Role of Ischemic Heart Disease in Major Adverse Renal and Cardiac Events Among Individuals With Heart Failure With Preserved Ejection Fraction (from the TOPCAT Trial)

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Despite improvements in the prognosis of patients with heart failure with reduced ejection fraction (HFrEF), established therapy for heart failure patients with preserved ejection fraction (HFpEF) is lacking. Additionally, ischemic heart disease adversely impacts the clinical course of HFrEF patients; however, its role in HFpEF is not fully understood. We conducted a post hoc analysis of propensity score matched patients from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial to compare HFpEF patients with versus without myocardial ischemia in terms of major adverse renal and/or cardiac events (MARCE). Of 3,445 participants, the prevalence of ischemia was 59%. For this analysis, we included 1,747 ischemic patients and 1,207 propensity matched nonischemic patients. Ischemia was associated with a 20% increased risk (HR = 1.20, 95% confidence interval [CI] = 1.042 to 1.382, p value = 0.0112) of major adverse renal and/or cardiac events (MARCE) in adjusted analyses. Other important predictors of MARCE were diabetes (hazard ratio [HR] = 1.60, 95% CI = 1.38 to 1.87, p <0.0001), dyslipidemia (HR = 1.30, 95% CI = 1.10 to 1.52, p = 0.001) and smoking (HR = 1.33, 95% CI = 1.04 to 1.69, p = 0.0197). Revascularization was not significantly associated with MARCE in the subgroup of ischemic HFpEF patients. Future work is warranted to develop tailored interventions for patients with both HFpEF and ischemic heart disease to mitigate the risk of MARCE . **(Am J Cardiol 2021;142:91−96)**

Several studies demonstrate that approximately 50% of all patients with heart failure (HF) have normal left ventricular function.[1−3] Although the epidemiology and pathophysiology of HF with preserved ejection fraction (HFpEF) is an ongoing challenge, it is generally accepted that women and older patients are more susceptible to its development.[4−8] Further, ischemic heart disease (IHD) is 1 of many identified risk factors for HF.[9] However, current evidence on the prognostic role of ischemia in HFpEF is conflicting.[10−14] Additionally, HFpEF is linked to both cardiac and renal outcomes.[15] Similarly, revascularization is strongly associated with acute kidney injury and may lead to the progression of kidney disease. Thus, both cardiac and renal outcomes are of interest in this population. Despite improvements in the prognosis of HFrEF through medical management, there has been no such established therapy for HFpEF. Moreover, no consensus exists on the influence of myocardial ischemia in HFpEF patients.[16] Additionally, the interconnectedness of heart and kidney dysfunction is well-documented and is believed to limit the effectiveness of CHF therapy. Accordingly, it is of interest to quantify the impact of ischemia on major adverse renal and/or cardiac events (MARCE) in patients with HFpEF, which is the purpose of this study. MARCE is a particularly useful outcome for patient populations at high risk for adverse events in both cardiac and renal systems, such as the 1 in this study.

Methods

The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT) rationale and design have been previously described.[10] In brief, TOPCAT was a multinational, double-blind, randomized, placebo-controlled trial that collectively enrolled 3,445 patients from 6 countries: United States, Canada, Russia, Republic of Georgia, Argentina, and Brazil. The primary objective of the trial was to evaluate the efficacy of spironolactone relative to placebo for the primary composite end point of cardiovascular death, aborted cardiac arrest, and/or HF hospitalization. Patients were eligible to participate if they satisfied the following criteria: ≥50 years old, symptomatic HF with LVEF≥45%, and either a history of HF hospitalization within the previous year, or a Brain Natriuretic Peptide ≥100 pg/mL in the previous 60 days. Participants were followed for an average of 3.3 years.[17]

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Patients' medical histories including cardiac procedures and hospitalizations within 1 year were reviewed as part of the screening process. For this analysis, patients were considered to have history of myocardial ischemia if they had a history of myocardial infarction (MI), coronary artery bypass graft surgery, or percutaneous coronary revascularization (PCI) at baseline. Demographic information including age, gender, race, and body mass index was obtained during the screening interview. In addition, patients were asked about their smoking status and alcohol consumption. We defined smokers as those who reported "currently smoking" at baseline. The number of alcoholic drinks per week was recorded as "none, 1 to 4, 5 to 10, 11 to 20, more than 20." The presence of other cardiac risk factors such as hypertension, diabetes, thyroid disease, and dyslipidemia were confirmed by reviewing medical records. Laboratory data including creatinine, estimated glomerular filtration rate, and complete blood counts were serially collected.

The trial received institutional review board approval at all participating sites; the post-hoc analysis was approved by the Baylor Scott & White Research Institute's Institutional Review Board.

Cardiac and renal outcomes were documented in TOPCAT, with major adverse cardiac events (and its components) adjudicated by a panel of experts. For this analysis, we considered MARCE as the primary outcome of interest, which included the adjudicated MACE outcome (including MI, stroke, congestive HF, aborted cardiac arrest, CV, and non-CV death) as well as renal worsening (doubling of creatinine values between 2 consecutive visits) and hospitalization for other cardiac or renal problems. Cardio-renal hospitalization is a composite of either hospitalization attributed to decompensation of renal function or cardiac problems (other than HF, ACA, and MI).

Descriptive statistics including mean ± standard deviation and frequency (%) were used to summarize continuous and categorical variables, respectively. Histograms and Q-Q plots were used to assess normality of the continuous factors. Differences in continuous patient characteristics between ischemic and nonischemic patients were assessed with Student's *t* test or Wilcoxon rank-sum test, as appropriate. Additionally, Chi-square or Fisher's Exact tests were used to determine differences in baseline proportions between study groups. In order to adjust for potential bias due to imbalance between the 2 groups, we conducted propensity score matching, specifying a caliper width of 0.2. Matching was performed using age, gender, race, study drug (Spironolactone vs placebo), and co-morbidities. Linear mixed models and (exact) conditional logistic regression were used for baseline comparisons between matched cohorts. We utilized survival analysis to identify the independent predictors of time-to-MARCE. To incorporate serial laboratory measurements, we utilized extended Cox models and accounted for the within-subject correlations with a robust sandwich estimator. Survival time was defined as time in years from randomization until the occurrence of first MARCE or end of follow-up (censored). After estimating the direct hazard of ischemia on MARCE through an unadjusted model, we developed an adjusted Cox model, accounting for possible confounders. We considered a broad set of possible predictors for developing the adjusted cox model including age, gender, race, body mass index (BMI), estimated glomerular filtration rate, smoking, alcohol consumption, co-morbidities, and complete blood counts. We used similar methods to perform a subgroup analysis in which we determined whether ischemic patients who received revascularization at any time prior to baseline had different outcomes compared to ischemic patients without history of revascularization. We used SAS version 9.4 for all statistical analyses with a level of significance of 0.05.

Results

There were 3,445 participants in TOPCAT. A total of 2,023 (59%) had IHD at the time of enrollment. Before matching, ischemic patients were younger and had higher rates of diabetes, hypertension and dyslipidemia (Table 1). They were also predominantly male and had lower BMI than patients without IHD. After matching, there were 1,747 patients with IHD and 1,207 patients without IHD (Table 1). The average age of matched participants was 68.6 ± 9.6 years, with females (52%), and Caucasians (90%) comprising the majority of the sample. Over a median follow-up of 2.39 years (25th, 75th percentiles = 1.01, 4.11), a total of 1,075 (36%) patients experienced at least 1 MARCE (Table 2).

There was no significant difference in time-to-MARCE between ischemic versus nonischemic participants in unadjusted analyses (p value = 0.33; Figure 1); however, ischemia was associated with a 20% (hazard ratio [HR] = 1.20, 95% confidence interval [CI] = 1.042 to 1.382, p value = 0.0112) increased risk of MARCE in adjusted analyses (Table 3). Additionally, diabetes increased the risk of MARCE by approximately 60% (HR = 1.60, 95% CI = 1.38 to 1.87, p value <0.0001), dyslipidemia did so by 30% (HR = 1.30, 95% CI = 1.10 to 1.52, p value = 0.001), and smoking by 33% (HR = 1.33, 95% CI = 1.04 to 1.69, p value = 0.0197).

In the subgroup analysis, considering only the 1,747 participants who had IHD at baseline, 660 (38%) had history of revascularization. Although unadjusted analysis suggested that revascularized patients had more than double the risk (HR = 2.19, 95% CI = 1.87 to 2.57, p value<0.0001) of experiencing MARCE than those who had not undergone revascularization, the effect lost significance after adjusting for confounders (Table 4).

Discussion

In this post hoc analysis of TOPCAT data, we found that the prevalence of IHD in this trial of patients with HFpEF was 59%, and that the participants with IHD had a 20% higher risk of MARCE compared to those without. Factors including BMI, smoking, diabetes mellitus and dyslipidemia were also found to contribute to the risk of MARCE. To our knowledge, this is the first study to examine the relationship between myocardial ischemia and MARCE in HFpEF patients.

The observed IHD prevalence in HFpEF of 59% is similar to that reported by Gottdiener et al, as well as Pernenkil et al.[11,18] However, there is no consensus regarding prevalence, and estimates range between 25% to 76%.[12,19–21] The high variability in prevalence estimates may be due to

Table 1
Baseline characteristics of ischemic and nonischemic TOPCAT participants

Variable	Entire Cohort				Propensity Matched Cohort			
	With Ischemia (n=2023)	Without Ischemia (n=1422)	Standardized Difference	p Value	With Ischemia (n=1747)	Without Ischemia (n=1207)	Standardized Difference	p Value
Age (years)	67.94± 9.37	69.43± 9.81	−0.15	<.0001	68.25± 9.32	69.28± 9.98	−0.10	0.0039
Men	1075 (53.14%)	595 (41.84%)	0.22	<.0001	880 (50.37%)	548 (45.40%)	0.10	0.8432
Body mass index (kg/m^2)	31.64± 6.47	32.69± 7.86	−0.14	<.0001	31.54± 6.58	32.69± 7.81	−0.15	<.0001
Race								
Black	103 (5.09%)	199 (13.99%)	−0.30	<.0001	103 (5.90%)	111 (9.20%)	−0.12	0.1544
White	1886 (93.23%)	1176 (82.70%)	0.32		1611 (92.22%)	1054 (87.32%)	0.16	
Other	34 (1.68%)	47 (3.31%)	−0.10		33 (1.89%)	42 (3.48%)	−0.09	
Current smoker	238 (11.76%)	122 (8.58%)	0.10	0.0029	198 (11.33%)	110 (9.12%)	0.07	0.1652
Alcoholic drinks/week								
0	1620 (80.08%)	1061 (74.61%)	0.13	0.0003	1407 (80.54%)	890 (73.74%)	0.16	<.0001
1-4	309 (15.27%)	271 (19.06%)	−0.10		261 (14.94%)	246 (20.38%)	−0.14	
5-10	67 (3.31%)	59 (4.15%)	−0.04		58 (3.32%)	47 (3.89%)	−0.03	
>11	26 (1.29%)	26 (1.83%)	−0.04		20 (1.14%)	22 (1.82%)	−0.05	
NYHA class 3 or 4	708 (35.01%)	428 (30.20)	0.10	0.0032	622 (35.62%)	354 (29.35%)	0.13	0.0003
Hypertension	1895 (93.67%)	1252 (88.05%)	0.19	<.0001	1619 (92.67%)	1081 (89.56%)	0.10	0.2955
Diabetes mellitus	701 (34.65%)	417 (29.32%)	0.11	0.0012	577 (33.03%)	380 (31.48%)	0.03	0.7877
Thyroid disease	305 (15.08%)	235 (16.53%)	−0.04	0.2385	260 (14.88%)	207 (17.15%)	−0.06	0.1412
Dyslipidemia*	1363 (67.38%)	710 (49.93%)	0.35	<.0001	1090 (62.39%)	653 (54.10%)	0.17	0.8359
eGFR (mL/min/1.73 m^2)	68.02±19.88	67.15±20.53	0.04	0.2166	67.87±20.15	66.99±20.70	0.04	0.2467
Creatinine (mg/dL)	1.09±0.29	1.09±0.31	0.001	0.9670	1.09±0.29	1.10±0.31	−0.02	0.4011
Sodium (mEq/L)	141.5±4.35	140.8±3.96	0.17	<.0001	141.60±4.29	140.80±4.01	0.17	<.0001
Potassium (mmol/L)	4.28±0.43	4.20±0.46	0.18	<.0001	4.28±0.43	4.20±0.46	0.16	<.0001
Blood urea nitrogen (mg/dL)	20.81±11.15	21.80±11.37	−0.08	0.0175	20.56±11.10	22.00±11.48	−0.12	0.0009

eGFR = Estimated Glomerular Filtration Rate; NYHA = New York Heart Association.
* Dyslipidemia was defined as abnormal level of lipids in the blood.

Table 2
Breakdown of events experienced by ischemic versus nonischemic participants

	Ischemic Patients (n=1747)	Non-Ischemic Patients (n=1207)	p Value
Major adverse renal and/or cardiac events	632 (36.18%)	443 (36.70%)	0.5819
Myocardial infarction	52 (2.98%)	17 (1.41%)	0.0054
Stroke	31 (1.77%)	24 (1.99%)	0.6760
Congestive heart failure	148 (8.47%)	114 (9.44%)	0.2487
Aborted cardiac arrest	3 (0.17%)	0 (0%)	0.2500
Renal worsening	91 (5.21%)	107 (8.86%)	0.0003
Cardio-renal hospitalization	206 (11.79%)	125 (10.36%)	0.2011
All cause death	101 (5.78%)	56 (4.64%)	0.2354

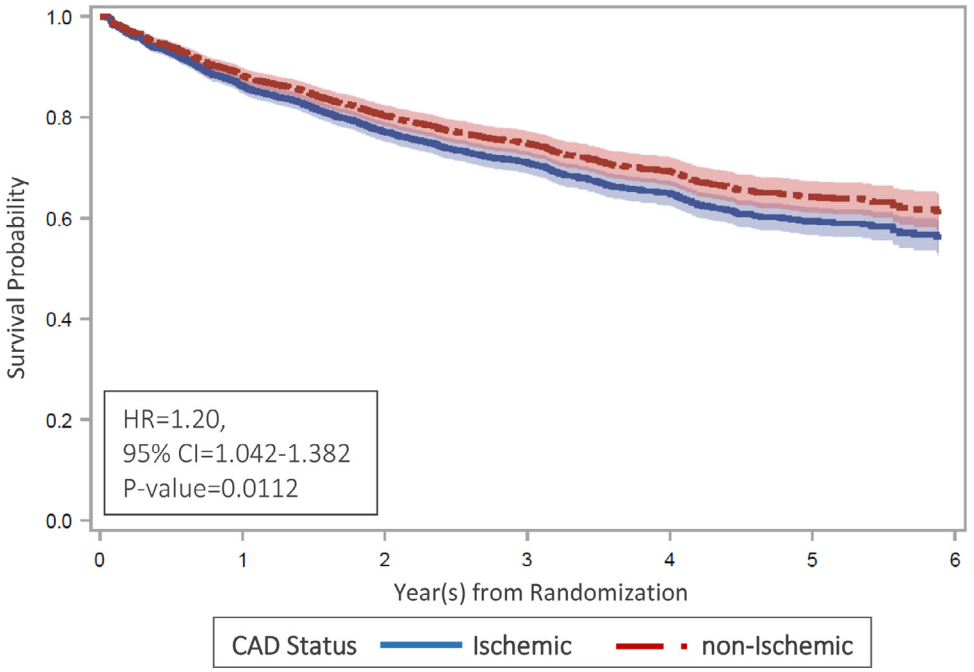

Figure 1. Adjusted major adverse renal and/or cardiac event − free survival curves comparing ischemic versus nonischemic patients.

patient characteristics or the actual definition of IHD. Previous studies have shown that demographic and clinical characteristics of persons with IHD are different from those without IHD.[23,28] In the HFpEF population, ischemic patients are typically older and more likely to be men.[23,28] Our results confirm the higher likelihood of ischemia in males; however, the ischemic participants in TOPCAT were slightly younger than those without ischemia. African Americans are disproportionately affected by HFpEF, yet the sample examined in this study was predominantly Caucasian. The underrepresentation of minorities in clinical trials is well-documented and the trial on which this work is based is no exception. As such, the results may not be widely generalizable to other races. For a detailed analysis of differences in patient characteristics and outcomes by race in this trial, please see the work of Lewis et al (2018).[22]

We found the typical cardiovascular risk factors (hypertension, diabetes, and dyslipidemia) to be more prevalent in ischemic participants than in nonischemic. These findings are in agreement with the reports based on I-Preserve trial and HF study in Somme, France[11,23] For example, in the I-Preserve trial, the majority of IHD patients were in New York Heart Association functional class III or IV. The 10-year longitudinal French study also reported higher rates of peripheral artery disease and lower rates of atrial fibrillation for HFpEF patients with IHD.

The pathophysiological effects of ischemia on HFpEF are still not fully understood.[24] Lee et al examined long term survival of HFpEF participants in the Framingham Heart Study, but failed to find excess risk due to ischemia.[13] Similarly, the results of a large community-based study in France failed to detect an association between ischemia and 5 year mortality in HFpEF patients.[14] Our study differs from others in that we considered MARCE as the primary outcome instead of mortality. We found a positive association between IHD and MARCE after adjusting for co-morbidities. The significance of ischemia in adjusted cox analysis points out the confounding effects of cardiovascular risk factors on adverse cardiorenal outcomes. These findings are confirmatory to that of the I-Preserve trial, as well as the studies utilizing the Swedish HF Registry, ETICs registry, and others.[11,12,20]

The pathogenic process of developing HF from IHD brings up the viability of revascularization as a potential preventive and/or therapeutic tool. There has been scarcity

Table 3
Risk associated with ischemia in heart failure participants with preserved ejection fraction: results of multivariate Cox analysis

Parameter	Parameter Estimate	Standard Error	p Value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Ischemia	0.18260	0.07197	0.0112	1.200	1.042	1.382
Age at entry	0.01551	0.00449	0.0006	1.016	1.007	1.025
Body mass index	0.01191	0.00502	0.0176	1.012	1.002	1.022
Blood urea nitrogen	0.01971	0.00210	<.0001	1.020	1.016	1.024
Serum carbon dioxide	0.01562	0.00281	<.0001	1.016	1.010	1.021
Serum sodium	−0.01245	0.00208	<.0001	0.988	0.984	0.992
Diabetes mellitus	0.47571	0.07660	<.0001	1.609	1.385	1.870
Dyslipidemia	0.26336	0.08222	0.0014	1.301	1.108	1.529
Smoking	0.28715	0.12309	0.0197	1.333	1.047	1.696

Table 4
Effect of revascularization in ischemic heart failure patients with preserved ejection fraction: results of multivariate Cox analysis

Parameter	Parameter Estimate	Standard Error	p value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Prior revascularization	0.17099	0.09422	0.0696	1.186	0.986	1.427
Age at entry	0.02219	0.00493	<.0001	1.022	1.013	1.032
Blood urea nitrogen	0.02188	0.00221	<.0001	1.022	1.018	1.027
Serum carbon dioxide	0.01131	0.00300	0.0002	1.011	1.005	1.017
Serum sodium	−0.01029	0.00316	0.0011	0.990	0.984	0.996
Diabetes mellitus	0.43302	0.08657	<.0001	1.542	1.301	1.827
Dyslipidemia	0.25342	0.10343	0.0143	1.288	1.052	1.578
Smoker	0.37768	0.13832	0.0063	1.459	1.112	1.913

of research investigating the impact of revascularization in HFpEF patients, the majority of which did not detect a significant improvement associated with revascularization.[25–27] Similarly, we did not find a significant difference in ischemic HFpEF patients' MARCE outcomes based on revascularization status at baseline. However, this could partially be due to limited details collected regarding the type of revascularization. Further, it is possible that the results could have been influenced by participants who received revascularization after the baseline assessment, and the analyses could not account for that. The results of a 2014 study suggested that complete revascularization could reduce the mortality rate of HFpEF patients with ischemia as well as preserve cardiac function.[28] Future studies are needed to better elucidate both short term and long term benefits and risks of revascularization with PCI and CABG for ischemic HFpEF patients.[29,30]

The ischemia prevalence in this analysis may not be generalizable, as the data were from a clinical trial and the definition for ischemia did not utilize angiographic information. We acknowledge that the phenotype of patients who have several ischemic events may be different from those who have only 1; however, participants were asked to report only their most recent ischemic event, rendering that potential analysis impossible. There was also a lack of data regarding the level of intervention and extent of treatment for patients who received revascularization. Additionally, we did not have information on either PCI or CABG that occurred over the course of participation in the trial. Furthermore, since the gap times between undergoing surgical treatment and joining the study were not the same for all patients, we could not disentangle the long-term and short-term effects of revascularization.

In conclusion, we found that IHD conferred an approximate 20% increase in the risk of MARCE for patients with HFpEF, after accounting for patient characteristics and comorbidities. The high prevalence of ischemia within the HFpEF population, as well as its association with increased risk of MARCE, suggest the need to create specific interventions for this sub-population.

Authors Contribution

Peter A. McCullough, MD, MPH: Conceptualization, Methodology, Design, Supervision, Interpretation, Critical revision, Final approval, Agreement to be accountable; Gelareh Rahimi, PhD: Data acquisition, Software, Formal analysis, Data Curation, Writing - Original Draft, Final approval, Agreement to be accountable; Kristen M. Tecson: Interpretation, Critical revision, Final approval, Agreement to be accountable; Osama Elsaid, MD: Interpretation, Critical revision, Final approval, Agreement to be accountable.

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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