Pharmacotherapy for diabetes and stroke risk: Results from ROCKET AF

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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 1.18–1.57). 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

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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,
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 CHA2DS2-VASc score did not dramatically improve its discriminatory capacity in stroke risk prediction.

hemostatic changes, and inflammation in patients with AF. This correlation has led to the inclusion of diabetes in stroke risk stratification schemes such as the CHA2DS2-VASc score.

The efficacy and safety of rivaroxaban compared to warfarin in patients with AF and diabetes has previously been examined. However, some uncertainty remains as to which aspect of diabetes contributes most to the increased risk of stroke in patients with AF. 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. 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). 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 ≤35%, hypertension, age ≥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.

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.

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. 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
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 CHA2DS2-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 CHA2DS2-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 diabetes.
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% 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% CI 1.01–1.58).

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**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%)             |
| CHADS2 score, mean (SD)               | 3.65 (1.01)                       | 3.67 (1.01)                            | 3.34 (0.87)          |
| CHADS2 score, n (%)                   | 1                                  | 0                                      | 3 (<1%)              |
|                                       | 2                                  | 63 (7%)                                | 353 (7%)             |
|                                       | 3                                  | 418 (48%)                              | 2255 (46%)           |
|                                       | 4                                  | 185 (21%)                              | 1173 (24%)           |
|                                       | 5                                  | 156 (18%)                              | 861 (18%)            |
|                                       | 6                                  | 41 (5%)                                | 241 (5%)             |
| CHA2DS2-VASc score, mean (SD)         | 5.13 (1.42)                       | 5.06 (1.42)                            | 4.72 (1.24)          |
| CHA2DS2-VASc score, alternative† mean (SD) | 5.13 (1.42)                       | 5.06 (1.42)                            | 4.72 (1.24)          |
| Presenting characteristics, median    |                                   |                                         |                      |
| (25th, 75th)                          |                                   |                                         |                      |
| BMI, kg/m²                            | 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.
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 CHA2DS2-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 CHA2DS2-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 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 observed that hemoglobin A1c was associated with a significant and linear increase in the risk of stroke. Similarly, Fangel and colleagues 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 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 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. In a 2019 analysis of the Medicare population, Mentias and colleagues found that patients had an incremental risk for stroke and
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. Finally, in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), 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.

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\textsubscript{2}-DS\textsubscript{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. 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.

| Efficacy outcomes                  | Insulin-treated diabetes vs non-insulin-treated diabetes | Non-insulin-treated diabetes vs no diabetes | Insulin-treated diabetes vs no diabetes |
|-----------------------------------|----------------------------------------------------------|-------------------------------------------|----------------------------------------|
| Stroke or SE                      | 1.14 (0.74–1.76)                                        | 1.27 (1.01–1.58)                           | 1.44 (0.88–2.37)                        |
| Stroke                            | 1.17 (0.75–1.82)                                        | 1.33 (1.06–1.68)                           | 1.56 (0.93–2.60)                        |
| Stroke, SE, vascular death, or MI | 1.15 (0.91–1.47)                                        | 1.37 (1.18–1.57)                           | 1.57 (1.19–2.08)                        |
| MI                                | 1.41 (0.89–2.22)                                        | 1.64 (1.17–2.30)                           | 2.31 (1.33–4.01)                        |
| All-cause death                   | 1.02 (0.79–1.32)                                        | 1.26 (1.08–1.46)                           | 1.28 (0.98–1.68)                        |
| Vascular death                    | 0.93 (0.67–1.31)                                        | 1.33 (1.11–1.60)                           | 1.25 (0.86–1.80)                        |

| Safety outcomes                  | Insulin-treated diabetes vs non-insulin-treated diabetes | Non-insulin-treated diabetes vs no diabetes | Insulin-treated diabetes vs no diabetes |
|----------------------------------|----------------------------------------------------------|-------------------------------------------|----------------------------------------|
| Major or NMCR bleeding           | 1.01 (0.84–1.20)                                        | 1.01 (0.92–1.11)                           | 1.02 (0.85–1.21)                        |
| Major bleeding                   | 0.96 (0.68–1.34)                                        | 1.05 (0.88–1.26)                           | 1.01 (0.71–1.43)                        |
| Hemoglobin drop ≥2 g/dL          | 0.84 (0.57–1.23)                                        | 1.06 (0.86–1.31)                           | 0.89 (0.60–1.31)                        |
| Transfusion ≥2 units             | 0.92 (0.57–1.48)                                        | 0.96 (0.73–1.26)                           | 0.88 (0.55–1.43)                        |

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

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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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