Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation

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)

Sameer Bansilal, MD,[a] Zachary Bloomgarden, MD,[a] Jonathan L. Halperin, MD,[a] Anne S. Hellkamp, MS,[b] Yuliya Lokhnygina, PhD,[b] Manesh R. Patel, MD,[b] Richard C. Becker, MD,[c] Günter Breithardt, MD,[d] Werner Hacke, MD,[e] Graeme J. Hankey, MD,[f] Christopher C. Nessel, MD,[g] Daniel E. Singer, MD,[h] Scott D. Berkowitz, MD,[i] Jonathan P. Piccini, MD,[b] Kenneth W. Mahaffey, MD,[j] and Keith A. A. Fox, MB, ChB[k], on behalf of the ROCKET AF Steering Committee and Investigators ***New York, NY; Durham, NC; Cincinnati, OH; Münster, Heidelberg, Germany; Crawley, Australia; Raritan, Whippany, NJ; Boston, MA; Stanford, CA; and Edinburgh, United Kingdom***

Background The prevalence of both atrial fibrillation (AF) and diabetes mellitus (DM) are rising, and these conditions often occur together. Also, DM is an independent risk factor for stroke in patients with AF. We aimed to examine the safety and efficacy of rivaroxaban vs warfarin in patients with nonvalvular AF and DM in a prespecified secondary analysis of the ROCKET AF trial.

Methods We stratified the ROCKET AF population by DM status, assessed associations with risk of outcomes by DM status and randomized treatment using Cox proportional hazards models, and tested for interactions between randomized treatments. For efficacy, primary outcomes were stroke (ischemic or hemorrhagic) or non–central nervous system embolism. For safety, the primary outcome was major or nonmajor clinically relevant bleeding.

Results The 5,695 patients with DM (40%) in ROCKET AF were younger, were more obese, and had more persistent AF, but fewer had previous stroke (the $CHADS_2$ score includes DM and stroke). The relative efficacy of rivaroxaban and warfarin for prevention of stroke and systemic embolism was similar in patients with (1.74 vs 2.14/100 patient-years, hazard ratio [HR] 0.82) and without (2.12 vs 2.32/100 patient-years, HR 0.92) DM (interaction $P = .53$). The safety of rivaroxaban vs warfarin regarding major bleeding (HRs 1.00 and 1.12 for patients with and without DM, respectively; interaction $P = .43$), major or

From the [a]Icahn School of Medicine at Mount Sinai, New York, NY, [b]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, [c]University of Cincinnati College of Medicine, Cincinnati, OH, [d]Department of Cardiovascular Medicine, Division of Electrophysiology, University Hospital Münster, Münster, Germany, [e]Ruprecht-Karls University, Heidelberg, Germany, [f]School of Medicine and Pharmacology, University of Western Australia, Crawley, Australia, [g]Janssen Research & Development, Raritan, NJ, [h]Massachusetts General Hospital and Harvard Medical School, Boston, MA, [i]Bayer HealthCare Pharmaceuticals, Whippany, NJ, [j]Department of Medicine, Stanford University, Stanford, CA, and [k]University of Edinburgh and Royal Infirmary of Edinburgh, Edinburgh, United Kingdom.

William G. Stevenson, MD served as guest editor for this article.

RCT No. NCT00403767

Previous presentation: These data were previously presented as an abstract poster at the American Heart Association's annual conference in 2012.

Potential conflicts of interest: Bansilal: consulting fees from AstraZeneca; institutional research grants from AstraZeneca. Bloomgarden: consulting fees from Astra Zeneca, Janssen, NovoNordisk, Merck, Amgen, and Novartis; speaker's bureau for Astra Zeneca, Janssen, NovoNordisk, and Merck; and ownership interest in Baxter International, CVS Caremark, Roche Holdings, St Jude Medical, and Novartis. Halperin: consulting fees from AstraZeneca, Bayer AG HealthCare, Biotronik, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Janssen, Johnson & Johnson, Medtronic, Ortho-McNeil-Janssen Pharmaceuticals, Pfizer, and Sanofi Aventis. Hellkamp and Lokhnygina: nothing to report. Patel: consultant/advisory board for Bayer, Janssen, AstraZeneca, and Genzyme; institutional research grant for Johnson & Johnson and AstraZeneca. Becker: consulting fees/honoraria from Portola, Daiichi-Sankyo, Bristol-Myers Squibb, and Boehringer Ingelheim; research grants from AstraZeneca and Johnson & Johnson. Breithardt: honoraria from Bayer HealthCare and BMS/Pfizer; consultant/advisory board for Bayer HealthCare, BMS/Pfizer, and Sanofi Aventis. Hacke: consulting fees from Boehringer Ingelheim, Bayer HealthCare, and Daiichi Sankyo; research grants from Boehringer Ingelheim. Hankey: honoraria/consulting fees from Bayer and Medscape (theheart.org). Nessel: employee of Janssen Research & Development. Singer: consulting/advisory board for Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, Merck, and Pfizer; research grants from Bristol-Myers Squibb and Johnson & Johnson. Berkowitz: employee of Bayer HealthCare Pharmaceuticals. Piccini: research grants from ARCA Biopharma, Boston Scientific, GE Healthcare, Janssen Scientific, Johnson & Johnson, and ResMed; consultant/advisory boards for ChanRx, Johnson & Johnson, and Spectranetics. Mahaffey: full disclosures prior to August 1, 2013, available at www.dcri.org; disclosures after August 1, 2013, available at http://med.stanford.edu/profiles/kenneth_mahaffey. Fox: consulting fees/honoraria from Boehringer Ingelheim, Sanofi-Aventis, Astra Zeneca, Johnson & Johnson/Bayer, and Janssen; research grants from Eli Lilly.

Submitted June 9, 2015; accepted July 13, 2015.

Reprint requests: Jonathan L. Halperin, MD, The Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, Mount Sinai Medical Center, Box 1030, Fifth Avenue at 100th Street, New York, NY 10029-6574.

E-mail: jonathan.halperin@mssm.edu

0002-8703

http://dx.doi.org/10.1016/j.ahj.2015.07.006

nonmajor clinically relevant bleeding (HRs 0.98 and 1.09; interaction $P = .17$), and intracerebral hemorrhage (HRs 0.62 and 0.72; interaction $P = .67$) was independent of DM status. Adjusted exploratory analyses suggested 1.3-, 1.5-, and 1.9-fold higher 2-year rates of stroke, vascular mortality, and myocardial infarction in DM patients.

Conclusions and Relevance The relative efficacy and safety of rivaroxaban vs warfarin was similar in patients with and without DM, supporting use of rivaroxaban as an alternative to warfarin in diabetic patients with AF. (Am Heart J 2015;170:675-682.e8.)

The prevalence of both atrial fibrillation (AF) and diabetes mellitus (DM) are rising. The 2 conditions commonly occur together, and DM is an independent risk factor for stroke in patients with AF (relative risk 1.7).[1] Diabetic patients with a stroke have higher mortality rates than nondiabetic patients.[2] Intensive activation of the coagulation system, decreased fibrinolytic activity, and alterations in platelet and endothelial function, accompanied by increased levels of tissue plasminogen activator antigen and factor VIII activity, may serve as links between diabetes and AF-related stroke.[3] Diabetic patients demonstrate a larger left atrial diameter and left atrial appendage size with higher prevalence of left atrial or appendage thrombi than do nondiabetic patients.[4] Traditionally, diabetic patients with AF have been treated with vitamin K antagonists with good efficacy. Rivaroxaban, the first oral factor Xa inhibitor approved as an alternative to warfarin, was noninferior to adjusted-dose warfarin (target international normalized ratio [INR] 2.0-3.0) in ROCKET AF[5,6] among patients with nonvalvular AF at moderate-to-high risk of stroke and caused less intracranial and fatal bleeding. The efficacy and safety of rivaroxaban in patients with AF and DM has not been specifically described. We compared rates of stroke and systemic embolism (primary events) as well as safety end points (bleeding on treatment) in those randomized to rivaroxaban or warfarin to ascertain the influence of DM on these outcomes.

Materials and methods

The design and results of the ROCKET AF trial (ClinicalTrials.gov NCT00403767) have been described. Briefly, this was an international, multicenter, double-blind, double-dummy, randomized noninferiority trial that compared rivaroxaban—20 mg once daily (or 15 mg daily in patients with creatinine clearance 30-49 mL/min)—with adjusted-dose warfarin (target INR 2.5, range 2.0-3.0) in patients with nonvalvular AF. Patients with electrocardiographic documentation of AF, at moderate-to-high risk of stroke, were eligible for enrollment. *Stroke risk* was defined by $CHADS_2$ risk score ≥ 2: (clinical heart failure, hypertension, age ≥ 75 years, DM [1 point each], and prior stroke or transient ischemic attack [TIA; 2 points]). Enrollment of patients with only 2 risk factors was capped at 10% for each clinical site. Key exclusion criteria included prosthetic heart valves, hemodynamically significant mitral stenosis, creatinine clearance <30 mL/min, recent embolic event, and an elevated risk of bleeding. The institutional review boards at each participating site approved the protocol, and all patients provided written consent. The ROCKET AF trial was sponsored by Johnson & Johnson Pharmaceutical Research & Development (Raritan, NJ) and Bayer HealthCare AG (Leverkusen, Germany).

Definition of diabetes

The diagnosis of DM was based on either prior documentation of DM or treatment with glucose-lowering medications. Measures of glycemic control, including glycated hemoglobin and blood glucose, were not systematically recorded.

Outcomes definitions

The primary efficacy outcome for the ROCKET AF trial and this prespecified analysis was stroke (ischemic or hemorrhagic) or non–central nervous system embolism. Detection of primary end points was enhanced by a standardized stroke symptom questionnaire, computed tomography or magnetic resonance brain imaging, and additional evaluation by local study-affiliated neurologists or stroke specialists blinded to treatment. The secondary efficacy outcomes included all-cause death, myocardial infarction (MI), and the composite (and individual components) of stroke, systemic embolism, or vascular death. The intention-to-treat population was used for all efficacy analyses. Ninety-three patients from one site were excluded because of violations of Good Clinical Practice guidelines. Efficacy end points were measured until the time of site notification of study termination.

The primary safety end point was major or nonmajor clinically relevant (NMCR) bleeding. Secondary safety end points were intracranial hemorrhage (ICH) and hemorrhagic stroke. Safety analyses were based on the safety population of randomized patients who received ≥ 1 dose of study drug. A per-protocol sensitivity analysis used the subset of patients from the safety population without protocol violations. For safety and per-protocol analyses, end points were measured from the first dose until 2 days after the last dose of study medication. All events were adjudicated by an independent clinical events committee blinded to treatment assignment.

Statistical analysis

Categorical data are summarized as counts and percentages, and differences were tested with the Pearson χ^2 test; continuous variables are summarized as medians with

Table I. Baseline characteristics by treatment assignment

	Diabetic patients (n = 5695)		Nondiabetic patients (n = 8569)	
	Rivaroxaban (n = 2878)	Warfarin (n = 2817)	Rivaroxaban (n = 4253)	Warfarin (n = 4316)
Baseline characteristics				
Age (y), median (25th, 75th)	71 (64, 77)	71 (64, 77)	74 (66, 79)	74 (66, 79)
Female, no. (%)	1128 (39.2)	1114 (39.5)	1702 (40.0)	1716 (39.8)
AF, no. (%)				
Persistent	2358 (81.9)	2326 (82.6)	3428 (80.6)	3436 (79.6)
Paroxysmal	475 (16.5)	447 (15.9)	770 (18.1)	822 (19.0)
Newly diagnosed	45 (1.6)	44 (1.6)	55 (1.3)	58 (1.3)
Type of diabetes control, no. (%)				
Diet	747 (26.0)	707 (25.1)		
Oral medication	1675 (58.2)	1626 (57.7)		
Thiazolidinedione	88 (5.3)	101 (6.2)		
Biguanide	931 (55.6)	933 (57.4)		
Sulfonylurea	902 (53.9)	913 (56.2)		
Other/unspecified	57 (3.4)	60 (3.7)		
Insulin	456 (15.8)	483 (17.2)		
Presenting characteristics				
BMI (kg/m^2), median (25th, 75th)	30.0 (26.6, 34.2)	29.8 (26.4, 34.2)	27.3 (24.4, 30.7)	27.2 (24.4, 30.4)
Systolic BP (mm Hg), median (25th, 75th)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)
Diastolic BP (mm Hg), median (25th, 75th)	80 (70, 85)	80 (70, 85)	80 (70, 85)	80 (72, 86)
CrCl (mL/min), median (25th, 75th)	73 (56, 94)	72 (54, 93)	65 (50, 83)	65 (51, 82)
eGFR (mL/min), no. (%)				
<30	6 (0.2)	5 (0.2)	6 (0.1)	11 (0.3)
30-60	920 (32.0)	956 (34.0)	1813 (42.7)	1808 (41.9)
>60	1950 (67.8)	1853 (65.8)	2428 (57.2)	2494 (57.8)
Other baseline comorbidities				
Prior stroke/TIA, no. (%)	922 (32.0)	884 (31.4)	2832 (66.6)	2830 (65.6)
Hypertension, no. (%)	2738 (95.1)	2695 (95.7)	3698 (87.0)	3779 (87.6)
Congestive HF, no. (%)	1893 (65.8)	1899 (67.4)	2574 (60.5)	2542 (58.9)
COPD, no. (%)	325 (11.3)	337 (12.0)	429 (10.1)	406 (9.4)
$CHADS_2$ score, median (25th, 75th)	3 (3, 4)	3 (3, 4)	3 (3, 4)	3 (3, 4)
$CHADS_2$ score, mean (SD)	3.7 (1.0)	3.7 (1.0)	3.3 (0.9)	3.3 (0.9)
Medications, no. (%)				
Prior VKA	1870 (65.0)	1847 (65.6)	2573 (60.5)	2614 (60.6)
Prior chronic ASA	1114 (38.7)	1116 (39.6)	1612 (37.9)	1643 (38.1)
ACE inhibitor/ARB	2345 (81.5)	2281 (81.0)	2973 (69.9)	2984 (69.1)
β-Blocker	1912 (66.4)	1922 (68.2)	2683 (63.1)	2733 (63.3)
Calcium-channel blocker	917 (31.9)	890 (31.6)	1100 (25.9)	1051 (24.4)
Diuretic	1921 (66.7)	1899 (67.4)	2345 (55.1)	2325 (53.9)

Abbreviations: BMI, Body mass index; BP, blood pressure; CrCl, creatinine clearance; HF, heart failure; VKA, vitamin K antagonist; ASA, aspirin; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

interquartile ranges, and differences were tested with the Wilcoxon rank sum test. Outcomes are presented as events per 100 patient-years. Cox proportional hazards models were used to assess the associations with risk of outcomes for patients with vs without DM and for rivaroxaban vs warfarin within diabetic and nondiabetic subgroups. Models for the latter included a term for the interaction between randomized treatment and the subgroup of interest.

All models included covariates identified as predictive of outcomes by modeling in the full ROCKET AF cohort. For efficacy end points, these included age, sex, body mass index, geographical region, previous stroke or TIA, previous MI, peripheral arterial disease, carotid occlusive disease, hypertension, chronic obstructive pulmonary disease (COPD), paroxysmal AF, left ventricular ejection fraction, heart rate, diastolic blood pressure, estimated glomerular filtration rate (eGFR) at baseline (calculated using the Cockroft-Gault formula), and abstinence from alcohol use. In the safety analysis, the following variables were entered into the model: age, sex, region, previous stroke or TIA, gastrointestinal bleeding, COPD, diastolic blood pressure, eGFR, anemia, platelet count, albumin, prior aspirin use, and prior use of a vitamin K antagonist or thienopyridine. An additional per-protocol sensitivity analysis examined the primary efficacy end point, major or NMCR bleeding, and hemorrhagic stroke in the per-protocol population, with models performed in the same manner. Risk relationships are presented as

Table II. Observed and predicted 2-year event rates (95% CIs)

	Diabetic		Nondiabetic	
	2-y Kaplan-Meier rate	Predicted 2-y rate with covariate values from the nondiabetic group	2-y Kaplan-Meier rate	Predicted 2-y rate with actual covariate values
Efficacy outcomes				
Stroke or SE	3.85 (3.31-4.40)	5.26 (5.21-5.31)	4.40 (3.93-4.86)	4.44 (4.40-4.48)
Ischemic stroke or SE	2.99 (2.51-3.47)	4.01 (3.97-4.05)	3.52 (3.10-3.94)	3.53 (3.50-3.57)
Stroke/SE/vascular death	8.97 (8.16-9.78)	11.52 (11.42-11.63)	8.30 (7.66-8.94)	8.33 (8.25-8.41)
Stroke/SE/vascular death/MI	10.73 (9.85-11.60)	13.26 (13.13-13.38)	9.41 (8.73-10.08)	9.39 (9.31-9.48)
Stroke	3.62 (3.09-4.14)	5.32 (5.27-5.36)	4.08 (3.63-4.53)	4.10 (4.07-4.14)
Ischemic stroke	2.75 (2.29-3.21)	4.07 (4.03-4.10)	3.20 (2.80-3.60)	3.20 (3.17-3.23)
SE	0.28 (0.12-0.43)	0.17 (0.17-0.17)	0.37 (0.23-0.51)	0.39 (0.38-0.40)
Vascular death	6.23 (5.55-6.92)	7.91 (7.80-8.02)	5.12 (4.61-5.63)	5.15 (5.08-5.22)
MI	2.60 (2.16-3.04)	2.92 (2.87-2.96)	1.57 (1.28-1.85)	1.51 (1.49-1.54)
Safety outcomes				
Major or NMCR bleeding	24.74 (23.41-26.08)	25.67 (25.47-25.87)	24.08 (23.01-25.15)	24.16 (23.97-24.35)
Major bleeding	7.22 (6.41-8.04)	7.52 (7.42-7.63)	6.11 (5.51-6.71)	6.35 (6.27-6.44)
Intracranial hemorrhage	1.30 (0.93-1.66)	1.72 (1.69-1.75)	1.10 (0.84-1.36)	1.18 (1.16-1.20)
Hemorrhagic stroke	0.68 (0.42-0.95)	0.91 (0.89-0.94)	0.65 (0.46-0.84)	0.71 (0.69-0.73)

Abbreviation: SE, Systemic embolism.

adjusted hazard ratios (HRs) with 95% CIs derived from the adjusted Cox models.

To address covariate imbalance, we calculated mean predicted event rates at 1 and 2 years to compare rates for nondiabetic patients vs rates expected in diabetic patients with the same prevalence of comorbid conditions as the nondiabetic group. We also performed a propensity score–matched analysis for the primary efficacy and safety outcomes to test the robustness of the multivariable adjusted models (see Supplementary Information for detailed methods).

The time anticoagulation was in the therapeutic range among patients treated with warfarin calculated using the linear interpolation method of Rosendaal et al.[7] Statistical significance was accepted at the 95% confidence level ($P < .05$). All analyses were performed with the SAS version 9.2 statistical software (SAS Institute, Cary, NC).

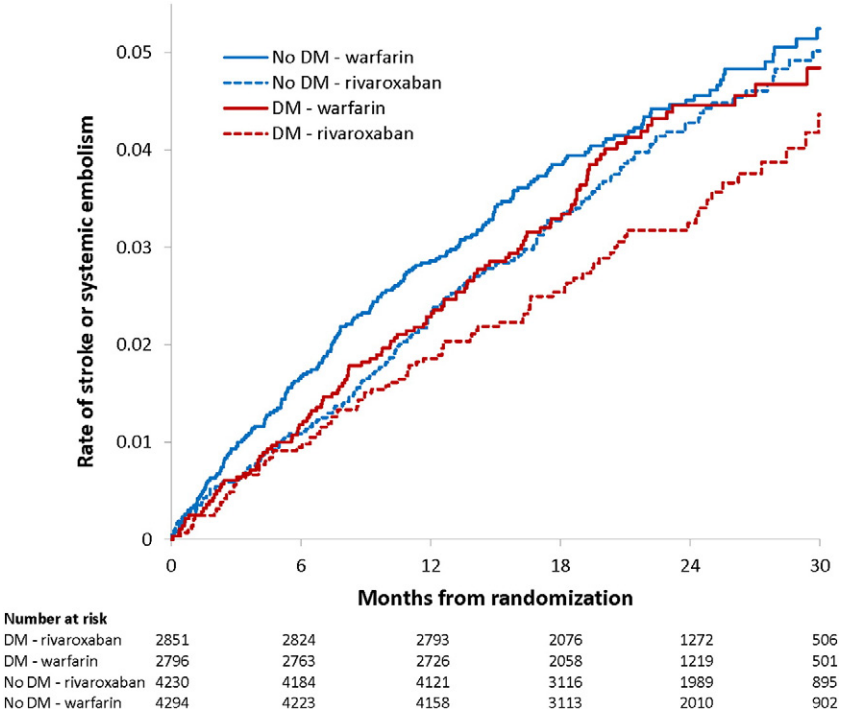
Results

The ROCKET AF trial included 14,264 patients, of whom 5,695 (39.9%) had DM, with a median follow-up of 1.9 years. Because DM was one of the entry criteria associated with risk of stroke in patients with AF, participants with DM were younger, on average, and less than half as often had prior stroke or TIA, but more often had a $CHADS_2$ score of 5 or 6 (Table I and online Appendix Supplementary Table I). In addition, diabetic participants had a higher body mass index and higher frequency of hypertension, heart failure, COPD, and use of angiotensin inhibitor, β-adrenergic antagonist, calcium-channel blocker, and diuretic medications at baseline. Glucose-lowering therapy was not used for 25.5% of diabetic study participants; 16.5% were treated with insulin, with or without concomitant oral agents, and 58% received oral agents alone (5.7% thiazolidinediones, 65.5% biguanides, and 55% sulfonylureas). Guided by renal function, the dose of rivaroxaban assigned to patients with DM was 20 mg once daily in 84% and reduced to 15 once daily in 16%, compared with 76% and 24% in patients without DM.

Outcomes in patients with and without diabetes

Vascular death rates were 3.24 vs 2.63 ($P = .0001$) and MI rates were 1.35 vs 0.75 ($P < .0001$) per 100 patient-years in diabetic vs nondiabetic patients, respectively (online Appendix Supplementary Table II). In evaluating the unadjusted risk for stroke associated with each of the $CHADS_2$ risk factors, DM was not a significant predictor (online Appendix Supplementary Table III). Observed rates of stroke, systemic embolism, and bleeding among diabetic patients were either similar to or lower than among nondiabetic patients (online Appendix Supplementary Table II). We used Cox regression modeling to predict outcomes for diabetic patients with the same prevalence of comorbid conditions as nondiabetic patients at 2 years. By this extrapolation, patients with DM faced a 1.3-fold higher risk of stroke, 1.5-fold higher risk of vascular death, and 1.9-fold higher risk of MI. Rates of major bleeding, hemorrhagic stroke, and ICH were 1.2, 1.3, and 1.5 times greater than those in nondiabetic patients, respectively (Table II).

Figure



Primary events in patients with and without diabetes randomized to warfarin vs rivaroxaban. The efficacy of rivaroxaban compared with warfarin in diabetic participants was similar to that in nondiabetic patients. Diabetic patients appear to have a lower rate of events than do nondiabetic patients due to covariate imbalance. Please see Table II for covariate adjusted rates.

Outcomes by diabetes and treatment assignment

In patients with DM randomized to rivaroxaban vs warfarin, rates of primary events (1.74 vs 2.14 per 100 patient-years) were similar to those in patients without DM (2.12 vs 2.32 per 100 patient-years; interaction $P = .53$) (Figure and Table III). The same was true for rates of ischemic stroke and systemic embolism (1.48 vs 1.55 per 100 patient-years in patients with DM, and 1.71 vs 1.80 per 100 patient-years in those without DM; interaction $P = .91$). Additional efficacy outcomes were independent of DM status (online Appendix Supplementary Figure 1). Results were similar across multiple subgroups (online Appendix Supplementary Table IVA-D).

Rates of major bleeding in patients with DM randomized to rivaroxaban vs warfarin (3.79 vs 3.90 per 100 patient-years) were similar to those in patients without DM (3.47 vs 3.17 per 100 patient-years; interaction $P = .43$). The same was true for rates of NMCR bleeding (14.81 vs 15.44 per 100 patient-years in patients with DM, and 14.99 vs 13.94 per 100 patient-years in those without DM; interaction $P = .17$) and ICH (0.50 vs 0.82 per 100 patient-years in patients with DM, and 0.49 vs 0.69 per 100 patient-years in those without DM; interaction $P = .67$) (Table III and online Appendix Supplementary Figure 2). Additional safety outcomes were similar regardless of DM status (online Appendix Supplementary Figure 2), and results were also similar across multiple subgroups (online Appendix Supplementary Table IVC and D).

When examined in propensity score–matched cohorts, the results were unchanged (online Appendix Supplementary Tables V and VIA-D). Similarly, the efficacy and safety impact of rivaroxaban compared with warfarin was not affected by diet or use of oral hypoglycemic agents or insulin therapy for glycemic control (online Appendix Supplementary Table IVA-D; interaction *P*, not significant).

Discussion

ROCKET AF enrolled a greater proportion of patients with DM (5,695 [39.9%]) than did other completed contemporary trials of novel oral anticoagulants (4,221 [23.3%] in the Randomized Evaluation of Long-term Anticoagulant Therapy [RE-LY] trial with dabigatran; 1,096 [19.2%] in the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes [AVERROES] trial; 4,547 [25%] in the Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE] trial; and 7,624 [36%] in Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–

Table III. Treatment comparisons for efficacy and safety end points in diabetic and nondiabetic patients

	Diabetic patients			Nondiabetic patients			
	Rivaroxaban events/100 pt-yrs (total events)	Warfarin events/100 pt-yrs (total events)	Rivaroxaban vs warfarin HR (95% CI)	Rivaroxaban events/100 pt-yrs (total events)	Warfarin events/100 pt-yrs (total events)	Rivaroxaban vs warfarin HR (95% CI)	*P* value for interaction*
Efficacy outcomes							
Stroke or SE	1.74 (95)	2.14 (114)	0.82 (0.63-1.08)	2.12 (174)	2.32 (192)	0.92 (0.75-1.13)	.53
Ischemic stroke or SE	1.48 (81)	1.55 (83)	0.97 (0.72-1.32)	1.71 (141)	1.80 (150)	0.95 (0.76-1.20)	.91
Stroke/SE/vascular death	4.23 (224)	5.17 (267)	0.84 (0.70-1.00)	4.34 (348)	4.22 (342)	1.03 (0.89-1.19)	.081
Stroke/SE/vascular death/MI	5.15 (270)	6.26 (320)	0.84 (0.72-0.99)	4.88 (389)	4.83 (389)	1.01 (0.88-1.17)	.097
Stroke	1.61 (88)	2.05 (109)	0.80 (0.60-1.06)	2.01 (165)	2.07 (172)	0.97 (0.79-1.21)	.27
Ischemic stroke	1.35 (74)	1.45 (78)	0.94 (0.69-1.30)	1.60 (132)	1.56 (130)	1.03 (0.81-1.31)	.67
SE	0.14 (8)	0.11 (6)	1.37 (0.48-3.96)	0.14 (12)	0.25 (21)	0.58 (0.29-1.19)	.19
Vascular death	2.83 (152)	3.65 (192)	0.80 (0.64-0.99)	2.73 (223)	2.53 (209)	1.08 (0.89-1.30)	.037
MI	1.19 (65)	1.51 (81)	0.82 (0.59-1.14)	0.78 (65)	0.72 (61)	1.09 (0.77-1.54)	.25
Safety outcomes							
Major or NMCR bleeding	14.81 (582)	15.44 (596)	0.98 (0.88-1.10)	14.99 (893)	13.94 (853)	1.09 (0.99-1.20)	.17
Major bleeding	3.79 (165)	3.90 (169)	1.00 (0.81-1.24)	3.47 (230)	3.17 (217)	1.12 (0.93-1.35)	.43
Intracranial hemorrhage	0.50 (22)	0.82 (36)	0.62 (0.36-1.05)	0.49 (33)	0.69 (48)	0.72 (0.46-1.12)	.67
Hemorrhagic stroke	0.23 (10)	0.46 (20)	0.51 (0.24-1.09)	0.28 (19)	0.43 (30)	0.65 (0.37-1.16)	.61
Intraocular/retinal bleeding	0.14 (6)	0.25 (11)	0.53 (0.20-1.45)	0.16 (11)	0.19 (13)	0.89 (0.40-1.99)	.43

Abbreviations; pt-yrs, Patient-years; SE, systemic embolism.
* *P* value for interaction of diabetes and treatment.

Thrombolysis In Myocardial Infarction 48 [ENGAGE AF-TIMI 48] trial with edoxaban), allowing robust assessment of an alternative to warfarin in diabetic patients with nonvalvular AF. The adjusted rates of stroke and systemic embolism and bleeding were higher for patients with DM vs without DM. The efficacy and safety of rivaroxaban compared with warfarin evident in the overall ROCKET AF study extended to patients with DM, and these effects were not significantly impacted by the use of oral agents or insulin for glucose control. Our results are consistent with findings from a subanalysis of the RELY trial in diabetic patients, which showed that diabetic status does not appear to impact the relative safety and efficacy of dabigatran compared with warfarin.[8]

In the Atherosclerosis Risk in Communities (ARIC) study of 13,025 persons, DM was associated with a 35% increase in the incidence of AF, and risk was greater in those with elevated levels of glycated hemoglobin.[9] These observations are supported by a population-based study and meta-analysis of more than 100,000 cases of AF among more than 1.6 million persons.[10,11] In the United Kingdom Prospective Diabetes Study (UKPDS), diabetic patients with AF had an 8-fold greater risk of stroke than did patients without this risk factor.[12] In cohorts of patients with AF, those with DM had stroke rates ranging from 3.6% to 8.6% per year.[13,14] In the Stroke Prevention in Atrial Fibrillation (SPAF) studies, of 196 diabetic patients without hypertension, prior stroke, or TIA, other than in women older than 75 years, the ischemic stroke rate was 2.6% per year.[15] The mechanism by which DM raises stroke risk independent of other established risk factors is unknown, but a hypercoagulable milieu mediated through increased levels of tissue plasminogen activator antigen and factor VIII activity and decreased fibrin breakdown is one postulated factor.[16]

Inferences about differences in clinical characteristics or intrinsic risk of stroke in the diabetic subpopulations in recent trials must be tempered because DM is a component of the $CHADS_2$ stroke risk schema used to define eligibility for enrollment. Although we found similar rates of stroke and systemic embolism in patients with and without DM, the latter group was more likely to have had prior stroke. As would be expected, patients with DM had a higher likelihood of MI and vascular death than did nondiabetic participants. The lack of robust association between DM and stroke in this analysis may be driven by high thromboembolism risk in the ROCKET AF population (mean $CHADS_2$ score 3.5). Given the considerably less frequent history of stroke, the diabetic subpopulation of the ROCKET AF cohort might be expected to have a lower event rate than the nondiabetic group; yet, the rates were comparable, suggesting that DM is associated with considerable risk. Modeling 2-year event rates for diabetic patients using the comorbid profiles of nondiabetic patients unmasked a higher risk of events associated with DM. The results of this analysis suggest that DM influences stroke risk in patients with AF as much as it raises the risk of coronary events in patients with atherosclerosis, but whether these associations share common mechanisms is speculative.

Limitations

The results reported here are derived from prespecified, post hoc subgroup analyses of a randomized trial in which DM was among the criteria used to establish eligibility for entry. Although the time in therapeutic range in ROCKET AF was lower than reported in some studies, the efficacy of rivaroxaban was favorable across groups defined by INR control in the overall trial population. The especially high mean $CHADS_2$ risk score required for enrollment provides a robust test of the drug's efficacy and safety in high-risk patients, but may limit generalizability to patients with DM at lower thromboembolism risk. Finally, we have inadequate information regarding the influence of glycemic control on clinical outcomes to assess whether more aggressive management of blood glucose influences the risk of ischemic or hemorrhagic events in patients with DM and AF.

Conclusions

The relative efficacy and safety of rivaroxaban compared with warfarin was similar in patients with and without DM, supporting the use of rivaroxaban as an alternative to warfarin for prevention of stroke and systemic embolism in diabetic patients with AF.

Author contributions

J.L.H. as guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. Study conception and design: J.L.H., Z.B., A.S.H., Y.L., M.R.P.

Acquisition of data: A.S.H., Y.L., M.R.P., K.W.M., K.A.A.F.

Analysis and interpretation of data: S.B., Z.B., J.L.H., A.S.H., Y.L., M.R.P., R.C.B., G.B., W.H., G.J.H., C.S.N., D.E.S., S.D.B., J.P.P., K.W.M., K.A.A.F.

Drafting of manuscript: S.B., Z.B., J.L.H., A.S.H., Y.L.

Critical revision: S.B., Z.B., J.L.H., A.S.H., Y.L., M.R.P., R.C.B., G.B., W.H., G.J.H., C.S.N., D.E.S., S.D.B., J.P.P., K.W.M., K.A.A.F.

Data access and responsibility

Dr Halperin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Bansilal and Halperin take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. All authors have approved the final article.

Disclosures

The ROCKET AF trial was sponsored by Johnson & Johnson Pharmaceutical Research & Development (Raritan, NJ) and Bayer HealthCare AG (Leverkusen, Germany). All analyses were conducted at the Duke Clinical Research Institute (Durham, NC), and the authors had full access to all data. The Duke Clinical Research Institute coordinated the trial, managed the database, and performed the secondary and post hoc analyses for this manuscript independent of the sponsors. An international executive committee designed the trial and was responsible for oversight of study conduct and reporting of all results and takes responsibility for the accuracy and completeness of data analyses. The authors are fully responsible for the study design, data collection, analysis and interpretation of the manuscript, and writing of the manuscript. The sponsor played no role in the decision to submit the manuscript for publication.

References

1. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 2007;69:546-54.
2. Stegmayr B, Asplund K. Diabetes as a risk factor for stroke. A population perspective. Diabetologia 1995;38:1061-8.
3. Wang TD, Chen WJ, Su SS, et al. Increased levels of tissue plasminogen activator antigen and factor VIII activity in nonvalvular atrial fibrillation: relation to predictors of thromboembolism. J Cardiovasc Electrophysiol 2001;12:877-84.
4. Klem I, Wehinger C, Schneider B, et al. Diabetic atrial fibrillation patients: mortality and risk for stroke or embolism during a 10-year follow-up. Diabetes Metab Res Rev 2003;19:320-8.
5. Rocket AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. Am Heart J 2010;159: 340-347.e1.
6. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
7. Rosendaal FR, Cannegieter SC, van der Meer FJ, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-9.
8. Brambatti M, Darius H, Oldgren J, et al. Comparison of dabigatran versus warfarin in diabetic patients with atrial fibrillation: results from the RE-LY trial. Int J Cardiol 2015;196:127-31.
9. Huxley RR, Alonso A, Lopez FL, et al. Type 2 diabetes, glucose homeostasis and incident atrial fibrillation: the Atherosclerosis Risk in Communities study. Heart 2012;98:133-8.
10. Dublin S, Glazer NL, Smith NL, et al. Diabetes mellitus, glycemic control, and risk of atrial fibrillation. J Gen Intern Med 2010;25:853-8.
11. Huxley RR, Filion KB, Konety S, et al. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol 2011;108:56-62.
12. Davis TM, Millns H, Stratton IM, et al. Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 29. Arch Intern Med 1999;159:1097-103.
13. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 2003;290: 2685-92.

14. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449-57.
15. Hart RG, Pearce LA, McBride R, et al. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Stroke 1999;30:1223-9.
16. Varughese GI, Patel JV, Tomson J, et al. The prothrombotic risk of diabetes mellitus in atrial fibrillation and heart failure. J Thromb Haemost 2005;3:2811-3.

Appendix. Supplementary information

Supplementary Table I. Baseline characteristics by diabetes status

	All patients enrolled (N = 14,264)	Diabetic patients (n = 5695)	Nondiabetic patients (n = 8569)	*P*
Baseline characteristics				
Age (y), median (25th, 75th)	73 (65, 78)	71 (64, 77)	74 (66, 79)	<.0001
Female, no. (%)	5660 (39.7)	2242 (39.4)	3418 (39.9)	.53
AF, no. (%)				.0007
Persistent	11,548 (81.0)	4684 (82.2)	6864 (80.1)	
Paroxysmal	2514 (17.6)	922 (16.2)	1592 (18.6)	
Newly diagnosed	202 (1.4)	89 (1.6)	113 (1.3)	
Diabetes controlled* by, no. (%)				
Diet		1454 (25.5)		
Oral medication†		3301 (58.0)		
Thiazolidinedione		189 (5.7)		
Biguanide		1864 (56.5)		
Sulfonylurea		1815 (55.0)		
Other/unspecified		117 (3.5)		
Insulin		939 (16.5)		
Presenting characteristics, median (25th, 75th)				
Body mass index (kg/m^2)	28.2 (25.1, 32.0)	29.9 (26.5, 34.2)	27.2 (24.4, 30.5)	<.0001
Systolic blood pressure	130 (120, 140)	130 (120, 140)	130 (120, 140)	<.0001
Diastolic blood pressure	80 (70, 85)	80 (70, 85)	80 (71, 86)	<.0001
Creatinine clearance	67 (52, 87)	72 (55, 94)	65 (50, 83)	<.0001
eGFR (mL/min)				<.0001
<30	28 (0.2)	11 (0.2)	17 (0.2)	
30-60	5497 (38.6)	1876 (33.0)	3621 (42.3)	
>60	8725 (61.2)	3803 (66.8)	4922 (57.5)	
Other baseline comorbidities				
Prior stroke/TIA, no. (%)	7468 (52.4)	1806 (31.7)	5662 (66.1)	<.0001
Hypertension, no. (%)	12,910 (90.5)	5433 (95.4)	7477 (87.3)	
Congestive heart failure, no. (%)	8908 (62.5)	3792 (66.6)	5116 (59.7)	<.0001
COPD, no. (%)	1497 (10.5)	662 (11.6)	835 (9.8)	.0003
$CHADS_2$ score, median (25th, 75th)	3 (3, 4)	3 (3, 4)	3 (3, 4)	<.0001
$CHADS_2$ score, mean (SD)	3.5 (0.9)	3.7 (1.0)	3.3 (0.9)	
Medications, no. (%)				
Prior vitamin K antagonist use	8904 (62.4)	3717 (65.3)	5187 (60.5)	<.0001
Prior chronic ASA use	5485 (38.5)	2230 (39.2)	3255 (38.0)	.16
ACE inhibitor/ARB	10,583 (74.2)	4626 (81.2)	5957 (69.5)	<.0001
β-Blocker	9250 (64.8)	3834 (67.3)	5416 (63.2)	<.0001
Calcium-channel blocker	3958 (27.7)	1807 (31.7)	2151 (25.1)	<.0001
Diuretic	8490 (59.5)	3820 (67.1)	4670 (54.5)	<.0001

Abbreviations: eGFR, Estimated glomerular filtration rate; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ASA, aspirin; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

* Patients may have reported more than one type of diabetes control. In this table, patients are placed in mutually exclusive categories with the priority order of (1) insulin, (2) oral, and (3) no treatment.

† Percents for individual drug types are calculated among those with diabetes controlled by oral medication. Patients could report more than 1 medication. In total, 438 (13%) of those reporting control by oral medication did not have any diabetes-specific medication reported.

Supplementary Table II. Efficacy and safety end points in diabetic and nondiabetic patients

	Diabetic patients events/100 pt-yrs (total events)	Nondiabetic patients events/100 pt-yrs (total events)	Diabetic patients vs nondiabetic patients HR (95% CI)	*P*
Efficacy outcomes				
Stroke or SE	1.94 (209)	2.22 (366)	1.13 (0.94-1.35)	.20
Ischemic stroke or SE	1.52 (164)	1.76 (291)	1.15 (0.94-1.41)	.18
Stroke/SE/vascular death	4.69 (491)	4.28 (690)	1.27 (1.13-1.44)	.0001
Stroke/SE/vascular death/MI	5.70 (590)	4.86 (778)	1.32 (1.18-1.49)	<.0001
Stroke	1.83 (197)	2.04 (337)	1.18 (0.98-1.43)	.085
Ischemic stroke	1.40 (152)	1.58 (262)	1.23 (0.99-1.52)	.063
SE	0.13 (14)	0.20 (33)	0.67 (0.34-1.33)	.25
Vascular death	3.24 (344)	2.63 (432)	1.35 (1.16-1.57)	.0001
MI	1.35 (146)	0.75 (126)	1.70 (1.31-2.20)	<.0001
Safety outcomes				
Major or NMCR bleeding	15.12 (1178)	14.46 (1746)	1.02 (0.94-1.10)	.62
Major bleeding	3.85 (334)	3.32 (447)	1.13 (0.97-1.31)	.12
Intracranial hemorrhage	0.66 (58)	0.59 (81)	1.36 (0.94-1.96)	.10
Hemorrhagic stroke	0.34 (30)	0.36 (49)	1.14 (0.69-1.88)	.62
Intraocular/retinal bleed	0.19 (17)	0.18 (24)	1.04 (0.52-2.06)	.91

Event rates (events per 100 pt-yrs) are unadjusted. HRs and *P* values are from adjusted Cox models.
Abbreviations: pt-yrs, Patient-years; HR, hazard ratio; MI, myocardial infarction; SE, systemic embolism; NMCR, nonmajor clinically relevant.

Supplementary Table III. Risk associated with diabetes compared with other components of the $CHADS_2$ score

	Stroke/SE		Ischemic stroke/SE	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Diabetes	1.14 (0.95-1.37)	.16	1.16 (0.94-1.42)	.17
Other $CHADS_2$ risk factors				
Age >75 y	1.22 (1.01-1.47)	.034	1.22 (0.99-1.50)	.063
Hypertension	1.26 (0.93-1.71)	.14	1.09 (0.79-1.51)	.61
LV dysfunction or heart failure	0.93 (0.78-1.11)	.41	0.96 (0.79-1.17)	.71
Chronic kidney disease (CrCl 30-49 mL/min)	1.26 (1.02-1.56)	.030	1.39 (1.10-1.75)	.0059
Female sex	1.29 (1.08-1.55)	.0044	1.36 (1.12-1.66)	.0024
Warfarin treatment assignment	1.13 (0.96-1.34)	.13	1.05 (0.87-1.26)	.64

Each model adjusted for other known predictors of efficacy end points.
Abbreviations: HR, Hazard ratio; SE, systemic embolism; LV, left ventricle; CrCl, creatinine clearance.

Supplementary Table IV. End points by treatment in diabetic subgroups

	N	Rivaroxaban events/100 pt-yrs (total events)	Warfarin events/100 pt-yrs (total events)	Rivaroxaban vs warfarin HR (95% CI)	*P* value for interaction of subgroup* with treatment
A. Stroke or systemic embolism					
Diabetic subgroup					
Diabetes controlled by					
Insulin	930	1.88 (16)	1.73 (16)	1.18 (0.59-2.36)	.62
Oral medication	3283	1.80 (58)	2.27 (70)	0.78 (0.55-1.10)	
Diet	1433	1.53 (21)	2.13 (28)	0.72 (0.41-1.27)	
Body mass index (kg/m^2)					
≥30	2793	1.68 (46)	1.66 (44)	1.01 (0.67-1.53)	.32
<30	2849	1.81 (49)	2.62 (70)	0.69 (0.48-1.00)	
Prior stroke or TIA					
Yes	1785	2.80 (47)	3.24 (52)	0.86 (0.58-1.28)	.75
No	3862	1.27 (48)	1.67 (62)	0.78 (0.53-1.14)	
Hypertension					
Yes	5389	1.76 (91)	2.15 (109)	0.82 (0.62-1.09)	.78
No	258	1.44 (4)	2.05 (5)	0.72 (0.19-2.68)	
Heart failure					
Yes	3764	1.62 (57)	2.07 (73)	0.80 (0.56-1.13)	.78
No	1882	1.97 (38)	2.29 (41)	0.85 (0.55-1.33)	
Prior VKA					
Yes	3687	1.54 (56)	1.87 (67)	0.84 (0.59-1.20)	.76
No	1960	2.17 (39)	2.72 (47)	0.77 (0.51-1.19)	
Concurrent ASA use					
Yes	2104	1.67 (33)	1.90 (37)	0.89 (0.56-1.43)	.72
No	3543	1.78 (62)	2.28 (77)	0.78 (0.56-1.09)	
Baseline renal function					
eGFR ≤60 (mL/min)	1860	2.25 (39)	3.14 (56)	0.72 (0.47-1.08)	.56
eGFR >60 (mL/min)	3782	1.51 (56)	1.64 (58)	0.91 (0.63-1.31)	
Nondiabetic subgroup	8524	2.12 (174)	2.32 (192)	0.92 (0.75-1.13)	–
B. Ischemic stroke					
Diabetic subgroup					
Diabetes controlled by					.55
Insulin	930	1.76 (15)	1.40 (13)	1.37 (0.65-2.87)	
Oral medication	3283	1.42 (46)	1.48 (46)	0.94 (0.62-1.42)	
Diet	1433	0.94 (13)	1.43 (19)	0.66 (0.33-1.35)	
Body mass index (kg/m^2)					.037
≥30	2793	1.35 (37)	0.86 (23)	1.56 (0.93-2.63)	
<30	2849	1.36 (37)	2.04 (55)	0.66 (0.43-1.01)	
Prior stroke or TIA					
Yes	1785	2.44 (41)	2.28 (37)	1.06 (0.68-1.66)	.63
No	3862	0.87 (33)	1.10 (41)	0.81 (0.51-1.28)	
Hypertension					.66
Yes	5389	1.37 (71)	1.43 (73)	0.96 (0.69-1.33)	
No	258	1.08 (3)	2.05 (5)	0.53 (0.13-2.24)	
Heart failure					.25
Yes	3764	1.34 (47)	1.18 (42)	1.16 (0.76-1.75)	
No	1882	1.39 (27)	2.01 (36)	0.68 (0.41-1.12)	
Prior VKA					.89
Yes	3687	1.26 (46)	1.38 (50)	0.93 (0.62-1.39)	
No	1960	1.54 (28)	1.60 (28)	0.93 (0.55-1.58)	
Concurrent ASA use					.63
Yes	2104	1.26 (25)	1.12 (22)	1.14 (0.64-2.02)	
No	3543	1.40 (49)	1.65 (56)	0.85 (0.58-1.25)	
Baseline renal function (mL/min)					.43
eGFR ≤60	1860	1.72 (30)	2.28 (41)	0.75 (0.47-1.21)	
eGFR >60	3782	1.18 (44)	1.04 (37)	1.12 (0.72-1.74)	
Nondiabetic subgroup	8524	1.60 (132)	1.56 (130)	1.03 (0.81-1.31)	–

(continued on next page)

Supplementary Table IV (*continued*)

	N	Rivaroxaban events/100 pt-yrs (total events)	Warfarin events/100 pt-yrs (total events)	Rivaroxaban vs warfarin HR (95% CI)	*P* value for interaction of subgroup* with treatment
C. Major or NMCR bleeding					
Diabetic subgroup					
Diabetes controlled by					.27
Insulin	937	16.54 (98)	16.19 (106)	1.03 (0.78-1.37)	
Oral medication	3292	14.80 (345)	14.64 (330)	1.05 (0.90-1.22)	
Diet	1453	13.83 (139)	16.81 (160)	0.85 (0.68-1.07)	
Body mass index (kg/m^2)					.16
≥30	2810	13.82 (280)	15.64 (303)	0.91 (0.77-1.08)	
<30	2868	15.90 (302)	15.20 (292)	1.08 (0.92-1.27)	
Prior stroke or TIA					.30
Yes	1800	14.93 (182)	14.66 (176)	1.08 (0.87-1.33)	
No	3883	14.76 (400)	15.79 (420)	0.96 (0.84-1.10)	
Hypertension					.053
Yes	5422	14.50 (543)	15.58 (575)	0.97 (0.86-1.09)	
No	261	21.35 (39)	12.25 (21)	1.74 (1.00-3.01)	
Heart failure					.15
Yes	3787	14.05 (356)	15.82 (403)	0.93 (0.81-1.08)	
No	1895	16.24 (226)	14.69 (193)	1.13 (0.93-1.37)	
Prior VKA					.37
Yes	3708	15.67 (413)	15.64 (414)	1.02 (0.88-1.17)	
No	1975	13.07 (169)	15.00 (182)	0.94 (0.76-1.16)	
Concurrent ASA use					.43
Yes	2108	16.62 (225)	17.35 (233)	1.01 (0.84-1.22)	
No	3575	13.86 (357)	14.41 (363)	0.98 (0.84-1.14)	
Baseline renal function (mL/min)					.45
eGFR ≤60	1880	17.69 (205)	18.85 (227)	0.99 (0.82-1.20)	
eGFR >60	3798	13.62 (377)	13.91 (369)	0.99 (0.86-1.15)	
Nondiabetic subgroup	8553	14.99 (893)	13.94 (853)	1.09 (0.99-1.20)	–
D. Intracranial hemorrhage					
Diabetic subgroup					
Diabetes controlled by					
Insulin	937	0.30 (2)	0.54 (4)	0.57 (0.10-3.11)	.27
Oral medication	3292	0.46 (12)	1.05 (27)	0.45 (0.23-0.89)	
Diet	1453	0.70 (8)	0.45 (5)	1.64 (0.54-5.03)	
Body mass index (kg/m^2)					
≥30	2810	0.35 (8)	0.81 (18)	0.44 (0.19-1.02)	.49
<30	2868	0.65 (14)	0.82 (18)	0.83 (0.41-1.68)	
Prior stroke or TIA					
Yes	1800	0.66 (9)	1.03 (14)	0.64 (0.28-1.48)	.95
No	3883	0.42 (13)	0.72 (22)	0.63 (0.32-1.26)	
Hypertension					
Yes	5422	0.50 (21)	0.83 (35)	0.64 (0.37-1.10)	.95
No	261	0.45 (1)	0.51 (1)	0.72 (0.05-11.6)	
Heart failure					
Yes	3787	0.35 (10)	0.83 (24)	0.47 (0.22-0.99)	.47
No	1895	0.74 (12)	0.80 (12)	0.92 (0.41-2.04)	
Prior VKA					
Yes	3708	0.43 (13)	0.69 (21)	0.64 (0.32-1.28)	.95
No	1975	0.63 (9)	1.09 (15)	0.63 (0.27-1.45)	
Concurrent ASA use					
Yes	2108	0.52 (8)	0.77 (12)	0.69 (0.28-1.69)	.92
No	3575	0.48 (14)	0.84 (24)	0.60 (0.31-1.17)	
Baseline renal function (mL/min)					
eGFR ≤60	1880	0.75 (10)	1.01 (14)	0.75 (0.33-1.68)	.83
eGFR >60	3798	0.39 (12)	0.73 (22)	0.56 (0.28-1.14)	
Nondiabetic subgroup	8553	0.49 (33)	0.69 (48)	0.72 (0.46-1.12)	–

Abbreviations: pt-yrs, Patient-years; HR, hazard ratio; TIA, transient ischemic attack; VKA, vitamin K antagonist; ASA, aspirin; eGFR, estimated glomerular filtration rate.
*Includes nondiabetic patients as one of the subgroups.

Supplementary Table V. Confirmatory analyses in propensity score–matched groups

Confirmatory analysis. A sensitivity analysis was conducted in which a subset of nondiabetic group was chosen to most closely match the diabetic group, using propensity score matching.

Matching process:

As diabetic patients were the smaller group, patients were selected from the nondiabetic group to match those in the diabetic group, in a 1:1 ratio, using the following process:

1. *Candidate covariates*. Variables in online Appendix Supplementary Table I, except for diabetes-specific variables and $CHADS_2$ score, comprised the starting list. Any variable missing in 15% or more of patients in either group was dismissed from further consideration. For any variable missing in <15% of patients in both groups, missing values were imputed using the group-specific median for continuous variables and mode for categorical variables.
2. *Trimming*. For continuous variables remaining after the first step, nondiabetic patients whose value was below the minimum or above the maximum for diabetic patients were excluded.
3. *Propensity model*. A propensity model was developed using multiple logistic regression in which the dependent (outcome) variable was an indicator of whether each patient is diabetic, and the independent (predictor) variables were the baseline variables remaining after step 1. Continuous predictors were evaluated for the linearity of their relationship with the outcome, and restricted cubic splines used as needed to accommodate nonlinearity. From this model, an estimated probability of being a diabetic patient and a corresponding logit ($\log_e[p/(1-p)]$) were calculated for each patient.
4. *Matching (Rosenbaum and Rubin method*[*]*)*. A caliper width of 0.15*(standard deviation of the logit) was used. For a given diabetic patient, all nondiabetic patients were considered whose logit differed from the diabetic patient's logit by less than the caliper width; among these patients, the nondiabetic patient with the shortest Mahalanobis distance from the diabetic patient was selected as the match. (Variables used in calculating Mahalanobis distance were all significant predictors from the propensity model.) If there were no nondiabetic patients within the caliper width, the diabetic patient was omitted from the analysis. Each nondiabetic patient could be selected only once. The multiplier for the caliper width (0.15) was chosen to allow the largest sample size while ensuring a standardized difference of <10% on the key variables of age, body mass index, estimated glomerular filtration rate, and prior stroke or TIA, and, as far as possible, all $P > .05$ for these 4 variables. Standardized difference is defined as the difference in means (or proportions) divided by the average standard deviation.

This matching process resulted in a cohort of 3999 diabetic patients (70% of the original cohort) and the same number of matched nondiabetic patients. The matched cohorts were then compared as in the main analyses. Baseline characteristics before and after matching are shown in online Appendix Supplementary Table VIA and B, and model results are shown in online Appendix Supplementary Table VIC and D.

---

[*] Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 1985;39(1):33–38.

Supplementary Table VI. Propensity score–matched cohorts

A. All

Baseline characteristic	All nondiabetic patients (n = 8569)	All diabetic patients (n = 5695)	% Standardized difference	*P*
Age (y)	74 (66, 79)	71 (64, 77)	16	<.0001
Female	40% (3418)	39% (2242)	1	.53
Persistent AF	80% (6864)	82% (4684)	5	.0013
Baseline BMI (kg/m^2)	27 (24, 30)	30 (27, 34)	53	<.0001
Baseline—systolic pressure	130 (120, 140)	130 (120, 140)	7	<.0001
Baseline—diastolic pressure	80 (71, 86)	80 (70, 85)	9	<.0001
GFR (Cockcroft and Gault)	65 (50, 83)	72 (55, 94)	31	<.0001
History—stroke or TIA	66% (5662)	32% (1806)	73	<.0001
History—hypertension	87% (7477)	95% (5433)	29	<.0001
History—CHF	60% (5116)	67% (3792)	14	<.0001
History—COPD	10% (835)	12% (662)	6	.0004
VKA use at screening	61% (5187)	65% (3717)	10	<.0001
Chronic ASA at screening	36% (3093)	37% (2112)	2	.23
ACE inhibitor/ARB at baseline	70% (5957)	81% (4626)	27	<.0001
β-Blocker at baseline	63% (5416)	67% (3834)	9	<.0001
Calcium-channel blocker at baseline	25% (2151)	32% (1807)	15	<.0001
Diuretic at baseline	54% (4670)	67% (3820)	26	<.0001
CHADS2 score 5 or 6*	9% (801)	23% (1294)	37	<.0001

B. Matched

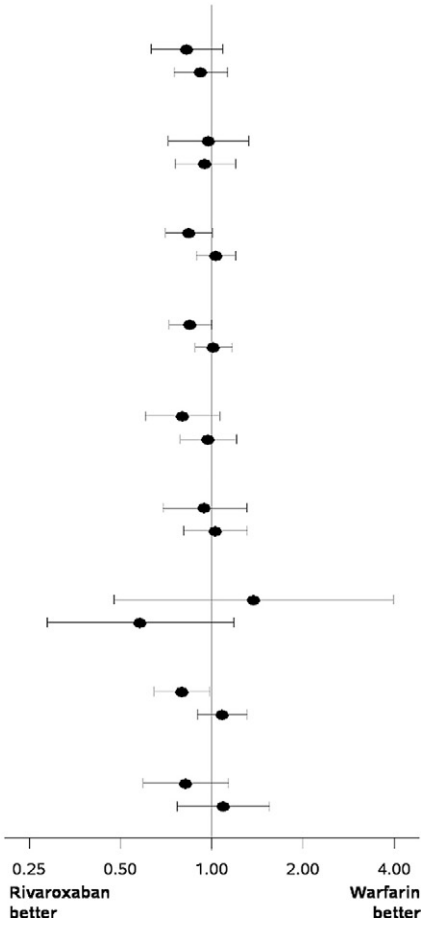
Baseline characteristic	Matched nondiabetic patients (n = 3999)	Matched diabetic patients (n = 3999)	% Standardized difference	*P*
Age (y)	75 (67, 78)	73 (66, 78)	7	.0011
Female	41% (1622)	41% (1631)	0	.84
Persistent AF	83% (3329)	82% (3262)	4	.049
Baseline BMI (kg/m^2)	29 (26, 32)	28 (26, 32)	0	.97
Baseline—systolic pressure	130 (120, 140)	130 (120, 140)	0	.94
Baseline—diastolic pressure	80 (70, 85)	80 (70, 85)	2	.41
GFR (Cockroft and Gault)	66 (52, 84)	67 (52, 86)	4	.099
History—stroke or TIA	46% (1844)	44% (1778)	3	.14
History—hypertension	94% (3771)	94% (3752)	2	.37
History—CHF	64% (2565)	64% (2567)	0	.95
History—COPD	11% (454)	11% (432)	2	.43
VKA use at screening	64% (2572)	64% (2543)	2	.50
Chronic ASA at screening	36% (1450)	37% (1488)	2	.38
ACE inhibitor/ARB at baseline	78% (3121)	77% (3097)	1	.52
β-Blocker at baseline	65% (2598)	66% (2624)	1	.54
Calcium-channel blocker at baseline	30% (1180)	29% (1154)	1	.52
Diuretic at baseline	64% (2545)	62% (2486)	3	.17
CHADS2 score = 5 or 6*	7% (275)	31% (1254)	66	<.0001

Outcomes	Diabetic patients vs nondiabetic patients, HR (95% CI)	*P* value for diabetic vs nondiabetic patients	Diabetic patients—rivaroxaban vs warfarin HR (95% CI)	Nondiabetic patients—rivaroxaban vs warfarin HR (95% CI)	*P* value for interaction of diabetes and treatment
C. Diabetic vs matched nondiabetic patients					
Primary efficacy: stroke or systemic embolism	1.23 (0.99-1.53)	.066	0.81 (0.60-1.10)	0.95 (0.69-1.30)	.49
Primary safety: major or NMCR bleeding	0.99 (0.90-1.09)	.82	1.00 (0.87-1.15)	1.16 (1.01-1.32)	.13
D. Original results using the unmatched patients					
Primary efficacy: stroke or systemic embolism	1.13 (0.94-1.35)	.20	0.82 (0.63-1.08)	0.92 (0.75-1.13)	.53
Primary safety: major or NMCR bleeding	1.02 (0.94-1.10)	.62	0.98 (0.88-1.10)	1.09 (0.99-1.20)	.17

% Standardized difference = 100*(mean(Diab) – mean(NonDiab))/sqrt((var(Diab) + var(NonDiab))/2).
Overall, the 2 sets of results were nearly identical.
Abbreviations: HR, hazard ratio; NMCR, nonmajor clinically relevant.
*Included for illustration but not used in matching.

Supplementary Figure 1

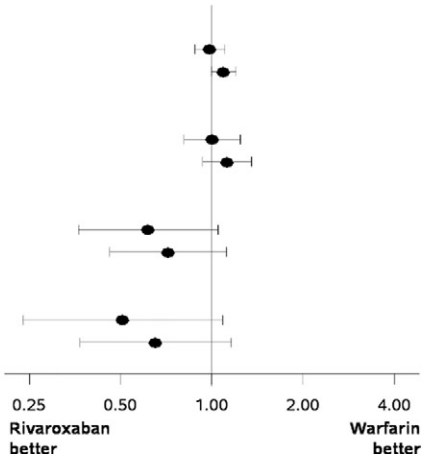
Outcome	Rivaroxaban Events per 100 pt-yrs	Warfarin Events per 100 pt-yrs	Interaction P-Value	Hazard Ratio	95% CI
Stroke/systemic embolism			0.54		
Diabetic	1.89	2.33		0.83	0.63, 1.08
Non-diabetic	2.27	2.48		0.92	0.75, 1.13
Ischemic stroke/SE			0.90		
Diabetic	1.61	1.69		0.97	0.72, 1.32
Non-diabetic	1.84	1.93		0.95	0.75, 1.20
Stroke/SE/vasc death			0.086		
Diabetic	4.45	5.45		0.84	0.70, 1.00
Non-diabetic	4.55	4.41		1.03	0.89, 1.20
Stroke/SE/vasc death/MI			0.11		
Diabetic	5.43	6.60		0.85	0.72, 1.00
Non-diabetic	5.11	5.06		1.01	0.88, 1.17
Stroke			0.27		
Diabetic	1.75	2.22		0.80	0.60, 1.06
Non-diabetic	2.15	2.21		0.97	0.79, 1.20
Ischemic stroke			0.69		
Diabetic	1.47	1.58		0.95	0.69, 1.30
Non-diabetic	1.72	1.67		1.03	0.81, 1.31
Systemic embolism			0.19		
Diabetic	0.16	0.12		1.37	0.48, 3.96
Non-diabetic	0.15	0.27		0.58	0.29, 1.18
Vascular death			0.036		
Diabetic	2.98	3.86		0.80	0.64, 0.99
Non-diabetic	2.87	2.65		1.08	0.90, 1.31
Myocardial infarction			0.24		
Diabetic	1.29	1.65		0.82	0.59, 1.14
Non-diabetic	0.84	0.78		1.09	0.77, 1.55



Efficacy end points.

Supplementary Figure 2

Outcome	Rivaroxaban Events per 100 pt-yrs	Warfarin Events per 100 pt-yrs	Interaction P-Value	Hazard Ratio	95% CI
Major or NMCR bleeding			0.17		
Diabetic	14.81	15.44		0.98	0.88, 1.10
Non-diabetic	14.99	13.94		1.09	0.99, 1.20
Major bleeding			0.43		
Diabetic	3.79	3.90		1.00	0.81, 1.24
Non-diabetic	3.47	3.17		1.12	0.93, 1.35
ICH			0.67		
Diabetic	0.50	0.82		0.62	0.36, 1.05
Non-diabetic	0.49	0.69		0.72	0.46, 1.12
Hemorrhagic stroke			0.61		
Diabetic	0.23	0.46		0.51	0.24, 1.09
Non-diabetic	0.28	0.43		0.65	0.37, 1.16



Safety end points.