Pharmacotherapy for diabetes and stroke risk: Results from ROCKET AF

Francis E. Ugowe, MD,[*] Anne S. Hellkamp, MS,[†] Allen Wang, BS,[‡] Richard C. Becker, MD,[§] Scott D. Berkowitz, MD,[‖] Günter Breithardt, MD,[¶] Keith A.A. Fox, MB ChB,[#] Jonathan L. Halperin, MD,[**] Graeme J. Hankey, MD,[††] Kenneth W. Mahaffey, MD,[‡‡] Christopher C. Nessel, MD,[§§] Daniel E. Singer, MD,[‖‖] Manesh R. Patel, MD,[*†] Jonathan P. Piccini, MD, MHS, FHRS,[*†] on behalf of the ROCKET AF Steering Committee and Investigators

*From the *Duke University Medical Center, Duke University School of Medicine, Durham, North Carolina, [†]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, [‡]Duke Center for Atrial Fibrillation, Department of Medicine, Duke University Medical Center, Durham, North Carolina, [§]University of Cincinnati College of Medicine, Cincinnati, Ohio, [‖]Bayer U.S. LLC, Parsippany, New Jersey, [¶]Hospital of the University of Münster, Münster, Germany, [#]University of Edinburgh and Royal Infirmary of Edinburgh, Edinburgh, United Kingdom, **Mount Sinai School of Medicine, New York, New York, [††]School of Medicine and Pharmacology, The University of Western Australia, Crawley, Australia, [‡‡]Stanford Center for Clinical Research, Stanford University, School of Medicine, Stanford, California, [§§]Janssen Research & Development, Raritan, New Jersey, and [‖‖]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.*

BACKGROUND Insulin use may be a better predictor of stroke risk and morbidity and mortality than diabetes in patients with atrial fibrillation (AF).

OBJECTIVES Determine if the increased risk of stroke observed in patients with AF and diabetes is restricted to those treated with insulin.

METHODS We analyzed the association between diabetes and treatment and the occurrence of stroke/systemic embolism, myocardial infarction (MI), all-cause death, vascular death, composite outcomes, and bleeding risk in the ROCKET AF trial.

RESULTS In a cohort of 14,264 patients, there were 40.3% (n = 5746) with diabetes, 5.9% (n = 842) on insulin, 18.9% (n = 2697) on oral medications, and 11.9% (n = 1703) diet-controlled. Compared to those without diabetes, patients with non–insulin-treated diabetes had increased risks of stroke (hazard ratio [HR] 1.33, 95% confidence interval [CI] 1.06–1.68), MI (HR 1.64, 95% CI 1.17–2.30), all-cause death (HR 1.26, 95% CI 1.08–1.46), vascular death (HR 1.33, 95% CI 1.11–1.60), and composite outcomes (HR 1.37, 95% CI 1.18–1.157). Patients with insulin-treated diabetes had a significantly higher risk of MI (HR 2.31, 95% CI 1.33–4.01) and composite outcomes (HR 1.57, 95% CI 1.19–2.08) compared to those without diabetes. There were no significant differences between insulin-treated and non–insulin-treated diabetes for any outcome.

CONCLUSION Among patients with AF and diabetes, there were no significant differences in outcomes in insulin-treated diabetes compared to non–insulin-treated diabetes.

KEYWORDS Atrial fibrillation; Diabetes; Rivaroxaban; Stroke; Warfarin

(Heart Rhythm O^2 2021;2:215–222)

Introduction

Atrial fibrillation (AF) is a complex disorder that is the result of interactions between genetics, environmental influences, comorbid illness, and, most importantly, modifiable risk factors such as hypertension, obesity, and diabetes mellitus. Patients with diabetes have a 34% higher risk of developing AF than those without diabetes, and the estimated risk increases approximately 3% per year of diabetes duration.[1,2] Diabetes is also associated with increased thromboembolic risk mediated through mechanisms such as oxidative stress,

ClinicalTrials.gov: NCT00403767. **Address reprint requests and correspondence:** Dr Jonathan P. Piccini, Electrophysiology Section, Duke University Medical Center, Duke Clinical Research Institute, P.O. Box 17969, Durham, NC 27710. E-mail address: jonathan.piccini@duke.edu.

2666-5018/

https://doi.org/10.1016/j.hroo.2021.04.001

KEY FINDINGS

- Patients with diabetes mellitus possess an increased risk of developing atrial fibrillation. The comorbidity of atrial fibrillation and diabetes leads to a heightened thromboembolic risk and worse cardiovascular outcomes.
- In the ROCKET AF cohort, there were no significant differences in the occurrence of stroke/systemic embolism, myocardial infarction, all-cause death, and other outcomes in patients with diabetes whether or not they were treated with insulin.
- The substitution of insulin-treated diabetes (instead of any diabetes) into the CHA_2DS_2-VASc score did not dramatically improve its discriminatory capacity in stroke risk prediction.

hemostatic changes, and inflammation in patients with AF.[3] This correlation has led to the inclusion of diabetes in stroke risk stratification schemes such as the CHA_2DS_2-VASc score.[4,5]

The efficacy and safety of rivaroxaban compared to warfarin in patients with AF and diabetes has previously been examined.[6] However, some uncertainty remains as to which aspect of diabetes contributes most to the increased risk of stroke in patients with AF.[6,7] A recent analysis from the PREFER registry demonstrated that the association between diabetes and stroke in patients with AF is greatest in those treated with insulin.[8] In this study we aimed to explore the external validity of this observation in a large, independent cohort of patients with AF. The objectives of the current analysis were to investigate whether insulin therapy in patients with AF is associated with an increased risk of stroke/systemic embolism, as well as to assess the contribution of insulin-treated diabetes (vs any diabetes) to discriminate risk of thromboembolic events.

Methods

The design and primary results of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism (ROCKET AF) trial have previously been described (NCT00403767).[8,9] Briefly, ROCKET AF was an international, randomized, prospective, double-blind, placebo-controlled trial of rivaroxaban compared with dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular AF. To be enrolled in ROCKET AF, patients were required to have electrocardiographic evidence of AF and an elevated risk of stroke, as defined by a history of stroke, transient ischemic attack (TIA), systemic embolism, or at least 2 of the following risk factors: heart failure or left ventricular ejection fraction $\leq$35%, hypertension, age $\geq$75 years, or diabetes mellitus. Patients with a high risk of bleeding, such as those with gastrointestinal bleeding within 6 months and previous intracranial bleeding, were excluded from the study. The study conformed to the principles outlined in the Declaration of Helsinki, as revised in 2013, and was approved by each participating site's ethics committee or institutional review board. All patients provided written informed consent.

The present study is a post hoc analysis of all patients randomized in ROCKET AF. We defined diabetes based on whether it was reported in the medical history at baseline or if the use of diabetes medications was documented in the medical record. Measures of glycemic control, including blood glucose and glycated hemoglobin, were not systematically recorded. Efficacy endpoints such as stroke, systemic embolism, myocardial infarction (MI), all-cause death, and vascular death were collected from randomization through the end of the study. Safety endpoints such as major or nonmajor clinically relevant bleeding were collected from the first dose of study medication to the last dose plus 2 days. The efficacy and safety outcomes were previously defined and were adjudicated by a clinical events committee whose members were unaware of treatment assignment.[9]

Statistical analysis

Summary statistics are presented for frequency of diabetes and diabetes treatment. Patient medications were reviewed, and patients were classified by their baseline status as those with insulin-treated diabetes, non–insulin-treated diabetes, or no diabetes. Patients with non–insulin-treated diabetes were further classified as being on oral medication or using diet to control their diabetes. Baseline characteristics are presented for each group with categorical variables as counts (percentages) and continuous variables as medians (25th, 75th percentiles).

Cox proportional hazards models were used to assess the relation of diabetes group with outcomes; patients were included in models for as long as they remained in their baseline group. Patients with diabetes who changed their treatment or patients who did not have diabetes at baseline and subsequently developed diabetes were censored at those time points. Patients who were on both oral agents and insulin were included in the insulin-treated group. Because a change in diabetes therapy can be influenced by patient characteristics or intervening events that might also be related to outcomes, patients were weighted by the inverse probability of continuing in their therapy group. Weights were applied to the Cox models with a robust sandwich variance estimator.[10]

Event rates (per 100 patient-years), which are weighted but unadjusted, and total number of events are presented for all outcomes. Group comparisons made using Cox models were adjusted for previously identified predictors of each endpoint.[11–14] Efficacy outcomes models included the following covariates: age, sex, body mass index (BMI), region, previous stroke/TIA, vascular disease, congestive heart failure, hypertension, chronic obstructive pulmonary disease (COPD), paroxysmal AF, diastolic blood pressure, creatinine clearance (calculated using the Cockcroft-Gault

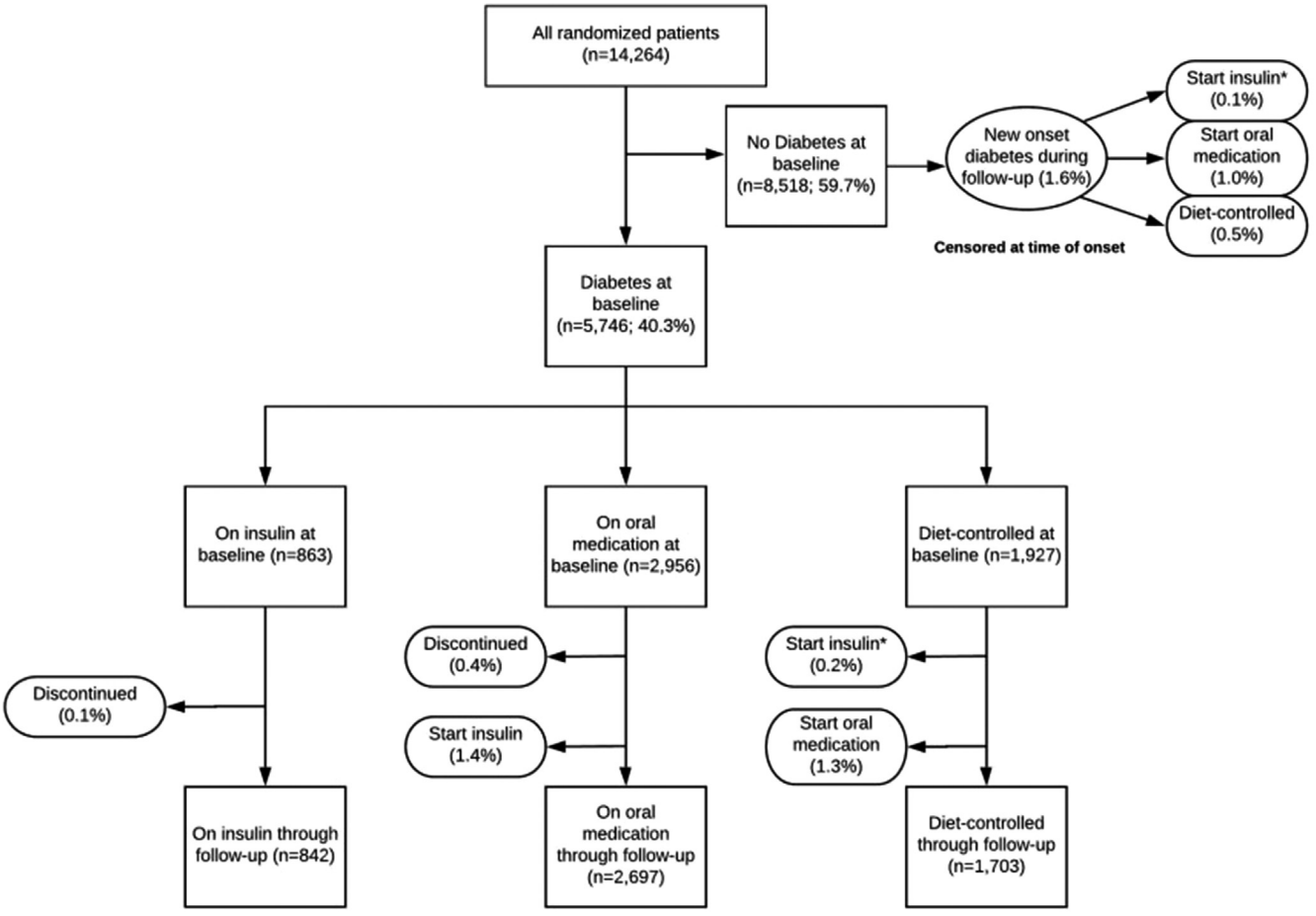

Figure 1 Presence of diabetes in the ROCKET AF cohort. *Patient may also have been on oral medication at some time.

equation), heart rate, and abstinence from alcohol. Safety outcomes models included the following covariates: age, sex, region, previous stroke/TIA, anemia, previous gastrointestinal bleed, COPD, diastolic blood pressure, creatinine clearance, platelets, albumin, previous aspirin use, previous vitamin K antagonist use, and previous thienopyridine use. Rates of missing data were quite low; when missing, covariates were imputed using the median for continuous variables and the mode for categorical variables within groups of patients within each diabetic group. All models contained randomized treatment (rivaroxaban vs dose-adjusted warfarin).

Two types of models were generated for the comparison of outcomes: (1) comparison among patients with insulin-treated diabetes, patients with non–insulin-treated diabetes, and patients with no diabetes; and (2) further comparisons of diabetes treatment among groups defined by insulin therapy, oral medication, and diet control. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) and *P* values are presented for all models.

To assess the contribution of any diabetes compared with insulin-treated diabetes on the ability of the CHA_2DS_2-VASc score to discriminate risk of thromboembolic event, the score was calculated 2 ways: (1) the conventional way, using any diabetes for the diabetes criterion; and (2) an alternative, using only diabetes with insulin for the diabetes criterion. Each score was entered into a Cox model with stroke/systemic embolism as the outcome and adjusted for other known predictors that are not part of the score (geographic region, BMI, heart rate, creatinine clearance, paroxysmal AF, COPD, and alcohol use). For each model, the c-index and its 95% CI were calculated, reflecting the ability of the model to discriminate higher- from lower-risk patients.

Results

Patient characteristics

Of the 14,264 patients randomized in ROCKET AF, 5746 patients (40.3%) were reported to have diabetes at baseline (Figure 1). There were 842 (5.9%) patients on insulin at baseline and through follow-up, 2697 (18.9%) patients on oral hypoglycemic agents at baseline and through follow-up, and 1703 (11.9%) who were using diet control (Figure 1). Patients without diabetes were slightly older; otherwise, overall demographics were similar between groups (Table 1). Types of AF and CHA_2DS_2-VASc scores were also comparable between groups. Patients with insulin-treated diabetes had a higher BMI than patients on oral agents and those using diet control to manage their

Table 1 Baseline characteristics by diabetes and treatment group

Variable	Insulin-treated diabetes (n = 863)	Non–insulin-treated diabetes (n = 4883)	No diabetes (n = 8518)
Randomized to rivaroxaban, n (%)	430 (50%)	2474 (51%)	4227 (50%)
Age, median (25th, 75th), y	70 (65, 76)	71 (64, 77)	74 (66, 79)
Female, n (%)	314 (36%)	1953 (40%)	3393 (40%)
Type of AF, n (%)			
Persistent	692 (80%)	4037 (83%)	6819 (80%)
Paroxysmal	156 (18%)	771 (16%)	1587 (19%)
New onset / newly diagnosed	15 (2%)	75 (2%)	112 (1%)
$CHADS_2$ score, mean (SD)	3.65 (1.01)	3.67 (1.01)	3.34 (0.87)
$CHADS_2$ score, n (%)			
1	0	0	3 (<1%)
2	63 (7%)	353 (7%)	1443 (17%)
3	418 (48%)	2255 (46%)	3543 (42%)
4	185 (21%)	1173 (24%)	2733 (32%)
5	156 (18%)	861 (18%)	796 (9%)
6	41 (5%)	241 (5%)	0
CHA_2DS_2-VASc score, mean (SD)	5.13 (1.42)	5.06 (1.42)	4.72 (1.24)
CHA_2DS_2-VASc score, alternative[†] mean (SD)	5.13 (1.42)	4.06 (1.42)	4.72 (1.24)
Presenting characteristics, median (25th, 75th)			
BMI, kg/m^2	31.2 (27.6, 35.9)	29.7 (26.3, 33.8)	27.2 (24.4, 30.5)
Systolic BP, mm Hg	130 (120, 140)	130 (120, 140)	130 (120, 140)
Diastolic BP, mm Hg	79 (70, 82)	80 (70, 85)	80 (71, 86)
Heart rate, beats/min	76 (67, 85)	76 (68, 87)	76 (67, 85)
Creatinine clearance,[‡] mL/min	71 (53, 95)	72 (55, 94)	65 (50, 82)
Baseline comorbidities, n (%)			
Prior stroke, TIA, or non-CNS embolism	284 (33%)	1663 (34%)	5864 (69%)
CAD, PAD, or carotid disease	392 (45%)	1495 (31%)	2160 (25%)
Hypertension	830 (96%)	4649 (95%)	7431 (87%)
Congestive HF	600 (70%)	3220 (66%)	5088 (60%)
COPD	128 (15%)	539 (11%)	830 (10%)
Medications, n (%)			
Prior VKA use	620 (72%)	3125 (64%)	5159 (61%)
Prior chronic ASA use	323 (37%)	1811 (37%)	3071 (36%)
ACE inhibitor/ARB at baseline	742 (86%)	3922 (80%)	5919 (69%)
Beta blocker at baseline	626 (73%)	3242 (66%)	5382 (63%)
Digitalis at baseline	381 (44%)	2025 (41%)	3062 (36%)
Diuretic at baseline	675 (78%)	3172 (65%)	4643 (55%)

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; HF = heart failure; PAD = peripheral artery disease; SD = standard deviation; TIA = transient ischemic attack; VKA = vitamin K antagonist.

[†]Score calculated using insulin-treated diabetes, in place of diabetes alone. This has the effect of reducing the score by 1 point for each patient in the diabetes/no insulin group; scores in the other groups remain the same.

[‡]Cockcroft and Gault formula.

diabetes. Patients with insulin-treated diabetes had higher rates of heart failure and COPD. Notably, patients without diabetes were more likely to have had a prior stroke, TIA, and systemic embolism but less likely to have coronary artery disease and peripheral artery disease (Table 1).

Outcomes according to diabetes treatment

Unadjusted, raw frequencies of the efficacy and safety events are shown in Table 2. Notably, the event rates of stroke and systemic embolism were similar between the diabetes and no-diabetes groups. This difference is an artifact of the ROCKET AF inclusion criteria where enrolled patients had to have either a prior stroke, TIA, or systemic embolism or at least 2 other risk factors (congestive heart failure, low ejection fraction, hypertension, older age, or diabetes). Most patients tended to fall into 1 of 2 groups: patients with a prior thromboembolic event and no other risk factors; and patients with diabetes and another risk factor, but no prior thromboembolic history. This is largely responsible for the higher rate of stroke (and stroke composite) in the no-diabetes group. Adjusted outcomes are shown in Table 3.

Patients with non–insulin-treated diabetes had an increased risk of systemic embolism (HR 1.27, 95% CI 1.01–1.58), stroke (HR 1.33, 95% CI 1.06–1.68), MI (HR 1.64, 95% CI 1.17–2.30), all-cause death (HR 1.26, 95%

Table 2 Unadjusted frequency of safety and efficacy outcomes according to diabetes status and insulin use

	Events/100 patient-years (total events)		
	Insulin-treated diabetes	Non–insulin-treated diabetes	No diabetes
Efficacy outcomes			
N	858	4840	8473
Stroke or SE	2.36 (30)	2.09 (168)	2.42 (364)
Stroke	2.28 (28)	1.97 (159)	2.22 (335)
Stroke, SE, vascular death, or MI	6.82 (104)	5.81 (451)	5.14 (769)
MI	1.88 (33)	1.29 (102)	0.81 (124)
All-cause death	5.30 (93)	5.12 (402)	4.31 (661)
Vascular death	3.22 (56)	3.36 (263)	2.77 (425)
Safety outcomes			
N	862	4872	8502
Major or NMCR bleeding	16.41 (194)	14.98 (925)	14.64 (1702)
Major bleeding	4.02 (57)	3.61 (248)	3.31 (429)
Hemoglobin drop ≥2 g/dL	2.59 (41)	2.68 (184)	2.26 (294)
Transfusion ≥2 units	1.75 (28)	1.58 (107)	1.35 (176)

MI = myocardial infarction; NMCR = nonmajor clinically relevant; SE = systemic embolism.

CI 1.08–1.46), and vascular death (HR 1.33, 95% CI 1.11–1.60) compared to those with no diabetes. Compared to patients with no diabetes, those with insulin-treated diabetes had an increased risk of the composite outcome of stroke/systemic embolism, vascular death, or MI (HR 1.57, 95% CI 1.19–2.08) and of MI alone (HR 2.31, 95% CI 1.33–4.0) (Table 3). Notably, when efficacy outcomes were compared between patients with insulin-treated diabetes and those with non–insulin-treated diabetes, there were no significant differences (Table 3). In addition, there were no differences in safety outcomes between any of the diabetes groups.

In the comparison of patients with diabetes on insulin vs those on oral medications, there were no differences in safety or efficacy endpoints (Table 4). In insulin-treated diabetes compared to diet-controlled diabetes, there was an increased risk of the composite of stroke/systemic embolism, vascular death, or MI (HR 1.43, 95% CI 1.08–1.89) and MI alone (HR 2.13, 95% CI 1.16–3.91) (Table 4). Similarly, in diabetes treated with oral medications compared to diet-controlled diabetes, there was an increased risk of the composite of stroke/systemic embolism, vascular death, or MI (HR 1.38, 95% CI 1.13–1.70) and MI alone (HR 1.79, 95% CI 1.10–2.94) (Table 4).

Diabetes categorization and risk stratification

When CHA_2DS_2-VASc score was calculated using all patients with diabetes, the Cox model with stroke/systemic embolism as the outcome had a c-index of 0.610 (95% CI 0.59–0.63). When only insulin-treated diabetes was used for the diabetes criterion, the model c-index was 0.615 (95% CI 0.59–0.64).

Discussion

Prior research has suggested that insulin use in patients with diabetes confers significant risk for thromboembolism in patients with AF. Our analysis from an international trial that included more than 14,000 patients, 40% of whom had diabetes at baseline, revealed 3 major findings. First, these data confirm that patients with diabetes have increased risk of cardiovascular events, including stroke, when compared to patients without diabetes. Second, and importantly, there was no evidence of differential risk in patients treated with oral hypoglycemic agents or insulin. Moreover, substitution of insulin-treated diabetes (instead of any diabetes) in the CHA_2DS_2-VASc score did not dramatically improve discriminatory capacity.

Prior cohort studies have examined which factors carry the greatest stroke risk in patients with AF and diabetes. Ashburner and colleagues[6] observed the duration of diabetes was more strongly associated with the occurrence of ischemic stroke than glycemic control as measured by hemoglobin A1c. Conversely, Saliba and colleagues[15] observed that hemoglobin A1c was associated with a significant and linear increase in the risk of stroke. Similarly, Fangel and colleagues[16] observed, in patients with incident AF and type 2 diabetes mellitus, that increasing levels of HbA1c were associated with a higher risk of thromboembolism. This finding was also supported in a recent study by Patlolla and colleagues[17] that observed that patients with both diabetes and AF had a significant 32% higher risk of stroke compared to patients with AF and no diabetes and that higher A1c levels were associated with increased risk of mortality.

Regarding the type of diabetes treatment, investigators from the PREFER registry[7] reported that among a cohort of 5717 patients with AF, of whom 1288 had diabetes and 22.4% were on insulin, the risk of stroke/systemic embolism at 1 year was significantly higher in patients with insulin-treated diabetes compared to patients with no diabetes (5.2% vs 1.9%; HR 2.89, 95% CI 1.67–5.02) and those with non–insulin-treated diabetes (5.2% vs 1.8%; HR 2.96, 95% CI 1.49–5.87). Additionally, they also found that the risk of stroke/systemic embolism remained significant even after adjusting for the duration of diabetes.[7] In a 2019 analysis of the Medicare population, Mentias and colleagues[18] found that patients had an incremental risk for stroke and

Table 3 Adjusted hazards of efficacy and safety outcomes according to diabetes status and insulin use

	Insulin-treated diabetes vs non–insulin-treated diabetes		Non–insulin-treated diabetes vs no diabetes		Insulin-treated diabetes vs no diabetes	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Efficacy outcomes						
Stroke or SE	1.14 (0.74–1.76)	.56	1.27 (1.01–1.58)	.04	1.44 (0.88–2.37)	.15
Stroke	1.17 (0.75–1.82)	.50	1.33 (1.06–1.68)	.01	1.56 (0.93–2.60)	.09
Stroke, SE, vascular death, or MI	1.15 (0.91–1.47)	.25	1.37 (1.18–1.57)	<.001	1.57 (1.19–2.08)	.001
MI	1.41 (0.89–2.22)	.15	1.64 (1.17–2.30)	.004	2.31 (1.33–4.01)	.003
All-cause death	1.02 (0.79–1.32)	.89	1.26 (1.08–1.46)	.003	1.28 (0.98–1.68)	.07
Vascular death	0.93 (0.67–1.31)	.69	1.33 (1.11–1.60)	.002	1.25 (0.86–1.80)	.24
Safety outcomes						
Major or NMCR bleeding	1.01 (0.84–1.20)	.94	1.01 (0.92–1.11)	.85	1.02 (0.85–1.21)	.86
Major bleeding	0.96 (0.68–1.34)	.81	1.05 (0.88–1.26)	.56	1.01 (0.71–1.43)	.95
Hemoglobin drop ≥2 g/dL	0.84 (0.57–1.23)	.36	1.06 (0.86–1.31)	.58	0.89 (0.60–1.31)	.54
Transfusion ≥2units	0.92 (0.57–1.48)	.74	0.96 (0.73–1.26)	.77	0.88 (0.55–1.43)	.62

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; NMCR = nonmajor clinically relevant; SE = systemic embolism.

MI based on their diabetes status and insulin use, where insulin-treated diabetes had the highest risk, followed by non–insulin-treated and then those without diabetes. Their results differed slightly from the PREFER analysis, in that the risk of stroke between non-insulin diabetes and no diabetes in PREFER was similar.[18] Finally, in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF),[19] the presence of diabetes in patients with AF was linked with an increased burden of symptoms and higher risk of death and hospitalizations, but no increase in thromboembolic events.

From the numerous studies above, one can see that there are a limited number of studies in this space that all seemingly lead to different conclusions regarding the true culprit behind the increased thromboembolic risk seen in patients with AF and diabetes. Our analysis of ROCKET AF data aimed to explore the external validity of the complex interaction between diabetes and AF observed in prior studies. We found that patients with AF and diabetes experienced worse cardiovascular outcomes when compared to patients with no diabetes. These findings are somewhat expected given the pathophysiology of type 2 diabetes and its tendency to create a prothrombotic state mediated by increased inflammation, platelet activity, hypercoagulability, and endothelial dysfunction.[20]

In contrast with previous findings, we found no difference in outcomes in patients with AF and insulin-treated diabetes compared to those with non–insulin-treated diabetes. Likewise, we found that the discriminatory ability of the CHA_2DS_2-VASc score for stroke risk prediction was not improved with the addition of diabetes with insulin as a modifier to the diabetes criterion. While departing somewhat from the literature, our results are concordant with a recent study by Jensen and colleagues.[21] In their registry-based observational cohort study, researchers found that while patients with comorbid AF and diabetes had an increased risk of stroke compared to patients with AF alone, their stroke risk did not differ significantly based on whether insulin was used in their diabetes management.[21]

There are several possible reasons for the absence of differential risk in patients treated with insulin. Firstly, it could be that insulin use is a poor surrogate for diabetes severity and glycemic control; and instances in which insulin is prescribed may not always connote worse disease. For example, a patient with well-controlled diabetes may remain on insulin therapy despite an indication for de-escalation of therapy, or an individual with poorly controlled diabetes may not be prescribed insulin despite an appropriate indication owing to socioeconomic or behavioral barriers. Next, perhaps the key to incremental risk in patients with AF and diabetes is actually a composite measure of the level of severity of one's diabetes, the full duration of this metabolic derangement, and other nuanced patient characteristics. We know that the interaction between diabetes, AF, and the risk for stroke/systemic embolism is a complex one; thus our analysis and others have suffered from seeking out and trying to explain this relationship with one discrete, objective measure. Similarly, it may be comorbid illnesses such as hypertension and heart failure that accompany diabetes and insulin use, rather than insulin use itself, that increase thromboembolic risk and thus explains our findings. Fourth, the attenuation of differences in cardiovascular and thromboembolic risk seen in our study could be the result of effective anticoagulation, and anticoagulation may be successful in mitigating thromboembolic risk in most patients with diabetes regardless of insulin use. Finally, we cannot completely rule out type II error, as it is possible that we were unable to detect an existing difference owing to the sample size and event rate, as only 5.9% of our cohort was on insulin therapy.

When we compared patients with insulin-treated diabetes to those with diet-controlled diabetes, we observed an increased risk of composite outcomes and MI. An increased risk of composite outcomes and MI was also seen in the comparison of diabetes treated with oral medication and diabetes

Table 4 Adjusted hazards of efficacy and safety outcomes according to diabetes status and non-insulin treatment

	Diabetes – insulin vs Diabetes – oral med		Diabetes – oral med vs Diabetes – diet control		Diabetes – insulin vs Diabetes – diet control	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Efficacy outcomes						
Stroke or SE	1.03 (0.66–1.61)	.89	1.33 (0.95–1.86)	.10	1.37 (0.84–2.25)	.21
Stroke	1.06 (0.67–1.68)	.79	1.30 (0.92–1.83)	.14	1.38 (0.83–2.29)	.21
Stroke, SE, vascular death, or MI	1.03 (0.80–1.32)	.80	1.38 (1.13–1.70)	.002	1.43 (1.08–1.89)	.01
MI	1.19 (0.75–1.89)	.47	1.79 (1.10–2.94)	.02	2.13 (1.16–3.91)	.01
All-cause death	0.97 (0.74–1.27)	.82	1.15 (0.93–1.42)	.19	1.12 (0.84–1.49)	.46
Vascular death	0.87 (0.61–1.23)	.42	1.25 (0.96–1.62)	.10	1.08 (0.74–1.57)	.69
Safety outcomes						
Major or NMCR bleeding	1.08 (0.90–1.30)	.39	0.81 (0.70–0.93)	.003	0.88 (0.72–1.07)	.19
Major bleeding	1.01 (0.71–1.43)	.96	0.87 (0.66–1.14)	.31	0.87 (0.59–1.29)	.50
Hemoglobin drop $\geq$2 g/dL	0.86 (0.58–1.29)	.48	0.92 (0.66–1.27)	.60	0.79 (0.51–1.24)	.31
Transfusion $\geq$2 units	0.91 (0.56–1.47)	.69	1.09 (0.67–1.75)	.74	0.98 (0.54–1.79)	.95

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; NMCR = nonmajor clinically relevant; SE = systemic embolism.

treated with diet control. From our data, it appears that the observed increase in composite outcomes was largely mediated by the increased risk of MI. Diabetes is a known risk factor for coronary artery disease. Studies have shown that in patients without a prior history of MI, those patients with diabetes have a 7-year risk of MI of 20.2%, compared to 3.5% for patients without diabetes.[22] For patients with a prior history of MI, the 7-year risk of MI increased to 45.0% and 18.8% for patients with and without diabetes, respectively.[22] It follows that patients with diet-controlled diabetes, with the assumption being that they had better glycemic control, truly had a lower risk of morbidity and mortality compared to patients who require diabetes medications.

There are several potential limitations that need to be considered. Firstly, this was a post hoc subgroup analysis of the ROCKET AF trial database and was not powered for evaluation of outcomes in patients with diabetes and AF, especially considering the minority of patients treated with insulin. In addition, these data are derived from a trial that enrolled patients at moderate-to-high risk for stroke/systemic embolism, and therefore the results may not be generalizable to populations with lower risk. Third, although multivariable adjustments were performed, we cannot exclude unmeasured or residual confounding. More specifically, we were unable to account for glycemic control, length of insulin exposure, or the presence/control of other vascular risk factors such as hypertension, elevated cholesterol, tobacco use, diet, and exercise. Finally, we also conducted multiple comparisons and it is possible that some associations were the result of type I error.

Conclusion

Diabetes mellitus is associated with worse outcomes in patients with AF, and these data from a large international clinical trial confirm that patients with diabetes have increased risk of cardiovascular events. However, there was no evidence of differential risk in patients treated with oral hypoglycemic agents or insulin. Whether a patient receives insulin for treatment of their diabetes does not appear to meaningfully improve stroke risk stratification. Further work is needed to better understand how to improve outcomes in patients with AF and diabetes.

Funding Sources

ROCKET AF was funded by Johnson & Johnson and Bayer.

Disclosures

Ugowe, Hellkamp, Wang: Nothing to report. Becker: Consulting fees/Honoraria from Boehringer Ingelheim, Daiichi-Sankyo, Portola; Research grants from AstraZeneca. Berkowitz: Employee of Bayer U.S. LLC. Breithardt: Consulting fees/Honoraria from Bayer Health Care, J&J, Sanofi-Aventis. Fox: Consulting fees/Honoraria from Astra Zeneca, Bayer, Janssen, Merck & Co, Inc, Sanofi-Aventis/Regeneron; Research grants from Eli Lilly, GSK. Halperin: Consulting fees/Honoraria from Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Medtronic, Inc, Ortho-McNeil-Janssen Pharmaceuticals, Inc, Pfizer, Inc. Hankey: Speaker's bureau for Bayer Healthcare Pharmaceuticals. Mahaffey: Available at https://profiles.stanford.edu/kenneth-mahaffey?tab=research-and-scholarship. Nessel: Employee of Janssen Research & Development. Singer: Consulting fees/Honoraria from Boehringer Ingelheim, Bristol-Myers Squibb, CVS Health, Johnson & Johnson, Inc, Medtronic, Merck, Pfizer; Research grants from Boehringer Ingelheim, Bristol-Myers Squibb, Medtronic. Patel: Institutional research grants from AstraZeneca, CSL, HeartFlow, Janssen Research. Piccini: Research grants from Abbott, American Heart Association, Boston Scientific, Gilead, Janssen Pharmaceuticals, and the NHLBI; consulting fees from Abbott, Allergan, ARCA Biopharma, Biotronik, Boston Scientific, Johnson & Johnson, LivaNova, Medtronic, Milestone, Oliver Wyman Health, Sanofi, Philips, and Up-to-Date.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All patients provided written informed consent.

Ethics Statement

The study conformed to the principles outlined in the Declaration of Helsinki, as revised in 2013, and was approved by each participating site's ethics committee or institutional review board.

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