Baseline Characteristics of Patients in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial

Shah et al: TOPCAT Baseline Characteristics

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Abstract

Background—Treatment of Preserved Cardiac Function with an Aldosterone Antagonist (TOPCAT) is an ongoing randomized controlled trial of spironolactone versus placebo for heart failure with preserved ejection fraction (HFpEF). We sought to describe the baseline clinical characteristics of subjects enrolled in TOPCAT relative to other contemporary observational studies and randomized clinical trials of HFpEF.

Methods and Results—Between August 2006 and January 2012, 3445 patients with symptomatic HFpEF from 270 sites in 6 countries were enrolled in TOPCAT. At the baseline study visit, all subjects provided a detailed medical history and underwent physical examination, electrocardiography, quality of life, and laboratory assessment. Key parameters were compared to other large, contemporary HFpEF studies. The mean age was 68.6±9.6 years with a slight female predominance (52%); mean body mass index was 32 kg/m²; and comorbidities were common. History of hypertension (91% prevalence in TOPCAT) exceeded all other major HFpEF clinical trials. However, baseline blood pressure was well controlled (129/76 mmHg; systolic blood pressure 7-16 mmHg lower than other similar trials). Other common comorbidities included coronary artery disease (57%), atrial fibrillation (35%), chronic kidney disease (38%) and diabetes (32%). Self-reported activity levels were low, quality of life scores were comparable to those reported for patients with end-stage renal disease, and the prevalence of moderate or greater depression was 27%.

Conclusions—TOPCAT subjects share many common characteristics with contemporary HFpEF cohorts. Low activity level, significantly decreased quality of life, and depression were common at baseline in TOPCAT, underscoring the continued unmet need for evidence-based treatment strategies in HFpEF.

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

Key Words: diastolic heart failure, randomized controlled trial, mineralocorticoid receptor, aldosterone, spironolactone
Heart failure with preserved ejection fraction (HFpEF), which currently represents approximately half of all HF cases, is a common clinical syndrome and a leading cause of morbidity and mortality, especially amongst the elderly.\textsuperscript{1-4} Although recent data suggest that the prevalence of HFpEF is increasing as the population ages, no evidence-based effective treatments are available.\textsuperscript{5} Epidemiologic studies and observational registries have found that patients with HFpEF are predominantly elderly and female, with a high prevalence of comorbidities including systemic hypertension, obesity, diabetes mellitus, chronic kidney disease, coronary artery disease, and atrial fibrillation.\textsuperscript{5-10} Like their counterparts with heart failure and reduced EF (HFrEF), patients with HFpEF are functionally limited and frequently require hospitalization, resulting in a generally poor quality of life.\textsuperscript{11-13}

Whereas annualized mortality rates have decreased in the last decade for patients with HFrEF, similar improvements in patient outcomes have not been observed for those with HFpEF.\textsuperscript{5,7} These differential trends may be related to the relative paucity of evidence-based treatment options for HFpEF. Thus far, clinical trials of digoxin,\textsuperscript{14} beta-blockers,\textsuperscript{15, 16} angiotensin converting enzyme (ACE)-inhibitors,\textsuperscript{17} and angiotensin receptor blockers (ARBs)\textsuperscript{18} have all failed to show a significant benefit, leaving the treatment of HFpEF largely empiric, symptom-based, and focused on comorbidities.\textsuperscript{10}

There is strong rationale for testing the impact of mineralocorticoid receptor antagonists (MRAs) such as spironolactone in HFpEF in the context of an adequately-powered, prospective randomized trial of HFpEF.\textsuperscript{19} Prior studies have demonstrated that MRAs improve clinical outcomes in patients with symptomatic HFrEF\textsuperscript{20, 21} and those with HF or left ventricular (LV) systolic dysfunction complicating myocardial infarction.\textsuperscript{22}
Small studies have suggested improvements in cardiac structure and function during treatment with MRAs in HFpEF as well as improvements in diastolic function in elderly patients, patients with hypertension, and patients with early stage chronic kidney disease.\textsuperscript{23-26} Despite these promising preliminary data,\textsuperscript{19} no prior large randomized trials have specifically evaluated the effect of an MRA on clinical outcomes in patients with HFpEF. Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Study is the first large randomized controlled trial of spironolactone versus placebo for HFpEF adequately powered to examine clinical outcomes.\textsuperscript{27} Although the inclusion and exclusion criteria were designed to select a representative sample of the larger population of patients with HFpEF, the patients enrolled in TOPCAT likely reflect a narrower spectrum of HFpEF patients than those enrolled in all-encompassing epidemiologic studies and observational registries. Therefore, our objective in the present report is to: (1) describe the baseline characteristics of the TOPCAT study participants; and (2) compare TOPCAT to recent HFpEF epidemiologic studies, observational registries, and clinical trials.

**Methods**

**TOPCAT study design and objectives**

The study objectives and study design of the TOPCAT study have been described in detail previously.\textsuperscript{27} Briefly, TOPCAT was designed as a multi-center, international, randomized, double blind, placebo-controlled trial of spironolactone in adults with HFpEF recruited from over 270 clinical sites. The trial was funded by the National Heart, Lung, and Blood Institute as a contract with the Brigham and Women’s Hospital (Clinical Coordinating Center) and the New England Research Institute (Data Coordinating Center). Enrollment began in August 2006 and
ended in January 2012. The trial duration is approximately 7 years (follow-up is currently ongoing), with a goal mean follow-up of 3.5 years. The primary aim of the TOPCAT study is to determine whether treatment with spironolactone, compared to placebo, can produce a clinically meaningful reduction in a composite outcome of cardiovascular mortality, aborted cardiac arrest, or HF hospitalization in adults with symptoms of HF and documented LVEF ≥ 45%. Secondary aims of TOPCAT include evaluation of the effect of spironolactone on clinical comorbidities (e.g., new atrial fibrillation, diabetes mellitus), all-cause mortality, and patient-reported health-related quality of life. These potential benefits will be viewed in the context of a safety evaluation afforded by the blinded comparison to placebo.

**Selection of study patients: inclusion criteria, and exclusion criteria**

Inclusion criteria for TOPCAT are as follows: age ≥ 50 years; diagnosis of HF based on at least one HF symptom at the time of study screening and at least one HF sign within the 12 months prior to screening (Table 1); LVEF ≥ 45% (per local reading), preferably obtained from echocardiography (although radionuclide ventriculography and angiography were acceptable); at least 1 HF hospitalization in the 12 months prior to study screening or B-type natriuretic peptide (BNP) > 100 pg/ml or N-terminal pro-BNP > 360 pg/ml (in the absence of an alternative explanation for elevated natriuretic peptide level) within the 60 days prior to screening; controlled systolic blood pressure (< 140 mmHg or 140-160 mmHg if the patient is taking at least 3 antihypertensive medications to control blood pressure); serum potassium < 5.0 mmol/L prior to randomization.27

There were multiple exclusion criteria for TOPCAT, as detailed previously.27 Examples of exclusion criteria include severe systemic illness with a life expectancy of less than 3 years,
significant chronic pulmonary disease, infiltrative or hypertrophic cardiomyopathy, constrictive pericarditis, prior cardiac transplant or left ventricular assist device, known chronic hepatic disease, severe chronic kidney disease, a history of significant hyperkalemia, known intolerance to aldosterone antagonists, and recent myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention.

**Baseline data**

Each patient enrolled in the TOPCAT study underwent a detailed baseline visit, that included medical history (based on patient self-report and chart review). The following medical history variables were collected: prior hospitalization for HF, myocardial infarction, stroke, coronary artery bypass surgery, percutaneous coronary intervention, angina pectoris, chronic obstructive pulmonary disease, asthma, hypertension, peripheral arterial disease, dyslipidemia, defibrillator, pacemaker, atrial fibrillation, thyroid disease, diabetes mellitus (including type of diabetes and presence of known microvascular complications), and bone fracture after the age of 45 years. Social history variables collected by self-report included smoking history, alcohol intake, activity level (pattern of exercise), pattern of nutrition, and living situation. Physical activity was computed as metabolic equivalents per week using the duration per week of various forms of self-reported exercise, weighting each activity by its intensity level.28 All medications were also documented at the time of the baseline study visit.

Physical examination and laboratory data collected at baseline included heart rate, blood pressure, height, weight, waist circumference, electrolytes, blood urea nitrogen, creatinine, liver function tests, complete blood count, and urine microalbumin. Natriuretic peptide levels were recorded in the subset of patients who were recruited on the basis of elevated natriuretic peptide
levels. Other baseline examinations included a resting 12-lead electrocardiogram (interpreted locally at each site by the site principal investigator) and health-related quality of life and functional status questionnaires. The latter included the Kansas City Cardiomyopathy Questionnaire (KCCQ), the EuroQOL EQ-5D Visual Analog Scale, and the Patient Health Questionnaire-9 (PHQ-9; a depression scale). The range of possible scores on the KCCQ and EQ5D is 0 to 100, and lower scores indicate a worse quality of life. The range of possible scores on the PHQ-9 is 0 to 27, and higher scores indicate a higher number of depressive symptoms. For comparison purposes, Minnesota Living with Heart Failure Questionnaire scores from prior HFP EF studies were converted to estimated KCCQ scores based on data from the original study describing the KCCQ.

Results

Enrollment of TOPCAT study participants

The first TOPCAT study patient was enrolled on August 10, 2006, and enrollment concluded on January 31, 2012 with a total of 3445 subjects from 270 active clinical sites worldwide. Of the 270 sites, 155 were in the United States (subjects enrolled [N]=1151 [33% of subjects]), 36 were in Russia (N=1066 [31%]), 9 were in the Republic of Georgia (N=612 [18%]), 35 were in Canada (N=326 [9%]), 17 were in Brazil (N=167 [5%]), and 18 were in Argentina (N=123 [4%]). Of the 3,445 subjects enrolled, 2480 (72%) met the eligibility criterion for HF hospitalization within the past year, and the remaining 965 (28%) were eligible by elevated natriuretic peptide levels. Table 2 displays the baseline evidence of heart failure (symptoms, signs, natriuretic peptide levels) and ejection fraction for the study participants. Dyspnea with mild or moderate exertion was the most common symptom present in the study participants (>
99% frequency at time of randomization or within the prior year); lower extremity edema was the most common sign of HF. At the time of enrollment, most patients had New York Heart Association (NYHA) class II (63%) or III (33%) symptoms (Table 2).

**Baseline demographics, comorbidities, medications, and lifestyle factors**

In TOPCAT, there was a slight female predominance (52%) and mean age was 68.6±9.6 years (Table 3). Overall, 89% of the study subjects were white, 9% were of African origin, and 9% were Hispanic. In the United States, 23% of the study subjects were of African origin. As shown in Tables 3 and 4, study patients were typically obese, and comorbidities were common. The frequency of hypertension history was especially high (91%) in study participants. Blood pressure was well controlled at time of study enrollment (mean 129/76 mmHg, median 130/80 mmHg, and interquartile range 120-140/70-80 mmHg).

The majority of patients (82%) were taking diuretics at the time of enrollment. In addition, use of beta-blockers (78%) and ACE-inhibitors /ARBs (84%) was also very common, indicating that the majority of TOPCAT patients were already treated with antagonists of the renin/angiotensin system. Evaluation of lifestyle factors revealed that the majority of patients enrolled reported living with others in the household and eating home-cooked meals. Most study participants were adding salt to cooked meals, and overall activity level was low (median 9.3 metabolic equivalent [MET]-hours/week).

**Baseline laboratory and electrocardiographic data**

In the 28% of TOPCAT study subjects who were enrolled in the study through the elevated natriuretic peptide inclusion criterion, median BNP and NT-proBNP levels were 234 pg/ml and
950 pg/ml, respectively. Although patients with severe chronic kidney disease (estimated glomerular filtration rate < 30 ml/min/1.73m²) were excluded from TOPCAT, the prevalence of chronic kidney disease was high (39% had stage 3 or worse chronic kidney disease, defined as eGFR < 60/ml/min/1.73m²), and the majority of TOPCAT participants had evidence of microalbuminuria. The majority of patients had a normal heart rate and QRS duration on the baseline electrocardiogram; however, most (74%) had one or more electrocardiographic abnormalities (Table 4).

**Baseline quality of life**

The median KCCQ clinical summary score was 54, and the median EQ-5D Visual Analog Scale score was 60. Results from the PHQ-9 indicated that approximately 27% of the TOPCAT study subjects endorsed symptoms of moderate or greater depression (Table 5).

**Comparison to prior HFpEF clinical trials and observational studies**

Overall, characteristics of TOPCAT participants were similar to those reported in recent clinical trials (Table 6). TOPCAT exceeded all other trials in frequency of hypertension history (91%), but mean systolic blood pressure was 7-16 mmHg lower compared to prior HFpEF trials. Mean BMI was higher than in all other clinical trials and observational studies with available BMI data. Compared with prior observational studies (Table 7), TOPCAT participants were younger (though still elderly with a mean age of 69 years) and less commonly women but had higher prevalence of hypertension and coronary artery disease.
Discussion

TOPCAT is the first large, randomized trial of treatment with an MRA in HFpEF. As expected in a trial population, the baseline characteristics of HFpEF participants selected for enrollment in TOPCAT were not exactly matched to those of epidemiologic and observational studies. Nevertheless, TOPCAT participants display several features that are typical of the broader population with HFpEF. Namely, the mean age of patients enrolled in TOPCAT was 68.6 years at baseline, with a female predominance and a very high prevalence of multiple comorbidities, especially a history of systemic hypertension. TOPCAT participants were selected to be at high risk for adverse outcomes, with greater than 70% hospitalized for HF within the 12 months prior to enrollment and the rest with relatively high natriuretic peptide levels. Although the majority of patients had NYHA functional class II symptoms, quality of life scores were quite poor, with a high prevalence of depressive symptoms. In addition, self-reported physical activity was very low (median 9 MET-hours/week) and the majority of participants were still adding salt to home-cooked meals despite carrying a heart failure diagnosis. Thus, the TOPCAT participants mirror the typical challenges of HFpEF.

The baseline characteristics of TOPCAT participants were as expected when taken in the context of a clinical trial setting which excluded patients with specific competing comorbidities (such as significant chronic lung disease), or drug-specific exclusion criteria (e.g., significant chronic kidney disease). Thus, the observed baseline characteristics reflect the clinical trial setting superimposed on the epidemiology of HFpEF. Despite these limitations, it is notable that the prevalence of comorbidities was very high and almost universal in the study subjects.

A relatively large proportion of patients of African origin (9% overall and 23% in the United States) were enrolled in TOPCAT, a proportion much higher than in recent HFpEF
clinical trials (2% and 4% in I-PRESERVE\textsuperscript{34} and CHARM-Preserved\textsuperscript{18}, respectively) and prior trials of eplerenone in HFrEF (1% and 2% in EPHESUS\textsuperscript{22} and EMPHASIS-HF,\textsuperscript{21} respectively), but lower than a prior trial of spironolactone in HFrEF (13.5% in RALES\textsuperscript{20}). The enrollment of patients of African origin is especially important in clinical trials of MRAs, given data showing higher aldosterone levels in hypertensive individuals of African ancestry.\textsuperscript{37}

Comparison of TOPCAT to contemporary HFpEF clinical trials and observational studies

Compared to prior large HFpEF clinical trials, characteristics of TOPCAT participants were generally similar with some notable differences (Table 6) which may be in part related to differences in study design. Both I-PRESERVE (irbesartan vs. placebo)\textsuperscript{33,34} and TOPCAT included only those patients with HF and LVEF \( \geq 45\% \). However, I-PRESERVE required more recent hospitalization (within the 6 months prior to enrollment vs. within the prior 12 months in TOPCAT) or more symptomatic HF (NYHA class III or IV with abnormal objective testing on chest x-ray, electrocardiogram, or echocardiogram). Enrollment criteria for DIG-PEF (digoxin vs. placebo),\textsuperscript{14} CHARM-Preserved (candesartan vs. placebo),\textsuperscript{18} and PEP-CHF (perindopril vs. placebo)\textsuperscript{17} were based primarily on clinical symptoms at time of enrollment and/or prior cardiovascular hospitalization, with less reliance on prior HF hospitalization compared to I-PRESERVE and TOPCAT. In addition, the minimum LVEF in CHARM-Preserved and PEP-CHF of \( > 40\% \) was more liberal, raising the possibility that some patients in those trials had primarily HFrEF physiology.

On review of clinical characteristics, there are also important differences between TOPCAT and epidemiologic/observational HFpEF studies. As stated previously, TOPCAT study patients were younger and had less of a female predominance than these prior observational
studies. However, TOPCAT is one of the few HF clinical trials which contains a majority of female patients. Overall, the frequencies of several comorbidities were similar to prior large observational studies. Prevalence of systemic hypertension history was strikingly high (91%) in TOPCAT, but blood pressure was well controlled at baseline, which reflects the requirement of a controlled blood pressure in TOPCAT. This was a key eligibility criterion for TOPCAT, given the desire to determine whether spironolactone was beneficial in HFpEF independent of its effects on blood pressure. Indeed, if the TOPCAT data are interpreted in the context of a large trial of antihypertensive agents, the difference in systolic blood pressure in TOPCAT versus other HFpEF clinical trials suggests that TOPCAT participants were on the equivalent of 1-2 additional antihypertensive agents.

Renal function in TOPCAT, while similar to other HFpEF clinical trials, was better than some observational studies of HFpEF (Table 7). This likely has to do with the exclusion of patients with severe chronic kidney disease (GFR < 30 ml/min/1.73 m²) in TOPCAT, as well as the differences in setting (i.e, the studies with the highest creatinine levels, such as ADHERE, enrolled inpatients with HFpEF, whereas TOPCAT patients were enrolled as outpatients).

Based on differences in enrollment criteria, NT-proBNP levels were much lower in I-PRESERVE (median 339 pg/ml) where they were measured at baseline for all participants compared to levels in the subset of TOPCAT patients who met eligibility criteria due to elevated baseline levels (median 950 pg/ml). However, I-PRESERVE subjects had higher NYHA functional class (79% NYHA class III or IV in I-PRESERVE compared to only 34% NYHA class III or IV in TOPCAT).
Health-related quality of life

The baseline data on self-reported activity level, quality of life, and depressive symptoms in TOPCAT paint a bleak picture of the HFpEF patient population and underscore the urgent need for new therapies to enhance the quality of life in these sick patients with multiple debilitating comorbidities. The KCCQ score in TOPCAT was lower than that of patients with HFrEF, where the median KCCQ score is typically in the mid 60s.²⁹ As a comparison, NYHA class IV patients undergoing left ventricular assist device placement typically have a median score of approximately 35.⁴⁰ On Visual Analog Scale testing, the median score was 60, which is similar to the quality of life score for patients with end-stage renal disease.⁴¹ This last statistic is quite sobering; the fact that the sickest and most frail HFpEF patients (including those with more severe chronic kidney disease) were excluded from TOPCAT suggests that quality of life in HFpEF patients in the community may in fact be worse than in dialysis patients. Thus, it is not surprising that over one-quarter of TOPCAT participants reported moderate or greater depression, as noted on the PHQ-9 questionnaire.

Health-related quality of life in HFpEF patients has been previously reported in the CHARM-Preserved and I-PRESERVE trials.¹³,³² In both CHARM and I-PRESERVE, the quality of life was studied using the Minnesota Living with Heart Failure questionnaire (MLHFQ; mean score in CHARM-Preserved = 41; mean score in I-PRESERVE = 43). Although the KCCQ is not directly comparable to MLHFQ, based on data from the original KCCQ development study,²⁹ which examined patients with HF and included MLHFQ testing, the mean KCCQ summary score in TOPCAT of 55 may indicate an even worse health-related quality of life than in CHARM-Preserved and I-PRESERVE.
**Strengths and limitations**

The strengths of TOPCAT include the large number of patients with evidence of HF and documented preserved LVEF, their advanced age and multiple comorbidities, the wealth of baseline data collected to help inform the use of spironolactone in HFpEF patients, and the breadth of quality of life data. Despite these strengths, certain limitations should be taken into consideration when interpreting the baseline TOPCAT data. Due to the TOPCAT study design and funding, detailed screening logs and data on screen failures were not recorded. Thus, we cannot determine how the TOPCAT study patients differed from those patients with HFpEF who did not enroll in the study. In addition, the inclusion criteria for TOPCAT were quite broad and required only signs and symptoms of HF with a preserved ejection fraction in the setting of a prior HF hospitalization or elevated natriuretic peptide level. However, despite the broad inclusion criteria, patients enrolled in TOPCAT were quite similar to those identified in contemporary HFpEF studies. Nevertheless, we are not able to compare severity of comorbidities between TOPCAT and other HFpEF trials/studies, and there may be differences among the HFpEF trials/studies for variables that were not collected or reported. Finally, some of the comparison studies\(^7\-9\) were observational registries of inpatients admitted with acute HFpEF and therefore differ from TOPCAT, which was conducted in the outpatient setting.

**Conclusions**

The TOPCAT study successfully enrolled a large number of participants with HFpEF with baseline characteristics that, for the most part, are similar to contemporary epidemiologic and observational registry studies of such individuals. Older age, multiple comorbidities, low activity level, significantly decreased quality of life, and depression were common in HFpEF patients
enrolled in TOPCAT; these data underscore the continued pressing need to find evidence-based therapies for patients with HFpEF.

Sources of Funding

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Disclosures

None.

References


8. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated
heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol.* 2006;47:76-84.


Table 1. Criteria for diagnosing heart failure in the TOPCAT study

<table>
<thead>
<tr>
<th>Symptoms (at least one present at time of screening)</th>
<th>Signs (at least one in the past 12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Paroxysmal nocturnal dyspnea</td>
<td>• Any rales post cough</td>
</tr>
<tr>
<td>• Orthopnea</td>
<td>• Jugular venous pressure $\geq 10$ cm H$_2$O</td>
</tr>
<tr>
<td>• Dyspnea on mild or moderate exertion</td>
<td>• Lower extremity edema</td>
</tr>
<tr>
<td></td>
<td>• Chest radiography demonstrating pleural effusion, pulmonary congestion, or cardiomegaly</td>
</tr>
</tbody>
</table>
Table 2. Baseline evidence of heart failure and preserved ejection fraction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Present at screening</th>
<th>Experienced in past year or present at screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure symptoms, n/N(%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Paroxysmal nocturnal dyspnea</td>
<td>409/3394 (12)</td>
<td>1140/3139 (36)</td>
</tr>
<tr>
<td>• Orthopnea</td>
<td>729/3410 (21)</td>
<td>1475/3243 (45)</td>
</tr>
<tr>
<td>• Dyspnea on mild or moderate exertion</td>
<td>3406/3443 (99)</td>
<td>3427/3434 (&gt;99)</td>
</tr>
<tr>
<td>Heart failure signs, n/N(%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Any rales post cough</td>
<td>521/3400 (15)</td>
<td>1538/2739 (56)</td>
</tr>
<tr>
<td>• Jugular venous pressure ≥ 10 cm H₂O</td>
<td>308/1744 (18)</td>
<td>605/1330 (45)</td>
</tr>
<tr>
<td>• Lower extremity edema</td>
<td>2067/3438 (60)</td>
<td>2832/3371 (84)</td>
</tr>
<tr>
<td>• Chest radiography demonstrating pleural effusion, pulmonary congestion, or cardiomegaly</td>
<td>482/1748 (28)</td>
<td>1659/2195 (76)</td>
</tr>
<tr>
<td>New York Heart Association functional class, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Class I</td>
<td>109 (3)</td>
<td>—</td>
</tr>
<tr>
<td>• Class II</td>
<td>2193 (63)</td>
<td>—</td>
</tr>
<tr>
<td>• Class III</td>
<td>1122 (33)</td>
<td>—</td>
</tr>
<tr>
<td>• Class IV</td>
<td>15 (&lt;1)</td>
<td>—</td>
</tr>
<tr>
<td>Natriuretic peptide levels used for eligibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• B-type natriuretic peptide (BNP), pg/ml (N=466)</td>
<td>234.0 (145.0, 398.0)**</td>
<td>—</td>
</tr>
<tr>
<td>• N-terminal pro-BNP, pg/ml (N=403)</td>
<td>950.0 (588.0, 1920.0)**</td>
<td>—</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>57.1±7.4</td>
<td>—</td>
</tr>
</tbody>
</table>

Values for continuous variables represent mean±SD unless otherwise specified.
*For heart failure symptoms and signs, case report forms included the options ‘yes’, ‘no’, and ‘unknown’; frequencies shown in table reflect proportion of study participants who had available data (either ‘yes’ or ‘no’ answer, with ‘unknown’ excluded).
**Median (25th, 75th percentile)
Table 3. Baseline demographics, comorbidities, medications, and lifestyle factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=3445</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.6±9.6</td>
</tr>
<tr>
<td>Female gender, n(%)</td>
<td>1775(52)</td>
</tr>
<tr>
<td>Race/ethnicity*, n(%)</td>
<td></td>
</tr>
<tr>
<td>- Native American/Alaskan native</td>
<td>10(&lt;1)</td>
</tr>
<tr>
<td>- Asian</td>
<td>19(1)</td>
</tr>
<tr>
<td>- Black/African American</td>
<td>302(9)</td>
</tr>
<tr>
<td>- Hispanic</td>
<td>321(9)</td>
</tr>
<tr>
<td>- Native Hawaiian/Other Pacific Islander</td>
<td>1(&lt;1)</td>
</tr>
<tr>
<td>- White</td>
<td>3062(89)</td>
</tr>
<tr>
<td>- Other</td>
<td>70(2)</td>
</tr>
<tr>
<td>Comorbidities, n(%)</td>
<td></td>
</tr>
<tr>
<td>- Hypertension</td>
<td>3147(91)</td>
</tr>
<tr>
<td>- Myocardial infarction</td>
<td>893(26)</td>
</tr>
<tr>
<td>- Percutaneous coronary intervention</td>
<td>500(15)</td>
</tr>
<tr>
<td>- Coronary artery bypass grafting</td>
<td>443(13)</td>
</tr>
<tr>
<td>- Angina pectoris**</td>
<td>1613(47)</td>
</tr>
<tr>
<td>- Coronary artery disease**</td>
<td>2023(59)</td>
</tr>
<tr>
<td>- Atrial fibrillation</td>
<td>213(6)</td>
</tr>
<tr>
<td>- Pacemaker</td>
<td>269(8)</td>
</tr>
<tr>
<td>- Implanted cardioverter-defibrillator</td>
<td>44(1)</td>
</tr>
<tr>
<td>- Diabetes mellitus</td>
<td>1114(32)</td>
</tr>
<tr>
<td>- Chronic kidney disease</td>
<td>1332(39)</td>
</tr>
<tr>
<td>- Obesity</td>
<td>1902(55)</td>
</tr>
<tr>
<td>- Dyslipidemia</td>
<td>2073(60)</td>
</tr>
<tr>
<td>- Chronic obstructive pulmonary disease</td>
<td>403(12)</td>
</tr>
<tr>
<td>- Asthma</td>
<td>223(6)</td>
</tr>
<tr>
<td>- Stroke</td>
<td>265(8)</td>
</tr>
<tr>
<td>- Peripheral arterial disease</td>
<td>319(9)</td>
</tr>
<tr>
<td>- Thyroid disease</td>
<td>540(16)</td>
</tr>
<tr>
<td>- Bone fracture</td>
<td>380(11)</td>
</tr>
<tr>
<td>Medications, n(%)</td>
<td></td>
</tr>
<tr>
<td>- Diuretic</td>
<td>2817(82)</td>
</tr>
<tr>
<td>- Angiotensin converting enzyme inhibitor (ACE-I)</td>
<td>2251(65)</td>
</tr>
<tr>
<td>- Angiotensin receptor blocker (ARB)</td>
<td>688(20)</td>
</tr>
<tr>
<td>- ACE-I or ARB</td>
<td>2889(84)</td>
</tr>
<tr>
<td>- Beta-blocker</td>
<td>2676(78)</td>
</tr>
<tr>
<td>- Calcium channel blocker</td>
<td>1295(38)</td>
</tr>
<tr>
<td>- Hypoglycemic agent</td>
<td>963(28)</td>
</tr>
<tr>
<td>- Aspirin</td>
<td>2250(65)</td>
</tr>
<tr>
<td>- Statin</td>
<td>1817(53)</td>
</tr>
<tr>
<td>- Warfarin</td>
<td>791(23)</td>
</tr>
<tr>
<td>- Long-acting nitrate</td>
<td>501(15)</td>
</tr>
<tr>
<td>- Other cardiovascular medication</td>
<td>1542(45)</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td></td>
</tr>
<tr>
<td>Smoking, n(%)</td>
<td></td>
</tr>
<tr>
<td>- Current</td>
<td>360(10)</td>
</tr>
<tr>
<td>- Past</td>
<td>1268(37)</td>
</tr>
<tr>
<td>- Never</td>
<td>1813(53)</td>
</tr>
<tr>
<td>Alcohol drinks in the past week, n(%)</td>
<td></td>
</tr>
<tr>
<td>- 0</td>
<td>2681(78)</td>
</tr>
<tr>
<td>- 1-4</td>
<td>580(17)</td>
</tr>
<tr>
<td>Activity level (MET-hours/week)</td>
<td>126(4)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>5-10</td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>42(1)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>10(&lt;1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cooking salt score†</th>
<th>4.0 (0.0, 8.0)‡</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Home meals, n(%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost none</td>
<td>164(5)</td>
</tr>
<tr>
<td>25%</td>
<td>115(3)</td>
</tr>
<tr>
<td>50%</td>
<td>264(8)</td>
</tr>
<tr>
<td>75%</td>
<td>513(15)</td>
</tr>
<tr>
<td>Almost all</td>
<td>2371(69)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Living situation, n(%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently living alone</td>
<td>782(23)</td>
</tr>
<tr>
<td>Currently living with a spouse or significant other</td>
<td>2321(67)</td>
</tr>
<tr>
<td>Currently living with someone other than spouse or significant other</td>
<td>335(10)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7(&lt;1)</td>
</tr>
</tbody>
</table>

Values for continuous variables represent mean±SD unless otherwise specified; MET = metabolic equivalent

*Participants could mark ‘Yes’ for more than one race/ethnicity

**Coronary artery disease = prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or angina pectoris (which referred to a history of angina; the symptom of angina at time of enrollment was not recorded)

†Cooking salt score = sum of salt added to staple foods, soup, meat and vegetables during cooking. Range is 0-12 (None=0, 1/8 tsp=1, ¼ tsp=2, ½ tsp or more=3 for each food category).

‡Median (25th, 75th percentile)
Table 4. Baseline physical examination, laboratory, and electrocardiographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=3445</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>- Weight, kg</td>
<td>89.7±22.1</td>
</tr>
<tr>
<td>- Height, cm</td>
<td>167.0±10.2</td>
</tr>
<tr>
<td>- Waist circumference, cm</td>
<td>105.0±16.8</td>
</tr>
<tr>
<td>- Body-mass index, kg/m²</td>
<td>32.1±7.3</td>
</tr>
<tr>
<td>- Heart rate, beats/min</td>
<td>69.1±10.4</td>
</tr>
<tr>
<td>- Systolic blood pressure, mmHg</td>
<td>129.2±14.0</td>
</tr>
<tr>
<td>- Diastolic blood pressure, mmHg</td>
<td>75.8±10.6</td>
</tr>
<tr>
<td><strong>Electrolytes, renal function, and glucose</strong></td>
<td></td>
</tr>
<tr>
<td>- Sodium, mEq/L</td>
<td>141.2±4.2</td>
</tr>
<tr>
<td>- Potassium, mEq/L</td>
<td>4.3±0.4</td>
</tr>
<tr>
<td>- Chloride, mEq/L</td>
<td>102.6±5.2</td>
</tr>
<tr>
<td>- Bicarbonate, mEq/L</td>
<td>28.3±3.6</td>
</tr>
<tr>
<td>- Blood urea nitrogen, mg/dl</td>
<td>21.3±11.3</td>
</tr>
<tr>
<td>- Creatinine, mg/dl</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>- Estimated glomerular filtrate rate, ml/min/1.73m²</td>
<td>67.7±20.1</td>
</tr>
<tr>
<td>- Urine microalbumin (mg/g creatinine)</td>
<td>20.0 (7.0, 88.4)*</td>
</tr>
<tr>
<td>- Fasting blood glucose, mg/dl</td>
<td>109.6±38.0</td>
</tr>
<tr>
<td>- Random blood glucose, mg/dl</td>
<td>126.0±59.8</td>
</tr>
<tr>
<td><strong>Complete blood count</strong></td>
<td></td>
</tr>
<tr>
<td>- White blood cells, K/μl</td>
<td>7.0±2.2</td>
</tr>
<tr>
<td>- Hemoglobin, g/dl</td>
<td>13.3±1.7</td>
</tr>
<tr>
<td>- Hematocrit, %</td>
<td>40.1±5.1</td>
</tr>
<tr>
<td>- Platelets, K/μl</td>
<td>231.5±66.6</td>
</tr>
<tr>
<td><strong>Liver function tests</strong></td>
<td></td>
</tr>
<tr>
<td>- Alanine transaminase (ALT), U/L</td>
<td>25.2±14.4</td>
</tr>
<tr>
<td>- Aspartate transaminase (AST), U/L</td>
<td>25.4±12.7</td>
</tr>
<tr>
<td>- Alkaline phosphatase, U/L</td>
<td>105.7±59.2</td>
</tr>
<tr>
<td>- Total bilirubin, mg/dl</td>
<td>0.6 (0.5, 0.9)*</td>
</tr>
<tr>
<td>- Albumin, g/dl</td>
<td>4.2±1.4</td>
</tr>
<tr>
<td><strong>Electrocardiography</strong></td>
<td></td>
</tr>
<tr>
<td>- Heart rate, beats/min</td>
<td>68.1±11.9</td>
</tr>
<tr>
<td>- QRS duration, msec</td>
<td>99.6±28.3</td>
</tr>
<tr>
<td>- Abnormal electrocardiogram, n(%)</td>
<td>2541(74)</td>
</tr>
<tr>
<td>- Abnormalities present on electrocardiogram, n(%)</td>
<td></td>
</tr>
<tr>
<td>- Atrial fibrillation/flutter</td>
<td>702(28)</td>
</tr>
<tr>
<td>- Right bundle branch block</td>
<td>287(11)</td>
</tr>
<tr>
<td>- Left bundle branch block</td>
<td>204(8)</td>
</tr>
<tr>
<td>- Intraventricular conduction delay</td>
<td>109(4)</td>
</tr>
<tr>
<td>- Ventricular paced rhythm</td>
<td>182(7)</td>
</tr>
<tr>
<td>- Pathological Q waves</td>
<td>399(16)</td>
</tr>
<tr>
<td>- Left ventricular hypertrophy</td>
<td>742(29)</td>
</tr>
<tr>
<td>- Other abnormality</td>
<td>1304 (51)</td>
</tr>
</tbody>
</table>

Values represent means±SD unless otherwise specified;
*Median (25th, 75th percentile)
**All electrocardiograms were interpreted locally by the site principal investigator, and data were entered into a standardized electrocardiogram abstraction form. TOPCAT did not require investigators to input specific criteria for electrocardiogram diagnoses such as left ventricular hypertrophy.
Table 5. Baseline quality of life

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>N=3445</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kansas City Cardiomyopathy Questionnaire, overall summary score</td>
<td>54.8±20.5</td>
</tr>
<tr>
<td>EQ5D</td>
<td>60.3±17.4</td>
</tr>
<tr>
<td>PHQ, n(%)*</td>
<td></td>
</tr>
<tr>
<td>• Minimal symptoms (0-4 points)</td>
<td>632(44)</td>
</tr>
<tr>
<td>• Mild symptoms (5-9 points)</td>
<td>417(29)</td>
</tr>
<tr>
<td>• Moderate depression (10-14 points)</td>
<td>227(16)</td>
</tr>
<tr>
<td>• Moderate-to-severe depression (15-19 points)</td>
<td>113(8)</td>
</tr>
<tr>
<td>• Severe depression (20-27 points)</td>
<td>42(3)</td>
</tr>
</tbody>
</table>

EQ5D = EuroQOL-5D Visual Analog Scale ; PHQ = Patient Health Questionnaire-9

*PHQ was only available in English-speaking countries (N=1431)
Table 6. Comparison of clinical characteristics and risk factors: TOPCAT vs. recent large clinical trials

<table>
<thead>
<tr>
<th>Characteristic/Risk factor</th>
<th>TOPCAT</th>
<th>I-PRESERVE</th>
<th>CHARM-Preserved</th>
<th>DIG-PEF</th>
<th>PEP-CHF</th>
<th>SENIORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (N)</td>
<td>3445</td>
<td>4133</td>
<td>3023</td>
<td>988</td>
<td>850</td>
<td>752</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69</td>
<td>72</td>
<td>67</td>
<td>67</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Women (%)</td>
<td>52</td>
<td>60</td>
<td>40</td>
<td>41</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>Hypertension history (%)</td>
<td>91</td>
<td>88</td>
<td>64</td>
<td>60</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>Coronary artery disease (%)*</td>
<td>59</td>
<td>48</td>
<td>60</td>
<td>56</td>
<td>27</td>
<td>77</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>32</td>
<td>27</td>
<td>28</td>
<td>29</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>35</td>
<td>29</td>
<td>29</td>
<td>0</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>39†</td>
<td>31⁺</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NYHA functional class (%)</td>
<td>3/63/33/3&lt;1</td>
<td>0/21/76/3</td>
<td>0/61/37/2</td>
<td>—</td>
<td>3.5/62.5/32.2</td>
<td></td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>32</td>
<td>30</td>
<td>29</td>
<td>28</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>129/76</td>
<td>136/79</td>
<td>136/78</td>
<td>138/80</td>
<td>145/83</td>
<td>—</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.1</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
<td>1.2</td>
<td>—</td>
</tr>
<tr>
<td>B-type natriuretic peptide</td>
<td>234</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>N-terminal pro-B-type natriuretic peptide (pg/ml)§</td>
<td>950</td>
<td>339</td>
<td>—</td>
<td>—</td>
<td>453; 335⁺</td>
<td>—</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>57</td>
<td>59</td>
<td>54</td>
<td>&gt;45**</td>
<td>64</td>
<td>49</td>
</tr>
</tbody>
</table>

*Includes prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or angina pectoris; **Mean ejection fraction not reported; 
†In TOPCAT, chronic kidney disease was defined as estimated glomerular filtration rate < 60 ml/min/1.73m² whereas in I-PRESERVE, chronic kidney disease diagnosis was based on chart review / patient self-report;  
§Median value; for TOPCAT, values represent data for patients who were enrolled based on natriuretic peptide data (N=466 for B-type natriuretic peptide and N=403 for N-terminal pro-B-type natriuretic peptide);  
¶Median values for the placebo and treatment arms, respectively (natriuretic peptides were only measured in a subset of patients).
Table 7. Comparison of clinical characteristics and risk factors: TOPCAT vs. recent epidemiologic studies and observational registries

<table>
<thead>
<tr>
<th>Characteristic/Risk Factor</th>
<th>TOPCAT</th>
<th>Olmstead County</th>
<th>EFFECT Study</th>
<th>Framingham</th>
<th>CHS</th>
<th>OPTIMIZE</th>
<th>ADHERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (N)</td>
<td>3445</td>
<td>2167</td>
<td>880</td>
<td>220</td>
<td>170</td>
<td>10072</td>
<td>26332</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69</td>
<td>74</td>
<td>75</td>
<td>80</td>
<td>75</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>Women (%)</td>
<td>52</td>
<td>56</td>
<td>66</td>
<td>65</td>
<td>56</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td>Hypertension history (%)</td>
<td>91</td>
<td>63</td>
<td>55</td>
<td>59</td>
<td>59</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>Coronary artery disease (%)*</td>
<td>59</td>
<td>53</td>
<td>36</td>
<td>37</td>
<td>58</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>32</td>
<td>33</td>
<td>32</td>
<td>22</td>
<td>27</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>35</td>
<td>41</td>
<td>32</td>
<td>29</td>
<td>15</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>39†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA functional class (%)</td>
<td>3/63/33/&lt;1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>32</td>
<td>30</td>
<td>27</td>
<td>156/76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>129/76</td>
<td>156/76</td>
<td>145/76</td>
<td>138/69</td>
<td>150/75</td>
<td>153/79</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.1</td>
<td>1.6</td>
<td>1.5</td>
<td>1.2</td>
<td>1.3</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)§</td>
<td>234</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-terminal pro-B-type natriuretic peptide (pg/ml)§</td>
<td>950</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>57</td>
<td>61</td>
<td>62</td>
<td>≥45**</td>
<td>≥55**</td>
<td>62</td>
<td>≥40**</td>
</tr>
</tbody>
</table>

*Includes prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or angina pectoris;

**Mean ejection fraction not reported;

†In TOPCAT, chronic kidney disease was defined as estimated glomerular filtration rate < 60 ml/min/1.73m² whereas in EFFECT, chronic kidney disease diagnosis was based on chart review

§Median value; for TOPCAT, values represent data for patients who were enrolled based on natriuretic peptide data (N=466 for B-type natriuretic peptide and N=403 for N-terminal pro-B-type natriuretic peptide)
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