A RIVA-DM Subanalysis Investigating Patients With Nonvalvular Atrial Fibrillation and Type 2 Diabetes Aged Under Versus Over 80 Years

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Abstract

Background: Advanced age and type 2 diabetes (T2D) are common in patients with nonvalvular atrial fibrillation (NVAF). We evaluated the impact of age on the effectiveness and safety of rivaroxaban versus warfarin in this population.

Methods: We analyzed electronic health record data from November 2010, to December 2019 including adults with NVAF and T2D, newly started on rivaroxaban or warfarin. Propensity score-overlap weighted hazard ratios (HRs) for stroke/systemic embolism (SSE), hospitalization for major or clinically relevant nonmajor bleeding (CRNMB), vascular death, major adverse limb events (MALE), major bleeding, and intracranial hemorrhage (ICH) were calculated for older (≥80 years) and younger (<80 years) cohorts.

Results: We included 32,078 rivaroxaban and 83,971 warfarin users (6,606 rivaroxaban and 25,335 warfarin patients were aged ≥80 years). No significant interaction for rivaroxaban versus warfarin by age was observed for any outcome, including SSE (HR = 1.05 vs 0.95), hospitalization for major or CRNMB (HR = 1.06 vs 0.90), vascular death (HR = 0.92 vs 0.90), MALE (HR = 0.80 vs 0.76), major bleeding or ICH.

Conclusions: The effectiveness and safety of rivaroxaban versus warfarin remained consistent across patient age subgroups.

Keywords
atrial fibrillation, anticoagulant, rivaroxaban, warfarin, diabetes

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Introduction

Patients with diabetes have a 49% increased risk of developing atrial fibrillation (AF) compared with those without.¹,² These patients, specifically those with nonvalvular AF (NVAF), are at a fivefold increased risk of stroke and up to a twofold increased risk of mortality.³,⁴ Additionally, in patients aged 80 years and older, more than 1 in 5 strokes are attributable to AF, while a quarter of patients >60 years old have diabetes.³ To reduce the risk of morbidity and mortality in these patients, oral anticoagulants (OACs) such as vitamin K antagonists (VKA) and direct-acting OACs (DOACs) are typically prescribed. These agents decrease thrombus formation and subsequently decrease mortality.

Data from randomized controlled trials, administrative claim database analyses, and electronic health record (EHR) studies have demonstrated that DOACs, such as rivaroxaban, are at...
least as effective and safe as warfarin in preventing stroke and systemic embolism (SSE) in patients with NVAF and type 2 diabetes (T2D).\(^3\)-\(^8\) Data comparing outcomes associated with rivaroxaban and warfarin use in NVAF patients with T2D stratified by advanced age are scarce. These data are important given the increased risk of AF and T2D with age, the attributable risk of stroke due to AF when T2D in present, and older patients’ baseline risk of bleeding compared to a younger population.\(^3\)-\(^9\),\(^10\)

In this study, we aimed to assess the incidence rates of thrombosis, vascular death, and bleeding events in patients with NVAF and T2D who were prescribed rivaroxaban or warfarin and were stratified by age under versus over 80 years.

**Methods**

The rivaroxaban in diabetes and NVAF study (RIVA-DM, Trial Registration: NCT04509193) was a retrospective cohort study that utilized the US Optum® De-Identified EHR data from November 1, 2010, through December 31, 2019. The US Food and Drug Administration approval date of rivaroxaban for NVAF was in November 2011; therefore, utilization back to November 2010 was needed to have a 12-month pre-index information for all patients. The EHR data set utilized included longitudinal patient-level medical record data for more than 90 million patients seen at over 700 hospitals and 7000 clinics across the United States.\(^11\) It contains data on insured and uninsured patients of all ages, which provide a representative sample of US patients. Records of prescriptions and over-the-counter medications (as prescribed or self-reported by patients), laboratory results, vital signs, anthropometrics, clinical diagnostic codes (International Classification of Diseases, Ninth Revision [ICD-9] and Tenth Revision [ICD-10]), and procedural codes (ICD-9, ICD-10, CPT-4, Healthcare Common Procedure Coding System, Revenue codes) are contained in the data set. The use of Optum® De-Identified EHR data has been determined by the New England Institutional Review Board to not constitute research involving human subjects and was therefore exempt from institutional review board oversight.

Patients were included if they were aged ≥18 years, diagnosed with NVAF and T2D, were OAC naive, newly initiated on rivaroxaban or warfarin after November 1, 2011 (defined as the index date), were active in the data set for at least 12 months prior to the index data, and had documented care in the EHR from at least one provider in the 12 months prior to the index date. Patients were excluded if there was presence of valvular heart disease, any prior OAC use, received rivaroxaban dose other than 15 mg or 20 mg once daily, had venous thromboembolism as an alternative indication for OAC use, underwent recent orthopedic surgery, or were pregnant. Both the specificity and sensitivity for billing codes to identify NVAF were high (≥98% and ≥80%, respectively).\(^12\) The specificity for billing codes to identify T2D was high (≥94%), but the sensitivity was low (≤59%).\(^13\) To address the lower sensitivity of T2D codes, we also included patients in this study if they had both hemoglobin A1c ≥6.5% and were receiving a noninsulin antihyperglycemic medication at baseline.

To adjust for potential confounding between the rivaroxaban and warfarin cohorts, propensity scores were calculated using a multivariable logistic regression model.\(^14\) The propensity score model consisted of commonly used variables and risk factors for differential OAC exposure identified at baseline, including demographics, comorbidities, laboratory values, vital signs, and outpatient medication use. The complete list of covariates used in the propensity score can be seen in Table 1. Comorbid disease presence was determined via billing codes and/or supporting laboratory and clinical data. The absence of data suggesting a comorbidity exists was assumed to mean the absence of the disease. When dependence on billing codes was required to identify a disease, we utilized validated coding algorithms (ie, Centers for Medicare and Medicaid Services Chronic Conditions Data Warehouse, Elixhauser or Charlson Comorbidity Indices) whenever possible.\(^15\)-\(^18\)

Baseline characteristics were analyzed and reported using descriptive statistics. Categorical variables were reported as percentages and continuous variables as means ± standard deviations (SDs). Propensity score-overlap weighted Cox proportional hazards regression models using a robust estimator were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for all outcomes. Patients were censored in the Cox models at the time of outcome occurrence, end-of-EHR activity, or end-of-data availability (December 31, 2019).

The study’s primary outcomes included the incidence rates (%/year) of developing SSE (effectiveness outcome defined by a diagnosis code for stroke in the primary position associated with a hospitalization) and hospitalization due to major or clinically relevant nonmajor bleeding (CRNMB; safety outcome defined per the Cunningham algorithm).\(^22\) Secondary outcomes included the composite of SSE/vascular death, any major bleeding (a Cunningham algorithm bleeding-related billing code in the primary coding position associated with an inpatient or outpatient encounter), and major adverse limb events (MALE; defined as revascularization or major amputation of the lower limbs and identified by ≥1 inpatient or outpatient diagnosis or procedural billing code in the primary or nonprimary position), along with individual components of composite outcomes.

All outcomes were compared between rivaroxaban and warfarin for a population aged <80 years and ≥80 years. Statistical
Table 1. Unweighted and Weighted Baseline Characteristics of Included Patients in Subgroup Analysis.

| Demographics                                      | Unweighted baseline characteristics | Overlap-weighted baseline characteristics |
|----------------------------------------------------|-------------------------------------|-------------------------------------------|
| Age, years (mean ± SD)                             | Age <80 years | Age ≥80 years | Age <80 years | Age ≥80 years |
|                                                   | Rivaroxaban, % | Warfarin, %   | Rivaroxaban, % | Warfarin, %   |
|                                                   | N = 25,472     | N = 58,636    | N = 25,472     | N = 58,636    |
|                                                    | N = 6606       | N = 25,335    |
| Demographics                                      |                          |               |
| Age, years (mean ± SD)<sup>a</sup>                | 66±9                | 68±8          | 67±9                | 67±8          | 83±2                | 83±2          |
| Age 65-74 years                                    | 43.1               | 45.1          | 44.5               | 44.5          | 44.5               | 44.5          |
| Age ≥75 years                                      | 19.9               | 25.7          | 22.3               | 22.3          | 22.3               | 22.3          |
| Female                                             | 37.0               | 37.3          | 37.3               | 37.3          | 50.5               | 50.5          |
| White race, self-reported                          | 84.8               | 85.0          | 85.5               | 85.5          | 89.3               | 89.3          |
| Hospital frailty score, intermediate risk          | 36.9               | 39.1          | 38.0               | 38.0          | 38.7               | 38.7          |
| Hospital frailty score, high risk                  | 13.6               | 22.5          | 15.9               | 15.9          | 25.6               | 25.6          |
| Hospitalizations in prior 12 months (mean ± SD)    | 0.98±1.90         | 1.29±2.10     | 1.07±1.96         | 1.07±1.89     | 1.07±1.96         | 1.07±1.89     |
| Medical history                                    | 25.472            | 58,636        |
| Ablation                                           | 2.5                | 3.0           | 2.6                | 2.6           | 2.6                | 2.6           |
| Active cancer                                      | 4.8                | 5.1           | 5.0                | 5.0           | 5.0                | 5.0           |
| Acute coronary syndrome                            | 10.6               | 14.2          | 11.6               | 11.6          | 9.9                | 9.9           |
| Anxiety                                            | 16.9               | 15.7          | 15.9               | 15.9          | 11.3               | 11.3          |
| Any bleeding in prior 90 days                      | 6.2                | 12.6          | 11.4               | 11.4          | 8.0                | 8.0           |
| Asthma                                             | 2.8                | 4.9           | 3.3                | 3.3           | 4.0                | 4.0           |
| Hemoglobin A1c <7%                                  | 49.9               | 52.4          | 50.6               | 50.6          | 50.6               | 50.6          |
| Hemoglobin A1c 7-8%                                 | 23.4               | 22.6          | 23.3               | 23.3          | 23.3               | 23.3          |
| Hemoglobin A1c >8%                                 | 26.7               | 25.0          | 26.1               | 26.1          | 17.5               | 17.5          |
| BMI 30-39.9 kg/m<sup>2</sup>                       | 47.4               | 44.9          | 46.4               | 46.4          | 35.3               | 35.3          |
| BMI ≥40 kg/m<sup>2</sup> or body weight >120 kg     | 31.6               | 29.5          | 31.1               | 31.1          | 6.3                | 6.3           |
| Cardioversion                                      | 8.1                | 9.1           | 8.2                | 8.2           | 5.4                | 5.4           |
| Carotid endarterectomy and/or stent                | 0.7                | 1.0           | 0.8                | 0.8           | 1.1                | 1.1           |
| Chronic obstructive pulmonary disease              | 24.3               | 28.5          | 25.9               | 25.9          | 23.5               | 23.5          |
| Coagulopathy                                       | 5.6                | 10.8          | 6.8                | 6.8           | 7.1                | 7.1           |
| Crohn's disease or ulcerative colitis              | 0.8                | 0.8           | 0.8                | 0.8           | 0.7                | 0.7           |
| Chronic venous insufficiency                       | 4.8                | 6.6           | 5.2                | 5.2           | 5.3                | 5.3           |
| Dementia                                           | 3.0                | 4.4           | 3.5                | 3.5           | 12.6               | 12.6          |
| Depression                                         | 17.9               | 19.7          | 18.5               | 18.5          | 14.1               | 14.1          |
| Diverticular disease                               | 6.2                | 6.9           | 6.4                | 6.4           | 7.7                | 7.7           |
| eGFR 30-50 mL/min                                  | 7.9                | 11.9          | 9.4                | 9.4           | 17.0               | 17.0          |
| eGFR <30 mL/min                                    | 3.0                | 14.2          | 4.2                | 4.2           | 5.3                | 5.3           |
| Kidney transplant or dialysis                      | 0.8                | 0.8           | 1.3                | 1.3           | 0.8                | 0.8           |
| Excessive alcohol consumption                      | 0.9                | 1.1           | 0.9                | 0.9           | 0.2                | 0.2           |
| Gastroesophageal reflux disease                    | 25.1               | 26.3          | 25.5               | 25.5          | 25.8               | 25.8          |
| Heart failure                                      | 32.2               | 44.9          | 36.2               | 36.2          | 41.0               | 41.0          |
| H. pylori infection                                | 0.3                | 0.3           | 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          | 43.8               | 43.8          | 52.5               | 52.5          |

(continued)
|                          | Overlap-weighted baseline characteristics | Unweighted baseline characteristics |
|--------------------------|------------------------------------------|------------------------------------|
|                          | Age <80 years | Age ≥80 years | N = 56,636 | N = 33,717 |
| Rivaroxaban, %          | N = 25,472   | N = 25,472   | 25,472     | 25,472    |
| Warfarin, %             | N = 58,636   | N = 58,636   | 58,636     | 58,636    |
| Hypercoagulable state   | 0.5          | 0.9          | 0.6        | 0.6       |
| Hyperlipidemia          | 82.8         | 81.5         | 82.4       | 82.4      |
| Hypertension            | 90.9         | 90.1         | 90.7       | 90.3      |
| SBP ≥160 mm Hg          | 3.7          | 3.4          | 3.4        | 3.4       |
| DBP ≥100 mm Hg          | 5.5          | 3.5          | 4.5        | 4.5       |
| Stroke                  | 6.9          | 9.6          | 7.9        | 7.9       |
| Liver dysfunction       | 6.0          | 8.4          | 7.9        | 7.9       |
| Major bleed             | 0.1          | 0.1          | 0.1        | 0.1       |
| Major adverse limb events | 0.1        | 0.1          | 0.1        | 0.1       |
| Major surgery in prior 90 days | 0.1   | 0.1          | 0.1        | 0.1       |
| Osteoarthritis or rheumatoid arthritis | 0.1 | 0.1          | 0.1        | 0.1       |
| Sleep apnea             | 10.8         | 15.2         | 12.1       | 12.1      |
| Major surgery in prior 90 days | 0.1   | 0.1          | 0.1        | 0.1       |
| Osteoarthritis or rheumatoid arthritis | 0.1 | 0.1          | 0.1        | 0.1       |
| Vascular disease (prior MI, PAD, or aortic plaque) | 0.1 | 0.1          | 0.1        | 0.1       |
| Body weight <60 kg      | 2.1          | 2.9          | 2.3        | 2.3       |
| Anti-hyperglycemic medications | 0.1          | 0.1          | 0.1        | 0.1       |
| Dipeptidyl peptidase-4 inhibitor | 11.6        | 9.5          | 9.5        | 9.5       |
| GLP-1 analog            | 5.8          | 3.1          | 3.1        | 3.1       |
| Insulin                 | 30.6         | 40.0         | 33.0       | 33.0      |
| Metformin               | 55.0         | 42.5         | 51.6       | 51.6      |
| Sodium-glucose cotransporter-1 inhibitor | 4.1          | 1.4          | 2.6        | 2.6       |
| Thiazolidinediones      | 4.8          | 3.9          | 4.4        | 4.4       |
| Other medications       | 11.6         | 9.5          | 9.5        | 9.5       |
| Amiodarone              | 12.1         | 17.4         | 13.9       | 13.9      |
| ACE inhibitor or ARB    | 7.1          | 7.4          | 7.1        | 7.4       |
| Alpha blocker           | 1.6          | 1.5          | 1.6        | 1.5       |
| Aspirin                 | 25.5         | 39.7         | 24.8       | 24.8      |
| Barbiturate             | 9.3          | 7.3          | 9.3        | 7.3       |
| Beta-blocker            | 5.2          | 7.7          | 4.8        | 4.8       |
| Digoxin                 | 9.3          | 7.3          | 9.3        | 7.3       |
| Diuretics               | 9.3          | 7.3          | 9.3        | 7.3       |
Table I. (continued)

| Unweighted baseline characteristics | Age <80 years | Age ≥80 years | Overlap-weighted baseline characteristics | Age <80 years | Age ≥80 years |
|------------------------------------|--------------|--------------|------------------------------------------|--------------|--------------|
| Rivaroxaban, %                     | N = 25,472   | N = 58,636   | Rivaroxaban, %                            | N = 25,472   | N = 58,636   |
| Warfarin, %                        | N = 58,636   | N = 25,472   | Warfarin, %                               | N = 58,636   | N = 25,472   |
| Dronedarone                        |              |              | Rivaroxaban, %                            | N = 6606     | N = 25,335   |
|                                    |              |              | Warfarin, %                               |              |              |
| Estrogen                           | 1.6          | 1.3          | 1.5                                      | 1.5          | 1.5          |
| Histamine-2 receptor antagonist    | 9.2          | 11.5         | 9.9                                      | 9.9          | 9.7          |
| Levothyroxine                      | 14.8         | 16.8         | 15.4                                     | 15.4         | 23.6         |
| Loop diuretic                      | 36.5         | 51.1         | 41.8                                     | 41.8         | 47.0         |
| Nonsteroidal anti-inflammatory drug| 24.7         | 18.2         | 22.3                                     | 22.3         | 17.0         |
| Other anti-arrhythmic agent        | 9.6          | 6.6          | 8.7                                      | 8.7          | 5.4          |
| Other antidepressant               | 10.1         | 11.4         | 10.5                                     | 10.5         | 9.9          |
| Other antiplatelet agent           | 1.1          | 1.2          | 1.1                                      | 1.1          | 1.8          |
| Other cholesterol medication       | 14.1         | 14.7         | 14.2                                     | 14.2         | 11.1         |
| P2Y12 inhibitor                    | 7.0          | 7.5          | 7.1                                      | 7.1          | 6.3          |
| Proton pump inhibitor              | 35.1         | 38.6         | 35.9                                     | 35.9         | 37.5         |
| SSRI or SNRI                       | 23.0         | 24.3         | 23.3                                     | 23.3         | 18.6         |
| Statin                             | 70.1         | 70.7         | 70.3                                     | 70.3         | 69.1         |
| Thiazide diuretic                  | 31.1         | 27.1         | 29.8                                     | 29.8         | 27.2         |
| Verapamil                          | 1.8          | 1.8          | 1.9                                      | 1.9          | 1.8          |
| Time in therapeutic INR range (mean ± SD) |              | 43.3 ± 27.8  | 46.2 ± 28.2                               | 46.2 ± 28.2  | 47.6 ± 27.7  |
| CHA2DS2-VASc score (mean ± SD)     | 3.6 ± 1.2    | 4.0 ± 1.3    | 3.8 ± 1.3                                | 3.8 ± 1.3    | 4.4 ± 1.2    |
| CHADS2 score (mean ± SD)           | 2.5 ± 0.8    | 2.7 ± 0.8    | 2.6 ± 0.8                                | 2.6 ± 0.8    | 3.4 ± 0.7    |
| Modified HAS-BLED score (mean ± SD)| 1.3 ± 0.8    | 1.5 ± 0.9    | 1.4 ± 0.8                                 | 1.4 ± 0.8    | 1.7 ± 0.7    |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, Age 65–74, Sex category (female); CHADS2, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischaemic attack (2 points), DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide; H. pylori, Helicobacter pylori; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; INR, international normalized ratio; MI, myocardial infarction; 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.

*Covariate not included in the propensity score model.*
comparison of age population results was made using the Benjamini and Yekutieli adjustment method for multiple hypothesis testing, with a \( P < .05 \) considered statistically significant in all cases.\(^{23} \) Statistical analysis and database management was done using IBM SPSS version 27.0 (IBM Corp., Armonk, NY) and R Studio version 4.0.2.

## Results

We identified 32,078 rivaroxaban patients (25,472 aged <80, 6606 aged ≥80) and 83,971 warfarin patients (58,636 aged <80, 25,335 aged ≥80) with NVAF and T2D. Baseline characteristics prior to propensity score-overlap weighting are depicted in Table 1. After propensity score-overlap weighting, rivaroxaban and warfarin cohorts had identical (standardized difference = 0 for all) comorbidity incidences and mean laboratory and clinical parameters as intended by methodology. In the age <80 population, the mean age was 67 ± 9, CHA2DS2-VASc (Congestive heart failure, Hypertension, Age ≥75 years [2 points], Diabetes mellitus, Stroke or transient ischaemic attack [2 points], Vascular disease, Age 65-74, Sex category [female]) was 3.8 ± 1.3 and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly) was 1.4 ± 0.8. In the age ≥80 cohort, the mean age was 83 ± 2, CHA2DS2-VASc was 4.41 ± 1.2, and HAS-BLED was 1.7 ± 0.7. In both age cohorts, approximately 38% of patients (31,961 patients aged <80 years and 12,361 patients aged ≥80 years) had an intermediate hospital frailty score, while 8177 (25.6%) of patients aged ≥80 years and 13,373 (15.9%) aged >80 years were determined to be highly frail (20,538 (64.3%) of patients aged ≥80 years had intermediate to high frailty scores). The mean follow-up time for rivaroxaban and warfarin patients was 2.9 ± 1.9 and 2.9 ± 2.0 years, respectively.

Propensity score-overlap weighted analyses found no significant interaction for the relative effectiveness or safety of rivaroxaban versus warfarin across the older or younger age groups for the outcomes of SSE (HR: 1.05, 95% CI: 0.92-1.19 vs HR: 0.95*, 95% CI: 0.87-1.04) and hospitalization for major or CRNMB (HR: 1.06, 95% CI: 0.96-1.18 vs HR: 0.90; 95% CI: 0.84-0.96) (Table 2). No significant interaction for rivaroxaban versus warfarin across the older or younger age groups for the composite outcome of SSE or vascular death or MALE were observed (Table 3). Vascular death, MALE, as well as major bleeding and intracranial hemorrhage (ICH) were observed significantly less frequently with rivaroxaban compared with warfarin regardless of patient age.

## Discussion

In this study of more than 116,000 patients with NVAF and comorbid T2D, patients aged ≥80 years or older and aged <80 years received a consistent incidence rates of SSE and hospitalization for major or CRNMB when receiving rivaroxaban compared with warfarin. Moreover, rivaroxaban use was associated with significantly lower rates of vascular death, MALE, any major bleeding, and ICH versus warfarin, regardless of patient age. These data support the use of rivaroxaban as an efficacious and safe alternative to warfarin in older patients with NVAF with concomitant T2D. Rivaroxaban has the advantages of easier dosing, no need for drug monitoring, and fewer drug-drug or drug-food interactions compared to warfarin.

Our study findings are very much in-line with current AF treatment guidelines.\(^{24} \) The European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) collaborative guidelines on the management of diabetest, pre-diabetes, and cardiovascular diseases recommend DOACs (such as rivaroxaban) over a VKA in patients with diabetes aged >65 years with NVAF and a CHA2DS2-VASc score ≥ 2, (class 1A recommendation).\(^{24} \) Given the accumulating data on the safety of DOACs in patients of advanced age with T2D, the practice of preferentially using DOACs over a VKA in a patient with diabetes would seem warranted.

The present study reinforces findings from the phase 3 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) and the bleeding risk in elderly Subjects Aged more than

### Table 2. Primary Outcomes.

| Outcome                  | Age ≥80 Years | Age <80 Years |
|--------------------------|---------------|---------------|
|                          | Rivaroxaban N = 6606 | Warfarin N = 25,335 | HR (95% CI) | Rivaroxaban N = 25,472 | Warfarin N = 58,636 | HR (95% CI) |
|                          | Incidence rate (%/year) | Incidence rate (%/year) |             | Incidence rate (%/year) | Incidence rate (%/year) |             |
| 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 CRNMB | 3.29          | 3.09          | 1.06        | (0.96-1.18)            | 2.00          | 2.22          | 0.90*        | (0.84-0.96)            |

Abbreviations: CI, confidence interval; CRNMB, clinically relevant nonmajor bleeding; HR, hazard ratio; SSE, stroke or systemic embolism.

*P-interaction ≥ 0.23.
Our study has limitations worthy of discussion. First, the presence or absence of diabetes, 40% of patients with diabetes at the time of treatment initiation. The substudy demonstrated the relative effect of rivaroxaban and warfarin on SSE, major bleeding, major or CRNMB, and ICH occurred less frequently in rivaroxaban-treated patients than in VKA-treated patients in a propensity score–matched analysis (HR: 0.26, 95% CI: 0.63-0.90). Although propensity score–based methods may serve to balance comparison groups, residual confounding due to variables not included or unavailable for inclusion (ie, time since diabetes diagnosis) into the propensity score model cannot be ruled out. Second, the cause of death was also not available in the data set; therefore, we had to utilize an algorithm consisting of hospitalization due to vascular cause within 365 days of death to identify “vascular” mortality. This method has been shown in previous observational studies to provide vascular mortality rates similar to those reported in “like” randomized controlled trials. Third, the EHR data set utilized for this study included only US patients. Our results may be less generalizable to populations outside the United States. Finally, the EHR data set used for this study did not capture prescription medication claims but rather information on medications prescribed or self-reported. The lack of formal prescription claims data (generated when a patient picks up their medication at a pharmacy) makes ascertainment of OAC exposure (persistence and adherence) difficult. Consequently, we did not perform an on-treatment analysis.

## Conclusion

The effectiveness and safety of rivaroxaban relative to warfarin remained consistent across older and younger patient subgroups, supporting rivaroxaban as an alternative for older patients with NVAF with concomitant T2D. Vascular death, may impact its internal validity. We attempted to mitigate misclassification bias by using validated coding schema and leveraging objective laboratory and clinical observation data available in an EHR but not claims data sets. We used propensity score–overlap weighting to balance patients on numerous important demographics, clinical and medication covariates to reduce the risk of confounding bias. Although propensity score–based methods may serve to balance comparison groups, residual confounding due to variables not included or unavailable for inclusion (ie, time since diabetes diagnosis) into the propensity score model cannot be ruled out. Second, the cause of death was also not available in the data set; therefore, we had to utilize an algorithm consisting of hospitalization due to vascular cause within 365 days of death to identify “vascular” mortality. This method has been shown in previous observational studies to provide vascular mortality rates similar to those reported in “like” randomized controlled trials. Third, the EHR data set utilized for this study included only US patients. Our results may be less generalizable to populations outside the United States. Finally, the EHR data set used for this study did not capture prescription medication claims but rather information on medications prescribed or self-reported. The lack of formal prescription claims data (generated when a patient picks up their medication at a pharmacy) makes ascertainment of OAC exposure (persistence and adherence) difficult. Consequently, we did not perform an on-treatment analysis.
MALE, major bleeding, and ICH were observed less frequently with rivaroxaban versus warfarin regardless of patient age.

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Ethics Approval
The use of the Optum EHR data set was reviewed by the New England Institutional Review Board and was determined to be exempt from oversight, as this research project did not involve human subject research and the investigators were supplied only de-identified and HIPAA-compliant data.

Declaration of Conflicting Interests
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References
1. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019;74(1):104-132.
2. Xiong Z, Liu T, Tse G, et al. A machine learning aided systematic review and meta-analysis of the relative risk of atrial fibrillation in patients with diabetes mellitus. Front Physiol. 2018;9:835.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The framingham study. Stroke. 1991;22(8):983-988.
4. Oudotuyo A, Wong CX, Hsiao AJ, et al. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: Systematic review and meta-analysis. Br Med J. 2016;354:i4482.
5. Bansilal S, Bloomgarden Z, Halperin JL, et al. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: 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). Am Heart J. 2015;170(4):675-682.
6. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-891.
7. Baker WL, Beyer-Westendorf J, Bunz TJ, et al. Effectiveness and safety of rivaroxaban and warfarin for prevention of major adverse cardiovascular or limb events in patients with non-valvular atrial fibrillation and type 2 diabetes. Diabetes Obes Metab. 2019;21(9):2107-2114.
8. Coleman CI, Costa OS, Brescia CW, et al. Thromboembolism, bleeding and vascular death in nonvalvular atrial fibrillation patients with type 2 diabetes receiving rivaroxaban or warfarin. Cardiovasc Diabetol. 2021;20(1):52.
9. Toader D. Treating atrial fibrillation in very old patients with new oral anticoagulation drugs: arguments pro and contra. 2019. https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-17/treating-atrial-fibrillation-in-very-old-patients-with-new-oral-anticoagulation. Accessed August 10, 2022.
10. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: Systematic review and meta-analysis. Circulation. 2015;132(3):10.
11. Optum. Optum EHR offering. 2018. https://www.optum.com/campaign/is/data-new-era-of-visibility/download.html. Accessed August 11, 2022.
12. Yao R, Andrade J, Deyell MW, et al. Sensitivity, specificity, positive and negative predictive values of identifying atrial fibrillation using administration data: A systematic review and meta-analysis. J Clin Epidemiol. 2019;11:14.
13. Khokhar B, Jette N, Metcalfe A, et al. Systematic review of validated case definitions for diabetes in ICD-9-coded and ICD-10-coded data in adult populations. BMJ Open. 2016;6(8):e009952.
14. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46(3):399-424.
15. Services CFmM. Chronic conditions data warehouse. https://www2.ccwdata.org/web/guest/home/. Accessed August 11, 2022.
16. Elkhoury A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998;36(1):8-27.
17. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):16.
18. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a hospital frailty risk score focusing on older people in acute care settings using electronic hospital records: An observational study. Lancet. 2018;391:7.
19. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. Br Med J. 2009;338:b2393.
20. Thomas LE, Li F, Pencina MJ. Overlap weighting: A propensity score method that mimics attributes of a randomized clinical trial. JAMA. 2020;323(23):2417-2418.
21. Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. Am J Epidemiol. 2019;188(1):250-257.
22. Cunningham A, Stein CM, Chung CP, et al. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf*. 2011;20(6):560-566.

23. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. *Ann Statist*. 2001;29(4):23.

24. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41(2):255-323.

25. Halperin JL, Hankey GJ, Wojdyla DM, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonist for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation*. 2014;130(2):138-146.

26. Hanon O, Vidal JS, Pisica-Donose G, et al. Bleeding risk with rivaroxaban compared with vitamin K antagonists in patients aged 80 years or older with atrial fibrillation. *Heart*. 2021;107(17):1376-1382.

27. Gandhi S, Salmon JW, Kong SX, Zhao SZ. Administrative databases and outcomes assessment: An overview of issues and potential utility. *J Manag Care Pharm*. 1999;5(3):215-222.