JACC: HEART FAILURE VOL. 6, NO. 8, 2018

PUBLISHED BY ELSEVIER

Sudden Death in Heart Failure With Preserved Ejection Fraction

A Competing Risks Analysis From the TOPCAT Trial

Muthiah Vaduganathan, MD, MPH,[a] Brian L. Claggett, PhD,[a] Neal A. Chatterjee, MD, MSc,[b] Inder S. Anand, MD, PhD,[c] Nancy K. Sweitzer, MD, PhD,[d] James C. Fang, MD,[e] Eileen O'Meara, MD,[f] Sanjiv J. Shah, MD,[g] Sheila M. Hegde, MD, MPH,[a] Akshay S. Desai, MD, MPH,[a] Eldrin F. Lewis, MD, MPH,[a] Jean Rouleau, MD,[f] Bertram Pitt, MD,[h] Marc A. Pfeffer, MD, PhD,[a] Scott D. Solomon, MD[a]

ABSTRACT

OBJECTIVES This study investigated the rates and predictors of SD or aborted cardiac arrest (ACA) in HFpEF.

BACKGROUND Sudden death (SD) may be an important mode of death in heart failure with preserved ejection fraction (HFpEF).

METHODS We studied 1,767 patients with HFpEF (EF ≥45%) enrolled in the Americas region of the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial. We identified independent predictors of composite SD/ACA with stepwise backward selection using competing risks regression analysis that accounted for nonsudden causes of death.

RESULTS During a median 3.0-year (25th to 75th percentile: 1.9 to 4.4 years) follow-up, 77 patients experienced SD/ACA, and 312 experienced non-SD/ACA. Corresponding incidence rates were 1.4 events/100 patient-years (25th to 75th percentile: 1.1 to 1.8 events/100 patient-years) and 5.8 events/100 patient-years (25th to 75th percentile: 5.1 to 6.4 events/100 patient-years). SD/ACA was numerically lower but not statistically reduced in those randomized to spironolactone: 1.2 events/100 patient-years (25th to 75th percentile: 0.9 to 1.7 events/100 patient-years) versus 1.6 events/100 patient-years (25th to 75th percentile: 1.2 to 2.2 events/100 patient-years); the subdistributional hazard ratio was 0.74 (95% confidence interval: 0.47 to 1.16; p = 0.19). After accounting for competing risks of non-SD/ACA, male sex and insulin-treated diabetes mellitus were independently predictive of composite SD/ACA (C-statistic = 0.65). Covariates, including eligibility criteria, age, ejection fraction, coronary artery disease, left bundle branch block, and baseline therapies, were not independently associated with SD/ACA. Sex and diabetes mellitus status remained independent predictors in sensitivity analyses, excluding patients with implantable cardioverter-defibrillators and when predicting SD alone.

CONCLUSIONS SD accounted for ~20% of deaths in HFpEF. Male sex and insulin-treated diabetes mellitus identified patients at higher risk for SD/ACA with modest discrimination. These data might guide future SD preventative efforts in HFpEF. (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function [TOPCAT]); NCT00094302 (J Am Coll Cardiol HF 2018;6:653–61) © 2018 by the American College of Cardiology Foundation.

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately one-half of prevalent heart failure (HF) (1) and is expected to rise with the aging population and the increasing burden of cardiometabolic risk factors worldwide (2). Three-quarters of older patients hospitalized for HFpEF in the United States die within 5 years, a mortality risk similar to that of HF with reduced ejection (HFrEF) (3). Unlike HFrEF, however, no medical therapies are currently available to alter

From the [a]Brigham and Women's Hospital, Boston, Massachusetts; [b]Massachusetts General Hospital, Boston, Massachusetts; [c]VA Medical Center and University of Minnesota, Minneapolis, Minnesota; [d]University of Arizona, Tucson, Arizona; [e]University of Utah, Salt Lake City, Utah; [f]Montreal Heart Institute and University of Montreal, Montreal, Quebec, Canada; [g]Northwestern University, Chicago, Illinois; and the [h]University of Michigan School of Medicine, Ann Arbor, Michigan. TOPCAT was supported by the National Heart, Lung, and Blood Institute (NHLBI) (HHSN268200425207C). Dr. Vaduganathan was supported by the NHLBI T32 postdoctoral training grant (T32HL007604). Dr. Sweitzer was supported by research grants from the National Institutes of Health.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2018.02.014

ABBREVIATIONS AND ACRONYMS

ACA = aborted cardiac arrest

BNP = brain natriuretic peptide

CI = confidence interval

DM = diabetes mellitus

EF = ejection fraction

eGFR = estimated glomerular filtration rate

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

MI = myocardial infarction

NP = natriuretic peptide

SD = sudden death

sHR = subdistributional hazard ratio

this natural history in HFpEF, perhaps due to incomplete understanding of the pathogenesis and progression of this disease entity. Sudden death (SD) appears to account for 40% of cardiovascular deaths and 20% of all deaths in recent global trials of HFpEF (4-6), and may represent a potential target for SD prevention strategies (7). Limited data are available for describing the profile of patients with HFpEF who experience SD (8,9), and SD risk prediction is particularly challenging because of the high rates of the competing risks of nonsudden causes of death. In this competing risks analysis, we investigated the incidence rates of composite SD or aborted cardiac arrest (ACA), unique predictors of SD/ACA, and response to spironolactone in the Americas region (United States, Canada, Brazil, Argentina) of the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial.

SEE PAGE 662

METHODS

TOPCAT AMERICAS AND PATIENT SELECTION. The TOPCAT trial (4,10) was a global phase 3, multicenter, double-blind, placebo-controlled randomized clinical trial that evaluated the safety and efficacy of spironolactone in HFpEF. Because of marked regional heterogeneity with respect to enrolled populations, and drug and protocol compliance (11), the study population for the present analysis focused on the 1,767 patients enrolled in the Americas region of TOPCAT. Eligible patients for enrollment included those 50 years and older with signs and symptoms of HF, left ventricular EF of ≥45%, well-controlled blood pressure, and a serum potassium <5.0 mmol/l. Enrollment was further stratified by the presence of 1 of 2 additional criteria: 1) HF hospitalization in the previous 12 months; or 2) elevated natriuretic peptide (NP) level in the previous 60 days. Relevant exclusion criteria included severe systemic disease expected to limit life expectancy to <3 years, known infiltrative or hypertrophic cardiomyopathy, or myocardial infraction (MI) in the previous 90 days. Patients were randomized 1:1 to either spironolactone or matching placebo, which was uptitrated up to 30 mg once daily at 4 weeks and up to 45 mg once daily at 4 months, as clinically tolerated.

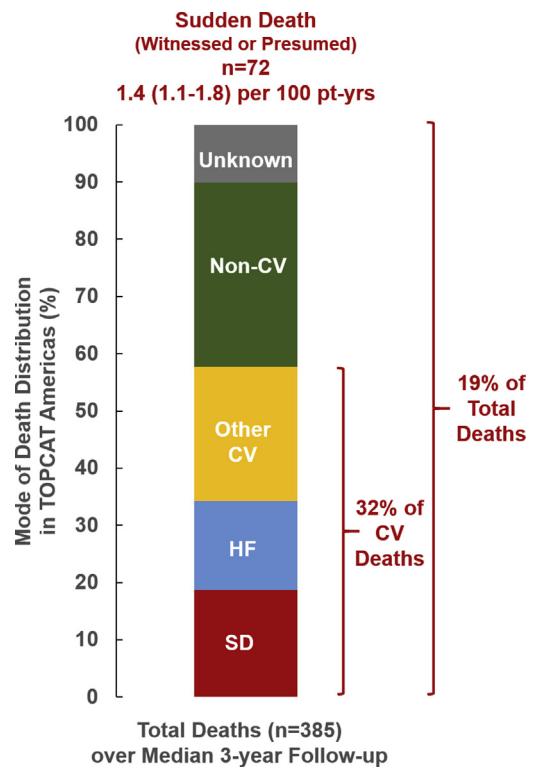
DEFINITION OF SD. Cause-specific deaths were independently adjudicated by a clinical events committee (Brigham and Women's Hospital, Boston, Massachusetts) that was blinded to treatment allocation. SD was defined as an unexpected death in an otherwise stable patient and was classified as either witnessed (if death was observed or if last seen within 24 h) or presumed (if last seen ≥24 h with the clinical context suggestive of SD). ACA, a pre-specified component of the primary composite endpoint for the overall TOPCAT trial, was defined as successful resuscitation after cardiac arrest (with or without antecedent MI or HF) with meaningful recovery. For the purposes of this analysis, all deaths not adjudicated as SD or ACA were considered to be non-SD/ACA and treated as a competing risk.

STATISTICAL ANALYSES. The clinical profiles of patients experiencing SD/ACA, non-SD/ACA, or who were alive throughout follow-up without

Dr. O'Meara has received subventions/research support and consulting fees from Novartis, Bayer, AstraZeneca, Servier, and Amgen. Dr. Shah has received research grants from Actelion, AstraZeneca, Corvia, and Novartis; and has received consulting fees from Actelion, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiora, Eisai, Ironwood, Merck, Novartis, Sanofi, and United Therapeutics. Dr. Desai has received research grant support from Novartis; and consulting fees from Novartis, AstraZeneca, Abbott, Relypsa, and DalCor Pharma. Dr. Lewis has received research grants from the NHLBI, Novartis, and Sanofi; and consulting fees from Novartis. Dr. Rouleau has been a consultant for Novartis, AstraZeneca, and Bayer. Dr. Pitt has received consulting fees from Amorcyte, AstraZeneca, Aurasense, Bayer, BG Medicine, Gambro, Johnson & Johnson, Mesoblast, Novartis, Pfizer, Relypsa, and Takeda; has received research grant support from Forest Laboratories; holds stock in Aurasense, Relypsa, BG Medicine, and Aurasense; and has a pending patent related to site-specific delivery of eplerenone to the myocardium. Dr. Pfeffer has received consulting fees from Amgen, AstraZeneca, Bayer, DalCor Pharma UK, Genzyme, Lilly, The Medicines Company, MedImmune, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Salix, Sanderling, Sanofi, Takeda, Teva, Thrasos, and Vericel; has received research grant support from Amgen, Celladon, Novartis, and Sanofi; and holds stock options in DalCor; Brigham and Women's Hospital has patents for the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction with Novartis Pharmaceuticals on which Dr. Pfeffer is a co-inventor and his share of the licensing agreement is irrevocably transferred to charity. Dr. Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Celladon, Gilead, GlaxoSmithKline, Ionis Pharmaceutics, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, Theracos; and has consulted for Alnylam, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Corvia, Gilead, GlaxoSmithKline, Ironwood, Merck, Novartis, Pfizer, Takeda, and Theracos. All other authors report no other relationships relevant to the contents of this paper to disclose.

Manuscript received February 6, 2018; revised manuscript received February 28, 2018, accepted February 28, 2018.

FIGURE 1 Mode of Death Distribution in the Americas Region of TOPCAT



Mode of death distribution in the Americas region of TOPCAT. CV = cardiovascular; HF = heart failure; SD = sudden death.

experiencing ACA were presented as mean ± standard deviation and proportions, and compared using Student's *t*-tests, 1-way analysis of variance tests, and chi-square tests, as appropriate. Incidence rates (per 100 patient-years of observation) were calculated for SD/ACA and non-SD/ACA overall and in key subgroups, including by treatment randomization (to spironolactone or placebo). To account for competing risks of non-SD/ACA, we used competing risks regression analysis by the proportional subhazards method developed by Fine and Gray (12).

The competing risks regression models were covariate adjusted to identify unique independent risk predictors of SD/ACA. The final model was fit using covariates identified by stepwise backward selection ($p < 0.05$ for retention), accounting for non-SD/ACA as competing risks. Candidate variables were selected based on previous TOPCAT-based analyses (13) and clinically relevant predictors of SD identified in previous studies (9): treatment arm, qualifying eligibility criteria, demographic characteristics (age, sex, race, ethnicity), clinical characteristics (body mass index, EF, New York Heart Association functional class, hypertension, diabetes mellitus [DM], coronary artery disease [defined as a composite of previous MI, angina, coronary artery bypass graft surgery, or percutaneous coronary intervention], atrial fibrillation/flutter, chronic obstructive pulmonary disease, peripheral artery disease, current or past smoking status), vital signs (systolic and diastolic blood pressures, heart rate), electrocardiographic measures (left bundle branch block, left ventricular hypertrophy, QRS duration), laboratory parameters (hemoglobin, estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2, serum potassium), baseline medical therapies, and baseline implantable cardioverter-defibrillator (ICD) use. Baseline electrocardiographic indexes were reported by the investigators and not specifically analyzed in a core laboratory. Self-reported race was classified as white, black, or Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander.

Model discrimination, the ability to discriminate who did and did not experience SD/ACA in follow-up, was assessed using Harrell's C-concordance statistic (C-statistic) of a Cox proportional hazards model (using predictors identified in the competing risks regression analysis).

Three sensitivity analyses were performed. First, a competing risks regression model was built after excluding the 42 patients with baseline ICD use. Second, because of variable ultimate outcomes after resuscitation in patients who experienced ACA, a separate competing risks regression model was fitted predicting SD alone (ACA events were analyzed accordingly to final vital status). Finally, a competing risks regression model was performed in patients with available NPs for analysis. NPs were available in 1,057 patients in the Americas region of TOPCAT (60%), including 687 patients enrolled in the NP strata and 370 in the hospitalization strata. Brain natriuretic peptide (BNP) was measured in 698 patients, whereas N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels were measured in 359 patients. In the subset of patients with available NP data, we evaluated the incremental predictive value of log-transformed and standardized NP values (either BNP or NT-proBNP), expressed per 1 standard deviation, beyond predictors identified in the full model. We compared Harrell's C statistics derived from a model including the original predictors with a model including those predictors and NPs.

The treatment effect of spironolactone on SD/ACA was estimated using unadjusted Cox proportional

JACC: HEART FAILURE VOL. 6, NO. 8, 2018
AUGUST 2018:653–61

TABLE 1 Baseline Characteristics by Vital Status in Follow-Up and Region (Americas)

	SD or ACA (n = 77)	Non-SD/ACA (n = 312)	p Value*	Alive (n = 1,378)	p Value†
Randomization to spironolactone	33 (42.9)	145 (46.5)	0.57	708 (51.4)	0.13
Eligibility criteria			0.34		0.06
Previous HF hospitalization in 12 months	50 (64.9)	184 (59.0)		742 (53.8)	
Elevated NP in 60 days	27 (35.1)	128 (41.0)		636 (46.2)	
Age, yrs	70.4 ± 9.2	75.4 ± 8.9	<0.001	70.7 ± 9.7	<0.001
Male	52 (67.5)	169 (54.2)	0.03	664 (48.2)	0.001
Race‡					
White	57 (74.0)	259 (83.0)	0.12	1,068 (77.5)	0.01
Black	15 (19.5)	34 (10.9)		253 (18.4)	
Asian, American Indian or Alaskan Native, Native Hawaiian/ Pacific Islander	5 (6.5)	19 (6.1)		57 (4.1)	
Hispanic ethnicity	12 (15.6)	45 (14.4)	0.80	261 (18.9)	0.15
Left ventricular ejection fraction (%)	56.1 ± 8.3	57.4 ± 7.6	0.20	58.5 ± 7.7	0.005
New York Heart Association functional class			0.74		0.02
I	3 (3.9)	17 (5.4)		79 (5.8)	
II	46 (59.7)	165 (52.9)		832 (60.6)	
III	27 (35.1)	125 (40.1)		458 (33.4)	
IV	1 (1.3)	5 (1.6)		4 (0.3)	
Hypertension	68 (88.3)	271 (86.9)	0.73	1,249 (90.8)	0.1
Diabetes mellitus	45 (58.4)	139 (44.6)	0.03	604 (43.9)	0.04
Insulin use	32 (71.1)	69 (49.6)	0.01	278 (46.0)	0.005
eGFR <60 ml/min/1.73 m^2	47 (61.0)	193 (61.9)	0.89	615 (44.6)	<0.001
Previous HF hospitalization	50 (64.9)	198 (63.5)	0.81	792 (57.6)	0.09
Previous myocardial infarction	22 (28.6)	74 (23.7)	0.38	263 (19.1)	0.04
Previous cerebrovascular accident	8 (10.4)	33 (10.6)	0.96	117 (8.5)	0.46
Coronary artery disease§	44 (57.1)	154 (49.4)	0.22	617 (44.8)	0.05
Peripheral artery disease	15 (19.5)	49 (15.7)	0.42	143 (10.4)	0.003
Atrial fibrillation	28 (36.4)	154 (49.4)	0.04	561 (40.8)	0.01
Dyslipidemia	56 (72.7)	215 (68.9)	0.51	979 (71.1)	0.68
Chronic obstructive pulmonary disease	13 (16.9)	63 (20.2)	0.51	215 (15.6)	0.14

Continued on the next page

hazards models and competing risks regression models. We graphically displayed the cumulative incidence functions of SD/ACA and non-SD/ACA by treatment group (spironolactone vs. placebo). Treatment interactions with identified risk predictors were tested.

All patients provided written informed consent to participate in TOPCAT, and study protocols were approved by local institutional review boards. TOPCAT was supported by the National Heart, Lung, and Blood Institute. All statistical analyses were performed using STATA 14.1 (StataCorp, College Station, Texas).

RESULTS

Clinical events were adjudicated and available in all 1,767 patients enrolled in the Americas region of TOPCAT. During a median of 3.0 (1.9 to 4.4) years, 385 patients died: 72 (19% of total deaths) of SD (63 witnessed, 9 presumed) and 313 (81% of total deaths) of non-SD (Figure 1). There were 6 adjudicated ACA events with variable ultimate outcomes after resuscitation (4 alive in follow-up, 1 SD, 1 infectious death). As such, the outcome of interest of composite SD or ACA occurred in 77 patients.

CLINICAL PROFILES OF HFpEF PATIENTS WHO DIED SUDDENLY. Compared with patients who experienced non-SD/ACA (Table 1), patients who experienced SD/ACA tended to be younger (70 ± 9 years vs. 75 ± 9 years), men (68% vs. 54%), with higher body mass indexes (35 ± 9 kg/m^2 vs. 32 ± 9 kg/m^2) and rates of DM (58% vs. 45%) ($p \leq 0.05$ for all comparisons). Left ventricular EF was similar in patients who experienced SD/ACA (56 ± 8%) and non-SD/ACA (57 ± 8%; $p = 0.20$). Rates of previous MI (29% vs. 24%) and coronary artery disease (57% vs. 49%) did not differ in those who experienced SD/ACA and non-SD/ACA ($p > 0.05$ for both comparisons). Baseline use of ICD therapy was low and not significantly different between patients who experienced SD/ACA or non-SD/ACA (1.3% vs. 2.6%; $p = 0.51$).

INCIDENCE RATES AND PREDICTORS OF SD OR ACA IN HFpEF. During 5,426 patient-years of total observation, incidence rates of SD/ACA and non-SD/ACA were 1.4 events/100 patient-years (25th to 75th percentile: 1.1 to 1.8 events/100 patient-years) and 5.8 events/100 patient-years (25th to 75th percentile: 5.1 to 6.4 events/100 patient-years), respectively. In the final competing risks regression model, male sex and insulin-treated DM were independent predictors of SD/ACA with modest discrimination (C-statistic = 0.65) (Figure 2). In sensitivity analyses, these 2 variables, along with smoking status, remained predictors of SD/ACA with similar discrimination (C-statistic = 0.66) in a competing risks regression model performed after excluding patients with baseline ICD use (n = 42). In addition, using a model fitted for SD alone (rather than SD/ACA), sex and DM status continued to be predictive, with similar magnitudes of association. eGFR <60 ml/min/1.73 m^2 (subdistributional hazard ratio [sHR]: 1.81; 95% confidence interval [CI]: 1.11 to 2.94; $p = 0.02$) was found to be an additional predictor of SD risk (final SD model C-statistic = 0.66).

NPs AND RISK OF SD OR ACA IN HFpEF. In patients with available NP data (n = 1,057), BNP (reported as median [25th to 75th percentile] [303 (17-301) pg/ml vs. 357 (225-541) pg/ml; p = 0.40]) did not vary by SD/ACA or non-SD/ACA. Similarly, NT-proBNP (877 [613-2,719] pg/ml vs. 1,431 [763-3,131] pg/ml; p = 0.35) was not significantly different by SD/ACA or non-SD/ACA. In this subset, 44 patients experienced SD/ACA and 174 experienced non-SD/ACA. In a competing risks regression model adjusted for enrollment strata (previous HF hospitalization or elevated NPs), standardized log-transformed NP (per 1 standard deviation) was not associated with increased SD/ACA risk when tested alone (sHR: 1.24; 95% CI: 0.92 to 1.67; p = 0.16) or when added to sex and DM status (sHR: 1.24; 95% CI: 0.89 to 1.73; p = 0.19). In the subset with available NPs, the C-statistic of the competing risks model with sex and DM status was 0.67 and improved to 0.69 after addition of NP measurements (p = 0.46 for difference in C-statistics).

TREATMENT EFFECT OF SPIRONOLACTONE ON SD OR ACA. Overall, 33 SD/ACA events occurred in patients randomized to spironolactone and 44 SD/ACA events occurred in patients randomized to placebo. Incidence rates in spironolactone- and placebo-treated patients were 1.2 per 100 patient-years (25th to 75th percentile: 0.9 to 1.7 per 100 patient-years) and 1.6 per 100 patient-years (25th to 75th percentile: 1.2 to 2.2 per 100 patient-years), respectively. In competing risks regression analysis, SD/ACA was numerically, but not statistically, reduced in those randomized to spironolactone (unadjusted sHR: 0.74; 95% CI: 0.47 to 1.16; p = 0.19) (Figure 3). Treatment effects with spironolactone did not differ by sex or DM status (all interaction terms p > 0.05). Traditional Cox proportional hazards model yielded similar estimates of treatment effects on SD/ACA (unadjusted HR: 0.73; 95% CI: 0.46 to 1.14; p = 0.17).

TABLE 1 Continued

	SD or ACA (n = 77)	Non-SD/ACA (n = 312)	p Value*	Alive (n = 1,378)	p Value†
Smoking status			0.14		0.07
Current	8 (10.4)	25 (8.0)		84 (6.1)	
Past	47 (61.0)	159 (51.1)		693 (50.4)	
Never	22 (28.6)	127 (40.8)		599 (43.5)	
Electrocardiographic parameters					
Left bundle branch block	4 (5.2)	28 (9.0)	0.28	80 (5.8)	0.11
Left ventricular hypertrophy	10 (13.0)	26 (8.3)	0.21	131 (9.5)	0.45
QRS duration (ms)	105.3 ± 31.5	112.0 ± 34.1	0.12	104.8 ± 30.8	0.001
Body mass index, kg/m^2	34.8 ± 9.1	32.0 ± 8.7	0.01	34.3 ± 8.3	<0.001
Systolic blood pressure, mm Hg	126.2 ± 18.2	124.2 ± 16.2	0.35	128.3 ± 15.6	<0.001
Diastolic blood pressure, mm Hg	69.2 ± 13.1	68.9 ± 11.7	0.85	72.0 ± 11.2	<0.001
Heart rate, beats/min	69.8 ± 12.0	70.3 ± 10.7	0.72	68.8 ± 11.3	0.07
BNP, pg/ml	303 (173-501) (n = 25)	357 (225-541) (n = 117)	0.40	236 (144-423) (n = 556)	<0.001
NT-proBNP, pg/ml	877 (613-2,719) (n = 19)	1,431 (763-3,131) (n = 57)	0.35	914 (528-1,813) (n = 283)	0.008
Hemoglobin, g/dl	12.7 ± 1.9	12.5 ± 1.8	0.40	12.9 ± 1.6	0.001
Potassium, mmol/l	4.2 ± 0.5	4.2 ± 0.4	0.65	4.2 ± 0.4	0.39
Creatinine, mg/dl	1.3 ± 0.4	1.3 ± 0.4	0.22	1.1 ± 0.3	<0.001
Implantable cardioverter-defibrillator	1 (1.3)	8 (2.6)	0.51	33 (2.4)	0.80
Permanent pacemaker	8 (10.4)	53 (17.0)	0.15	181 (13.2)	0.14
Medication use					
β-blocker	63 (81.8)	249 (79.8)	0.69	1,075 (78.1)	0.63
Calcium-channel blocker	27 (35.1)	97 (31.1)	0.50	558 (40.6)	0.007
Diuretic	69 (89.6)	286 (91.7)	0.57	1,218 (88.5)	0.27
ACEi/ARB	65 (84.4)	235 (75.3)	0.09	1,095 (79.6)	0.12
Statin	49 (63.6)	199 (63.8)	0.98	900 (65.4)	0.83
Aspirin	47 (61.0)	172 (55.1)	0.35	808 (58.7)	0.45

Values are n (%), mean ± standard deviation, or median (25th to 75th percentiles). *Comparison between sudden death/aborted cardiac arrest (SD/ACA) versus non-SD/ACA. †Comparison across all 3 vital status groups. ‡Race categories were self-reported. §Composite of previous myocardial infarction, angina, coronary artery bypass graft surgery, or percutaneous coronary intervention.

ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BNP = brain natriuretic peptide; eGFR = estimated glomerular filtration rate; HF = heart failure; NP = natriuretic peptide; NT-proBNP = N-terminal prohormone of BNP; SD = sudden death.

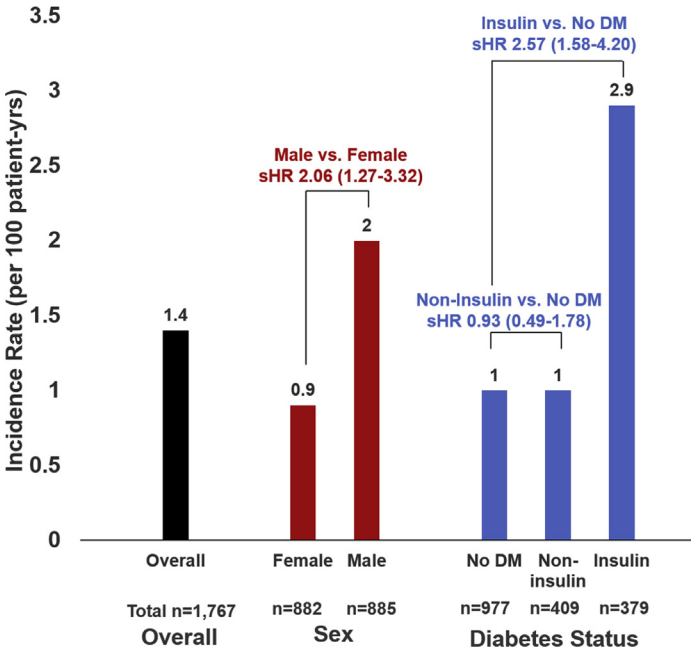
DISCUSSION

We described incidence rates and unique predictors of SD/ACA in HFpEF patients enrolled in the Americas region of TOPCAT. We highlighted several important findings: 1) SD accounted for ~20% of total deaths; 2) accounting for risks of non-SD/ACA, male sex and insulin-treated DM identified patients at higher risk for SD/ACA with modest discrimination; 3) SD/ACA was numerically, but not statistically, reduced in patients randomized to spironolactone compared with placebo.

DEFINING SD IN HFpEF CLINICAL TRIALS. Risks of cause-specific deaths might vary considerably across a spectrum of EF in patients with chronic HF (14), but SD appeared to be a consistent major mode of death in recent HFpEF trials. SD accounted for 39% of cardiovascular deaths and 28% of all deaths in the CHARM-Preserved (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) trial during an average follow-up of 37 months (5). Similarly, 43% of cardiovascular deaths and 26% of all deaths were adjudicated as SD in I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study) during an average follow-up of 50 months (6).

The higher estimates of SD in these earlier trials (CHARM-Preserved and I-PRESERVE) compared with

FIGURE 2 Independent Predictors of SD or ACA in TOPCAT



Incidence rates are reported per 100 patient-years of observation. Covariate-adjusted subdistributional hazard ratios (sHRs) were derived from competing risks regression models (accounting for nonsudden causes of death). Candidate variables included treatment arm, qualifying eligibility criteria, demographic characteristics (age, sex, race, ethnicity), clinical characteristics (body mass index, ejection fraction, New York Heart Association functional class, hypertension, diabetes mellitus [DM], coronary artery disease [defined as composite of previous myocardial infarction, angina, coronary artery bypass graft surgery, or percutaneous coronary intervention], atrial fibrillation/flutter, chronic obstructive pulmonary disease, peripheral artery disease, and current or past smoking status), vital signs (systolic and diastolic blood pressure, heart rate), electrocardiographic measures (left bundle branch block, left ventricular hypertrophy, QRS duration), laboratory parameters (hemoglobin, estimated glomerular filtration rate <60 ml/min/1.73 m^2, serum potassium), baseline medical therapies, and baseline implantable cardioverter-defibrillator use.

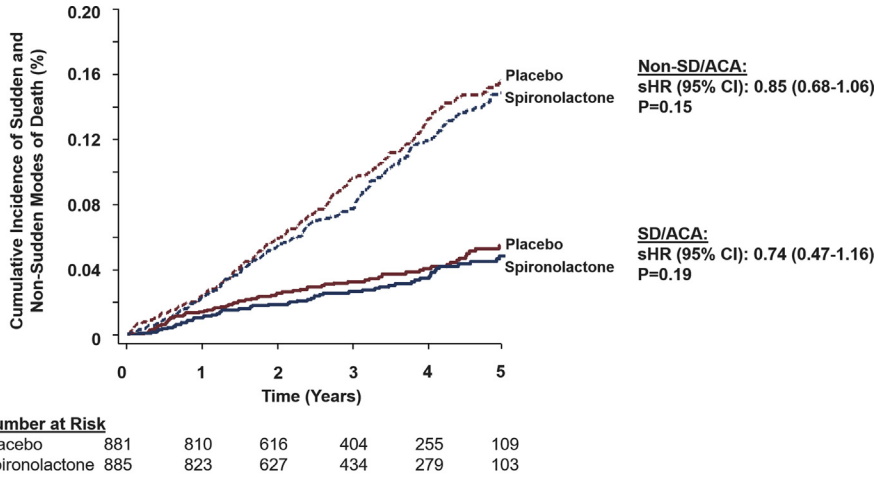
in TOPCAT might be related to variations in the definitions of SD. CHARM-Preserved defined SD as unexpected death of a stable patient without further qualifying parameters (5). I-PRESERVE further required recent human contact and characterized SD based on antecedent cardiovascular symptoms (however, this information was not available in many patients) (6). TOPCAT Americas also enrolled higher proportions of older patients aged 75 years or more (41%) compared with CHARM-Preserved (27%) and I-PRESERVE (34%) which might have contributed to higher global risk, including for nonsudden modes of death. Rates of SD observed in contemporary HFpEF trials were comparably higher than those reported in large epidemiological studies, which may be related to more complete capture and ascertainment of events in trials, more liberal definitions applied in trials, or higher rates of deaths related to noncardiac comorbidities in epidemiological studies (8).

MECHANISMS UNDERLYING SD IN HFpEF. Mechanistic data from animal models described repolarization abnormalities (15) in HFpEF that might increase susceptibility to ventricular arrhythmias. In patients with HFpEF, electrocardiographic measures, including indexes of repolarization, intraventricular conduction delays, and bundle branch pathology, have been closely linked to diastolic dysfunction, abnormal myocardial mechanics, and potentially worse outcomes (16–20). Microvascular disease and myocardial injury, as evidenced by low-level cardiac biomarker detection in hospitalized and ambulatory HFpEF cohorts, may contribute to disease progression and influence arrhythmic risk (21). However, these putative mechanisms have been corroborated with limited clinical data evaluating arrhythmic burden and risk of SD in HFpEF.

Because many patients with HFpEF die outside the immediate health care setting and few have cardiac implantable electronic devices, limited corroborating rhythm information is available at the time of event adjudication. Although considered synonymous with arrhythmic death, SD in contemporary HF trials encompasses a broad range of pathological processes. Similar to patients with post-MI left ventricular dysfunction or HF (22), acute MI may contribute to SD presentations in HFpEF, which might explain the higher incidence in men and DM in our experience. Although established infiltrative cardiomyopathy was an exclusion criterion in TOPCAT, undiagnosed amyloid heart disease might have contributed to heightened SD risk. Many causes of SD in HFpEF might not be remediable by ICD, which is perhaps mediated by bradyarrhythmias and/or asystole or nonarrhythmic modes of death (e.g., circulatory collapse or electromechanical dissociation). These nonarrhythmic mechanisms of SD might be relatively more common in older patients with HFpEF. Large-scale autopsy experiences and rhythm monitoring studies, as are being conducted in the ongoing VIP-HF (Ventricular Tachyarrhythmia Detection by Implantable Loop Recording in Patients with Heart Failure with Preserved Ejection Fraction; NCT01989299) study, are required to better define the clinical course and primary drivers of SD in HFpEF.

PREDICTING SD IN HFpEF. Previous work from the I-PRESERVE trial (9) identified 6 independent predictors of SD (older age, male sex, DM, previous MI, left branch bundle block on electrocardiogram, and

FIGURE 3 Treatment Effects of Spironolactone on Risks of SD/ACA and Non-SD/ACA in TOPCAT



Estimates of SD/aborted cardiac arrest (ACA) and non-SD/ACA risks were based on cumulative incidence function methods and accounted for competing risks of other modes of death. Unadjusted subdistributional hazard ratios (sHRs) with corresponding 95% confidence intervals (CIs) were calculated for the treatment effect of spironolactone versus placebo based on competing risks regression analyses.

NP level). Our competing risks analysis was restricted to the Americas region of TOPCAT and accounted for nonsudden modes of death, and identified male sex and DM as important predictors of SD/ACA in this population.

The diabetic HFpEF phenotype (23) might have distinct clinical, structural, and electrical aspects that contribute to risk of SD. DM might directly contribute to repolarization abnormalities and heterogeneous electrical dispersion, which represent potential mechanisms of increased SD risk in this population (24,25). DM was previously identified as an important predictor of SD risk in young patients in the community (26,27), by being potentially related to nocturnal hypoglycemic events and absent intact angina warning systems, and after acute MI with or without LV dysfunction or HF (28,29). Insulin treatment in DM represents a proxy of disease duration and identifies HFpEF patients at higher risk of cardiovascular events based on recent data from I-PRESERVE (30).

It is possible that the limited overall number of SD/ACA events (n = 77) and the limited available samples of biomarkers in our study might explain why certain other factors (including NPs, coronary artery disease, presence of left bundle branch block) were not predictive in final models. NPs might predict both SD and non-SD (namely, deaths related to worsening HF), and thus, might not uniquely identify at-risk patients for SD. Similar to our TOPCAT experience, the previous work from I-PRESERVE demonstrated that NPs distinguished patients who experienced SD from those patients alive in follow-up, but did not distinguish cause-specific deaths (SD vs. non-SD) (9). Enriching SD risk based on some of these factors, the MADIT S-ICD (Multicenter Automatic Defibrillator Implantation Trial with Subcutaneous Implantable Cardioverter Defibrillator; NCT02787785) is evaluating the usefulness of subcutaneous ICD on overall survival in patients with previous MI, DM, and EFs of 36% to 50%, although we recognize these patients might be clinically distinct from those with prevalent HFpEF (31). Because of the strong co-association of clinical parameters in HFpEF with both sudden and nonsudden modes of death, markers more proximate to the biology of SD might enrich risk prediction (32), including biomarkers, novel imaging modalities (defining substrate characteristics) (33–35), and electrical risk markers (electrocardiographic indexes, presence of nonsustained ventricular tachycardia, or electrophysiological study testing).

Although spironolactone appeared to reduce clinical events, including cardiovascular mortality, in the Americas region of TOPCAT (11), spironolactone did not significantly reduce risk of SD/ACA compared with placebo. These findings might be related to limited number of captured events or predominant treatment effects of spironolactone on nonsudden modes of cardiovascular death (e.g., worsening HF).

STUDY LIMITATIONS. The aggregate number of SD/ACA events was modest, thus limiting our risk prediction analysis. The TOPCAT trial was not powered to detect differences in rates of SD/ACA between treatment arms. Because of significant issues with the interpretation of data generated from Russia and Georgia in TOPCAT, this analysis was restricted to patients enrolled in the Americas region, which limited the number of captured SD/ACA events. Although TOPCAT Americas enrolled a more racially diverse cohort than previous HFpEF trials, more complete reporting and representative sampling of racial and ethnic minorities are needed to understand the burden of SD in these groups. Missing data for baseline NP levels and lack of availability of serial NP measurements or other biomarkers (e.g., troponin) reduced the robustness of our predictive models. No information was available regarding the presence of preceding cardiovascular symptoms. Similarly, no autopsy data were available for analysis to define pathological processes that contributed to SD/ACA. Reasons for baseline ICD used were not captured, but only 42 patients had ICDs at baseline, and sensitivity analysis revealed consistency of risk predictors of SD/ACA even after excluding them.

CONCLUSIONS

SD accounted for up 20% of all deaths in HFpEF, and male sex and insulin-treated DM identified patients at heightened risk for SD/ACA. Further studies are required to define mechanisms that contribute to SD, to build more robust SD risk prediction models that integrate imaging and biomarkers, and to develop strategies to attenuate SD risk in HFpEF.

ACKNOWLEDGMENTS The authors would like to acknowledge the contributions of the TOPCAT participants, site investigators, and leadership, including the clinical events committee (Brigham and Women's Hospital, Boston, Massachusetts).

ADDRESS FOR CORRESPONDENCE: Dr. Scott D. Solomon, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: ssolomon@rics.bwh.harvard.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: SD accounts for ~20% of deaths in HFpEF. Male sex and insulin-treated DM identified patients at higher risk for SD. In the Americas region of the TOPCAT trial, composite SD/ACA was numerically lower, but not statistically reduced, in those randomized to spironolactone.

TRANSLATIONAL OUTLOOK: Further studies are required to define mechanisms that contribute to SD, to build more robust SD risk prediction models that integrate imaging and biomarkers, and to develop strategies to attenuate SD risk in HFpEF.

REFERENCES

1. Vaduganathan M, Michel A, Hall K, et al. Spectrum of epidemiological and clinical findings in patients with heart failure with preserved ejection fraction stratified by study design: a systematic review. Eur J Heart Fail 2016;18:54–65.

2. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63:1123–33.

3. Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol 2017;70:2476–86.

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

5. Solomon SD, Wang D, Finn P, et al. Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart failure Assessment of Reduction in Mortality and Norbidity (CHARM) program. Circulation 2004;110:2180–3.

6. Zile MR, Gaasch WH, Anand IS, et al. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE) trial. Circulation 2010;121:1393–405.

7. Vaduganathan M, Patel RB, Shah SJ, Butler J. Sudden cardiac death in heart failure with preserved ejection fraction: a target for therapy? Heart Fail Rev 2016;21:455–62.

8. Vaduganathan M, Patel RB, Michel A, et al. Mode of death in heart failure with preserved ejection fraction. J Am Coll Cardiol 2017;69:556–69.

9. Adabag S, Rector TS, Anand IS, et al. A prediction model for sudden cardiac death in patients with heart failure and preserved ejection fraction. Eur J Heart Fail 2014;16:1175–82.

10. 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.

11. 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.

12. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601–9.

13. Hegde SM, Claggett B, Shah AM, et al. Physical activity and prognosis in the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist). Circulation 2017;136:982–92.

14. Bajaj NS, Claggett B, Lewis EF, et al. Influence of ejection fraction on cause-specific mortality in heart failure with preserved ejection fraction. Eur J Heart Fail 2018;20:815–6.

15. Cho JH, Zhang R, Kilfoil PJ, et al. Delayed repolarization underlies ventricular arrhythmias in rats with heart failure and preserved ejection fraction. Circulation 2017;136:2037–50.

16. Selvaraj S, Ilkhanoff L, Burke MA, et al. Association of the frontal QRS-T angle with adverse cardiac remodeling, impaired left and right ventricular function, and worse outcomes in heart failure with preserved ejection fraction. J Am Soc Echocardiogr 2014;27:74–82 e2.

17. Sauer A, Wilcox JE, Andrei AC, Passman R, Goldberger JJ, Shah SJ. Diastolic electromechanical coupling: association of the ECG T-peak to T-end interval with echocardiographic markers of diastolic dysfunction. Circ Arrhythm Electrophysiol 2012;5:537–43.

18. Sauer AJ, Selvaraj S, Aguilar FG, et al. Relationship between repolarization heterogeneity and abnormal myocardial mechanics. Int J Cardiol 2014;172:289–91.

19. Wilcox JE, Rosenberg J, Vallakati A, Gheorghiade M, Shah SJ. Usefulness of electrocardiographic QT interval to predict left ventricular diastolic dysfunction. Am J Cardiol 2011;108:1760–6.

20. Joseph J, Claggett BC, Anand IS, et al. QRS duration is a predictor of adverse outcomes in heart failure with preserved ejection fraction. J Am Coll Cardiol HF 2016;4:477–86.

21. Pandey A, Golwala H, Sheng S, et al. Factors associated with and prognostic implications of cardiac troponin elevation in decompensated heart failure with preserved ejection fraction: findings from the American Heart Association Get With The Guidelines-Heart Failure Program. JAMA Cardiol 2017;2:136–45.

22. Pouleur AC, Barkoudah E, Uno H, et al. Pathogenesis of sudden unexpected death in a clinical trial of patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. Circulation 2010;122:597–602.

23. Lindman BR, Davila-Roman VG, Mann DL, et al. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. J Am Coll Cardiol 2014;64:541–9.

24. Okin PM, Devereux RB, Lee ET, et al. Electrocardiographic repolarization complexity and abnormality predict all-cause and cardiovascular mortality in diabetes: the Strong Heart Study. Diabetes 2004;53:434–40.

25. Jani Y, Kamberi A, Xhunga S, et al. The influence of type 2 diabetes and gender on ventricular repolarization dispersion in patients with subclinic left ventricular diastolic dysfunction. Am J Cardiovasc Dis 2015;5:155–66.

26. Secrest AM, Becker DJ, Kelsey SF, Laporte RE, Orchard TJ. Characterizing sudden death and dead-in-bed syndrome in type 1 diabetes: analysis from two childhood-onset type 1 diabetes registries. Diabet Med 2011;28:293–300.

27. Sovik O, Thordarson H. Dead-in-bed syndrome in young diabetic patients. Diabetes Care 1999;22 Suppl 2:B40–2.

28. Junttila MJ, Barthel P, Myerburg RJ, et al. Sudden cardiac death after myocardial infarction in patients with type 2 diabetes. Heart Rhythm 2010;7:1396–403.

29. Solomon SD, Zelenkofske S, McMurray JJ, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. N Engl J Med 2005;352:2581–8.

30. Kristensen SL, Mogensen UM, Jhund PS, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-PRESERVE Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). Circulation 2017;135:724–35.

31. Kutyifa V, Beck C, Brown MW, et al. Multicenter Automatic Defibrillator Implantation Trial-Subcutaneous Implantable Cardioverter Defibrillator (MADIT S-ICD): design and clinical protocol. Am Heart J 2017;189:158–66.

32. Chugh SS. Disrupting the approach to sudden cardiac death: from vulnerable ejection fraction to vulnerable patient. Circulation 2018;137:7–9.

33. Kato S, Saito N, Kirigaya H, et al. Prognostic significance of quantitative assessment of focal myocardial fibrosis in patients with heart failure with preserved ejection fraction. Int J Cardiol 2015;191:314–9.

34. Halliday BP, Gulati A, Ali A, et al. Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. Circulation 2017;135:2106–15.

35. Fallavollita JA, Heavey BM, Luisi AJ Jr., et al. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. J Am Coll Cardiol 2014;63:141–9.

KEY WORDS heart failure with preserved ejection fraction, risk prediction, sudden death