Observational Study Information

Title	Evaluation of Clinical outcomes among non-valvular Atrial fibriLLatIon PatiEnts with Renal dysfunction treated with warfarin or reduced dose rivaroxaban (CALLIPER)
Protocol version identifier	1.0
Date of last version of protocol	08.11.2017
IMPACT study number	19721
Study type/Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☐ NO
EU PAS register number	
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Product reference	
Procedure number	
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen Please note that, effective 1st January 2017, Bayer Pharma AG transfers its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change
Research question and objectives	The objective of the study is to evaluate the effectiveness and safety of the reduced dose rivaroxaban (15 mg once daily) as compared to warfarin in non-valvular atrial fibrillation patients with renal dysfunction in routine clinical practice
Country(-ies) of study	USA (claims data from Truven MarketScan)
Author	Tatsiana Vaitsiakhovich (Bayer AG)

Marketing authorization holder *(table below mandatory for PASS studies)*

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
MAH contact person	

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

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of Contents

2. List of abbreviations

ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
ARB	Angiotensin-receptor blockers
DVT	Deep vein thrombosis
CAD	Coronary artery disease
CKD	Chronic kidney disease
CI	Confidence interval
CPT	Current Procedural Technology
CrCl	Creatinine clearance
GFR	Glomerular filtration rate
HCPCS	Healthcare Common Procedure Coding System
ICD-CM	International Classification of Diseases – Clinical Modification
ICD-PCS	International Classification of Diseases – Procedure Coding System
ICH	Intracranial hemorrhage
IPTW	Inverse probability of treatment weighting
IS	Ischemic stroke
GI	Gastrointestinal
HR	Hazard ratio
NOAC	Non-vitamin K antagonist oral anticoagulant
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulation
OD	Once daily
OS	Observational study
PAD	Peripheral artery disease
PASS	Post-authorization safety study
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PY	Person-year
RI	Renal impairment
TIA	Transient ischemic attack
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

3. Responsible parties

Tatsiana Vaitsiakhovich, Bernhard Schaefer, Craig I. Coleman, Evelyn Weber, Tomasz Dyszynski, Sebastian Kloss, Yanina Lenz

See Annex 4 for responsibilities and contact details.

4. Abstract

Evaluation of clinical outcomes among non-valvular atrial fibrillation patients with renal dysfunction treated with warfarin or reduced dose rivaroxaban

Rationale and background: Non-valvular atrial fibrillation (NVAF) is a common cardiac arrhythmia. NVAF substantially increases patients' risk of stroke and mortality. Renal impairment is a common comorbidity in patients with NVAF; it intensifies the risk of stroke, and increases the bleeding risk during the established oral anticoagulant (OAC) treatment with either a vitamin K antagonist (VKA) or non-VKA oral anticoagulant (NOAC). Various degree of renal insufficiency enforces NOACs reduced dosing regimen for NVAF patients with kidney dysfunction. Clinical and "real world" data on treatment outcomes in these patients are scarce. Available real world studies investigate often effectiveness and safety of NOACs irrespective of dose prescribed, or focus not only on renal impairment but require a combination of this condition with other phenotypes. Failure to reduce the dose for NVAF patients with severe kidney disease may increase bleeding risk, whereas off-label dose reduction may decrease the effectiveness of NOACs. In response to this, the proposed study aims to examine effectiveness and safety of the reduced dose rivaroxaban (15 mg once daily (OD), called also *AF renal impairment dose*) compared to warfarin in patients with NVAF and renal dysfunction in routine clinical practice.

Research question and objectives: The objective of the study is to evaluate the risk of ischemic stroke (IS), intracranial hemorrhage (ICH) (individually and as a composite endpoint) and bleeding-related hospitalization in NVAF patients with renal dysfunction treated with the reduced dose rivaroxaban (15 mg OD) compared to warfarin in routine clinical practice.

Study design: A retrospective cohort study in the Truven Health MarketScan Commercial Claims and Medicare Supplemental Databases will be conducted.

Population: To be included in the present study, patients have to be adults (≥18 years of age) newly-initiated on warfarin or rivaroxaban 15 mg (index event, index drug) for treatment of NVAF between August 1, 2011 and December 31, 2016. The date of the first fill of OAC will be defined as the index date. Patients need to have at least 365 days of continuous medical and pharmacy benefits prior to the index date (baseline period), at least two diagnosis codes for NVAF on two different days and at least one diagnosis code indicating renal dysfunction in the baseline period.

Variables: Patient baseline characteristics such as age, gender, comorbidities and comedications, stroke and bleeding scores will be collected at the index date. The outcomes of interest are ischemic stroke, intracranial hemorrhage (individually and as a composite endpoint) and bleeding-related hospitalization events. Baseline characteristics and outcome events will be assessed using diagnosis and procedure codes, as well as drug names. Bleeding-related hospitalizations will be identified by using the Cunningham algorithm [17].

Data sources: Truven Health MarketScan databases. Individuals enrolled in the MarketScan databases are largely representative of the United States population.

Study size: Preliminary estimates yielded a sample of approximately 11,000 naïve users of OACs under investigation (9,500 warfarin; 1,500 rivaroxaban 15 mg) with NVAF and a diagnosis code for a clinical renal condition for the period between August 1, 2011 and September 30, 2016.

Data analysis: Individuals will be followed from the index date until an event of interest occurs (IS, ICH, bleeding-related hospitalization), the end of the continuous health plan enrollment, the end of data availability or the end of the study period (August 1, 2011 – December 31, 2016), whichever comes first. Descriptive statistics will be generated to summarize the baseline characteristics of the study population. We will utilize stabilized inverse probability of treatment weighting (IPTW) approach based on the propensity score to adjust for potential confounding resulting from imbalances in baseline patient characteristics. IPTW based analysis will be accomplished by the propensity score matching analysis, as well as by a conventional multiple logistic regression analysis. The incidence rates of IS, ICH and bleeding-related hospitalizations will be reported as the number of events per 100 person-years. Cox proportional hazards regression model will be applied in the rivaroxaban cohort compared to the warfarin (reference) cohort to estimate adjusted hazard ratios (HRs) with accompanying 95% confidence intervals (CIs) and *p*-values.

Milestones: This study will be conducted between November 2017 and December 2018.

5. Amendments and updates

6. Milestones

Milestones	**Planned date**
Start of data collection	December 2017
End of data collection	May 2018
Final report of study results	December 2018

7. Rationale and background

Non-valvular atrial fibrillation is a common cardiac arrhythmia, with one in four middle-aged adults in the United States (US) and Europe likely to be diagnosed. NVAF substantially increases patients' risk of stroke by five-fold and mortality by two-fold [1], [2].

Oral anticoagulation (OAC) with either a vitamin K antagonist (VKA) or non-VKA oral anticoagulant (NOAC), such as apixaban, dabigatran, edoxaban or rivaroxaban, significantly decreases the risk of clot formation and is used to prevent ischemic stroke in NVAF population [1],

[2], reducing thus morbidity, mortality and economic burden for patients and healthcare systems world-wide.

Renal impairment is a common comorbidity in patients with NVAF, especially in the elderly population. Patients with NVAF and renal dysfunction are at increased risk of systemic embolic events as compared to those having NVAF "only" [3]. Established OAC treatment for stroke prevention in this sub-group of NVAF patients is not straightforward. VKA and NOACs are partially excreted by kidneys, causing higher plasma level in patients with moderate-to-severe renal impairment and leading to potential increase of bleeding events. Reduced dose of NOACs is therefore recommended in NVAF patients with renal dysfunction. The NOACs have individual pharmacokinetic profiles with variable proportion of renal elimination for each compound, being reflected in prescription guidelines of the products [10]-[13]. Rivaroxaban is the only NOAC with a dose reduction solely based on renal function measured by a creatinine clearance (CrCl) level, when used for the prevention of stroke in AF.

NVAF patients were included in the randomized clinical trials (RCTs) comparing NOACs with warfarin [4]-[6]. Nearly 20% of the patients enrolled in these trials had a creatinine clearance CrCl<50 mL/min. NOACs are in general not recommended in patients with CrCl<15 mL/min, the level which indicates the end-stage renal disease. All NOACs showed at least a trend towards risk reduction of systemic embolic events as compared to warfarin in NVAF patients with moderate renal impairment. Major bleeding risk was reduced with apixaban relative to warfarin, and was similar to warfarin for dabigatran or rivaroxaban [14]. However, each of the mentioned RCTs included different patient populations in terms of underlying comorbidities and risks. Therefore, any comparison across the individual RCTs results should be avoided.

Supplementary to RCTs, generation of real-world evidence is of importance in reinforcing safety perceptions and gaining knowledge on differences between treatments used in routine clinical practice, e.g. between individual OACs. Available real world studies investigated effectiveness and safety of NOACs irrespective of dose prescribed (e.g. rivaroxaban 15 mg and 20 mg OD [9]) dealing partly with the drugs' off-label use, or focused not only on renal impairment but required a combination of that condition with other phenotypes. Failure to reduce the NOAC dose for NVAF patients with severe kidney disease may increase bleeding risk, whereas off-label dose reduction may decrease the effectiveness of these drugs [20].

Interpretation of a real-world study results requires understanding of the strengths and limitations of data assets and analytic methods used. While clinical studies have the advantage of predefined phenotypes and/or endpoints (e.g. chronic kidney disease definition by the National Kidney Foundation [15]; the International Society of Thrombosis and Haemostasis (ISTH) definition of major bleeding) and the ability to adjudicate events, retrospective claims database analyses depend on the structure and the quality of data collected for reimbursement and not for research purposes.

Widely used administrative claims databases provide limited information on whether NOAC prescription is consistent with labeling in real life. For instance, most claims databases do not have data on individual creatinine clearance (or serum creatinine, or glomerular filtration rate) needed to verify the appropriateness of the NOAC dosing regimen prescribed in routine clinical practice. Thus, alternative approaches suitable for database analysis of OAC use in patients with renal insufficiency

need to be developed. It has recently been suggested to identify NVAF patients with renal dysfunction in databases with no lab information by employing specific diagnosis codes for clinical renal conditions [9], [16], assuming they affect renal function to such an extent that a prescription of a reduced dose NOAC according to its label can be justified.

Existing (although sparse) real-world studies have provided evidence that NOACs in general and rivaroxaban in particular are more effective and at least as safe as warfarin in NVAF patients with renal impairment [8], [16]. Nevertheless, it is known that clinicians often hesitate to prescribe NOACs to patients with even moderate renal impairment. Therefore, it is imperative for us to investigate effectiveness and safety of the reduced dose rivaroxaban (15 mg OD) compared to warfarin in NVAF patients with renal dysfunction in real life setting.

8. Research questions and objectives

8.1 Primary objective

The primary objective of this study is to evaluate effectiveness and safety of the reduced dose rivaroxaban (15 mg OD) as compared to warfarin in routine clinical care by assessing the risk of ischemic stroke (IS), intracranial hemorrhage (ICH) and bleeding-related hospitalization in NVAF patients with renal dysfunction.

8.2 Secondary objectives

The secondary objective of this study is:

- To evaluate the risk of a composite endpoint defined as the occurrence of IS or ICH

9. Research methods

9.1 Study design

A retrospective cohort study in the US Truven Health MarketScan Commercial Claims and Medicare Supplemental Databases will be conducted.

The study outcomes will be defined based on the International Classification of Diseases, 9th- and 10th-revision, Clinical Modification (ICD-9/10-CM) diagnosis codes, Current Procedural Technology, 4th-revision (CPT-4) and Healthcare Common Procedure Coding System (HCPCS) procedure codes. IS or ICH related diagnosis codes will be required to appear on inpatient claims in the primary diagnosis position. The validated Cunningham algorithm [17] will be used to identify bleeding-related hospitalizations and the site of bleeds: upper, lower or unspecified gastrointestinal (GI), cerebral, genitourinary and other.

We will utilize stabilized inverse probability of treatment weighting (IPTW) methodology based on the propensity score [18] to adjust for potential confounding. Additionally, we will conduct a

propensity score matching analysis, as well as a conventional multiple logistic regression analysis. The incidence rates of IS, ICH and bleeding-related hospitalizations will be reported as the number of events per 100 person-years. Cox proportional hazards regression model will be applied in the reduced dose rivaroxaban (15 mg OD) users compared to warfarin users to estimate adjusted hazard ratios (HRs) with accompanying 95% confidence intervals (CIs) and *p*-values.

9.2 Setting

The source population of this study will be all the insured individuals included in the Truven Health MarketScan databases.

9.2.1 Study time frame

We will use Truven MarketScan claims data from August 1, 2011 to December 31, 2016.

9.2.2 Selection criteria

To be included in the present study, patients have to be adults (≥18 years of age) newly-initiated on warfarin or rivaroxaban 15 mg (index event, index drug), have at least 365 days of continuous medical and prescription benefits prior to the index event (baseline period), at least two diagnosis codes for NVAF (on outpatient or inpatient claims, at two different days) and at least one diagnosis code (inpatient or outpatient) indicating renal dysfunction in the baseline period. The date of the first fill of OAC will be defined as the index date.

Renal dysfunction will be assessed during the baseline period. While there are no data on individual CrCl, or estimated glomerular filtration rate (eGFR), or serum creatinine in the MarketScan database, we will make an assumption that the presence of particular, carefully chosen diagnosis codes in patients data at baseline reflects their reduced renal function and influences lab results, leading to the treatment initiation with the anticipated reduced dose of rivaroxaban as per label [8], [16], [21].

In our analysis two different lists of ICD codes will be used to define patients with renal dysfunction.

Approach 1:

To start with, it is straightforward to classify patients with a diagnosis of chronic kidney disease (CKD) as having renal dysfunction. CKD is defined as either the presence of kidney damage or eGFR less than 60 mL/min/1.73m^2 for three or more months [15], and has five severity stages.

Contemporary guidelines for stroke prevention in AF with rivaroxaban recommend 15 mg OD dosing regimen for patients with CrCl level 15-49 mL/min; rivaroxaban (OAC in general) is not recommended in patients with CrCl below 15 mL/min. An accepted substitute for CrCl is a Modification of Diet in Renal Disease (MDRD) Study equation of eGFR [22]. Therefore, in our study we need to capture patients with a potential measure of eGFR 15-49 mL/min/1.73m^2.

Different levels of eGFR correspond to different CKD stages [15]. CKD stage 3 and 4 cover the level of eGFR 15-59 mL/min/1.73m^2. Therefore, we will define patients with ICD codes for CKD stage 3 and 4 (see Annex 3) as having renal dysfunction and being eligible for rivaroxaban 15 mg OD treatment, although those having eGFR level 50-59 mL/min/1.73m^2 need to be treated by rivaroxaban 20 mg OD according to the product labelling.

Approach 2:

Fleet et al. [21] developed and validated an "algorithm" to detect patients with eGFR<45 mL/min/1.73m^2 in the population-based administrative healthcare database in Ontario, Canada. The approach requires presence of at least one of eleven ICD codes for different kidney diseases in rather recent longitudinal patients data, has positive and negative predictive values of 65.4% and 88.8%, respectively, and can be applied to other claims databases with ICD system used to collect diagnoses related information. We will utilize ICD codes of this validated approach despite of small difference in eGFR threshold level set in [21] and in the rivaroxaban label, and despite of two out of eleven codes in the Fleet approach which cannot be applied to the MarketScan data. Furthermore, we will include additional ICD codes, following Nielsen et al. [8] and Weir et al. [16] argumentation on definition of patients with renal dysfunction in claims databases.

Summarizing, we will categorize not only patients with chronic kidney disease stage 3 and 4 as in Approach 1, but also those with cystic kidney disease, unspecified kidney failure, chronic or unspecified nephritic syndrome, nephrotic syndrome, recurrent and persistent hematuria, nephropathy (diabetic, hypertensive, hereditary), chronic tubulo-interstitial nephritis, diabetes mellitus with kidney complications as having renal dysfunction (see Annex 3).

Patients will be **excluded** from the study if they have a diagnosis of:

- Valvular atrial fibrillation (at least one inpatient diagnosis in the baseline period)
- Pregnancy (inpatient or outpatient diagnosis in the baseline period)
- Transient cause of AF (inpatient or outpatient diagnosis in the baseline period)
- Venous thromboembolism (VTE) (pulmonary embolism PE or deep vein thrombosis DVT) (one inpatient or outpatient diagnosis 60 days prior to or on the index date)

or

- Overcame a hip or knee replacement (one inpatient diagnosis or procedure code 60 days prior to or on the index date)
- Have a pharmacy claim for an OAC dispensation (warfarin, apixaban, dabigatran, edoxaban or rivaroxaban) in the baseline period
- Receive both warfarin and rivaroxaban 15 mg on the index date

- Have end-stage kidney disease or be on dialysis (one inpatient or outpatient diagnosis or procedure code in the baseline period).

For the main analysis, patients having malignant cancers (inpatient or outpatient diagnosis in the baseline period) will be excluded. One year baseline allows to classify such patients as having active cancer. A sensitivity analysis, omitting this exclusion criterion, will additionally be perfomed.

See Annex 3 for the corresponding diagnosis and procedure codes.

9.2.3 Study population

MarketScan data is a convenience sample [19], its overall extensive sample size including more than 150,000 NVAF patients enables the creation of a nationally representative data sample of the US population with employer-provided health insurance and Medicaid with ample statistical power to evaluate potential differences in both effectiveness and safety endpoints between rivaroxaban 15 mg OD and warfarin-managed NVAF patients with renal dysfunction.

9.3 Variables

9.3.1 Baseline characteristics

Patient baseline characteristics such as age, gender, comorbidities and comedications, stroke and bleeding scores will be collected at the index date or from the last recorded value within the baseline period.

Number of patients, total

Demographic characteristics

- Gender
- Age
- Age group: 18–39, 40–44, 45–49, …, 75–79, 80+

Clinical characteristics

Presence of the following clinical characteristics (see Annex 3) will be assessed from the patients medical and pharmacy claims in the baseline period:

- $CHADS_2$ score
- CHA_2DS_2-VASc score
- HAS-BLED score (the international normalized ratio INR will not be included in the calculation of the score because of the non-availability of the lab data in MarketScan)

- Comorbidities
    - Acute coronary syndrome
    - Alcohol abuse
    - Aortic plaque
    - Anemia
    - Coronary heart disease
    - Dementia
    - Depression
    - Diabetes mellitus
    - Drug abuse
    - Gastric or peptic ulcer disease/diseases of gastrointestinal tract
    - Heart failure
    - History of major bleeding
    - Hyperlipidemia
    - Hypertension
    - Hypothyroidism
    - Infection with helicobacter pylori
    - Inflammatory bowel disease
    - IS or transient ischemic attack (TIA)
    - Liver disease
    - Mechanical heart valve
    - Mitral stenosis
    - Myocardial infarction (MI)
    - Obesity
    - Peripheral arterial disease (PAD)
    - Psychosis
    - Pulmonary disease
    - Rheumatoid arthritis/collagen vascular disease
    - Tobacco abuse
    - Vascular disease

- Comedications

- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARB)
- Antiarrhythmics
- Antidepressants
- Antiplatelets
- Antiulcer drugs (except PPIs)
- Calcium channel blockers
- Diabetes drugs
- Diuretics
- Erythropoietin-simulating agents
- Estrogens
- NSAIDs
- Proton-pump inhibitors (PPIs)
- Statins

- Number of hospitalizations
- Cohort entry date, 12 months period

See Annex 3 for the corresponding diagnosis and procedure codes.

9.3.2 Exposure

There will be two **exposure groups**: new users of warfarin and new users of rivaroxaban 15 mg. **Exposure** is defined as the presence of at least one dispensation event for the study drugs, found on the patients pharmacy claims.

Exposure time starts at the index date and is calculated as the sum of days supply, days of potential hospitalizations and a gap period (if no prescription immediately follows). Hospitalizations related to the outcome measures will terminate exposure time, and patients will be censored.

Patients will be considered to have **discontinued** oral anticoagulant therapy if a **gap period** of ≥14-days will be detected between the most recent anticoagulant fill date and the date when there will be no days of anticoagulant supply anticipated to be remaining. The date of discontinuation will be defined as the end of exposure, and patients will be censored.

Patients having a pharmacy claim for OAC different to the index drug during the follow-up period will be considered as **switchers** if the claim date is prior to the end of supply of the current drug or within the gap period after the end of supply. Patients dispensing rivaroxaban other than the dosage at index will also be considered as switchers. The dispense date of the new OAC will be defined as the end of exposure, and patients will be censored.

9.3.3 Outcome measures

The study outcomes will be defined based on ICD-9/10-CM diagnosis codes, CPT-4, HCPCS, ICD-9/10-PCS procedure codes, see Annex 3.

- *Effectiveness outcomes*

  IS or ICH related diagnosis codes will be required to appear in the primary diagnosis position on inpatient claims.

  To evaluate the risk of a composite endpoint defined as the occurrence of IS or ICH, a respective ICD code for either of two diagnoses needs to be present in the primary position of inpatient data.

- *Safety outcomes*

  The validated Cunningham algorithm [17] will be applied to identify bleeding-related hospitalizations and sites of bleeds by using inpatient and outpatient claims data.

  The Cunningham algorithm determines bleeding-related hospitalizations from the primary and secondary discharge diagnoses. Site of bleeding is classified as gastrointestinal (upper, lower, unspecified), cerebral, genitourinary, or other.

9.4 Data sources

The Truven Health MarketScan Research Databases capture person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services. Individuals enrolled in the MarketScan databases are largely representative of the United States population in terms of age, sex, and type of health insurance coverage. The data contain claims from approximately 100 employers, health plans, and government and public organizations representing about 50 million covered lives. The data elements to be used in the proposed study will include health plan enrollment records, participant demographics, inpatient and outpatient medical claims and outpatient prescription drug dispensing records. The data included in the MarketScan database are de-identified and are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 to preserve participant anonymity and confidentiality.

9.5 Study Size

Preliminary estimates yielded a sample of around 11,000 naïve users of OACs under investigation (9,500 warfarin; 1,500 rivaroxaban 15 mg) with NVAF and a diagnosis code for a clinical renal condition for the period between August 1, 2011 and September 30, 2016. Sample size depends strongly on the definition of “renal dysfunction”, i.e. on the choice of ICD codes used to identify patients with renal insufficiency. The feasibility counts given above have been obtained by applying Approach 2 from Section 9.2. If Approach 1 is used instead, the sample size is reduced to appr. 4,500 new users of warfarin and 850 new users of rivaroxaban 15 mg. Furthermore, sample size is expected to increase by 15-20% in the sensitivity analysis including cancer patients.

9.6 Data management

Database management will be performed using Aetion platform and SAS version 9.4 (SAS Inc., Cary, NC, USA). Aetion platform facilitates observational studies execution for the data assets

licensed by Bayer AG and linked to the platform. Aetion use is expected to accelerate the study conduct as compared to the SAS option based on the availability of the pre-defined and consistent definitions of measures (covariates, outcomes) and complex algorithms (e.g. Cunningham bleeding algorithm), which have been implemented on the platform during the study initiation and feasibility assessment phase in collaboration with Aetion's scientific team. SAS will be used to support the study execution by Aetion.

9.7 Data analysis

Individuals will be followed from the index date until a study event occurs (IS, ICH, bleeding-related hospitalization), the end of the continuous health plan enrollment, the end of data availability or the end of the study period (August 1, 2011 – December 31, 2016), whichever comes first.

Descriptive statistics will be generated to summarize the baseline characteristics of the study population. For continuous variables the mean, median, upper and lower quartiles and the standard deviation will be reported. For discrete variables absolute counts and proportions of patients with given characteristics will be given. Proportions will be calculated relative to the total sample size of each treatment group. The differences between two treatment groups will be assessed by the standardized mean difference estimate. Patients initiated on warfarin will be used as a reference group.

We will utilize **stabilized inverse probability of treatment weighting** (IPTW) approach based on the propensity score to adjust for potential confounding resulting from imbalances in baseline patient characteristics. The objective of IPTW based analysis is to create a weighted sample, for which the distribution of either the confounding variables or the prognostically important covariates is approximately the same between comparison groups [18].

Propensity score (PS) is defined as the patient's probability to receive a treatment under investigation (rivaroxaban 15 mg) given a set of known patient's baseline characteristics. Propensity scores will be calculated outcome blinded by utilizing multiple logistic regression on a relevant set of patient characteristics listed in Section 9.3.1.

Let Z be an indicator variable relating to the treatment received by a patient, $Z = 1$ for an active treatment (rivaroxaban 15 mg), $Z = 0$ for a control treatment (warfarin), and let X denote a vector of observed patient baseline characteristics. Then the propensity score is $e = P(Z = 1 \mid X)$. The inverse probability of treatment weight is defined as $w = \frac{Z}{e} + \frac{1-Z}{1-e}$, i.e.

$w = \frac{1}{e}$ for patients receiving the active treatment, and

$w = \frac{1}{1-e}$ for patients receiving the control treatment.

Weighting by the inverse probability of treatment results in an artificial population or synthetic sample, in which treatment assignment is independent of measured baseline characteristics. Obviously, a very low propensity score of subjects receiving an active treatment, or a propensity score close to 1 of subjects receiving a control treatment result in large weights. Such weights

increase the variability of the estimated treatment effect. Moreover, it is known [24] that the sample size of the synthetic sample is always greater that the sample size of the original data. Consequently, regression estimates with IPTW tend to reject the null hypothesis too often because of the inflated sample sizes. In our analysis we will deploy IPTW with stabilized weights (SWs), given in e.g. [18], which ensure more robust effect estimates. The use of stabilized weights in the synthetic data preserves the sample size of the original data, and provides an appropriate estimate of treatment effect from the conventional regression with SWs [24].

By applying IPTW method using the propensity score assessment needs to be done, whether weighting procedure succeeded to balance patient characteristics between treatment groups. We will assess the balance by using standardized mean differences. The distributions of propensity scores and stabilized weights will be inspected for initial and synthetic samples. A standardized difference of 0.1 or less will be considered as a negligible difference between groups.

In this study we will additionally conduct an analysis by matching on a propensity score technique, and by utilizing a conventional multiple logistic regression model. A 1:*n* matching will be performed using the nearest neighbor without replacement approach, where *n* will depend on the number of warfarin and rivaroxaban users in the study cohort.

The incidence rates of IS, ICH and bleeding-related hospitalizations will be reported as the number of events per 100 person-years. Cox proportional hazards regression model will be applied in the rivaroxaban group compared to warfarin (reference) group in order to estimate the adjusted hazard ratios (HRs) with accompanying 95% confidence intervals (CIs) and *p*-values, which should be interpreted as exploratory only. Kaplan-Meier cumulative incidence plots will be generated to characterize risk of events of interest over time.

No actions will be taken to deal with missing data related issues.

Data analysis will be performed using Aetion platform and SAS version 9.4 (SAS Inc., Cary, NC, USA).

The statistical concept of the study described above will be supplemented by the more detailed statistical analysis plan.

9.8 Quality control

The MarketScan databases are created by combining the standard variables of the individual data sets from various contributors and by linking years of data across all data types. The MarketScan data are a snapshot in time and are based on a calendar-year incurred period. The quality of diagnosis and procedure coding, claims lag periods etc. vary among the approximately 100 payers or administrators represented in the MarketScan databases. Every effort is made to select the data contributors with the best coding; the diagnosis and procedure codes are validated and edited by the Truven Health Analytics company, if necessary.

9.9 Limitations of the research methods

As with any data source, MarketScan claims databases have limitations. Some have to do with the nature of claims data and others with the nature of the MarketScan sample population. Key limitations include:

Laboratory results are not available in the MarketScan databases. Data sources containing this type of information are very limited and, to the best of our knowledge, cannot provide a reasonable sample size of NVAF patients with renal dysfunction treated with rivaroxaban 15 mg OD. Our attempt to develop a strategy of identifying these patients without involving lab measures can be useful for future RWE studies involving various data sources.

The MarketScan databases largely cover employees and their dependents, so patients with conditions that prevent them to be employed may be underrepresented. The data mostly come from large employers; medium and small firms are underrepresented. This may lead to underrepresentation of particular population groups.

The MarketScan patients sample is not random, it may contain biases or fail to generalize well to other populations.

The results which will be derived from the MarketScan database are only valid for the population described by the in- and exclusion criteria.

In the database analysis where the randomization is not possible, such PS based methods as matching or IPTW serve to harmonize comparison groups with respect to patient characteristics. However, residual confounding caused by e.g. unmeasured factors, missing data, miscoding or tactical coding issues, over-the-counter drugs use etc. remains present.

Two approaches to identify patients with renal dysfunction will be used in this study. Although all efforts will be made to capture population with characteristics close to those eligible for rivaroxaban 15 mg OD dosing regimen, there will be no possibility to estimate patients CrCl level, i.e. to assess their true renal status. The interpretation of the results should accommodate this limitation.

9.10 Other aspects

None.

10. Protection of human subjects

The data included in the MarketScan database are de-identified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality.

11. Management and reporting of adverse events/adverse reactions

For non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. Reports of adverse events/reactions will be summarized in the study report, where applicable.

12. Plans for disseminating and communicating study results

The results of the study are intended for publication and will follow the International Committee of Medical Journal Editors guidelines [23]. In addition, communication in appropriate scientific meetings will be considered.

13. List of references

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Annex 1. List of stand-alone documents

Annex 2. ENCePP checklist for study protocols *(mandatory for PASS studies)*

Annex 3. Additional information

This Annex provides ICD-CM, ICD-PCS, CPT-4, HCPCS codes and drug names used in the study.

Section 9.2, Inclusion criteria:

NVAF diagnosis codes:

ICD-10	Code description	ICD-9	Code description
I48.0	Paroxymal atrial fibrillation	427.31	Atrial fibrillation
I48.1	Persistent atrial fibrillation		
I48.2	Chronic atrial fibrillation		
I48.91	Unspecified atrial fibrillation		

Identification of patients with renal dysfunction:

Approach 1.

ICD-10	Code description	ICD-9	Code description
N18.3	Chronic kidney disease, stage 3 (moderate)	585.3	Chronic kidney disease, Stage III (moderate)
N18.4	Chronic kidney disease, stage 4 (severe)	585.4	Chronic kidney disease, Stage IV (severe)

Approach 2.

ICD-10	Code description	ICD-9	Code description
D63.1	Anemia in chronic kidney disease	285.21	Anemia in chronic kidney disease
E08.22	Diabetes mellitus due to underlying condition with diabetic chronic kidney disease	249.40	Secondary diabetes mellitus with renal manifestations, not stated as uncontrolled, or unspecified

		581.81	Nephrotic syndrome in diseases classified elsewhere
E09.22	Drug or chemical induced diabetes mellitus with diabetic chronic kidney disease	249.40 581.81 583.81	Secondary diabetes mellitus with renal manifestations, not stated as uncontrolled, or unspecified Nephrotic syndrome in diseases classified elsewhere Nephritis and nephropathy not specified as acute or chronic in diseases classified elsewhere
E10.2 E10.21 E10.22 E10.29	Type 1 diabetes mellitus with kidney complications Type 1 diabetes mellitus with diabetic nephropathy Type 1 diabetes mellitus with diabetic chronic kidney disease Type 1 diabetes mellitus with other diabetic kidney complication	250.41 250.43	Diabetes with renal manifestations type I [juvenile type] not stated as uncontrolled Diabetes with renal manifestations type I [juvenile type] uncontrolled
E11.2 E11.21 E11.22 E11.29	Type 2 diabetes mellitus with kidney complications Type 2 diabetes mellitus with diabetic nephropathy Type 2 diabetes mellitus with diabetic chronic kidney disease Type 2 diabetes mellitus with other diabetic kidney complication	250.40 250.42	Diabetes with renal manifestations type II or unspecified type not stated as uncontrolled Diabetes with renal manifestations type II or unspecified type uncontrolled
E13.21 E13.22 E13.29	Other specified diabetes mellitus with diabetic nephropathy Other specified diabetes mellitus with diabetic chronic kidney disease Other specified diabetes mellitus with other diabetic kidney complication	249.40 250.40	Secondary diabetes mellitus with renal manifestations, not stated as uncontrolled, or unspecified Diabetes with renal manifestations, type ii or unspecified type, not stated as uncontrolled
I12.9	Hypertensive chronic kidney disease with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	403.00 403.10 403.90	Hypertensive chronic kidney disease malignant with chronic kidney disease stage I through stage IV or unspecified Hypertensive kidney disease benign with chronic kidney disease stage I through stage IV or unspecified Hypertensive chronic kidney disease unspecified with chronic kidney disease stage I through stage IV or unspecified
I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic	404.00	Hypertensive heart and chronic kidney disease malignant without heart failure with chronic kidney disease stage I through stage

	kidney disease, or unspecified chronic kidney disease		IV or unspecified
I13.10	Hypertensive heart and chronic kidney disease without heart failure, with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	404.01	Hypertensive heart and chronic kidney disease malignant with heart failure with chronic kidney disease stage I through stage IV or unspecified
		404.10	Hypertensive heart and chronic kidney disease benign without heart failure with chronic kidney disease stage I through stage IV or unspecified
		404.90	Hypertensive heart and chronic kidney disease unspecified without heart failure with chronic kidney disease stage I through stage IV or unspecified
		404.91	Hypertensive heart and chronic kidney disease unspecified with heart failure with chronic kidney disease stage I through stage IV or unspecified
N02.xx	Recurrent and persistent hematuria	581.1	Nephrotic syndrome with lesion of membranous glomerulonephritis
		581.2	Nephrotic syndrome with lesion of membranoproliferative glomerulonephritis
		581.3	Nephrotic syndrome with lesion of minimal change glomerulonephritis
		581.89	Other nephrotic syndrome with specified pathological lesion in kidney
		581.9	Nephrotic syndrome with unspecified pathological lesion in kidney
N03.xx	Chronic nephritic syndrome	582.0	Chronic glomerulonephritis with lesion of proliferative glomerulonephritis
		582.1	Chronic glomerulonephritis with lesion of membranous glomerulonephritis
		582.2	Chronic glomerulonephritis with lesion of membranoproliferative glomerulonephritis
		582.4	Chronic glomerulonephritis with lesion of rapidly progressive glomerulonephritis
		582.89	Other chronic glomerulonephritis with specified pathological lesion in kidney
		582.9	Chronic glomerulonephritis with unspecified pathological lesion in kidney
N04.xx	Nephrotic syndrome	581.0	Nephrotic syndrome with lesion of proliferative glomerulonephritis
		581.1	Nephrotic syndrome with lesion of membranous glomerulonephritis
		581.2	Nephrotic syndrome with lesion of membranoproliferative glomerulonephritis
		581.3	Nephrotic syndrome with lesion of minimal

			change glomerulonephritis
		581.89	Other nephrotic syndrome with specified pathological lesion in kidney
		581.9	Nephrotic syndrome with unspecified pathological lesion in kidney
N05.xx	Unspecified nephritic syndrome	583.0	Nephritis and nephropathy not specified as acute or chronic with lesion of proliferative glomerulonephritis
		583.1	Nephritis and nephropathy not specified as acute or chronic with lesion of membranous glomerulonephritis
		583.2	Nephritis and nephropathy not specified as acute or chronic with lesion of membranoproliferative glomerulonephritis
		583.4	Nephritis and nephropathy not specified as acute or chronic with lesion of rapidly progressive glomerulonephritis
		583.89	Other nephritis and nephropathy not specified as acute or chronic with specified pathological lesion in kidney
		583.9	Nephritis and nephropathy not specified as acute or chronic with unspecified pathological lesion in kidney
N07.xx	Hereditary nephropathy, not elsewhere classified	583.1	Nephritis and nephropathy not specified as acute or chronic with lesion of membranous glomerulonephritis
		583.2	Nephritis and nephropathy not specified as acute or chronic with lesion of membranoproliferative glomerulonephritis
		583.89	Other nephritis and nephropathy not specified as acute or chronic with specified pathological lesion in kidney
		583.9	Nephritis and nephropathy not specified as acute or chronic with unspecified pathological lesion in kidney
N08	Glomerular disorders in diseases classified elsewhere	583.81	Nephritis and nephropathy, not specified as acute or chronic, in diseases classified elsewhere
N11.xx	Chronic tubulo-interstitial nephritis	590.00	Chronic pyelonephritis without lesion of renal medullary necrosis
		590.01	Chronic pyelonephritis with lesion of renal medullary necrosis
		590.80	Pyelonephritis unspecified
		593.3	Stricture or kinking of ureter
		593.4	Other ureteric obstruction
N14.xx	Drug- and heavy-metal-induced tubulo-interstitial and tubular conditions	583.89	Other nephritis and nephropathy not specified as acute or chronic with specified pathological lesion in kidney
N18.1	Chronic kidney disease, stage 1	585.1	Chronic kidney disease stage I

N18.2 N18.3 N18.4 N18.9	Chronic kidney disease, stage 2 (mild) Chronic kidney disease, stage 3 (moderate) Chronic kidney disease, stage 4 (severe) Chronic kidney disease, unspecified	585.2 585.3 585.4 585.9	Chronic kidney disease stage II (mild) Chronic kidney disease stage III (moderate) Chronic kidney disease stage IV (severe) Chronic kidney disease unspecified
N19	Unspecified kidney failure	586	Unspecified kidney failure
Q61.xx	Cystic kidney disease	753.xx	Congenital anomalies of urinary system

Section 9.2, Exclusion criteria:

- Valvular atrial fibrillation

  ICD-9-CM: 394.0, 394.1, 394.2, 394.9, 395.0, 395.1, 395.2, 395.9, 396.0, 396.1, 396.2, 396.3, 396.8, 396.9, 397.0, 397.1, 397.9, 424.0, 424.1, 424.2, 424.3, 424.9, 424.90, 424.91, 424.99, 746.00, 746.01, 746.02, 746.09, 746.1, 746.2, 746.3, 746.4, 746.5, 746.6, 746.7, V42.2, V42.3

  ICD-10-CM: I05 – I08, I09.1, I09.89, I34 – I39, Q23.0 – Q23.3, Z95.2 – Z95.4

  CPT-4: 33400, 33401, 33403 – 33406, 33410 – 33420, 33422, 33425 – 33427, 33430, 33460, 33463 – 33465, 33468, 33470 – 33472, 33474 – 33476, 33478

- Pregnancy
  ICD-9-CM: 630 – 676, V22, V23, V27
  ICD-10-CM: O00 – O9A, Z34 – Z39

- Malignant cancers
  ICD-9-CM: 140 – 208, 230 – 234
  ICD-10-CM: C00 – C80, C7A, C7B, C81 – C96, D00 – D09, E31.20 – E31.23

- Transient cause of AF
  ICD-9-CM: 429.4
  ICD-10-CM: I97.0, I97.110, I97.130, I97.190
  CPT-4: 33400 – 33999

- Venous thromboembolism (VTE) (pulmonary embolism PE or deep vein thrombosis DVT)
  PE, ICD-9-CM: 415.1
  PE, ICD-10-CM: I26

  DVT, ICD-9-CM: 451.1, 451.2, 453.4, 463.8, 453.9
  DVT, ICD-10-CM: I80, I81, I82.210, I82.220, I82.290, I83, I84, I82.90

- Hip or knee replacement
  ICD-10-PCS: 0SR9019, 0SR9019, 0SR901A, 0SR901Z, 0SR9029, 0SR902A, 0SR902Z, 0SR9039, 0SR903A, 0SR903Z, 0SR9049, 0SR904A, 0SR904Z, 0SR907Z, 0SR90J9, 0SR90JA, 0SR90JZ, 0SR90KZ, 0SRA009, 0SRA00A, 0SRA00Z, 0SRA019, 0SRA01A, 0SRA01Z, 0SRA039, 0SRA03A, 0SRA03Z, 0SRA07Z, 0SRA0J9, 0SRA0JA, 0SRA0JZ, 0SRA0KZ, 0SRB019, 0SRB01A, 0SRB01Z, 0SRB029, 0SRB02A, 0SRB02Z, 0SRB039, 0SRB03A, 0SRB03Z, 0SRB049, 0SRB04A, 0SRB04Z, 0SRB07Z, 0SRB0J9, 0SRB0JA, 0SRB0JZ, 0SRB0KZ, 0SRC07Z, 0SRC0J9, 0SRC0JA, 0SRC0JZ, 0SRC0KZ, 0SRC0L9, 0SRC0LA, 0SRC0LZ, 0SRD07Z, 0SRD0J9, 0SRD0JA, 0SRD0JZ, 0SRD0KZ, 0SRD0L9, 0SRD0LA, 0SRD0LZ, 0SRE009, 0SRE00A, 0SRE00Z, 0SRE019, 0SRE01A, 0SRE01Z, 0SRE039, 0SRE03A, 0SRE03Z, 0SRE07Z, 0SRE0J9, 0SRE0JA, 0SRE0JZ, 0SRE0KZ, 0SRR01A, 0SRR01Z, 0SRR039, 0SRR03A, 0SRR03Z, 0SRR07Z, 0SRR0J9, 0SRR0JA, 0SRR0JZ, 0SRR0KZ, 0SRS019, 0SRS01A, 0SRS01Z, 0SRS039, 0SRS03A, 0SRS03Z, 0SRS07Z, 0SRS0J9, 0SRS0JA, 0SRS0JZ, 0SRS0KZ, 0SRT07Z, 0SRT0J9, 0SRT0JA, 0SRT0JZ, 0SRT0KZ, 0SRU07Z, 0SRU0J9, 0SRU0JA, 0SRU0JZ, 0SRU0KZ, 0SRV07Z, 0SRV0J9, 0SRV0JA, 0SRV0JZ, 0SRV0KZ, 0SRW07Z, 0SRW0J9, 0SRW0JA, 0SRW0JZ, 0SRW0KZ

  CPT-4: 27090, 27091, 27125, 27130, 27132, 27134, 27137, 27138, 27438, 27440 – 27447, 27486 – 27488

- End-stage kidney disease or dialysis

  ICD-9-CM: 403.01, 403.91, 585.5, 585.6, 586, 996.81, V42.0, V45.1, V45.11, V45.12, V56.0, V56.1, V56.2, V56.31, V56.32, V56.8

  ICD-10-CM: I12.0, I13.11, I13.2, I95.3, N18.5, N18.6, R88.0, T81.502, T82.4, T85.611, T85.621, T85.631, T85.691, T85.71, Y62.2, Y84.1, Z49, Z91.15, Z94.0

  ICD-10-PCS: B50W0ZZ, B50W1ZZ, B50WYZZ, B51W0ZA, B51W0ZZ, B51W1ZA, B51W1ZZ, B51WYZZ, B51WZZA, B51WZZZ

  CPT-4: 00868, 0505F, 0507F, 4052F, 4053F, 4054F, 4055F, 50360, 50365, 50366, 50370, 75791, 76778, 90918 – 90925, 90935, 90937, 90939 – 90945, 90947, 90951 – 90970, 90976 – 90979, 90982 – 90985, 90988 – 90995, 90998, 90999, 99512, 99559

  HCPC: A4655, A4663, A4672, A4690, A4700, A4705, A4720, A4721 – A4726, A4728, A4760, A4765, A4766, A4780, A4790, A4800, A4820, A4910, A4913, A4919, A4929, C1037, C1750, C1752, C1881, E1510, E1570, E1590, E1592, E1594, E1632, E1634, E1635, E1637 – E1639, E1699, G0257, G0308 – G0319, G0321 – G0327, G8075 – G8082, G8085, G8387, G8388, G8488, G8714, G8715, G8727, G9013, G9014, G9231, J0882, J0886, J0887, K0610, K0612, Q0139, Q4054, Q4055, Q4081, Q9972, S9335, S9339

Below only ICD-10 diagnosis codes will be provided. The corresponding ICD-9 codes can obtained by the General Equivalence Mappings, see https://www.asco.org/practice-guidelines/billing-coding-reporting/icd-10/general-equivalence-mappings-gems

Section 9.3.1, Baseline characteristics:

Comorbidities

- Alcohol abuse

  ICD-10-CM: F10

- Anemia

  ICD-10-CM: D50 – D53, D63, D64.9

- Aortic plaque

  ICD-10-CM: I70.0

- Coronary artery disease (CAD)

  Angina pectoris

  ICD-10-CM: I20, I25.1

  Myocardial infarction

  ICD-10-CM: I21 – I23, I25.2

  Acute ischemic heart diseases

  ICD-10-CM: I24

  Chronic ischemic heart disease

  ICD-10-CM: I25.1, I25.3 – I25.6, I25.8, I25.9

  Coronary artery bypass graft(s)

  ICD-10-CM: I25.7, I25.810

  ICD-10-PCS: B20.2, B20.3, B21.2, B21.3, B22.3, 021

  CPT-4: 00566, 00567, 33510 – 33525, 33528, 33530, 33533 – 33536, 35600, 4110F, 75762, 75764, 75766, 75767, 93551, C9604, C9606, G8158 – G8172, G8497, G8544, G8573, G8574

  Percutaneous coronary intervention (PCI)

  ICD-10-CM: Z95.5, Z98.61

  ICD-10-PCS: 027.0 – 027.3

  CPT-4: 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, C9600 – C9608

- Dementia

  ICD-10-CM: F01 – F03, G30, G31.0

- Depression

  ICD-10-CM: F32 – F34, F43.21

- Diabetes mellitus

ICD-10-CM: E08 – E11, E13

- Drug abuse

  ICD-10-CM: F11 – F19, F55

- Gastric or peptic ulcer disease/diseases of gastrointestinal trackt

  ICD-10-CM: K21, K25.4 – K25.9, K26.4 – K26.9, K27.4 – K27.9, K28.4 – K28.9, K29, K30, K31.89, K51, K52, K64, Z87.11

- Heart failure

  ICD-10-CM: I09.81, I11.0, I13.0, I13.2, I25.5, I42, I43, A36.84, B33.24

  CPT-4: 0001F, J1250, J1265, J1940, J2260, Q4076

- History of major bleeding

  Will be assessed by application of the Cunnigham algorithm to the patients baseline data

- Hypertension

  ICD-10-CM: I10 - I12, I13.0, I13.10, I13.11, I13.2, I15, I67.4

- Hypothyroidism

  ICD-10-CM: E00, E01.8, E02, E03, E89.0

- Infection with helicobacter pylori

  ICD-10-CM: B96.81

  CPT-4: 83009, 83013, 83014, 86677, 87338, 87339

- Inflammatory bowel disease

  ICD-10-CM: K58

- IS or transient ischemic attack (TIA)

  ICD-10-CM: I63, G45.0 – G45.2, G45.4 – G45.9, Z86.73

- Liver disease

  ICD-10-CM: B18.0, B18.1, B18.2, I85, K70.0, K70.2, K70.3, K70.4, K70.9, K72.10, K72.11, K72.90, K73, K74, K75.4, K75.81, K76.0, K76.6, K76.89, K76.9, Z94.4

- Mechanical heart valve

  ICD-10-CM: Z95.2 – Z95.4

- Metabolic disorders

  Hyperlipidemia

  ICD-10-CM: E78.0 – E78.5

  Volume depletion

  ICD-10-CM: E86

Other metabolic disorders

ICD-10-CM: E87

- Mitral stenosis

  ICD-10-CM: I05

- Obesity

  ICD-10-CM: E66, R93.9, Z68.3, Z68.4

- Peripheral artery disease (PAD)

  ICD-10-CM: I70.2 – I70.9, I71, I73.9

- Psychosis

  ICD-10-CM: F20, F22 – F25, F28, F29 – F31, F32.3 – F32.5, F33.3, F33.4, F34.8, F34.9, F39, F44.89

- Pulmonary disease

  ICD-10-CM: I26, I27, I28.9, J44, T80.0XXA, T82.817A, T82.818A

- Rheumatoid arthritis/collagen vascular disease

  ICD-10-CM: M05, M06, M08, L90.0, L94.0, L94.1, L94.3, M32 – M35, M45, M46, M48, M49

- Tobacco abuse

  ICD-10-CM: F17.2, Z72.0

  CPT-4: 0002F, 0004F, 1032F, 1034F, 4000F, 4001F, C9801, C9802, D1320, G0375, G0376, G00436, G0437, G8455, G9276

- Vascular disease

  ICD-10-CM: I70 – I72, I73.1, I73.8, I73.9, I74, I76, I77, I79, K55.1, K55.8, K55.9, Z95

- Comedications

  - Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARB)

    ACE inhibitors

    benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, moexipril, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, zofenopril

    ARB

    azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan

  - Antiarrhythmics

ajmaline, amiodarone, aprindine, bretylium, bunaftine, cibenzoline, disopyramide, dofetilide, dronedarone, encainide, ethacizine, flecainide, ibutilide, lidocaine, lorajmine, lorcainide, mexiletine, moracizine, prajmaline, procainamide, propafenone, quinidine, sparteine, tedisamil, tocainide, vernakalant

- Antidepressants

  agomelatine, alaproclate, amineptine, amitriptyline, amoxapine, bifemelane, bupropion, butriptyline, citalopram, clomipramine, desipramine, desvenlafaxine, dibenzepin, dimetacrine, dosulepin, doxepin, duloxetine, escitalopram, etoperidone, fluoxetine, fluvoxamine, gepirone, hyperici herba, imipramine, imipramine oxide, iprindole, iproclozide, iproniazide, isocarboxazid, lofepramine, maprotiline, medifoxamine, melitracen, mianserin, milnacipran, minaprine, mirtazapine, moclobemide, nefazodone, nialamide, nomifensine, nortriptyline, opipramol, oxaflozane, oxitriptan, paroxetine, phenelzine, pivagabine, protriptyline, quinupramine, reboxetine, selegiline, sertraline, tianeptine, toloxatone, tranylcypromine, trazodone, trimipramine, tryptophan, venlafaxine, vilazodone, viloxazine, vortioxetine, zimelidine

- Antiplatelets

  abciximab, acetylsalicylic acid, aloxiprin, beraprost, cangrelor, carbasalate calcium, cilostazol, clopidogrel, cloricromen, dipyridamole, ditazole, epoprostenol, eptifibatide, iloprost, indobufen, picotamide, prasugrel, selexipag, ticagrelor, ticlopidine, tirofiban, treprostinil, triflusal, vorapaxar

- Antiulcer drugs (except PPI)

  aluminum hydroxide, amoxicillin, atropine, azithromycin, bismuth subsalicylate, calcium carbonate, cimetidine, clarithromycin, doxycycline, erythromycin, magnesium hydroxide, metronidazole, misoprostol, ranitidine, rebamipide, sodium bicarbonate, sucralfate

- Beta blockers

  acebutolol, alprenolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, bupranolol, carteolol, carvedilol, celiprolol, cloranolol, epanolol, esmolol, labetalol, mepindolol, metoprolol, nadolol, nebivolol, oxprenolol, penbutolol, pindolol, practolol, propranolol, sotalol, talinolol, tertatolol, timolol

- Calcium channel blockers

  amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine, nilvadipine, manidipine, barnidipine, lercanidipine, cilnidipine, benidipine, clevidipine, nifedipine, mibefradil, verapamil, gallopamil, diltiazem, fendiline, bepridil, lidoflazine, perhexiline

- Diabetes drugs

  insulin, acarbose, acetohexamide, albiglutide, alogliptin, benfluorex, buformin, canagliflozin, carbutamide, chlorpropamide, dapagliflozin, dulaglutide, empagliflozin, exenatide, gemigliptin, glibenclamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepide, glymidine, guar gum, linagliptin,

liraglutide, lixisenatide, metahexamide, metformin, miglitol, mitiglinide, nateglinide, phenformin, pioglitazone, pramlintide, repaglinide, rosiglitazone, saxagliptin, simvastatin, sitagliptin, tolazamide, tolbutamide, troglitazone, vildagliptin, voglibose

- Diuretics

  altizide, amiloride, bumetanide, butizide, canrenone, chlorothiazide, chlortalidone, cicletanine, clofenamide, clopamide, clorexolone, conivaptan, cyclopenthiazide, cyclothiazide, epitizide, eplerenone, etacrynic acid, etozolin, fenquizone, furosemide, hydrochlorothiazide, hydroflumethiazide, indapamide, mebutizide, mefruside, mersalyl, methyclothiazide, meticrane, metolazone, muzolimine, piretanide, polythiazide, potassium canrenoate, quinethazone, spironolactone, sulfonamides, theobromine, tienilic acid, tolvaptan, torasemide, triamterene, trichlormethiazide, xipamide

- Erythropoietin-simulating agents

  darbepoetin, epoetin, epogen, eprex, erythropoietin, procrit

- Estrogens

  chlorotrianisene, conjugated estrogens, dienestrol, diethylstilbestrol, estradiol, estriol, estrone, ethinylestradiol, methallenestril, methallenestril, moxestrol, promestriene, tibolone

- NSAIDs

  aceclofenac, acemetacin, alclofenac, alminoprofen, azapropazone, benoxaprofen, benzydamine, bufexamac, bumadizone, celecoxib, chondroitin sulfate, dexibuprofen, dexketoprofen, diacerein, diclofenac, difenpiramide, droxicam, etodolac, etoricoxib, fenbufen, fenoprofen, fentiazac, feprazone, flunoxaprofen, flurbiprofen, glucosamine, glucosaminoglycan polysulfate, ibuprofen, ibuproxam, indometacin, indoprofen, ketoprofen, ketorolac, lonazolac, lornoxicam, lumiracoxib, meloxicam, morniflumate, nabumetone, naproxcinod, naproxen, niflumic acid, nimesulide, orgotein, oxaceprol, oxametacin, oxaprozin, parecoxib, piroxicam, pirprofen, proglumetacin, proquazone, rofecoxib, sulindac, suprofen, tenidap, tenoxicam, tiaprofenic acid, tolmetin, valdecoxib, zomepirac

- Proton-pump inhibitors (PPI)

  dexlansoprazole, dexrabeprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

- Statins

  acipimox, alipogene tiparvovec, aluminium clofibrate, aluminium nicotinate, atorvastatin, atorvastatin, atorvastatin, atorvastatin, bezafibrate, cerivastatin, choline fenofibrate, ciprofibrate, clofibrate, colesevelam, colestipol, colestyramine, colextran, dextrothyroxine, etofibrate, evolocumab, ezetimibe, fenofibrate, fluvastatin, gemfibrozil, lomitapide, lovastatin, magnesium pyridoxal

5-phosphate glutamate, meglutol, mipomersen, niceritrol, nicofuranose, nicotinic acid, nicotinyl alcohol (pyridylcarbinol), omega-3-triglycerides, pitavastatin, policosanol, pravastatin, probucol, ronifibrate, rosuvastatin, simfibrate, simvastatin, tiadenol

Section 9.3.3, Outcome measures:

- Ischemic stroke: ICD-10: I63
- Intracranial hemorrhage: ICD-10: I60 – I62

Annex 4. Signature pages

Signature Page - Study Conduct Responsible

Title	Evaluation of clinical outcomes among non-valvular atrial fibrillation patients with renal dysfunction treated with warfarin or reduced dose rivaroxaban
Protocol version identifier	1.0
Date of last version of protocol	08 November 2017
IMPACT study number	19721
Study type	☒ PASS ☐ non PASS
Active substance (medicinal product)	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Marketing authorization holder(s)	Bayer AG

Function	RLE Strategy & Outcomes Data Generation
Name	Tatsiana Vaitsiakhovich
Title	Dr. rer. nat.
Address	Bayer AG, 13342 Berlin, Germany

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

Date, Signature: _____,_____

Signature Page – Study RWE Strategy Leader

Title	Evaluation of clinical outcomes among non-valvular atrial fibrillation patients with renal dysfunction treated with warfarin or reduced dose rivaroxaban
Protocol version identifier	1.0
Date of last version of protocol	08 November 2017
IMPACT study number	19721
Study type	☒ PASS ☐ non PASS
Active substance (medicinal product)	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Marketing authorization holder(s)	Bayer AG
Function	RLE Strategy & Outcomes Data Generation
Name	Bernhard Schaefer
Address	Bayer AG, 13342 Berlin, Germany

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

Date, Signature: _____,_____

Signature Page – Study External Partner

Title	Evaluation of clinical outcomes among non-valvular atrial fibrillation patients with renal dysfunction treated with warfarin or reduced dose rivaroxaban
Protocol version identifier	1.0
Date of last version of protocol	08 November 2017
IMPACT study number	19721
Study type	☒ PASS ☐ non PASS
Active substance (medicinal product)	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Marketing authorization holder(s)	Bayer AG
Name	Craig I. Coleman
Title	PharmD
Address	Meta-Evidence LLC, 1050 Halladay Avenue West, Suffield, CT, 06078, USA

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

Date, Signature: _____,_____

Signature Page – Study Medical Expert

Title	Evaluation of clinical outcomes among non-valvular atrial fibrillation patients with renal dysfunction treated with warfarin or reduced dose rivaroxaban
Protocol version identifier	1.0
Date of last version of protocol	08 November 2017
IMPACT study number	19721
Study type	☒ PASS ☐ non PASS
Active substance (medicinal product)	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Marketing authorization holder(s)	Bayer AG

Function	Medical Affairs TA Xarelto
Name	Evelyn Weber
Title	MD
Address	Bayer AG, 13342 Berlin, Germany

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

Date, Signature: _____,_____

Signature Page – Study Safety Leader

Title	Evaluation of clinical outcomes among non-valvular atrial fibrillation patients with renal dysfunction treated with warfarin or reduced dose rivaroxaban
Protocol version identifier	1.0
Date of last version of protocol	08 November 2017
IMPACT study number	19721
Study type	☒ PASS ☐ non PASS
Active substance (medicinal product)	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Marketing authorization holder(s)	Bayer AG
Function	Pharmacovigilance
Name	Tomasz Dyszynski
Title	MD, PhD
Address	Bayer AG, 13342 Berlin, Germany

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

Date, Signature: _____,_____

Signature Page – Study Statistician

Title	Evaluation of clinical outcomes among non-valvular atrial fibrillation patients with renal dysfunction treated with warfarin or reduced dose rivaroxaban
Protocol version identifier	1.0
Date of last version of protocol	08 November 2017
IMPACT study number	19721
Study type	☒ PASS ☐ non PASS
Active substance (medicinal product)	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Marketing authorization holder(s)	Bayer AG
Function	RLE Strategy & Outcomes Data Generation
Name	Sebastian Kloss
Address	Bayer AG, 13342 Berlin, Germany

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

Date, Signature: _____,_____

Signature Page – Study Epidemiologist

Title	Evaluation of clinical outcomes among non-valvular atrial fibrillation patients with renal dysfunction treated with warfarin or reduced dose rivaroxaban
Protocol version identifier	1.0
Date of last version of protocol	08 November 2017
IMPACT study number	19721
Study type	☒ PASS ☐ non PASS
Active substance (medicinal product)	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Marketing authorization holder(s)	Bayer AG
Function	Epidemiology
Name	Yanina Lenz
Title	MD, MSc PhD
Address	Bayer AG, 13342 Berlin, Germany

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

Date, Signature: _____,_____

Signature Page – Study Data Manager

Title	Evaluation of clinical outcomes among non-valvular atrial fibrillation patients with renal dysfunction treated with warfarin or reduced dose rivaroxaban
Protocol version identifier	1.0
Date of last version of protocol	08 November 2017
IMPACT study number	19721
Study type	☒ PASS ☐ non PASS
Active substance (medicinal product)	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Marketing authorization holder(s)	Bayer AG

Function	RLE Strategy & Outcomes Data Generation
Name	Tatsiana Vaitsiakhovich
Title	Dr. rer. nat.
Address	Bayer AG, 13342 Berlin, Germany

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

Date, Signature: _____,_____