Observational Study Information

Title	Real-world comparative effectiveness of stroke prevention in patients with AF treated with Rivaroxaban vs VKA (RELOAD)
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Active substance	Rivaroxaban (ATC Code: B01AF01) Phenprocoumon (ATC Code: B01AA04)
Product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Product reference	
Procedure number	
Marketing authorisation holder(s)	Bayer Healthcare AG, 51368 Leverkusen, Germany
Joint PASS	*No*

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

Author	

Table of Contents

List of Figures and Tables

1. Abstract

Title

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

Keywords

Claims data, Rivaroxaban, atrial fibrillation, safety, effectiveness

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 was 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 was 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 was 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 were:

- 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 were also analyzed separately.

Study design

To address the objectives, this study was 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.

Setting

Subjects and Study Size, including dropouts

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 January 1, 2011 and September 30, 2015 being eligible for the planned cohort study.

Variables and Data sources

The study was 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 (ICD-10-GM codes) 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).

Demographic characteristics, co-morbidities, relevant co-medications, bleeding and stroke risk scores as well as the clinical outcome parameters were analyzed. The primary outcome parameters were ischemic stroke and ICH; Secondary outcome parameters were 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 were analyzed as part of the secondary objective. Components of ICH (subarachnoid hemorrhage, intracerebral hemorrhage, other and unspecified non-traumatic intracranial hemorrhage) were assessed separately as well.

Results

Patient characteristics were analyzed descriptively and showed that Rivaroxaban patients were slightly younger and healthier than Phenprocoumon patients. The mean of CHA2DS2-VASc Score and modified HAS-BLED score was slightly higher in the Phenprocoumon group.

The mean follow-up time for the primary effectiveness endpoint in the main analyses (derived by the empirical defined daily dose) was 367 days for Rivaroxaban patients and 408 days for Phenprocoumon patients.

The mean follow-up time for the primary effectiveness endpoint in the sensitivity analyses (1 tablet per day (3mg) for Phenprocoumon) was 367 days for Rivaroxaban patients and 241 days for Phenprocoumon patients.

The unadjusted incidence rate for the primary effectiveness endpoint ischemic stroke was 1.76 per 100 person years and for primary safety endpoint intracranial hemorrhage 0.49 per 100 person years in the Rivaroxaban group.

The unadjusted incidence rate for the primary effectiveness endpoint ischemic stroke was 1.62 per 100 person years and for primary safety endpoint intracranial hemorrhage 0.51 per 100 person years in the Phenprocoumon group.

Results of primary endpoints in the main analysis (empirical defined daily dose) based on a multivariate regression showed lower risks for Rivaroxaban for both, ischemic stroke and intracranial hemorrhage. However, results were statistically not significant.

Results of primary endpoints in the sensitivity analysis (1 tablet per day (3mg)) based on a multivariate regression showed a significant risk reduction for ischemic stroke of 23% for patients receiving Rivaroxaban. Results for the primary safety endpoint were consistent with the main analysis.

These results were consistent across different models, i.e. propensity score matching and IPTW.

A sensitivity analysis was conducted, where only patients diagnosed with renal impairment were included. 1954 Rivaroxaban patients were compared with 3871 Phenprocoumon patients.

The mean follow-up time for the primary effectiveness endpoint in this analysis using the empirical defined daily dose was 346 days for Rivaroxaban patients and 367 days for Phenprocoumon patients.

The mean follow-up time for the primary effectiveness endpoint in this analysis using the 1 tablet per day (3mg) definition for Phenprocoumon was 367 days for Rivaroxaban patients and 203 days for Phenprocoumon patients.

The unadjusted incidence rate for the primary effectiveness endpoint ischemic stroke was 2.60 per 100 person years and for primary safety endpoint intracranial hemorrhage 0.53 per 100 person years in the Rivaroxaban group.

The unadjusted incidence rate for the primary effectiveness endpoint ischemic stroke was 2.98 per 100 person years and for primary safety endpoint intracranial hemorrhage 0.71 per 100 person years in the Phenprocoumon group.

Results of primary endpoints in this analysis was consistent across different models. Results showed a strong trend towards lower risks for Rivaroxaban for both, ischemic stroke and intracranial hemorrhage, although results were statistically not significant.

Further sensitivity analyses were conducted for 20mg Rivaroxaban initiators (sensitivity analysis 1), patients without any events from the combined endpoints (sensitivity analysis 2) and including cancer patients (sensitivity analysis 3). Results in these sensitivity analyses were consistent with overall findings.

Other analyses:

As a further exploratory analysis a more recent data cut of the underlying data source was used to additionally look into a renal subgroup population. With the inclusion of additional data, collected up to December 2016, a total of 4164 patients with renal impairment were prescribed rivaroxaban and 7002 were prescribed phenprocoumon.

Patients with renal impairment prescribed rivaroxaban or phenprocoumon were of similar age (76.9 years and 77.2 years, respectively), had similar CHA_2DS_2-VASc (4.4 and 4.5, respectively) and $CHADS_2$ (2.9 in both groups) scores, and received similar baseline medication

Discussion

In the main analysis of this study, the use of Rivaroxaban was not associated with significant differences regarding safety and effectiveness compared to Phenprocoumon when applying an algorithm for an empirical defined daily dose for Phenprocoumon exposure time calculation. When applying the literature based defined daily dose for Phenprocoumon the exposure time differed substantially. Results showed a significant reduction in risk for ischemic stroke for patients receiving Rivaroxaban.

As a conclusion, results showed differences depending on how exposure time in Phenprocoumon patients was measured, however results within renal impaired patients showed a consistent trend across all different models towards better effectiveness and safety of Rivaroxaban vs. Phenprocoumon. Further analyses with more recent data cuts are necessary to confirm these findings.

Sensitivity analyses for a renal impaired subgroup showed a strong trend towards a protective effect of Rivaroxaban vs. Phenprocoumon. As of the small sample size, there was not enough power to show significance. Although patient numbers in this subgroup were low, the results presented here suggest that rivaroxaban is more effective and safer than phenprocoumon in patients with NVAF and renal impairment. The results of this subgroup analysis were generally consistent with the trends observed in the main analysis, showing evidence for the improved effectiveness and safety profile of rivaroxaban versus phenprocoumon in this patient population.

Marketing Authorisation Holder(s)

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Names and affiliations of principal investigators

Sponsor

Investigator, Statistical Expert

Data Management

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
PSM	Propensity Score Matching
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. Investigators

4. Other responsible parties

5. Milestones

Milestone	Planned date	Actual Date	Comments
Start of data collection	Oct 15, 2016	Oct 15, 2016	-
End of data collection	Dec 15, 2016	Dec 31, 2016	-
Final report of study results	Feb 28, 2017	Oct 6, 2017	-

6. 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 was 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 aimed to add insights about the real world effectiveness and safety of Rivaroxaban compared to Phenprocoumon, whose pharmacokinetic profile differs from Warfarin. This study included the analysis of ICH as a safety parameter and is therefore designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Bayer Vital.

7. Research Question and objective

The aim of this study was 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.

Primary objective

The primary objective of this study was 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 were defined as hospitalizations with the respective ICD-10-GM diagnosis.

Secondary objectives

The secondary objectives of this study were:

- To assess the cerebral benefit in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon. The combined endpoint was defined as the occurrence of a hospitalization with 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 were also analyzed separately. The composite event was defined as the occurrence of a hospitalization with the following diagnoses
  - ischemic stroke
  - systemic embolism
  - TIA.

8. Amendments and updates

Nr.	Date	Section of study protocol	Amendment or Update	Reason
1.0	April 2016	Major changes included revision of the study objectives and the conditions and comments of the PRC were addressed	Amendment	PRC review
2.0	12 September 2016	Changes included the revision of exclusion criteria, definition of switch, and adding a sensitivity analysis for cancer patients	Amendment	Adaption to the database structure and generation of further insights

9. Research methods

9.1 Study design

This study was 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 were 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 was conducted using a longitudinal claims data base representing routine care in Germany
- New user design, multivariate adjusted analyses, propensity score matching, and IPTW to reduce and control for confounding.

9.2 Setting

The study included data from the inpatient and outpatient setting as well as information on drug prescriptions from a sample of German sick funds.

Two study cohorts were 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 of the study was January 1, 2011 through March 31, 2016.

For both groups (Rivaroxaban and Phenprocoumon), the date of the first Rivaroxaban or Phenprocoumon dispensing reflected the index date and marked the beginning of the observation period. Patient baseline characteristics were measured during one year (365 days, four quarters) preceding the index date (baseline period). The observation (follow-up) period spanned 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 consisted 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, see Table 71) or Phenprocoumon (PZN based, see Table 70) between January 1, 2012 and December 31, 2015
- At least two verified outpatient diagnoses or one inpatient diagnosis (main or secondary diagnosis) of NVAF in the individual time frame of 4 quarters before the index date (pre-index period) or within the index quarter (see Table 72, Type of AF)

- Patients were 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)
- ≥ 18 years of age at the dispense date of Rivaroxaban or Phenprocoumon.

Exclusion criteria:

- Patients with valvular AF [inpatient diagnosis: 4 quarters before and index quarter up to index date] (see Table 72, Evidence of valvular AF)
- Pregnancy [inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis: 4 quarters before and index quarter] (see Table 77, Pregnancy)
- Malignant cancers [inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis: 4 quarters before and index quarter) in addition "condition after diagnosis" for outpatient diagnoses (4 quarter before and index quarter] (see Table 77, Cancer)
- Transient cause of AF [inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis: 4 quarters before and index quarter] (see Table 72, Transient causes of AF)
- Patients with VTE (pulmonary embolism or DVT) [inpatient diagnosis: 60 days before index date – outpatient diagnosis: within index quarter] (see Table 77, Deep thrombosis on leg and pelvic veins)
- Patients with major surgery defined as hip or knee replacement [inpatient diagnosis: 60 days before index date] (see Table 77, Hip or knee replacement procedure)
- Prescriptions of anticoagulant substances (VKA, Phenprocoumon, Dabigatran, Rivaroxaban, Apixaban) before index date [4 quarters before and index quarter up to index date] (see Table 81)
- Patients receiving more than one anticoagulant substance (VKA (not including Phenprocoumon), Phenprocoumon, Dabigatran, Rivaroxaban, Apixaban) (see Table 70 and Table 81) or more than one dosage of Rivaroxaban on the index date (see Table 71)
- Patients with dialysis [inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis: 4 quarters before and index quarter] (see Table 77, Dialysis).

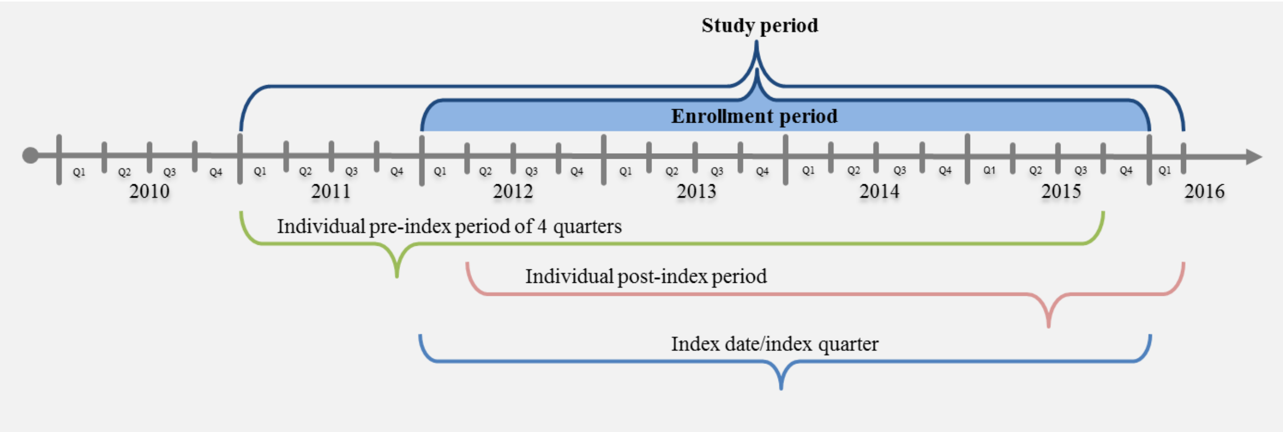
9.2.3 Study population

The study population was 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).

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

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

Figure 1. Selection of the study population



9.3 Subjects

Main results

1. All patients meeting the selection criteria from 9.2.2 were included in the main analysis.

Sensitivity Analyses

1. Patients receiving 20mg Rivaroxaban only (standard-dose analysis) were included in the first sensitivity analysis. Patients were censored once a different dose was prescribed compared to the index dose of 20mg.
2. Patients with any of the events defined in the combined endpoints (see Table 73) within the baseline period were excluded from the second sensitivity analyses.
3. Patients with evidence of cancer (ICD-10-GM C00-C97) (see Table 79) in the baseline period were included in the study population of the third sensitivity analysis.

9.4 Variables

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

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 was used to determine whether patients had a

NVAF diagnosis, to verify that patients were new users and to assess baseline demographic and clinical characteristics of the patients included in the study population.

The following demographics were reported for each cohort:

- Gender
- Age group
    - 18-29, 30-39, 40-49, 50-59, 60-64, 65-74, ≥75.

Stroke risk score CHADS$_2$ and CHA$_2$DS$_2$-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 74).

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 (see Table 1) 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 were assessed.

Co-medications

Prescriptions of relevant co-medications including anticoagulation therapy, antiarrhythmic drugs, and other medications (see Table 1) in the individual 4 quarters before the index quarter (pre-index period) were assessed.

Table 1. Definition of covariates

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

Number 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 was 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 80.
CHA_2DS_2-VASc score	continuous	The CHA_2DS_2-VASc score was 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 were used to assess the CHA_2DS_2-VASc score. For a complete list of all ICD-10 codes which were used to form the CHA_2DS_2-VASc score please refer to Table 74.
$CHADS_2$ score	continuous	The $CHADS_2$ Score was derived by assigning one point each for hypertension, heart failure, age 75 years and older, diabetes mellitus. A preliminary stroke/TIA was 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 were to assess the $CHADS_2$ score. For a complete list of all ICD-10 codes which was used to form the $CHADS_2$ score please refer to Table 74.

Charlson Comorbidity Index (CCI)	continuous	The Charlson Comorbidity Index (CCI) was 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 were used to build the CCI score. A list of included conditions and their assigned weights can be found in Table 75. 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 was 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) was not included in the HAS-BLED score. For a complete list of all ICD codes which were used to form the HAS-BLED score please refer to Table 78.
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 were used to assess whether patients suffered from a previous myocardial infarction. MI was 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 were used to assess whether patients suffered from a chronic renal insufficiency. Chronic renal insufficiency was 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 was used to assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage I was 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 were used to assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage II was 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 were used to assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage III was 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 were used to assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage IV was 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 were used to assess whether patients suffered from a chronic renal insufficiency, stage I. Chronic renal insufficiency, stage V was 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 were used assess whether patients suffered from other chronic renal insufficiency. Other chronic renal insufficiency was 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 were used to assess whether patients suffered from an unspecified renal insufficiency. Unspecified chronic renal insufficiency was 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 were used to assess whether patients suffered from diabetes mellitus. Diabetes mellitus was 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 were used to assess whether patients suffered from hypertension. Hypertension was 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 were used to assess whether patients suffered from congestive heart failure. Congestive heart failure was 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 were used to assess whether patients suffered from peripheral vascular disease. Peripheral vascular disease was 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 were used to assess whether patients suffered from ischemic stroke or TIA. Ischemic stroke or TIA was 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 were used to assess whether patients suffered from coronary heart disease. Coronary heart disease was defined using the ICD-10-GM code I20*(angina pectoris), I24*(other acute ischemic heart diseases) and I25* (chronic ischemic 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 were used to assess whether patients suffered from a mild liver disease. Mild liver disease was defined using the ICD-10 GM codes according to the Charlson Comorbidity Index (Table 75).
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 were used to assess whether patients suffered from a moderate or severe liver disease. Moderate or severe liver disease was defined using the ICD-10 GM codes according to the Charlson Comorbidity Index (Table 75).
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 were used to assess whether patients used tobacco. Tobacco use was 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 were used to assess whether patients abused alcohol. Alcohol abuse was 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 were used to assess whether patients suffered from depression. Depression was 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 were used to assess whether patients suffered from somatoform disorder. Somatoform disorder was 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 were used to assess whether patients suffered from anxiety disorder. Anxiety disorder was 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 were used to assess whether patients suffered from substance abuse. Substance abuse was 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 were used to assess whether patients suffered from dementia. Dementia was 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 were used to assess whether patients suffered from cancer. Cancer types were defined using the ICD-10-GM codes (see Table 79).
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 were used to assess whether patients suffered from obesity. Obesity was defined using the ICD-10 GM codes E66.
Proton-pump-inhibitors	categorical	It was assessed whether patients received at least one prescription for proton-pump-inhibitors (ATC: A02BC) in the 365 days before or on the index date.
Coronary angioplasty	categorical	It was 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*) was used to determine whether the procedure has been performed in the patient individual baseline period.
Antiplatelet medication	categorical	It was 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 was used is B01AC.
Prescription of acetylsalicylic acid (ASS)	categorical	It was 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 was assessed whether patients received at least one prescription for NSAIDs (ATC Code: M01A*) in the 365 days before or on the index date.

Exposure

There are two exposures: New use of Rivaroxaban and new use of Phenprocoumon. Exposure was defined as one or more prescriptions for the target drug (Phenprocoumon or Rivaroxaban). These prescriptions were identified using the anatomical therapeutic chemical (ATC) and Pharmazentralnummer (PZN) drug codes including dose and package size (listed in the Annex 2, Table 70 and Table 71).

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

Exposure time
The exposure time was defined as the days of supply. If the days of supply were lower than the days between the prescriptions, the gap period (if no prescription immediately followed) was added. If necessary, the days of potential hospitalizations was additionally added resulting in the following formula: Time from index date: Days of supply + Gap period + Days of potential hospitalizations

Hospitalizations related to outcome measures were considered as outcome event.

Gap period
A gap period was allowed when treatment was discontinued before censoring the patient for discontinuation. Patients were 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 correspond 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 was 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 was calculated.

The Phenprocoumon PZN code was 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 was 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 received a prescription for an OAC other than the index OAC prescription (including other NOACs) during the follow- up period were 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 was defined as the date of switch and patients were censored. Patients who received a prescription of Rivaroxaban other than the dosage at index date during the follow- up period were considered as switchers. The dispense date of the new dosage was defined as the date of switch and patients were censored.

Date of discontinuation

Discontinuation was 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 were also considered to have terminated the treatment.

The last day of the exposure time was defined as the date of discontinuation and patients were censored.

9.5 Data sources and measurement

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.

9.6 Bias

All patients from the HRI database who met the inclusion criteria were included in the analysis. Both in- and outpatient data were assessed for the identification of the study populations to ensure complete reporting. Patients were required to have 4 quarters of enrollment for the assessment of baseline characteristics and to be observable and insured in the database for at least one day after their individual index date (post-index period). Therefore, the risk of selection bias could be minimized. In order to eliminate the effect i.a. of the two most important confounding variables age and gender, the study cohorts were matched by applying the propensity score matching. The propensity score was calculated as the predicted probability of exposure (i.e. probability of receiving Rivaroxaban), given all that is known about a patient (i.e. patient characteristics and covariates).The probability itself was derived from a multivariate logistic regression using the parameters thought to act as confounding variables. This minimized confounding by observed baseline covariates by removing any potential relationship between cofounders and exposure group. Furthermore, multivariate regression models were applied to compare the composite endpoints of Rivaroxaban vs. Phenprocoumon by controlling e.g. for patients' demographic and clinical characteristics.

9.7 Study Size

All patients identified in the HRI research database meeting the inclusion criteria were 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 January 1, 2011 and September 30, 2015 for the planned cohort study. However, this preliminary assessment did not consider all of the above listed inclusion and exclusion criteria. We estimated that the actual number of patients might be up to 25% lower.

Rivaroxaban: ~ 17,000 patients

Phenprocoumon: ~ 30,000 patients

Power considerations

Table 2. 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

Table 3. 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	1.0000
Larsen et al.	-	-	0.56	0.9995

9.8 Data transformation

A completely anonymized file comprising all observations and variables required for the planned analyses was created from information contained exclusively within the source material. It is required that all analyses are conducted on the site of the data provider. Data files from the HRI database must stay in-house due to data protection regulations. All statistical processing was performed using SAS® Enterprise Guide Version 9.2.

9.9 Statistical Methods

9.9.1 Main Summary Measures

This section provides a detailed overview about the statistical methods which were 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.

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

9.9.2 Main Statistical Methods

Demographic and clinical characteristics:

In a first step the demographic and clinical characteristics of the patients in both treatment groups were determined. All variables were 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) are reported. The differences between the treatment groups were 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 was used as the reference group.

For categorical variables:

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

Primary and secondary objectives:

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

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

Rivaroxaban was compared to Phenprocoumon. Hence, Phenprocoumon was the reference category in the analysis. A subset of the variables depicted in Table 1 which were selected on an empirical basis, were included as covariates in the Cox proportional hazards model.

Propensity Score Matching

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

The probability itself was derived from a multivariate logistic regression model using the parameters thought to act as confounding variables. The propensity score acts 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 minimized confounding by observed baseline covariates by removing any potential relationship between cofounders and exposure group.

In this study, we estimated propensity scores from all measured factors noted above. These factors were 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 predicted probability of treatment for each patient; this probability of treatment was each patient’s estimated propensity score.

We performed a 1:1 nearest-neighbor matching. After matching, we expected to see balance between the Rivaroxaban and VKA groups with respect to all measured factors. To ensure this, we examined 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 were censored in the follow-up period as follows:

Patients were 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 experiencing any event, whichever occurred first.

9.9.3 Missing Values

Missing data was not imputed.

9.9.4 Sensitivity Analyses

For this study, sensitivity analyses were conducted according to dosing regimen, patients with prior events of any of the events defined in the combined endpoints, and the inclusion of cancer patients in the study population.

1. One separate analysis was conducted for patients receiving 20mg Rivaroxaban only (standard-dose analysis). Patients were censored once a different dose was prescribed compared to the index dose of 20mg. For patients who initiated treatment with 15mg Rivaroxaban baseline characteristics were outlined descriptively.
2. Additionally, a separate analysis was conducted where patients with any of the events defined in the combined endpoints (see Table 73) within the baseline period [inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis (verified or condition after): 4 quarters before and index quarter] were excluded from the analyses.
3. A separate analysis was conducted where patients with evidence of cancer (ICD-10-GM C00-C97) (see Table 79) in the baseline period [(inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis: 4 quarters before and index quarter) in addition “condition after diagnosis” for outpatient diagnoses (4 quarters before and index quarter)] were included in the study population.

Therefore, sensitivity analyses resulted in three separate cohorts and patient time datasets for which a propensity score matching, a multivariate analysis and a IPTW was performed according to 9.9.2.

Two other sensitivity post hoc analyses were conducted to 1) understand the sensitivity of Phenprocoumon exposure time calculation and 2) understand trends and differences in a subgroup of patients diagnosed as renally impaired. For primary effectiveness and primary safety endpoint a multivariate regression model was calculated related to different daily doses of Phenprocoumon (i.e. 3mg, 4,5mg as well as 1,5mg once daily).

Other analyses:
In order to further research potential effects in renal impaired patients an approach following [22 Nielsen et al.], and [21 Weir et al.] was used. We categorized not only patients with chronic kidney disease, but also those with cystic kidney disease, unspecified kidney failure, chronic or unspecified nephritic syndrome, nephrotic syndrome, recurrent and persistent hematuria, nephropathy (diabetic, hypertensive, hereditary), chronic tubulo-interstitial nephritis, diabetes mellitus with kidney

complications as having renal dysfunction. This subanalysis included patients with renal impairment (defined by International Classification of Diseases, Tenth Revision [ICD-10] codes D61.3, E08.22, E09.22, E10.2, E11.2, I12, I13, I95.3, N02, N03, N04, N05, N07, N11, N14, N18, N19, O10, Q61 or R88.0). We were able to obtain a new data cut of the underlying research database to increase the sample size, utlizing data from January 2012 until December 2016. Two different types of analyses were conducted utilizing this new data cut. Patients initiating Rivaroxaban 15mg or 20mg were compared to patients treated with Phenprocoumon. The same analysis was done for patients initiating Rivaroxaban 15mg only, respectively.

9.9.5 Amendments to Statistical Analysis Plan

The core statistical elements (analysis populations, definition and measurement of endpoints and other key variables and statistical methodology) were adequately detailed within the study protocol. Therefore, no separate SAP was needed.

9.10 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.

10. Results

10.1 Participants

The following table depicts the identification of the study population showing every step of inclusion and exclusion and the corresponding patient counts.

Table 4. Identification of study population

	Rivaroxaban	**Phenprocoumon**
Inclusion criteria		
First dispense date of Rivaroxaban (15mg – 20 mg) or Phenprocoumon between January 1, 2012 and December 31, 2015	52,896	138,272
At least two verified outpatient diagnoses or one inpatient diagnosis (main or secondary diagnosis) of NVAF (ICD-10-GM codes 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	33,316	90,156
4 quarters of enrollment before index date up to at least one day after individual index date	32,952	89,689
>=18 years of age at dispense date of Rivaroxaban or Phenprocoumon	32,952	89,687
Total included (first index date with Rivaroxaban or Phenprocoumon)	**23,814**	**87,782**
Exclusion criteria		
Patients with valvular AF (OPS code: 5351/5352/5353/5358/535a)	200	2,356

(inpatient diagnosis: 4 quarters before and index quarter up to index date)		
Pregnancy (ICD-10-GM codes: O*/Z34*/Z35*) (inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis: 4 quarters before and index quarter)	26	74
Malignant cancers (ICD-10-GM codes: C00-C97) (inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis: 4 quarters before and index quarter) in addition "condition after diagnosis" for outpatient diagnosis (4 quarter before and index quarter)	5,965	21,726
Transient cause of AF (ICD-10-GM codes: I27/I97) (inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis: 4 quarters before and index quarter)	2,144	8,955
Patients with VTE (ICD-10-GM codes: I26*/I81*/I82*/I80* and not I800) (inpatient diagnosis : 60 days before index date – outpatient diagnosis: within index quarter)	1,603	4,254
Patients with major surgery defined as hip or knee replacement (OPS codes: 5820/5821/5822/5823) (inpatient diagnosis: 60 days before index date)	331	361
Prescriptions of anticoagulant substances (VKA, Phenprocoumon, Dabigatran, Rivaroxaban, Apixaban) before index date (ATC codes: B01AF01/B01AF02/B01AA*/B01AE07/B01AX06/B01AX08) (4 quarters before and index quarter up to index date)	3,316	53,615
Patients receiving more than one anticoagulant substance (VKA (not including Phenprocoumon), Phenprocoumon, Dabigatran, Rivaroxaban, Apixaban) (ATC codes: B01AF01/B01AF02/B01AA*/B01AE07/B01AX06/B01AX08)	7	89
Patients with more than one dosage of a substance on the index date (only Rivaroxaban)	160	0
Patients with dialysis (ICD-10-GM codes: Z490/Z491/Z492) (inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis: 4 quarters before and index quarter)	40	1,020
Total excluded	10,659	67,269
Total remained	**13,155**	**20,513**

The following table shows the study population after propensity score matching:

Table 5. Study population after propensity score matching

	Rivaroxaban	**Phenprocoumon**
Total study population	13,155	20,513
Total remaining after matching	11,353	11,353

The following tables depict the study populations for the sensitivity analyses:

1. Inclusion of patients with Rivaroxaban 20mg:

Table 6. Sensitivity analysis – Study population including patients with Rivaroxaban 20mg

	Rivaroxaban	Phenprocoumon
Total remained with patients receiving 20 mg only (Rivaroxaban)	9,539	20,513

2. Inclusion of patients without any previous combined endpoints events:

Table 7. Sensitivity analysis – Study population including patients without any previous endpoints

	Rivaroxaban	Phenprocoumon
Total remained without events within the baseline period	11,138	17,393

3. Inclusion of cancer patients:

Table 8. Sensitivity analysis – Study population including cancer patients

	Rivaroxaban	Phenprocoumon
Total remaining after including cancer patients	17,236	27,004

10.2 Descriptive Data

In the following, the descriptive data including demographic and clinical characteristics before matching are reported.

Table 9. Demographic characteristics Rivaroxaban patients before matching

Age groups	Rivaroxaban patients N=13,155					
	Female		Male		Total	
	n	%	n	%	n	%
18-29	6	0.05	22	0.17	28	0.21
30-39	18	0.14	97	0.74	115	0.87
40-49	88	0.67	395	3	483	3.67
50-59	359	2.73	1,064	8.09	1,423	10.82
60-64	454	3.45	782	5.94	1,236	9.40

65-74	1,676	12.74	2,109	16.03	3,785	28.77
≥75	3,801	28.89	2,284	17.36	6,085	46.26
Total	6,402	48.67	6,753	51.33	13,155	100.00

Table 10. Demographic characteristics Phenprocoumon patients before matching

Age groups	**Phenprocoumon patients** **N=20,513**					
	Female		**Male**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**
18-29	<5		9	0.04	13	0.06
30-39	12	0.06	48	0.23	60	0.29
40-49	67	0.33	247	1.20	314	1.53
50-59	351	1.71	1,089	5.31	1,440	7.02
60-64	532	2.59	1,038	5.06	1,570	7.65
65-74	2,832	13.81	3,608	17.59	6,440	31.39
≥75	6,352	30.97	4,324	21.08	10,676	52.05
Total	10,150	49.48	10,363	50.52	20,513	100.00

Table 11. Demographic characteristics – age distribution for Rivaroxaban patients before matching

	Rivaroxaban patients **N=13,155**				
Gender	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
Female	75.56	10.35	18	77	103
Male	68.29	12.17	20	70	97
Total	71.83	11.89	18	74	103

Table 12. Demographic characteristics – age distribution for Phenprocoumon patients before matching

	Phenprocoumon patients

	N=20,513				
Gender	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
Female	76.32	8.78	20	77	102
Male	71.28	10.15	21	73	99
Total	73.77	9.82	20	75	102

Table 13. Type of AF diagnosis before matching

ICD-10-GM Code	**Type of AF**	**Rivaroxaban patients N=13,155**		**Phenprocoumon patients N=20,513**	
		n	**%**	**n**	**%**
I48.0	Paroxysmal	7,201	54.74	8,083	39.40
I48.1	Persistent	5,655	42.99	12,442	60.65
I48.2	Permanent	2,242	17.04	2,717	13.25
I48.9	Unknown*	1,316	10.00	1,675	8.17
	Total	13,155	100.00	20,513	100.00
* Only patients whose diagnosis was not specified					

Table 14. $CHADS_2$ risk score before matching

$CHADS_2$ risk score value	**Rivaroxaban patients N=13,155**		**Phenprocoumon patients N=20,513**	
	n	**%**	**n**	**%**
0	1,237	9.40	1,227	5.98
1	3,498	26.59	4,733	23.07
2	3,655	27.78	6,260	30.52
3	2,523	19.18	4,583	22.34
4	1,370	10.41	2,420	11.80
5	645	4.90	941	4.59
6	227	1.73	349	1.70

Mean score	2.16		2.31	
SD	1.39		1.32	

Table 15. CHA_2DS_2-VASC risk score before matching

CHA_2DS_2-VASC risk score value	**Rivaroxaban patients N=13,155**		**Phenprocoumon patients N=20,513**	
	n	**%**	**n**	**%**
0	580	4.41	427	2.08
1	1,483	11.27	1,439	7.02
2	2,053	15.61	2,827	13.78
3	2,565	19.50	4,340	21.16
4	2,632	20.01	4,754	23.18
5	1,940	14.75	3,529	17.20
6	1,111	8.45	2,010	9.80
7	563	4.28	858	4.18
8	203	1.54	284	1.38
9	25	0.19	45	0.22
Mean score	3.49	-	3.78	-
SD	1.86	-	1.7	-

Table 16. Summary statistics for hospitalizations (overall) before matching

	Rivaroxaban patients N=13,155					
n (% of patients)	**Sum**	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
9,765 (74.23%)	15,979	1.21	1.19	0	1	18
	Phenprocoumon patients N=20,513					
n (% of patients)	**Sum**	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
14,434 (70.36%)	23,724	1.16	1.18	0	1	33

Table 17. Summary statistics of the duration of hospitalizations (overall) before matching (in days)

	Rivaroxaban patients N=13,155					
n (% of patients)	**Sum**	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
9,765 (74.23%)	157,914	16.17	20.85	1	9	291
	Phenprocoumon patients N=20,513					
n (% of patients)	**Sum**	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
14,434 (70.36%)	246,723	17.09	19.34	1	11	477

Table 18. Co-medications before matching

Medication		**Rivaroxaban patients N=13,155**		**Phenprocoumon patients N=20,513**	
		n	**%**	**n**	**%**
Anticoagulation therapy	VKA	0	0.00	0	0.00
	Phenprocoumon	0	0.00	0	0.00

	Thrombin inhibitors*	0	0.00	<5	<0.03
	Rivaroxaban	0	0.00	0	0.00
	Apixaban	0	0.00	0	0.00
	ASA	2,108	16.02	3,497	17.05
	Other anticoagulants	1,612	12.25	3,058	14.91
Antiarrhythmic drugs	Class I: Sodium channel blockers	396	3.01	482	2.35
	Class II: Beta-blockers	3,633	27.62	6,266	30.55
	Class III: Potassium channel blockers	427	3.25	792	3.86
	Class IV: Calcium antagonists	406	3.09	608	2.96
	Digitalis	448	3.41	913	4.45
	Other	86	0.65	137	0.67
Other medications	ACE-inhibitors	5,448	41.41	9,934	48.43
	ATII-antagonists	3,197	24.30	4,914	23.96
	Beta-blocker	7,254	55.14	12,238	59.66
	Calcium-antagonists	413	3.14	615	3.00
	Diuretics	4,260	32.38	8,027	39.13
	Nitrates	918	6.98	1,823	8.89
	Statins	707	5.37	1,529	7.45
	Antidiabetic medications	2,494	18.96	4,557	22.22
	Thyroid medications	2,382	18.11	3,655	17.82
	NSAIDs	4,798	36.47	7,457	36.35
*Other than B01AE07					

10.3 Outcome Data

In the following, the outcome data including the primary and secondary endpoints before matching are reported.

Table 19. Primary endpoints before matching

Description	Rivaroxaban patients N=13,155			Phenprocoumon patients N=20,513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	233	13,205.34	1.76	372	22,939.74	1.62	1.068 (0.906 - 1.258)	0.4344
Intracranial hemorrhage (ICH) (safety)	66	13,337.93	0.49	119	23,107.38	0.51	0.935 (0.692 - 1.264)	0.6633

Table 20. Secondary endpoints before matching

Description	Rivaroxaban patients N=13,155			Phenprocoumon patients N=20,513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	286	13,191.86	2.17	475	22,905.69	2.07	1.023 (0.883 - 1.185)	0.7635
Systemic embolism (SE) (effectiveness)	51	13,324.07	0.38	69	23,122.93	0.30	1.263 (0.879 - 1.816)	0.2074
Transient ischemic attack (TIA) (effectiveness)	77	13,302.51	0.58	102	23,069.32	0.44	1.259 (0.936 - 1.693)	0.1273
Subarachnoid hemorrhage (safety)	8	13,348.33	0.06	21	23,138.06	0.09	0.628 (0.278 - 1.418)	0.2631
Intracerebral hemorrhage (safety)	44	13,345.75	0.33	79	23,127.94	0.34	0.934 (0.646 - 1.351)	0.7175
Other and unspecified	17	13,348.69	0.13	31	23,128.3	0.13	0.945 (0.522 -	0.8511

nontraumatic intracranial hemorrhage (safety)							1.709)	
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	345	13,135.15	2.63	523	22,848.33	2.29	1.122 (0.979 - 1.286)	0.0975

10.4 Main Results

Table 21. Primary and secondary endpoints - Multivariate Analysis (eDDD)

Description	Rivaroxaban patients N=13,155			Phenprocoumon patients N=20,513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	233	13,205.34	1.76	372	22,939.74	1.62	0.930 (0.779 - 1.111)	0.4239
Intracranial hemorrhage (ICH) (safety)	66	13,337.93	0.49	119	23,107.38	0.51	0.881 (0.637 - 1.219)	0.4459
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	286	13,191.86	2.17	475	22,905.69	2.07	0.905 (0.772 - 1.061)	0.2194
Systemic embolism (SE) (effectiveness)	51	13,324.07	0.38	69	23,122.93	0.30	1.158 (0.781 - 1.717)	0.4653
Transient ischemic attack (TIA) (effectiveness)	77	13,302.51	0.58	102	23,069.32	0.44	1.189 (0.859 - 1.645)	0.2964

Subarachnoid hemorrhage (safety)	8	13,348.33	0.06	21	23,138.06	0.09	0.678 (0.281 - 1.632)	0.3857
Intracerebral hemorrhage (safety)	44	13,345.75	0.33	79	23,127.94	0.34	0.914 (0.614 - 1.361)	0.6583
Other and unspecified nontraumatic intracranial hemorrhage (safety)	17	13,348.69	0.13	31	23,128.3	0.13	0.839 (0.442 - 1.593)	0.5921
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	345	13,135.15	2.63	523	22,848.33	2.29	0.994 (0.858 - 1.153)	0.9407

Table 22. Primary and secondary endpoints - Multivariate Analysis (alternative VKA exposure time calculation methods)

Description	**Rivaroxaban patients N=13,155**				**Phenprocoumon patients N=20,513**				**HR (95% CI)**	**p-value**
	No. of events	**Person-years of follow up**		**Events/100 person-years**	**No. of events**	**Person-years of follow up**		**Events/100 person-years**		
		Mean	**Median**			**Mean**	**Median**			
Exposure Time of VKA with 1 tablet per day (3mg)										
Ischemic stroke (effectiveness)	233	366.9	275	1.76	295	241.3	160	2.18	0.768 (0.632-0.933)	0.0077
Intracranial hemorrhage (ICH) (safety)	66	370.6	279	0.49	82	242.4	161	0.6	0.855 (0.593-1.234)	0.4034
Exposure Time of VKA with 1.5 tablet per day (4.5mg)										
Ischemic stroke (effectiveness)	233	366.9	275	1.76	230	143.4	101.33	2.86	0.619 (0.496-0.772)	<0.0001

Intracranial hemorrhage (ICH) (safety)	66	370.6	279	0.49	60	143.5	101.67	0.74	0.772 (0.504-1.182)	0.2339
Exposure Time of VKA with 0.5 tablet per day (1.5 mg)										
Ischemic stroke (effectiveness)	233	366.9	275	1.76	439	533.8	430	1.47	0.982 (0.827-1.166)	0.8381
Intracranial hemorrhage (ICH) (safety)	66	370.6	279	0.49	156	638.5	431	0.52	0.861 (0.633-1.172)	0.3421

Table 23. Sensitivity analysis: renal impaired: Primary endpoints - Multivariate Analysis (alternative VKA exposure time calculation methods)

Description	**Rivaroxaban patients N=1,954**				**Phenprocoumon patients N=3,871**				**HR (95% CI)**	**p-value**
	No. of events	**Person-years of follow up**		**Events/100 person-years**	**No. of events**	**Person-years of follow up**		**Events/100 person-years**		
		Mean	**Median**			**Mean**	**Median**			
Exposure Time of VKA with eDDD										
Ischemic stroke (effectiveness)	48	345.73	257	2.6	116	366.98	282	2.98	0.818 (0.566-1.184)	0.2876
Intracranial hemorrhage (ICH) (safety)	10	352.77	263	0.53	28	371.92	290.39	0.71	0.538 (0.241-1.200)	0.1298
Exposure Time of VKA with 1 tablet per day (3mg)										
Ischemic stroke (effectiveness)	48	345.73	257	2.6	83	202.82	146	3.86	0.846 (0.559-1.280)	0.4279
Intracranial hemorrhage (ICH) (safety)	10	352.77	263	0.53	19	204.12	147	0.88	0.531 (0.212-1.329)	0.1761
Exposure Time of VKA with 1.5 tablet per day (4.5mg)										
Ischemic stroke (effectiveness)	48	345.73	257	2.6	62	134.13	103.3	4.36	0.716 (0.452-1.134)	0.1548
Intracranial hemorrhage (ICH)	10	352.77	263	0.53	14	134.33	103.67	0.98	0.529 (0.191-	0.2212

(safety)									1.467)	
Exposure Time of VKA with 0.5 tablet per day (1.5mg)										
Ischemic stroke (effectiveness)	48	345.73	257	2.6	129	447.16	353	2.72	0.867 (0.605-1.243)	0.4379
Intracranial hemorrhage (ICH) (safety)	10	352.77	263	0.53	36	453.33	362	0.75	0.486 (0.228-1.038)	0.0624

10.4.1 Main Results – Propensity Score Matching

In the following the main results from the analyses are reported, including c-statistics before and after propensity score matching, demographic and clinical characteristics after propensity score matching, as well as the results for the primary and secondary endpoints after propensity score matching.

Figure 2. Pre- and post-matching propensity score overlap plots

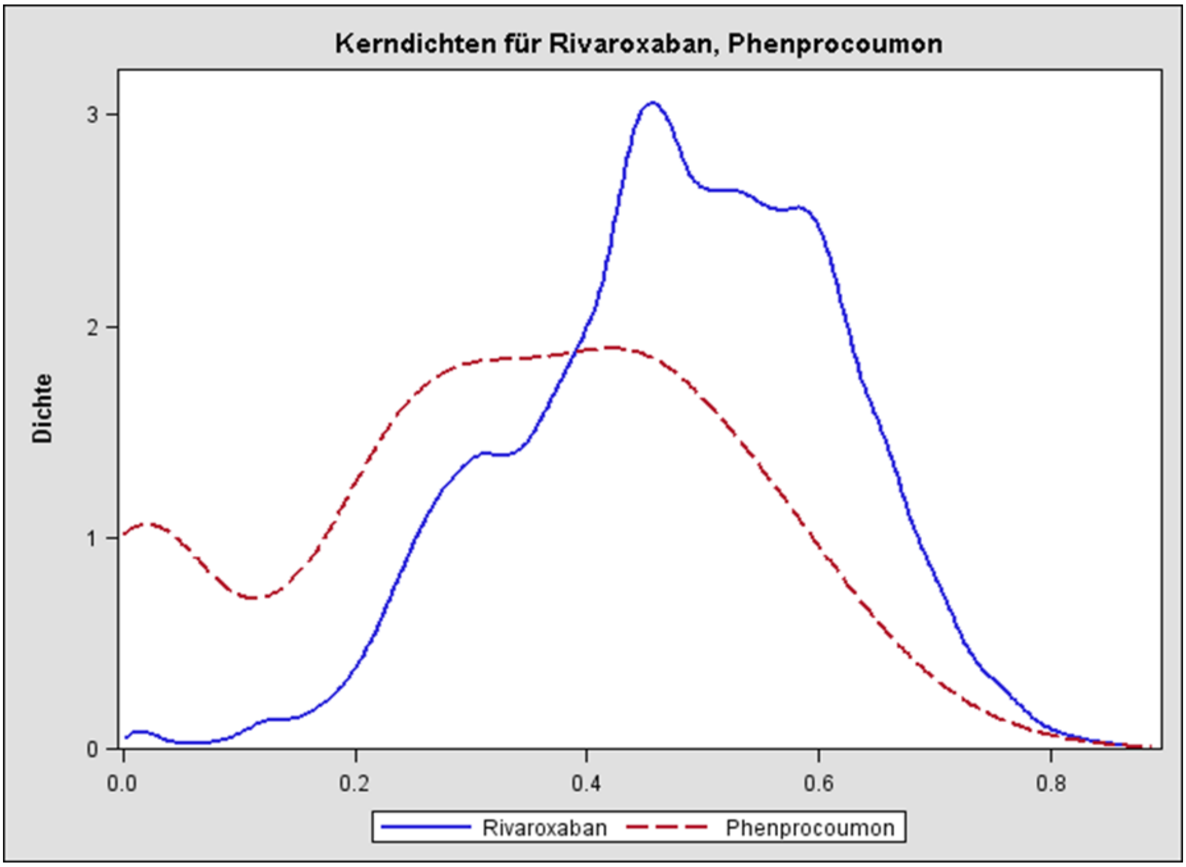


Figure 3. Propensity score distributions by treatment group after matching

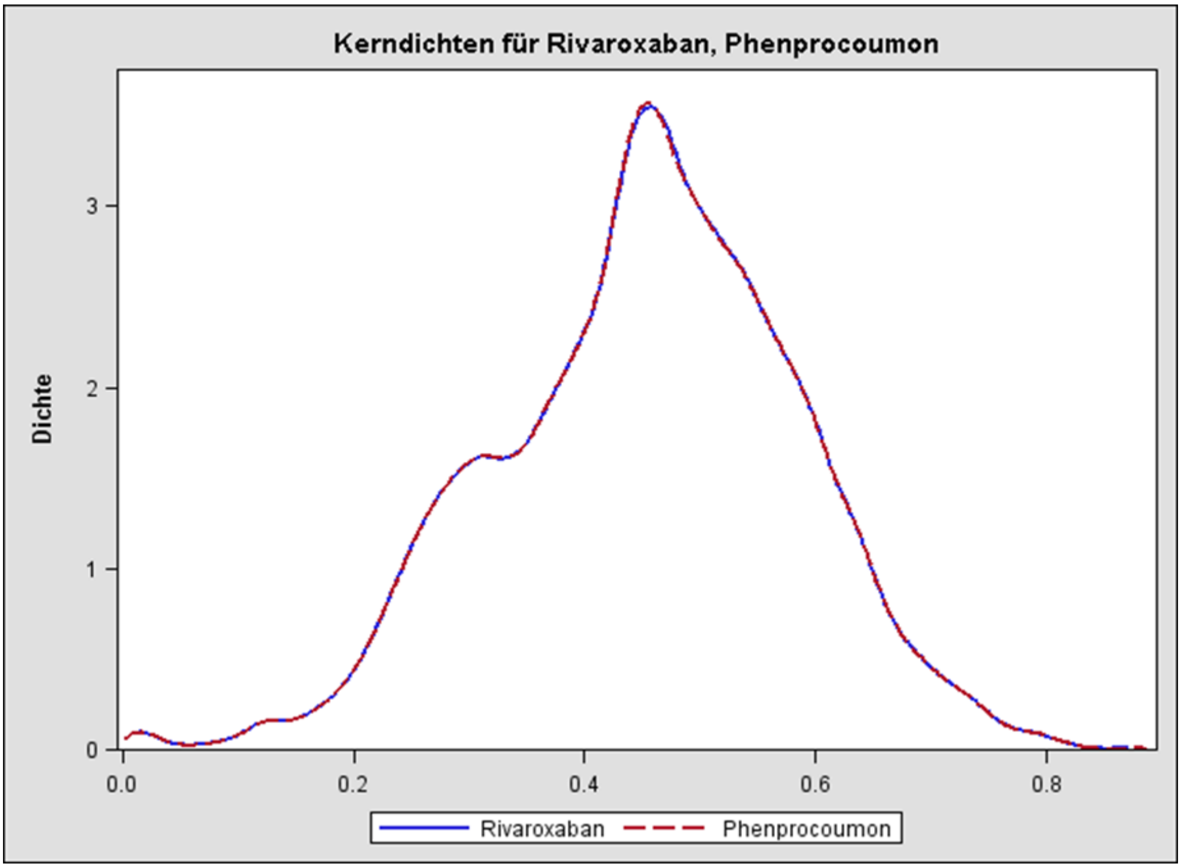


Table 24. C-statistics before matching

Description	Number of usable pairs	Number of concordant pairs	Number of discordant pairs	Total of observations	C-Index*	Lower 95%CI	Upper 95%CI
Ischemic stroke (effectiveness)	18,954,521	18,513,094	441,427	33,668	0.97671	0.94375	0.99683
Intracranial hemorrhage (ICH) (safety)	5,891,725	5,837,397	54,328	33,668	0.99078	0.92901	1.01127
Systemic embolism (SE) (effectiveness)	3,602,369	3,377,979	224,390	33,668	0.93771	0.80723	1.00954
Transient ischemic attack (TIA) (effectiveness)	5,555,055	5,249,923	305,132	33,668	0.94507	0.85007	1.00047

Subarachnoid hemorrhage (safety)	841,675	784,067	57,608	33,668	0.93156	0.573	1.08721
Intracerebral hemorrhage (safety)	3,939,039	3,885,333	53,706	33,668	0.98637	0.89573	1.01706
Other and unspecified nontraumatic intracranial hemorrhage (safety)	1,548,682	1,528,468	20,214	33,668	0.98695	0.7922	1.04231
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	23,937,237	23,573,660	363,577	33,668	0.98481	0.9602	0.99906
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	26,899,933	25,995,349	904,584	33,668	0.96637	0.93615	0.98771
* proposed by Pencina and D'Agostino							

Table 25. C-statistics after matching

Description	Number of usable pairs	Number of concordant pairs	Number of discordant pairs	Total of observations	C-Index*	Lower 95%CI	Upper 95%CI
Ischemic stroke (effectiveness)	8,854,950	8,714,007	140,943	22,706	0.98408	0.94653	1.00294
Intracranial hemorrhage (ICH) (safety)	2,520,255	2,453,292	66,963	22,706	0.97343	0.86802	1.01754
Systemic embolism (SE) (effectiveness)	1,612,055	1,481,974	130,081	22,706	0.91931	0.73776	1.01897

Transient ischemic attack (TIA) (effectiveness)	2,497,550	2,348,356	149,194	22,706	0.94026	0.81347	1.00957
Subarachnoid hemorrhage (safety)	272,460	245,108	27,352	22,706	0.89961	0.30151	1.18574
Intracerebral hemorrhage (safety)	1,702,875	1,660,277	42,598	22,706	0.97498	0.83445	1.02724
Other and unspecified nontraumatic intracranial hemorrhage (safety)	635,740	617,919	17,821	22,706	0.97197	0.66718	1.07351
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	11,011,925	10,858,271	153,654	22,706	0.98605	0.95496	1.00198
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	12,442,340	12,081,175	361,165	22,706	0.97097	0.93486	0.99406
* proposed by Pencina and D'Agostino							

Table 26. Standardized Differences before and after matching

Characteristics	**Pre-matching**			**Post-matching**		
	Rivaroxaban patients N=13,155	Phenprocoumon patients N=20,513	Standardized Difference	Rivaroxaban patients N=11,353	Phenprocoumon patients N=11,353	Standardized Difference
Age	71.83 ± 11.89	73.77 ± 9.82	-0.182	72.71 ± 11.26	72.80 ± 10.51	-0.008

Characteristics	Pre-matching			Post-matching		
	Rivaroxaban patients N=13,155	Phenprocoumon patients N=20,513	Standardized Difference	Rivaroxaban patients N=11,353	Phenprocoumon patients N=11,353	Standardized Difference
Number of hospitalizations	1.21 ± 1.19	1.16 ± 1.18	0.042	1.18 ± 1.15	1.16 ± 1.21	0.017
Number of unique medications	8.28 ± 5.07	8.75 ± 5.05	-0.093	8.19 ± 5.00	8.15 ± 5.13	0.008
CHA2DS2 VASc score	3.49 ± 1.86	3.78 ± 1.70	-0.164	3.56 ± 1.81	3.56 ± 1.75	0
CHADS2 score	2.16 ± 1.39	2.31 ± 1.32	-0.111	2.18 ± 1.38	2.18 ± 1.35	0
Charlson Comorbidity Index (CCI)	2.20 ± 2.12	2.41 ± 2.15	-0.098	2.19 ± 2.10	2.19 ± 2.11	0
Comorbidity Index (modified Charlson Comorbidity Index)	1.74 ± 1.83	1.82 ± 1.81	-0.044	1.71 ± 1.80	1.70 ± 1.80	0.005
Bleeding history (modified HAS BLED score)	2.50 ± 1.21	2.67 ± 1.13	-0.146	2.55 ± 1.18	2.56 ± 1.16	-0.008
Gender						
Female	48.67%	49.48%	-1.62	49.28%	48.95%	0.66
Male	51.33%	50.52%	1.62	50.72%	51.05%	-0.66
Insurance status						
Family insured	2.96%	2.33%	3.93	2.75%	2.68%	0.43
Regular insurance	21.57%	13.92%	20.12	17.88%	17.90%	-0.052
Retired	75.46%	83.74%	-20.66	79.36%	79.42%	-0.148
Unknown	0.01%	0.01%	0	0.01%	0.01%	0
Interaction with co-medications – Boost						
Boost (yes)	31.90%	54.43%	-46.71	36.33%	35.67%	1.38

Characteristics	Pre-matching			Post-matching		
	Rivaroxaban patients N=13,155	Phenprocoumon patients N=20,513	Standardized Difference	Rivaroxaban patients N=11,353	Phenprocoumon patients N=11,353	Standardized Difference
Boost (no)	68.10%	45.57%	46.71	63.67%	64.33%	-1.38
Interaction with co-medications – Attenuation						
Attenuation (yes)	0.35%	15.08%	-57.43	0.41%	0.43%	-0.31
Attenuation (no)	99.65%	84.92%	57.43	99.59%	99.57%	0.31
Comorbidities						
Myocardial infarction	4.58%	7.51%	-12.31	4.89%	4.81%	0.37
Chronic renal insufficiency	14.85%	18.87%	-10.75	15.54%	15.46%	0.22
Chronic renal insufficiency stage I	0.71%	0.71%	0	0.70%	0.77%	-0.82
Chronic renal insufficiency stage II	3.95%	4.40%	-2.25	3.99%	3.95%	0.2
Chronic renal insufficiency stage III	8.65%	11.39%	-9.13	9.11%	9.22%	-0.38
Chronic renal insufficiency stage IV	1.23%	2.55%	-9.71	1.38%	1.38%	0
Chronic renal insufficiency stage V	0.08%	0.35%	-5.83	0.09%	0.05%	1.51
Other chronic renal insufficiency	1.58%	2.27%	-5.02	1.74%	1.74%	0
Unspecified chronic renal insufficiency	2.17%	3.35%	-7.21	2.33%	2.40%	-0.46
Diabetes	31.41%	34.91%	-7.44	29.99%	29.69%	0.66

Characteristics	**Pre-matching**			**Post-matching**		
	Rivaroxaban patients N=13,155	Phenprocoumon patients N=20,513	Standardized Difference	Rivaroxaban patients N=11,353	Phenprocoumon patients N=11,353	Standardized Difference
Hypertension	83.31%	86.84%	-9.92	84.39%	84.16%	0.63
Congestive heart failure	30.29%	34.20%	-8.37	30.58%	30.49%	0.19
Atherosclerosis of arteries of extremities	4.62%	5.97%	-6.03	4.76%	5.17%	-1.89
Ischemic stroke or TIA during baseline	12.18%	11.35%	2.58	12.20%	12.02%	0.55
Coronary heart disease	33.67%	42.24%	-17.73	35.53%	35.41%	0.25
Mild liver disease	13.05%	13.12%	-0.21	12.63%	12.58%	0.15
Moderate or severe liver disease	0.32%	0.44%	-1.95	0.33%	0.29%	0.72
Depression	17.26%	15.89%	3.68	16.65%	16.40%	0.67
Somatoform disorder	8.94%	8.52%	1.49	8.91%	8.95%	-0.14
Anxiety disorder	4.81%	4.09%	3.49	4.64%	4.46%	0.86
Dementia	8.06%	5.87%	8.61	6.96%	6.69%	1.07
Cancer	0%	0%	0	0%	0%	0
Obesity	22.08%	23.38%	-3.1	21.75%	21.67%	0.19
Prescriptions						
Proton-pump-inhibitors	41.57%	41.56%	0.02	40.90%	40.62%	0.57
Antiplatelet medication	22.95%	26.18%	-7.51	23.31%	23.16%	0.36
Acetylsalicylic acid (ASS)	18.24%	20.44%	-5.57	18.47%	18.39%	0.21

Characteristics	Pre-matching			Post-matching		
	Rivaroxaban patients N=13,155	Phenprocoumon patients N=20,513	Standardized Difference	Rivaroxaban patients N=11,353	Phenprocoumon patients N=11,353	Standardized Difference
Non-steroidal antiinflammatory drugs (NSAIDs)	36.66%	36.83%	-0.35	36.22%	36.38%	-0.33
Interventions						
Coronary angioplasty	2.42%	6.71%	-20.66	2.78%	2.77%	0.06
Other						
Smoking	5.37%	5.03%	1.53	5.20%	4.86%	1.56
Alcohol abuse	2.57%	2.09%	3.18	2.39%	2.38%	0.07
Substance abuse	0.67%	0.68%	-0.12	0.62%	0.67%	-0.62

Table 27. Demographic characteristics Rivaroxaban patients after matching

Age groups	Rivaroxaban patients N=11,353					
	Female		Male		Total	
	n	%	n	%	n	%
18-29	<5		13	0.11	14	0.12
30-39	12	0.11	64	0.56	76	0.67
40-49	62	0.55	264	2.33	326	2.87
50-59	267	2.35	764	6.73	1,031	9.08
60-64	347	3.06	616	5.43	963	8.48
65-74	1,514	13.34	1,940	17.09	3,454	30.42
≥75	3,392	29.88	2,097	18.47	5,489	48.35
Total	5,595	49.28	5,758	50.72	11,353	100

Table 28. Demographic characteristics Phenprocoumon patients after matching

Age groups	Phenprocoumon patients N=11,353					
	Female		Male		Total	
	n	%	n	%	n	%
18-29	<5		9	0.08	13	0.11
30-39	8	0.07	41	0.36	49	0.43
40-49	54	0.48	200	1.76	254	2.24
50-59	251	2.21	772	6.80	1,023	9.01
60-64	332	2.92	660	5.81	992	8.74
65-74	1,562	13.76	1,900	16.74	3,462	30.49
≥75	3,346	29.47	2,214	19.50	5,560	48.97
Total	5,557	48.95	5,796	51.05	11,353	100

Table 29. Demographic characteristics – age distribution for Rivaroxaban patients after matching

Gender	Rivaroxaban patients N=11,353				
	Mean	SD	Minimum	Median	Maximum
Female	76.04	9.84	24	77	103
Male	69.47	11.61	20	71	97
Total	72.71	11.26	20	74	103

Table 30. Demographic characteristics – age distribution for Phenprocoumon patients after matching

Gender	Phenprocoumon patients N=11,353				
	Mean	**SD**	**Minimum**	**Median**	**Maximum**
Female	75.74	9.31	20	77	101
Male	69.98	10.83	21	72	98
Total	72.8	10.51	20	74	101

Table 31. Type of AF diagnosis after matching

ICD-10-GM Code	Type of AF	Rivaroxaban patients N=11,353		Phenprocoumon patients N=11,353	
		n	**%**	**n**	**%**
I48.0	Paroxysmal	6,133	54.02	4,526	39.87
I48.1	Persistent	4,866	42.86	6,844	60.28
I48.2	Permanent	1,942	17.11	1,427	12.57
I48.9	Unknown*	1,173	10.33	959	8.45
	Total	11,353	100.00	11,353	100.00
* Only patients whose diagnosis was not specified					

Table 32. CHADS$_2$ risk score after matching

CHADS$_2$ risk score value	Rivaroxaban patients N=11,353		Phenprocoumon patients N=11,353	
	n	%	n	%
0	973	8.57	921	8.11
1	3,006	26.48	2,959	26.06
2	3,214	28.31	3,358	29.58
3	2,223	19.58	2,225	19.60
4	1,199	10.56	1,228	10.82
5	554	4.88	478	4.21
6	184	1.62	184	1.62
Mean score	2.18	-	2.18	-
SD	1.38	-	1.35	-

Table 33. CHA_2DS_2-VASC risk score after matching

CHA_2DS_2-VASC risk score value	Rivaroxaban patients N=11,353		Phenprocoumon patients N=11,353	
	n	%	n	%
0	403	3.55	354	3.12
1	1,149	10.12	1,064	9.37
2	1,763	15.53	1,784	15.71
3	2,285	20.13	2,395	21.10
4	2,372	20.89	2,481	21.85
5	1,729	15.23	1,697	14.95
6	975	8.59	1,001	8.82
7	489	4.31	410	3.61
8	164	1.44	147	1.29
9	24	0.21	20	0.18
Mean score	3.56	-	3.56	-
SD	1.81	-	1.75	-

Table 34. Summary statistics for hospitalizations (overall) after matching

	Rivaroxaban patients N=11,353					
n (% of patients)	Sum	Mean	SD	Minimum	Median	Maximum
8,331 (73.40%)	13,359	1.18	1.15	0	1	12
	Phenprocoumon patients N=11,353					
n (% of patients)	Sum	Mean	SD	Minimum	Median	Maximum
8,029 (70.72%)	13,219	1.16	1.21	0	1	33

Table 35. Summary statistics of the duration of hospitalizations (overall) after matching (in days)

	Rivaroxaban patients N=11,353					
n (% of patients)	**Sum**	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
8,331 (73.40%)	131,582	15.79	20.06	1	9	291
	Phenprocoumon patients N=11,353					
n (% of patients)	**Sum**	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
8,029 (70.72%)	139,648	17.39	20.46	1	11	451

Table 36. Co-medications after matching

Medication		**Rivaroxaban patients N=11,353**		**Phenprocoumon patients N=11,353**	
		n	**%**	**n**	**%**
Anticoagulation therapy	VKA	0		0	
	Phenprocoumon	0		0	
	Thrombin inhibitors*	0		0	
	Rivaroxaban	0		0	
	Apixaban	0		0	
	ASA	1,848	16.28	1,790	15.77
	Other anticoagulants	1,426	12.56	1,482	13.05
Antiarrhythmic drugs	Class I: Sodium channel blockers	313	2.76	283	2.49
	Class II: Beta-blockers	3,129	27.56	3,299	29.06
	Class III: Potassium channel blockers	364	3.21	378	3.33
	Class IV: Calcium antagonists	353	3.11	304	2.68
	Digitalis	383	3.37	230	2.03
	Other	73	0.64	60	0.53

Other medications	ACE-inhibitors	4,723	41.60	5,193	45.74
	ATII-antagonists	2,820	24.84	2,600	22.9
	Beta-blocker	6,266	55.19	6,486	57.13
	Calcium-antagonists	359	3.16	309	2.72
	Diuretics	3,714	32.71	4,001	35.24
	Nitrates	807	7.11	892	7.86
	Statins	602	5.30	386	3.40
	Antidiabetic medications	2,044	18.00	1,739	15.32
	Thyroid medications	2,038	17.95	1,574	13.86
	NSAIDs	4,047	35.65	4,138	36.45
*Other than B01AE07					

Table 37. Primary endpoints after matching

Description	**Rivaroxaban patients N=11,353**			**Phenprocoumon patients N=11,353**			**HR (95% CI)**	**p-value**
	No. of events	**Person-years of follow up**	**Events/100 person-years**	**No. of events**	**Person-years of follow up**	**Events/100 person-years**		
Ischemic stroke (effectiveness)	200	11,520.08	1.74	213	12,591.05	1.69	1.013 (0.835 - 1.230)	0,8935
Intracranial hemorrhage (ICH) (safety)	59	11,628.22	0.51	57	12,704.06	0.45	1.091 (0.758 - 1.571)	0.6379

Table 38. Secondary endpoints after matching

Description	**Rivaroxaban patients N=11,353**			**Phenprocoumon patients N=11,353**			**HR (95% CI)**	**p-value**
	No. of events	**Person-years of follow up**	**Events/100 person-years**	**No. of events**	**Person-years of follow up**	**Events/100 person-years**		
Composite endpoint cerebral	248	11,509.18	2.15	264	12,571.53	2.10	1.008 (0.847 -	0.9262

benefit (Ischemic stroke and Intracranial hemorrhage (ICH))							1.200)	
Systemic embolism (SE) (effectiveness)	44	11,614.98	0.38	32	12,709.99	0.25	1.461 (0.926 - 2.305)	0.103
Transient ischemic attack (TIA) (effectiveness)	64	11,597.09	0.55	53	12,684.15	0.42	1.285 (0.892 - 1.850)	0.1783
Subarachnoid hemorrhage (safety)	7	11,636.02	0.06	7	12,720.93	0.06	1.055 (0.370 - 3.010)	0.9201
Intracerebral hemorrhage (safety)	40	11,634.16	0.34	38	12,714.12	0.30	1.102 (0.707 - 1.719)	0.6672
Other and unspecified nontraumatic intracranial hemorrhage (safety)	14	11,638.02	0.12	15	12,714.13	0.12	0.999 (0.482 - 2.070)	0.9972
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	294	11,459.56	2.57	289	12,541.2	2.30	1.095 (0.930 - 1.288)	0.2757

Figure 4. Kaplan-Maier Survival Curves – Primary endpoints – Ischemic Stroke (effectiveness)

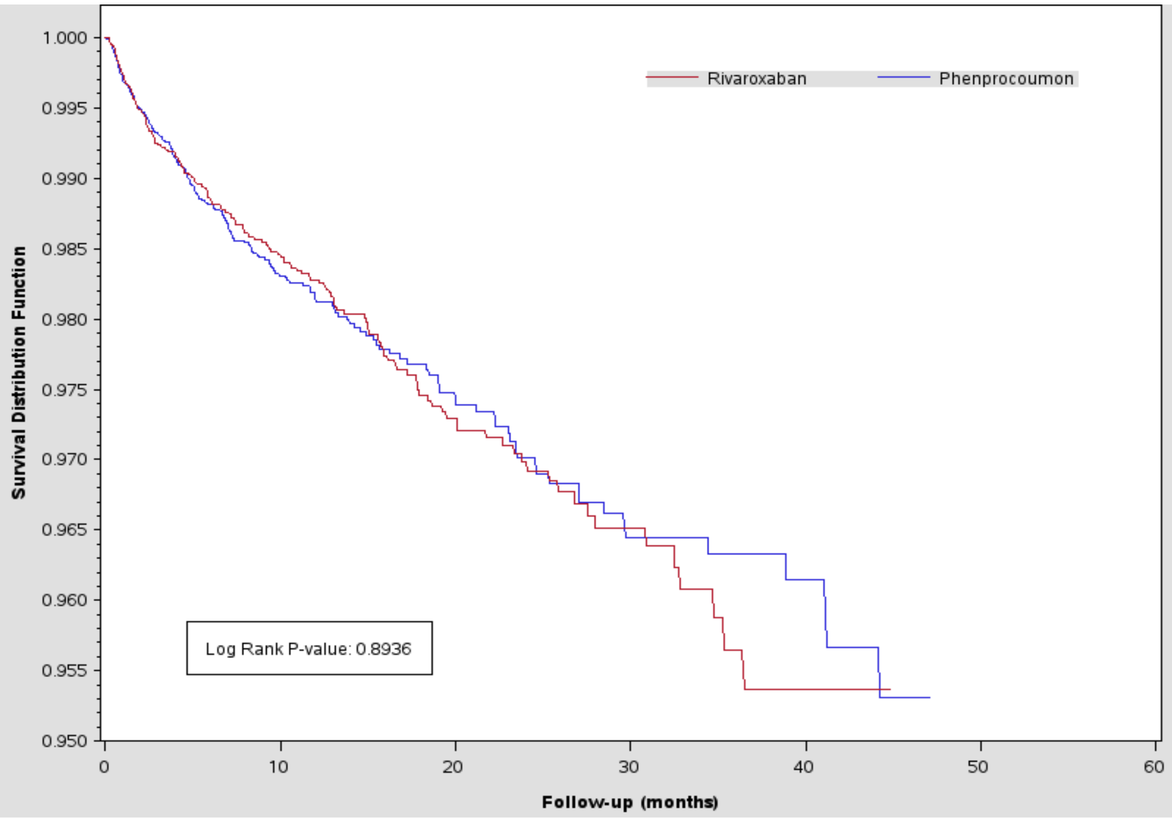


Figure 5. Kaplan-Maier Survival Curves – Primary endpoints – Intracranial hemorrhage (ICH) (safety)

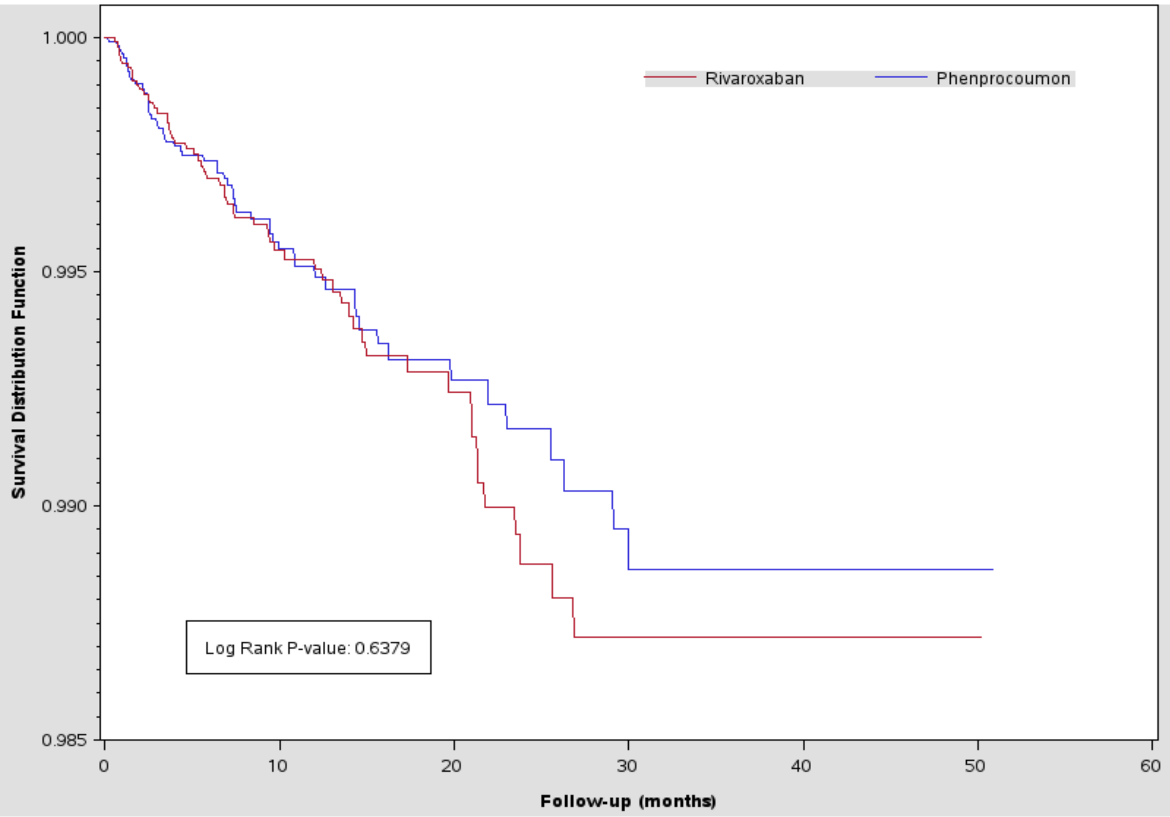


Figure 6. Kaplan-Maier Survival Curves – Secondary endpoints – Composite endpoint cerebral benefit (Ischemic stroke and ICH)

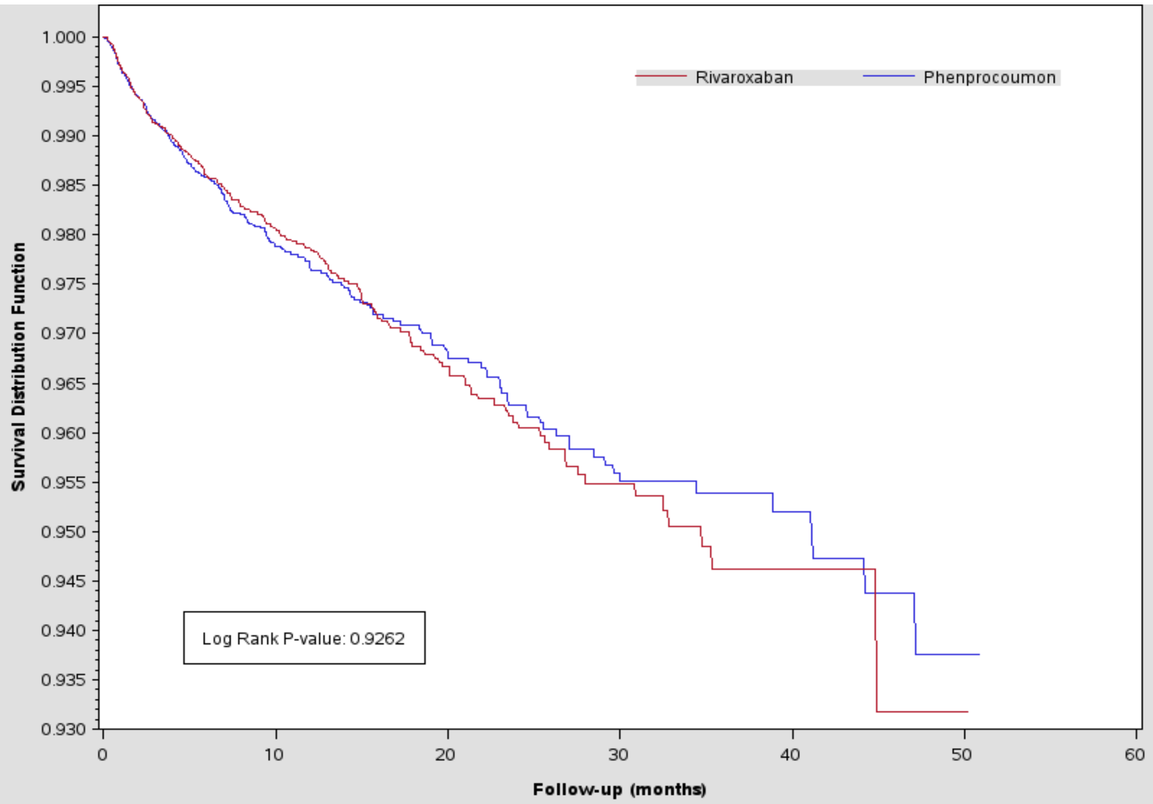


Figure 7. Kaplan-Maier Survival Curves – Secondary endpoints – Composite endpoint effectiveness (Ischemic stroke, SE and TIA)

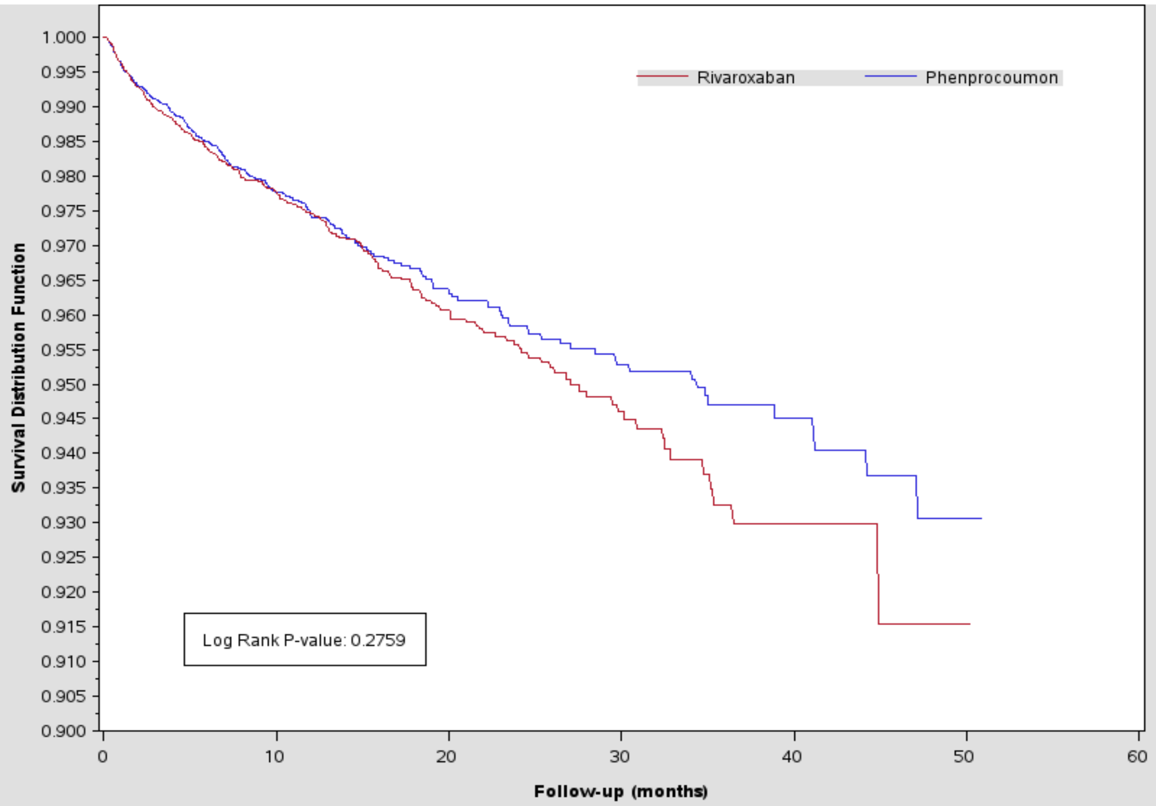


Figure 8. Kaplan-Maier Survival Curves – Secondary endpoints – Systemic embolism (SE) (effectiveness)

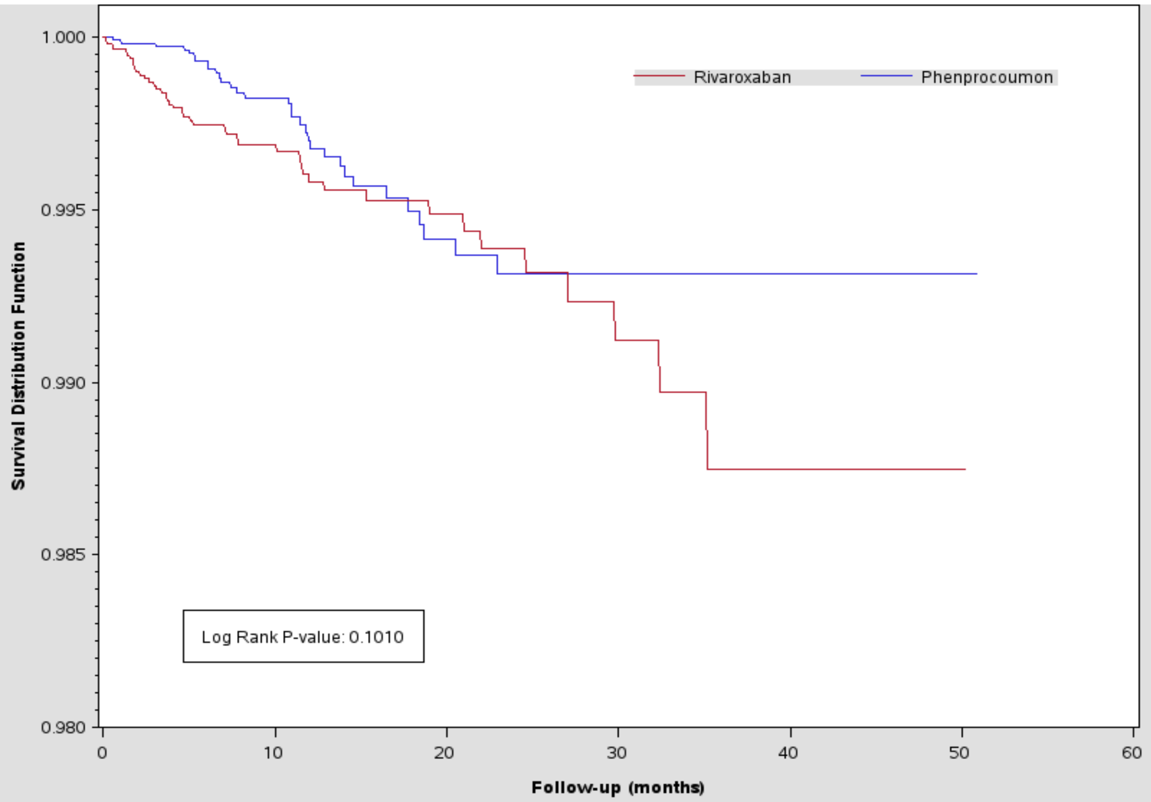


Figure 9. Kaplan-Maier Survival Curves – Secondary endpoints – Transient ischemic attack (TIA) (effectiveness)

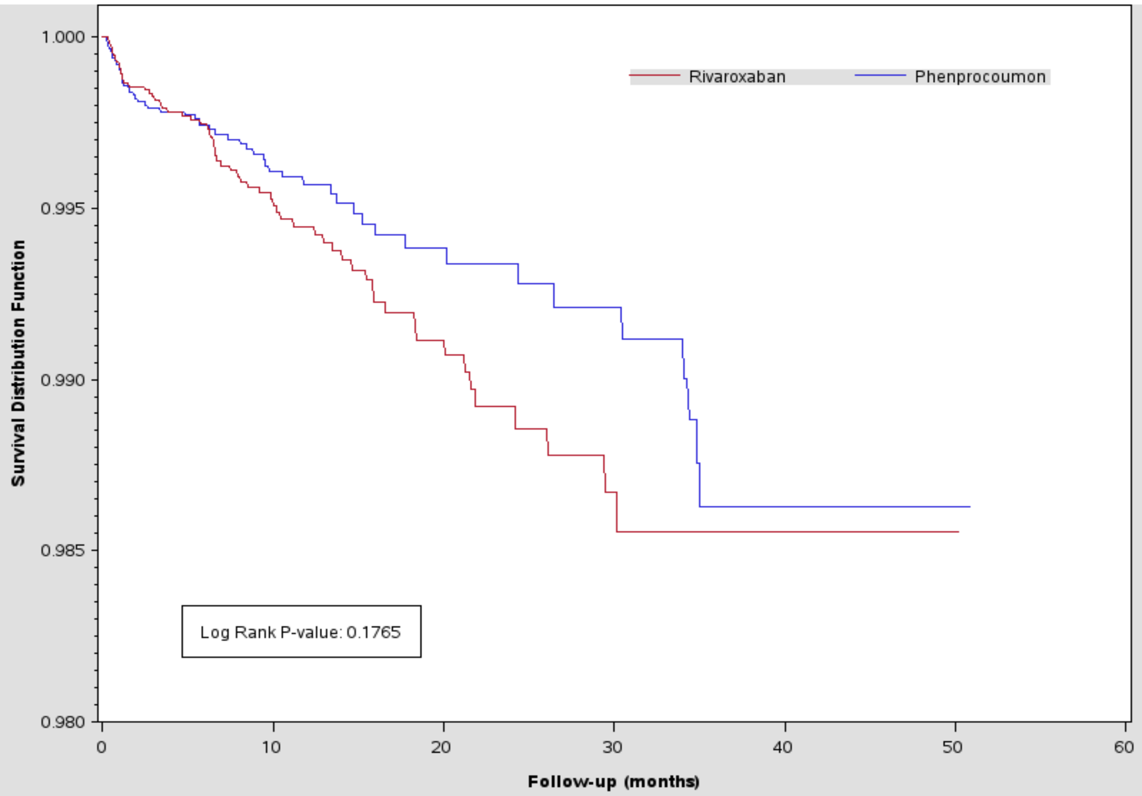


Figure 10. Kaplan-Maier Survival Curves – Secondary endpoints – Subarachnoid hemorrhage (safety)

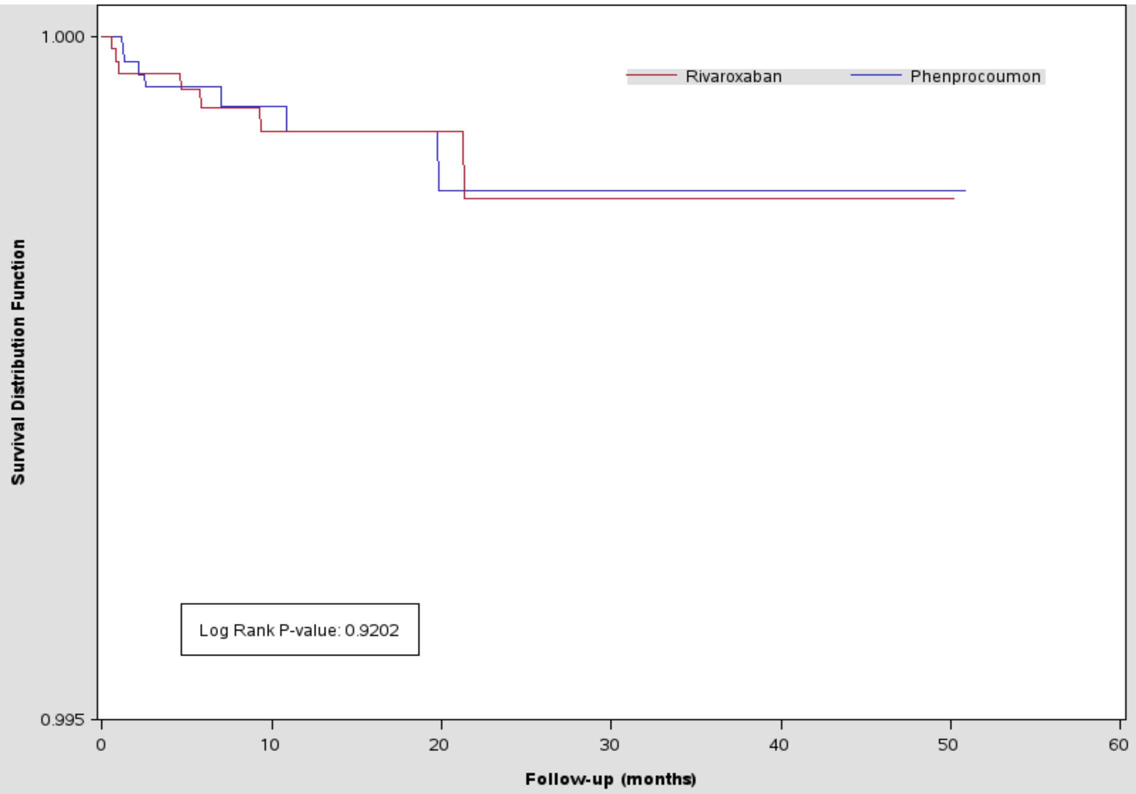


Figure 11. Kaplan-Maier Survival Curves – Secondary endpoints – Intracerebral hemorrhage (safety)

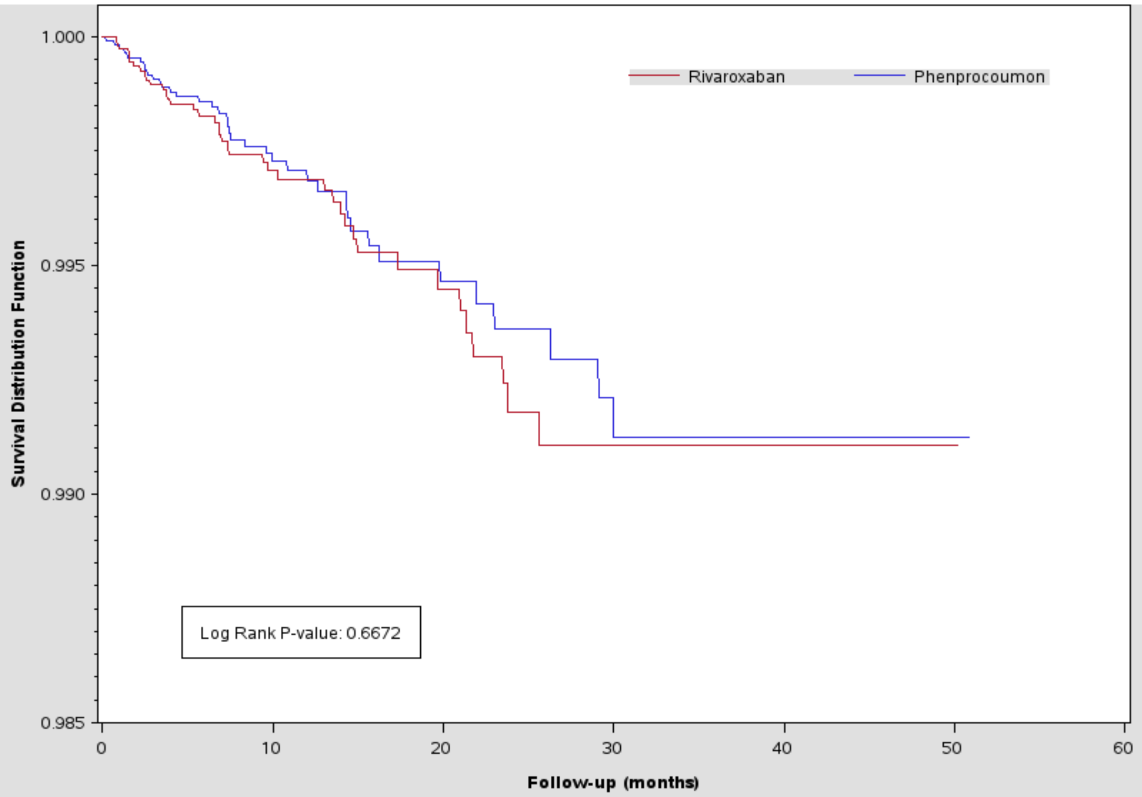
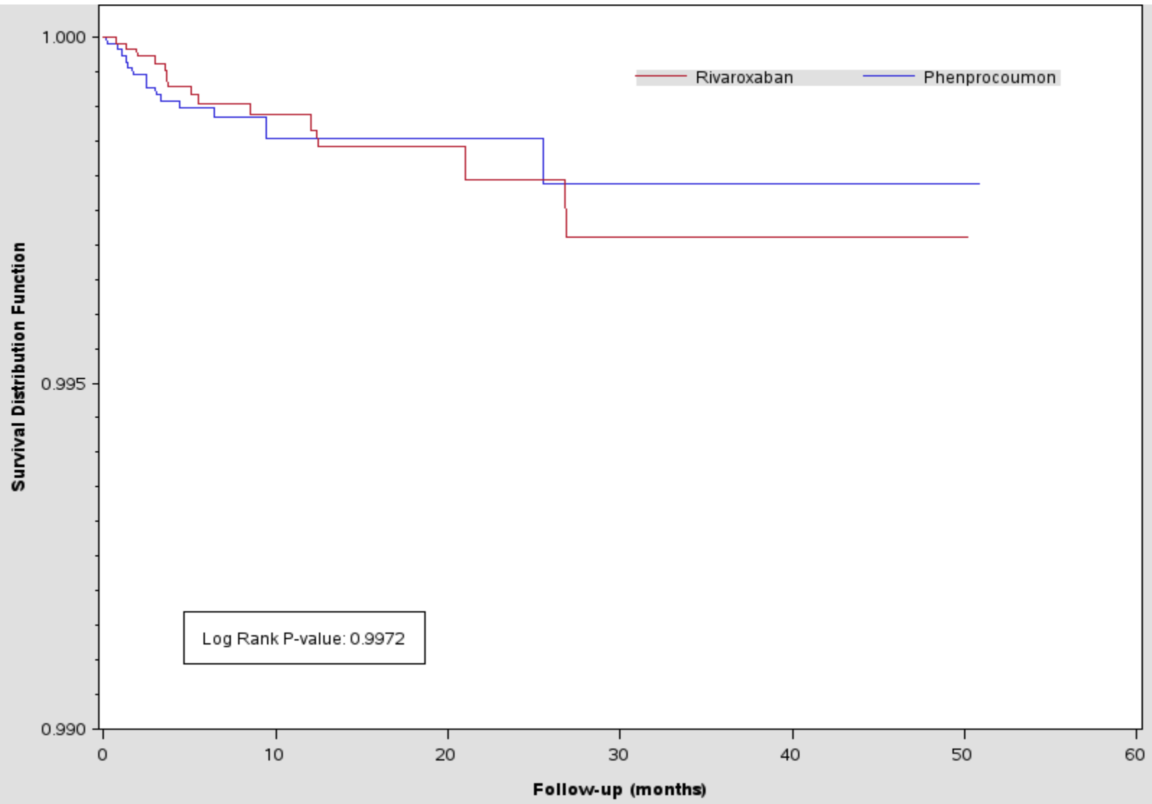


Figure 12. Kaplan-Maier Survival Curves – Secondary endpoints – Other and unspecified non traumatic intracranial hemorrhage (safety)



10.4.2 Main Results – Multivariate Analysis and IPTW weighted

In the following the main results from the multivariate analysis are reported including primary and secondary endpoints from the multivariate analysis as well as IPTM weighted.

Table 39. Primary endpoints – Multivariate analysis

Description	Rivaroxaban patients N=13,155			Phenprocoumon patients N=20,513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	233	13,205.34	1.76	372	22,939.74	1.62	0.930 (0.779 - 1.111)	0.4239
Intracranial hemorrhage (ICH) (safety)	66	13,337.93	0.49	119	23,107.38	0.51	0.881 (0.637 - 1.219)	0.4459

Table 40. Secondary endpoints – Multivariate analysis

Description	Rivaroxaban patients N=13,155			Phenprocoumon patients N=20.513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	286	13,191.86	2.17	475	22,905.69	2.07	0.905 (0.772 - 1.061)	0.2194
Systemic embolism (SE) (effectiveness)	51	13,324.07	0.38	69	23,122.93	0.30	1.158 (0.781 - 1.717)	0.4653
Transient ischemic attack (TIA) (effectiveness)	77	13,302.51	0.58	102	23,069.32	0.44	1.189 (0.859 - 1.645)	0.2964
Subarachnoid hemorrhage (safety)	8	13,348.33	0.06	21	23,138.06	0.09	0.678 (0.281 - 1.632)	0.3857
Intracerebral hemorrhage (safety)	44	13,345.75	0.33	79	23,127.94	0.34	0.914 (0.614 - 1.361)	0.6583
Other and unspecified nontraumatic intracranial hemorrhage (safety)	17	13,348.69	0.13	31	23,128.3	0.13	0.839 (0.442 - 1.593)	0.5921
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	345	13,135.15	2.63	523	22,848.33	2.29	0.994 (0.858 - 1.153)	0.9407

Table 41. Primary endpoints – IPTW weighted

Description	Rivaroxaban patients N=13,155			Phenprocoumon patients N=20,513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	233	13,205.34	1.76	372	22,939.74	1.62	1.020 (0.868 - 1.199)	0.8077
Intracranial hemorrhage (ICH) (safety)	66	13,337.93	0.49	119	23,107.38	0.51	0.852 (0.626 - 1.161)	0.3105

Table 42. Secondary endpoints – IPTW weighted

Description	Rivaroxaban patients N=13,155			Phenprocoumon patients N=20.513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	286	13,191.86	2.17	475	22,905.69	2.07	0.967 (0.836 - 1.118)	0.6498
Systemic embolism (SE) (effectiveness)	51	13,324.07	0.38	69	23,122.93	0.30	1.063 (0.727 - 1.553)	0.7531
Transient ischemic attack (TIA) (effectiveness)	77	13,302.51	0.58	102	23,069.32	0.44	1.113 (0.817 - 1.515)	0.4987
Subarachnoid hemorrhage (safety)	8	13,348.33	0.06	21	23,138.06	0.09	0.502 (0.204 - 1.233)	0.1328
Intracerebral hemorrhage (safety)	44	13,345.75	0.33	79	23,127.94	0.34	0.903 (0.623 - 1.309)	0.5918
Other and unspecified	17	13,348.69	0.13	31	23,128.3	0.13	0.777 (0.414 -	0.4334

nontraumatic intracranial hemorrhage (safety)							1.460)	
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	345	13,135.15	2.63	523	22,848.33	2.29	1.041 (0.908 - 1.193)	0.5635

10.4.3 Main Results – Sensitivity Analyses

For this study sensitivity analyses were conducted according to dosing regimen, patients with prior events of any of the events defined in the combined endpoints, and assessing the inclusion of cancer patients in the study population. The results of the sensitivity analyses are reported in the following sections.

10.4.3.1 Sensitivity Analysis 1 Results – Patients receiving 20mg Rivaroxaban only

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

The results for propensity score matching and the multivariate analysis are reported in the following tables.

Table 43. Sensitivity analysis – Number of patients receiving 20mg Rivaroxaban only

	Rivaroxaban	**Phenprocoumon**
Sensitivity analysis		
Total remained with patients receiving 20 mg only (Rivaroxaban)	9,539	20,513
Total remained with patients receiving 15 mg (Rivaroxaban)	3,616	

Table 44. Sensitivity analysis – Patients receiving 20mg Rivaroxaban only: Primary endpoints before matching

Description	Rivaroxaban patients N=9,539			Phenprocoumon patients N=20,513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	195	9,035.53	2.16	372	22,939.74	1.62	1.291 (1.085 - 1.537)	0.0039
Intracranial hemorrhage (ICH) (safety)	45	9,107.67	0.49	119	23,107.38	0.51	0.922 (0.654 - 1.300)	0.6443

Table 45. Sensitivity analysis – Patients receiving 20mg Rivaroxaban only: Secondary endpoints before matching

Description	Rivaroxaban patients N=9,539			Phenprocoumon patients N=20,513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	229	9,025.96	2.54	475	22,905.69	2.07	1.184 (1.011 - 1.387)	0.0361
Systemic embolism (SE) (effectiveness)	37	9,107.32	0.41	69	23,122.93	0.30	1.345 (0.901 - 2.008)	0.1473
Transient ischemic attack (TIA) (effectiveness)	61	9,081.95	0.67	102	23,069.32	0.44	1.452 (1.057 - 1.995)	0.0215
Subarachnoid hemorrhage (safety)	5	9,116.32	0.05	21	23,138.06	0.09	0.562 (0.212 - 1.490)	0.2464
Intracerebral hemorrhage (safety)	35	9,110.39	0.38	79	23,127.94	0.34	1.082 (0.726 - 1.612)	0.6977

Other and unspecified nontraumatic intracranial hemorrhage (safety)	7	9,116.3	0.08	31	23,128.3	0.13	0.555 (0.244 - 1.262)	0.1597
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemich attack (TIA))	278	8,995.31	3.09	523	22,848.33	2.29	1.309 (1.132 - 1.515)	0.0003

Table 46. Sensitivity analysis – Patients receiving 20mg Rivaroxaban only: Primary endpoints after matching

Description	Rivaroxaban patients N=8,556			Phenprocoumon patients N=8,556			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	141	8,746.14	1.61	140	9,954.71	1.41	1.109 (0.877 - 1.402)	0.3885
Intracranial hemorrhage (ICH) (safety)	42	8,827.59	0.48	42	10,041.05	0.42	1.091 (0.711 - 1.675)	0.6886

Table 47. Sensitivity analysis – Patients receiving 20mg Rivaroxaban only: Secondary endpoints after matching

Description	Rivaroxaban patients N=8,556			Phenprocoumon patients N=8,556			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	174	8,738.98	1.99	178	9,942.7	1.79	1.074 (0.871 - 1.324)	0.5049
Systemic embolism (SE) (effectiveness)	28	8,823.65	0.32	25	10,040.53	0.25	1.232 (0.718 - 2.114)	0.4489
Transient ischemic attack (TIA) (effectiveness)	49	8,800.82	0.56	34	10,018.7	0.34	1.576 (1.016 - 2.442)	0.042
Subarachnoid hemorrhage (safety)	5	8,833.92	0.06	9	10,048.65	0.09	0.593 (0.199 - 1.770)	0.3492
Intracerebral hemorrhage (safety)	32	8,829.43	0.36	29	10,045.13	0.29	1.206 (0.729 - 1.994)	0.4653
Other and unspecified nontraumatic intracranial hemorrhage (safety)	7	8,834.77	0.08	8	10,049.13	0.08	0.960 (0.348 - 2.649)	0.937
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	206	8,706.41	2.37	193	9,911.76	1.95	1.175 (0.965 - 1.431)	0.1082

Table 48. Sensitivity analysis – Patients receiving 20mg Rivaroxaban only: Primary endpoints – Multivariate analysis

Description	Rivaroxaban patients N=9,539			Phenprocoumon patients N=20,513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	195	9,035.53	2.16	372	22,939.74	1.62	1.006 (0.820 - 1.234)	0.9573
Intracranial hemorrhage (ICH) (safety)	45	9,107.67	0.49	119	23,107.38	0.51	0.936 (0.645 - 1.358)	0.7268

Table 49. Sensitivity analysis – Patients receiving 20mg Rivaroxaban only: Secondary endpoints – Multivariate analysis

Description	Rivaroxaban patients N=9,539			Phenprocoumon patients N=20,513			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	229	9,025.96	2.54	475	22,905.69	2.07	0.975 (0.812 - 1.171)	0.7842
Systemic embolism (SE) (effectiveness)	37	9,107.32	0.41	69	23,122.93	0.30	1.043 (0.653 - 1.666)	0.8606
Transient ischemic attack (TIA) (effectiveness)	61	9,081.95	0.67	102	23,069.32	0.44	1.308 (0.909 - 1.880)	0.1479
Subarachnoid hemorrhage (safety)	5	9,116.32	0.05	21	23,138.06	0.09	0.634 (0.224 - 1.796)	0.3913
Intracerebral hemorrhage (safety)	35	9,110.39	0.38	79	23,127.94	0.34	1.095 (0.705 - 1.701)	0.6847

Other and unspecified nontraumatic intracranial hemorrhage (safety)	7	9,116.3	0.08	31	23,128.3	0.13	0.640 (0.280 - 1.461)	0.2895
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	278	8,995.31	3.09	523	22,848.33	2.29	1.043 (0.879 - 1.237)	0.6278

Table 50. Characteristics of patients with Rivaroxaban 15mg

Characteristics	**Rivaroxaban patients (15mg) N=3,616**
Age	79.35 ± 9.09
Number of hospitalizations	1.40 ± 1.35
Number of unique medications	9.86 ± 5.28
CHA2DS2 VASc score	4.52 ± 1.65
CHADS2 score	2.84 ± 1.36
Charlson Comorbidity Index (CCI)	3.16 ± 2.38
Comorbidity Index (modified Charlson Comorbidity Index)	2.47 ± 2.03
Bleeding history (modified HAS BLED score)	3.03 ± 1.16
Gender	
Female	60.40%
Male	39.60%
Insurance status	
Family insured	1.80%
Regular insurance	6.64%
Retired	91.57%

Unknown	0.00%
Interaction with co-medications - Boost	
Boost (yes)	36.75%
Boost (no)	63.25%
Interaction with co-medications - Attenuation	
Attenuation (yes)	0.50%
Attenuation (no)	99.50%
Comorbidities	
Myocardial infarction	6.86%
Chronic renal insufficiency	31.36%
Chronic renal insufficiency stage I	1.24%
Chronic renal insufficiency stage II	6.39%
Chronic renal insufficiency stage III	20.74%
Chronic renal insufficiency stage IV	3.48%
Chronic renal insufficiency stage V	0.19%
Other chronic renal insufficiency	3.32%
Unspecified chronic renal insufficiency	4.78%
Diabetes	39.46%
Hypertension	87.61%
Congestive heart failure	43.94%
Atherosclerosis of arteries of extremities	7.19%
Ischemic stroke or TIA during baseline	16.48%
Coronary heart disease	43.50%
Mild liver disease	12.64%
Moderate or severe liver disease	0.47%
Depression	20.60%
Somatoform disorder	8.77%

Anxiety disorder	4.56%
Dementia	15.46%
Cancer	0%
Obesity	20.24%
Prescriptions	
Proton-pump-inhibitors	48.37%
Antiplatelet medication	32.69%
Acetylsalicylic acid (ASS)	25.66%
Non-steroidal antiinflammatory drugs (NSAIDs)	34.32%
Interventions	
Coronary angioplasty	3.73%
Other	
Smoking	3.82%
Alcohol abuse	2.60%
Substance abuse	0.83%

10.4.3.2 Sensitivity Analysis 2 Results – Patients without any events from the combined endpoints

A separate analysis was conducted where patients with any of the events defined in the combined endpoints (see Table 6) within the baseline period [inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis (verified or condition after): 4 quarters before and index quarter] were excluded from the analyses.

The results for propensity score matching and the multivariate analysis are reported in the following tables.

Table 51. Sensitivity analysis – Number of included patients without any combined endpoint events in the baseline period

	Rivaroxaban	Phenprocoumon
Sensitivity analysis		
Total remained without events within the baseline period (inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis (verified or condition after): 4 quarters before and index quarter)	11,138	17,393

Table 52. Sensitivity analysis – Patients without any combined endpoint events: Primary endpoints before matching

Description	Rivaroxaban patients N=11,138			Phenprocoumon patients N=17,393			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	110	11,092.49	0.99	209	19,848.34	1.05	0.919 (0.729 - 1.158)	0.4723
Intracranial hemorrhage (ICH) (safety)	41	11,144.22	0.37	81	19,923.13	0.41	0.883 (0.606 - 1.286)	0.5157

Table 53. Sensitivity analysis – Patients without any combined endpoint events: Secondary endpoints before matching

Description	Rivaroxaban patients N=11,138			Phenprocoumon patients N=17,393			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	142	11,085.26	1.28	282	19,822.75	1.42	0.877 (0.717 - 1.074)	0.2048
Systemic embolism (SE) (effectiveness)	34	11,134.88	0.31	54	19,935.62	0.27	1.115 (0.725 - 1.715)	0.6204

Transient ischemic attack (TIA) (effectiveness)	45	11,121.65	0.4	47	19,917.17	0.24	1.632 (1.084 - 2.457)	0.019
Subarachnoid hemorrhage (safety)	5	11,149.69	0.04	16	19,943.84	0.08	0.531 (0.194 - 1.449)	0.2164
Intracerebral hemorrhage (safety)	27	11,149.28	0.24	55	19,939.44	0.28	0.859 (0.541 - 1.363)	0.5185
Other and unspecified nontraumatic intracranial hemorrhage (safety)	11	11,150.92	0.10	20	19,936.59	0.10	0.959 (0.459 - 2.005)	0.9108
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	183	11,046.45	1.66	299	19,802.61	1.51	1.070 (0.890 - 1.287)	0.4705

Table 54. Sensitivity analysis – Patients without any combined endpoint events: Primary endpoints after matching

Description	Rivaroxaban patients N=9,500			Phenprocoumon patients N=9,500			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	93	9,625.4	0.97	105	10,831.49	0.97	0.978 (0.739 - 1.294)	0.8762
Intracranial hemorrhage (ICH) (safety)	36	9,669.66	0.37	38	10,869.93	0.35	1.028 (0.651 - 1.621)	0.9072

Table 55. Sensitivity analysis – Patients without any combined endpoint events: Secondary endpoints after matching

Description	Rivaroxaban patients N=9,500			Phenprocoumon patients N=9,500			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	121	9,619.36	1.26	139	10,816.66	1.29	0.954 (0.747 - 1.218)	0.7054
Systemic embolism (SE) (effectiveness)	29	9,662.15	0.30	26	10,876.68	0.24	1.265 (0.742 - 2.155)	0.3881
Transient ischemic attack (TIA) (effectiveness)	39	9,651.25	0.40	19	10,869.82	0.17	2.233 (1.290 - 3.866)	0.0041
Subarachnoid hemorrhage (safety)	5	9,673.93	0.05	8	10,881.73	0.07	0.677 (0.221 - 2.069)	0.4932
Intracerebral hemorrhage (safety)	22	9,674.72	0.23	22	10,878.56	0.20	1.086 (0.601 - 1.963)	0.7834
Other and unspecified nontraumatic intracranial hemorrhage (safety)	11	9,675.17	0.11	12	10,875.96	0.11	0.991 (0.437 - 2.247)	0.9828
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	157	9,586.91	1.64	147	10,810.06	1.36	1.186 (0.946 - 1.486)	0.1389

Table 56. Sensitivity analysis – Patients without any combined endpoint events: Primary endpoints – Multivariate analysis

Description	Rivaroxaban patients N=11,138			Phenprocoumon patients N=17,393			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	110	11,092.49	0.99	209	19,848.34	1.05	0.920 (0.716 - 1.181)	0.5118
Intracranial hemorrhage (ICH) (safety)	41	11,144.22	0.37	81	19,923.13	0.41	0.955 (0.637 - 1.432)	0.8248

Table 57. Sensitivity analysis – Patients without any combined endpoint events: Secondary endpoints – Multivariate analysis

Description	Rivaroxaban patients N=11,138			Phenprocoumon patients N=17,393			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	142	11,085.26	1.28	282	19,822.75	1.42	0.891 (0.716 - 1.108)	0.2993
Systemic embolism (SE) (effectiveness)	34	11,134.88	0.31	54	19,935.62	0.27	1.007 (0.630 - 1.611)	0.9757
Transient ischemic attack (TIA) (effectiveness)	45	11,121.65	0.40	47	19,917.17	0.24	1.608 (1.022 - 2.530)	0.04
Subarachnoid hemorrhage (safety)	5	11,149.69	0.04	16	19,943.84	0.08	0.631 (0.214 - 1.862)	0.4045
Intracerebral hemorrhage (safety)	27	11,149.28	0.24	55	19,939.44	0.28	1.020 (0.620 - 1.680)	0.9372

Other and unspecified nontraumatic intracranial hemorrhage (safety)	11	11,150.92	0.10	20	19,936.59	0.10	0.861 (0.392 - 1.891)	0.7092
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemich attack (TIA))	183	11,046.45	1.66	299	19,802.61	1.51	1.052 (0.861 - 1.286)	0.6182

10.4.3.3 Sensitivity Analysis 3 Results – Patients with cancer

A separate analysis was conducted where patients with evidence of cancer (ICD-10-GM codes C00-C97) (see Table 79) in the baseline period [(inpatient diagnosis: 4 quarters before and index quarter up to index date – outpatient diagnosis: 4 quarters before and index quarter) in addition “condition after diagnosis” for outpatient diagnoses (4 quarters before and index quarter)] were included in the study population.

The results for propensity score matching and the multivariate analysis are reported in the following tables.

Table 58. Sensitivity analysis – Number of included cancer patients

	Rivaroxaban	**Phenprocoumon**
Sensitivity analysis		
Total remained after including cancer patients	17,236	27,004

Table 59. Sensitivity analysis – Patients with cancer: Primary endpoints before matching

Description	Rivaroxaban patients N=17,236			Phenprocoumon patients N=27,004			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	329	17,151.29	1.92	506	30,113.14	1.68	1.118 (0.973 - 1.285)	0.1157
Intracranial hemorrhage (ICH) (safety)	98	17,324.62	0.57	178	30,329.53	0.59	0.940 (0.734 - 1.203)	0.6217

Table 60. Sensitivity analysis – Patients with cancer: Secondary endpoints before matching

Description	Rivaroxaban patients N=17,236			Phenprocoumon patients N=27,004			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	409	17,121.22	2.39	661	30,054.35	2.20	1.063 (0.939 - 1.203)	0.3347
Systemic embolism (SE) (effectiveness)	78	17,312.65	0.45	109	30,355.89	0.36	1.225 (0.915 - 1.639)	0.1727
Transient ischemic attack (TIA) (effectiveness)	104	17,289.58	0.60	142	30,292.09	0.47	1.250 (0.970 - 1.610)	0.0852
Subarachnoid hemorrhage (safety)	11	17,351.94	0.06	27	30,383.79	0.09	0.685 (0.339 - 1.381)	0.2897
Intracerebral hemorrhage (safety)	67	17,339.68	0.39	120	30,361.46	0.40	0.948 (0.703 - 1.278)	0.7247
Other and unspecified	26	17,346.28	0.15	47	30,366.71	0.15	0.959 (0.593 -	0.8635

nontraumatic intracranial hemorrhage (safety)							1.550)	
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	489	17,049.01	2.87	727	29,985.91	2.42	1.157 (1.031 - 1.298)	0.0131

Table 61. Sensitivity analysis – Patients with cancer: Primary endpoints after matching

Description	Rivaroxaban patients N=14,961			Phenprocoumon patients N=14,961			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Ischemic stroke (effectiveness)	285	15,001.46	1.90	279	16,512.18	1.69	1.111 (0.941 - 1.311)	0.2132
Intracranial hemorrhage (ICH) (safety)	89	15,155.02	0.59	87	16,634.16	0.52	1.094 (0.814 - 1.471)	0.5516

Table 62. Sensitivity analysis – Patients with cancer: Secondary endpoints after matching

Description	Rivaroxaban patients N=14,961			Phenprocoumon patients N=14,961			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	357	14,975.66	2.38	355	16,481.91	2.15	1.090 (0.940 - 1.263)	0.2531
Systemic embolism (SE)	63	15,143.55	0.42	65	16,640.87	0.39	1.050 (0.742 -	0.7831

(effectiveness)							1.487)	
Transient ischemic attack (TIA) (effectiveness)	95	15,119.89	0.63	64	16,621.48	0.39	1.624 (1.181 - 2.233)	0.0028
Subarachnoid hemorrhage (safety)	10	15,177.17	0.07	15	16,661.13	0.09	0.708 (0.318 - 1.577)	0.3986
Intracerebral hemorrhage (safety)	63	15,167.08	0.42	53	16,650.95	0.32	1.257 (0.872 - 1.812)	0.2209
Other and unspecified nontraumatic intracranial hemorrhage (safety)	22	15,174.5	0.14	27	16,652.29	0.16	0.893 (0.508 - 1.572)	0.6956
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	421	14,909.94	2.82	391	16,447.41	2.38	1.174 (1.022 - 1.348)	0.0231

Table 63. Sensitivity analysis – Patients with cancer: Primary endpoints – Multivariate analysis

Description	**Rivaroxaban patients N=17,236**			**Phenprocoumon patients N=27,004**			**HR (95% CI)**	**p-value**
	No. of events	**Person-years of follow up**	**Events/100 person-years**	**No. of events**	**Person-years of follow up**	**Events/100 person-years**		
Ischemic stroke (effectiveness)	329	17,151.29	1.92	506	30,113.14	1.68	0.982 (0.844 - 1.141)	0.8089
Intracranial hemorrhage (ICH) (safety)	98	17,324.62	0.57	178	30,329.53	0.59	0.898 (0.689 - 1.170)	0.4259

Table 64. Sensitivity analysis – Patients with cancer: Secondary endpoints – Multivariate analysis

Description	Rivaroxaban patients N=17,236			Phenprocoumon patients N=27,004			HR (95% CI)	p-value
	No. of events	Person-years of follow up	Events/100 person-years	No. of events	Person-years of follow up	Events/100 person-years		
Composite endpoint cerebral benefit (Ischemic stroke and Intracranial hemorrhage (ICH))	409	17,121.22	2.39	661	30,054.35	2.20	0.952 (0.833 - 1.088)	0.4688
Systemic embolism (SE) (effectiveness)	78	17,312.65	0.45	109	30,355.89	0.36	1.133 (0.826 - 1.554)	0.4389
Transient ischemic attack (TIA) (effectiveness)	104	17,289.58	0.60	142	30,292.09	0.47	1.208 (0.916 - 1.593)	0.1799
Subarachnoid hemorrhage (safety)	11	17,351.94	0.06	27	30,383.79	0.09	0.721 (0.341 - 1.526)	0.3927
Intracerebral hemorrhage (safety)	67	17,339.68	0.39	120	30,361.46	0.40	0.930 (0.675 - 1.283)	0.6588
Other and unspecified nontraumatic intracranial hemorrhage (safety)	26	17,346.28	0.15	47	30,366.71	0.15	0.894 (0.532 - 1.499)	0.6699
Composite endpoint effectiveness (Ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA))	489	17,049.01	2.87	727	29,985.91	2.42	1.038 (0.916 - 1.175)	0.5596

10.5 Other Analyses – renal impaired subanalysis with new data cut

Table 65. Patient characteristics: new definition of renal impaired, new data cut Jan 2012-December2016: Rivaroxaban 15mg and 20mg, cancer patients excluded

Characteristics	Rivaroxaban (N= 4164)	Phenprocoumon (N= 7002)
Age	76,89 ± 9,42	77,16 ± 8,43
Number of hospitalizations	1,6 ± 1,42	1,53 ± 1,37
Number of unique medications	10,55 ± 5,50	10,91 ± 5,40
CHA2DS2 VASc Score	4,43 ± 1,72	4,53 ± 1,60
CHADS2 Score	2,86 ± 1,36	2,91 ± 1,29
Charlson Comorbidity Index (CCI)	4,09 ± 2,33	4,2 ± 2,28
Comorbidity Index (modified Charlson Comorbidity Index)	3,04 ± 2,03	2,99 ± 1,93
Bleeding history (modified HAS BLED Score)	3,37 ± 1,14	3,44 ± 1,08
Sex		
female	52,26%	49,23%
male	47,74%	50,77%
Insurance status		
family insured	1,71%	1,64%
regular insurance	9,85%	6,84%
retired	88,45%	91,50%
unknown	0,00%	0,01%
Interaction with co-medications - Boost		
Boost (yes)	37,25%	40,07%
Boost (no)	62,75%	59,93%
Interaction with co-medications - Attenuation		
Attenuation (yes)	0,53%	0,54%
Attenuation (no)	99,47%	99,46%
Comorbidities		

Myocardial infarction	7,61%	11,57%
Chronic renal insufficiency	57,28%	62,07%
Chronic renal insufficiency stage I	2,93%	2,34%
Chronic renal insufficiency stage II	15,87%	14,25%
Chronic renal insufficiency stage III	33,38%	37,92%
Chronic renal insufficiency stage IV	4,63%	8,60%
Chronic renal insufficiency stage V	0,31%	1,14%
Other chronic renal insufficiency	6,08%	7,37%
Unspecified chronic renal insufficiency	7,68%	10,63%
Cancer	0,00%	0,00%
Diabetes	47,05%	48,60%
Hypertension	91,35%	93,02%
Congestive heart failure	49,38%	51,13%
Atherosclerosis of arteries of extremities	8,84%	10,64%
Ischemic stroke or TIA during baseline	14,75%	13,82%
Coronary heart disease	46,88%	54,71%
Mild liver disease	16,35%	16,54%
Moderate or severe liver disease	0,53%	0,59%
Depresion	21,04%	19,39%
Somatoform disorder	9,68%	8,57%
Anxiety disorder	5,24%	4,23%
Dementia	14,58%	9,48%
Obesity	28,46%	29,33%
Prescriptions		
Proton-pump-inhibitors	51,71%	51,57%
Antiplatelet medication	33,26%	35,28%
Acetylsalicylic acid (ASS)	26,32%	27,38%

Non-steroidal antiinflammatory drugs (NSAIDs)	36,72%	36,25%
Interventions		
Coronary angioplasty	3,63%	9,10%
Other		
Smoking	5,19%	4,96%
Alcohol abuse	2,55%	2,13%
Substance abuse	0,96%	1,00%

Table 66. Patient characteristics: new definition of renal impaired, new data cut Jan 2012-Dec 2016: Rivaroxaban 15mg only, cancer patients included

Characteristics	Rivaroxaban 15mg (N= 2786)	Phenprocoumon (N= 9871)
Age	80,75 ± 7,61	77,67 ± 8,07
Number of hospitalizations	1,79 ± 1,57	1,61 ± 1,47
Number of unique medications	11,69 ± 5,49	11,10 ± 5,43
CHA2DS2 VASc Score	4,90 ± 1,54	4,52 ± 1,57
CHADS2 Score	3,21 ± 1,28	2,92 ± 1,28
Charlson Comorbidity Index (CCI)	5,07 ± 2,61	4,66 ± 2,55
Comorbidity Index (modified Charlson Comorbidity Index)	3,90 ± 2,35	3,43 ± 2,23
Bleeding history (modified HAS BLED Score)	3,62 ± 1,07	3,46 ± 1,07
Sex		
female	54,99%	45,86%
male	45,01%	54,14%
Insurance status		
family insured	1,26%	1,49%
regular insurance	3,84%	6,01%
retired	94,90%	92,49%

unknown	0,00%	0,01%
Interaction with co-medications - Boost		
Boost (yes)	39,95%	40,44%
Boost (no)	60,05%	59,56%
Interaction with co-medications - Attenuation		
Attenuation (yes)	0,61%	0,53%
Attenuation (no)	99,39%	99,47%
Cancer		
C00-C14	0,36%	0,41%
C15-C26	3,55%	3,52%
C30-C39	1,33%	0,86%
C40-C41	0,04%	0,06%
C43-C44	5,74%	5,45%
C45-C49	0,07%	0,23%
C50-C63	7.75%	7,63%
C64-C68	3,37%	3,71%
C69-C72	0,22%	0,09%
C73-C75	0,43%	0,26%
C76-C80	2,87%	2,22%
C81-C96	1,97%	1,95%
C97	0,29%	0,19%
Comorbidities		
Myocardial infarction	8,08%	11,25%
Chronic renal insufficiency	68,95%	62,51%
Chronic renal insufficiency stage I	3,02%	2,56%
Chronic renal insufficiency stage II	15,22%	14,58%
Chronic renal insufficiency stage III	45,48%	37,75%

Chronic renal insufficiency stage IV	7,50%	8,93%
Chronic renal insufficiency stage V	0,32%	1,15%
Other chronic renal insufficiency	8,26%	8,03%
Unspecified chronic renal insufficiency	10,70%	11,32%
Diabetes	49,89%	47,76%
Hypertension	92,53%	93,13%
Congestive heart failure	56,82%	50,45%
Atherosclerosis of arteries of extremities	11,02%	10,56%
Ischemic stroke or TIA during baseline	16,62%	13,52%
Coronary heart disease	52,05%	55,54%
Mild liver disease	16,26%	16,66%
Moderate or severe liver disease	0,65%	0,60%
Depresion	22,51%	19,42%
Somatoform disorder	9,55%	9,00%
Anxiety disorder	4,81%	4,60%
Dementia	18,02%	8,98%
Obesity	24,95%	28,01%
Prescriptions		
Proton-pump-inhibitors	56,82%	51,75%
Antiplatelet medication	38,23%	35,51%
Acetylsalicylic acid (ASS)	30,29%	27,68%
Non-steroidal antiinflammatory drugs (NSAIDs)	34,71%	36,02%
Interventions		
Coronary angioplasty	4,49%	9,02%
Other		
Smoking	3,98%	4,90%
Alcohol abuse	2,12%	2,07%

Substance abuse	1,01%	1,05%

Table 67. Sensitivity analysis: new definition of renal impaired, new data cut Jan 2012-Dec 2016: Primary endpoints – Rivaroxaban 15mg and 20mg, Multivariate Analysis, cancer patients exlcuded

Description	Rivaroxaban patients N=4,164				Phenprocoumon patients N=7,002				HR (95% CI)	p-value
	No. of events	Person-years of follow up		Events/100 person-years	No. of events	Person-years of follow up		Events/100 person-years		
		Mean	Median			Mean	Median			
Exposure Time of VKA with 1 tablet per day (3mg)										
Ischemic stroke (effectiveness)	104	380,82	275	2,4	149	221,29	148	3,51	0,715 (0,545 - 0,937)	0,0149
Intracranial hemorrhage (ICH) (safety)	25	386,98	281	0,57	38	222,46	149	0,89	0,662 (0,384 - 1,143)	0,1391
Combined endpoint cerebral benefit: stroke and ICH	125	380,38	275	2,88	184	220,95	147	4,35	0,689 (0,539 - 0,880)	0,0029
Exposure Time of VKA with eDDD										
Ischemic stroke (effectiveness)	104	380,82	275	2,4	198	419,15	313	2,47	0,857 (0,671 - 1,094)	0,2156
Intracranial hemorrhage (ICH) (safety)	25	386,98	281	0,57	67	424,45	318,6	0,82	0,588 (0,367 - 0,943)	0,0276
Combined endpoint cerebral benefit: stroke and ICH	125	380,38	275	2,88	254	418,35	311,33	3,17	0,797 (0,640 - 0,994)	0,0443

Table 68. Sensitivity analysis: new definition of renal impaired, new data cut Jan 2012-Dec 2016: Primary endpoints – Rivaroxaban 15mg and 20mg, Multivariate Analysis, cancer patients included

Description	Rivaroxaban patients N=5,878			Phenprocoumon patients N=9,871			HR (95% CI)	p-value
	No. of	Person-years of	Events/100	No. of	Person-years of	Events/100		

	events	follow up		person-years	events	follow up		person-years		
		Mean	**Median**			**Mean**	**Median**			
Exposure Time of VKA with 1 tablet per day (3mg)										
Ischemic stroke (effectiveness)	168	377,33	269	2,77	201	219,56	148	3,39	0,844 (0,677 - 1,052)	0,1313
Intracranial hemorrhage (ICH) (safety)	39	384,06	278,5	0,63	59	220,82	149	0,99	0,665 (0,430 - 1,029)	0,0667
Combined endpoint cerebral benefit: stroke and ICH	201	376,37	269	3,32	255	219,21	148	4,31	0,793 (0,650 - 0,968)	0,0226
Exposure Time of VKA with eDDD										
Ischemic stroke (effectiveness)	168	377,33	269	2,77	276	415,4	308	2,46	0,983 (0,807 - 1,197)	0,8667
Intracranial hemorrhage (ICH) (safety)	39	384,06	278,5	0,63	98	420,54	312	0,86	0,666 (0,455 - 0,974)	0,0363
Combined endpoint cerebral benefit: stroke and ICH	201	376,37	269	3,32	357	414,5	306,62	3,19	0,917 (0,768 - 1,095)	0,3399

Table 69. Sensitivity analysis: new definition of renal impaired, new data cut Jan 2012-December 2016: Primary endpoints – Rivaroxaban 15mg only, Multivariate Analysis, cancer patients included

Description	**Rivaroxaban patients N=1,954**				**Phenprocoumon patients N=3,871**				**HR (95% CI)**	**p-value**
	No. of events	**Person-years of follow up**		**Events/100 person-years**	**No. of events**	**Person-years of follow up**		**Events/100 person-years**		
		Mean	**Median**			**Mean**	**Median**			
Exposure Time of VKA with 1 tablet per day (3mg)										
Ischemic stroke (effectiveness)	90	347,27	238,5	3,4	201	219,56	148	3,39	0,838 (0,636 - 1,104)	0,2086
Intracranial hemorrhage (ICH) (safety)	21	354,76	247	0,78	59	220,82	149	0,99	0,609 (0,351 - 1,057)	0,0781

Combined endpoint cerebral benefit: stroke and ICH	108	346,96	238	4,08	255	219,21	148	4,31	0,782 (0,609 - 1,003)	0,0524
Exposure Time of VKA with eDDD										
Ischemic stroke (effectiveness)	90	347,27	238,5	3,4	276	415,4	308	2,46	1,015 (0,790 - 1,305)	0,9053
Intracranial hemorrhage (ICH) (safety)	21	354,76	247	0,78	98	420,54	312	0,86	0,637 (0,389 - 1,044)	0,0737
Combined endpoint cerebral benefit: stroke and ICH	108	346,96	238	4,08	357	414,5	306,62	3,19	0,932 (0,743 - 1,169)	0,5411

10.6 Adverse Events/Adverse Reactions

Not applicable.

11. Discussion

11.1 Key Results

The aim of this study was 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.

Patients characteristics before matching:

- In total, 13,155 patients initiating treatment with Rivaroxaban and 20,513 patients initiating treatment with Phenprocoumon met the specified inclusion and exclusion criteria.
- 83.4% of the Phenprocoumon patients were above the age of 64, whereas patients initiating treatment with Rivaroxaban were slightly younger, 75.0% were above the age of 64.
- Mean age was 71.8 years in the Rivaroxaban and 73.8 years in the Phenprocoumon group.
- The assessment of type of AF diagnosis showed that most Rivaroxaban and Phenprocoumon patients either had a paroxysmal (54.7% vs. 39.4%) or persistent (43.0% vs. 60.7%) type of AF.
- The mean $CHADS_2$ risk score before matching was slightly higher in the Phenprocoumon group than in the Rivaroxaban group (2.31 vs. 2.16).
- Similarly, the mean CHA_2DS_2-VASC risk score before matching was higher for patients initiating treatment with Phenprocoumon in comparison to Rivaroxaban (3.78 vs. 3.49).
- The analysis of all-cause hospitalizations in the baseline period showed that 74.2% of the Rivaroxaban patients and 70.4% of the Phenprocoumon patients were hospitalized. Mean number of hospitalizations was slightly higher for the Rivaroxaban group with 1.21 vs. 1.16,

whereas the mean duration of hospitalization was 16.1 and 17.1 days for the Rivaroxaban patients and the Phenprocoumon patients, respectively.

- The analysis of co-medications in the baseline period showed that beta-blockers were the most frequently prescribed co-medications in both groups (Rivaroxaban 55.1% vs. Phenprocoumon 59.7%), followed by prescriptions for ACE-inhibitors (Rivaroxaban 41.4% vs. Phenprocoumon 48.4%).

Primary objective:

The primary objective of this study was 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. The events were defined as hospitalizations with the respective ICD-10-GM diagnosis.
To assess the primary objective, propensity score matching, multivariate regression analysis, and IPTW were performed.

- Before matching, the HR for ischemic stroke and intracranial hemorrhage were 1.068 (95% CI 0.906-1.258, p=0.4344) and 0.935 (95% CI 0.692-1.264, p=0.6633), respectively.
- Furthermore, before matching, the primary endpoint ischemic stroke per 100 person-years was higher in the Rivaroxaban group (1.76 vs. 1.62) and intracranial hemorrhage was higher in the Phenprocoumon group (0.51 vs. 0.49).
- After propensity score matching, 11,353 patients remained in each treatment group.
- Mean age was 72.7 years in the Rivaroxaban and 72.8 years in the Phenprocoumon group and most Rivaroxaban and Phenprocoumon patients either had a paroxysmal (54.0% vs. 39.9%) or persistent (43.9% vs. 60.3%) type of AF after propensity score matching.
- After PSM, the HR for ischemic stroke and intracranial hemorrhage were 1.013 (95% CI 0.835-1.230, p=0.8935) and 1.091 (0.758-1.571, p=0.6379), respectively.
- The events per 100 person-years for ischemic stroke were slightly higher in the Rivaroxaban group (1.74 vs. 1.69). When comparing the events per 100 person-years of intracranial hemorrhage, Rivaroxaban patients had a higher event rate than the Phenprocoumon patients (0.51 vs. 0.45).
- When assessing the primary endpoints by multivariate analysis, the Rivaroxaban patients had a lower chance for ischemic stroke (HR 0.930; 95% CI 0.779-1.111, p=0.4293) as well as for intracranial hemorrhage (HR 0.881; 95% CI 0.637-1.219, p=0.4459).
- The assessment of the primary endpoints by IPTW showed a higher chance of ischemic stroke for Rivaroxaban patients (HR 1.020; 95% CI 0.868-1.199, p=0.8077). The chance of intracranial hemorrhage was lower for Rivaroxaban patients (HR 0.852; 95% CI 0.626-1.161, p=0.3105).

Secondary objectives:

The secondary objectives of this study were to assess the cerebral benefit in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon. The combined endpoint was defined as hospitalizations with a diagnosis of ischemic stroke and ICH. Furthermore, secondary objective was to assess 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 composite event was defined

as the occurrence of a hospitalization with a diagnoses of ischemic stroke and systemic embolism and TIA.
To assess the secondary objectives, propensity score matching, multivariate analysis, and the IPTW were performed.

- Before matching, the HR of the composite endpoint cerebral benefit was 1.023 (95% CI 0.883-1.185, p=0.7635) and for the composite endpoint effectiveness 1.122 (95% CI 0.979-1.286, p=0.0975).
- Furthermore, before matching, the events per 100 person-years were slightly higher in the Rivaroxaban group for the composite endpoint cerebral benefit (2.17 vs. 2.07) and higher for the composite endpoint effectiveness (2.63 vs. 2.29).
- After PSM, the HR for the composite endpoint cerebral benefit was 1.008 (95% CI 0.847-1.200, p=0.9262) and 1.095 (0.930-1.288, p=0.2757) for effectiveness.
- The events per 100 person-years for the cerebral benefit were slightly higher in the Rivaroxaban group (2.15 vs. 2.10) and higher for the composite endpoint effectiveness (2.57 vs. 2.30).
- When assessing the secondary endpoints by multivariate analysis, the risk for the composite cerebral benefit for Rivaroxaban patients was lower (HR 0.905; 95% CI 0.772-1.061, p=0.2194), and the HR of the endpoint effectiveness was 0.994 (95% CI 0.858-1.153, p=0.9407).
- The assessment of the secondary endpoints by IPTW showed a lower composite effectiveness for Rivaroxaban patients (HR 1.041; 95% CI 0.908-1.193, p=0.5635) and a slightly higher benefit for the endpoint cerebral benefit (HR 0.967; 95% CI 0.836-1.118, p=0.6498).

Sensitivity analyses:

A sensitivity analysis was conducted, where only patients diagnosed with renal impairment were included. 1954 Rivaroxaban patients were compared with 3871 Phenprocoumon patients.

The mean follow-up time for the primary effectiveness endpoint in this analysis using the empirical defined daily dose was 346 days for Rivaroxaban patients and 367 days for Phenprocoumon patients.

The mean follow-up time for the primary effectiveness endpoint in this analysis using the 1 tablet per day (3mg) definition for Phenprocoumon was 367 days for Rivaroxaban patients and 203 days for Phenprocoumon patients.

The unadjusted incidence rate for the primary effectiveness endpoint ischemic stroke was 2.60 per 100 person years and for primary safety endpoint intracranial hemorrhage 0.53 per 100 person years in the Rivaroxaban group.

The unadjusted incidence rate for the primary effectiveness endpoint ischemic stroke was 2.98 per 100 person years and for primary safety endpoint intracranial hemorrhage 0.71 per 100 person years in the Phenprocoumon group.

Results of primary endpoints in this analysis was consistent across different models. Results showed a strong trend towards lower risks for Rivaroxaban for both, ischemic stroke and intracranial hemorrhage, although results were statistically not significant.

Further sensitivity analyses were conducted for 20mg Rivaroxaban initiators (sensitivity analysis 1), patients without any events from the combined endpoints (sensitivity analysis 2) and including cancer patients (sensitivity analysis 3). Results in these sensitivity analyses were consistent with overall findings.

Other analyses:

As a further exploratory analysis a more recent data cut of the underlying data source was used to additionally look into a renal subgroup population. With the inclusion of additional data, collected up to December 2016, a total of 4164 patients with renal impairment were prescribed rivaroxaban and 7002 were prescribed phenprocoumon.

Patients with renal impairment prescribed rivaroxaban or phenprocoumon were of similar age (76.9 years and 77.2 years, respectively), had similar CHA_2DS_2-VASc (4.4 and 4.5, respectively) and $CHADS_2$ (2.9 in both groups) scores, and received similar baseline medication.

When using the ‘one tablet per day’ definition to estimate drug exposure times for phenprocoumon, the mean follow-up for the primary effectiveness outcome in this analysis was 381 days (rivaroxaban) and 221 days (phenprocoumon).

The risk of the combined endpoint (Figure 3) was lower in patients prescribed rivaroxaban compared with those prescribed phenprocoumon (2.88%/year vs 4.35%/year, respectively; adjusted HR=0.69; 95% CI 0.54–0.88; p=0.0029)

The risk of the primary effectiveness outcome was significantly different between patient groups 2.40%/year in patients prescribed rivaroxaban vs 3.51%/year in patients prescribed phenprocoumon; adjusted HR=0.72; 95% CI 0.55–0.94; p=0.0149)

The risk of the primary safety outcome was lower, but not significantly different, in patients prescribed rivaroxaban compared with patients prescribed phenprocoumon (0.57%/year vs 0.89%/year, respectively; adjusted HR=0.66; 95% CI 0.38–1.14; p=0.139)

When using the eDDD definition of drug exposure time, the mean follow-up for the primary effectiveness outcome was 381 days for patients prescribed rivaroxaban and 419 days for patients prescribed phenprocoumon

All HRs showed a similarly consistent protective effect for rivaroxaban compared with phenprocoumon. A separate analysis was conducted, limiting the rivaroxaban group only to patients receiving the 15 mg od dose (Figure 4)

Despite the reduced statistical power, results were generally consistent.

11.2 Limitations

Claims data analyses can be appropriate tools for the assessment of pharmaceutical-use due to the recording of prescription data independently of any study purposes and due to the large panels of prescribers and associated population coverage. The HRI database includes patient characteristics such as age, gender, major diagnoses, and prescription records and is thus appropriate 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. However, the following limitations need to be mentioned:

A general limitation of this study includes the inability of claims data to observe the actual intake and dose of medications. This study assumed that patients always take the medications according to prescription. The analyses are therefore based on assumptions about the behaviour of the identified patients which in turn might lead to overestimating relevant endpoints. Furthermore, claims data analyses are not able to capture the reasons for switching therapies, such as treatment response, tolerability or physician beliefs.

In German claims data, prescriptions are not necessarily linked to the corresponding diagnosis. Therefore, it might be possible that a substance is prescribed for an indication other than the expected indication if there are several indications. To identify disease specific prescriptions, a claims data specific algorithm has to be applied, requesting, for example, a diagnosis within the same quarter of the prescription.

As the HRI database only includes SHI data, private health insurances data is not represented. As all sickness funds within SHI have the same level of reimbursement and the health insurance contribution is based on the salary, the HRI database selected for Germany is not subject to any selection bias compared to SHI with respect to access conditions.

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.

In Germany, outpatient data are only delivered on a quarterly basis. Date of diagnosis is not available, only the quarter of diagnosis.

11.3 Generalizability

This real world evidence study describes the characteristics of Rivaroxaban and Phenprocoumon users and the effectiveness of stroke prevention under real-life conditions and for the whole resource utilization reimbursed by the Statutory Health Insurance system in Germany.

Automated databases can be appropriate tools for drug-use studies due to the recording of diagnosis and prescription data independently of any study purposes. All patients were included who had at least one incident prescription of Rivaroxaban or Phenprocoumon within the study inclusion period spanning from January 1, 2012 to December 31, 2015 and meeting all inclusion and exclusion criteria.

As the data pool is representative in terms of age and gender for the German population (as of 31.12.2013), the results are generalizable to the German population keeping in mind the general limitation of claims data.

12. Other information

Not applicable.

13. Conclusion

Between 2012 and 2015, 13,155 patients initiated treatment with Rivaroxaban and 20,513 patients with Phenprocoumon. Rivaroxaban patients were slightly younger than Phenprocoumon patients (71.8 vs. 73.7 years) and marginally more patients were male in both treatment groups.

Sensitivity analyses for a renal impaired subgroup showed a strong trend towards a protective effect of Rivaroxaban vs. Phenprocoumon. As of the small sample size, there was not enough power to show significance.

As a conclusion, results showed differences depending on how exposure time in Phenprocoumon patients was measured, however results within renal impaired patients showed a consistent trend across all different models towards better effectiveness and safety of Rivaroxaban vs. Phenprocoumon. Further analyses with more recent data cuts are necessary to confirm these findings.

Renal subgroup analysis:
Although patient numbers in this subgroup were low, the results presented here suggest that rivaroxaban is more effective and safer than phenprocoumon in patients with NVAF and renal impairment. The results of this subgroup analysis were generally consistent with the trends observed in the main analysis, showing evidence for the improved effectiveness and safety profile of rivaroxaban versus phenprocoumon in this patient population.

This observation may be ascribed to limitations of claims data, e.g. no clinical parameters, no link between prescriptions and diagnoses, and outpatient diagnoses on a quarterly basis.

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15. Appendices

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	18735 Protocol version identifier	08 December 2016	PRC_OS_Secondary Data_SPAF_v3

Annex 2. List of ICD-10-GM, PZN, OPS, ATC codes

Table 70. 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 71. 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 72. Definition of types of AF

Type of AF	*ICD-10-GM code*
Paroxysmal	I48.0
Persistent	I48.1
Permanent	I48.2
Unknown	I48.9
Transient causes of AF	*ICD-10-GM code*
Other pulmonary heart diseases	I27.-
Intraoperative and postprocedural complications and disorders of circulatory system, not elsewhereclassified	I97.-
Evidence of valvular AF	*OPS code*
Replacement of heart valves by prosthesis	5-351.*
Replacement of heart valves protheses	5-352.*
Heart valvuloplasty	5-353.*
Operations of congential anomalies of heart valves	5-358.*
Minimally invasive operations of heart valves	5-35a.*

Table 73. Definition of primary and secondary outcomes

Outcome parameter	**ICD-10 GM code**	
Primary effectiveness: ischemic stroke	I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9	
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, I26.0, I26.9, I80.1, I80.2, I80.3, I80.9
	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 non-traumatic intracranial hemorrhage (safety)	I62.00, I62.01, I62.02, I62.09, I62.1, I62.9

Table 74. 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/emboli sm	2	2	I61/I63/I64/I 69/I82/G45/I 74/K55.0/N2 8.0/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/peripher al artery disease/aortic plaque)	0	1	I21/I22/I23/I 73	Acute myocardial infarction/ recurrent myocardial infarction/ Certain current complications following myocardial infarction/ Other peripheral vascular diseases
Female gender	0	1	-	

Table 75. 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	C77, C78, C79, C80	6	6
AIDS	B20, B21, B22, B24	6	6

Table 76. 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-GM codes as listed in Table 78
Alcohol use	F10
Non-steroidal anti-inflammatory drug	M01A
Antiplatelet agents	B01AC
Age >65	

Table 77. 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
Pregnancy	O00-O99, Z34, Z35

Table 78. 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 79. Type of cancer

No.	*ICD-10-GM*	*Name*
1	C00-C14	Malignant neoplasms of lip, oral cavity and pharynx
2	C15-C26	Malignant neoplasms of digestive organs
3	C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
4	C40-C41	Malignant neoplasms of bone and articular cartilage
5	C43-C44	Melanoma and other malignant neoplasms of skin
6	C45-C49	Malignant neoplasms of mesothelial and soft tissue
7	C50-C63	Malignant neoplasms of breast, Malignant neoplasms of female genital organs, Malignant neoplasms of male genital organs
8	C64-C68	Malignant neoplasms of urinary tract
9	C69-C72	Malignant neoplasms of eye, brain and other parts of central nervous system
10	C73-C75	Malignant neoplasms of thyroid and other endocrine glands
11	C76-C80	Malignant neoplasms of ill-defined, other secondary and unspecified sites
12	C81-C96	Malignant neoplasms of lymphoid, hematopoietic and related tissue
13	C97	Malignant neoplasms as primary tumors at several sites

Table 80. 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 81. Definition of anticoagulants

Medication	*ATC*
Anticoagulation therapy	
VKA	B01AA
VKA (not including Phenprocoumon)	B01AA01, B01AA02, B01AA03, B01AA07, B01AA08, B01AA09, B01AA10, B01AA11, B01AA12
Phenprocoumon	B01AA04
Dabigatran	B01AE07
Rivaroxaban	B01AF01, B01AX06
Apixaban	B01AF02, B01AX08

Table 82. 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 Phenprocoumon and other medications of interest (other anticoagulants, antiarrhythmics, digitalis, other medications such as diuretics, statins etc.)	ATC/PZN

Annex 3. Signature Pages

- Study Conduct responsible

Signature Page

Study 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)
Product:	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
IMPACT Study Number:	18735
Study Type:	PASS
EU PAS Register Number:	EUPAS15755
Development phase:	Post-Authorization
Sponsor's Name and Address:	Bayer Healthcare AG 51368 Leverkusen, Germany

Function:

Name:

Title:

Address:

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature