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

Amil M. Shah, MD, MPH; Sanjiv J. Shah, MD; Inder S. Anand, MD; Nancy K. Sweitzer, MD, PhD; Eileen O’Meara, MD; John F. Heitner, MD; George Sopko, MD, MPH; Guichu Li, PhD, RDACS; Susan F. Assmann, PhD; Sonja M. McKinlay, PhD; Bertram Pitt, MD; Marc A. Pfeffer, MD, PhD; Scott D. Solomon, MD; for the TOPCAT Investigators

Background—Heart failure with preserved ejection fraction (HFpEF) is associated with substantial morbidity and mortality. Existing data on cardiac structure and function in HFpEF suggest significant heterogeneity in this population.

Methods and Results—Echocardiograms were obtained from 935 patients with HFpEF (left ventricular ejection fraction ≥45%) enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial before initiation of randomized therapy. Average age was 70±10 years, 49% were women, 14% were of African descent, and comorbidities were highly prevalent. Centralized quantitative analysis in a blinded core laboratory demonstrated a mean left ventricular ejection fraction of 59.3±7.9%, with prevalent concentric left ventricular remodeling (34%) and hypertrophy (43%), and left atrial enlargement (53%). Diastolic dysfunction was present in 66% of gradable participants and was significantly associated with greater left ventricular hypertrophy and a higher prevalence of left atrial enlargement. Doppler evidence of pulmonary hypertension was present in 36%. At least 1 measure of structural heart disease was present in 93% of patients.

Conclusions—Patients enrolled in TOPCAT demonstrated heterogeneous patterns of ventricular remodeling, with high prevalence of structural heart disease, including left ventricular hypertrophy and left atrial enlargement, in addition to pulmonary hypertension, each of which has been associated with adverse outcomes in HFpEF. Diastolic function was normal in approximately one third of gradable participants, highlighting the heterogeneity of the cardiac phenotype in this syndrome. These findings deepen our understanding of the TOPCAT trial population and expand our knowledge of the diversity of the cardiac phenotype in HFpEF.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00094302.

(Circ Heart Fail. 2014;6:00-00.)

Key Words: diastolic heart failure ■ echocardiography ■ heart failure ■ randomized controlled trial ■ spironolactone

Received October 5, 2013; accepted October 21, 2013.

Division of Cardiovascular Medicine, Brigham and Women’s Hospital, Boston, MA (A.M.S., G.L., M.A.P., S.D.S.); Northwestern University Feinberg School of Medicine, Chicago, IL (S.J.S.); VA Medical Center, Minneapolis, MN (I.S.A.); University of Wisconsin Hospital and Clinics, Madison, WI (N.K.S.); Montreal Heart Institute, Montreal, Canada (E.O.); New York Methodist Hospital, Brooklyn, NY (J.F.H.); National Heart, Lung, and Blood Institute, Bethesda, MD (G.S.); New England Research Institutes, Watertown, MA (S.A., S.M.); and University of Michigan School of Medicine, Ann Arbor, MI (B.P.).

Correspondence to Amil M. Shah, MD, MPH, Division of Cardiovascular Medicine, Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115. E-mail ashah11@partners.org

© 2013 American Heart Association, Inc.

Circ Heart Fail is available at http://circheartfailure.ahajournals.org

DOI: 10.1161/CIRCHEARTFAILURE.113.000887
to determine whether treatment with spironolactone would reduce morbidity and mortality in patients with HFpEF. Assessment of cardiac structure and function by echocardiography at baseline was prespecified in a subset of participants, with a smaller portion undergoing additional assessment at 12 to 18 months after randomization to either spironolactone or placebo. In this analysis, we aimed to characterize the cardiac phenotype in HFpEF patients in the TOPCAT trial. We describe baseline cardiac structure and function in this HFpEF population and compare it with other HFpEF clinical trials and epidemiological studies. These findings deepen our understanding of the TOPCAT trial population and expand our knowledge of the diversity of the cardiac phenotype in HFpEF.

Methods

Patient Population

TOPCAT is a multicenter, international, randomized, double-blind, placebo-controlled trial testing the efficacy and safety of the aldosterone antagonist, spironolactone, to reduce cardiovascular morbidity and mortality in adults with signs and symptoms of heart failure and a LV ejection fraction (LVEF) ≥45% as previously described in detail. Briefly, TOPCAT enrolled 3445 patients at 270 sites in 6 countries, who met the following key inclusion criteria: (1) age ≥50 years old; (2) heart failure defined by the presence of ≥1 symptom at the time of screening and ≥1 sign in the previous 12 months; (3) LVEF ≥45% per local reading and obtained within 6 months before randomization and ≥26 months after myocardial infarction or other event that would affect LVEF; (4) controlled systolic blood pressure defined as systolic blood pressure <140 mm Hg or 140 to 160 mm Hg if on ≥2 antihypertensive medications; and (5) assignment to 1 of 2 strata within which subjects were randomized: either ≥1 hospitalization in the previous 12 months for which heart failure was a major component of hospitalization, or B-type natriuretic peptide (BNP) ≥360 pg/mL. This study was approved by an institutional review committee at each participating site. All patients provided written informed consent. Key exclusion criteria included chronic pulmonary disease requiring home O₂ or oral steroid therapy, infiltrative or hypertrophic obstructive cardiomyopathy, hemodynamically significant uncorrected obstructive or regurgitant valvular heart disease or any valvular disease expected to lead to surgery during the trial, atrial fibrillation with a resting heart rate >90 beats per minute, myocardial infarction or coronary artery bypass surgery in past 3 months, percutaneous coronary intervention in the past 30 days, and severe renal dysfunction defined as an estimated glomerular filtration rate <30 mL/min or serum creatinine ≥2.5 mg/dL.

Baseline demographics and clinical characteristics of the trial population have been previously described in detail. For quality control purposes, each enrolling site was required to submit echocardiograms from at least the first 2 randomized patients for quantification of LVEF by the echocardiographic core laboratory at the Brigham and Women’s Hospital. Studies were performed within 6 months of randomization and were not obtained using a uniform prespecified acquisition protocol. Consent for review of these echocardiograms was obtained in the main study consent form. At 27 sites, patients consenting to participate in the overall TOPCAT trial were separately consented to participate in the echocardiographic substudy. For participating sites, echocardiography was performed by a study-specific protocol at baseline and 12 to 18 months after randomization. From a combined total of 1017 baseline studies received from 204 sites, 935 studies were suitable for qualitative analysis and included in this report (Figure 1).

Echocardiographic Methods

Echocardiograms were sent in digital or analog format to the echocardiographic core laboratory at the Brigham and Women’s Hospital. Echocardiograms from videotape were digitized, and analyses were performed on an offline analysis workstation. Quantitative measures on all study echocardiograms were performed by dedicated analysts at the core laboratory, blinded to clinical information and randomized treatment assignment.

LV endocardial borders were manually traced at end-diastole and end-systole in the apical 4- and 2-chamber views and LV volumes derived according to the modified biplane Simpson rule. In cases where the Simpson method could not be used because of missing or poor quality apical views, LVEF was calculated using the Teicholz method. To minimize measurement variability and given the low prevalence of regional wall motion abnormalities, LV mass was calculated by the American Society of Echocardiography (ASE) recommended formula for estimation of LV mass from LV linear dimensions and indexed to body surface area. LV hypertrophy (LVH) was defined as LV mass indexed to body surface area (LV mass index) >115 g/m² in men or >95 g/m² in women. LV geometry was classified based on relative wall thickness (RWT), defined as (2×diastolic posterior wall thickness)/LV end-diastolic dimension, and LV mass index as recommended by the ASE: normal—RWT ≤0.42 and no LVH; eccentric hypertrophy—RWT ≥0.42 and LVH; concentric remodeling—RWT >0.42 and no LVH; concentric hypertrophy—RWT >0.42 and LVH. Mitral regurgitation (MR) was categorized by tracing the MR jet area (obtained with color Doppler imaging) occupying the left atrium (LA) in 4- and 2-chamber views and was expressed as a proportion of LA area. The presence of an eccentric jet raised the grade of MR by 1 degree.

LV volume was assessed by the biplane area-length method from apical 2- and 4-chamber views at end-systole from the frame preceding mitral valve opening and was indexed to body surface area (LA volume index, LAVI). LA enlargement was determined based on LA area, volume, and volume index based on guideline recommendations. Peak early diastolic tissue velocity (E′) was measured from the septal and lateral aspects of the mitral annulus. Mitral inflow velocity was assessed by pulsed wave Doppler from the apical 4-chamber view, by positioning the sample volume at the tip of the mitral leaflets. The deceleration time of the E-wave was measured as the interval from the peak E-wave to its extrapolation to the baseline. E/E′ ratio was calculated as E-wave divided by E′. Diastolic dysfunction grade was derived from mitral inflow E/A ratio, tissue Doppler E′, and deceleration time. Diastolic dysfunction was graded as follows: mild—reduced E′ (septal <8 cm/s or lateral <10 cm/s) and E/A ratio ≥0.8; moderate—reduced E′ and E/A ratio of 0.8 to 1.5; severe—reduced E′ and E/A ratio >1.5 or E′-wave deceleration time <160 ms. Diastolic dysfunction was only graded among participants in sinus rhythm at the time of echocardiography. Because of the limited feasibility of obtaining reliable pulmonary venous flow data, pulmonary venous Doppler pattern was not measured. Right ventricular (RV) function, expressed as the RV fractional area change (RV FAC), was assessed as the percent change in cavity area from end-diastole to end-systole in accordance with ASE guidelines.

Peak tricuspid regurgitation (TR) velocity was measured and peak RV-to-RA systolic gradient was calculated as 4×peak TR velocity. Pulmonary vascular resistance (PVR) was estimated as 0.1618×(10.006×peak TR velocity/right ventricular outflow time–velocity integral). An experienced echocardiographer (A.M.S.) over-read all quantitative measures and qualitatively assessed each study for the presence of regional wall motion abnormalities, in addition to the presence and severity of aortic insufficiency, mitral stenosis, TR, and RV enlargement. Aortic insufficiency grade was assessed.
primarily based on the width of the color Doppler jet at the level of the aortic valve in the parasternal long and short axis views, in addition to the percent of the LV outflow tract diameter occupied by the aortic regurgitation color Doppler signal in the parasternal long axis view. Mitral stenosis assessment was based on the mean antegrade transmural gradient from continuous wave Doppler, with mild defined as a mean gradient <5 mm Hg, moderate as 5 to 10 mm Hg, and severe as ≥10 mm Hg. TR severity was based primarily on the size of the regurgitant color Doppler signal relative to the right atrial size. Evaluations were performed only on images with color Doppler Nyquist limit ≥50 cm/s.

Three hundred five of 308 (99%) substudy echocardiograms and 630 of 704 (89%) quality assurance echocardiograms could be analyzed quantitatively (Figure 1). Of the 935 analyzable studies included in this analysis, complete 2-dimensional and Doppler data were available in 553 (59%), with all Doppler measures missing in 181 (19%) and tissue Doppler only missing in an additional 147 (16%) patients. Among the 78% of participants with Doppler measures, 76% were in sinus rhythm.

Each measure was performed by the same analyst for all study participants. Intraobserver variability in our laboratory, performed in 60 studies, was as follows: wall thickness: coefficient of variation 12%, bias 0.02±0.1 cm; LV end-diastolic volume: coefficient of variation 12%, bias 1.6±10.5 mL; LV end-systolic volume: coefficient of variation 18%, bias 2.6±5.9 mL; LVEF: coefficient of variation 6.6%, bias 2.0±4.3%; tissue Doppler imaging E': coefficient of variation 7.0%, bias 0.1±0.4 cm/s; E/E' ratio: coefficient of variation 11%, bias 0.2±1.2.

Statistical Analysis
Continuous variables are presented as mean and SDs or median and interquartile range as specified. Comparison of baseline clinical measures between TOPCAT participants included (n=935) and not included (n=2510) in the echocardiographic cohort, and comparison of cardiac structure and function based on TOPCAT entry criteria, was performed using a Fisher exact test for categorical variables and a t-test or Wilcoxon rank-sum test for continuous variables as specified. Two-sided P values of <0.05 were considered significant. All analyses were performed using SAS version 9.2 and Stata version 11.

Results
The average age of the 935 TOPCAT patients in the pooled echocardiographic analysis was 70±10 years, 49% were women, 14% were of African descent, and 11% were Hispanic. Comorbidities included hypertension (91%), coronary artery disease (57%), atrial fibrillation (38%), diabetes mellitus (40%), and chronic kidney disease (CKD; 42%). The majority of patients were receiving therapy with β-blockers (81%), inhibitors of the renin-angiotensin system (ACE inhibitors or angiotensin receptor blockers: 81%), and diuretics (83%). Compared with TOPCAT patients not in the pooled echocardiographic analysis, patients participating in the echocardiographic cohort were older, more frequently of African descent, had a higher BMI, and had a higher prevalence of comorbidities, including diabetes mellitus, CKD, previous coronary revascularization, atrial fibrillation, and chronic obstructive pulmonary disease or asthma (Table 1). Patients in the echocardiographic cohort were also more frequently enrolled in the United States (52%). Compared with patients in the echocardiographic cohort without missing echocardiographic data, participants with missing data were more frequently men and white, had a lower prevalence of CKD and previous percutaneous coronary intervention, and had higher diastolic blood pressure, estimated glomerular filtration rate, and hematocrit.

LV Structure and Systolic Function
Consistent with trial inclusion criteria, the mean LVEF was 59.3±7.9%, with core laboratory LVEF <50% in only 13% and an LVEF <45% in 5% (Table 2). Despite preserved ejection fraction, LV longitudinal shortening reflected in tissue Doppler imaging S' was significantly reduced. The majority of patients demonstrated normal LV size but increased wall thickness. Elevated LV RWT was present in 78%, and concentric LVH was present in 44% of patients (Figure 2A). Eccentric hypertrophy was also found in 9% of participants and was associated with lower LVEF. Focal regional wall motion abnormalities, suggestive of previous myocardial infarction, were noted in 7% of participants (n=70).

LV Diastolic Function
LA size was enlarged in 53% of patients (Figure 2B), with moderate or severe LA enlargement noted in 34% of participants. Including LA anterior-posterior dimension >4.0 cm as an additional criterion, the prevalence of LA enlargement increased to 80%. Only 7% of patients demonstrated normal LV and LA structure. Both lateral and septal tissue Doppler imaging E' were impaired in the majority of patients. Elevated LV filling pressure, defined by a septal E/E' ≥15 or lateral E/E' ≥12, was present in 51% and was associated with a higher prevalence of LA enlargement (62% with elevated E/E' ratio versus 52% without; P=0.03). Diastolic grade could not be determined in 445 participants, because of atrial fibrillation in 25%, no tissue Doppler measures in 72%, and, additionally, no mitral inflow Doppler E-wave in 3%. Among the 52% of patients in whom diastolic dysfunction grade could be determined, diastolic dysfunction was present in 66%, with moderate or severe dysfunction in 44% (Figure 2C). Worse diastolic dysfunction grade was significantly associated with higher prevalence of LVH (P=0.02), both concentric and eccentric.

Pulmonary Vasculature and the Right Ventricle
Among patients with measurable TR jet (n=450), the peak velocity was elevated to >2.9 m/s in 36%. Among the 162 of these participants with a jet velocity >2.9 m/s, the mean TR velocity was 3.28±0.33 m/s. TR jet was ≥3.5 m/s in 37 (8%) and ≥4.0 m/s in 8 (2%). TR jet velocity was significantly related to the E/E' ratio (septal: r=0.29; P<0.0001; lateral: r=0.23; P<0.0001). In the subset of 324 patients in whom PVR could be estimated echocardiographically, PVR exceeded 2.5 Wood units in 11%. RV FAC was within reference limits in the majority of participants (median, 0.49, Q1–Q3, 0.44 – 0.54). RV FAC was ≤0.45 in 31% of patients, ≤0.40 in 11%, and ≤0.35 (abnormal cut-off per ASE guidelines) in 4%. Some degree of RV enlargement was noted in 11% of patients and was moderate or severe in 5%.

Mitrall and Aortic Valve Disease
MR was detected in 61% of patients, with moderate or greater regurgitation present in 12% of patients overall. Mitrall stenosis was rare, noted in 1.2% and was mild in the large majority. Peak antegrade transaortic velocity was obtained in 623 patients, among whom mild aortic stenosis (peak velocity of 2.0–3.0 m/s) was present in 10% and moderate stenosis
Table 1. Baseline Characteristics of TOPCAT Patients Included Compared With Those Not Included in the Echocardiographic Substudy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N=3445)</th>
<th>Echo (n=935)</th>
<th>Nonecho (n=2510)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.6±9.6</td>
<td>69.9±9.7</td>
<td>68.1±9.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>1775 (52)</td>
<td>462 (49)</td>
<td>1313 (52)</td>
<td>0.14</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3062 (89)</td>
<td>770 (82)</td>
<td>2292 (91)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Black</td>
<td>302 (9)</td>
<td>127 (14)</td>
<td>175 (7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>321 (9)</td>
<td>103 (11)</td>
<td>218 (9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Native American/Alaskan</td>
<td>10 (&lt;1)</td>
<td>5 (&lt;1)</td>
<td>5 (&lt;1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Asian</td>
<td>19 (1)</td>
<td>4 (&lt;1)</td>
<td>15 (&lt;1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Native Hawaiian/Other Pacific Islander</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>70 (2)</td>
<td>31 (3)</td>
<td>39 (2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>1151 (33)</td>
<td>483 (52)</td>
<td>668 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Canada</td>
<td>326 (9)</td>
<td>101 (11)</td>
<td>225 (9)</td>
<td></td>
</tr>
<tr>
<td>Russia</td>
<td>1066 (31)</td>
<td>242 (26)</td>
<td>824 (33)</td>
<td></td>
</tr>
<tr>
<td>Republic of Georgia</td>
<td>612 (18)</td>
<td>39 (4)</td>
<td>573 (23)</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>167 (5)</td>
<td>42 (5)</td>
<td>125 (5)</td>
<td></td>
</tr>
<tr>
<td>Argentina</td>
<td>123 (4)</td>
<td>28 (3)</td>
<td>95 (4)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3147 (91)</td>
<td>854 (91)</td>
<td>2293 (91)</td>
<td>1.0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>893 (26)</td>
<td>253 (27)</td>
<td>640 (26)</td>
<td>0.36</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>500 (15)</td>
<td>164 (18)</td>
<td>336 (13)</td>
<td>0.003</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>443 (13)</td>
<td>144 (15)</td>
<td>299 (12)</td>
<td>0.007</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1613 (47)</td>
<td>391 (42)</td>
<td>1222 (49)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2023 (59)</td>
<td>533 (57)</td>
<td>1490 (59)</td>
<td>0.23</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1213 (35)</td>
<td>359 (38)</td>
<td>854 (34)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>269 (8)</td>
<td>94 (10)</td>
<td>175 (7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Implanted cardioverter-defibrillator</td>
<td>44 (1)</td>
<td>14 (2)</td>
<td>30 (1)</td>
<td>0.50</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1114 (32)</td>
<td>373 (40)</td>
<td>741 (30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1311 (38)</td>
<td>391 (42)</td>
<td>920 (37)</td>
<td>0.006</td>
</tr>
<tr>
<td>Obesity</td>
<td>1902 (55)</td>
<td>538 (58)</td>
<td>1364 (55)</td>
<td>0.11</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2073 (60)</td>
<td>639 (68)</td>
<td>1434 (67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>403 (12)</td>
<td>127 (14)</td>
<td>276 (11)</td>
<td>0.04</td>
</tr>
<tr>
<td>Asthma</td>
<td>223 (6)</td>
<td>74 (8)</td>
<td>149 (6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke</td>
<td>265 (8)</td>
<td>77 (8)</td>
<td>188 (8)</td>
<td>0.47</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>319 (9)</td>
<td>90 (10)</td>
<td>229 (9)</td>
<td>0.64</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>2785 (81)</td>
<td>774 (83)</td>
<td>2011 (80)</td>
<td>0.10</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>2260 (66)</td>
<td>566 (61)</td>
<td>1694 (68)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>672 (20)</td>
<td>203 (22)</td>
<td>469 (19)</td>
<td>0.053</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>2731 (79)</td>
<td>753 (81)</td>
<td>1978 (79)</td>
<td>0.30</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>1285 (37)</td>
<td>355 (38)</td>
<td>930 (37)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypoglycemic agent</td>
<td>959 (28)</td>
<td>331 (35)</td>
<td>628 (25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other cardiovascular medication</td>
<td>3115 (91)</td>
<td>853 (91)</td>
<td>2262 (90)</td>
<td>0.40</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>360 (10)</td>
<td>81 (9)</td>
<td>279 (11)</td>
<td>0.35</td>
</tr>
<tr>
<td>Past</td>
<td>1268 (37)</td>
<td>394 (42)</td>
<td>874 (35)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1813 (53)</td>
<td>459 (49)</td>
<td>1354 (54)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
(peak velocity 3.0–4.0 m/s) was present in 1.1%. Mild aortic regurgitation was noted in 9% and moderate regurgitation was noted in 1.3%. Previous replacement of the mitral or aortic valve was noted in 28 patients (3%; 6 mitral only, 19 aortic only, 3 both). Finally, at least moderate TR was noted in 55 patients (6%).

Impact of Trial Entry Criteria on Cardiac Structure and Function

Entry into TOPCAT required either hospitalization within the previous 12 months for which heart failure was a major component or BNP \( \geq 100 \) pg/mL or NT-proBNP \( \geq 360 \) pg/mL within the previous 60 days. Patients qualifying only by biomarker criteria (33%) tended to be older; had a higher prevalence of atrial fibrillation, CKD, and previous coronary revascularization; and were more likely to be enrolled in the United States or Canada. Despite these differences, LV structure differed modestly between groups. Participants with a heart failure hospitalization within the previous 12 months demonstrated slightly higher wall thickness (Table 3). Echocardiographic markers of elevated LV filling pressure, namely LAVi and E/A ratio, were higher among participants enrolled solely based on biomarker criteria. These differences in LAVi and E/A ratio remained significant after adjusting for age and history of atrial fibrillation. Participants enrolled based on biomarker criteria also demonstrated lower systolic longitudinal velocity despite similar LVEF.

**Discussion**

Among 935 patients enrolled in TOPCAT, we found a high prevalence of structural heart disease, including concentric LV remodeling, concentric hypertrophy, and LA enlargement. Only 7% of participants demonstrated normal LV geometry and normal LA size. Over one third of patients with measurable TR jet velocity demonstrated evidence of pulmonary hypertension. Each of these echocardiographic characteristics has been associated with an increased risk of adverse outcomes in HFpEF. Doppler-based diastolic function grade, which has only inconsistently been associated with outcomes in HFpEF, was normal in one third of evaluable participants. These findings enhance our understanding of the HFpEF population tested in TOPCAT and suggest that they may represent a particularly high-risk group within the HFpEF syndrome.

We noted a higher prevalence of LVH, increased LV wall thickness, and higher mass index in TOPCAT compared with epidemiological cohorts (Table 4). A notable exception is blacks with HFpEF from the Jackson (Mississippi) site of the National Heart, Lung, and Blood Institute’s Atherosclerosis Risk in Communities (ARIC) study, who demonstrated an even higher prevalence of LVH than seen in this cohort. In general, the pattern of ventricular remodeling noted in TOPCAT more closely approximated that from a large HFpEF registry.

Compared with data from the echocardiographic substudy of the Irbesartan for Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial, which is the most comparable in size and comprehensiveness, LV size was similar although wall thickness tended to be greater in TOPCAT, resulting in a higher prevalence of concentric remodeling and concentric hypertrophy. The reason for this difference is unclear, as the prevalence of major comorbidities, including hypertension, diabetes mellitus, and coronary disease, was similar between studies. The average estimated glomerular filtration rate
was modestly lower in TOPCAT. In addition, blacks seem to develop greater degrees of concentric LV remodeling and LVH for a set degree of hypertension and demonstrate greater hypertrophy in HFpEF. One potential contributor to the higher LV mass index and concentricity noted in TOPCAT might be the greater representation of blacks (14%) compared with I-PRESERVE (2%). Greater variability in ventricular structure exists when looking more broadly at HFpEF clinical trials (Table 5), with appreciably larger LV size observed in the CHARM Echocardiographic Substudy (CHARMES) and Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) trials.

Interestingly, we noted an eccentric pattern of hypertrophy in 9% of participants, consistent with findings from the PARAMOUNT trial (eccentric hypertrophy in 7%) and the Olmsted County epidemiological cohort (eccentric hypertrophy in 16%). Although increased wall thickness-to-cavity...
ratio with diminished cavity size is the commonly expected pattern of remodeling in HFpEF, these findings suggest heterogeneity of the cardiac phenotype in the HFpEF syndrome.

Doppler-based measures of diastolic function were normal in approximately one third of our patients in sinus rhythm. Previous, relatively small, invasive hemodynamic studies in select highly phenotyped HFpEF patients demonstrated a high prevalence of diastolic dysfunction, characterized by both prominent markers of elevated filling pressure, including larger LAVi and higher E/A ratio, among participants enrolled on the basis of elevated BNP or NT-proBNP levels, as opposed to recent hospitalization with heart failure. These findings could help account for the greater degree of LA enlargement noted in clinical trials with a uniform entry requirement for an elevated NT-proBNP, such as PARAMOUNT and Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX).30,32 The previously noted distinctions between clinical trials and observational epidemiological studies may also reflect trial-specific inclusion and exclusion criteria and inclusion of a broader range of patients, possibly with more comorbidities, in the observational studies.

Concomitant pulmonary hypertension is a risk factor for adverse outcomes in HFpEF.20 We found Doppler evidence of pulmonary hypertension in 36% of patients, likely consistent with findings from other HFpEF trials.7,30,32 At least moderate pulmonary hypertension, defined as a peak TR velocity of ≥3.5 m/s, was present in 8%. Concordant with data from the Olmsted County cohort, estimated pulmonary artery systolic pressure was significantly associated with E/E′ ratio as an index of LV filling pressure.20 Previous studies, however, have not assessed PVR in HFpEF. In the smaller subgroup of our participants in whom PVR could be estimated noninvasively, PVR was elevated in ≈11%. Relatively little is also known about RV performance in HFpEF. Gross RV dysfunction, based on the FAC, was uncommon. However, although guideline documents define abnormal RV FAC as <0.35,17 studies in heart failure with reduced EF have demonstrated the prognostic relevance of RV FAC <0.40,37 which was present in 11% of participants.

Limited data exists regarding the prevalence and prognostic implication of valvular disease in HFpEF. Most clinical trials and observational studies have excluded individuals with significant mitral or aortic valve disease from HFpEF studies. Of 619 HFpEF patients in the New York Heart Failure Registry, moderate-to-severe or greater degrees of MR was present in 10%.25 Similarly, in the Northwestern HFpEF Registry, moderate MR was noted in ≈14% of patients.27 Consistent with these findings, moderate or greater MR was noted in 12% of TOPCAT participants. Although hemodynamically significant valvular disease was an exclusion criterion, interobserver agreement for MR grading is known to be ≈83%, possibly explaining the discordance between site and core laboratory assessments in these cases.38 Consistent with TOPCAT trial inclusion criteria, no cases of severe mitral stenosis, aortic regurgitation, or aortic stenosis were detected.

Several limitations of this analysis should be noted. Although centrally analyzed, a portion of the echocardiograms included

![Pie charts demonstrating the prevalence of (A) left ventricular (LV) geometry (n=875), (B) left atrial enlargement (n=836), and (C) LV diastolic dysfunction grade in the TOPCAT echocardiographic study (n=490).](http://circheartfailure.ahajournals.org/)

the largest studies to provide normal ranges for healthy community dwelling individuals without prevalent cardiovascular risk factors included only ≈100 subjects >70 years.35,36 LA enlargement, considered an integrator of LV diastolic function and dependent on LA filling pressure, was present in the majority of TOPCAT participants.

The characteristics of patients with HFpEF have varied depending on the cohort studied, due both to the inherent heterogeneity of the syndrome and the cohort-specific inclusion criteria. Within TOPCAT, we also observed echocardiographic differences based on study inclusion criteria, with more prominent markers of elevated filling pressure, including larger LAVi and higher E/A ratio, among participants enrolled on the basis of elevated BNP or NT-proBNP levels, as opposed to recent hospitalization with heart failure. These findings could help account for the greater degree of LA enlargement noted in clinical trials with a uniform entry requirement for an elevated NT-proBNP, such as PARAMOUNT and Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX).30,32 The previously noted distinctions between clinical trials and observational epidemiological studies may also reflect trial-specific inclusion and exclusion criteria and inclusion of a broader range of patients, possibly with more comorbidities, in the observational studies.

Concomitant pulmonary hypertension is a risk factor for adverse outcomes in HFpEF.20 We found Doppler evidence of pulmonary hypertension in 36% of patients, likely consistent with findings from other HFpEF trials.7,30,32 At least moderate pulmonary hypertension, defined as a peak TR velocity of ≥3.5 m/s, was present in 8%. Concordant with data from the Olmsted County cohort, estimated pulmonary artery systolic pressure was significantly associated with E/E′ ratio as an index of LV filling pressure.20 Previous studies, however, have not assessed PVR in HFpEF. In the smaller subgroup of our participants in whom PVR could be estimated noninvasively, PVR was elevated in ≈11%. Relatively little is also known about RV performance in HFpEF. Gross RV dysfunction, based on the FAC, was uncommon. However, although guideline documents define abnormal RV FAC as <0.35,17 studies in heart failure with reduced EF have demonstrated the prognostic relevance of RV FAC <0.40,37 which was present in 11% of participants.

Limited data exists regarding the prevalence and prognostic implication of valvular disease in HFpEF. Most clinical trials and observational studies have excluded individuals with significant mitral or aortic valve disease from HFpEF studies. Of 619 HFpEF patients in the New York Heart Failure Registry, moderate-to-severe or greater degrees of MR was present in 10%.25 Similarly, in the Northwestern HFpEF Registry, moderate MR was noted in ≈14% of patients.27 Consistent with these findings, moderate or greater MR was noted in 12% of TOPCAT participants. Although hemodynamically significant valvular disease was an exclusion criterion, interobserver agreement for MR grading is known to be ≈83%, possibly explaining the discordance between site and core laboratory assessments in these cases.38 Consistent with TOPCAT trial inclusion criteria, no cases of severe mitral stenosis, aortic regurgitation, or aortic stenosis were detected.

Several limitations of this analysis should be noted. Although centrally analyzed, a portion of the echocardiograms included

![Pie charts demonstrating the prevalence of (A) left ventricular (LV) geometry (n=875), (B) left atrial enlargement (n=836), and (C) LV diastolic dysfunction grade in the TOPCAT echocardiographic study (n=490).](http://circheartfailure.ahajournals.org/)
in this analysis were clinical echocardiograms not obtained by a prespecified protocol and could have been performed within 6 months of randomization, which may introduce variability into measurements. Because of this, certain echocardiographic views or measures, particularly Doppler measures, were missing in a large proportion of patients. In addition, although the study protocol precluded intercurrent myocardial infarction, we cannot exclude that cardiac structure and function may have changed for other reasons during this period. Compared with TOPCAT participants not included in the echocardiographic study, those included differed in some baseline characteristics, which, although relatively minor, may limit the generalizability of these findings. Finally, clinical trials by necessity impose inclusion and exclusion criteria, and therefore these findings may not be generalizable to community-based cohorts.

Conclusions
Echocardiographic findings from the 935 patients enrolled in TOPCAT demonstrate a high prevalence of concentric LV remodeling and hypertrophy, LA enlargement, and pulmonary
hypertension. In the context of existing epidemiological and clinical trial studies, these findings suggest that the TOPCAT participants represent a particularly high-risk group within the HFpEF syndrome. Similar to other published HFpEF trials, diastolic function was normal in approximately one third, highlighting the heterogeneity of the cardiac phenotype in this syndrome.

Sources of Funding

TOPCAT was funded by the National Institutes of Health’s National Heart, Lung, and Blood Institute (NHLBI), Bethesda, MD, grant N01 HC45207. The work for this article was also supported by NHLBI grant 1K08HL116792-01A1 (to A.M.S.).

Disclosures

None.

References

Table 5. Cardiac Structure and Function in TOPCAT Compared With Select HFpEF Clinical Trials Enrolling $\geq 100$ Patients

<table>
<thead>
<tr>
<th></th>
<th>TOPCAT</th>
<th>PARAMOUNT$^{(a)}$</th>
<th>Aldo-DHF$^{(b)}$</th>
<th>RELAX$^{(c)}$</th>
<th>I-PRESERVE$^{(d)}$</th>
<th>CHARMES$^{(e)}$</th>
<th>PEP-CHF$^{(f)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>935</td>
<td>292</td>
<td>422</td>
<td>216</td>
<td>745</td>
<td>312</td>
<td>850</td>
</tr>
</tbody>
</table>

Key inclusion criteria

- LVEF $\geq 45\%$, heart failure hospitalization or BNP $\geq 100$, or NT-proBNP $\geq 360$ pg/mL

| Age, y          | 69.9±9.7$^*$ | 70.6±9.1 | 67±8  | 69 (62–77) | 72±7             | 66±11           | 75 (72–79)       |

Women

- 49%$^*$ | 56% | 52% | 48% | 62% | 34% | 56%$^*$ |

LV structure

- EDD, cm | 4.80±0.58 | 4.64±0.48 | 4.65±0.62 | 4.6 (4.3–5.1)$^*$ | 4.8±0.6 | 5.4±0.7$^*$ | 4.6 (4.2–5.1)$^*$ |
- ESD, cm | 3.37±0.51 | 2.99±0.70 | 2.55±0.64 | NA | 3.2±0.7 | 3.6±0.7$^*$ | NA |
- EDVI, mL/m$^2$ | 49.9±15.5 | 61.4±15.4 | NA | NA | 49±14 | NA | NA |
- ESVI, mL/m$^2$ | 20.7±9.8 | 26.5±10.4 | NA | NA | 18±9 | NA | NA |
- MWT, cm | 1.18±0.20 | 0.91±0.16 | NA | NA | 0.93±0.15 | NA | 1.3 (1.2–1.5)$^*$ |
- LV mass, g | 223±71 | 148±43 | NA | NA | 164±48 | 237±91$^*$ | NA |
- LVMI, g/m$^2$ | 111±31 | 79.1±22.2 | 109±28 | 78 (62–94)$^*$ | NA | 117±42$^*$ | NA |

Hypertrophy

- 52% | 14% | NA | 48%$^*$ | 29% | NA | NA |

Concentric form of remodeling

- 77% | 21% | NA | 46%$^*$ | 54% | NA | NA |

LV geometry

Normal

- 14% | 72% | NA | NA | 46% | NA | NA |

Concentric remodeling

- 34% | 14% | NA | NA | 25% | NA | NA |

Concentric hypertrophy

- 43% | 7% | NA | NA | 29% | NA | NA |

Eccentric hypertrophy

- 9% | 7% | NA | NA | 0% | NA | NA |

LV systolic function

EF, % | 59.6±8.0 | 57.7±7.9 | 67±8 | 60 (56–65)$^*$ | 64±9 | 50 (18–65)$^*$ | 65 (56–66)$^*$ |

LV diastolic function

LAVi, mL/m$^2$ | 29.8±12.5 | 35.9±13.5 | 28±8.4 | 44 (36–59)$^*$ | NA | 41.3±14.7$^*$ | NA |

LA area, cm$^2$ | 19.6±5.2 | 21±5 | NA | NA | NA | NA | NA |

LA diameter, cm | 4.3±0.6 | 3.7±0.5 | NA | NA | NA | NA | 4.5 (4.1–4.8)$^*$ |

E/A ratio | 1.2±0.7 | 1.1±0.62 | 0.9±0.33 | 1.5 (1.0–2.1)$^*$ | 1.05±0.74 | 1.1±0.7$^*$ | 0.7 (0.6–0.9)$^*$ |

TDI E’ septal, cm/s | 6.1±2.2 | 5.8±2.0 | 5.9±1.3 | 6 (5–8)$^*$ | 7.2±2.9 | NA | NA |

TDI E’ lateral, cm/s | 8.2±3.2 | 7.5±2.8 | NA | NA | 9.1±3.4 | NA | NA |

E/E’ ratio (septal) | 15.6±6.8 | 15.9±7.3 | 12.8±4.0 | 16 (11–24)$^*$ | NA | NA | NA |

E/E’ ratio (lateral) | 11.8±5.9 | 12.7±7.4 | NA | NA | 10.2±4.5 | NA | NA |

Diastolic dysfunction, any

- 66% | 92% | 100% | NA | 69% | 67% | NA |

None

- 34% | 8% | 0% | NA | 31% | 33% | NA |

Grade 1

- 22% | 31% | 77% | NA | 29% | 22% | NA |

Grade 2

- 34% | 43% | 21% | NA | 36% | 37% | NA |

Grade 3

- 10% | 18% | 2% | NA | 4% | 7% | NA |

Pulmonary pressure

TR velocity, m/s | 2.8±0.5 | 2.5±0.4 | NA | 41 (33–53)$^*$ (RVSP) | 37±13 (RVSP) | NA | NA |

$^*$Values were estimated from primary data provided in the referenced articles.

A-wave indicates peak late diastolic transmitral flow velocity; AF, atrial fibrillation; Aldo-DHF, Aldosterone Receptor Blockade in Diastolic Heart Failure; BNP, B-type natriuretic peptide; CHARMS, CHARM Echocardiographic Substudy; clin, clinical; DD, diastolic dysfunction; E-wave, peak early diastolic tissue velocity; E’ lateral, peak early diastolic mitral annular tissue velocity at lateral mitral annulus; E’ septal, peak early diastolic mitral annular tissue velocity at septal mitral annulus; EDD, end-diastolic dimension; EDVI, end-diastolic volume indexed to BSA; ESVI, end-systolic volume indexed to BSA; LAVI, left atrial (LA) volume indexed to BSA; LV, left ventricular (LV) ejection fraction; LVMI, LV mass index; MWT, mean wall thickness; NA, not available; NSR at echo, normal sinus rhythm at the time of echocardiography; NT-pBNP, N-terminal pro-BNP; PEP-CHF, Perindopril for Elderly People With Chronic Heart Failure; pred, predicted; pVO2, maximal oxygen consumption; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure; RVSP, right ventricular systolic pressure; RVWT, relative wall thickness; TDI, tissue Doppler imaging; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; and TR, tricuspid regurgitation.


14. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.


**CLINICAL PERSPECTIVE**

Heart failure with preserved ejection fraction (HFpEF) is associated with substantial morbidity and mortality. Existing data on cardiac structure and function in HFpEF suggest significant heterogeneity in this population. The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial was designed to determine whether treatment with spironolactone would reduce morbidity and mortality in 3445 patients with HFpEF. In this echocardiographic substudy, we aimed to characterize the cardiac phenotype in HFpEF patients in the TOPCAT trial. Among 935 patients enrolled in TOPCAT, we found a high prevalence of structural heart disease, including concentric left ventricular (LV) remodeling, concentric hypertrophy, and left atrial (LA) enlargement. Only 7% of participants demonstrated normal LV geometry and normal LA size. Over one third of patients with measurable tricuspid regurgitation jet velocity demonstrated evidence of pulmonary hypertension. Each of these echocardiographic characteristics has been associated with an increased risk of adverse outcomes in HFpEF. Diastolic function was normal in approximately one third of evaluable participants, highlighting the heterogeneity of the cardiac phenotype in this syndrome. These findings enhance our understanding of the HFpEF population tested in TOPCAT and suggest that they may represent a particularly high-risk group within HFpEF syndrome.
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. published online November 18, 2013;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/early/2013/11/18/CIRCHEARTFAILURE.113.000887

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/