Reference Number: RD-SOP-1216
Best Practice Document Version: 5

Observational Post Authorization Safety Study (PASS) Report

Study Information

Acronym/Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Report version and date	v 1.0, 05 NOV 2021
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS36634
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Product reference	Not applicable
Procedure number	Not applicable
Comparator / Reference therapy	Warfarin, Coumadin®
Study Initiator and Funder	Bayer AG
Research question and objectives	The objective of the study is to evaluate the effectiveness and safety of rivaroxaban as compared to warfarin in non-valvular atrial fibrillation patients with co-morbid diabetes mellitus in routine clinical practice
Country(-ies) of study	USA
Author	1) PPD MetaEvidence, LLC 2) PPD Bayer AG 3) APCER Life Sciences: PPD

Marketing authorization holder

Marketing authorization holder (MAH)	Bayer AG, 51368 Leverkusen, Germany
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1. Abstract

Acronym/Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Report version and date Author	v 1.0, 05 NOV 2021 1) PPD MetaEvidence, LLC 2) PPD Bayer AG 3) APCER: PPD
Keywords	NVAF, Rivaroxaban, Diabetes Mellitus, Effectiveness, Safety
Rationale and background	Patients with diabetes are at a greater risk of developing nonvalvular atrial fibrillation (NVAF). Comorbid diabetes and NVAF increases the risk of stroke and systemic embolism (SSE), lower extremity arterial disease, and progression to end-stage renal disease (ESRD)
Research question and objectives	What is the comparative effectiveness and safety of rivaroxaban versus warfarin in patients with NVAF and comorbid type 2 diabetes managed in routine clinical practice? The objectives of the study were to compare the effectiveness and safety of rivaroxaban versus warfarin by assessing the risk of major thrombotic adverse events and bleeding-related hospitalization in patients with NVAF and comorbid type 2 diabetes, as well as secondary endpoints (e.g., development of new-onset neurologic impairment, adverse renal outcomes)
Study design	A retrospective cohort study using the Optum EHR database.
Setting	The Optum EHR (electronic health record) database included data on insured and uninsured patients of all ages (≥18 years) to provide a representative sample of US patients with NVAF. Optum EHR data from 01 NOV 2010 to 31 DEC 2019 were used for the study.
Subjects and study size, including dropouts	NVAF patients with comorbid type 2 diabetes and those qualifying for study inclusion were identified in the Optum EHR database and analyzed for primary and secondary outcomes. After applying all of the defined selection criteria, 116,049 patients (32,078 rivaroxaban users and 83,971 warfarin users) were considered to evaluate primary

	outcomes and secondary outcomes (CV and bleeding). Of the 116,049 patients, 83,182 patients (24,912 rivaroxaban users and 58,270 warfarin users) were considered to evaluate secondary outcomes related to kidney, major adverse limb event (MALE), ophthalmic, and all-cause mortality. Of the 116,049 patients, a total of 88,227 patients (26,537 rivaroxaban users and 61,690 warfarin users) were considered to evaluate ophthalmic outcomes/complications (non-traumatic bleeding and/or diabetic retinopathy).
Variables and data sources	Patient baseline characteristics such as age, gender, comorbidities and comedications, stroke and bleeding scores were collected at the index date or from the last recorded value within the baseline period. The primary outcomes were: • Composite outcome of SSE • Major or clinically relevant non-major (CRNM) bleeding events resulting in hospitalization. The secondary outcomes were composite of stroke, systemic embolism, and vascular death; composite of stroke, systemic embolism, myocardial infarction (MI), and vascular death; major adverse cardiovascular event (stroke, MI, and vascular death); ischemic stroke (IS); systemic embolism; need for revascularization or major amputation of the lower limb; intracranial hemorrhage (ICH); critical organ bleeding; any extracranial bleeding; any hospitalization due to intracranial or critical organ bleeding or a bleed in another location associated with either a 2 g/dL drop in hemoglobin or need for transfusion; doubling of the serum creatinine level from baseline; decrease in eGFR>30% or 40%; development of an eGFR<15 mL/min or initiation of dialysis; development of ESRD; development of urine albumin-to-creatinine ratio (UACR) of 30-300 or >300; development of diabetic retinopathy; development of serum potassium > 5.6 or >6 mg/dL; MI; all-cause mortality; vascular mortality; composite stroke, systemic embolism, need for lower limb revascularization or major amputation; and composite of >40% decrease in eGFR from baseline, eGFR<15 mL/min, need for dialysis, renal transplant, MALE, retinopathy or all-cause death. Billing codes were required to identify covariates or outcomes and endorsed and/or validated coding algorithms (e.g., Centers for Medicare & Medicaid Services (CMS), agency for health research and Quality (AHRQ), Elixhauser

	or Charlson comorbidity indices, Cunningham bleeding algorithm) were utilized, whenever possible. United States Optum® de-identified EHR database that capture longitudinal patient-level medical record data for ~97 million patients at ~700 hospitals and ~7,000 clinics across the United States (US) were utilized for this study. This EHR database included patients from different geographical areas of the US and captured commercially insured, Medicare, Medicaid, and uninsured patients, providing a more accurate reflection of the general population than a traditional administrative claims data set.
Results	Rivaroxaban was associated with a reduced risk of SSE or vascular death (3.79 vs. 4.19; HR=0.91, 95% CI: 0.88, 0.95), driven mostly by 10% relative risk reduction (RRR) in vascular death (2.81 vs 3.18, HR=0.90, 95% CI: 0.86, 0.95) and 18% RRR in systemic embolism (0.13 vs. 0.16; HR=0.82, 95% CI: 0.66, 1.02). Major/CRNM bleeding was less frequent with rivaroxaban versus warfarin (2.17 vs. 2.31; HR=0.94, 95% CI: 0.89, 0.99) due to decreased critical organ bleeding (37% RRR) and intracranial hemorrhage (28% RRR). These findings remained consistent across subgroups such as baseline HbA1c level, with statistical interactions seen only when comparing the 20 mg versus 15 mg dosing subgroups for the SSE/vascular death outcome (an interaction based more on magnitude than direction of effect) and among patients with a well-controlled INRs (TTR≥75%). These findings also remained robust upon changes in confounding adjustment methodology employed and upon capping follow-up at a maximum of 2-years. The effectiveness and safety of rivaroxaban relative to warfarin remained consistent across older and younger patient subgroups for the outcomes of SSE or vascular death (HR=0.93 vs. 0.91), and hospitalization for major or CRNM bleeding (HR=1.06 vs. 0.90). Rivaroxaban was associated with a reduced hazard of the composite outcome of >40% decrease in eGFR from baseline, eGFR<15 mL/minute/1.73 m^2, need for dialysis or kidney transplant, MALE, diabetic retinopathy or death (HR=0.93, 95%CI: 0.91, 0.95) versus warfarin. Rivaroxaban was also associated with significant reductions in the relative hazard of a >40% decrease in eGFR from baseline (HR=0.96), need for dialysis or renal transplant (HR=0.81), and limb revascularization or major amputation (HR=0.85). Death occurred at a lower incidence rate with rivaroxaban

	(HR=0.92, 95%CI: 0.89, 0.95). These findings remained consistent across subgroups stratified by age, eGFR, HbA1c, morbid obesity, and antiplatelet use; as well as, when follow-up was capped at 2-years and 1:1 propensity score matching or sIPTW was alternatively used for between cohort confounder adjustment. Rivaroxaban was associated with a 15% (95%CI: 8%, 21%) relative hazard reduction of any ophthalmic complication (incidence rate=1.25 vs. 1.46 per 100 person years), driven by reductions in both ophthalmic bleeding (HR=0.80) and diabetic retinopathy (HR=0.85).
Discussion	In NVAF patients with T2DM, rivaroxaban was associated with an ~10% relative risk reduction in vascular mortality and fewer bleeding-related hospitalizations versus warfarin, including a significant 37% relative risk reduction in critical organ bleeding and a 28% relative risk reduction in intracranial hemorrhage. Rivaroxaban was associated with a significant 19.7 event/1,000 person years reduction in the composite outcome of >40% decrease in eGFR from baseline, eGFR<15 mL/minute/1.73 m^2, new need for dialysis or renal transplant, limb revascularization or major amputation, development of diabetic retinopathy, or all-cause mortality. These reductions in adverse events were due to reduced incidence rates of kidney and limb complications, as well as all-cause death. Rivaroxaban was associated with a reduction in ophthalmic complications compared to warfarin. The effectiveness and safety of rivaroxaban relative to warfarin remained consistent across older and younger patient subgroups, supporting rivaroxaban as an alternative for elderly NVAF patients with concomitant type 2 diabetes. The findings of the present study should provide clinicians with additional confidence in selecting rivaroxaban in NVAF patients with comorbid T2DM.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen, Germany

2. List of abbreviations

ACE	Angiotensin-converting enzyme
AG	Aktiengesellschaft
ARB	Angiotensin-receptor blockers
BMI	Body mass index
CABG	Coronary artery bypass graft
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 transient ischemic attack or Thromboembolism; V=Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque); A=Age 65–74 years; Sc: Sex category (i.e., female sex)
$CHADS_2$	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 transient ischemic attack or Thromboembolism
CI(s)	Confidence interval(s)
CKD	Chronic kidney disease
CMS	Centers for Medicare & Medicaid Services
CONSORT	Consolidated standards of reporting trials
CPT	Current procedural technology
CRNM	Clinically relevant non-major
CV	Cardiovascular
CYP	Cytochrome P450
DM	Diabetes mellitus
DOACs	Direct-acting oral anticoagulants
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
ESRD	End-stage renal disease
EU	European Union
GI	Gastrointestinal
GLP	Glucagon-like peptide
H. pylori	*Helicobacter pylori*
HAS-BLED	H=Hypertension; A=Abnormal renal and liver function; S=Stroke; B=Bleeding; L=Labile INR; E=Elderly; D=Drugs or alcohol
HCPCS	Healthcare common procedure coding system
HIPAA	Health insurance portability and accountability act
HR(s)	Hazard ratio(s)
ICD	International classification of diseases
ICD-CM	International classification of diseases – clinical modification
ICD-PCS	International classification of diseases – procedure coding system
ICH	Intracranial hemorrhage
INR	International normalized ratio
IPTW	Inverse probability of treatment weighting
IS	Ischemic Stroke
ISTH	International Society on Thrombosis and Haemostasis

MAH	Marketing authorization holder
MALE(s)	Major adverse limb event(s)
MI	Myocardial infarction
N/n	Number of patients/Number of patients with event
NOAC(s)	Non-vitamin K antagonist oral anticoagulant(s)
NSAIDs	Nonsteroidal anti-inflammatory drugs
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulation
OD	Once daily
OLW	Overlap weighted
OS	Observational study
PAD	Peripheral artery disease
PAS	Post-authorization study
PASS	Post-authorization safety study
PCI	Percutaneous coronary intervention
PPIs	Proton-pump inhibitors
PS(s)	Propensity score(s)
p-value	Probability value
PY(s)	Person-year(s)
QPPV	Qualified Person Responsible For Pharmacovigilance
RCTs	Randomized controlled trials
SD(s)	Standard deviation(s)
SNRI(s)	Serotonin-norepinephrine reuptake inhibitor(s)
sIPTW	Stabilized inverse probability of treatment weighting
SSE	Stroke or systemic embolism
SSRI(s)	Selective serotonin reuptake inhibitor(s)
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T2DM	Type 2 diabetes mellitus
TTR	Time in therapeutic range
UACR	Urine albumin-to-creatinine ratio
US	United States

3. Investigators

Role:	Principal Investigator (external)
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Address	MetaEvidence, LLC 559 North Stone Street, West Suffield, CT 06093, USA
E-mail:	PPD

4. Other responsible parties

Study Team (internal or external)

Role:	OS (Observational study) Conduct Responsible
Name:	PPD
E-mail:	PPD
Role:	OS Safety Lead
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Statistician
Name:	PPD
Role:	OS Epidemiologist
Name:	PPD
Role:	Qualified Person responsible for Pharmacovigilance (EU QPPV)
Name:	PPD
Role:	MAH contact person (Regulatory Affairs)
Name:	PPD

Contact details of the responsible parties are available upon request.

5. Milestones

Table 5-1: Milestones

Milestone	Planned date	Actual Date	Comments
Registration in the EU PAS register	AUG 2020	20 AUG 2020	Not applicable
Start of data collection	AUG 2020	21 AUG 2020	Not applicable
End of data collection	FEB 2021	31 JUL 2021	Not applicable
Final report of study results	AUG 2021	05 NOV 2021	Not applicable

6. Rationale and background

NVAF is a common cardiac arrhythmia. One in four middle-aged adults in the US and Europe is likely to be diagnosed with this clinical manifestation. NVAF substantially increases patients' risk of stroke by five-fold and mortality by two-fold [1], [2].

Oral anticoagulation (OAC) with either warfarin or a non-vitamin K antagonist oral anticoagulant (NOAC), such as apixaban, dabigatran, edoxaban, or rivaroxaban, significantly decreases the risk of clot formation and is used to prevent IS in NVAF population [1], [2], thus reducing morbidity, mortality and economic burden for patients and healthcare systems worldwide.

Data from randomized controlled trials (RCTs) [3], [4] and administrative claims database analyses [5], [6] show that the oral factor Xa inhibitor, rivaroxaban, is safe and effective in patients with NVAF and diabetes mellitus (DM); however, EHR-based evaluations of such patients (which provide more detailed patient data) are scarce.

Patients with diabetes are at a 49% greater risk of developing NVAF [7]. Comorbid diabetes and NVAF increase the risk of stroke and systemic embolism (SSE) compared with those without diabetes [4], [8]. Patients with NVAF and diabetes are at increased risk of death due to vascular causes. Data suggest that NOACs may be associated with a reduced risk of vascular death compared to VKA in the diabetic NVAF patient population [4], [9]. Diabetes also increases patients' risk of lower extremity arterial disease by two- to four-fold compared with the absence of diabetes; this includes MALE such as the need for amputation and revascularization procedures of the lower limbs [10]. Finally, vascular calcification is common in diabetic patients, and warfarin (when used to treat NVAF) has been associated with increased renovascular calcification and worsening renal function, and the need for dialysis [11], [12].

7. Research question and objectives

What is the comparative effectiveness and safety of rivaroxaban versus warfarin in patients with NVAF and comorbid type 2 diabetes managed in routine practice using Optum® De-Identified EHR data?

Primary objective

The primary objective of this study was to compare the effectiveness and safety of rivaroxaban versus warfarin in NVAF patients with comorbid type 2 diabetes using the Optum® De-Identified EHR dataset, including:

- The composite outcome of SSE;
- Any major or CRNM bleed resulting in hospitalization [13]

Secondary objectives

The secondary objectives of this study were to compare rivaroxaban versus warfarin in NVAF patients with comorbid type 2 diabetes for the risk of:

- IS;
- Systemic embolism;
- Need for revascularization or major amputation of the lower limb (i.e., MALE);
- ICH;
- Critical organ bleeding per International Society on Thrombosis and Haemostasis (ISTH) categories;
- Any extracranial bleeding;
- Any hospitalization due to intracranial or critical organ bleeding or a bleed in another location associated with either a 2 g/dL drop in hemoglobin or need for transfusion;
- New-onset vascular dementia;
- Doubling of the serum creatinine level from baseline;
- Decrease in eGFR>30% or 40%;
- Development of an eGFR<15 mL/min or the initiation of dialysis;
- Development of ESRD [14];
- Development of UACR of 30-300 or >300;
- Development of serum potassium > 5.6 or >6 mg/dL;
- Composite stroke, systemic embolism, need for lower limb revascularization or major amputation;
- MI;
- Development of diabetic retinopathy;
- Vascular mortality (a primary diagnosis/procedure code indicating cardiovascular (CV) condition(s) associated with hospital admission or emergency room visit within 365 days of death);
- Composite of stroke, systemic embolism, vascular death;
- Composite of stroke, systemic embolism, MI, vascular death;
- Major adverse CV event (stroke, MI, vascular death);
- Composite of >40% decrease in eGFR from baseline, eGFR<15 mL/min, need for dialysis, renal transplant, MALE, retinopathy or all-cause death;
- All-cause mortality.

8. Amendments and updates

On 9 NOV 2020, the following secondary outcomes were added due to medical insights:

- Composite of stroke, systemic embolism, vascular death;
- Composite of stroke, systemic embolism, MI, vascular death;
- Major adverse CV event (stroke, MI, vascular death);
- Diabetic retinopathy;
- Vascular mortality (a primary diagnosis/procedure code indicating CV condition(s) associated with hospital admission or emergency room visit within 365 days of death);
- Composite of >40% decrease in eGFR from baseline, eGFR<15 mL/min, need for dialysis, renal transplant, MALE, retinopathy, or all-cause death.

9. Research methods

9.1 Study design

This study was a retrospective cohort study based on the data from the US Optum® De-Identified EHR database.

Optum EHR data from 01 NOV 2010 to 31 DEC 2019 was used. Rivaroxaban was approved in the US for use in NVAF patients in NOV 2011, and thus data back to NOV 2010 was required to provide a full 12-month pre-period for all patients. Included patients were OAC-naïve, newly initiated on rivaroxaban or warfarin, be active in the data set for at least 12 months before the index event (based on the "First Month Active" field provided in the Optum data set), and had received care documented in the EHR database from at least one provider in the 12-months before the index date. The date of the first fill of OAC was defined as the index date (date of start of OAC).

9.2 Setting

The Optum EHR database [15] included longitudinal patient-level medical record data for 97 million patients seen at ~700 hospitals and ~7,000 clinics across the US. The database included records of prescriptions and over-the-counter medications as prescribed, administered, or self-reported by patients, laboratory results, vital signs, body measurements, other clinical observations, diagnosis (International classification of diseases [ICD]-9 and ICD-10), and procedures codes (ICD-9, ICD-10, Current procedural technology (CPT)-4, Healthcare common procedure coding system (HCPCS), Revenue codes).

9.3 Subjects

9.3.1 Selection criteria

To be included in the study, patients had to:

- be ≥18 years of age at the time of anticoagulation initiation;
- have diagnoses of type 2 diabetes and NVAF;

- given the high specificity (>98%) of billing codes for identifying diabetes, a code for diabetes was considered sufficient to indicate diabetes in this study, regardless of A1c value (which was also a treatment goal);
- due to the moderate sensitivity of billing codes for diabetes (~60-70%), patients without a billing code for diabetes, but having an A1c>6.5% and receiving an antihyperglycemic medication (oral medications, glucagon-like peptide [GLP]1-antagonists) were considered diabetics as well;

- have no record of prior OAC use in the prior 12-months;
- be newly initiated on rivaroxaban or warfarin (index date);
- have ≥12-months of EHR activity prior to the index date and received care documented in the EHR database from at least one provider in the 12-months prior.

Patients were excluded from the study if they had:

- evidence of valvular heart disease, defined as any rheumatic heart disease, mitral stenosis, or mitral valve repair/replacement;
- pregnancy;
- usage of rivaroxaban doses other than 15 mg once daily (OD) or 20 mg OD or the presence of other indication(s) for OAC use;
- any prior OAC utilization per written prescription or patient self-report at baseline.

9.3.2 Study population

The Optum EHR database [15] comprised data on insured and uninsured patients of all ages to provide a representative sample of US patients with NVAF. The study population of interest had NVAF and comorbid type 2 diabetes, were OAC-naïve and newly initiated on rivaroxaban or warfarin (defined as the index date), active in the data set for at least 12 months prior to the index event (based on the "First Month Active" field provided in the Optum data set) and had received care documented in the EHR database from at least one provider in the 12-months prior to the index date.

9.4 Variables

9.4.1 Baseline characteristics

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

Demographic characteristics collected for all patients included gender, race, age, and age group (<45, 45–64, 65-74, 75–79, 80+).

Clinical characteristics identified from the patients' medical and pharmacy claims in the baseline period were:

- $CHADS_2$ score;
- CHA_2DS_2-VASc score;
- Modified HAS-BLED score;

- Comorbidities included atrial fibrillation type (starting in 2016), IS, intracranial bleeding, systemic embolism, deep vein thrombosis, pulmonary embolism, mitral stenosis, heart valve/complications, aortic valve replacement, transcatheter aortic valve replacement, pulmonary valve replacement, mitral valve replacement, tricuspid valve replacement, valvotomy/valvuloplasty for mitral stenosis, heart failure, hypertension, prior IS (recent IS within 30-days prior of index event), transient ischemic attack, bariatric surgery, peripheral vascular disease, MI, percutaneous coronary intervention (PCI), coronary artery bypass grafting, any major bleed, MALE, major amputation, gastrointestinal (GI) bleeding, active cancer treatment, aortic plaque, central venous catheter, acute kidney injury, chronic kidney disease (CKD), ESRD or hemodialysis, liver disease, coagulopathy, gastroesophageal reflux disease/heartburn, anemia, asthma, chronic obstructive pulmonary disease, sleep apnea, smoker, hemorrhoids, alcohol abuse, anxiety, depression, lower extremity paralysis, psychosis, osteoarthritis, headache, diverticulitis, Crohn's or ulcerative colitis, *Helicobacter pylori (H. pylori)*, hypothyroidism, solid tumor, lymphoma, metastatic cancer, recent major surgery within 6-12 weeks of index event, dementia, vascular dementia, trauma, hypercoagulable state, prior history of venous thromboembolism, obesity, morbid obesity, varicose veins, chronic venous insufficiency, acute coronary syndrome, carotid stenosis, pneumonia, osteoporosis, orthopedic surgery, rheumatoid arthritis/collagen vascular disease, proteinuria, and ischemic (coronary) heart disease;
- Comedications were aspirin, P2Y12 inhibitors, other antiplatelet agents, nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2-specific NSAIDs, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), β-blockers, diltiazem, verapamil, dihydropyridine calcium channel blockers, loop diuretic, thiazide diuretic, digoxin, amiodarone, dronedarone, other antiarrhythmic drugs, statins, other cholesterol-lowering drugs, metformin, sulfonylureas or glinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 agonists, insulin, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitor (SNRIs), other antidepressants, proton pump inhibitors (PPIs), histamine-2 receptor antagonists, systemic corticosteroids, estrogens, strong Cytochrome P450 (CYP)3A4 inhibitors, and strong CYP3A4 inducers;
- Laboratory values and vital signs included systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, left ventricular ejection fraction, D-dimer, potassium, serum creatinine, reported eGFR, glycosylated hemoglobin (A1c), height, weight, body mass index (BMI), UACR, aspartate transaminase, alanine transaminase, total bilirubin, platelet count, blood urea nitrogen, total cholesterol, and low-density lipoprotein cholesterol;
- Number of hospitalizations;
- Hospital Frailty Risk Score [16].

9.4.2 Exposure

There were two exposure groups: new users of rivaroxaban and warfarin per written prescription, medication administration, or patient self-report of medication use (including over-the-counter medications) at baseline.

9.4.3 Outcome measures

The study outcomes were defined based on ICD-9/10-CM diagnosis codes, CPT-4, HCPCS, and ICD-9/10-PCS procedure codes or laboratory, vital sign, and other patient observation results; see Annex 1.

The primary outcomes included:

- The composite outcome of SSE;
- Any major or CRNM bleed resulting in hospitalization

The secondary outcomes included:

- Composite of stroke, systemic embolism, vascular death;
- Composite of stroke, systemic embolism, MI, vascular death;
- Major adverse CV event (stroke, MI, vascular death);
- IS;
- Systemic embolism;
- Need for revascularization or major amputation of the lower limb (i.e., MALE);
- ICH;
- Critical organ bleeding;
- Any extracranial bleeding;
- Any hospitalization due to intracranial or critical organ bleeding or a bleed in another location associated with either a 2 g/dL drop in hemoglobin or need for transfusion;
- Doubling of the serum creatinine level from baseline;
- Decrease in eGFR>30% or 40%;
- Development of an eGFR<15 mL/min or the initiation of dialysis;
- Development of ESRD per billing codes only [14];
- Development of UACR of 30-300 or >300;
- Development of diabetic retinopathy;
- Development of serum potassium > 5.6 or >6 mg/dL;
- MI;
- All-cause mortality;
- Vascular mortality (a primary diagnosis/procedure code indicating CV condition(s) associated with hospital admission or emergency room visit within 365 days of death);
- Composite stroke, systemic embolism, need for lower limb revascularization or major amputation;
- Composite of >40% decrease in eGFR from baseline, eGFR<15 mL/minute, need for dialysis, renal transplant, MALE, retinopathy or all-cause death.

9.5 Data sources and measurement

The Optum EHR database included longitudinal patient-level medical record data for ~97 million patients seen at ~700 hospitals and ~7,000 clinics across the US. The database included records of prescriptions as prescribed and administered, laboratory results, vital signs, body measurements, diagnosis, and procedures. This database contained data on insured and uninsured patients of all ages to provide a representative sample of US patients with NVAF.

Strengths of the data set included the ability to use clinical data as opposed to relying solely on billing codes disease classification/severity. Both prescribed and self-reported medication use was tracked, allowing for assessment of important over-the-counter medication use (e.g., aspirin, [PPIs] St John's Wort). Importantly, this EHR database included patients from different geographical areas of the US and captured commercially insured, Medicare, Medicaid, and uninsured patients that provided a more accurate reflection of the general population than a traditional administrative claims data set.

9.6 Bias

Like other databases, Optum EHR claims databases have limitations [15, 17].

Key limitations include:

- Misclassification bias could negatively impact the internal validity of database analyses.
- Optum EHR data patient sampling was not random and could contain biases or fail to generalize well to other populations.
- Data from Optum EHR represents only patients within the US.
- Patients may have received care at institutions that were not included in Optum EHR, allowing for potential incompleteness of data in the follow-up period.
- The EHR database lacked information on prescription fills as only written prescriptions were captured.
- The study was conducted as an intent to treat approach, and given the lack of prescription fills, it was difficult to ascertain treatment exposure.
- Data on time since diabetes diagnosis could not be assessed in this data set.
- New-onset neurologic impairment was assessed based on the presence of new billing codes for vascular dementia, which may have missed less severe cases of neurologic impairment.
- An EHR entry to initiate an OAC did not necessarily mean a patient filled their prescription and/or took it. Moreover, as the Optum® EHR did not provide data on adjudicated.

9.7 Study size

The NVAF patients with comorbid type 2 diabetes and those qualifying for study inclusion were identified in the Optum EHR database and analyzed for primary and secondary outcomes. After applying all the defined selection criteria, 116,049 patients (32,078 rivaroxaban users and 83,971 warfarin users) were considered to evaluate primary outcomes

and the secondary CV and bleeding outcomes. Of the 116,049 patients, 83,182 patients (24,912 rivaroxaban users and 58,270 warfarin users) were considered to evaluate secondary outcomes related to kidney, MALE, ophthalmic, and all-cause mortality.

Of the 116,049 patients, a total of 88,227 patients (26,537 rivaroxaban users and 61,690 warfarin users) were considered to evaluate ophthalmic outcomes/complications (non-traumatic bleeding and/or diabetic retinopathy).

For further details on the number of patients, refer to Section 10.1.

9.8 Data transformation

Database management was performed using SAS Enterprise Guide version 8.1 (SAS Inc., Cary, NC, USA). MetaEvidence LLC met all data maintenance and security requirements of Optum Inc (the data owners). The required data were de-identified and were compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and was provided by Optum Inc to MetaEvidence LLC via a secure, password-protected, temporary SharePoint link. Raw and processed data files were maintained by MetaEvidence LLC on a secure, password-protected (2 step verification required) network assessable server and made available only to members of the research team via unique logins and passwords.

9.9 Statistical methods

9.9.1 Main summary measures

This section provides a detailed overview of 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 within this section.

Propensity score matching was performed using the 'MatchIT' package and R statistical software (version 3.4.3, The R Project for Statistical Computing). Cox proportional hazards regression analysis will be performed using R statistical software (version 3.4.3, The R Project for Statistical Computing).

9.9.2 Main statistical methods

Individuals were followed from the index date until a study event occurred (primary and secondary outcomes), the end of EHR activity (based on "Last Month Active" data available in the Optum EHR), or until the end of follow-up data availability or reaches the end of data availability in the Optum data set (31 DEC 2019). Descriptive statistics were generated to summarize the baseline characteristics of the study population. Categorical data were reported as percentages and continuous data as medians with accompanying 25%, 75% ranges, or means ± standard deviations (SDs). The incidence rate of each outcome of interest was reported as events per 100 person years (%/year). Patients receiving rivaroxaban were 1:n matched to warfarin patients based on PSs. Stabilized IPTW, overlap weighting, and multivariable regression, competing risk regression approaches, as explained below were used to adjust for potential confounding. Cox proportional hazards regression models were used to compare event rates over time for the rivaroxaban and warfarin cohorts.

9.9.2.1 Propensity score-matched analysis

Patients receiving rivaroxaban were 1:n matched to warfarin patients based on PSs calculated via multivariable logistic regression where the probability of exposure (here: receiving

rivaroxaban) given patient characteristics were calculated [18]. PSs were estimated based upon commonly used variables and accepted risk factors for differential OAC exposure identified during the baseline period, including demographics, comorbidities, laboratory and vital signs, and concurrent outpatient co-medication use. All clinical characteristics listed in section 9.4 of this report were included in the PS model. Given the retrospective nature of the data analysis, the presence of a comorbid disease diagnosis was made based upon billing codes and/or supporting laboratory/observation data. The absence of data suggesting comorbidity exists was assumed to represent the absence of the disease (no missing data for binary comorbidity disease diagnoses). For continuous laboratory and observation data (e.g., eGFR, BMI, etc.), missing data were imputed using a "multiple imputation" approach based on a fully conditional specification linear regression model with all other available variables included in the model [19]. No imputation was performed for potentially missing outcomes/endpoint data. Separate PS models were fit once for the primary analysis and for each subgroup analysis. The presence of residual differences in measured covariates following cohort matching (using a caliper ≤0.5 SDs of the logit of the PS) was assessed by calculating standardized differences (with a difference <0.1 considered well-balanced for each covariate) [18].

All methods for confounder adjustment have potential limitations related to selecting a clinically relevant target population, covariate balance, and precision. PS matching operates by taking each treated study participant and finding the closest PS match among controls within a caliper (or bound).

9.9.2.2 IPTW and Overlap weighting

Conventional IPTW assigns a weight of 1/PS for treated and 1/ (1 − PS) for untreated patients, allowing individuals with underrepresented characteristics to count more in the analysis. IPTW can produce inflated variance estimates which can be addressed through a simple stabilization of weights (multiplying PSs of each participant by the relative proportion of the specific cohort makes up of the total study population). In observational data, in which the initial differences in treatment groups may be large, these methods can modify the target population, fail to achieve good balance, or substantially worsen precision.

Overlap weighting assigns weights to each patient that are proportional to the probability of that patient belonging to the opposite treatment group. Specifically, treated patients are weighted by the probability of not receiving treatment (1 − PS), and untreated patients are weighted by the probability of receiving the treatment (PS). These weights are smaller for extreme PS values so that outliers who are nearly always treated (PS near 1) or never treated (PS near 0) do not dominate results and worsen precision, as occurs with IPTW. These outliers contribute relatively less to the result, while patients whose characteristics are compatible with either treatment contribute relatively more. The resulting target population mimics the characteristics. Overlap weighting also leads to exact balance on the mean of every measured covariate when the PS is estimated by logistic regression. Like all PS-based methods, overlap weighting cannot adjust for patient characteristics that are not measured and included in the model for the PS. When initial imbalances in patient characteristics between treatment groups are modest, overlap weighting yields similar results to IPTW. The advantages of overlap weighting are greatest when comparator groups are initially very different.

Visual inspection of plots of PS distributions can aid in the determination of the best method to utilize.

9.9.2.3 Cox proportional hazards regression model

Cox regression (or proportional hazards regression) is a method for investigating the effect of variables upon the time a specified event takes to happen. Cox proportional hazards regression models were used to compare event rates over time for the rivaroxaban and warfarin cohorts. As PS-based methods were assumed to balance key characteristics of the treatment cohorts, the only independent variable that was included in Cox regression model was OAC received (rivaroxaban or warfarin); meaning that the analysis, adjusted for treatment only, was performed on an already matched population to keep baseline characteristics in balance. Results of Cox regression were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Cox proportional hazards regression analysis was performed using R statistical software (version 3.4.3, The R Project for Statistical Computing). The proportional hazard assumption was tested based on Schoenfeld residuals. Patients were censored in the Cox models at the first incidence a patient experienced end-of-EHR activity (based on "Last Month Active" data available in the Optum EHR) or reached the end of data availability in the Optum data set (31 DEC 2019). As the EHR dataset does not allow to calculate exposure times (prescriptions are not captured with all the relevant details for such an analysis), patients were analyzed using an intention-to-treat approach, where patients were evaluated based on their initial OAC prescription Time from treatment initiation to end of follow-up were then be considered the time under risk.

9.9.2.4 Subgroup analyses

The primary effectiveness and primary safety outcomes will be analyzed in the entire study cohort as well as stratified by the following subgroups:

- Hemoglobin A1c value closest and prior to baseline, <7%, 7% to <8%, ≥8% (Diabetes severity)
- Age≥75 years or <75 years
- Age ≥80 years or <80 years
- Sex
- BMI ≥40 kg/m2 and/or body weight ≥120 kg
- eGFR (value closest and prior to baseline, <15 ml, 15 to 30 ml, 30 to <45 ml, 45 to <60 ml (and < 50 ml), 60 to <90 ml, >=90 ml per minute per 1.73 m2) or CKD [14]
- Frailty risk using the Hospital Frailty Risk Score [16] (score <5 is low risk, 5-15 intermediate-risk, >15 high risk)
- Presence or absence of the following comorbid conditions (in addition to NVAF and type 2 diabetes):
    - Peripheral artery disease (PAD)
    - Coronary artery disease
    - Heart failure
    - Active cancer (e.g., active treatment in prior 6-months or metastatic disease)
    - Prior IS

- Concomitant antiplatelet utilization (aspirin, P2Y12 platelet inhibitor, dual antiplatelet therapy)
- Initial rivaroxaban dose (20 mg or 15 mg)

To limit the number of analyses performed (and the impact of multiple hypothesis testing), subgroup analyses were only performed on the primary effectiveness and primary safety endpoints. To allow for the assessment of statistical interaction in outcome rates across age groups, PS-overlap weighted (OLW) patients after stratification of eligible patients into older (≥80 years old) and younger (<80 years old) cohorts were evaluated. P-values for interaction across age subgroups were adjusted to control for false discovery rates due to multiple hypothesis testing. A p-value <0.05 was considered statistically significant in all cases.

9.9.3 Missing values

For continuous laboratory and observation data (e.g., eGFR, BMI, etc.) with <25% missing values, missing data were imputed using a "multiple imputation" approach based on a fully conditional specification linear regression model with all other available variables included in the model [19].

No imputation was performed for potentially missing outcomes/endpoint data.

9.9.4 Sensitivity analyses

To test the robustness of conclusions to various methods for confounding adjustment, sensitivity analyses were performed in which each analysis/outcome was assessed using a stabilized-IPTW [20], overlap weighting [21], and a competing risk model assessing the effect of covariates (anticoagulant choice) on the cause-specific hazard of outcome (death, stroke/systemic embolism, or major bleeding) [22, 23] approach. Because a competing risk scenario in which different event types, including nonfatal outcomes (stroke/systemic embolism, major bleeding) and death, was anticipated in this study, which event type occurred first was determined. Therefore, for this study, a cause-specific hazard model was used [23]. Competing risk regression was performed using 'cmprsk,' and 'riskRegression' in R. Results of the competing risk regression was reported as incidences over time for the cohorts and as HRs with 95% CIs. Finally, to assess the magnitude of confounding as well as the consistency and robustness of the results with the different analytical methods, unadjusted analyses were also reported.

Based on prior NVAF analyses, it was estimated the median follow-up for available patients using this approach was to exceed 2.5 years (like that of RCTs). An additional sensitivity analysis was performed whereby the SSE/vascular death and major/CRNM bleeding outcomes were assessed after applying stabilized IPTW and 1:1 PS matched (using a caliper of 0.25 SDs of the logit of the PS) approaches to confounding adjustment and capping the duration of patient follow-up at a maximum of 2-years. The data were analyzed using logistic regression instead of Cox proportional hazards regression. To reduce the chances of obtaining false positive results (type 1 error) because of multiple hypothesis testing, all p-values for subgroup and sensitivity analyses were adjusted using the Benjamini and Yekutieli method.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

When dependence on billing codes was required to identify covariates or outcomes, endorsed and/or validated coding algorithms (e.g., CMS, AHRQ, Elixhauser or Charlson comorbidity indices, Cunningham bleeding algorithm) were utilized whenever possible. All database coding was performed in SAS Enterprise Guide version 8.1 (SAS Inc., Cary, NC, USA). All coding was reviewed by a second trained investigator to assure its accuracy. Billing codes, generic drug names, laboratory values, and observation data used for this study are detailed in the supplied Annex 1.

10. Results

10.1 Participants

10.1.1 Patients considered for primary and secondary outcomes (CV and bleeding)

A total of 758,739 OAC-naive NVAF patients were available in the Optum EHR database from 01 NOV 2010 to 31 DEC 2019. Of these, 403,240 patients had initiated OAC on or after 01 NOV 2011, were older than 18 years of age, and identified with a claim for warfarin or rivaroxaban. After applying all other defined selection criteria (excluding patients who had non-atrial fibrillation dose, or valvular disease, or pregnancy, or were not type-2 diabetic), 116,049 patients (32,078 rivaroxaban users and 83,971 warfarin users) were considered to evaluate the primary outcomes and the secondary CV and bleeding outcomes. Of the 32,078 rivaroxaban users, 31% started with 15 mg OD, while 69% were prescribed with 20 mg OD.

Table 10-1 depicts the identification of the study population, showing every step of exclusion with corresponding patients analyzed for primary and secondary outcomes (CV and bleeding) of the study.

Table 10-1: Patient flow table (CONSORT-style) - analyzed for primary and secondary outcomes (CV and bleeding)

	Less Excluded Patients	Remaining Patients	
OAC-naive NVAF patients		758,739	
OAC initiation date prior to 01 NOV 2011	-92,936	665,803	
Being <18 years of age	-79	665,724	
Not being on rivaroxaban or warfarin	-262,484	403,240	
Use of a non-atrial fibrillation dose	-8,599	394,641	
Valvular disease	-26,797	367,844	
Pregnancy	-805	367,039	
Not being a type 2 diabetic	-250,990	116,049	
Patients analyzed for primary and secondary outcomes (CV and bleeding)		32,078 (Rivaroxaban)	83,971 (Warfarin)

CONSORT: Consolidated standards of reporting trials; CV: Cardiovascular; NVAF: Non-valvular atrial fibrillation; OAC: Oral anticoagulation

10.1.2 Patients considered for other secondary outcomes

Patients requiring prior renal transplant or dialysis, or had eGFR <15 mL/min/1.73m^2, or prior MALE, or prior diabetic retinopathy, were further excluded, and the remaining 83,182 patients (24,912 rivaroxaban users and 58,270 warfarin users) were considered to evaluate secondary outcomes related to kidney, MALE, ophthalmic, and all-cause mortality.

Table 10-2 depicts the identification of the study population, showing every step of inclusion/exclusion and the corresponding patient analyzed for other secondary outcomes (related to kidney, MALE, ophthalmic, and all-cause mortality) of the study.

Table 10-2: Patient flow table (CONSORT-style) - analyzed for other secondary outcomes (related to kidney, MALE, ophthalmic and all-cause mortality)

	Less Excluded Patients	Remaining Patients
OAC-naïve NVAF patients		758,739
OAC initiation date prior to Nov 1, 2011	-92,936	665,803
Being <18 years of age	-79	665,724
Not being on rivaroxaban or warfarin	-262,484	403,240
Use of a non-atrial fibrillation dose	-8,599	394,641
Valvular disease	-26,797	367,844
Pregnancy	-805	367,039
Not being a type 2 diabetic	-250,990	116,049
Prior renal transplant or dialysis, eGFR <15	-19,860	96,189
Prior MALE	-8513	87,676
Prior diabetic retinopathy	-4,494	83,182
Patients analysed for other secondary outcomes		24,912 (Rivaroxaban) 58,270 (Warfarin)

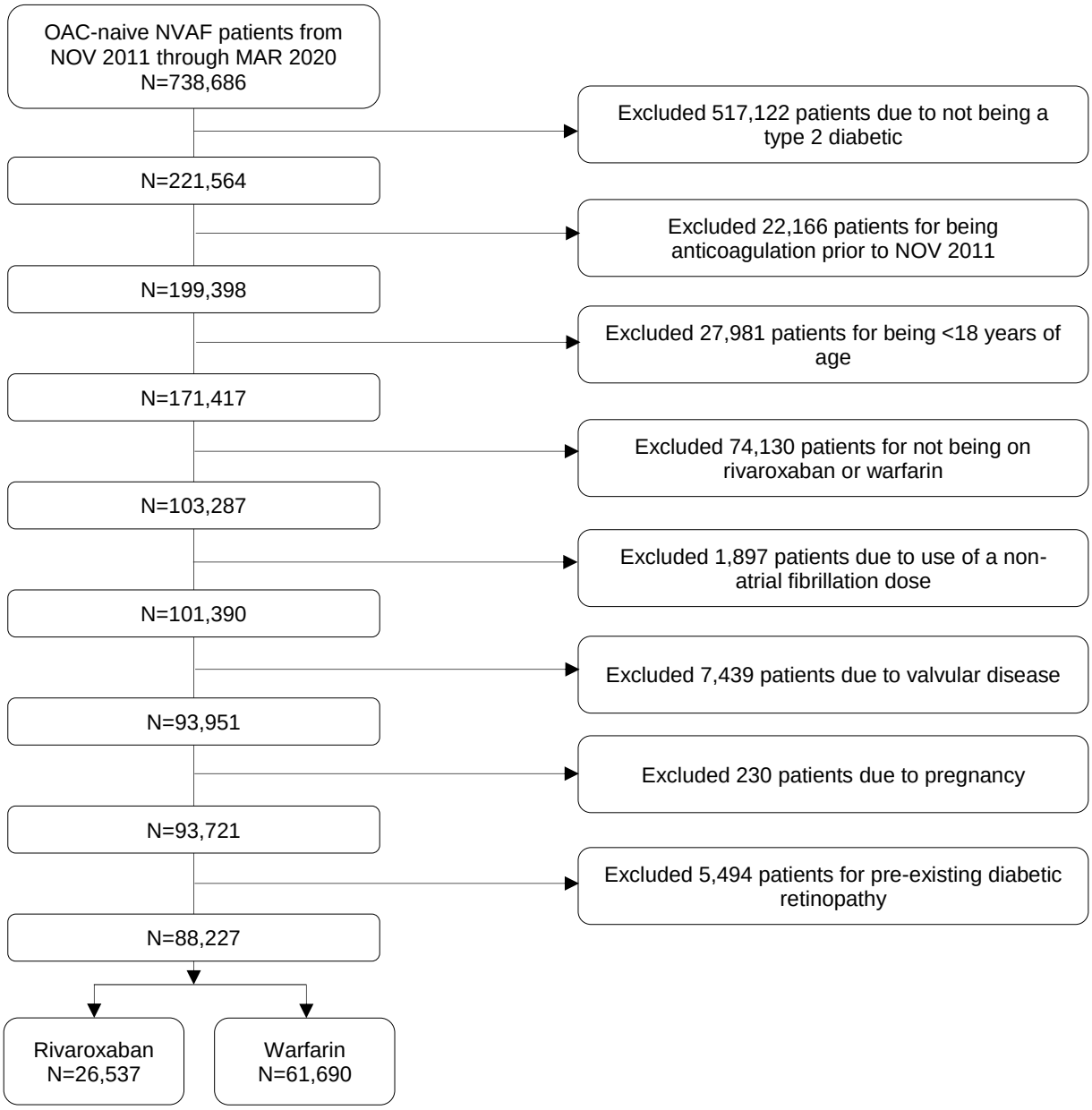
CONSORT: Consolidated standards of reporting trials; eGFR: Estimated glomerular filtration rate; MALE: Major adverse limb event; NVAF: Non-valvular atrial fibrillation ; OAC: Oral anticoagulation

10.1.3 Patients considered for secondary ophthalmic outcomes

In a separate analysis, data from NOV 2010-MAR 2020 were utilized and patients with pre-existing diabetic retinopathy were excluded resulting in the inclusion of a total 88,227 patients (26,537 rivaroxaban users and 61,690 warfarin users) to evaluate ophthalmic complications (non-traumatic bleeding and/or diabetic retinopathy) as secondary outcomes (Figure 10-1).

All the selected patients were followed until the occurrence of endpoint, end of EHR activity, or end of follow-up data availability.

Figure 10-1: Inclusion and Exclusion Criteria for Patient Selection for Ophthalmic complications in patients with NVAF and T2DM prescribed rivaroxaban or warfarin



N: Number of patients; NVAF: Non-valvular atrial fibrillation ; T2DM: Type 2 Diabetes Mellitus

10.2 Descriptive data

10.2.1 Baseline characteristics of patients considered for primary and secondary outcomes (CV and bleeding)

Table 10-3 presents the unweighted and PS-OLW baseline characteristics (gender, age, hospital frailty score, number of hospitalizations, medical history, concomitant, and other medications, time in therapeutic international normalized ratio (INR) range, $CHADS_2$ score, CHA_2DS_2-VASc score, and modified HAS-BLED score) of 83,971 warfarin patients and 32,078 rivaroxaban patients analyzed for following outcomes:

- Primary outcomes:

- Composite outcome of SSE;
- Any major or CRNM bleed resulting in hospitalization

- Secondary CV outcomes:
  - Composite of stroke, systemic embolism, vascular death;
  - Composite of stroke, systemic embolism, MI, vascular death;
  - IS;
  - Systemic embolism;
  - MI;
  - Vascular death
- Secondary bleeding outcomes:
  - Major or CRNM bleed
  - Major bleed
  - Critical organ bleed
  - ICH
  - Extracranial bleed
  - CRNM bleed

Patient Characteristics

After PS overlap weighting, the rivaroxaban and warfarin cohorts were identical (absolute standardized difference = 0 for all). Of the included patients, 99% had a diagnostic code for T2DM. The mean ±SD age of patients was 71±10 years, CHA2DS2VASc score was 4.3±1.5, and modified HAS-BLED score was 1.5±0.9. Thirty-one percent of rivaroxaban patients were initiated on the 15 mg dose, with the remainder prescribed 20 mg OD. Using an eGFR cut-off of 50 mL/min/1.75m^2, 6.4% of rivaroxaban patients were overdosed and 21.0% underdosed. Patients started on rivaroxaban were followed for an average of 1,048±693 days (2.9 years). Warfarin patients were followed for a mean of 1,044±727 days (2.9 years). Warfarin patients spent an average of 47±28% (median: 50%) of their time in the target therapeutic INR range (linear interpolated assuming a target range of 2.0 to 3.0).

Table 10-3: Unweighted and weighted baseline characteristics for population analyzed for primary and secondary outcomes (CV and bleeding)

	Unweighted			PS OLW		
	Rivaroxaban, % N=32,078	Warfarin, % N=83,971	ASD, %	Rivaroxaban, % N=32,078	Warfarin, % N=83,971	ASD, %
Demographics						
Age, years (mean±SD)[a]	70±10	73±10	30.0	71±10	71±10	0.0
Age 65-74 years	34.2	31.5	6.8	33.8	33.8	0.0
Age ≥75 years	36.4	48.1	26.6	41.0	41.0	0.0
Female	39.9	40.8	2.1	40.5	40.5	0.0
White race, self-reported	85.6	86.8	5.6	86.4	86.4	0.0

Table 10-3: Unweighted and weighted baseline characteristics for population analyzed for primary and secondary outcomes (CV and bleeding)

	Unweighted			PS OLW		
	Rivaroxaban, % N=32,078	Warfarin, % N=83,971	ASD, %	Rivaroxaban, % N=32,078	Warfarin, % N=83,971	ASD, %
Hospital frailty score, intermediate risk	37.3	39.0	4.0	38.1	38.1	0.0
Hospital frailty score, high risk	15.8	24.3	29.6	18.2	18.2	0.0
Hospitalizations in prior 12-months (mean±SD)	0.98±1.84	1.22±1.98	12.4	1.05±1.83	1.05±1.83	0.0
Medical history						
Ablation	2.6	3.1	10.0	2.7	2.7	0.0
Active cancer	5.1	5.4	3.3	5.3	5.3	0.0
Active gastric or duodenal ulcer in prior 90-days	0.2	0.4	3.8	0.2	0.2	0.0
Acute coronary syndrome	10.4	13.2	14.9	11.2	11.2	0.0
Anxiety	15.0	14.2	3.5	14.8	14.8	0.0
Any bleeding in prior 90-days	3.0	5.0	29.3	3.5	3.5	0.0
Asthma	10.9	10.0	5.3	10.5	10.5	0.0
Hemoglobin A1c <7%	52.1	54.7	5.8	52.9	52.9	0.0
Hemoglobin A1c 7-8%	23.3	22.8	1.6	23.0	23.0	0.0
Hemoglobin A1c >8%	24.6	22.5	6.4	24.0	24.0	0.0
BMI 30-39.9 kg/m^2	45.0	41.8	7.2	43.8	43.8	0.0
BMI ≥40 kg/m2 or body weight >120 kg	26.3	22.7	10.8	25.1	25.1	0.0
Cardioversion	7.5	7.9	3.1	7.5	7.5	0.0
Carotid endarterectomy and/or stent	0.8	1.1	17.7	0.9	0.9	0.0
Chronic obstructive pulmonary disease	24.0	27.4	9.8	25.2	25.2	0.0
Coagulopathy	5.8	10.2	33.8	6.9	6.9	0.0
Crohn's disease or ulcerative colitis	0.7	0.8	7.4	0.8	0.8	0.0
Chronic venous insufficiency	4.9	6.4	15.6	5.2	5.2	0.0
Dementia	4.9	7.2	22.6	5.7	5.7	0.0
Depression	17.1	17.9	3.1	17.4	17.4	0.0
Diverticular disease	6.5	7.1	5.2	6.7	6.7	0.0
eGFR 30-50 mL/minute	9.5	13.9	23.7	11.2	11.2	0.0
eGFR <30 mL/minute	3.3	13.6	84.3	4.6	4.6	0.0
Kidney transplant or dialysis	0.8	7.2	124.8	1.2	1.2	0.0
Excessive alcohol consumption	0.8	0.8	0.0	0.8	0.8	0.0
Gastroesophageal reflux disease	25.3	25.7	1.2	25.5	25.5	0.0
Heart failure	33.6	45.8	28.3	37.3	37.3	0.0
H. pylori infection	0.3	0.3	0.0	0.3	0.3	0.0
Hemoglobin <13 g/dL in men or <12 g/dL in women (anemia)	40.5	57.6	38.1	45.8	45.8	0.0
Hypercoagulable state	0.5	0.8	26.1	0.6	0.6	0.0
Hyperlipidemia	82.7	80.6	7.7	82.2	82.2	0.0
Hypertension	91.3	90.2	7.2	90.8	90.8	0.0
SBP ≥160 mm Hg	3.9	3.5	6.2	3.7	3.7	0.0
DBP ≥100 mm Hg	5.0	3.0	29.3	4.1	4.1	0.0
IS	7.7	10.1	16.4	8.6	8.6	0.0
IS in prior 12 months	2.3	3.0	15.1	2.0	2.0	0.0
Liver dysfunction	5.6	7.3	15.6	6.0	6.0	0.0
Major bleed	1.2	2.7	45.6	1.5	1.5	0.0
MALE	6.4	9.8	25.5	7.3	7.3	0.0

Table 10-3: Unweighted and weighted baseline characteristics for population analyzed for primary and secondary outcomes (CV and bleeding)

	Unweighted			PS OLW		
	Rivaroxaban, % N=32,078	Warfarin, % N=83,971	ASD, %	Rivaroxaban, % N=32,078	Warfarin, % N=83,971	ASD, %
Major surgery in prior 90-days	40.6	44.6	9.0	41.8	41.8	0.0
Osteo- or rheumatoid arthritis	23.3	22.3	3.1	23.2	23.2	0.0
Osteoporosis	6.7	8.2	12.0	7.3	7.3	0.0
Pneumonia	11.4	15.5	19.6	12.6	12.6	0.0
Psychosis	2.0	2.9	21.0	2.2	2.2	0.0
Proteinuria	3.8	3.9	1.5	3.8	3.8	0.0
Revascularization (CABG or PCI)	20.8	26.3	16.9	22.7	22.7	0.0
Sleep apnea	24.7	22.4	7.1	23.6	23.6	0.0
Smoker	13.8	11.5	11.5	13.0	13.0	0.0
Vascular disease (prior MI, PAD or aortic plaque)	26.8	33.1	16.6	28.7	28.7	0.0
Body weight <60 kg	3.7	5.2	19.6	4.2	4.2	0.0
Concomitant medications						
Anti-hyperglycemic medications						
Dipeptidyl peptidase-4 inhibitor	11.5	9.3	13.1	10.7	10.7	0.0
GLP-1 analog	4.9	2.4	40.8	3.7	3.7	0.0
Insulin	29.2	36.6	18.5	31.0	31.0	0.0
Metformin	51.5	38.6	28.9	47.8	47.8	0.0
Sodium-glucose cotransporter-2 inhibitor	3.4	1.0	68.8	2.2	2.2	0.0
Sulfonylurea or glinide	25.9	28.1	6.2	26.8	26.8	0.0
Thiazolidinediones	4.5	3.6	12.8	4.2	4.2	0.0
Other medications						
Amiodarone	11.8	15.4	17.0	13.1	13.1	0.0
ACE inhibitor or ARB	70.7	65.1	14.2	69.3	69.3	0.0
Alpha blocker	14.7	16.7	8.3	15.3	15.3	0.0
Aspirin	28.5	29.4	2.4	29.0	29.0	0.0
Barbiturate	1.2	1.2	0.0	1.3	1.3	0.0
Benzodiazepine	16.5	17.2	2.8	16.7	16.7	0.0
Beta blocker	73.2	74.0	2.3	73.3	73.3	0.0
Dihydropyridine calcium channel blocker	5.4	4.7	8.1	5.0	5.0	0.0
Digoxin	9.5	14.9	28.2	11.4	11.4	0.0
Diltiazem	20.0	17.7	8.3	19.3	19.3	0.0
Dronedarone	1.9	1.1	30.6	1.6	1.6	0.0
Estrogen	1.6	1.2	16.1	1.4	1.4	0.0
Histamine-2 receptor antagonist	9.3	11.0	10.3	9.8	9.8	0.0
Levothyroxine	16.7	18.6	7.2	17.3	17.3	0.0
Loop diuretic	38.1	52.0	31.2	43.0	43.0	0.0
Nonsteroidal anti-inflammatory drug	23.4	16.7	23.2	21.0	21.0	0.0
Other anti-arrhythmic agent	8.8	5.8	24.8	7.9	7.9	0.0
Other antidepressant	10.1	10.9	4.7	10.4	10.4	0.0
Other antiplatelet agent	1.3	1.3	0.0	1.3	1.3	0.0
Other cholesterol medication	13.6	13.5	0.5	13.5	13.5	0.0
P2Y12 inhibitor	6.9	7.0	0.9	6.9	6.9	0.0
Proton pump inhibitor	35.6	38.2	6.2	36.2	36.2	0.0
SSRI or SNRI	22.2	22.3	0.3	22.2	22.2	0.0
Statin	70.0	69.7	0.8	70.0	70.0	0.0
Thiazide diuretic	30.5	26.2	11.7	29.2	29.2	0.0
Verapamil	1.8	1.8	0.0	1.9	1.9	0.0

Table 10-3: Unweighted and weighted baseline characteristics for population analyzed for primary and secondary outcomes (CV and bleeding)

	Unweighted			PS OLW		
	Rivaroxaban, % N=32,078	**Warfarin, % N=83,971**	**ASD, %**	**Rivaroxaban, % N=32,078**	**Warfarin, % N=83,971**	**ASD, %**
Time in therapeutic INR range (mean±SD)[a]	--	46±28	--	--	47±28	--
Median (25%, 75%)		47 (21, 66)			50 (24, 69)	
CHA_2DS_2VASc score (mean±SD)[a]	4.2±1.5	4.6±1.5	--	4.3±1.5	4.3±1.5	--
$CHADS_2$ score (mean±SD)[a]	3.1±1.2	3.4±1.2	--	3.2±1.2	3.2±1.2	--
Modified HAS-BLED score (mean±SD)[a]	1.5±0.8	1.7±0.9	--	1.5±0.9	1.5±0.8	--

[a]Covariate not included in the propensity score model
ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blockers; ASD: Absolute standardized difference; BMI: Body mass index; CABG: Coronary artery bypass graft; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; GLP: Glucagon-like peptide; *H. pylori*: *Helicobacter pylori*; INR: International normalized ratio; IS: Ischemic stroke; MALE: Major adverse limb events; N: Number of patients; OLW: overlap weighted; PCI: Percutaneous coronary intervention; PS: Propensity score; SBP: Systolic blood pressure; SD: Standard deviation; SSRI: Selective serotonin reuptake inhibitor; SNRI: Serotonin-norepinephrine reuptake inhibitor

10.2.2 Baseline characteristics of patients considered for other secondary outcomes

Table 10-4 presents the unweighted and PS-OLW baseline characteristics (gender, age, hospital frailty score, number of hospitalizations, medical history, concomitant and other medications, time in therapeutic INR range, $CHADS_2$ score, CHA_2DS_2-VASc score, and modified HAS-BLED score) of 58,270 warfarin patients and 24,912 rivaroxaban patients analyzed for following secondary outcomes related to kidney, MALE, ophthalmic and all-cause mortality:

- Composite of >40% decrease in eGFR from baseline, eGFR<15 mL/minute, need for dialysis, renal transplant, MALE, retinopathy or death;
- eGFR <15 mL/min/1.73m2, need for dialysis or renal transplant;
- Need for dialysis or renal transplant;
- >40% decrease in eGFR from baseline;
- MALE (including limb amputation);
- Diabetic retinopathy;
- All-cause mortality

Patient Characteristics

After PS overlap weighting, the rivaroxaban and warfarin cohorts were identical (absolute standardized difference = 0 for all). Of included patients, 99% had a diagnostic code for T2DM and 34% had both an HbA1c≥6.5% (48 mmol/mol) and were receiving a non-insulin antihyperglycemic agent. The mean±SD age was 71±10 years, CHA2DS2VASc score was 4.3±1.5, and modified HAS-BLED score was 1.5±0.8. Thirty percent of rivaroxaban patients were started on 15mg OD, with the rest prescribed 20 mg. All patients had an eGFR value prior to multiple imputations (mean±SD=74±25). Patients were followed for a mean of 2.89±1.95 years. Warfarin patients had a mean time in therapeutic range (TTR) of 47±28%.

Table 10-4: Unweighted and weighted baseline characteristics for population analyzed for other secondary outcomes

	Unweighted			PS OLW		
	Rivaroxaban N=24,912	Warfarin N=58,270	ASD, %	Rivaroxaban N=24,912	Warfarin N=58,270	ASD, %
Demographics						
Age, years (mean±SD)[a]	70±11	73±10	29.1	71±10	71±10	--
Age 65-74 years	34.0	30.7	8.3	33.5	33.5	0
Age ≥75 years	36.1	50.0	31.5	41.2	41.2	0
Female sex	40.2	41.3	2.5	40.9	40.9	0
White race	85.8	88.5	13.3	86.9	86.9	0
Hospital frailty score, intermediate risk	39.7	41.2	3.4	40.4	40.4	0
Hospital frailty score, high risk	15.1	21.5	23.8	17.3	17.3	0
Hospitalizations in prior 12-months (mean±SD)	1.00±1.77	1.14±1.75	8.0	1.07±1.78	1.07±1.74	0
Medical history						
Ablation	2.6	3.0	40.8	2.7	2.7	0
Active cancer	5.3	5.5	2.2	5.5	5.5	0
Active gastric or duodenal ulcer in prior 90-days	0.2	0.3	22.9	0.2	0.2	0
Acute coronary syndrome	10.4	12.2	10.0	11.1	11.1	0
Anxiety	15.5	14.2	5.7	15.1	15.1	0
Any bleeding in prior 90-days	3.0	4.7	25.7	3.4	3.4	0
Asthma	11.3	10.2	6.3	10.9	10.9	0
Hemoglobin a1c <7% (53 mmol/mol)	53.5	55.9	5.3	54.5	54.5	0
Hemoglobin a1c 7-8% (53-64 mmol/mol)	23.2	22.7	1.6	23.0	23.0	0
Hemoglobin a1c >8% (>64 mmol/mol)	23.3	21.4	6.0	22.6	22.6	0
BMI 30-39.9 kg/m^2	45.1	41.9	7.2	43.8	43.8	0
BMI ≥40 kg/m^2 or weight > 120 kg	26.7	23.3	10.0	25.5	25.5	0
Cardioversion	7.6	7.6	0.0	7.5	7.5	0
Carotid endarterectomy and/or stent	0.7	1.1	25.1	0.9	0.9	0
Chronic obstructive pulmonary disease	24.3	27.5	9.2	25.5	25.5	0
Coagulopathy	5.6	9.1	28.9	6.7	6.7	0
Crohns disease or ulcerative colitis	0.7	0.8	7.4	0.8	0.8	0
Chronic venous insufficiency	4.4	5.5	12.9	4.8	4.8	0
Dementia	4.8	7.3	24.6	5.7	5.7	0
Depression	17.6	17.7	0.4	17.7	17.7	0
Diverticular disease	6.7	7.3	5.1	6.9	6.9	0

Table 10-4: Unweighted and weighted baseline characteristics for population analyzed for other secondary outcomes

	Unweighted			PS OLW		
	Rivaroxaban N=24,912	Warfarin N=58,270	ASD, %	Rivaroxaban N=24,912	Warfarin N=58,270	ASD, %
eGFR 30-50 mL/minute	9.4	14.6	27.5	11.1	11.1	0
eGFR <30 mL/minute	2.5	6.8	57.7	3.3	3.3	0
Excessive alcohol consumption	0.7	0.8	7.4	0.8	0.8	0
Gastroesophageal reflux disease	26.2	25.5	2.0	26.1	26.1	0
Heart failure	33.6	44.3	24.9	37.3	37.3	0
Hemoglobin <13 g/dL men, <12 g/dL women (anemia)	39.1	53.8	32.8	44.4	44.4	0
Hypercoagulable state	0.4	0.8	38.4	0.5	0.5	0
Hyperlipidemia	84.3	81.8	9.8	83.6	83.6	0
Hypertension	91.6	90.2	9.4	91.2	91.2	0
SBP ≥160 mm Hg	3.6	3.4	3.3	3.5	3.5	0
DBP ≥100 mm Hg	5.3	3.1	30.8	4.3	4.3	0
IS	7.5	9.9	16.8	8.5	8.5	0
IS in prior 12-months	2.3	3.1	16.9	2.6	2.6	0
Liver dysfunction	5.9	7.0	10.1	6.3	6.3	0
Major bleed	1.2	2.5	41.2	1.5	1.5	0
Major surgery in prior 90-days	42.0	43.4	3.2	42.6	42.6	0
Osteo- or rheumatoid arthritis	23.8	22.9	2.8	23.7	23.7	0
Osteoporosis	6.8	8.4	12.6	7.5	7.5	0
Pneumonia	11.7	15.1	16.2	12.9	12.9	0
Psychosis	2.0	3.0	22.9	2.3	2.3	0
Proteinuria	3.7	3.6	1.6	3.6	3.6	0
Revascularization (CABG or PCI)	20.4	25.1	14.8	22.3	22.3	0
Sleep apnea	25.5	22.1	10.4	24.1	24.1	0
Smoker	14.0	11.2	14.1	13.0	13.0	0
Vascular disease (prior MI, PAD or aortic plaque)	24.6	28.6	11.3	26.3	26.3	0
Body weight <60 kg	3.5	5.0	20.5	4.0	4.0	0
Medications						
Amiodarone	11.7	14.8	14.9	13.1	13.1	0
ACE inhibitor or ARB	71.5	67.2	11.2	70.2	70.2	0
Alpha blocker	14.7	16.5	7.5	15.3	15.3	0
Aspirin	28.9	29.0	0.3	29.3	29.3	0

Table 10-4: Unweighted and weighted baseline characteristics for population analyzed for other secondary outcomes

	Unweighted			PS OLW		
	Rivaroxaban N=24,912	Warfarin N=58,270	ASD, %	Rivaroxaban N=24,912	Warfarin N=58,270	ASD, %
Barbiturate	1.3	1.2	4.5	1.3	1.3	0
Benzodiazepine	16.8	17.4	2.3	17.1	17.1	0
Beta blocker	73.6	73.8	0.6	73.8	73.8	0
Dihydropyridine calcium channel blocker	5.5	4.3	14.3	5.0	5.0	0
Digoxin	9.6	15.6	30.6	11.6	11.6	0
Diltiazem	20.5	18.4	7.4	19.8	19.8	0
Dipeptidyl peptidase-4 inhibitor	11.6	9.6	1.7	10.8	10.8	0
Dronedarone	1.9	1.2	25.7	1.6	1.6	0
Estrogen	1.6	1.3	11.6	1.5	1.5	0
GLP-1 analog	4.8	2.5	37.3	3.6	3.6	0
Histamine-2 receptor antagonist	9.1	10.6	9.3	9.6	9.6	0
H. pylori treatment	0.3	0.3	0.0.	0.3	0.3	0
Insulin	28.0	33.1	13.3	29.6	29.6	0
Levothyroxine	16.7	18.6	7.2	17.4	17.4	0
Loop diuretic	37.8	52.1	32.1	42.9	42.9	0
Metformin	52.8	42.0	24.0	49.2	49.2	0
Nonsteroidal anti-inflammatory drug	24.3	18.0	21.0	21.9	21.9	0
Other anti-arrhythmic agent	9.0	6.3	21.3	8.1	8.1	0
Other antidepressant	10.1	10.8	4.1	10.4	10.4	0
Other antiplatelet agent	1.0	1.0	0.0	1.0	1.0	0
Other cholesterol medication	13.8	13.7	0.5	13.6	13.6	0
P2Y12 inhibitor	6.5	6.2	2.8	6.5	6.5	0
Proton pump inhibitor	36.2	37.7	3.6	36.8	36.8	0
Sodium-glucose cotransporter-2 inhibitor	3.4	1.1	63.5	2.2	2.2	0
SSRI or SNRI	22.6	22.1	1.6	22.5	22.5	0
Statin	70.3	69.7	1.6	70.2	70.2	0
Sulfonylurea or glinide	26.2	29.6	9.3	27.3	27.3	0
Thiazide diuretic	31.2	27.7	9.3	29.9	29.9	0
Thiazolidinediones	4.6	3.8	11.0	4.3	4.3	0
Verapamil	1.9	1.8	3.0	1.9	1.9	0

Table 10-4: Unweighted and weighted baseline characteristics for population analyzed for other secondary outcomes

	Unweighted			PS OLW		
	Rivaroxaban N=24,912	Warfarin N=58,270	ASD, %	Rivaroxaban N=24,912	Warfarin N=58,270	ASD, %
Time in therapeutic INR range (mean±SD)[a]	--	45.26±27.64	--	--	47±28	--
CHA_2DS_2VASc score (mean±SD)[a, b]	4.1±1.5	4.6±1.5	30.2	4.3±1.5	4.3±1.4	--
$CHADS_2$ score (mean±SD)[a, c]	3.1±1.2	3.5±1.2	32.8	3.2±1.2	3.2±1.2	--
Modified HASBLED score (mean±SD)[a, d]	1.4±0.8	1.6±0.8	15.4	1.5±0.8	1.5±0.8	--

[a]Covariate not included in the propensity score model
[b]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 thrombo-embolism, 2 points; vascular disease, 1 point; age 65–74 years, 1 point; female sex, 1 point.
[c]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.
[d]Modified HAS-BLED = 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.
ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blockers; ASD: Absolute standardized difference; BMI: Body mass index; CABG: Coronary artery bypass graft; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; GLP: Glucagon-like peptide; *H.pylori*: *Helocobacter pylori*; IS: Ischemic Stroke; N: Number of patients; OLW: Overlap weighted; PCI: Percutaneous coronary intervention; PS: Propensity score; SBP: Systolic blood pressure

10.2.3 Baseline characteristics of patients considered for secondary ophthalmic outcomes

Patient Characteristics

Patients were excluded if they received any OAC in the prior 12 months, had a valvular disease or pre-existing diabetic retinopathy, and about 61,690 warfarin and 26,537 rivaroxaban patients were selected in warfarin and rivaroxaban exposure groups, respectively, to evaluate ophthalmic complications including non-traumatic bleeding (choroidal, intraocular, retinal, vitreous) or diabetic retinopathy. Ophthalmic bleeds typically associated with trauma (hyphema, orbital) were excluded from these outcomes.

After PS overlap weighting, the mean±SD age of patients was 69±9 years, CHA2DS2VASc score was 4.1±1.5, and HAS-BLED 1.5±0.9. Thirty-two percent of patients had an HbA1c ≥7.0 and 16% an a1c≥8.0.

10.2.4 Baseline characteristics of patients in age subgroup

Table 10-5 presents the baseline characteristics of the subgroup by age.

Patient Characteristics

Of the 83,971 warfarin (TTR = 47±28%) and 32,078 rivaroxaban patients (31% initiated on 15 mg dose), there were 31,941 patients (28%) aged ≥80 years who were initiated on either warfarin (n=25,335) or rivaroxaban (n=6,606). Older patients had a higher mean CHA2DS2VASc (4.4±1.2 vs. 3.8±1.3) and modified HAS-BLED (1.7±0.7 vs. 1.4±0.8) score compared to younger patients. Mean follow-up time was 2.9±1.9 years for rivaroxaban and 2.9±2.0 years for warfarin patients.

Table 10-5: Unweighted and weighted baseline characteristics of included patients in subgroup analysis

	Unweighted baseline characteristics				Overlap-weighted baseline characteristics			
	Age<80 years		Age≥80 years		Age<80 years		Age≥80 years	
	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=6,606	Warfarin, % N=25,335
Demographics								
Age, years (mean±SD)[a]	66±9	68±8	83±2	83±2	67±9	67±8	83±2	83±2
Age 65-74 years	43.1	45.1	0	0	44.5	44.5	0	0
Age ≥75 years	19.9	25.7	100	100	22.3	22.3	100	100
Female	37.0	37.3	50.8	48.9	37.3	37.3	50.5	50.5
White race, self-reported	84.8	85.0	88.4	90.8	85.5	85.5	89.3	89.3
Hospital frailty score, intermediate risk	36.9	39.1	39.0	38.6	38.0	38.0	38.7	38.7
Hospital frailty score, high risk	13.6	22.5	24.6	28.4	15.9	15.9	25.6	25.6
Hospitalizations in prior 12-months (mean±SD)	0.98±1.90	1.29±2.10	0.98±1.63	1.07±1.66	1.07±1.96	1.07±1.89	1.01±1.63	1.01±1.66
Medical history								
Ablation	2.5	3.0	2.7	3.2	2.6	2.6	2.8	2.8
Active cancer	4.8	5.1	6.4	5.9	5.0	5.0	6.2	6.2
Active gastric or duodenal ulcer in prior 90-days	0.2	0.4	0.2	0.4	0.2	0.2	0.2	0.2
Acute coronary syndrome	10.6	14.2	9.7	10.8	11.6	11.6	9.9	9.9
Anxiety	16.0	15.7	11.5	10.6	15.9	15.9	11.3	11.3
Any bleeding in prior 90-days	2.8	4.9	3.7	5.2	3.3	3.3	4.0	4.0
Asthma	11.6	11.1	8.1	7.6	11.4	11.4	8.0	8.0
Hemoglobin A1c <7%	49.9	52.4	60.3	60.5	50.6	50.6	60.4	60.4
Hemoglobin A1c 7-8%	23.4	22.6	22.2	22.5	23.3	23.3	22.1	22.1
Hemoglobin A1c >8%	26.7	25.0	17.5	17.0	26.1	26.1	17.5	17.5
BMI 30-39.9 kg/m^2	47.4	44.9	35.5	34.6	46.4	46.4	35.3	35.3
BMI ≥40 kg/m^2 or body weight >120 kg	31.6	29.5	6.0	7.0	31.1	31.1	6.3	6.3
Cardioversion	8.1	9.1	5.5	5.3	8.2	8.2	5.4	5.4

Table 10-5: Unweighted and weighted baseline characteristics of included patients in subgroup analysis

	Unweighted baseline characteristics				Overlap-weighted baseline characteristics			
	Age<80 years		Age≥80 years		Age<80 years		Age≥80 years	
	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=6,606	Warfarin, % N=25,335
Carotid endarterectomy and/or stent	0.7	1.0	1.0	1.2	0.8	0.8	1.1	1.1
Chronic obstructive pulmonary disease	24.3	28.5	23.1	24.9	25.9	25.9	23.5	23.5
Coagulopathy	5.6	10.8	6.5	9.0	6.8	6.8	7.1	7.1
Crohn's disease or ulcerative colitis	0.8	0.8	0.7	0.8	0.8	0.8	0.7	0.7
Chronic venous insufficiency	4.8	6.6	5.2	5.9	5.2	5.2	5.3	5.3
Dementia	3.0	4.4	12.1	13.8	3.5	3.5	12.6	12.6
Depression	17.9	19.7	14.2	14.0	18.5	18.5	14.1	14.1
Diverticular disease	6.2	6.9	7.6	7.6	6.4	6.4	7.7	7.7
eGFR 30-50 mL/minute	7.9	11.9	16.2	18.7	9.4	9.4	17.0	17.0
eGFR <30 mL/minute	3.0	14.2	4.4	12.2	4.2	4.2	5.3	5.3
Kidney transplant or dialysis	0.8	8.8	0.6	3.3	1.3	1.3	0.8	0.8
Excessive alcohol consumption	0.9	1.1	0.2	0.2	0.9	0.9	0.2	0.2
Gastroesophageal reflux disease	25.1	26.3	26.3	24.5	25.5	25.5	25.8	25.8
Heart failure	32.2	44.9	39.0	47.7	36.2	36.2	41.0	41.0
H. pylori infection	0.3	0.3	0.3	0.2	0.3	0.3	0.3	0.3
Hemoglobin <13 g/dL in men or <12 g/dL in women (anemia)	38.0	56.8	50.4	59.5	43.8	43.8	52.5	52.5
Hypercoagulable state	0.5	0.9	0.4	0.5	0.6	0.6	0.4	0.4
Hyperlipidemia	82.8	81.5	82.6	78.7	82.4	82.4	81.7	81.7
Hypertension	90.9	90.1	92.6	90.4	90.4	90.4	92.1	92.1
SBP ≥160 mm Hg	3.7	3.4	4.4	3.8	3.5	3.5	4.2	4.2

Table 10-5: Unweighted and weighted baseline characteristics of included patients in subgroup analysis

	Unweighted baseline characteristics				Overlap-weighted baseline characteristics			
	Age<80 years		Age≥80 years		Age<80 years		Age≥80 years	
	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=6,606	Warfarin, % N=25,335
DBP ≥100 mm Hg	5.5	3.5	3.0	1.9	4.5	4.5	2.6	2.6
IS	6.9	9.6	11.0	11.0	7.9	7.9	11.1	11.1
IS in prior 12 months	2.1	2.8	3.1	3.6	2.4	2.4	3.3	3.3
Liver dysfunction	6.0	8.4	3.8	4.6	6.6	6.6	4.0	4.0
Major bleed	1.1	2.6	1.8	2.8	1.4	1.4	2.0	2.0
MALE	6.3	10.3	6.9	8.6	7.3	7.3	7.2	7.2
Major surgery in prior 90-days	41.0	45.6	38.8	42.5	42.3	42.3	39.8	39.8
Osteo- or rheumatoid arthritis	22.3	21.5	27.1	24.0	22.3	22.3	26.3	26.3
Osteoporosis	5.6	6.7	10.8	11.5	6.1	6.1	11.2	11.2
Pneumonia	10.8	15.2	13.7	16.4	12.1	12.1	14.2	14.2
Psychosis	1.9	2.7	2.4	3.5	2.1	2.1	2.6	2.6
Proteinuria	3.9	4.3	3.4	3.2	3.9	3.9	3.4	3.4
Revascularization (CABG or PCI)	20.1	27.1	23.4	24.3	22.5	22.5	23.7	23.7
Sleep apnea	27.9	27.1	12.5	11.5	27.2	27.2	12.1	12.1
Smoker	16.2	14.8	4.6	3.7	15.8	15.8	4.4	4.4
Vascular disease (prior MI, PAD or aortic plaque)	25.5	33.2	32.0	32.6	27.8	27.8	32.0	32.0
Body weight <60 kg	2.1	2.9	10.0	10.7	2.3	2.3	10.2	10.2
Anti-hyperglycemic medications								
Dipeptidyl peptidase-4 inhibitor	11.6	9.5	11.1	9.0	10.8	10.8	10.5	10.5
GLP-1 analog	5.8	3.1	1.3	0.7	4.6	4.6	1.2	1.2
Insulin	30.6	40.0	23.6	28.7	33.0	33.0	24.8	24.8
Metformin	55.0	42.5	38.3	29.4	51.6	51.6	36.1	36.1
Sodium-glucose cotransporter-2 inhibitor	4.1	1.4	0.9	0.3	2.6	2.6	0.6	0.6

Table 10-5: Unweighted and weighted baseline characteristics of included patients in subgroup analysis

	Unweighted baseline characteristics				Overlap-weighted baseline characteristics			
	Age<80 years		Age≥80 years		Age<80 years		Age≥80 years	
	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=6,606	Warfarin, % N=25,335
Sulfonylurea or glinide	25.5	27.2	27.5	30.3	26.5	26.5	28.1	28.1
Thiazolidinediones	4.8	3.9	3.5	3.1	4.4	4.4	3.4	3.4
Other medications								
Amiodarone	12.1	17.4	10.7	10.8	13.9	13.9	10.9	10.9
ACE inhibitor or ARB	71.4	66.6	68.0	61.6	70.2	70.2	66.5	66.5
Alpha blocker	13.6	15.6	18.8	19.2	14.2	14.2	18.8	18.8
Aspirin	28.5	30.6	28.7	26.6	29.4	29.4	28.3	28.3
Barbiturate	1.3	1.2	0.9	1.0	1.4	1.4	0.9	0.9
Benzodiazepine	16.9	18.0	14.6	15.2	17.3	17.3	14.9	14.9
Beta blocker	73.7	75.4	71.2	70.8	74.1	74.1	71.0	71.0
Dihydropyridine calcium channel blocker	5.2	4.7	6.0	4.5	4.8	4.8	5.5	5.5
Digoxin	9.3	14.5	10.2	15.8	11.3	11.3	11.5	11.5
Diltiazem	20.7	18.3	17.0	16.3	20.0	20.0	16.9	16.9
Dronedarone	2.1	1.2	1.2	0.8	1.8	1.8	1.1	1.1
Estrogen	1.6	1.3	1.3	1.2	1.5	1.5	1.2	1.2
Histamine-2 receptor antagonist	9.2	11.5	9.6	9.9	9.9	9.9	9.7	9.7
Levothyroxine	14.8	16.8	23.9	22.7	15.4	15.4	23.6	23.6
Loop diuretic	36.5	51.1	44.5	54.2	41.8	41.8	47.0	47.0
Nonsteroidal anti-inflammatory drug	24.7	18.2	18.5	13.5	22.3	22.3	17.0	17.0
Other anti-arrhythmic agent	9.6	6.6	5.8	4.0	8.7	8.7	5.4	5.4
Other antidepressant	10.1	11.4	10.0	9.8	10.5	10.5	9.9	9.9
Other antiplatelet agent	1.1	1.2	1.9	1.5	1.1	1.1	1.8	1.8
Other cholesterol medication	14.1	14.7	11.4	10.7	14.2	14.2	11.1	11.1
P2Y12 inhibitor	7.0	7.5	6.6	5.8	7.1	7.1	6.3	6.3

Table 10-5: Unweighted and weighted baseline characteristics of included patients in subgroup analysis

	Unweighted baseline characteristics				Overlap-weighted baseline characteristics			
	Age<80 years		Age≥80 years		Age<80 years		Age≥80 years	
	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=25,472	Warfarin, % N=58,636	Rivaroxaban, % N=6,606	Warfarin, % N=25,335
Proton pump inhibitor	35.1	38.6	37.7	37.2	35.9	35.9	37.5	37.5
SSRI or SNRI	23.0	24.3	19.0	17.8	23.3	23.3	18.6	18.6
Statin	70.1	70.7	69.7	67.4	70.3	70.3	69.1	69.1
Thiazide diuretic	31.1	27.1	28.1	24.2	29.8	29.8	27.2	27.2
Verapamil	1.8	1.8	1.7	1.7	1.9	1.9	1.8	1.8
Time in therapeutic INR range (mean±SD)[a]	**--**	**43.3±27.8**	**--**	**46.0±27.5**	**--**	**46.2±28.2**	**--**	**47.6±27.7**
CHA_2DS_2VASc score (mean±SD)[a]	**3.6±1.2**	**4.0±1.3**	**4.4 ± 1.2**	**4.5±1.2**	**3.8±1.3**	**3.8±1.3**	**4.4±1.2**	**4.4±1.2**
$CHADS_2$ score (mean±SD)[a]	**2.5±0.8**	**2.7±0.8**	**3.4 ± 0.7**	**3.5±0.7**	**2.6±0.8**	**2.6±0.8**	**3.4±0.7**	**3.4±0.7**
Modified HASBLED score (mean±SD)[a]	**1.3±0.8**	**1.5±0.9**	**1.7 ± 0.7**	**1.7±0.7**	**1.4±0.8**	**1.4±0.8**	**1.7±0.7**	**1.7±0.7**

ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blockers; ASD: Absolute standardized difference; CABG: Coronary artery bypass graft; DBP: Diastolic blood pressure; eGFR: estimated glomerular filtration rate; GLP: Glucagon-like peptide; *H. pylori*: *Helicobacter pylori*; INR: International normalized ratio; IS: Ischemic stroke; MALE: Major adverse limb events; MI: Myocardial infarction; N: Number of patients; PAD: Peripheral artery disease; PCI: Percutaneous coronary intervention; SBP: Systolic blood pressure; SD: Standard deviation; SNRI: Serotonin-norepinephrine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitors
[a]Covariate not included in the propensity score model

10.3 Outcome data

10.3.1 Primary outcomes

Refer to Section 10.4.1 for number of events and events per 100 person years (%/year) and hazard ratios (with 95% CI) for the primary outcomes (SSE and hospitalization for major or CRNM bleed) using PS-OLW method.

10.3.2 Secondary outcomes

Refer to Section 10.4.2 for number of events and events per 100 person years (%/year) or 1000 person years and hazard ratios (with 95% CI) for the secondary outcomes using PS-OLW method.

10.4 Main results

This retrospective cohort study evaluated the effectiveness and safety of the reduced dose rivaroxaban (15 mg OD) as compared to warfarin in NVAF patients with T2DM in a real-world setting. Individual-level data for warfarin- and rivaroxaban-naïve NVAF patients with T2DM were used from the Optum EHR database (from 01 NOV 2010 to 31 DEC 2019).

The incidence rates were captured as either the events per 100 person years [%/year] or 1000 person years throughout the study report.

The primary outcomes included the incidence rates of developing the composite of SSE (effectiveness) and hospitalization for major/CRNM bleed (safety). Composite of kidney, MALE, ophthalmic, or death; the individual components, and all-cause mortality were assessed as secondary outcomes. The patients were followed until the occurrence of endpoint, end of EHR activity, or end of follow-up data availability.

Patients receiving rivaroxaban were 1:n matched to warfarin patients based on PSs. To minimize selection bias, different analyses such as overlap weighting, stabilized inverse probability treatment weighting (sIPTW), multivariable regression, and competing risk regression were conducted to adjust for confounding. Falsification analysis using urinary tract infection as an outcome was also performed.

10.4.1 Primary outcomes

The number of events and events per 100 person years (%/year) and hazard ratios (with 95% CI) for the primary outcomes (SSE and hospitalization for major or CRNM bleed) using PS-OLW method are displayed in Table 10-6.

Hospitalization for any type of major/CRNM bleeding was less frequent in rivaroxaban users compared to warfarin users (2.17 vs. 2.31; HR=0.94, 95% CI: 0.89, 0.99) and there was no difference detected in SSE (1.31 vs 1.34, HR=0.97, 95% CI: 0.90, 1.04).

The use of an alternative PS-based method to adjust for confounding or applying a 2-year follow-up cap did not impact the major/CRNM bleed analysis results.

For analysis of primary outcomes by competing risk and multivariate cox regression, refer to Table 16-2 and Table 16-3, respectively.

Table 10-6: Primary outcomes- Number of events and events per 100 person-years (%/year) and Hazard ratios

Outcome	Rivaroxaban N=32,078 n (%/year)	Warfarin N=83,971 n (%/year)	PS-OLW HR (95% CI)
SSE	1219 (1.31)	3275 (1.34)	0.97 (0.90, 1.04)
Hospitalization for major or CRNM bleed	1989 (2.17)	5542 (2.31)	0.94 (0.89, 0.99)

CI: confidence interval; CRNM: clinically relevant non-major; HR: hazard ratio; OLW: overlap weighted; PS: propensity score; SSE: Stroke or systemic embolism

10.4.2 Secondary outcomes

CV and bleeding outcomes

The number of events and events per 100 person years (%/year) and hazard ratios (with 95% CI) for the secondary CV and bleeding outcomes using PS-OLW method are displayed in Table 10-7.

Rivaroxaban was associated with a reduced hazard of the composite outcome of SSE/vascular death compared to warfarin (3.79 vs. 4.19; HR=0.91, 95% CI: 0.88, 0.95). The favorable result for rivaroxaban was driven by a reduction in vascular death (2.81 vs 3.18, HR=0.90, 95% CI: 0.86, 0.95). Critical organ bleeding was less frequent in rivaroxaban users compared to warfarin users (0.35 vs. 0.54; HR=0.63, 95% CI: 0.55, 0.72) as was intracranial hemorrhage (0.29 vs. 0.40; HR=0.72, 95% CI: 0.62, 0.84). There was no difference in extracranial bleeding between rivaroxaban and warfarin (1.87 vs. 1.86; HR=1.00, 95% CI: 0.95, 1.07), including gastrointestinal bleeding (1.50 vs. 1.42; HR=1.06, 95% CI: 0.99, 1.13).

Rivaroxaban was associated with a reduced hazard of the composite outcome of SSE or MALE compared to warfarin (1.83 vs. 2.00, HR=0.91, 95% CI: 0.85, 0.97) as were hyperkalemia, >5.6 (5.21 vs. 5.49, HR=0.95, 95% CI: 0.91, 0.99), and hyperkalemia, >6.0 (2.42 vs. 2.66 , HR=0.91, 95% CI: 0.86, 0.96). There was no difference in new onset vascular dementia between rivaroxaban and warfarin (0.41 vs. 0.46, HR=0.89, 95% CI: 0.78, 1.02).

Table 10-7: CV and bleeding outcomes - Number of events and events per 100 person-years (%/year) and Hazard ratios

Outcome	Number of subjects		n (%/year)	n (%/year)	PS OLW HR (95%CI)
	Rivaroxaban	Warfarin			
CV outcomes					
Stroke, systemic embolism, vascular death	32,078	83,971	3497 (3.79)	10077 (4.19)	0.91 (0.88, 0.95)
Stroke, systemic embolism, MI, vascular death			4074 (4.42)	11420 (4.76)	0.94 (0.90, 0.97)
Stroke, MI, vascular death			4010 (4.34)	11252 (4.69)	0.94 (0.90, 0.97)
IS			1026 (1.10)	2519 (1.05)	1.05 (0.97, 1.14)
Systemic embolism			128 (0.13)	420 (0.16)	0.82 (0.66, 1.02)

Table 10-7: CV and bleeding outcomes - Number of events and events per 100 person-years (%/year) and Hazard ratios

Outcome	Number of subjects		n (%/year)	n (%/year)	PS OLW HR (95%CI)
	Rivaroxaban	Warfarin			
Myocardial infarction			898 (0.99)	2267 (0.95)	1.04 (0.96, 1.14)
Vascular death			2598 (2.81)	7641 (3.18)	0.90 (0.86, 0.95)
SSE or MALE[a]	30,017	75,744	(1.83)	(2.00)	0.91 (0.85, 0.97)
Hyperkalemia, >5.6[b]	28,320	74,778	(5.21)	(5.49)	0.95 (0.91, 0.99)
Hyperkalemia, >6.0[c]	28,390	75,040	(2.42)	(2.66)	0.91 (0.86, 0.96)
New onset vascular dementia[d]	30,508	77,890	(0.41)	(0.46)	0.89 (0.78, 1.02)
			n (%/year)	**n (%/year)**	**PS OLW HR (95%CI)**
Bleeding outcomes					
Major or CRNM bleed	32,078	83,971	6416 (6.95)	16710 (6.95)	1.00 (0.97, 1.03)
Major bleed[e]			834 (0.90)	2687 (1.11)	0.80 (0.74, 0.97)
CRNM bleed			5614 (6.09)	14443 (6.00)	1.02 (0.98, 1.05)
Critical organ bleed			321 (0.35)	1344 (0.54)	0.63 (0.55, 0.72)
ICH			257 (0.29)	1008 (0.40)	0.72 (0.62, 0.84)
Extracranial bleed			1732 (1.87)	4450 (1.86)	1.00 (0.95, 1.07)

CRNM: clinically relevant non-major; CV: Cardiovascular; ICH: Intracranial hemorrhage; IS: Ischemic stroke; ISTH: International Society on Thrombosis and Haemostasis; MALE: major adverse limb event; MI: Myocardial infarction; n: Number of events; SSE: Stroke or systemic embolism
[a]Excludes MALE at baseline.
[b]Excludes patients with potassium>5.6 or missing at baseline.
[c]Excludes patients with potassium>6.0 or missing at baseline.
[d]Excludes dementia and/or vascular dementia at baseline.
[e]Defined as an intracranial hemorrhage, critical organ per ISTH, or other bleed associated with a fall in hemoglobin level of ≥2 g/dL or requiring transfusion of ≥2 units of whole blood or red cells.

Kidney, MALE, and ophthalmic outcomes and all-cause mortality

The number of events and events per 1000 person years and hazard ratios (with 95% CI) for the kidney, MALE, ophthalmic outcomes, and all-cause mortality using PS-OLW method are displayed in Table 10-8.

Rivaroxaban was associated with 19.7 fewer cases of composite outcome/1,000 person years compared to warfarin (237.4 vs. 257.1; HR=0.93, 95% CI: 0.91, 0.95). This corresponds to a number needed-to-treat of 51. The incidence rate of eGFR<15, need for dialysis of kidney transplant was reduced with rivaroxaban versus warfarin (absolute rate reduction = -1.5 events per 1,000 person years; HR=0.96, 95% CI: 0.91, 1.01), due mostly to significant reductions in new dialysis of transplant (absolute incidence rate reduction = -1.9 events/1,000 person years; HR=0.81, 95% CI: 0.72, 0.90). Rivaroxaban was also associated with a statistically significant

reduction in the incidence rate of experiencing at least a 40% decrease in eGFR from baseline (absolute incidence rate reduction = -1.5 events/1,000 person years; HR=0.96, 95% CI: 0.93, 0.98) and at least a 30% decrease in eGFR from baseline (absolute incidence rate reduction = -12.4 events/1,000 person years; HR=0.96, 95% CI: 0.94, 0.98) compared to warfarin. There was no difference in doubling of serum creatinine levels between rivaroxaban and warfarin (55.2 vs. 57.4; HR=0.96, 95% CI: 0.92, 1.00).

The development of proteinuria, 30-300 was less frequent in rivaroxaban users compared to warfarin users (5.70 vs. 6.19 %/year, HR=0.92, 95% CI: 0.87, 0.97) as was development of proteinuria, <300 (0.66 vs. 0.79 %/year, HR=0.83, 95% CI: 0.71, 0.98).

For the MALE outcome (limb revascularization or major amputation), rivaroxaban was associated with a 15% relative incidence rate reduction (95% CI: 6, 24%), equating to a statistically significant absolute incidence rate reduction of -1.4 events/1,000 person years. All-cause mortality occurred 10.3/1,000 person years fewer in rivaroxaban users compared to warfarin users (HR=0.92, 95% CI: 0.89, 0.95).

Table 10-8: Kidney, MALE, ophthalmic outcomes, and all-cause mortality - Number of events and events per 1000 person-years and Hazard ratios

Outcome	Number of subjects		n (Events per 1,000 PY)		Incidence rate difference per 1000 PY (95%CI)	PS OLW HR (95%CI)
	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin		
Composite outcome						
>40% decrease in eGFR from baseline, eGFR<15 mL/minute, need for dialysis, renal transplant, MALE, retinopathy or death	24,912	58,270	12,331 (237.4)	30,359 (257.1)	-19.7 (-27.5 to -11.8)	0.93 (0.91, 0.95)
Components						
eGFR <15 mL/min/1.73 m^2, need for dialysis or renal transplant	24,912	58,270	2,342 (34.4)	5,662 (35.9)	-1.5 (-39.9 to -11.7)	0.96 (0.91, 1.01)
Need for dialysis or renal transplant			548 (7.5)	1,573 (9.4)	-1.9 (-3.1 to -0.6)	0.81 (0.72, 0.90)
>40% decrease in eGFR from baseline			8,744 (162.3)	21,035 (170.4)	-8.1 (-14.4 to -1.7)	0.96 (0.93, 0.98)
Doubling of serum creatinine			(55.2)	(57.4)		0.96 (0.92, 1.00)
Decrease in > 30% EGFR			(250.1)	(262.5)		0.96 (0.94, 0.98)
MALE (including limb amputation)			548 (7.7)	1,515 (9.1)	-1.4 (-2.6 to -0.2)	0.85 (0.76, 0.94)
All-cause mortality			6,203 (85.6)	16,257 (95.9)	-10.3 (-6.4 to -14.4)	0.92 (0.89, 0.95)
Diabetic retinopathy			1,221 (17.6)	2,972 (18.6)	-1.0	0.95 (0.88, 1.02)

Table 10-8: Kidney, MALE, ophthalmic outcomes, and all-cause mortality - Number of events and events per 1000 person-years and Hazard ratios

Outcome	Number of subjects		n (Events per 1,000 PY)		Incidence rate difference per 1000 PY (95%CI)	PS OLW HR (95%CI)
	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin		
					(-2.8 to 0.8)	
			%/year	%/year		PS OLW HR (95%CI)
Development of proteinuria, >300[a]	12,347	31,287	0.66	0.79		0.83 (0.71, 0.98)
Development of proteinuria, 30-300[a]			5.70	6.19		0.92 (0.87, 0.97)

CI: Confidence interval; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: Hazard ratio; MALE: Major adverse limb event(s); n: Number of events; OLW: Overlap weighted; PS: Propensity score; PY: person-years
[a]Excludes patients with proteinuria, missing, or ESRD at baseline

10.4.3 Subgroup analysis

10.4.3.1 Primary bleeding and secondary CV outcomes

Exploratory analyses did not show a statistically significant interaction across most subgroups for either the SSE/vascular death or major/CRNM bleed outcomes. One exception was the better relative effectiveness of rivaroxaban versus warfarin with the 20 mg rivaroxaban dose (compared to 15 mg) (p-interaction <0.05). A second exception was the better relative effectiveness of warfarin versus rivaroxaban when the warfarin cohort was restricted to patients with a TTR≥75% (11.6% of all warfarin users) during follow-up (p-interaction <0.05) (Table 10-9).

Table 10-9: Subgroup analysis: Primary bleeding and secondary CV outcomes - Hazard ratios

Subgroup	Hospitalization for major or CRNM bleed		SSE/Vascular Death	
	PS OLW HR	(95%CI)	PS OLW HR	(95%CI)
Age				
≥80 years	1.06	(0.96, 1.18)	0.93	(0.87, 1.00)
<80 years	0.90	(0.84, 0.96)	0.91	(0.86, 0.96)
Sex				
Female	0.97	(0.89, 1.06)	0.94	(0.88, 1.01)
Male	0.92	(0.85, 0.99)	0.89	(0.84, 0.94)
eGFR				
>50	0.92	(0.86, 0.98)	0.93	(0.89, 1.03)
30-50	1.03	(0.89, 1.19)	0.89	(0.80, 0.99)
<30	1.02	(0.82, 1.27)	0.79	(0.67, 0.93)
Hemoglobin A1c				
≥8.5	0.89	(0.77, 1.03)	0.86	(0.78, 0.95)
<8.5	0.95	(0.89, 1.01)	0.93	(0.86, 0.97)
Morbid obesity				
Yes	0.85	(0.75, 0.95)	0.89	(0.82, 0.99)
No	0.97	(0.91, 1.03)	0.92	(0.87, 0.96)

Table 10-9: Subgroup analysis: Primary bleeding and secondary CV outcomes - Hazard ratios

Subgroup	Hospitalization for major or CRNM bleed		SSE/Vascular Death	
	PS OLW HR	(95%CI)	PS OLW HR	(95%CI)
Heart failure				
Yes	1.02	(0.94, 1.11)	0.92	(0.87, 0.97)
No	0.87	(0.80, 0.94)	0.89	(0.83, 0.95)
Vascular disease				
Yes	1.03	(0.94, 1.31)	0.91	(0.85, 0.97)
No	0.89	(0.82, 0.95)	0.89	(0.85, 0.95)
PAD				
Yes	1.10	(0.98, 1.23)	0.92	(0.85, 1.00)
No	0.90	(0.84, 0.96)	0.91	(0.86, 0.95)
Revascularization				
Yes	0.99	(0.90, 1.10)	0.94	(0.87, 1.01)
No	0.97	(0.94, 1.01)	0.88	(0.84, 0.93)
Prior stroke				
Yes	0.98	(0.83, 1.17)	1.02	(0.93, 1.13)
No	0.93	(0.88, 0.99)	0.89	(0.85, 0.93)
Concomitant aspirin				
Yes	1.05	(0.97, 1.30)	0.92	(0.88, 1.01)
No	0.86	(0.80, 0.93)	0.86	(0.84, 0.93)
Frailty score				
Low	0.85	(0.77, 0.94)	0.86	(0.80, 0.94)
Moderate-to-high	0.99	(0.92, 1.05)	0.92	(0.87, 0.96)
Rivaroxaban dose				
20 mg	0.86	(0.80, 0.92)[a]	0.76	(0.72, 0.80)[a]
15 mg	0.93	(0.86, 1.02)	0.93	(0.88, 0.99)
Warfarin time in therapeutic INR				
<25%	0.64	(0.60, 0.69)	0.72	(0.69, 0.76)
25 to <50%	0.74	(0.69, 0.79)	0.72	(0.68, 0.76)
50 to <75%	1.03	(0.96, 1.11)	1.02	(0.97, 1.08)
≥75%	1.67	(1.48, 1.85)	1.33	(1.22, 1.44)

CRNM: Clinically relevant non-major; CI: Confidence interval; CV: Cardiovascular; eGFR: estimated glomerular filtration rate; HR: Hazard ratio; INR: international normalized ratio; OLW: overlap weighted; PAD: Peripheral artery disease; PS: Propensity score; SD: Standard deviation
[a]p-value for interaction <0.05 after adjustment for multiple comparisons using the Benjamini, Hochberg, and Yekutieli method to control for false discovery rates

10.4.3.2 Other secondary outcomes

No significant interaction was observed between subgroups upon stratification by age, eGFR, HbA1c, morbid obesity, or antiplatelet use for the composite kidney, MALE, and ophthalmic outcome (Table 10-10).

Table 10-10: Subgroup analyses: Other secondary outcomes (composite of kidney, MALE, or all-cause mortality) - Hazard ratios

Subgroup	Composite outcome of >40% decrease in eGFR from baseline, eGFR<15 mL/minute, need for dialysis, renal transplant, major adverse limb event, retinopathy, or death	
	PS OLW HR	(95%CI)
Age		
≥75 years	0.96	(0.93, 0.99)

Table 10-10: Subgroup analyses: Other secondary outcomes (composite of kidney, MALE, or all-cause mortality) - Hazard ratios

Subgroup	Composite outcome of >40% decrease in eGFR from baseline, eGFR<15 mL/minute, need for dialysis, renal transplant, major adverse limb event, retinopathy, or death	
	PS OLW HR	(95%CI)
<75 years	0.91	(0.89, 0.94)
eGFR		
≥60	0.93	(0.90, 0.95)
30 to 59	0.93	(0.89, 0.97)
15 to 29	0.99	(0.89, 1.10)
Hemoglobin A1c		
≥8.5% (69 mmol/mol)	0.91	(0.86, 0.96)
<8.5% (69 mmol/mol)	0.93	(0.91, 0.96)
Morbid obesity		
Yes	0.94	(0.90, 0.98)
No	0.93	(0.90, 0.95)
Concomitant antiplatelet		
Yes	0.95	(0.91, 0.98)
No	0.92	(0.89, 0.94)

CI: Confidence interval; eGFR: estimated glomerular filtration rate; HR: Hazard ratio; OLW: Overlap weighted; PS: Propensity score
[a]No significant interactions were observed across any subgroup

10.4.3.3 Age

To allow for the assessment of statistical interaction in outcome rates across age groups, patients were PS-OLW after stratification of eligible patients into older (≥80 years old) and younger (<80 years old) groups.

Primary and Secondary Outcomes

For number of events and rate per 100 person-years (%/year), stratified by warfarin and rivaroxaban exposure groups for each outcome, refer to Table 10-11 and Table 10-12.

Weighted incidence rates (%/year) of developing SSE, or vascular death; hospitalization for major or CRNM bleeding; and MALEs (need for revascularization or major amputation of the lower limbs) for rivaroxaban and warfarin users with type 2 diabetes patients either ≥80 or <80 years old were reported.

Propensity score-overlap weighted analyses found no statistically significant interaction for the relative effectiveness or safety of rivaroxaban versus warfarin across the older or younger age groups for the outcomes of stroke, systemic embolism, or vascular death (HR=0.93; 95% CI: 0.87, 1.00 vs. HR=0.91; 95% CI: 0.86, 0.96), hospitalization for major or CRNM bleeding (HR=1.06; 95% CI: 0.96, 1.18 vs. HR=0.90; 95% CI: 0.84, 0.96) or MALEs (HR=0.79; 95% CI: 0.68, 0.94 vs. HR=0.76; 95% CI: 0.70, 0.83). Major and intracranial bleeding were also observed significantly less frequently with rivaroxaban compared to warfarin regardless of patient age.

Table 10-11: Primary outcomes in subgroup analysis - Hazard ratios

Outcome	Age≥80 years			Age<80 years		
	Rivaroxaban N=6,606 Incidence rate (%/year)	Warfarin N=25,335 Incidence rate (%/year)	HR (95%CI)	Rivaroxaban N=25,472 Incidence rate (%/year)	Warfarin N=58,636 Incidence rate (%/year)	HR (95%CI)
SSE	2.08	1.98	1.05 (0.92, 1.19)	1.15	1.21	0.95 (0.87, 1.04)
Hospitalization for major or CRNM bleed	3.29	3.09	1.06 (0.96, 1.18)	2.00	2.22	0.90 (0.84, 0.96)

CI: Confidence interval; CRNM: Clinically relevant non-major; HR: Hazard ratio; N: Number of patients; SSE: Stroke or systemic embolism

Table 10-12: Secondary outcomes in subgroup analysis - Hazard ratios

Outcome	Age≥80 years			Age<80 years		
	Rivaroxaban N=6,606 Incidence rate (%/year)	Warfarin N=25,335 Incidence rate (%/year)	HR (95%CI)	Rivaroxaban N=25,472 Incidence rate (%/year)	Warfarin N=58,636 Incidence rate (%/year)	HR (95%CI)
CV outcomes						
SSE/vascular death	6.31	6.86	0.93 (0.87, 1.00)	3.24	3.62	0.91 (0.86, 0.96)
Vascular death	4.81	5.34	0.92 (0.85, 0.99)	2.26	2.58	0.90 (0.84, 0.95)
MALE	1.09	1.37	0.80 (0.68, 0.94)	1.10	1.44	0.76 (0.70, 0.83)
Bleeding outcomes						
Major bleed	1.11	1.43	0.77 (0.66, 0.91)	0.86	1.05	0.82 (0.74, 0.91)
Intracranial bleed	0.26	0.63	0.68 (0.52, 0.89)	0.26	0.34	0.75 (0.63, 0.90)

CI: Confidence interval; CV: Cardiovascular; HR: Hazard ratio; MALE: Major adverse limb event; N: Number of patients; SSE: Stroke or systemic embolism

10.4.4 Sensitivity analysis

Table 10-13: Sensitivity analysis: Primary bleeding and secondary CV outcome - Hazard ratios

	Hospitalization for major or CRNM bleed		SSE/Vascular Death	
	HR	(95%CI)	HR	(95%CI)
PS method				
OLW	0.94	(0.89-0.99)	0.91	(0.88, 0.95)
sIPTW	1.00	(0.92-1.08)	0.94	(0.91, 0.99)
1:1 PSM (caliper=0.25 SD)	0.89	(0.83-0.95)	0.89	(0.85, 0.94)
	PS OLW HR	**(95%CI)**	**PS OLW HR**	**(95%CI)**
2-year follow-up cap	**0.98**	**(0.92, 1.06)**	**0.93**	**(0.88, 0.98)**

CI: Confidence interval; HR: Hazard ratio; OLW: Overlap weighting; PS: Propensity score; SD: Standard deviation; sIPTW: Stabilized inverse probability weighting

Table 10-14: Sensitivity Analyses: Secondary outcome (composite of kidney, MALE, or all-cause mortality) - Hazard ratios

	Composite outcome of >40% decrease in eGFR from baseline, eGFR<15 mL/minute, need for dialysis, renal transplant, major adverse limb event, retinopathy, or death	
	HR	**(95%CI)**
PS method		
OLW	0.93	(0.91, 0.95)
sIPTW	0.95	(0.93, 0.97)
1:1 PSM	0.91	(0.89, 0.93)
Follow-up time	**PS OLW HR**	**(95%CI)**
Full intent-to-treat (base-case)	0.93	(0.91, 0.95)
2-years follow-up cap	0.95	(0.92, 0.97)

CI: Confidence interval; HR: Hazard ratio; OLW: Overlap weighting; PS: Propensity score; sIPTW: Stabilized inverse probability weighting

10.5 Other analyses

Ophthalmic outcomes

The number of events and events per 100 person years (%/year) and hazard ratios (with 95% CI) for the ophthalmic outcomes using PS-OLW method are displayed in Table 10-15.

Rivaroxaban was associated with a 15% (95% CI: 8%, 21%) relative hazard reduction of any ophthalmic complication (incidence rate=1.25 vs. 1.46%/year), driven by reductions in both ophthalmic bleeding (HR=0.80, 95% CI: 0.63, 1.00) and diabetic retinopathy (HR=0.85, 95% CI: 0.79, 0.93).

Among ophthalmic bleed outcomes, vitreous bleed was less frequent in rivaroxaban users compared to warfarin users (0.07 vs. 0.10%/year; HR=0.66, 95% CI: 0.47, 0.92) and there was no difference in choroidal bleed (0.003 vs. 0.005; HR=0.59, 95% CI: 0.11, 3.17), intraocular bleed (0.01 vs. 0.01; HR=0.75, 95% CI: 0.26, 2.13), and retinal bleed (0.08 vs. 0.09; HR=0.93, 95% CI: 0.68, 1.28) between rivaroxaban and warfarin.

Sensitivity analyses demonstrated the conclusions remained robust after implementation of a 2-year follow-up cap or changes in study methodology to adjust for confounding (both alternative methods also resulted in cohorts with absolute standardized differences <0.1 for all observed covariates).

For analysis of secondary outcomes by crude method, refer to Table 16-4 and Table 16-5.

Table 10-15: Ophthalmic complications - Events per 100 person-years (%/year) and Hazard ratios

Outcome	Rivaroxaban, N=26,537 %/year	Warfarin, N=61,690 %/year	PS OLW HR (95%CI)
Any ophthalmic complication	**1.25**	**1.46**	**0.85 (0.79, 0.92)**
Any ophthalmic bleed	**0.15**	**0.19**	**0.80 (0.63, 1.00)**
Choroidal bleed	0.003	0.005	0.59 (0.11, 3.17)

Table 10-15: Ophthalmic complications - Events per 100 person-years (%/year) and Hazard ratios

Outcome	Rivaroxaban, N=26,537 %/year	Warfarin, N=61,690 %/year	PS OLW HR (95%CI)
Intraocular bleed	0.01	0.01	0.75 (0.26, 2.13)
Retinal bleed	0.08	0.09	0.93 (0.68, 1.28)
Vitreous bleed	0.07	0.10	0.66 (0.47, 0.92)
Any type of diabetic retinopathy	**1.15**	**1.34**	**0.85 (0.79, 0.93)**
Diabetic retinopathy, non-proliferative	0.35	0.44	0.80 (0.69, 0.93)
Diabetic retinopathy, proliferative	0.09	0.12	0.79 (0.59, 1.05)
Diabetic retinopathy, unspecified	0.82	0.94	0.87 (0.79, 0.97)

CI: Confidence interval; HR: Hazard ratio; N: number of patients; OLW: Overlap weighted; PS: Propensity score

10.6 Safety data (Adverse events/adverse reactions)

Not applicable.

11. Discussion

11.1 Key results

This retrospective cohort study evaluated the effectiveness and safety of rivaroxaban as compared to warfarin in NVAF patients with T2DM in a real-world setting. Individual-level data for warfarin- and rivaroxaban-naïve NVAF patients with T2DM were used from the Optum EHR database (from 01 NOV 2010 to 31 DEC 2019).

The current analyses by PS-OLW method demonstrated that rivaroxaban was associated with a reduced risk of SSE or vascular death (3.79 vs. 4.19; HR=0.91, 95% CI: 0.88, 0.95), driven mostly by 10% relative risk reduction (RRR) in vascular death (2.81 vs 3.18, HR=0.90, 95% CI: 0.86, 0.95) and 18% RRR in systemic embolism (0.13 vs. 0.16; HR=0.82, 95% CI: 0.66, 1.02). Major/CRNM bleeding was less frequent with rivaroxaban versus warfarin (2.17 vs. 2.31; HR=0.94, 95% CI: 0.89, 0.99) due to decreased critical organ bleeding (37% RRR) and intracranial hemorrhage (28% RRR). These findings remained consistent across subgroups including baseline HbA1c level, with statistical interactions seen only when comparing the 20 mg versus 15 mg dosing subgroups for the SSE/vascular death outcome (an interaction based more on magnitude than direction of effect) and among patients with a well-controlled INRs (TTR≥75%). These findings also remained robust upon changes in confounding adjustment methodology employed and upon capping follow-up at a maximum of 2-years.

Rivaroxaban was associated with a reduced hazard of the composite outcome of >40% decrease in eGFR) from baseline, eGFR<15 mL/minute/1.73 m^2, need for dialysis or kidney transplant, MALE, diabetic retinopathy, or death (HR=0.93, 95% CI: 0.91, 0.95) versus warfarin. Rivaroxaban was also associated with significant reductions in the relative hazard of a >40% decrease in eGFR from baseline (HR=0.96), need for dialysis or renal transplant (HR=0.81), and limb revascularization or major amputation (HR=0.85). Death occurred at a lower incidence rate with rivaroxaban (HR=0.92, 95% CI: 0.89, 0.95). These findings remained consistent across subgroups stratified by age, eGFR, HbA1c, morbid obesity, and antiplatelet use; as well as, when follow-up was capped at 2-years and 1:1 propensity score matching or sIPTW was alternatively used for between cohort confounder adjustment. Of the 19.7 event/1,000 person years fewer adverse events observed with rivaroxaban versus warfarin use, all-cause death (10.3 fewer events/1,000 person years) and >40% decrease in eGFR from baseline (8.1 fewer events/1,000 person years) were substantial drivers of the overall effect. However, the need for dialysis or kidney transplant (1.9 fewer events/1,000 person-years) and need for limb revascularization or major amputation (1.4 fewer events/1,000 person years) components were also significantly reduced in the rivaroxaban cohort.

Rivaroxaban was associated with a 15% (95%CI: 8%, 21%) relative hazard reduction of any ophthalmic complication (incidence rate=1.25 vs. 1.46 100 person years), driven by reductions in both ophthalmic bleeding (HR=0.80) and diabetic retinopathy (HR=0.85).

The effectiveness and safety of rivaroxaban relative to warfarin remained consistent across older and younger patient subgroups for the outcomes of stroke, systemic embolism, or vascular death (HR=0.93 vs. 0.91), hospitalization for major or CRNM bleeding (HR=1.06 vs. 0.90) or MALEs (HR=0.79 vs. 0.76).

A falsification analysis using urinary tract infection as an outcome was performed. The analysis did not detect a difference between the two cohorts in the development of using urinary tract infection (HR=0.97, 0.95-1.00).

11.2 Limitations

As with any data source, Optum EHR database has limitations worth discussion:

- Due to the non-randomized, retrospective nature of the study, biases including misclassification, sampling, and confounding could have impacted the internal validity.
- Due to the observational nature of this study, there was no control over warfarin dosing or target INR chosen (though an assumption of a target range of 2.0-3.0 for the purposes of TTR calculation was done). However, the TTR observed in this study (mean: 47%, median: 50%) was not dissimilar to that of warfarin patients enrolled in ROCKET AF (mean: 55%, median: 58%) or to that observed in routine clinical practice (mean: 55%).
- Time since diabetes diagnosis was not accurately ascertained within the available data; and therefore, it was not included in the propensity score model.
- Cause of death was also not available in the database. However, prior studies have suggested that 8 out of every 10 diabetes die from cardiovascular causes. Notably, the vascular mortality rates observed in this study (rivaroxaban=2.81%, warfarin=3.18%) were similar to the vascular mortality rate in the diabetic sub-analysis of ROCKET AF (rivaroxaban=2.83%, warfarin=3.65%).
- The EHR data set utilized for this study included only US patients making the findings most generalizable to a US population.
- The EHR data sets lacked information on prescription medication claims. Instead, they provided data only on medications prescribed or self-reported (the latter proved to being an advantage of EHRs as they allowed for detection of over-the-counter medication use such as aspirin). The lack of prescription claims data made ascertainment of OAC exposure (persistence and adherence) problematic. As a result, the present study only performed intent-to-treat (and not on-treatment) analyses.
- Finally, although Optum EHR data covered both insured and uninsured patients, it did not cover all institutions and therefore possible follow-up events could have been missed.

Measures taken to mitigate the limitations:

- The probability of misclassification bias was reduced by using objective data points (i.e., laboratory and vital signs) rather than relying solely on billing codes to identify comorbidities and outcomes. When billing codes were used in the identification of comorbidities or outcomes, efforts to utilize validated coding schema were taken whenever possible. Propensity score-overlap weighting was used to reduce the risk of confounding bias. Overlap weighting was used as the primary method of cofounder adjustment as it retained all patients in the dataset (unlike propensity score matching which typically decrease the sample size of at least one cohort) and it provided more weight to patients with unpredictable treatment and less weight to patients with extreme propensity scores which prevented outliers from steering the analysis (a concern seen within inverse probability weighting). While such propensity score-based methods serve to harmonize comparison groups with respect to patient characteristics, residual

confounding cannot be ruled out. A falsification analysis was also performed that found, as anticipated, no difference between rivaroxaban and warfarin users for the outcome of urinary tract infection.

- To identify "vascular" mortality, an algorithm consisting of hospitalization due to vascular cause within 365 days of death was used.

11.3 Interpretation

Detailed EHR data was utilized to evaluate >116,000 patients with NVAF and comorbid T2DM newly started on rivaroxaban or warfarin for a mean of ~2.9 years of follow-up. Rivaroxaban use was associated with effectiveness and safety benefits versus warfarin; most notably, significant reductions in vascular death (10% relative risk reduction [RRR]), critical organ bleeding (37% RRR) and intracranial hemorrhage (28% RRR). These findings remained consistent across subgroups including baseline HbA1c level, with statistical interactions seen only when comparing the 20 mg versus 15 mg dosing subgroups for the SSE/vascular death outcome (an interaction based more on magnitude than direction of effect) and among patients with a well-controlled INRs (TTR≥75%). Current findings also remained robust upon changes in confounding adjustment methodology employed and upon capping follow-up at a maximum of 2-years.

The findings of current report are generally consistent with those from the diabetes subanalysis of the rivaroxaban once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial) (3, 4). Bansilal and colleagues (4) evaluated 5,695 subjects with diabetes from ROCKET AF (mean $CHADS_2$ score=3.7±1.0) and demonstrated rivaroxaban reduced the incidence rate of SSE/vascular death (4.23 vs. 5.17%/year, HR=0.84 (0.70-1.00) and vascular death alone (2.83 vs. 3.65%/year, HR=0.80, 95% CI=0.64-0.99). Of note, the vascular mortality reduction with rivaroxaban compared to warfarin in ROCKET AF was observed in diabetics but not in those without diabetes (HR=1.08, 95% CI=0.89-1.30) (p-interaction=0.037 for diabetic vs. non-diabetic subgroup comparison) (3, 4).

An administrative claims database study performed by Baker and colleagues (6) of nearly 24,000 patients provided confirmatory evidence to ROCKET AF (3, 4), suggesting rivaroxaban was at least as effective and safe as warfarin in NVAF patients with comorbid T2DM. The investigators reported no statistically significant differences in ischemic stroke (HR=0.83, 95% CI=0.59-1.17) or major bleeding (HR=0.95, 95% CI=0.79-1.15) between the two inverse probability of treatment weighted (IPTW) OAC cohorts. Unfortunately, the IBM MarketScan claims data set utilized by the investigators does not provide mortality data, so vascular death could not be assessed (6). This is noteworthy, since vascular death occurs in at least 7 out of 10 NVAF patients with diabetes (24) and appears to be the outcome most benefited by the preferential use of rivaroxaban in diabetics in ROCKET AF (3, 4) and in the present EHR study.

Another retrospective database study was performed by Chan et al. and investigated all direct-acting oral anticoagulants (DOACs) versus warfarin in patients with comorbid NVAF and diabetes (25). This study found no significant difference in SSE between DOACs and warfarin (HR=0.89, 95% CI=0.79-1.02) but did find DOACs to be associated with a reduction in major bleeding (HR=0.67, 95% CI=0.59-0.76). These findings were not inconsistent with those in our study, though our study importantly added the outcome of vascular mortality. Our observed reduction in vascular mortality with rivaroxaban versus warfarin was bolstered by

the findings of a meta-analysis performed by Patti and colleagues that demonstrated a reduction in vascular mortality with DOACs versus vitamin K antagonists in patients with comorbid NVAF and diabetes using data from four phase III RCTs (4.97 vs. 5.99%; relative reduction=0.83, 95% CI=0.72-0.96) (9).

United States and European atrial fibrillation guidelines (26, 27) state that for stroke prevention, patients who are eligible for OAC should receive a DOAC in preference to a vitamin K antagonist (VKA) except in patients with mechanical heart valves or moderate-to-severe mitral stenosis (class 1A recommendations). European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) collaborative guidelines on the management of diabetes, pre-diabetes, and cardiovascular diseases additionally recommend (class 1A) DOACs over a VKA in patients with diabetes aged >65 years with NVAF and a CHA2DS2VASc score ≥2, (if not otherwise contraindicated) (28). Given vascular mortality is substantially increased in NVAF patients with comorbid T2D and the accumulating data suggesting DOACs (9) may be associated with up to a 17% relative and ~1% absolute risk reduction in vascular death, the practice of preferentially using DOACs over a VKA in a diabetic appears warranted (29).

In this EHR study, rivaroxaban was associated with a significant reduction in our composite outcome (7% relative hazard reduction, 1.97% absolute risk reduction, number needed-to-treat of 51). Our conclusions remained consistent (no interaction noted) across subgroups stratified by age, eGFR, HbA1c, morbid obesity and antiplatelet use; as well as, when follow-up was capped at 2-years and 1:1 propensity score matching or sIPTW was alternatively used for between cohort confounder adjustment. Of the 19.7 event/1,000 person-years fewer adverse events observed with rivaroxaban versus warfarin use, all-cause death (10.3 fewer events/1,000 person-years) and >40% decrease in eGFR from baseline (8.1 fewer events/1,000 person-years) were substantial drivers of the overall effect. However, the need for dialysis or kidney transplant (1.9 fewer events/1,000 person-years) and need for limb revascularization or major amputation (1.4 fewer events/1,000 person-years) components were also significantly reduced in the rivaroxaban cohort.

Progressive renal decline is frequently seen in patients with type 2 diabetes and is hypothesized as being due to atherosclerotic calcification associated with increased oxidative stress and the release of inflammatory cytokines (12). Because VKA use inhibits the vitamin k-dependent matrix Gla protein (MGP), this class of anticoagulants has been linked to renovascular calcification and more rapid kidney decline (12). Data from prior RCTs (30, 31, 32) and real-world evaluations (5, 33) provide conflicting data regarding the comparative effect of using DOACs versus VKA on kidney complications in NVAF patients (with or without comorbid diabetes). This conflict may be the result of different study designs employed, the kidney outcome definitions evaluated and/or variation in study sample sizes. Available RCTs of DOACs versus warfarin (with <40% incidence of type 2 diabetes) have primarily focused on surrogate outcomes of renal decline including mean change in creatinine clearance (CrCL) or >20 to 40% decline in CrCl from baseline. While data for RCTs is collected prospectively, change in renal function was not a pre-specified outcome, and therefore, CrCL data was not collected in all patients, at regular time intervals or at the same frequency (30, 31, 32). In kidney outcome trials (34, 35) the primary outcome of interest is often a composite of surrogate and terminal outcomes including kidney failure (eGFR<15 mL/min/1.73 m^2) confirmed by a second measurement at least 4 weeks after the initial measurement, initiation of chronic dialysis, or need for renal transplantation), a sustained decrease of eGFR≥40% from baseline over at least 4 weeks, or death. The “sustained”

requirement of the outcome definitions is particularly important for surrogate outcomes (e.g., change in kidney function or attainment of an absolute value) because these outcomes may more likely be associated with misclassification bias in the absence of subsequent verification. Real-world evaluations will likely suffer from this same bias, but notably, the present study also reports results for terminal kidney outcomes not dependent on laboratory measures and their measurement intervals (i.e., need for dialysis or renal transplant was reduced with rivaroxaban by 19%). Previously, Yao and colleagues performed an analysis of each DOAC versus warfarin in an integrated claim and EHR data set (33). While they evaluated development of end-stage kidney disease (which included an eGFR<15 mL/minute/1.73 m2) as one of their outcomes, the use of the integrated data set resulted in small sample sizes (n for DOAC cohorts=1,216 to 2,485) and only a handful of kidney failure events (n range=4 to 58) observed in the various DOAC cohorts. Importantly, our study exclusively evaluated >80,000 type 2 diabetes patients.

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial demonstrated rivaroxaban (2.5 mg twice daily) given with low-dose aspirin could reduce the risk of major adverse limb events by 60% (p=0.005) in patients with stable coronary or peripheral arterial disease versus aspirin alone (36). About 38% of COMPASS patients had diabetes and subgroup analysis of COMPASS showed the limb benefits observed with rivaroxaban was seen in the presence or absence of diabetes (p-interaction=0.27) (36). Prior claims database studies (6, 25) have also suggested DOACs, including rivaroxaban, can reduce major adverse limb events compared to warfarin. The present study thus provides further support to hypothesize that rivaroxaban's reduction in adverse limb events is maintained in NVAF patients with comorbid type 2 diabetes. It should be noted; however, that rivaroxaban doses vary across the NVAF and stable CAD/PAD indications, as does the use of low dose aspirin therapy.

Diabetic patients often develop ophthalmic complications, most commonly, diabetic retinopathy. It is estimated that >28% of diabetics >40-year-old have diabetic retinopathy. While the exact mechanism by which diabetes causes retinopathy has not been fully elucidated, microaneurysms and hemorrhages are among the earliest signs of disease (37). A host of hematologic abnormalities are also common in diabetics (e.g., increased erythrocyte aggregation, increased platelet aggregation, and adhesion) which could lead to capillary occlusion, retinal ischemia, and finally diabetic retinopathy (37). While either of these mechanisms (bleeding or occlusion) might be impacted by OAC use, data regarding the association between DOAC use and diabetic retinopathy are scarce. A meta-analysis (38) of 12 DOAC NVAF or venous thromboembolism trials, with or without diabetes) demonstrated DOACs were associated with a 22% relative reduction in intraocular bleeding compared with warfarin (risk ratio=0.78; 95% CI=0.61 to 0.99). In a diabetes subanalysis of ROCKET AF, Bansilal and colleagues observed a non-significant 47% relative hazard reduction for intraocular or retinal bleeding with rivaroxaban compared to warfarin (HR=0.53, 95% CI=0.20-1.45) although the event rates were low in both groups (0.14 versus 0.25%/year) [10]. The present study found a 1.0 event/1,000 person-year reduction in diabetic retinopathy (95% CI=-2.8 to 0.8). While the present study's findings are consistent with the absolute rate reduction observed in the ROCKET AF diabetes substudy, it is worth noting, our study looked for the diagnosis of diabetic retinopathy rather than simply intraocular bleeding. While our findings for this outcome were not statistically significant, we believe further investigation into the impact of DOACs versus warfarin on the development of diabetic retinopathy is warranted.

11.4 Generalizability

The Optum EHR Database capture person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services. Individuals enrolled in such databases are largely representative of the US population in terms of age, sex, and type of health insurance coverage. Therefore, generalizability of the results of this study in the US population should be considered acceptable.

12. Other information

Not applicable.

13. Conclusion

In NVAF patients with T2DM, rivaroxaban was associated with an ~10% relative risk reduction in vascular mortality and fewer bleeding-related hospitalizations versus warfarin, including a significant 37% relative risk reduction in critical organ bleeding and a 28% relative risk reduction in intracranial hemorrhage. However, there was no difference detected in SSE.

Rivaroxaban was associated with a significant 19.7 event/1,000 person years reduction in the composite outcome of >40% decrease in eGFR from baseline, eGFR<15 mL/minute/1.73 m^2, new need for dialysis or renal transplant, limb revascularization or major amputation, development of diabetic retinopathy, or all-cause mortality. These reductions in adverse events were due to reduced incidence rates of kidney and limb complications, as well as all-cause death.

Rivaroxaban was associated with a reduction in ophthalmic complications compared to warfarin. The effectiveness and safety of rivaroxaban relative to warfarin remained consistent across older and younger patient subgroups, supporting rivaroxaban as an alternative for elderly NVAF patients with concomitant type 2 diabetes.

The findings of the present study should provide clinicians with additional confidence in selecting rivaroxaban in NVAF patients with comorbid T2DM.

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15. Annexures

15.1 Annex 1: List of stand-alone documents

Table 15-1: List of stand-alone documents

Document Name	Final version and date (if available)*
ICD_optum_coding.xlxs	19 OCT 2020

15.2 Annex 2: Additional information

PASS protocol

Reference Number: RD-SOP-1216
Best Practice Document Version: 5

15.3 Annex 3: Signature Pages

Signature Page – OS Outcomes Data Generation

Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Report version and date	v 1.0, 05 NOV 2021
IMPACT study number	21449
Study type / Study phase	Observational, Phase IV PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO
Medicinal product / Active substance / Medical Device / Combination Product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®/ Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Comparator / Reference therapy	Warfarin, Coumadin®
Study Initiator and Funder	Bayer AG

The signatories confirm that they agree that the study will be conducted under the conditions described in the protocol.

Signatories

- PPD (Principal Investigator)
- PPD (OS Conduct Responsible)
- PPD (OS Safety Lead)
- PPD (OS Medical Expert)
- PPD (OS Epidemiologist)
- PPD (OS Statistician)

16. Appendices

Table 16-1: Primary outcomes: Analysis by the crude method

Outcome	Rivaroxaban N=32,078 %/year	Warfarin N=83,971 %/year	HR (95%CI)
SSE	1.28	1.50	0.45 (0.36, 0.55)
Hospitalization for major or CRNM bleed	2.11	2.88	0.70 (0.66, 0.73)

CI: Confidence interval; CRNM: Clinically relevant non-major; HR: Hazard ratio; N: Number of patients; SSE: Stroke or systemic embolism

Table 16-2: Competing risk of SSE, hospitalization for major or CRNM bleed, or CV Death - Number of events and events per 100 person-years (%/year)[a] and Hazard ratios

Outcome	Rivaroxaban N=30,597 %/year	Warfarin N=30,597 %/year	HR (95%CI)
SSE	1.91	1.88	1.01 (0.92, 1.12)
Hospitalization for major or CRNM bleed	3.91	4.57	0.89 (0.83, 0.95)
CV Death[b]	7.75	8.48	0.85 (0.79, 0.91)

N: number of patients; CI: confidence interval; CRNM: clinically relevant non-major; CV: Cardiovascular; HR: hazard ratio; SSE: Stroke or systemic embolism
[a]This population utilized propensity score matching.
[b]Secondary outcome

Table 16-3: Multivariate Cox regression - Number of events and events per 100 person-years (%/year)[a] and Hazard ratios[b]

Outcome	Rivaroxaban N=32,078 %/year	Warfarin N=83,971 %/year	HR (95%CI)
SSE	1.28	1.50	0.94 (0.88, 1.01)
Hospitalization for major or CRNM bleed	2.11	2.88	0.89 (0.85, 0.95)

N: number of patients; CI: confidence interval; CRNM: clinically relevant non-major; HR: hazard ratio; SSE: Stroke or systemic embolism
[a]Crude incidences reported incorporate all covariates used for weighting.
[b]Hazard ratios (and 95% CIs) incorporate all covariates used for weighting.

Table 16-4: Secondary CV and bleeding outcomes

Outcome	Number of subjects		%/year		HR
	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin	(95%CI)
CV outcomes					
Stroke, systemic embolism, vascular death	32,078	83,971	3.26	5.23	0.63 (0.61, 0.66)
Stroke, systemic embolism, MI, vascular death			4.27	6.30	0.67 (0.65, 0.70)
Stroke, MI, vascular death			4.19	6.16	0.68 (0.66, 0.71)
IS			1.07	1.13	0.90 (0.83, 0.97)

Table 16-4: Secondary CV and bleeding outcomes

Outcome	Number of subjects		%/year		HR (95%CI)
	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin	
Systemic embolism			0.12	0.24	0.45 (0.36, 0.55)
MI			1.00	1.06	0.90 (0.93, 0.97)
Vascular death			2.50	4.42	0.59 (0.57, 0.62)
Stroke, systemic embolism, MALE[a]	30,017	75,744	1.75	2.33	0.72 (0.68, 0.77)
Hyperkalemia, >5.6[b]	28,320	74,778	4.89	7.13	0.65 (0.63, 0.68)
Hyperkalemia, >6.0[c]	28,390	75,040	2.25	3.62	0.59 (0.56, 0.62)
New onset vascular dementia[d]	30,508	77,890	0.36	0.51	0.72 (0.64, 0.82)
Bleeding outcomes					
Hospitalization for major or CRNM bleed	32,078	83,971	8.04	8.51	0.90 (0.87, 0.93)
Major bleed			0.86	1.31	0.63 (0.58, 0.68)
CRNM bleed			6.98	6.91	0.96 (0.93, 0.99)
Critical organ bleed			0.33	0.62	0.51 (0.45, 0.58)
ICH			0.28	0.47	0.57 (0.50, 0.66)
Extracranial bleed			1.79	2.33	0.73 (0.69, 0.77)

CI: Confidence interval; CRNM: Clinically relevant non-major; HR: Hazard ratio; ICH: Intracranial hemorrhage; IS: Ischemic stroke; MALE: Major adverse limb event
[a]excludes MALE at baseline
[b]excludes patients with potassium>5.6 or missing at baseline
[c]excludes patients with potassium>6.0 or missing at baseline
[d]excludes excludes dementia and/or vascular dementia at baseline

Table 16-5: Kidney, MALE, ophthalmic outcomes, and all-cause mortality

Outcome	Number of patients		Events per 1,000 PY	Events per 1,000 PY	Incidence rate difference per 1000 PY (95%CI)	HR (95%CI)
	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin		
Composite outcome						
>40% decrease in eGFR from baseline, eGFR<15 mL/minute, need for dialysis, renal transplant, MALE, retinopathy or death	24,912	58,270	224.0	289.1	-65.1 (-66.8, -63.4)	0.76 (0.75, 0.78)
Components						
eGFR <15 mL/min/1.73 m^2, need for dialysis or renal transplant	24,912	58,270	31.5	45.1	-13.6 (-14.4, 12.8)	0.66 (0.63, 0.70)
Need for dialysis or renal transplant			6.7	11.8	-5.1 (-5.6, -4.6)	0.56 (0.50, 0.62)
>40% decrease in eGFR from baseline			155.1	184.3	-29.2 (-30.4, 28.1)	0.81 (0.79, 0.83)
Doubling of serum creatinine			52.0	63.2	-11.2 (-11.9, 10.5)	0.80 (0.77, 0.83)
Decrease in > 30% EGFR			240.7	279.4	-38.7 (-40.0, -37.4)	0.83 (0.81, 0.84)
MALE (including limb amputation)			7.5	10.0	-2.5 (-2.9, 2.2)	0.74 (0.67, 0.82)
Diabetic retinopathy			17.5	18.2	-0.7 (-0.9, -0.5)	0.94 (0.87, 1.00)
All-cause mortality			77.1	117.6	-40.5) (-41.9, -39.2	0.72 (0.70, 0.74)
			%/year	%/year		
Development of proteinuria, >300[a]	12,347	31,287	0.64	0.79		0.82 (0.71, 0.96)
Development of proteinuria, 30-300[a]			5.80	5.61		1.02 (0.96, 1.07)

CI: Confidence interval; eGFR: estimated glomerular filtration rate; ESRD: End-stage renal disease; HR: Hazard ratio; MALE: Major adverse limb event(s); PY: person-years
[a]Excludes patients with proteinuria, missing, or ESRD at baseline

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Reason for signing: Approved	Name: PPD Role: OS Conduct Responsible Date of signature: 04-Jan-2022 20:29:19 GMT+0000
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Reason for signing: Approved	Name: PPD Role: OS Epidemiologist Date of signature: 05-Jan-2022 09:15:52 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Statistician Date of signature: 05-Jan-2022 12:23:25 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Safety Lead Date of signature: 06-Jan-2022 18:35:14 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Medical Expert Date of signature: 12-Jan-2022 22:05:38 GMT+0000

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