Observational Study Information

Title	Real-world comparative effectiveness of stroke prevention in patients with AF treated with Rivaroxaban vs VKA (RELOAD)
Local Project identifier	HEOR0215
IMPACT-No.	18735
Protocol version identifier	2.0
Date of last version of protocol	12 September 2016
Active substance	Rivaroxaban (ATC Code: B01AF01) Phenprocoumon (ATC Code: B01AA04)
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Marketing authorization holder(s)	Bayer Healthcare AG, 51368 Leverkusen, Germany
Research question and objectives	The aim of this study is to assess the real world comparative effectiveness of Rivaroxaban prescribed in non-valvular atrial fibrillation (NVAF) routine care patients in Germany The primary objective of this study is to assess the risk of ischemic stroke (effectiveness) and intracranial hemorrhage (ICH, safety) in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon The secondary objectives of this study are: - To assess the cerebral benefit defined as the combined endpoints of ischemic stroke and ICH in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon. - To assess combined effectiveness defined as the endpoints of ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA) in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon. The components of this combined endpoint will also be analyzed separately.

Country(-ies) of study	Germany
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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.

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2. List of abbreviations

ATC	Anatomical Therapeutic Chemical Classification System
CCI	Charlson Comorbidity Index
CHA_2DS_2-VASc	C=Congestive heart failure; H=Hypertension, A=Age (≥75); D=Diabetes mellitus; S=Stroke or TIA or thromboembolism; V=Vascular diseases; A=Age (65-74); Sc=Sex category
$CHADS_2$	C=Congestive heart failure; H=Hypertension, A=Age; D= Diabetes mellitus; S= Stroke or TIA
CI	Confidence Interval
DDD	Defined Daily Dose
DESTATIS	Federal Statistical Office
DRG	Diagnosis-Related Group
DVT	Deep Vein Thrombosis
EBM	Einheitlicher Bewertungsmaßstab
EMA	European Medicine Agency
EU	European Union
HRI	Health Risk Institute
ICD-10 GM	International Classification of Diseases, 10th Revision, German Modification
ICH	Intracranial Hemorrhage
INR	International Normalized Ratio
MI	Myocardial infarction
NI	Non-Interventional
NOAC	Non vitamin-K antagonist
NSAID	Non-Steroidal Anti-Inflammatory Drug
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulants
OPS	International Classification of Procedures in Medicine – German modification (Operationen- und Prozedurenschlüssel)
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PE	Pulmonary Embolism
PZN	National central pharmaceutical number (Pharmazentralnummer)
RR	Relative risk
SAP	Statistical Analysis Plan
SE	Systemic Embolism
SHI	Statutory Health Insurance
TIA	Transitory Ischemic Attack
TIA	Transient Ischemic Attack
UK	United Kingdom
US	United States
VKA	Vitamin K Antagonists
VTE	Venous Thromboembolism

3. Responsible parties

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4. Abstract

Title

Real-world comparative effectiveness of stroke prevention in patients with AF treated with Rivaroxaban vs VKA (RELOAD)

Rationale and background

Non-Valvular Atrial fibrillation (NVAF), the most common cardiac arrhythmia worldwide, affects approximately 1-2% of the general population and is a major risk factor for ischemic stroke. Xarelto® (Rivaroxaban) is a Factor Xa inhibitor which is marketed for stroke prevention in patients with NVAF. This study will be conducted to obtain a better understanding on the comparative effectiveness of Rivaroxaban versus Phenprocoumon for stroke prevention in patients with NVAF in a routine care setting.

Research question and objectives

The aim of this study is to assess the real world comparative effectiveness of Rivaroxaban prescribed in non-valvular atrial fibrillation (NVAF) routine care patients in Germany

The primary objective of this study is to assess the risk of ischemic stroke (effectiveness) and intracranial hemorrhage (ICH, safety) in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon

The secondary objectives of this study are:

- To assess the cerebral benefit defined as the combined endpoints of ischemic stroke and ICH in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon.

- To assess combined effectiveness defined as the endpoints of ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA) in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon. The components of this combined endpoint will also be analyzed separately.

Study design

To address the objectives, this study will be conducted as a retrospective, new user cohort study based on a longitudinal claims database using insurance claims data from the Health Risk Institute's (HRI) research database.

Population

The study population will consist of patients, newly initiated with Rivaroxaban or Phenprocoumon with an NVAF diagnosis from January 1, 2012 through December 31, 2015. Patients will be identified from the HRI research database, a complete longitudinal dataset of patients under statutory health insurance in Germany

Variables

Demographic characteristics, co-morbidities, relevant co-medications, bleeding and stroke risk scores as well as the clinical outcome parameters will be analyzed. The primary outcome parameters are ischemic stroke and ICH; Secondary outcome parameters are the combined endpoints cerebral benefit (ischemic stroke or ICH) as well as combined effectiveness (ischemic stroke, SE or TIA). Single events included in all combined endpoints will be analyzed as part of the secondary objective. Components of ICH (subarachnoid hemorrhage, intracerebral hemorrhage, other and unspecified non-traumatic intracranial hemorrhage) will be assessed separately as well.

Data sources

The study will be conducted using data from the HRI research database. This database includes information about the utilization of services on a case-by-case individual level. To support claims, indications (ICD10-GM) and procedure codes are provided together with costs. The size of the dataset has been reduced to a sample of approximately 4 million patients per year, representative of the German population in terms of age and gender (as of 31.12.2013).

Study size

A preliminary feasibility assessment using the HRI database identified a total of approximately 39,600 treatment naïve users of Phenprocoumon and 22,800 treatment naïve users of Rivaroxaban between Jan 1, 2011 and Sep 30, 2015 being eligible for the planned cohort study.

Data analysis

Patient characteristics will be analyzed descriptively. Incidence rates for the primary and secondary objectives will be estimated as the number of events per 100 person years (% per year). Time-to-event analyses using unadjusted and adjusted multivariate cox proportional hazard models and a 1:1 propensity score matched analyses will be conducted to estimate Hazard Ratios and corresponding confidence intervals.

Milestones

- Final protocol: Oct 15, 2016
- Start of data analyses: Oct 15, 2016
- End of data analyses: Dec 15, 2016
- Final study report: Feb 28, 2017

5. Amendments and updates

This is version 2 of the protocol, modified after initial PRC review in April 2016. Major changes include revising of study objectives and addressing comments of the PRC.

6. Milestones

The following timelines are estimated for the study development, data collection in the database and report of the final study results:

Table 1 – Timelines

Milestone	*Planned date*
Final protocol	Oct 15, 2016
Start of data analyses	Oct 15, 2016
End of data analyses	Dec 15, 2016
Final study report	Feb 28, 2017

7. Rationale and background

Atrial fibrillation (NVAF) is the most common cardiac arrhythmia, with a prevalence of 1-2% in the general population. NVAF prevalence increases with age (1,2) and is a major risk factor for stroke and death. NVAF confers a 5-fold risk of stroke compared to patients without NVAF patients. The appropriate and timely anticoagulant therapy of patients at risk of stroke is one of the core principles of modern NVAF management (1).

Vitamin-K antagonists (VKA) have long been the standard of care of patients with NVAF. However, narrow therapeutic control, high inter- and intrapersonal variation of VKA exposure, multiple drug und food interactions, the need of extensive monitoring, and the associated risk of bleeding limit their use in practice (3,4).

Rivaroxaban (Xarelto®) is a Factor Xa inhibitor which is marketed for stroke prevention in patients with non-valvular atrial fibrillation. The clinical phase III study ROCKET-AF has shown that Rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism [Patel 2011]. However, all relevant efficacy endpoints showed a trend towards better efficacy (partly significant) of Rivaroxaban compared to VKA in the on-treatment analysis. Regarding safety, a significant reduction in ICH was demonstrated in ROCKET-AF.

Recently conducted observational studies using secondary data sources in Germany (IMS® Disease Analyzer) showed significantly better persistence in patients using Rivaroxaban compared to VKA [Evers 2013]. Corresponding results based on claims data in US were published by Laliberté et al. and Nelson et al in 2014 [Laliberte 2014, Nelson 2014].

Similarly, a published comparative effectiveness analysis by Laliberté and colleagues using US claims data suggests a trend towards better effectiveness for most effectiveness endpoints – even though not always significant [Laliberte 2014; Ruff 2014]. One reason for the non-significant findings are the relatively low absolute event numbers of the individual endpoints. Likewise, the NACORA study which was communicated in July 2014 by the French authorities confirmed the favorable trend of Rivaroxaban compared to VKA in the prevention of e.g. ischemic stroke, intracranial hemorrhage, MI. [NACORA 2014] Overall, some publications consistently confirm a trend towards better effectiveness of Rivaroxaban compared to VKA in NVAF in real world. Because of the low event numbers these effects are rarely significant. This trend was also supported by the RELIEF-study that was conducted using German electronic medical records (IMS® Disease Analyzer) as well [Coleman 2016].

The aim of this study is to gain further insight into the real world effectiveness and safety profile of Rivaroxaban compared to VKA (Phenprocoumon) prescribed in NVAF patients in Germany. Internationally, Warfarin is the most commonly used VKA whereas in Germany, Phenprocoumon accounts for the majority of VKA prescriptions in NVAF. This retrospective observational database study therefore aims to add insights about the real world effectiveness and safety of Rivaroxaban compared to Phenprocoumon, whose pharmacokinetic profile differs from Warfarin. This study includes the analysis of ICH as a safety parameter and is therefore designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Bayer Vital.

8. Research questions and objectives

The aim of this study is to evaluate the comparative effectiveness of Rivaroxaban versus VKA (Phenprocoumon) in the prevention of ischemic and cerebral events after treatment initiation in NVAF routine care patients in Germany.

8.1 Primary objectives

The primary objective of this study is to assess the risk of the single components ischemic stroke (effectiveness) and ICH (safety) in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon.

Events are defined as hospitalizations with the respective ICD-10-GM diagnosis.

8.2 Secondary objective(s)

The secondary objectives of this study are:

- To assess the cerebral benefit in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon. The combined endpoint is defined as the occurrence of a hospitalization with one of the following diagnoses
    - ischemic stroke
    - ICH

- To assess the real world effectiveness defined as the combined endpoint of ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA) in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon. The components of this combined endpoint will also be analyzed separately. The composite event is defined as the occurrence of a hospitalization with one of the following diagnoses
    - ischemic stroke
    - systemic embolism
    - TIA

9. Research methods

9.1 Study design

This study will be conducted as a retrospective, new user cohort study based on a longitudinal claims database using German insurance claims data from the Health Risk Institute's (HRI) research database.

New users of Rivaroxaban will be compared with new users of Phenprocoumon to assess the risk for ischemic stroke, ICH, cerebral benefit and the combined effectiveness endpoint of ischemic stroke, SE and TIA.

Strengths of the study design are:

- Study will be conducted using a longitudinal claims data base representing routine care in Germany

- New user design, multivariate adjusted analyses and propensity score matching to reduce and control for confounding

9.2 Setting

The study will include inpatient and outpatient setting as well as drug prescriptions from a sample of German sick funds.

Two study cohorts will be observed:

- NVAF patients who were initiated on Rivaroxaban for stroke prevention
- NVAF patients who were initiated on Phenprocoumon for stroke prevention

9.2.1 Study time frame

The evaluation time frame the study will be January 1, 2011 through March 31, 2016.

For both groups (Rivaroxaban and Phenprocoumon), the date of the first Rivaroxaban or Phenprocoumon dispensing will reflect the index date and mark the beginning of the observation period. Patient baseline characteristics will be measured during the 12 months (365 days, four quarters) preceding the index date (baseline period). The observation (follow-up) period will span from the index date up until the end of data, disenrollment, discontinuation of index treatment (30 day gap period allowed), occurrence of event or switch of treatment.

9.2.2 Selection criteria

The study population will consist of all patients, newly initiated on Rivaroxaban or Phenprocoumon with an NVAF diagnosis meeting the following inclusion and exclusion criteria

Inclusion criteria:

- First dispense date of Rivaroxaban (15mg or 20mg - PZN based) or Phenprocoumon (PZN based) between January 1, 2012 and December 31, 2015
- At least two verified outpatient diagnoses or one inpatient diagnosis (main or secondary diagnosis) of NVAF (ICD-10 GM I48.0/ I48.1/I48.2/I48.9) in the individual time frame of 4 quarters before the index date (pre-index period) or within the index quarter
- Patients will be required to have 4 quarters of enrollment for the assessment of baseline characteristics and be observable and insured in the database for at least one day after their individual index date (post-index period)
- $\geq$ 18 years of age

Exclusion criteria:

- Patients with valvular AF [4 quarters prior to the index date] (see Table 5)
- Pregnancy [4 quarters prior to index date]

- Malignant cancers [4 quarters prior to the index date or "condition after"] (see Table 10)
- Transient cause of AF [4 quarters prior to index date] (see Table 5)
- Patients with VTE (pulmonary embolism or DVT) [60 days before index] (see Table 10)
- Patients with major surgery defined as hip or knee replacement [60 days before index] (see Table 10)
- Prescriptions of OACs (Rivaroxaban, VKA, Dabigatran, Apixaban) before index date [4 quarters prior to index date] (see Table 3, Table 4)
- Patients receiving more than one anticoagulant substance (Apixaban, Dabigatran, Rivaroxaban or Phenprocoumon) or more than one dosage of a substance on the index date (see Table 3, Table 4)
- *For sensitivity analysis* (see data analysis section) : Patient with any of the events defined in the combined endpoints [4 quarters prior to index date or "condition after" (see Table 6)
- Patients with dialysis [4 quarters prior to index date] (see Table 10)

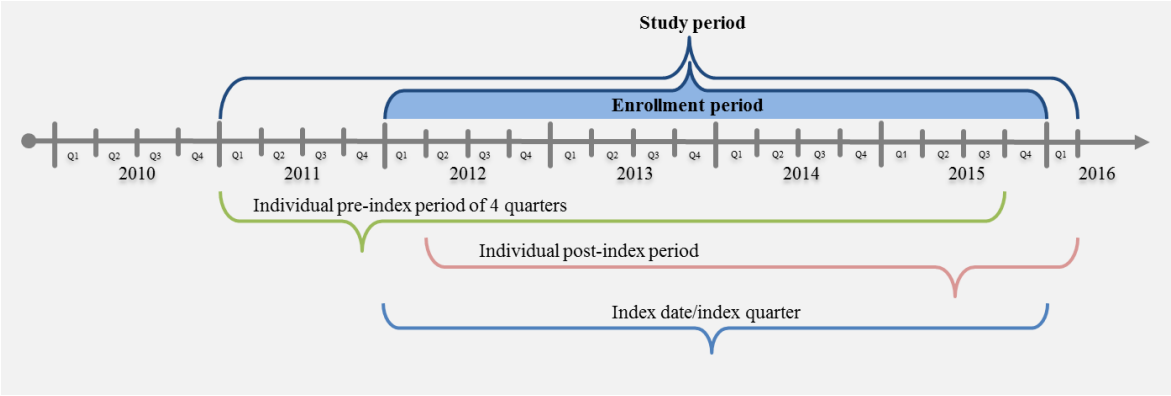
9.2.3 Study population

The study population will be drawn from the HRI database which comprises approximately 4 million covered lives in 2013 on an anonymized case-by-case individual level. Almost 80% of the insured individuals in the database are observable for the entire available observation period of up to six years (most currently from 2010 to 2015). This sample represents 4.8% of the German population and 5.6% of the German SHI population. The insured individuals are distributed all over Germany and the database is already structured to be representative for the German population in terms of age and gender (structure of age and gender as per 31.12.2013 / DESTATIS).

This subset of patients will be used for the purposes of this study. Since this study will use only de-identified patient records and will not involve the collection, use, or transmittal of individually identifiable data, institutional review board approval is not required.

The study population will consist of incident Rivaroxaban or Phenprocoumon users with NVAF in the enrollment period spanning from 1 January 2012 through 31 December 2015.

Figure 1. Selection of the study population



9.3 Variables

9.3.1 Baseline characteristics

Baseline period:
365 days prior to index date for hospital diagnoses and prescriptions and four quarters prior to the index quarter for ambulatory diagnosis. This period will be used to determine whether patients have an NVAF diagnosis, to verify that patients are new users and to assess baseline demographic and clinical characteristics of the patients included in the study population.

The following demographics will be reported for each cohort:

- Gender
- Age
- Age group
    - 18-65, 65-74, ≥75

The following clinical characteristics will be reported for each cohort:

- 4-quarter Charlson comorbidity index (CCI)
- CKD, which is important as risk of adverse events among patients receiving NOACs tends to differ according to renal function)
- $CHADS_2$ score, including Congestive heart failure, hypertension, age, diabetes, stroke
- CHA_2DS_2-Vasc score
- HASBLED score, as measurable without lab values
- Prior non-CNS systemic embolism
- Prior oral anticoagulant use (expected to be 0 with 180-day covariate look back)
- Other relevant co-morbidities:
    - Congestive heart failure
    - DVT
    - Essential hypertension
    - Diabetes mellitus
    - Pulmonary embolism
    - Unstable angina
    - Hyperthyroidism
    - Functional dyspepsia
    - Renal failure

- Other cardiovascular drugs:
  - Antiarrythmics
  - Beta blockers
  - ACE inhibitors
  - ARBs
  - Calcium channel blockers
  - Diuretics
  - Anti-platelet drug classes
  - NSAIDS

Stroke risk score $CHADS_2$ and CHA_2DS_2-VASc

Stroke risk scores in the individual pre-index period of 4 quarters before the index quarter with defined risk factors and corresponding ICD-10-GM codes including heart failure, hypertension, age groups, diabetes mellitus, stroke/TIA/embolism, vascular disease and gender (listed in Annex 2, Table 7).

To include Health Care Proxies

- Number of hospitalizations in the baseline period
- Number of unique medications in the baseline period

Comorbidities

Presence of relevant comorbidities e.g. hemorrhagic diathesis due to anticoagulants and antibodies, coagulopathy, hyperthyroidism, etc. (see Annex 2, Table 6) in the inpatient sector (main and secondary diagnoses) or in the outpatient sector (verified diagnoses and in addition "condition after diagnoses" for stroke, bleedings and MI) in the patient's medical history in the individual pre-index period of 4 quarters before the index quarter will be assessed.

Co-medications

Prescription medications of relevant comedications including antigoagulation therapy, antiarrhythmic drugs, and other medications (see Annex 2, Table 13) in the individual 4 quarters before the index quarter (pre-index period) will be assessed.

Table 2 – Definition of covariates

Variable	Category	Operational definition
Age	continuous	Age in the index quarter.
Gender	categorical	Sex on the index date.

Insurance status	categorical	Insurance status on the index date: • regular insurance • retired • family insured • unknown
Number of hospitalizations	continuous	Total number of hospitalizations, independent of admission diagnosis, during the baseline period.
No of unique medications	continuous	Number of unique pharmaceutical substances (unique ATC 5 Codes) per patient received during the baseline period, based on the prescriptions documented in the database.
Interactions with co-medications	categorical	In order to determine whether patients were concurrently treated with other medication interacting with Rivaroxaban or Phenprocoumon, it will be assessed whether patients received any of the relevant substances in the 90 days before the Index date. For a list of medications with interaction potential see Table 12.
CHA_2DS_2-VASc Score	continuous	The CHA_2DS_2-VASc score will be derived by assigning one point each for hypertension, diabetes mellitus, and heart failure, vascular disease (peripheral artery disease, myocardial infarction, aortic plaque), age 65-74 years, female sex and two points for age 75 years or older, previous stroke or transient ischemic attack (TIA), with a total possible score of nine [Trappe 2012]. Ambulatory verified as well as primary and secondary hospital discharge diagnoses within in the 12 months before the index date will be used to assess the CHA_2DS_2-VASc score. For a complete list of all ICD-10 codes which will be used to form the CHA_2DS_2-VASc score please refer to Annex 2. Tables.

$CHADS_2$ Score	continuous	The $CHADS_2$ Score will be derived by assigning one point each for hypertension, heart failure, age 75 years and older, diabetes mellitus. A preliminary stroke/TIA will be assigned two points, with a total possible score of six [Trappe 2012]. Ambulatory verified as well as primary and secondary hospital discharge diagnoses within in the 12 months before the Index date will be used to assess the $CHADS_2$ score. For a complete list of all ICD-10 codes which will be used to form the $CHADS_2$ score please refer t to Annex 2. Tables.
Charlson Comorbidity Index (CCI)	continuous	The Charlson Comorbidity Index (CCI) will be used to weigh comorbidities in the baseline period depending on their severity. Ambulatory verified as well as primary and secondary hospital discharge diagnoses within the 12 months before the index date will be used to build the CCI score. A list of included conditions and their assigned weights can be found in Annex 2. Tables. Please consider the following publications for further information regarding the applied methodology: - Charlson ME, Pompei P, Ales KL, MacKenzie CR. "A new method of classifying prognostic comorbidity in longitudinal studies: development and validation", Journal of Chronic Disease, 1987, Vol. 40(5), pp. 373-383. - Quan et al., "Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data", Medical Care, Nov 2005, Vol. 43(11), pp. 1130-1139.

Comorbidity Index (modified Charlson Comorbidity Index)	continuous	In order to avoid a high degree of correlation between some covariates a separate Comorbidity Index was defined, which includes only disease categories which are not already measured by the HAS BLED score. This modified Comorbidity Index contains all Charlson disease categories except hypertension, congestive heart failure, cerebrovascular disease, mild, moderate or severe liver disease and moderate or severe renal disease.
Bleeding history (modified HAS BLED Score)	continuous	The HAS-BLED score is derived for each patient in the baseline period_by assigning one point and summing the score across the following conditions: hypertension, renal disease, cirrhosis, and stroke, major bleeding event, age 65 and older, use of non-steroidal anti-inflammatory drug, intake of antiplatelet agents, alcohol abuse. Since the HRI database does not contain any laboratory parameters, the international normalized ratio (INR) will not be included in the HAS-BLED score. For a complete list of all ICD codes which will be used to form the HAS-BLED score please refer to Annex 2. Tables.
Myocardial infarction (MI)	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used to assess whether patients suffered from a previous myocardial infarction. MI will be defined using the ICD-10 GM code I21.* and I22.*.
Chronic renal insufficiency	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from a chronic renal insufficiency. Chronic renal insufficiency will be defined using the ICD-10 GM code N18.*.

Chronic renal insufficiency stage I	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage I will be defined using the ICD-10 GM code N18.1.
Chronic renal insufficiency stage II	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage II will be defined using the ICD-10 GM code N18.2.
Chronic renal insufficiency stage III	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage III will be defined using the ICD-10 GM code N18.3.
Chronic renal insufficiency stage IV	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage IV will be defined using the ICD-10 GM code N18.4.
Chronic renal insufficiency stage V	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage V will be defined using the ICD-10 GM code N18.5.

Other chronic renal insufficiency	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from other chronic renal insufficiency. Other chronic renal insufficiency will be defined using the ICD-10 GM code N18.8.
Unspecified chronic renal insufficiency	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from an unspecified renal insufficiency. Unspecified chronic renal insufficiency will be defined using the ICD-10 GM code N18.9.
Diabetes	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from diabetes mellitus. Diabetes mellitus will be defined using the ICD-10 GM code E10.*-E14.*.
Hypertension	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from hypertension. Hypertension will be defined using the ICD-10 GM code I10.*.
Congestive heart failure	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from congestive heart failure. Congestive heart failure will be defined using the ICD-10 GM code I50.*.

Atherosclerosis of arteries of extremities	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from peripheral vascular disease. Peripheral vascular disease will be defined using the ICD-10 GM code I70.2.
Ischemic stroke or TIA during baseline	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from ischemic stroke or TIA. Ischemic stroke or TIA will be defined using the ICD-10 GM code I63, I64, G45.9 and G45.8.
Coronary heart disease	categorical	Ambulatory verified diagnoses in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from coronary heart disease. Coronary heart disease will be defined using the ICD-10 GM code I20*(angina pectoris), I24.*(other acute ischemic heart diseases) and I25* (chronic ischaemic heart disease).
Liver disease		
Mild liver disease	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from a mild liver disease. Mild liver disease will be defined using the ICD-10 GM codes according to the Charlson Comorbidity Index (Table 8).

Moderate or severe liver disease	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from a moderate or severe liver disease. Moderate or severe liver disease will be defined using the ICD-10 GM codes according to the Charlson Comorbidity Index (Table 8).
Severe liver disease	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from a severe liver disease. Severe liver disease will be defined using the ICD-10 GM codes K70.4 Alcoholic hepatic disease K71.1 Toxic liver disease with hepatic necrosis K72.1 Chronic hepatic failure K72.9 Hepatic failure, unspecified K76.5 Hepatic veno-occlusive disease K76.6 Portal hypertension K76.7 Hepatorenal syndrome I85.0 Oesophageal varices with bleeding I85.9 Oesophageal varices without bleeding I86.4 Gastric varices I98.2 Oesophageal varices without bleeding in diseases classified elsewhere
Smoking	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients used tobacco. Tobacco use will be defined using the ICD-10 GM codes F17.*, Z71.6, Z72.0.

Alcohol abuse	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients abused alcohol. Alcohol abuse will be defined using the ICD-10 GM codes F10.*, Z71.4, Z50.2, Z72.1.
Depression	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from depression. Depression will be defined using the ICD-10 GM codes F32*, F33.*, F34.1.
Somatoform disorder	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from somatoform disorder. Somatoform disorder will be defined using the ICD-10 GM codes F45.*.
Anxiety disorder	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from anxiety disorder. Anxiety disorder will be defined using the ICD-10 GM codes F40.* and F41.*.
Substance abuse	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from substance abuse. Substance abuse will be defined using the ICD-10 GM codes F11*, F12*, F13*, F14*, F15*, F16*, F18*, F19*.

Dementia	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from dementia. Dementia will be defined using the ICD-10 GM codes F00, F01, F02, F03.
Cancer	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from cancer. Cancer will be defined using the ICD-10 GM code C*.
Obesity	categorical	Ambulatory verified diagnosis in the four quarters prior to the index quarter as well as primary and secondary hospital discharge diagnoses within the 365 days before or on the index date will be used assess whether patients suffered from obesity. Obesity will be defined using the ICD-10 GM codes E66.
Proton-pump-inhibitors (omeprazol)	categorical	It will be assessed whether patients received at least one prescription for proton-pump-inhibitors in the 365 days before or on the index date. For a complete list of all relevant ATC Codes please refer to Table 13.
Coronary angioplasty	categorical	It will be assessed whether patients underwent a percutaneous transluminal coronary angioplasty (PTCA) in the 365 days before or on the index date. The OPS Code 8837 (*perkutan-transluminale Gefäßintervention an Herz und Koronargefäßen*) will be used to determine whether the procedure has been performed in the patient individual baseline period.
Antiplatelet medication	categorical	It will be assessed whether patients received at least one prescription for antiplatelet medications in the 365 days before or on the index date. The relevant ATC code that will be used is B01AC.

Prescription of acetylsalicylic acid (ASS)	categorical	It will be assessed whether patients received at least one prescription for ASS (ATC Code: B01AC06) in the 365 days before or on the index date.
Prescription of non- steroidal anti-inflammatory drugs (NSAIDs)	categorical	It will be assessed whether patients received at least one prescription for NSAIDs (ATC Code: M01A*) in the 365 days before or on the index date.

9.3.2 Exposure

There are two exposures: New use of Rivaroxaban and new use of Phenprocoumon. Exposure will be defined as one or more prescriptions for the target drug (Phenprocoumon or Rivaroxaban). These prescriptions will be identified using the anatomical therapeutic chemical (ATC) and Pharmazentralnummer (PZN) drug codes including dose and package size (listed in the Annex 2, Table 3 and Table 4).

The exposure start date (index date in the index quarter) for each patient will be defined as the dispense date of the first Rivaroxaban or Phenprocoumon prescription.

Exposure time
Time from index date: Days of supply + Days of potential hospitalizations + Gap period (if no prescription immediately follows). Hospitalizations related to outcome measures will be considered as outcome event.

Gap period
A gap period is allowed when treatment is discontinued before censoring the patient for discontinuation. Patients will be considered as being exposed until 30 days after the end of supply.

Days of supply
Since Rivaroxaban is prescribed with a fixed dose, the number of days of supply corresponds to the size of the package, or the number of days until new prescription, if smaller. Assessing the number of days of supply for Phenprocoumon will be different.

Phenprocoumon Days of Supply:

To account for the intra- and interpersonal variability of the Phenprocoumon treatment regime (INR control and potential titration of Phenprocoumon) an empirical DDD (eDDD) based on the observed Phenprocoumon prescription patterns in the HRI database will be calculated.

The Phenprocoumon PZN code will be used to compute the Amount of Active Ingredient (AAI) dispensed to each patient of the Phenprocoumon group for each prescription. A personalized prescribed daily dose (pPDD) representing the daily dose taken during follow-up will be computed for each patient *i*:

$$\mathrm{pDDD}_i = \frac{\sum_{k=1}^{K-1} AAI_{i,k}}{T_i}$$

k: index of the Phenprocoumon prescriptions during follow-up ($k \in \{1, K\}$)

T: number of days between the first and the last prescription during follow-up

The eDDD corresponds to the median of the distribution of the pPDD estimated over all patients who were solely treated with Phenprocoumon during the study period. The Exposure Time (ET) corrected from the intra- and interpersonal variability of Phenprocoumon treatments can be computed for each patient *i* as:

$$\mathrm{ET}_i = \frac{\sum_{k=1}^{K} AAI_{i,k}}{eDDD}$$

Date of switch
Patients who receive a prescription for an OAC other than the index OAC prescription (including other NOACs) during the follow- up period will be considered as switchers if the new prescription occurred either before the end of supply of the current prescription or within the gap period after the end of supply. The dispense date of the new OAC will be defined as the date of switch and patients will be censored.

Date of discontinuation
Discontinuation will be defined as no follow-up prescription for either Rivaroxaban or Phenprocoumon at the end of the gap period after the end of supply. Patients receiving prescriptions for Rivaroxaban 10 mg will also be considered to have terminated the treatment. The last day of the exposure time will be defined as the date of discontinuation and patients will be censored.

9.3.3 Outcome measures

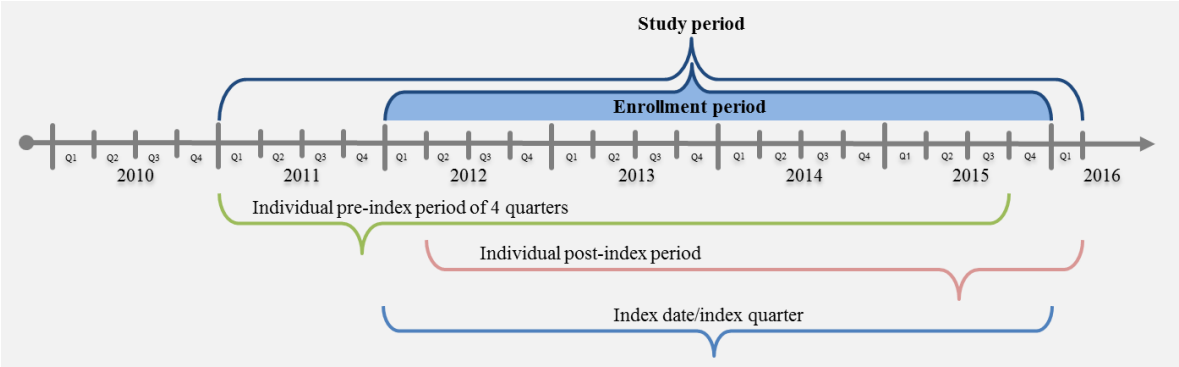
All outcomes will be identified by using inpatient hospital data with either primary and or secondary discharge diagnoses.

The primary effectiveness outcome of this study is ischemic stroke and the primary safety outcome of this study is ICH.

Events are defined as hospitalizations with the respective ICD-10-GM diagnosis (see Table 6).

The secondary outcome will be occurrence of any one single event (as listed above). Incidence rates, as well as adjusted and unadjusted hazard ratios will be estimated comparing the risk for a cardiovascular endpoint in patients initiating Rivaroxaban versus Phenprocoumon.

Figure 2. Study Period and Outcome Variables



9.4 Data sources

Health insurance in Germany

Approximately 86% of the German population, corresponding to about 70 million individuals, is insured in the statutory health insurance (SHI). Out of the remaining 14%, 11% of the German population is covered by the private health insurances and 3% are covered by special programs which include soldiers and policemen. The SHI is structured in ~120 different and independent health insurances. All individual health insurances offer the same comprehensive benefit package, as the contents to be reimbursed are set in Social Law. Nearly full coverage for all health care related services is provided as only little co-payments exist. Therefore, the funds paid by the SHI to any provider of health care (hospital, physician or pharmacist) represent almost the complete spectrum of total health care cost on an individual patient basis. All data can be linked to patients' demographics including age, gender, and the type of occupation for individuals within the workforce. However, health insurances in Germany do not have knowledge of any clinical data, such as clinical parameters (e.g. lab test results, results of bone density tests, quality of life data, severity grades of a disease, symptom scores etc.). A health insurance has a record for the test or procedure in every case as they have to pay for it but no record of the clinical finding as mentioned.

Description of the database

The HRI research database comprises claims data from about 75 different health insurances, which represents a high percentage of the overall number of health insurances in Germany. Data on patients and physicians is anonymized, as are the providers and the sickness funds, before data is made available to the HRI. The analysis sample of the HRI database includes the utilization and costs of services for approximately 4 million covered lives in 2013 on an anonymized case-by-case individual level. This sample represents 4.8% of the German population and 5.6% of the German SHI population. The insured individuals are distributed all over Germany. Furthermore, the sample is already structured to be representative for the German population in terms of age and gender (structure of age and gender as per 31.12.2013 / DESTATIS).

Almost 80% of the insured individuals in the database are observable for the entire available observation period of up to six years. Thus, analyses including comparatively large study populations with a long observation period are possible.

The HRI database is updated on an annual basis, guaranteeing studies with the most recent data. As the database has an administrative time lag until completion and clean up for all areas of health care of about 9 months, most data will be available for the preceding year, mid of the following calendar year.

Structure of the database

The database refers to different health care sectors such as the inpatient, outpatient, and pharmacy sector, and provides detailed information on the resource use and cost of these services. It includes amongst others, the following data:

- Patient Demographics: Record of continuous enrollment for a unique set of demographics (e.g. insurance begin and end, age, gender, date of death, which relates to the beginning of the quarter) for each individual. In addition, the insurance status (e.g. retired, family insurance), region of residence, and the type of occupation are included.
- Inpatient Care: Contains records that summarize hospital admission information such as ICD-10-GM (German Modification of the ICD-10 codes) codes in primary or secondary position, and Diagnosis Related Groups (DRG) code. It also includes the length of stay (date of hospital admission and end of hospital stay) and all performed procedures and surgeries (OPS). Furthermore, discharge diagnosis code or death in hospital, and costs of inpatient stay are included.
- Outpatient Care: Contains services that were rendered in a physician's office in the quarter in which the diagnosis (ICD-10-GM code) was documented. In addition, the procedures performed (e.g. laboratory, radiology echocardiography) by EBM codes and day of performance. Furthermore, the type of specialist that documented the diagnosis and performed the procedure (e.g. cardiologist, general practitioner) and costs of outpatient care are available.
- Pharmaceutical Claims: Contains drug dispensed by PZN (package level) – this is mapped to ATC codes and DDDs, day of prescription, day of dispensing, and costs of drugs dispensed from a statutory health insurance perspective without individual deductibles between single sickness funds and pharmaceutical companies. Furthermore, the type of doctor prescribing (e.g. cardiologist, general practitioner) is included.
- Devices and Aids: Contains type of device/aid (code and text) (e.g. massage, occupational therapy, walker, wheel chair), quantity prescribed, type of care provider, start and end date, and costs of device/aids.
- Incapacity to Work and Sick Leave Payments: This includes ICD-10-GM diagnoses that cause sick leave, duration of sick leave, and the corresponding start and end date of sick leave. In addition, the type of physician that filled-out the sick leave (e.g., cardiologist, general practitioner) and the cost of sick leave payments are incorporated.

9.5 Study Size

All patients identified in the HRI research database meeting the inclusion criteria will be included in the study. A preliminary feasibility assessment using the HRI database identified a total of approximately 39,600 treatment naïve users of Phenprocoumon and 22,800 treatment

naïve users of Rivaroxaban between Jan 1, 2011 and Sep 30, 2015 for the planned cohort study. However, this preliminary assessment did not consider all of the above listed inclusion and exclusion criteria. We estimate that the actual number of patients might be up to 25% lower.

Rivaroxaban: ~ 17,000 patients

Phenprocoumon: ~ 30,000 patients

Power considerations

Primary effectiveness endpoint – ischemic stroke

Source study	Incidence rate Rivaroxaban	Incidence rate Phenprocoumon	Hazard Ratio	Power
Rocket-AF	0.0134	0.0126	0.94	0.1105
REVISIT-US	0.0054	0.0083	0.65	0.9581
Larsen et al	-	-	0.86	0.2702

Primary safety endpoint – ICH

Source study	Incidence rate Rivaroxaban	Incidence rate Phenprocoumon	Hazard Ratio	Power
Rocket-AF	0.005	0.007	0.71	0.7601
REVISIT	0.0054	0.0096	0.53	1.000
Larsen et al	-	-	0.56	0.9995

9.6 Data management

A completely anonymized file comprising all observations and variables required for the planned analyses will be created from information contained exclusively within the source material. It is required that all analyses will be conducted on the site of the data provider. Data files from the HRI research database must stay in-house due to data protection regulations. Results will be available on an aggregated level.

All statistical processing will be performed using SAS® Enterprise Guide Version 9.2 unless otherwise stated.

It is required that all analyses be conducted on the site of the data provider due to data protection requirements. An independent review of study results will be performed by Xcenda GmbH.

9.7 Data analysis

This section will provide a detailed overview about the statistical methods which will be used in order to answer the research questions. The core statistical elements (analysis populations, definition and measurement of endpoints and other key variables and statistical methodology) are adequately detailed within this section and there will not be a separate SAP.

All analyses will be performed by the Health Risk Institute in coordination with Elsevier Health Analytics and Xcenda GmbH.

9.7.1.1 Demographics and clinical characteristics

In a first step the demographic and clinical characteristics of the patients in both treatment groups will be determined. All variables will be derived in the baseline period.

For continuous variables:

For continuous variables such as age and number of hospitalizations, the mean, median, minimum (min), maximum (max) and the standard deviation (SD) will be reported. The differences between the treatment groups will be estimated by calculating the standardized difference in means (SMD):

$$\frac{\overline{X_1} - \overline{X_2}}{\sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}}$$

Phenprocoumon will be used as the reference group.

For categorical variables:

The absolute number and relative proportion of patients with the respective characteristic will be reported. Proportions will be relative to the total sample size of each treatment group. The differences between the treatment groups will be estimated by calculating the standardized difference in means (SMD). Phenprocoumon will be used as the reference group

9.7.1.2 Primary and secondary objectives

The incidence rate and corresponding confidence intervals of the primary and secondary endpoints will be estimated as the number of events per 100 person years (% per year). Cox proportional hazard regression will be used to estimate unadjusted and adjusted hazard ratios (multivariate adjusted as well as 1:1 propensity matched). For all models, hazard ratios (HRs), 95% confidence intervals (CIs) and all other regression coefficients will be reported.

Kaplan-Meier curves will be generated to evaluate the time-to-first event associated with the initial treatment.

Rivaroxaban will be compared to Phenprocoumon. Hence, Phenprocoumon will be the reference category in the analysis. A subset of the variables depicted in Table 2 which were selected on an empirical basis, will be included as covariates in the Cox proportional hazards model.

Propensity Score Matching

In this study, we will additionally use propensity score matching. The propensity score will be calculated as the predicted probability of exposure (i.e. probably of receiving Rivaroxaban), given all that is known about a patient (i.e. patient characteristics and covariates).

The probability itself will be derived from a multivariate logistic regression using the parameters thought to act as confounding variables. The propensity score act as a "balancing score" in that all factors that contribute to the score are expected to be independent between treatment groups if the patient population is matched on propensity score and a stratified table of patient characteristics is examined. That is, after propensity score matching all other factors included in the score are expected to be balanced between the two treatment groups. This will minimize confounding by observed baseline covariates by removing any potential relationship between cofounders and exposure group.

In this study, we will estimate propensity scores from all measured factors noted above. These factors will be entered into a logistic regression model, with the factors as the independent variables (with no further variable selection) and the treatment as the dependent variable. From the resulting model, we will predict probability of treatment for each patient; this probability of treatment will be each patient's estimated propensity score.

We will perform 1:1 nearest-neighbor matching. After matching, we expect to see balance between the Rivaroxaban and VKA groups with respect to all measured factors. To ensure this, we will examine propensity score balance diagnostics including: (1) pre- and post-matching propensity score overlap plots; (2) pre- and post-matching c-statistics and (3) pre- and post-standardized mean differences (SMD) between the two treatment groups.

Patient time under risk and censoring

Patients will be censored in the follow-up period as follows:

Patients will be followed from index date to date of discontinuation of treatment, switch of treatment, death, end of continuous enrollment in the sick fund or end of study period without experiences any event, whichever occurs first.

Sensitivity Analyses

For this study sensitivity analyses are planned according to dosing regimen and patients with prior events of any of the events defined in the combined endpoints.

One separate analysis will be conducted for patients receiving 20mg Rivaroxaban only (standard-dose analysis). Patients will be censored once a different dose was prescribed compared to the index dose of 20mg. For patients receiving initiating 15mg Rivaroxaban baseline characteristics will be outlined descriptively.

Additionally, a separate analysis will be planned where patients with any of the events defined in the combined endpoints within the baseline period 4 quarters prior to index date or "condition after") will be included in the analyses.

Therefore, sensitivity analyses will result in four separate cohort and patient time datasets for which a propensity score matching and a multivariate analysis will be performed.

Handling of Missing Data

Missing data will not be imputed.

Statistical Software

All analyses will be performed with SAS 9.2.

9.8 Quality control

Data quality management comprises data collection, management, and verification processes, including quality control processes and documentation of the quality control steps. Data quality management is built in to the core processing systems. In addition SAS is used to process data extracted from the production process to determine quality metrics.

As part of the management strategy the HRI documents and implements:

1. Quality control processes around reference data
2. Rules for raw data checks for completeness reasonability and volume
3. Control processes for production files and outputs
4. Process flow and maintenance processes including standard operating procedures
5. Database metrics including quality and completeness
6. Procedures for handling internal inquiries.

The HRI routinely applies data quality assurance across data life-cycle stages. The following process is typical:

Data acquisition

The acquisition of the data follows a predefined statistical data-collection design/plan. The first control is the assurance that this plan is executed, i.e. all the required data items have been acquired and are in the collected-data-repository.

Data completeness checks

1. Checking the file for completeness
2. Ensuring the file format consistency with a predefined standard
3. Checking the file for data content (e.g. check for corresponding values in each field).

Data-processing checks

1. Control for correctness of the format and any input files format transformations
2. Control of correctness of the bridged data.

Processed-data checks

1. Control of individual data-suppliers - total data volume versus expected and previous periods
2. Checks for missing data estimations
3. Check for aggregated data by analysis unit, e.g. values for surgeries, hospitals, regions.

Indicator Quality Assurance

The HRI will provide a series of descriptive statistics derived from the underlying data to validate the integrity of the field content. A sample of these statistics includes but is not limited to:

1. Record counts with each data table
2. Unique counts of patients
3. Unique counts of patients continuously enrolled for specified one year increments
4. Percentage of missing values in key data fields (e.g. patient date of birth, patient gender, billing and diagnosis codes, dates of service, etc.)
5. Percentage of valid values in key data fields
6. Verify that a unique patient identifier is linked to only one individual.

9.9 Limitations of the research methods

As with any data source, the HRI research database has limitations. Some have to do with the nature of claims data and others with the nature of the German sick funds claims.

Key limitations include:

- The HRI research database is based on a large sample. Because the sample is not random, it may contain biases or fail to generalize well to other populations. However, these data can complement other datasets or be used as benchmarks against them.
- For the comorbidities of interest, the level of precision in the coding system of the database may impact the level of precision of the results and also, may limit the comparability of results across databases. The proportions of patients with a given comorbidity may differ greatly, only due to the structure of the diagnosis coding system. Also, the reason for prescribing is not captured.
- Claims data are recorded for accounting purposes and not for clinical research. As a result, it is not possible to characterize patients by clinical parameters or to see the physician's intention for each intervention.
- The HRI research databases do not provide information on lifestyle variables such as smoking, but recording of lifestyle factors should be non-differential with respect to exposure, and PS matching is expected to generate balance between cohorts on

measured confounders (some of which will strongly correlate with unmeasured factors).

- In Germany, outpatient data is only delivered on a quarterly basis. Date of diagnosis is not available, only the quarter of diagnosis.
- The results which will be derived from this study are only valid for the population described by the in- and exclusion criteria.

9.10 Other aspects

Not applicable.

10. Protection of human subjects

Data on patients and physicians is anonymized, as are the providers and the sickness funds, before data is made available to the HRI. Therefore, this classifies it as exempt for IRB approval.

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidances, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar standards.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required.

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), 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 (European Medicines Agency 2012).

12. Plans for disseminating and communicating study results

The study will be posted on clinicaltrials.gov. The results will be presented in form of a study report and separately in form of a MS-PowerPoint presentation in English following the STROBE checklist [von Elm et. al 2008]. The results of the study are considered for publication and will follow the International Committee of Medical Journal Editors [ICMJE 2015] guidelines. In addition, communication in appropriate scientific meetings will be considered.

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Annex 1. List of stand-alone documents

None.

Annex 2. Tables

Table 3 – Phenprocoumon PZN codes

Description		*Pack size*	*PZN*
FALITHROM 1,5 mite Filmtabletten	20	St	972890
FALITHROM 1,5 mite Filmtabletten	100	St	972915
FALITHROM Filmtabletten	20	St	3011932
FALITHROM Filmtabletten	20	St	4421721
FALITHROM Filmtabletten	50	St	4421738
FALITHROM Filmtabletten	100	St	4421744
MARCOUMAR Tabletten	50	St	3352194
MARCOUMAR Tabletten	100	St	3352202
MARCOUMAR Tabletten	50	St	4334620
MARCOUMAR Tabletten	100	St	4334637
MARCOUMAR Tabletten	100	St	9726170
MARCOUMAR Tabletten	50	St	4958705
MARCOUMAR Tabletten	100	St	4958711
MARCOUMAR Tabletten	100	St	4386479
MARCUMAR Tabletten	14	St	5541315
MARCUMAR Tabletten	30	St	1300649
MARCUMAR Tabletten	49	St	5541321
MARCUMAR Tabletten	56	St	7768135
MARCUMAR Tabletten	92	St	7768170
MARCUMAR Tabletten	98	St	5541338
MARCUPHEN-CT 3 mg Tabletten	20	St	7636008
MARCUPHEN-CT 3 mg Tabletten	50	St	7636014
MARCUPHEN-CT 3 mg Tabletten	98	St	6588626
MARCUPHEN-CT 3 mg Tabletten	100	St	7636020
PHENPRO AbZ 3 mg Tabletten	98	St	6811219
PHENPRO AbZ 3 mg Tabletten	100	St	2059517
PHENPRO ratiopharm 3 mg Tabletten	20	St	4582128
PHENPRO ratiopharm 3 mg Tabletten	50	St	4582134
PHENPRO ratiopharm 3 mg Tabletten	98	St	6575233
PHENPRO ratiopharm 3 mg Tabletten	100	St	4582140
PHENPROCOUMON acis 3 mg Tabletten	20	St	10269507
PHENPROCOUMON acis 3 mg Tabletten	50	St	10269513
PHENPROCOUMON acis 3 mg Tabletten	100	St	10269542
PHENPROGAMMA 3 Tabletten	14	St	9404207
PHENPROGAMMA 3 Tabletten	20	St	2704892
PHENPROGAMMA 3 Tabletten	50	St	2704900
PHENPROGAMMA 3 Tabletten	100	St	2704917
MARCOUMAR Tabletten	100	St	8874891
MARCOUMAR Tabletten	100	St	3352202
MARCOUMAR Tabletten	50	St	4334620
MARCOUMAR Tabletten	100	St	4334637
MARCOUMAR Tabletten	100	St	9726170
MARCOUMAR Tabletten	50	St	4958705

MARCOUMAR Tabletten	100	St	4958711
MARCOUMAR Tabletten	100	St	4386479
MARCOUMAR Tabletten	50	St	8874885
MARCOUMAR Tabletten	2X25	St	3422256
MARCOUMAR Tabletten	100	St	3422262
MARCOUMAR Tabletten	50	St	4386462
MARCOUMAR Tabl.	50	St	1835787
MARCOUMAR Tabl.	100	St	1837390
MARCOUMAR Tabl.	50	St	4446773
MARCOUMAR Tabl.	100	St	4446796
MARCOUMAR Tabl.	50	St	6969475
MARCOUMAR Tabl.	100	St	6969481
MARCOUMAR Tabl.	20	St	2499417
MARCOUMAR Tabl.	50	St	2021408
MARCOUMAR Tabl.	100	St	3215540

Table 4 – Xarelto® PZN codes

Description	*Pack size*		*PZN*
XARELTO 2,5 mg Filmtabletten	1X10X10	St	8461290
XARELTO 2,5 mg Filmtabletten	1X28	St	9647915
XARELTO 2,5 mg Filmtabletten	1X30	St	8717186
XARELTO 10 mg Filmtabletten	5	St	9154791
XARELTO 10 mg Filmtabletten	5	St	2088536
XARELTO 10 mg Filmtabletten	10	St	5995074
XARELTO 10 mg Filmtabletten	10	St	9721534
XARELTO 10 mg Filmtabletten	10	St	7799012
XARELTO 10 mg Filmtabletten	10	St	7610606
XARELTO 10 mg Filmtabletten	10	St	7572633
XARELTO 10 mg Filmtabletten	10	St	7536850
XARELTO 10 mg Filmtabletten	10	St	10852626
XARELTO 10 mg Filmtabletten	10	St	10743771
XARELTO 10 mg Filmtabletten	10	St	10381894
XARELTO 10 mg Filmtabletten	10	St	10764520
XARELTO 10 mg Filmtabletten	30	St	5995080
XARELTO 10 mg Filmtabletten	30	St	6410420
XARELTO 10 mg Filmtabletten	30	St	7799029
XARELTO 10 mg Filmtabletten	30	St	5459513
XARELTO 10 mg Filmtabletten	30	St	9777888
XARELTO 10 mg Filmtabletten	30	St	5748766
XARELTO 10 mg Filmtabletten	30	St	7572662
XARELTO 10 mg Filmtabletten	30	St	7536927
XARELTO 10 mg Filmtabletten	30	St	6454481
XARELTO 10 mg Filmtabletten	30	St	10402662
XARELTO 10 mg Filmtabletten	30	St	10852632
XARELTO 10 mg Filmtabletten	30	St	10339455
XARELTO 10 mg Filmtabletten	30	St	10381902
XARELTO 10 mg Filmtabletten	30	St	11617270

XARELTO 10 mg Filmtabletten	30	St	11565001
XARELTO 10 mg Filmtabletten	100	St	5995097
XARELTO 10 mg Filmtabletten	10X10	St	9941276
XARELTO 15 mg Filmtabletten	14	St	8461344
XARELTO 15 mg Filmtabletten	14	St	10101682
XARELTO 15 mg Filmtabletten	14	St	10058590
XARELTO 15 mg Filmtabletten	14	St	10012139
XARELTO 15 mg Filmtabletten	14	St	10852649
XARELTO 15 mg Filmtabletten	14	St	10297679
XARELTO 15 mg Filmtabletten	14	St	10853560
XARELTO 15 mg Filmtabletten	14	St	10381919
XARELTO 15 mg Filmtabletten	14	St	10999312
XARELTO 15 mg Filmtabletten	14	St	11015708
XARELTO 15 mg Filmtabletten	14	St	10964153
XARELTO 15 mg Filmtabletten	28	St	8461350
XARELTO 15 mg Filmtabletten	28	St	9724515
XARELTO 15 mg Filmtabletten	28	St	4369423
XARELTO 15 mg Filmtabletten	28	St	10058609
XARELTO 15 mg Filmtabletten	28	St	10012145
XARELTO 15 mg Filmtabletten	28	St	10072093
XARELTO 15 mg Filmtabletten	28	St	10852655
XARELTO 15 mg Filmtabletten	28	St	10393650
XARELTO 15 mg Filmtabletten	28	St	10948987
XARELTO 15 mg Filmtabletten	28	St	10381925
XARELTO 15 mg Filmtabletten	28	St	7605019
XARELTO 15 mg Filmtabletten	28	St	11724729
XARELTO 15 mg Filmtabletten	42	St	8461404
XARELTO 15 mg Filmtabletten	42	St	9724521
XARELTO 15 mg Filmtabletten	42	St	10102144
XARELTO 15 mg Filmtabletten	42	St	10012151
XARELTO 15 mg Filmtabletten	42	St	10393667
XARELTO 15 mg Filmtabletten	42	St	4369452
XARELTO 15 mg Filmtabletten	42	St	10200906
XARELTO 15 mg Filmtabletten	42	St	10948970
XARELTO 15 mg Filmtabletten	42	St	10381931
XARELTO 15 mg Filmtabletten	42	St	10964176
XARELTO 15 mg Filmtabletten	42	St	10999329
XARELTO 15 mg Filmtabletten	42	St	10852661
XARELTO 15 mg Filmtabletten	42	St	11565018
XARELTO 15 mg Filmtabletten	98	St	8461367
XARELTO 15 mg Filmtabletten	98	St	9724538
XARELTO 15 mg Filmtabletten	98	St	10132139
XARELTO 15 mg Filmtabletten	98	St	10005926
XARELTO 15 mg Filmtabletten	98	St	10012168
XARELTO 15 mg Filmtabletten	98	St	7089598
XARELTO 15 mg Filmtabletten	98	St	10762403
XARELTO 15 mg Filmtabletten	98	St	10072101

XARELTO 15 mg Filmtabletten	98	St	10852678
XARELTO 15 mg Filmtabletten	98	St	10393696
XARELTO 15 mg Filmtabletten	98	St	4369475
XARELTO 15 mg Filmtabletten	98	St	10200912
XARELTO 15 mg Filmtabletten	98	St	10743794
XARELTO 15 mg Filmtabletten	98	St	10381948
XARELTO 15 mg Filmtabletten	98	St	10999335
XARELTO 15 mg Filmtabletten	98	St	11096606
XARELTO 15 mg Filmtabletten	98	St	11864962
XARELTO 15 mg Filmtabletten	98	St	11559348
XARELTO 15 mg Filmtabletten	100	St	9333393
XARELTO 15 mg Filmtabletten	10X10	St	9941282
XARELTO 20 mg Filmtabletten	14	St	8461410
XARELTO 20 mg Filmtabletten	14	St	10106863
XARELTO 20 mg Filmtabletten	14	St	10057490
XARELTO 20 mg Filmtabletten	14	St	10012174
XARELTO 20 mg Filmtabletten	14	St	10852684
XARELTO 20 mg Filmtabletten	14	St	10297685
XARELTO 20 mg Filmtabletten	14	St	10853577
XARELTO 20 mg Filmtabletten	14	St	10381954
XARELTO 20 mg Filmtabletten	14	St	10964182
XARELTO 20 mg Filmtabletten	14	St	10999341
XARELTO 20 mg Filmtabletten	14	St	11015714
XARELTO 20 mg Filmtabletten	28	St	8461427
XARELTO 20 mg Filmtabletten	28	St	9724544
XARELTO 20 mg Filmtabletten	28	St	10106886
XARELTO 20 mg Filmtabletten	28	St	4369481
XARELTO 20 mg Filmtabletten	28	St	10057509
XARELTO 20 mg Filmtabletten	28	St	10012180
XARELTO 20 mg Filmtabletten	28	St	10072118
XARELTO 20 mg Filmtabletten	28	St	10852690
XARELTO 20 mg Filmtabletten	28	St	10393638
XARELTO 20 mg Filmtabletten	28	St	10318631
XARELTO 20 mg Filmtabletten	28	St	10381983
XARELTO 20 mg Filmtabletten	28	St	7605025
XARELTO 20 mg Filmtabletten	28	St	10999358
XARELTO 20 mg Filmtabletten	98	St	8461433
XARELTO 20 mg Filmtabletten	98	St	9724550
XARELTO 20 mg Filmtabletten	98	St	10106892
XARELTO 20 mg Filmtabletten	98	St	10005932
XARELTO 20 mg Filmtabletten	98	St	10012197
XARELTO 20 mg Filmtabletten	98	St	7089606
XARELTO 20 mg Filmtabletten	98	St	10762426
XARELTO 20 mg Filmtabletten	98	St	10072124
XARELTO 20 mg Filmtabletten	98	St	10852709
XARELTO 20 mg Filmtabletten	98	St	10393644
XARELTO 20 mg Filmtabletten	98	St	4369498

XARELTO 20 mg Filmtabletten	98	St	10200929
XARELTO 20 mg Filmtabletten	98	St	10743802
XARELTO 20 mg Filmtabletten	98	St	10382008
XARELTO 20 mg Filmtabletten	98	St	10999364
XARELTO 20 mg Filmtabletten	98	St	11096612
XARELTO 20 mg Filmtabletten	98	St	11559354
XARELTO 20 mg Filmtabletten	100	St	9333401
XARELTO 20 mg Filmtabletten	10X10	St	9941299

Table 5 – Definition of types of AF

Type of AF	*ICD-10-GM code*
Paroxysmal	I48.0
Persistent	I48.1
Permanent	I48.2
Typical	I48.3
Atypical	I48.4
Unknown	I48.9

Table 6 – Definition of primary and secondary outcomes

Outcome parameter	**ICD-10 GM code**	
Primary effectiveness: ischemic stroke	I630, I631, I632, I633, I634, I635, I636, I638, I639	
Primary safety: Intracranial hemorrhage (ICH)	I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I62.00, I62.01, I62.02, I62.09, I62.1, I62.9	
Secondary	combined endpoint cerebral benefit	ischemic stroke and ICH
	systemic embolism (SE) (effectiveness)	I26, I260, I269, I801, I802, I803, I809
	transient ischemic attack (TIA) (effectiveness)	G45.8, G45.9
	combined endpoint effectiveness	ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA)
	subarachnoid hemorrhage (safety)	I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9
	intracerebral hemorrhage (safety)	I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9
	other and unspecified nontraumatic intracranial hemorrhage (safety)	I62.00, I62.01, I62.02, I62.09, I62.1, I62.9

Table 7 – Definition of stroke risk score $CHADS_2$ and CHA_2DS_2-VASc

Risk factor	*$CHADS_2$ risk score value*	*CHA_2DS_2-VASc risk score value*	*ICD-10-GM code*	*Description*
Heart failure	1	1	I50	Heart Failure
Hypertension	1	1	I10	Essential (primary) hypertension
Age 65-74 years	0	1	-	
Age ≥75 years	1	2	-	
Diabetes mellitus	1	1	E11/E10/ E12	Type 2 diabetes mellitus/ Type 1 diabetes mellitus/ Diabetes mellitus in combination with malnutrition
Stroke/TIA/embolism	2	2	I61/I63/I64/ I69/I82/G45 /I74/K55.0/ N28.0/H34	Non-traumatic intracerebral hemorrhage/ Cerebral infarction/stroke/ Sequelae of cerebrovascular disease/ Other venous embolism and thrombosis/ Transient cerebral ischemic attacks and related syndromes/ Arterial embolism and thrombosis/ Acute vascular disorders of intestine/ Ischemia and infarction of kidney/ Retinal vascular occlusions
Vascular disease (prior myocardial infarction/peripheral artery disease/aortic plaque)	0	1	I21/I22/I23/ I73	Acute myocardial infarction/ recurrent myocardial infarction/ Certain current complications following myocardial infarction/ Other peripheral vascular diseases
Female gender	0	1	-	

Table 8 – Comorbidities included in the Charlson Comorbidity Index (CCI) and modified comorbidity index

Conditions	ICD-10 GM code	Assigned weights CCI	Assigned weights modified comorbidity index
Myocardial Infarction	I21, I22, I252	1	1
Congestive heart failure	I43, I50, I099, I110, I130, I132, I255, I420, I425, I 426, I427, I428, I429, P290	1	0
Peripheral vascular disease	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959	1	1
Cerebrovascular disease	G45, G46, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, H340	1	0
Dementia	F00, F01, F02, F03, G30, F051, G311	1	1
Chronic pulmonary disease	J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, I278, I279, J684, J701, J703	1	1
Connective tissue disease	M05, M32, M33, M34, M06, M315, M351, M353, M360	1	1
Ulcer disease	K25, K26, K27, K28	1	1
Mild liver disease	B18, K73, K74, K700, K701, K702, K703, K709, K717, K713, K714, K715, K760, K762, K763, K764, K768, K769, Z944	1	0
Diabetes	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149	1	1
Hemiplegia	G81, G82, G041, G114, G801, G802, G830, G831, G832, G833, G834, G839	2	2
Moderate or severe renal disease	N18, N19, N052, N053, N054, N055, N056, N057, N250, I120, I131, N032, N033, N034, N035, N036, N037, Z490, Z491, Z492, Z940, Z992	2	0
Diabetes with end organ damage	E102, E103, E104, E105, E107, E112, E113, E11 4, E115, E117, E122, E123, E124, E125, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145, E147	2	2

Any tumor	C00, C01, C02, C03, C04, C05, C06, C07, C08, C0 9, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C3 1, C32, C33, C34, C37, C38, C39, C40, C41, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C5 4, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C7 4, C75, C76, C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96, C97	2	2
Moderate or severe liver disease	K704, K711, K721, K72 9, K765, K766, K767, I850, I859, I864, I982	3	0
Metastatic solid tumor or AIDS	C77, C78, C79, C80, B20, B21, B22, B24	6	6

Table 9 – Operationalization HAS-BLED Score

Criteria	**ICD-10 GM code**
Hypertension	I10.*, I11.*, I12.*, I13.*, I14.*, I15.*
Renal disease	N18.*, N19.*
Cirrhosis	K70.3, K71.7, K74.*
Stroke	I63.*
Major bleeding event	Primary or secondary hospital discharge of ICD-10 codes as listed in Table 11
Alcohol use	F10.*
Non-steroidal anti-inflammatory drug	M01A*
Antiplatelet agents	B01AC*
Age >65	

Table 10 – Definition of comorbidities

Comorbidity	*ICD-10-GM code / OPS Code*
Hemorrhagic diathesis due to anticoagulants and antibodies	D68.3
Coagulopathy, not specified	D68.9
Hyperthyroidism	E05
Diabetes mellitus	E10-E14
Hyperlipidemia	E78.0-E78.5
Cerebral transitory ischemia and related problems	G45
Essential hypertension	I10
Angina pectoris	I20
Myocardial infarction	I21-I22
Other acute ischaemic heart disease	I24
Chronic ischaemic heart disease	I25
Pulmonary embolisms	I26
Heart failure	I50
Intracerebral hemorrhage	I61
Other non-traumatic intracranial bleeding	I62
Cerebral infarction	I63
Stroke, not referred to as bleeding or infarction	I64
Hemorrhage or intracranial bleeding or cerebral infarction or stroke	I61-I64
Peripheral vascular disease, not specified	I73.9
Embolism and thrombosis of unspecified artery	I74.9
Deep thrombosis on leg and pelvic veins	I80-I82 without I80.0
Functional dyspepsia	K30
Hepatic insufficiency	K72
Renal insufficiency	N17-N18
Chronic renal disease, stage 1	N18.1
Chronic renal disease, stage 2	N18.2
Chronic renal disease, stage 3	N18.3
Chronic renal disease, stage 4	N18.4
Chronic renal disease, stage 5	N18.5
Cancer	C00-C97
Gastrointestinal bleeding*	K92.0.-K92.2
Dialysis	Z49.0, Z49.1, Z49.2
Hip or knee replacement procedure	OPS 5820, OPS 5821, OPS 5822, OPS 5823

Table 11 – Definition of major bleeding events for HAS-BLED Score

Primary or secondary hospital discharge diagnosis ICD-10-GM code	*ICD-10-GM code*
Conjunctival haemorrhage	H11.3
Otorrhagia	H92.2
Oesophageal varices with bleeding	I85.0
Oesophageal varices without bleeding in diseases classified elsewhere with bleeding	I98.21
Other specified diseases of oesophagus	K22.8
Gastric ulcer with bleeding	K25.0, K25.2, K25.4, K25.6
Duodenal ulcer with bleeding	K26.0, K26.2, K26.4, K26.6
Peptic ulcer, site unspecified with bleeding	K27.0, K27.2, K27.4, K27.6
Gastrojejunal ulcer with bleeding	K28.0, K28.2, K28.4, K28.6
Acute haemorrhagic gastritis	K29.0
Other specified diseases of stomach and duodenum and bleeding	K31.82
Angiodysplasia of colon with bleeding	K55.22
Diverticular disease of small intestine with perforation and abscess and bleeding	K57.01, K57.03
Diverticular disease of small intestine without perforation and abscess and bleeding	K57.11, K57.13
Diverticular disease of large intestine with perforation and abscess and bleeding	K57.21, K57.23
Diverticular disease of large intestine without perforation or abscess with bleeding	K57.31, K57.33
Diverticular disease of both small and large intestine with perforation and abscess and bleeding	K57.41, K57.43
Diverticular disease of both small and large intestine without perforation or abscess with bleeding	K57.51, K57.53
Diverticular disease of intestine, part unspecified, with perforation and abscess and bleeding	K57.81, K57.83
Diverticular disease of intestine, part unspecified, without perforation or abscess with bleeding	K57.91, K57.93
Haemorrhage of anus and rectum	K62.5
Haemoperitoneum	K66.1
Haematemesis	K92.0
Melaena	K92.1
Gastrointestinal haemorrhage, unspecified	K92.2
Recurrent and persistent haematuria	N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9
Congestion and haemorrhage of prostate	N42.1
Haematosalpinx	N83.6
Haematometra	N85.7
Haematocolpos	N89.7
Other abnormal uterine and vaginal bleeding	N93.0, N93.8, N93.9
Postmenopausal bleeding	N95.0

Haemorrhage from respiratory passages	R04.0, R04.1, R04.2, R04.8, R04.9
Spontaneous ecchymoses	R23.3
Unspecified haematuria	R31
Haemorrhage, not elsewhere classified	R58
Open wound of vagina and vulva	S31.4
Acute posthaemorrhagic anaemia	D62
Hyphaema	H21.0
Cyst of iris, ciliary body and anterior chamber	H31.3, H31.30, H31.31
Retinal haemorrhage	H35.6
Vitreous haemorrhage	H43.1
Vitreous haemorrhage in diseases classified elsewhere	H45.0
Haemopericardium, not elsewhere classified	I31.2
Haemothorax	J94.2
Gastro-oesophageal laceration-haemorrhage syndrome	K22.6
Haemarthrosis	M25.0, M25.00, M25.01, M25.02, M25.03, M25.04, M25.05, M25.06, M25.07, M25.09

Table 12 – Pharmaceutical substances interacting with the OAC therapy by treatment group

Treatment group	Effect	ATC_Code	Name
Phenprocoumon	Boost	B01AC	Thrombozytenaggregationshemmer
Phenprocoumon	Boost	M01A	Nichtsteroidale Antiphlogistika und Antirheumatika
Phenprocoumon	Boost	B01AB	Heparingruppe
Phenprocoumon	Boost	M04AA01	Allopurinol
Phenprocoumon	Boost	C01BD01	Amiodaron
Phenprocoumon	Boost	C01BA01	Chinidin
Phenprocoumon	Boost	C01BA51	Chinidin, Kombinationen exkl. Psycholeptika
Phenprocoumon	Boost	C01BA71	Chinidin, Kombinationen mit Psycholeptika
Phenprocoumon	Boost	C08DA81	Verapamil in Kombination mit Chinidin
Phenprocoumon	Boost	C01BC03	Propafenon
Phenprocoumon	Boost	J01G	Aminoglykosid Antibiotika
Phenprocoumon	Boost	S01AA01	Chloramphenicol
Phenprocoumon	Boost	J01A	Tetracycline
Phenprocoumon	Boost	J01E	Sulfonamid und Trimethoprim
Phenprocoumon	Boost	J01CF01	Cloxacillin
Phenprocoumon	Boost	J01FA	Makrolide
Phenprocoumon	Boost	J01DB	Cephalosporine der 1. Generation
Phenprocoumon	Boost	J01DC	Cephalosporine der 2. Generation
Phenprocoumon	Boost	J01DD	Cephalosporine der 3. Generation
Phenprocoumon	Boost	J01DE	Cephalosporine der 4. Generation
Phenprocoumon	Boost	C01AB	Fibrate
Phenprocoumon	Boost	G01AF	Imidazolderivate
Phenprocoumon	Boost	G01AG	Triaolderivate
Phenprocoumon	Boost	L04AA13	Leflunomid
Phenprocoumon	Boost	M01AA01	Phenylbutazon

Phenprocoumon	Boost	M01AA51	Phenylbutazon, Kombinationen
Phenprocoumon	Boost	M01AC01	Piroxicam
Phenprocoumon	Boost	M01AH	Coxibe
Phenprocoumon	Boost	N02AX02	Tramadol
Phenprocoumon	Boost	A14A	Andere anabole Steroide
Phenprocoumon	Boost	H03AA	Schilddrüsenhormone
Phenprocoumon	Boost	L02BA01	Tamoxifen
Phenprocoumon	Boost	L01BC06	Capecitabin
Phenprocoumon	Boost	N06AA	Nichtselektive Monoamin-Wiederaufnahmehemmer
Phenprocoumon	Attenuation	L04AX01	Azathioprin
Phenprocoumon	Attenuation	N01AF	Barbiturate, rein
Phenprocoumon	Attenuation	N01AG	Barbiturate in Kombination mit anderen Mitteln
Phenprocoumon	Attenuation	N03AF01	Carbamazepin
Phenprocoumon	Attenuation	C10AC01	Colestyramin
Phenprocoumon	Attenuation	C01AA	Digitalisglykoside
Phenprocoumon	Attenuation	C03	Diuretika
Phenprocoumon	Attenuation	H02	Corticosteroide zur systemischen Anwendung
Phenprocoumon	Attenuation	L01BB02	Mercaptopurin
Phenprocoumon	Attenuation	J04AB02	Verapamil in Kombination mit Chinidin
Phenprocoumon	Attenuation	A10BA02	Metformin
Phenprocoumon	Attenuation	H03BA	Thiouracile
Rivaroxaban	Boost	G01AF02	Clotrimazol
Rivaroxaban	Boost	G01AF05	Econazol
Rivaroxaban	Boost	J02AC01	Fluconazol
Rivaroxaban	Boost	J02AC02	Itraconazol
Rivaroxaban	Boost	G01AF11	Ketoconazol
Rivaroxaban	Boost	J02AB02	Ketoconazol
Rivaroxaban	Boost	G01AF17	Oxiconazol
Rivaroxaban	Boost	J02AC04	Posaconazol
Rivaroxaban	Boost	J02AC03	Voriconazol
Rivaroxaban	Boost	J05AE	Proteasehemmer
Rivaroxaban	Boost	B01	Antithrombotische Mittel
Rivaroxaban	Boost	M01A	Nichtsteroidale Antiphlogistika und Antirheumatika
Rivaroxaban	Boost	R05GB07	Erythromycin, Kombinationen
Rivaroxaban	Boost	J01FA01	Erythromycin
Rivaroxaban	Boost	S01AA17	Erythromycin
Rivaroxaban	Attenuation	J04AB02	Rifampicin
Rivaroxaban	Attenuation	J04AM02	Rifampicin und Isoniazid
Rivaroxaban	Attenuation	J04AM05	Rifampicin, Pyrazinamid und Isoniazid
Rivaroxaban	Attenuation	J04AM06	Rifampicin, Pyrazinamid, Ethambutol und Isoniazid
Rivaroxaban	Attenuation	N03AA02	Phenobarbital
Rivaroxaban	Attenuation	N03AF01	Carbamazepin
Rivaroxaban	Attenuation	N03AB02	Phenytoin

Table 13 – Definition of co-medications

Medication	*ATC*
Anticoagulation therapy	
VKA	B01AA
Phenprocoumon	B01AA04
Thrombin inhibitors	B01AE
Rivaroxaban	B01AF01, B01AX06
Apixaban	B01AF02, B01AX08
ASA	B01AC06
Other anticoagulants	B01AB or B01AX or B01AC excl. B01AC06
None	No B01A
Antiarrhythmic drugs	
Class I: Sodium channel blockers	C01BA01 Chinidin
	C01BA02 Procainamid
	C01BA05 Ajmalin
	C01BA03 Disopyramid
	C01BC03 Propafenon
	C01BA08 Prajmalin
	C01BB01 Lidocain
	N03AB02 Phenytoin
	C01BB02 Mexiletin
	C01BB04 Aprindin
	C01BB03 Tocainid
	C01BC04 Flecainid
	C01BC07 Lorcainid
Class II: Beta-blockers	C07AB04 Acebutolol
	C07AB03 Atenolol
	C07AB02 Metoprolol
	C07AA05 Propranolol
	C07AA07 Sotalol
Class III: Potassium channel blockers	C01BD01 Amiodaron
	C01BD05 Ibutilid
	C07AA07 Sotalol
	C01BD07 Dronedaron
Class IV: Calcium antagonists	C08DA01 Verapamil
	C08DA02 Gallopamil
	C08DB01 Diltiazem
Digitalis	C01AA05 Digoxin
	C01AA04 Digitoxin
Other	C01EB10 Adenosin
	A12CC* Magnesium
	Parasympatholytika (A03BA01/G04BD15 Atropin,
	C01CX10 Ipratropiumbromid)
	R03C* Sympathomimetics for systemic use
	C01CA24 Epinehrin
	C01CA03 Norepinephrin
	R03CB03 Orciprenaline

	C01EB10 Ivabradine (If-channel-blocker)
Other medications	
ACE-inhibitors	C09A ACE-inhibitors, pure C09B ACE-inhibitors, combinations
ATII-antagonists	C09C Angiotensin II antagonists, pure C09D Angiotensin II antagonists, combinations
Beta-blocker	C07A Beta-adrenoceptor-antagonists
Calcium-antagonists	C08D Selective calcium channel blocker with main effect on the heart
Diuretics	C03 Diuretics
Nitrates	C01DA Organic nitrates
Statines	C01AA HMG-CoA-reductase inhibitor
Antidiabetic medications	A10 Antidiabetics
Thyroid medications	H03A Thyroid preparations
NSAIDs	M01A* Antiinflammatory and antirheumatic products, non-steroids

Table 14 – Definition of anticoagulants

Medication	*ATC*
Anticoagulation therapy	
VKA	B01AA
Phenprocoumon	B01AA04
Thrombin inhibitor	B01AE
Rivaroxaban	B01AF01, B01AX06
Apixaban	B01AF02, B01AX08
ASA	B01AC06
Other anticoagulants	B01AB or B01AX or B01AC excl. B01AC06

Table 15 – Availability of variables of interest

	Variable	*Germany*
Patient's characteristics	Age	yes
	Gender	yes
	Death	yes
Diagnosis	Atrial fibrillation, stroke risk scores $CHADS_2$ and CHA_2DS_2-VASc, comorbidities including cardiovascular events and GI-bleedings	ICD-10-GM
Prescription drugs	Xarelto® and VKA and other medications of interest (other anticoagulants, antiarrhythmics, digitalis, other medications such as diuretics, statins etc.)	ATC/PZN

Table 16 – Demographic characteristics before matching

Age groups	*Rivaroxaban patients (n, %)*			*VKA patients (n, %)*		
	Female	Male	Total	Female	Male	Total
0-19						
20-29						
30-39						
40-49						
50-59						
60-64						
65-74						
≥75						
Total						

Table 17 – Demographic characteristics - statistics before matching

Age		*Mean*	*Standard deviation*	*Minimum*	*Median*	*Maximum*
Rivaroxaban patients	Female					
	Male					
	Total					
VKA patients	Female					
	Male					
	Total					

Table 18 – Type of AF diagnosis before matching

ICD-10-GM code	*Type of AF*	*Rivaroxaban patients (n, %)*	*VKA patients (n, %)*
I48.0	Paroxysmal		
I48.1	Persistent		
I48.2	Permanent		
I48.3	Typical		
I48.4	Atypical		
I48.9	Unknown		
Total			

Table 19 – $CHADS_2$ risk score before matching

$CHADS_2$ risk score value	*Rivaroxaban patients (n, %)*	*VKA patients (n, %)*
0		
1		
2		
3		
4		
5		
6		

Table 20 – CHA_2DS_2-VASc risk score before matching

CHA_2DS_2-VASc risk score value	*Rivaroxaban patients (n, %)*	*VKA patients (n, %)*
0		
1		
2		
3		
4		
5		
6		
7		
8		
9		

Table 21 – Co-morbidities before matching

Comorbidity	*Rivaroxaban patients (n, %)*	*VKA patients (n, %)*
Hemorrhagic diathesis due to anticoagulants and antibodies		
Coagulopathy, not specified		
Hyperthyroidism		
Diabetes mellitus		
Hyperlipidemia		
Cerebral transitory ischemia and related problems		
Essential hypertension		
Angina pectoris		
Myocardial infarction		
Other acute ischemic heart disease		
Chronic ischemic heart disease		
Pulmonary embolisms		
Heart failure		
Intracerebral hemorrhage		
Other non-traumatic intracranial bleeding		
Cerebral infarction		
Stroke, not referred to as bleeding or infarction		
Hemorrhage or intracranial bleeding or cerebral infarction or stroke		
Peripheral vascular disease, not specified		
Deep thrombosis on leg and pelvic veins		
Functional dyspepsia		
Hepatic insufficiency		
Renal insufficiency		
Chronic renal disease, stage 1		
Chronic renal disease, stage 2		
Chronic renal disease, stage 3		
Chronic renal disease, stage 4		
Chronic renal disease, stage 5		
Cancer		
Gastrointestinal bleeding*		

Table 22 – Co-medications before matching

	Rivaroxaban patients (n, %)	*VKA patients (n, %)*
Anticoagulation therapy		
VKA		
Thrombin inhibitors		
Rivaroxaban		
Apixaban		
ASA		
Other anticoagulants		
None		
Antiarrhythmic drugs		
Class I		
Class II		
Class III		
Class IV		
Digitalis		
Other		
Other medications		
ACE-inhibitors		
ATII-antagonists		
Beta-blocker		
Calcium-antagonists		
Diuretics		
Nitrates		
Statines		
Antidiabetic medications		
Thyroid medications		

Table 23 – Demographic characteristics after matching

Age groups	*Rivaroxaban cohort (n, %)*			*VKA cohort (n, %)*		
	Female	Male	Total	Female	Male	Total
0-19						
20-29						
30-39						
40-49						
50-59						
60-64						
65-74						
≥75						
Total						

Table 24 – Demographic characteristics - statistics after matching

Age		*Mean*	*Standard deviation*	*Minimum*	*Median*	*Maximum*
Rivaroxaban cohort	Female					
	Male					
	Total					
VKA cohort	Female					
	Male					
	Total					

Table 25 – Type of AF diagnosis after matching

ICD-10-GM code	*Type of AF*	*Rivaroxaban cohort (n, %)*	*VKA cohort (n, %)*
I48.0	Paroxysmal		
I48.1	Persistent		
I48.2	Permanent		
I48.3	Typical		
I48.4	Atypical		
I48.9	Unknown		
Total			

Table 26 – $CHADS_2$ risk score after matching

$CHADS_2$ risk score value	*Rivaroxaban cohort (n, %)*	*VKA cohort (n, %)*
0		
1		
2		
3		
4		
5		
6		

Table 27 – CHA_2DS_2-VASc risk score after matching

CHA_2DS_2-VASc risk score value	*Rivaroxaban cohort (n, %)*	*VKA cohort (n, %)*
0		
1		
2		
3		
4		
5		
6		
7		
8		
9		

Table 28 – Comorbidities after matching

Comorbidity	*Rivaroxaban cohort (n, %)*	*VKA cohort (n, %)*
Hemorrhagic diathesis due to anticoagulants and antibodies		
Coagulopathy, not specified		
Hyperthyroidism		
Diabetes mellitus		
Hyperlipidemia		
Cerebral transitory ischemia and related problems		
Essential hypertension		
Angina pectoris		
Myocardial infarction		
Other acute ischemic heart disease		
Chronic ischemic heart disease		
Pulmonary embolisms		

Heart failure Intracerebral hemorrhage Other non-traumatic intracranial bleeding Cerebral infarction Stroke, not referred to as bleeding or infarction Hemorrhage or intracranial bleeding or cerebral infarction or stroke Peripheral vascular disease, not specified Deep thrombosis on leg and pelvic veins Functional dyspepsia Hepatic insufficiency Renal insufficiency Chronic renal disease, stage 1 Chronic renal disease, stage 2 Chronic renal disease, stage 3 Chronic renal disease, stage 4 Chronic renal disease, stage 5 Cancer	

Table 29 – Co-medications after matching

	Rivaroxaban cohort (n, %)	*VKA cohort (n, %)*
Anticoagulation therapy		
VKA		
Thrombin inhibitors		
Rivaroxaban		
Apixaban		
ASA		
Other anticoagulants		
None		
Antiarrhythmic drugs		
Class I		
Class II		
Class III		
Class IV		
Digitalis		
Other		
Other medications		

ACE-inhibitors
ATII-antagonists
Beta-blocker
Calcium-antagonists
Diuretics
Nitrates
Statines
Antidiabetic medications
Thyroid medications

Table 30 – Standardized Differences before and after matching

Demographic and characteristics	*Standardized differences before matching*	*Standardized differences before matching*
Age		
Gender		
Type of atrial fibrillation		
I48.0		
I48.1		
I48.2		
I48.3		
I48.4		
I48.9		
Stroke risk score CHA2DS2 VASc		
1		
…		
9		
No of Comorbidities		
1		
… >10		
Separate Comorbidites		
Cancer		
...		

Table 31 – Primary endpoints after matching

Description	*Rivaroxaban cohort (n, %)*	*VKA cohort (n, %)*	*HR (HR, CI)*
Ischemic stroke			
Intracranial hemorrhage (ICH)			

Table 32 – Composite cerebral benefit endpoint after matching

Description	*Rivaroxaban cohort (n, %)*	*VKA cohort (n, %)*	*HR (HR, CI)*
Composite cerebral			

benefit (Ischemic stroke and Intracranial hemorrhage (ICH))			

Table 33 – Single events of the composite effectiveness endpoint after matching

Description	*Rivaroxaban cohort (n, %)*	*VKA cohort (n, %)*	*HR (HR, CI)*
Ischemic stroke			
Transient ischemic attack (TIA)			
Systemic embolism			
subarachnoid hemorrhage (safety)			
intracerebral hemorrhage (safety)			
other and unspecified nontraumatic intracranial hemorrhage (safety)			
Composite effectiveness endpoint			

Table 34 – Composite cerebral benefit endpoint after matching

Description	*Rivaroxaban cohort (n, %)*	*VKA cohort (n, %)*	*HR (HR, CI)*
Composite cerebral benefit			

Table 35 – Summary statistics for hospitalizations (overall) after matching

All-cause hospitalizations (number)	*n (%) of patients*	*Sum*	*Mean*	*Standard deviation*	*Minimum*	*Median*	*Maximum*
Rivaroxaban cohort							
VKA cohort							

Table 36 – Summary statistics of the duration of hospitalizations (overall) after matching

Days	*Sum*	*Mean*	*Standard deviation*	*Minimum*	*Median*	*Maximum*
Rivaroxaban cohort						
VKA cohort						

Table 37 – Co-medications (anticoagulants) after matching

	Rivaroxaban cohort (n, %)	*VKA cohort (n, %)*
Anticoagulation therapy		
VKA		
Thrombin		
Rivaroxaban		
Apixaban		
ASA		
Other anticoagulants		

Annex 3. Signature pages

Core OS Team

- Study Conduct Responsible, Study Health Economics and Outcomes Research (HEOR) Responsible: Maria Huelsebeck
- Study Medical Expert: Evelyn Weber
- Study Safety Leader: Nils Konieczny
- Study Statistician: Sebastian Kloss
- Study Epidemiologist: Christian Jacob

For PASS studies, additional signature page for:

- Qualified Person responsible for Pharmacovigilance (QPPV) – Michael Kayser

For local studies, additional signature page for:

- Country Medical Director – Robin Wegener

Bayer HealthCare

Signature Page - Study Conduct Responsible, HEOR Responsible

Title	A retrospective claims database analysis to compare stroke prevention and cardiovascular events in patients with atrial fibrillation treated with rivaroxaban vs. vitamin k antagonists Revised title: Real-world comparative effectiveness of stroke prevention in patients with AF treated with Rivaroxaban vs VKA (RELOAD)
Protocol version identifier	18735
Date of last version of protocol	12 Sept 2016
IMPACT study number	NA
Study type	☒ PASS ☐ non PASS
EU PAS register number	NA
Active substance (medicinal product)	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Market Access
Name	Maria Hülsebeck
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Address	Bayer Vital GmbH, 51368 Leverkusen - Germany

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

Date, Signature: 20 September 2016 ___, _____

Bayer HealthCare

Signature Page - Study Medical Expert

Title	A retrospective claims database analysis to compare stroke prevention and cardiovascular events in patients with atrial fibrillation treated with rivaroxaban vs. vitamin k antagonists Revised title: Real-world comparative effectiveness of stroke prevention in patients with AF treated with Rivaroxaban vs VKA (RELOAD)
Protocol version identifier	18735
Date of last version of protocol	12 Sept 2016
IMPACT study number	NA
Study type	☒ PASS ☐ non PASS
EU PAS register number	NA
Active substance (medicinal product)	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Marketing authorization holder(s)	Bayer Healthcare AG
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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: September 2016, 21.,

Signature Page

Title	A retrospective claims database analysis to compare stroke prevention and cardiovascular events in patients with atrial fibrillation treated with rivaroxaban vs. vitamin k antagonists Revised title: Real-world comparative effectiveness of stroke prevention in patients with AF treated with Rivaroxaban vs VKA (RELOAD)
Protocol version identifier	18735
Date of last version of protocol	12 Sept 2016
IMPACT study number	NA
Study type	☒ PASS ☐ non PASS
EU PAS register number	NA
Active substance (medicinal product)	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Study safety lead
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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: 12 Sept 2016____,_____

Signature Page - Study Statistician

Title	A retrospective claims database analysis to compare stroke prevention and cardiovascular events in patients with atrial fibrillation treated with rivaroxaban vs. vitamin k antagonists Revised title: Real-world comparative effectiveness of stroke prevention in patients with AF treated with Rivaroxaban vs VKA (RELOAD)
Protocol version identifier	18735
Date of last version of protocol	12 Sept 2016
IMPACT study number	NA
Study type	☒ PASS ☐ non PASS
EU PAS register number	NA
Active substance (medicinal product)	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
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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: September 2016 21, _____

Signature Page - Study Epidemiologist

Title	A retrospective claims database analysis to compare stroke prevention and cardiovascular events in patients with atrial fibrillation treated with rivaroxaban vs. vitamin k antagonists Revised title: Real-world comparative effectiveness of stroke prevention in patients with AF treated with Rivaroxaban vs VKA (RELOAD)
Protocol version identifier	18735
Date of last version of protocol	12 Sept 2016
IMPACT study number	NA
Study type	☒ PASS ☐ non PASS
EU PAS register number	NA
Active substance (medicinal product)	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Marketing authorization holder(s)	Bayer Healthcare AG
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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: September 2016 23, C. Jacob

Bayer HealthCare

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Title	A retrospective claims database analysis to compare stroke prevention and cardiovascular events in patients with atrial fibrillation treated with rivaroxaban vs. vitamin k antagonists Revised title: Real-world comparative effectiveness of stroke prevention in patients with AF treated with Rivaroxaban vs VKA (RELOAD)
Protocol version identifier	18735
Date of last version of protocol	12 Sept 2016
IMPACT study number	NA
Study type	☒ PASS ☐ non PASS
EU PAS register number	NA
Active substance (medicinal product)	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Marketing authorization holder(s)	Bayer Healthcare AG
Function	
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Address	

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

Date, Signature: 23 September 2016, Michael Kayser

Bayer HealthCare

Signature Page - Country Medical Director

Title	A retrospective claims database analysis to compare stroke prevention and cardiovascular events in patients with atrial fibrillation treated with rivaroxaban vs. vitamin k antagonists Revised title: Real-world comparative effectiveness of stroke prevention in patients with AF treated with Rivaroxaban vs VKA (RELOAD)
Protocol version identifier	18735
Date of last version of protocol	12 Sept 2016
IMPACT study number	NA
Study type	☒ PASS ☐ non PASS
EU PAS register number	NA
Active substance (medicinal product)	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Medical Affairs
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Title	
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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: 28 September 2016, _____