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Prognostic Implications of N-Terminal Pro–B-Type Natriuretic Peptide and High-Sensitivity Cardiac Troponin T in EMPEROR-Preserved

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ABSTRACT

BACKGROUND N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) are associated with disease severity and outcomes among patients with heart failure (HF) with preserved ejection fraction.

OBJECTIVES The authors evaluated associations between both biomarkers and clinical outcomes in the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial.

METHODS Of 5,988 study participants, 5,986 (99.9%) and 5,825 (97.3%) had available baseline NT-proBNP and hs-cTnT; postbaseline NT-proBNP was also available. Baseline characteristics were expressed by biomarker quartiles. The effect of empagliflozin on cardiovascular death/ HF hospitalization, the individual components, total HF hospitalizations, slope of decline of estimated glomerular filtration rate (eGFR), and a composite renal endpoint were examined across biomarker quartiles. Change in NT-proBNP across study visits as a function of treatment assignment was also assessed.

RESULTS Higher baseline NT-proBNP and hs-cTnT concentrations were associated with more comorbidities and worse HF severity. Incidence rates for cardiac and renal outcomes were 2- to 5-fold higher among those in the highest vs lowest NT-proBNP or hs-cTnT quartiles. Empagliflozin consistently reduced the risk for cardiovascular events and reduced slope of eGFR decline across NT-proBNP or hs-cTnT quartiles. Empagliflozin treatment modestly lowered NT-proBNP; by 100 weeks, the adjusted mean difference in NT-proBNP from placebo was 7%. Increase in NT-proBNP from baseline to 12 weeks was strongly associated with risk of cardiovascular death/HF hospitalization.

CONCLUSIONS The benefit of empagliflozin on cardiac outcomes and decline of eGFR is preserved across the wide range of baseline NT-proBNP and hs-cTnT evaluated. Empagliflozin modestly reduces NT-proBNP in HF with preserved ejection fraction. (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction [EMPEROR-Preserved]; NCT03057951) (J Am Coll Cardiol HF 2022;10:512–524) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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Evaluation and management of individuals with heart failure and preserved ejection fraction (HFpEF) may be challenging, and assessing risk in those with the diagnosis via clinical means may be difficult. To assist in the clinical assessment of those with heart failure (HF), physicians have increasingly relied on testing of biomarkers, including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin (hs-cTn). These 2 biomarkers have a powerful and well-established prognostic role in persons across the range of ejection fraction (EF) in HF, including those with HFpEF.[1,2]

In addition to their prognostic importance, it is possible that baseline values of NT-proBNP or hs-cTn can be used to identify patients for effective treatments for HF. Although this has been more explored in heart failure with reduced ejection fraction (HFrEF), among those with HFpEF, previous biomarker analyses in randomized trials of treatments for HFpEF (such as angiotensin receptor blockers or spironolactone) have detected heterogeneity between baseline NT-proBNP values and subsequent response to these therapies.[3,4] Specifically, in these analyses, the most obvious benefit of studied therapies was observed among those with only modest elevation of the NT-proBNP. However, those with very low or very high concentrations of NT-proBNP appeared to have less benefit from both irbesartan or spironolactone. This ambiguity has led to confusion about the pharmacological management in HFpEF and whether biomarkers have a role for predicting response to treatment.[5] More information is needed regarding the proper utilization of HF biomarkers to inform evaluation and management in HFpEF, particularly with the advent of effective treatments.

The effect of sodium glucose cotransporter (SGLT2) inhibitor treatment on HFpEF outcome was recently evaluated in EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction).[6] In this randomized comparison of 10 mg of empagliflozin vs placebo for treatment of persons with HF and a left ventricular ejection fraction (LVEF) >40%, significant reductions in the primary composite endpoint of cardiovascular (CV) death/HF hospitalization along with reduction in total burden of HF hospitalization was observed in those treated with SGLT2 inhibition. We therefore sought to understand the prognostic meaning of baseline NT-proBNP and high-sensitivity cardiac troponin T (hs-cTnT) in patients with HFpEF and how levels of these biomarkers might influence the response to empagliflozin; we also evaluated the effect of empagliflozin on serially measured concentrations of NT-proBNP during long-term follow-up.

ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

HFpEF = heart failure with preserved ejection fraction

hs-cTn = high-sensitivity cardiac troponin

hs-cTnT = high-sensitivity cardiac troponin T

KCCQ = Kansas City Cardiomyopathy Questionnaire

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

SGLT2 = sodium/glucose cotransporter 2

METHODS

The institutional review board of each study site approved of all study procedures, and all patients provided informed consent.

STUDY DESIGN. The design and primary results of the EMPEROR-Preserved Trial (NCT03057951) have been recently reported.[6,7] The study included HF patients with an LVEF >40% and New York Heart Association functional class II-IV functional class. Study participants were randomized in a double-blind manner to receive placebo or empagliflozin 10 mg daily. The protocol required an NT-proBNP concentration >300 ng/L for participation; this concentration was increased to >900 ng/L in the presence of atrial fibrillation at baseline.

The primary endpoint of EMPEROR-Preserved was time-to-first event in a composite of CV death or hospitalization for HF. The first secondary endpoint was the occurrence of all (first and recurrent) hospitalizations for HF. The second endpoint was the slope of the change in estimated glomerular filtration rate (eGFR) during double-blind treatment. In addition, time-to-first composite renal endpoint (consisting as progression to any of the following: chronic dialysis; renal transplantation; a sustained eGFR <15 mL/min/1.73 m^2 for patients with baseline

eGFR ≥30 or sustained eGFR <10 mL/min/1.7 3m^2 for patients with baseline eGFR <30 mL/min/1.73 m^2; or sustained reduction of eGFR by 40% or greater

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics of Study Participants as a Function of Quartiles of NT-proBNP

	Quartile 1 <499 ng/L (n = 1,496)	Quartile 2 499 to <974 ng/L (n = 1,495)	Quartile 3 974 to <1,731 ng/L (n = 1,498)	Quartile 4 ≥1,731 ng/L (n = 1,497)	*P* Value for Trend
Age, y	69.5 ± 9.4	71.1 ± 9.4	73.1 ± 8.8	74.0 ± 9.3	<0.001
Female	704 (47.1)	653 (43.7)	664 (44.3)	655 (43.8)	0.11
Race					<0.001
White	1,159 (77.5)	1,134 (75.9)	1,157 (77.2)	1,091 (72.9)	
Black	81 (5.4)	69 (4.6)	48 (3.2)	59 (3.9)	
Asian	146 (9.8)	203 (13.6)	215 (14.4)	260 (17.4)	
Other or missing	110 (7.4)	89 (6.0)	78 (5.2)	87 (5.8)	
Region					<0.001
North America	167 (11.2)	175 (11.7)	181 (12.1)	195 (13.0)	
Latin America	440 (29.4)	402 (26.9)	319 (21.3)	354 (23.6)	
Europe	701 (46.9)	664 (44.4)	713 (47.6)	610 (40.7)	
Asia	105 (7.0)	163 (10.9)	193 (12.9)	225 (15.0)	
Other	83 (5.5)	91 (6.1)	92 (6.1)	113 (7.5)	
Clinical course of HF					
Duration of heart failure, y	2.4 (0.9, 5.8)	2.6 (1.1, 6.0)	3.0 (1.0, 6.3)	2.4 (0.9, 5.3)	0.55
NYHA functional class III-IV	215 (14.4)	238 (15.9)	289 (19.3)	359 (24.0)	0.001
Hospitalization for HF within 12 mo	253 (16.9)	288 (19.3)	365 (24.4)	462 (30.9)	<0.001
Left ventricular ejection fraction	55.0 ± 8.7	54.4 ± 9.0	54.3 ± 8.6	53.7 ± 8.8	<0.001
Left ventricular ejection fraction <50%	442 (29.5)	504 (33.7)	490 (32.7)	547 (36.5)	<0.001
Body mass index, kg/m^2	30.8 ± 5.7	29.9 ± 5.9	30.0 ± 6.0	28.6 ± 5.7	<0.001
Heart rate, beats/min	67.7 ± 10.4	68.6 ± 11.2	71.8 ± 12.0	73.4 ± 12.8	<0.001
Systolic blood pressure, mm Hg	132.5 ± 14.8	132.6 ± 15.9	131.9 ± 15.7	130.3 ± 16.1	<0.001
Medical history					
Ischemic cause of HF	645 (43.1)	580 (38.8)	462 (30.8)	429 (28.7)	<0.001
History of myocardial infarction	561 (37.5)	508 (34.0)	363 (24.2)	347 (23.2)	<0.001
Diabetes mellitus	764 (51.1)	779 (52.1)	708 (47.3)	685 (45.8)	<0.001
History of atrial fibrillation	376 (25.1)	621 (41.5)	1,053 (70.3)	1,085 (72.5)	<0.001
Atrial fibrillation at baseline	348 (23.3)	603 (40.3)	1,038 (69.3)	1,068 (71.3)	<0.001
Hypertension	1,383 (92.4)	1,357 (90.8)	1,352 (90.3)	1,330 (88.8)	<0.001
HF management, baseline					
ACEi/ARB	1,274 (85.2)	1,199 (80.2)	1,154 (77.0)	1,077 (71.9)	<0.001
ARNI	27 (1.8)	42 (2.8)	34 (2.3)	30 (2.0)	0.97
Beta-blocker	1,268 (84.8)	1,293 (86.5)	1,303 (87.0)	1,301 (86.9)	0.08
Mineralocorticoid receptor antagonist	525 (35.1)	527 (35.3)	584 (39.0)	607 (40.5)	<0.001
Loop diuretic agent	837 (55.9)	926 (61.9)	1,084 (72.4)	1,205 (80.5)	<0.001
Laboratory findings					
eGFR, mL/min/1.73 m^2	66.2 ± 19.6	63.3 ± 19.8	60.1 ± 18.8	53.0 ± 18.7	<0.001
eGFR <60 mL/min/1.73 m^2	581 (38.8)	655 (43.8)	755 (50.4)	997 (66.6)	<0.001
Hemoglobin, g/dL	13.5 ± 1.5	13.4 ± 1.5	13.4 ± 1.6	13.1 ± 1.7	<0.001
hs-cTnT, ng/L	14.0 (9.5, 20.9)	16.6 (11.5, 24.2)	17.9 (11.9, 27.2)	24.1 (16.1, 37.7)	<0.001
Kansas City Cardiomyopathy Questionnaire					
Clinical summary score	75.5 (56.8, 89.6)	76.8 (57.8, 89.6)	72.3 (55.7, 87.5)	70.3 (52.6, 85.4)	<0.001
Overall summary score	74.3 (54.9, 87.5)	75.0 (57.6, 88.0)	70.8 (55.2, 85.9)	68.3 (50.5, 83.4)	<0.001
Total symptom score	77.6 (60.4, 92.7)	81.3 (60.4, 93.8)	77.1 (59.4, 91.7)	75.0 (55.6, 89.6)	<0.001

Values are mean ± SD, n (%), or median (Q1, Q3). *P* value compares group means using analysis of variance for continuous variables and chi-square test for categorical variables.

ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; eGFR = estimated glomerular filtration rate; HF = heart failure; hs-cTnT = high sensitivity cardiac troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

from baseline) was evaluated. Last, changes from baseline in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) to 52 weeks of follow-up were also evaluated.

As part of the study design, blood was collected for measurement of NT-proBNP and hs-cTnT (Roche Diagnostics) at baseline. Additionally, NT-proBNP results were also available at weeks 4, 12, 52, and 100.

TABLE 2 Baseline Characteristics of Study Participants as a Function of Quartiles of hs-cTnT

	Quartile 1 <11.6 ng/L (n = 1,439)	Quartile 2 11.6 to <17.8 ng/L (n = 1,473)	Quartile 3 17.8 to <27.0 ng/L (n = 1,448)	Quartile 4 ≥27.0 ng/L (n = 1,465)	*P* Value for Trend
Age, y	68.5 ± 9.5	72.3 ± 8.4	73.3 ± 9.0	73.4 ± 9.9	<0.001
Female	916 (63.7)	701 (47.6)	560 (38.7)	425 (29.0)	<0.001
Race					0.008
White	1,070 (74.4)	1,127 (76.5)	1,101 (76.0)	1,112 (75.9)	
Black	61 (4.2)	53 (3.6)	73 (5.0)	66 (4.5)	
Asian	197 (13.7)	204 (13.8)	208 (14.4)	211 (14.4)	
Other or missing	111 (7.7)	89 (6.0)	66 (4.6)	76 (5.2)	
Region					<0.001
North America	136 (9.5)	138 (9.4)	180 (12.4)	240 (16.4)	
Latin America	414 (28.8)	360 (24.4)	352 (24.3)	337 (23.0)	
Europe	629 (43.7)	718 (48.7)	662 (45.7)	600 (41.0)	
Asia	164 (11.4)	172 (11.7)	179 (12.4)	168 (11.5)	
Other	96 (6.7)	85 (5.8)	75 (5.2)	120 (8.2)	
Clinical course of HF					
Duration of heart failure, y	2.4 (1.0, 5.6)	2.7 (1.0, 5.8)	2.9 (1.0, 6.1)	2.5 (0.9, 5.8)	0.43
NYHA functional class III-IV	214 (14.9)	223 (15.1)	257 (17.7)	354 (24.2)	<0.001
Hospitalization for HF within 12 mo	234 (16.3)	307 (20.8)	338 (23.3)	458 (31.3)	<0.001
Left ventricular ejection fraction	54.9 ± 8.7	54.4 ± 8.7	54.1 ± 8.9	53.9 ± 8.7	0.001
Left ventricular ejection fraction <50%	423 (29.4)	485 (32.9)	506 (34.9)	522 (35.6)	<0.001
Body mass index, kg/m^2	30.0 ± 5.9	29.6 ± 5.8	29.9 ± 6.0	29.9 ± 5.9	0.93
Heart rate, beats/min	70.3 ± 11.7	70.5 ± 11.7	70.0 ± 12.2	70.6 ± 11.8	0.74
Systolic blood pressure, mm Hg	130.9 ± 14.9	131.8 ± 15.6	132.9 ± 15.6	131.9 ± 16.4	0.02
Medical history					
Ischemic cause of HF	453 (31.5)	518 (35.2)	555 (38.3)	530 (36.2)	<0.001
History of myocardial infarction	392 (27.2)	410 (27.8)	490 (33.8)	430 (29.4)	0.02
Diabetes mellitus	565 (39.3)	675 (45.8)	725 (50.1)	887 (60.5)	<0.001
History of atrial fibrillation	701 (48.7)	804 (54.6)	771 (53.2)	781 (53.3)	0.03
Atrial fibrillation at baseline	680 (47.3)	787 (53.4)	755 (52.1)	757 (51.7)	0.04
Hypertension	1,261 (87.6)	1,329 (90.2)	1,322 (91.3)	1,354 (92.4)	<0.001
HF management, baseline					
ACEi/ARB	1,153 (80.1)	1,189 (80.7)	1,154 (79.7)	1,080 (73.7)	<0.001
ARNI	33 (2.3)	31 (2.1)	29 (2.0)	33 (2.3)	0.90
Beta-blocker	1,288 (89.5)	1,290 (87.6)	1,242 (85.8)	1,208 (82.5)	<0.001
Mineralocorticoid receptor antagonist	504 (35.0)	550 (37.3)	537 (37.1)	598 (40.8)	0.003
Loop diuretic agent	801 (55.7)	910 (61.8)	1,034 (71.4)	1,201 (82.0)	<0.001
Laboratory findings					
eGFR, mL/min/1.73 m^2	70.5 ± 17.8	63.2 ± 17.9	57.8 ± 18.9	51.3 ± 19.5	<0.001
eGFR <60 mL/min/1.73 m^2	428 (29.7)	654 (44.4)	818 (56.5)	1,003 (68.5)	<0.001
Hemoglobin, g/dL	13.5 ± 1.4	13.4 ± 1.5	13.4 ± 1.6	13.0 ± 1.7	<0.001
NT-proBNP, ng/L	697 (369, 1,282)	833 (464, 1,446)	1,023 (536, 1,821)	1,468 (774, 2,755)	<0.001
Kansas City Cardiomyopathy Questionnaire					
Clinical summary score	77.1 (58.3, 89.6)	75.2 (59.4, 89.6)	75.0 (56.3, 88.5)	68.8 (50.5, 84.5)	<0.001
Overall summary score	74.8 (56.3, 87.5)	74.0 (57.6, 87.5)	72.7 (55.7, 86.6)	67.7 (49.0, 83.9)	<0.001
Total symptom score	79.2 (60.4, 91.7)	79.2 (62.5, 93.8)	78.1 (60.4, 91.7)	75.0 (54.2, 88.5)	<0.001

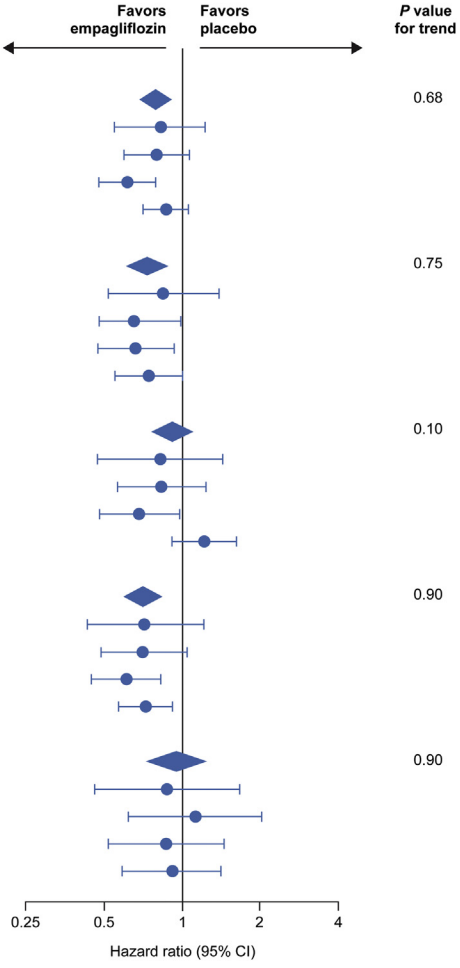
Values are mean ± SD, n (%), or median (Q1, Q3). *P* value compares group means using analysis of variance for continuous variables and chi-square test for categorical variables.
Abbreviations as in Table 1.

STATISTICAL ANALYSIS. Study participants were categorized by quartiles of NT-proBNP and hs-cTnT, and baseline characteristics were compared. Time-to-event analyses were performed using Cox proportional hazards models, adjusting for age, sex, region, baseline diagnosis of diabetes, LVEF and eGFR at baseline and treatment-by-cardiac biomarker (quartile) interaction. A joint frailty model was used for the analysis of first and recurrent events, incorporating the same variables as the time-to-event analyses and including CV death as a competing risk. Changes in eGFR slope were analyzed using a

FIGURE 1 Forest Plots for Key Cardiovascular or Renal Endpoints in the EMPEROR-Preserved Trial

A

NT-proBNP group	Empagliflozin: n with event/ N analyzed (%)[a]	Empagliflozin: Rate per 100 patient-years	Placebo: n with event/ N analyzed (%)[a]	Placebo: Rate per 100 patient-years	HR (95% CI)	*P* value for trend
Time to first event of CV death or hospitalization for HF						
All patients	415/2997 (13.8)	6.9	511/2991 (17.1)	8.7	0.79 (0.69, 0.90)	0.68
<499 ng/L	44/747 (5.9)	2.8	54/749 (7.2)	3.4	0.83 (0.55, 1.23)	
≥499–<974 ng/L	80/719 (11.1)	5.4	107/776 (13.8)	6.9	0.80 (0.60, 1.07)	
≥974–<1731 ng/L	105/777 (13.5)	6.5	149/721 (20.7)	10.6	0.62 (0.48, 0.79)	
≥1731 ng/L	186/754 (24.7)	13.6	199/743 (26.8)	15.0	0.87 (0.71, 1.06)	
First and recurrent hospitalization for HF						
All patients	407	-	541	-	0.73 (0.61, 0.88)	0.75
<499 ng/L	39	-	46	-	0.84 (0.52, 1.38)	
≥499–<974 ng/L	54	-	93	-	0.65 (0.48, 0.99)	
≥974–<1731 ng/L	109	-	148	-	0.66 (0.47, 0.93)	
≥1731 ng/L	205	-	253	-	0.74 (0.55, 1.00)	
Time to first event of CV death						
All patients	219/2997 (7.3)	3.4	244/2991 (8.2)	3.8	0.91 (0.76, 1.09)	0.10
<499 ng/L	23/747 (3.1)	1.4	28/749 (3.7)	1.7	0.82 (0.47, 1.43)	
≥499–<974 ng/L	43/719 (6.0)	2.8	56/776 (7.2)	3.4	0.83 (0.56, 1.23)	
≥974–<1731 ng/L	53/777 (6.8)	3.1	72/721 (10.0)	4.7	0.68 (0.48, 0.97)	
≥1731 ng/L	100/754 (13.3)	6.6	86/743 (11.6)	5.6	1.21 (0.91, 1.61)	
Time to first event of hospitalization for HF						
All patients	259/2997 (8.6)	4.3	352/2991 (11.8)	6.0	0.71 (0.60, 0.83)	0.90
<499 ng/L	24/747 (3.2)	1.5	34/749 (4.5)	2.1	0.72 (0.43, 1.22)	
≥499–<974 ng/L	43/719 (6.0)	2.9	66/776 (8.5)	4.2	0.71 (0.49, 1.05)	
≥974–<1731 ng/L	69/777 (8.9)	4.3	99/721 (13.7)	7.0	0.61 (0.45, 0.83)	
≥1731 ng/L	123/754 (16.3)	9.0	152/743 (20.5)	11.5	0.73 (0.57, 0.92)	
Time to first renal composite outcome						
All patients	108/2997 (3.6)	2.1	112/2991 (3.7)	2.2	0.95 (0.73, 1.24)	0.90
<499 ng/L	17/747 (2.3)	1.3	21/749 (2.8)	1.6	0.88 (0.46, 1.67)	
≥499–<974 ng/L	22/719 (3.1)	1.8	21/776 (2.7)	1.6	1.12 (0.62, 2.04)	
≥974–<1731 ng/L	29/777 (3.7)	2.2	29/721 (4.0)	2.4	0.87 (0.52, 1.46)	
≥1731 ng/L	40/754 (5.3)	3.4	41/743 (5.5)	3.6	0.92 (0.59, 1.42)	



Outcomes and treatment effect are expressed as a function of **(A)** N-terminal pro-B-type natriuretic peptide (NT-proBNP) or **(B)** high sensitivity cardiac troponin T (hs-cTnT) quartile. *Number with total heart failure hospitalization events. CV = cardiovascular; HF = heart failure.

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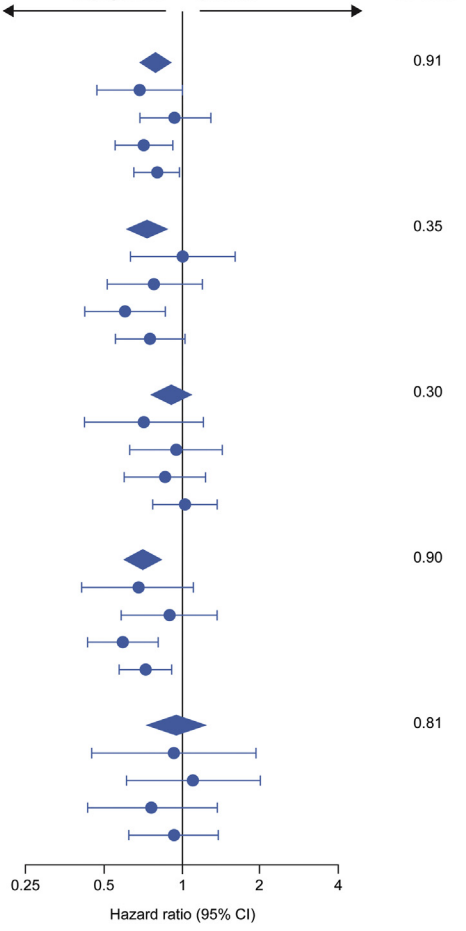
random coefficient model using on-treatment data, with age and baseline eGFR as linear covariates and sex, region, LVEF, diabetes status, baseline eGFR-by-time, treatment-by-cardiac biomarker (quartile), and treatment-by-time-by-cardiac biomarker (quartile) interaction terms as fixed effects. The relationship of cardiac biomarker (continuous) with outcomes was analyzed by the incidence rates using a Poisson model for primary outcome, adjusted with the same covariates as the Cox model and log-transformed cardiac biomarker as well as log-transformed cardiac biomarker-by-treatment interaction in addition.

Geometric mean concentration of NT-proBNP were analyzed across study visits using a mixed model with repeated measures, adjusted for age, baseline eGFR, region, baseline diagnosis of diabetes, sex, LVEF, last projected visit based on dates of randomization and trial closure, baseline log-transformed cardiac biomarker concentration, treatment-by-visit interaction, and baseline log-transformed cardiac biomarker-by-visit interaction. Comparisons between treatment groups at various timepoints were made using adjusted geometric mean ratio. This approach allows for an understanding of the adjusted change in the geometric mean concentration (superior to

FIGURE 1 Continued

B

hs-TnT group	Empagliflozin: n with event/ N analyzed (%)[a]	Empagliflozin: Rate per 100 patient-years	Placebo: n with event/ N analyzed (%)[a]	Placebo: Rate per 100 patient-years	HR (95% CI)	*P* value for trend
Time to first event of CV death or hospitalization for HF						
All patients	415/2997 (13.8)	6.9	511/2991 (17.1)	8.7	0.79 (0.69, 0.90)	0.91
<11.6 ng/L	44/714 (6.2)	2.9	66/725 (9.1)	4.3	0.69 (0.47, 1.00)	
≥11.6–<17.7 ng/L	80/763 (10.5)	5.0	78/710 (11.0)	5.3	0.94 (0.69, 1.29)	
≥17.7–<26.9 ng/L	103/711 (14.5)	7.2	143/737 (19.4)	10.0	0.71 (0.55, 0.92)	
≥26.9 ng/L	175/726 (24.1)	13.2	211/739 (28.6)	16.5	0.80 (0.65, 0.97)	
First and recurrent hospitalization for HF						
All patients	407	-	541	-	0.73 (0.61, 0.88)	0.35
<11.6 ng/L	48	-	53	-	1.00 (0.63, 1.59)	
≥11.6–<17.7 ng/L	57	-	68	-	0.78 (0.51, 1.19)	
≥17.7–<26.9 ng/L	89	-	145	-	0.60 (0.42, 0.86)	
≥26.9 ng/L	199	-	264	-	0.75 (0.55, 1.02)	
Time to first event of CV death						
All patients	219/2997 (7.3)	3.4	244/2991 (8.2)	3.8	0.91 (0.76, 1.09)	0.30
<11.6 ng/L	23/714 (3.2)	1.5	33/725 (4.6)	2.1	0.71 (0.42, 1.21)	
≥11.6–<17.7 ng/L	45/763 (5.9)	2.7	45/710 (6.3)	2.9	0.95 (0.63, 1.43)	
≥17.7–<26.9 ng/L	55/711 (7.7)	3.6	67/737 (9.1)	4.3	0.86 (0.60, 1.23)	
≥26.9 ng/L	93/726 (12.8)	12.8	92/739 (12.4)	6.2	1.03 (0.77, 1.37)	
Time to first event of hospitalization for HF						
All patients	259/2997 (8.6)	4.3	352/2991 (11.8)	6.0	0.71 (0.60, 0.83)	0.90
<11.6 ng/L	26/714 (3.6)	1.7	40/725 (5.5)	2.6	0.68 (0.41, 1.11)	
≥11.6–<17.7 ng/L	42/763 (5.5)	2.6	43/710 (6.1)	2.9	0.89 (0.58, 1.36)	
≥17.7–<26.9 ng/L	60/711 (8.4)	4.2	100/737 (13.6)	7.0	0.59 (0.43, 0.81)	
≥26.9 ng/L	121/726 (16.7)	9.1	162/739 (21.9)	12.7	0.72 (0.57, 0.91)	
Time to first renal composite outcome						
All patients	108/2997 (3.6)	2.1	112/2991 (3.7)	2.2	0.95 (0.73, 1.24)	0.81
<11.6 ng/L	14/714 (2.0)	1.1	15/725 (2.1)	1.2	0.93 (0.45, 1.93)	
≥11.6–<17.7 ng/L	23/763 (3.0)	1.7	20/710 (2.8)	1.6	1.10 (0.61, 2.01)	
≥17.7–<26.9 ng/L	20/711 (2.8)	1.7	28/737 (3.8)	2.3	0.76 (0.43, 1.36)	
≥26.9 ng/L	48/726 (6.6)	4.2	49/739 (6.6)	4.4	0.93 (0.62, 1.38)	



arithmetic means for repeated measure comparisons over time) by expressing it as a ratio of the concentration at the present time point/concentration at baseline.

To assess the association between change in NT-proBNP from baseline to week 12 and subsequent primary endpoint events occurring after week 12, a landmark analysis was performed adjusted for same covariates as the Cox model, baseline log-transformed NT-proBNP and NT-proBNP relative change from baseline to week 12.

All analyses were performed using SAS version 9.4 (SAS Institute). The *P* values reported are 2-sided, with $P < 0.05$ considered statistically significant. No adjustments for multiple testing were made.

DATA SHARING. Data will be made available on request in adherence with transparency conventions in medical research and through requests to the corresponding author. Following execution of pre-specified analyses a full database will be made available in adherence with the transparency policy of the sponsor (available online[8]).

RESULTS

The study flow for the present analysis is detailed in Supplemental Figure 1. At baseline, of 5,988 overall study participants in EMPEROR-Preserved, 5,986 (99.9%) and 5,825 (97.3%) had available NT-proBNP and hs-cTnT concentrations, respectively. The overall median baseline (Q1, Q3) concentration of NT-proBNP and hs-cTnT were 974 ng/L (499, 1,731 ng/L) and 17.8 ng/L (11.6, 26.9 ng/L), respectively; 3,767 (65.7%) had an hs-cTnT >14 ng/L (the 99th percentile concentration for a healthy reference population).

BIOMARKERS AND BASELINE CHARACTERISTICS. Characteristics of the study participants by baseline NT-proBNP quartiles are described in **Table 1**. Patients with higher NT-proBNP values were older and had a greater medical severity of heart failure, including more longstanding HF, lower LVEF, worse symptoms, and more prevalent atrial fibrillation. In addition, those with higher baseline concentration for NT-proBNP had worse health status, with meaningfully lower scores for the KCCQ-CSS, KCCQ overall summary score, and KCCQ total symptom score, and they were more likely to have worse kidney function and higher hs-cTnT concentration ($P < 0.001$ for all comparisons). Those with higher baseline NT-proBNP concentrations were less likely to be treated with angiotensin-converting enzyme inhibitors, but they were more likely to be treated with mineralocorticoid receptor antagonists or loop diuretic agents.

The baseline characteristics of study participants by baseline hs-cTnT are detailed in **Table 2**, which shows generally similar patterns; higher hs-cTnT concentrations were associated with more severe HF and comorbidities. Those with higher hs-cTnT were notably less likely to be women ($P < 0.001$); in distinction, there were no obvious differences in sex across NT-proBNP quartiles. Notably, despite associations between hs-cTnT and prevalent coronary artery disease and a majority of study participants with a baseline hs-cTnT above the 99th percentile for a healthy population, most study participants with higher hs-cTnT concentrations did not have a history of either coronary artery disease or prior myocardial infarction.

BASELINE NT-proBNP AND STUDY OUTCOMES. Across quartiles of baseline NT-proBNP concentration, there was stepwise increase in the subsequent rates of the primary endpoint of CV death/HF hospitalization and its individual components (**Figure 1**). Among those randomized to placebo in the highest NT-proBNP quartile, there was >4-fold higher incidence rate for the CV death, HF hospitalization, or the combined risk of both events (from 3.4 to 15.0 events per 100 patient-years), with comparable patterns of considerably higher risk for the time to first renal composite outcome. Treatment with empagliflozin reduced events across NT-proBNP quartiles without interaction with baseline NT-proBNP (P for trend > 0.05); those with more substantial NT-proBNP elevation accrued similar relative benefits as those with lower values. However, because patients with higher NT-proBNP had more elevated event rates, the absolute risk reduction with empagliflozin was greater in those patients with higher NT-proBNP concentrations (**Figure 2**). In a similar fashion, among patients in the placebo group, there was a stepwise increase in total hospitalizations for HF with higher NT-proBNP concentrations at baseline, with a 5-fold higher total number of hospitalizations (from 46 to 253) in the highest quartile of NT-proBNP (**Figure 1**). Empagliflozin reduced total HF hospitalizations without statistical heterogeneity across NT-proBNP concentrations, but with largest absolute reductions in patients in the highest quartiles.

Rates of the renal composite endpoint were slightly more than twice higher between lowest and highest NT-proBNP quartiles, but eGFR declined to a similar degree across NT-proBNP strata (**Table 3**): the mean slope of change among placebo patients was −2.56 mL/min/1.73 m^2/y in quartile 1 and −2.47 mL/min/1.73 m^2/y in quartile 4. In adjusted models, consistent with the main result of EMPEROR-Preserved, no significant reduction in the composite renal outcome was observed across any of the NT-proBNP quartiles (**Figure 1**). Yet, empagliflozin slowed the rate of eGFR in each quartile without significant heterogeneity (effect size ranging from 0.92 to 1.69 mL/min/1.73 m^2/y), P for trend = 0.66).

Last, the effect of empagliflozin on adjusted mean KCCQ-CSS was comparable across NT-proBNP quartiles, with no interaction (Supplemental Table 1).

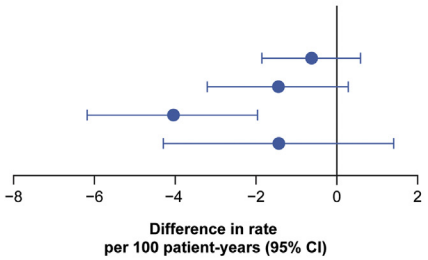
CHANGE IN NT-proBNP. Increase in NT-proBNP from baseline to 12-weeks was strongly associated with risk for the primary endpoint in those treated with placebo (HR: 1.88 per log unit NT-proBNP increase [95% CI: 1.57-2.26]; $P < 0.001$) and empagliflozin (HR: 1.57 per log unit NT-proBNP increase [95% CI: 1.30-1.90]; $P < 0.001$). From baseline to week 100, a minor (albeit statistically significant from week 12 onward) reduction in adjusted geometric mean NT-proBNP was seen, when compared with placebo; adjusted geometric mean reductions were 2%, 4%, 5%, and 7% larger than placebo at weeks 4, 12, 52, and 100, respectively (Supplemental Figure 2). A histogram demonstrating absolute NT-proBNP change from baseline to week 52 is included as Supplemental Figure 3.

BASELINE HS-cTnT AND STUDY OUTCOMES. Similar to the results for baseline NT-proBNP concentrations, there was a significant and clinically meaningful increase in the rates of subsequent primary endpoint of CV death/HF hospitalization events and its individual components across baseline hs-cTnT quartiles (**Figure 1**). There was a nearly 4-fold higher incidence rate per 100 patient-years for CV death, HF

FIGURE 2 Adjusted Rate Differences for the Primary Endpoint of the EMPEROR-Preserved Trial Across Biomarker Quartiles

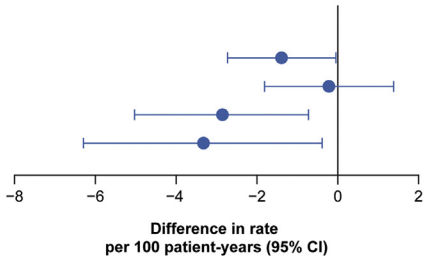
A

NT-proBNP group	Empagliflozin n with event/N analyzed	Placebo n with event/N analyzed	Difference in rate per 100 patient-years (95% CI)	*P* value for trend
Time to first event of CV death or hospitalization for HF				
<499 ng/L	44/747	54/749	−0.63 (−1.85, 0.59)	0.31
≥499–<974 ng/L	80/719	107/776	−1.43 (−3.19, 0.33)	
≥974–<1731 ng/L	105/777	149/721	−4.04 (−6.15, −1.93)	
≥1731 ng/L	186/754	199/743	−1.43 (−4.28, 1.43)	



B

hs-TnT group	Empagliflozin n with event/N analyzed	Placebo n with event/N analyzed	Difference in rate per 100 patient-years (95% CI)	*P* value for trend
Time to first event of CV death or hospitalization for HF				
<11.6 ng/L	44/714	66/725	−1.39 (−2.72, −0.05)	0.10
≥11.6–<17.7 ng/L	80/763	78/710	−0.23 (−1.83, 1.38)	
≥17.7–<26.9 ng/L	103/711	143/737	−2.87 (−5.02, −0.72)	
≥26.9 ng/L	175/726	211/739	−3.33 (−6.29, −0.38)	



Relative risk reduction was the same across biomarker concentration; however, given greater risk for events at higher concentrations of **(A)** NT-proBNP or **(B)** hs-cTnT, reduction in absolute event rate from empagliflozin was greater with higher biomarker concentrations. Abbreviations as in Figure 1.

hospitalization, or the combined risk of both events in placebo-treated study participants in the highest hs-cTnT quartile (from 4.3 to 16.5 events per 100 patient-years), with comparable patterns of higher risk for the time to first renal composite outcome in those with the highest quartile. Empagliflozin reduced events comparably across baseline hs-cTnT quartiles; no treatment by baseline hs-cTnT interaction was detected, and relative reduction in events was similar regardless of baseline hs-cTnT. As in the case of NT-proBNP, study participants with highest baseline hs-cTnT had the largest absolute risk reductions with empagliflozin for the primary endpoint, as shown in Figure 2. With higher baseline hs-cTnT there was increasing total number of hospitalizations for heart failure, with a 5-fold higher number of events between quartiles 1 and 4 in those randomized to placebo (from 53 to 264 events) (Figure 1). Regardless of baseline hs-cTnT, empagliflozin reduced total HF hospitalizations without statistical heterogeneity.

Rates of the composite renal outcome were nearly 4 times higher in the highest hs-cTnT quartile compared with the lowest quartile in placebo-treated participants. As shown in Figure 1, however, no difference in the composite renal outcome across hs-cTnT quartiles was observed. Similar to NT-proBNP, empagliflozin slowed the rate of eGFR decline in each hs-cTnT quartile without significant heterogeneity (Table 3) (P for trend = 0.45).

Adjusted mean KCCQ-CSS change was comparable across study visits and hs-cTnT quartiles without interaction by baseline biomarker concentration (Supplemental Table 1).

DISCUSSION

In this planned analysis from the EMPEROR-Preserved trial, we have made several important findings (Central Illustration). Higher baseline concentrations of NT-proBNP and hs-cTnT were strongly associated with a greater risk profile and more severe HF in patients with an EF >40%. Higher concentrations of NT-proBNP and hs-cTnT were associated with a 4- to 5-fold higher rate of the primary composite endpoint of CV death/HF hospitalization as well as the secondary endpoint of total HF hospitalizations. Higher baseline concentrations of both of these

TABLE 3 Mean Slope of Change in eGFR Relative to NT-proBNP or hs-cTnT Quartile and Treatment Assignment

Biomarker Quartile	Empagliflozin eGFR Slope, mL/min/1.73 m^2/y	Placebo eGFR Slope, mL/min/1.73m^2/y	Slope Difference (95% CI)	*P* Value for Trend
NT-proBNP				
Q1 (<499 ng/L)	−1.38	−2.56	1.18 (0.60-1.76)	0.66
Q2 (499-<974 ng/L)	−0.86	−2.54	1.68 (1.09-2.27)	
Q3 (974-<1,731 ng/L)	−1.28	−2.96	1.69 (1.09-2.28)	
Q4 (≥1,731 ng/L)	−1.55	−2.47	0.92 (0.29-1.55)	
hs-cTnT				
Q1 (<11.6 ng/L)	−1.48	−2.79	1.31 (0.73-1.90)	0.45
Q2 (11.6-<17.7 ng/L)	−1.37	−2.38	1.02 (0.43-1.60)	
Q3 (17.7-<26.9 ng/L)	−1.06	−2.50	1.44 (0.83-2.05)	
Q4 (≥26.9 ng/L)	−1.24	−2.79	1.54 (0.90-2.19)	

Empagliflozin reduced decline in kidney function regardless of biomarker quartile.
Abbreviations as in Table 1.

cardiac biomarkers were also highly associated with a greater likelihood for the composite renal endpoint during follow-up care. Moreover, unlike in other analyses of irbesartan or spironolactone treatment in HFpEF, no biomarker-based heterogeneity in response to treatment with empagliflozin was seen: the relative risk reductions attributable to empagliflozin were comparable across baseline biomarker quartiles, with notably higher absolute reductions in those with higher biomarker concentrations. Change in NT-proBNP after baseline was associated with the primary outcome, and treatment with empagliflozin was associated with a small relative reduction in NT-proBNP concentration across 100 weeks of treatment. These results illustrate the importance of biomarkers reflecting wall stress and cardiomyocyte necrosis for the risk stratification of both cardiac and renal outcomes in individuals with HFpEF and supports the benefit of empagliflozin regardless of biomarker concentration in HFpEF.

The results of this study provide strong evidence for both NT-proBNP and hs-cTnT as important disease markers and prognostic indicators in HFpEF. Although concentrations of both NT-proBNP and hs-cTnT were lower in the EMPEROR-Preserved Trial when compared with the concentrations of both biomarkers in EMPEROR-Reduced,[9] a substantial percentage of study participants had significant elevation of both NT-proBNP or hs-cTnT, and greater values for either were associated with a higher-risk clinical profile characterized by more advanced age, worse HF symptoms, higher antecedent hospitalization rates, and higher prevalence of comorbidities that might be expected to complicate subsequent HF course and treatment. In adjusted models, higher baseline concentrations of both NT-proBNP and hs-cTnT remained independently associated with HF and renal outcomes.

Previous studies regarding NT-proBNP and therapeutic interventions for HFpEF have yielded conflicting patterns of results. Although natriuretic peptide concentrations were directly associated with the primary outcomes of the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction)[4] and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist)-Americas[3] studies, in both trials, Anand et al[3,4] reported an "inverted U shape" association between NT-proBNP and reduction in risk from treatment: benefits of irbesartan and spironolactone were most obvious in those with only modest natriuretic peptide elevation. Although study participants in I-PRESERVE had substantially lower NT-proBNP than in the present analysis, in TOPCAT-Americas, the median concentration was comparable to EMPEROR-Preserved (900 ng/L vs 974 ng/L); yet, in a manner similar to I-PRESERVE, the most obvious benefit from spironolactone in TOPCAT was seen in those in the lower third of NT-proBNP (median 480 ng/L, again very similar to the present analysis). These findings led to the hypothesis that marked elevation of NT-proBNP in HFpEF might identify a patient population whose HF was too advanced to respond to HF therapies or might have HF that was related to infiltrative cardiomyopathies and other restrictive heart muscle disorders, which might respond poorly to neurohormonal antagonists. However, in contrast to these earlier findings, we found no such interaction between baseline NT-proBNP and subsequent response to empagliflozin, that is, the relative reduction in risk from empagliflozin treatment was similar across NT-proBNP concentrations, with

CENTRAL ILLUSTRATION **A Summary of Findings in the EMPEROR-Preserved N-Terminal Pro-B-Type Natriuretic Peptide and High-Sensitivity Cardiac Troponin T Analysis**

5,988 patients with heart failure → **Blood drawn for NT-proBNP and hs-cTnT** → **Assessments**

- LVEF >40%
- Treated with empagliflozin vs placebo

- NT-proBNP at baseline and serially
- hs-cTnT at baseline only

- Baseline clinical status
- HF/renal events follow-up

Findings

Higher baseline concentrations of NT-proBNP and hs-cTnT strongly associated with risk profile and more severe HF

↑NT-proBNP and hs-cTnT was associated with a 4- to 5-fold higher rate of CV death/HF hospitalization, total HF hospitalization, and the composite renal endpoint

Unlike other therapies, relative risk reductions attributable to empagliflozin were comparable across baseline marker quartiles

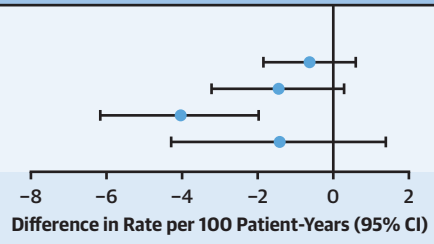
Change in NT-proBNP after baseline was associated with the primary outcome, and treatment with empagliflozin was associated with a small relative reduction in NT-proBNP concentration across 100 weeks of treatment

Outcome Across Biomarker Strata

Absolute Event Rate Difference, Empagliflozin vs Placebo

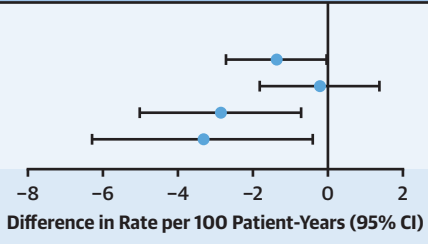
NT-proBNP

NT-proBNP Group	Empagliflozin n With Event/N Analyzed	Placebo n With Event/N Analyzed	Difference in Rate per 100 Patient-Years (95% CI)	*P* Value for Trend
Time to first event of CV death or hospitalization for HF				
<499 ng/L	44/747	54/749	−0.63 (−1.85 to 0.59)	0.31
≥499–<974 ng/L	80/719	107/776	−1.43 (−3.19 to 0.33)	
≥974–<1,731 ng/L	105/777	149/721	−4.04 (−6.15 to −1.93)	
≥1,731 ng/L	186/754	199/743	−1.43 (−4.28 to 1.43)	



hs-cTnT

hs-cTnT Group	Empagliflozin n With Event/N Analyzed	Placebo n With Event/N Analyzed	Difference in Rate per 100 Patient-Years (95% CI)	*P* Value for Trend
Time to first event of CV death or hospitalization for HF				
<11.6 ng/L	44/714	66/725	−1.39 (−2.72 to −0.06)	0.10
≥11.6–<17.7 ng/L	80/763	78/710	−0.23 (−1.83 to 1.38)	
≥17.7–<26.9 ng/L	103/711	143/737	−2.87 (−5.02 to −0.72)	
≥26.9 ng/L	175/726	211/739	−3.33 (−6.29 to −0.38)	



Januzzi Jr. JL, et al. J Am Coll Cardiol HF. 2022;10(7):512–524.

CV = cardiovascular; HF = heart failure; hs-cTnT = high-sensitivity cardiac troponin T; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

greatest absolute reduction in events seen in those with highest concentrations for NT-proBNP.

The data from the present analysis suggest that hs-cTnT is also a powerful biomarker of disease severity and outcomes in HFpEF and that empagliflozin reduces risk across the spectrum of hs-cTnT concentrations. The results from the present analysis are consistent with prior studies indicating that myocardial necrosis is common among individuals with HFpEF, and this finding is associated with higher risk for noncoronary outcomes, such as hospitalization.[10,11] In the present study, placebo-treated patients with higher hs-cTnT values had a 4-fold increased risk for the primary endpoint, reminiscent of results from TOPCAT.[2] Importantly, empagliflozin reduced risk across the wide range of hs-cTnT results in this study, even in those with the most elevated concentrations.

We noted a strong association between change in NT-proBNP and risk for the primary endpoint of EMPEROR-Preserved. These results are consistent with prior results in HFpEF, and they provide important support for the role of NT-proBNP measurement as a tool for longitudinal risk assessment. In the I-PRESERVE trial, an increase or decrease in NT-proBNP concentration between baseline and 6 months was directionally associated with an increased risk of CV death or HF hospitalization,[12] whereas in the more recent PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) trial of sacubitril/valsartan in HFpEF, Cunningham et al[10] reported that a decrease in NT-proBNP from a median concentration of 911 ng/L (comparable to that in EMPEROR-Preserved) by 16 weeks postrandomization was associated with lower subsequent risk of the primary endpoint of total HF hospitalizations or CV death. We observed similar patterns of response in the EMPEROR-Preserved Trial, even though empagliflozin produced only a small reduction in NT-proBNP. Following randomization, concentrations of NT-proBNP in both study arms fell initially; however, both arms showed a gradual rise over the duration of the trial. At each time point, NT-proBNP was lower in those treated with empagliflozin. This may reflect effects of empagliflozin to reduce disease progression over time; similar patterns of natriuretic peptide concentrations have been reported in those treated with SGLT2 inhibitors versus placebo in earlier trials of diabetes and HFrEF.[13,14]

Prior mechanistic studies help to contextualize the present clinical results. Among those with HFpEF, concentrations of natriuretic peptides are associated with increased LV end-diastolic pressure, cardiac hypertrophy and fibrosis, left atrial hypertension, pulmonary venous congestion, plasma volume expansion, and worse kidney function.[15] Similarly, hs-cTn has been associated with left atrial and LV remodeling and worse kidney function in HFpEF;[11,16] it is also linked to impairment in myocardial functional reserve, marked by greater abnormalities in Doppler-derived measures of systolic and diastolic function and impairment in cardiac output response, and accompanied by greater degrees of congestion.[17] Mechanistic studies elucidating the benefit of SGLT2 inhibitor therapy in HFpEF and how these mechanisms are informed by circulating or imaging biomarkers are needed.

STUDY LIMITATIONS. Although this analysis provides strong evidence that empagliflozin exerts similar relative benefits across the wide spectrum of NT-proBNP and hs-cTnT and represents the largest single-trial biomarker analysis of individuals with HFpEF to date, it has limitations. First, although Secular trends in NT-proBNP predict subsequent risk in the trial, the magnitude of NT-proBNP lowering in EMPEROR-Preserved from empagliflozin treatment was modest relative to the clinical benefits observed; further study of the mechanisms by which SGLT2 inhibitors lower NT-proBNP is needed. Further, although NT-proBNP and hs-cTnT were both important predictors of risk in those with HFpEF, it is not clear whether these 2 biomarkers add to clinical factors for risk prediction. Last, we currently have only baseline values for hs-cTnT; further testing of banked samples for postrandomization changes in hs-cTnT is planned.

CONCLUSIONS

In the EMPEROR-Preserved trial, higher baseline concentrations of both NT-proBNP and hs-cTnT were associated with disease severity and prognosis. Empagliflozin reduced CV events and slowed decline in kidney function regardless of baseline biomarker concentrations and showed similar relative benefits across the wide range of biomarker values recorded in the trial. These results provide further support for both NT-proBNP and hs-cTnT as disease markers and prognostic indicators in HFpEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Elevations of baseline levels of both NT-proBNP and hs-cTnT were associated with significantly increased risk of both cardiac and renal outcomes in EMPEROR-Preserved, underscoring their prognostic value in HFpEF populations. NT-proBNP increases over time are associated with rise in risk. Empagliflozin only modestly reduced levels of NT-proBNP, but nevertheless showed consistent benefit on both cardiac outcomes and eGFR slope.

TRANSLATIONAL OUTLOOK: Prior studies suggested heterogeneity of therapeutic response in HFpEF based on NT-proBNP concentrations. The EMPEROR-Preserved trial found no such association between baseline NT-proBNP and subsequent benefit of empagliflozin. The modest impact of empagliflozin, an SGLT2-inhibitor, on NT-proBNP levels over time paired with its prognostic benefits independent of baseline levels of NT-proBNP and hs-cTnT underscores the alternative pathways through which the benefits of this drug class are likely mediated. Further research into the mechanisms of action of empagliflozin in patients with HFpEF are warranted.

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KEY WORDS empagliflozin, heart failure, high-sensitivity cardiac troponin (hs-cTn), N-terminal pro-B-type natriuretic peptide (NT-proBNP), prognosis

APPENDIX For a supplemental table and figures, please see the online version of this paper.