Circulation: Heart Failure

ORIGINAL ARTICLE

Sex-Related Differences in Heart Failure With Preserved Ejection Fraction

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BACKGROUND: To describe characteristics and outcomes in women and men with heart failure with preserved ejection fraction.

METHODS: Baseline characteristics (including biomarkers and quality of life) and outcomes (primary outcome: composite of first heart failure hospitalization or cardiovascular death) were compared in 4458 women and 4010 men enrolled in CHARM-Preserved (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) (EF≥45%), I-Preserve (Irbesartan in heart failure with Preserved ejection fraction), and TOPCAT-Americas (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial).

RESULTS: Women were older and more often obese and hypertensive but less likely to have coronary artery disease or atrial fibrillation. Women had more symptoms and signs of congestion and worse quality of life. Despite this, the risk of the primary outcome was lower in women (hazard ratio, 0.80 [95% CI, 0.73–0.88]), as was the risk of cardiovascular death (hazard ratio, 0.70 [95% CI, 0.62–0.80]), but there was no difference in the rate for first hospitalization for heart failure (hazard ratio, 0.92 [95% CI, 0.82–1.02]). The lower risk of cardiovascular death in women, compared with men, was in part explained by a substantially lower risk of sudden death (hazard ratio, 0.53 [0.43–0.65]; $P<0.001$). E/A ratio was lower in women (1.1 versus 1.2).

CONCLUSIONS: There are significant differences between women and men with heart failure with preserved ejection fraction. Despite worse symptoms, more congestion, and lower quality of life, women had similar rates of hospitalization and better survival than men. Their risk of sudden death was half that of men.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00853658, NCT01035255.

Key Words: coronary artery disease ■ death, sudden ■ heart failure ■ quality of life ■ sex

Although much has been written about differences in the characteristics of, and outcomes in, men and women with heart failure (HF) with reduced ejection fraction (HFrEF), much less is known about these differences in HF with preserved ejection fraction (HFpEF).[1–3] In part, this reflects the few large trials in patients with the latter phenotype. Moreover, the first major report on women with HFpEF was from CHARM-Preserved (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) trial, which enrolled patients with a left ventricular ejection fraction (LVEF) >40%.[4] Subsequent large trials have used 45% as the threshold for the identification of HFpEF and, in retrospect, it is clear that many patients in CHARM-Preserved had characteristics more typical of HFrEF than HFpEF.[5] The second of the large HFpEF trials to report, the I-Preserve (Irbesartan in heart failure

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WHAT IS NEW?

- Women with heart failure with preserved ejection fraction (HFpEF) live longer when compared with men with HFpEF but have a poorer quality of life and a greater symptom burden.
- Hospital admission rates are not lower in women, compared with men. This differs from mortality (which is lower in women than men) and from heart failure with reduced ejection fraction (where heart failure hospitalization is less frequent in women than men).

WHAT ARE THE CLINICAL IMPLICATIONS?

- While no pharmacological therapy to date has been approved for the treatment of patients with HFpEF overall, recent evidence suggests there may be benefit from certain agents in women with this heart failure phenotype.
- The former findings, plus the striking contrasts reported here, between the characteristics and outcomes of women compared with men with HFpEF, argue for intensified efforts to understand and explain these sex-related differences. This should be a clinical priority given the worse quality of life and symptoms experienced by women with HFpEF and the fact that this is the major type of heart failure affecting women.

Nonstandard Abbreviations and Acronyms

BNP	B-type natriuretic peptide
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
eGFR	estimated glomerular filtration rate
HFpEF	heart failure with preserved ejection fraction
HR	hazard ratio
I-Preserve	Irbesartan in heart failure with Preserved ejection fraction
LV	left ventricular
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PARAGON-HF	Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction
QoL	quality of life
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial

with Preserved ejection fraction trial), described outcomes in women compared with men, but that analysis was limited by inclusion of only 1637 men.[6] With the availability of a third large trial, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT), and using CHARM data on patients with a LVEF≥45%, it is now possible in an individual patient data meta-analysis, using a common definition of HFpEF, to conduct a more comprehensive analysis of outcomes according to sex (4458 women and 4010 men) in all 3 trials.[5,7,8] Although there was an echocardiographic sub-study in (I-Preserve), cardiac structure and function were not analyzed by sex.[6] TOPCAT also had an echocardiographic substudy meaning that, along with I-Preserve, information on cardiac structure and function is available for 774 women and 625 men with HFpEF.[9]

METHODS

The data that support the findings of this study for I-Preserve and CHARM-Preserved are available from the corresponding author on request. The data for TOPCAT is available upon request from a third party (The National Heart, Lung, and Blood Institute, Biologic Specimen and Data Repository Information Coordinating Center).

Study Population

For the present analyses, we pooled patients enrolled in CHARM-Preserved, I-Preserve, and TOPCAT. The designs and results of these trials are published.[5,10,11] Briefly, in CHARM-Preserved 3023 patients with HF in New York Heart Association (NYHA), class II to IV with a LVEF >40% were randomized to receive candesartan or placebo. I-Preserve compared irbesartan with placebo in 4128 patients aged ≥60 years in NYHA functional class II to IV, a LVEF ≥45% and echocardiographic, electrocardiographic or radiological evidence supporting a diagnosis of HF. Patients in NYHA functional class II were required to have had a HF hospitalization within the previous 6 months. TOPCAT compared spironolactone with placebo in 3445 patients aged ≥50 years in functional class II to IV with a LVEF ≥45%; patients were also required to have been hospitalized within the previous 12 months for HF or to have an elevated natriuretic peptide level within 60 days before randomization (ie, BNP [brain natriuretic peptide] ≥100 pg/mL or NT-proBNP [N-terminal pro brain natriuretic peptide ≥360 pg/mL]).

For this analysis, we excluded 450 patients from CHARM-Preserved who had a LVEF<45% to ensure a consistent lower LVEF threshold across trials. Patients from TOPCAT who were randomized in Russia (N=1066) and Georgia (N=612) were also excluded because of doubts about diagnosis raised by the substantially lower event rates in this region, compared with those in the Americas, as well as doubts about treatment adherence.[12] Accordingly, we have analyzed 2573 patients enrolled in CHARM-preserved, 4128 patients from I-Preserve, and 1767 patients enrolled in TOPCAT-Americas.

Each trial was approved by the ethics committee at participating centers and all patients provided written informed consent.

The median duration of follow-up was 41.3 months in the pooled cohort (36.6 months in CHARM-Preserved, 52.9 months in I-Preserve, and 41.1 months in TOPCAT).

Outcomes

The primary outcome was a composite of cardiovascular death or HF hospitalization in CHARM-Preserved, all-cause death or cardiovascular hospitalization in I-Preserve, and a composite of cardiovascular death, HF hospitalization or aborted cardiac arrest in TOPCAT. In the present study, we used a composite of cardiovascular death or HF hospitalization as the primary outcome as this is now the most widely used end point in HF trials. We also analyzed each of the components of this composite, the 2 main modes of cardiovascular death (sudden death and death due to worsening HF), noncardiovascular death, and all-cause death. In addition, risk of other hospitalizations (cardiovascular, noncardiovascular and all-cause) and fatal or nonfatal myocardial infarction and stroke were examined. Last, given the high burden of hospitalization in HFpEF, we examined recurrent as well as first admissions (for HF, all cardiovascular causes, noncardiovascular causes, and any cause).

HF hospitalization and causes/modes of death were adjudicated by a central end point committee according to similar prespecified criteria in each trial (the same committee adjudicated the events in CHARM-Preserved and TOPCAT).

Statistical Analyses

Baseline characteristics are presented as means with SDs or medians with interquartile ranges for continuous variables and frequencies and percentages for categorical variables. Baseline characteristics according to sex were compared using Student *t* test or Mann-Whitney *U* test as appropriate for continuous variables, and χ^2 test for categorical variables.

Competing risk regression using the Fine-Gray method was used to analyze outcomes (to account for the risk of multiple potential competing events). All outcomes are reported as number of events and subdistribution hazard ratios (HRs) with 95% CIs. Both the primary outcome and cardiovascular death were tested for the competing risk of noncardiovascular death. First hospitalization for HF was tested for competing risk of all-cause death. Sudden death was tested for the competing risk of nonsudden death and death due to worsening HF was tested for death not caused by worsening HF. Noncardiovascular death was tested for competing risk of cardiovascular death. Fatal and nonfatal myocardial infarction and strokes were tested for competing risk of all cause death not due to myocardial infarction or stroke. HRs adjusted for trial, randomized treatment, region, age, heart rate, systolic blood pressure, body mass index, NYHA functional class, LVEF, estimated glomerular filtration rate (eGFR), and NT-proBNP (with missing indicator method used to handle missing eGFR and NT-proBNP values) have been reported (Model 1).[13] We have also reported outcomes adjusted for a second model which includes comorbidities in addition to variables incorporated in model 1.

A sensitivity analysis for unobserved confounding (potentially not otherwise corrected by covariate adjustment) for the main outcomes by propensity score matching to balance available baseline covariates was also carried out. This analysis only included I-Preserve and TOPCAT so that eGFR, which was missing in >50% of patients in CHARM-Preserved, could be used as one of the matching covariates. We matched 830 women with 830 men based on the propensity scores so derived.

Recurrent hospitalizations were analyzed using negative binomial regression, which is a counting method for the analysis of recurrent events and incidence risk ratios with 95% CIs adjusted for the 2 models as mentioned above are reported. Event rates per 1000 person-years are also reported, calculated by dividing the total number of events in each patient for each type of hospitalization by the total follow-up time for each patient.

All analyses were performed using Stata version 15 (Stata Corp, College Station, TX). A 2-sided $P<0.05$ was considered significant.

Analysis of Echocardiography Subset

Measures of left ventricular (LV) structure were indexed to body surface area, and diastolic dysfunction is described as recommended in current guidelines.[14] Baseline characteristics of the patients in the echocardiography subset are reported in the Data Supplement. The outcomes of interest were further adjusted for in the echocardiography subgroup by adding E wave velocity, LV mass index, and left atrial volume index to Model 1.

RESULTS

There were 4010 men and 4458 women in our analysis, accounting for 47.4% and 52.6% of the cohort, respectively.

Baseline Characteristics

The baseline characteristics in men and women have been shown in Table 1. Women were an average 2.5 years older than men, had higher systolic blood pressure, heart rate, and body mass index. A greater proportion of women than men (48.7% versus 41.2% men) were obese.[15]

Comorbidities

Apart from hypertension (86.6% women versus 76.6% men), women were less likely to have a history of major comorbidities such as atrial fibrillation (30.6% versus 33.9%), and coronary heart disease (49.1% versus 62.9%). Electrocardiographically documented atrial fibrillation was also less common in women than men (16.9% versus 20.4%). Among noncardiovascular comorbidities, women had a similar prevalence of diabetes mellitus (30.7% versus 32.0%) but a lower prevalence of chronic obstructive pulmonary disease/asthma (11.2% versus 13.8%).

Women were also less likely to be current smokers (6.8% versus 13.2%) and had lower intake of alcohol than men.

Heart Failure Characteristics and Investigations

As shown in Table 1, women had been hospitalized for HF as often as men within the 6 months before randomization. Women had more symptoms of HF than men, with a higher prevalence of orthopnea (28.9% versus 21.0%)

Table 1. Characteristics of Women and Men With HFpEF

	Women, N=4458 (52.6%)	Men, N=4010 (47.4%)	*P* Value
Baseline characteristics			
Age, mean±SD	71.4±8.7	68.9±9.6	<0.001
Age groups, no. (%)			<0.001
≤40 y	9 (0.2)	24 (0.6)	
41–55 y	177 (4.0)	312 (7.8)	
56–70 y	1800 (40.4)	1852 (46.2)	
>70 y	2472 (55.5)	1822 (45.4)	
Region, no. (%)			<0.001
North America	1332 (29.9)	1483 (37.0)	
Latin America	679 (15.2)	327 (8.2)	
Western Europe and other	1351 (30.3)	1361 (33.9)	
Central Europe	1019 (23.9)	735 (18.3)	
Asia-Pacific	77 (1.7)	104 (2.6)	
Race, no. (%)			<0.001
White	3925 (88.0)	3671 (91.5)	
Black	327 (7.3)	165 (4.1)	
Asian	48 (1.1)	70 (1.7)	
Other	158 (3.5)	104 (2.6)	
SBP, mm Hg; mean±SD	136.0±16.4	133.0±17.1	<0.001
DBP, mm Hg; mean±SD	77.0±10.4	77.0±10.7	0.27
HR, bpm; mean±SD	72.0±11.2	70.0±11.6	<0.001
BMI, kg/m^2; median (Q1–Q3)	29.8 (26.1–34.4)	28.7 (25.9–32.7)	<0.001
Weight category, no. (%)			<0.001
Underweight	31 (0.7)	18 (0.5)	
Normal	753 (17.0)	687 (17.2)	
Overweight	1493 (33.6)	1643 (41.2)	
Obese	2165 (48.7)	1642 (41.2)	
Comorbidities, no. (%)			
Cardiovascular			
Atrial fibrillation (history)	1362 (30.6)	1359 (33.9)	<0.001
Hypertension	3859 (86.6)	3071 (76.6)	<0.001
Coronary artery disease	2191 (49.1)	2522 (62.9)	<0.001
Myocardial infarction	879 (19.7)	1505 (37.5)	<0.001
Angina	1834 (41.1)	1950 (48.7)	<0.001
PCI or CABG	681 (15.3)	1263 (31.5)	<0.001
Stroke or TIA	393 (8.8)	386 (9.6)	0.20
Other systems			
Type II diabetes mellitus	1369 (30.7)	1284 (32.0)	0.1887
COPD/asthma	498 (11.2)	553 (13.8)	0.0003
Peripheral arterial disease*	733 (21.7)	567 (22.5)	0.481
Anemia*	553 (16.4)	628 (24.9)	<0.001
Any alcohol intake*	291 (8.6)	617 (24.5)	<0.001
Current smoker†	134 (6.8)	313 (13.2)	<0.001
Heart failure characteristics, investigations, and treatment			
HF hospitalization within past 6 mo, no. (%)	1883 (42.2)	1625 (40.5)	0.11
NYHA III/IV, no. (%)	2801 (62.8)	2059 (51.3)	<0.001
Quality of life scores			
MLWHF; median (Q1–Q3)	44.0 (29.0–61.0)	37.0 (22.0–54.0)	<0.001
KCCQ clinical summary score; median (Q1–Q3)	56.3 (39.1–72.9)	64.6 (45.8–82.3)	<0.001
Markers of congestion, no. (%)			
Dyspnea on effort†	1922 (97.7)	2312 (97.5)	0.61
Orthopnea†	565 (28.9)	496 (21.0)	<0.001
PND†	279 (14.3)	282 (12.0)	0.02
Peripheral edema	2371 (53.2)	1920 (47.9)	<0.001
JVD	410 (9.2)	428 (10.7)	0.02
Rales	1033 (23.2)	830 (20.7)	0.008
ECG, no. (%)			
Atrial fibrillation	752 (16.9)	816 (20.4)	<0.001
LVH	1043 (23.5)	760 (19.0)	<0.001
Echocardiography and other investigations			
LVEF, %; mean±SD	59.8±9.0	56.3±8.3	<0.001
CXR demonstrating pleural effusion or pulmonary congestion	1057 (23.7)	611 (15.2)	<0.001
NT-proBNP, pg/mL; median (Q1–Q3)*‡	348 (133–967)	484 (177–1159)	<0.001
No atrial fibrillation on ECG* (1934/2800)	261 (115–619)	340 (138–796)	0.001
Atrial fibrillation on ECG* (574/569)	1349 (816–2155)	1231 (733–2015)	0.20
Sodium, mmol/L; mean±SD	139.8±3.1	139.7±3.0	0.05
Potassium, mmol/L; mean±SD	4.36±0.5	4.37±0.46	0.21
eGFR, mL/min per 1.73 m^2; mean±SD§	68.8±23.2	72.4±23.0	<0.001
eGFR <60 mL/min per m^2, no. (%)	1454 (38.9)	972 (32.4)	<0.001
Drugs and interventions, no. (%)			
Diuretic	3772 (84.7)	3143 (78.5)	<0.001
Loop diuretics	2675 (60.1)	2449 (61.1)	0.32
Thiazide diuretics	1417 (31.8)	942 (23.5)	<0.001
Digoxin	688 (15.5)	764 (19.1)	<0.001
β-Blocker	2709 (60.8)	2523 (63.0)	0.04
Calcium channel blocker	1784 (40.1)	1372 (34.2)	<0.001
Antiarrhythmics	380 (8.5)	382 (9.5)	0.11
Antiplatelets	2482 (55.7)	2577 (64.3)	<0.001
Anticoagulants	977 (21.9)	1078 (26.9)	<0.001
History of atrial fibrillation (n=1362/1359)	819 (60.1)	870 (64.0)	0.04
Statins	1628 (36.6)	1902 (47.5)	<0.001
Pacemaker	319 (7.2)	363 (9.1)	0.001
ICD	29 (0.7)	42 (1.0)	0.045

COPD/asthma in CHARM derived from patients using bronchodilators at baseline. BMI indicates body mass index; CABG, coronary artery bypass graft; CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; DBP, diastolic blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; ICD, implantable cardioverter defibrillator; I-Preserve, Irbesartan in heart failure with Preserved ejection fraction; IQR, interquartile range; JVD, jugular venous distension; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MLWHF, Minnesota Living With Heart Failure questionnaire; NT-proBNP, N-terminal pro B-type natriuretic peptide—only available in I-Preserve and TOPCAT; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PND, paroxysmal nocturnal dyspnea; SBP, systolic blood pressure; TIA, transient ischemic attack; and TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial.

*Only I-Preserve and TOPCAT (2522 men, 3373 women).

†Only CHARM-Preserved and TOPCAT (2373 men, 1967 women).

‡Missing: 2057.

§Missing:1732.

and paroxysmal nocturnal dyspnea (14.3% versus 12.0%; only recorded in I-Preserve and TOPCAT-Americas) and more evidence of congestion (peripheral edema and rales). Women were considerably more likely to be in a worse NYHA functional class (62.8% NYHA class III/IV versus 51.3% in men) and had poorer health-related quality-of-life (QoL), that is, lower (worse) median Kansas City Cardiomyopathy Questionnaire scores (56.3 versus 64.6 in men) or higher (worse) Minnesota Living with Heart Failure questionnaire scores (44.0 versus 37.0). Each individual Kansas City Cardiomyopathy Questionnaire domain score was also lower in women (Figure I in the Data Supplement) and each of the Minnesota Living with Heart Failure domains and majority of the scores to questions in the Minnesota Living with Heart Failure questionnaire were higher in women (Figures II and III in the Data Supplement).

Women had a significantly higher LVEF (59.8% versus 56.3%) than men and a lower median NT-proBNP (women, 348 pg/mL versus men, 484 pg/mL), although the latter difference was confined to patients without atrial fibrillation.

Mean eGFR was lower in women than men and a higher proportion of women had an eGFR <60 mL/minute per 1.73 m^2 (38.9% versus 32.4% in men). There was no other difference in measures of blood chemistry.

Background Treatment

The proportion treated with a diuretic was larger in women than in men (84.7% versus 78.5%; Table 1). Women were less likely to receive digoxin (15.5% versus 19.1%). β-Blocker use was also slightly less in women (60.8% versus 63.0%) whereas use of calcium channel blockers was more frequent (40.1% versus 34.2%). The differences between men and women in the proportions using statins, aspirin, and anticoagulants were larger (all used less commonly in women).

Echocardiographic Measurements (I-Preserve and TOPCAT-Americas only)

Women in the echocardiography subset were older, were more obese, and had fewer major comorbidities apart from hypertension similar to what was observed in the main cohort (Table 2; Table II in the Data Supplement). As shown in Table 2, indexed LV volumes and LV mass were lower in women than in men. Indexed left atrial volume was increased above normal in both sexes but did not differ between men and women (even though men had greater LV volumes). Stroke volume was low in both sexes. While peak E wave velocity was similar in both sexes, women had a higher peak A wave velocity (83.7 versus 73.2 cm/s). Consequently, E/A ratio was lower in women (1.1 versus 1.2). Other measures of diastolic function, generally, did not differ notably between men and women.

Table 2. Echocardiographic Parameters in Women and Men With HFpEF (I-Preserve and TOPCAT)

	Women, N=774 (55.3%)	Men, N=625 (44.7%)	*P* Value
Age, y	71.8±8.3	71.2±8.7	0.17
LV structure			
End-diastolic diameter, cm	4.7±0.6	5.0±0.6	<0.001
End-diastolic diameter index, cm/m^2	2.5±0.4	2.4±0.4	<0.001
End-diastolic volume, mL	82.3±28.6	110.3±36.1	<0.001
End-diastolic volume index, mL/m^2	43.6±14.6	52.2±16.8	<0.001
End-systolic diameter, cm	3.1±0.6	3.5±0.6	<0.001
End-systolic diameter index, cm/m^2	1.7±0.3	1.7±0.3	0.59
End-systolic volume, mL	30.6±14.5	44.6±20.0	<0.001
End-systolic volume index, mL/m^2	16.2±7.7	21.2±9.7	<0.001
Interventricular septum thickness, cm	1.0±0.2	1.2±0.2	<0.001
LV mass, g	191.5±58.7	241.5±65.6	<0.001
LV mass index, g/m^2	101.7±29.4	113.7±28.9	<0.001
Relative wall thickness, cm	0.4±0.1	0.5±0.1	0.02
LV systolic properties			
Ejection fraction, %	61.8±8.5	58.2±7.9	<0.001
Stroke volume, mL	51.7±18.1	65.6±22.0	<0.001
LV diastolic properties			
Diastolic dysfunction,* no. (%)			0.65
Grade I	202 (6.1)	152 (24.3)	
Grade II	32 (4.1)	20 (3.2)	
Grade III	62 (8.0)	50 (8.0)	
Undetermined	278 (61.8)	403 (64.5)	
Peak E wave velocity, cm/s	81.1±28.6	78.8±28.0	0.18
E/E' lateral ratio	11.3±5.6	10.3±5.0	0.01
E/E' septal ratio	14.3±6.6	14.1±6.8	0.75
E/E' average ratio	12.1±5.4	11.6±5.1	0.20
Peak A wave velocity, cm/s	83.7±26.6	73.2±23.9	<0.001
E/A ratio	1.1±0.7	1.2±0.8	0.01
Lateral early diastolic myocardial velocity, cm/s	8.6±3.4	9.2±3.5	0.01
Septal early diastolic myocardial velocity, cm/s	6.8±2.9	6.9±2.7	0.71
Mitral deceleration time, ms	212.7±73.8	203.9±65.6	0.02
Left atrial volume, mL	69.0±30.1	77.3±35.6	<0.001
Left atrial volume index, mL/m^2	37.1±16.8	36.9±17.9	0.85

All values expressed as mean±SD except where indicated. HFpEF indicates heart failure with preserved ejection fraction; I-Preserve, Irbesartan in heart failure with Preserved ejection fraction; LV, left ventricular; and TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial.

*Missing: 627.

Outcomes

Women had a significantly lower risk of the primary composite outcome with an HR (model 1) of 0.80 (95% CI,

Table 3. Clinical Outcomes in Women and Men With HFpEF

	Women; N=4458 (52.6%)	Men; N=4010 (47.4%)	Adjusted Heart Rate (Model 1)	Adjusted Heart Rate (Model 2)
	Total Patients With Events		*P* Value	*P* Value
Primary composite outcome	1087	1069	0.80 (0.73–0.88)	0.84 (0.76–0.92)
			<0.001	<0.001
Hospitalization				
Heart failure	787	703	0.92 (0.82–1.02)	0.95 (0.85–1.06)
			0.123	0.385
Cardiovascular	1690	1682	0.86 (0.80–0.92)	0.90 (0.83–0.96)
			<0.001	0.004
Noncardiovascular	1622	1525	0.90 (0.84–0.97)	0.92 (0.85–0.99)
			0.008	0.032
All-cause	2517	2359	0.91 (0.85–0.96)	0.94 (0.88–1.00)
			0.001	0.040
Death				
Cardiovascular	533	583	0.70 (0.62–0.80)	0.72 (0.63–0.82)
			<0.001	<0.001
Sudden death	161	243	0.53 (0.43–0.65)	0.53 (0.43–0.66)
			<0.001	<0.001
Death due to worsening HF	129	139	0.69 (0.54–0.89)	0.72 (0.55–0.93)
			0.005	0.012
Noncardiovascular	261	301	0.62 (0.52–0.74)	0.63 (0.53–0.75)
			<0.001	<0.001
All-cause (HR)	794	884	0.65 (0.59–0.72)	0.67 (0.60–0.74)
			<0.001	<0.001
Others				
Fatal/nonfatal MI	154	193	0.75 (0.60–0.94)	0.80 (0.64–1.00)
			0.011	0.054
Fatal/nonfatal stroke	193	179	0.87 (0.70–1.07)	0.88 (0.71–1.09)
			0.191	0.242

Hazard ratios are reported with 95% CIs within parentheses and represent comparison of women to men. All outcomes have been adjusted for trial, randomized treatment, and region at baseline. Adjustment Model 1: age, heart rate, SBP, DBP, BMI, NYHA classes III/IV, LVEF, eGFR, NT-proBNP. Adjustment Model 2: age, heart rate, SBP, DBP, BMI, NYHA classes III/IV, LVEF, eGFR, NT-proBNP, H/o atrial fibrillation, H/o coronary heart disease, H/o hypertension, H/o stroke, H/o diabetes mellitus. All outcomes were tested for competing risks of all-cause and noncardiovascular death. Sudden death was tested for competing risk of all nonsudden deaths and death due to worsening HF for all deaths not due to worsening HF. Noncardiovascular death was tested for competing risk of cardiovascular death. Missing indicator method was used to handle missing eGFR and NT-proBNP values. BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; H/o, history of; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; and SBP, systolic blood pressure.

0.73–0.88), as shown in Table 3 and Figures 1 and 2.

Looking at the components of this composite, the risk of first hospitalization for HF did not differ significantly between women and men (HR, 0.92 [95% CI, 0.82–1.02]).

By contrast, the risk of cardiovascular death (HR, 0.70 [95% CI, 0.62–0.80]) was lower, as were each of the 2 major modes of cardiovascular death, that is sudden death and death due to worsening HF. The risk of sudden death in women was about half that in men (HR, 0.53 [95% CI, 0.43–0.65]).

The risk of noncardiovascular death was also lower in women and, as a result, so was the risk of all-cause death (HR, 0.62 [95% CI, 0.52–0.74] and 0.65 [95% CI, 0.59–0.72], respectively).

While women were less likely to have a fatal/nonfatal myocardial infarction than men (HR, 0.75 [95% CI, 0.60–0.94]), the risk of stroke was similar (HR, 0.87 [95% CI, 0.70–1.07]).

The results were not altered in the subset of patients with echocardiographic data or in a sensitivity analysis using propensity score to match men and women (Tables III and IV and Figure IV in the Data Supplement).

Recurrent Events

During a median follow-up of 1255 (1–2278) days, there were a total of 6610 hospitalizations for any cause in women and 6507 hospitalizations for any cause in men (Table 4). Of these, 1479 (22.4%) were due to HF

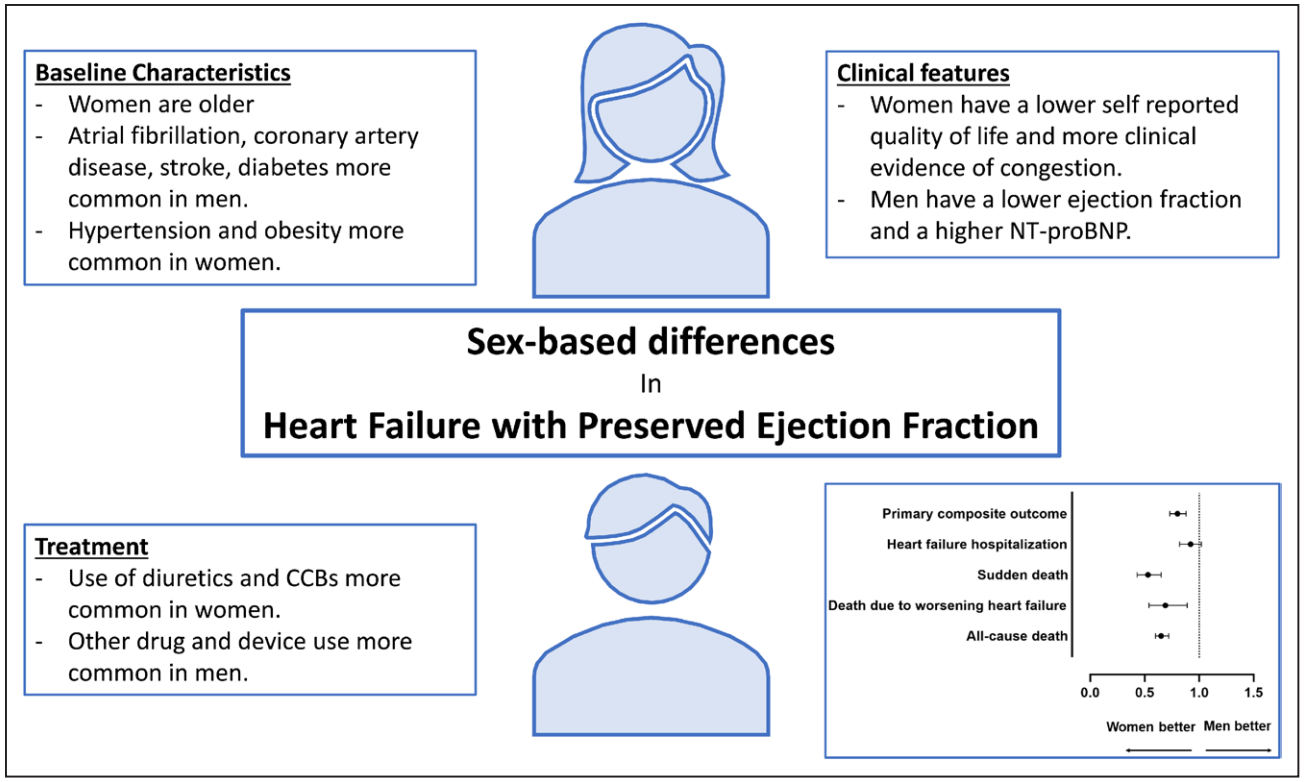

Figure 1. Sex-based differences in heart failure with preserved ejection fraction.
CCB indicates calcium channel blocker; and NT-proBNP, N-terminal pro B-type natriuretic peptide.

in women and 1327 (20.4%) were due to HF in men. Among women, 7.4% had >1 hospitalization for HF and the same was true for 7.2% of men (Table I in the Data Supplement).

The incidence risk ratio for recurrent HF hospitalization for women compared with men was 0.87 (95% CI, 0.77–1.00). The incidence risk ratios for cardiovascular hospitalization (0.84; 0.77–0.91), all-cause hospitalization (0.85; 0.79–0.90), and noncardiovascular hospitalizations (0.86; 0.79–0.93) were similar to those for HF hospitalization.

DISCUSSION

Epidemiological and registry studies show that women are as likely as men to suffer from HFpEF and this is what we also found in our pooled clinical trial cohort.[16,17] Among the 8468 individuals randomized, 4458 (53%) were women. There were notable differences between men and women: in our study, women were older than men, more often had a history of hypertension and were more often obese than men (but did not have a greater prevalence of diabetes mellitus). Most comorbid conditions were less common in women than in men, with a particularly large difference in prevalence of CAD. These differences are consistent with prior studies.[18,19] More novel were our findings related to the impact of HF on women, compared with men. Women had worse NYHA functional class, worse symptoms, and more signs of congestion (and more often received diuretics) than men. These physician reported/recorded indicators of worse heart failure status in women were supported by patient reported outcomes. Specifically, health-related QoL (as measured by Kansas City Cardiomyopathy Questionnaire in TOPCAT-Americas and Minnesota Living with Heart Failure questionnaire in I-Preserve and CHARM-Preserved) was worse in women than men and all domains of QoL were worse in women compared with men. Interestingly, this worse clinical picture was apparent despite a lower median NT proBNP and higher LVEF (and smaller indexed LV volumes and mass) in women, compared with men. How one interprets this dissociation between symptoms/signs/QoL and physiological measures of cardiac function in women compared with men is uncertain. Is it that women experience worse symptoms of HF for any given level of cardiac dysfunction? Or is it that their symptoms and signs of congestion reflect an inadequate natriuretic peptide response in women? Alternatively, are women relatively undertreated with diuretics? While the proportion of patients treated with a loop diuretic was similar in men and women, more women were treated with a thiazide diuretic. Arguably, diuretics were underutilized in view of the greater congestion in women. Renal function may be relevant here too as it was worse in women.

With respect to outcomes, women were at a lower risk of the primary composite end point than men, due

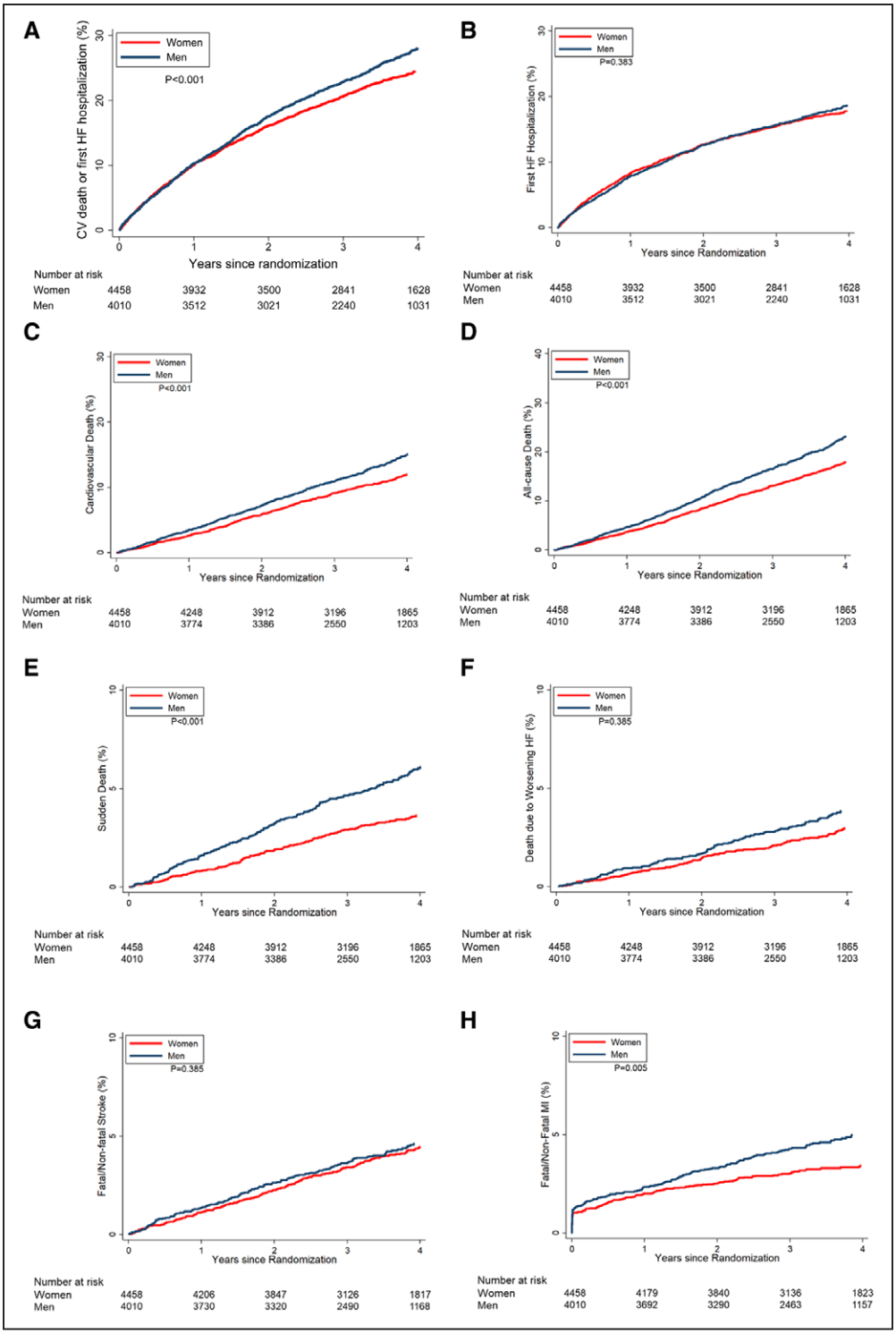

Figure 2. Clinical outcomes in women and men with heart failure with preserved ejection fraction.
A, Primary composite outcome. **B**, Hospitalization for heart failure. **C**, Cardiovascular death. **D**, All-cause death. **E**, Sudden death. **F**, Death due to worsening HF. **G**, Fatal/nonfatal stroke. **H**, Fatal/nonfatal MI. All figures are cumulative incidence plots except all-cause death (Kaplan-Meier). HF indicates heart failure; and MI, myocardial infarction.

to a substantially lower risk of cardiovascular death (and not HF hospitalization). This was also true for the 2 main modes of cardiovascular death, noncardiovascular death and, therefore, death overall. However, the most striking difference between women and men was in the risk of sudden death, which occurred almost twice as frequently in men as in women. This may be explained the lower prevalence of CAD in women and because sudden death is linked to CAD.[20] However, this may not be the whole answer as when just individuals with CAD were

Table 4. Analysis of Repeat Hospitalizations in Women and Men With HFpEF (Negative Binomial Model)

	Women; N=4458 (52.6%)	Men; N=4010 (47.4%)	Women; N=4458 (52.6%)	Men; N=4010 (47.4%)	Adjusted IRR (Model 1)	Adjusted IRR (Model 2)
	Total Events		Admissions Per 100 Patient-Years (95% CI)			
HF hospitalization	1479	1327	9.14 (8.68–9.62)	9.91 (9.39–10.46)	0.87 (0.77–1.00)	0.87 (0.77–0.99)
					0.045	0.040
Cardiovascular hospitalization	3560	3590	22.0 (21.29–22.73)	26.81 (25.95–27.70)	0.84 (0.77–0.91)	0.87 (0.80–0.94)
					<0.001	<0.001
Noncardiovascular hospitalization	3054	2919	18.87 (18.21–19.55)	21.80 (21.02–22.60)	0.86 (0.79–0.93)	0.88 (0.81–0.95)
					<0.001	0.002
All-cause hospitalization	6610	6507	40.84 (39.87–41.84)	48.59 (47.43–49.79)	0.85 (0.79–0.90)	0.87 (0.82–0.93)
					<0.001	<0.001

IRRs denotes 95% CIs within parentheses. All outcomes adjusted for trial, randomized treatment and region at baseline. Adjustment Model 1: age, HR, SBP, DBP, BMI, NYHA classes III/IV, LVEF, eGFR, NT-proBNP. Adjustment Model 2: age, HR, SBP, DBP, BMI, NYHA classes III/IV, LVEF, eGFR, NT-proBNP, H/o atrial fibrillation, H/o coronary heart disease, H/o hypertension, H/o stroke, H/o diabetes mellitus. Missing indicator method used to handle missing eGFR and NT-proBNP. BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; H/o, history of; HR, heart rate; IRR, incidence rate ratio; LVEF, left ventricular ejection fraction; NYHA, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; and SBP, systolic blood pressure.

examined, women still appeared less likely than men to die suddenly.

By contrast, the proportion of patients experiencing one or more hospitalization for HF did not differ between women and men. When HF admissions were examined (using both first and repeat hospitalizations), taking account of the competing risk of death, women still had a similar rate of events to men in the unadjusted analysis.

Overall, therefore, the impact of HFpEF seems to differ in men and women with women having worse symptoms and QoL, similar rates of hospital admission but lower rates of death than men. This raises the possibility that the goals of management of HFpEF in men and women might have a different emphasis, with women needing relatively more attention paid to well-being than men. This difference in impact may also extend to and have implications for pharmacological therapy in HFpEF. An analysis of TOPCAT showed that while there was no sex-based difference in the risk of the primary composite outcome according to randomized treatment, women who received spironolactone had a lower risk of all-cause and cardiovascular death while no such benefit was seen in men.[21] Similarly, in the recent PARAGON-HF trial (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction), only women receiving sacubitril/valsartan had a statistically significant reduction in risk of the primary outcome while there was no risk reduction observed in men.[22]

Finally, it is also of interest to compare these findings in HFpEF with a recent similar analysis in HFrEF.[23] Both men and women with HFpEF were quite different than people with HFrEF; for example, people with HFpEF were 6 years older on average and had a 12 mmHg higher average systolic blood pressure.[23] Obesity was more common in HFpEF than HFrEF and this difference was more marked in women (48.7% in HFpEF versus 33.4% in HFrEF) than men (41.2% versus 29.2%, respectively). Women had more symptoms/signs of congestion in both HFpEF and HFrEF. QoL was worse in HFpEF than in HFrEF, overall, but worse in women than men in both HF phenotypes. A notable distinction between HFpEF and HFrEF, with respect to sex differences, was the similar rate of hospital admission in women and men with HFpEF (contrasting with the lower risk in women, compared with men, with HFrEF). The risk of sudden death was less in women with HFrEF than in men with HFrEF, although the between-sex difference was smaller than in HFpEF.[23]

Strengths and Limitations

We studied patients enrolled in clinical trials who had to fulfil specific inclusion and exclusion criteria and they may not be representative of patients with HFpEF more generally. However, because these patients were enrolled in trials, they were well characterized at baseline and had systematic and complete follow-up, with adjudication of clinical outcomes. Not all data were available in all 3 trials.

In conclusion, we found significant sex-based differences in patients with HFpEF. Women were older and more likely than men to be hypertensive and obese (but less likely to have CAD). Despite worse symptoms, more evidence of congestion, and lower QoL, women had similar rates of hospitalization to men and a better survival. Their risk of sudden death was half that of men.

ARTICLE INFORMATION

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REFERENCES

1. Ghali JK, Krause-Steinrauf HJ, Adams KF, Khan SS, Rosenberg YD, Yancy CW, Young JB, Goldman S, Peberdy MA, Lindenfeld J. Gender differences in advanced heart failure: insights from the BEST study. *J Am Coll Cardiol*. 2003;42:2128–2134. doi: 10.1016/j.jacc.2003.05.012
2. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med*. 2002;347:1403–1411. doi: 10.1056/NEJMoa021266
3. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Circulation*. 2001;103:375–380. doi: 10.1161/01.cir.103.3.375
4. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Piña IL, Granger CB, Ostergren J, Michelson EL, Solomon SD, Pocock S, Yusuf S, Swedberg K, Pfeffer MA; CHARM Investigators. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation*. 2007;115:3111–3120. doi: 10.1161/CIRCULATIONAHA.106.673442
5. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362:777–781. doi: 10.1016/S0140-6736(03)14285-7
6. Lam CS, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M, McKelvie RS, McMurray JJ, Zile MR, Massie BM, et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in heart failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ Heart Fail*. 2012;5:571–578. doi: 10.1161/CIRCHEARTFAILURE.112.970061
7. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, et al; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456–2467. doi: 10.1056/NEJMoa0805450
8. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, et al; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392. doi: 10.1056/NEJMoa1313731
9. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O'Meara E, Heitner JF, Sopko G, Li G, Assmann SF, McKinlay SM, 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;7:104–115. doi: 10.1161/CIRCHEARTFAILURE.113.000887
10. Carson P, Massie BM, McKelvie R, McMurray J, Komajda M, Zile M, Ptaszynska A, Frangin G; I-PRESERVE Investigators. The irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial: rationale and design. *J Card Fail*. 2005;11:576–585. doi: 10.1016/j.cardfail.2005.06.432
11. Desai AS, Lewis EF, Li R, Solomon SD, Assmann SF, Boineau R, Clausell N, Diaz R, Fleg JL, Gordeev I, 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;162:966–972.e10. doi: 10.1016/j.ahj.2011.09.007
12. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, 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. doi: 10.1161/CIRCULATIONAHA.114.013255
13. Huberman M, Langholz B. Application of the missing-indicator method in matched case-control studies with incomplete data. *Am J Epidemiol*. 1999;150:1340–1345. doi: 10.1093/oxfordjournals.aje.a009966
14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, et al; Houston, Texas; Oslo, Norway; Phoenix, Arizona; Nashville, Tennessee; Hamilton, Ontario, Canada; Uppsala, Sweden; Ghent and Liège, Belgium; Cleveland, Ohio; Novara, Italy; Rochester, Minnesota; Bucharest, Romania; and St. Louis, Missouri. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1321–1360. doi: 10.1093/ehjci/jew082
15. The World Health Orginisation. WHO Mean Body Mass Index (BMI). WHO. 2017. Available at: https://www.who.int/gho/ncd/risk_factors/bmi_text/en/. Accessed September 28, 2019.
16. Lam CSP, Gamble GD, Ling LH, Sim D, Leong KTG, Yeo PSD, Ong HY, Jaufeerally F, Ng TP, Cameron VA, et al. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. *Eur Heart J*. 2018;39:1770–1780. doi: 10.1093/eurheartj/ehy005
17. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, Hillege HL, van Veldhuisen DJ, van Gilst WH. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J*. 2013;34:1424–1431. doi: 10.1093/eurheartj/eht066
18. Lloyd-Jones DM, Allen NB, Greenland P, Ayers C, Kuller LH, Eaton CB, Klein L, LaMonte M, Pandey A, Berry JD, et al. Sex and race differences in lifetime risk of heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. *Circulation*. 2018;137:1814–1823. doi: 10.1161/CIRCULATIONAHA.117.031622
19. Gori M, Lam CS, Gupta DK, Santos AB, Cheng S, Shah AM, Claggett B, Zile MR, Kraigher-Krainer E, Pieske B, et al; PARAMOUNT Investigators. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2014;16:535–542. doi: 10.1002/ejhf.67
20. Yarnoz MJ, Curtis AB. More reasons why men and women are not the same (gender differences in electrophysiology and arrhythmias). *Am J Cardiol*. 2008;101:1291–1296. doi: 10.1016/j.amjcard.2007.12.027
21. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex differences in outcomes and responses to spironolactone in heart failure with preserved ejection fraction: a secondary analysis of TOPCAT Trial. *JACC Heart Fail*. 2019;7:228–238. doi: 10.1016/j.jchf.2019.01.003
22. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, et al; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–1620. doi: 10.1056/NEJMoa1908655
23. Dewan P, Rørth R, Jhund PS, Shen L, Raparelli V, Petrie MC, Abraham WT, Desai AS, Dickstein K, Køber L, et al. Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol*. 2019;73:29–40. doi: 10.1016/j.jacc.2018.09.081