JAMA Cardiology | Brief Report

Association of Natriuretic Peptides With Cardiovascular Prognosis in Heart Failure With Preserved Ejection Fraction
Secondary Analysis of the TOPCAT Randomized Clinical Trial

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IMPORTANCE Contemporary clinical trials of heart failure with preserved ejection fraction (HFpEF) apply natriuretic peptide (NP) thresholds to identify patients who are more likely to have the disease of interest and to enrich the baseline risk of the enrolled cohort.

OBJECTIVE To determine whether age, race/ethnicity, obesity, renal function, and atrial fibrillation (AF) affect the levels of NPs in HFpEF and whether the prognostic significance of NPs varies in these clinically important subgroups.

DESIGN, SETTING, AND PARTICIPANTS This secondary analysis of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT) evaluated the distribution and prognostic significance of NPs across 6 subgroups comprising 1057 adult patients (60%) in the Americas region of TOPCAT with symptomatic heart failure (HF) and a left ventricular ejection fraction of 45% or more with available NPs at baseline.

EXPOSURES Natriuretic peptides were log-transformed and standardized (expressed per 1 SD, *z* score) and assessed in 6 subgroups: age (cutoff, 70 years), black race, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared; cutoff, 30 kg/m^2), waist circumference (cutoff, 102 cm for men, 88 cm for women), estimated glomerular filtration rate (cutoff, 60 mL/min/1.73 m^2), and a history of AF.

MAIN OUTCOMES AND MEASURES Time to composite cardiovascular death, hospitalization for HF, or aborted cardiac arrest at mean (SD) 2.4-year (1.5) follow-up.

RESULTS Of 1057 participants, the mean (SD) age was 72 (10) years, 183 (17.3%) were black, the mean (SD) BMI was 33.4 (8.6) kg/m^2, the mean (SD) estimated glomerular filtration rate was 64.6 (21.8) mL/min/1.73 m^2, and 472 (45%) had a history of AF. Median B-type NP (n = 698) and N-terminal pro-B-type NP concentrations (n = 359) were 257 (interquartile range, 149-443) ng/L and 959 (interquartile range, 554-2015) ng/L, respectively. Natriuretic peptide concentrations varied by up to 0.5 SD within the 6 subgroups, being higher in older patients with nonblack race, a lower BMI, a lower waist circumference, a lower estimated glomerular filtration rate, and a history of AF. Elevated NP levels (per 1-SD increase) were independently associated with an increased risk of the primary outcome (adjusted hazard ratio, 1.36; 95% CI, 1.22-1.54; $P < .001$) consistently across all investigated subgroups (interaction $P > .05$). In TOPCAT Americas (n = 1767), 791 (45%) were enrolled based on elevated NP levels as the qualifying criterion (as opposed to a history of HF hospitalization). This proportion was 31% (93 of 302), 34% (258 of 760), and 39% (443 of 1144) for black race, younger than 70 years, and a BMI of 30 kg/m^2 or greater, respectively.

CONCLUSIONS AND RELEVANCE Natriuretic peptides remain important biomarkers of prognosis in HFpEF, even in subgroups who tend to have lower NP levels. A single, absolute NP threshold for inclusion in contemporary HFpEF trials may lead to an underrepresentation of certain demographic and clinical subgroups.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT00094302

JAMA Cardiol. 2018;3(10):1000-1005. doi:10.1001/jamacardio.2018.2568
Published online August 22, 2018.

Supplemental content

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Concentrations of circulating natriuretic peptides (NPs) are incorporated in diagnostic criteria for heart failure with preserved ejection fraction (HFpEF)[1] and serve as important markers of cardiovascular prognosis.[2] Contemporary clinical trials of HFpEF apply NP thresholds to identify patients who are more likely to have the disease of interest and to enrich baseline risk.[3] However, NP levels are influenced by various clinical factors, including age, race/ethnicity, obesity, renal function, and the presence of atrial fibrillation (AF).[4,5] It is uncertain whether the risk associated with a given NP level varies in these clinically important subgroups and whether heterogeneity in NP distributions alters the relative representation of these patients in contemporary HFpEF trials. As such, we examined the distribution and associated cardiovascular prognosis of baseline concentrations of NPs in subgroups of HFpEF that were defined by age, race/ethnicity, obesity, renal function, and AF status that were enrolled in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT).

Key Points

Question How do age, race/ethnicity, obesity, renal function, and atrial fibrillation influence natriuretic peptides (NP) in heart failure with preserved ejection fraction and does the prognostic significance of NPs vary in these clinically important subgroups?

Findings In this secondary analysis of the Americas region of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT), 1057 participants had available NP concentrations that varied markedly across key subgroups and were consistently associated with excess cardiovascular risk.

Meaning Natriuretic peptides represent important biomarkers of prognosis, even in populations with lower distributions of levels; single, absolute NP thresholds for inclusion in contemporary heart failure with preserved ejection fraction trials may lead to an underrepresentation of certain demographic and clinical subgroups.

Methods

TOPCAT was a global, phase-3, double-blind, placebo-controlled randomized clinical trial of spironolactone in HFpEF.[6] Given significant regional heterogeneity,[7] this analysis was restricted to the 1057 patients who were enrolled in the Americas region (United States, Canada, Brazil, and Argentina) with available NPs. Patients who were 50 years or older with symptomatic heart failure (HF) and a left ventricular ejection fraction of 45% or greater, well-controlled blood pressure, and a serum potassium of less than 5.0 mEq/L (to convert potassium to millimoles per liter, multiply by 1) were considered for enrollment. In addition, either HF hospitalization within 12 months or elevated NP concentration (B-type natriuretic peptide [BNP] ≥100 ng/L or N-terminal pro-BNP [NT-proBNP] ≥360 ng/L) within 60 days was required. The primary outcome for TOPCAT and for this analysis was time to composite cardiovascular death, hospitalization for HF, or aborted cardiac arrest.

Analyses were performed in all patients with available NPs, which were locally collected and processed as previously described.[8] Before the analysis, we selected 6 key subgroups and relevant cutoffs a priori based on available clinical consensus documents[9,10] and prior data in HFpEF[2]: age (cutoff, 70 years), black race, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) (cutoff, 30 kg/m^2), waist circumference (cutoff, 102 cm for men; 88 cm for women), estimated glomerular filtration rate (eGFR) (cutoff, 60 mL/min/1.73 m^2), and a history of AF. Consistent with a prior report,[2] BNP and NT-proBNP levels were log-transformed and standardized (expressed per 1 SD; z score). Multivariable Cox proportional hazards models that accounted for age, sex, race/ethnicity, BMI, eGFR, history of AF, enrollment strata, and treatment randomization were used to assess the association between NP levels and the primary outcome. Interactions by key subgroups on the association between NPs and risk were assessed by linear regression. The incremental value of NPs in predicting the primary outcome was evaluated using the change in Harrell C-statistics. Restricted cubic splines models with 3 knots were used to plot the flexible association between log-transformed, standardized NP as a continuous variable and the incidence of the primary end point for each of the key subgroups. All patients provided written informed consent, and the study was approved by institutional review boards or ethics committees at each participating institution. Statistical analyses were performed using Stata, version 14.1 (Stata Corp).

Results

There was minor variation across the key characteristics in those with (1057 [60%]) and without available NPs (710 [40%]) in TOPCAT Americas (eTable in the Supplement). As expected, patients with available NPs levels were more frequently enrolled in the NP strata (687 [65%]) than the hospitalization for HF strata (370 [35%]). In patients with available NP levels, the mean (SD) age was 72 (10) years, 514 (49%) were men, and 183 (17%) were black. The mean (SD) BMI was 33.4 (8.6) kg/m^2, mean (SD) eGFR was 64.6 (21.8) mL/min/1.73 m^2, and 472 (45%) had a history of AF (of whom 289 [61%] had AF on an inclusion electrocardiogram).

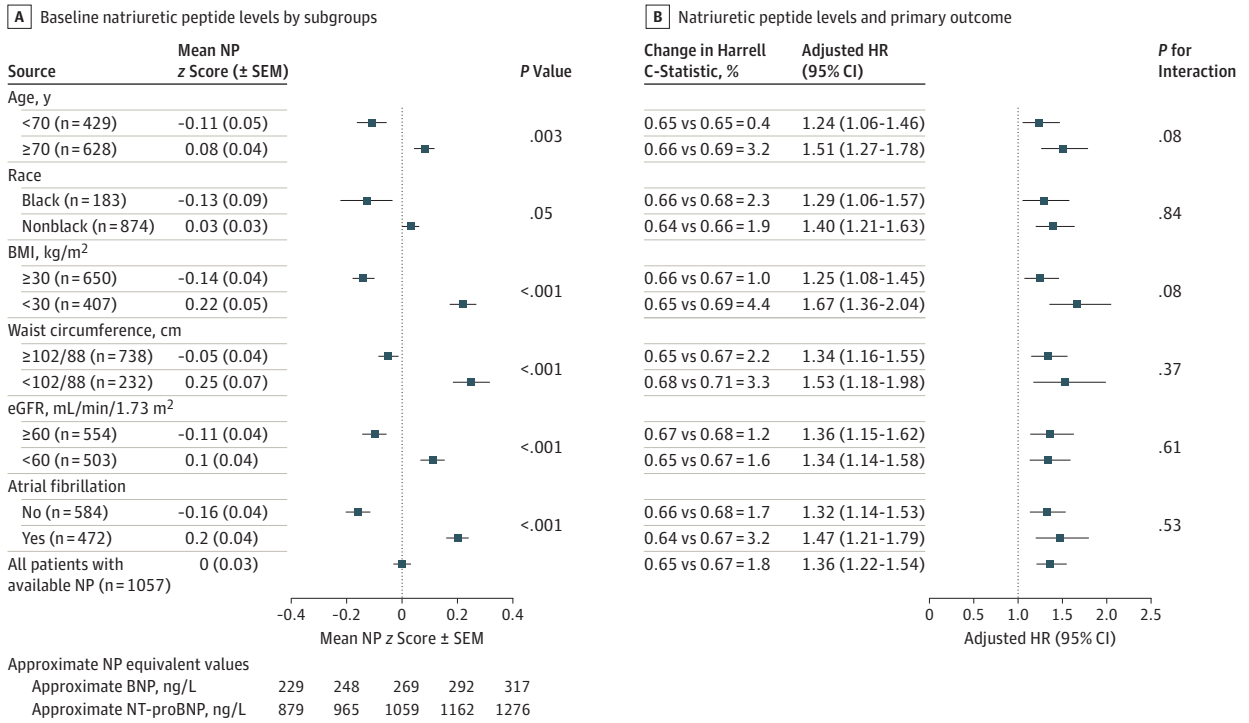
Overall, median BNP (n = 698) and NT-proBNP concentrations (n = 359) were 257 (interquartile range, 149-443) ng/L and 959 (interquartile range, 554-2015) ng/L, respectively (**Table**), and there were no differences in NP levels between the enrollment strata (eFigure 1 in the Supplement). The NP concentrations varied by up to 0.5 SDs within the 6 subgroups and were significantly higher in older patients with nonblack race, a lower BMI, a lower waist circumference, lower eGFR, and a history of AF (**Figure 1**). A similar variation was observed between patients with and without AF on a presenting electrocardiogram (z score [SD] 0.28 [0.90] vs −0.06 [1.03], respectively). In sensitivity analyses, similar qualitative differences across these subgroups were observed when analyzing concentrations of NPs in patients who were enrolled in the hospitalization stratum (n = 370; eFigure 2 in the Supplement) and in Russia and Georgia with available NPs (n = 366; eFigure 3 in the Supplement).

Table. Concentrations of BNP and NT-proBNP and Incidence Rate of the Primary Outcome in 6 Subgroups of the Americas Region of the TOPCAT Trial

Characteristic	Median (IQR) BNP, ng/L	Median (IQR) NT-proBNP, ng/L	Incidence Rate of the Primary Outcome per 100 Patient-Years (95% CI)
Total population (N = 1057)	257 (149-443)	959 (554-2015)	11.6 (10.3-13.0)
Age, y			
<70 (n = 429)	235 (136-427)	937 (487-1813)	12.7 (10.7-15.2)
≥70 (n = 628)	276 (165-461)	962 (631-2027)	10.9 (9.4-12.6)
Race			
Black (n = 183)	208 (128-454)	1274 (599-2582)	16.1 (12.5-20.6)
Nonblack (n = 874)	268 (157-443)	918 (554-1937)	10.8 (9.5-12.3)
BMI, kg/m^2			
≥30 (n = 650)	240 (143-402)	885 (500-1611)	12.5 (10.9-14.4)
<30 (n = 407)	285 (170-518)	1140 (665-2308)	10.2 (8.4-12.3)
Waist circumference, cm			
≥102/88 (n = 738)	252 (152-439)	893 (502-1641)	11.4 (9.9-13.0)
<102/88 (n = 232)	282 (149-504)	1229 (700-2720)	10.8 (8.4-13.9)
eGFR, mL/min/1.73 m^2			
≥60 (n = 554)	239 (146-414)	882 (496-1720)	8.9 (7.5-10.6)
<60 (n = 503)	273 (162-484)	1077 (672-2276)	14.9 (12.8-17.3)
Atrial fibrillation			
No (n = 584)	234 (138-429)	761 (475-1592)	11.9 (10.2-13.8)
Yes (n = 472)	293 (175-478)	1275 (731-2276)	11.3 (9.5-13.4)

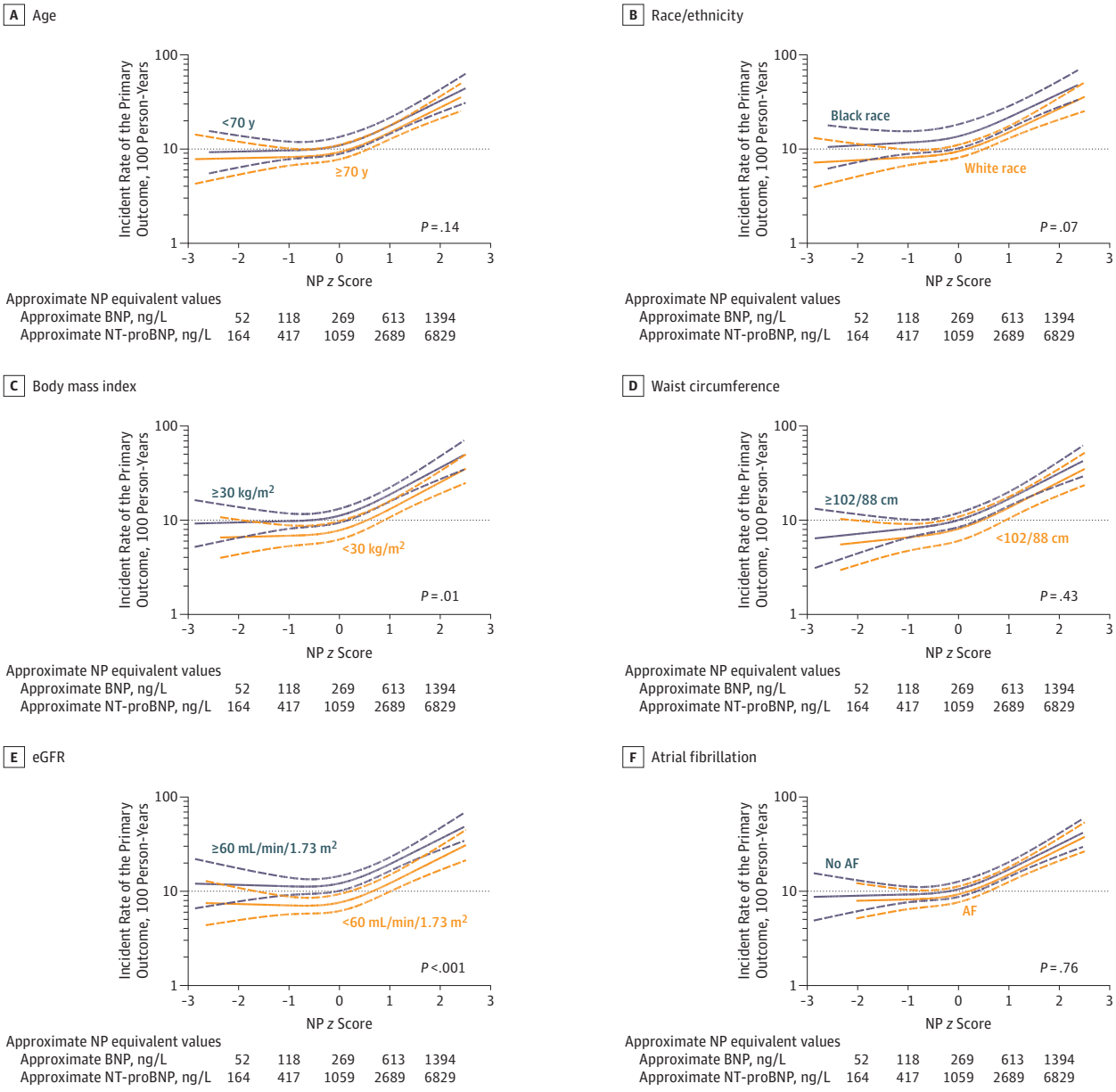
Abbreviations: AF, atrial fibrillation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Figure 1. Baseline Natriuretic Peptides and Subsequent Cardiovascular Risk in 6 Subgroups of the Americas Region of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial



Overall, 1057 patients had natriuretic peptides (NPs) available for analysis. Multivariate Cox regression models and risk reclassification models accounted for the following covariates: age, sex, race/ethnicity, body mass index (calculated as weight in kilograms divided by height in meters squared), estimated glomerular filtration rate (eGFR), history of atrial fibrillation (AF), enrollment strata, and treatment randomization. BNP indicates B-type natriuretic peptide; HR, hazard ratio; SEM, standard error of the mean.

Figure 2. Association Between Natriuretic Peptide (NP) Levels and Incidence of Primary Outcome in 6 Subgroups of the Americas Region of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial



Restricted cubic splines models with 3 knots were constructed to display the association between log-transformed, standardized NP concentrations as a continuous variable and the incidence of the primary end point for each of the key subgroups. The dotted lines reflect the 95% confidence intervals. BNP indicates B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide. Body mass index is calculated as weight in kilograms divided by height in meters squared.

Over a mean (SD) 2.4-year (1.5) follow-up, 300 primary outcome events occurred (incidence rate, 11.6; 95% CI, 10.3-13.0 per 100 patient-years) (Table). Elevated NP levels (per 1-SD increase in log-transformed, standardized NP) were independently associated with an increased risk of the primary outcome (adjusted hazard ratio, 1.36; 95% CI, 1.22-1.54; $P < .001$). The excess risk that was associated with NP levels was consistent in all the investigated subgroups (no significant interactions across subgroups). The incremental value of NP levels in predicting the primary outcome beyond the covariate set was modest (a 1.8% increase in C statistic) and was comparable across investigated subgroups (Figure 1).

The incidence of the primary outcome at a given level of NP was higher in subgroups with left-shifted distributions of baseline NP concentrations (young, black, obese, higher eGFR, and no AF) compared with their respective counterparts (**Figure 2**). Overall, in TOPCAT Americas (n = 1767), 791 (45%) were enrolled based on elevated NP levels as the qualifying

criterion (as opposed to a history of hospitalization for HF). This proportion was 31% (93 or 302), 34% (258 of 760), and 39% (443 of 1144) for black race, age younger than 70 years, and a BMI of 30 kg/m^2 or greater, respectively.

Discussion

The factors associated with variations in NP levels in the general population and in HF with reduced ejection fraction also appeared to modify NP levels in HFpEF.[4,5,11] Key clinical subgroups (young, black, obese, better renal function, and no AF) have, on average, lower NP levels in HFpEF. Nevertheless, elevated NP concentrations are consistently associated with adverse cardiovascular outcomes, even in these populations with lower distributions of levels.

Applying a single NP threshold for trial entry may contribute to unbalanced selection and may result in an underrepresentation of certain subgroups. Natriuretic peptide thresholds are often used in trials as a risk enrichment strategy, but this approach may exclude patients in these subsets who truly have HFpEF and who experience high rates of cardiovascular events. For instance, most black patients (~70%) in TOPCAT Americas were eligible for enrollment based on prior hospitalization for HF as opposed to elevated NP levels (~30%), and enrolled black patients faced higher rates of the primary outcome compared with white patients across a broad range of NP levels. In addition, patients with lower NPs may potentially stand to benefit most from investigational therapies,[2,12] perhaps due to improved responsiveness earlier in the natural history of HFpEF, which adds to the importance of identifying appropriate NP-based pathways to enroll these subgroups. Ongoing global advanced-phase pharmacological trials of HFpEF (NCT01920711, NCT03057951, and NCT02901184) are applying differential NP thresholds based on AF status, while select device trials (NCT03499236) are adjusting screening NP levels for BMI in determining trial eligibility. As high-quality data from global registries of HFpEF accrue, greater information regarding the typical distributions of NP levels across various clinical subgroups should be ascertained, and these identified factors should be considered in modifying NP-based trial entry criteria. Beyond this, markers are needed that are less sensitive to systematic variation across heterogeneous subsets for use in screening for therapeutic trials.

The mechanisms that drive NP distributions in HFpEF are varied. Natriuretic peptides are known to increase with age and with atrial arrhythmias, which are thought to be mediated by increased atrial and ventricular wall stress. Genetic polymorphisms that regulate NP levels may partially explain lower NP distributions in black patients.[13,14] Obesity has been mechanistically linked with lower NP levels that are associated with increased adipocyte-mediated clearance, hyperinsulinemia, sex hormonal activity, and local epicardial adipose tissue-related effects.[11,15] Because only a proportion of NPs are renally cleared, elevations in NP levels in renal impairment are likely multifactorial and are incompletely understood.

Limitations

The limitations in this exploratory analysis include restricting the study sample to patients with NP data available at baseline in a randomized clinical trial that used an NP threshold as one of the trial eligibility criteria. We evaluated NPs on a standardized scale given variation in circulating levels of BNP and NT-proBNP; however, the validity and prognostic utility of NPs appear independent of assay. Given the selected nature of this trial population, clear NP thresholds of risk for individual subgroups were not able to be established.

Conclusions

The burden of HFpEF is high in subgroups who tend to have lower NP levels, including black patients and patients with obesity. Natriuretic peptides remain important biomarkers of prognosis in HFpEF, even in these subgroups with lower distributions of levels. However, as the global population of HFpEF grows and becomes more heterogeneous, single, absolute NP thresholds for inclusion in contemporary HFpEF trials may bias against enrolling certain demographic and clinical subgroups.

ARTICLE INFORMATION

Accepted for Publication: July 3, 2018.

Published Online: August 22, 2018. doi:10.1001/jamacardio.2018.2568

Author Contributions: Drs Myhre, Vaduganathan, and Solomon had full access to all the data in the study and take responsibility for its integrity and the accuracy of the data analysis. Drs Myhre and Vaduganathan contributed equally as co-first authors.
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Statistical analysis: Myhre, Vaduganathan, Claggett.
Obtained funding: Solomon.
Administrative, technical, or material support: Myhre, Anand.
Study supervision: Desai, Pitt, Solomon.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Myhre has received speaker fees from Novartis and is supported by a postdoctoral research grant from the South-Eastern Norway Regional Health Authority (Dr Røsjø), Akershus University Hospital (Dr Omland), the Norwegian Medical Association, and the Unger Vetlesen Medical Fund. Dr Vaduganathan is supported by the National Heart, Lung, and Blood Institute (NHLBI) T32 postdoctoral training grant T32HL007604 and receives consulting fees from Bayer AG and Baxter Healthcare. Dr Sweitzer has received research grants from the National Institutes of Health (NIH). Dr Fang is a member of the data and safety monitoring board for Novartis, Amgen, NIH, and Johnson & Johnson. Dr O'Meara has received subventions/research support and consulting fees from Novartis, Bayer, AstraZeneca, Servier, and Amgen. Dr Shah has received research grants from Actelion, AstraZeneca, Corvia, and Novartis and consulting fees from Actelion, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiora, Eisai, Ironwood, Merck, Novartis, Sanofi, and United Therapeutics. Dr Desai has received research grant support from Novartis and consulting fees from Novartis, AstraZeneca, Abbott, Relypsa, and DalCor Pharma. Dr Lewis has received research grants from the NHLBI, Novartis, and Sanofi and consulting fees

from Novartis. Dr Rouleau reports receiving consulting fees from Novartis and AstraZeneca. Dr Pitt reports receiving consulting fees and/or stock options from AstraZeneca, Bayer, Sanofi, Stealth Peptides, Relypsa/Vifor, scPharmaceuticals, Sarfez, Tricida, and KBP Pharmaceuticals, reports a patent related to a site-specific delivery of eplerenone to the myocardium (9931412), and is a member of the data and safety monitoring board for Johnson & Johnson. Dr Pfeffer has received consulting fees from Amgen, AstraZeneca, Bayer, DalCor Pharma UK, Genzyme, Lilly, Medicines Company, MedImmune, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Salix, Sanderling, Sanofi, Takeda, Teva, Thrasos, and Vericel and has received research grant support from Amgen, Celladon, Novartis, and Sanofi. The Brigham and Women's Hospital has patents for the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction with Novartis Pharmaceuticals, for which Dr Pfeffer is a coinventor. His share of the licensing agreement is irrevocably transferred to charity. Dr Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Celladon, Gilead, GlaxoSmithKline, Ionis Pharmaceutics, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, and Theracos and has consulted for Alnylam, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Corvia, Gilead, GlaxoSmithKline, Ironwood, Merck, Novartis, Pfizer, Takeda, and Theracos. No other disclosures are reported.

Funding/Support: TOPCAT was supported by the NHLBI (grant HHSN268200425207C).

Role of the Funder/Sponsor: The NHLBI had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the TOPCAT participants, site investigators, and leadership, including the clinical events committee. These individuals were not compensated for their contributions.

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