NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	**Non-interventional study describing direct costs related to anticoagulation treatment in patients with nonvalvular atrial fibrillation (NVAF) in secondary stroke prevention prescribed apixaban or warfarin treatment**
Protocol number	**B0661121**
Protocol version identifier	1.2
Date	5. November 2018
Active substance	B01AF02 apixaban
Medicinal product	**Eliquis**
Research question and objectives	To describe the direct costs related to warfarin/apixaban treatment during the first 6 months of the secondary stroke prevention in NVAF patients.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse events
AEM	adverse event monitoring
AF	atrial fibrillation
BMI	body-mass index
e-CRF	electronic case report form
EDP	exposure during pregnancy
FXa	coagulation factor Xa
IEC	Independent Ethics Committee
INR	international normalized ratios
IRB	Institutional Review Board
LSLV	last subject last visit
NIS	non-interventional study
NOAC	non-vitamin K antagonist oral anticoagulant
NVAF	non-valvular atrial fibrillation
SAE	serious adverse events
TIA	transient ischemic attack
VKA	vitamin K antagonists

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
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3. ABSTRACT

None.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	September 2018
Start of data collection	July 2020
End of data collection	September 2020
Final study report	November 2020

6. RATIONALE AND BACKGROUND

Patients with atrial fibrillation (AF) are at increased risk for stroke. AF is associated with a four to fivefold increase in risk of stroke and thromboembolic events, resulting in significant morbidity, mortality, and costs.[1,2] Stroke is the second most common cause of death and major cause of disability worldwide.[3] About 30% of strokes occur in individuals with a previous transient ischemic attack (TIA) or stroke[4], and more than 50% occur in individuals with previous vascular events of any kind.[5]

Warfarin is a highly effective treatment, reducing the risk of stroke by about two thirds, but its effectiveness in clinical practice is challenged by its variable dose response, drug-food and drug-drug interactions, need for frequent monitoring of international normalized ratios (INR), and associated risk of hemorrhage.[6] Bleeding complications are relatively frequent, and a high proportion of patients discontinues or receives suboptimal therapy in clinical practice.[7] In recent, carefully monitored trials, patients treated with warfarin spent only 63–68% of the time in the therapeutic INR range.[8] Warfarin is associated with bleeding and drug related hospitalizations relate to a narrow therapeutic window and difficulties in adjusting the dose. Among elderly patients (65 years and older) warfarin was the most common drug leading to drug related hospitalizations followed by insulins, oral antiplatelet agents, and oral hypoglycemic agents.[9]

Bleeding among patients on anticoagulant therapy often leads to cessation of anticoagulant treatment, which may increase the risk of subsequent thrombotic events. Termination of warfarin after a gastrointestinal bleed was shown in one study to increase the risk of death and thrombotic events.[10] In a real-world registry, patients who experienced serious bleeding had a threefold increase in the risk of thrombotic events even though the majority of patients did not permanently stop oral anticoagulation.[11]

Non-vitamin K antagonist oral anticoagulants (NOACs) that have emerged in recent years as alternatives to warfarin are proven to reduce these events, similar to or more than warfarin, with a similar or lower risk of hemorrhage.[14,15,16,17] Additionally NOACs have predictable effect without need for routine monitoring, and fewer food and drug interactions compared with vitamin K antagonists (VKA). Apixaban is a direct oral factor Xa inhibitor with rapid absorption, a 12-hour half-life, and 27% renal excretion.[19] In patients with AF and at least one additional risk factor for stroke, the use of apixaban, as compared with warfarin, significantly reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11%.[18] In the patients with AF who were not candidates for VKA treatment, apixaban was compared to aspirin (ASA) and showed significant reduction in rate of stroke and systemic embolism by 55% without increasing the risk of major bleeding.[15]

Real-world clinical observations are justifying that improved clinical profile of NOACs is translated to hard end-points in clinical practice. Favorable effectiveness and safety together with easiness of monitoring and improved adherence are generating important savings in cost of healthcare services. According to *Laliberté et al.* the NOACs´ (rivaroxaban) users have

significantly less AF-related hospitalization days than those patients who use warfarin.[20] Apixaban was found to be a cost-effective alternative to warfarin for stroke prevention in patients with AF in Sweden, Portugal as well as in the USA[21,22,24] and also (compared to warfarin) apixaban is a cost-saving medicine with significantly lower rates of stroke and major bleeding in a real-world nonvalvular atrial fibrillation (NVAF) population in the USA.[23,24] In the group of NOACs apixaban seems to be the most cost-effective alternative in comparison to rivaroxaban and dabigatran.[25,26]

NOACs are indicated for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [28]. When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a VKA as stated in guidelines of European Society of Cardiology (endorsed by Czech Society of Cardiology) [28].
Nonetheless NOACs were categorized as a second line treatment due to the restriction of SUKL (local regulatory authority) in Czech Republic and therefore Czech patients are primarily treated with warfarin (including patient post stroke/TIA) and NOACs treatment can be initiated only in case of defined contraindication. Czech Cardiology Society, Society of Ambulatory Specialist together with main Czech Public Insurance House (VZP) defined number of conditions where safe and efficacious anticoagulation therapy by VKA cannot be adequately ensured[29]. Prescription of NOACs as first line therapy is allowed in these defined situations [29]. One of the situations is described as higher sensitivity to warfarin. There are two variants of two genes, CYP2C9 and VKORC1, account for 30-50% of the variability in dosing of warfarin.[12] The prevalence of CYP2C9 (allele *1, *2 and *3) and VKORC1 (-1639 G and A alleles), and their combinations in Czech population was analyzed and about 30% of the Czech healthy subjects have genetically determined higher sensitivity to warfarin.[13]
Individuals with higher sensitivity to warfarin are eligible for first line NOACs treatment in secondary prevention of stroke.

Additionally there is no healthcare resource use (hospitalization days, outpatient visits, and clinical events) comparison of apixaban to warfarin available in the Czech Republic. The most intensive resource use is expected in the first 6 months after stroke, especially because of a high risk of the event recurrence. Considering that there are less outpatient visits, less monitoring needed and lower risk of the complications and adverse events expected with apixaban. Real-world data about the impact of different treatment strategies on healthcare resource use and costs are essential arguments for establishing the clinical value of new therapies.

In the light of this situation we have designed this study to compare the healthcare resource use in patients who use warfarin or apixaban in secondary stroke prevention as a first line therapy.

7. RESEARCH QUESTION AND OBJECTIVES

The primary objective of the study is:

- Description of direct costs related to warfarin/apixaban treatment during the first 6 months of the secondary stroke prevention in NVAF patients.

The secondary objectives of this study are:

- Comparison of direct costs related to warfarin/apixaban treatment during the first 6 months of the secondary stroke prevention in NVAF patients;
- Number of hospitalization days in the first 6 months of the treatment;
- Number of ischemic/hemorrhagic strokes in the first 6 months of the treatment;
- Number of ischemic events in the first 6 months of the treatment;
- Number of major/minor hemorrhagic events in the first 6 months of the treatment;
- Mortality rates in both cohorts;
- Number and costs of medical procedures directly related to the treatment in the first 6 months (visits, hospitalizations, labs, diagnostics, etc.);
- Overall safety (adverse events) of the treatment.

8. RESEARCH METHODS

8.1. Study design

This is a double arm, non-interventional, single-center retrospective study according to Czech legal definitions (Law 378/2007 Sb.). For the description of the direct costs related to warfarin/apixaban treatment, retrospective data will be used for both, the warfarin treatment arm and the apixaban treatment arm.

The study follows two cohorts of NVAF patients, who used either warfarin or apixaban as a secondary stroke/TIA prevention.

The data to be collected retrospectively:

- Consecutive data of the 6 months after the first prescription of warfarin/apixaban (indicated as a secondary stroke/TIA prevention).

Considering the retrospective design of data collection, the non-interventional study will not impose any additional procedures, assessments or changes to the routine management of subjects. Data for the study will be obtained from clinical practice records and transcribed to an anonymous electronic case report form (e-CRF).

8.2. Setting

In total, this non-interventional study follows the population of 240 patients with nonvalvular atrial fibrillation. From 240 NVAF patients, 120 patients are treated with warfarin and 120 patients are treated with apixaban.

The study will follow the period of 6 months after the prescription of warfarin or apixaban for the secondary stroke/TIA prevention.

The data will be collected retrospectively from clinical practice hospital records.

It´s expected that the data will be collected within 3 months from the start of the study – the data collection will be closed as soon as there are 120 patients enrolled in each study arm. If there are not 120 patients enrolled in each study arm after 3 months of the data collection, the period can be prolonged up to 6 months from the start of the study.

Requirements for the center´s eligibility are as followed: center able to genetically determine patients´ higher sensitivity to warfarin; neurologists, who work in cerebrovascular center in a hospital; satisfactory experience in the care of patients with NVAF and treatment with warfarin and NOAC; sufficient number of patients with NVAF diagnosis fulfilling eligibility criteria.

8.2.1. Inclusion criteria

The data will be collected for patients who have met all of the following inclusion criteria:

1. Diagnosis of non-valvular atrial fibrillation (NVAF);
2. New initiation of anticoagulation therapy (apixaban or warfarin) due to the ischemic event (stroke/TIA) meaning patients previously not anticoagulated due to diagnosis of NVAF;
3. Indication to anticoagulation therapy as a secondary stroke prevention within 7 to 30 days after the stroke/TIA event;
4. Apixaban arm: genetically determined higher sensitivity to warfarin;
5. Patients whose status allowed oral treatment with apixaban/warfarin;
6. Age ≥ 18;
7. Access to patient´s records of the first 6 months of the warfarin/apixaban treatment.

8.2.2. Exclusion criteria

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

8. Diagnosis of valvular disease;
9. Treatment with other anticoagulants in previous 6 months due to other the NVAF indication;
10. Treatment or prophylaxis of deep vein thrombosis or pulmonary embolism;
11. Contraindications according SmPC of Eliquis.

8.3. Variables

Table 1: Table of variables

Variable	Role	Data source(s)	Operational definition
Age, Sex, BMI, date of index event (stroke/TIA diagnosis), date of indication to warfarin/apixaban treatment (index date)	Demographic data	Medical records	Specified in e-CRF
CHA2-DS2-Vasc score, HAS-BLED score	Outcome	Medical records	Specified in e-CRF
Therapy after index event, prior to warfarin/apixaban treatment	Exposure	Medical records	Specified in e-CRF
Warfarin/apixaban therapy information (dosage; number of INR measurements in warfarin arm)	Exposure	Medical records	Specified in e-CRF
Number and type of resource use during the first 6 months of warfarin/apixaban treatment (outpatient visits, diagnostic procedures, labs, medication, hospital admissions)	Outcome	Medical records	Specified in e-CRF
Amount, type, severity and cost of ischemic events	Outcome	Medical records	Specified in e-CRF

Amount, type, severity and cost of major/minor hemorrhagic events	Outcome	Medical records	Specified in e-CRF
Adverse events	Outcome	Medical records	Specified in e-CRF

Index date = The index date will be the first date of OAC prescription indicated for secondary stroke/TIA prevention.
Index event = The index event will be the first stroke/TIA event based on which the OAC treatment will be initiated.
Index event date = The index event date will be the date of first stroke/TIA event based on which the OAC treatment will be initiated
Therapy after index event, prior to warfarin/apixaban treatment (Aspirin, clopidigrel, Trombolytics (rhu-tPA - alteplase, urokinase), Anticoagulans (heparin, heparinoids), other)

8.4. Data sources

The data will be obtained retrospectively from hospital medical records, this study will not impose any additional procedures, assessments or changes to the routine management of subjects. The data will be transcribed to an anonymous e-CRF.

8.5. Study size

The study will be descriptive in nature. No sample size was statistically determined. Based on experience of experts on anticoagulant treatment the data from 120 patients per study arm can be collected.

8.6. Data management

The data will be transcribed by the physician to an anonymous electronic Case Report Form from the patient´s medical records. The data will be obtained retrospectively and no patient data identification will be possible.

8.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

8.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

8.7. Data analysis

The statistical analyses will be descriptive and exploratory. Given the nature of the study, which is exploratory, it is not designed to confirm or reject predetermined hypotheses.

Categorical outcomes will be summarized by the number and percentage in each category. Continuous outcomes will be summarized by mean, standard deviation, median, minimum and maximum values.

All analyses will be based on the full analysis set, comprising all subjects enrolled into the study.

The paired tests will be applied in the detailed analyses. Relevant endpoints will be compared using the differences in mean / median or proportion. Statistical significance will be assessed at a significance level of 0.05. All statistical analyses will be conducted using STATA version 13.1.

Table 2: Table of descriptive analyses

Variable	Categorical outcome	Continuous outcome
Age		X
Sex	X	
Body height, weight, BMI		X
Period between stroke/TIA and start of secondary stroke prevention (duration in days)		X
Period between stroke/TIA and start of secondary stroke prevention (medication)	X	
CHA2-DS2-VASc Score		X
Stratification: (0, 1, 2-9)	X	
HAS-BLED Score		X
Stratification: (0-2, 3-9)	X	
Warfarin/apixaban dosage		X
INR measurements	X	
Number and type of outpatient visits, diagnostic procedures, labs, hospital admissions	X	
Cost of outpatient visits, diagnostic procedures, labs, medication, hospital admissions		X
Amount, type and severity of ischemic events	X	
Cost of ischemic events		X
Amount, type, severity of major/minor hemorrhagic events	X	

Cost of major/minor hemorrhagic events		X
Adverse events	X	

8.8. Quality control

Data entry into eCRF and Electronic Data Record will be accomplished by qualified subjects only. Entered data will be reviewed by CRO for consistency and logic via implemented quality checks and by manual reviews, as well.

8.9. Strengths and limitations of the research methods

The study design is considered to be the main strength of this study. It brings a unique opportunity to compare the outcomes of two cohorts of patients fulfilling the same inclusion criteria. Another strength of the design is data collection in real-world setting without any patient's selection according subgroups characteristics. The main limitation of the research may be a random distribution of patients on warfarin/apixaban treatment.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff has access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study,

linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

9.2. Patient Consent

As this study involves anonymized structured or unstructured 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.

9.3. Patient Withdrawal

Not Applicable.

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

The study will be reviewed by Independent Ethics Committee of the study site.

9.5. Ethical Conduct of the Study

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

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The investigator is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed

information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the the e-CRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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 investigator 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.
In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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13. LIST OF TABLES

14. LIST OF FIGURES

None.

15. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.