NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	The use of NOAC for atrial fibrillation in patients after biologic valvular replacement or valvuloplasty.
Protocol number	B0661136
Protocol version identifier	1
Date	06 December 2019
EU Post Authorization Study (PAS) register number	EUPAS31606
Active substance	Warfarin-B01AA03 Dabigatran-B01AE07 Rivaroxaban-B01AF01 Apixaban-B01AF02 Edoxaban-B01AF03
Medicinal product	Waran® - warfarin Pradaxa® - dabigatran Xarelto® - rivaroxaban Eliquis® - apixaban Lixiana® - edoxaban.
Product reference	EU/1/11/691/001-015
Procedure number	EMEA/H/C/002148
Marketing Authorization Holder(s) (MAH)	Bristol-Myers Squibb/Pfizer European Economic Interest Group (EEIG)
Joint PASS	No

Research question and objectives	*Research question:* Describe the patterns of OACs and outcomes for patients with AF after biological valve surgery, transcatheter valve intervention or after valvuloplasty. *Main objectives:* 1. To create descriptive data on NOAC (and separately for each NOAC) and warfarin treatment in patients with AF after biological valve surgery, transcatheter valve intervention or after valvuloplasty 2. To assess the feasibility, with respect to data quality, crude event counts by type of OAC and power estimation, to conduct a comparative analysis between apixaban and warfarin using the specified data. 3. To evaluate the association between apixaban versus warfarin treatment and the combination of all-cause death,-stroke (ischemic and hemorrhagic)/systemic embolization and major bleeding from 3 months post intervention to the end of follow up. 4. To evaluate the association between apixaban versus warfarin treatment and the combination of all-cause death, stroke (ischemic and hemorrhagic)/systemic embolization and major bleeding from hospital discharge post intervention to the end of follow up. 5. To evaluate the association between apixaban versus warfarin treatment on the separated endpoints, such as all-cause death, ischemic stroke, systemic embolization and myocardial infarction, major bleeding, gastrointesitinal bleeding, urogenital bleeding, hemorrhagic stroke and intracranial bleeding from hospital discharge post intervention and from 3 months post intervention.
Country(-ies) of study	Sweden
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial fibrillation
ATC	Anatomic Therapeutic Chemical classification system
ICD	International Statistical Classification of Diseases and Related Health Problems
NOAC	Non-vitamin K oral anticoagulants
NPR	National Patient Register
OAC	Oral anticoagulants
PASS	Post Authorization Safety Study
SAP	Statistical Analysis Plan
TAVI	Transcatheter aorta valve intervention
UCR	Uppsala Research Center

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title

The use of NOAC for atrial fibrillation in patients after biologic valvular replacement or valvuloplasty

Version and date: 1.0, 06 Dec 2019

Main author

Christina Christersson, MD, PhD; Uppsala University; Department of Medical Sciences, Uppsala; Sweden

Rationale and background

Non-vitamin K oral anticoagulants (NOACs) as primary prevention of stroke in atrial fibrillation (AF) is well established and is given high priority in the current guidelines and is recommended over warfarin as the first choice of treatment. However, patients with valvular AF have been excluded from randomized trials and the registered indications for treatment therefore exclude patients with valvular AF.

The spectrum of valvular disease is broad, including native as well as corrected valvular diseases. In patients with AF and native valvular disease, a recent meta-analysis showed NOACs (i.e., Factor Xa-inhibitors) to be superior to warfarin in reducing stroke or systemic embolism. Apixaban and edoxaban were also associated with lower rates of major bleeding than warfarin.

The majority of the patients with valvular disease that need intervention are treated with biological valve prosthesis including open heart surgery or transcatheter valve interventions. In valvular regurgitation lesions, valvular repair techniques including valvuloplasty is an alternative if the anatomy is suitable.

The guidelines for antithrombotic treatment after valve surgery are based on expert recommendations due to lack of appropriately sized randomized clinical trials. If the patient has other indications for anticoagulant treatment, e.g. AF, oral anticoagulant treatment is recommended. Patients with AF and concomitant valvular disease are often older, have more comorbidities and higher CHA_2DS_2-VASc score compared to patients without valvular disease. The guidelines recommend warfarin over NOACs in patients with AF and prosthetic valves.

Taken together, there is scientific value in further evaluating NOAC treatment in patients with valve interventions. There is also a clinical need to clarify whether NOAC could be an alternative to warfarin in this group of patients and if the time-point from intervention, surgery or transcatheter aorta valve intervention (TAVI) influences the clinical outcomes. The current study will include all patients in Sweden who have undergone a valvular intervention with biological prosthesis or valvuloplasty and will represent a real-world group of patients with indication for anticoagulant treatment.

Research question

Describe the patterns of OACs and outcomes for patients with AF after biological valve surgery, transcatheter valve intervention or after valvuloplasty.

Main objectives:

1. To create descriptive data on NOAC (and separately for each NOAC) and warfarin treatment in patients with AF after biological valve surgery, transcatheter valve intervention or after valvuloplasty.

2. To assess the feasibility, with respect to data quality and power estimation, to conduct a comparative analysis between apixaban and warfarin using the specified data.

3. To evaluate the association between apixaban versus warfarin treatment and the combination of all-cause death, stroke (ischemic and hemorrhagic), systemic embolization and major bleeding from 3 months post intervention.

4. To evaluate the association between apixaban versus warfarin treatment and the combination of all-cause death, stroke (ischemic and hemorrhagic), systemic embolization and major bleeding from hospital discharge post intervention to the end of follow-up.

5. To evaluate the association between apixaban versus warfarin treatment on separated endpoints: all-cause death, ischemic stroke, systemic embolization and myocardial infarction, major bleeding, gastrointesitinal bleeding, urogenital bleeding, hemorrhagic stroke and intracranial bleeding from hospital discharge post intervention and from 3 months post intervention.

Study design

A retrospective registry-based observational study using data from the SWEDEHEART, and Swedish administrative health databases.

Population

All patients treated with either biological valve surgery, transcatheter valve intervention, or valvuloplasty in Sweden during 2010-2016, identified through SWEDEHEART, excluding patients with mechanical valves.

Variables

Exposure: Treatment with NOAC or warfarin

Outcomes:

Primary:

The combination of all-cause death, stroke (ischemic and hemorrhagic), systemic embolization and major bleeding.

Secondary:

The separate endpoints; all-cause death, ischemic stroke, systemic embolization, myocardial infarction, major bleeding, gastrointestinal bleeding, urogenital bleeding, hemorrhagic stroke and intracranial bleeding

Data sources

- SWEDEHEART national quality register: all patients treated with either biological valve surgery, transcatheter valve intervention, or valvuloplasty in Sweden during 2010-2016.
- National Patient Register: medical history during the last three years prior to the intervention and during follow-up after the index intervention (2007-2017)
- National Cause of Death Register: mortality data, including cause of death (2010-2018).
- National Prescribed Drug Register: Dispensing data and dosage for prescribed pharmaceuticals (2009-2017).

Study size

After exclusion of patients with mechanical valves, the estimated number of patients included in the study cohort is 15 511. The proportion patients with AF is estimated to 30% in the group planned for open heart surgery and 40% in the group planned for TAVI. The estimated number of patients with AF in the study cohort is approximately 5000. During follow-up the proportion of patients with AF will increase.

Data analysis

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

Milestones

- Ethical approval obtained: Q4 2018
- Application sent to register holder(s) National Board of Health and Welfare/SWEDEHEART: Q1 2019

- The study protocol will be finalized and approved by Pfizer: Q4 2019
- Start of data collection: August 2019
- End of data collection: Q4 2019
- Preliminary study report: Q4 2019
- Final study report: Q4 2019

5. AMENDMENTS AND UPDATES

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

6. MILESTONES

Milestone	Planned date
Application to Independent Ethics Committee	November 2018
Application sent to register holders (National Board of Health and Welfare/ Swedeheart)	March 2019
Registration in the EU PAS register	30 November 2019
Final study protocol	Q4 2019
Start of data collection	August 2019
End of data collection	Q4 2019
Preliminary study report	Q4 2019
Final study report	Q4 2019

7. RATIONALE AND BACKGROUND

NOAC as primary prevention of stroke in atrial fibrillation (AF) is well established. NOAC treatment is given high priority in the current guidelines and is recommended over warfarin as the first choice of treatment (1-3). However, patients with valvular AF were excluded from randomized trials on NOACs in patients with AF, and the registered indications for treatment hence exclude patients with valvular AF.

The spectrum of valvular disease is broad, including native as well as corrected valvular diseases. In a recent meta-analysis, NOACs were superior compared to warfarin in reducing stroke or systemic embolism in patients with AF and native valvular disease for prevention of stroke (4). Apixaban, edoxaban, and dabigatran, but not rivaroxaban, were also associated with lower rates of major bleeding than warfarin.

The majority of the patients with valvular disease that need intervention are treated with biological valve prostheses, including open heart surgery and transcatheter valve interventions (5). In regurgitation lesions, valve repair techniques including valvuloplasty is an alternative if the anatomy is suitable (6-8). The guidelines for antithrombotic treatment after valve surgery are based on expert recommendations and if the patient has other indications, oral anticoagulant treatment is recommended (5).

In patients with mechanical valve prostheses, one randomized trial comparing dabigatran and warfarin has been performed (9). The study included two categories of patients; i) patients included within 7 days after surgery with an aortic or mitral valve prosthesis, ii) patients with previous intervention (> 3 months) with a mechanical mitral prosthesis. The study was stopped prematurely due to a higher frequency of thrombosis and bleeding events in the group treated with dabigatran. NOAC treatment is therefore not recommended for patients with mechanical valve prostheses.

Patients with biological valve prostheses are considered to have a lower risk of valve thrombosis, even though recent data describe a higher incidence of subclinical leaflet thrombosis than previously known (10). However, further investigation on the clinical relevance of these findings is needed. Suboptimal oral anticoagulant treatment in AF patients has been described as a risk factor for valve thrombosis in patients with biological prostheses (11). No prospective randomized trial have evaluated the efficacy and safety of NOACs compared to warfarin in patients with AF treated with surgical biological valve prostheses or valvuloplasty. Recruitment of patients treated with transcatheter aortic valve intervention (TAVI) and an indication for OAC are ongoing in two randomized trials comparing NOAC versus warfarin (12-13).

Patients with AF and concomitant valvular disease are often older, have more comorbidities and higher CHA_2DS_2-VASc score compared to patients without valvular disease. The guidelines recommend warfarin before NOACs in AF patients with prosthetic valves and the American guidelines also include valvuloplasty in this recommendation, based on the design of previous randomized trials. In clinical trials evaluating NOACs in AF, only a minority of

patients (1.4-5.7%) had a history of valvular intervention before randomization. Based on these studies the European guidelines state that treatment with NOACs could not be recommended until more than 3 months has passed since intervention.

There is scientific value in further evaluating NOAC treatment in patients with valve interventions. There is also a clinical need to clarify whether NOACs could be an alternative to warfarin in this group of patients and if time from intervention influences the results. This study will include all patients in Sweden who have received a valvular intervention with biological prosthesis or valvoplasty and will represent a real-world group of patients with indication for anticoagulant treatment.

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

8. RESEARCH QUESTION AND OBJECTIVES

Research question:

Describe the patterns of OACs and outcomes for patients with AF after biological valve surgery, transcatheter valve intervention or after valvuloplasty.

Main objectives:

Step 1:

1. Create descriptive data on NOAC (and separately for each NOAC) and warfarin treatment in patients with AF after biological valve surgery, transcatheter valve intervention or after valvuloplasty.

Step 2:

2. To assess the feasibility, with respect to data quality, crude event counts by type of OAC and power estimation, to conduct a comparative analysis between apixaban and warfarin using the specified data.

Step 3:

3. To evaluate the association between apixaban versus warfarin treatment and the combination of all-cause death, stroke (ischemic and hemorrhagic), systemic embolization and major bleeding from 3 months post intervention to the end of follow up.

4. To evaluate the association between apixaban versus warfarin treatment and the combination of all cause-death, stroke (ischemic and hemorrhagic), systemic embolization and major bleeding from hospital discharge post intervention to the end of follow up.

5. To evaluate the association between apixaban versus warfarin treatment on the separated endpoints, such as all-cause death, ischemic stroke, systemic embolization and myocardial infarction, major bleeding, gastrointesitinal bleeding, urogenital bleeding, hemorrhagic stroke and intracranial bleeding from hospital discharge post intervention and from 3 months post intervention.

9. RESEARCH METHODS

9.1. Study design

Register-based observational study. The patient cohort will be identified using the SWEDEHEART national quality register and will include all patients treated with either biological valve surgery, transcatheter valve intervention, or valvuloplasty during 2010-2017 at discharge. Patients with mechanical valves will be excluded. For a schematic presentation of the study design, please see Figure 1.

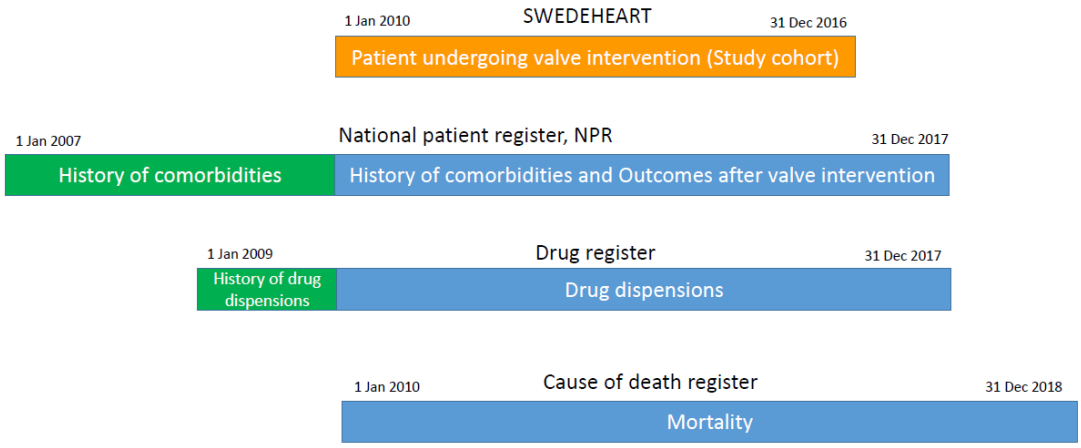


Figure 1. Schematic presentation of the study design.

9.2. Setting

The patient cohort will be identified using the SWEDEHEART national quality register and will include all patients treated with either biological valve surgery, transcatheter valve intervention, or valvuloplasty performed during 2010-2017. See separate statistical analysis plan (SAP) 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. > 18 years at discharge.

2. Valvular disease requiring valve surgery, transcatheter valve intervention, or valvuloplasty

3. Registred in SWEDEHEART for the index valve intervention

4. Atrial fibrillation/flutter registred in SWEDEHEART or in the National Patient Register (NPR) before index intervention or during follow-up.

9.2.2. Exclusion criteria

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

1. Treatment with a mechanical valve prosthesis

2. Prescription of more than one type of OAC at discharge

3. Death before discharge from the index valve intervention

9.3. Variables

A list of covariates with definition according to the ICD-10 and ATC coding systems has been included in the statistical analysis plan.

Covariates are defined by diagnoses, medication or other conditions observed or documented before or on index date. Endpoints are events that occurred after discharge from the index intervention. See separate SAP.

9.4. Data sources

Data from the following national registers will be extracted and linked:

- SWEDEHEART: The patient cohort will be identified using the SWEDEHEART national quality register and will include all patients treated with either biological valve surgery, transcatheter valve intervention, or valvuloplasty during 2010-2016.

- National Patient Register (NPR): Information on medical history during the last three years prior to the intervention and during follow-up will be collected from the NPR 2007-2017. The NPR will also be used to identify outcome events during follow-up after the index intervention.

- Cause of Death Register: Cause of death will be collected from the Cause of Death Register.

- Prescribed Drug Register: Information on expedited drugs the year before and during follow-up will be collected from the Prescribed Drug Register 2009-2017.

9.5. Study size

The estimated number of patients included in the study cohort is 15 511 after exclusion of patients with mechanical valves. The proportion of patients with AF is estimated to 30% in the group planned for open heart surgery and 40% in the group planned for transcatheter aortic valve intervention (TAVI). The estimated number of patients with AF in the study cohort is approximately 5000. During follow-up, the proportion of patients with AF will increase.

9.6. Data management

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

The study will be performed by associated professor Christina Christersson, researcher Gorav Batra, and professor Claes Held, all at the Department of Medical Sciences, Cardiology, Uppsala University and Uppsala Clinical Research Center (UCR) in collaboration with statisticians at UCR.

The linkage of registers will be performed by the National Board of Health and Welfare (Socialstyrelsen). All data will be completely de-identified for this study (secondary data collection, structured data analysis).

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.

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, including cox regression analysis. Full operational definition for each variable, and the analytic strategy, including variables for inclusion in the cox regression analysis are described in the SAP.

STEP 1

Objective 1

Descriptive statistics will be calculated for two sets of groups, where the patients either are split by the onset of AF or by which anticoagulant treatment was given (NOAC separated in

the different the different groups). The AF population is divided into AF prior to or during hospitalization for valvular intervention and new-onset AF after discharge. The population will also be described according to which OAC they were prescribed at discharge (NOAC, separately for apixaban and warfarin), during follow-up and a separate non OAC-treated group.

Description of exposures; % by total follow up time, patient years, treatment cross over during follow up in relation to antithrombotic treatment at baseline.

Cohort: The patient cohort is identified within the SWEDEHEART registry (Swedish cardiac surgery registry and SWENTRY) and includes all patients with biological valvular surgery, transcatheter valve intervention or valvuloplasty during the years 2010 – 2017. The group of interest in this cohort is patients with atrial fibrillation (AF), including both patients with known AF at the time of intervention and patients with AF obtained after intervention.

Methodology: Patients will be described overall and by exposure cohort. Continuous variables will be summarized using categories and/or means/medians as appropriate. Categorical variables will be summarized using frequencies and proportions.

STEP 2

Objective 2

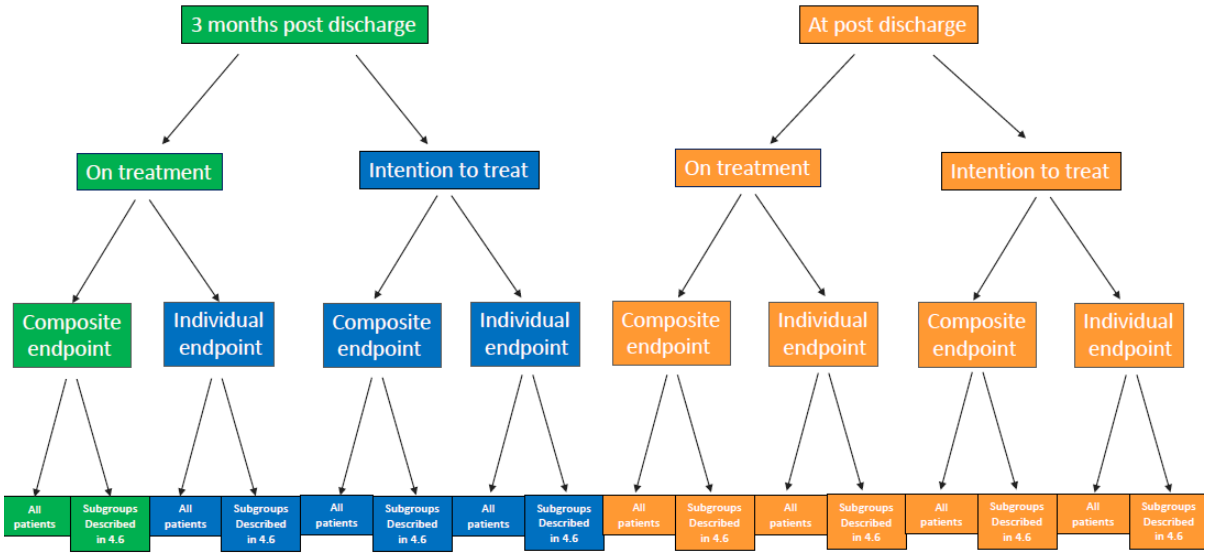
To assess the feasibility, with respect to data quality, crude event counts by type of OAC and power estimation, to conduct a comparative analysis between apixaban and warfarin using the specified data.

Cohort: Apixaban and warfarin treated patients from the cohort described above.

Methodology: To assess the feasibility of conducting comparative analyses, involving an assessment of raw event counts by type of OAC (apixaban and warfarin) and power calculations

STEP 3

Overview of the comparativeanalyses described in objective 3-5. The green boxes describe the main analysis.



Objective 3

To evaluate the association between apixaban versus warfarin treatment on the composite endpoint of all-cause death, stroke (ischemic and hemorrhagic), systemic embolization and major bleeding *from 3 months post intervention to* the end of follow up.

Cohort: Apixaban and warfarin treated patients from the cohort described above (Step 1).

Methodology: To compare the risk of outcome events across the study cohorts, time to event analysis will be undertaken, using adjusted Cox regression models for intention to treat and time-varying Cox regression models for on treatment analyses. Performed in all patients and in predefined subgroups described in the SAP 4.6

Objective 4

To evaluate the association between apixaban versus warfarin treatment on the composite endpoint of all-cause death, stroke (ischemic and hemorrhagic), systemic embolization and major bleeding *from hospital discharge post intervention* to the end of follow up.

Cohort: Apixaban and warfarin treated patients from the cohort described above (Step 1).

Methodology: To compare the risk of outcome events across the study cohorts, time to event analysis will be undertaken, using adjusted Cox regression models for intention to treat and time-varying Cox regression models for on treatment analyses. Performed in all patients and in predefined subgroups described in the SAP 4.6

Objective 5

To evaluate the association between apixaban versus warfarin treatment on the individual endpoints: all-cause death, ischemic stroke, systemic embolization and myocardial infarction, major bleeding, gastrointesitinal bleeding, urogenital bleeding, hemorrhagic stroke and intracranial bleeding *from hospital discharge post intervention* and *from 3 months post intervention.*

Cohort: Apixaban and warfarin treated patients from the cohort described above (Step 1).

Methodology: To compare the risk of outcome events across the study cohorts, time to event analysis will be undertaken, using adjusted Cox regression models for intention to treat and time-varying Cox regression models for on treatment analyses. Performed in all patients and in predefined subgroups described in the SAP 4.6

9.8. Quality control

All data used in the present study originates from national registers of very high coverage and quality previously published (14). Quality control will be performed continously during the data management and statistical analysis. 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. 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, including cox regression analysis. Full operational definition for each variable, and the analytic strategy, including variables for inclusion in the cox regression analysis are described in the SAP.

9.9. Limitations of the research methods

Given the retrospective observational study design, there are some limitations that have to be taken into consideration when interpreting the results. First, 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, and a major limitation for non-randomized registry studies is vulnerability to confounding by indication. More specifically; patients will not be randomized to the different treatment arms and we have no information regarding provider rationale for treatment choices. These factors might not be apparent from registry data and therefore not possible to adjust for. In order to minimize this effect, several relevant clinical variables will be taken

into account and adjusted for when assessing outcomes. Still, unknown and unmeasured confounders may exist, and the results should be interpreted with caution.

The assessment of drug exposure during follow up will not be as exact as in prospective randomized studies were pill counts are used. Purchase 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. Patients may stop taking a drug while still having more of it in supply. Drug exposure will be assessed by a combination of counting medicine possession ratios and intervals between purchases. As a sensitivity analysis, patients will therefore be analysed both according to the drug combination at baseline (in analogy with intention to treat) and with censoring when combination treatment is assumed to have stopped (in analogy with on treatment or per protocol analyses).

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.

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

The results will be presented at international conferences and submitted to international peer-reviewed journals for publication.

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. Jernberg T et al Heart 2010;96:1617-1621)

14. LIST OF TABLES

Not applicable.

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: The use of NOAC for atrial fibrillation in patients after biologic valvular replacement or valvuloplasty.

EU PAS Register® number: To be added
Study reference number (if applicable): B0661136

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	n/a
1.1.4 Interim report(s) 12/11-19	☒	☒	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

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Comments:

Section 2: Research question		Yes	No	N/A	Section Number
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	n/a
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4,9.1-9.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	n/a
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	n/a

Comments:

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.6
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

3.5: 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.

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.1-9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1-9.2
	4.2.2 Age and sex	☒	☐	☐	9.1-9.2
	4.2.3 Country of origin	☒	☐	☐	9.1-9.2
	4.2.4 Disease/indication	☒	☐	☐	9.1-9.2

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Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.5 Duration of follow-up	☒	☐	☐	9.1-9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1-9.2

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	SAP 2.2.5
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	n/a
5.3 Is exposure categorised according to time windows?	☒	☐	☐	SAP 2.2.5
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	SAP 2.2.5
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	n/a
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	~~SAP 4~~ 8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	3, SAP 4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	n/a
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	~~☒~~	☐	☒	n/a

12/11-19

12/11-19

Comments:

6.4 Treatment and disease management for this subgroup of patients.

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	~~☒~~	☐	~~n/a~~ 9.7 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	~~☒~~	☐	~~n/a~~ 9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	~~☒~~	☐	~~n/a~~ 9.9

12/11-19

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	SAP 4.6

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	n/a
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	n/a
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☒	☐	n/a
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	SAP 2.2.5
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	SAP 3.1
9.3.3 Covariates and other characteristics?	☒	☐	☐	SAP 3.2
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9,4, 9.6, SAP 2.2

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Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	SAP 4
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	SAP 4.1
10.4 Are stratified analyses included?	☒	~~☒~~	☐	~~n/a~~ SAP 4.1.2, 4.3
10.5 Does the plan describe methods for analytic control of confounding?	☒	~~☒~~	☐	~~n/a~~ SAP 4.3 12/11-19
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	n/a
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	SAP 4.5
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	~~SAP 4.6~~ 9.9 12/11-19

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	~~☒~~	☐	9.6 ~~n/a~~ 9.7
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	n/a

Comments:

11.3. Study results are reviewed by study team and Pfizer publication subcommittee

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	n/a
12.1.2 Information bias?	☐	☒	☐	n/a
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	n/a
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8

Comments:

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Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	n/a
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments: 12/11-19

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author(s) of the protocol: Christina Christersson, Angelo Modica

Date: 12/November/2019

Signature:

Signature:

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.