HAL open science

Prognostic Importance of NT-proBNP and Effect of Empagliflozin in the EMPEROR-Reduced Trial

James L Januzzi, Faiez Zannad, Stefan D Anker, Javed Butler, Gerasimos Filippatos, Stuart J Pocock, João Pedro Ferreira, Naveed Sattar, Subodh Verma, Ola Vedin, et al.

To cite this version:

James L Januzzi, Faiez Zannad, Stefan D Anker, Javed Butler, Gerasimos Filippatos, et al.. Prognostic Importance of NT-proBNP and Effect of Empagliflozin in the EMPEROR-Reduced Trial. Journal of the American College of Cardiology, 2021, 78 (13), pp.1321-1332. 10.1016/j.jacc.2021.07.046 . hal-03357955

HAL Id: hal-03357955

https://hal.univ-lorraine.fr/hal-03357955v1

Submitted on 29 Sep 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 78, NO. 13, 2021
© 2021 THE AUTHORS. PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION. THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY-NC-ND LICENSE (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Prognostic Importance of NT-proBNP and Effect of Empagliflozin in the EMPEROR-Reduced Trial

James L. Januzzi, Jr, MD,[a,b,c] Faiez Zannad, MD, PhD,[d] Stefan D. Anker, MD, PhD,[e] Javed Butler, MD, MPH,[f] Gerasimos Filippatos, MD,[g] Stuart J. Pocock, PhD,[h] João Pedro Ferreira, MD,[i] Naveed Sattar, MD,[j] Subodh Verma, MD, PhD,[k] Ola Vedin, MD, PhD,[l] Janet Schnee, MD,[m] Tomoko Iwata, MSc,[n] Dan Cotton, MSc,[m] Milton Packer, MD,[o,p] on behalf of the EMPEROR-Reduced Trial Committees and Investigators

ABSTRACT

BACKGROUND The relationship between the benefits of empagliflozin in heart failure with reduced ejection fraction (HFrEF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) has not been reported.

OBJECTIVES The authors sought to evaluate the relationship between NT-proBNP and empagliflozin effects in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction).

METHODS Patients with HFrEF were randomly assigned to placebo or empagliflozin 10 mg daily. NT-proBNP was measured at baseline, 4 weeks, 12 weeks, 52 weeks, and 100 weeks. Patients were divided into quartiles of baseline NT-proBNP.

RESULTS Incidence rates for each study outcome were 4- to 6-fold higher among those in the highest versus lowest NT-proBNP quartiles (≥3,480 vs <1,115 pg/mL). Study participants with higher NT-proBNP had 2- to 3-fold total hospitalizations higher than the lowest NT-proBNP quartile. Empagliflozin reduced risk for major cardiorenal events without heterogeneity across NT-proBNP quartiles (primary endpoint $P_{interaction} = 0.94$; renal composite endpoint $P_{interaction} = 0.71$). Empagliflozin treatment significantly reduced NT-proBNP at all timepoints examined; by 52 weeks, the adjusted mean difference from placebo was 13% ($P < 0.001$). An NT-proBNP in the lowest quartile (<1,115 pg/mL) 12 weeks after randomization was associated with lower risk for subsequent cardiovascular death or heart failure hospitalization regardless of baseline concentration. Treatment with empagliflozin resulted in 27% higher adjusted odds of an NT-proBNP concentration of <1,115 pg/mL by 12 weeks compared with placebo ($P = 0.01$).

CONCLUSIONS In EMPEROR-Reduced, higher baseline NT-proBNP concentrations were associated with greater risk for adverse heart failure or renal outcomes, but empagliflozin reduced risk regardless of baseline NT-proBNP concentration. The NT-proBNP concentration after treatment with empagliflozin better informs subsequent prognosis than pretreatment concentrations. (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction [EMPEROR-Reduced]; NCT03057977) (J Am Coll Cardiol 2021;78:1321–1332) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts, USA; [b]Harvard Medical School, Boston, Massachusetts, USA; [c]Baim Institute for Clinical Research, Boston, Massachusetts, USA; [d]Université de Lorraine, Inserm Investigation Network Initiative-Cardiovascular and Renal Clinical Trialists, Centre Hospitalier Régional Universitaire, Nancy, France; [e]Department of Cardiology and Berlin Institute of Health Center for Regenerative Therapies, German Centre for Cardiovascular Research Partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany; [f]Department of Medicine, University of Mississippi School of Medicine, Jackson, Mississippi, USA; [g]National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, Athens, Greece; [h]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom; [i]Université de Lorraine, Inserm, Centre d'Investigation Clinique Plurithématique 1433, Centre Hospitalier Régional Universitaire de Nancy, French Clinical Research Infrastructure Network, Investigation Network Initiative-Cardiovascular and Renal Clinical Trialists, Nancy, France; [j]British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [k]Division of Cardiac Surgery, St Michael's Hospital and University of Toronto, Toronto, Ontario, Canada; [l]Boehringer Ingelheim AB, Stockholm, Sweden; [m]Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Connecticut, USA; [n]Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany; [o]Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, Texas, USA; and the [p]Imperial College, London, United Kingdom.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2021.07.046

JACC VOL. 78, NO. 13, 2021
SEPTEMBER 28, 2021:1321–1332

ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

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

SGLT2 = sodium-glucose cotransporter-2

Among patients affected by heart failure (HF) with reduced ejection fraction (HFrEF), elevated concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) are associated with more severe symptoms, worse health status, and a higher risk for hospitalization for HF or cardiovascular (CV) death (1). Elevated or rising concentrations of NT-proBNP in patients with HFrEF are associated with a more decompensated hemodynamic profile, higher filling pressures, and greater risk for progressive adverse cardiac remodeling, hospitalization, and death (1-4). In contrast, a reduction of NT-proBNP values following treatment for HFrEF predicts an improved outcome, better health status, and a higher likelihood for favorable reverse cardiac remodeling (1,2,5). Most treatments that reduce mortality or hospitalization in HFrEF produce some reduction in NT-proBNP concentrations (6).

SEE PAGE 1333

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been added to the foundational treatments for chronic HFrEF. When added to standard HF care, both empagliflozin and dapagliflozin reduced rates of hospitalization or CV death and improved health status (7,8); recent data have also suggested that empagliflozin may lead to reverse cardiac remodeling in HF (9-12), which may, in turn, contribute to lower NT-proBNP concentrations.

Although a reduction in the concentration of NT-proBNP has been reported following treatment with SGLT2 inhibitors among patients with type 2 diabetes (most of whom did not have HFrEF) (13), the significance of NT-proBNP measurement among patients with chronic HFrEF treated with SGLT2 inhibitors is not well understood. In this context, we explored whether baseline NT-proBNP concentrations influence the efficacy of SGLT2 inhibitors in HFrEF, how and over what timescale and pattern SGLT2 inhibitors affect concentrations of NT-proBNP in HFrEF, and how changes in NT-proBNP after empagliflozin treatment are related to subsequent outcomes.

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-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; NCT03057977) trial have been recently reported (8,14). In brief, the study included HF patients with a left ventricular ejection fraction (LVEF) of ≤40% and New York Heart Association functional class II to IV and randomized them in a double-blind manner to receive placebo or empagliflozin 10 mg daily. To prioritize the recruitment of patients at higher risk, either a hospitalization within 12 months of study enrollment or an elevated NT-proBNP concentration was required for study inclusion. The NT-proBNP inclusion criteria were ≥600; 1,000; and 2,500 pg/mL in patients with an LVEF of ≤30%, 31%-35%, and 36%-40%, respectively; these thresholds were doubled in patients with atrial fibrillation.

The primary endpoint of EMPEROR-Reduced was the time to first event in a composite of CV death or hospitalization for HF. Two secondary endpoints were included into the study testing hierarchy: 1) the occurrence of all (first and recurrent) hospitalizations for HF; and 2) the slope of the change in estimated glomerular filtration rate (eGFR) during double-blind treatment. Major adverse renal outcomes were assessed by the need for renal replacement therapy or transplant or by the occurrence of sustained severe reductions in eGFR of ≥40% or reduction to <15 mL/min/1.73 m^2 (if baseline eGFR was ≥30 mL/min/1.73 m^2) or eGFR of <10 mL/min/1.73 m^2 (if baseline eGFR was <30 mL/min/1.73 m^2). Changes in the Kansas City Cardiomyopathy Questionnaire Clinical Summary score across 52 weeks of follow-up were also evaluated.

As part of the study design, blood was collected for measurement of NT-proBNP (Roche Diagnostics) at baseline and again at 4, 12, 52, and 100 weeks.

Scott Solomon, MD, served as Guest Associate Editor for this paper. Christie Ballantyne, MD, served as Guest Editor-in-Chief for this paper.
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.

Manuscript received June 15, 2021; revised manuscript received July 12, 2021, accepted July 16, 2021.

TABLE 1 Characteristics of the Study Participants Categorized by NT-proBNP Quartiles at Baseline

	Quartile 1 <1,115 pg/mL (n = 930)	Quartile 2 1,115-1,909 pg/mL (n = 932)	Quartile 3 1,910-3,479 pg/mL (n = 934)	Quartile 4 ≥3,480 pg/mL (n = 932)	*P* Value
Age, y	64.4 ± 11.0	66.6 ± 10.7	67.6 ± 11.0	68.8 ± 11.0	<0.001
Female	211 (22.7)	230 (24.7)	225 (24.1)	227 (24.4)	0.76
Race					0.72
White	657 (70.6)	670 (71.9)	659 (70.6)	641 (68.8)	
Black	70 (7.5)	60 (6.4)	58 (6.2)	69 (7.4)	
Asian	161 (17.3)	152 (16.3)	181 (19.4)	178 (19.1)	
Other or missing	42 (4.5)	50 (5.4)	36 (3.9)	44 (4.7)	
Region					0.02
North America	114 (12.3)	116 (12.4)	94 (10.1)	101 (10.8)	
Latin America	334 (35.9)	287 (30.8)	318 (34.0)	346 (37.1)	
Europe	327 (35.2)	372 (39.9)	342 (36.6)	311 (33.4)	
Asia	104 (11.2)	116 (12.4)	139 (14.9)	134 (14.4)	
Other	51 (5.5)	41 (4.4)	41 (4.4)	40 (4.3)	
Clinical course of heart failure					
Duration of heart failure, y	3.4 (1.3-8.9)	4.3 (1.5-9.2)	4.2 (1.5-8.4)	4.1 (1.5-9.0)	0.37
NYHA functional class III-IV	163 (17.5)	209 (22.4)	231 (24.7)	326 (35.0)	<0.001
Hospitalization for heart failure within 12 months	246 (26.5)	275 (29.5)	288 (30.8)	342 (36.7)	<0.001
Left ventricular ejection fraction, %	27.6 ± 5.5	27.4 ± 6.0	27.7 ± 6.1	27.1 ± 6.5	0.16
KCCQ-CSS	75.2 ± 20.3	72.0 ± 20.8	70.1 ± 22.3	65.6 ± 23.2	<0.001
Body mass index, kg/m^2	28.8 ± 5.3	28.7 ± 5.5	27.6 ± 5.3	26.4 ± 5.1	<0.001
Heart rate, beats/min	70.1 ± 10.5	70.4 ± 11.3	71.4 ± 12.0	73.2 ± 12.8	<0.001
Systolic blood pressure, mm Hg	123.0 ± 15.2	122.3 ± 15.3	121.9 ± 15.8	120.8 ± 16.2	0.03
Medical history					
Ischemic cause of heart failure	516 (55.5)	496 (53.2)	457 (48.9)	459 (49.2)	0.01
History of myocardial infarction	426 (45.8)	423 (45.4)	388 (41.5)	385 (41.3)	0.08
History of coronary revascularization	391 (42.0)	389 (41.7)	373 (39.9)	369 (39.6)	0.62
Diabetes mellitus	460 (49.5)	458 (49.1)	462 (49.5)	474 (50.9)	0.88
History of atrial fibrillation or flutter	226 (24.3)	363 (38.9)	425 (45.5)	427 (45.8)	<0.001
Atrial fibrillation at baseline	52 (5.6)	178 (19.1)	257 (27.5)	246 (26.4)	<0.001
Hypertension	653 (70.2)	682 (73.2)	676 (72.4)	686 (73.6)	0.37
HF management, baseline					
ACE inhibitor/ARB	661 (71.1)	645 (69.2)	672 (71.9)	621 (66.6)	0.06
ARNI	212 (22.8)	204 (21.9)	157 (16.8)	154 (16.5)	<0.001
Beta blocker	890 (95.7)	885 (95.0)	877 (93.9)	880 (94.4)	0.34
Mineralocorticoid receptor antagonist	694 (74.6)	661 (70.9)	671 (71.8)	633 (67.9)	0.02
Loop diuretic	745 (80.1)	773 (82.9)	800 (85.7)	831 (89.2)	<0.001
ICD (including CRT-D)	301 (32.4)	311 (33.4)	303 (32.4)	255 (27.4)	0.02
Laboratory findings					
eGFR, mL/min/1.73 m^2	69.8 ± 21.3	63.8 ± 21.0	59.8 ± 20.3	54.6 ± 21.1	<0.001
eGFR of <60 mL/min/1.73 m^2	308 (33.1)	425 (45.6)	479 (51.3)	587 (63.0)	<0.001
Uric acid, mg/dL	6.71 ± 1.79	6.90 ± 1.93	7.16 ± 2.10	7.66 ± 2.33	<0.001

Values are mean ± SD, n (%), or median (interquartile range). *P* values compare group means using analysis of variance for continuous variables and the chi-square test for categorical variables.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; CRT-D = cardiac resynchronization therapy-defibrillator; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

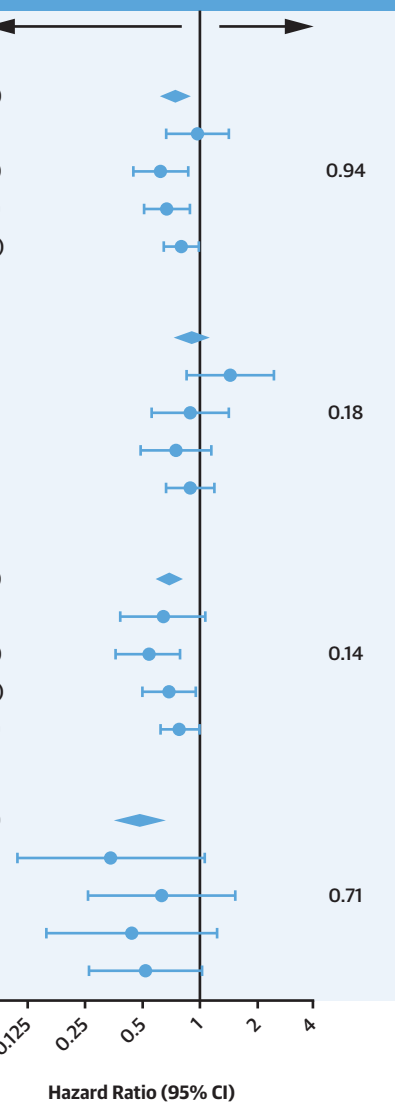
STATISTICAL ANALYSIS. Study participants were categorized by NT-proBNP quartiles, and baseline characteristics were compared.

Geometric mean concentrations 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 NT-proBNP, treatment-by-visit interaction, and baseline log-transformed NT-proBNP-by-visit interaction. Comparisons between treatment groups at various timepoints were made using the adjusted geometric mean ratio.

JACC VOL. 78, NO. 13, 2021
SEPTEMBER 28, 2021:1321–1332

FIGURE 1 Forest Plots for Key CV or Renal Endpoints in EMPEROR-Reduced Trial

NT-proBNP Group	Empagliflozin n with Event/ N Analyzed (%)	Empagliflozin Rate per 100 Patient-Years	Placebo n with Event/ N Analyzed (%)	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	361/1,863 (19.4)	15.8	462/1,867 (24.7)	21.0	0.75 (0.65-0.86)	
<1,115 pg/mL	54/488 (11.1)	8.5	51/442 (11.5)	8.9	0.97 (0.66-1.42)	
1,115-1,909 pg/mL	57/454 (12.6)	9.5	92/478 (19.2)	15.3	0.62 (0.45-0.87)	0.94
1,910-3,479 pg/mL	80/459 (17.4)	14.2	122/475 (25.7)	21.3	0.67 (0.51-0.89)	
≥3,480 pg/mL	170/461 (36.9)	34.7	196/471 (41.6)	43.7	0.80 (0.65-0.98)	
Time to first event of CV death						
All patients	187/1,863 (10.0)	7.6	202/1,867 (10.8)	8.1	0.92 (0.75-1.12)	
<1,115 pg/mL	34/488 (7.0)	5.2	22/442 (5.0)	3.6	1.44 (0.84-2.47)	
1,115-1,909 pg/mL	32/454 (7.0)	5.1	37/478 (7.7)	5.6	0.89 (0.56-1.43)	0.18
1,910-3,479 pg/mL	35/459 (7.6)	5.8	51/475 (10.7)	7.8	0.75 (0.49-1.16)	
≥3,480 pg/mL	86/461 (18.7)	14.7	91/471 (19.3)	16.2	0.89 (0.66-1.19)	
Time to first event of hospitalization for HF						
All patients	246/1,863 (13.2)	10.8	342/1,867 (18.3)	15.6	0.69 (0.59-0.81)	
<1,115 pg/mL	24/488 (4.9)	3.8	34/442 (7.7)	5.9	0.64 (0.38-1.07)	
1,115-1,909 pg/mL	39/454 (8.6)	6.5	74/478 (15.5)	12.3	0.54 (0.36-0.79)	0.14
1,910-3,479 pg/mL	59/459 (12.9)	10.5	88/475 (18.5)	15.3	0.69 (0.50-0.96)	
≥3,480 pg/mL	124/461 (26.9)	25.3	146/471 (31.0)	32.6	0.78 (0.62-1.00)	
Time to first renal composite outcome						
All patients	30/1,863 (1.6)	1.6	58/1,867 (3.1)	3.1	0.50 (0.32-0.77)	
<1,115 pg/mL	4/488 (0.8)	0.8	11/442 (2.5)	2.3	0.34 (0.11-1.06)	
1,115-1,909 pg/mL	8/454 (1.8)	1.6	12/478 (2.5)	2.4	0.63 (0.26-1.54)	0.71
1,910-3,479 pg/mL	5/459 (1.1)	1.1	13/475 (2.6)	2.6	0.44 (0.16-1.23)	
≥3,480 pg/mL	13/461 (2.8)	3.0	22/471 (4.7)	5.3	0.52 (0.26-1.03)	



Outcomes and treatment effect are expressed as a function of NT-proBNP quartile. CV = cardiovascular; EMPEROR-Reduced = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

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. A joint frailty model was used for the analysis of total (ie, first and potentially recurrent) events, incorporating the same variables as the time-to-event analyses and including death as a competing risk. Changes in eGFR slope were analyzed using a 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-NT-proBNP (quartile), and treatment-by-time-by-NT-proBNP (quartile) interaction terms as fixed effects. Given the stratified NT-proBNP inclusion criteria for those with an LVEF of >30%, a sensitivity analysis that focused only on those patients with an LVEF of ≤30% was also performed.

TABLE 2 Total Number of Heart Failure Hospitalizations Expressed in NT-proBNP Quartiles and Treatment Assignment

NT-proBNP Quartile	Empagliflozin, Total Hospitalizations	Empagliflozin Events per 100 Patient-Years	Placebo, Total Hospitalizations	Placebo Events per 100 Patient-Years	HR (95% CI)	*P* Value for Trend
Q1: <1,115 pg/mL	35	5.4	51	8.5	0.67 (0.41-1.11)	0.49
Q2: 1,115-1,909 pg/mL	57	9.1	118	18.0	0.52 (0.35-0.77)	
Q3: 1,910-3,479 pg/mL	107	17.7	136	20.9	0.85 (0.60-1.22)	
Q4: ≥3,480 pg/mL	189	32.5	248	44.5	0.71 (0.52-0.970)	

Values are n unless otherwise indicated. Empagliflozin reduced heart failure hospitalization similarly across NT-proBNP quartiles.
NT-proBNP = N-terminal pro-B type natriuretic peptide; Q = quartile.

In an effort to understand how the change in NT-proBNP informs outcome, study participants in pooled empagliflozin and placebo groups were categorized as "low" (if in the lowest quartile) or "high" (if in quartiles 2-4) at both baseline and at 12 weeks after randomization; this yielded 4 NT-proBNP categories (low/low, high/low, low/high, and high/high). Time to the primary endpoint was evaluated across these 4 groups by landmark analysis using Cox proportional hazards modeling, as described, with the landmarked data beginning at week 12, to assess the association between NT-proBNP at 2 time points and the differences in the risk of subsequent events after 12 weeks. The 12-week visit was scheduled in a visit window of 12 weeks ± 7 days, with values of NT-proBNP mapped to the closest planned visit, where used (if no other values were available), that was closer to the planned measurement. This way, NT-proBNP values were measured at as early as 8 weeks or as late as 16 weeks. Because the quartiles of NT-proBNP were ordered, trend tests were used for the calculation of *P* values to evaluate the influence of baseline values for NT-proBNP on CV and renal outcomes, using the covariate adjustments as described.

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 prespecified analyses, a full database will be made available in adherence with the transparency policy of the sponsor.

RESULTS

Baseline NT-proBNP results were available in 3,728 study participants; the median NT-proBNP value at baseline was 1,910 pg/mL (interquartile range: 1,115-3,480 pg/mL).

NT-proBNP 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 greater medical complexity, including more atrial fibrillation, higher rates of recent hospitalization, and poorer health status ($P < 0.001$ for all comparisons). Consistent with the design of the study (with higher inclusion NT-proBNP concentrations for those with higher LVEF), no significant difference in the LVEF was found across quartiles. Those with higher baseline NT-proBNP concentrations were less likely to be treated with neurohormonal antagonists but were more likely to be treated with loop diuretics.

BASELINE NT-proBNP AND STUDY OUTCOME. Across NT-proBNP quartiles, there was a significant and clinically meaningful increase in the rates of the primary endpoint of CV death/HF hospitalization and its individual components. Among those randomized to placebo in the highest NT-proBNP quartile, there was >4-fold higher incidence rate/100 patient-years for the CV death, HF hospitalization, or the combined risk of both events. Treatment with empagliflozin reduced events across NT-proBNP quartiles without interaction with baseline NT-proBNP (*P* value for trend >0.05) (Figure 1).

There was a stepwise increase in total HF hospitalizations with a doubling of total hospitalizations across NT-proBNP among patients treated with placebo (Table 2). Empagliflozin reduced the risk of total hospitalizations for HF by approximately 30% in the lowest and highest NT-proBNP quartiles, with no significant treatment-by-NT-proBNP heterogeneity (*P* value for trend = 0.49). Similar results were seen if all-cause (rather than CV) mortality was used in the joint frailty model (HR: 0.66, 0.52, 0.84, and 0.73 across quartiles, respectively).

JACC VOL. 78, NO. 13, 2021
SEPTEMBER 28, 2021:1321–1332

TABLE 3 Mean Slope of Change in Estimated Glomerular Filtration Rate Relative to NT-proBNP Quartile and Treatment Assignment

	Slope			
NT-proBNP Quartile	Empagliflozin (n = 1,799)	Placebo (n = 1,792)	Slope Difference (95% CI)	*P* Value for Trend
Q1: <1,115 pg/mL	-0.58	-1.65	1.07 (-0.16 to 2.30)	0.27
Q2: 1,115-1,909 pg/mL	-0.58	-2.47	1.89 (0.67 to 3.12)	
Q3: 1,910-3,479 pg/mL	-0.02	-1.94	1.92 (0.67 to 3.17)	
Q4: ≥3,480 pg/mL	-1.14	-3.29	2.15 (0.79 to 3.51)	

Empagliflozin reduced decline in kidney function regardless of NT-proBNP quartile.
Abbreviations as in Table 2.

The rate of decline in eGFR was related to the baseline NT-proBNP, with the largest decrease in renal function noted among those with higher NT-proBNP values (Table 3); specifically, the mean slope of change among placebo patients in NT-proBNP was −1.65 mL/min/1.73 m^2/year in quartile 1 and −3.29 mL/min/1.73 m^2/year in quartile 4. Empagliflozin slowed the rate of eGFR decline in each quartile, with no significant treatment-by-NT-proBNP heterogeneity (*P* value for trend = 0.27). In addition, rates of the renal composite endpoint were associated with baseline NT-proBNP, with the largest decrease in renal function among those with higher NT-proBNP concentrations ($P < 0.001$) (Figure 1); empagliflozin reduced rates of the renal composite endpoint without treatment interaction with NT-proBNP. In a sensitivity analysis using a shared random effects model with all-cause mortality considered as a competing risk, the mean slope of change of eGFR was greatest at higher NT-proBNP concentrations (Supplemental Table 1).

Changes in the adjusted mean Kansas City Cardiomyopathy Questionnaire Clinical Summary scores were comparable across study visits and NT-proBNP quartiles, with generally larger improvements seen in those treated with empagliflozin (Supplemental Figure 1).

CHANGE IN NT-proBNP OVER TIME AND EFFECT OF EMPAGLIFLOZIN. NT-proBNP concentrations at study visits in the 2 treatment groups are shown in Figure 2 and Supplemental Table 2. At 4 weeks following randomization, treatment with empagliflozin 10 mg lowered NT-proBNP concentrations (as compared to placebo) (adjusted geometric mean ratio: 0.95; 95% CI: 0.92-0.99; $P = 0.009$); this difference persisted across all study timepoints, with the largest difference being seen at 52 weeks (adjusted geometric mean ratio: 0.87; 95% CI: 0.82-0.93; $P < 0.001$). A histogram visualizing absolute NT-proBNP change from baseline to 52 weeks is shown in Supplemental Figure 2; those randomized to empagliflozin 10 mg were more likely to show a reduction in NT-proBNP concentrations by 52 weeks, whereas those randomized to placebo were more likely to show an increase in NT-proBNP concentrations.

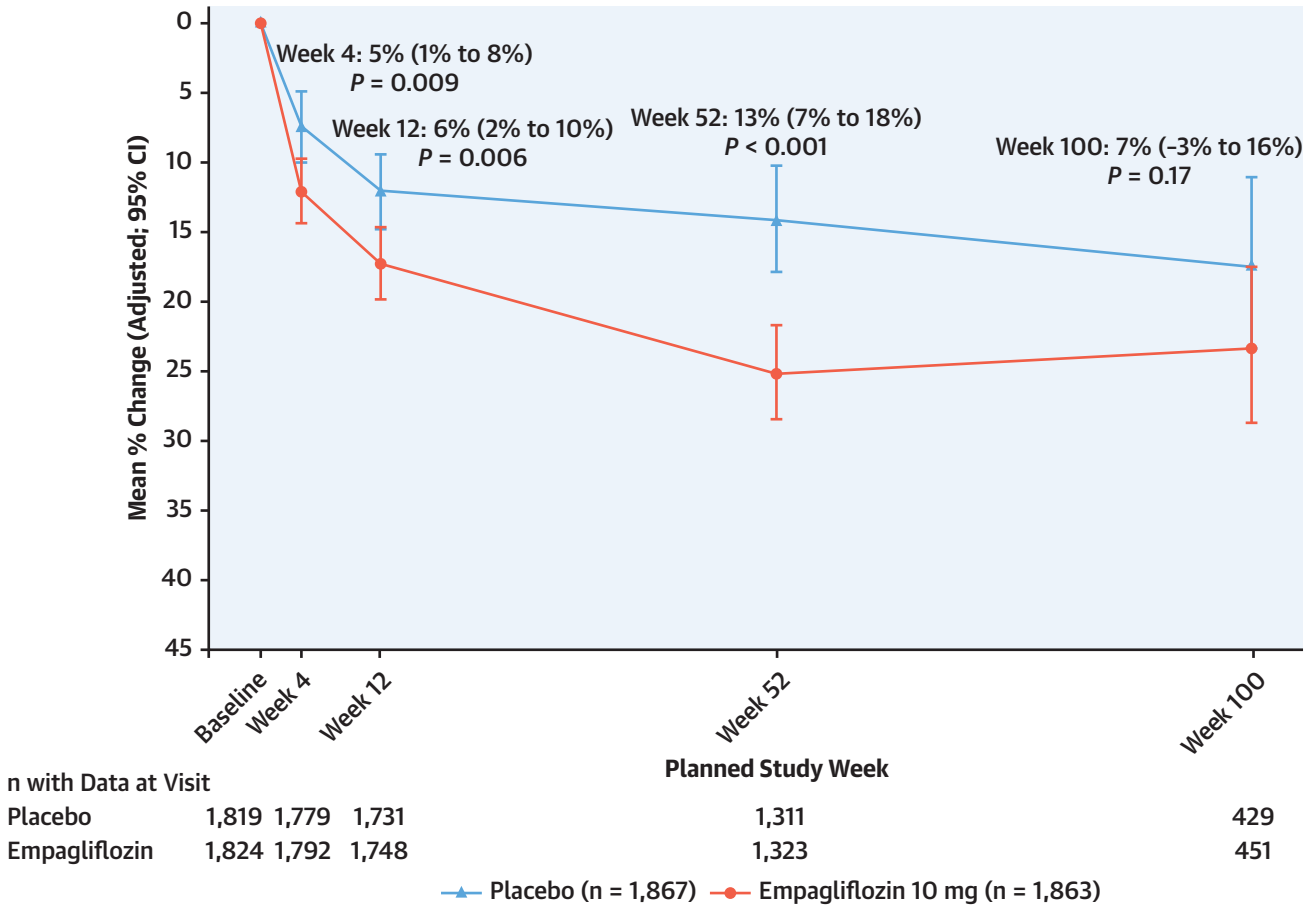
CHANGE IN NT-proBNP BY 12 WEEKS AND OUTCOME. Change in NT-proBNP between baseline and 12 weeks and subsequent outcome was evaluated in a landmark analysis of study participants free of primary endpoint events starting at 12 weeks after randomization; 87% of 3,730 randomized patients were included in the analysis. Patients in pooled empagliflozin and placebo groups were categorized according to their absolute values of NT-proBNP at these 2 timepoints; that is, they were grouped as "low" (quartile 1: <1,115 pg/mL) or "high" (quartiles 2-4: ≥1,115 pg/mL), thus yielding 4 groups: "low/low," "high/low," "low/high," and "high/high."

Using data landmarked beginning at week 12, Kaplan-Meier plots show that the risk for the primary endpoint of CV death/HF hospitalization was lower for those with NT-proBNP values of <1,115 pg/mL at this timepoint when compared to those in higher quartiles (Supplemental Figure 3). When patients were categorized by their baseline and 12-week NT-proBNP, we found that patients were at lower risk if they had an NT-proBNP of <1,115 pg/mL, regardless of the baseline value of NT-proBNP (Figure 3). When compared to the referent category of "high/high," those with an NT-proBNP of <1,115 pg/mL by 12 weeks had a lower adjusted hazard for CV death/HF hospitalization, regardless of their baseline value for NT-proBNP ("low/low" HR: 0.35; 95% CI: 0.26-0.46; $P < 0.001$; "high/low" HR: 0.23; 95% CI: 0.15-0.35; $P < 0.001$). Notably, in those who started "low" but by 12 weeks had an NT-proBNP of ≥1,115 pg/mL, the HR was 0.61 (95% CI: 0.41-0.91; $P = 0.01$) (Figure 4).

The number and proportion of patients in each category are shown in Supplemental Table 3, which shows the effect of empagliflozin in lowering NT-proBNP concentrations at 12 weeks. In a model adjusted for age, sex, LVEF, region, diabetes, baseline eGFR, and baseline NT-proBNP as compared with placebo, treatment with empagliflozin resulted in a 27% (95% CI: 5.6-52.6) higher likelihood of having an NT-proBNP of <1,115 pg/mL ($P = 0.01$). Furthermore, among those with an NT-proBNP of ≥1,115 pg/mL at baseline, across the entire time of the study, treatment with empagliflozin resulted in an adjusted 35% (95% CI: 17-56) higher likelihood of achieving an NT-proBNP of <1,115 pg/mL compared with the placebo group ($P < 0.001$).

SENSITIVITY ANALYSIS. No significant relative difference in NT-proBNP reduction after study entry was

FIGURE 2 Effect of Empagliflozin on NT-proBNP Concentrations



Treatment with empagliflozin resulted in a significant reduction of NT-proBNP compared to placebo as early as 4 weeks and lasting across study visits.
NT-proBNP = N-terminal pro-B-type natriuretic peptide.

observed across LVEF categories (Supplemental Table 4). Reduction of NT-proBNP as a function of treatment assignment across LVEF categories is shown in Supplemental Table 5. Finally, when evaluating only those patients with an LVEF of <30% at inclusion, the outcome results for the primary endpoint and effect of empagliflozin were similar across NT-proBNP categories (Supplemental Table 6).

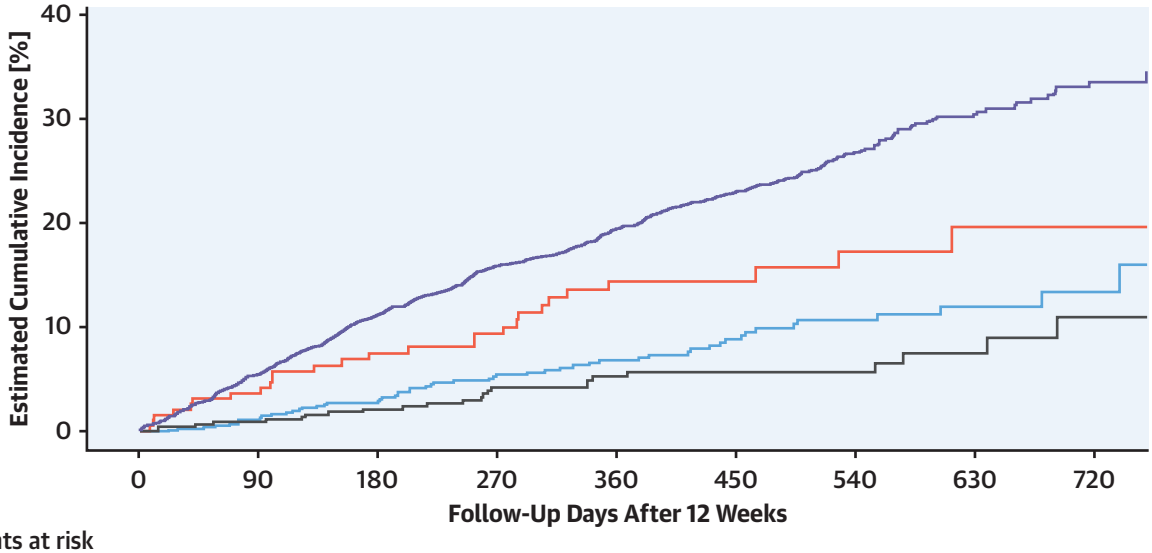
DISCUSSION

In this planned analysis of NT-proBNP concentrations measured from HFrEF patients in the recent EMPEROR-Reduced study, we have made 3 key observations (**Central Illustration**). First, in those with higher baseline NT-proBNP, there was a more severe clinical presentation and higher risk for study endpoints, but the effect of empagliflozin on reducing the risk of adverse CV and renal outcomes was similar across NT-proBNP quartiles. Second, compared to placebo, empagliflozin resulted in greater reductions of NT-proBNP concentrations; this finding was observed early in the study and persisted until the end of follow-up. Third, an NT-proBNP of <1,115 pg/mL by 12 weeks in the study (a finding more frequently present in those treated with empagliflozin) was associated with lower subsequent risks. These results add considerable information to the understanding regarding the role and pattern of NT-proBNP measurements in HFrEF patients treated with SGLT2 inhibitors.

Through its design, the EMPEROR-Reduced trial intended enrollment of higher-risk patients with HFrEF. Reflecting this, the average NT-proBNP concentration at baseline in this study was 1,910 pg/mL, one of the higher concentrations among

JACC VOL. 78, NO. 13, 2021
SEPTEMBER 28, 2021:1321–1332

FIGURE 3 Trial Outcome Relative to Baseline and Follow-Up NT-proBNP Concentrations



Patients at risk Baseline/12 Weeks									
Low/Low	664	654	570	471	388	263	175	93	42
Low/High	190	183	155	142	103	69	50	27	15
High/Low	442	434	367	305	241	178	123	67	33
High/High	1,937	1,813	1,514	1,246	963	716	460	257	121

Cumulative incidence of cardiovascular death or heart failure hospitalization is landmarked beginning at 12 weeks. Patients were categorized as "low" if they had an NT-proBNP of <1,115 pg/mL at baseline or the 12-week mark; if they were above this cutoff, they were categorized as "high." Regardless of starting concentration, if a patient demonstrated an NT-proBNP of <1,115 pg/mL at 12 weeks, the prognosis was substantially better. NT-proBNP = N-terminal pro-B-type natriuretic peptide.

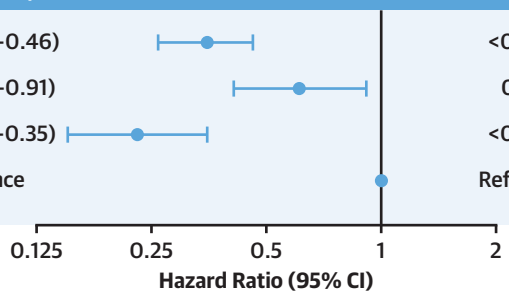
recent trials of ambulatory HFrEF patients (15-17) and, to our knowledge, the highest among ambulatory SGLT2 inhibitor trials reported thus far. In EMPEROR-Reduced, higher baseline concentrations of NT-proBNP were associated with more advanced age and a more decompensated HF profile characterized by worse New York Heart Association functional class, greater burden of recent HF hospitalization, poorest health status, and more prevalent atrial arrhythmia or kidney dysfunction. In keeping with this clinical profile, patients in the highest NT-proBNP quartile were also least likely to receive renin-angiotensin-aldosterone inhibitors and most likely to be treated with loop diuretics.

A stepwise relationship was observed between the baseline value of NT-proBNP and the risk for the primary endpoint in placebo recipients. When compared to those in the lowest NT-proBNP quartile (<1,115 pg/mL), those in the highest NT-proBNP quartile (≥3,480 pg/mL) had a 4- to 6-fold excess rate of CV death, HF hospitalization, or the composite of both endpoints; they also had more than twice the total number of HF hospitalizations. Higher NT-proBNP concentrations were also associated with worse decline in renal function and higher rates of the composite renal endpoint. Treatment with empagliflozin reduced the risk for each adverse outcome across NT-proBNP quartiles without statistical heterogeneity. The large size of the EMPEROR-Reduced trial allows for a comprehensive assessment of treatment modification by baseline NT-proBNP and suggests a consistent relative effect of SGLT2 inhibition to reduce key CV and renal endpoints across NT-proBNP concentrations. Importantly, these results also demonstrate a consistent benefit of empagliflozin in those with the highest NT-proBNP concentrations, an important finding in light of recent data suggesting the attenuation of the benefit of vericiguat in patients with the highest NT-proBNP values before treatment (18).

SGLT2 inhibitors may reduce concentrations of NT-proBNP in patients with type 2 diabetes (13,19), but recent smaller trials have returned conflicting results as to the effect of SGLT2 inhibitors on natriuretic peptides in HF (20,21), where considerably higher concentrations of these biomarkers are

FIGURE 4 NT-proBNP Categories at Baseline and 12 Weeks and Risk for Study Outcome

NT-proBNP Category at Baseline/Week 12	Patients with Event, n/N	Patients with Event, %	Rate per 100 Patient-Years	HR (95% CI)	*P* Value
Low/Low	55/664	8.3	7.49	0.35 (0.26-0.46)	<0.001
Low/High	27/190	14.2	13.04	0.61 (0.41-0.91)	0.01
High/Low	24/442	5.4	4.95	0.23 (0.15-0.35)	<0.001
High/High	438/1,937	22.6	22.00	Reference	Reference



Study participants with NT-proBNP concentrations of <1,115 pg/mL by 12 weeks had lower risk for the primary endpoint of the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) trial, regardless of starting NT-proBNP concentration. NT-proBNP = N-terminal pro-B-type natriuretic peptide.

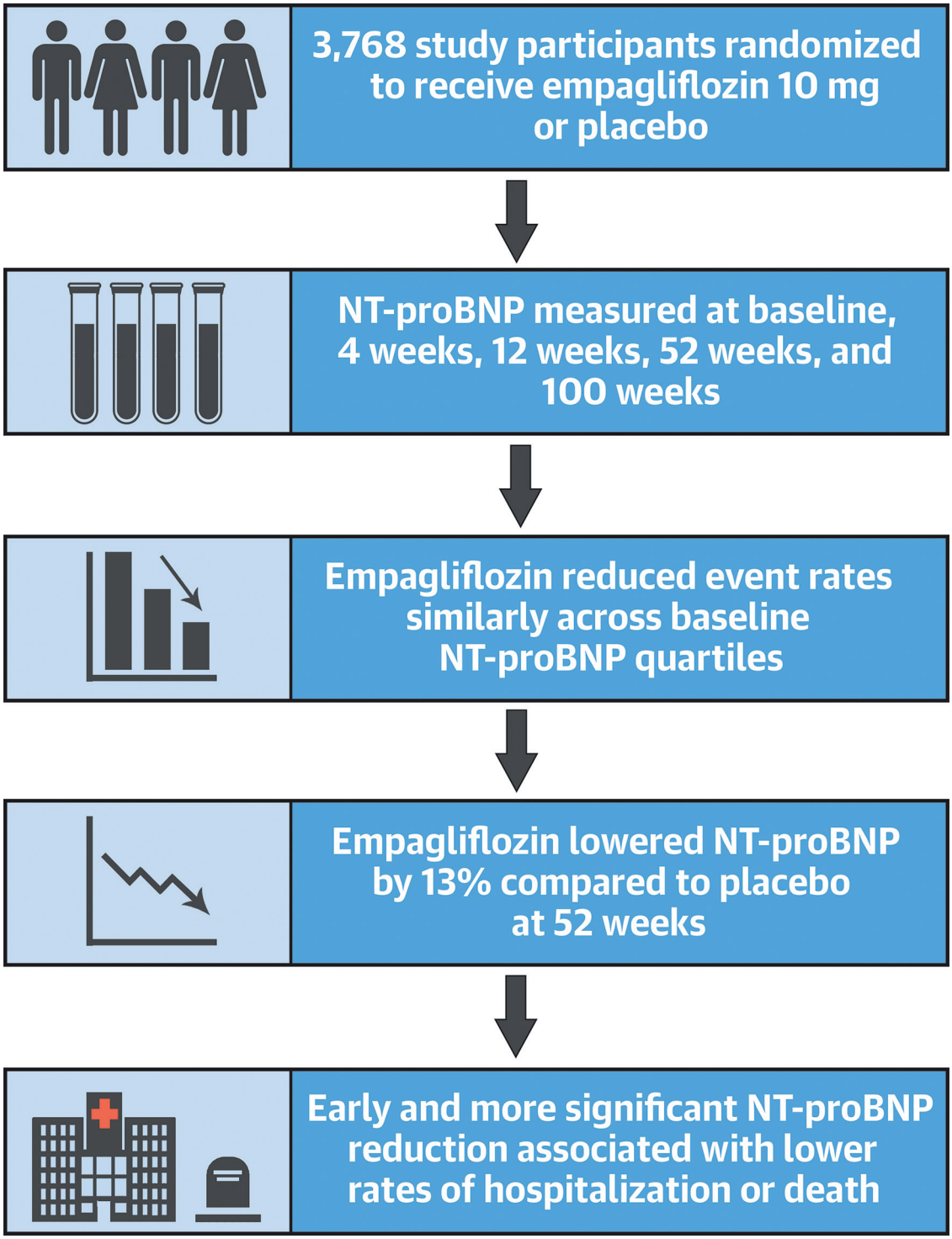
expected. Thus, an important finding in this analysis was evidence for a treatment effect of empagliflozin to reduce NT-proBNP in HFrEF. A difference in biomarker values was already significant by 4 weeks after randomization, which became increasingly apparent over time. By 52 weeks, empagliflozin treatment resulted in an average 13% difference of adjusted NT-proBNP concentrations compared to placebo.

Serial measurement of NT-proBNP is frequently used for risk monitoring in chronic HFrEF; therefore, our results are clinically meaningful. We found that those receiving empagliflozin were 27% more likely than placebo-treated patients to have an NT-proBNP below 1,115 pg/mL by 12 weeks. Prior studies have identified an NT-proBNP concentration of <1,000 pg/mL after HF treatment to be predictive of substantially reduced risk in HFrEF compared to higher achieved values and to be the point at which the magnitude and speed of reverse cardiac remodeling are more pronounced (1,5), so this finding is noteworthy. Of similar importance is the finding that prognosis for CV death/HF hospitalization is better informed by the 12-week NT-proBNP, regardless of the baseline concentration. Similar data focused on treatment with sacubitril/valsartan suggested that a reduction of NT-proBNP to <1,000 pg/mL by 30 days was also predictive of lower risk for CV death/HF hospitalization regardless of baseline values (22), but to our knowledge, these data are the first to show an association between early change in NT-proBNP and improved outcomes after treatment with an SGLT2 inhibitor. We further extend the understanding of how empagliflozin influences NT-proBNP concentrations by showing that through the entire course of the study among those with an NT-proBNP of ≥1,115 pg/mL at baseline, treatment with empagliflozin led to a 35% higher likelihood for an NT-proBNP of <1,115 pg/mL compared with placebo. Mechanistically, early and sustained longitudinal reduction in NT-proBNP following treatment for HFrEF may inform reverse cardiac remodeling after treatment for HFrEF (3,5). Empagliflozin has recently been shown to produce reverse remodeling in randomized trials (9,12), but whether reduction in NT-proBNP owing to treatment with an SGLT2 inhibitor is associated with reverse cardiac remodeling cannot be answered by this analysis. Nonetheless, these results may be of use for clinicians serially measuring NT-proBNP concentrations for risk monitoring and remodeling status.

Our data add to the evidence that treatments reducing risk in HFrEF tend to durably reduce concentrations of NT-proBNP in parallel with reduced risk for CV events and increase the likelihood for reverse cardiac remodeling. Although more modest than the effects of sacubitril/valsartan in reducing NT-proBNP (23), the reduction of NT-proBNP due to treatment with empagliflozin in this study is comparable to that seen with several other drug therapies for HFrEF (24-27). Such early and sustained reduction in NT-proBNP may have implications for risk reduction related to treatment with empagliflozin. To fully contextualize how change in NT-proBNP reflects the benefit of empagliflozin in this trial, a full mediation analysis relating change in all variables affected by SGLT2 inhibition to the primary endpoint would be necessary. This was previously done in a trial of

JACC VOL. 78, NO. 13, 2021
SEPTEMBER 28, 2021:1321–1332

CENTRAL ILLUSTRATION **Key Findings of the EMPEROR-Reduced NT-proBNP Analysis**



Januzzi, Jr., J.L. et al. J Am Coll Cardiol. 2021;78(13):1321–1332.

Treatment with empagliflozin reduced cardiac and renal events equally, regardless of baseline NT-proBNP; however, empagliflozin reduced NT-proBNP concentrations compared to placebo, and early NT-proBNP after empagliflozin treatment was associated with a greater reduction in events. EMPEROR-Reduced = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction trial; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

canagliflozin therapy in type 2 diabetes mellitus (13), where reduction of NT-proBNP accounted for a small percentage of the mediation of HF reduction. Indeed, although we report that empagliflozin resulted in a reduction of NT-proBNP that predicted a posttreatment reduction in risk, in this (as in other studies), the magnitude of early benefit from SGLT2 inhibition in HFrEF appears larger than the modest early reduction in NT-proBNP related to treatment. Mechanistic data are needed to better elucidate how NT-proBNP change reflects a benefit from SGLT2 inhibitors in HFrEF and how other biomarkers might add meaningful information regarding the mediation of reduced risk related to treatment with these agents. A full mediation analysis, considering all variables affected by empagliflozin in EMPEROR-Reduced, is planned to address this complex issue.

STUDY LIMITATIONS. The results from this analysis should be considered in the context of its strengths and limitations. This analysis provides the first large-scale data of serial NT-proBNP measurement among patients with HFrEF treated with empagliflozin. To our knowledge, these data represent the first report of the longer-term effects of empagliflozin on NT-proBNP concentrations and potential prognostic ramifications of such changes. However, the mechanism of the lowering of NT-proBNP by empagliflozin cannot be answered by this data set. An important feature of the EMPEROR-Reduced trial was an inclusion criterion requirement of a higher NT-proBNP for those with an LVEF closer to 40%, whereas those with an LVEF of ≤30% could be enrolled regardless of their NT-proBNP. Given the potential for a reduced treatment effect among those with higher NT-proBNP concentrations, this design might have biased the result of the trial toward the null, but the results of this analysis indicate otherwise. It is also noteworthy that results for the primary endpoint relative to NT-proBNP value were similar whether patients had an LVEF of ≤30% or >30%.

CONCLUSIONS

Among patients in the EMPEROR-Reduced Trial, treatment with empagliflozin reduced risk for CV and renal endpoints similarly across NT-proBNP concentrations, including among the patients at highest risk with most elevated baseline NT-proBNP concentrations. Treatment with empagliflozin lowered NT-proBNP concentrations, and the achievement of a low-risk NT-proBNP concentration by 12 weeks was more predictive of study endpoints than the baseline NT-proBNP.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The EMPEROR-Reduced trial was supported by Boehringer Ingelheim and Eli Lilly and Company. Dr Januzzi is supported in part by the Hutter Family Professorship at Harvard Medical School; is a Trustee of the American College of Cardiology; is a board member of Imbria Pharmaceuticals; has received grant support from Applied Therapeutics, Innolife, Novartis Pharmaceuticals, and Abbott Diagnostics; has received consulting income from Abbott, Janssen, Novartis, and Roche Diagnostics; and participates in Clinical Endpoint Committees/Data Safety Monitoring Boards for Abbott, AbbVie, Amgen, Bayer, CVRx, Janssen, MyoKardia, and Takeda. Dr Zannad has recently received Steering Committee or Advisory Board fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cardior, CVRx, Janssen, LivaNova, Merck, Mundipharma, Novartis, Novo Nordisk, and Vifor Fresenius. Dr Anker has received fees from Abbott, Bayer, Boehringer Ingelheim, Cardiac Dimension, Cordio, Impulse Dynamics, Novartis, Occlutech, Servier, and Vifor Pharma; and has received grant support from Abbott and Vifor Pharma. Dr Butler is a consultant for Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, V-Wave Limited, and Vifor. Dr Filippatos has lectured for and/or has Committee Member contributions in trials sponsored by Medtronic, Vifor, Servier, Novartis, Bayer, Amgen, and Boehringer Ingelheim. Dr Pocock is a consultant for Boehringer Ingelheim. Dr Ferreira is a consultant for Boehringer Ingelheim. Dr Sattar has consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp and Dohme, Novo Nordisk, Novartis, Sanofi, and Pfizer; and has received grant support from Boehringer Ingelheim. Drs Vedin and Schnee, Mr Cotton, and Ms Iwata are employees of Boehringer Ingelheim Pharmaceuticals. Dr Packer has received personal fees from Boehringer Ingelheim during the conduct of the study; and has received personal fees from AbbVie, Akcea, Amarin, AstraZeneca, Amgen, Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, Lilly, Novartis, ParatusRx, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr James L. Januzzi, Jr, Massachusetts General Hospital, 32 Fruit Street, Yawkey 5984, Boston, Massachusetts 02114, USA. E-mail: jjanuzzi@partners.org. Twitter: @JJHeart_doc.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In EMPEROR-Reduced, empagliflozin exerted benefits on cardiorenal outcomes irrespective of baseline NT-proBNP levels. Moreover, empagliflozin treatment resulted in reductions in NT-proBNP, which was associated with improved outcomes.

TRANSLATIONAL OUTLOOK: Further studies generating mechanistic insights on the benefits of empagliflozin treatment in heart failure, in addition to the association with natriuretic peptides, are warranted.

JACC VOL. 78, NO. 13, 2021
SEPTEMBER 28, 2021:1321–1332

REFERENCES

1. Januzzi JL, Jr. Ahmad T, Mulder H, et al. Natriuretic peptide response and outcomes in chronic heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;74:1205–1217.

2. Januzzi JL, Jr. Camacho A, Pina IL, et al. Reverse cardiac remodeling and outcome after initiation of sacubitril/valsartan. *Circ Heart Fail*. 2020;13:e006946.

3. Januzzi JL, Jr. Prescott MF, Butler J, et al. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA*. 2019;322(11):1085–1095.

4. Pina IL, Camacho A, Ibrahim NE, et al. Improvement of health status following initiation of sacubitril/valsartan in heart failure and reduced ejection fraction. *J Am Coll Cardiol HF*. 2021;9:42–51.

5. Daubert MA, Adams K, Yow E, et al. NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFrEF. *J Am Coll Cardiol HF*. 2019;7:158–168.

6. Ferreira JP, Duarte K, Graves TL, et al. Natriuretic peptides, 6-min walk test, and quality-of-life questionnaires as clinically meaningful endpoints in HF trials. *J Am Coll Cardiol*. 2016;68:2690–2707.

7. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.

8. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.

9. Lee MMY, Brooksbank KJM, Wetherall K, et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation*. 2021;143:516–525.

10. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin ameliorates diastolic dysfunction and left ventricular fibrosis/stiffness in nondiabetic heart failure: a multimodality study. *J Am Coll Cardiol Img*. 2021;14:393–407.

11. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. *J Am Coll Cardiol*. 2019;73:1931–1944.

12. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, et al. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2021;77:243–255.

13. Januzzi JL, Jr. Xu J, Li J, et al. Effects of canagliflozin on amino-terminal pro-B-type natriuretic peptide: implications for cardiovascular risk reduction. *J Am Coll Cardiol*. 2020;76:2076–2085.

14. Packer M, Butler J, Filippatos GS, et al. Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. *Eur J Heart Fail*. 2019;21:1270–1278.

15. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382:1883–1893.

16. McMurray JJ, Packer M, Solomon SD. Neprilysin inhibition for heart failure. *N Engl J Med*. 2014;371:2336–2337.

17. Teerlink JR, Diaz R, Felker GM, et al. Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction: GALACTIC-HF baseline characteristics and comparison with contemporary clinical trials. *Eur J Heart Fail*. 2020;22:2160–2171.

18. Ezekowitz JA, O'Connor CM, Troughton RW, et al. N-terminal pro-B-Type natriuretic peptide and clinical outcomes: Vericiguat Heart Failure With Reduced Ejection Fraction Study. *J Am Coll Cardiol HF*. 2020;8:931–939.

19. Januzzi Jr JL, Butler J, Jarolim P, et al. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. *J Am Coll Cardiol*. 2017;70:704–712.

20. Nassif ME, Windsor SL, Tang F, et al. dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. *Circulation*. 2019;140:1463–1476.

21. Tanaka A, Hisauchi I, Taguchi I, et al. Effects of canagliflozin in patients with type 2 diabetes and chronic heart failure: a randomized trial (CANDLE). *ESC Heart Fail*. 2020;7:1585–1594.

22. Zile MR, Claggett BL, Prescott MF, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. *J Am Coll Cardiol*. 2016;68:2425–2436.

23. Myhre PL, Vaduganathan M, Claggett B, et al. B-type natriuretic peptide during treatment with sacubitril/valsartan: the PARADIGM-HF trial. *J Am Coll Cardiol*. 2019;73:1264–1272.

24. Anand IS, Fisher LD, Chiang YT, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). *Circulation*. 2003;107:1278–1283.

25. Olsson LG, Swedberg K, Cleland JG, et al. Prognostic importance of plasma NT-pro BNP in chronic heart failure in patients treated with a beta-blocker: results from the Carvedilol or Metoprolol European Trial (COMET) trial. *Eur J Heart Fail*. 2007;9:795–801.

26. Rosenberg J, Gustafsson F, Remme WJ, Riegger GA, Hildebrandt PR. Effect of beta-blockade and ACE inhibition on B-type natriuretic peptides in stable patients with systolic heart failure. *Cardiovasc Drugs Ther*. 2008;22:305–311.

27. Udelson JE, Feldman AM, Greenberg B, et al. Randomized, double-blind, multicenter, placebo-controlled study evaluating the effect of aldosterone antagonism with eplerenone on ventricular remodeling in patients with mild-to-moderate heart failure and left ventricular systolic dysfunction. *Circ Heart Fail*. 2010;3:347–353.

KEY WORDS heart failure, NT-proBNP, prognosis

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