Observational Post-Authorization Safety Study (PASS) Report

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)
Report version and date	v 1.0, 07 JUL 2020
IMPACT study number	19859
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO N/A
EU PAS register number	EUPAS21800
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Medicinal product	Xarelto®
Comparator / Reference therapy	Vitamin-K antagonist (Warfarin, B01AA03)
Study Initiator and Funder	Bayer AG
Research question and objectives	The overall goal of this study was to evaluate the comparative safety and effectiveness of rivaroxaban vs. VKA for stroke prevention in patients with NVAF across the risk profiles and comorbidities that reflected on everyday clinical practice.
Country(-ies) of study	USA
Author	MetaEvidence, LLC: PPD Bayer AG: PPD PPD PPD APCER: PPD, PPD, PPD

Marketing authorization holder

Marketing authorization holder (MAH)	Bayer AG, 51368 Leverkusen, Germany
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Confidentiality statement:

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1. Abstract

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)
Report version and date **Author**	v 1.0, 15 NOV 2019 MetaEvidence, LLC: PPD Bayer AG: PPD, PPD, PPD APCER: PPD, PPD, PPD
IMPACT study number	19859
Keywords	NVAF, Rivaroxaban, Renal dysfunction, Effectiveness, Safety
Rationale and background	This proposed study was 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 a routine clinical practice. Specifically, the aim of the study was to evaluate the safety and effectiveness of rivaroxaban in multi-morbid patients, such as those with renal impairment. Subgroup analyses from ROCKET-AF (The Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin-K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) had 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 (HF), diabetes, hypertension, abnormal body weight, frailty, low stroke risk (CHA_2DS_2-VASc=1), moderate cytochrome P450 3A4 (CYP3A4) inhibitor use (diltiazem or verapamil), or the elderly.

Research question and objectives	The overall goal of this study was to evaluate the comparative safety and effectiveness of rivaroxaban vs. VKA for stroke prevention in patients with NVAF across the risk profiles and comorbidities that reflected on everyday clinical practice.
Study design	A cohort study using administrative claims data was conducted. The aim of the study was to compare rivaroxaban with VKA for stroke prevention in patients with NVAF across the risk profiles and comorbidities that reflected on everyday clinical practice in the United States of America (USA).
Setting	The source population of this study included all the insured individuals in the IBM Watson MarketScan Commercial Claims and Medicare Supplemental Databases. The study time frame spanned from January 1, 2011 to December 31, 2017 (or until the most recent available data). The date of the first fill of oral anticoagulant (OAC) (rivaroxaban or VKA) was defined as the index date.
Subjects and study size, including dropouts	A total of 78,517 NVAF patients were identified who were OAC-naïve (newly initiated on warfarin or rivaroxaban) and had ≥365 days of continuous medical and prescription insurance coverage (study baseline period) prior to the initiation of oral anticoagulation (index date). Patients who were <18 years of age, had <2 ICD-9 or ICD-10 diagnosis codes for NVAF, or had valvular heart disease, VTE, hip or knee arthroplasty, malignant cancer, pregnancy, transient cause of NVAF, or >1 oral anticoagulant prescribed on index date, were excluded. The patients were further assigned to 7 distinctive cohorts on the basis of existing comorbidities (like renal impairment, diabetes, coronary artery disease (CAD)/PAD, HF, or low stroke risk) or comedications at baseline.
Variables and data sources	Patients' baseline characteristics such as age, sex, comorbidities, and comedications were collected at the index date. The outcomes of interest were combined endpoints of stroke or systemic embolism (SSE), ischemic stroke (IS), hemorrhagic stroke, acute kidney injury, kidney failure, major adverse cardiovascular events (MACEs), major adverse limb events (MALEs), major bleeding, and subtypes of major bleeding. Baseline characteristics and outcome events were assessed using diagnostic procedure as

	well as drug codes. Bleeding-related hospitalizations were identified using the Cunningham's algorithm. IBM Watson MarketScan databases that capture longitudinal, individual-level administrative claims data of the US population were utilized for this study. The data elements that were used in the study included health plan enrollment records, participant demographics, inpatient and outpatient medical claims, and outpatient prescription drug-dispensing records. The data included both Medicare supplemental-covered and employer-paid portions of the healthcare encounter.
Results	In NVAF patients of Cohort 1 (excluding those with Stage 5 chronic kidney disease [CKD]/receiving hemodialysis), rivaroxaban was associated with significant risk reductions of acute kidney injury (AKI) by 19%, progression to Stage 5 CKD or hemodialysis by 18%, SSE and IS each by 33%, and intracranial hemorrhage (ICH) by 42%, in comparison with warfarin. No significant difference in major bleeding was observed between rivaroxaban and warfarin users (hazard ratio [HR] 0.98). In NVAF patients with type 1 or type 2 diabetes mellitus (Cohort 2 had T2DM patients >97%), rivaroxaban was associated with a significant risk reduction of AKI by 17%, progression to Stage 5 CKD or hemodialysis by 18%, MACE by 25%, MALE by 63%, major limb amputation by 80%, and endovascular revascularization by 73% in comparison with warfarin. The risk reductions of IS (17-22%), myocardial infarction (MI) (23%), minor limb amputation (28%), SSE (32%), surgical revascularization (34%), hemorrhagic stroke (34%), and ICH (41%) were better with rivaroxaban in comparison with warfarin; however, they did not reach statistical significance. No significant difference in major bleeding was observed between rivaroxaban and warfarin users (HR 0.95-0.97). In NVAF patients with concomitant CAD and/or PAD (Cohort 3), rivaroxaban was associated with a significant risk reduction of major thrombotic vascular event (MTVEs) by 32% and adverse limb events by 56%. Although the rate of major bleeding with rivaroxaban was higher in comparison to warfarin (HR 1.13), it was of no statistical significance (95% CI: 0.84 - 1.52). In NVAF patients with renal impairment (CKD stages 4 or 5 or undergoing hemodialysis) (Cohort 4), rivaroxaban use was associated with a significant 32% lower risk of major

	bleeding compared with warfarin. Rivaroxaban was also associated with a 45% reduction in the risk of SSE vs. warfarin, albeit the 95% confidence intervals (CIs) crossed the line of unity. In NVAF patients with heart failure (Cohort 5), the risk reductions of SSE (18%) and IS (23%) were better with rivaroxaban in comparison with warfarin; however, they did not reach statistical significance. No significant difference in major bleeding was observed between rivaroxaban and warfarin users (HR 0.98). These findings were consistent with those from a sub-analysis from the ROCKET-AF trial. In NVAF patients experiencing polypharmacy (≥5 chronic medications) (Cohort 6), rivaroxaban was associated with a significant risk reduction of SSE by 34% and IS by 40% in comparison with warfarin. In NVAF patients experiencing substantial polypharmacy (≥10 chronic medications), the risk reductions of SSE (56%) and IS (38%) were better with rivaroxaban in comparison with warfarin; however, they did not reach statistical significance. No significant difference in major bleeding was observed between rivaroxaban and warfarin users (HR 1.07-1.08). In NVAF patients with low stroke risk (CHA_2DS_2-VASc score = 1) (Cohort 7), rivaroxaban was associated with a significant risk reduction of SSE (by 59% and 54% at 1-year and 2-year follow-up, respectively) in comparison with warfarin. The risk reduction of IS (51% and 37% at 1-year and 2-year follow-up) and major bleeding (26% and 35% at 1-year and 2-year follow-up) were better with rivaroxaban in comparison with warfarin; however, they did not reach statistical significance.
Discussion	When used in a routine practice in NVAF patients, rivaroxaban vs. warfarin appears to be associated with lower risks of AKI or renal impairment (in those with or without diabetes mellitus), MACE and MALE (in those with diabetes), MTVEs (in those with CAD and/or PAD), and SSE and IS (in those with heart failure or a lower risk of stroke). Moreover, in the setting of polypharmacy, rivaroxaban in NVAF patients is an effective and safe alternative to warfarin. The risk of major bleeding with rivaroxaban is generally comparable to warfarin. Rivaroxaban use in patients with NVAF and Stage 4 or 5 CKD and among those receiving hemodialysis, appears to be associated with less major bleeding compared with warfarin, although additional studies are needed to confirm

	the effectiveness and safety of rivaroxaban in patients with severe kidney dysfunction and to help determine optimal dosing in this population. The fact that the real-world findings in this study are generally consistent with those from Phase III randomized trials of rivaroxaban vs. warfarin in NVAF should provide additional reassurance to clinicians regarding the use of rivaroxaban in people with comorbidities that reflected on everyday clinical practice. As the study used the US claims data, the results therefore are generalizable to an insured US population with NVAF.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen, Germany
Names and affiliations of principal investigators	Not applicable

2. List of abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
ATC	Anatomical Therapeutic Chemical (classification system)
CAD	Coronary artery disease
$CHADS_2$	C=Congestive heart failure; H=Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication); A=Age ≥75 years; D=Diabetes mellitus; S_2=Prior Stroke or TIA or Thromboembolism
CHA_2DS_2-VASc	C=Congestive heart failure; H=Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication); A_2=Age ≥75 years; D=Diabetes mellitus; S_2=Prior Stroke or TIA or Thromboembolism; V=Vascular disease (e.g., PAD, MI, aortic plaque); A=Age 65-74 years; Sc: Sex category (i.e., female sex)
CI	Confidence interval
CKD	Chronic kidney disease
CPT	Current Procedural Technology
CYP3A4	Cytochrome P450 3A4
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
EU	European Union
EU PAS	European Union Post-Authorization Study
HAS-BLED	H=Hypertension; A=Abnormal renal and liver function; S=Stroke; B=Bleeding; L=Labile INR; E=Elderly; D=Drugs or alcohol
HF	Heart failure
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
IBM	International Business Machines
ICD	International Classification of Diseases
ICD-CM	ICD - Clinical Modification
ICH	Intracranial hemorrhage
INR	International normalized ratio
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
IS	Ischemic stroke
ITT	Intention to treat
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular event
MAH	Marketing Authorization Holder
MALE	Major adverse limb event
MI	Myocardial infarction
MTVE	Major thrombotic vascular event

N	Number
N/A	Not applicable
NOAC	Non-vitamin-K-antagonist oral anticoagulant
NSAIDs	Nonsteroidal anti-inflammatory drugs
NVAF	Nonvalvular atrial fibrillation
NYHA	New York Heart Association
OAC	Oral anticoagulation
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
OS	Observational study
p	Probability
PAD	Peripheral artery disease
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PPIs	Proton-pump inhibitors
PPV	Positive predictive values
PS	Propensity score
ROCKET-AF	The Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin-K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RRT	Renal replacement therapy
RWE	Real-world evidence
SAS	Statistical Analysis System
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter-2
SNRI	Serotonin-norepinephrine reuptake inhibitor
SPAF	Stroke Prevention in Atrial Fibrillation
SSE	Stroke or systemic embolism
SSRI	Selective serotonin reuptake inhibitor
T2DM	Type 2 diabetes mellitus
TIA	Transient ischemic attack
TTR	Times in the therapeutic range
TWANG	Threshold of Weighted intensity And seed-Normal Gradient dot product image
UCL	Upper confidence limit
US(A)	United States (of America)
VKA	Vitamin-K antagonist
VTE	Venous thromboembolism

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5. Milestones

Table 5–1: Milestones

Milestone	Planned date	Actual date
Study protocol finalization	JAN 2019	JAN 2019
Complete analysis	MAR 2019	MAR 2019
Final report of the study results	OCT 2019	JUL 2020

6. Rationale and background

This proposed study was 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 a routine clinical practice. Specifically, the aim of the study was to evaluate the safety and effectiveness of rivaroxaban in multi-morbid patients, such as 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 (SSE) in patients with atrial fibrillation and one or more risk factors for stroke.

Subgroup analyses from ROCKET-AF (The Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin-K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) had demonstrated consistent treatment effect for rivaroxaban vs. VKA across a wide range of patient types, including those with prior stroke or transient ischemic attack (TIA), reduced renal function, prior myocardial infarction (MI), peripheral artery disease (PAD), heart failure (HF), diabetes, hypertension, abnormal body weight, frailty, low stroke risk (CHA_2DS_2-VASc=1), moderate cytochrome P450 3A4 (CYP3A4) inhibitor use (diltiazem or verapamil), or the elderly [1-9]. However, sample sizes were small, and the extent to which these results applied to a routine clinical practice was unclear.

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

7. Research question and objectives

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

Multi-morbidity, risk profiles, and comorbidities were primarily being assessed using one-dimensional measures (see Section 9.3). Additionally, the strength of this research was in assessing the renally impaired patients, who were assessed using robust algorithms that have been validated against clinical measures.

Objectives

The objectives of the study were to evaluate the following outcomes in the NVAF patients treated with rivaroxaban vs. VKA:

- Combined endpoint of SSE
- Ischemic stroke (IS)
- Hemorrhagic stroke
- Major bleeding
- Subtypes of major bleeding
- Acute kidney injury (AKI)
- Kidney failure
- Major adverse cardiovascular events (MACEs) and major adverse limb events (MALEs)

8. Amendments and updates

Table 8–1: Amendments and updates

Number	Date	Section of study protocol	Amendment or Update	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	02 JAN 2019	Throughout document	Updates to team composition and timelines	Protocol amendment
2.0	02 JAN 2019	8.2 and 9.3	Addition to secondary objectives	As above
2.0	31 JAN 2019	9.3.2, 9.3.3, and 9.7	Editorial changes and clarifications	Response to PRC-OS comments

9. Research methods

9.1 Study design

A cohort study using administrative claims data was conducted. The aim of the study was to compare rivaroxaban with VKA for stroke prevention in patients with NVAF across the risk profiles and comorbidities that reflected on everyday clinical practice in the United States of America (USA).

9.2 Setting

The source population of this study included all the insured individuals in the IBM Watson MarketScan Commercial Claims and Medicare Supplemental Databases.

The study time frame spanned from January 1, 2011 to December 31, 2017 (or until the most recent available data). The date of the first fill of OAC (rivaroxaban or VKA) was defined as the index date.

9.3 Subjects

Selection criteria

Selection criteria was assessed during the study baseline period. To be included in this study a patient would have to:

- Be oral anticoagulant naïve 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 the 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 (ICD-9/10-CM) Diagnosis codes for atrial fibrillation. Two separate coding instances were required to reduce the possibility of false positive identification (misclassification).
- Valvular heart disease
- Transient cause of NVAF
- Venous thromboembolism (VTE)
- Hip or knee arthroplasty
- Malignant cancer
- Pregnancy
- >1 oral anticoagulant prescribed (on index date)

Variable definitions defining eligibility criteria are presented in Table 9–1:

Table 9–1: 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]
Transient causes of atrial fibrillation	429.4; CPT-4: 33400-33999	[11]
VTE	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]
OACs	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)

9.4 Variables

Both ICD-9-CM and ICD-10-CM were used in this study.

Exposure definition

Rivaroxaban (15/20 mg) and VKA comprised the study drugs of interest. The study cohort comprised of two groups of patients: those who initiated OAC treatment with rivaroxaban and those who initiated with VKA.

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

Subgroups definition

Subgroup analyses included patients' types as defined in Table 9–2. Results were further stratified by rivaroxaban dose (e.g., reduced dose in patients with renal impairment according to label) and risk factors such as age and CHA_2DS_2-VASc. Similar to assessment of patient characteristics, subgroups were defined using data over the baseline period.

Table 9–2: Variable definitions: Subgroups

Criteria	Comment/Reference
Diabetes	Variables were categorized as YES (present) or NO (absent).
CAD/PAD	Variables were categorized as YES (present) or NO (absent).
Renal impairment	A recently validated algorithm for detecting CKD in administrative claims data was used (detection of an estimated glomerular filtration rate [eGFR] <45 mL/min per 1.73 m^2). While the algorithm underestimated the prevalence of disease (sensitivity of 33%), it was most useful for detecting CKD as a baseline characteristic (positive predicated value of 65%). This study used a validated subset of the algorithm, specific codes for CKD, which pushes the positive predictive values (PPVs) up to 81% [13]. Another definition was also considered that allowed 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, and 5 and Renal replacement therapy [RRT] [hemodialysis]).
HF	Variables were categorized as YES (present) or NO (absent).
Polypharmacy*†	Polypharmacy, or the use of multiple medications, is associated with a number of adverse outcomes, such as drug-drug interactions and mortality [14]. This study will use the commonly used definition concurrent use of five or more medications [15-17].
Low stroke risk (CHA_2DS_2-VASc=1)	Variables were categorized as numeric or integers.

*Concomitant use (with index drug)
†Anatomical Therapeutic Chemical (ATC) classification system Level 4 were 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.

Outcomes definition

The effectiveness endpoints for this study were stroke or systemic embolism. Major bleeding was safety endpoint.

The occurrence of SSE during the observation period was determined by the presence of an appropriate ICD-9/10-CM discharge diagnosis code in the primary position. Major bleeding was determined using the Cunningham's algorithm.

Covariate definition

Patient characteristics will be assessed as per specified International Classification of Diseases (ICD) codes, including medical history, medications, and risk scores (CHA_2DS_2-VASc and HAS-BLED scores). Unless otherwise indicated, the characteristics will be evaluated over the baseline period.

9.5 Data sources and measurement

The IBM Watson MarketScan data capture 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 [19]. The data elements that were used in the study included health plan enrollment records, participant demographics, inpatient and outpatient medical claims, and outpatient prescription drug-dispensing records. The data included both the Medicare supplemental-covered and employer-paid portions of the healthcare encounter. The data included in the MarketScan database were de-identified and were in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 to preserve participant anonymity and confidentiality.

9.6 Bias

Like other databases, samples from IBM Watson MarketScan Commercial Claims and Medicare Supplemental Databases were not random and could contain biases or could fail to generalize well to other populations.

The results derived from the MarketScan database were only valid for the population described by the inclusion/exclusion criteria.

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

Furthermore, adjustments were made for baseline differences with propensity score (PS)-matching between rivaroxaban and VKA (warfarin) users. Nonetheless, in the absence of randomization, our results might be subject to residual confounding.

9.7 Study size

A total of 78,517 OAC-naïve (newly initiated on warfarin or rivaroxaban) adult NVAF patients were identified in the IBM Watson MarketScan databases who were further assigned to distinctive cohorts on the basis of presence of other comorbidities (like renal impairment, diabetes, coronary artery disease (CAD)/PAD, HF, or low stroke risk) or comedications at baseline [28]. Additional exclusion/inclusion criteria were applied to select the patients in the respective cohort.

Table 9–3: Number of patients in each of the distinctive cohort

Cohort ID	Comorbidities or comedications at baseline	Number of patients
Cohort 1	All-inclusive except Stage 5 CKD/receiving hemodialysis	N=36,318 (R) N=36,281 (W)
Cohort 2 (NVAF + Diabetes): Diabetic population I	Diabetes (type 1 or 2)	N=10,017 (R) N=11,665 (W)
Cohort 2 (NVAF + Diabetes): Diabetic population II	T2DM	N=10,700 (R) N=13,946 (W)
Cohort 2 (NVAF + Diabetes): Diabetic population III	Diabetes (type 1 or 2)	N=5,517 (R) N=5,517 (W)
Cohort 3 (NVAF + CAD/PAD)	CAD and/or PAD	N=3,257 (R) N=5,046 (W)
Cohort 4 (NVAF + Renal impairment)	Severe kidney disease (CKD Stage 4 and 5) or receiving hemodialysis	N=1,896 (R) N=4,848 (W)
Cohort 5 (NVAF + HF)	HF	N=3,418 (R) N=3,418 (W)
Cohort 6 (NVAF + Polypharmacy)	≥5 Concomitant chronic medications	N=13,981 (R) N=13,981 (W)
	≥10 Concomitant chronic medications	N=1,765 (R) N=1,765 (W)
Cohort 7 (NVAF + CHA_2DS_2-VASc score = 1)	Non-sex-related CHA_2DS_2-VASc score of 1	N=3,319 (R) N=3,319 (W)

R: Rivaroxaban; W: Warfarin

9.8 Data transformation

The data elements used in the proposed study included health plan enrollment records, participant demographics, inpatient and outpatient medical claims, and outpatient prescription drug-dispensing records. The data included in the MarketScan database were de-identified and were in compliance with the HIPAA of 1996 to preserve participant anonymity and confidentiality. Database management was performed using Statistical Analysis System (SAS) Version 9.4 (SAS Inc., Cary, NC, USA).

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 elements (analysis populations, definition and measurement of endpoints and other key variables, and statistical methodology) are adequately detailed in this section.

9.9.2 Main statistical methods

Propensity scores were estimated using generalized boosted models based on 10,000 regression trees using the "Threshold of Weighted intensity And seed-Normal Gradient dot product image (TWANG)" package (version 1.5) and R statistical software (version 3.4.3, The R Project for Statistical Computing) which implemented an automated, nonparametric machine learning method [20]. The weights were derived to obtain estimates of the population average treatment effect. Moreover, PSs were estimated using multivariable logistic regression incorporating frequently used variables and potential risk factors for differential oral anticoagulant exposure [21-25] including patient demographics (age and sex), comorbidities, concomitant monorail anticoagulant medications, and individual components of the $CHADS_2$, CHA_2DS_2-VASc, and modified HAS-BLED risk stratification scores measured during the baseline period [18]. Each eligible rivaroxaban user underwent through *1:1* PS matching (using greedy nearest-neighbor matching without replacement and a caliper of 1%) to a VKA user to minimize the presence of baseline differences between cohorts. The proportion of rivaroxaban-treated patients that could be matched was reported. Residual differences in characteristics between the matched cohorts were assessed by calculating the standardized differences between cohorts (<10% considered well balanced). Based on the PSs, IPTW approach was utilized to adjust for potential confounding resulting from imbalances in baseline patient characteristics. The objective of IPTW based analysis was to create a weighted sample, for which the distribution of either the confounding variables or the prognostically important covariates was approximately the same between comparison groups [26]. In our study, IPTW method was used for Cohort 1, Cohort 2 (Diabetic population I and Diabetic Population II), Cohort 3, and Cohort 4 whereas PS matching was used for Cohort 2 (Diabetic Population III), Cohort 5, Cohort 6, and Cohort 7.

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

The incidence of study endpoints were 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 cohort's time at risk. Cox proportional hazards regression was performed on the matched cohorts, and the results were reported as hazard ratios (HRs) and 95% confidence intervals (CIs).

The regression analysis included only oral anticoagulant treatment as an independent variable as it was anticipated that all baseline characteristics were balanced after PS matching. Statistical analyses were 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 was considered statistically significant.

9.9.3 Missing values

No actions were taken to deal with the missing-data-related issues.

9.9.4 Sensitivity analyses

An intention-to-treat (ITT) approach (patients were followed until endpoint of interest occurrence, end-of-database activity, or through the end of data availability [end of data cut]), with 12 months, 24 months, and the maximum available follow-up, was also considered for sensitivity analysis.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

The IBM Watson MarketScan databases are created by combining the standard variables of the individual databases (data contributors) and also creating links between the years of data and across all data types [19]. The MarketScan databases were created as a snapshot in time and were 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 were collected when close to 100% of claims had been paid, which took about 6 months after the year end.

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

10. Results

10.1 Participants

Utilizing the IBM Watson MarketScan databases in the study time frame of 01 JAN 2011 to 31 DEC 2017, a total of 78,517 adult patients were identified after applying general inclusion/exclusion criteria as described in Section 9.3. These patients were OAC naïve (newly initiated on warfarin or rivaroxaban) and had ≥365 days of continuous medical and prescription insurance coverage (study baseline period) prior to the initiation of oral anticoagulation (index date). Patients who were <18 years of age, had <2 ICD-9 or ICD-10 diagnosis codes for NVAF, or had valvular heart disease, VTE, hip or knee arthroplasty, malignant cancer, pregnancy, transient cause of NVAF, or >1 oral anticoagulant prescribed on index date, were excluded.

The identified patients were assigned to distinctive cohorts on the basis of existing comorbidities/co-medications at baseline. Patients with Stage 5 CKD or requiring hemodialysis were further excluded in Cohort 1 and Cohort 2 Diabetic Population I. All the selected patients in each of the cohort were followed until an event, anticoagulant discontinuation/switch, insurance disenrollment, or end-of-data availability. Table 10–1 presents an overview of the study cohorts.

10.1.1 Cohort 1

A total of 36,318 rivaroxaban- and 36,281 warfarin-naïve patients with NVAF were selected in Cohort 1. The patients with Stage 5 CKD or receiving hemodialysis during the baseline period were excluded. The following endpoints (incidences of events per 100 person-years) were analyzed to evaluate the effectiveness and safety of rivaroxaban over warfarin (as exhibited by HR) in Cohort 1 [27]:

- AKI
- Composite of progression to Stage 5 CKD or need for hemodialysis
- Composite of SSE (IS [ICD-10 codes: I63, I64.9], hemorrhagic stroke [ICD-10 codes: I60-I62], or systemic embolism [ICD-10 code: I74])
- Major bleeding (intracranial and gastrointestinal)

10.1.2 Cohort 2 (NVAF + Diabetes)

Diabetic Population I

A total of 10,017 rivaroxaban- and 11,665 warfarin-naïve patients with NVAF and diabetes (type 1 or 2) were selected in diabetic population I of Cohort 2. The proportion of patients with type 2 diabetes mellitus (T2DM) was 99.4%. Patients had to have a baseline history of type 1 or 2 diabetes mellitus, whereas those with Stage 5 CKD or receiving hemodialysis at baseline were excluded. Patients with alternate indications for full-dose OAC during the baseline period were also excluded.

The following endpoints (incidences of events per 100 person-years) were analyzed to evaluate the effectiveness and safety of rivaroxaban over warfarin in diabetic population I [28]:

- AKI
- Composite of progression to Stage 5 CKD or need for hemodialysis

Diabetic Population II

A total of 10,700 rivaroxaban- and 13,946 warfarin-naïve patients with NVAF and T2DM were selected in diabetic population II of Cohort 2. Patients had to have an inpatient or outpatient diagnosis code in any position for T2DM.

The following endpoints (incidences of events per 100 person-years) were analyzed to evaluate the effectiveness and safety of rivaroxaban over warfarin in diabetic population II [29]:

- MACE
- MALE
- Major bleeding (intracranial and gastrointestinal)

Diabetic Population III

Initially, a total of 8,424 rivaroxaban- and 11,348 warfarin-naïve patients with NVAF and diabetes were selected in diabetic population III of Cohort 2. After a PS-based *1:1* matched analysis, 5,517 patients were available in both exposure groups. Patients had to have an inpatient or outpatient diagnosis code in any position for diabetes. Individuals were excluded if they had a history of VTE or orthopedic arthroplasty, were pregnant, had a transient cause of nonvalvular atrial fibrillation, or were prescribed >1 oral anticoagulant.

The following endpoints (incidences of events per 100 person-years) were analyzed to evaluate the effectiveness and safety of rivaroxaban over warfarin in diabetic population III [30]:

- Composite of SSE
- Major bleeding (intracranial and gastrointestinal)

10.1.3 Cohort 3 (NVAF + CAD/PAD)

A total of 3,257 rivaroxaban- and 5,046 warfarin-naïve patients with NVAF and CAD/PAD were selected in Cohort 3. The patients had to have ≥1 billing code, indicative of CAD and/or PAD, before index OAC initiation. Patients with alternate indications for full-dose OAC during the baseline period were excluded.

The following endpoints (incidences of events per 100 person-years) were analyzed to evaluate the effectiveness and safety of rivaroxaban over warfarin in Cohort 3 [31]:

- Composite of major thrombotic vascular events (MTVEs; including IS, MI, and need for lower limb revascularization/major amputation)
- MACE
- MALE
- Major bleeding (intracranial and gastrointestinal)

10.1.4 Cohort 4 (NVAF + Renal impairment)

A total of 1,896 rivaroxaban- (38.7% received a dose <20 mg/day) and 4,848 warfarin-naïve patients with NVAF and severe kidney disease or receiving hemodialysis were selected in Cohort 4. The patients had to have billing codes indicative of Stage 4 or 5 CKD or the receipt of hemodialysis. Patients with alternate indications for full-dose OAC during the baseline period were excluded.

The following endpoints (incidences of events per 100 person-years) were analyzed to evaluate the effectiveness and safety of rivaroxaban over warfarin in Cohort 4 [32]:

- Composite of SSE
- IS
- Major bleeding (intracranial and gastrointestinal)

10.1.5 Cohort 5 (NVAF + Heart failure)

Initially, a total of 4,533 rivaroxaban- and 8,222 warfarin-naïve patients with NVAF and HF were selected in Cohort 5. After PS-based *1:1* matched analysis, 3,418 patients were available in both exposure groups. In the rivaroxaban exposure group, 32% received the reduced dose of 15 mg once/day. The patients had to have an inpatient or outpatient diagnosis code in any position for HF (ICD-10 = I50, I09.81). Individuals were excluded if they had a history of VTE or orthopedic arthroplasty, were pregnant, had a transient cause of NVAF, or were prescribed >1 OAC.

The following endpoints (incidences of events per 100 person-years) were analyzed to evaluate the effectiveness and safety of rivaroxaban over warfarin in Cohort 5 [33]:

- Composite of SSE
- IS
- Major bleeding (intracranial)

10.1.6 Cohort 6 (NVAF + Polypharmacy)

Cohort 6 included the patients who were experiencing polypharmacy (defined as having concomitant prescription claims for ≥5 unique chronic medications). A separate secondary analysis defining substantial polypharmacy (≥10 chronic medications) was also performed.

In the polypharmacy analysis, a total of 13,981 naïve patients with NVAF, who were also receiving ≥5 concomitant medications, were selected in each of the rivaroxaban and warfarin exposure groups after PS-based *1:1* matched analysis. In the rivaroxaban exposure group, 24.1% received the reduced dose of 15 mg once/day. Individuals were excluded if they had a history of VTE or orthopedic arthroplasty, were pregnant, had a transient cause of NVAF, or were prescribed more than one OAC. In the separate secondary analysis (≥10 chronic medications), a total of 1,765 naïve patients with NVAF, who were also receiving ≥10 concomitant medications, were selected in each of the rivaroxaban and warfarin exposure groups after PS-based *1:1* matched analysis.

The following endpoints (incidences of events per 100 person-years) were analyzed to evaluate the effectiveness and safety of rivaroxaban over warfarin in Cohort 6 [34]:

- Composite of SSE
- IS
- Major bleeding

10.1.7 Cohort 7 (NVAF + CHA_2DS_2-VASc score = 1)

A total of 3,319 naïve patients with NVAF and a non-sex-related CHA_2DS_2-VASc score of 1 (low stroke risk) were selected in each of the rivaroxaban and warfarin exposure groups after PS-based *1:1* matched analysis. The patients had to have a single non-sex-related risk factor that was assigned 1 point in the CHA_2DS_2-VASc score (congestive heart failure, hypertension, diabetes, vascular disease, and age 65-74 years). Individuals were excluded if they were ≥75 years old; had a history of stroke/TIA, VTE, or orthopedic arthroplasty; were pregnant; had a transient cause of NVAF; or were prescribed >1 oral anticoagulant.

The following endpoints (incidences of events per 100 person-years) were analyzed to evaluate the effectiveness and safety of rivaroxaban over warfarin in Cohort 7 [35]:

- Composite of SSE
- IS
- Major bleeding (intracranial and gastrointestinal)

Table 10–1: Overview of study cohorts

Cohort	Time frame* / Adjustment method**	Basis of cohort formation - Existence of comorbidities/co-medications at baseline	Patients with Stage 5 CKD or requiring hemodialysis - Incl./Excl.	Patients with CKD stages Incl./Excl.	Additional Incl./Excl. criteria
Cohort 1 (N=36,318 (R) N=36,281 (W))	JAN 2012-DEC 2017 / IPTW	Patients with NVAF	Excluded	Patients with CKD stages 3 and 4 were included	
Cohort 2 - Diabetic population I (N=10,017 (R) N=11,665 (W))	JAN 2011-DEC 2017 / IPTW	NVAF Patients with Type 1 or 2 diabetes	Excluded	Patients with CKD stages 3 and 4 were included	
Cohort 2 - Diabetic population II (N=10,700 (R) N=13,946 (W))	JAN 2012-DEC 2017 / IPTW	NVAF Patients with Type 2 diabetes	Included	Patients with CKD stages 3 ,4, and 5 were included	
Cohort 2 - Diabetic population III (N=5,517 (R) N=5,517 (W))	NOV 2011-DEC 2016 / 1:1 PS-based matching	NVAF Patients with Type 1 or 2 diabetes	Included	Patients with CKD stages 3 ,4, and 5 were included	
Cohort 3 (NVAF + CAD/PAD) (N=3,257 (R) N=5,046 (W))	JAN 2012-DEC 2017 / IPTW	NVAF Patients with CAD/PAD	Included	Patients with CKD stages 3, 4, and 5 were included	
Cohort 4 (NVAF + Renal impairment) (N=1,896 (R) N=4,848 (W))	JAN 2012-DEC 2017 / IPTW	NVAF Patients with CKD stages 4 or 5 or requiring hemodialysis	Included	Patients with CKD stages 4 and 5 were included	
Cohort 5 (NVAF + Heart failure) (N=3,418 (R) N=3,418 (W))	NOV 2011-DEC 2016 / 1:1 PS-based matching	NVAF Patients with heart failure	Included	Patients with CKD stages 3 ,4, and 5 were included	
Cohort 6 (NVAF + Poly-pharmacy) (N=13,981 (R) N=13,981 (W)) Cohort 6 (NVAF + Poly-pharmacy) (N=1,765 (R) N=1,765 (W))	NOV 2012-MAR 2017 / 1:1 PS-based matching	NVAF Patients having ≥5 Concomitant chronic medications NVAF Patients having ≥10 Concomitant chronic	Included	Patients with CKD stages 3 ,4, and 5 were included	
Cohort 7 (NVAF + CHA2DS2-VASc score = 1) (N=3,319 (R) N=3,319 (W))	NOV 2011-DEC 2016 / 1:1 PS-based matching	NVAF Patients with Non-sex-related CHA2DS2-VASc score of 1	Included	Patients with CKD stages 3 ,4, and 5 were included	Patients with a history of stroke/TIA were excluded.

* time period of collected data from IBM Watson MarketScan database
** adjustment method for baseline covariates

10.2 Descriptive data

10.2.1 Cohort 1

Table 10–2 summarizes the descriptive statistics of the patient baseline characteristics (gender, age, comorbidities, and comedications) in Cohort 1. Baseline covariates were well balanced after inverse probability of treatment weighting (IPTW) (absolute standardized differences ≤0.1 for all covariates). There were more men than women in both rivaroxaban (61.6%) and warfarin (61.0%) exposure groups. Median (25%, 75% range) values for age, duration of available patient follow-up, time on OAC, and CHA_2DS_2-VASc score were 69 (60, 79) years, 1.8 (0.8, 3.3) years, 141 (54, 355) days, and 3 (2, 4), respectively. At baseline, Stage 3 and Stage 4 CKDs were present in 5% and 1% of the patients, respectively, and proteinuria was present in 2% of the patients.

Table 10–2: Patient baseline characteristics stratified by exposure status and before and after IPTW: Cohort 1

	Before IPTW			After IPTW		
	Rivaroxaban N=36,318 (%)	Warfarin N=36,281 (%)	Absolute standardized difference	Rivaroxaban N=36,318 (%)	Warfarin N=36,281 (%)	Absolute standardized difference
Demographics						
Age (years)						
18-49	7.5	3.7	0.16	5.7	5.4	0.01
50-64	40.7	28.0	0.27	34.8	34.1	0.02
65-74	22.8	22.7	0.00	22.7	22.8	0.00
75-79	11.6	14.9	0.10	13.6	13.4	0.01
80	17.4	30.6	0.31	23.2	24.3	0.03
Male sex	63.6	59.4	0.09	61.6	61.0	0.01
Past medical history						
Acute decompensate heart failure	1.4	2.9	0.10	2.2	2.2	0.00
AKI	5.6	8.4	0.11	6.8	7.0	0.01
Anal fistula	0.2	0.2	0.01	0.2	0.2	0.01
Anemia	10.4	14.8	0.13	12.5	12.8	0.01
Anxiety	9.0	7.6	0.05	8.5	8.3	0.01
Asthma	7.1	6.1	0.04	6.7	6.6	0.01
Barrett's esophagus	1.2	1.0	0.02	1.1	1.1	0.00
Gastrointestinal bleeding	0.8	1.2	0.04	1.0	1.0	0.01
Genital urinary bleeding	0.1	0.1	0.01	0.1	0.1	0.01
ICH	0.1	0.1	0.02	0.1	0.1	0.00
IS	5.1	9.1	0.15	7.0	7.2	0.01
Coronary artery bypass grafting	7.3	10.7	0.12	9.1	9.2	0.01
Cancer	10.4	12.0	0.05	11.0	11.2	0.01
Carotid stenosis	6.1	8.2	0.08	7.3	7.2	0.00
CKD						
Stage 3	3.7	6.3	0.12	4.9	5.1	0.01
Stage 4	0.5	1.8	0.13	1.0	1.2	0.02

Table 10–2: Patient baseline characteristics stratified by exposure status and before and after IPTW: Cohort 1

	Before IPTW			After IPTW		
	Rivaroxaban N=36,318 (%)	Warfarin N=36,281 (%)	Absolute standardized difference	Rivaroxaban N=36,318 (%)	Warfarin N=36,281 (%)	Absolute standardized difference
Chronic obstructive pulmonary disease	11.0	14.8	0.11	12.7	13.1	0.01
CAD	2.7	3.7	0.06	3.2	3.3	0.01
Coagulopathy	2.4	4.3	0.11	3.3	3.4	0.01
Crohn's disease	0.8	1.2	0.04	1.0	1.1	0.01
Dementia	3.7	6.0	0.10	4.8	4.9	0.01
Depression	8.2	8.9	0.03	8.5	8.6	0.01
Diverticulitis	7.1	6.9	0.01	7.1	7.0	0.01
Type 1 diabetes	5.6	7.8	0.09	6.6	6.8	0.01
Type 2 diabetes	27.4	32.0	0.10	29.2	29.7	0.01
Ethanol abuse	2.1	1.7	0.03	2.0	1.8	0.01
Falls	5.4	4.9	0.02	5.2	5.3	0.00
Gastroesophageal reflux disease	13.4	11.4	0.06	12.5	12.2	0.01
Hemorrhoids	3.8	3.6	0.02	3.7	3.7	0.00
HF	19.6	27.5	0.19	23.1	23.7	0.01
Hypertension	73.6	74.1	0.01	74.1	74.0	0.00
Hypothyroidism	14.2	14.4	0.01	14.6	14.3	0.01
Joint pain or stiffness	34.0	34.8	0.02	35.0	34.8	0.00
Liver dysfunction	3.7	3.5	0.01	3.6	3.7	0.01
MI	5.3	8.3	0.12	6.7	6.8	0.01
Osteoarthritis	21.1	21.8	0.02	22.3	22.0	0.01
Obesity	18.2	13.2	0.14	15.7	15.5	0.01
Other kidney disease	0.1	0.2	0.03	0.1	0.2	0.01
Proteinuria	2.0	2.1	0.01	2.0	2.1	0.01
Peripheral artery disease	5.8	8.1	0.09	6.8	7.1	0.01
Percutaneous coronary intervention	2.9	3.3	0.02	3.2	3.1	0.00
Psychosis	2.3	3.4	0.06	2.6	2.9	0.01
Rheumatoid arthritis	15.8	15.5	0.01	16.1	15.8	0.01
Sleep apnea	16.7	13.1	0.10	15.1	14.8	0.01
Smoker	6.2	5.5	0.03	5.9	6.0	0.00
Ulcerative colitis	0.5	0.6	0.01	0.6	0.6	0.00
Upper gastrointestinal testing	5.2	5.7	0.02	5.5	5.5	0.00
Medications						
α-glucosidase inhibitors	0.1	0.1	0.02	0.1	0.1	0.01
Amiodarone	4.3	4.2	0.00	4.4	4.3	0.00
ACEI or ARB	52.8	53.1	0.01	53.1	53.1	0.00
Aspirin	1.8	1.6	0.02	1.7	1.7	0.00
β-blockers	56.3	54.4	0.04	55.6	55.3	0.01

Table 10–2: Patient baseline characteristics stratified by exposure status and before and after IPTW: Cohort 1

	Before IPTW			After IPTW		
	Rivaroxaban N=36,318 (%)	Warfarin N=36,281 (%)	Absolute standardized difference	Rivaroxaban N=36,318 (%)	Warfarin N=36,281 (%)	Absolute standardized difference
Cyclooxygenase-2 inhibitors	2.9	2.8	0.01	2.9	2.9	0.00
Dihydropyridine calcium channel blockers	22.1	23.3	0.03	22.8	22.9	0.00
Digoxin	5.5	6.9	0.06	6.1	6.3	0.01
Diltiazem	12.3	11.0	0.04	11.9	11.6	0.01
Dipeptidyl peptidase-4 inhibitors	3.0	3.1	0.00	3.2	3.0	0.01
Dronedarone	2.6	1.5	0.08	2.1	2.1	0.00
Glucagon-like peptide-1 analogues	1.4	1.0	0.04	1.3	1.2	0.01
Histamine-2 receptor antagonists	3.6	4.0	0.02	3.8	3.9	0.01
Helicobacter pylori treatment	0.4	0.5	0.01	0.5	0.5	0.01
Hypnotics	6.3	5.8	0.02	6.2	6.1	0.01
Insulin	5.3	6.9	0.07	6.0	6.2	0.01
Loop diuretics	14.2	20.7	0.17	17.2	17.7	0.01
Metformin	15.2	14.8	0.01	15.1	14.9	0.01
NSAIDs	20.4	16.9	0.09	18.9	18.6	0.01
Other antiarrhythmic agents	11.4	7.0	0.15	9.4	9.2	0.01
Other lipid drugs	9.1	9.0	0.00	9.3	9.0	0.01
Other antidepressants	7.0	7.5	0.02	7.2	7.4	0.01
P2Y12 platelet inhibitors	9.7	11.0	0.05	10.5	10.5	0.00
PPIs	22.7	22.0	0.02	22.6	22.4	0.00
SGLT2 inhibitors	0.6	0.2	0.07	0.4	0.4	0.01
SSRI or SNRI	13.5	13.6	0.00	13.6	13.6	0.00
Statins	49.4	50.8	0.03	50.1	50.1	0.00
Sulfonylureas or glinides	7.3	9.7	0.09	8.3	8.6	0.01
Systemic corticosteroids	20.7	18.8	0.05	20.0	19.8	0.01
Thiazides	27.7	27.8	0.00	27.7	27.7	0.00
Thiazolidinediones	1.9	2.5	0.05	2.2	2.2	0.00
Warfarin inhibitors	64.4	63.2	0.03	64.1	64.0	0.00
Warfarin inducers	27.1	27.1	0.00	27.3	27.4	0.00
Verapamil	2.0	2.1	0.01	0.02	0.02	0.00

10.2.2 Cohort 2 (NVAF + Diabetes)

Diabetic Population I

Table 10–3 summarizes the descriptive statistics of the patient baseline characteristics (gender, age, comorbidities, and comedications) stratified by exposure status after IPTW of the study population in diabetic population I of Cohort 2.

Baseline covariates were well balanced after IPTW (absolute standardized differences ≤0.1 for all covariates). There were more men than women in both rivaroxaban (63.8%) and warfarin (63.6%) exposure groups. Median (25%, 75% range) values for age, duration of available patient follow-up, time on OAC, and CHA_2DS_2-VASc score were 70 (62, 79) years, 1.7 (0.76, 3.2) years, 153 (58, 366) days, and 3 (2, 5), respectively. At baseline, the proportions of patients with CAD, PAD, prior MACE, and prior MALE were 11%, 5.1%, 9.0% and 1.4%, respectively. At baseline, Stage 3 and Stage 4 CKD were present in 8.5% and 2.2% of the patients, respectively; and proteinuria was present in 4.2% of the patients.

Table 10–3: Patient baseline characteristics stratified by exposure status after IPTW: Cohort 2 (diabetic population I)

Variables	Rivaroxaban N=10,017 (%)	Warfarin N=11,665 (%)	Absolute standardized difference
Demographics			
Age (years)			
Age 18-49 years	3.3	3.1	0.01
Age 50-64 years	33.4	33.0	0.01
Age 65-74 years	26.0	26.1	0.00
Age 75-79 years	14.9	15.2	0.01
Age ≥80 years	22.3	22.7	0.01
Male sex	63.8	63.6	0.01
Index year 2015-2017 (vs. 2012-2014)	28.4	27.4	0.02
Past medical history			
Acute decompensated heart failure (90 days since hospitalization)	2.9	2.9	0.00
AKI	11.2	11.3	0.01
Anal fistula	0.1	0.1	0.00
Anemia	16.4	16.9	0.01
Anxiety	8.0	7.9	0.00
Asthma	7.2	7.3	0.00
Barrett's esophagus	1.1	1.1	0.01
Gastrointestinal bleeding	1.1	1.1	0.01
ICH	0.1	0.2	0.01
Genital urinary bleeding	0.1	0.1	0.00
IS	8.5	8.7	0.01
Coronary artery bypass grafting	12.7	12.9	0.01
Cancer	12.2	12.2	0.00
Carotid stenosis	9.2	9.3	0.01
CKD, Stage 3	8.3	8.5	0.01
CKD, Stage 4	1.9	2.2	0.02
Chronic obstructive pulmonary disease	15.8	16.1	0.01
CAD	4.6	4.7	0.01
Coagulopathy	3.8	3.9	0.01
Crohn's disease	1.1	1.2	0.01
Dementia	5.5	5.6	0.01

Table 10–3: Patient baseline characteristics stratified by exposure status after IPTW: Cohort 2 (diabetic population I)

Variables	Rivaroxaban N=10,017 (%)	Warfarin N=11,665 (%)	Absolute standardized difference
Depression	9.7	9.9	0.01
Diverticulitis	7.2	7.2	0.00
Ethanol abuse	1.4	1.4	0.00
Falls	6.4	6.2	0.01
Gastroesophageal reflux disease	11.5	11.4	0.01
Hemorrhoids	3.8	3.7	0.00
HF	29.6	30.0	0.01
Hypertension	85.5	85.5	0.00
Hypothyroidism	16.7	16.6	0.00
Joint pain or stiffness	39.1	39.2	0.00
Liver dysfunction	4.6	4.6	0.00
MI	3.8	4.0	0.01
MALE	0.7	0.8	0.01
Osteoarthritis	23.0	23.1	0.00
Obesity	23.3	22.9	0.01
Other kidney disease	0.2	0.3	0.01
Proteinuria	4.0	4.0	0.00
Peripheral artery disease	10.0	10.1	0.00
Percutaneous coronary intervention	4.4	4.3	0.01
Psychosis	3.6	3.6	0.00
Rheumatoid arthritis	16.4	16.3	0.01
Sleep apnea	20.5	20.2	0.01
Smoker	5.8	5.8	0.00
Ulcerative colitis	0.5	0.6	0.01
Upper gastrointestinal testing	6.3	6.3	0.00
Medications			
α-glucosidase inhibitors	0.3	0.3	0.00
Amiodarone	4.8	4.7	0.00
ACEI or ARB	70.3	70.3	0.00
β-blockers	61.3	61.2	0.00
Cyclooxygenase-2 inhibitors	2.9	2.9	0.00
Dihydropyridine calcium channel blockers	28.9	28.6	0.01
Digoxin	7.6	7.7	0.00
Diltiazem	11.5	11.3	0.00
Dipeptidyl peptidase-4 inhibitors	9.9	9.7	0.01
Dronedarone	1.6	1.5	0.01
Glucagon-like peptide-1 analogues	4.0	3.9	0.00
Histamine-2 receptor antagonists	4.5	4.7	0.01
Helicobacter pylori treatment	0.5	0.5	0.00
Hypnotics	6.5	6.5	0.00
Insulin	19.7	19.8	0.00
Loop diuretics	26.0	26.4	0.01
Metformin	47.2	46.7	0.01
NSAIDs	19.9	19.6	0.01
Other antiarrhythmic agents	6.8	6.6	0.01
Other lipid drugs	14.2	14.2	0.00
Other antidepressants	8.6	8.7	0.00
P2Y12 platelet inhibitors	14.8	14.7	0.00
PPIs	24.7	24.7	0.00

Table 10–3: Patient baseline characteristics stratified by exposure status after IPTW: Cohort 2 (diabetic population I)

Variables	Rivaroxaban N=10,017 (%)	Warfarin N=11,665 (%)	Absolute standardized difference
SGLT2 inhibitors	1.4	1.4	0.00
SSRIs or SNRIs	15.6	15.6	0.00
Statins	65.9	65.9	0.00
Sulfonylureas or glinides	27.1	27.2	0.00
Systemic corticosteroids	19.9	19.9	0.00
Thiazides	33.6	33.4	0.00
Thiazolidinediones	6.7	6.9	0.01
Warfarin inhibitors	71.4	71.3	0.00
Warfarin inducers	32.6	32.7	0.00
Verapamil	2.1	2.1	0.00

Diabetic Population II

Table 10–4 summarizes the descriptive statistics of the patient baseline characteristics (gender, age, comorbidities, and comedications) stratified by exposure status after IPTW analysis of the study population in diabetic population II of Cohort 2.

Baseline covariates were well balanced after IPTW (absolute standardized differences ≤0.02 for all covariates). There were more men than women in both rivaroxaban (64.7%) and warfarin (62.7%) exposure groups. Median (25%, 75% range) values for age, duration of available patient follow-up, and CHA_2DS_2-VASc score were 70 (62, 79) years, 1.4 (0.6, 2.7) years, and 4 (3, 5), respectively. At baseline, the proportions of patients with CAD, PAD, prior MACE, and prior MALE were 11%, 5.1%, 9.0% and 1.4%, respectively. Notably, the proportion of patients with CKD stage ≥3 was 20.8% at baseline.

Table 10–4: Patient baseline characteristics stratified by exposure status after IPTW: Cohort 2 (diabetic population II)

Variables	Rivaroxaban N=10,700 (%)	Warfarin N=13,946 (%)	Absolute standardized difference
Demographics			
Age (years)			
18-49	3.2	3.0	0.01
50-64	33.0	32.8	0.00
65-74	26.5	26.7	0.01
75-79	15.1	15.2	0.00
≥80	22.3	22.3	0.00
Men	64.7	62.7	0.01
Medical history			
AKI			
Anal fistula	0.1	0.2	0.01
Anemia	20.7	21.7	0.03
Anxiety	8.7	8.5	0.01
Gastrointestinal bleeding	1.4	1.4	0.00
ICH	0.2	0.2	0.00
Genital urinary bleeding	0.1	0.1	0.01
IS	9.3	9.3	0.00

Table 10–4: Patient baseline characteristics stratified by exposure status after IPTW: Cohort 2 (diabetic population II)

Variables	Rivaroxaban N=10,700 (%)	Warfarin N=13,946 (%)	Absolute standardized difference
Coronary artery bypass grafting	14.1	14.2	0.00
Cancer	13.5	13.6	0.00
Carotid stenosis	9.7	9.6	0.00
CKD			
Stage 3	10.5	10.4	0.00
Stage 4	3.5	4.0	0.02
CAD	5.3	5.1	0.01
Coagulopathy	4.7	5.0	0.01
Crohn's disease	1.4	1.6	0.01
Depression	11.0	11.0	0.00
Diverticulitis	7.5	7.6	0.01
Ethanol abuse	1.5	1.4	0.00
Falls	7.2	7.0	0.01
Gastroesophageal reflux disease	12.1	11.9	0.01
Hemorrhoids	3.8	3.8	0.00
HF	33.0	33.4	0.01
Hypertension	86.5	86.5	0.00
Hypothyroidism	17.2	16.8	0.01
Joint pain or stiffness	41.4	41.2	0.01
Liver dysfunction	5.1	5.2	0.01
MI	10.0	10.4	0.01
Osteoarthritis	23.3	23.5	0.01
Obesity	23.8	23.7	0.00
Peripheral artery disease	10.7	11.2	0.02
Percutaneous coronary intervention	4.6	4.5	0.00
Psychosis	3.8	4.1	0.01
Rheumatoid arthritis	16.7	16.2	0.01
Sleep apnea	20.7	20.5	0.00
Smoker	6.1	6.1	0.00
Ulcerative colitis	0.6	0.7	0.02
Upper gastrointestinal testing	6.9	7.1	0.01
Medication			
α-glucosidase inhibitors	0.3	0.3	0.01
Amiodarone	5.5	5.4	0.01
ACEIs or ARBs	69.7	69.1	0.02
β-blockers	62.5	62.2	0.01
Cyclooxygenase-2 inhibitors	2.8	2.8	0.00
Dihydropyridine calcium channel blockers	30.0	29.7	0.01
Digoxin	7.4	7.6	0.01
Diltiazem	11.5	11.5	0.00
Dipeptidyl peptidase-4 inhibitors	9.9	9.8	0.00
Dronedarone	1.5	1.4	0.01
Glucagon-like peptide-1 analogues	3.9	3.8	0.00
Histamine-2 receptor antagonists	5.1	5.0	0.00
Helicobacter pylori treatment	0.6	0.6	0.00
Hypnotics	7.0	6.9	0.01
Insulin	21.6	21.8	0.01
Loop diuretics	28.6	28.7	0.00
Metformin	45.0	44.2	0.02

Table 10–4: Patient baseline characteristics stratified by exposure status after IPTW: Cohort 2 (diabetic population II)

Variables	Rivaroxaban N=10,700 (%)	Warfarin N=13,946 (%)	Absolute standardized difference
NSAIDs	19.4	19.1	0.01
Other antiarrhythmic agents	6.5	6.2	0.01
Other lipid drugs	14.2	14.4	0.00
Other antidepressants	9.0	9.2	0.01
P2Y12 platelet inhibitors	16.2	16.1	0.01
PPIs	25.8	26.0	0.00
SGLT2 inhibitors	1.4	1.3	0.01
SSRIs or SNRIs	16.2	16.2	0.00
Statins	65.7	65.6	0.00
Sulphonylureas or glinides	27.0	27.1	0.00
Systemic corticosteroids	20.9	21.1	0.01
Thiazides	32.9	32.7	0.00
Thiazolidinediones	6.5	6.7	0.01
Warfarin inhibitors	72.8	72.4	0.01
Warfarin inducers	33.3	33.8	0.01
Verapamil	2.1	2.1	0.00

Diabetic Population III

Table 10–5 summarizes the descriptive statistics of the patient baseline characteristics (gender, age, comorbidities, $CHADS_2$ score, CHA_2DS_2-VASc score, modified HAS-BLED score, and comedications) of the study population in Cohort 2 (diabetic population I) before PS matching.

Table 10–5: Patient baseline characteristics stratified by exposure status before PS matching: Cohort 2 (diabetic population III)

Variable	Rivaroxaban N=8,424 (%)	Warfarin N=11,348 (%)	Absolute standardized difference
Demographics			
Age, years, median (IQR)*	67 (60, 76)	72 (63, 80)	
65-74 years	26.0	27.5	0.03
≥75 years	30.0	42.9	0.27
Male sex	64.4	62.1	0.05
Type 2 diabetes diagnosis	97.4	97.4	0.00
Comorbidities			
HF	21.3	32.9	0.26
Hypertension	86.4	84.7	0.05
Peripheral vascular disease	15.3	20.4	0.13
IS	5.9	10.4	0.17
MI	6.7	10.9	0.15
Percutaneous coronary intervention	3.9	4.0	0.01
Coronary artery bypass grafting	11.4	14.6	0.09
History of major bleeding	3.3	5.2	0.09
Gastrointestinal bleeding	0.8	1.5	0.07
ICH	0.1	0.2	0.03
AKI	6.9	13.5	0.22
CKD	13.3	24.7	0.30
ESRD	6.8	17.3	0.33

Table 10–5: Patient baseline characteristics stratified by exposure status before PS matching: Cohort 2 (diabetic population III)

Variable	Rivaroxaban N=8,424 (%)	Warfarin N=11,348 (%)	Absolute standardized difference
Liver disease	4.8	5.1	0.01
Coagulopathy	3.0	6.0	0.15
Gastroesophageal reflux disease	12.5	11.2	0.04
Upper gastrointestinal testing	6.8	7.6	0.03
Anemia	15.2	25.0	0.25
Asthma	8.4	7.2	0.04
Chronic obstructive pulmonary disease	13.7	19.3	0.15
Sleep apnea	21.8	18.7	0.08
Smoker	5.8	5.3	0.02
Hemorrhoids	3.9	3.9	0.00
Alcohol abuse	1.5	1.3	0.02
Anxiety	8.7	7.7	0.04
Depression	9.7	11.3	0.05
Psychosis	3.2	4.6	0.07
Obesity	24.8	19.8	0.12
Osteoarthritis	22.4	22.4	0.00
Back pain	19.2	17.9	0.03
Joint pain and stiffness	36.8	39.5	0.06
Headache	7.5	8.2	0.03
Diverticulitis	7.3	7.7	0.02
Crohn’s or ulcerative colitis	1.9	1.9	0.02
Helicobacter pylori	0.5	0.3	0.02
Hypothyroidism	17.4	16.3	0.03
Solid tumor	11.2	13.1	0.06
Lymphoma	1.5	1.7	0.02
Metastatic cancer	1.6	2.1	0.04
Medication use			
Antiplatelet drugs	14.7	16.0	0.03
NSAIDs	22.3	16.9	0.14
Cyclooxygenase-2-specific NSAIDs	3.3	2.7	0.04
ACEIs or ARBs	70.6	66.9	0.08
β-blockers	62.6	61.6	0.02
Diltiazem	12.8	11.4	0.04
Verapamil	2.2	2.1	0.01
Dihydropyridine calcium channel blockers	28.6	29.5	0.02
Loop diuretic	23.2	31.6	0.19
Thiazide diuretic	34.2	31.8	0.05
Digoxin	7.1	8.4	0.05
Amiodarone	5.4	5.4	0.00
Dronedarone	2.3	1.3	0.08
Other antiarrhythmic drugs	9.1	5.1	0.16
Statins	65.4	64.9	0.01
Other cholesterol-lowering drugs	14.5	14.1	0.01
Benzodiazepines	16.0	14.9	0.03
SSRIs or SNRIs	16.0	16.0	0.00

Table 10–5: Patient baseline characteristics stratified by exposure status before PS matching: Cohort 2 (diabetic population III)

Variable	Rivaroxaban N=8,424 (%)	Warfarin N=11,348 (%)	Absolute standardized difference
Other antidepressants	8.5	9.3	0.03
PPIs	26.6	25.6	0.03
Histamine-2 receptor antagonists	4.5	4.9	0.02
Systemic corticosteroids	21.2	20.4	0.02
Warfarin inducer	33.4	33.4	0.00
Warfarin inhibitor	73.3	70.9	0.05
Diabetes medications			
Metformin	49.2	39.1	0.21
Sulfonylureas or glinides	24.9	27.5	0.06
Thiazolidinediones	5.6	7.0	0.02
Dipeptidyl peptidase-4 inhibitors	10.4	8.9	0.05
Glucagon-like peptide-1 agonists	4.7	2.9	0.09
SGLT2 inhibitors	1.9	0.5	0.13
Insulin	18.3	22.0	0.09
α-glucosidase inhibitor	0.2	0.3	0.02
Risk stratification scores			
$CHADS_2$, median (IQR)	2 (2, 3)	2 (2, 3)	
0-1	12.3	19.8	0.21
2-3	75.6	69.6	0.13
≥4	12.1	10.6	0.05
CHA_2DS_2-VASc, median (IQR)	3 (2, 4)	4 (3, 5)	
0-1	6.0	3.8	0.10
2-3	52.6	39.8	0.26
≥4	41.4	56.4	0.30
Modified HAS-BLED, median (IQR)	2 (1, 3)	2 (2, 3)	
≥3	30.2	40.0	0.21

CHADS2=congestive heart failure, 1 point; hypertension, 1 point; age ≥75 y, 1 point; diabetes mellitus, 1 point; previous stroke or transient ischemic attack, 2 points.

CHA2DS2-VASc=congestive heart failure, 1 point; hypertension, 1 point; age ≥75 y, 2 points; diabetes mellitus, 1 point; previous stroke, transient ischemic attack or thromboembolism, 2 points; vascular disease, 1 point; age 65-74 y, 1 point; female sex, 1 point.

Modified HASBLED=hypertension, 1 point; age >65 y, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; liable international normalized ratio, not assessed; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point.

*Median age and $CHADS_2$, CHA_2DS_2-VASc, and modified HAS-BLED risk scores were not included in the propensity-score model; instead individual components of CHA_2DS_2-VASc, and modified HAS-BLED were used.

Table 10–6 summarizes the descriptive statistics of the patient baseline characteristics (gender, age, comorbidities, CHA_2DS_2-VASc score, modified HAS- BLED score, and comedications) of the study population in Cohort 2 (diabetic population I) after PS matching.

After PS-based *1:1* matched analysis, 5,517 patients were available in both exposure groups; there were more men than women in both rivaroxaban (63.3%) and warfarin (63.5%) exposure groups. Baseline covariates were well balanced after PS matching (absolute standardized differences ≤0.1 for all covariates). Median (25%, 75% range) values for age,

CHA_2DS_2-VASc score, and HAS-BLED score were 70 (62.00, 78.00) years, 3 (3, 4), and 2 (1, 3), respectively. The most common antidiabetic agents prescribed were metformin (45%), sulfonylureas (26%), and insulin (20%).

Table 10–6: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 2 (diabetic population III)

Variables	Rivaroxaban N=5,517 (%)	Warfarin N=5,517 (%)	Absolute standardized difference
Demographics			
Median (IQR) age* (years)	70 (62, 78)	70 (62, 78)	
65-74	27.9	27.7	0.00
≥75	36.7	36.5	0.00
Male	63.3	63.5	0.01
Type 2 diabetes diagnosis	97.3	97.0	0.02
Comorbidities			
HF	24.7	25.7	0.02
Hypertension	85.6	85.9	0.01
Peripheral vascular disease	20.3	21.1	0.02
IS	7.4	7.4	0.00
MI	8.0	8.1	0.00
Percutaneous coronary intervention	4.2	4.5	0.01
Coronary artery bypass grafting	13.0	13.3	0.01
History of major bleeding	4.0	3.8	0.01
Gastrointestinal bleeding	1.0	1.0	0.00
ICH	0.2	0.2	0.00
AKI	8.6	8.3	0.01
CKD	16.2	16.0	0.01
ESRD	9.2	9.0	0.01
Liver disease	4.7	4.9	0.01
Coagulopathy	3.6	3.5	0.01
Gastroesophageal reflux disease	11.6	12.2	0.02
Upper gastrointestinal testing	6.8	6.8	0.00
Anemia	17.9	17.7	0.01
Asthma	7.5	7.7	0.01
Chronic obstructive pulmonary disease	15.8	15.8	0.00
Sleep apnea	20.4	20.5	0.00
Smoker	5.7	5.5	0.01
Hemorrhoids	4.0	3.9	0.01
Alcohol abuse	1.4	1.5	0.01
Anxiety	8.0	8.3	0.01
Depression	10.3	9.9	0.01
Psychosis	3.7	3.6	0.00
Obesity	22.4	21.9	0.01
Osteoarthritis	22.7	22.8	0.00
Back pain	18.6	18.9	0.01
Joint pain and stiffness	37.2	38.2	0.02
Headache	7.8	7.8	0.00
Diverticulitis	7.5	7.4	0.00
Crohn's or ulcerative colitis	2.0	1.9	0.01
Helicobacter pylori	0.4	0.3	0.02
Hypothyroidism	17.1	16.9	0.01
Solid tumor	12.2	11.9	0.01
Lymphoma	1.7	1.7	0.00
Metastatic cancer	1.8	1.7	0.01

Table 10–6: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 2 (diabetic population III)

Variables	Rivaroxaban N=5,517 (%)	Warfarin N=5,517 (%)	Absolute standardized difference
Medication use			
Antiplatelet drugs	15.7	15.8	0.00
Non-steroidal anti-inflammatory drugs	21.5	21.8	0.01
Cyclooxygenase-2-specific NSAIDs	2.9	3.0	0.00
ACEIs or ARBs	69.2	70.5	0.03
β-blockers	61.6	61.6	0.00
Diltiazem	12.9	12.2	0.02
Verapamil	2.2	2.0	0.01
Dihydropyridine calcium channel blockers	29.5	29.2	0.01
Loop diuretic	26.4	26.4	0.00
Thiazide diuretic	33.1	33.3	0.00
Digoxin	8.0	7.4	0.02
Amiodarone	5.2	5.1	0.01
Dronedarone	1.8	1.6	0.02
Other antiarrhythmic drugs	6.3	6.4	0.00
Statins	65.5	65.1	0.01
Other cholesterol-lowering drugs	14.4	14.3	0.00
Benzodiazepines	15.4	15.3	0.00
SSRIs or SNRIs	16.1	16.1	0.00
Other antidepressants	9.0	8.9	0.00
PPIs	26.0	26.2	0.01
Histamine-2 receptor antagonists	4.6	5.0	0.02
Systemic corticosteroids	20.7	20.3	0.01
Warfarin inducer	33.3	32.2	0.02
Warfarin inhibitor	72.8	71.5	0.03
Diabetes medications			
Metformin	44.9	45.0	0.00
Sulfonylureas or glinides	26.4	26.2	0.00
Thiazolidinediones	6.9	6.0	0.04
Dipeptidyl peptidase-4 inhibitors	9.7	10.2	0.02
Glucagon-like peptide-1 agonists	3.7	3.6	0.01
SGLT2 inhibitors	1.1	0.9	0.02
Insulin	19.2	20.0	0.02
α-glucosidase inhibitor	0.2	0.3	0.01
Risk stratification scores			
Median (IQR)	2 (2, 3)	2 (2, 3)	
CHADS2[*†]			
0-1	10.5	11.6	0.04
2-3	75.2	72.9	0.05
≥4	14.3	15.5	0.03
Median (IQR)	3 (3, 4)	3 (2, 4)	
CHA_2DS_2-VASc score			
CHA_2DS_2-VASc score 0-1	4.5	5.2	0.03
CHA_2DS_2-VASc score 2-3	46.5	46.2	0.01
CHA_2DS_2-VASc score ≥4	51.0	51.4	0.00
Median (IQR)	2 (1, 3)	2 (1, 3)	

Table 10–6: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 2 (diabetic population III)

Variables	Rivaroxaban N=5,517 (%)	Warfarin N=5,517 (%)	Absolute standardized difference
Modified HAS-BLED			
HAS-BLED score ≥3	33.1	34.4	0.03

CHADS2: congestive heart failure, 1 point; hypertension, 1 point; age ≥75 years, 1 point; diabetes mellitus, 1 point; previous stroke or transient ischemic attack, 2 points.
CHA_2DS_2-VASc: congestive heart failure, 1 point; hypertension, 1 point; age ≥75 years, 2 points; diabetes mellitus, 1 point; previous stroke, transient ischemic attack or thromboembolism, 2 points; vascular disease, 1 point; age 65-74 years, 1 point; female sex, 1 point. Modified HASBLED: hypertension, 1 point; age >65 years, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; liable international normalized ratio, not assessed; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point.
*Median age and $CHADS_2$, CHA_2DS_2-VASc, and modified HAS-BLED risk scores were not included in the PS model; instead individual components of CHA_2DS_2-VASc and modified HAS-BLED were used.

10.2.3 Cohort 3 (NVAF + CAD/PAD)

Table 10–7 summarizes the descriptive statistics of the patient baseline characteristics (gender, age, comorbidities, and comedications) stratified by exposure status after IPTW of the study population in Cohort 3. Approximately, 47% of the patients had CAD (~10% has a history of MI) and 45% had PAD, with 21% having both CAD and PAD. Nearly 11% of all patients had a prior history of IS. Among the patients with a PAD diagnosis, ~19% had a prior MALE. Over 46% of the patients had diabetes at baseline and about one-third of patients had Stage 3 or worse CKD.

Baseline covariates were well balanced after IPTW (absolute standardized differences ≤0.07 for all covariates). There were more men than women in both rivaroxaban (64.1%) and warfarin (63.8%) exposure groups. Median (25%, 75% range) values for age, CHA_2DS_2-VASc score, and modified HAS-BLED score were 74 (65, 81) years, 3 (2, 4), and 2 (2, 3), respectively.

Table 10–7: Patient baseline characteristics stratified by exposure status after IPTW: Subgroup Cohort 3

Variable	Rivaroxaban N=3,257 (%)	Warfarin N=5,046 (%)	Absolute standardized difference
Demographics			
Age (years)			
50-64	23.6	22.6	0.02
65-74	26.0	26.2	0.01
75-79	17.4	17.2	0.00
≥80	31.2	32.4	0.03
Male sex	64.1	63.8	0.01
Receiving reduced dose	30.4	NA	NA
Comorbidities			
CAD	47.3	47.0	0.02
Peripheral artery disease	45.8	45.3	0.02
MALE in prior 12 months	18.7	19.6	0.05
HF	39.4	41.8	0.05
Hypertension	86.1	86.0	0.00
IS	11.0	11.5	0.02
Diabetes mellitus	45.8	46.6	0.02

Table 10–7: Patient baseline characteristics stratified by exposure status after IPTW: Subgroup Cohort 3

Variable	Rivaroxaban N=3,257 (%)	Warfarin N=5,046 (%)	Absolute standardized difference
MI	9.5	10.2	0.03
Percutaneous coronary intervention	10.5	10.5	0.00
Coronary artery bypass grafting	40.4	40.3	0.00
History of major bleeding	2.0	2.0	0.00
History of ICH	0.1	0.1	0.02
AKI	15.7	17.6	0.05
Stage 3 CKD	9.9	10.3	0.02
Stage 4 CKD	2.7	3.9	0.07
Stage 5 CKD or dialysis	12.1	14.4	0.07
Liver disease	4.6	4.6	0.00
Coagulopathy	5.8	6.7	0.04
Gastroesophageal reflux disease	15.2	14.9	0.01
Upper gastrointestinal testing	9.3	8.9	0.01
Anemia	22.2	23.8	0.04
Chronic lung disease	30.5	31.8	0.03
Sleep apnea	16.3	15.8	0.01
Smoker	9.0	9.3	0.01
Hemorrhoids	3.8	4.0	0.01
Alcohol abuse	1.8	1.8	0.00
Anxiety	9.9	9.6	0.01
Depression	11.0	11.1	0.00
Dementia	7.9	8.4	0.02
Psychosis	3.6	4.4	0.04
Obesity	17.5	16.6	0.02
Osteoarthritis	23.4	23.6	0.01
Joint pain and/or stiffness	44.8	46.1	0.03
Rheumatoid arthritis	15.7	15.6	0.01
Diverticulitis	8.9	8.6	0.01
Crohn’s disease	1.7	1.9	0.02
Ulcerative colitis	0.7	0.7	0.01
Hypothyroidism	16.4	15.9	0.01
Solid tumor	12.8	13.1	0.01
Lymphoma	1.5	1.4	0.00
Metastatic cancer	1.8	1.9	0.01
Medication use			
P2Y12 inhibitors	28.3	28.1	0.00
NSAIDs	17.7	17.0	0.02
Cyclooxygenase-2-specific NSAIDs	3.0	2.9	0.01
Cilostazol	2.6	2.8	0.01
Dipyridamole	0.2	0.2	0.01
ACEIs or ARBs	61.5	61.4	0.00
β-blockers	65.5	65.6	0.00
Diltiazem	11.9	11.0	0.03
Verapamil	1.9	1.8	0.01
Dihydropyridine calcium channel blockers	29.4	29.6	0.00
Loop diuretic	29.5	30.8	0.03
Thiazide diuretic	29.3	28.5	0.02
Digoxin	6.3	6.9	0.03
Amiodarone	7.3	7.3	0.00

Table 10–7: Patient baseline characteristics stratified by exposure status after IPTW: Subgroup Cohort 3

Variable	Rivaroxaban N=3,257 (%)	Warfarin N=5,046 (%)	Absolute standardized difference
Dronedarone	1.5	1.4	0.01
Other antiarrhythmic drugs	6.3	5.8	0.02
Statins	64.7	63.9	0.02
Other cholesterol-lowering drugs	13.0	12.6	0.01
Metformin	18.3	17.6	0.02
Sulfonylureas or glinides	12.8	13.7	0.03
Thiazolidinediones	2.7	2.9	0.01
Dipeptidyl peptidase-4 inhibitors	4.9	4.9	0.00
Glucagon-like peptide-1 agonists	1.6	1.4	0.02
Insulin	12.8	13.3	0.02
SSRIs or SNRIs	15	15.1	0.00
Other antidepressants	9.3	9.7	0.01
PPIs	29.3	28.6	0.02
Histamine-2 receptor antagonists	5.7	6.3	0.03
Systemic corticosteroids	25.1	23.8	0.03
Warfarin inducer	32.5	33.0	0.01
Warfarin inhibitor	74.1	73.2	0.02

10.2.4 Cohort 4 (NVAF + Renal impairment)

Table 10–8 summarizes the descriptive statistics of the patient baseline characteristics (gender, age, comorbidities, and comedications) of the study population in Cohort 4.

Baseline covariates were well balanced after IPTW (absolute standardized differences ≤0.1 for all covariates). There were more men than women in both rivaroxaban (58.4%) and warfarin (61.6%) exposure groups. Median (25%, 75% range) values for age, duration of available patient follow-up, time on OAC, and CHA_2DS_2-VASc score were 72 (63, 80) years, 1.4 (0.6, 2.7) years, 112 (38, 260) days, and 4 (2, 5), respectively. At baseline, nearly 9 out of every 10 patients (88%) were diagnosed with CKD Stage 5 or underwent hemodialysis.

Table 10–8: Patient baseline characteristics stratified by exposure status after IPTW: Cohort 4

	Rivaroxaban N = 1896 %	Warfarin N = 4848 %	Absolute standardized difference
Demographics			
Age, years	72 (63, 80)	72 (63, 80)	
18-49	2.9	2.9	0.002
50-64	26.5	27.7	0.027
65-74	27.7	26.7	0.022
75-79	15.9	15.7	0.005
80	27	27	0
Female sex	41.6	38.4	0.033
Past medical history			
Anal fistula	0.1	0.1	0.008
Anemia	44	47.6	0.072
Anxiety	12.5	11	0.045
Barrett's esophagus	1.4	1.2	0.016

Table 10–8: Patient baseline characteristics stratified by exposure status after IPTW: Cohort 4

	Rivaroxaban N = 1896 %	Warfarin N = 4848 %	Absolute standardized difference
Gastrointestinal bleeding	2.5	3.1	0.035
ICH	0.4	0.4	0
Genital urinary bleeding	0.2	0.3	0.015
IS	11.2	12.1	0.027
Coronary artery bypass grafting	19.3	19.9	0.016
Carotid stenosis	12	11.8	0.007
Chronic lung disease	36.6	34.6	0.043
Coagulopathy	10.2	11.3	0.034
Crohn's disease	3.9	4.4	0.025
Dementia	10.3	11.2	0.029
Depression	15.3	15.4	0.003
Diverticulitis	11.1	11	0.004
Diabetes mellitus	53.3	54.4	0.022
Ethanol abuse	2.2	2	0.016
Falls	12	10.5	0.047
Gastroesophageal reflux disease	16.1	15.7	0.011
Hemorrhoids	4.4	4.5	0.002
HF	49.8	51.1	0.027
Hypertension	87.8	88.4	0.019
Hypothyroidism	19.7	17.9	0.047
Joint pain or stiffness	49.6	48.9	0.014
Liver dysfunction	8.2	9.8	0.025
MI	16.3	16	0.016
Osteoarthritis	24.7	25.1	0.009
Obesity	20.1	20.9	0.018
Peripheral artery disease	12.7	14.5	0.053
Percutaneous coronary intervention	4.8	5	0.006
Psychosis	5.5	5.9	0.015
Rheumatoid arthritis	17	16.4	0.017
Sleep apnea	18.8	18.1	0.019
Smoker	7.7	7.4	0.011
Stage 4 CKD	11.4	12.5	0.033
Ulcerative colitis	1.5l	2.1	0.04
Upper gastrointestinal testing	10.6	11.2	0.019
Medications			
α-glucosidase inhibitors	4	3	0.016
Amiodarone	10.3	9.5	0.027
ACEIs or ARBs	59	55	0.079
Antiplatelet agents	18.2	18.3	0.004
β-blockers	66.1	66.4	0.006
Cyclooxygenase-2 inhibitors	2.3	2.3	0.005
Dihydropyridine calcium channel blockers	32.3	34	0.036
Digoxin	6	6.2	0.011
Diltiazem	11.5	11.5	0.002
Dipeptidyl peptidase-4 inhibitors	6.3	6	0.013
Dronedarone	1.1	1.1	0.006
Glucagon-like peptide-1 analogues	1.7	1.6	0.003
Histamine-2 receptor antagonists	7.3	6.1	0.049
Helicobacter pylori treatment	0..3	0.3	0.003

Table 10–8: Patient baseline characteristics stratified by exposure status after IPTW: Cohort 4

	Rivaroxaban N = 1896 %	Warfarin N = 4848 %	Absolute standardized difference
Hypnotics	8.5	8.7	0.007
Insulin	19.7	20.1	0.01
Loop diuretics	39.1	39.9	0.015
Metformin	14.3	13.4	0.027
NSAIDs	16.3	15.6	0.019
Other antiarrhythmic agents	5.2	4	0.059
Other lipid drugs	13.1	12.1	0.028
Other antidepressants	10.3	11.5	0.039
PPIs	31.7	33	0.027
SGLT2 inhibitors	0.6	0.4	0.03
SSRIs or SNRIs	17.9	18.5	0.017
Statins	56.7	58.2	0.031
Sulfonylurea or glinides	14	14.2	0.006
Systemic corticosteroids	28.6	3	0.031
Thiazides	24.8	24.9	0.003
Thiazolidinediones	2.4	2.8	0.022
Warfarin inhibitors	78.5	77.6	0.023
Warfarin inducers	37	38.2	0.025

10.2.5 Cohort 5 (NVAF + Heart failure)

Table 10–9 summarizes the descriptive statistics of the patient baseline characteristics (gender, age, comorbidities, $CHADS_2$ score, CHA_2DS_2-VASc score, modified HAS-BLED score, and comedications) of the study population in Cohort 5 after PS matching.

Baseline covariates were well balanced after PS matching (absolute standardized differences ≤0.04 for all covariates). There were more men than women in both rivaroxaban (58.6%) and warfarin (58.8%) exposure groups. Median (25%, 75% range) values for age, duration of available patient follow-up, time on OAC, and CHA_2DS_2-VASc score were 74 (63, 82) years, 1.4 (0.6, 2.5) years, 112 (38, 260) days, and 4 (3, 5), respectively. At baseline, Common HF medications included β-blockers (64%), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs; 62%), loop diuretics (46%), digoxin (11%), and aldosterone receptor antagonists (10%).

Table 10–9: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 5

	Rivaroxaban N = 3418 (%)	Warfarin N = 3418 (%)	Absolute standardized difference
Demographics			
Age, years, median (IQR)*	74 (63, 82)	74 (63, 82)	
65-74 years	22.3	22.1	0
≥75 years	55.8	56.1	0.01
Male sex	58.6	58.8	0
Comorbidities			
Diabetes mellitus	35.2	35.6	0.01
Hypertension	82.9	83.3	0.01

Table 10–9: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 5

	Rivaroxaban N = 3418 (%)	Warfarin N = 3418 (%)	Absolute standardized difference
Peripheral vascular disease	4.9	4.7	0.01
IS	7.7	8.1	0.01
MI	13.2	12.8	0.01
Percutaneous coronary intervention	5.1	5.1	0
Coronary artery bypass grafting	16.2	16.2	0
History of major bleeding	5.1	4.6	0.02
Gastrointestinal bleeding	1.7	1.5	0.02
ICH	0.2	0.2	0.01
AKI	13.1	12.7	0.01
CKD	17.2	16.6	0.02
ESRD	12.4	12.1	0.01
Liver disease	4.4	4.5	0.01
Coagulopathy	5.2	5.1	0
Gastroesophageal reflux disease	12.8	12.4	0.01
Upper gastrointestinal testing	6.9	7.3	0.01
Anemia	21.9	21.1	0.02
Asthma	9.6	8.8	0.03
Chronic obstructive pulmonary disease	27	27.3	0.01
Sleep apnea	18	17.7	0.01
Smoker	8.2	7.7	0.02
Hemorrhoids	3.7	3.3	0.02
Alcohol abuse	2.8	2.6	0.01
Anxiety	9.6	9.9	0.01
Depression	11.9	11.8	0.01
Psychosis	4.3	4.6	0.01
Obesity	20.3	19.5	0.02
Osteoarthritis	23.2	22.4	0.02
Back pain	18.6	18.5	0
Joint pain and stiffness	37.2	38	0.02
Headache	7	6.9	0.01
Diverticulitis	7.3	6.9	0.02
Crohn’s disease or ulcerative colitis	2.5	2.4	0.01
Helicobacter pylori	0.5	0.3	0.04
Hypothyroidism	16.8	17.2	0.01
Solid tumor	11.5	11.9	0.01
Lymphoma	1.9	2	0.01
Metastatic cancer	1.7	1.9	0.01
Medication use			
Antiplatelet drugs	16.9	17.9	0.03
NSAIDs	17.3	17.2	0
Cyclooxygenase-2-specific NSAIDs	2.6	2.8	0.01
ACEIs or ARBs	61.6	62.3	0.01
Aldosterone receptor antagonists	10.2	10	0.01
β-Blockers	64.5	64.3	0
Diltiazem	12	12.9	0.03

Table 10–9: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 5

	Rivaroxaban N = 3418 (%)	Warfarin N = 3418 (%)	Absolute standardized difference
Verapamil	2	1.9	0
Dihydropyridine calcium channel blockers	25.3	25.3	0
Loop diuretic	45.8	45.6	0
Thiazide diuretic	27	27.2	0
Digoxin	11.1	11.1	0
Amiodarone	8.7	8.5	0.01
Dronedarone	1.4	1.1	0.03
Other antiarrhythmic drugs	5.7	5	0.03
Statins	54	54.1	0
Other cholesterol-lowering drugs	10.2	10.3	0.01
Benzodiazepines	16.4	16.2	0.01
SSRIs or SNRIs	16.1	16.9	0.02
Other antidepressants	9.2	8.8	0.01
PPIs	25.6	24.9	0.02
Histamine-2 receptor antagonists	5	5.3	0.01
Systemic corticosteroids	25.3	24.9	0.01
Warfarin inducer	31.8	30.8	0.02
Warfarin inhibitor	67.6	68.3	0.02
Metformin	16.9	16.9	0
Sulfonylureas or glinides	11.6	12.2	0.02
Thiazolidinediones	2.5	2.2	0.02
Dipeptidyl peptidase-4 inhibitors	4.7	4.5	0.01
Glucagon-like peptide-1 agonists	1.2	1.2	0
SGLT2 inhibitors	0.2	0.2	0.01
Insulin	11.1	10.9	0
α-glucosidase inhibitor	0.2	0.1	0.01
Risk stratification scores			
$CHADS_2$, median (IQR)	3 (2,3)	3 (2,3)	
Mean ± SD	2.8 ± 1.0	2.9 ± 1.0	
1	8.6	7.7	0.03
2	27.9	27.8	
3	42.7	43.9	
≥4	20.8	20.5	0.01
CHA_2DS_2-VASc, median (IQR)	4 (3, 5)	4 (3,5)	
Mean ± SD	3.9 ± 1.4	4.0 ± 1.4	
1	4.5	3.8	0.04
2	13	12.8	
3	19.7	19.7	0
≥4	62.7	63.6	0.02
Modified HAS-BLED, median (IQR)	2 (2,3)	2 (2,3)	
Mean ± SD	2.3 ± 1.2	2.3 ± 1.1	
≥3	37.7	37.1	0.01

*Median age and $CHADS_2$, CHA_2DS_2-VASc, and modified HAS-BLED risk scores were not included in the PS model; instead individual components of CHA_2DS_2-VASc and modified HAS-BLED were used.

10.2.6 Cohort 6 (NVAF + Polypharmacy)

Table 10–10 summarizes the descriptive statistics of the patient baseline characteristics (gender, age, comorbidities, $CHADS_2$ score, CHA_2DS_2-VASc score, modified HAS-BLED score, and comedications) of the study population in Cohort 6 after PS matching.

Baseline covariates were well balanced after PS matching (absolute standardized differences ≤0.08 for all evaluated covariates). There were more men than women in both rivaroxaban (59.2%) and warfarin (59.2%) exposure groups. Median (25%, 75% range) values for age, duration of available patient follow-up, CHA_2DS_2-VASc score, and modified HAS-BLED scores were 71 (62, 80) years, 1.7 (0.7, 3.0) years, 3 (2, 4), and 2 (1, 3), respectively. At baseline, the most common interacting medications prescribed included warfarin inhibitors (75%), warfarin inducers (35%), diltiazem (13%), and amiodarone (6%). In this analysis, rivaroxaban was associated with significant 34% and 40% hazard reductions in SSE and IS alone vs. warfarin, respectively.

For the secondary analysis of patients, substantial polypharmacy (≥10 concomitant medications) included a total of 3,530 patients. After *1:1* PS-based matching, 1,765 patients were available in both rivaroxaban and warfarin groups. There were more men than women in both rivaroxaban (56.2%) and warfarin (57.7%) exposure groups. Median (25%, 75% range) values for age, duration of available patient follow-up, CHA_2DS_2-VASc score, and modified HAS-BLED scores were 72 (63, 79) years, 1.4 (0.6, 2.7) years, 4 (3, 5), and 2 (2, 3), respectively.

Table 10–10: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 6

Variable	Polypharmacy ≥5 concomitant chronic medications			Polypharmacy ≥10 concomitant chronic medications		
	Rivaroxaban (N=13,981) (%)	Warfarin (N=13,981) (%)	Absolute standardized difference	Rivaroxaban (N=1765) (%)	Warfarin (N=1765) (%)	Absolute standardized difference
Demographics						
Age (years), median (IQR)	71 (62, 79)	72 (63, 80)	NA	71 (63, 79)	72 (64, 80)	NA
65-74	25.8	25.8	0	29.9	30.5	0.01
≥75	38.5	42.5	0.08	39.6	41.5	0.04
Male sex	59.2	59.2	0	56.2	57.7	0.03
Receiving reduced dose of rivaroxaban	24.1	NA	NA	30.4	NA	NA
Comorbidities						
HF	29.6	32.9	0.07	46.9	50	0.06
Hypertension	83.6	83.4	0	88.2	88.6	0.01
IS	7.2	8.4	0.05	8.2	9.4	0.04
Diabetes mellitus	34.7	35.2	0.01	58.7	56.8	0.04
Peripheral vascular disease	3.8	4.3	0.03	4.9	5.3	0.02
MI	8.5	9.9	0.05	13.3	15.7	0.07
Percutaneous coronary intervention	4.6	5.1	0.02	7.4	8.2	0.03
Coronary artery bypass grafting	12.2	13.5	0.04	17.7	20.2	0.06
History of major bleeding	4	3.9	0	5.6	5.6	0
Gastrointestinal bleeding	1.2	1.4	0.02	1.4	1.3	0.01

Table 10–10: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 6

Variable	Polypharmacy ≥5 concomitant chronic medications			Polypharmacy ≥10 concomitant chronic medications		
	Rivaroxaban (N=13,981) (%)	Warfarin (N=13,981) (%)	Absolute standardized difference	Rivaroxaban (N=1765) (%)	Warfarin (N=1765) (%)	Absolute standardized difference
ICH	0.1	0.1	0	0.1	0.2	0.02
AKI	7.2	8.8	0.06	13.6	15.1	0.04
CKD	12.1	14.3	0.07	20	22.9	0.07
ESRD	7.2	9.3	0.08	12.8	14.6	0.05
Liver disease	4.5	4.7	0.01	5.9	5.8	0
Coagulopathy	3.5	4	0.03	3.9	4.1	0.01
Gastroesophageal reflux disease	14.3	14.3	0	18	16.8	0.03
Upper gastrointestinal testing	6.7	7.1	0.02	10	9.3	0.03
Anemia	15.4	17.7	0.06	22.8	23.9	0.03
Asthma	8.7	8.1	0.02	14.1	12.3	0.05
Chronic obstructive pulmonary disease	17.3	18.6	0.04	31.4	31.6	0
Sleep pane	17.6	16.9	0.02	27.7	27.1	0.01
Smoker	6.4	6.1	0.01	7.1	7	0.01
Hemorrhoids	3.8	3.8	0	4.2	4.7	0.02
Alcohol abuse	1.9	1.8	0	1.4	1.3	0.01
Anxiety	9.4	9.1	0.01	11.3	10.9	0.01
Depression	10.3	10.7	0.01	16.2	15.8	0.01
Psychosis	3.5	3.7	0.01	5.9	6	0
Obesity	17.8	16.8	0.03	24.8	24.1	0.02
Osteoarthritis	23.1	23.6	0.01	28.6	28.1	0.01
Back pain	18.4	18.1	0.01	24	22.8	0.03
Joint pain and stiffness	37.9	38.2	0.01	47.7	46.7	0.02
Headache	7.1	7.4	0.01	8.2	9.2	0.04
Diverticulitis	7.6	7.5	0	8.3	8.5	0.01
Crohn's disease or ulcerative colitis	2.6	2.6	0	5.1	5.8	0.03
Helicobacter pylori	0.4	0.3	0.01	0.4	0.3	0.01
Hypothyroidism	17.6	17.7	0	24.7	23.7	0.02
Solid tumor	12.3	12.4	0	13.4	14.5	0.03
Lymphoma	1.5	1.6	0.01	1.7	2.3	0.04
Metastatic cancer	1.9	2.1	0.02	2.4	2.6	0.01
Medication use						
Antiplatelet drugs	16.3	16.8	0.01	28.8	28.8	0
P2Y12 inhibitors	15.8	16.2	0.01	27.8	27.9	0
NSAIDs	22.2	20.4	0.04	25.6	23.9	0.04
Cyclooxygenase-2-specific NSAIDs	3.8	3.6	0.01	6.2	6	0.01
ACEIs or ARBs	67.9	66.5	0.03	80.3	79.6	0.02
β-Blockers	65.7	64.7	0.02	74.4	74.1	0.01
Diltiazem	13.5	12.5	0.03	16.1	15.3	0.02
Verapamil	2.6	2.3	0.02	3.3	3	0.02
Dihydropyridine calcium channel blockers	30.6	30.7	0	40.7	41	0.03
Loop diuretic	24.9	26.7	0.04	50.7	51.1	0.01
Thiazide diuretic	35.7	34.4	0.03	41.2	40.3	0.02
Digoxin	8.2	7.9	0.01	11.1	11.6	0.02
Amiodarone	5.9	5.8	0	8.7	8.1	0.02
Dronedarone	2.6	1.7	0.07	2	1.3	0.06

Table 10–10: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 6

Variable	Polypharmacy ≥5 concomitant chronic medications			Polypharmacy ≥10 concomitant chronic medications		
	Rivaroxaban (N=13,981) (%)	Warfarin (N=13,981) (%)	Absolute standardized difference	Rivaroxaban (N=1765) (%)	Warfarin (N=1765) (%)	Absolute standardized difference
Other antiarrhythmic drugs	9.7	7.6	0.08	7.5	6.6	0.03
Statins	64	63.7	0.01	77.7	77.7	0
Other cholesterol-lowering drugs	13.1	12.6	0.02	19.5	18.2	0.03
Metformin	22.7	21.7	0.02	40.9	38.9	0.04
Sulfonylureas or glinides	12.8	13.2	0.01	27.7	28.6	0.02
Thiazolidinediones	3.3	3.1	0.01	6.6	6.5	0
Dipeptidyl peptidase-4 inhibitors	5.1	4.9	0.01	11.4	10.5	0.03
Glucagon-like peptide-1 agonists	2.1	1.8	0.02	5	4.5	0.02
Insulin	9.7	10.4	0.02	26.5	26.4	0
Benzodiazepines	18	17.2	0.02	26	25.3	0.02
SSRIs or SNRIs	18.4	18.2	0.01	30.4	29.5	0.02
Other antidepressants	9.8	9.9	0	17.7	17.4	0.01
PPIs	31	30.4	0.01	48.2	45.7	0.05
Histamine-2 receptor antagonists	5.2	5.4	0.01	9.6	10.1	0.02
Systemic corticosteroids	24.5	24.2	0.01	35.4	35.5	0
Warfarin inducer	35.2	34.9	0.01	53.8	52.5	0.03
Warfarin inhibitor	75.2	74.1	0.03	87	86.5	0.02
Risk stratification scores						
$CHADS_2$, median (IQR)	2 (1, 3)	2 (1, 3)	NA	2 (2, 3)	3 (2, 3)	NA
CHA_2DS_2-VASc, median (IQR)	3 (2, 4)	3 (2, 4)	NA	4 (3, 5)	4 (3, 5)	NA
Modified HAS-BLEDa[1], median (IQR)	2 (1, 3)	2 (2, 3)	NA	2 (2, 3)	2 (2, 3)	NA

[1] Modified HAS-BLED scores = hypertension, 1 point; age > 65 years, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; liable international normalized ratio, not assessed; ethanol or drug abuse, 1 point; and drug predisposing to bleeding, 1 point.

10.2.7 Cohort 7 (NVAF + CHA_2DS_2-VASc score = 1)

Table 10–11 summarizes the descriptive statistics of the patient baseline characteristics (gender, age, comorbidities, modified HAS-BLED, and comedications) of the study population in Cohort 7 after PS matching.

Baseline covariates were well balanced after PS matching (absolute standardized differences ≤0.05 for all evaluated covariates). There were more men than women in both rivaroxaban (69.1%) and warfarin (69.8%) exposure groups. Median (25%, 75% range) values for age, duration of available patient follow-up, and modified HAS-BLED scores were 60 (55, 64) years, 1.6 (0.7, 2) years, and 1 (0, 1), respectively. At baseline, the most common qualifying

non-sex-CHA_2DS_2-VASc risk factor was hypertension (68.3%), followed by age 65-74 years (19.1%), diabetes (6.1%), and HF (5.1%). Table 2 depicts event rates at 1- and 2-year follow-up.

Table 10–11: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 7

Variable No. of patients	Rivaroxaban N=3319	Warfarin N=3319	Standardized n (%) difference
Demographics			
Age (years) median (IQR)*	60 (55, 64)	60 (56, 64)	0
Male sex	2295 (69.1)	2318 (69.8)	0.02
Comorbidities			
HF	168 (5.1)	170 (5.1)	0
Hypertension	2279 (68.7)	2253 (67.9)	0.02
Age 65-74 years	631 (19.0)	640 (19.3)	0.01
Diabetes mellitus	203 (6.1)	209 (6.3)	0.01
Peripheral vascular disease	46 (1.4)	51 (1.5)	0.01
MI	116 (3.5)	116 (3.5)	0
Percutaneous coronary intervention	63 (1.9)	67 (2.0)	0.01
Coronary artery bypass grafting	192 (5.8)	195 (5.9)	0
History of major bleeding	14 (0.4)	14 (0.4)	0
Gastrointestinal bleeding	11 (0.3)	10 (0.3)	0
ICH	0 (0)	0 (0)	0
AKI	67 (2.0)	55 (1.7)	0.02
CKD	184 (5.5)	157 (4.7)	0.04
ESRD	48 (1.5)	43 (1.3)	0.02
Liver disease	126 (3.8)	125 (3.8)	0
Coagulopathy	66 (2.0)	54 (1.6)	0.03
Gastroesophageal reflux disease	391 (11.8)	391 (11.8)	0
Upper gastrointestinal testing	141 (4.3)	158 (4.8)	0.02
Anemia	239 (7.2)	224 (6.8)	0.02
Asthma	218 (6.6)	222 (6.7)	0
Chronic obstructive pulmonary disease	214 (6.5)	243 (7.3)	0.03
Sleep apnea	572 (17.2)	569 (17.1)	0
Smoker	228 (6.9)	237 (7.1)	0.01
Hemorrhoids	140 (4.2)	146 (4.4)	0.01
Alcohol abuse	74 (2.2)	81 (2.4)	0.01
Anxiety	281 (8.5)	292 (8.8)	0.01
Depression	278 (8.4)	268 (8.1)	0.01
Psychosis	71 (2.1)	61 (1.8)	0.02
Obesity	612 (18.4)	583 (17.6)	0.02
Osteoarthritis	559 (16.8)	578 (17.4)	0.02
Back pain	436 (13.1)	455 (13.7)	0.02
Joint pain and stiffness	917 (27.6)	935 (28.2)	0.01
Headache	211 (6.4)	217 (6.5)	0
Diverticulitis	213 (6.4)	217 (6.5)	0
Crohn’s or ulcerative colitis	56 (1.7)	62 (1.9)	0.02
Helicobacter pylori	7 (0.2)	16 (0.5)	0.05
Hypothyroidism	352 (10.6)	363 (10.9)	0.01
Solid tumor	217 (6.5)	226 (6.8)	0.01
Lymphoma	23 (0.7)	23 (0.7)	0
Metastatic cancer	34 (1.0)	37 (1.1)	0.01

Table 10–11: Patient baseline characteristics stratified by exposure status after PS matching: Cohort 7

Variable No. of patients	Rivaroxaban N=3319	Warfarin N=3319	Standardized n (%) difference
Medication use			
Antiplatelet drugs	194 (5.9)	188 (5.7)	0.01
NSAIDs	739 (22.3)	750 (22.6)	0.01
Cyclooxygenase-2-specific NSAIDs	77 (2.3)	75 (2.3)	0
ACEIs or ARBs	1522 (45.9)	1544 (46.5)	0.01
β-blockers	1795 (54.1)	1737 (52.3)	0.04
Diltiazem	457 (13.8)	448 (13.5)	0.01
Verapamil	68 (2.1)	76 (2.3)	0.01
Dihydropyridine calcium channel blockers	583 (17.6)	558 (16.8)	0.02
Loop diuretic	247 (7.4)	271 (8.2)	0.03
Thiazide diuretic	878 (26.5)	855 (25.8)	0.02
Digoxin	173 (5.2)	160 (4.8)	0.02
Amiodarone	117 (3.5)	117 (3.5)	0
Dronedarone	92 (2.8)	85 (2.6)	0.01
Other antiarrhythmic drugs	440 (13.3)	455 (13.7)	0.01
Statins	1321 (39.8)	1327 (40.0)	0
Other cholesterol-lowering drugs	250 (7.5)	248 (7.5)	0
Metformin	202 (6.1)	215 (6.5)	0.02
Sulfonylureas or glinides	80 (2.4)	72 (2.2)	0.01
Thiazolidinediones	22 (0.7)	24 (0.7)	0
Dipeptidyl peptidase-4 inhibitors	28 (0.8)	23 (0.7)	0.01
Glucagon-like peptide-1 agonists	13 (0.4)	17 (0.5)	0.01
Insulin	48 (1.5)	47 (1.4)	0.01
Benzodiazepines	461 (13.9)	480 (14.5)	0.02
SSRIs or SNRIs	427 (12.9)	432 (13.0)	0
Other antidepressants	240 (7.2)	248 (7.5)	0.01
PPIs	661 (19.9)	666 (22.0)	0.05
Histamine-2 receptor antagonists	98 (3.0)	93 (2.8)	0.01
Systemic corticosteroids	663 (20.0)	634 (19.1)	0.02
Warfarin inducer	821 (24.7)	809 (24.4)	0.01
Warfarin inhibitor	1992 (60.0)	1975 (59.5)	0.01
Risk stratification scores			
Modified HAS-BLED, median (IQR)	1 (0.1)	1 (0.1)	0

[a] Modified HAS-BLED indicates hypertension, 1 point; age >65 years, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; labile international normalized ratio, not assessed; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point.

10.3 Outcome data (incidence rate per 100 person-years)

Table 10–12 to Table 10–20 present the basic rate parameters (events rate per 100 person-years) for Cohort 1 to Cohort 7, stratified by exposure status.

Table 10–12: Summary of basic rate parameters, stratified by exposure status after IPTW: Cohort 1

	Rate per 100 person-years	
Parameter	**Rivaroxaban (N=36,318)**	**Warfarin (N=36,281)**
Stroke or systemic embolism	0.62	1.19
IS	0.49	0.90
Major bleeding	1.91	2.67
ICH	0.13	0.33
Gastrointestinal bleeding	1.49	1.80
AKI	4.91	8.45
Stage 5 CKD or dialysis	2.67	4.12

Table 10–13: Summary of basic rate parameters, stratified by exposure status after IPTW: Cohort 2 (diabetic population I)

	Rate per 100 person-years	
Parameter	**Rivaroxaban (N=10,017)**	**Warfarin (N=11,665)**
AKI	7.70	13.45
Stage 5 CKD or hemodialysis	3.74	6.03

Table 10–14: Summary of basic rate parameters, stratified by exposure status after IPTW: Cohort 2 (diabetic population II)

	Rate per 100 person-years	
Parameter	**Rivaroxaban (N=10,700)**	**Warfarin (N=13,946)**
Major adverse cardiac events	1.26	2.07
Ischemic stroke	0.66	1.01
MI	0.77	1.20
MALEs	0.19	0.75
Major limb amputation	0.03	0.18
Surgical revascularization	0.12	0.27
Endovascular revascularization	0.07	0.39
Minor limb amputation	0.14	0.27
Major bleeding	2.38	3.37
Intracranial	0.17	0.36
Gastrointestinal	1.85	2.44

Table 10–15: Summary of basic rate parameters, stratified by exposure status after 1:1 PS matching: Cohort 2 (diabetic population III)

	Rate per 100 person-years	
Parameter	**Rivaroxaban**	**Warfarin**
All doses	**N=5517**	**N=5517**
Stroke or systemic embolism	0.87	1.35
IS	0.69	1.93
Hemorrhagic stroke	0.20	0.33

Table 10–15: Summary of basic rate parameters, stratified by exposure status after 1:1 PS matching: Cohort 2 (diabetic population III)

	Rate per 100 person-years	
Parameter	**Rivaroxaban**	**Warfarin**
Major bleeding	2.71	3.01
ICH	0.24	0.39
Gastrointestinal bleeding	2.05	2.19
Standard dose	**N=4418**	**N=4418**
Stroke or systemic embolism	0.91	1.50
IS	0.68	1.04
Hemorrhagic stroke	0.22	0.34
Major bleeding	2.53	2.82
ICH	0.26	0.38
Gastrointestinal bleeding	1.95	1.85
Reduced dose	**N=1099**	**N=1099**
Stroke or systemic embolism	0.62	1.99
IS	0.35	1.76
Hemorrhagic stroke	0.35	0.23
Major bleeding	4.00	3.27
ICH	0.44	0.46
Gastrointestinal bleeding	3.10	2.45

Table 10–16: Summary of basic rate parameters, stratified by exposure status after IPTW: Cohort 3

	Rate per 100 person-years	
Parameter	**Rivaroxaban (N=3,257)**	**Warfarin (N=5,046)**
MTVE	4.21	7.15
IS	1.30	2.00
MI	2.18	3.14
Adverse limb event	0.87	2.44
Major bleeding	6.27	7.40
ICH	0.27	0.70
Gastrointestinal bleeding	5.01	5.12

Table 10–17: Summary of basic rate parameters, stratified by exposure status after IPTW: Cohort 4

	Rate per 100 person-years	
Parameter	**Rivaroxaban (N=1896)**	**Warfarin (N=4848)**
Stroke or systemic embolism	1.10	2.16
IS	0.85	1.44
Major bleeding	3.73	6.16
ICH	0.08	0.28
Gastrointestinal bleeding	3.39	4.52

Table 10–18: Summary of basic rate parameters, stratified by exposure status after 1:1 PS matching: Cohort 5

	Rate per 100 person-years	
Parameter	**Rivaroxaban (N=3418)**	**Warfarin (N=3418)**
Stroke or systemic embolism	0.98	1.28
IS	0.70	1.02
Major bleeding	3.86	4.23
ICH	0.27	0.36

Table 10–19: Summary of basic rate parameters, stratified by exposure status after 1:1 PS matching: Cohort 6

Polypharmacy ≥5 concomitant chronic medications				
	Rivaroxaban cohort (N=13,981) (%)		**Warfarin cohort (N=13,981) (%)**	
	Events	**Event Rate***	**Events**	**Event rate***
SSE	90	0.74 (0.60-0.91)	105	1.22 (1.01-1.47)
IS	65	0.53 (0.41-0.68)	83	0.97 (0.77-1.19)
Major bleeding	339	2.80 (2.50-3.10)	246	2.88 (2.52-3.24)
Polypharmacy ≥10 concomitant chronic medications				
	Rivaroxaban cohort (N=1765) (%)		**Warfarin cohort (N=1765) (%)**	
	Events	**Event rate***	**Events**	**Event rate***
SSE	7	0.49 (0.22-0.98)	13	1.26 (0.70-2.11)
IS	6	0.42 (0.17-0.88)	8	0.78 (0.36-1.48)
Major bleeding	62	4.42 (3.42-5.63)	46	4.55 (3.37-6.02)

*Event rates are reported as no. of events/100 patient-years.

Table 10–20: Summary of basic rate parameters, stratified by exposure status after 1:1 PS matching: Cohort 7

	Rivaroxaban		**Warfarin**	
	Events	**Event rate***	**Events**	**Event rate***
1-year follow-up				
Stroke or systemic embolism	7	0.25	17	0.63
IS	6	0.22	12	0.44
Major bleeding	24	0.88	32	1.19
Hemorrhagic stroke	1	0.04	3	0.11
ICH	1	0.04	3	0.11
Gastrointestinal bleeding	19	0.69	24	0.89
2-year follow-up				
Stroke or systemic embolism	12	0.26	25	0.57
IS	11	0.24	17	0.39
Major bleeding	33	0.73	49	1.12
Hemorrhagic stroke	1	0.02	6	0.14
ICH	1	0.02	7	0.16
Gastrointestinal bleeding	25	0.55	33	0.76

*Event rates are reported as no. of events/100 patient-years.

10.4 Main results (hazard ratios)

10.4.1 Cohort 1

By Cox proportional hazards regression analysis, HRs (and 95% CI) were evaluated as 0.67 (0.54, 0.84) for SSE, 0.67 (0.52, 0.86) for IS, 0.98 (0.86, 1.12) for major bleeding, 0.58 (0.37, 0.91) for intracranial hemorrhage (ICH), 0.81 (0.75, 0.87) for AKI, and 0.82 (0.74, 0.91) for progression to Stage 5 CKD or hemodialysis.

Table 10–21: Main results: Cohort 1

Model	Hazard ratio	CI
Stroke or systemic embolism (SSE)	0.67	(0.54, 0.84)
IS	0.67	(0.52, 0.86)
AKI	0.81	(0.75, 0.87)
Renal impairment (Kidney failure/Stage 5 CKD or dialysis)	0.82	(0.74, 0.91)
Major bleeding	0.98	(0.86, 1.12)
Gastrointestinal	1.12	(0.96, 1.30)
Cerebral including ICH	0.58	(0.37, 0.91)

Population stratified by age, ACEI/ARB use, and CHA_2DS_2-VASc score

For AKI, HRs (and 95% CI) were evaluated as 0.84 (0.72, 0.98) in <70 years of age, 0.78 (0.72, 0.86) in ≥70 years of age, 0.78 (0.71, 0.85) in the patients with ACEI/ARB use, 0.81 (0.71, 0.92) in the patients without ACEI/ARB use, 0.82 (0.64, 1.04) in the patients with CHA_2DS_2-VASc score 0-1, 0.83 (0.74, 0.93) in the patients with CHA_2DS_2-VASc score 2-3, and 0.78 (0.70, 0.87) in the patients with CHA_2DS_2-VASc score 4-8.

For Stage 5 CKD or hemodialysis, HRs (and 95% CI) were evaluated as 0.83 (0.70, 0.98) in <70 years of age, 0.88 (0.72, 1.06) in ≥70 years of age, 0.87 (0.72, 1.06) in the patients with ACEI/ARB use, 0.80 (0.67, 0.95) in the patients without ACEI/ARB use, 0.64 (0.48, 0.86) in the patients with CHA_2DS_2-VASc score 0-1, 0.89 (0.76, 1.04) in the patients with CHA_2DS_2-VASc score 2-3, and 0.93 (0.70, 1.22) in the patients with CHA_2DS_2-VASc score 4-8.

Table 10–22: Results of the sub-population of Cohort 1, stratified by age, ACEI/ARB use, and CHA_2DS_2-VASc scores

	AKI			Stage 5 CKD or hemodialysis		
	Hazard ratio	CI	$P_{interaction}$	Hazard ratio	CI	$P_{interaction}$
<70 years of age	0.84	(0.72, 0.98)	0.41	0.83	(0.70, 0.98)	0.65
≥70 years of age	0.78	(0.72, 0.86)		0.88	(0.72, 1.06)	
ACEI/ARB use	0.78	(0.71, 0.85)	0.64	0.87	(0.72, 1.06)	0.53
No ACEI/ARB use	0.81	(0.71, 0.92)		0.80	(0.67, 0.95)	
CHA_2DS_2-VASc 0-1	0.82	(0.64, 1.04)		0.64	(0.48, 0.86)	
CHA_2DS_2-VASc 2-3	0.83	(0.74, 0.93)	0.73	0.89	(0.76, 1.04)	0.11
CHA_2DS_2-VASc 4-8	0.78	(0.70, 0.87)		0.93	(0.70, 1.22)	

10.4.2 Cohort 2 (NVAF + Diabetes)

Diabetic population I

By Cox proportional hazards regression analysis, HRs (and 95% CI) were evaluated as 0.83 (0.74, 0.92) for AKI and 0.82 (0.70, 0.96) for Stage 5 CKD or hemodialysis.

Sensitivity analyses

For AKI, HRs (and 95% CI) were evaluated as 0.86 (0.79, 0.93) in patients who met ITT data scope, 0.82 (0.72, 0.94) in patients with no AKI at baseline, and 0.80 (0.67, 0.96) in patients with >365 days follow-up available.

For Stage 5 CKD or hemodialysis, HRs (and 95% CI) were evaluated as 0.82 (0.73, 0.91) in patients who met ITT data scope, 0.82 (0.68, 0.98) in patients with no AKI at baseline, and 0.75 (0.58, 0.96) in patients with >365 days follow-up available.

Population stratified by age, sex, presence of Stage 3 or 4 CKD, or hypertension

For AKI, the HRs (and 95% CI) were evaluated as 0.86 (0.75, 0.98) in patients >70 years, 0.81 (0.68, 0.96) in patients ≤70 years, 0.77 (0.67, 0.88) in males, 0.88 (0.73, 1.06) in females, 0.63 (0.49, 0.79) in patients with Stage 3-4 CKD, 0.89 (0.78, 1.00) in patients without Stage 3-4 CKD, 0.84 (0.75, 0.94) in patients with hypertension, and 0.75 (0.53, 1.06) in patients without hypertension.

For Stage 5 CKD or hemodialysis, the HRs (and 95% CI) were evaluated as 0.80 (0.64, 0.99) in patients >70 years, 0.87 (0.69, 1.09) in patients ≤70 years, 0.82 (0.65, 1.00) in males, 0.79 (0.60, 1.03) in females, 0.66 (0.46, 0.94) in patients with Stage 3-4 CKD, 0.87 (0.73, 1.04) in patients without Stage 3-4 CKD, 0.79 (0.67, 0.94) in patients with hypertension, and 0.97 (0.67, 1.60) in patients without hypertension.

Table 10–23: Main results: Cohort 2 (diabetic population I)

	AKI		Stage 5 CKD or hemodialysis	
Analyses	**Hazard ratio**	**CI**	**Hazard ratio**	**CI**
Overall analysis	0.83	(0.74, 0.92)	0.82	(0.70, 0.96)
Sensitivity analyses				
ITT (N=21,682)	0.86	(0.79, 0.93)	0.82	(0.73, 0.91)
No AKI at baseline (N=19,228)	0.82	(0.72, 0.94)	0.82	(0.68, 0.98)
>365 days follow-up (N=5,438)	0.80	(0.67, 0.96)	0.75	(0.58, 0.96)
Subgroup analyses				
Age >70 (N=10,602)	0.86	(0.75, 0.98)	0.80	(0.64, 0.99)
Age ≤70 (N=11,080)	0.81	(0.68, 0.96)	0.87	(0.69, 1.09)
Male (N=13,805)	0.77	(0.67, 0.88)	0.82	(0.65, 1.00)
Female (N=7,876)	0.88	(0.73, 1.06)	0.79	(0.60, 1.03)
Stage 3-4 CKD (N=2,037)	0.63	(0.49, 0.79)	0.66	(0.46, 0.94)
No Stage 3-4 CKD (N=19,645)	0.89	(0.78, 1.00)	0.87	(0.73, 1.04)
Hypertension (N=18,537)	0.84	(0.75, 0.94)	0.79	(0.67, 0.94)
No hypertension (N=3,645)	0.75	(0.53, 1.06)	0.97	(0.67, 1.60)

Diabetic population II

By Cox proportional hazards regression analysis, HRs (and 95% CI) were evaluated as 0.75 (0.59, 0.96) for MACE, 0.83 (0.59, 1.17) for IS, 0.77 (0.56, 1.06) for MI, 0.37 (0.21, 0.65) for

MALE, 0.20 (0.06, 0.69) for major limb amputation, 0.66 (0.31, 1.39) for surgical revascularization, 0.27 (0.11, 0.67) for endovascular revascularization, 0.72 (0.34, 1.53) for minor limb amputation, 0.95 (0.79, 1.15) for major bleeding, 0.59 (0.30, 1.13) for ICH, and 1.04 (0.84, 1.30) for gastrointestinal bleeding.

Population stratified by sex, with/without MTVE, with/without PAD, with/without CAD, with/without CKD, and with/without smoking.

A subgroup analysis was performed for MACE, MALE, and major bleeding. No statistical significant interactions were observed, p-value ≥0.17 for all subgroup analyses. The associations were consistent in men and women, in patients with major thrombovascular events and in those without, in patients with PAD and in those without, in those with CAD and in those without, in patients with CKD and in those without, and in smokers and those who did not smoke. Among those who received reduced dose rivaroxaban, rates of MALE were lower than with warfarin (HR 0.36, 95% CI 0.13-1.01) with similar rates of MACE (HR 1.05, 95% CI 0.73-1.51) and major bleeding (HR 1.10, 95% CI 0.82-1.47) observed between groups.

Table 10–24: Main results: Cohort 2 (diabetic population II)

	Hazard ratio	CI	$P_{interaction}$
Main analysis			
Major adverse cardiac events	0.75	(0.59, 0.96)	-
Ischemic stroke	0.83	(0.59, 1.17)	-
MI	0.77	(0.56, 1.06)	-
MALEs	0.37	(0.21, 0.65)	-
Major limb amputation	0.20	(0.06, 0.69)	-
Surgical revascularization	0.66	(0.31, 1.39)	-
Endovascular revascularization	0.27	(0.11, 0.67)	-
Minor limb amputation	0.72	(0.34, 1.53)	-
Major bleeding	0.95	(0.79, 1.15)	-
Intracranial	0.59	(0.30, 1.13)	-
Gastrointestinal	1.04	(0.84, 1.30)	-
Subgroup analysis			
MACE			
Men	0.82	(0.61, 1.10)	0.69
Women	0.63	(0.40, 1.01)	
MTVE	0.75	(0.40, 1.42)	0.99
No MTVE	0.75	(0.58, 0.99)	
PAD	0.99	(0.54, 1.80)	0.40
No PAD	0.71	(0.54, 0.93)	
CAD	0.45	(0.19, 1.06)	0.19
No CAD	0.77	(0.60, 1.00)	
CKD	0.75	(0.43, 1.31)	0.99
No CKD	0.75	(0.57, 0.99)	
Smoking	0.82	(0.33, 2.03)	0.86
No smoking	0.74	(0.57, 0.95)	
MALE			
Men	0.32	(0.14, 0.59)	0.84
Women	0.38	(0.13, 1.17)	
MTVE	0.59	(0.23, 1.54)	0.49
No MTVE	0.34	(0.17, 0.70)	
PAD	0.45	(0.19, 1.03)	0.60
No PAD	0.32	(0.15, 0.67)	

Table 10–24: Main results: Cohort 2 (diabetic population II)

	Hazard ratio	CI	$P_{interaction}$
CKD	0.27	(0.10, 0.71)	0.41
No CKD	0.47	(0.23, 0.94)	
Major bleeding			
Men	0.94	(0.73, 1.21)	0.58
Women	1.05	(0.78, 1.41)	
MTVE	1.32	(0.77, 2.25)	0.47
No MTVE	0.92	(0.75, 1.13)	
PAD	1.46	(0.87, 2.44)	0.17
No PAD	0.89	(0.72, 1.10)	
CAD	0.62	(0.24, 1.61)	0.32
No CAD	0.98	(0.80, 1.19)	
CKD	0.84	(0.57, 1.22)	0.39
No CKD	1.02	(0.82, 1.28)	
Smoking	1.02	(0.53, 1.93)	0.87
No smoking	0.96	(0.78, 1.17)	

Diabetic population III

In the any-dose analysis (by Cox proportional hazards regression), HRs (and 95% CI) were evaluated as 0.68 (0.44, 1.05) for SSE, 0.78 (0.48, 1.30) for IS, 0.66 (0.27, 1.60) for hemorrhagic stroke, 0.96 (0.74, 1.37) for major bleeding, 0.68 (0.30, 1.53) for ICH, and 1.00 (0.72, 1.37) for gastrointestinal bleeding.

In standard-dose analysis (by Cox proportional hazards regression), HRs (and 95% CI) were evaluated as 0.64 (0.40, 1.02) for SSE, 0.71 (0.41, 1.23) for IS, 0.65 (0.25, 1.71) for hemorrhagic stroke, 0.97 (0.71, 1.32) for major bleeding, 0.68 (0.27, 1.69) for ICH, and 1.15 (0.79, 1.66) for gastrointestinal bleeding.

In reduced-dose analysis (by Cox proportional hazards regression), HRs (and 95% CI) were evaluated as 0.33 (0.13, 0.79) for SSE, 0.20 (0.07, 0.62) for IS, 1.74 (0.32, 9.60) for hemorrhagic stroke, 1.35 (0.84, 2.18) for major bleeding, 1.05 (0.28, 3.93) for ICH, and 1.41 (0.82, 2.42) for gastrointestinal bleeding.

Analysis of participants with chronic kidney disease at baseline

The relative hazards for SSE (HR 0.76, 95% CI: 0.31, 1.87) and major bleeding (HR 0.98, 95% CI: 0.58, 1.66) for rivaroxaban vs. warfarin were similar in the subgroup analysis of participants with CKD at baseline.

Table 10–25: Main results: Cohort 2 (diabetic population III)

Model	Hazard ratio	CI
All doses	**N=5517**	**N=5517**
Stroke or systemic embolism (SSE)	0.68	(0.44, 1.05)
IS	0.78	(0.48, 1.30)
Hemorrhagic stroke	0.66	(0.27, 1.60)
Major bleeding	0.96	(0.74, 1.37)
Gastrointestinal	1.00	(0.72, 1.37)
Cerebral including ICH	0.68	(0.30, 1.53)

Table 10–25: Main results: Cohort 2 (diabetic population III)

Model	Hazard ratio	CI
Standard dose	**N=4418**	**N=4418**
Stroke or systemic embolism (SSE)	0.64	(0.40, 1.02)
IS	0.71	(0.41, 1.23)
Hemorrhagic stroke	0.65	(0.25, 1.71)
Major bleeding	0.97	(0.71, 1.32)
Gastrointestinal	1.15	(0.79, 1.66)
Cerebral including ICH	0.68	(0.27, 1.69)
Reduced dose	**N=1099**	**N=1099**
Stroke or systemic embolism (SSE)	0.33	(0.13, 0.79)
IS	0.20	(0.07, 0.62)
Hemorrhagic stroke	1.74	(0.32, 9.60)
Major bleeding	1.35	(0.84, 2.18)
Gastrointestinal	1.41	(0.82, 2.42)
Cerebral including ICH	1.05	(0.28, 3.93)

10.4.3 Cohort 3 (NVAF + CAD/PAD)

By Cox proportional hazards regression analysis, HRs (and 95% CI) were evaluated as 0.68 (0.50, 0.92) for MTVE, 0.69 (0.38, 1.26) for IS, 0.88 (0.56, 1.38) for MI, 0.44 (0.25, 0.79) for adverse limb event, 1.13 (0.84, 1.52) for major bleeding, 0.50 (0.15, 1.72) for ICH, and 1.33 (0.94, 1.88) for gastrointestinal bleeding.

Table 10–26: Main results: Cohort 3

Model	Hazard ratio	CI
MTVE	0.68	(0.50, 0.92)
IS	0.69	(0.38, 1.26)
MI	0.88	(0.56, 1.38)
MALE	0.44	(0.25, 0.79)
Major bleeding	1.13	(0.84, 1.52)
Gastrointestinal	1.33	(0.94, 1.88)
Cerebral including ICH	0.50	(0.15, 1.72)

Analyses for the MTVE and major bleeding endpoints stratified by age, presence or absence of baseline diabetes, Stage 3 or worse CKD, P_2Y_{12} platelet inhibitor use, and atherosclerosis type

Significant risk reductions were observed in patients without diabetes mellitus (42%; CI: 0.37, 0.89), with PAD only (33%; CI: 0.46, 0.98), without CKD (37%; CI: 0.41, 0.95), and with P_2Y_{12} platelet inhibitor use (38%, CI: 0.39, 0.98) ($P_{interaction} \geq 0.35$ for all).

There were no significant interactions observed for major bleeding in any of the subgroups analyzed ($P_{interaction} \geq 0.09$ for all subgroups).

Table 10–27: Results of the population of Cohort 3, stratified by age, diabetes mellitus, atherosclerotic disease, chronic kidney disease, and P_2Y_{12} inhibitor use

	Major thrombotic vascular events			Major bleeding events		
	Hazard ratio	CI	$P_{interaction}$	Hazard ratio	CI	$P_{interaction}$
Age						
<65 years	0.60	(0.35, 1.02)		0.69	(0.32, 1.47)	
65-74 years	0.64	(0.37, 1.14)	0.97	1.07	(0.57, 2.00)	0.37
≥75 years	0.66	(0.41, 1.07)		1.26	(0.88, 1.81)	
Diabetes mellitus						
Yes	0.75	(0.49, 1.15)	0.41	1.11	(0.71, 1.72)	0.75
No	0.58	(0.37, 0.89)		1.01	(0.69, 1.48)	
Atherosclerotic disease						
CAD only	0.70	(0.38, 1.29)		0.61	(0.33, 1.12)	
PAD only	0.67	(0.46, 0.98)	0.49	1.34	(0.94, 1.90)	0.09
CAD and PAD	0.32	(0.10, 1.08)		0.98	(0.36, 2.68)	
CKD						
Yes	0.85	(0.53, 1.35)	0.35	1.11	(0.69, 1.79)	>0.99
No	0.63	(0.41, 0.95)		1.11	(0.76, 1.62)	
P_2Y_{12} inhibitor						
Yes	0.62	(0.39, 0.98)	0.70	1.26	(0.77, 2.09)	0.54
No	0.70	(0.46, 1.06)		1.04	(0.73, 1.50)	

10.4.4 Cohort 4 (NVAF + Renal impairment)

By Cox proportional hazards regression analysis, HRs (and 95% CI) were evaluated as 0.55 (0.27, 1.10) for SSE, 0.67 (0.30, 1.50) for IS, 0.68 (0.47, 0.99) for major bleeding, 0.19 (0.02, 1.56) for ICH, 0.87 (0.58, 1.30) for gastrointestinal bleeding.

Table 10–28: Main results: Cohort 4

Model	Hazard ratio	CI
Stroke or systemic embolism	0.55	(0.27, 1.10)
IS	0.67	(0.30, 1.50)
Major bleeding	0.68	(0.47, 0.99)
ICH	0.19	(0.02, 1.56)
Gastrointestinal bleeding	0.87	(0.58, 1.30)

10.4.5 Cohort 5 (NVAF + Heart failure)

By Cox proportional hazards regression analysis, HRs (and 95% CI) were evaluated as 0.82 (0.47, 1.44) for SSE, 0.77 (0.41, 1.46) for IS, 0.98 (0.73, 1.31) for major bleeding, and 0.73 (0.25, 2.08) for ICH.

Table 10–29: Main results: Cohort 5

Model	Hazard ratio	CI
Stroke or systemic embolism	0.82	(0.47, 1.44)
IS	0.77	(0.41, 1.46)
Major bleeding	0.98	(0.73, 1.31)
ICH	0.73	(0.25, 2.08)

10.4.6 Cohort 6 (NVAF + Polypharmacy)

By Cox proportional hazards regression analysis, HRs (and 95% CI) were evaluated as 0.66 (0.50, 0.88) for SSE, 0.60 (0.43-0.84) for IS, and 1.08 (0.92-1.28) for major bleeding in ≥5 concomitant medication cohort.

By Cox proportional hazards regression analysis, HRs (and 95% CI) were evaluated as 0.44 (0.17, 1.12) for SSE, 0.62 (0.22, 1.78) for IS, and 1.07 (0.73, 1.58) for major bleeding in the ≥10 concomitant medication cohort.

Sensitivity analysis

In the sensitivity analysis, the results for ≥5 and ≥10 concomitant medication Cox regression analyses were further adjusted by age (continuous), sex, and either stroke or bleeding risk score.

Upon sensitivity analysis in the ≥5 concomitant medication cohort, HRs (and 95% CI) were evaluated as 0.71 (0.53, 0.94) for SSE, 0.65 (0.47, 0.90) for IS, and 1.14 (0.97, 1.35) for major bleeding.

Upon sensitivity analysis in the ≥10 concomitant medication cohort, HRs (and 95% CI) were evaluated as 0.45 (0.18, 1.14) for SSE, 0.67 (0.23, 1.94) for IS, and 1.08 (0.73, 1.59) for major bleeding.

Table 10–30: Main results: Cohort 6

	Hazard ratio	(95% CI)
Polypharmacy ≥5 concomitant chronic medications		
SSE	0.66	(0.50, 0.88)
IS	0.60	(0.43, 0.84)
Major bleeding	1.08	(0.92, 1.28)
Sensitivity analysis		
SSE	0.71	(0.53, 0.94)
IS	0.65	(0.47, 0.90)
Major bleeding	1.14	(0.97, 1.35)
Polypharmacy ≥10 concomitant chronic medications		
SSE	0.44	(0.17, 1.12)
IS	0.62	(0.22, 1.78)
Major bleeding	1.07	(0.73, 1.58)
Sensitivity analysis		
SSE	0.45	(0.18, 1.14)
IS	0.67	(0.23, 1.94)
Major bleeding	1.08	(0.73, 1.59)

10.4.7 Cohort 7 (NVAF + CHA_2DS_2-VASc score = 1)

By Cox proportional hazards regression analysis, HRs (and 95% CI) were evaluated as 0.41 (0.17, 0.98) for SSE, 0.49 (0.19, 1.31) for IS, 0.74 (0.44, 1.26) for major bleeding, 0.33 (0.03, 3.17) for Hemorrhagic stroke, 0.33 (0.03, 3.17) for intracranial stroke, and 0.78 (0.43, 1.43) for gastrointestinal bleeding at 1-year follow-up.

By Cox proportional hazards regression analysis, HRs (and 95% CI) were evaluated as 0.46 (0.23, 0.92) for SSE, 0.63 (0.29, 1.33) for IS, 0.65 (0.42, 1.02) for major bleeding, 0.16 (0.02, 1.34) for hemorrhagic stroke, 0.14 (0.02, 1.11) for intracranial stroke, and 0.74 (0.44, 1.24) for gastrointestinal bleeding at 2-year follow-up.

Table 10–31: Main results: Cohort 7

	HR	(95% CI)
1-year follow-up		
Stroke or systemic embolism	0.41	(0.17, 0.98)
IS	0.49	(0.19, 1.31)
Major bleed	0.74	(0.44, 1.26)
Hemorrhagic stroke	0.33	(0.03, 3.17)
ICH	0.33	(0.03, 3.17)
Gastrointestinal bleeding	0.78	(0.43, 1.43)
2-year follow-up		
Stroke or systemic embolism	0.46	(0.23, 0.92)
IS	0.63	(0.29, 1.33)
Major bleed	0.65	(0.42, 1.02)
Hemorrhagic stroke	0.16	(0.02, 1.34)
ICH	0.14	(0.02, 1.11)
Gastrointestinal bleeding	0.74	(0.44, 1.24)

10.5 Other analyses

Not applicable.

10.6 Safety data (adverse events/adverse reactions)

Not applicable.

11. Discussion

11.1 Key results

11.1.1 Cohort 1

Upon Cox regression analysis, rivaroxaban was associated with a significant risk reduction of AKI by 19%, progression to Stage 5 CKD or hemodialysis by 18%, SSE and IS each by 33%, and ICH by 42%, in comparison with warfarin. No significant difference in major bleeding was observed between rivaroxaban and warfarin users (0.02%).

According to the analysis in the study population stratified by age, ACEI/ARB use, and CHA_2DS_2-VASc score, the results for AKI and progression to Stage 5 CKD or hemodialysis showed associations that were consistent with the base-case analyses (no significant statistical interactions were observed; p-values ≥0.11 for all subgroup analyses) in patients <70 or ≥70 years of age; in patients with/without prior ACEIs/ARBs use; and according to the baseline CHA_2DS_2-VASc score.

11.1.2 Cohort 2 (NVAF + Diabetes)

Diabetic population I

According to the overall analysis, rivaroxaban was associated with a significant risk reduction of AKI and Stage 5 CKD or hemodialysis by Cox regression analysis (17% and 18%, respectively), in comparison with warfarin.

Upon sensitivity analysis (patients who met ITT data scope, exclusion of patients with AKI at baseline, and limiting inclusion to patients with >365 days of available follow-up), rivaroxaban was also associated with a significant risk reduction of AKI and Stage 5 CKD or hemodialysis (14-20% and 18-25%, respectively), in comparison with warfarin.

Upon Cox regression analysis in the stratified population, both renal outcomes did not show any statistical interaction when rivaroxaban vs. warfarin cohorts were further stratified by age, sex, presence of Stage 3 or 4 CKD, or hypertension ($P_{interaction}$ >0·01 for all AKI analyses and >0·17 for development of Stage 5 CKD or need for hemodialysis).

Note: A more conservative p-value for interaction (also referred to as a Q statistic p-value) was used (i.e., <0.01 instead of <0.05) for the analysis on stratified population. The approach was used to account for multiple hypothesis testing that was based upon the number of comparisons/subgroups assessed [40].

Diabetic population II

Upon Cox regression analysis, rivaroxaban was associated with significant risk reductions in MACE (25%), MALE (63%), major limb amputation (80%), and endovascular revascularization (73%), in comparison with warfarin. The risk reductions of IS (17%), ICH (41%), MI (23%), surgical revascularization (34%), and minor limb amputation (28%) were better with rivaroxaban in comparison with warfarin; however, they did not reach statistical significance (UCL: 1.17, 1.13, 1.06, 1.39, and 1.53, respectively).

Overall, no significant difference in major bleeding was observed between rivaroxaban and warfarin users (HR=0.95). Similarly, no difference was also observed in gastrointestinal bleeding (HR=1.04).

Diabetic population III

In any-dose analysis, the risk reductions of SSE (32%), IS (22%), and hemorrhagic stroke (34%) were better with rivaroxaban in comparison with warfarin; however, they did not reach statistical significance (UCL: 1.05, 1.30, and 1.60, respectively).

Overall, in any-dose analysis, no significant difference in major bleeding was observed between rivaroxaban and warfarin users (HR=0.96). Similarly, no difference was also observed in gastrointestinal bleeding (HR=1.00). Although, the risk reduction of ICH (32%) was better with rivaroxaban vs. warfarin, but did not reach statistical significance (UCL: 1.53).

In reduced-dose analysis, rivaroxaban was associated with a significant risk reduction of SSE (67%) and IS (80%), in comparison with warfarin.

An analysis stratified by dose showed that rivaroxaban had similar effectiveness and safety to those of warfarin across any-dose and standard-dose analyses. For the reduced dose rivaroxaban vs. warfarin analysis, rivaroxaban was associated with a significantly reduced hazard of the combined outcome of SSE and IS alone. No significant differences were observed between rivaroxaban and warfarin users for any bleeding related outcomes.

11.1.3 Cohort 3 (NVAF + CAD/PAD)

In patients with CAD/PAD, rivaroxaban was associated with a significant risk reduction of MTVE (32%; CI: 0.50, 0.92) and adverse limb events (56%; CI: 0.25, 0.79), in comparison with warfarin.

The rates of major bleeding (13%) and gastrointestinal bleeding (33%) were higher with rivaroxaban in comparison to warfarin (HR 1.13 and 1.33, respectively), however, the differences were of no statistical significance. Rivaroxaban was also associated with a risk reduction of ICH (50%) vs. warfarin, but did not reach statistical significance.

11.1.4 Cohort 4 (NVAF + Renal impairment)

Upon Cox regression analysis, rivaroxaban was associated with a risk reduction of SSE (45%) vs. warfarin, though the 95% CIs crossed the line of unity.

Rivaroxaban was also associated with an overall 32% (95% CI = 1-53%) risk reduction in major bleeding compared with warfarin, driven directionally by reductions in both intracranial and gastrointestinal bleeding (albeit neither subtype was reduced significantly with rivaroxaban compared with warfarin on its own).

11.1.5 Cohort 5 (NVAF + Heart failure)

In patients with heart failure, rivaroxaban was associated with risk reductions in SSE (18%) and IS (23%) alone vs. warfarin, though the 95% CIs crossed the line of unity.

No significant difference in the overall major bleeding (HR = 0.98) was observed between the treatment cohorts.

ICH occurred less frequently with rivaroxaban compared with warfarin (0.27 events/100 person-years vs. 0.36 events/100 person-years); however, the 95% CIs for the HR included 1.0.

11.1.6 Cohort 6 (NVAF + Polypharmacy)

In polypharmacy (≥5 concomitant chronic medications), rivaroxaban was associated with a significant risk reduction of SSE (34%) and IS (40%), in comparison with warfarin. In substantial polypharmacy (≥10 concomitant chronic medications), rivaroxaban was again associated with a risk reduction of SSE (56%) and IS (38%) vs. warfarin, although did not reach statistical significance (95% CIs crossed 1.0 for each outcome).

No significant difference in major bleeding was observed between rivaroxaban and warfarin users in either polypharmacy (HR 1.08, 95% CI 0.92-1.28) or substantial polypharmacy (HR 1.07, 95% CI 0.73-1.58) analyses.

Results of the sensitivity analyses in which ≥5 and ≥10 concomitant medications were further adjusted by age (continuous), sex, and either stroke or bleeding risk score were consistent with our base-case results.

11.1.7 Cohort 7 (NVAF + CHA_2DS_2-VASc score = 1)

In 1-year and 2-year follow-up, rivaroxaban was associated with a significant risk reduction of SSE (59% and 54%, respectively), in comparison with warfarin. The risk reduction of IS with rivaroxaban vs. warfarin was 51% in 1-year follow-up and 37% in 2-year follow-up, though the 95% CIs crossed the line of unity.

The event rates for IS were qualitatively lower at 1-year with rivaroxaban vs. warfarin (HR 0.49, 95% CI 0.19-1.31).

The risk reduction for major bleeding was non-significantly lower with rivaroxaban vs. warfarin at 1-year (HR = 0.74, 95% CI 0.44-1.26) and at 2-year follow-up (HR 0.65, 95% CI 0.42-1.02).

Major bleeding subtypes were similar between the treatment cohorts at both time points.

11.2 Limitations

The source population of this study included all the insured individuals in the IBM Watson MarketScan databases. As with any data source, IBM Watson MarketScan databases have limitations worth discussion:

- As with all retrospective claims database analyses, misclassification (measurement error) and selection bias (selection of patients in a non-randomized fashion) may have affected the study's internal validity.
- As the study used US claims data, the results, therefore, are generalizable to an insured US population with NVAF and comorbidities like diabetes, CAD and/or PAD, HF, or low CHA_2DS_2-VASc score.
- While PS matching can generate cohorts that are comparable in key characteristics, only the variables that are measured in MarketScan databases could be used in the generation of PSs. Therefore, further residual confounding is possible.

- Despite the sophistication of the methodology and the number of covariates used in developing PSs, residual confounding could not be fully excluded due to the possibility of confounding from unobserved or unmeasured covariates. However, a machine learning method was implemented that required the researcher to specify only which pretreatment covariates need to be balanced between the treatment cohorts. The TWANG algorithm, and not the researcher, then determined the most appropriate main effects, interactions, and higher-order terms that made up the optimal PS model.
- Laboratory results including serum creatinine values were not available in the IBM Watson MarketScan databases licensed. Patients' renal function was assessed based solely on the diagnosis or procedural codes. Therefore, end points such as >30% increase in estimated glomerular filtration rate or a doubling in serum creatinine could not be assessed. However, data sources containing this type of information are very limited and, to the best of our knowledge, could not provide a reasonable sample size of NVAF patients with renal dysfunction treated with rivaroxaban.
- Laboratory data such as international normalized ratio (INR) data were not available in the IBM Watson MarketScan databases licensed, and, therefore, times in the therapeutic range (TTRs) could not be calculated. While the inability to assess patients' INRs/TTRs is a limitation of the current analysis, it is important to note that most patients in the US achieve TTRs significantly lower (−9.1%, 95% CI −4.3% to −13.9%) than that observed in randomized controlled trials [36] and, 55% of the patients on an average fall well below the ≥70% value, which is thought to be associated with maximal VKA benefit. Moreover, data from the prospective Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) have raised the question of whether patients receiving VKA therapy who have stable INR values remain stable over time [37]. In an analysis of 3,749 patients taking warfarin in the ORBIT-AF performed by Pokorney et al., 26% of the patients were found to have ≥80% of their INR values in the 2.0-3.0 range during the first 6 months of the therapy, and, notably of these patients, only 34% (95% CI 31-37%) remained stable over the subsequent 12 months of treatment. Consequently, it was unlikely that availability of INR data for adjustment in the current analyses would have substantially impacted the overall conclusions [37].
- Data on the out-of-hospital mortality were not available in the IBM Watson MarketScan databases, thereby the outcome of the all-cause or cardiovascular mortality could not be evaluated, especially while evaluating the MACE and MALE event rates in diabetic population II of Cohort 2.
- In Cohort 1, available data did not allow attributing a specific cause to the development of AKI events, and AKI could have occurred for reasons other than the anticoagulant received (including pre-renal azotemia due to changes in antihypertensive and diuretic use, worsening HF, volume depletion, and kidney infection).
- In diabetic population I of Cohort 2, no subgroup analyses in patients with high- vs. low- dose rivaroxaban doses or patients with or without proteinuria could be performed due to limited sample sizes.

- In Cohort 2 (diabetic population III) and Cohort 5, only ~65% and ~75% of rivaroxaban users, respectively, could be PS-based *1:1* matched to warfarin users due to the small PS caliper (1%). Using a small caliper makes it more difficult to match patients but likely results in a higher quality of matching. Moreover, due to lack of hemoglobin A1c data, the quality of glycemic control experienced by diabetic population III and the impact that varying glycemic control may have had on outcomes could not be determined.
- In the Cohort 3 and Cohort 4 population, the impact of aspirin on MTVE or major bleeding could not be determined, as being an over-the-counter product its claim in MarketScan was not trackable.
- In Cohort 5, the ICD-9 or -10 diagnosis coding did not allow for adequate assessment of left ventricular ejection fraction (LVEF) or New York Heart Association (NYHA) class, and the lack of coding specificity was further compounded by the lack of laboratory data available in the database. As a result, the impact of HF severity or functional status on outcomes (SSE, IS, and major bleeding) could not be evaluated. Interestingly, the HF patient sub-analysis from ROCKET-AF did not show a statistical interaction by LVEF (≥40% vs. <40%) or NYHA classification (I - II vs. III - IV) and trial endpoints (including SSE and clinical relevant bleeding) [8]. Consequently, it is less likely that lack of specific detail on HF severity in IBM Watson MarketScan data set would have substantially impacted the findings.
- In Cohort 6, medication adherence to rivaroxaban vs. warfarin could have played a role in the superior effectiveness seen with rivaroxaban. No attempt was made to assess medication adherence in this study, as the frequent dosing changes seen with warfarin makes claims-based assessments difficult.

11.3 Interpretation

11.3.1 Cohort 1

In patients with NVAF and without Stage 5 CKD or receiving dialysis at baseline, rivaroxaban use was associated with significant risk reductions of undesirable renal endpoints in comparison with warfarin. This included a 19% risk reduction in developing AKI (absolute risk of 2.1%) and an 18% risk reduction in the progression to Stage 5 CKD or need for dialysis (absolute risk of 0.9%). These findings were consistent across all identified subgroups. Results of secondary end point analyses demonstrated effectiveness and safety results that were generally consistent with ROCKET-AF [6] and earlier real-world analyses of rivaroxaban vs. warfarin in patients with NVAF [23]. This included significant risk reductions in SSE as well as IS and ICH in rivaroxaban compared with warfarin users, without a difference in the overall major bleeding risk between the treatment cohorts.

11.3.2 Cohort 2 (NVAF + Diabetes)

Diabetic population I

In patients with NVAF and diabetes rivaroxaban was shown to be associated with a ~17% risk reduction in both AKI and Stage 5 CKD or need for hemodialysis vs. warfarin. Sensitivity

analyses showed that findings were robust to changes in study methodology employed including use of ITT methods, exclusion of patients with AKI at baseline and limiting analysis to patient with >365 days of available follow-up. Subgroup analysis by age, sex, presence or absence of Stage 3 or 4 CKD or hypertension demonstrated results similar to the base case (no statistical interactions).

Diabetic population II

Analysis of ~24,000 patients with NVAF and T2DM treated in routine practice suggested that rivaroxaban was associated with significant risk reductions of MACE (25%) and MALE (63%) when compared with warfarin, without a difference in the overall major bleeding risk between the treatment cohorts. The risk reductions of major limb amputation and endovascular revascularization separately were also better with patients treated with rivaroxaban vs. warfarin. These findings have important implications for clinicians managing patients with comorbid NVAF and T2DM, in that anticoagulant choice may affect outcome risk beyond the traditional NVAF endpoints of stroke and systemic embolism. Patients who previously experienced MALE have a high risk of hospitalization, vascular amputations and death within 1 year of the event [38]. These risks appear to be lower when receiving rivaroxaban compared with warfarin use, although mortality rates were not directly evaluated in the present study.

Diabetic population III

In patients with NVAF and concomitant diabetes, rivaroxaban had similar rates of SSE and major bleeding compared with warfarin. The findings were consistent with those from a sub-analysis from the ROCKET-AF trial [1], which showed that the relative efficacy of rivaroxaban and warfarin for prevention of SSE was similar in people with diabetes (1.74 vs. 2.14/100 person-years; HR 0.82, 95% CI 0.63-1.08), as were the relative effects of the two oral anticoagulants on major bleeding (3.79 vs. 3.90/100 person-years; HR 1.00, 95% CI 0.81-1.24).

11.3.3 Cohort 3 (NVAF + CAD/PAD)

In patients with NVAF and concomitant CAD and/or PAD, rivaroxaban 20 mg/15 mg was associated with a significant risk reductions of MTVEs by 32%, in comparison with warfarin. No significant difference in the overall major bleeding was observed between rivaroxaban and warfarin users. No statistical interactions were noted upon subgroup analyses performed on either the MTVE or the major bleeding endpoint.

11.3.4 Cohort 4 (NVAF + Renal impairment)

In patients with NVAF and Stage 4 or 5 CKD or undergoing hemodialysis, rivaroxaban use was associated with a significant risk reduction of major bleeding by 32%, in comparison with warfarin. Rivaroxaban was also associated with a risk reduction of SSE by 45% vs. warfarin, albeit the 95% CIs crossed the line of unity.

11.3.5 Cohort 5 (NVAF + Heart failure)

In patients with NVAF and comorbid HF, rivaroxaban was associated with similar rates of SSE, IS, and major bleeding vs. warfarin. The findings were consistent with those from a sub-analysis from the ROCKET-AF trial, which showed the relative efficacy of rivaroxaban and warfarin for prevention of SSE was similar in people with HF or a LVEF of <40%

(SSEs/100 person-years = 1.90 vs. 2.09; HR = 0.91, 95% CI = 0.74-1.13) as were the relative rates of developing bleeding complications (major or non-major clinical relevant bleeds/100 person-years = 14.22 vs. 14.02; HR = 1.05, 95% CI = 0.95-1.15) [8].

11.3.6 Cohort 6 (NVAF + Polypharmacy)

In patients with NVAF taking ≥5 concomitant non-OAC chronic medications, rivaroxaban was associated with lower rates of SSE and IS and similar rates of major bleeding vs. warfarin. In patients taking ≥10 concomitant chronic medications (substantial polypharmacy), lower rates of SSE and IS were seen in rivaroxaban users, but 95% CIs crossed 1.0 for each outcome. No significant difference in major bleeding events was observed between rivaroxaban and warfarin users in either the polypharmacy or substantial polypharmacy analyses.

11.3.7 Cohort 7 (NVAF + CHA_2DS_2-VASc score = 1)

In patients with NVAF and a non-sex-related CHA_2DS_2-VASc score of 1 (low stroke risk), rivaroxaban was associated with a risk reduction of SSE by 59% at 1-year vs. warfarin without impacting the hazard of major bleeding. Similar results for both effectiveness and bleeding outcomes were seen when the follow-up was extended to 2 years.

11.4 Generalizability

As the study used the US claims data, the results therefore are generalizable to an insured US population with NVAF.

12. Other information

Not applicable.

13. Conclusion

When used in a routine practice in NVAF patients, rivaroxaban vs. warfarin appears to be associated with lower risks of AKI or renal impairment (in those with or without diabetes mellitus), MACE and MALE (in those with diabetes), MTVEs (in those with CAD and/or PAD), and SSE and IS (in those with heart failure or a lower risk of stroke). Moreover, in the setting of polypharmacy, rivaroxaban in NVAF patients is an effective and safe alternative to warfarin. The risk of major bleeding with rivaroxaban is generally comparable to warfarin.

Rivaroxaban use in patients with NVAF and Stage 4 or 5 CKD and among those receiving hemodialysis, appears to be associated with less major bleeding compared with warfarin, although additional studies are needed to confirm the effectiveness and safety of rivaroxaban in patients with severe kidney dysfunction and to help determine optimal dosing in this population.

The fact that the real-world findings in this study are generally consistent with those from Phase III randomized trials of rivaroxaban vs. warfarin in NVAF should provide additional reassurance to clinicians regarding the use of rivaroxaban in people with comorbidities that reflected on everyday clinical practice.

As the study used the US claims data, the results therefore are generalizable to an insured US population with NVAF.

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15. Appendices

Annex 1: List of stand-alone documents

Not applicable.

Annex 2: Additional information

PASS protocol.

Annex 3: Signature Pages

Signature Page - OS Conduct Responsible

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).
Report version and date	v 1.0, 07 JUL 2020
IMPACT study number	19859
Study type/Study phase	Observational Post Authorization Safety Study (PASS)
EU PAS register number	EUPAS21800
Medicinal product	Xarelto®
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Name: PPD

Date: 7/15/2020 | 1:30:50 AM PDT

Signature: PPD

Signature Page - OS Safety Lead

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).
Report version and date	v 1.0, 07 JUL 2020
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Study type/Study phase	Observational Post Authorization Safety Study (PASS)
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Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Name: PPD

Date: 7/16/2020 | 6:36:17 AM PDT

Signature: PPD

Signature Page - OS Medical Expert

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).
Report version and date	v 1.0, 07 JUL 2020
IMPACT study number	19859
Study type/Study phase	Observational Post Authorization Safety Study (PASS)
EU PAS register number	EUPAS21800
Medicinal product	Xarelto®
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Name: PPD

Date: 7/20/2020 | 11:55:42 AM CEST

Signature: PPD

Signature Page - OS Statistician

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).
Report version and date	v 1.0, 07 JUL 2020
IMPACT study number	19859
Study type/Study phase	Observational Post Authorization Safety Study (PASS)
EU PAS register number	EUPAS21800
Medicinal product	Xarelto®
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Name: PPD

Date: 7/20/2020 | 12:41:05 PM CEST

Signature: PPD

Signature Page - OS Epidemiologist

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).
Report version and date	v 1.0, 07 JUL 2020
IMPACT study number	19859
Study type/Study phase	Observational Post Authorization Safety Study (PASS)
EU PAS register number	EUPAS21800
Medicinal product	Xarelto®
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Name: PPD

Date: _____ 7/21/2020 | 9:49:21 AM CEST

Signature: _____

PPD

Signature Page - Study External Partner

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).
Report version and date	v 1.0, 07 JUL 2020
IMPACT study number	19859
Study type/Study phase	Observational Post Authorization Safety Study (PASS)
EU PAS register number	EUPAS21800
Medicinal product	Xarelto®
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Name: PPD

Date: _____ 7/21/2020 | 7:19:16 AM EDT

Signature: _____

PPD