicable competent authority in any area of the world, nor was the Investigator aware of any new information which might have influenced the evaluation of the benefits and risks of a Pfizer product. Otherwise, Pfizer would have been informed immediately.

15. GENERALIZABILITY

Not applicable.

16. OTHER INFORMATION

Not applicable.

16.1. Other Analyses

As this study does not involve data subject to privacy laws, according to applicable legal requirements, obtaining informed consent from patients by Pfizer was not required.

16.2. Adverse Adverse Events/Adverse Reactions

Not applicable.

17. REFERENCES

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18. LIST OF SOURCE TABLES AND FIGURES

Not applicable.

19. LIST OF TABLES

20. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
Number 1	Section 1	19 Sep 2023	Abstract: *Major bleeding in patients with atrial fibrillation treated with apixaban versus warfarin in combination with amiodarone: the APIXAMIO study Rheumatoid Arthritis.*

APPENDIX 1. SIGNATURES

APPENDIX 2.1. PROTOCOL

APPENDIX 2.2. PACL (Not applicable)

APPENDIX 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

APPENDIX 3.1. LIST OF INVESTIGATORS BY COUNTRY (Not applicable)

APPENDIX 3.2. LIST OF INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB) AND CORRESPONDING PROTOCOL APPROVAL DATES (Not applicable)

APPENDIX 4. STATISTICAL ANALYSIS PLAN

APPENDIX 5. SAMPLE CASE REPORT FORM (CRF) / DATA COLLECTION TOOL (DCT) (Not applicable)

APPENDIX 6: SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD) (Not applicable)

APPENDIX 7. LIST OF SUBJECT DATA LISTINGS (Not applicable)

APPENDIX 7.1 WITHDRAWN SUBJECTS (Not applicable)

APPENDIX 7.2 PROTOCOL DEVIATIONS (Not applicable)

APPENDIX 7.3 SUBJECTS EXCLUDED FROM ANALYSIS (Please see APPENDIX 8 for STUDY RESULTS/STATISTICAL RESPORT)

APPENDIX 7.4 DEMOGRAPHIC DATA (Please see APPENDIX 8 for STUDY RESULTS/STATISTICAL RESPORT)

APPENDIX 7.5 MEDICATION/TREATMENT DATA (Please see APPENDIX 8 for STUDY RESULTS/STATISTICAL RESPORT)

APPENDIX 7.6 ENDPOINT DATA (Please see APPENDIX 8 for STUDY RESULTS/STATISTICAL RESPORT)

APPENDIX 7.7 ADVERSE EVENTS (Not applicable)

APPENDIX 7.8 LABORATORY LISTINGS (Not applicable)

APPENDIX 8. ADDITIONAL DOCUMENTS (STUDY RESULTS/STATISTICAL REPORT)