Post Authorization Study Information

Acronym/Title	Comparative effectiveness of rivaroxaban and warfarin for stroke prevention in multi-morbid patients with nonvalvular atrial fibrillation (Short title: Rivaroxaban vs warfarin for SPAF in multi-morbid patients)
Protocol version and date	v2.0; 31 Jan, 2019
IMPACT study number	19859
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO N/A
EU PAS register number	N/A
Active substance	BAY 597939, Rivaroxaban Factor Xa Inhibitor
Medicinal product	Xarelto
Comparator / Reference therapy	Vitamin K antagonist
Study Initiator and Funder	Bayer AG
Research question and objectives	The overall goal of this study is to evaluate the comparative safety and effectiveness of rivaroxaban vs. VKA for stroke prevention in patients with NVAF across risk profiles and comorbidities that reflect everyday clinical practice.
Country(-ies) of study	USA
Author	PPD (MetaEvidence, LLC) PPD PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	PPD 13342 Berlin

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

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

1. Table of contents

2. List of abbreviations

AF	Atrial fibrillation
CKD	Chronic kidney disease
ICD	International Classification of Diseases
ICH	Intracranial hemorrhage
NOAC	Non-vitamin K antagonist
NVAF	Nonvalvular atrial fibrillation
N/A	Not applicable
VKA	Vitamin K antagonist

3. Responsible parties

Role: OS Conduct Responsible
Name: PPD
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Role: RWE Strategy & Outcomes Data Generation
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Role: OS Safety Lead
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Role: OS Medical Expert
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Role: Qualified Person responsible for Pharmacovigilance
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Collaborator

Name: PPD
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4. Abstract

Acronym/Title	Comparative effectiveness of rivaroxaban and warfarin for stroke prevention in multi-morbid patients with nonvalvular atrial fibrillation
Rationale and background	The study aims to evaluate the safety and effectiveness of rivaroxaban in multi-morbid patients, such as the elderly and those with renal impairment.
Research question and objectives	The overall goal of this study is to evaluate the comparative safety and effectiveness of rivaroxaban vs. vitamin K antagonist (VKA) for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) across risk profiles and comorbidities that reflect everyday clinical practice. The primary objective in this study is to evaluate the combined end point of stroke or systemic embolism (SSE), and major bleeding in NVAF patients treated with rivaroxaban vs. VKA.
Study design	A cohort study using administrative claims data will be conducted.
Population	The source population of this study will be all the insured individuals included in the Truven Health MarketScan Commercial Claims and Medicare Supplemental Databases. The study time frame will span January 1, 2011 to December 31, 2017 (or until the most recent available data). The day of the first qualifying oral anticoagulant (rivaroxaban or VKA) dispensing will constitute the index date. To be included in this study patients would have to have ≥365 days of continuous medical and prescription coverage before initiation of oral anticoagulation (which serves as the study's baseline period).
Variables	The study cohort will comprise two groups of patients: those who initiated OAC treatment with rivaroxaban and those who initiated with VKA. Patients will be followed until the first occurrence of an outcome event, switch or discontinuation of oral anticoagulant therapy, leaving the insurance plan or end of study follow-up (an on-treatment approach). Similar to assessment of patient characteristics, subgroups will be defined using data over the baseline period. Subgroups (risk profiles and comorbidities) will primarily be

	assessed using one-dimensional measures. Additionally, the strength of this research is in assessing the renally impaired and frail patients, both of which will be assessment using robust algorithms that have been validated against clinical measures.
Data sources	The Truven MarketScan data come from a selection of large employers, health plans, and government and public organizations and contain claims from approximately 100 employers, health plans, and government and public organizations representing about 170 million covered lives across all age groups, including retirees with Medicare supplemental insurance.
Study size	Preliminary estimates yielded a cohort of over 75,000 OAC-naive patients with an NVAF diagnosis for the period 2012–2015 Q3, of which 53,000 are treated with either rivaroxaban or VKA.
Data analysis	Propensity scores will be calculated using multivariable logistic regression incorporating frequently used variables and potential risk factors for differential oral anticoagulant exposure. The incidence of outcomes will be reported as the number of events per 100 person-years anticoagulant exposure and calculated as the number of patients with ≥1 documented event divided by each respective cohorts' time at risk. Cox proportional hazards regression will be performed on the matched cohorts and results reported as hazard ratios and 95% confidence intervals.
Milestones	Study protocol is expected to be updated in January 2019, followed by analysis completion in March 2019.

5. Amendments

Table 1: Amendments and updates

Number	Date	Section of study protocol	Amendment	Reason
1.0	18 Oct, 2017	Throughout document	Editorial changes and clarifications	PRC-OS recommendation
1.0	18 Oct, 2017	9.3.2	Clarification and reference to the addition of Annex 2	Response to PRC-OS comments
1.1	22 Nov, 2017	3	Updates to team composition and timelines	As above
1.1	22 Nov, 2017	9.5	Clarification made	As above
1.1	22 Nov, 2017	9.7	Details on analytical approach added	As above
2.0	2 Jan, 2019	Throughout document	Updates to team composition and timelines	Protocol amendment
2.0	2 Jan, 2019	8.2, 9.3	Addition to secondary objectives	As above
2.0	31 Jan, 2019	9.3.2, 9.3.3, 9.7	Editorial changes and clarifications	Response to PRC-OS comments

6. Milestones

Table 2: Milestones

Milestone	Planned date
Study protocol finalization	January 2019
Complete analysis	March 2019
Final report of study results	October 2019

7. Rationale and background

This proposed study will be conducted to obtain a better understanding on the comparative safety and effectiveness of rivaroxaban vs. Vitamin K antagonist (VKA) for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) in routine clinical practice. Specifically, the study aims to evaluate the safety and effectiveness of rivaroxaban in multi-morbid patients, such as the elderly and those with renal impairment.

Oral anticoagulant (OAC) treatment with either VKA or non-vitamin K antagonist oral anticoagulants (NOACs) is essential for the prevention of stroke or systemic embolism in patients with atrial fibrillation and one or more risk factors for stroke.

Subgroup analyses from ROCKET-AF have demonstrated consistent treatment effect for rivaroxaban vs. VKA across a wide range of patient types, including those with prior stroke or transient ischemic attack, reduced renal function, prior myocardial infarction, peripheral artery disease (PAD), heart failure, diabetes, hypertension, abnormal body weight, frailty, low stroke risk (CHA2DS2-VASc=1), moderate CYP3A4 inhibitor use (diltiazem or verapamil) or the elderly [1-9]. However, sample sizes were small and the extent to which these results apply to routine clinical practice is unclear.

The past few years have seen a significant number of real-world evidence (RWE) publications on NOACs. While insufficient for demonstrating causal relationships, these studies provide valuable insight into the effectiveness and safety of anticoagulants in routine clinical practice, helping to ensure that clinicians are well-informed to make patient-tailored clinical decisions.

8. Research questions and objectives

The overall goal of this study is to evaluate the comparative safety and effectiveness of rivaroxaban vs. VKA for stroke prevention in patients with NVAF across risk profiles and comorbidities that reflect everyday clinical practice.

Multi-morbidity, risk profiles and comorbidities, will primarily be assessed using one-dimensional measures (see 9.3.2). Additionally, the strength of this research is in assessing the renally impaired and frail patients, both of which will be assessment using robust algorithms that have been validated against clinical measures.

8.1 Primary objective

The primary objective in this study is to evaluate the combined end point of stroke or systemic embolism (SSE), and major bleeding in NVAF patients treated with rivaroxaban vs. VKA.

8.2 Secondary objective(s)

The secondary objectives in this study are to:

- evaluate the secondary endpoints ischemic stroke, hemorrhagic stroke, and subtypes of major bleeding,
- evaluate the secondary endpoints acute kidney injury and kidney failure,
- evaluate the secondary endpoints major adverse cardiovascular and limb events, and

- evaluate the comparative safety and effectiveness (as above) between individuals who switched from a VKA to rivaroxaban (switchers) and those who remained on a VKA (non-switchers).

9. Research methods

9.1 Study design

A cohort study using administrative claims data will be conducted. The study aims to compare rivaroxaban with VKA for stroke prevention in patients with NVAF across risk profiles and comorbidities that reflect everyday clinical practice in the USA.

9.2 Setting

9.2.1 Study population

The source population of this study will be all the insured individuals included in the Truven Health MarketScan Commercial Claims and Medicare Supplemental Databases (Truven MarketScan).

9.2.2 Study time frame

The study time frame will span January 1, 2011 to December 31, 2017 (or until the most recent available data). The day of the first qualifying oral anticoagulant (rivaroxaban or VKA) dispensing will constitute the index date.

9.2.3 Selection criteria

Selection criteria will be assessed during the study baseline period. To be included in this study patients would have to:

- be oral anticoagulant naive during the 365 days before the day of the first qualifying oral anticoagulant (rivaroxaban or VKA) dispensing, and
- have ≥365 days of continuous medical and prescription coverage before initiation of oral anticoagulation (which serves as the study's baseline period)

Exclusion criteria:

- <18 years of age
- <2 International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification diagnosis codes for atrial fibrillation
- valvular heart disease
- transient cause of NVAF
- venous thromboembolism
- hip or knee arthroplasty
- malignant cancer
- pregnancy
- >1 oral anticoagulant prescribed (on index date)

9.2.4 Representativeness

The Truven MarketScan databases capture person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services. Individuals enrolled in the MarketScan databases are largely representative of the United States population in terms of age, sex, and type of health insurance coverage.

9.3 Variables

Both revisions 9 and 10 International Classification of Diseases, Clinical Modification (ICD-9/10-CM) are used in this study. In the following sections ICD-9 codes are provided. A cross-walk file is used to derive ICD-10 codes (stand-alone document).

9.3.1 Exposure definition

Rivaroxaban (15/20 mg) and VKA comprise the study drugs of interest. The study cohort, further detailed in 9.2.3 and 9.3.2, will comprise two groups of patients: those who initiated OAC treatment with rivaroxaban and those who initiated with VKA. The latter group will form the cohort used to address the secondary objective on switching.

Patients will be followed until the first occurrence of an outcome event, switch or discontinuation of oral anticoagulant therapy, leaving the insurance plan or end of study follow-up (an on-treatment approach).

Patients will be considered to have discontinued oral anticoagulant therapy if a gap ≥30 days is detected between the most recent anticoagulant fill date and the date when there are no days of anticoagulant supply anticipated to be remaining (14 days will be considered as a sensitivity analysis). Switching is defined as starting another OAC within the gap period. No attempts to control for dose adjustments will be made; rather it will be assumed that patients are treated during the time periods for which they had a supply. Oral anticoagulant therapy will be identified using product names and generic names.

An intention-to-treat approach, with 12 months, 24 months and maximum available follow-up, will be run as a sensitivity analysis.

9.3.2 Eligibility criteria and subgroups definition

This section provides a detailed description of variable definitions of the study cohort (as defined in 9.2.3) and subgroups. Similar to assessment of patient characteristics (see 9.3.4), subgroups will be defined using data over the baseline period. Definitions for eligibility criteria are listed in Table 3.

Table 3. Variable definitions: Eligibility criteria

Criteria	Codes*	Reference/Comment
Atrial fibrillation	427.31	[10]
Valvular heart disease	394.x–397.x, 424.x, 746.0x–746.7x, V42.2, V43.3; CPT-4: 33400–33478	[11]

Criteria	Codes*	Reference/Comment
Transient causes of atrial fibrillation	429.4; CPT-4: 33400-33999	[11]
Venous thromboembolism	453.x, 415.1x	[11]
Hip or knee arthroplasty	CPT-4: 27090, 27091, 27125, 27130, 27132, 27134, 27136-27137-27138, 27438,27446, 27447, 27486-27488	[12]
Malignant cancers	140.x-208.xx, 230.x-234.x 4	[11]
Pregnancy	630.x-676.x, V22, V23, V27	[11]
Oral anticoagulants	apixaban, dabigatran, edoxaban, rivaroxaban, VKA (warfarin)	Identified using product names and generic names
*Codes are International Classification of Diseases (9th Revision) unless otherwise specified CPT=Current Procedural Technology (4th Edition)		

Subgroup analyses will include patients types as defined in Table 4 with additional codes provided in Table 7 (stand-alone document). Results will further be stratified by rivaroxaban dose (e.g. reduced dose in patients with renal impairment according to label) and risk factors such as age and CHA2DS2-VASc (Table 6).

Table 4. Variable definitions: Subgroups

Criteria	Comment/Reference
Renal impairment	A recently validated algorithm for detecting CKD in administrative claims data will be used (detection of an eGFR < 45 mL/min per 1.73 m^2). While the algorithm underestimates the prevalence of disease (sensitivity of 33%), it is most useful for detecting CKD as a baseline characteristic (positive predicated value of 65%). This study will use a validated subset of the algorithm, specific codes for CKD, that pushes the PPV up to 81%. [13] Please see Annex2: for a brief overview of the literature[14] and that illustrates the validity of identifying patients with renal impairment using administrative claims data. Another definition will also be considered that allows for detection of an eGFR < 50 mL/min per 1.73 m^2 and eGFR < 60 mL/min per 1.73 m^2 (including CKD stage 3A-B, 4, 5, and RRT [hemodialysis]).
Frailty**	Frailty can be operationalized in several ways, but is commonly characterized by a set of signs and symptoms in geriatrics and gerontology research. While

Criteria	Comment/Reference
	difficult to assess in administrative claims data, the recently validated Claims-based Frailty Indicator will be used in this study. [15] This algorithm is validated using against the frailty phenotype, which is the most widely used instrument for assessing frailty.
CAD/PAD	See 9.3.4.
Heart failure	See 9.3.4.
Diabetes	See 9.3.4.
Polypharmacy[+#]	Polypharmacy, or the use of multiple medications, is associated with a number of adverse outcomes, such as drug–drug interactions and mortality[16]. This study will use the commonly used definition concurrent use of five or more medications[17-19].
Prior stroke or transient ischemic attack	See [20]
Prior myocardial infarction	See 9.3.4.
Hypertension	See 9.3.4.
Low stroke risk (CHA2DS2-VASc=1)	See 9.3.4.
Moderate CYP3A4 inhibitor use[+]	Concomitant use of nondihydropyridine calcium channel blockers (non-DHP CCBs) and rivaroxaban may be associated with a drug–drug interaction (due to the former's moderate CYP3A4 enzyme inhibition and the latter being a substrate for the CYP3A4 isoenzyme pathway. Exposure will be defined as use of either verapamil or diltiazem[9].

[*]Codes are International Classification of Diseases (9th Revision) unless otherwise specified
[**]Including the elderly (aged ≥80 years) and abnormal body weight (Table 7).
[+]Concomitant use (with index drug)
[#]Anatomical Therapeutic Chemical (ATC) classification system Level 4 will be used to classify drugs; in theory, this grouping results in groups of different chemicals that work in the same way to treat similar medical conditions.. The ATC system divides drugs into groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.

9.3.3 Outcomes definition

The primary effectiveness end point for this study is stroke or systemic embolism. Major bleeding is primary safety end point. Definitions are provided in Table 5.

The occurrence of SSE during the observation period will be determined by the presence of an appropriate International Classification of Diseases, Clinical Modification (ICD-9/10-CM) discharge diagnosis code in the primary position. Major bleeding will be determined using the Cunningham algorithm.

Table 5. Variable definitions: Outcomes

Criteria	Codes*	Reference/Comment
Ischemic stroke**	I63; I64.9	
Hemorrhagic stroke**	I60; I61; I62	
Systemic embolism**	I74	
Adverse cardiovascular and limb events#	Combination of procedure and diagnosis codes	Myocardial infarction or ischemic stroke; need for revascularization of the limb or major amputation[21]
Acute kidney injury^	N17	[22]
Renal impairment^	Combination of procedure and diagnosis codes	End-stage kidney disease, or renal replacement therapy based on KDIGO guidelines[23]
Major bleeding Stratified by site of bleeding: Gastrointestinal Genitourinary Cerebral, including ICH Other	Bleeds identified using the Cunningham algorithm.	Without access to clinical information and event adjudication in administrative claims data, major bleeding will operationalized as hospital-related bleeding using a clinically validated algorithm[24].

*Codes are International Classification of Diseases (10th Revision) unless otherwise specified; for additional details, see stand-alone document
**Component of SSE
#Assessed in patients with CAD and/or PAD. Adverse limb events also assessed in patients with diabetes.
^See [25] for background and rationale for this outcome (assessed in patients with CKD stages 1–4, and diabetes)

9.3.4 Covariate definition

Patient characteristics will be assessed as per Table 6. Codes, including medications and variables to derive the components of the propensity scores, are specified in a stand-alone document (Table 7). Unless otherwise indicated, the characteristics will be evaluated over the baseline period.

Table 6. Variable definitions: Covariates

Variable	Categorization
Demographics	
Age at the index date (years)	18-34, 35-44, 45-54,55-64, 65-74, 75-84, ≥85 <30, 30-39, 40-49, 50-59, 60-69, 70-79, ≥80
Sex	Man, Woman
Medical history	
Acute coronary syndrome (i.e. MI and unstable angina)	Yes, No
Alcohol abuse*	Yes, No
Atrial Fibrillation	Yes, No
Angina	Yes, No
Angina – Stable	Yes, No
Angina – Unstable	Yes, No
Obesity**	Yes, No
CAD (i.e. acute coronary syndrome, stable angina or sudden cardiac death)	Yes, No
Cerebrovascular disease (i.e. ischemic stroke, transient ischemic attack, hemorrhagic stroke	Yes, No
Chronic kidney disease	Yes, No
COPD (Chronic Obstructive Pulmonary Disease) and respiratory failure	Yes, No
Diabetes	Yes, No
Duodenitis	Yes, No
Gastritis	Yes, No

Variable	**Categorization**
HF	Yes, No
Hyperlipidemia	Yes, No
Hypertension	Yes, No
Myocardial infarction	Yes, No
NSTEMI (Non-ST Elevation Myocardial Infarction)	Yes, No
STEMI (ST Elevation Myocardial Infarction)	Yes, No
Other vascular disease (i.e. aneurysms, splanchnic beds, vasculitis)	Yes, No
PAD	Yes, No
Prior bleed	Yes, No
Ulcer	Yes, No
Past-Year Medication Use	
ACE (Angiotensin Converting Enzyme) Inhibitors	Yes, No
Alpha-blocker or other vasodilator	Yes, No
Anticoagulant	Yes, No
Antiplatelet	Yes, No
Antithrombotic	Yes, No
ARBs (Angiotensin II Receptor Blockers)	Yes, No
ARNI (Angiotensin Receptor Neprilysin Inhibitors) (i.e. Entresto)	Yes, No
Beta-blockers	Yes, No

Variable	Categorization
Calcium channel blockers	Yes, No
Diuretic	Yes, No
Hypoglycemic agents	Yes, No
Lipid Lowering Agents	Yes, No
NSAIDs (Non Steroidal Anti Inflammatory Drugs)	Yes, No
Proton Pump Inhibitors	Yes, No
Risk Scores	
CHADS2	Numeric, integers
CHA2DS2-VASc Score	Numeric, integers
Charlson Comorbidity Index[26]	Numeric, integers 2–3, ≥4
HASBLED (modified)	Numeric, integers
SAMe-TT2R2 (modified), and	Numeric, integers ≥3
*Will be under-reported in claims **Captured through diagnosis codes, will be under-reported.	

9.4 Data sources

The Truven MarketScan data come from a selection of large employers, health plans, and government and public organizations and contain claims from approximately 100 employers, health plans, and government and public organizations representing about 170 million covered lives across all age groups[27]. The data elements to be used in the proposed study will include health plan enrollment records, participant demographics, inpatient and outpatient medical claims and outpatient prescription drug dispensing records. Data include both the Medicare supplemental-covered and employer-paid portions of the healthcare encounter. The data included in the MarketScan database are de-identified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality.

9.5 Study size

This cohort study is based on the entire source population of the MarketScan database covering 170 million lives across all age groups in the United States. Thus no formal sample size calculations were considered.

Preliminary estimates yielded a cohort of over 75,000 OAC-naive patients with an NVAF diagnosis for the period 2012–2015 Q3, of which 53,000 are treated with either rivaroxaban or VKA. Consequently, this well-powered study will include more than five times the number of patients that were included in the pivotal RCT[6].

9.6 Data management

The data elements to be used in the proposed study will include health plan enrollment records, participant demographics, inpatient and outpatient medical claims and outpatient prescription drug dispensing records. The data included in the MarketScan database are de-identified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality. Database management will be performed using SAS version 9.4 (SAS Inc., Cary, NC, USA).

9.7 Data analysis

Propensity scores (PSs) will be calculated using multivariable logistic regression incorporating frequently used variables and potential risk factors for differential oral anticoagulant exposure [28-32] including patient demographics (age and sex), comorbidities, concomitant nonoral anticoagulant medications, individual components of the CHADS2, CHA2DS2-VASc and modified HASBLED risk stratification scores and modified SAMe-TT2R2, and Charlson Comorbidity Index measured during the baseline period (Table 6)[26]. Each eligible rivaroxaban user will be 1:1 propensity score matched (using greedy nearest-neighbor matching without replacement and a caliper of 1%; weighting using the PS will be considered as a sensitivity analysis and for subgroups with few patients) to a VKA user to minimize the presence of baseline differences between cohorts. The proportion of rivaroxaban treated patients that could be matched will be reported. Residual differences in characteristics between matched cohorts will be assessed by calculating standardized differences between cohorts (<10% considered well balanced)[33]. Further details and information on the analyses, including additional subgroups and outcomes, are described in a stand-alone document (see Table 7).

To address the secondary objective on switching, separate PS-matching will be carried out between the switchers (VKA to rivaroxaban) and those who remain on a VKA (non-switchers).

Baseline patient characteristics will be analyzed using descriptive statistics. Categorical data will be reported as proportions, while continuous data will be reported as means±standard deviations or medians with interquartile ranges.

The incidence of primary and secondary study end points will be reported as the number of events per 100 person-years anticoagulant exposure and calculated as the number of patients with ≥1 documented event divided by each respective cohorts' time at risk. Cox proportional hazards regression will be performed on the matched cohorts and results reported as hazard ratios and 95% confidence intervals.

The regression analysis will include only oral anticoagulant treatment as an independent variable as it is anticipated that all baseline characteristics will be balanced after propensity score matching.

Statistical analyses will be performed using SAS version 9.4 (SAS Inc, Cary, NC) and IBM SPSS Statistics version 22.0 (IBM Corp, Armonk, NY). In all cases, a P value <0.05 will be considered significant.

9.8 Quality control

The MarketScan databases are created by combining the standard variables of the individual databases (data contributors) and also creating links between years of data and across all data types[27]. The MarketScan databases are created as a snapshot in time and are based on a calendar-year incurred period.

Claims lag periods (the amount of time between the date of service on the claim and the date payment is made) vary considerably across the approximately 100 insurance carriers in the MarketScan databases. Because of this, the data are collected when close to 100% of claims have been paid, which takes about 6 months after year end.

Additional enhancements are made by the data provider data during the creation process of the MarketScan databases.

9.9 Limitations of the research methods

As with all observational research, there are inherent limitations in the use of administrative claims databases. One such limitation is the assessment of drug exposure. In this study no attempt to control for dosing changes on VKA will be made. A major limitation includes the potential for misclassification of diseases and of the outcomes. This study tries to minimize this bias by, to the extent possible, use claims-based algorithms that have been validated against clinical data.

Furthermore adjustments will be made for baseline differences with propensity score-matching between rivaroxaban and VKA users. Nonetheless, in the absence of randomization, our results may be subject to residual confounding.

Although the combined end point of ischemic stroke or intracranial hemorrhage, as used in this study, is not the primary end point in the typical stroke prevention RCT that focuses on ischemic and hemorrhagic stroke, the ability to differentiate between hemorrhagic strokes and other types of ICH is challenging when relying on International Classification of Diseases, Clinical Modification coding alone, since many ICH events are coded as unspecified ICH (432.9). Moreover, this combined end point of ischemic stroke or ICH is the a priori primary end point in the US Food and Drug Administration Mini-Sentinel postmarketing surveillance protocol[28]. Although composite end points can simplify risk–benefit assessment, it is possible that the stroke prevention effectiveness could come at the cost of increased bleeding risk. For this reason, ischemic stroke and ICH are assessed separately as secondary end points.

Some specific notes on the data source are also of relevance. The MarketScan claims databases are based on a large sample. Because the sample is not random, it may contain biases or fail to generalize well to other populations. However, these data can complement other datasets or be used as benchmarks against them. The databases largely cover employees and their dependents, so patients with conditions that prevent them to be employed may be underrepresented. The data mostly come from large employers; medium and small firms are underrepresented. This may lead to

underrepresentation of particular population groups. Finally, the results which will be derived from the MarketScan database are only valid for the population described and by the eligibility criteria.

10. Protection of human subjects

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

11. Management and reporting of adverse events/adverse reactions

The reporting of suspected adverse reactions in the form of individual care report forms (ICSRs) is not required for studies using secondary data. Reports of adverse events/reactions will be summarized in the study report, where applicable.

12. Plans for disseminating and communicating study results

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

13. References

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Annex 1: List of stand-alone documents

Table 7: List of stand-alone documents

Document Name	Final version and date (if available)
Covariates, diagnoses and procedures coding list: disease states and medications	31 January 2019
Analytical plan complementing section 9.7	31 January 2019

Annex2: Claims-based definitions of renal impairment

The use of the MarketScan database for identifying patients with renal impairment (and frailty) was deemed appropriate based on a review of the literature. A systematic literature review of studies that compared the accuracy of codes for CKD in administrative databases with a reference standard was the primary source for informing the decision to include patients with renal impairment[14].

In short, this review identified 19 validation studies of CKD with ICD-9 coding used in the majority of studies (all but five studies were from the United States)[14]. Sensitivity varied across studies and was generally poor (median, 41%; range, 3–88%). However, and importantly for the present study, positive predictive values (PPVs) often were reasonable (median, 78%; range, 29–100%).

It is important to acknowledge the limitations of observational studies, and specifically the use of administrative data for studying patients with renal impairment. For example, administrative data are generally not helpful in understanding the prevalence of non-dialysis-dependent CKD because the sensitivity is poor. In other words, any incidence/prevalence estimates derived using codes in administrative databases will underestimate the overall burden. This is especially true in early stages of CKD since mild renal impairment is generally under-diagnosed in routine clinical practice.

However, for the current study it is not of interest to obtain a valid prevalence estimate. Rather, the primary objective is to use a definition that is as selective as possible for renal impairment to ensure that patients who have normal renal function are not classified as having CKD. That is, instead of focusing on sensitivity, the primary interest is to use a definition of CKD with a high PPV.

In summary, the literature provides confidence in the ability to create a cohort of individuals who truly have the condition of interest, i.e. renal impairment. The definition of CKD chosen for this study comes from a more recent Canadian validation study[13]. While there is a distinct difference between the healthcare systems of United States and Canada, the characteristics of data are similar, namely health information collected by the administration of a health service, used primarily for financial or record-keeping purposes. Importantly, both countries use standardized International Statistical Classification of Diseases and Related Health Problems (ICD-9/10 codes). Reassuringly, the performance of the definition for use in the current study is consistent with the results of the systematic literature review mentioned above[14]. As has been reported earlier, by reducing the number of codes used to identify patients with renal impairment, PPV increases. This is also reflected in the Canadian validation study, in which the PPV reaches 80.1% when restricting the codes to the ICD-10 group N18 (equivalent ICD-9 585)[13]. Finally, the advantage of the definition for use in this study is that it is validated against the detection of an eGFR < 45 mL/min per 1.73 m^2, which is comparable to the label for treating rivaroxaban patients with renal impairment (15 < CrCl ≤ 50 mL/min).

Annex 3: Signature pages

Signature Page - OS Conduct Responsible

Title	Rivaroxaban vs warfarin for SPAF in multi-morbid patients
Protocol version and date	v2.0; 31 Jan, 2019
IMPACT study number	19859
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	N/A
Medicinal product / Active substance	Xarelto/BAY 597939, Rivaroxaban Factor Xa Inhibitor
Comparator / Reference therapy	Vitamin K antagonist
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 12 APR 2019 , PPD

Signature Page - RWE Strategy & Outcomes Data Generation

Title	Rivaroxaban vs warfarin for SPAF in multi-morbid patients
Protocol version and date	v2.0; 31 Jan, 2019
IMPACT study number	19859
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	N/A
Medicinal product / Active substance	Xarelto/BAY 597939, Rivaroxaban Factor Xa Inhibitor
Comparator / Reference therapy	Vitamin K antagonist
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD PPD

Date, Signature: 26.02.19 _____

Signature Page - OS Safety Lead

Title	Rivaroxaban vs warfarin for SPAF in multi-morbid patients
Protocol version and date	v2.0; 31 Jan, 2019
IMPACT study number	19859
Study type / Study phase	Observational PASS · Joint PASS: ☐ YES ☒ NO
EU PAS register number	N/A
Medicinal product / Active substance	Xarelto/BAY 597939, Rivaroxaban Factor Xa Inhibitor
Comparator / Reference therapy	Vitamin K antagonist
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD PPD

Date, Signature: 7.03.2019

Signature Page - OS Medical Expert

Title	Rivaroxaban vs warfarin for SPAF in multi-morbid patients
Protocol version and date	v2.0; 31 Jan, 2019
IMPACT study number	19859
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	N/A
Medicinal product / Active substance	Xarelto/BAY 597939, Rivaroxaban Factor Xa Inhibitor
Comparator / Reference therapy	Vitamin K antagonist
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees PPD
described in the protocol.

Print Name: PPD

Date, Signature: 06.03.19 , _____

Signature Page - OS Statistician

Title	Rivaroxaban vs warfarin for SPAF in multi-morbid patients
Protocol version and date	v2.0; 31 Jan, 2019
IMPACT study number	19859
Study type / Study phase	*Observational* PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	N/A
Medicinal product / Active substance	Xarelto/BAY 597939, Rivaroxaban Factor Xa Inhibitor
Comparator / Reference therapy	Vitamin K antagonist
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 1 Feb 26, 2019, PPD

Signature Page - OS Epidemiologist

Title	Rivaroxaban vs warfarin for SPAF in multi-morbid patients
Protocol version and date	v2.0; 31 Jan, 2019
IMPACT study number	19859
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	N/A
Medicinal product / Active substance	Xarelto/BAY 597939, Rivaroxaban Factor Xa Inhibitor
***Comparator* / Reference therapy**	Vitamin K antagonist
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 04-03-2019, PPD

Signature Page - Qualified Person responsible for Pharmacovigilance

Title	Rivaroxaban vs warfarin for SPAF in multi-morbid patients
Protocol version and date	v2.0; 31 Jan, 2019
IMPACT study number	19859
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	N/A
Medicinal product / Active substance	Xarelto/BAY 597939, Rivaroxaban Factor Xa Inhibitor
Comparator / Reference therapy	Vitamin K antagonist
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 26. 2. 2019 , PPD