

# Impact of Sex on Ventricular-Vascular Stiffness and Long-Term Outcomes in Heart Failure With Preserved Ejection Fraction: TOPCAT Trial Substudy

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**Background**—Women have higher vascular stiffness with aging. The aim of this study was to characterize sex differences in vascular and ventricular structure and function, and to investigate the impact on the primary outcome in the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial).

**Methods and Results**—Data from the Americas cohort of the TOPCAT trial were analyzed. Patients with echocardiography ( $n=654$ ) were compared according to sex, and achievement of the primary end point (a composite of death from cardiovascular causes and heart failure hospitalization) assessed. Echocardiography revealed higher arterial, systolic, and diastolic ventricular elastance and worse ventricular-vascular coupling in women. Women had better overall survival and heart failure hospitalization outcomes (hazard ratio 0.74, 95% CI 0.57–0.98,  $P=0.034$ ), however, determinants of achievement of the primary outcome differed between the sexes. Pulse pressure was a key determinant of outcome in women (hazard ratio 1.04, 95% CI 1–1.09,  $P=0.034$ ) whereas in men heart rate (hazard ratio 1.61, 95% CI 1.02–2.52 per 10 mm Hg increase,  $P=0.04$ ) and B-type natriuretic peptide (hazard ratio 1.01, 95% CI 1–1.02 per 10 ng/mL increase  $P=0.02$ ) were associated with poorer outcome.

**Conclusions**—Outcomes in patients with heart failure with preserved ejection fraction appear to be differentially influenced by key physiological factors that vary according to sex. In women, ventricular-vascular stiffening was the most significant determinant of outcome, whereas in men overall survival was influenced by heart rate and B-type natriuretic peptide; this highlights key sex differences in the pathophysiology and outcomes of heart failure with preserved ejection fraction and warrants further exploration.

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**Key Words:** health outcomes • heart failure • pulse pressure • sex differences

Sex is an important determinant of cardiovascular structure and function, with attendant implications for phenotypes of coronary disease and heart failure. Women are less likely to develop heart failure with reduced ejection fraction,<sup>1</sup> however, they are overrepresented amongst patients with heart failure with preserved ejection fraction (HFpEF).<sup>2</sup> Postulated mediators of the sex difference in cardiovascular

pathology include differences in cardiac remodeling, with prominent concentric rather than eccentric remodeling<sup>3</sup> and less apoptosis in response to myocardial injury.<sup>4</sup> There are also considerable differences in the relative impact of risk factors for cardiovascular disease in men and women; diabetes mellitus increases heart failure risk 5-fold in women compared with 2.4-fold in men,<sup>5</sup> and obesity has a greater impact on diastolic function in women.<sup>6</sup>

There are substantial differences in the epidemiology and impact of hypertension across sexes. While women have a lower prevalence of hypertension during childbearing years, this rises substantially after menopause and surpasses that of men.<sup>7</sup> With aging, metrics of vascular stiffening, including arterial elastance calculated from echocardiography,<sup>8</sup> compliance derived from tonometry,<sup>9</sup> and pulse wave velocity,<sup>10</sup> are higher in women. The effect of vascular stiffening also has a greater impact on left ventricular elastance in women than men,<sup>8</sup> which may explain poorer diastolic function with aging. Women have higher augmentation indices between their peripheral and central pressures,<sup>11</sup> a contributor to the impact of hypertension on

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## Clinical Perspective

### What Is New?

- Women with heart failure with preserved ejection fraction (HFpEF) have better overall survival than men with HFpEF, however the factors influencing hospitalization and survival in HFpEF differ between the sexes; in women, pulse pressure is an important determinant of outcome whereas in men, heart rate and B-type natriuretic peptide are significant.
- Women had greater arterial and ventricular elastance and poorer ventricular-vascular coupling than men, echoing findings in elderly populations without heart failure and indicating that this enhanced vascular stiffness with aging may be a key component of the underlying pathophysiology of HFpEF in women and could be responsible for the overrepresentation of women in the HFpEF population.

### What Are the Clinical Implications?

- This research implies that risk factors for vascular stiffening such as hypertension should be aggressively targeted in women, who are more susceptible to the effects of increased pulse pressure and vascular stiffness on myocardial remodeling.

ventricular stiffness and the development of HFpEF.<sup>12</sup> Greater pulse pressure in women with aging<sup>8</sup> causes a lower coronary perfusion pressure, leading to ischemia in the setting of pre-existing coronary disease including coronary microvascular disease, which is more common in women.<sup>13</sup> Thus vascular stiffness with aging is more prominent, and may have greater adverse impact, in women.

Previous studies of HFpEF have demonstrated higher arterial stiffness in women, accompanied by greater left ventricular systolic and diastolic stiffening, however, long-term outcomes have not been evaluated.<sup>14</sup> We sought to characterize sex differences in arterial and ventricular mechanics, and their impact on outcomes, in a large and well-characterized cohort of HFpEF patients.

## Methods

### Study Design and Participants

The TOPCAT trial<sup>15</sup> studied the utility of spironolactone for the treatment of patients with HFpEF. The inclusion and exclusion criteria have been published previously.<sup>15</sup> In brief HFpEF was defined as defined as symptoms of heart failure in the setting of an ejection fraction (EF)  $\geq 45\%$ . Subjects aged  $>50$  years were recruited on the basis of a previous hospitalization for heart failure or elevated natriuretic peptide levels. Exclusion criteria included uncontrolled hypertension, stage 4 to 5 renal

failure, elevated serum potassium, or other significant comorbid conditions limiting life expectancy to  $<3$  years. Because of previously published data on regional heterogeneity,<sup>16</sup> we studied subjects from the Americas cohort only. All participants in the TOPCAT trial gave informed consent, and ethics approval for this analysis of the TOPCAT data was obtained from the local human research ethics committee.

### Echocardiographic and Hemodynamic Measurements

An echocardiographic sub-study was performed within the TOPCAT cohort, comprising 654 patients from the Americas.<sup>17</sup> Transthoracic echocardiography studies followed a protocol that reflected standard clinical echocardiography assessments. Baseline studies only were analyzed to compare raw differences between men and women.

Pulse pressure (PP) was calculated as the difference between systolic blood pressure (SBP) and diastolic blood pressure. Left ventricular wall stress was calculated according to the invasively validated Meridional method,<sup>18</sup> using the formula end-diastolic wall stress =  $(0.334 \times \text{left ventricular end diastolic pressure} \times \text{LVEDD} [\text{left ventricular end diastolic diameter}] / (\text{PWT} \times [1 + \text{PWT} / \text{LVEDD}]))$  and end-systolic wall stress =  $(0.334 \times [0.9 \times \text{SBP}] \times \text{LVESD} [\text{left ventricular end systolic diameter}] / (\text{PWT} \times [1 + \text{PWT} / \text{LVEDD}]))$  as previously described.<sup>19</sup> Left ventricular end diastolic pressure was estimated using previously a validated equation (left ventricular end diastolic pressure =  $11.96 + (0.596 \times \text{mean } E/e')$ ).<sup>20</sup> Arterial elastance (Ea) was calculated as  $0.9 \times \text{SBP}$  divided by the stroke volume.<sup>21</sup> Ventricular end diastolic elastance (Ed) was calculated as left ventricular end diastolic pressure divided by the left ventricular end diastolic volume (LVEDV [left ventricular end diastolic volume]).<sup>22</sup> Ventricular end systolic elastance (Ees) was calculated as the  $0.9 \times \text{SBP}$  divided by the left ventricular end systolic volume. The ratio of Ea to Ees was used to assess ventricular-vascular coupling.<sup>23</sup> In those with increased LVMI (left ventricular mass index) (LVMI  $\geq 95$  g/m<sup>2</sup> in women, LVMI  $\geq 115$  g/m<sup>2</sup> in men), concentric remodeling was defined as a left ventricular mass/LVEDV ratio  $\geq 1.5$ ; eccentric remodeling was defined as a ratio  $\leq 1.5$ .<sup>14</sup>

### Primary Outcome

The primary outcome for this study was to examine the differences between men and women in comorbidities, echocardiographic parameters, and outcome defined as a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure.

### Statistical Analysis

Normally distributed data are presented as mean  $\pm$  SD and non-parametric data as median (interquartile range). Baseline

and echocardiographic characteristics are compared between sexes using the Student *t* test if normally distributed and the Wilcoxon signed-rank test for non-parametric data. The analyses of the primary outcome were performed with the use of Kaplan–Meier estimates, with the log-rank test for comparison of sexes, and a Cox proportional hazards model to calculate hazard ratios and 95% CIs. A *P* value of <0.05 was considered statistically significant. All statistical analysis was performed with R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

## Ethics Approval

Ethics approval was obtained by the local human research ethics committee for this analysis. Data were obtained via the United States National Heart, Lung, and Blood Institute BioLINCC (Biologic Specimen and Data Repository Information Coordinating Center) data repository information coordinating center. Data are available from BioLINCC; analytic methods and study materials will be made available on request to other researchers on request.

## Results

Table 1 outlines baseline demographics of the echocardiographic cohort. Men were more likely to have a history of myocardial infarction, angina, or diabetes mellitus. Women had a higher body mass index ( $35\pm 9$  versus  $33\pm 7$  kg/m<sup>2</sup>, *P*=0.027). A greater proportion of women (95%) had an elevated waist circumference compared with men (84%), *P*<0.001. Men had a higher B-type natriuretic peptide (BNP) than women, however, this did not remain different after indexing to left ventricular mass ( $1.2$  [0.75–2.1] men versus  $1.3$  [0.8–2.8] women, *P*=0.27). These characteristics are similar to cohorts of HFpEF patients studied previously.<sup>24</sup>

Echocardiography revealed substantial differences between the sexes, detailed in Table 2. Women had a significantly higher EF than men, accompanied by more negative global longitudinal strain and higher right ventricular fractional area change, as well as higher tricuspid regurgitation velocities. Men had a greater left ventricular mass index, relative wall thickness, and end systolic and diastolic volumes. However, the proportion of patients meeting sex-specific criteria for moderate or severely abnormal ventricular end-diastolic and end-systolic volumes according to American Society of Echocardiography criteria<sup>25</sup> was higher in women than men (9% versus 2%, *P*=0.002 for LVEDV; 27% versus 9%, *P*<0.001 for left ventricular end systolic volume). There was no difference in the proportion with eccentric or concentric remodeling in those with increased LVMI. The proportion with abnormal relative wall thickness was similar in women and men (80% men versus 77% women, *P*=0.44). Women had lower cardiac output and index. Left

**Table 1.** Baseline Demographics

	Men (339)	Women (315)	<i>P</i> Value
Randomized to spironolactone, n (%)	173 (51)	159 (50.5)	0.95
Age, y	71±10	72±10	0.42
History of myocardial infarction, n (%)	96 (28)	42 (13)	<0.001
Angina, n (%)	107 (32)	62 (20)	0.001
Atrial fibrillation, n (%)	158 (47)	123 (39)	0.057
Diabetes mellitus, n (%)	175 (52)	133 (42)	0.018
Smoker, n (%)	26 (8)	15 (5)	0.17
Body mass index, kg/m <sup>2</sup>	33±7	35±9	0.027
Waist circumference, cm	112±18	106±16	<0.001
Estimated glomerular filtration rate, mL/min	66±21	62±25	0.024
BNP, ng/mL	289 [177–473]	211 [135–442]	0.032
Heart rate, bpm	69±11	70±12	0.41
Systolic blood pressure, mm Hg	126±15	128±17	0.15
Diastolic blood pressure, mm Hg	71±11	71±11	0.54
Pulse pressure, mm Hg	55±13	57±15	0.26

BNP indicates B-type natriuretic peptide.

ventricular wall stress did not differ between sexes. Indices of vascular and ventricular elastance were consistently higher in women, with a lower Ea/Ees ratio in women suggestive of poorer ventricular-vascular coupling. These findings persisted after indexing Ea, Ed, and Ees to body surface area.

## Outcomes

Survival analyses for time to primary end point revealed significantly better overall survival in women than men (hazard ratio [HR] 0.74, 95% CI 0.57–0.98, *P*=0.034), depicted in Figure 1. In a multivariate Cox proportional hazards analysis incorporating comorbidities that differed between the sexes, sex was no longer a significant predictor of time to primary end point. In a multivariate Cox analysis incorporating comorbidities, BNP, and echocardiographic parameters that differed between men and women, global longitudinal strain (HR 1.08 [1–1.16]) and septal E/e' (HR 1.04 [1.01–1.08]) remained independent predictors of primary outcome.

When considering factors affecting achievement of the primary end point in men and women separately, there were different predictors of outcome, depicted in Table 3. None of the calculated variables of wall stress or elastance were predictors of outcome in men or women.

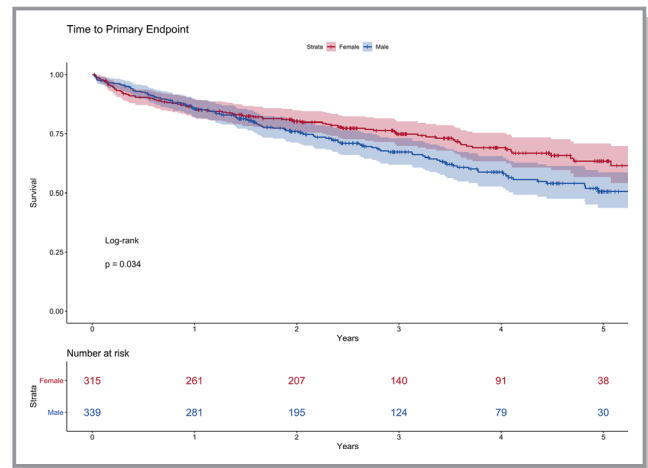
**Table 2.** Baseline Echocardiography

	Men (339)	Women (315)	P Value
Ejection fraction, %	58±8	61±7	<0.001
LVMI, g/m <sup>2</sup>	114±30	99±29	<0.001
Increased LVMI, n (%)	147 (43)	149 (47)	0.35
Relative wall thickness	0.49 [0.44–0.54]	0.47 [0.42–0.53]	0.047
Concentric remodeling, n (%)	130 (99)	140 (99)	0.95
Eccentric remodeling, n (%)	2 (1)	1 (1)	0.95
LVEDV, mL	105 [86–125]	79 [64–96]	<0.001
LVESV, mL	43 [33–55]	30 [23–38]	<0.001
Stroke volume, mL	63±18	50±15	<0.001
Cardiac output, L/min	4.3±1.3	3.5±1.2	<0.001
Cardiac index, L/min per m <sup>2</sup>	2±0.6	1.8±0.5	<0.001
Global longitudinal strain	−15.1±3.4	−16±3.5	0.02
Left atrial volume index, mL/kg per m <sup>2</sup>	30.5±13.6	29.9±12.6	0.59
Significant valvular disease, n (%)	42 (13)	53 (17)	0.16
Septal E/e' ratio	16.1±7.3	16.7±7	0.37
Lateral E/e' ratio	11.8±5.9	13±6.1	0.06
Right ventricular FAC	0.47±0.08	0.5±0.08	<0.001
Peak TR velocity, m/s	273±46	289±46	0.001
EDWS, kdyne	30.2±8.6	31.5±8.5	0.2
ESWS, kdyne	111.5±30.7	112.4±29	0.68
Ea	1.8 [1.5–2.3]	2.4 [1.9–2.9]	<0.001
Ees	2.7 [2.1–3.5]	3.8 [3.1–5]	<0.001
Ed	0.19 [0.15–0.24]	0.26 [0.21–0.33]	<0.001
Ea/Ees	0.7 [0.6–0.8]	0.6 [0.5–0.7]	<0.001

Ea indicates arterial elastance; Ed, end-diastolic elastance; EDWS, end-diastolic wall stress; Ees, end-systolic elastance; ESWS, end-systolic wall stress; FAC, fractional area change; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end systolic volume; LVMI, left ventricular mass index; TR, tricuspid regurgitation.

## Women

PP was a predictor of outcome in women (HR 1.2 per 10 mm Hg increase, CI 1.04–1.37), but not men. As pictured in Figure 2, dichotomizing men and women into 2 groups according to whether their PP was > or <50 mm Hg found a difference in survival in women, but not men. In univariate survival analyses, other significant predictors of outcome in women included heart rate, LVMI, global longitudinal strain, E/e' (mean, lateral and septal), cardiac output, BNP, and diabetes mellitus. In a multivariate Cox regression analysis incorporating these variables, PP alone remained an independent predictor of

**Figure 1.** Time to primary end point in women and men.

achievement of the primary outcome in women (HR 1.54 per 10 mm Hg increase, 95% CI 1.03–2.28,  $P=0.034$ ).

## Men

Conversely in men, predictors of primary outcome in univariate cox regression analyses differed from women and included: heart rate, age, smoking status, global longitudinal strain, E/e' septal and mean, and BNP. In multivariate regression analysis incorporating all univariate predictors of outcome, heart rate (HR 1.61, 95% CI 1.02–2.52 per 10 mm Hg increase,  $P=0.04$ ) and BNP (HR 1.01, 95% CI 1–1.02 per 10 ng/mL increase  $P=0.02$ ) remained independent predictors of outcome.

## Discussion

In this study, we examined sex differences in echocardiographic parameters and measures of arterial and ventricular stiffness in patients with HFpEF, and studied their association with long-term outcomes. Overall women were less likely to meet the primary end point than men, however PP had a greater impact. Women had greater arterial and ventricular elastance and poorer ventricular-vascular coupling. Women also had a higher ejection fraction, more negative global longitudinal strain, and better right ventricular systolic function, but a greater proportion with elevated ventricular volumes according to sex-specific criteria, lower stroke volume and lower cardiac index.

Greater arterial stiffness with aging has been well established in women without HFpEF. Redfield and colleagues demonstrated higher arterial elastance and PP in women than men, with a steeper age-arterial elastance association in women, regardless of the presence of cardiovascular disease.<sup>8</sup> These findings are consistent with a study in a younger cohort of patients with brachial blood pressure, PWV and

**Table 3.** Univariate and Multivariate Regression Analyses for Primary Outcome in Men and Women

Predictors of Primary Outcome	Univariate			Multivariate		
	Men	Women	All	Men	Women	All
Pulse pressure (per 10 mm Hg increase)	1.06 (0.93–1.22)	1.2 (1.04–1.37)*	1.12 (1.02–1.23)*	...	1.54 (1.03–2.28)*	1.04 (0.88–1.23)
DBP (per 10 mm Hg increase)	0.97 (0.83–1.5)	0.88 (0.73–1.07)	0.9 (0.82–1.06)	...	...	...
Heart rate (per 10 bpm increase)	1.2 (1.03–1.4)*	1.23 (1.04–1.47)*	1.21 (1.07–1.34)*	1.61 (1.02–2.52)*	1.2 (0.65–2.32)	1.2 (0.94–1.52)
EF, %	1 (0.98–1.02)	0.99 (0.97–1.02)	0.99 (0.98–1.01)	...	...	...
LVMI, g/m <sup>2</sup>	1.01 (0.99–1.01)	1.01 (1–1.02)*	1.01 (1–1.01)*	...	1 (0.976–1.02)	1 (0.996–1.01)
Cardiac output, L	1.02 (0.88–1.17)	1.25 (1.04–1.51)*	1.12 (1.01–1.24)*	...	1.6 (0.92–2.76)	1.1 (0.91–1.36)
GLS	1.12 (1.04–1.22)*	1.13 (1.04–1.22)*	1.13 (1.07–1.19)*	1.07 (0.94–1.22)	1.09 (0.82–1.45)	1.08 (1–1.16)*
Septal E/e'	1.05 (1.02–1.09)*	1.06 (1.03–1.1)*	1.06 (1.03–1.08)*	1.05 (0.99–1.11)	1.05 (0.97–1.14)	1.04 (1.01–1.08)*
BNP (per 10 ng/mL increase)	1.01 (1–1.01)*	1.01 (1–1.01)*	1 (0.99–1)	1.01 (1–1.02)*	1.07 (0.99–1.02)	...
Age, y	1.03 (1.01–1.05)*	1.001 (0.98–1.02)	1.01 (0.99–1.03)	1 (0.95–1.06)	...	...
Diabetes mellitus	1.23 (0.86–1.77)	2.18 (1.43–3.31)*	1.64 (1.24–2.16)*	...	0.28 (0.04–1.89)	1.1 (0.67–1.84)
Smoker	2.45 (1.42–4.22)*	1.26 (0.46–3.46)	2.08 (1.29–3.34)*	0.87 (0.18–4.34)	...	1.48 (0.66–3.32)

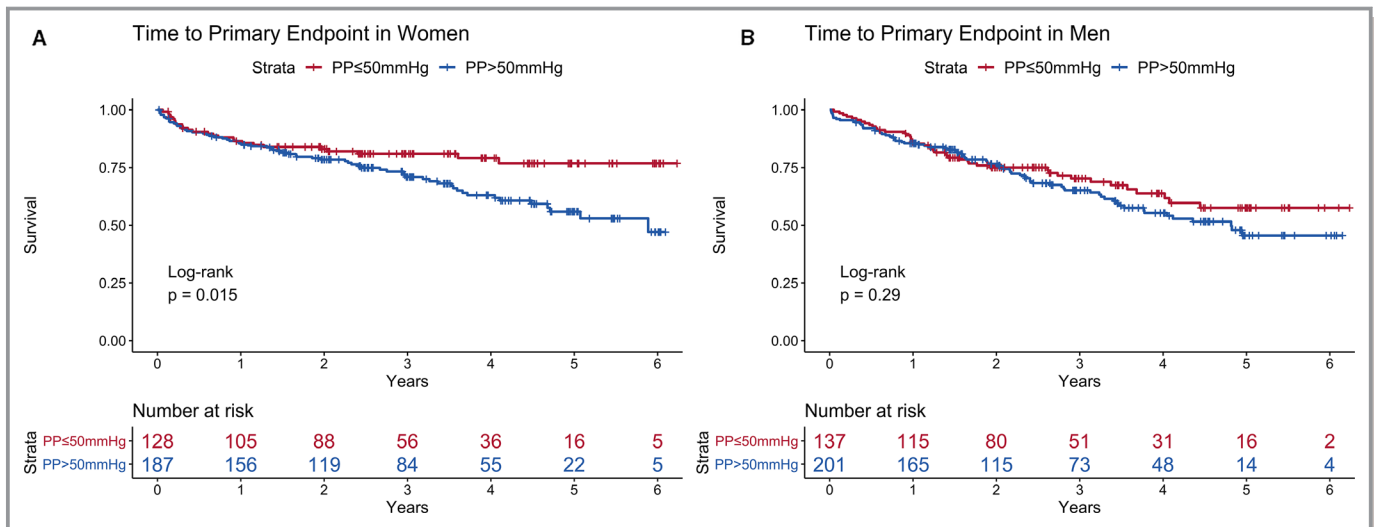
BNP indicates B-type natriuretic peptide; DBP, diastolic blood pressure; EF, ejection fraction; GLS, global longitudinal strain; LVMI, left ventricular mass index.  
\*Statistically significant associations.

aortic wave form analysis, finding greater PP and a closer relationship between PP and PWV in women than men.<sup>10</sup> Similarly, arterial stiffness and wave reflection were demonstrated to be greater in women than men in a large community study.<sup>9</sup>

Vascular stiffness is closely related to the development of HFpEF. Lam and colleagues performed an analysis of the Olmsted County community cohort of patients with HFpEF or hypertension without heart failure, and controls with echocardiographically derived ventricular-vascular function. Arterial elastance and PP were higher in patients with HFpEF and hypertension, as was Ees.<sup>26</sup> Kawaguchi et al used pressure-volume loops to assess ventricular-vascular stiffening in patients with HFpEF and controls with hypertension, finding that Ees and Ea were substantially higher in patients with HFpEF compared with hypertensive controls.<sup>27</sup> Desai and colleagues performed echocardiography and tonometry on HFpEF patients, hypertensives and controls, and found increased central aortic stiffness in hypertensives and HFpEF patients. Importantly, carotid-femoral pulse wave velocity was markedly higher in HFpEF patients compared with hypertensives and controls; persisting after adjusting for BMI, SBP, and renal function, and correlating with left ventricular mass index and BNP.<sup>28</sup> Taken together, these studies underscore the importance of vascular stiffness, particularly of the central vasculature, in the pathogenesis of HFpEF.

That sex differences in indices of arterial stiffness persist amongst patients with HFpEF is of interest, therefore, as it could be expected that men with HFpEF have a degree of vascular and ventricular stiffness similar to that of women given its role in the pathophysiology of HFpEF. However, women are more sensitive to the effects of vascular stiffening. Redfield et al established that the greater arterial elastance resulted in worse ventricular-vascular coupling and worse diastolic function in women than men.<sup>8</sup> Furthermore, women have a greater degree of left ventricular remodeling, based on LVMI and relative wall thickness, in response to hypertension than men.<sup>3</sup> Gori and colleagues analyzed patients in the PARAMOUNT (Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) study of an angiotensin receptor neprilysin inhibitor versus angiotensin receptor blocker in patients with HFpEF according to sex, a study including 279 participants.<sup>14</sup> They found that women had higher arterial elastance and were far more likely to have concentric and eccentric remodeling than men in the PARAMOUNT study.<sup>14</sup> We did not demonstrate similar sex differences in the proportion of patients with elevated LVMI, or eccentric or concentric remodeling, in this larger cohort. However, the LVMI was considerably lower in both men and women in the aforementioned study, which may suggest that the TOPCAT trial incorporated a population with more advanced ventricular remodeling, blunting the sex differences. Importantly, in the current analysis of the TOPCAT trial,





**Figure 2.** Time to primary end point in women (A) and men (B) according to pulse pressure category. PP indicates pulse pressure.

arterial stiffness as indicated by PP was an independent predictor of achievement of the primary outcome in women, but not men. This reinforces the notion that ventricular-vascular stiffening plays a greater role in HFpEF pathophysiology and severity in women than men, in whom other mechanisms are more active.

There is mounting evidence in the literature regarding the clinical significance of PP in determining the prognosis of cardiovascular conditions. A recent analysis of the TOPCAT trial indicated that low diastolic blood pressure is associated with greater adverse outcomes in HFpEF patients.<sup>29</sup> Higher PP is also associated with a greater burden of coronary disease and increased mortality after percutaneous coronary intervention compared with those with narrow PP.<sup>30</sup> These associations could be explained by subclinical myocardial ischemia attributable to the combination of increased myocardial oxygen demand and systemic hypertension, in concert with lower diastolic coronary perfusion pressure.<sup>31</sup> In women, a higher prevalence of coronary microvascular disease<sup>13</sup> may render them more susceptible to these reductions in coronary perfusion, and could help to explain the greater impact of increasing PP on primary outcome.

Achievement of the primary outcome was higher in men than women, with poor outcomes driven most strongly by heart rate and BNP in men. This is consistent with a study of 260 patients with HFpEF finding that men were more likely to die of cardiovascular causes than women, and tended to achieve the combined end point of cardiac death or heart failure hospitalization at greater rates.<sup>32</sup> Likewise, Lam et al analyzed the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial of irbesartan in HFpEF (EF ≥45%) with regard to sex differences in survival, and found that women had a 21% lower risk of all-cause events than men, which persisted after adjusting for differences in

baseline characteristics. In analyses investigating sex differences in predictors of all-cause events, comorbidities played an important role in distinguishing predictors between men and women; for example, smoking and a history of coronary revascularization were predictive of poor outcome in men.<sup>24</sup> Often poorer survival in men has been attributed to higher rates of ischemic heart disease, which drives adverse outcomes across all phenotypes of heart failure.<sup>33</sup> A history of myocardial infarction or angina did not predict outcome in our analysis despite being more common in men, however, this may have been because of lack of statistical power.

An important predictor of outcome in HFpEF is natriuretic peptide level. A key study of heart failure patients in Singapore and New Zealand found that while overall HFpEF patients had lower mortality than heart failure with reduced ejection fraction patients, stratifying according to NT-proBNP quartile overrode the differences in prognosis according to heart failure phenotype.<sup>34</sup> BNP and NT-proBNP are released in response to myocardial wall stress,<sup>35</sup> and in HFpEF this is driven by increased relative wall thickness attributable to myocardial remodeling, and afterload. However, there are other active contributors to natriuretic peptide levels;  $e'$  has been associated with BNP levels even in the setting of the same left ventricular wall stress, as has  $s'$  which may reflect alterations to the structure of the left ventricular myocardium reflecting fibrosis and cellular hypertrophy.<sup>35</sup> In our analysis of the TOPCAT data, BNP levels were significantly higher in men; however, this did not persist after indexing BNP to left ventricular mass, and wall stress did not differ between men and women. Similarly, blood pressure and the proportion with abnormal relative wall thickness did not differ between men and women. BNP was an independent predictor of outcome in men but not women when considered separately, and wall stress was not a predictor of outcome in either sex. This may

indicate that factors contributing to BNP release other than wall stress, afterload and myocardial wall thickness are responsible for the poorer prognosis in men with HFpEF.

Another determinant of achievement of the primary outcome in men was heart rate. This finding mirrors a large study of propensity-matched subjects from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry of outcomes according to heart rate strata (<70 versus  $\geq$ 70 beats/min), finding that heart rate was independently associated with all-cause mortality in HFpEF patients.<sup>36</sup> Interestingly, when analyzing in subgroups according to sex, heart rate was clearly associated with outcome in women but not men, contrary to our findings. Thus, further investigation may help to delineate the relevance of heart rate in determining outcomes in men and women with HFpEF.

## Clinical Implications

This study emphasizes sex differences in ventricular-vascular stiffening, even within the HFpEF population, by demonstrating greater indices of arterial stiffness in women with a significant impact on their achievement of the primary outcome in the TOPCAT trial. In particular, we demonstrate that despite similar overall blood pressures, measures of vascular stiffness were more impaired in women with a greater impact on long-term outcomes. Thus, better understanding the processes that lead to increased vascular stiffness is integral to preventing HFpEF and mitigating adverse outcomes in women in particular. Given the close relationship between hypertension and vascular stiffness, aggressive blood pressure management is key in women. However, hypertension may not fully explain differences in pulsatility and arterial elastance with aging, albeit this is without taking into consideration blood pressure variability.<sup>10</sup> Further research will benefit from identifying mechanisms to reduce ventricular-vascular stiffening.

Furthermore, these findings may suggest that sex can be used to better characterize patients with HFpEF into phenogroups with different characteristics, and for whom outcome is affected by different factors. Just as there are different mechanisms behind HFpEF which warrant divergent therapeutic approaches,<sup>37</sup> the relative importance of, for example, extracellular matrix involvement versus cardiomyocyte dysfunction in men and women could be further explored to better understand the molecular mechanisms behind these processes.

## Limitations

This study has inherent limitations associated with being a post-hoc analysis of a previous study. Given the substantial heterogeneity between geographic regions, we selected only

patients from the Americas region, significantly limiting the number of patients with echocardiographic data. This is likely to have affected our statistical power, and may have introduced confounders not adjusted for in our analysis given the more select nature of the cohort. Certainly, further statistical investigation of the interaction between sex, hemodynamics, and outcome was potentially limited by the modest sample size.

Another limitation of the study is the EF cut-off of 45%; although this was the accepted definition of HFpEF at the time of trial design, the definition has since been revised to an EF  $\geq$ 50%.<sup>38</sup> Given women have higher EFs,<sup>39</sup> and there are strong associations between EF and outcome in heart failure, this may have affected our results. Finally, the study is limited by its retrospective nature, and future studies could build on these results with the addition of invasive hemodynamic data including invasive measures of central arterial pressure, along with pulmonary arterial and pulmonary capillary wedge measurements.

## Conclusions

This analysis reveals overall more favorable prognosis in women compared with men in the TOPCAT trial. Numerous differences in vascular function, natriuretic peptides, comorbidities, and echocardiographic parameters between men and women are active in mediating this survival benefit in women. Importantly, women have greater metrics of ventricular-vascular stiffness, and arterial elastance as indicated by PP is an important predictor of outcome in women, but not men. This indicates divergent phenotypes within this selective trial population according to sex and may represent an opportunity for further research into sex-specific mechanisms and therapies for vascular stiffness with a view to preventing and treating HFpEF.

## Disclosures

None.

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