Pharmacologie médicale

Bordeaux Pharmacoépi
CIC Bordeaux CIC1401

BROTHER

Benefit-Risk Of arterial THrombotic prEvention with Rivaroxaban for atrial fibrillation in daily clinical practice.

A French cohort within the nationwide claims and hospital database

Protocol

Final version 1.0, 18 December 2015

Sponsor: Bayer Pharma AG

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PASS INFORMATION

Title	Benefit-Risk Of arterial THrombotic prEvention with Rivaroxaban for atrial fibrillation in daily clinical practice. A French cohort within the nationwide claims and hospital database (BROTHER).
Protocol version identifier	Version 1.0
Date of last version of protocol	18 December 2015
IMPACT study number	18656
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Active substance	Rivaroxaban (ATC code B01AF01)
Medicinal product	Xarelto® 15 mg (CIP: 34009 219 225 1 6, 34009 219 226 8 4, 34009 219 227 4 5, 34009 219 228 0 6, 34009 581 416 7 6 Xarelto® 20 mg (CIP code: 34009 219 229 7 4, 34009 219 230 5 6, 34009 219 231 1 7, 34009 581 419 6 6,
Product reference	Xarelto® 15 mg: EU/1/08/472/011 to EU/1/08/472/016, EU/1/08/472/023, EU/1/08/472/036 Xarelto® 20 mg: EU/1/08/472/017 to EU/1/08/472/022, EU/1/08/472/024, EU/1/08/472/037
Procedure number	N/A
Marketing authorisation holder(s)	Bayer HealthCare AG
Joint PASS	No
Research question and objectives	The research question is to assess the one-year and two-year benefit-risk of rivaroxaban for stroke prevention in atrial fibrillation (SPAF) compared to vitamin K antagonists (VKA) and dabigatran among new anticoagulant users. The main objective is to compare the one-year and two-year risk of the following individual outcomes: Stroke and systemic embolism (SE), major bleeding and death, between new users of anticoagulant for SPAF during drug exposure: rivaroxaban versus VKA, and rivaroxaban versus dabigatran.
Country(-ies) of study	France
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
ANSM	French Medicines Agency (*Agence Nationale de Sécurité du Médicament et des produits de santé*)
BPE	Bordeaux PharmacoEpi, the Pharmacoepidemiology research platform of the University of Bordeaux - INSERM CIC1401
CIF	Cumulative Incidence Function
CHA_2DS_2-VASc	Risk score of stroke in patients with atrial fibrillation
CNAMTS	French national health insurance fund for salaried worker (*Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés*)
CNIL	French data protection commission (*Commission Nationale de l'Informatique et des Libertés*)
CRB	Clinically Relevant Bleeding
DEP	Data Extraction Plan
DOAC	Direct Oral AntiCoagulants
DRG	Diagnosis-Related Groups (*or GHM for Groupes Homogènes de Malades*)
DVT	Deep Vein Thrombosis
EGB	1/97 random sample of the national health insurance database (*Echantillon Généraliste de Bénéficiaires*)
HAS	*Haute Autorité de Santé*
HAS-BLED	Risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation
hdPS	High-dimensional Propensity Score
IDS	Institute of Health Data (*Institut des Données de Santé*)
LTD	Long-Term Disease (registration for major chronic diseases with full insurance coverage of all claims related to disease)
MSA	French national health insurance fund for farmers and agricultural workers (*Mutuelle Sociale Agricole*)
MI	Myocardial Infarction
N	Number
NVAF	Non-Valvular Atrial Fibrillation
PE	Pulmonary Embolism (PE)
PMSI	National hospital discharge summary database (*Programme de Médicalisation des Systèmes d'Information*)
PY	Person-Years
RSI	French national health insurance fund for independent workers (*Régime Social des Indépendants*)
SAP	Statistical Analysis Plan
SNIIRAM	National healthcare insurance system database (*Système National d'Information Inter-Régimes de l'Assurance Maladie*)
SPAF	Stroke Prevention in Atrial Fibrillation
SPC	Summary of Product Characteristics
VKA	Vitamin K Antagonists
VTE	Venous Thromboembolic Events

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4. ABSTRACT

TITLE

Benefit-Risk Of arterial THrombotic prEvention with Rivaroxaban for atrial fibrillation in daily clinical practice. A French cohort within the nationwide claims and hospital database (BROTHER).

RATIONAL AND BACKGROUND

Atrial fibrillation (AF) is an abnormal heart rhythm characterized by irregular beating. AF is associated with a five-fold increased risk of ischemic stroke, and accounts for up to 15% of strokes in persons of all ages and 30% in those over 80 years. Vitamin K antagonists (VKA) were the reference treatment for stroke prevention in AF (SPAF) and recommended for persons at increased risk of stroke.

Since 2012, three direct oral anticoagulants (DOAC), with a different mode of action from VKA, received a European market authorization for the prevention of stroke and systemic embolism in adult patients with non-valvular AF (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack.

In France, Xarelto® (rivaroxaban 15 and 20 mg once daily) and Pradaxa® (dabigatran 110 and 150 mg twice daily) were launched in this indication in August 2012, and Eliquis® (apixaban 2.5 and 5 mg twice daily) in January 2014. The Transparency Committee of the HAS (*Haute Autorité de Santé*) gave a positive opinion for the reimbursement in this indication. As part of this procedure, the HAS requested Bayer to provide additional data documenting the therapeutic benefit of Xarelto® under actual conditions of use compared with the normal treatment of at-risk patients with NVAF.

In order to provide additional information to answer the HAS requests, especially the impact on morbidity and mortality, with a longer follow-up than for the NACORA studies, a rivaroxaban versus VKA comparison, as well as a face to face comparison between the two DOAC (rivaroxaban versus dabigatran), Bayer committed to a cohort study to be initiated about six months after the launch of the two first DOAC for SPAF using the national claims and hospitalisation database.

RESEARCH QUESTION AND OBJECTIVES

Research question: To assess the one-year and two-year benefit-risk of rivaroxaban for SPAF compared to VKA and dabigatran among new anticoagulant users.

Main objective: To compare the one-year and two-year risk of each of the following individual outcomes: Stroke and systemic embolism (SE), major bleeding and death between new users of anticoagulant for SPAF during drug exposure: rivaroxaban versus VKA, and rivaroxaban versus dabigatran.

Secondary objectives:

- To describe the drug exposure to rivaroxaban, dabigatran, and VKA for SPAF in new users, as well as and pattern of use;
- To compare the one-year and two-year risk of the following individual outcomes: a composite of stroke and SE, major bleeding and death, clinically relevant bleeding (CRB) and acute coronary syndrome (ACS) between new users of anticoagulant for SPAF during drug exposure: rivaroxaban versus VKA, and rivaroxaban versus dabigatran;
- To estimate the cumulative incidence and the incidence rate of each

individual main and secondary outcome (stroke and SE, major bleeding, CRB, death, composite criteria, and ACS), as well as according to individual diagnose of each of these outcomes, during drug exposure for rivaroxaban, dabigatran, and VKA;

- To estimate the cumulative incidence of each individual main and secondary outcome (stroke and SE, major bleeding, CRB, death, composite criteria, and ACS), as well as according individual diagnose of each of these outcomes during post-anticoagulant exposure for rivaroxaban, dabigatran, and VKA (i.e. after anticoagulant discontinuation);
- To assess outcome risk factors, including (but not limited to), gender, age, stroke and bleeding risk scores (CHA_2DS_2-VASc and HAS-BLED), low or high dosage at index date for DOAC, drug predisposing to bleeding during drug exposure and significant baseline characteristics;
- To describe and compare healthcare resources utilisation related to SPAF during rivaroxaban, dabigatran, and VKA exposure, including outcomes, and their related costs from the societal perspective and from the French healthcare insurance perspective.

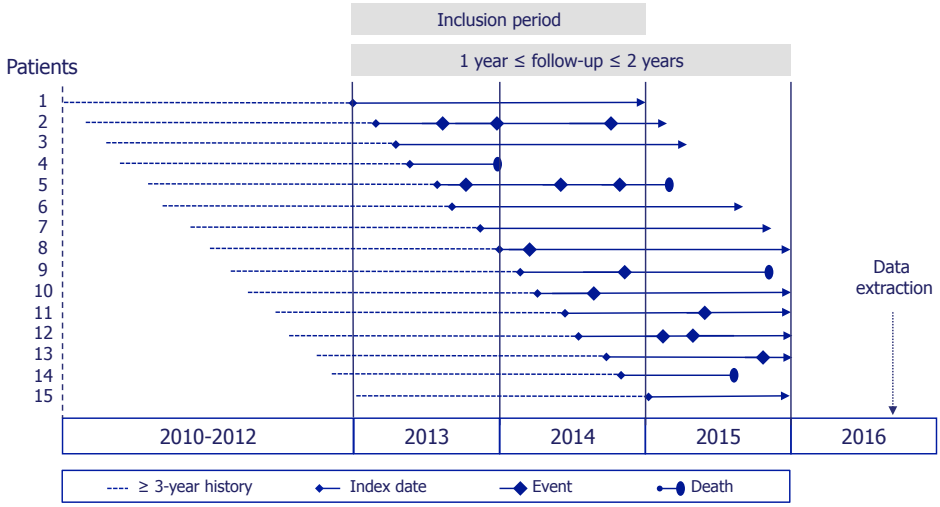
STUDY DESIGN

A cohort study in a healthcare claims and hospitalisation database including new users of rivaroxaban, dabigatran, or VKA for SPAF with a follow-up for at least one year and up to two years per subject.

Data will be extracted from 1 January 2010 to 31 December 2015:

- The index date will be the first reimbursed dispensation of rivaroxaban, dabigatran, or VKA in 2013 or 2014, and without dispensation of any of them within the 3 years before index date.
- The study follow-up period will start on the study index date and will end two years later, or until the date of death with a right censoring on 31 December 2015 (at least a one-year follow-up period except for death).
- Rivaroxaban, dabigatran, or VKA exposure will be defined during the study follow-up period, as well as the occurrence of each of the study outcome.

The overall design of the study is presented in the following figure.



POPULATION

Subjects with a first reimbursed dispensation of rivaroxaban (15 or 20 mg),

dabigatran (110 or 150 mg), or VKA in 2013 or 2014 and no previous anticoagulant dispensation during the previous three years, with a specific or sensitive diagnosis of non-valvular AF (NVAF). Two NVAF cohorts will be defined:

- Specific NVAF cohort (for the main analysis) will include definite NVAF subjects as defined below (to minimize the risk of false positives);
- Sensitive NVAF cohort (as secondary analysis) will include definite NVAF and probable NVAF subjects as defined below (to minimize the risk of false negatives).

Definite NVAF subjects: Definite AF information in the database, and no other indication for the use of anticoagulant (treatment of venous thromboembolic events (VTE), prevention of VTE after orthopaedic surgery), or history of rheumatic valve disease or valve replacement.

Probable NVAF subjects: Probable AF information in the database (using the development of an AF disease score), and no other indication for use of anticoagulant (treatment of VTE, prevention of VTE after orthopaedic surgery), or history of rheumatic valve disease or valve replacement.

VARIABLES

Disease definition

- Definite AF: Hospitalisation with an AF diagnosis (primary, linked or associated) or a procedure for AF (cardioversion, catheter ablation), or a Long-Term Disease (LTD) registration for AF in the 36 months before the index date or within six months after index date.
- Probable AF: Subjects without definite AF, and with anticoagulant and amiodarone or dronedarone co-prescription, or having a high probability of AF, using an AF disease score based on a logistic regression of the definite AF population with the following parameters (see statistical analysis):
  - Gender and age of the subject at index date,
  - Cardiologist or hospital physician prescriber of the first DOAC or VKA dispensation,
  - Investigation within 2 months before index date: Holter ECG monitoring or echocardiography, T3-T4 thyroid hormone test, D-dimer test or venous echo-doppler,
  - ≥ 1 drug dispensation within 3 months before index date for acetylsalicylic acid (ASA), ASA in association, clopidogrel, heparin or low-molecular-weight heparin (LMWH),
  - ≥ 1 drug dispensation within 2 months before or 2 months after index date of sotalol, other beta-blockers excluding associations, beta-blockers in association, verapamil or diltiazem, digoxin or digitoxin, other antiarrhythmic drug, other calcium channel blocker, agents acting on the renin-angiotensin system, diuretic.

Disease definitions for exclusion criteria

- Rheumatic valve disease (subjects excluded): Hospitalisation or LTD registration with rheumatic valve disease diagnosis, before index date (three-year history).
- Valve replacement (subjects excluded): Hospitalisation with diagnosis-related group of valve replacement or medical procedure for valve replacement (three-year history).
- Other probable indications of first anticoagulant dispensation (subjects excluded):
  - Treatment of VTE: index date within 2 months after hospital discharge

for pulmonary embolism or deep vein thrombosis;
- Prevention of VTE after orthopaedic surgery: index date within 2 months after hospital discharge for an orthopaedic surgery.

Exposure

- Treatment group: Defined by the first anticoagulant dispensation during the inclusion period, i.e. rivaroxaban high or low dosage, dabigatran high or low dosage, or VKA.
- Index date: Date of the first dispensation of anticoagulant in the treatment group.
- Duration of a drug dispensation will be defined as the number of daily doses for DOAC and 30 days for VKA;
- Drug exposure (rivaroxaban, dabigatran, or VKA): Period starting at the index date and ending at the date of the last drug dispensation plus the duration of the last drug dispensation for subject with a drug discontinuation or at the date of another anticoagulant dispensation (switch) or at the end of follow-up, whichever is the earliest.
- Drug (DOAC or VKA) discontinuation: with a grace period of 60 days for the main analysis and 30 days for a sensitive analysis after a "last" dispensation plus the duration of the last drug dispensation.
- Drug (DOAC or VKA) switch: Dispensation of another anticoagulant, including heparin and LMWH dispensation for subject with a drug discontinuation.
- Post drug (DOAC or VKA) exposure: Period starting at date of the end of drug exposure and ending at the date a new prescription of an anticoagulant or at the end of follow-up, whichever is the earliest.
- DOAC compliance: Estimated using Medication Possession Ratio (MPR) during drug exposure defined by the number of defined daily doses dispensed, divided by the number of days of drug exposure for DOAC.
- During a hospitalisation, drugs are provided by the hospital, and this time will be taken into account for calculation of drug exposure and drug discontinuation.

Outcomes

- Stroke and SE: Hospitalisation with one of the two following primary diagnoses:
  - Ischemic or undefined stroke,
  - Other systemic arterial embolism or surgical procedure for systemic arterial embolism.
- Major bleeding: Hospitalisation with one of the three following primary diagnoses:
  - Haemorrhagic stroke,
  - Other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular),
  - Other bleeding with a transfusion during hospital stay, or resulting in death.
- Clinically relevant bleeding (CRB): Hospitalisation with one of the five following primary diagnoses:
  - Haemorrhagic stroke,
  - Other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular),
  - Gastro-intestinal bleeding,
  - Urogenital bleeding,

  - Other bleeding.
- Death: All-cause death.
- ACS: Hospitalisation with one of the two following primary diagnoses:
  - Myocardial infarction (MI),
  - Unstable angina.

Potential confounding

- Gender and age at index date,
- CHA2DS2-VASc score (stroke risk factor score) at index date: Sum of points from congestive heart failure (+1), hypertension (+1), age ≥ 75 years (+2), diabetes mellitus (+1), stroke or transient ischemic attack history (+2), vascular disease history (+1), age 65-74 years (+1), female gender (+1),
- CHADS2 score (stroke risk factor score for descriptive analysis) at index date: Sum of points from congestive heart failure (+1), hypertension (+1), age ≥ 75 years (+1), diabetes mellitus (+1), stroke or transient ischemic attack history (+2),
- HAS-BLED score (bleeding risk factor score) at index date: Sum of points from hypertension (+1), abnormal renal function (+1), abnormal liver function (+1), stroke history (+1), bleeding history (+1), age > 65 years (+1), drug predisposing to bleeding (+1),
- High dimensional Propensity Scores (hdPS) at index date for the probability of being treated by one of the studied drugs (rivaroxaban versus VKA, rivaroxaban versus dabigatran),
- Drug predisposing to bleeding during drug exposure: ASA, NSAIDs, antiplatelet agent and heparin or LMWH.

Healthcare resources

- Cardiovascular hospitalisations: Hospitalisations with primary diagnosis or diagnosis-related group of cardiovascular disease,
- Non-cardiovascular hospitalisations: Hospitalisations other than those defined above,
- Medical visits and technical acts,
- Cardiovascular and antidiabetic drugs reimbursed,
- Non-cardiovascular/antidiabetic drugs reimbursed,
- Lab tests,
- Products and services,
- Nursing acts,
- Physiotherapy acts,
- Transports,
- Sick leave daily allowances, disability allowances, pension,
- Other medical resources.

Healthcare resources related to AF

- Specific Hospitalisations: Hospitalisations with primary diagnosis of AF, or cardioversion, or catheter ablation procedure, or stroke or systemic embolism, or CRB,
- Specific drugs: DOAC, VKA, beta-blockers, amiodarone, dronedarone, other antiarrhythmics,
- Specific lab tests: INR, haemostasis tests, creatinine, creatinine clearance, ALAT, ASAT, including sampling,
- Specific medical visits: cardiologist visit, other medical visits with date

corresponding to the date of prescription of specific drugs or lab tests, neurologist visit after stroke event,

- Specific transport: Transport with date corresponding to the date of a specific hospitalisation, medical visit, medical procedure, or lab test.

Healthcare resources cost

- From a societal perspective: Diagnosis-related group cost for hospitalisations and total cost for other healthcare resources.
- From the French healthcare insurance perspective: Stay-related group cost for hospitalisations and reimbursed cost for other healthcare resources.

DATA SOURCES

The SNIIRAM database is the national healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system (PMSI) and the national death registry. It currently includes more than 96% of the French population of 65 million persons. To the extent that the SNIIRAM is a national database, all subjects are followed-up until they died, or for some people until they leave the country to live abroad. It contains individual anonymised information on:

- Demographic characteristics: gender, year of birth, area of residence;
- Date of death;
- Long-term disease (LTD and associated ICD-10 codes) registration for full insurance coverage (with start and end dates);
- Outpatient reimbursed healthcare expenditures with dates and codes (but not the medical indication nor result): visits, medical procedures, lab tests, drugs and medical devices, etc;
- Hospital-discharge summaries from PMSI: ICD-10 diagnosis codes (primary, linked and associated diagnoses) for all medical, obstetric and surgery hospitalisations, with the date and duration, medical procedures and cost coding system.

Access to SNIIRAM is regulated and needs approval from IDS (Institute of health data) and CNIL (French data protection commission). Hospital data are uploaded once a year and made available in the third quarter following the last year considered (i.e. the third quarter of 2016 for the extraction relating to the 2015 follow-up period).

STUDY SIZE

Using a previous study of VKA for SPAF, about 100 000 and 150 000 subjects are expected, respectively for the specific NVAF population and the sensitive NVAF population for a two-year inclusion period.

The number of subjects treated with rivaroxaban, dabigatran, and VKA, as well as the number of subjects who can be matched for each comparison (rivaroxaban versus VKA, rivaroxaban versus dabigatran) will be a result of the study, but it should be clearly higher than the 7 131 and 7 133 subjects randomized in the rivaroxaban and VKA arms of the ROCKET AF trial.

DATA ANALYSIS

A statistical analysis plan (SAP) will be developed and validated by the scientific committee before analysis. The statistical analysis will be performed using SAS® software (latest current version), following the SAP.

Probable AF will be estimated using AF disease score with a logistic regression model to predict AF diagnosis among subjects without history of rheumatic valve disease or valve replacement, or other probable indications, using variables defined above (see disease definition).

The probability to be treated by rivaroxaban or VKA, as well as rivaroxaban or dabigatran will be estimated with hdPS. The hdPS will be estimated using a logistic regression model with a large set of variables at index date and three-year history before inclusion, including gender, age, CHA2DS2-VASc and HAS-BLED scores.

For the rivaroxaban versus VKA comparison, subjects will be matched 1:1 on hdPS and index date within each population (specific and sensitive); For the rivaroxaban versus dabigatran comparison, subjects will be matched 1:1 on high or low DOAC dosage at index date, hdPS and index date within each population (specific and sensitive).

The main analysis will be performed with the specific NVAF matched cohorts and a grace period of 30 days for the drug discontinuation definition. A secondary analysis will be performed using a statistical adjustment with all specific NVAF subjects, and a grace period of 30 days for the drug discontinuation definition.

The following sensitive analyses will be performed for matched cohorts, as well as all for statistical adjustment with all subjects:

- With a grace period of 60 days for drug discontinuation definition, in order to take into account the drug supply in real life, or short discontinuation and poor drug adherence;
- With the sensitive NVAF subjects and the two grace periods for drug discontinuation definition;
- With unspecified bleeding classified as haemorrhagic stroke for the specific and the sensitive NVAF cohorts.

The following statistical analyses will be performed:

- A flow chart depicting the total number of subjects available in the database, those satisfying the cohort criteria according to the treatment group, and the number of matched subjects for each comparison, and in each population;
- Description of baseline characteristics, three-year history previous the inclusion, follow-up duration for all and matched subjects according to the treatment group, with standardised difference for each comparison;
- Description of drug use patterns including drug MPR for DOAC, dosage, treatment discontinuation, switch to another anticoagulant, co-dispensation of drug predisposing to bleeding and one-year and two-year treatment maintenance for all and matched subjects according to the treatment group, with standardised difference for each comparison;
- Outcomes will be analysed using survival methods for the first occurrence of each outcome:
  - Estimation of the one-year and two-year cumulative incidence of each outcome, and according to individual diagnose of each outcome, during drug exposure for rivaroxaban, dabigatran, and VKA; using Kaplan-Meier estimate for death, cumulative incidence function for clinical outcomes, in order to take into account death as a competing risk.
  - Estimation of the incidence rate (per 100 PY exposed) of each outcome, and according to individual diagnose of each outcome, during drug exposure or if the risk is not constant over the time, during periods with a constant risk.
  - Comparison of the one-year and two-year risk of each outcome during drug exposure: rivaroxaban versus VKA, and rivaroxaban versus dabigatran, using Cox proportional hazard risk model (Cox 1972) for death and Fine and Gray model (Fine 1999) for clinical outcomes in

order to take into account death as a competing risk. Hazard ratio will presented as point estimate with their 95% confidence interval:

- ✓ Main analysis will compare the incidence of each outcome for matched subjects with adjustment for drugs predisposing to bleeding during drug exposure (time dependant variables).
- ✓ Secondary analysis will compare the incidence of each outcome with all subjects, with adjustment for hdPS and drugs predisposing to bleeding during drug exposure (time dependant variable) for the rivaroxaban versus VKA comparison, and plus low or high DOAC dosage at index date for the rivaroxaban versus dabigatran comparison.
- ✓ Prognostic analysis will be done with all subjects to assess outcome risk factors, including gender, age, CHA2DS2-VASc and HAS-BLED scores, low or high dosage at index date for DOAC, drug predisposing to bleeding during drug exposure (time dependant variable) and significant baseline characteristics. The significant baseline characteristics will be identified firstly with univariate analyses, and therefore using a forward stepwise (taking into account the size of the database, the p threshold will be set at 1/1000 for variables selection and at 5% for the stepwise procedure).

• Estimation of cumulative incidence of each outcome during post-anticoagulant exposure period for rivaroxaban, dabigatran, and VKA (i.e. after anticoagulant discontinuation), using Kaplan-Meier estimate for death, cumulative incidence function for clinical outcomes (stroke and SE, ACS, CRB), in order to take into account death as a competing risk.

– Description of healthcare resources use and cost, for all and matched subjects according to the treatment group rivaroxaban dabigatran, and VKA during the first year of follow-up for all patients, and during two years of follow-up for those included in 2013. Comparison (rivaroxaban versus VKA, and rivaroxaban versus dabigatran) will be done for matched cohorts.

MILESTONES		
	Study protocol	Sept-Dec 2015
	IDS and CNIL authorisation	Q4 2015-Q3 2016
	Development of SAP	Q2-Q3 2016
	SNIIRAM data extraction	Q3-Q4 2016
	Data management and statistical analysis	Q4 2016-Q1 2017
	Final report	Q2 2017

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason

6. MILESTONES

Milestones	Planned Date
Study protocol	Sep-Dec 2015
IDS and CNIL authorisation	Q4 2015-Q3 2016
Development of the Statistical Analysis Plan	Q2-Q3 2016
SNIIRAM data extraction	Q3-Q4 2016
Data management and statistical analysis	Q4 2016-Q1 2017
Final report	Q2 2017
Manuscript	Q3-Q4 2017

7. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is an abnormal heart rhythm characterized by irregular beating. AF is associated with a five-fold increased risk of ischemic stroke, and accounts for up to 15% of strokes in persons of all ages and 30% in those over 80 years (Wolf 1987, Camm 2010). Ischemic stroke in AF is often severe and results in long-term disability or death (Camm 2010). Vitamin K antagonists (VKA) were the reference treatment for stroke prevention in AF (SPAF) and recommended for persons at increased risk of stroke (Camm 2010, Steinberg 2014).

Xarelto® (rivaroxaban) is a direct oral anticoagulant (DOAC) with a different mode of action from VKA. Xarelto®, 15 mg or 20 mg once daily, received a European market authorization for the prevention of stroke and systemic embolism in adult patients with non-valvular AF (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack (EMA/CHMP/753436/2011, 22 September 2011). Two other DOAC received a European market authorization for the same indication: Pradaxa® (dabigatran) 110 mg or 150 mg twice daily (EMA/CHMP/ 304146/2011, 14 April 2011) and Eliquis® (apixaban) 2.5 mg or 5 mg twice daily (EMA/CHMP/ 608476/2012, 20 September 2012).

The market authorization of rivaroxaban is based on the ROCKET AF trial which randomized 14,264 subjects with NVAF at increased risk of stroke, to receive either rivaroxaban (at a daily dose of 20 mg) or adjusted-dose warfarin (Patel 2011). In the primary analysis, the incidence of stroke or systemic embolism was 1.71% per year in the rivaroxaban group and 2.16% per year in the warfarin group (hazard ratio, 0.79; 95%CI, 0.66 to 0.96; $p < 0.001$ for non-inferiority). Major and non-major clinically relevant bleeding incidence was 14.9% per year in the rivaroxaban group and 14.5% per year in the warfarin group (hazard ratio, 1.03; 95%CI, 0.96 to 1.11), with significant reductions in intracranial haemorrhage (0.5% vs. 0.7%, $p = 0.02$) and fatal bleeding (0.2% vs. 0.5%, $p = 0.003$) in the rivaroxaban group.

In France, Xarelto® and Pradaxa® were launched in this indication in August 2012, and Eliquis® in January 2014. The Transparency Committee of the *Haute Autorité de Santé (*HAS) gave a positive opinion for the reimbursement in this indication with a substantial medical benefit (SMR important) but no improvement in existing benefit (ASMR V), no expected public health impact, and a target population of 500 000 patients. As part of this procedure, the Transparency Committee requested Bayer to provide additional data documenting the therapeutic benefit of Xarelto® under actual conditions of use compared with the normal treatment of at-risk patients with NVAF:

- The characteristics of the treated patients, in particular age, gender, history and cardiovascular risk factors,
- The conditions of use of Xarelto®: reasons for starting treatment (particularly, first-line or second-line prescription, and risk factors associated with AF), any previous anticoagulant treatment and level of control thus obtained, concomitant treatments (in particular, antiplatelet agents and medicines with a risk of interaction), prescribed dosage (dose, amount administered daily and duration of prescription), frequency and reasons for any discontinuation of treatment and treatments started as a back-up,
- The impact on morbidity and mortality (events avoided and adverse effects, particularly bleeding), treatment compliance and quality of life in the medium and long term.

ANSM,[1] the French medicines agency, commissioned two studies using the French national claims and hospital database:

- The NACORA-BR study, performed by the CNAMTS,[2] was a cohort study with a main objective to compare the short-term risk of major bleeding for new NOAC users naive of VKA during the second half of 2012 to new users of VKA during the second half of 2011. Secondary objectives were to compare the risk of arterial events (stroke, systemic embolism), the risk of myocardial infarction (MI) over the same period in patients starting treatment within the AF indication, and the 30-day survival for patients hospitalized for major bleeding. This study concluded to no significant statistical difference between NOACs, dabigatran or rivaroxaban, and VKAs for the short-term risk of bleeding or arterial thromboembolic short-term risk during the early phase of anticoagulant therapy in NVAF patients (CNAMTS 2014, Maura 2015).
- The NACORA-Switch study, led by the ANSM, was a cohort study with the same main and secondary objectives for patients who switched from VKA to NOAC compared to matched patients who remained on VKA. The authors concluded that the short-term risk of severe bleeding, stroke and systemic embolism, myocardial infarction was not increased for patients switching from VKA to DOAC compared to those remaining on VKA (ANSM 2014).

The two study underline that they were conducted at the early phase of dabigatran and rivaroxaban marketing for SPAF with a short-term follow-up (3 months). The early period of marketing of a new drug is generally considered as a learning period during which disease severity and history, drug prescription and utilisation do not necessary reflect the use of the drug in daily practice some months later.

In order to provide additional information to answer the HAS requests, especially the impact on morbidity and mortality, with a longer follow-up than for the NACORA studies, a rivaroxaban versus VKA comparison, as well as a face to face comparison between the two DOAC (rivaroxaban versus dabigatran). Bayer committed to a cohort study to be initiated about six months after the launch of the two first DOAC for SPAF with two years of follow-up, using the French national claims and hospital database.

8. RESEARCH QUESTION AND OBJECTIVES

The research question is to assess the one-year and two-year benefit-risk of rivaroxaban for SPAF compared to VKA and dabigatran among new anticoagulant users.

The main study objective is to compare the one-year and two-year risk of each of the following individual outcomes: Stroke and systemic embolism (SE), major bleeding and death between new users of anticoagulant for SPAF during drug exposure: rivaroxaban versus VKA, and rivaroxaban versus dabigatran.

Secondary objectives are:

- To describe the drug exposure to rivaroxaban, dabigatran, and VKA for SPAF in new users, as well as pattern of use;

[1] *Agence Nationale de Sécurité du Médicament et des produits de santé* (French Medicines Agency)
[2] *Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés* (French National Health Insurance Fund for Salaried Workers)

- To compare the one-year and two-year risk of the following individual outcomes: a composite of stroke and SE, major bleeding and death, clinically relevant bleeding (CRB) and acute coronary syndrome (ACS) between new users of anticoagulant for SPAF during drug exposure: rivaroxaban versus VKA, and rivaroxaban versus dabigatran;
- To estimate the cumulative incidence and the incidence rate of each individual main and secondary outcome (stroke and SE, major bleeding, CRB, death, composite criteria, and ACS), as well as according individual diagnose of each of these outcomes, during drug exposure for rivaroxaban, dabigatran, and VKA;
- To estimate the cumulative incidence of each individual main and secondary outcome (stroke and SE, major bleeding, CRB, death, composite criteria, and ACS), as well as according individual diagnose of each of these outcomes during post-anticoagulant exposure for rivaroxaban, dabigatran, and VKA (i.e. after anticoagulant discontinuation);
- To assess outcome risk factors, including (but not limited to), gender, age, stroke and bleeding risk scores (CHA_2DS_2-VASc and HAS-BLED), low or high dosage at index date for DOAC, drug predisposing to bleeding during drug exposure and significant baseline characteristics;
- To describe and compare healthcare resources utilisation related to SPAF during rivaroxaban, dabigatran, and VKA exposure, including outcomes, and their related costs from the societal perspective and from the French healthcare insurance perspective.

9. RESEARCH METHODS

9.1. STUDY DESIGN

The design is a cohort study in a healthcare claims and hospitalisation database including new users of rivaroxaban, dabigatran, or VKA for SPAF with a follow-up for at least one year and up to two years per subject. The overall design of the study is presented in the following figure (Figure 1).

Data will be extracted from 1 January 2010 to 31 December 2015. The index date will be the first reimbursed dispensation of rivaroxaban, dabigatran, or VKA in 2013 or 2014, without dispensation of any of them within the 3 years before index date. The study follow-up period will start on the study index date and will end two years later, or until the date of death with a right censoring on 31 December 2015 (at least a one year follow-up period except for death). Rivaroxaban, dabigatran, and VKA exposure will be defined during the study follow-up period, as well as the occurrence of each of the study outcome.

The main advantages of this study are that data are collected independently of the research question, allowing the conduct of a nationwide population-based historical cohort. Limits of database analyses are discussed later (Section 9.9 Limitations of the research methods).

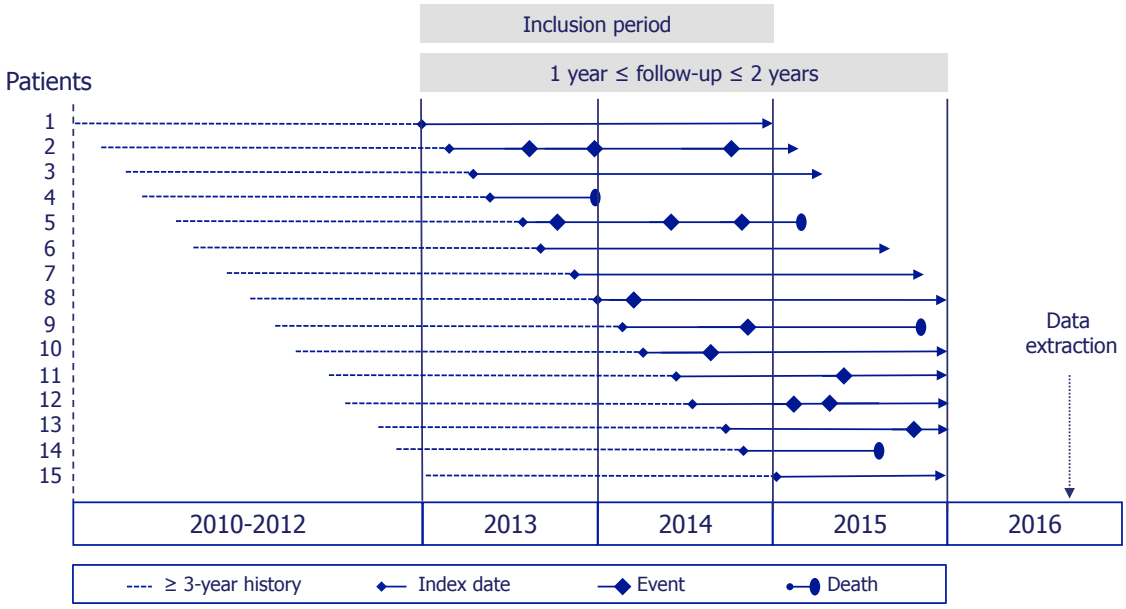


Figure 1: Study design

9.2. SETTING

This is a study of subjects with a first dispensation of an anticoagulant (VKA or DOAC) for SPAF in a real world setting, identified and followed in the French national claims and hospital database (SNIIRAM).

Population definition

All subjects with a first reimbursed dispensation of rivaroxaban (15 or 20 mg), dabigatran (110 or 150 mg) or VKA in 2013 or 2014 will be extracted from the database. Among them, some will have clear AF diagnosis information, some an indication other than AF and other no clear information about anticoagulant indication. To overcome this obstacle, we will use two diagnosis definitions for AF, a specific definition in order to minimize the risk of false positives, and a sensitive definition in order to minimize the risk of false negatives, in such a way that two NVAF cohorts will be defined:

- **Specific NVAF cohort** (for the main analysis) will include definite NVAF subjects as defined below;
- **Sensitive NVAF cohort** (as secondary analysis) will include definite NVAF and probable NVAF subjects as defined below.

Definite NVAF subjects will be defined with all the following inclusion criteria:

- A first reimbursed dispensation of rivaroxaban, dabigatran, or VKA in 2013 or 2014, and
- No previous DOAC (rivaroxaban, dabigatran, apixaban) or VKA dispensation during the previous three years,
- Definite AF information in the database (see variable definition below),
- No other indication for the use of anticoagulant (treatment of venous thromboembolic events (VTE), prevention of VTE after orthopaedic surgery),
- No history of rheumatic valve disease or valve replacement (non-valvular AF definition from the 2012 European Society of cardiology guidelines, Camm 2012).

Probable NVAF subjects will be defined with all the following inclusion criteria:

- A first reimbursed dispensation of rivaroxaban, dabigatran, or VKA in 2013 or 2014, and
- No previous DOAC (rivaroxaban, dabigatran, apixaban) or VKA dispensation during the previous three years,
- Probable AF information in the database (using the development of an AF disease score, see variables definition below),
- No other indication for the use of anticoagulant (treatment of VTE, prevention of VTE after orthopaedic surgery),
- No history of rheumatic valve disease or valve replacement (non-valvular AF definition from the 2012 European Society of cardiology guidelines, Camm 2012).

9.3. VARIABLES

9.3.1. Disease definitions

Definite AF will be defined as a hospitalisation with an AF diagnosis (primary, linked, or associated, I48 ICD-10 code) or a procedure for AF (cardioversion, catheter ablation), or a Long-Term Disease (LTD) registration for AF (I48 ICD-10 code) in the 36 months before the index date or within six months after index date.

Probable AF will be defined as subjects without definite AF, and with anticoagulant and amiodarone or dronedarone co-prescription, or having a high probability of AF, using an AF disease score based on a logistic regression of the definite AF population with the following parameters (see statistical analysis):

- Gender and age of the subject at index date,
- Cardiologist or hospital physician prescriber of the first DOAC or VKA dispensation,
- Investigation within 2 months before index date: Holter ECG monitoring or echocardiography, T3-T4 thyroid hormone test, D-dimer test or venous echo-doppler,
- ≥ 1 drug dispensation within 3 months before index date for acetylsalicylic acid (ASA), ASA in association, clopidogrel, fondaparinux, heparin or low-molecular-weight heparin (LMWH),
- ≥ 1 drug dispensation within 2 months before or 2 months after index date for sotalol, other beta-blockers excluding associations, beta-blockers in association, verapamil or diltiazem, digoxin or digitoxin, other antiarrhythmic drug, other calcium channel blocker, agents acting on the renin-angiotensin system, diuretic.

9.3.2. Disease definitions for exclusion criteria

Rheumatic valve disease will be defined as a hospitalisation with rheumatic valve disease diagnosis (primary, linked or associated I05-I09 ICD-10 codes) or LTD registration for rheumatic valve disease (I05-I09 ICD-10 codes), before index date (three-year history).

Valve replacement will be defined as a hospitalisation with diagnosis-related group of valve replacement or medical procedure for valve replacement (three-year history).

Other probable indications of first anticoagulant dispensation:

- **Treatment of VTE** will be defined as index date within 2 months after hospital discharge for a pulmonary embolism (primary or associated diagnosis I26 ICD-10

code) or deep vein thrombosis (primary or associated diagnosis I80, I81, I82 ICD-10 codes);

- **Prevention of VTE after orthopaedic surgery** will be defined as index date within 2 months after hospital discharge for an orthopaedic surgery (using diagnosis-related group codes).

9.3.3. Exposure

Exposure definitions will use the following variables:

- **VKA** will be defined as B01AA ATC code;
- **DOAC** will be defined as B01AF01 ATC code for rivaroxaban and B01AE07 ATC code for dabigatran;
- **DOAC high dosage** will be defined using CIP codes for rivaroxaban 20mg and dabigatran 150mg;
- **DOAC low dosage** will be defined using CIP codes for rivaroxaban 15mg and dabigatran 110mg;
- **Treatment group** will be defined by the first anticoagulant dispensation during the inclusion period, i.e. rivaroxaban high or low dosage, dabigatran high or low dosage, or VKA;
- **Index date** will be defined as the date of the first dispensation of the anticoagulant in the treatment group;
- **Duration of a drug dispensation** will be defined as the number of daily doses for DOAC and 30 days for VKA;
- **Drug (DOAC or VKA) exposure** will be defined as the period starting at the index date and ending at the date of the last drug dispensation plus the duration of the last drug dispensation for subject with a drug discontinuation (defined below) or at the date of drug switch (defined below), or at the end of follow-up, whichever is the earliest;
- **Drug (DOAC or VKA) discontinuation** will be defined with a grace period of 60 days for the main analysis and 30 days for a sensitive analysis after the last dispensation plus the duration of the last drug dispensation;
- **Drug (DOAC or VKA) switch** defined as a dispensation of another anticoagulant, including heparin and LMWH dispensation (B01AB ATC code), for subject with a drug discontinuation;
- **Post drug (DOAC or VKA) exposure** will be defined as the period starting at date of the end of drug exposure (see above) and ending at the date a new prescription of an anticoagulant or at the end of follow-up, whichever is the earliest;
- **DOAC compliance** will be estimated using Medication Possession Ratio (MPR) during drug exposure defined by the number of defined daily doses dispensed, divided by the number of days of drug exposure for DOAC. Considering the variable dosage of VKA between subjects and over time in individual subjects, no defined daily dose can be defined, and therefore no MPR for VKA exposure.
- During a hospitalisation, drugs are provided by the hospital, and this time will be taken into account for calculation of drug exposure and drug discontinuation.

9.3.4. Outcomes

The primary outcomes are:

- **Stroke and systemic embolism (SE)** will be defined as a hospitalisation with one of the two following primary diagnoses:
  - ✓ Ischemic or undefined stroke (Giroud 2015),
  - ✓ Other systemic arterial embolism or surgical procedure for systemic arterial embolism.
- **Major bleeding,** based on International Society on Thrombosis and Haemostasis definition (Schulman 2005) and modified* to take into account the availability of information in the database, will be defined as a hospitalisation with one of the three following primary diagnoses:
  - ✓ Haemorrhagic stroke,
  - ✓ Other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular),
  - ✓ Other bleeding with a transfusion during hospital stay, or resulting in death,

  * Causes of death and haemoglobin result are not available to take into account not hospitalized fatal bleeding and bleeding causing a fall in haemoglobin level of 20g/l.
- **Clinically relevant bleeding (CRB)** will be defined as a hospitalisation with one of the five following primary diagnoses:
  - ✓ Haemorrhagic stroke,
  - ✓ Other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular),
  - ✓ Gastro-intestinal bleeding,
  - ✓ Urogenital bleeding,
  - ✓ Other bleeding (ICD-10 codes in annex 1).
- **Death** defined as all-cause death (cause of death not available in the database).
- **Acute coronary syndrome (ACS)** will be defined as a hospitalisation with one of the two following primary diagnoses (Bezin 2015):
  - ✓ Myocardial infarction (MI),
  - ✓ Unstable angina.

9.3.5. Potential confounding

The potential confounders considered will be:

- **Gender and age** at index date;
- **CHA_2DS_2-VASc score** (Lip GY 2010) at index date, modified to take into account the availability of information in the database, and defined as the sum of points from following stroke risk factors: congestive heart failure (+1), hypertension (+1), age ≥ 75 years (+2), diabetes mellitus (+1), stroke or transient ischemic attack (TIA) history (+2), vascular disease history (+1), age 65-74 years (+1), female gender (+1), within tree-year database history;
- **$CHADS_2$ score** (for descriptive analysis, Waterman 2001) at index date, modified to take into account the availability of information in the database, and defined as the sum of points from following stroke risk factors: congestive heart failure (+1), hypertension (+1), age ≥ 75 years (+1), diabetes mellitus (+1), stroke or transient ischemic attack history (+2);
- **HAS-BLED score** (Pisters 2010, Lip GY 2011), modified to take into account the availability of information in the database, and defined as the sum of points from bleeding risk factors: hypertension (+1), abnormal renal function (+1), abnormal liver function (+1), stroke history (+1), bleeding history (+1), age > 65 years (+1), drug predisposing to bleeding (+1), within tree-year database history;

- **High dimensional Propensity Scores (hdPS)**: the probability to be treated by one of the studied drugs (rivaroxaban versus VKA, rivaroxaban versus dabigatran), will be estimated using hdPS taking into account all information of the database, with multiple data dimensions from subjects and disease characteristics, other LTD, other comorbidities using one-year history of hospitalisation (primary, linked, or associated diagnosis), three-year history of number of systemic drugs dispensed by therapeutic class (ATC 3 digit, including antacids A02A and drugs for peptic ulcer A02B) and of healthcare reimbursements (number of GP visits, specialist visits, emergency room visits, days of hospitalisation, nurse care and lab tests).
- **Drug predisposing to bleeding** during drug exposure: ASA, NSAIDs, antiplatelet agent and heparin or LMWH.

9.3.6. Healthcare resources

Healthcare resources use will be described from reimbursed claims and hospitalisation information, and classified as:

- Cardiovascular hospitalisations defined as all hospitalisations with cardiovascular primary diagnosis or diagnosis-related group of cardiovascular disease,
- Non-cardiovascular hospitalisations defined as all hospitalisations other than those defined above,
- Medical visits and technical acts,
- Cardiovascular and antidiabetic drugs reimbursed,
- Non-cardiovascular/antidiabetic drugs reimbursed,
- Lab tests,
- Products and services,
- Nursing acts,
- Physiotherapy acts,
- Transports,
- Sick leave daily allowances, disability allowances, pension,
- Other medical resources.

Healthcare resources related to AF will be:

- Specific Hospitalisations: Hospitalisations with primary diagnosis of AF, or cardioversion, or catheter ablation procedure, or stroke or systemic embolism, or CRB,
- Specific drugs: DOAC, VKA, beta-blockers, amiodarone, dronedarone, other antiarrhythmics,
- Specific lab tests: INR, haemostasis tests, creatinine, creatinine clearance, ALAT, ASAT, including sampling,
- Specific medical visits: cardiologist visit, other medical visits with date corresponding to the date of prescription of specific drugs or lab tests, neurologist visit after stroke event,
- Specific transport: Transport with date corresponding to the date of a specific hospitalisation, medical visit, medical procedure, or lab test.

Healthcare resources cost will be estimated using the French HAS methodological guide for economic evaluations (2011):

- From a societal perspective using diagnosis-related group (DRG) cost for hospitalisations and total cost for other healthcare resources.
- From the French healthcare insurance perspective using stay-related group (STG) cost for hospitalisations and reimbursed cost for other healthcare resources.

9.4. DATA SOURCES

The SNIIRAM database is the national healthcare insurance system database linked to the national hospital-discharge summary database (*Programme de Médicalisation des Systèmes d'Information*, PMSI) and the national death registry, using a unique pseudonimized identifier. It includes the three main healthcare insurance funds (CNAMTS[3], MSA[4], RSI[5]), which represent about 96% of the French population, and currently some of the 19 other smaller French healthcare insurances for specific professional organisations such as militaries, deputies and senators, priests, Opera... (Moulis 2015). To the extent that the SNIIRAM is a national database, all subjects are followed-up until they died. The only dropouts are subjects who leave the country to live abroad and those who join one of the smaller French healthcare insurance organisations not yet included in the SNIIRAM, which is rare and not linked with a disease or healthcare package. The SNIIRAM contains individual pseudonymised information on (Tuppin 2010, Moulis 2015):

- General characteristics: gender, year of birth, affiliation scheme, area of residence;
- Month and year of death;
- Long-term disease (LTD, or ALD in French, and associated ICD-10 codes) with starting and ending date. There is a list of 30 LTD for a total of 3448 available ICD-10 codes, which includes most of chronic diseases with long term and/or expensive treatment; e.g. a disease such as AF is specified by the ICD-10 code within LTD. Registration with a LTD is obtained at the request of a patient's general practitioner and must be validated by the health insurance system physician. Once registered, patients receive full (i.e. 100%) reimbursement for expenditure related to the LTD, as defined by the health authorities. The LTD information is specific for the diagnosis (very low risk of false positives), but not sensitive because not all patients with the disease ask to benefit from a LTD;
- Outpatient reimbursed healthcare expenditures: visits, medical procedures, medical imageries, lab tests, drugs, medical devices, transports, sick leaves… with prescriber and professional caregiver information (medical or paramedical specialty, private/public practice), dates (prescription and dispensation), and codes (but not the medical indication nor result);
- Hospital-discharge summaries from the PMSI: ICD-10 diagnosis codes (primary, linked and associated diagnosis) for all medical, obstetric and surgery hospitalisations, with the date and duration, medical procedures and cost coding system. The hospital discharge summary includes the medical unit summaries when the patient is hospitalized successively in several medical units.

[3] *Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés* (French national health insurance fund for salaried workers)
[4] *Mutuelle Sociale Agricole* (French national health insurance fund for farmers and agricultural workers)
[5] *Régime Social des Indépendants* (French national health insurance fund for independent workers)

Primary diagnosis is the health problem that motivated the admission in the hospital. It is determined at hospital discharge. For patients hospitalized successively in several medical units, the primary diagnosis of the hospitalisation, as well as all medical unit primary diagnoses, are generally taken into account to define the occurrence of an outcome in a pharmacoepidemiology study.

A linked diagnosis can exist only if the primary diagnosis is a care procedure with a code Z of the ICD-10 classification (e.g. chemotherapy session) for a chronic or LTD disease. It indicates the pathology at the origin of the care procedure. Linked diagnoses can be used to define chronic diseases but are generally not taken into account to define the occurrence of an outcome in a pharmacoepidemiology study (many being false positives for the studied outcome).

Associated diagnoses are specified if they represent specific healthcare resources. They are mainly underlying chronic diseases. Associated diagnoses can be used to define chronic diseases but are generally not taken into account to define the occurrence of an outcome in a pharmacoepidemiology study (many being false positives for the studied outcome).

The CNAMTS proposes algorithms to define 56 diseases (CNAMTS 2015), including stroke and ACS. Furthermore, ICD-10 code validation in the SNIIRAM was recently published for ACS and stroke (Bezin 2015, Giroud 2015), and others validation works are on-going.

Non-hospital data are updated every month and hospital-discharge summaries yearly at end of Q3 for the previous year. Access to SNIIRAM is regulated and needs approval from Institute of Health Data (*Institut des Données de Santé* - IDS) and French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

9.5. STUDY SIZE

The Bordeaux Pharmacoépi (BPE) has performed a previous VKA study in the EGB database, a 1/97 permanent random sample of the SNIIRAM, using similar definitions used in this protocol (Blin 2015). Between 2007 and 2011, the numbers of subjects who initiated a VKA for SPAF were 2 197 for the specific NVAF population and 3 345 for the sensitive NVAF population, which represent about 50 000 and 75 000 subjects respectively in the SNIIRAM each year, and 100 000 and 150 000 respectively for a two-year inclusion period.

Among them, the number of subjects treated with rivaroxaban, dabigatran, and VKA, as well as the number of subjects who can be matched for each comparison (rivaroxaban versus VKA, rivaroxaban versus dabigatran) will be a result of the study. Anyway, it should be clearly higher than the 7 131 and 7 133 subjects randomized in the rivaroxaban and VKA arms of the ROCKET AF trial (Patel 2011).

In the previous VKA study cited above (Blin 2015), the outcome incidence rate during VKA exposure was estimated in the specific NVAF population (with similar results for the sensitive NVAF population):

- Stroke and systemic arterial embolism: 1.6 per 100 person-years (PY), 95%CI [1.1-2.1],
- ACS: 1.6 per 100 PY, 95%CI [1.0-2.1],
- CRB: 2.6 per 100 PY, 95%CI [1.9-3.3], with 0.5 [0.3-0.9] cerebral bleeding hospitalisation, 0.8 [0.4-1.1] digestive bleeding hospitalisation, and 1.3 [0.9-1.8] other bleeding hospitalisation,
- Death: 3.5 per 100 PY, 95%CI [2.7-4.3].

Within the ranges of incidence rates of ROCKET AF trial outcomes, the following table shows the minimum hazard ratio that can be identified with a 95% confidence interval excluding 1, for the study group compared to a reference group, according to the incidence of an outcome in the reference group and the sample size for each group for analysis of matched subjects (1:1).

Minimum hazard ratio (< 1 and > 1) with a 95% confidence interval excluding 1, for the study group compared to a reference group, according to the incidence of an outcome in the reference group, sample size for each group (1:1 matching) and normal distribution

Incidence in the reference group	Hazard ratio	Sample size			
		5 000	10 000	15 000	20 000
0.5%	< 1 / >1	0.24 / 2.19	0.43 / 1.78	0.58 / 1.52	0.65 / 1.42
1.0%	< 1 / >1	0.43 / 1.78	0.58 / 1.52	0.70 / 1.35	0.75 / 1.28
1.5%	< 1 / >1	0.53 / 1.61	0.66 / 1.41	0.75 / 1.28	0.79 / 1.23
2.0%	< 1 / >1	0.59 / 1.52	0.70 / 1.35	0.78 / 1.24	0.82 / 1.20
2.5%	< 1 / >1	0.63 / 1.46	0.73 / 1.31	0.81 / 1.21	0.84 / 1.17
3.0%	< 1 / >1	0.66 / 1.41	0.75 / 1.28	0.82 / 1.19	0.89 / 1.16
4.0%	< 1 / >1	0.70 / 1.35	0.78 / 1.24	0.85 / 1.17	0.87 / 1.13
5.0%	< 1 / >1	0.73 / 1.31	0.81 / 1.21	0.86 / 1.15	0.89 / 1.12

9.6. DATA MANAGEMENT

Database extraction criteria will be described in a data extraction plan (DEP) approved prior to initiating extraction. Data extraction will be done by the CNAMTS. The BPE data manager in charge of the project will validate the population extracted by the CNAMTS using the EGB data extraction.

Data transformation, including decision rules, disease definition, exposure definition, outcomes, risk factors, healthcare resources and calculated variables will be detailed in a statistical analysis plan (SAP).

9.7. DATA ANALYSIS

Statistical analysis will be performed using SAS® software (SAS Institute, latest current version, North Carolina, USA), and followed the SAP developed and validated by the scientific committee before analysis.

9.7.1. Generalities

The main analysis will be performed with the specific NVAF matched cohorts and a grace period of 30 days for the drug discontinuation definition. A secondary analysis will be performed using a statistical adjustment with all specific NVAF subjects, and a grace period of 30 days for the drug discontinuation definition.

The following sensitive analyses will be performed for matched cohorts, as well as all for statistical adjustment with all subjects:

- With a grace period of 60 days for drug discontinuation definition, in order to take into account the drug supply in real life, or short discontinuation and poor drug adherence;

- With the sensitive NVAF subjects and the two grace periods for drug discontinuation definition;
- With unspecified bleeding classified as haemorrhagic stroke for the specific and the sensitive NVAF cohorts.

9.7.2. AF disease score

Probable AF will be estimated using AF disease score with a logistic regression model to predict AF diagnosis among subjects without history of rheumatic valve disease or valve replacement, or other probable indications, using variables defined above (see disease definition). This model will be secondary applied to subjects without AF diagnosis, and the threshold for probable AF will be defined with specificity greater than 65%.

9.7.3. Propensity score

The probability to be treated by rivaroxaban or VKA, as well as rivaroxaban or dabigatran will be estimated with hdPS at index date (Schneeweiss 2009, Rassen 2012). The hdPS will be estimated using a logistic regression model with a large set of variables at index date and three-year history before inclusion, including gender, age, CHA_2DS_2-VASc and HAS-BLED scores. The subjects without correspondence between both hdPS distributions will be considered as outliers (two extremities of the hdPS distribution).

9.7.4. Matching

For the rivaroxaban versus VKA comparison, subjects will be matched 1:1 on hdPS and index date within each population (specific and sensitive); For the rivaroxaban versus dabigatran comparison, subjects will be matched 1:1 on high or low DOAC dosage at index date, hdPS and index date within each population (specific and sensitive). The matching will use the logit of the hdPS with calipers of width equal to 0.2 of the standard deviation of the logit of the hdPS (Austin 2011).

9.7.5. Population description

The population description will include the following analyses:

- A flow chart depicting the total number of subjects available in the database, those satisfying the cohort criteria according to the treatment group, outliers (if any), and the number of matched subjects for each comparison, and in each cohort;
- Description of baseline characteristics, three-year history previous to inclusion, follow-up duration for all and matched subjects according to the treatment group (rivaroxaban, dabigatran, VKA), with standardised difference for each comparison planned (rivaroxaban versus VKA, and rivaroxaban versus dabigatran).

9.7.6. Drug exposure

Description of drug use patterns including drug MPR for DOAC, dosage, treatment discontinuation, switch to another anticoagulant, co-dispensation of drug predisposing to bleeding, and one-year and two-year treatment maintenance for all and matched subjects according to the treatment group, with standardised difference for each comparison planned (rivaroxaban versus VKA, and rivaroxaban versus dabigatran).

9.7.1. Outcomes

Outcomes will be analysed using survival methods for the first occurrence of each outcome:

- Estimation of the one-year and two-year cumulative incidence of each outcome, and according to individual diagnose of each outcome, during drug exposure for rivaroxaban, dabigatran, and VKA, using Kaplan-Meier estimate for death and cumulative incidence function for clinical outcomes, in order to take into account death as a competing risk.
- Estimation of the incidence rate (per 100 PY exposed) of each outcome, and according to individual diagnose of each outcome, during drug exposure or if the risk is not constant over the time, during periods with a constant risk.
- Comparison of the one-year and two-year risk of each outcome during drug exposure, rivaroxaban versus VKA, and rivaroxaban versus dabigatran, using Cox proportional hazard risk model (Cox 1972) for death and Fine and Gray model (Fine 1999) for clinical outcomes, in order to take into account death as a competing risk. Hazard ratio will presented as a point estimate with its 95% confidence interval.
  - Main analysis will compare the incidence of each outcome for matched subjects with time dependant variables adjustment for drug predisposing to bleeding during drug exposure (time dependant variable),
  - Secondary analysis will compare the incidence of each outcome with all subjects, except outliers, with adjustment for hdPS and drug predisposing to bleeding during drug exposure (time dependant variable) for the rivaroxaban versus VKA comparison; and plus low or high DOAC dosage at index date for the rivaroxaban versus dabigatran comparison.
  - Prognostic analysis will be done with all subjects, but outliers, to assess outcome risk factors, including gender, age, CHA_2DS_2-VASc and HAS-BLED scores, low or high dosage at index date for DOAC, drug predisposing to bleeding during drug exposure (time dependant variable) and significant baseline characteristics. The significant baseline characteristics will be identified firstly with univariate analyses, and therefore using a forward stepwise (taking into account the size of the database, the p threshold will be set at 1/1000 for variables selection and at 5% for the stepwise procedure).
- Estimation of cumulative incidence of each outcome during post-anticoagulant exposure period for rivaroxaban, dabigatran, and VKA (i.e. after anticoagulant discontinuation), using Kaplan-Meier estimate for death, cumulative incidence function for clinical outcomes (stroke and SE, ACS, CRB), in order to take into account death as a competing risk.

9.7.2. Healthcare resources and cost

Healthcare resources and cost will be described for all and matched subjects according to the treatment group (rivaroxaban, dabigatran, VKA) during the first year of follow-up for all patients, and during two years of follow-up for those included in 2013. Comparison (rivaroxaban versus VKA, and rivaroxaban versus dabigatran) will be done for matched cohorts.

9.8. QUALITY CONTROL

The Bordeaux Pharmacoépi, INSERM CIC1401, has implemented a quality management system for all its activities. CNAMTS data extraction will be validated

using the expected population size estimated using the EGB. An independent double programming will be performed for main criteria and analyses, and the results compared for validation. All statistical logs are kept and can be provided. In the case of interim analyses, the database for the interim analysis is locked and kept for ulterior validation if needed. The statistical analysis report (SAR) is included in the final study report.

9.9. LIMITATIONS OF THE RESEARCH METHODS

The SNIIRAM is a national healthcare claims database linked to the national hospital discharge summaries database that covers more than 95% of the French population. It provides a unique opportunity to identify all new users of DOAC or VKA in NVAF in 2013-2014, with exhaustive information about reimbursed treatments out of hospital and use of reimbursed healthcare resources, as well as all hospitalisations for the outcomes of interest. Furthermore, the SNIIRAM has the advantage of any study extracting patient records from an existing database that are not impacted by the study.

This is also the main limit of this claims and hospitalisation database that was built for administrative and reimbursement purposes with a lack of clinical data and biological results, including some risk factors such as smoking status, body mass index, blood pressure, and cholesterol values, that could be impact the patient prognosis. However, statistical methods such as PS and hdPS were developed to improve control of confounding using a large number of covariates ascertained from patients' healthcare claims data, as these variables may collectively be proxies for unmeasured confounders (Schneeweiss 2009, Rassen 2012).

Selection bias

Since all subjects identified with extraction criteria in 2013-2014 will be extracted from a national database, there is no study selection bias, nor attrition bias, except very rare withdrawals from one of the healthcare insurance systems including and covering more than 95% of the French population.

Information bias

- **AF indication**: Anticoagulants are prescribed for several medical conditions. The main analysis will be done using the specific NVAF population, with a highly specific definition of the disease (LTD for AF or a hospitalisation with an AF diagnosis before the index date). Nevertheless, several subjects with an AF do not have an LTD and are not hospitalized or hospitalized for another primary diagnosis without AF reported in the linked or associated diagnosis, during the 3 years before index date. To assess the robustness of the main analysis results, secondary analyses will be performed using a sensitive definition for NVAF (sensitive NVAF population) defined as the subjects of the specific NVAF population, plus those with probable information using an AF disease score. In terms of bias, there is no reason that the specificity of AF definition will be different according to the treatment group.
- **Drug exposure**: VKA and DOAC exposure will be assessed using exhaustive non-hospital drug claims. Drugs prescribed during hospital stays are not recorded and could represent a potential risk of exposure underestimation. However, it should concern few subjects for a very short period of time, and the impact over a 3-year study period should be negligible. Drug expose is defined as the time between index date and the end of follow-up for subjects without drug withdrawal, i.e. as the time between index date and last dispensation + 90 days (30 days for the duration of the

last dispensation or less for small DOAC packaging, plus a grace period of 60 days), or before in case of drug switch. Two grace periods will be considered (60 and 30 days) to estimate the true drug withdrawal, in order to take into account the drug supply in real life, or short discontinuation and bad drug adherence that could be a risky situation for ischemic event, directly in relation with the use of the DOAC or VKA. This would also cover short hospital stays.

- **Outcomes**: Since deaths are recorded in the database using the national death registry, there is no information bias for this outcome. Death is a competing risk of other clinical outcomes (stroke and SE, ACS, CRB). To take into account this, the model proposed by Fine and Gray will be used to analyse clinical outcomes (Fine 1999). Clinical outcomes will be defined using the ICD-10 discharge primary diagnosis. Miscoding cannot be excluded but should be sparse for the clearly defined events studied. Nevertheless, the PMSI coding is fully independent from the study and there is no reason that a potential miscoding will be different between anticoagulant drugs, excluding an information bias. For strokes classified as undefined because CT scan or NMR were not performed, it was decided to classify undefined stroke with ischemic stroke but some could be cases of haemorrhagic stroke. A sensitivity analysis will be performed by classifying undefined stroke as haemorrhagic stroke.

Counfouding bias

The choice between a VKA and a DOAC could be related to potential confounding. To control this potential bias, the main analysis will use 1:1 matching on high dimensional propensity score (hdPS), which includes main known risk factors (gender, age, AF risk factor score, bleeding risk factor score). Indeed, one of the main limits of this database, as for many administrative databases, is the lack of information for some risk factors (e.g. smoking status, body mass index, biological results, etc.), which may or not be confounders. Without such information, it is not possible to compare the distribution of these risks factors between treatment groups, or to take it into account in the matching.

The propensity score is a statistical technique that attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that predict receiving the treatment. The propensity score, and more recently hdPS (Schneeweiss 2009, Rassen 2012), were developed to summarise a large set of variables that characterize each subject for status and unmeasured confounders not recorded in a database (i.e. drugs, medical status, hospitalisation, other co-morbidities directly, or indirectly linked with unmeasured confounders). Adjusting for large numbers of covariates ascertained from subject healthcare claims data may improve control of confounding, as these variables may collectively be proxies for unobserved factors.

9.10. OTHER ASPECTS

None.

10. PROTECTION OF HUMAN SUBJECTS

This project is a database analysis with individual anonymous information for which subject informed consent is not required. Data extraction from the SNIIRAM is regulated and needs approval from Institute of Health Data (*Institut des Données de Santé* - IDS)

and French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This project is a database analysis using anonymous individual information without any spontaneous reporting. Study outcomes will be reported in aggregate in the final study report, and no individual or expedited reporting is required, according to the EMA Guideline on good pharmacovigilance practices cited above (GVP IV*), as well as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

* The latest revision of the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) from EMA (coming into effect 16 Sept 2014) specifies: *For Non-interventional post-authorisation studies based on secondary use of data (VI.C.1.2.1.b): "The design of such studies is characterised by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses. For these studies, the reporting of suspected adverse reactions in the form of ICSRs is not required. Reports of adverse events/reactions should be summarised as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting*".

12. PLANS FOR DISSEMINATING AND COMMUNATING STUDY RESULTS

This database analysis will be performed by the Bordeaux Pharmacoépi, INSERM CIC1401, an academic research organization (ARO), for which scientific communication and publication is a major component of its activities. Study methods and results will be submitted to scientific meetings and for publication in international scientific journals.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Title
1	List of ICD-10 codes for bleeding

ANNEX 2. ENCEPP CHEKLIST FOR STUDY PROTOCOLS

A copy of the ENCePP Checklist for Study protocols available at website encepp.eu/standards_and_guidances completed and signed by the main author of the study protocol is included in ANNEX 2.

ANNEX 3. ADDITIONAL INFORMATION

None.

ANNEX 4. SIGNATURE PAGES

ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

Number 1: List of ICD-10 codes for bleeding leading to an hospitalization

1) All ICD codes with the following label were selected: “hémorragie (hemorrhage), hémorragique (hemorrhagic), saignement (bleeding), épistaxis (epistaxis), otorragie (otorrhagia), hématémèse (hematemesis), rectorragie (proctorrhagia), melena (melena), hematuria (hematuria), hémoptysie (hemoptysis), métrorragies (metrorrhagia), hémopéritoine (hemoperitonea), hémothorax (hemothorax), hémopéricarde (hemopericardia)”.

2) ICD label that do not correspond to a bleeding event were excluded (grey list), such as:
- No bleeding
- Chronic disease with bleeding in the definition
- Infectious diseases with bleeding in the definition
- Aftereffect of cerebral haemorrhage
- Accident during surgical and medical care, including other events than a bleeding.

3) ICD code for bleeding during abortion or delivery are also excluded (grey list):

ICD-10 code	ICD label (French)	ICD label (English)	Key word
Selected Codes			
D62	Anémie posthémorragique aiguë	Acute posthaemorrhagic anaemia	Hémorragique
D683	Troubles hémorragiques dus à des anticoagulants circulants	Haemorrhagic disorder due to circulating anticoagulants	Hémorragique
D698	Autres affections hémorragiques précisées	Other specified haemorrhagic conditions	Hémorragique
D699	Affection hémorragique, sans précision	Haemorrhagic condition, unspecified	Hémorragique
H113	Hémorragie conjonctivale	Conjunctival haemorrhage	Hémorragie
H313	Hémorragie et rupture de la choroïde	Choroidal haemorrhage and rupture	Hémorragie
H356	Hémorragie rétinienne	Retinal haemorrhage	Hémorragie
H431	Hémorragie du corps vitré	Vitreous haemorrhage	Hémorragie
H450	Hémorragie du corps vitré au cours de maladies classées ailleurs	Vitreous haemorrhage in diseases classified elsewhere	Hémorragie
H922	Otorragie	Otorrhagia	Otorragie
I230	Hémopéricarde comme complication récente d'un infarctus aigu du myocarde	Haemopericardium as current complication following acute myocardial infarction	Hémopéricarde
I312	Hémopéricarde, non classé ailleurs	Haemopericardium, not elsewhere classified	Hémopéricarde
I600	Hémorragie sous-arachnoïdienne de la bifurcation et du siphon carotidien	Subarachnoid haemorrhage from carotid siphon and bifurcation	Hémorragie
I601	Hémorragie sous-arachnoïdienne de l'artère cérébrale moyenne	Subarachnoid haemorrhage from middle cerebral artery	Hémorragie

I602	Hémorragie sous-arachnoïdienne de l'artère communicante antérieure	Subarachnoid haemorrhage from anterior communicating artery	Hémorragie
I603	Hémorragie sous-arachnoïdienne de l'artère communicante postérieure	Subarachnoid haemorrhage from posterior communicating artery	Hémorragie
I604	Hémorragie sous-arachnoïdienne de l'artère basilaire	Subarachnoid haemorrhage from basilar artery	Hémorragie
I605	Hémorragie sous-arachnoïdienne de l'artère vertébrale	Subarachnoid haemorrhage from vertebral artery	Hémorragie
I606	Hémorragie sous-arachnoïdienne d'autres artères intracrâniennes	Subarachnoid haemorrhage from other intracranial arteries	Hémorragie
I607	Hémorragie sous-arachnoïdienne d'une artère intracrânienne, sans précision	Subarachnoid haemorrhage from intracranial artery, unspecified	Hémorragie
I608	Autres hémorragies sous-arachnoïdiennes	Other subarachnoid haemorrhage	Hémorragie
I609	Hémorragie sous-arachnoïdienne, sans précision	Subarachnoid haemorrhage, unspecified	Hémorragie
I610	Hémorragie intracérébrale hémisphérique, sous-corticale	Intracerebral haemorrhage in hemisphere, subcortical	Hémorragie
I611	Hémorragie intracérébrale hémisphérique, corticale	Intracerebral haemorrhage in hemisphere, cortical	Hémorragie
I612	Hémorragie intracérébrale hémisphérique, non précisée	Intracerebral haemorrhage in hemisphere, unspecified	Hémorragie
I613	Hémorragie intracérébrale du tronc cérébral	Intracerebral haemorrhage in brain stem	Hémorragie
I614	Hémorragie intracérébrale cérébelleuse	Intracerebral haemorrhage in cerebellum	Hémorragie
I615	Hémorragie intracérébrale intraventriculaire	Intracerebral haemorrhage, intraventricular	Hémorragie
I616	Hémorragie intracérébrale, localisations multiples	Intracerebral haemorrhage, multiple localized	Hémorragie
I618	Autres hémorragies intracérébrales	Other intracerebral haemorrhage	Hémorragie
I619	Hémorragie intracérébrale, sans précision	Intracerebral haemorrhage, unspecified	Hémorragie
I620	Hémorragie sous-durale (aiguë) (non traumatique)	Subdural haemorrhage (acute)(nontraumatic)	Hémorragie
I621	Hémorragie extradurale non traumatique	Nontraumatic extradural haemorrhage	Hémorragie
I629	Hémorragie intracrânienne (non traumatique), sans précision	Intracranial haemorrhage (nontraumatic), unspecified	Hémorragie
I850	Varices œsophagiennes hémorragiques	Oesophageal varices with bleeding	Hémorragique
I983	Varices œsophagiennes hémorragiques au cours de maladies classées ailleurs	Oesophageal varices with bleeding in diseases classified elsewhere	Hémorragique
J942	Hémothorax	Haemothorax	Hémothorax
K226	Syndrome de dilacération hémorragique gastro-œsophagienne	Gastro-oesophageal laceration-haemorrhage syndrome	Hémorragique
K250	Ulcère de l'estomac aigu, avec hémorragie	Gastric ulcer: Acute with haemorrhage	Hémorragie
K252	Ulcère de l'estomac aigu, avec hémorragie et perforation	Gastric ulcer: Acute with both haemorrhage and perforation	Hémorragie
K254	Ulcère de l'estomac chronique ou non précisé, avec hémorragie	Gastric ulcer: Chronic or unspecified with haemorrhage	Hémorragie
K256	Ulcère de l'estomac chronique ou non précisé, avec hémorragie et perforation	Gastric ulcer: Chronic or unspecified with both haemorrhage and perforation	Hémorragie
K260	Ulcère du duodénum aigu, avec hémorragie	Duodenal ulcer: Acute with haemorrhage	Hémorragie
K262	Ulcère du duodénum aigu, avec hémorragie et perforation	Duodenal ulcer: Acute with both haemorrhage and perforation	Hémorragie

K264	Ulcère du duodénum chronique ou non précisé, avec hémorragie	Duodenal ulcer: Chronic or unspecified with haemorrhage	Hémorragie
K266	Ulcère du duodénum chronique ou non précisé, avec hémorragie et perforation	Duodenal ulcer: Chronic or unspecified with both haemorrhage and perforation	Hémorragie
K270	Ulcère digestif, de siège non précisé, aigu avec hémorragie	Peptic ulcer, site unspecified: Acute with haemorrhage	Hémorragie
K272	Ulcère digestif, de siège non précisé, aigu avec hémorragie et perforation	Peptic ulcer, site unspecified: Acute with both haemorrhage and perforation	Hémorragie
K274	Ulcère digestif, de siège non précisé, chronique ou non précisé, avec hémorragie	Peptic ulcer, site unspecified: Chronic or unspecified with haemorrhage	Hémorragie
K276	Ulcère digestif, de siège non précisé, chronique ou non précisé, avec hémorragie et perforation	Peptic ulcer, site unspecified: Chronic or unspecified with both haemorrhage and perforation	Hémorragie
K280	Ulcère gastro-jéjunal aigu, avec hémorragie	Gastrojejunal ulcer: Acute with haemorrhage	Hémorragie
K282	Ulcère gastro-jéjunal aigu, avec hémorragie et perforation	Gastrojejunal ulcer: Acute with both haemorrhage and perforation	Hémorragie
K284	Ulcère gastro-jéjunal chronique ou non précisé, avec hémorragie	Gastrojejunal ulcer: Chronic or unspecified with haemorrhage	Hémorragie
K286	Ulcère gastro-jéjunal chronique ou non précisé, avec hémorragie et perforation	Gastrojejunal ulcer: Chronic or unspecified with both haemorrhage and perforation	Hémorragie
K290	Gastrite hémorragique aiguë	Acute haemorrhagic gastritis	Hémorragique
K625	Hémorragie de l'anus et du rectum	Haemorrhage of anus and rectum	Hémorragie
K661	Hémopéritoine	Haemoperitoneum	Hémopéritoine
K762	Nécrose hémorragique centrale du foie	Central haemorrhagic necrosis of liver	Hémorragique
K920	Hématémèse	Haematemesis	Hématémèse
K921	Mélæna	Melaena	mélaena
K922	Hémorragie gastro-intestinale, sans précision	Gastrointestinal haemorrhage, unspecified	Hémorragie
M250	Hémarthrose	Haemarthrosis	Hémarthrose
N020	Hématurie récidivante et persistante avec anomalies glomérulaires mineures	Recurrent and persistent haematuria: Minor glomerular abnormality	Hématurie
N021	Hématurie récidivante et persistante avec lésions glomérulaires segmentaires et focales	Recurrent and persistent haematuria: Focal and segmental glomerular lesions	Hématurie
N022	Hématurie récidivante et persistante avec glomérulonéphrite membraneuse diffuse	Recurrent and persistent haematuria: Diffuse membranous glomerulonephritis	Hématurie
N023	Hématurie récidivante et persistante avec glomérulonéphrite proliférative mésangiale diffuse	Recurrent and persistent haematuria: Diffuse mesangial proliferative glomerulonephritis	Hématurie
N024	Hématurie récidivante et persistante avec glomérulonéphrite proliférative endocapillaire diffuse	Recurrent and persistent haematuria: Diffuse endocapillary proliferative glomerulonephritis	Hématurie
N025	Hématurie récidivante et persistante avec glomérulonéphrite mésangiocapillaire diffuse	Recurrent and persistent haematuria: Diffuse mesangiocapillary glomerulonephritis	Hématurie
N026	Hématurie récidivante et persistante avec maladie à dépôt dense	Recurrent and persistent haematuria: Dense deposit disease	Hématurie
N027	Hématurie récidivante et persistante avec glomérulonéphrite diffuse en croissant	Recurrent and persistent haematuria: Diffuse crescentic glomerulonephritis	Hématurie
N028	Hématuries récidivantes et persistantes avec autres lésions	Recurrent and persistent haematuria: Other	Hématurie

	morphologiques		
N029	Hématurie récidivante et persistante, sans précision	Recurrent and persistent haematuria: Unspecified	Hématurie
N421	Congestion et hémorragie prostatiques	Congestion and haemorrhage of prostate	Hémorragie
N920	N920 « Menstruation trop abondante et trop fréquente avec cycle menstruel régulier »	Excessive and frequent menstruation with regular cycle	Menstruation trop abondante
N920	N921 « Menstruation trop abondante et trop fréquente avec cycle menstruel irrégulier »	Excessive and frequent menstruation with irregular cycle	Menstruation trop abondante
N923	Saignements de l'ovulation	Ovulation bleeding	Saignement
N924	Saignements abondants de la préménopause	Excessive bleeding in the premenopausal period	Saignement
N930	Saignements post-coïtaux et de contact	Postcoital and contact bleeding	Saignement
N938	Autres saignements anormaux précisés de l'utérus et du vagin	Other specified abnormal uterine and vaginal bleeding	Saignement
N939	Saignement anormal de l'utérus et du vagin, sans précision	Abnormal uterine and vaginal bleeding, unspecified	Saignement
N950	Saignements post-ménopausiques	Postmenopausal bleeding	Saignement
O031	Avortement spontané incomplet, compliqué d'une hémorragie retardée ou sévère	Spontaneous abortion: Incomplete, complicated by delayed or excessive haemorrhage	Hémorragie
O036	Avortement spontané complet ou sans précision, compliqué d'une hémorragie retardée ou sévère	Spontaneous abortion: Complete or unspecified, complicated by delayed or excessive haemorrhage	Hémorragie
O041	Avortement médical incomplet, compliqué d'une hémorragie retardée ou sévère	Medical abortion: Incomplete, complicated by delayed or excessive haemorrhage	Hémorragie
O046	Avortement médical complet ou sans précision, compliqué d'une hémorragie retardée ou sévère	Medical abortion: Complete or unspecified, complicated by delayed or excessive haemorrhage	Hémorragie
O051	Autres formes d'avortement incomplet, compliqué d'une hémorragie retardée ou sévère	Other abortion: Incomplete, complicated by delayed or excessive haemorrhage	Hémorragie
O056	Autres formes d'avortement complet ou sans précision, compliqué d'une hémorragie retardée ou sévère	Other abortion: Complete or unspecified, complicated by delayed or excessive haemorrhage	Hémorragie
O061	Avortement sans précision, incomplet, compliqué d'une hémorragie retardée ou sévère	Unspecified abortion: Incomplete, complicated by delayed or excessive haemorrhage	Hémorragie
O066	Avortement sans précision, complet ou sans précision, compliqué d'une hémorragie retardée ou sévère	Unspecified abortion: Complete or unspecified, complicated by delayed or excessive haemorrhage	Hémorragie
O071	Échec d'une tentative d'avortement médical, compliqué d'une hémorragie retardée ou sévère	Failed medical abortion, complicated by delayed or excessive haemorrhage	Hémorragie
O076	Échec d'une tentative d'avortement, autres et sans précision, compliqués d'une hémorragie retardée ou sévère	Other and unspecified failed attempted abortion, complicated by delayed or excessive haemorrhage	Hémorragie
O081	Hémorragie retardée ou sévère consécutive à un avortement, une grossesse extra-utérine et molaire	Delayed or excessive haemorrhage following abortion and ectopic and molar pregnancy	Hémorragie
O208	Autres hémorragies du début de la grossesse	Other haemorrhage in early pregnancy	Hémorragie
O209	Hémorragie du début de la grossesse, sans précision	Haemorrhage in early pregnancy, unspecified	Hémorragie

O441	Placenta prævia avec hémorragie	Placenta praevia with haemorrhage	Hémorragie
O460	Hémorragie précédant l'accouchement avec anomalie de la coagulation	Antepartum haemorrhage with coagulation defect	Hémorragie
O468	Autres hémorragies précédant l'accouchement	Other antepartum haemorrhage	Hémorragie
O469	Hémorragie précédant l'accouchement, sans précision	Antepartum haemorrhage, unspecified	Hémorragie
O670	Hémorragie pendant l'accouchement avec anomalie de la coagulation	Intrapartum haemorrhage with coagulation defect	Hémorragie
O678	Autres hémorragies pendant l'accouchement	Other intrapartum haemorrhage	Hémorragie
O679	Hémorragie pendant l'accouchement, sans précision	Intrapartum haemorrhage, unspecified	Hémorragie
O720	Hémorragie de la délivrance (troisième période)	Third-stage haemorrhage	Hémorragie
O721	Autres hémorragies immédiates du post-partum	Other immediate postpartum haemorrhage	Hémorragie
O722	Hémorragie du post-partum, tardive et secondaire	Delayed and secondary postpartum haemorrhage	Hémorragie
R040	Épistaxis	Epistaxis	Epistaxis
R041	Hémorragie de la gorge	Haemorrhage from throat	Hémorragie
R042	Hémoptysie	Haemoptysis	Hémoptysie
R048	Hémorragie d'autres parties des voies respiratoires	Haemorrhage from other sites in respiratory passages	Hémorragie
R049	Hémorragie des voies respiratoires, sans précision	Haemorrhage from respiratory passages, unspecified	Hémorragie
R31	Hématurie, sans précision	Unspecified haematuria	Hématurie
R58	Hémorragie, non classée ailleurs	Haemorrhage, not elsewhere classified	Hémorragie
S064	Hémorragie épidurale	Epidural haemorrhage	Hémorragie
S065	Hémorragie sous-durale traumatique	Traumatic subdural haemorrhage	Hémorragie
S066	Hémorragie sous-arachnoïdienne traumatique	Traumatic subarachnoid haemorrhage	Hémorragie
S260	Lésion traumatique du cœur avec hémopéricarde	Injury of heart with haemopericardium	Hémopéricarde
S271	Hémothorax traumatique	Traumatic haemothorax	Hémothorax
T792	Hémorragie traumatique secondaire et récidivante	Traumatic secondary and recurrent haemorrhage	Hémorragie
T810	Hémorragie et hématome compliquant un acte à visée diagnostique et thérapeutique, non classés ailleurs	Haemorrhage and haematoma complicating a procedure, not elsewhere classified	Hémorragie

Unselected Codes:

1. No bleeding

D473	Thrombocytémie essentielle (hémorragique)	Essential (haemorrhagic) thrombocythaemia	Hémorragique
I694	Séquelles d'accident vasculaire cérébral, non précisé comme étant	Sequelae of stroke, not specified as haemorrhage or infarction	Hémorragique

	hémorragique ou par infarctus		
I859	Varices oesophagiennes, (non hémorragiques)	Oesophageal varices without bleeding	Hémorragique
I982	Varices oesophagiennes non hémorragiques au cours de maladies classées ailleurs	Oesophageal varices without bleeding in diseases classified elsewhere	Hémorragique
2. Chronic disease with bleeding in the definition			
I780	Télangiectasie hémorragique héréditaire	Hereditary haemorrhagic telangiectasia	**I780**
K518	Autres recto-colites hémorragiques	Other ulcerative colitis	Hémorragique
K519	Recto-colite hémorragique, sans précision	Ulcerative colitis, unspecified	Hémorragique
3. Infectious diseases with bleeding in the definition			
A043	Infection entéro-hémorragique à Escherichia coli	Enterohaemorrhagic Escherichia coli infection	Hémorragique
A270	Leptospirose ictéro-hémorragique	Leptospirosis icterohaemorrhagica	Hémorragique
A91	Fièvre hémorragique due au virus de la dengue	Dengue haemorrhagic fever	Hémorragique
A960	Fièvre hémorragique de Junin	Junin haemorrhagic fever	Hémorragique
A961	Fièvre hémorragique de Machupo	Machupo haemorrhagic fever	Hémorragique
A968	Autres fièvres hémorragiques à arénavirus	Other arenaviral haemorrhagic fevers	Hémorragique
A969	Fièvre hémorragique à arénavirus, sans précision	Arenaviral haemorrhagic fever, unspecified	Hémorragique
A980	Fièvre hémorragique de Crimée [du Congo]	Crimean-Congo haemorrhagic fever	Hémorragique
A981	Fièvre hémorragique d'Omsk	Omsk haemorrhagic fever	Hémorragique
A985	Fièvre hémorragique avec syndrome rénal	Haemorrhagic fever with renal syndrome	Hémorragique
A988	Autres fièvres hémorragiques virales précisées	Other specified viral haemorrhagic fevers	Hémorragique
A99	Fièvre hémorragique virale, sans précision	Unspecified viral haemorrhagic fever	Hémorragique
B303	Conjonctivite hémorragique (aiguë épidémique) (entérovirale)	Acute epidemic haemorrhagic conjunctivitis (enteroviral)	Hémorragique
G361	Leucoencéphalite hémorragique aiguë et subaiguë [Hurst]	Acute and subacute haemorrhagic leukoencephalitis [Hurst]	Hémorragique
4. After effect of cerebral hemorrhage			
I690	Séquelles d'hémorragie sous-arachnoïdienne	Sequelae of subarachnoid haemorrhage	Hémorragie
I691	Séquelles d'hémorragie intracérébrale	Sequelae of intracerebral haemorrhage	Hémorragie
I692	Séquelles d'autres hémorragies intracrâniennes non traumatiques	Sequelae of other nontraumatic intracranial haemorrhage	Hémorragie

5. Accident during surgical and medical care, including other events than a bleeding			
T810	Hémorragie et hématome compliquant un acte à visée diagnostique et thérapeutique, non classés ailleurs	Haemorrhage and haematoma complicating a procedure, not elsewhere classified	Hémorragie
Y60	Coupure, piqûre, perforation ou hémorragie accidentelles au d'un intervention chirurgical ou d'un acte médical	Unintentional cut, puncture, perforation or haemorrhage during surgical and medical care	
Y600	• Au cours d'une intervention chirurgicale	• During surgical operation	Hémorragie
Y601	• Au cours d'une perfusion ou transfusion	• During infusion or transfusion	Hémorragie
Y602	• Au cours d'une dialyse rénale ou autre perfusion	• During kidney dialysis or other perfusion	Hémorragie
Y603	• Au cours d'une injection ou vaccination	• During injection or immunization	Hémorragie
Y604	• Au cours d'une endoscopie	• During endoscopic examination	Hémorragie
Y605	• Au cours d'un cathétérisme cardiaque	• During heart catheterization	Hémorragie
Y606	• Au cours d'une aspiration, d'une ponction et d'un autre cathétérisme	• During aspiration, puncture and other catheterization	Hémorragie
Y607	• Au cours de l'administration d'un lavement	• During administration of enema	Hémorragie
Y608	• Au cours d'autres actes médicaux et chirurgicaux	• During other surgical and medical care	Hémorragie
Y609	• Au cours d'un acte médical et chirurgical, sans précision	• During unspecified surgical and medical care	Hémorragie
6. ICD code for bleeding during abortion or delivery			
O031	Avortement spontané incomplet, compliqué d'une hémorragie retardée ou sévère	Spontaneous abortion: Incomplete, complicated by delayed or excessive haemorrhage	Hémorragie
O036	Avortement spontané complet ou sans précision, compliqué d'une hémorragie retardée ou sévère	Spontaneous abortion: Complete or unspecified, complicated by delayed or excessive haemorrhage	Hémorragie
O041	Avortement médical incomplet, compliqué d'une hémorragie retardée ou sévère	Medical abortion: Incomplete, complicated by delayed or excessive haemorrhage	Hémorragie
O046	Avortement médical complet ou sans précision, compliqué d'une hémorragie retardée ou sévère	Medical abortion: Complete or unspecified, complicated by delayed or excessive haemorrhage	Hémorragie
O051	Autres formes d'avortement incomplet, compliqué d'une hémorragie retardée ou sévère	Other abortion: Incomplete, complicated by delayed or excessive haemorrhage	Hémorragie
O056	Autres formes d'avortement complet ou sans précision, compliqué d'une hémorragie retardée ou sévère	Other abortion: Complete or unspecified, complicated by delayed or excessive haemorrhage	Hémorragie
O061	Avortement sans précision, incomplet, compliqué d'une hémorragie retardée ou sévère	Unspecified abortion: Incomplete, complicated by delayed or excessive haemorrhage	Hémorragie
O066	Avortement sans précision, complet ou sans précision, compliqué d'une hémorragie retardée ou sévère	Unspecified abortion: Complete or unspecified, complicated by delayed or excessive haemorrhage	Hémorragie
O071	Échec d'une tentative d'avortement médical, compliqué d'une hémorragie retardée ou sévère	Failed medical abortion, complicated by delayed or excessive haemorrhage	Hémorragie
O076	Échec d'une tentative d'avortement, autres et sans précision, compliqués d'une hémorragie retardée ou sévère	Other and unspecified failed attempted abortion, complicated by delayed or excessive haemorrhage	Hémorragie
O081	Hémorragie retardée ou sévère consécutive à un avortement, une grossesse extra-utérine et molaire	Delayed or excessive haemorrhage following abortion and ectopic and molar pregnancy	Hémorragie

O208	Autres hémorragies du début de la grossesse	Other haemorrhage in early pregnancy	Hémorragie
O209	Hémorragie du début de la grossesse, sans précision	Haemorrhage in early pregnancy, unspecified	Hémorragie
O441	Placenta prævia avec hémorragie	Placenta praevia with haemorrhage	Hémorragie
O460	Hémorragie précédant l'accouchement avec anomalie de la coagulation	Antepartum haemorrhage with coagulation defect	Hémorragie
O468	Autres hémorragies précédant l'accouchement	Other antepartum haemorrhage	Hémorragie
O469	Hémorragie précédant l'accouchement, sans précision	Antepartum haemorrhage, unspecified	Hémorragie
O670	Hémorragie pendant l'accouchement avec anomalie de la coagulation	Intrapartum haemorrhage with coagulation defect	Hémorragie
O678	Autres hémorragies pendant l'accouchement	Other intrapartum haemorrhage	Hémorragie
O679	Hémorragie pendant l'accouchement, sans précision	Intrapartum haemorrhage, unspecified	Hémorragie
O720	Hémorragie de la délivrance (troisième période)	Third-stage haemorrhage	Hémorragie
O721	Autres hémorragies immédiates du post-partum	Other immediate postpartum haemorrhage	Hémorragie
O722	Hémorragie du post-partum, tardive et secondaire	Delayed and secondary postpartum haemorrhage	Hémorragie

ANNEX 4: ENCEPP CHEKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

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 page number(s) 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). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Benefit-Risk Of arterial THrombotic prEvention with Rivaroxaban for atrial fibrillation in daily clinical practice. A French cohort within the nationwide claims and hospital database (BROTHER)

Study reference number:
18656

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	15
1.1.2 End of data collection[2]	☒	☐	☐	15
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	2
1.1.6 Final report of study results.	☒	☐	☐	15

Comments:
1.1.3, 1.1.4: These items are not planned for this study.

[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.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
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)	☒	☐	☐	16-17
2.1.2 The objective(s) of the study?	☒	☐	☐	17-18
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	18-19
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.5: There is a hypothesis: the therapeutic benefit of DOAC would be better than that of VKA (results observed in the premarketing clinical trials).

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	21-22
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	28

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	19
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	18-19
4.2.2 Age and sex?	☒	☐	☐	19
4.2.3 Country of origin?	☒	☐	☐	19
4.2.4 Disease/indication?	☒	☐	☐	19
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19-20

Comments:

4.2.5: This item is not clearly described in the protocol, but included in the section 9.7.5 "Population description" (page 27) with the description of the 3-year history previous to inclusion. This item will be more defined in the statistical analysis plan.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and	☒	☐	☐	21

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
categorising exposure)				
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	29-30
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	21
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

5.4, 5.5: Drug exposures will be assessed using exhaustive non-hospital drug claims.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	21-22
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	25-30

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	22-23
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

7.2: No effect modifiers known.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	21-24
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	21-22-24
8.1.3 Covariates?	☒	☐	☐	24-25
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	24
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	24-25

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	24-25
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	24
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	24
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	21
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	24

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	25-26

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	28
10.2 Is the choice of statistical techniques described?	☒	☐	☐	26 to 28
10.3 Are descriptive analyses included?	☒	☐	☐	27
10.4 Are stratified analyses included?	☒	☐	☐	26 to 28
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	26to28-30
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

10.6: See item 7.2.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	28-29
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	29-30
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	26-31

Comments:

11.1: The SNIIRAM (data sources) contains exhaustive information about reimbursed treatments out of hospital and use of reimbursed healthcare resources.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	29
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	29-30
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	29-30

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	30-31
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	30-31

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	15

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	31
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	31

Comments:

Name of the main author of the protocol: Dr Patrick BLIN

Date: 18/12/20

Signature: [redacted]

ENCePP Checklist for Study Protocols (Revision 2) 5

ANNEX 4: SIGNATURE PAGES

Signature Page – Sponsor

Title	Benefit-Risk Of arterial THrombotic prEvention with Rivaroxaban for atrial fibrillation in daily clinical practice. A French cohort within the nationwide claims and hospital database (BROTHER).
Protocol version identifier	Version 1.0
Date of last version of protocol	18 December 2015
IMPACT study number	18656
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not registered
Active substance (medicinal product)	Xarelto® 15 mg (CIP: 34009 219 225 1 6, 34009 219 226 8 4, 34009 219 227 4 5, 34009 219 228 0 6, 34009 581 416 7 6 Xarelto® 20 mg (CIP code: 34009 219 229 7 4, 34009 219 230 5 6, 34009 219 231 1 7, 34009 581 419 6 6
Marketing authorization holder(s)	Bayer HealthCare AG
Function	Qualified person responsible for pharmacovigilance
Name	Miachael Kayser
Title	Doctor
Address	Bayer Pharma AG D-13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 18.12.2015 [redacted] Gerhard Reille
Deputy - QPPV

Signature Page – Coordinating centre

Title	Benefit-Risk Of arterial THrombotic prEvention with Rivaroxaban for atrial fibrillation in daily clinical practice. A French cohort within the nationwide claims and hospital database (BROTHER).
Protocol version identifier	Version 1.0
Date of last version of protocol	18 December 2015
IMPACT study number	18656
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not registered
Active substance (medicinal product)	Xarelto® 15 mg (CIP: 34009 219 225 1 6, 34009 219 226 8 4, 34009 219 227 4 5, 34009 219 228 0 6, 34009 581 416 7 6 Xarelto® 20 mg (CIP code: 34009 219 229 7 4, 34009 219 230 5 6, 34009 219 231 1 7, 34009 581 419 6 6
Marketing authorization holder(s)	Bayer HealthCare AG
Function	Head of CIC1401
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The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 18/12/2015 [redacted]

Signature Page – Coordinating centre

Title	Benefit-Risk Of arterial THrombotic prEvention with Rivaroxaban for atrial fibrillation in daily clinical practice. A French cohort within the nationwide claims and hospital database (BROTHER).
Protocol version identifier	Version 1.0
Date of last version of protocol	18 December 2015
IMPACT study number	18656
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not registered
Active substance (medicinal product)	Xarelto® 15 mg (CIP: 34009 219 225 1 6, 34009 219 226 8 4, 34009 219 227 4 5, 34009 219 228 0 6, 34009 581 416 7 6 Xarelto® 20 mg (CIP code: 34009 219 229 7 4, 34009 219 230 5 6, 34009 219 231 1 7, 34009 581 419 6 6
Marketing authorization holder(s)	Bayer HealthCare AG
Function	Scientific and medical director
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Title	Doctor
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Marketing authorization holder(s)	Bayer HealthCare AG
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Date, Signature: 18th December 2015 [redacted]