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Interaction Between Spironolactone and Natriuretic Peptides in Patients With Heart Failure and Preserved Ejection Fraction

From the TOPCAT Trial

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CME Objective for This Article: After reading this article, the reader should understand: 1) the prognostic utility of natriuretic peptides in heart failure with preserved ejection fraction; 2) present available data regarding the use of spironolactone in heart failure with preserved ejection fraction; and 3) the implications of these data related to clinical practice and future research.

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ABSTRACT

OBJECTIVES The aims of this study were to explore the relationship of baseline levels of natriuretic peptides (NPs) with outcomes and to test for an interaction between baseline levels of NPs and the effects spironolactone.

BACKGROUND Plasma NPs are considered to be helpful in the diagnosis of heart failure (HF) with preserved ejection fraction (HFpEF), and elevated levels are associated with adverse outcomes. Levels of NPs higher than certain cutoffs are often used as inclusion criteria in clinical trials of HFpEF to increase the likelihood that patients have HF and to select patients at higher risk for events. Whether treatments have a differential effect on outcomes across the spectrum of NP levels is unclear.

METHODS The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) trial randomized patients with HFpEF and either prior hospitalization for HF or elevated natriuretic peptide levels (B-type NP [BNP] ≥100 pg/ml or N-terminal proBNP ≥360 pg/ml) to spironolactone or placebo. Baseline BNP (n = 430) or N-terminal proBNP (n = 257) levels were available in 687 patients enrolled from the Americas in the elevated-NP stratum of TOPCAT.

RESULTS Higher levels of NPs were independently associated with an increased risk for TOPCAT's primary endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for HF when analyzed either continuously or grouped by terciles, adjusting for region of enrollment, age, sex, atrial fibrillation, diabetes, renal function, body mass index, and heart rate. There was a significant interaction between the effect of spironolactone and baseline NP terciles for the primary outcome (p = 0.017), with greater benefit of the drug in the lower compared with higher NP terciles.

CONCLUSIONS Similar to the effects of irbesartan in the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) trial, a greater benefit of spironolactone was observed in the group with lower levels of NPs and overall risk in TOPCAT. Elevated NPs in HFpEF identify patients at higher risk for events but who may be less responsive to treatment. The mechanism of this apparent interaction between disease severity and response to therapy requires further exploration. (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function [TOPCAT]; NCT00094302) (J Am Coll Cardiol HF 2017;5:241–52) © 2017 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Plasma natriuretic peptides (NPs) are elevated in patients with heart failure (HF) and preserved ejection fraction (HFpEF) and are associated with adverse outcomes (1,2). Clinical trials for the treatment of HF are often designed to include patients with plasma concentrations of NPs higher than certain cutoff levels to increase the likelihood that patients have HF and to select patients at higher risk for clinical events (3,4). Such an inclusion criterion is particularly relevant to patients with HFpEF, in whom the diagnosis of HF is often uncertain (5–7). However, the requirement for elevated NP levels comes at the expense of excluding approximately one-third of patients with HFpEF who have

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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CI = confidence interval

eGFR = estimated glomerular filtration rate

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

LV = left ventricular

LVEF = left ventricular ejection fraction

NP = natriuretic peptides

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NP levels lower than thresholds for abnormal B-type natriuretic peptide (BNP), which are based primarily on studies of patients with HF and reduced ejection fraction (HFrEF) (8).

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Whether the benefit of HF therapies varies according to levels of NPs is unclear. In I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study), the angiotensin receptor blocker irbesartan had no benefit in the overall population of patients with HFpEF, but in a post hoc analysis, irbesartan significantly reduced all outcomes in patients with low but not high NP levels (2). In TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) patients with HFpEF had no overall benefit of spironolactone compared with placebo on the primary composite endpoint of cardiovascular death, HF hospitalization, or aborted cardiac arrest (7). However, spironolactone did appear to be beneficial among the subgroup of patients enrolled in the Americas, among whom event rates were nearly 4-fold higher than in the cohort enrolled in Russia and Georgia (9). We conducted post hoc analyses of data from TOPCAT to explore the relationship of baseline levels of NPs with outcomes and to test for an interaction between baseline levels of NPs and the effects spironolactone.

METHODS

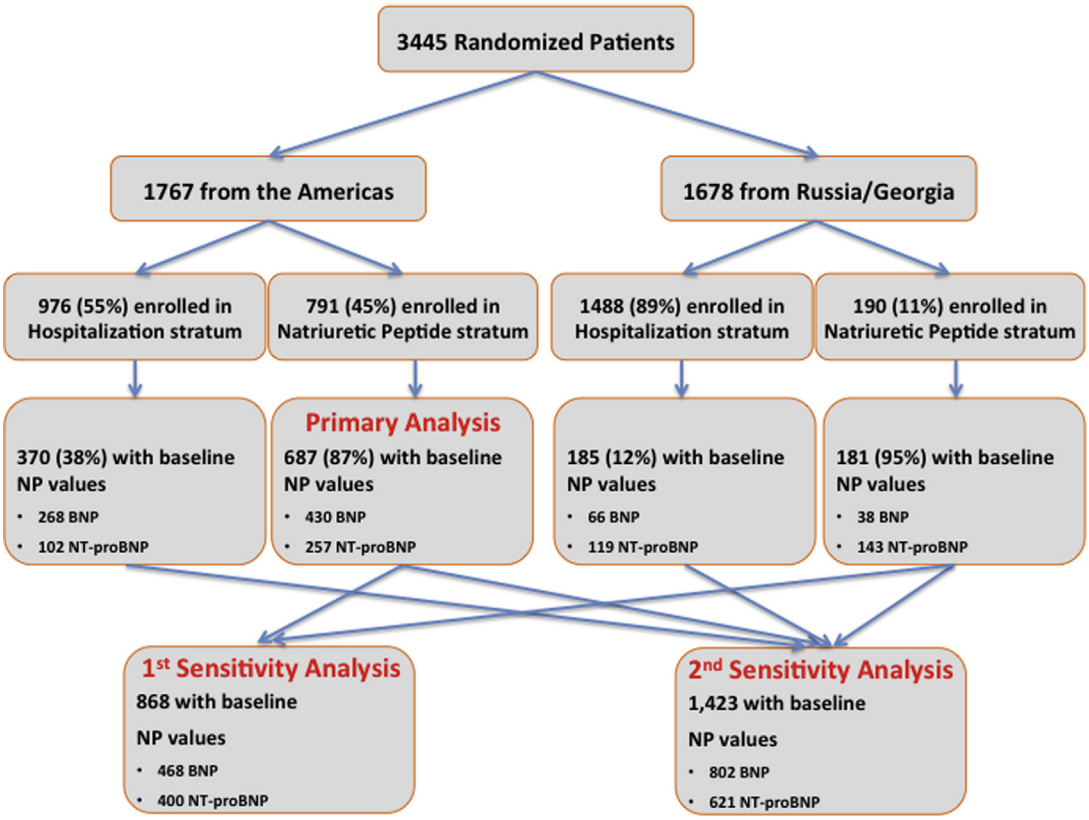
STUDY DESIGN AND PATIENT SELECTION. TOPCAT was an international, randomized, placebo-controlled, double-blind, multicenter trial designed to evaluate the efficacy and safety of the aldosterone antagonist spironolactone to reduce cardiovascular morbidity in patients with symptomatic HFpEF. Patients older than 50 years with signs and symptoms of HF and left ventricular (LV) ejection fractions (LVEF) ≥45% could be randomized, provided they fulfilled at least 1 of the following inclusion criteria: 1) at least 1 hospitalization in the prior 12 months for which HF was a major component (hospitalization stratum); and 2) an elevated NP level (BNP ≥100 pg/ml or N-terminal pro-B-type natriuretic peptide [NT-proBNP] ≥360 pg/ml) in the prior 60 days (NP stratum). Major exclusions were uncontrolled hypertension, serum potassium ≥5.0 mmol/l, creatinine ≥2.5 mg/dl, estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 body surface area, recent acute events, and other severe comorbidities defined previously (7). A total of 3,445 patients were enrolled in the study, 1,767 (51%) from North America and South America (United States, n = 1,151; Canada, n = 326; Brazil, n = 167; Argentina, n = 123) and 1,678 (49%) from Russia (n = 1,066) and Georgia (n = 612).

The primary endpoint was the composite of cardiovascular death, HF hospitalization, and aborted cardiac arrest. Secondary endpoints included the individual components of the primary outcome and all-cause mortality. All events were independently adjudicated by the clinical endpoints committee using pre-specified criteria. The study was approved by the institutional review board at each participating site, and all patients provided written informed consent. The study protocol and primary findings have been published (7).

PLASMA BNP AND NT-proBNP MEASUREMENTS. Of the 3,445 patients enrolled in TOPCAT, 2,464 (72%) were enrolled in the hospitalization stratum and 981 (28%) in the elevated NP stratum. The majority (81%) of the patients in the NP stratum came from the Americas, where 791 (45%) were enrolled in the NP stratum and 976 (55%) were enrolled in the hospitalization stratum (**Figure 1**). In contrast, sites in Russia and Georgia enrolled only 190 patients (11%) in the NP stratum and 1,488 (89%) in the hospitalization stratum. The study-qualifying BNP or NT-proBNP values were available in the case report forms in 868 of the 981 patients (88.5%) enrolled in the NP stratum. The remaining 113 patients (11.5%) (104 from the Americas and 9 from Russia and Georgia) were enrolled before a requirement to report NP values in the case report form was implemented in August 2007. Therefore, 687 patients from Americas and only 181 patients from Russia and Georgia had baseline BNP or NT-proBNP values available for analysis. Of the 687 patients from the Americas with available NP measurements, 430 had BNP values (206 in the spironolactone group and 224 in the placebo group) and 257 had NT-proBNP values (126 in the spironolactone group and 131 in the placebo group). There were 148 primary events in the 687 patients from the Americas and only 11 events from the 181 patients from Russia and Georgia. In addition, another 555 NP values (334 BNP and 221 NT-proBNP) were available at baseline in patients randomized in the hospitalization stratum. Therefore, a total of 1,423 patients had baseline NP values available in the case report forms for analysis, of which 1,057 were from the Americas (698 BNP and 359 NT-proBNP) and 366 from Russia and Georgia (104 BNP and 262 NT-proBNP).

ECHOCARDIOGRAPHIC MEASUREMENTS. Of the 1,423 patients with measurement of NP available at baseline, 476 also had measurements of echocardiographic

FIGURE 1 Consolidated Standards of Reporting Trials Diagram Showing the Patients Studied in the Primary and the 2 Sensitivity Analyses



BNP = B-type natriuretic peptide; NP = natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

variables. Details of the methods and findings of the TOPCAT echocardiographic substudy on 935 patients have been published (10).

DATA ANALYSIS. Baseline characteristics are described and compared using tercile groupings of BNP and NT-proBNP using means and SDs, medians and interquartile ranges, or percentages as appropriate for the levels of measurement and distributions of the variables. The NP terciles were compared using analysis of variance for continuous variables and the chi-square test for categorical variables.

Because of the previously reported significant regional differences between the Americas and Russia and Georgia, and with very few events in Russia and Georgia, the primary analysis was carried out on the 687 patients from the Americas with BNP or NT-proBNP values in the pre-specified NP stratum (**Figure 1**). Similar sensitivity analyses were then repeated on all 868 patients, including those from Russia and Georgia with BNP or NT-proBNP values, in the NP stratum, and in all the 1,423 patients who had BNP or NT-proBNP values available at baseline from the NP or hospitalization stratum. First, we compared the relationships of log-transformed standardized (z-score) baseline BNP or NT-proBNP levels with the incidence rate of the primary endpoint using a Poisson regression model in the 868 patients with BNP or NT-proBNP values, in the NP stratum, controlling for region, age, sex, atrial fibrillation, diabetes, eGFR, body mass index, and heart rate. Restricted cubic spline transformations were used to assess the linearity of the relationships using likelihood ratio tests to compare models with linear or curvilinear NP terms. Observing similar linear risk relationships for BNP and NT-proBNP levels, the groups were combined for further analyses. The combined NP was related to each study endpoint using Cox proportional hazards and Poisson regression models adjusting for region, age, sex, atrial fibrillation, diabetes, eGFR, body mass index, and heart rate. The continuous relationship between the effect of spironolactone and NP was

TABLE 1 Baseline Demographics, Comorbidities, Physical Examination Results, Laboratory Results, and Medications in Patients From the Americas Randomized in the Natriuretic Peptide Stratum With Available B-Type Natriuretic Peptide or N-Terminal Pro-B-Type Natriuretic Peptide Values (N = 687)

	NP Tercile 1 (BNP <166 pg/ml, NT-proBNP <682 pg/ml) (n = 230)	NP Tercile 2 (BNP 166-322 pg/ml, NT-proBNP 684-1,431 pg/ml) (n = 230)	NP Tercile 3 (BNP >322 pg/ml, NT-proBNP >1,431 pg/ml) (n = 227)	p Value for Trend
BNP, pg/ml	132	234	505	
NT-proBNP, median pg/ml	480	900	2,339	
Age, yrs	72 ± 9	74 ± 9	75 ± 9	<0.001
Female	119 (51.7)	116 (50.4)	120 (52.9)	0.81
Ejection fraction, %	60 ± 8	58 ± 8	58 ± 7	0.005
Race/ethnicity				
White	186 (80.9)	202 (87.8)	182 (80.2)	0.85
NYHA functional class				
I or II	164 (71.3)	146 (63.8)	157 (69.5)	0.67
III or IV	66 (28.7)	83 (36.2)	69 (30.5)	
Comorbidities				
Hypertension	205 (89.1)	204 (89.1)	198 (87.2)	0.52
Ischemic heart disease*	111 (48.3)	118 (51.5)	100 (44.1)	0.37
Atrial fibrillation	78 (33.9)	115 (50.2)	127 (55.9)	<0.001
Pacemaker or ICD	38 (16.5)	37 (16.1)	44 (19.4)	0.42
Diabetes mellitus	80 (34.8)	83 (36.2)	81 (35.7)	0.84
Chronic kidney disease	90 (39.1)	101 (43.9)	108 (47.6)	0.07
Obesity	143 (62.2)	137 (59.8)	101 (44.7)	<0.001
COPD or asthma	51 (22.2)	45 (19.6)	51 (22.5)	0.94
Stroke	21 (9.1)	22 (9.6)	26 (11.5)	0.41
PAD	29 (12.6)	25 (10.9)	29 (12.8)	0.96
Physical examination				
Body mass index, kg/m^2	32.7 ± 7.0	32.5 ± 7.0	30.2 ± 7.1	<0.001
Heart rate, beats/min	67 ± 10	67 ± 10	69 ± 11	0.003
SBP, mm Hg	128 ± 14	127 ± 16	126 ± 16	0.16
DBP mm Hg	71 ± 10	71 ± 12	71 ± 11	0.68
HF symptoms and signs				
PND	24 (10.4)	26 (11.3)	29 (12.8)	0.43
Orthopnea	60 (26.1)	70 (30.4)	50 (22.0)	0.33
Dyspnea†	229 (99.6)	226 (98.3)	223 (98.2)	0.21
Rales	31 (13.5)	30 (13.0)	31 (13.7)	0.96
JVP ≥10 cm H_2O	46 (20.0)	47 (20.4)	47 (20.7)	0.85
Ankle edema	175 (76.1)	178 (77.4)	177 (78.0)	0.63
Pulmonary congestion (CXR)	22 (9.6)	33 (14.3)	34 (15.0)	0.08

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modeled using nonlinear restricted cubic spline terms along with the previously listed covariates. Testing for interaction between randomized treatment (spironolactone or placebo) and NP values was conducted using the NP tercile variable as a linear predictor and also through the use of likelihood ratio tests in the restricted cubic spline models.

The values of $p < 0.05$ were considered to indicate statistical significance. All analyses were performed using Stata version 14 (StataCorp LP, College Station, Texas).

RESULTS

BASELINE PATIENT DEMOGRAPHICS IN RELATION TO NP LEVELS. At baseline, BNP (n = 430) ranged from 100 to 4,943 pg/ml (median 234 pg/ml; interquartile range: 145 to 391 pg/ml). NT-proBNP (n = 257) ranged from 360 to 17,410 pg/ml (median 900 pg/ml; interquartile range: 557 to 1,920 pg/ml). The median and range of the NP values by tercile distribution are shown in Table 1, which also shows the baseline characteristics of the 687 patients from the Americas by NP tercile. Patients with higher NP levels were older and more likely to have atrial fibrillation, chronic kidney disease, microalbuminuria, and lower albumin and less likely to be obese. They were also less likely to be taking aspirin but more likely to be taking long-acting nitrates.

A SINGLE, COMBINED NP SCORE. Baseline levels of both BNP and NT-proBNP in the 868 patients from the NP stratum had a similar linear relationship with the incidence of the primary outcome (p = 0.54 for difference in overall risk relationship by NP type, p = 0.33 for difference

TABLE 1 Continued

	NP Tercile 1 (BNP <166 pg/ml, NT-proBNP <682 pg/ml) (n = 230)	NP Tercile 2 (BNP 166–322 pg/ml, NT-proBNP 684–1,431 pg/ml) (n = 230)	NP Tercile 3 (BNP >322 pg/ml, NT-proBNP >1,431 pg/ml) (n = 227)	p Value for Trend
Laboratory variables				
Sodium, mEq/l	140 ± 3	139 ± 3	140 ± 3	0.72
Potassium, mEq/l	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	0.47
eGFR, ml/min/1.73 m^2	21.98 ± 10.39	23.22 ± 9.87	24.45 ± 10.39	0.017
Microalbuminuria, mg/g Cr	1.08 ± 0.29	1.13 ± 0.31	1.16 ± 0.30	0.003
Hemoglobin, g/dl	117 ± 56	117 ± 46	114 ± 45	0.59
Total bilirubin, mg/dl	7.0 ± 1.8	7.2 ± 2.3	7.3 ± 2.1	0.21
Albumin, g/dl	13.2 ± 1.5	13.2 ± 1.5	12.9 ± 1.7	0.043
LVH on ECG	22 (13.9)	18 (10.2)	30 (16.2)	0.49
Medications				
Diuretic agents	73 (31.7)	73 (31.7)	75 (33.0)	0.77
ACE inhibitors or ARBs	183 (79.6)	208 (90.4)	201 (88.5)	0.005
Beta-blockers	170 (73.9)	171 (74.3)	170 (74.9)	0.81
Calcium-channel blockers	177 (77.0)	185 (80.4)	185 (81.5)	0.23
Aspirin	89 (38.7)	87 (37.8)	81 (35.7)	0.51
Statins	138 (60.0)	130 (56.5)	103 (45.4)	0.002
Warfarin	145 (63.0)	157 (68.3)	123 (54.2)	0.05
Long-acting nitrate agents	62 (27.0)	95 (41.3)	101 (44.5)	<0.001

Values are median, mean ± SD, or n (%). *Any of the following: coronary artery disease, myocardial infarction, coronary artery bypass grafting, angina pectoris, and percutaneous coronary intervention. †Dyspnea on mild or moderate exertion.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; COPD = Chronic obstructive pulmonary disease; Cr = creatinine; CXR = chest x-ray; DBP = diastolic blood pressure; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter defibrillator; JVP = jugular venous pressure; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PAD = peripheral arterial disease; PND = paroxysmal nocturnal dyspnea; SBP = systolic blood pressure.

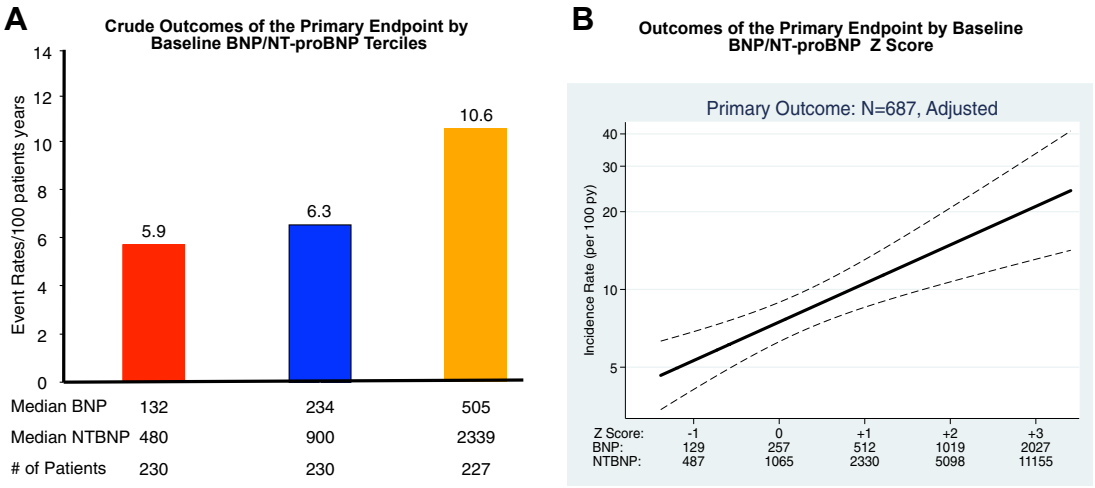
in slopes) (Online Figure 1), suggesting that the values of BNP and NT-proBNP could be analyzed together using the respective standardized *z*-scores of the logarithms. No evidence of nonlinearity was detected when using standardized BNP, NT-proBNP, or the combined NP variable (p for nonlinearity = 0.60, 0.38, and 0.50, respectively).

ASSOCIATION BETWEEN BASELINE NP AND OUTCOME EVENTS. During a median follow-up period of 35 months (interquartile range: 23 to 48 months), 148 patients (21.5% of the 687) had primary endpoints, 125 died (18.2%), and 111 (16.2%) had hospitalizations for HF. The incidence rate for outcomes increased across NP terciles (**Figure 2A**, **Table 2**). After adjusting for region, age, sex, stratum, atrial fibrillation, diabetes, eGFR, body mass index, and heart rate, the baseline NP *z*-score as a continuous variable was independently associated with an increased risk for the primary endpoint (adjusted hazard ratio [HR]: 1.41 per unit; 95% confidence interval [CI]: 1.20 to 1.65; $p < 0.001$) (**Figure 2B**), all-cause mortality (adjusted HR: 1.48; 95% CI: 1.25 to 1.76; $p < 0.001$), and hospitalization for HF (adjusted HR: 1.49; 95% CI: 1.24 to 1.78; $p < 0.001$) (**Table 2**).

INTERACTION BETWEEN BASELINE BNP AND NT-proBNP LEVELS AND EFFECT OF SPIRONOLACTONE. As previously reported, spironolactone did not have a significant effect on the primary outcome in the entire TOPCAT cohort or in any of the 22 prespecified subgroups defined by baseline characteristics, except the randomization stratum, for which a significant benefit of spironolactone was seen in the 981 patients randomized in the NP stratum (HR: 0.65; 95% CI: 0.49 to 0.87; $p = 0.003$) but not in hospitalization stratum (HR: 1.01; 95% CI: 0.84 to 1.21; $p = 0.92$) (7). In the 687 patients from the Americas with NP available at baseline analyzed in this report, the effect of spironolactone was very similar to that seen in overall NP stratum (HR: 0.64; 95% CI: 0.46 to 0.90; $p < 0.01$) (**Figure 3**). However, most of the beneficial effect of spironolactone was restricted to the lowest NP tercile. There was a significant interaction between the effect of spironolactone and the tercile grouping of the baseline NP for the primary outcome ($p = 0.017$) (**Figure 3**). When the continuous relationship between the NP *z*-score and treatment effect was modeled using restricted cubic splines, a significant treatment effect was also seen only at low NP levels, with no significant effect at higher NP levels (**Figure 4**).

Similar findings were seen when the analyses were conducted separately in the smaller BNP (n = 430) and NT-proBNP (n = 257) subgroups of patients (**Figure 3**). When the analysis was repeated in the 868

FIGURE 2 Crude Outcomes of the Primary Endpoint by Baseline B-Type Natriuretic Peptide and N-Terminal Pro-B-Type Natriuretic Peptide Terciles and *z*-Scores



(A) Bar diagram showing the crude rates (per 100 patient-years) of the primary outcome by baseline terciles of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the 687 patients enrolled in the natriuretic peptide stratum from the Americas. The median values of BNP and NT-proBNP and the number of patients for each tercile are shown on the x-axis. **(B)** Linear relationship of the log-transformed standardized (*z*-score) baseline natriuretic peptide (NP) levels, as a continuous variable, to the incidence rate of the primary endpoint in 687 patients enrolled in the NP stratum from the Americas, controlling for region, age, sex, atrial fibrillation, diabetes, estimated glomerular filtration rate, body mass index, and heart rate. The values of BNP and NT-proBNP for each of the *z*-scores are shown on the x-axis.

patients enrolled in the NP stratum from both the Americas and Russia and Georgia, similar findings were seen, with a significant interaction between treatment and level of baseline NP (p = 0.015) (Online Figures 2 and 3). Further sensitivity analyses in all 1,423 patients with available NP levels at baseline or restricted to the 1,057 patients from the Americas with available NP levels at baseline showed similar findings, with significant treatment × NP level interaction p values of 0.023 and 0.028, respectively (Online Figures 4 and 5).

TABLE 2 Multivariable Analysis* of Events by Baseline B-Type Natriuretic Peptide or N-Terminal Pro-B-Type Natriuretic Peptide as a Continuous Variable (*z*-Score) and by Tercile Grouping in 687 Patients With B-Type Natriuretic Peptide or N-Terminal Pro-B-Type Natriuretic Peptide Values Available at Baseline in the Natriuretic Peptide Stratum

	Events/Patients (% Events)	HR	95% CI	p Value
Primary endpoint				
ln BNP/NT-proBNP (*z*-score)	148/687 (22.0)	1.41	1.20–1.65	<0.001
BNP/NT-proBNP T1	40/230 (17.0)	Reference		
BNP/NT-proBNP T2	40/230 (17.0)	1.01	0.65–1.58	0.95
BNP/NT-proBNP T3	68/227 (30.0)	1.89	1.25–2.84	0.002
All-cause mortality				
ln BNP/NT-proBNP (*z*-score)	125/687 (18.0)	1.48	1.25–1.76	<0.001
BNP/NT-proBNP T1	28/230 (12.0)	Reference		
BNP/NT-proBNP T2	39/230 (17.0)	1.34	0.82–2.21	0.24
BNP/NT-proBNP T3	58/227 (26.0)	2.01	1.25–3.22	0.004
HF hospitalization				
ln BNP/NT-proBNP (*z*-score)	111/687 (16.0)	1.49	1.24–1.78	<0.001
BNP/NT-proBNP T1	28/230 (12.0)	Reference		
BNP/NT-proBNP T2	28/230 (12.0)	1.00	0.59–1.70	0.99
BNP/NT-proBNP T3	55/227 (24.0)	2.21	1.37–3.55	0.001

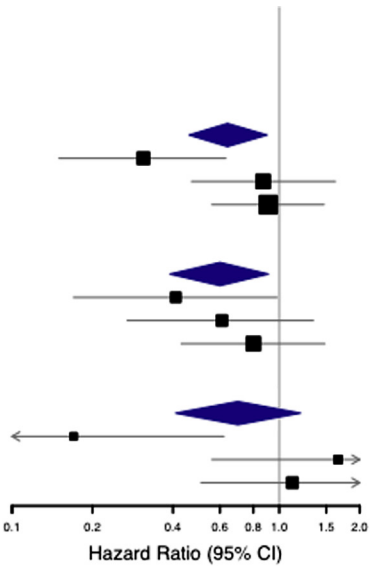
*Adjusted for age, sex, stratum, region, atrial fibrillation, diabetes, estimated glomerular filtration rate, body mass index, and heart rate.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

BASELINE ECHOCARDIOGRAPHIC VARIABLES BY TERCILE OF BASELINE BNP AND NT-proBNP LEVELS. The TOPCAT echocardiographic substudy was carried out in 935 patients (10). Of these, 473 patients also had baseline measurements of NPs (321 BNP and 152 NT-proBNP). Selected baseline echocardiographic variables in these 473 patients are shown in Online Table 1. LV volumes and LV systolic function were not related to tercile of NP. However, higher NP tercile was associated with higher LV mass index and prevalence of LV hypertrophy, worse diastolic function (lower e′, higher E/e′ ratio, larger left atrial volume index), and higher pulmonary pressure. In the 868 patients with NP levels available in the pre-specified NP stratum, only 268 had echocardiographic measurements at baseline, and only a few of them had full measurements of diastolic function. Nevertheless, even in this small group, higher NP tercile was associated with worse LV diastolic dysfunction (Online Table 2).

FIGURE 3 Forest Plot of the Effect of Spironolactone in Patients Randomized in the Natriuretic Peptide Stratum

Subgroup	Placebo No. of Events/Patients	Spironolactone No. of Events/Patients	Hazard Ratio (95% CI)	P Value for Interaction
BNP/NTBNP (n=687)				
Overall	**91/355 (25.6%)**	**57/332 (17.2%)**	**0.64 (0.46, 0.90)**	**0.017**
Tertile 1	30/117 (25.6%)	10/113 (8.8%)	0.31 (0.15, 0.63)	
Tertile 2	21/110 (19.1%)	19/120 (15.8%)	0.87 (0.47, 1.62)	
Tertile 3	40/128 (31.2%)	28/99 (28.3%)	0.91 (0.56, 1.47)	
BNP (n=430)				
Overall	**60/224 (26.8%)**	**34/206 (16.5%)**	**0.60 (0.39, 0.91)**	**0.216**
Tertile 1	19/79 (24.1%)	7/65 (10.8%)	0.41 (0.17, 0.98)	
Tertile 2	16/70 (22.9%)	10/74 (13.5%)	0.61 (0.27, 1.34)	
Tertile 3	25/75 (33.3%)	17/67 (25.4%)	0.80 (0.43, 1.48)	
NTBNP (n=257)				
Overall	**31/131 (23.7%)**	**23/126 (18.3%)**	**0.70 (0.41, 1.20)**	**0.027**
Tertile 1	11/38 (28.9%)	3/48 (6.2%)	0.17 (0.05, 0.62)	
Tertile 2	5/40 (12.5%)	9/46 (19.6%)	1.66 (0.56, 4.97)	
Tertile 3	15/53 (28.3%)	11/32 (34.4%)	1.12 (0.51, 2.46)	



The upper part of the plot shows the results in the overall 687 patients from the Americas **(diamonds)** and by tercile grouping (**solid squares** with associated confidence intervals [CIs]). The lower 2 plots show the similar data separately for the patients with B-type natriuretic peptide (BNP) or N-terminal pro–B-type natriuretic peptide (NTBNP) measurements. Interaction p values refer to tests of trend in the treatment effect across terciles.

DISCUSSION

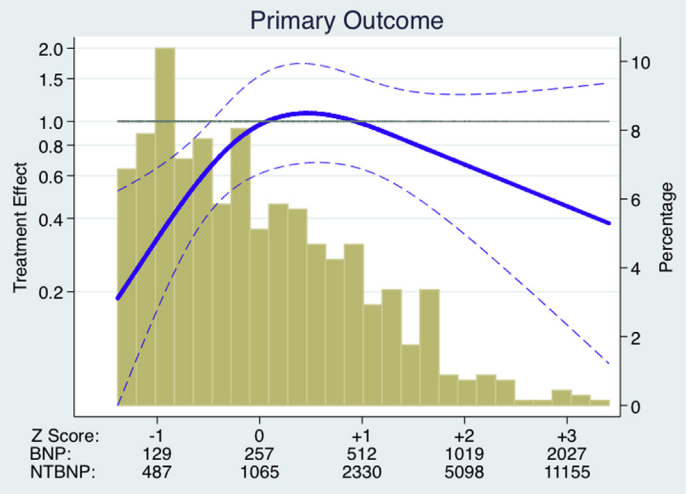
This post hoc analysis of patients with HFpEF enrolled in TOPCAT shows that NPs analyzed either continuously or grouped by terciles are independently associated with an increased risk for the primary endpoint, all-cause mortality, and hospitalization for HF, confirming previous findings that NPs are important prognostic markers in patients with HFpEF (1,2).

However, the new finding is the observation of a significant interaction between the effect of spironolactone treatment and NP levels, with most of the beneficial effects of spironolactone seen in patients with low levels of NPs and no effect in the patients with high NP levels. The results persisted whether the analyses were done separately in patients with BNP or NT-proBNP levels and when repeated in all patients randomized in the NP stratum, including those from Russia and Georgia. Moreover, sensitivity analyses confirmed the treatment interaction with NP levels when the analyses were done in all 1,423 patients with available NP levels (both NP and hospitalization strata) or restricted to the 1,056 higher risk patients from the Americas.

Although post hoc subgroup analyses are generally considered to be hypothesis generating, it should be pointed out that our analyses of 868 TOPCAT subjects were based on the 981 patients in the NP stratum, 113 of whom did not have NP values. However, despite that, because they came from the NP stratum, the patients in the placebo and spironolactone groups were similar in all regards except treatment, because of randomization. As a consequence, the results derived within the NP stratum could be considered as "true" randomized evidence, and as expected, these patients were similar in all regards except treatment (Online Table 3). Therefore, it is possible to draw stronger conclusions and with greater reassurance than from other subgroup analyses that are not from a pre-specified randomized stratum (11–13).

Several complementary analyses of these data confirm that the beneficial effects of the mineralocorticoid receptor antagonist spironolactone are more likely to be seen in patients with lower rather than higher levels of NPs. These data support the previous findings from the I-PRESERVE trial, in which the angiotensin receptor blocker irbesartan was shown to have no benefit in the overall population of patients with HFpEF but significantly reduced all outcomes in patients with low but not high NP levels (2). How can we explain these intriguing findings? In both I-PRESERVE and TOPCAT, patients with higher NP

FIGURE 4 Spironolactone Treatment Effect, Incidence Rate Ratio for the Primary Outcome, by Standardized Log-Transformed B-Type Natriuretic Peptide and N-Terminal Pro-B-Type Natriuretic Peptide Variable (*z*-Score) as a Continuous Variable in all 687 Patients From the Americas Enrolled in the Natriuretic Peptide Stratum



Stronger protective drug effects are seen at lower *z*-scores. The **bars** represent a histogram showing the percentage of patients at different *z*-scores. BNP = B-type natriuretic peptide; NTBNP = N-terminal pro-B-type natriuretic peptide.

levels were older and had more comorbidities and features of worse HF. It is therefore likely that patients with HFpEF and higher levels of NT-proBNP have more advanced structural heart disease. The TOPCAT echocardiographic substudy supports this notion; although echocardiographic measurements were available in only a subset of 473 patients with NP levels at baseline, the data showed that the highest levels of NP were seen in patients with greater LV mass, worse LV diastolic dysfunction, and higher pulmonary pressure, confirming previous studies in patients with HFpEF (14–16). Recently, Paulus and Tschöpe (17) suggested that comorbidities such as overweight or obesity, diabetes mellitus, and chronic obstructive pulmonary disease, common in HFpEF, contribute to a systemic inflammatory state, which induces oxidative stress, reduces myocardial nitric oxide bioavailability, and leads to reduced protein kinase G activity in cardiomyocytes, which accelerates prohypertrophic signaling and promotes hypophosphorylation of titin, worsening diastolic dysfunction, increasing ventricular stiffening, and causing HFpEF. More recently, Zile et al. (18) confirmed that compared with patients with hypertension and no HFpEF (n = 31), those with hypertension and HFpEF (n = 22) have increased LV end-diastolic pressure; left atrial volume; NP levels; total, collagen-dependent, and titin-dependent stiffness; insoluble collagen; and biomarkers of inflammation. Such structural changes may represent an irreversible stage in the natural history of HFpEF that may not be amenable to pharmaceutical interventions. Further studies are required to confirm this contention.

Although the benefit of spironolactone in reducing cardiovascular events appears to be greatest in those patients in whom BNP or NT-proBNP was in the lower tercile, independent of LVEF, it should be pointed out that in a previous analysis of the TOPCAT data (19), the benefits of spironolactone appeared to be greater in patients with LVEFs >45% to ≤60%, compared with those with LVEFs ≥60%. The number of patients in TOPCAT in whom serial measurements of both BNP or NT-proBNP and LVEF were available was, however, relatively small and insufficient to reach any definitive conclusion regarding the value of measurement of the combination of BNP or NT-proBNP and LVEF to predict the beneficial effects of spironolactone. Thus, future prospective studies are required to understand and evaluate the effectiveness of the combination of BNP or NT-proBNP and LVEF to predict the effectiveness of spironolactone in patients with HFpEF.

Do these findings differ from those in patients with HFrEF? Only a few studies have examined an interaction of HF drugs with NP levels in patients with HFrEF. Whereas the beta-blocker, carvedilol had a significantly greater treatment effect in higher risk patients with higher than median baseline BNP in the ANZ (Australia New Zealand) carvedilol trial (20), the same could not be confirmed in COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) (21). In Val-HeFT (Valsartan Heart Failure Trial), valsartan had a similar effect in high- and low-risk patients (22). In a small 261-patient substudy from the RALES (Randomized Aldactone Evaluation Study) trial, Zannad et al. (23) found that higher levels of serum procollagen type I carboxyterminal peptide, procollagen type I aminoterminal peptide, and procollagen type III aminoterminal peptide, markers of collagen turnover, were associated with an increased risk for death. Spironolactone significantly reduced mortality only in patients with higher levels of markers of collagen turnover, although a significant treatment interaction was not reported. These studies suggest that response to drugs by levels of biomarkers may be different in patients with HFrEF and those with HFpEF who have such differences in the pattern of ventricular remodeling.

Furthermore, studies of the interaction between biomarker levels and treatment effect for neurohormonal antagonists in HF (including ours in TOPCAT) suggest that biomarkers (or patterns of biomarkers)

could be used as a way to more precisely tailor specific therapies for patients with HF who may benefit most, a strategy that requires further testing in future clinical trials.

STUDY LIMITATIONS. The analysis was restricted to a minority of TOPCAT patients who had NP values available at baseline. Moreover, the inclusion criteria for the NP stratum required BNP or NT-proBNP levels beyond a certain cutoff level, excluding patients with less severe HFpEF. Furthermore, post hoc analyses of TOPCAT indicate marked regional differences in the patient populations from the Americas and Russia and Georgia, who had a 4-fold lower event rate and substantially lower magnitude of the effects of spironolactone relative to placebo on blood pressure, potassium, and creatinine (9). These findings call into question whether some of these patients even had HFpEF and were receiving spironolactone, confounding the interpretation of our findings in the overall population.

Despite these limitations, analyses of the data on all patients with available NP values or separately only on the Americas confirm the findings that the significant beneficial effects of spironolactone were observed only in patients with lower rather than higher levels of NP. Finally, although we adjusted for several covariates, there may be residual unmeasured confounders as well as some spurious differences that might have affected the results.

CONCLUSIONS

This study confirmed that elevated NP levels in patients with HFpEF are associated with adverse outcomes. Use of spironolactone in TOPCAT was associated with improved outcomes only in patients with HFpEF and mildly elevated NP levels. This apparent benefit of spironolactone in lower risk patients with HFpEF is similar to that previously reported for irbesartan in the I-PRESERVE trial and suggests that drug intervention may be successful early but not later in the natural history of the HFpEF syndrome, when structural changes in the heart might not be responsive to a therapeutic intervention. These data also suggest that we should not assume that patients at higher risk are always more likely to benefit from a treatment but do not provide the best NP cutoff for selecting more responsive patients. Nevertheless, the findings of this study need to be confirmed, and the strategy of using elevated plasma concentrations of NPs as a patient selection criterion in trials of HFpEF needs to be carefully reexamined in prospectively designed clinical trials, particularly to determine specific thresholds at which treatment effects become more or less prominent.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Clinical trials of HFpEF have excluded patients with low NP levels to increase the likelihood of enrolling high-risk patients with larger numbers of outcome events. However, the notion that high-risk patients with HFpEF are more likely to benefit from treatments is not well established. We tested this hypothesis in patients from TOPCAT who had baseline measurements of BNP or NT-proBNP. Overall, spironolactone had no significant effect on the primary endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for HF in the entire population. However, a significant interaction was observed between the effect of spironolactone and NP levels (interaction $p < 0.02$), with most of the benefit of spironolactone seen in patients with low levels of NPs and no effect in patients with high NP levels. This apparent beneficial effect of the spironolactone in lower risk patients with HFpEF suggests that drug intervention may be successful early but not later in the natural history of HFpEF, when structural changes in the heart may not be responsive to a therapeutic intervention. These data also suggest that the concept that patients at higher risk are more likely to benefit from treatment may not be correct. Thus, the strategy of using elevated plasma concentrations of NPs as a patient selection criterion in trials of HFpEF needs to be re-examined in prospectively designed clinical trials.

TRANSLATIONAL OUTLOOK: One of the important objectives in HF research is to identify patients to more precisely tailor specific therapies for those who are most likely to benefit from certain pharmaceutical agents or strategies of care. Several strategies are being considered, including the use of single or multiple biomarkers to guide approaches to categorizing patients. In this study, we show that the strategy of excluding patients with HFpEF with plasma NP concentrations less than certain thresholds from clinical trials to ensure enrollment of high-risk patients, who may not only have more outcomes but also be more likely to show a greater response to therapy, may need to be re-examined. We found that the beneficial effect of spironolactone was seen only in patients with low, not high, NP levels. Further studies are required to test the interaction between biomarker levels and treatment effect.

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KEY WORDS biomarkers, heart failure, natriuretic peptides, preserved ejection fraction, prognosis

APPENDIX For supplemental figures and tables, please see the online version of this article.

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