Comparison of Outcomes in Patients With Diabetes Mellitus Treated With Versus Without Insulin + Heart Failure With Preserved Left Ventricular Ejection Fraction (from the TOPCAT Study)

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We aimed to evaluate the impact of diabetes mellitus (DM) and insulin treatment on clinical outcomes in patients with heart failure and preserved left ventricular ejection fraction enrolled in the TOPCAT study. We investigated the influence of DM status (insulin-treated [ITDM], non-insulin treated [NITDM], and no diabetes [non-DM]) at baseline on time to development of the primary end point, a composite of cardiovascular (CV) mortality, heart failure hospitalization, and aborted cardiac arrest. Secondary end points included the individual components of the primary end point, myocardial infarction, stroke, all-cause mortality, hyperkalemia, and worsened renal function. Due to marked regional differences in characteristics and outcomes of the TOPCAT patients, with much lower events in patients enrolled in Russia/Georgia, we restricted our analyses on findings from patients enrolled from the Americas.

Compared to patients without DM, patients with ITDM had approximately 2-fold increased risk for the primary end point, heart failure hospitalization, and myocardial infarction (hazard ratios: 1.80, 1.97, and 2.27, respectively) and approximately 50% increases in all-cause and CV mortality. The risks for these outcomes were also increased in patients with ITDM in comparison to patients with NITDM as well (hazard ratios: 1.63, 1.65, and 2.73, respectively, and approximately 40% increases in all-cause and CV mortality). Patients with NITDM had similar risks for the primary end point and all secondary end points as patients without DM. In conclusion, the apparent increased risk of adverse outcomes in patients with heart failure and preserved left ventricular ejection fraction and ITDM merits future research to improve the prognosis of these high-risk patients.

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Approximately 50% of patients with heart failure have preserved systolic function of the left ventricle (HFpEF).[1] In these patients, diabetes mellitus (DM) is associated with increases in cardiovascular (CV) morbidity and mortality.[2−9] DM may accelerate the progression of HFpEF by deleterious effects of tissue advanced glycation end products and/or long-term microvascular coronary endothelial inflammation on diastolic cardiac function.[10−13] Currently, the impact of insulin treatment on outcomes has not been adequately clarified in patients with HFpEF and DM.[3−9] The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) was a randomized-controlled trial evaluating whether spironolactone would improve clinical outcomes in patients with HFpEF.[14−16] Our primary objective was to evaluate the relation of DM, with or without insulin treatment, with time to the primary end point in TOPCAT patients with HFpEF. Our secondary objectives were to evaluate the impact of type of DM on time to the occurrence of CV death, hospitalization for heart failure, myocardial infarction (MI), stroke, all-cause mortality, hyperkalemia, and elevated serum creatinine. Since spironolactone was associated with reduction in the primary end point in patients from the Americas,[16] we also sought to examine the impacts of randomization to spironolactone on the prognosis of patients with HFpEF and DM.

Methods

Due to marked regional differences and lower primary outcome event rates between the patients enrolled from

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Table 1
Baseline characteristics of TOPCAT patients enrolled from the Americas, stratified by diabetes mellitus status

Baseline characteristics*	Patients enrolled in the Americas			p Value
	ITDM (n = 390)	NITDM (n = 406)	No DM (n = 969)	
Age (years)	67 (61,74)	71 (64,78)	75 (66,81)	<0.001
Women	174 (45%)	185 (46%)	523 (54%)	<0.001
White	280 (72%)	313 (77%)	789 (81%)	<0.001
Body mass index (kg/m^2)	36.9 (32.1,42.4)	33.7 (29.3,39.7)	30.7 (26.3,35.4)	<0.001
Duration of diabetes (year)	15 (10,21)	8 (3,12)	Non-applicable	<0.001
Systolic blood pressure (mm Hg)	130 (118,140)	130 (118,140)	128 (116,138)	0.002
Diastolic blood pressure (mm Hg)	68 (60,78)	72 (63,80)	71 (64,80)	<0.001
Current smoker	24 (6%)	25 (6%)	68 (7%)	0.77
Fasting glycemia (mg/dL)	136 (100,197)	122 (100,156)	97 (89,107)	<0.001
Glomerular filtration rate (ml/min/1.73 m)	55 (44,70)	61 (49,79)	64 (51,78)	<0.001
New York Heart Association Class III/IV	186 (48%)	142 (35%)	292 (30%)	<0.001
Left ventricular ejection fraction (%)	58 (53,61)	58 (52,64)	59 (53,65)	0.52
LV mass body indexed	110.8 (92.3,124.9)	111.0 (94.1,129.8)	103.3 (83.5,125.1)	0.04
Hypertension	371 (95%)	382 (94%)	835 (86%)	<0.001
Myocardial infarction	91 (23%)	106 (26%)	162 (17%)	<0.001
Atrial fibrillation	122 (31%)	154 (38%)	467 (48%)	<0.001
Stroke	48 (12%)	30 (7%)	80 (8%)	0.03
Peripheral arterial disease	64 (16%)	51 (13%)	92 (9%)	0.001
Medication use				
Diuretic	370 (95%)	371 (91%)	832 (86%)	<0.001
Angiotensin converting enzyme inhibitor	215 (55%)	220 (54%)	455 (47%)	0.01
Angiotensin receptor blocker	143 (37%)	136 (33%)	272 (28%)	0.005
Beta-blocker	333 (85%)	312 (77%)	741 (77%)	0.001
Calcium channel blocker	184 (47%)	163 (40%)	335 (35%)	<0.001
Metformin	102 (26%)	232 (57%)	Non-applicable	<0.001
Sulfonylurea	78 (20%)	198 (49%)	Non-applicable	<0.001
Aspirin	266 (68%)	257 (63%)	503 (52%)	<0.001
Statin	320 (82%)	312 (77%)	515 (53%)	<0.001
Long acting nitrate	95 (24%)	95 (23%)	115 (12%)	<0.001
Warfarin	91 (23%)	123 (30%)	378 (39%)	<0.001
TOPCAT randomization				
Stratum: Hospitalized for heart failure during the 12 months prior to randomization	277 (71%)	240 (59%)	458 (47%)	<0.001
Treatment: spironolactone	198 (51%)	197 (49%)	491 (51%)	0.74

Americas = United States of America, Canada, Brazil, Argentina; DM = diabetes mellitus; ITDM = insulin-treated diabetes mellitus; NITDM = noninsulin-treated diabetes mellitus.

* Values for continuous variables represent median (twenty-fifth, seventy-fifth percentile) and number (percent) are presented for categorical variables.

Russia/Georgia,[17,18] we focused mainly on patients from the Americas. The TOPCAT Study was an international, randomized, double-blind, and placebo-controlled of spironolactone (15 to 45 mg) in 1,767 patients with HFpEF (left ventricle's ejection fraction of ≥45%). The primary end point of TOPCAT was time to first composite end point of CV mortality, hospitalization for heart failure, or aborted cardiac arrest. The secondary end points included the individual components of the primary end point plus MI, stroke, and all-cause mortality. The TOPCAT drug safety end points included hyperkalemia (defined as potassium ≥ 5.5 mmol/L) and serum creatinine ≥3.0 mg/dl. Patients were classified as insulin-treated DM (ITDM), noninsulin treated DM (oral therapy, diet control, or other; NITDM), and no DM based on the presence of DM at baseline, medical history and baseline use of oral hypoglycemic agents.

We compared baseline characteristics by DM status via chi-square tests for categorical variables and ANOVA for continuous variables. We used Cox proportional hazards regression models to investigate the influence of DM status at baseline on time to first primary end point and time to each of the secondary end points and safety end points. We used stepwise-selection for the multivariable models, starting with a model that included all baseline covariates except for baseline medications. DM status, TOPCAT randomization stratum, and treatment group were included in all models. Given the already-documented differences in primary outcome rates between regions,[16] we also investigated the interaction between regions, DM status, and outcomes. For patients with available echocardiographic data (n:653), we compared Left ventricle (LV) mass index and diastolic parameters in the 3 groups.

To determine whether the impact of spironolactone on outcome was similar in patients with and without DM, a Cox model was used to evaluate the interaction between TOPCAT treatment group and DM, separately for each outcome and adjusting for TOPCAT randomization stratum. For all analyses, a 2-tailed p <0.05 was required for

Table 2
Outcomes by diabetes mellitus status in TOPCAT patients enrolled from the Americas

Outcomes	Number and % of participants with event, and incidence rate per 100 person-years			Adjusted* hazard ratio (95% CI), p value			Global test p value
	ITDM (n = 390)	NITDM (n = 406)	No DM (n = 969)	ITDM vs non-DM	NITDM vs non-DM	ITDM vs NITDM	
Primary TOPCAT end point	173 (44%) 20.7 / 100py	113 (28%) 10.9 / 100py	236 (24%) 8.8 / 100py	1.80 (1.43-2.26) <0.001	1.11 (0.88-1.40) 0.40	1.63 (1.27-2.08) <0.001	<0.001
Secondary end points							
Cardiovascular mortality	60 (15%) 5.5 / 100py	45 (11%) 3.8 / 100py	118 (12%) 4.0 / 100py	1.47 (1.02-2.13) 0.04	1.01 (0.70-1.44) 0.97	1.46 (0.98-2.18) 0.06	0.08
Hospitalization for heart failure	143 (37%) 17.0 / 100py	89 (22%) 8.5 / 100py	168 (17%) 6.3 / 100py	1.97 (1.52-2.56) <0.001	1.20 (0.92-1.57) 0.19	1.65 (1.25-2.17) <0.001	<0.001
Myocardial infarction	34 (9%) 3.3 / 100py	14 (3%) 1.2 / 100py	46 (5%) 1.6 / 100py	2.27 (1.33-3.88) 0.003	0.83 (0.45-1.55) 0.57	2.73 (1.43-5.18) 0.002	0.002
Stroke	19 (5%) 1.8 / 100py	18 (4%) 1.6 / 100py	40 (4%) 1.4 / 100py	1.50 (0.80-2.83) 0.21	1.15 (0.65-2.06) 0.63	1.30 (0.67-2.54) 0.44	0.45
All-cause mortality	102 (26%) 8.9 / 100py	80 (20%) 6.5 / 100py	203 (21%) 6.7 / 100py	1.44 (1.09-1.91) 0.01	1.07 (0.82-1.40) 0.62	1.35 (0.99-1.83) 0.06	0.03
Safety end points							
Hyperkalemia	87 (22%) 9.9 / 100py	82 (20%) 8.3 / 100py	132 (14%) 5.0 / 100py	1.66 (1.21-2.29) 0.002	1.77 (1.33-2.36) <0.001	0.94 (0.68-1.29) 0.70	<0.001
Creatinine ≥3.0 mg/dL	71 (18%) 7.2 / 100py	49 (12%) 4.4 / 100py	47 (5%) 1.6 / 100py	2.08 (1.35-3.20) <0.001	2.04 (1.34-3.08) <0.001	1.02 (0.69-1.51) 0.92	<0.001

Americas = United States of America, Canada, Brazil, Argentina; DM = diabetes mellitus; ITDM = insulin treated diabetes mellitus; NITDM = noninsulin treated diabetes mellitus.

* Adjusted for randomized treatment, randomization strata, age, gender, race, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, smoking status, potassium, estimated glomerular filtration, QRS duration, New York Heart Association class, atrial fibrillation, peripheral arterial disease and left ventricular ejection fraction.

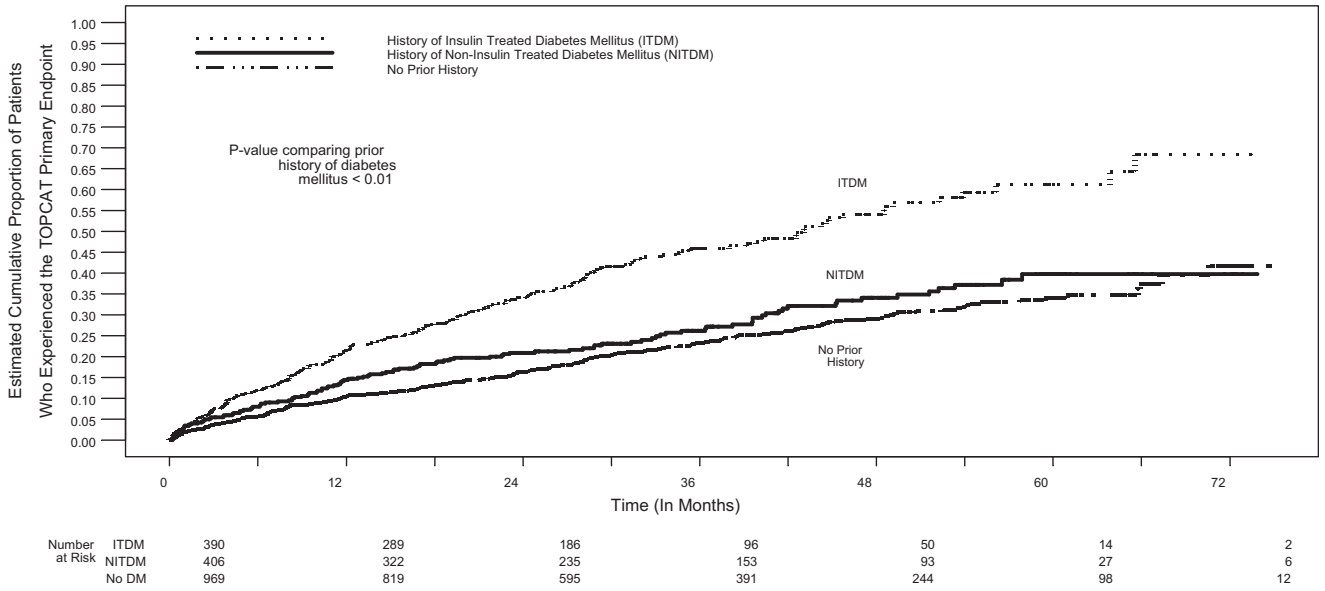

Figure 1. Kaplan-Meier plot of time to the TOPCAT primary end point, stratified by history of diabetes mellitus, in TOPCAT patients enrolled from the Americas.

significance. Statistical analyses were performed at the Data Coordinating Center (New England Research Institute, Watertown, Massachusetts) and the Brigham and Women's Hospital, Boston, Massachusetts with SAS software, release 9.3 (SAS Institute Inc., Cary, North Carolina).

Results

Compared to patients with NITDM, patients with ITDM had longer duration of DM. As compared to patients without DM and NITDM, patients with ITDM were younger, more patients belonging to ethnic minorities, with more impaired renal function, New York Heart Association class III/IV, and higher body mass index (Table 1). Patients with DM also used more diuretics and all other types of CV medications than patients without DM.

During a mean follow-up of 3.3 years, one-third of the patients had at least 1 confirmed primary end point and 22% had died (Table 2). The incidence rate for the primary end point was the highest in ITDM patients, followed by NITDM patients and patients without DM (Table 2 and Figure 1). The incidence rates for all-cause mortality and for all other secondary and safety end points followed a similar descending pattern across ITDM, NITDM, and non-diabetic patients (Table 2 and Figure 2).

The risks of the primary end point and all other secondary end points (except for stroke) were increased in patient with ITDM compared to patients without DM (Table 2). Compared to patients without DM, patients

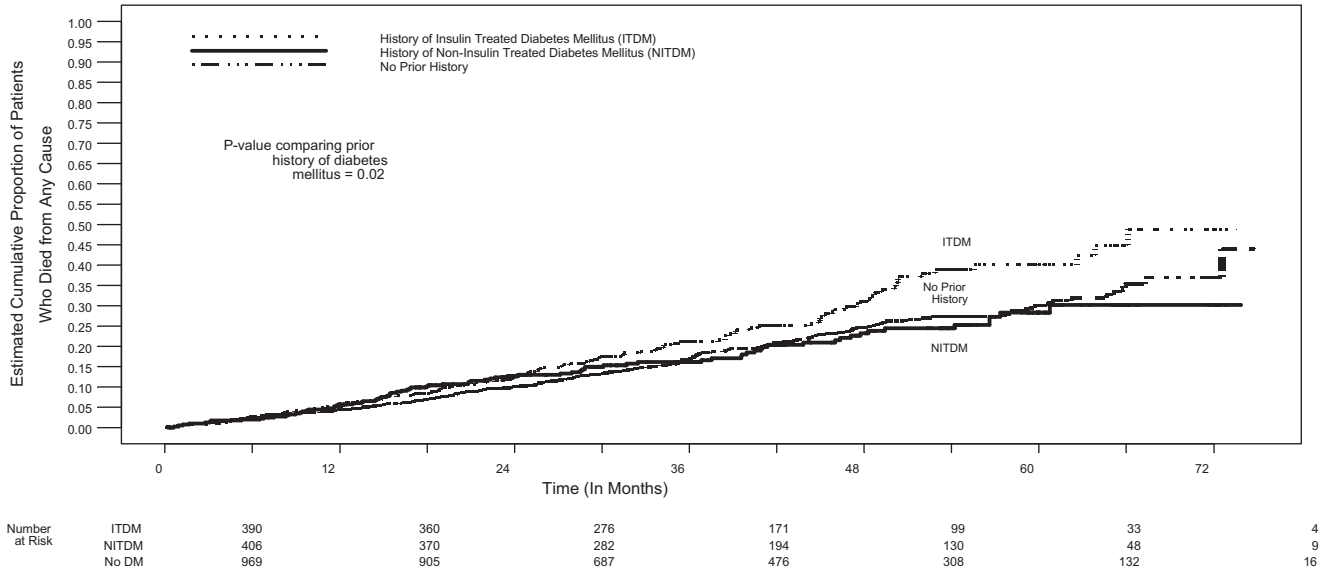

Figure 2. Kaplan-Meier plot of time to all-cause mortality, stratified by history of diabetes mellitus, in TOPCAT patients enrolled from the Americas.

Table 3
Impact of spironolactone on outcome in TOPCAT patients enrolled from the Americas with heart failure and preserved ejection by diabetes mellitus status

Outcome	Treatment-DM interaction (p value)*	HR, (95% CI), p value		
		ITDM (n = 390)	NITDM (n = 406)	No DM (n = 969)
Primary TOPCAT end point	0.73	0.76 (0.56-1.03) 0.07	0.91 (0.63-1.32) 0.62	0.77 (0.59-0.99) 0.04
Secondary end points				
Cardiovascular mortality	0.11	0.65 (0.39-1.08) 0.10	1.28 (0.71-2.30) 0.41	0.61 (0.42-0.88) 0.01
Hospitalization for heart failure	0.99	0.80 (0.58-1.11) 0.18	0.82 (0.54-1.24) 0.34	0.78 (0.57-1.06) 0.11
Myocardial infarction	0.56	1.26 (0.64-2.50) 0.50	1.16 (0.41-3.32) 0.78	0.79 (0.44-1.41) 0.43
Stroke	0.47	1.52 (0.60-3.87) 0.38	0.67 (0.26-1.72) 0.4	0.86 (0.46-1.60) 0.63
All-cause mortality	0.52	0.71 (0.48-1.05) 0.09	1.03 (0.67-1.61) 0.88	0.80 (0.61-1.05) 0.11
Safety end points				
Hyperkalemia	0.09	3.99 (2.40-6.63) <.001	2.10 (1.33-3.29) 0.001	3.73 (2.47-5.63) <.001
Creatinine ≥ 3.0 mg/dL	0.28	1.43 (0.89-2.30) 0.14	0.87 (0.49-1.53) 0.62	0.92 (0.52-1.62) 0.76

Americas = United States of America, Canada, Brazil, Argentina; DM = diabetes mellitus; ITDM = insulin treated diabetes mellitus; NITDM = noninsulin treated diabetes mellitus.
* Adjusted for TOPCAT randomization stratum.

with ITDM had approximately 2-fold increase in risks for the primary end point, hospitalization for heart failure and MI and 50% increases in all-cause and CV mortality compared to patients without DM. Compared to patients with NITDM, the incidence rates of the primary end point, hospitalization for heart failure, MI, and all-cause mortality were also increased in patients with ITDM. Patients with NITDM had similar risks for the primary and secondary end points as patients without DM. There was no significant interaction between DM and spironolactone use on the primary and secondary outcomes (Table 3). In patients with ITDM, the risk of hyperkalemia was approximately 4-fold higher in those randomized to spironolactone compared with those on placebo. The risk of hyperkalemia was 2-fold higher in patients with NITDM randomized to spironolactone compared with those on placebo.

We presented the available echocardiographic results in Table 4. Many relevant echocardiographic data were missing in a large proportion of patients (E/A ratio, diastolic dysfunction grading, and longitudinal strain). In restricting to echocardiographic data with less than 15% of missing values, patients with DM had increased LV mass indexed for body surface area, higher E wave, increased end-diastolic volume and stroke volume compared to patients without DM (Table 4).

Discussion

Our findings extended previous studies of patients with HFpEF and DM[1−9] by providing additional insights into the characteristics and outcomes of patients with ITDM compared to those with NITDM and without DM. Patients with ITDM had at least 50% increases in risks of the primary end point, CV mortality, and all-cause mortality compared to patients without DM and patients with NITDM. Compared to patients without DM, patients with DM had greater increases in risks of hyperkalemia and increased serum creatinine.

Although previous authors reported worse outcomes in patients with DM compared to patients without DM, the association of insulin with adverse outcomes had not been described in patients with heart failure (with or without reduced EF). Insulin's use may be just a marker of higher risk patients or it also may be directly aggravating HFpEF. Although our multivariate models adjusted for many pertinent covariates (age, body mass index, New York Heart Association, glomerular filtration rate, and left ventricle's ejection fraction), we did not adjust for DM's end organs damages and CV medications. Therefore, it remained possible that at least one or more of these residual confounders may have influenced the impact of insulin therapy on the TOPCAT patients with DM and HFrEF.

Use of oral hypoglycemic agents may have also confounded the outcomes of patients with ITDM. Compared to sulfonylurea, metformin reduced mortality, and morbidity in patients with heart failure,[19] patients with ITDM may have had less CV protection with lesser use of metformin. In contrast, they were less likely to be exposed to medications which may have worsened heart failure (such as thiazolidinediones and inhibitors of dipeptidyl peptidase 4).[20,21] The worse outcomes of patients with ITDM compared to patients without DM and with NITDM were even more notable considering the higher uses of cardio-protective medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and β blockers in patients with ITDM.

Our subgroup analysis of echocardiographic parameters shed additional mechanistic insights. The increased E wave and stroke volume may be secondary to a restricted LV (impaired relaxation of the LV). Although these findings were mainly hypothesis generating, the abnormal diastolic parameters and increased LV mass in patients with heart failure and ITDM may have contributed to their worse outcomes.

The similar adverse outcomes between patients with NITDM and patients without DM were also noteworthy. Despite a relatively long duration of DM (median of 8 years) and more previous MIs, patients with NITDM had comparable prognosis as patients without DM. Compared to patients with NITDM, patients without DM were older with more females, more atrial fibrillation, higher use of

Table 4
Baseline echocardiographic measurements by diabetes mellitus status

Baseline echo measurements*	Patients enrolled in the Americas n = 635				
	Missing data (%)	Insulin-treated diabetes n = 164	Noninsulin treated diabetes n = 148	No diabetes n = 341	p Value
Left ventricle mass indexed for body surface area	2	110.8 (92.3,124.9)	111.0 (94.1,129.8)	103.3 (83.5,125.1)	0.04
Peak E wave velocity	13	101.4 (83.7,123.5)	95.3 (73.3,113.5)	85.4 (67.6,106.1)	<0.001
E wave deceleration time	14	196.7 (166.7,235.0)	200.0 (170.0,240.0)	190.0 (150.0,228.3)	0.08
E/A ratio	38	1.3 (1.0,1.7)	1.1 (0.8,1.6)	1.1 (0.8,1.6)	0.02
Simpson ejection fraction	9	60.5 (57.4,65.2)	61.0 (57.5,64.5)	60.3 (55.6,65.3)	0.57
End-diastolic volume	9	99.9 (79.4,120.5)	89.9 (73.9,114.6)	85.7 (69.5,110.4)	<0.001
End-systolic volume	9	38.2 (28.8,47.4)	35.0 (28.2,47.4)	33.7 (24.8,46.0)	0.05
Left atria volume	10	53.1 (43.6,69.2)	58.7 (46.3,72.8)	60.7 (45.0,79.1)	0.09
Stroke volume	9	60.9 (47.4,74.4)	56.2 (46.1,65.6)	51.6 (41.8,64.1)	<0.001
Abnormal E' (septal or lateral)	28	93 (75%)	84 (76%)	149 (64%)	0.03
Diastolic dysfunction grade	43				0.03
• Grade = 0		31 (32%)	27 (30%)	84 (44%)	
• Grade = 1		8 (8%)	16 (18%)	31 (16%)	
• Grade = 2		44 (46%)	33 (37%)	55 (29%)	
• Grade = 3		13 (14%)	13 (15%)	20 (11%)	
Diastolic dysfunction grade (modified Olmsted criteria)	57				0.02
• Grade = 0		4 (5%)	4 (5%)	16 (12%)	
• Grade = 1		9 (12%)	21 (28%)	37 (28%)	
• Grade = 2		39 (51%)	31 (41%)	51 (39%)	
• Grade = 3		24 (32%)	20 (26%)	26 (20%)	
Longitudinal strain	48	−14.8 (−17.4,−12.7)	−15.0 (−17.7,−13.4)	−16.2 (−18.6,−13.3)	0.06
Abnormal longitudinal strain	48	43 (59%)	47 (61%)	90 (48%)	0.07
Quartile of longitudinal strain	48				0.03
• 1st Quartile		12 (16%)	14 (18%)	55 (29%)	
• 2nd Quartile		18 (25%)	16 (21%)	50 (26%)	
• 3rd Quartile		21 (29%)	30 (39%)	38 (20%)	
• 4th Quartile		22 (30%)	17 (22%)	46 (24%)	
Significant valvular disease	3	20 (12%)	20 (14%)	55 (17%)	0.43

* Values for continuous variables represent median (twenty-fifth, seventy-fifth percentile) and number (percent) are presented for categorical variables.

warfarin, and lesser uses of CV medications. Our multivariate model did adjust for age and sex but atrial fibrillation, previous MI, stroke, and peripheral arterial disease were not retained in our stepwise model selection due to their lacks of significance. Residual confounders such as differences in baseline characteristics, and lesser uses of CV medications may have increased the rates of adverse outcomes in patients without DM.

Previous reports on the effects of spironolactone in patients with DM and/or heart failure were conflicting. Spironolactone reduced microalbuminuria in patients with DM.[22,23] In contrast, the use of spironolactone was associated with more renal insufficiency, hyperkalemia, and impaired glycemic control in patients with heart failure and DM.[24,25] The 20% reduction in risk of the primary composite end point associated with spironolactone for TOPCAT patients enrolled from the Americas was not affected by DM status, suggesting that spironolactone may be beneficial in these patients, regardless of DM status. Therefore, spironolactone should be considered in patients with DM and HFpEF, but clinicians must remain vigilant with close monitoring of renal function and electrolytes in patients with DM treated with spironolactone.

Our study has some limitations worth mentioning. First, stratification of DM status was based on reports by patients and/or study physicians and their reported use of hypoglycemic agents. Therefore, the prevalence of DM in our cohort may have been underestimated. Suskin et al reported 8% of patients with undiagnosed DM in a heart failure trial.[26] Second, classification of ITDM status versus NITDM was based on the use of insulin at baseline and may not accurately reflect insulin-dependency. Third, we did not capture, and therefore could not evaluate the later use of insulin during the study period. Fourth, we could not adjust entirely for DM's control and end-organs damages and severity of HFpEF since we did not measurement glycosylated hemoglobin; brain natriuretic peptide (BNP)/N Terminal (NT)-BNP, and proteinuria were also missing in the majority of patients. Finally, in limiting our analyses only to patients enrolled from the Americas, our findings may not be applicable to patients with HFpEF from other regions of the world and would require confirmation by future studies.

In conclusion, our analysis provides valuable insights into the different risks profiles associated with ITDM and NITDM in patients with HFpEF. ITDM was associated with markedly increases in risks of the primary end point and other adverse outcomes, including all-cause mortality in patients with HFpEF, whereas patients with NITDM had similar risks of adverse outcomes as those without DM.

Disclaimer

The content of this article does not necessarily represent the views of the National Heart, Lung, and Blood Institute or of the Department of Health and Human Services. All authors have participated in the research and/or article preparation.

Conflicts of Interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.11.022.

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