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Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction

The TOPCAT Trial

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ABSTRACT

OBJECTIVES This study assessed the relationship between atrial fibrillation (AF) and outcomes in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, to evaluate whether AF modified the treatment response to spironolactone and whether spironolactone influenced post-randomization AF.

BACKGROUND AF is common in heart failure with preserved ejection fraction (HFpEF) and likely contributes to increased risk of adverse outcomes.

METHODS A total 1,765 patients enrolled in TOPCAT trial in North and South America were divided into 3 groups: no known AF, history of AF without AF at enrollment, and AF found on the electrocardiogram (ECG) at enrollment. We assessed outcomes and treatment response to spironolactone in all groups, and the association between post-randomization AF and outcomes in patients free of AF at baseline. The primary outcome of the TOPCAT trial was a composite of cardiovascular mortality, aborted cardiac arrest, or heart failure hospitalization.

RESULTS A total of 760 patients (43%) had a history of AF (18%) or AF on ECG at enrollment (25%). The highest adjusted risk was associated with AF at enrollment (primary outcome, hazard ratio: 1.34; 95% confidence interval: 1.09 to 1.65; $p = 0.006$; and an increased early risk of secondary outcomes). Neither history of AF nor AF at enrollment modified the beneficial treatment effect of spironolactone. Post-randomization AF, which occurred in 6.3% of patients, was not influenced by spironolactone treatment, but was associated with an increased early risk of the primary outcome (hazard ratio: 2.32; 95% confidence interval: 1.59 to 3.40; $p < 0.0001$) and secondary outcomes.

CONCLUSIONS AF at enrollment was associated with increased cardiovascular risk in HFpEF patients in the TOPCAT study. Post-randomization AF, which was associated with an increased risk of morbidity and mortality, was not influenced by spironolactone. (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist [TOPCAT]; NCT00094302) (J Am Coll Cardiol HF 2018;6:689-97) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BNP = B-type natriuretic peptide

CI = confidence interval

ECG = electrocardiogram

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro–B-type natriuretic peptide

RVFAC = right ventricular fractional area change

The prevalence of heart failure (HF) with preserved ejection fraction (HFpEF) is increasing, particularly in the older adult population, which is simultaneously burdened by rising rates of atrial fibrillation (AF) (1,2). AF is highly prevalent in HFpEF, and patients with HFpEF are at increased risk of developing AF. Based on data from randomized clinical trials and registries, the prevalence of AF in HFpEF patients ranges between 15% and 41% (3), with a reported incidence between 5% and 32% (4,5). Furthermore, comorbidities such as arterial hypertension and increased body mass index, which are common and may play an etiological role in patients with HFpEF, are also considered to represent the greatest attributable risk for the development of AF (6).

SEE PAGE 698

The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) study assessed the efficacy of the mineralocorticoid receptor antagonist spironolactone in patients with HFpEF. Although spironolactone did not reduce the composite primary outcome of cardiovascular mortality, aborted cardiac arrest, or HF hospitalization in the overall population (7), post hoc analyses performed on the patients enrolled in the United States, Canada, Brazil, and Argentina (the Americas) demonstrated a significant reduction in the primary and several secondary endpoints with spironolactone treatment (8). We used data from the Americas component of the TOPCAT study to compare characteristics between patients without AF and those with a history of AF or AF confirmed on an electrocardiogram (ECG) at enrollment, to assess whether AF modified the treatment response to spironolactone and to determine whether spironolactone influenced post-randomization AF.

METHODS

STUDY POPULATION. The design and results of the TOPCAT study were previously published (7,9). Briefly, the TOPCAT study enrolled 3,445 patients at 233 centers in the Americas, Russia, and Georgia. These were patients 50 years of age or older, had HFpEF (left ventricular ejection fraction [LVEF] ≥45%) and at least 1 sign and symptom of HF, and had controlled systolic blood pressure, a serum potassium level <5.0 mmol/l, and an estimated glomerular filtration rate (eGFR) of ≥30 ml/min per 1.73 m^2 of body surface area. Patients were enrolled if they had a history of hospitalization for HF within 12 months before enrollment (hospitalization stratum), or if not, an elevated level of natriuretic peptide within 60 days before randomization (a B-type natriuretic peptide [BNP] level of ≥100 pg/ml or N-terminal pro-BNP [NT-proBNP] of ≥360 pg/ml (natriuretic peptide stratum). Eligible patients were randomly assigned to receive spironolactone or placebo and were followed for a mean period of 3.3 years. The main aim was to determine whether treatment with spironolactone provided a clinically meaningful reduction in the primary composite outcome of cardiovascular mortality, aborted cardiac arrest, or HF hospitalization compared with placebo. Cardiovascular death alone and HF hospitalization alone were defined as secondary outcomes. All events recognized as individual components of the primary outcome and stroke were independently adjudicated by the Clinical Endpoints Center (7,9). The number of patients with AF at screening was not limited in this trial. The protocol was approved by the institutional review board at each of the participating centers, and each subject gave written informed consent.

For the present study, we excluded patients enrolled at the Russian and Georgian sites due to the significant differences in the study population that originated from these regions (8,10).

ASCERTAINMENT OF AF. Patients were classified into 3 groups according to AF status at enrollment: 1) those with no known history of AF nor AF on ECG at enrollment; 2) those with a history of AF, but without AF on ECG at enrollment; and 3) those with AF on ECG at enrollment. During the screening visit, the enrolling physicians entered information on history of AF, when present. During the same visit, an ECG was taken and read by the enrolling physician. The presence of AF or atrial flutter as the underlying rhythm was noted in the electronic case report forms; we used these forms to classify the patients into the group with AF on ECG on enrollment. We also analyzed the occurrence of post-randomization AF during the trial; potential AF events were adjudicated by the clinical endpoints committee and were defined as an irregular rhythm with no discernible P waves confirmed by a physician as AF after ECG or rhythm strip review (9).

ECHOCARDIOGRAPHY. At 27 sites, patients separately consented for participation in the echocardiographic substudy. The present analysis pooled all baseline echocardiograms with quality suitable for quantitative analysis from the echocardiographic

substudy and the quality assurance studies, which provided data of adequate quality for 653 patients for this subanalysis. Differences between TOPCAT participants included in the echocardiographic study compared with those not included were previously reported (11). Standard echocardiographic and Doppler parameters were analyzed using an offline analysis workstation at a dedicated core laboratory blinded to clinical information as previously described (11). All measurements were made in accordance with the recommendations of the American Society of Echocardiography (12,13). Left ventricular deformation was also measured at the core laboratory using a B-mode speckle tracking vendor-independent software (TomTec Imaging Systems, Unterschleissheim, Germany), as previously described (14).

STATISTICAL ANALYSIS. Baseline characteristics were expressed as counts and percentages for categorical variables or as mean ± SD (alternatively, median and 25th to 75th percentiles) if they were non-normally distributed) for continuous variables. The intergroup differences were assessed using the chi-square test and analysis of variance (or Kruskal-Wallis test for non-normally distributed variables) for categorical and continuous variables, respectively. All analyses were performed using the primary endpoint and its components of HF hospitalization and cardiovascular death, as well as all-cause death and stroke. Incidence rates were estimated for each of these endpoints across 3 AF categories, as well the condensed category of patients with either a history of AF or AF at enrollment; hazard ratios (HRs) were estimated using the Cox proportional hazards model with the group of patients with no known AF serving as the referent group. Multivariable models were adjusted for age, sex, randomization to spironolactone, enrollment through HF hospitalization stratum, race, diabetes category, heart rate, smoker status, LVEF, and QRS duration. Cox proportional hazards regression analyses were performed to estimate the treatment effect on the primary endpoint. A Cox regression model using a stepwise selection process with a significance level of 0.10 was used to test the association of post-randomization AF with the following baseline covariates: age, sex, black race, body mass index, resting heart rate, systolic blood pressure, diastolic blood pressure, New York Heart Association functional class, LVEF, eGFR, history of myocardial infarction, diabetes mellitus, chronic obstructive pulmonary disease, peripheral artery disease, thyroid disease, and smoking status. A time-varying analysis with post-randomization AF as the time-varying covariate was performed to assess the association between post-randomization

TABLE 1 Baseline Characteristics of Patients by AF Strata at Enrollment

	No AF (n = 1,005)	History of AF Alone (n = 314)	AF on ECG at Enrollment (n = 446)	Global p Value
Randomization to spironolactone	503 (50.0)	169 (53.8)	214 (48.0)	0.28
Enrollment through HF hospitalization stratum	590 (58.7)	172 (54.8)	213 (47.8)	<0.001
Age, yrs	70 ± 10	73 ± 9	74 ± 8	<0.001
Female	531 (52.8)	155 (49.4)	196 (43.9)	0.007
White race	726 (72.2)	268 (85.4)	388 (87.0)	<0.001
Heart rate, beats/min	69 ± 12	67 ± 11	70 ± 10	<0.001
SBP, mm Hg	130 ± 16	127 ± 15	123 ± 14	<0.001
DBP, mm Hg	72 ± 12	70 ± 11	72 ± 11	0.023
BMI, kg/m^2	35 ± 9	34 ± 8	33 ± 7	<0.001
NYHA functional class				0.18
I	66 (6.6)	15 (4.8)	18 (4.0)	
II	582 (58.1)	201 (64.2)	259 (58.1)	
III	347 (34.6)	96 (30.7)	167 (37.4)	
IV	7 (0.7)	1 (0.3)	2 (0.4)	
QRS duration, ms	103 ± 30	116 ± 38	105 ± 29	<0.001
Comorbidities				
Previous HF hospitalization	597 (59.4)	189 (60.2)	189 (60.2)	0.60
Previous MI	22 (22.0)	81 (25.8)	57 (12.8)	<0.001
Hypertension	914 (90.9)	278 (88.5)	396 (88.8)	0.29
Diabetes	510 (50.7)	122 (38.9)	156 (35.0)	<0.001
Smoking				0.003
Current	8 (0.8)	12 (3.8)	19 (4.3)	
Previous	490 (48.8)	163 (52.1)	246 (55.2)	
Never	181 (40.6)	138 (44.1)	181 (40.6)	
Laboratory values				
Hemoglobin, mg/dl	12.7 ± 1.7	12.7 ± 1.6	13.2 ± 1.7	<0.001
Serum potassium, mg/dl	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.5	0.14
Serum creatinine, mg/dl	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	0.37
eGFR, ml/min	66.0 ± 23.2	61.1 ± 19.1	63.3 ± 18.6	<0.001
BNP, pg/ml	234 (138–432) (n = 394)	260 (170–453) (n = 136)	311 (184–483) (n = 167)	<0.001
NT-proBNP, pg/ml	758 (475–1,592) (n = 183)	853 (614–2,273) (n = 54)	1,367 (851–2,308) (n = 122)	<0.001
Medication				
ACE inhibitor	515 (51.3)	147 (46.8)	228 (51.1)	0.36
ARB	309 (30.8)	108 (34.4)	134 (30.0)	0.40
Beta-blocker	784 (78.1)	244 (77.7)	358 (80.3)	0.59
Calcium channel blocker	390 (38.8)	121 (38.5)	171 (38.3)	0.98
Diuretic	875 (87.2)	280 (89.2)	418 (93.7)	0.001
Warfarin	59 (5.9)	187 (59.6)	346 (77.6)	<0.001
Aspirin	681 (67.8)	174 (55.4)	171 (38.3)	<0.001

Values are n (%), mean ± SD, or median (range).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; BMI = body mass index; DBP = diastolic blood pressure; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; HF = heart failure; MI = myocardial infarction; NT-proBNP = N-terminal pro-BNP; NYHA = New York Heart Association; SBP = systolic blood pressure.

TABLE 2 Baseline Characteristics of the Echocardiography Cohort by AF Strata at Enrollment

	No AF (n = 364)	History of AF Alone (n = 121)	AF on ECG at Enrollment (n = 168)	Global p Value
Mean LV wall thickness, mm	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.0
LVMi, g/m^2	111 ± 31	110 ± 31	109 ± 31	0.77
LVEDVi, ml/m^2	55 ± 14	54 ± 13	54 ± 16	0.71
LVESVi, ml/m^2	24 ± 8	24 ± 7	24 ± 8	0.99
LVEF, %	60 ± 8	59 ± 8	59 ± 8	0.08
Longitudinal strain, %	−16.3 ± 3.5	−15.6 ± 3.4	−14.1 ± 3.1	<0.001
RVFAC, %	50 ± 8	48 ± 8	46 ± 8	<0.001
LAVi, ml	27 ± 10	34 ± 17	37 ± 15	<0.001
MR jet area/LA area	0.03 (0.00–0.10)	0.08 (0.00–0.14)	0.08 (0.03–0.13)	<0.001
TR jet velocity, m/s	2.8 ± 4.7	2.8 ± 4.6	2.8 ± 4.6	0.92

Values are mean ± SD or median (range).

LA = left atrial; LAVi = left atrial volume index; LV = left ventricular; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end systolic volume index; LVMi = left ventricular mass index; MR = mitral regurgitation, RVFAC = right ventricular fractional area change; TR = tricuspid regurgitation; other abbreviations as in Table 1.

AF and the occurrence and time course of the primary outcome, adjusted for history of AF, age, sex, and body mass index, following an AF episode.

A p value of <0.05 was considered statistically significant. The statistical analyses were performed in Stata version 14 (StataCorp, College Station, Texas).

RESULTS

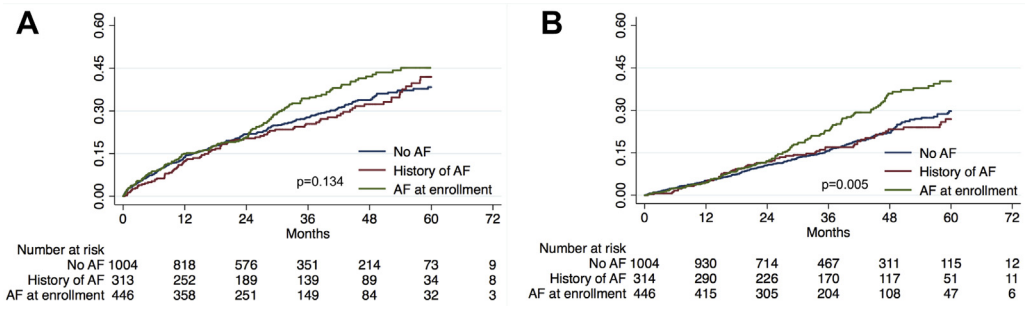
BASELINE CHARACTERISTICS. After excluding 1,678 patients from Russia and Georgia and 2 patients with missing data on AF status, the studied population consisted of 1,765 patients. A total of 760 patients (43.1%) had known AF either by history only (n = 314; 17.8%) or confirmed by ECG at enrollment (n = 446; 25.3%). Baseline characteristics of the studied population stratified by AF category are shown in Table 1. Patients with AF at enrollment were less likely to have been enrolled in the HF hospitalization strata. They were predominantly men and were older than patients without AF or patients with only a history of AF. Patients with AF at enrollment had significantly lower body mass index, lower systolic blood pressure, and significantly higher heart rate compared with the other 2 AF strata. Patients with AF on ECG also had the lowest incidence of diabetes and were less likely to have a history of myocardial infarction. There was no significant difference in history of arterial hypertension or New York Heart Association functional class among the 3 studied groups. Baseline eGFR values were the highest in the group of patients without known AF. The natriuretic peptide levels at baseline were the highest in patients with AF on ECG, followed by those with a history of AF, and the lowest in patients without known AF. The use of diuretics and warfarin was significantly higher in patients with AF at enrollment, and the lowest in patients without known AF, whereas the inverse was true for the use of aspirin.

ECHOCARDIOGRAPHIC CHARACTERISTICS. Baseline echocardiographic data were available in 653 patients (Table 2). The standard descriptors of left ventricular structure and function such as left ventricular wall thickness, mass, left ventricular volumes, and LVEF did not differ significantly among the 3 studied groups, although there was a trend toward lower LVEF in the patients with AF on ECG at enrollment. However, longitudinal strain was significantly reduced in this group, followed by patients with a history of AF and those with no known AF. Patients with AF on ECG also had a greater degree of mitral regurgitation and larger left atrial volumes. Right ventricular fractional area change (RVFAC) was also the most impaired in patients with ongoing AF, with no differences between the groups in peak tricuspid regurgitation jet velocities.

OUTCOMES BASED ON AF AND INFLUENCE OF AF ON THE EFFICACY OF SPIRONOLACTONE. Over a mean follow-up of 2.9 years, the primary composite outcome occurred in 522 patients: in 281 (28.0%) patients with no known AF, in 93 (29.6%) patients with a history of AF, and in 148 (33.2%) patients with AF on ECG at enrollment. Patients with AF at enrollment had the highest rates of both the primary composite outcome and all-cause mortality, with similar rates observed for these endpoints in patients with a history of AF only or without any AF history (Figure 1). The crude incidence rate of the primary outcome, all-cause mortality, and HF hospitalization was highest in those with AF on ECG at enrollment (Table 3). The treatment effect of spironolactone on the primary and secondary outcomes were similar irrespective of AF status at enrollment, with no significant interactions for any of the endpoints (p ≥ 0.42) (Figure 2).

After adjusting for baseline covariates, AF confirmed by ECG at enrollment was associated with a significant increase in the risk for the primary endpoint, cardiovascular mortality, HF hospitalization, and all-cause mortality, compared with those without known AF (Table 3). Patients with a history of AF or AF on ECG at enrollment appeared to have a nominally significant crude increased risk of stroke (Table 3) that was no longer significant when warfarin use was added to the adjusted model (HR: 1.47; 95%

FIGURE 1 Kaplan-Meier Plots



(A) Kaplan-Meier plot of time to first primary outcome (composite outcome of cardiovascular mortality, aborted cardiac arrest, or heart failure hospitalization) event, according to atrial fibrillation (AF) status. **(B)** Kaplan-Meier plot of time to all-cause mortality, according to AF status.

confidence interval [CI]: 0.76 to 2.85; p = 0.25). There was no effect of spironolactone on the risk of stroke in patients with any known AF at enrollment (HR: 1.17; 95% CI: 0.64 to 2.16; p = 0.60).

Over the follow-up period, post-randomization AF, confirmed on ECG, occurred in 85 (8.5%) patients with no known history of AF nor AF on ECG at enrollment, and in 27 (8.6%) patients with a history of

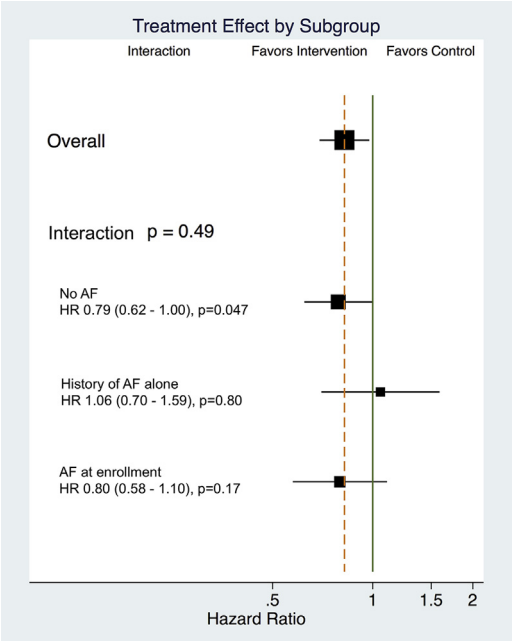
TABLE 3 Event Rates and HRs for the Primary Endpoint, Cardiovascular Mortality, HF Hospitalization, All-Cause Mortality, and Stroke by AF Groups

	No AF (n = 1,005)	History of AF Alone (n = 314)	AF on ECG at Enrollment (n = 446)	Any Known AF at Enrollment (n = 760)
Primary outcome				
Participants with event	281 (28.0)	93 (29.6)	148 (33.2)	241 (31.7)
Event rate per 100 person-yrs	11.0 (9.8-12.3)	10.6 (8.7-13.0)	13.3 (11.3-15.6)	12.1 (10.7-13.7)
Unadjusted HR (95% CI)	Referent	0.98 (0.78-1.25) (p = 0.90)	1.21 (0.99-1.48) (p = 0.06)	1.11 (0.94-1.32) (p = 0.23)
Adjusted HR (95% CI)*	Referent	1.01 (0.79-1.29) (p = 0.93)	1.34 (1.09-1.65) (p = 0.006)	1.19 (0.99-1.43) (p = 0.06)
Cardiovascular mortality				
Participants with event	113 (11.2)	36 (11.5)	74 (16.6)	110 (14.5)
Event rate per 100 person-yrs	3.8 (3.2-4.6)	3.6 (2.6-5.0)	5.7 (4.6-7.2)	4.8 (4.0-5.8)
Unadjusted HR (95% CI)	Referent	0.90 (0.62-1.31) (p = 0.58)	1.50 (1.12-2.01) (p = 0.007)	1.23 (0.95-1.60) (p = 0.12)
Adjusted HR (95% CI)*	Referent	0.85 (0.58-1.26) (p = 0.43)	1.43 (1.05-1.94) (p = 0.024)	1.17 (0.89-1.55) (p = 0.26)
HF hospitalization				
Participants with event	215 (21.4)	73 (23.3)	112 (25.1)	185 (24.3)
Event rate per 100 person-yrs	8.4 (7.3-9.6)	8.4 (6.6-10.5)	10.0 (8.3-12.1)	9.3 (8.1-10.7)
Unadjusted HR (95% CI)	Referent	1.02 (0.79-1.34) (p = 0.86)	1.19 (0.95-1.50) (p = 0.13)	1.12 (0.92-1.36) (p = 0.25)
Adjusted HR (95% CI)*	Referent	1.05 (0.80-1.39) (p = 0.72)	1.36 (1.07-1.73) (p = 0.012)	1.22 (0.99-1.50) (p = 0.06)
All-cause mortality				
Participants with event	197 (19.6)	68 (22.0)	120 (26.9)	188 (24.7)
Event rate per 100 person-yrs	6.4 (5.6-7.4)	6.6 (5.2-8.3)	9.1 (7.6-10.8)	8.0 (6.9-9.2)
Unadjusted HR (95% CI)	Referent	0.99 (0.75-1.31) (p = 0.97)	1.43 (1.14-1.79) (p = 0.002)	1.23 (1.01-1.51) (p = 0.040)
Adjusted HR (95% CI)*	Referent	0.86 (0.64-1.15) (p = 0.32)	1.27 (1.00-1.62) (p = 0.047)	1.09 (0.88-1.35) (p = 0.42)
Stroke				
Participants with event	35 (3.5)	17 (5.4)	25 (5.6)	42 (5.5)
Event rate per 100 person-yrs	1.2 (0.9-1.7)	1.7 (1.1-2.8)	2.0 (1.3-2.9)	1.9 (1.4-2.5)
Unadjusted HR (95% CI)	Referent	1.43 (0.80-2.55) (p = 0.23)	1.63 (0.98-2.73) (p = 0.06)	1.54 (0.99-2.42) (p = 0.06)
Adjusted HR (95% CI)*	Referent	1.58 (0.87-2.89) (p = 0.14)	1.63 (0.95-2.79) (p = 0.08)	1.61 (1.00-2.58) (p = 0.048)

Values are n (%) or median (range), unless otherwise indicated. *Adjusted for age, sex, randomization to spironolactone, enrollment through HF hospitalization stratum, race category, diabetes category, heart rate, smoker status category, left ventricular ejection fraction, and QRS duration.

CI = confidence interval; HR = hazard ration; other abbreviations as in Table 1.

FIGURE 2 The Effect of Treatment With Spironolactone



The effect of treatment with spironolactone, compared with placebo, on the primary composite outcome of cardiovascular mortality, aborted cardiac arrest, or heart failure hospitalization, for each of the AF subgroups. AF = atrial fibrillation; HR = hazard ratio.

AF (but without AF on ECG at enrollment). In those who developed post-baseline AF, the mean time to an event was 1.9 years. In a stepwise multiple regression model, heart rate and age remained the only significant baseline characteristics predictive of post-randomization AF (HR per 10 beats/min change in heart rate: 0.78; 95% CI: 0.64 to 0.94; p = 0.008; HR per 1 year change in age: 1.03; 95% CI: 1.01 to 1.05; p = 0.011). Randomization to spironolactone did not influence post-randomization AF in an intention-to-treat (HR: 0.98; 95% CI: 0.68 to 1.42; p = 0.92) or on-treatment analysis (HR: 0.93; 95% CI: 0.59 to 1.46; p = 0.74).

In a time-varying analysis adjusted for history of AF, age, sex, and body mass index, in those with either no history of AF or history of AF but not AF at enrollment, post-randomization AF was associated with a 2.3-fold increased subsequent risk of the composite primary outcome (HR: 2.32; 95% CI: 1.59 to 3.40; p < 0.0001) and a significant increase in risk of cardiovascular mortality (HR: 2.84; 95% CI: 1.86 to 4.35; p < 0.0001), hospitalization for HF (HR: 2.50; 95% CI: 1.62 to 3.88; p < 0.0001), all-cause mortality (HR: 2.53; 95% CI: 1.80 to 3.55; p < 0.0001), and all-cause hospitalization (HR: 1.90; 95% CI: 1.20 to 3.02; p = 0.006). The risk of the primary outcome was the greatest in the first 90 days post-incident AF (HR: 5.3; 95% CI: 2.9 to 10.0) and declined between 90 days and 1 year (HR: 2.0; 95% CI: 1.0 to 4.1) and after 1 year (HR: 1.6; 95% CI: 0.9 to 2.9). Nine patients (8%) with post-baseline AF developed a stroke.

DISCUSSION

In patients with HFpEF enrolled in the TOPCAT trial in the Americas, the presence of AF confirmed by ECG at enrollment was associated with an increased adjusted risk of the composite primary outcome and a significant increase in the risk for cardiovascular mortality, HF hospitalization, and all-cause mortality compared with patients without AF. In contrast, patients with a history of AF (but without AF on ECG at enrollment) did not demonstrate an increased risk of these adverse outcomes compared with those without known AF. The potentially beneficial effects of spironolactone on the primary outcome, its components, and several of the secondary outcomes in the patients enrolled in the Americas was independent of history of AF or AF at enrollment. Post-randomization AF was associated with a substantial increase in risk for all outcomes. Spironolactone treatment did not influence post-randomization AF.

The prevalence of AF in TOPCAT was somewhat higher than that reported in previous clinical trials and a smaller community-based cohort, yet it was consistent with data from a large multicenter cohort of patients with HF (Cardiovascular Research Network PRESERVE Study) that included >14,000 patients with HFpEF (4,5,15,16). The rates of post-randomization AF that we reported were comparable to those reported in patients with preserved LVEF from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) cohort and the PRESERVE study (4,15).

Although baseline echocardiographic data did not reveal significant differences in standard measurements of left ventricular structure and function among the studied subgroups, global longitudinal strain was significantly reduced in patients with AF on ECG at enrollment, who also exhibited significant left atrial enlargement. Although the reproducibility of ventricular strain measures in AF was reduced (17), it was nevertheless prognostic (18). Additional echocardiographic predictors of adverse events in HF, such as reduced RVFAC and increased severity of mitral regurgitation were also more pronounced in

patients with AF on ECG at enrollment. Although the association between atrial enlargement and AF were well described (19), our results supported several studies that demonstrated a significant association between AF and right ventricular dysfunction in HFpEF (20,21).

The association between both prevalent and incident AF with increased morbidity and mortality was reported in HFpEF (4,5,15). The 28% increase in relative risk for all-cause mortality in patients with AF at enrollment in the present study was comparable to existing data (5). Somewhat lower rates of adverse outcomes were noted in patients with pre-existing AF in the PRESERVE study. However, pre-existing AF was defined as AF documented at any time during the 5 years before cohort entry; the patients with only a history of AF might have possibly attenuated the increase in risk (15), which was a finding confirmed by our data.

An association between prevalent AF and increased risk of morbidity and mortality was demonstrated in symptomatic HF patients irrespective of LVEF in CHARM; however, there was an even higher risk attributable to AF in HFpEF—specifically, a 37% increase in risk of all-cause mortality (4). In patients with only a history of AF, we did not find an increased risk for adverse outcomes compared with patients without AF. Such a subgroup was not investigated in the mentioned HFpEF studies. However, recent data from 2 large heart failure with reduced ejection fraction (HFrEF) trials suggested a higher risk of the composite endpoint (cardiovascular death or HF hospitalization), HF hospitalization alone, or stroke in patients with paroxysmal AF compared with patients without AF, whereas permanent and/or persistent AF at enrollment was not associated with an increased risk (22).

Importantly, we found that post-randomization AF in HFpEF patients indicated an especially high morbidity and mortality risk in those with either no history of AF or history of AF who were not in AF at enrollment, particularly in the first 90 days following the occurrence of AF. Interestingly, the rates of post-randomization AF were identical in patients with no history of AF and those with history of AF but without AF at enrollment. Our data confirmed previous findings of a greater mortality risk associated with incident AF following the diagnosis of HFpEF than with AF on ECG at enrollment, (i.e., a 2.2-fold increase in risk) compared with patients without AF (5). The PRESERVE study also recognized that incident AF complicating HF was associated with the highest risk for adverse outcomes (albeit lower than in the TOPCAT cohort) with comparable multivariable adjusted HRs for ischemic stroke, hospitalization for HF, hospitalization for any cause, and AF-associated death among patients with HFpEF and those with HFrEF (15). In the CHARM study, although the absolute risk of cardiovascular mortality or HF hospitalization was shown to be the highest in patients with HFrEF, patients with HFpEF and incident AF had a greater relative increase in risk than those with HFrEF (4). In our cohort, lower heart rate and higher age were the only significant baseline characteristics predictive of post-randomization AF. Although lower resting heart rate was suggested as a risk factor for AF in a community-based cohort (23) and in healthy young adults (possibly associated with increased vagal tone and high stroke volumes) (24), it was inconsistent as a predictor of AF risk in previous studies (25). However, due to the relatively small number of AF events in our cohort, we could not exclude the possibility that this finding was aberrant. In a recent TOPCAT subanalysis that studied echocardiographic predictors of AF, diastolic parameters of left atrial function appeared to be relevant predictors of AF risk (26).

We did not observe a reduction in post-randomization AF in patients randomized to spironolactone. In contrast, a reduced risk of developing AF in patients with HFrEF and HFpEF treated with candesartan (27) and a reduced incidence of new-onset AF with eplerenone in HFrEF were reported (28). In addition, in a smaller cohort of patients with refractory paroxysmal AF and preserved LVEF but without symptoms of HF, combined spironolactone and beta-blocker treatment appeared beneficial in preventing recurrent AF episodes (29).

STUDY LIMITATIONS. We focused our subanalysis only on the cohort enrolled in the Americas due to concerns that many patients enrolled in Russia and Georgia might not have had HF (8,10). The stratification of patients according to investigator-reported history of AF at enrollment was suboptimal, and some patients with history of AF might not have been recognized as such. Although specific AF classification and progression of AF standards exist, we opted for the current stratification because we could not determine if those with a history of AF had paroxysmal or persistent AF, or if those with AF at enrollment had persistent or permanent AF. The small subgroup with post-randomization AF limited our ability to determine the patient characteristics that were predictive of AF, including the association of spironolactone with AF occurrence, as well as the association between post-randomization AF and outcomes. The true rate of post-randomization AF

was likely higher than documented by the schedule of study visits; continuous ECG monitoring could provide reliable results. Although such studies in HFpEF are still lacking, they might provide much better insight to the complex interrelation between AF and HFpEF and the influence of therapies on incident AF. We also acknowledge the lack of formal data on antiarrhythmic drug use that would ideally be accounted for. Finally, inherent to clinical trials with specific entry criteria, the generalizability of these results might be limited. This analysis should be considered post hoc and thus hypothesis-generating.

CONCLUSIONS

In a well-defined HFpEF cohort, we reported a significant association between AF confirmed by ECG at enrollment (but not a history of AF) and morbidity and mortality. We also found a markedly increased risk following development of post-randomization AF during the course of the trial, in particular during the first 90 days after the episode of post-randomization AF. These data underscore the need for further understanding the inter-relationship between AF and HFpEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a population of patients with HFpEF from the TOPCAT trial, we noted a significant association between AF confirmed by ECG at enrollment in TOPCAT and morbidity and mortality. This increased risk was not observed in patients with only a history of AF but without AF at enrollment. The potentially beneficial treatment effect of spironolactone on the primary outcome was not modified by either history of AF alone or AF on ECG at enrollment. Patients who developed post-randomization AF during the course of the trial were at substantially higher risk of adverse outcomes after an AF event, particularly during the first 90 days following the episode. Our data confirm that AF portends an additional increase in cardiovascular risk in patients with HFpEF. The beneficial effects of spironolactone appear to be retained irrespective of AF status, and might thus be a valid therapeutic strategy in the wider HFpEF population.

TRANSLATIONAL OUTLOOK: Prospective studies using ECG monitoring devices are required to detect incident AF and thus improve the understanding of its association with cardiovascular outcomes. Furthermore, prospective studies are needed to assess the effect of spironolactone on incident AF in HFpEF patients.

REFERENCES

1. Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. Circ Cardiovasc Qual Outcomes 2012;5:85–93.

2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.

3. Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins. J Am Coll Cardiol 2016;68:2217–28.

4. Olsson LG, Swedberg K, Ducharme A, et al., CHARM Investigators. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol 2006;47:1997–2004.

5. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. Circulation 2013;128:1085–93.

6. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2011;123:1501–8.

7. Pitt B, Pfeffer MA, Assmann SF, et al., TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.

8. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34–42.

9. Desai AS, Lewis EF, Li R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. Am Heart J 2011;162:966–72.e10.

10. de Denus S, O'Meara E, Desai AS, et al. Spironolactone metabolites in TOPCAT - New insights into regional variation. N Engl J Med 2017;376:1690–2.

11. Shah AM, Shah SJ, Anand IS, et al., TOPCAT Investigators. Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial. Circ Heart Fail 2014;7:104–15.

12. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165–93.

13. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.e14.

14. Shah AM, Claggett B, Sweitzer NK, et al. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. Circulation 2015;132:402–14.

15. McManus DD, Hsu G, Sung SH, et al., Cardiovascular Research Network PRESERVE Study. Atrial fibrillation and outcomes in heart failure with preserved versus reduced left ventricular ejection fraction. J Am Heart Assoc 2013;2:e005694.

16. Oluleye OW, Rector TS, Win S, et al. History of atrial fibrillation as a risk factor in patients with heart failure and preserved ejection fraction. Circ Heart Fail 2014;7:960–6.

17. Kotecha D, Mohamed M, Shantsila E, Popescu BA, Steeds RP. Is echocardiography valid and reproducible in patients with atrial fibrillation? A systematic review. Europace 2017;19:1427–38.

18. Su HM, Lin TH, Hsu PC, et al. Global left ventricular longitudinal systolic strain as a major predictor of cardiovascular events in patients with atrial fibrillation. Heart 2013;99:1588–96.

19. Patel RB, Vaduganathan M, Shah SJ, Butler J. Atrial fibrillation in heart failure with preserved ejection fraction: insights into mechanisms and therapeutics. Pharmacol Ther 2017;176:32–9.

20. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J 2014;35:3452–62.

21. Gorter TM, van Melle JP, Rienstra M, et al. Right heart dysfunction in heart failure with preserved ejection fraction: the impact of atrial fibrillation. J Card Fail 2018;24:177–85.

22. Mogensen UM, Jhund PS, Abraham WT, Desai AS, et al., PARADIGM-HF and ATMOSPHERE Investigators and Committees. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. J Am Coll Cardiol 2017;70:2490–500.

23. Morseth B, Graff-Iversen S, Jacobsen BK, et al. Physical activity, resting heart rate, and atrial fibrillation: the Tromsø Study. Eur Heart J 2016;37:2307–13.

24. Grundvold I, Skretteberg PT, Liestøl K, et al. Low heart rates predict incident atrial fibrillation in healthy middle-aged men. Circ Arrhythm Electrophysiol 2013;6:726–31.

25. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009;373:739–45.

26. O'Neil WT, Sandesara P, Patel N, et al. Echocardiographic predictors of atrial fibrillation in patients with heart failure with preserved ejection fraction. Eur Heart J Cardiovasc Imaging 2017;18:725–9.

27. Ducharme A, Swedberg K, Pfeffer MA, et al., CHARM Investigators. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Am Heart J 2006;152:86–92.

28. Swedberg K, Zannad F, McMurray JJ, et al., EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. J Am Coll Cardiol 2012;59:1598–603.

29. Dabrowski R, Borowiec A, Smolis-Baket E, et al. Effect of combined spironolactone–blocker enalapril treatment on occurrence of Symptomatic Atrial Fibrillation Episodes in Patients With a History of Paroxysmal Atrial Fibrillation (SPIR-AF Study). Am J Cardiol 2010;106:1609–14.

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