The Prognostic Significance of Diabetes and Microvascular Complications in Patients With Heart Failure With Preserved Ejection Fraction

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OBJECTIVE

This study examined the prognostic significance of diabetes and microvascular complications in patients with heart failure with preserved ejection fraction (HFpEF).

RESEARCH DESIGN AND METHODS

This analysis included 3,385 patients (mean age 69 ± 9.6 years; 49% male; 89% white) with HFpEF from the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT). Diabetes and microvascular complications were ascertained by self-reported history and medical record review. Microvascular complications included neuropathy, nephropathy, and retinopathy. Outcomes included hospitalization, hospitalization for heart failure, death, and cardiovascular death. Cox regression was used to examine the risk of each outcome associated with diabetes and microvascular complications.

RESULTS

Of the 1,109 subjects (32%) with diabetes, 352 (32%) had at least one microvascular complication. Patients with diabetes and microvascular complications had an increased risk for hospitalization (no diabetes: referent; diabetes + no microvascular complication: hazard ratio [HR] 1.18, 95% CI 1.01, 1.37; diabetes + microvascular complications: HR 1.54, 95% CI 1.25, 1.89; *P*-trend <0.001), hospitalization for heart failure (no diabetes: referent; diabetes + no microvascular complication: HR 1.51, 95% CI 1.14, 1.99; diabetes + microvascular complications: HR 1.97, 95% CI 1.38, 2.80; *P*-trend <0.001), death (no diabetes: referent; diabetes + no microvascular complication: HR 1.35, 95% CI 1.04, 1.75; diabetes + microvascular complications: HR 1.73, 95% CI 1.22, 2.45; *P*-trend = 0.0017), and cardiovascular death (no diabetes: referent; diabetes + no microvascular complication: HR 1.34, 95% CI 0.96, 1.86; diabetes + microvascular complications: HR 1.70, 95% CI 1.09, 2.65; *P*-trend = 0.018). When the analysis was limited to participants who reported prior hospitalization for heart failure (*n* = 2,449), a higher risk of rehospitalization for heart failure was observed across diabetes categories (no diabetes: referent; diabetes + no microvascular complication: HR 1.40, 95% CI 1.01, 1.96; diabetes + microvascular complications: HR 1.78, 95% CI 1.18, 2.70; *P*-trend = 0.0036).

CONCLUSIONS

Diabetes is associated with adverse cardiovascular outcomes in HFpEF, and the inherent risk of adverse outcomes in HFpEF patients with diabetes varies by the presence of microvascular complications.

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Heart failure with preserved ejection fraction (HFpEF) is a growing health care concern with rising prevalence (1). Nearly half of all patients with heart failure symptoms have HFpEF (2). Diabetes is a common comorbid condition that is present in almost half of HFpEF patients, and its presence plays an important role in the development of HFpEF (1). In addition, diabetes confers a nearly twofold increase in morbidity and mortality in patients with HFpEF (3).

Diabetes is associated with various microvascular complications, such as autonomic and peripheral neuropathy, retinopathy, and nephropathy, and these complications are associated with adverse cardiovascular outcomes (4). Although diabetes is associated with poor outcomes in HFpEF (5), diabetes is not a uniform disorder, and the risk of adverse cardiovascular outcomes may vary by disease severity (e.g., presence of microvascular complications). Therefore, we examined the prognostic significance of diabetes and microvascular complications in patients with HFpEF in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT).

RESEARCH DESIGN AND METHODS

Study Design and Patients

TOPCAT was a multicenter, international, randomized, double-blind, placebo-controlled study to examine the efficacy of spironolactone in patients with HFpEF. The design, inclusion criteria, and baseline characteristics of the trial have been published previously (6,7). Briefly, 3,445 patients with symptomatic HFpEF from 270 sites in 6 countries were enrolled between August 2006 and January 2012. The primary goal of the trial was to determine whether spironolactone was associated with a reduction in the composite outcome of cardiovascular mortality, aborted cardiac arrest, or heart failure hospitalization in patients with HFpEF (e.g., documented ejection fraction $\geq$45%). In this analysis, we examined the relationship between total microvascular disease burden in diabetes and the risk of hospitalization, hospitalization for heart failure, death, and cardiovascular death.

Baseline Characteristics

Patients who participated in TOPCAT underwent a detailed baseline evaluation (7). Age, sex, race, and smoking were obtained by self-reported history. Smoking was defined as the current use of cigarettes. Medical histories for the following diagnoses were obtained by self-report and medical record review: coronary heart disease, stroke, New York Heart Association Functional Classification, and prior heart failure hospitalization. Systolic blood pressure and BMI were obtained by trained staff, and laboratory data included serum creatinine, glomerular filtration rate, hemoglobin, and the urine albumin-to-creatinine ratio. Medication data also were obtained during the initial study visit, and the following were included in this analysis: aspirin, β-blockers, ACE inhibitors/angiotensin II receptor blockers, and statins.

Diabetes and Microvascular Complications

Patients were asked about their diabetes status and characteristics related to diabetes severity during the baseline visit. History of diabetes, duration of diabetes, diabetes medications (insulin vs. noninsulin), and microvascular complications were ascertained by follow-up medical record review. Microvascular complications included neuropathy, nephropathy, and retinopathy.

Outcomes

Outcomes in TOPCAT were adjudicated by a clinical end point committee, and the details of this process and definitions for each outcome examined have been described (6,8). The outcomes examined in this analysis included hospitalization, hospitalization for heart failure, death, and cardiovascular death. Briefly, hospitalization for heart failure was defined as the unexpected presentation to an acute care facility requiring an overnight stay with symptoms and physical examination findings consistent with heart failure and treatment with intravenous vasodilators, inotropes, mechanical fluid removal, or hemodynamic support. Cardiovascular death was defined as death caused by one of the following: myocardial infarction, worsening heart failure, sudden death, stroke, pulmonary embolism, death occurring during a cardiovascular-related procedure, or other cardiovascular death. Death included the composite of cardiovascular and noncardiovascular death.

Statistical Analysis

Diabetes was categorized as *1*) no diabetes, *2*) diabetes + no microvascular complication, or *3*) diabetes + microvascular complications. Baseline characteristics were compared across these categories. Categorical variables were reported as frequency and percentage, and continuous variables were reported as mean $\pm$ SD. Characteristics were compared between all groups using the χ^2 method for categorical data and the ANOVA procedure for continuous variables. Comparisons were also made between diabetes + no microvascular complication and diabetes + microvascular complications using the χ^2 method and Student *t* test. Follow-up time was defined as the time from randomization until one of the following: outcome of interest, death, loss to follow-up, or end of follow-up. Kaplan-Meier estimates were used to examine the unadjusted cumulative incidence estimates of each outcome associated with diabetes and microvascular complications. Cox regression was used to examine the risk of each outcome associated with each diabetes category (referent: no diabetes).

Multivariable models were constructed as follows: model 1, adjusted for age, sex, and race; model 2, adjusted for model 1 covariates plus smoking, systolic blood pressure, serum creatinine, BMI, aspirin, ACE inhibitors/angiotensin II receptor blockers, β-blockers, statin, randomization group, New York Heart Association Functional Classification, coronary heart disease, stroke, prior heart failure hospitalization, insulin, duration of diabetes, and hemoglobin; and model 3, adjusted for model 2 covariates plus the urine albumin-to-creatinine ratio.

A secondary analysis was performed in which we limited patients to those who reported prior heart failure hospitalization to determine whether the magnitude of the association between diabetes and each outcome was dependent on prior admission. Also, to determine whether the risk of adverse events increased incrementally with the number of microvascular complications, we performed an analysis limited to patients with diabetes (n = 1,109) across the following categories: *1*) no microvascular complications (referent); *2*) one microvascular complication; *3*) two or more microvascular complications. In addition, as a result of the differences in the baseline characteristics and event rates observed between patients recruited in Russia and Georgia versus the Americas (9), we examined

whether the association of diabetes and its microvascular complications with outcomes varied by region of enrollment (Russia/Georgia vs. the Americas). Statistical significance was defined as $P < 0.05$. SAS 9.4 software (SAS Institute Inc., Cary, NC) was used for all analyses.

RESULTS

This analysis included 3,385 patients (mean age 69 ± 9.6 years; 49% male; 89% white). A total of 1,109 (32%) had diabetes, and 352 (32%) had at least one microvascular complication. Of these patients with diabetes, neuropathy was present in 232 (21%), nephropathy in 120 (11%), and retinopathy in 167 (15%). The baseline characteristics across diabetes categories are reported in Table 1.

During a median follow-up of 3.4 years (25%, 75% = 2.0, 4.9), a total of 1,524 hospitalizations, 437 hospitalizations for heart failure, 516 deaths, and 330 cardiovascular deaths occurred. The cumulative incidence estimates for hospitalization, hospitalization for heart failure, death, and cardiovascular death by diabetes status are depicted in Figs. 1 and 2. An increased risk for hospitalization (*P*-trend <0.001), hospitalization for heart failure (*P*-trend <0.001), death (*P*-trend = 0.0017), and cardiovascular death (*P*-trend = 0.018) was observed across categories of diabetes and microvascular complications (Table 2).

When the analysis was limited to participants who reported prior hospitalization for heart failure (*n* = 2,449), a higher risk of rehospitalization for heart failure was observed in patients with diabetes + microvascular complications than in those with diabetes + no microvascular complication (no diabetes: referent; diabetes + no microvascular complication: hazard ratio [HR] 1.40, 95% CI 1.01, 1.96; diabetes + microvascular complications: HR 1.78, 95% CI 1.18, 2.70; *P*-trend = 0.0036). In a secondary analysis limited to persons with diabetes, a higher risk of hospitalization (*P*-trend <0.001), hospitalization for heart failure (*P*-trend = 0.0063), and death (*P*-trend = 0.037) was observed with a higher number of microvascular complications (Supplementary Table 1). The risk of cardiovascular death did not increase with a higher number of microvascular complications (*P*-trend = 0.45). When we examined the association between diabetes and each outcome by country of origin (Russia/Georgia vs. the Americas), similar findings were observed in the patients from Russia/Georgia compared with the Americas (data not shown).

CONCLUSIONS

This analysis from TOPCAT found diabetes was associated with an increased risk for hospitalization, hospitalization for heart failure, death, and cardiovascular death in patients with HFpEF, and the risk for these adverse events was greater among patients with diabetes who had known microvascular complications. Overall, our findings provide evidence that diabetes represents an important comorbid condition in HFpEF with regard to

Table 1—Baseline characteristics (*N* = 3,385)

		Diabetes			
	No diabetes	Microvascular complications			
Characteristic	(*n* = 2,294)	No (*n* = 739)	Yes (*n* = 352)	*P* value*	*P* value†
Age, years	69 ± 10	68 ± 9.1	67 ± 8.6	0.0089	0.026
Male	1,084 (47)	354 (48)	205 (58)	<0.001	0.0014
White	2,114 (92)	611 (83)	284 (81)	<0.001	0.42
Current smoker	272 (12)	58 (8)	29 (8)	0.0027	0.82
Coronary heart disease	715 (31)	329 (45)	169 (48)	<0.001	0.28
Stroke	157 (7)	65 (9)	39 (11)	0.0098	0.23
Systolic blood pressure, mmHg	129 ± 13	131 ± 15	129 ± 15	0.0067	0.044
BMI, kg/m^2	30 ± 6.2	35 ± 7.8	37 ± 7.3	<0.001	<0.001
Serum creatinine, mg/dL	1.05 ± 0.27	1.12 ± 0.32	1.26 ± 0.37	<0.001	<0.001
Glomerular filtration rate, mL/min/1.73 m^2	69 ± 20	67 ± 21	60 ± 19	<0.001	<0.001
New York Heart Association class III–IV	668 (29)	287 (39)	163 (46)	<0.001	0.019
Prior heart failure hospitalization	1,647 (72)	529 (72)	273 (78)	0.069	0.037
Aspirin use	1,463 (64)	499 (68)	256 (73)	0.0019	0.082
β-Blockers	1,765 (77)	573 (78)	298 (85)	0.0050	0.0061
ACE inhibitors/ARBs	1,898 (83)	650 (88)	304 (86)	0.0017	0.46
Statin	1,012 (44)	488 (66)	268 (76)	<0.001	<0.001
Insulin	—	215 (29)	203 (58)	—	<0.001
Oral diabetes medications	—	488 (66)	215 (61)	—	0.11
Diabetes duration, years	—	9.3 ± 8.8	14.2 ± 10	—	<0.001
Log(urine albumin-to-creatinine ratio), mg/g	3.4 ± 1.6	3.8 ± 1.9	4.1 ± 1.9	<0.001	0.028
Hemoglobin, g/dL	13.5 ± 1.7	13.0 ± 1.7	12.7 ± 1.6	<0.001	0.0023
Spironolactone	1,141 (50)	378 (51)	178 (51)	0.79	0.86
Russia/Georgia	1,340 (58)	244 (33)	84 (24)	<0.001	0.0021

Data are presented as mean ± SD or as *n* (%). ARBs, angiotensin II receptor blockers. **P* value reflects comparison between all groups using the χ^2 method for categorical variables and the ANOVA test for continuous variables. †*P* value reflects comparison between those with diabetes with and without microvascular complications using the χ^2 method for categorical variables and the Student *t* test for continuous variables.

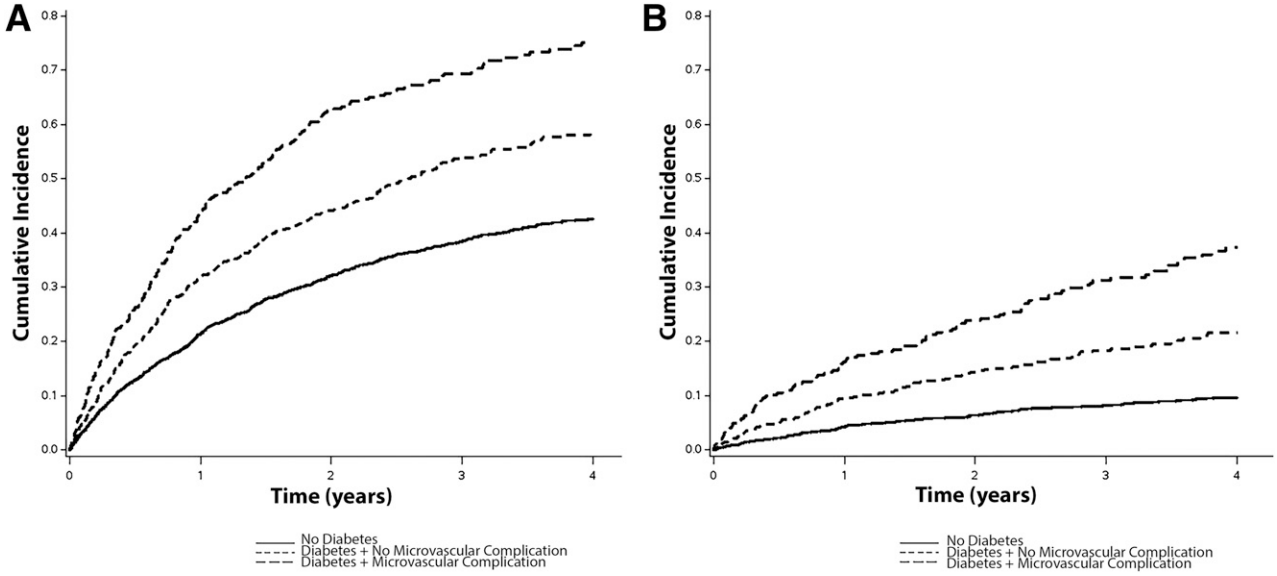

Figure 1—Unadjusted cumulative incidence curves are shown for hospitalization (*A*) (log-rank $P < 0.001$) and hospitalization for heart failure (*B*) (log-rank $P < 0.001$).

prognosis and utilization of health care resources and that the inherent risk of adverse outcomes in HFpEF patients with diabetes varies by the presence of microvascular complications.

Several secondary analyses of clinical trial data have demonstrated that the presence of diabetes is associated with adverse outcomes in HFpEF. In a post hoc analysis from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) study, diabetes was associated with a twofold increased risk of cardiovascular death or heart failure hospitalization (10). Similarly, in the Irbesartan in Heart Failure with Preserved Ejection Fraction Trial (I-PRESERVE) study, patients with diabetes had a 1.75-fold increased risk of cardiovascular death or heart failure hospitalization (5). The findings in this analysis demonstrated that the risk of adverse events increased linearly with the number of microvascular complications. These data enhance our understanding of the adverse risk profile among individuals with diabetes who have HFpEF, as we have shown that microvascular complications have important prognostic information in this group. Furthermore, we have demonstrated that microvascular complications represent an important marker for heart failure rehospitalization, a finding that has not been previously reported.

The mechanisms that link diabetes and the presence of microvascular complications with adverse events in patients with HFpEF are unknown. Microvascular disease results from significant hyperglycemia in tissues where glucose uptake occurs independently of insulin. Subsequently, tissue damage occurs as a result of glucose-mediated damage, oxidative stress, and advanced glycation end products (11). Hyperglycemia also leads to the development of atherosclerosis through endothelial dysfunction and

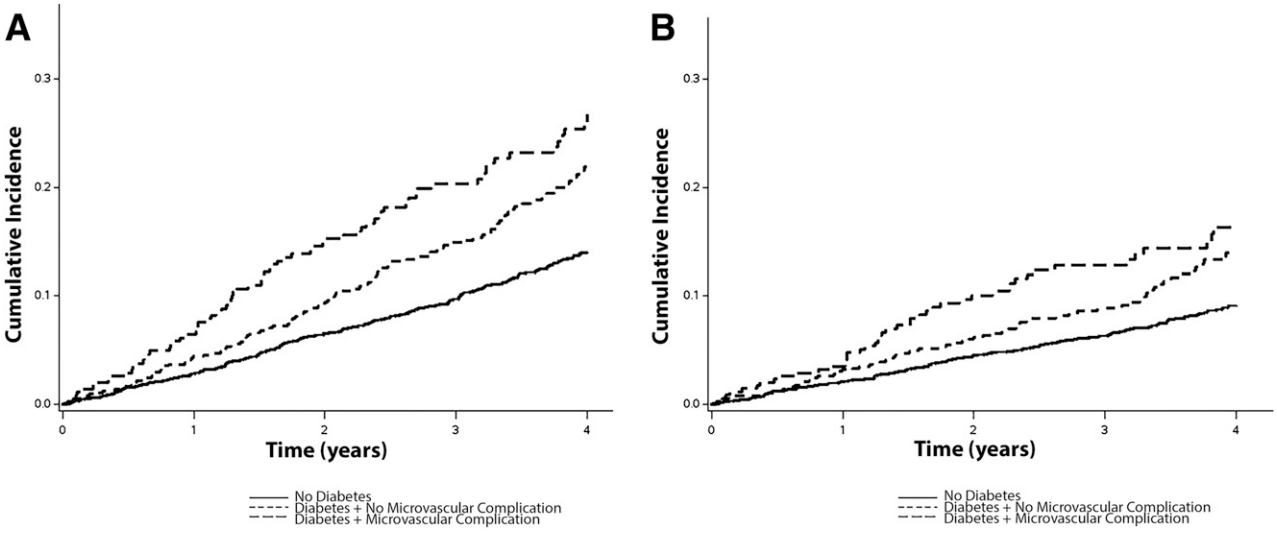

Figure 2—Unadjusted cumulative incidence curves are shown for death (*A*) (log-rank $P < 0.001$) and cardiovascular death (*B*) (log-rank $P < 0.001$).

Table 2—Risk of hospitalization and death with diabetes (N = 3,385)

Outcome	Events/*n* at risk	Model 1* HR (95% CI)	*P* value	Model 2† HR (95% CI)	*P* value	Model 3‡ HR (95% CI)	*P* value	*P*-trend§
Hospitalization								
No diabetes	896/2,294	Ref	—	Ref	—	Ref	—	<0.001
Diabetes + no microvascular complication	388/739	1.49 (1.32, 1.68)	<0.001	1.18 (1.01, 1.37)	0.036	1.16 (0.99, 1.35)	0.051	
Diabetes + microvascular complications	240/352	2.30 (1.99, 2.66)	<0.001	1.54 (1.25, 1.89)	<0.001	1.52 (1.24, 1.87)	<0.001	
Hospitalization for heart failure								
No diabetes	197/2,294	Ref	—	Ref	—	Ref	—	<0.001
Diabetes + no microvascular complication	134/739	2.19 (1.76, 2.74)	<0.001	1.51 (1.14, 1.99)	0.0042	1.46 (1.10, 1.94)	<0.001	
Diabetes + microvascular complications	106/352	3.98 (3.12, 5.08)	<0.001	1.97 (1.38, 2.80)	<0.001	1.90 (1.33, 2.72)	0.0094	
Death								
No diabetes	298/2,294	Ref	—	Ref	—	Ref	—	0.0017
Diabetes + no microvascular complication	128/739	1.51 (1.22, 1.86)	<0.001	1.35 (1.04, 1.75)	0.025	1.34 (1.03, 1.74)	0.028	
Diabetes + microvascular complications	90/352	2.29 (1.80, 2.92)	<0.001	1.73 (1.22, 2.45)	0.0019	1.72 (1.21, 2.43)	0.0023	
Cardiovascular death								
No diabetes	198/2,294	Ref	—	Ref	—	Ref	—	0.018
Diabetes + no microvascular complication	79/739	1.38 (1.06, 1.80)	0.016	1.34 (0.96, 1.86)	0.083	1.33 (0.96, 1.85)	0.090	
Diabetes + microvascular complications	53/352	1.98 (1.45, 2.69)	<0.001	1.70 (1.09, 2.65)	0.020	1.68 (1.08, 2.63)	0.022	

*Adjusted for age, sex, and race. †Adjusted for model 1 covariates plus smoking, systolic blood pressure, serum creatinine, BMI, aspirin, ACE inhibitors/angiotensin II receptor blockers, β-blockers, statin, randomization group, New York Heart Association class, coronary heart disease, stroke, prior heart failure hospitalization, insulin, duration of diabetes, and hemoglobin. ‡Adjusted for model 2 covariates plus urine albumin-to-creatinine ratio. §Represents the *P*-trend across categories. Computed using model 2 covariates.

promotion of elevated blood cholesterol. Subclinical myocardial damage is often present in patients with diabetes without clinically apparent manifestations (12,13). Therefore, microvascular complications signify that subclinical cardiovascular disease is present and that future events will likely develop (4). This is supported by the findings of this analysis, because an increased risk of death from cardiovascular causes was observed in patients with diabetes and microvascular complications.

The observed findings also possibly were related to diabetes medications that are associated with an increased risk of heart failure events. Saxagliptin and rosiglitazone have both been associated with an increased risk for hospitalization for heart failure (14,15), and the increased risk for heart failure–specific outcomes was possibly related to medications or therapies received by patients in this study. However, we were unable to account for individual diabetes medications and their effect on adverse events in this study because TOPCAT did not ascertain the specific oral agents. Nonetheless, our data demonstrate an important finding regarding the risk of adverse outcomes in HFpEF patients with diabetes, and further investigation is needed to elucidate the underlying pathophysiologic link.

The coexistence of diabetes and HFpEF portends an increased risk of morbidity and mortality. Accordingly, optimizing medical and lifestyle therapies for both conditions, while balancing the potential for adverse effects of medications, is important. Although specific recommendations do not exist regarding the management of HFpEF patients who have diabetes and microvascular complications (16), our data suggest that careful attention is needed in this heart failure population. Possibly, more frequent clinic visits or frequent monitoring of volume status is needed in HFpEF patients with diabetic microvascular complications to reduce acute decompensation and heart failure–specific outcomes. In addition, as a result of the increased risk of cardiovascular death, HFpEF patients with diabetic microvascular complications possibly merit closer evaluation if symptoms suggest underlying coronary heart disease. Although the findings of this analysis support this claim, further research is needed to determine the optimal management strategies of patients in this high-risk group before changes in clinical practice are made.

Several limitations merit attention in our analysis. Several baseline characteristics were self-reported and subjected our analysis to recall bias. Diabetes and the presence of microvascular complications were ascertained by self-reported history and review of relevant of medical records. Despite rigorous attempts to identify all patients with diabetes, it is possible that some were missed. However, the potential for misclassification of patients with diabetes did not likely result in significant bias other than reducing effect estimates toward the null. Rigorous attempts were also made to ascertain all adverse events in TOPCAT, but it is possible that events were missed. Furthermore, we included several characteristics in our multivariable models in an attempt to account for diabetes severity, yet other markers, such as hemoglobin A_{1c}, were not collected, and we acknowledge that these factors possibly introduced residual confounding into our analysis.

In conclusion, we have demonstrated that diabetes and its microvascular complications have important prognostic information regarding adverse outcomes in HFpEF. In addition, microvascular disease burden predicts heart failure rehospitalization in this high-risk group. Further investigation is needed to develop preventive strategies to reduce the morbidity and mortality in these high-risk patients and to determine optimal treatment strategies to improve outcomes in HFpEF patients with diabetes.

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