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CLINICAL RESEARCH

Influence of NT-proBNP on Efficacy of Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction

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ABSTRACT

BACKGROUND N-terminal pro-B-type natriuretic peptide (NT-proBNP) is used for diagnostic and prognostic evaluation in heart failure (HF). Previous clinical trials in heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF) have shown potential heterogeneity in the treatment response by baseline NT-proBNP levels.

OBJECTIVES The purpose of this study was to assess the treatment effect of dapagliflozin across baseline levels of NT-proBNP among patients with HFmrEF or HFpEF.

METHODS This was a post hoc analysis from DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure), a randomized, placebo-controlled trial of dapagliflozin in patients with HFmrEF or HFpEF. Elevated NT-proBNP was part of the inclusion criteria (≥300 ng/L for non-atrial fibrillation or flutter [AFF]; ≥600 ng/L for AFF). Baseline NT-proBNP was categorized in quartiles and additionally analyzed continuously. The primary composite outcome was cardiovascular death or worsening HF events.

RESULTS Among the 6,262 included patients (mean: 71.7 years and 3,516 [56%] men), the median baseline concentration of NT-proBNP was 716 (Q1-Q3: 469-1,280) ng/L and 1,399 (Q1-Q3: 962-2,212) ng/L for non-AFF and AFF, respectively. Higher NT-proBNP levels were linearly associated with a greater risk of the primary outcome (adjusted HR for $\log_2$NTpro-BNP was 1.53 [95% CI: 1.46-1.62] and Q4 vs Q1: 3.46 [95% CI: 2.48-4.22]; $P < 0.001$), with consistent results regardless of AFF status. The clinical benefit of dapagliflozin was present irrespective of baseline NT-proBNP concentration (P value for interaction = 0.40 by quartiles and = 0.19 continuously for the primary outcome) and the absolute risk reduction was, therefore, greater with higher NT-proBNP concentrations. The effect on health status and safety of dapagliflozin was similarly consistent across NT-proBNP quartiles.

CONCLUSIONS Dapagliflozin is safe and improves outcomes irrespective of baseline NT-proBNP concentrations in HFmrEF or HFpEF, with the greatest absolute benefit likely seen in patients with higher NT-proBNP concentrations. (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure [DELIVER]; NCT03619213) (J Am Coll Cardiol HF 2022;10:902-913) © 2022 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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The prognostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been well established in heart failure (HF), and measurement of natriuretic peptides for risk stratification has a Class 1a recommendation in current guidelines.[1] However, patients with heart failure with preserved ejection fraction (HFpEF) typically have lower levels than patients with heart failure with reduced ejection fraction (HFrEF), and there are specific patient populations (such as Black patients or those who are obese) who may have NT-proBNP concentrations within the normal range despite definitely having elevated filling pressures and the clinical syndrome of HF.[2,3] Furthermore, common comorbidities in HFpEF, such as atrial fibrillation or flutter (AFF) and chronic kidney disease, are associated with higher levels of NT-proBNP.[3] Diagnostic algorithms for HFpEF are less dependent on NT-proBNP,[4] and clinical trials typically use lower NT-proBNP thresholds as inclusion criteria in HFpEF compared with HFrEF.[5] As such, the prognostic relevance of NT-proBNP even among those patients with relatively lower NT-proBNP levels needs to be affirmed in a contemporary setting.

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Several clinical trials in HF, both in HFrEF and HFpEF, have raised concern that patients at the higher end of the natriuretic peptide spectrum might derive less benefit from therapies than those with lower natriuretic peptides.[6-8] Although this may be specific to the biological pathways of the drugs in these trials, this has raised the question that some patients may be too sick to benefit from therapies that might otherwise be efficacious. Whether the same may be true with sodium glucose cotransporter-2 (SGLT-2) inhibition in HF with ejection fraction >40% is less certain. The DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; NCT03619213) trial randomized patients with heart failure with mildly reduced ejection fraction (HFmrEF) (41%-49%) or HFpEF (≥50%) to dapagliflozin 10 mg daily or placebo, and showed that dapagliflozin reduced the composite of cardiovascular death or worsening HF in this population.[9] This analysis explores the efficacy and safety of dapagliflozin according to baseline NT-proBNP concentrations in HFmrEF or HFpEF.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The DELIVER trial was a multicenter, randomized, double-blind trial in patients with chronic HF and left ventricular ejection fraction (LVEF) >40%, comparing the effect of dapagliflozin 10 mg daily vs matching placebo.[10,11] Ambulatory or hospitalized patients ≥40 years of age with signs and symptoms of HF (New York Heart Association functional class II-IV) were eligible for enrollment. Patients with and without type 2 diabetes mellitus were eligible, and randomization was stratified by diabetes status. Patients were required to have evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy) and elevated NT-proBNP: ≥300 ng/L for patients in sinus rhythm (SR) and ≥600 ng/L for patients in AFF on baseline electrocardiogram. Failure to meet the NT-proBNP threshold criteria was the primary reason for screen failure (n = 3,373 of 4,155; 81%). Key exclusions included uncorrected primary valvular disease, known infiltrative heart disease, hypertrophic cardiomyopathy, myocarditis, hypotension (systolic blood pressure <95 mm Hg), severe hypertension, type 1 diabetes mellitus, or estimated glomerular filtration rate (eGFR) <25 mL/min per 1.73 m^2. The study was approved by institutional review boards or ethics committees at individual study sites, and all patients signed written informed consent.

OUTCOME MEASURES. The primary outcome in the DELIVER trial was a composite of cardiovascular death or worsening HF events (either unplanned hospitalization or urgent HF visit requiring intravenous therapy), analyzed as time to first event. The

ABBREVIATIONS AND ACRONYMS

AFF = atrial fibrillation or flutter

eGFR = estimated glomerular filtration rate

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

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

SGLT2 = sodium glucose cotransporter-2

SR = sinus rhythm

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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 According to Quartiles of NT-proBNP

	NT-proBNP Q1 (300-623 ng/L) (n = 1,570)	NT-proBNP Q2 (624-1,010 ng/L) (n = 1,563)	NT-proBNP Q3 (1,011-1,751 ng/L) (n = 1,565)	NT-proBNP Q4 (1,752-31,290 ng/L) (n = 1,564)	*P* Value for Trend
Age, y	70.0 ± 9.7	70.7 ± 9.4	72.6 ± 9.1	73.4 ± 9.6	<0.001
Male	845 (53.8)	897 (57.4)	881 (56.3)	893 (57.1)	0.170
Race					<0.001
White	1,095 (69.7)	1,112 (71.1)	1,116 (71.3)	1,115 (71.3)	
Asian	293 (18.7)	339 (21.7)	323 (20.6)	319 (20.4)	
Black or African American	57 (3.6)	35 (2.2)	29 (1.9)	38 (2.4)	
American Indian or Alaska Native	69 (4.4)	40 (2.6)	41 (2.6)	39 (2.5)	
Other	56 (3.6)	37 (2.4)	56 (3.6)	53 (3.4)	
Body mass index, kg/m^2	30.3 ± 6.2	30.5 ± 6.3	29.8 ± 6.1	28.7 ± 5.7	<0.001
NYHA functional class III/IV	259 (16.5)	346 (22.1)	375 (23.9)	568 (36.3)	<0.001
LVEF	55.1 ± 9.0	54.7 ± 8.7	54.3 ± 8.6	52.5 ± 8.4	<0.001
Systolic BP, mm Hg	130.2 ± 15.7	128.4 ± 15.4	127.6 ± 15.0	126.6 ± 15.1	<0.001
eGFR, mL/min/1.73 m^2	64.6 ± 19.7	64.6 ± 18.4	60.8 ± 18.4	54.2 ± 18.2	<0.001
Geographic region					<0.001
Europe and Saudi Arabia	720 (45.9)	760 (48.6)	772 (49.3)	752 (48.1)	
Asia	283 (18.0)	328 (21.0)	312 (19.9)	303 (19.4)	
Latin America	370 (23.6)	279 (17.9)	262 (16.7)	270 (17.3)	
North America	197 (12.5)	196 (12.5)	219 (14.0)	239 (15.3)	
Comorbidities					
Type 2 diabetes mellitus	769 (49.0)	748 (47.9)	665 (42.5)	623 (39.8)	<0.001
Myocardial infarction	522 (33.2)	377 (24.1)	364 (23.3)	376 (24.0)	<0.001
Hypertension	1,401 (89.2)	1,396 (89.3)	1,393 (89.0)	1362 (87.1)	0.160
Prior HF hospitalization	539 (34.3)	588 (37.6)	633 (40.4)	778 (49.7)	<0.001
Coronary artery disease	918 (58.5)	771 (49.3)	737 (47.1)	737 (47.1)	<0.001
AFF at baseline ECG	35 (2.2)	708 (45.3)	925 (59.1)	975 (62.3)	<0.001
COPD	158 (10.1)	156 (10.0)	175 (11.2)	203 (13.0)	0.026
Baseline medication					
Loop diuretics	1,089 (69.5)	1,152 (73.7)	1,236 (79.0)	1,333 (85.2)	<0.001
Angiotensin-converting enzyme inhibitor	586 (37.4)	568 (36.3)	582 (37.2)	559 (35.7)	0.760
Angiotensin receptor blocker	616 (39.3)	586 (37.5)	550 (35.1)	519 (33.2)	0.002
Angiotensin receptor neprilysin inhibitor	73 (4.7)	82 (5.2)	59 (3.8)	87 (5.6)	0.100
Beta-blocker	1,275 (81.3)	1,274 (81.5)	1,303 (83.3)	1,324 (84.7)	0.043
Mineralocorticoid receptor antagonist	614 (39.2)	681 (43.6)	677 (43.3)	694 (44.4)	0.015

Values are mean ± SD or n (%), unless otherwise noted.

AFF = atrial fibrillation or flutter; BP = blood pressure; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

outcome measures were adjudicated by an independent Cardiovascular Endpoint Committee blinded to treatment assignment. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores from baseline to week 32 was used to assess changes in health status.

NT-proBNP MEASUREMENTS. NT-proBNP was measured from venous blood samples drawn at the enrollment visit (1 to 21 days before randomization) using the Roche Elecsys proBNP II immunoassay (Roche Diagnostics GmbH) in a central study laboratory (Covance). The measuring range for the assay was 10 ng/L to 35,000 ng/L. The DELIVER trial did not collect serial blood samples during follow-up.

STATISTICAL ANALYSIS. Patients were categorized into quartiles (Q) of baseline NT-proBNP, and the baseline characteristics are presented for each quartile. Categorical and continuous variables were compared by trend across quartiles using Pearson chi-squared tests and analysis of variance tests. NT-proBNP levels were non-normally distributed (assessed by visual inspection of the distribution) and are presented as median (and IQR, Q1-Q3). The other continuous variables are presented as mean ± SD. The association between baseline NT-proBNP and time to first event was analyzed by Cox proportional hazards models using either log2-transformed NT-proBNP or quartiles of NT-proBNP (with Q1 as the reference). The Cox proportional hazards models were adjusted for covariates based on clinical factors known to influence NT-proBNP: age, sex, race (White, Asian, Black or African

TABLE 2 Incidence of Study Outcomes by Baseline NT-proBNP Quartiles and Continuously (Log_2-Transformed)

	NT-proBNP Q1 (300-623 ng/L)	NT-proBNP Q2 (624-1,010 ng/L)	NT-proBNP Q3 (1,011-1,751 ng/L)	NT-proBNP Q4 (1,752-31,290 ng/L)	*P* Value for Trend	Log_2 NT-proBNP Continuously
Primary composite	171 events	210 events	281 events	460 events		HR: 1.53 (95% CI: 1.45-1.61)
	(5.0/100 py)	(6.3/100 py)	(8.6/100 py)	(16.1/100 py)		*P* < 0.001
	Ref.	HR: 1.38 (95% CI: 1.12-1.70)	HR: 1.92 (95% CI: 1.57-2.36)	HR: 3.45 (95% CI: 2.83-4.21)	<0.001	
CV death	74 events	88 events	110 events	220 events		HR: 1.55 (95% CI: 1.43-1.67)
	(2.1/100 py)	(2.5/100 py)	(3.1/100 py)	(6.8/100 py)		*P* < 0.001
	Ref.	HR: 1.31 (95% CI: 0.96-1.81)	HR: 1.61 (95% CI: 1.17-2.20)	HR: 3.20 (95% CI: 2.38-4.30)	<0.001	
HF hospitalization	104 events	137 events	190 events	316 events		HR: 1.54 (95% CI: 1.45-1.64)
	(3.0/100 py)	(4.1/100 py)	(5.8/100 py)	(10.9/100 py)		*P* < 0.001
	Ref.	HR: 1.45 (95% CI: 1.12-1.89)	HR: 2.08 (95% CI: 1.61-2.69)	HR: 3.78 (95% CI: 2.95-4.85)	<0.001	
All-cause death	173 events	191 events	251 events	408 events		HR: 1.42 (95% CI: 1.34-1.50)
	(4.9/100 py)	(5.4/100 py)	(7.1/100 py)	(12.7/100 py)		*P* < 0.001
	Ref.	HR: 1.22 (95% CI: 0.98-1.50)	HR: 1.53 (95% CI: 1.24-1.88)	HR: 2.48 (95% CI: 2.03-3.04)	<0.001	

The associations are adjusted for age, sex, race, geographic region, body mass index, systolic BP, LVEF, AFF on ECG, COPD, mineralocorticoid receptor antagonist use, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor use, and eGFR.

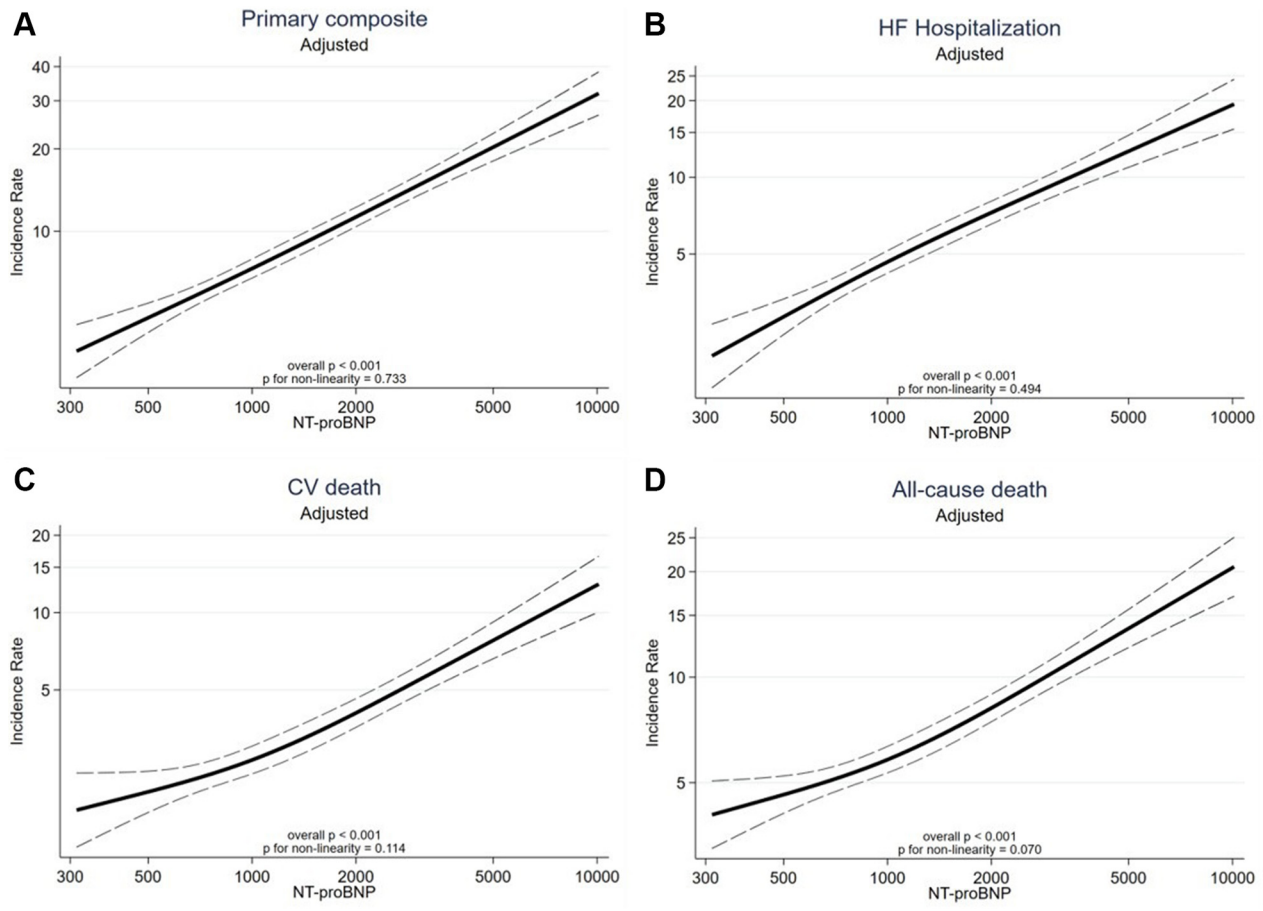
CV = cardiovascular; HF = heart failure; py = person-years; Q = quartile; Ref. = reference; other abbreviations as in Table 1.

American, American Indian or Alaska Native, or other), geographic region (North America, Latin America, Asia, or Europe and Saudi Arabia), body mass index, systolic blood pressure, LVEF, AFF, chronic obstructive pulmonary disease, mineralocorticoid receptor antagonist use, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor use, and eGFR (all assessed at baseline). Sensitivity analyses accounting for competing risks of non-cardiovascular death (for the primary endpoint and cardiovascular death alone) and all-cause death (for HF hospitalization) using the Fine-Gray competing risk models were performed. In an additional sensitivity analysis, to address violations in the proportional hazards assumption, we assessed the associations between NT-proBNP levels and clinical events during different time intervals. We used Cox models truncated at 9 months since randomization, as well as corresponding Cox models landmarked at 9 months since randomization. Flexible cubic splines with 3 knots for the association between log2-transformed NT-proBNP and each outcome, adjusted for the same covariates, were generated. To compare the effects of dapagliflozin vs placebo on the clinical outcomes according to NT-proBNP quartiles and continuously, time-to-event data were evaluated with Cox proportional hazards models, and flexible cubic splines with 3 knots for the treatment effect across levels of log2-transformed baseline NT-proBNP were generated. By applying a consistent relative risk reduction with dapagliflozin (observed in the overall population) to event rates seen in placebo-treated participants, the differences in incidence rate of the primary outcome were calculated continuously across the spectrum of log_2-transformed NT-proBNP. To compare the effects of dapagliflozin vs placebo on changes in health status by baseline NT-proBNP quartiles, we analyzed changes in KCCQ total symptom score, clinical summary score, and overall summary score from baseline to the 8-month visit (ie, difference in each score between patients randomized to dapagliflozin and placebo, adjusted for baseline values). Statistical analyses were performed using STATA 17.1.

RESULTS

BASELINE CHARACTERISTICS ACCORDING TO NT-proBNP CONCENTRATIONS. Of 6,263 patients randomized in the DELIVER trial, 6,262 (99.9%) had available baseline concentrations of NT-proBNP. The median concentration of NT-proBNP was 1,011 (Q1-Q3: 623-1,751) ng/L. NT-proBNP was ≥5,000 ng/L in 251 (4.0%) patients and ≥10,000 ng/L in 65 (1.0%) patients, and the highest registered value was 31,290 ng/L (Supplemental Figure 1). Higher concentrations of NT-proBNP were associated with older age, White race, lower body mass index, lower blood pressure, and lower eGFR (Table 1). Patients with higher NT-proBNP had a lower prevalence of type 2 diabetes mellitus or prior myocardial infarction, and a higher prevalence of prior HF hospitalization, New York Heart Association class III/IV functional class, and lower ejection fractions. NT-proBNP was higher in patients with AFF (median 1,399 [Q1-Q3 962-2,212] ng/L) compared with SR (716 [469-1,280] ng/L; *P* < 0.001) and only 2% of patients had AFF in the lowest quartile of NT-proBNP compared with 45%, 59%, and 62% in quartiles 2, 3, and 4, respectively.

FIGURE 1 Association Between Baseline Concentrations of NT-proBNP and Cardiovascular Events

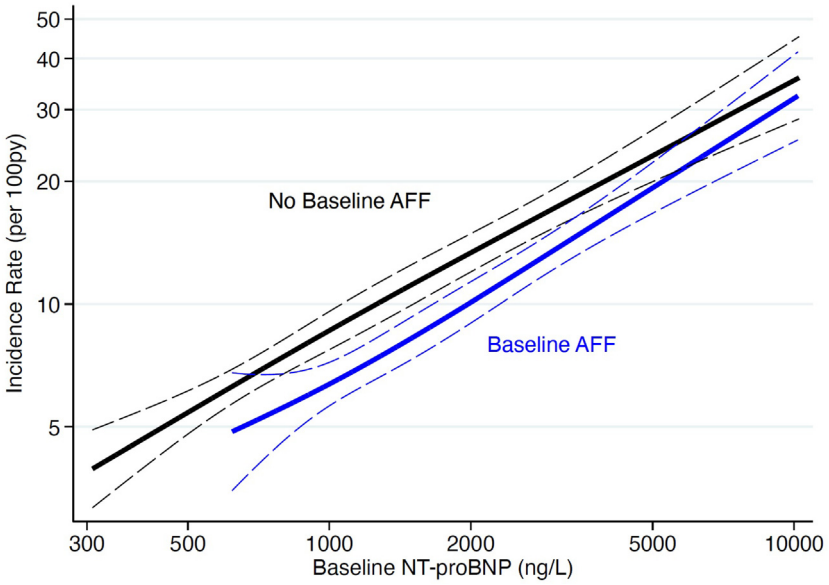


The figure represents fitted cubic splines using 3 knots for the association between $\log_2$-tranformed baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and the incidence rate for **(A)** the primary composite outcome, **(B)** heart failure (HF) hospitalization, **(C)** cardiovascular (CV) death, and **(D)** all-cause death. All models are adjusted for age, sex, race, geographic region, and baseline measures of body mass index, systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate, chronic obstructive pulmonary disease, mineralocorticoid receptor antagonist use, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor use, and atrial fibrillation or flutter on electrocardiogram.

ASSOCIATIONS BETWEEN BASELINE NT-proBNP LEVELS AND OUTCOMES. The median follow-up time was 2.3 (Q1-Q3: 1.7-2.8) years. The incidence rate (per 100 patient-years) of the primary composite outcome increased linearly (*P* value for nonlinearity = 0.73) with increasing baseline levels of log-transformed NT-proBNP: 5.0 for Q1, 6.3 for Q2, 8.6 for Q3, and 16.1 for Q4 (Table 2, Figure 1). The association persisted after adjusting for age, sex, geographic region, body mass index, blood pressure, LVEF, AFF, and eGFR. Strong and linear associations were also observed between baseline log-transformed NT-proBNP and other study outcomes, such as HF hospitalization, cardiovascular death, and all-cause death (Table 2). Consistent associations between NT-proBNP and outcomes were found using competing risk models (Supplemental Table 1). NT-proBNP was associated with the primary outcome irrespective of AFF status (adjusted HR for overall population: 1.53 [95% CI: 1.45-1.61]; $P < 0.001$ per doubling of NT-proBNP); *P* value for interaction = 0.62 (Figure 2). Baseline NT-proBNP levels were found to be most strongly prognostic for events occurring closer to the time of randomization, but remained significantly associated with events occurring later during study follow-up as well (Supplemental Table 2).

TREATMENT EFFECT OF DAPAGLIFLOZIN ACCORDING TO BASELINE NT-proBNP. Dapagliflozin reduced the

FIGURE 2 Association Between Baseline NT-proBNP Levels and Incidence of the Primary Outcome in Patients With and Without AFF at Baseline



The figure represents fitted cubic splines using 3 knots for the association between $\log_2$-tranformed baseline NT-proBNP levels and the composite primary outcome. AFF = fibrillation or flutter; other abbreviations as in Figure 1.

incidence of the primary outcome irrespective of baseline NT-proBNP concentration (*P* interaction 0.40 across NT-proBNP quartiles and *P* interaction 0.19 continuously for log-transformed NT-proBNP) (Table 3, Figure 3). The same consistency in the treatment effect across the range of NT-proBNP was seen for cardiovascular death, HF hospitalization, and all-cause death. The results were similar in competing risk models (Supplemental Table 3). The absolute rate difference between dapagliflozin and placebo was greater in patients with higher levels of baseline NT-proBNP as a result of the higher event rate (Central Illustration).

KCCQ data were available at baseline and at the 8-month visit in 4,411 patients (79% of surviving patients remaining in the study). Dapagliflozin improved health status as measured by KCCQ from baseline to the 8-month visit across quartiles of NT-proBNP: *P* value for interaction was 0.44, 0.68, and 0.42 for total symptom score, clinical summary score, and overall summary score, respectively (Table 4).

Drug discontinuation and reported adverse events were more frequent in the higher quartiles of NT-proBNP but were similar between dapagliflozin and placebo across the quartiles of NT-proBNP (Table 5).

DISCUSSION

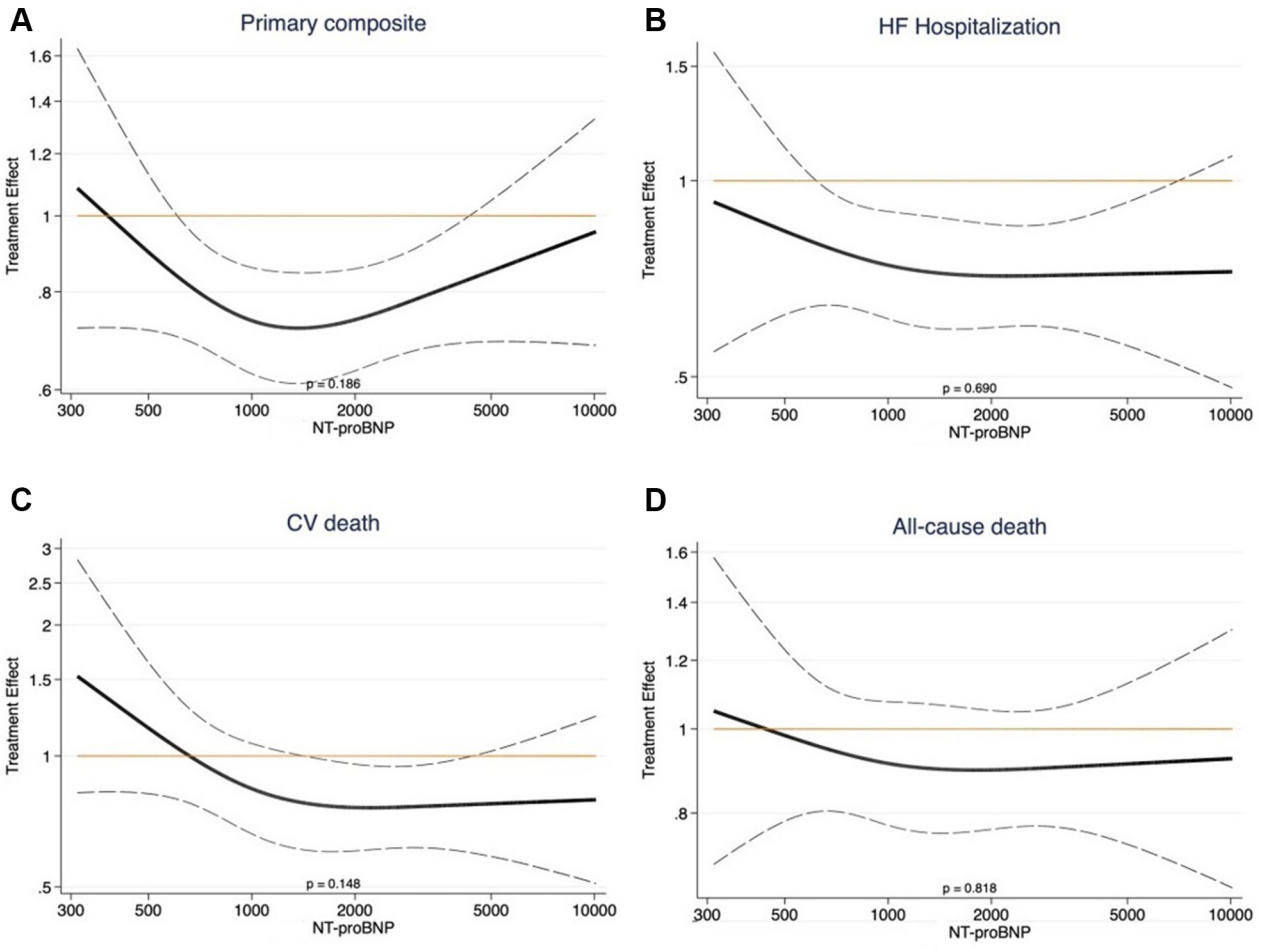
Treatment with dapagliflozin improved outcomes and was well-tolerated across the range of NT-proBNP concentrations at baseline in this contemporary

TABLE 3 Treatment Effect of Dapagliflozin vs Placebo on Study Outcomes by Quartiles of Baseline Concentrations of NT-proBNP

	Total Population	NT-proBNP Q1 (300-623 ng/L)	NT-proBNP Q2 (624-1,010 ng/L)	NT-proBNP Q3 (1,011-1,751 ng/L)	NT-proBNP Q4 (1,752-31,290 ng/L)	*P* Value for Interaction
Primary composite	0.82 (0.73-0.92) *P* = 0.0008	0.99 (0.74-1.34)	0.72 (0.55-0.95)	0.74 (0.58-0.94)	0.82 (0.68-0.98)	*P* = 0.40
CV death	0.88 (0.74-1.05) *P* = 0.17	1.29 (0.81-2.04)	0.88 (0.58-1.34)	0.79 (0.54-1.15)	0.80 (0.61-1.04)	*P* = 0.33
HF hospitalization	0.77 (0.67-0.89) *P* = 0.0004	0.88 (0.60-1.30)	0.72 (0.52-1.02)	0.75 (0.57-1.00)	0.73 (0.58-0.91)	*P* = 0.86
All-cause death	0.94 (0.83-1.07) *P* = 0.34	1.07 (0.79-1.44)	0.84 (0.63-1.12)	0.87 (0.68-1.12)	0.96 (0.79-1.17)	*P* = 0.64

Values are HR (95% CI).
Abbreviations as in Tables 1 and 2.

FIGURE 3 Treatment Effect of Dapagliflozin vs Placebo by Baseline Concentrations of NT-proBNP

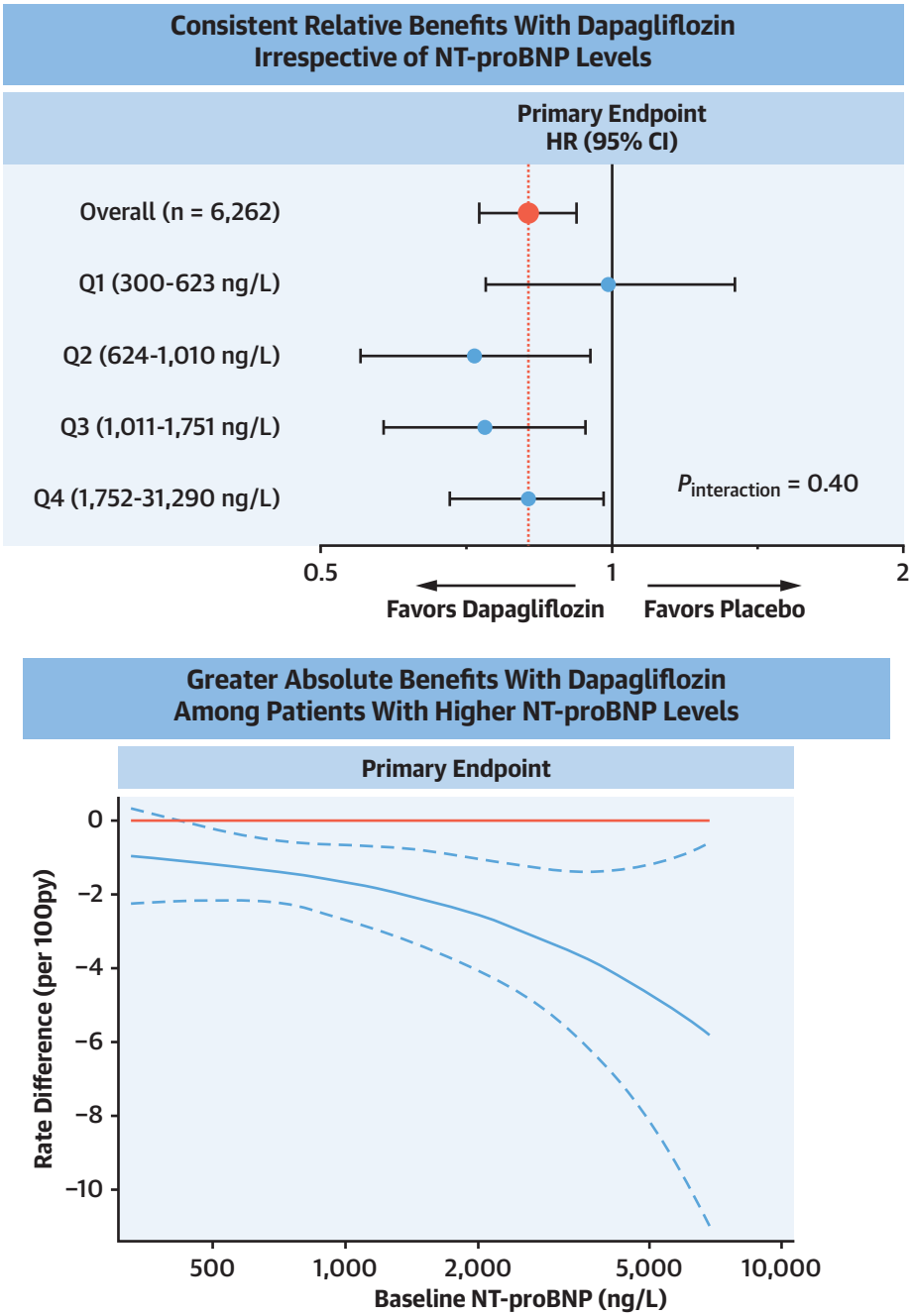


NT-proBNP was $\log_2$-transformed, and the panels represent the association with **(A)** the primary composite outcome, **(B)** HF hospitalization, **(C)** CV death, and **(D)** all-cause death using restricted cubic splines. Abbreviations as in Figure 1.

trial of patients with HFmrEF or HFpEF. Higher concentrations of NT-proBNP were associated with a greater risk of cardiovascular death and worsening HF events, with approximately 3-fold greater risk in the highest compared with the lowest quartile. As such, the greatest absolute risk reductions from dapagliflozin may be seen in patients with higher NT-proBNP baseline concentrations.

Natriuretic peptides are the most common biomarkers used in contemporary HF care and represent one of the strongest risk factors in HF. This analysis, which evaluates the treatment effects of dapagliflozin according to baseline NT-proBNP levels in patients with HFmrEF or HFpEF. This is particularly relevant, as elevated NT-proBNP levels were a key inclusion criterion in most recent contemporary trials of HF, and guidelines have also included elevated natriuretic peptides as a diagnostic criterion for HFpEF.[12] In HFrEF, this criterion is primarily used to enhance risk, but in HFpEF the NT-proBNP elevation together with a structural cardiac abnormality is critical to increase the certainty that patients have HF. On the other hand, some patients with HFpEF (defined by invasive hemodynamic exercise test) have NT-proBNP levels within the normal range.[2] Accordingly, the NT-proBNP threshold for inclusion in HFpEF trials must be low enough to also allow inclusion of these patients and was therefore set to

CENTRAL ILLUSTRATION **NT-proBNP Levels, Clinical Outcomes, and Response to Dapagliflozin in the DELIVER Trial**



Myhre PL, et al. J Am Coll Cardiol HF. 2022;10(12):902–913.

Rate differences for the incidence rate of the primary composite were calculated by applying a consistent relative risk reduction with dapagliflozin (observed in the overall population) to placebo-treated participants across the spectrum of log_2-transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP). DELIVER = Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure.

TABLE 4 Changes in KCCQ Scores From Baseline to the 8-Month Visit in Patients Randomized to Dapagliflozin and Placebo by Quartiles of Baseline NT-proBNP

	NT-proBNP Q1	NT-proBNP Q2	NT-proBNP Q3	NT-proBNP Q4	*P* Value for Interaction
Total symptom score	1.2 (−0.8 to 3.2)	3.2 (1.3 to 5.1)	3.1 (1.3 to 5.0)	2.1 (0.0 to 4.3)	0.44
Clinical summary score	1.7 (−0.1 to 3.5)	2.8 (1.1 to 4.6)	2.9 (1.2 to 4.6)	1.8 (−0.1 to 3.8)	0.68
Overall summary score	1.2 (−0.8 to 3.2)	3.3 (1.3 to 5.2)	3.4 (1.5 to 5.3)	2.1 (0.0 to 4.2)	0.42

Presented is the difference in each score between patients randomized to dapagliflozin and placebo, adjusted for baseline values, the associated 95% CI, and the *P* value for interaction by quartiles of baseline NT-proBNP.

KCCQ = Kansas City Cardiomyopathy Questionnaire; other abbreviations as in Tables 1 and 2.

300 ng/L in DELIVER and EMPEROR-Preserved (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction). As AFF directly increases NT-proBNP, the threshold was higher for patients with AFF at the baseline electrocardiogram (600 ng/L in DELIVER and 900 ng/L in EMPEROR-Preserved). Level of NT-proBNP below the enrollment threshold was the main reason for screen failure in DELIVER. Natriuretic peptide–based eligibility criteria remain important in contemporary trials to affirm the diagnosis of HF and to enrich risk for clinical events. In the current analysis, we demonstrate that NT-proBNP is strongly and linearly associated with cardiovascular events in both AFF and SR and this remained true for all the study outcomes even after comprehensive adjustment for other prognostic variables. The absolute risk for a given NT-proBNP level was indeed lower in patients with AFF and the doubling of the entry NT-proBNP requirement for patients with AFF was appropriate, as the concentration associated with a given risk of the primary outcome was approximately double that for patients with AFF compared with those without. These observations argue for elevation of thresholds of natriuretic peptides as an inclusion criterion in clinical trials for patients with AFF.[5]

Patients in DELIVER had a wide range of baseline NT-proBNP concentrations, from 300 ng/L to more than 30,000 ng/L. Patients in the highest quartile of NT-proBNP had the highest absolute risk. Few patients had very high levels (ie, only 1% had above 10,000 ng/L), and whether these patients had undiagnosed conditions such as hypertrophic or infiltrative cardiomyopathy is unknown. Patients in the lowest quartile of NT-proBNP in our study (<623 ng/L; median 440 ng/L) had the absolute lowest risk, but still 171 of 1,570 patients (11%) experienced a cardiovascular death or worsening HF event over the median 2.3 years of follow-up. This highlights that patients with HFpEF are at substantial risk, even if the NT-proBNP concentrations are low. These patients were younger, with more obesity, diabetes, and coronary artery disease, and substantially less AFF than patients in the higher NT-proBNP quartiles. However, no significant treatment interaction was observed for baseline NT-proBNP, either when analyzed by quartiles or continuously. Similar results with respect to baseline NT-proBNP were also seen in EMPEROR-Preserved[13] and in PRESERVED-HF (Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients With PRESERVED Ejection Fraction Heart Failure),[14] supporting the consistent effect of SGLT2 inhibition across the range of baseline NT-proBNP.

Prior trials of HFmrEF or HFpEF have suggested potentially greater treatment response in those with lower natriuretic peptide levels; however, these observations were based on small sample sizes and with

TABLE 5 Adverse Events in Patients Treated With Dapagliflozin and Placebo, Stratified by Quartiles of Baseline NT-proBNP

	NT-proBNP Q1		NT-proBNP Q2		NT-proBNP Q3		NT-proBNP Q4	
	Placebo	Dapa	Placebo	Dapa	Placebo	Dapa	Placebo	Dapa
Serious adverse events leading to death	67 (8.5)	74 (9.5)	82 (10.4)	69 (8.9)	110 (14.0)	95 (12.2)	162 (21.1)	163 (20.5)
Serious adverse events (all)	306 (38.8)	329 (42.4)	351 (44.7)	291 (37.5)	351 (44.8)	336 (43.2)	415 (54.0)	405 (50.9)
Discontinuation of study drug caused by adverse event	37 (4.7)	46 (5.9)	31 (3.9)	37 (4.8)	46 (5.9)	40 (5.1)	67 (8.7)	59 (7.4)
Interruption of study drug caused by adverse event	104 (13.2)	96 (12.4)	130 (16.6)	102 (13.1)	124 (15.8)	114 (14.7)	136 (17.7)	124 (15.6)

Values are n (%).

Dapa = dapagliflozin; other abbreviations as in Tables 1 and 2.

nominal interaction terms.[7,8] In DELIVER, to date the largest trial in HFmrEF or HFpEF, with more than 1,500 patients with NT-proBNP levels in the lowest quartile (~300-600 ng/L), we observed no such heterogeneity in treatment effects with dapagliflozin across a range of NT-proBNP levels. These findings are highly concordant with the largest outcomes trial of SGLT2 inhibitors, DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events-Thrombolysis In Myocardial Infarction 58), which similarly did not find differential treatment response of dapagliflozin by baseline natriuretic peptide levels.[15] In HFrEF there was a signal of a greater efficacy from dapagliflozin in the lowest baseline NT-proBNP quartile (<857 ng/L); however, without consistent significant interaction for the different outcomes.[16]

Dapagliflozin improved health status compared with placebo, irrespective of baseline NT-proBNP, which is similar to what was seen for empagliflozin in EMPEROR-Preserved.[13] With respect to safety and tolerability, patients in the higher NT-proBNP quartiles were more likely to report adverse events and discontinue both dapagliflozin and placebo, compared with patients in the lower quartiles. However, the proportion of patients with adverse events was not different between dapagliflozin and placebo, and this was consistent across all quartiles of NT-proBNP, again supporting the drug is safe and well-tolerated.

STUDY LIMITATIONS. The DELIVER trial did not collect serial blood samples, so the effect of dapagliflozin on changes in NT-proBNP concentrations cannot be determined. Previous trials across the ejection fraction spectrum of HF have demonstrated modest reductions in NT-proBNP with SGLT2 inhibitors (5%-10%),[13,16] which is less pronounced than other HF drugs.[17] Although NT-proBNP (dichotomized at the median level) was prespecified, this assessment of NT-proBNP by quartiles and as a continuous measure was carried out post hoc. Because of the NT-proBNP inclusion criterion, we are not able to assess the treatment effect in this population with NT-proBNP <300 ng/L in SR and <600 ng/L in AFF. NT-proBNP was measured between 1 and 21 days before randomization, and given the well-known variability in NT-proBNP,[18] this may have influenced the level, particularly in patients who were enrolled during or shortly after hospitalization.

CONCLUSIONS

In HFmrEF or HFpEF, higher NT-proBNP concentrations were consistently and linearly associated with a higher risk of cardiovascular events. Dapagliflozin was safe and well-tolerated, and reduced the relative risk of cardiovascular events across the range of NT-proBNP studied (300 to 31,290 ng/L). Although these data suggest that patients with HFmrEF or HFpEF benefited from dapagliflozin, irrespective of NT-proBNP level at baseline, the absolute reductions in risk were especially large in patients with a high NT-proBNP.

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The DELIVER trial was funded by AstraZeneca. Dr Myhre has consulted for Amgen, Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, and Novo Nordisk. Dr Vaduganathan has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; speaker engagements with AstraZeneca, Novartis, and Roche Diagnostics; and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. Dr Claggett has received consulting fees from Amgen, Cardurion, Corvia, and Novartis. Dr Jhund's employer has been remunerated for his work on the DELIVER and DAPA-HF trials by AstraZeneca; consulting and speaker fees from Novartis, AstraZeneca, and Boehringer Ingelheim; research funding from Boehringer Ingelheim; and remuneration for clinical trial work from NovoNordisk and Bayer. Dr De Boer has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Ionis Pharmaceuticals, Inc, Novo Nordisk, and Roche; and has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Novartis, and Roche. Dr Hernandez has received research grants from American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Somologic and Verily; and has served as a consultant or on the advisory board for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cytokinetics, Eidos, Intercept, Merck, and Novartis. Dr Inzucchi has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lexicon, Merck, Pfizer, vTv Therapeutics, Abbott, and Esperion; and has given lectures sponsored by AstraZeneca and Boehringer Ingelheim. Dr Kosiborod has received research grant support from AstraZeneca, and Boehringer Ingelheim; has served as a consultant or on an advisory board for Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Sanofi, Pharmacosmos, and Vifor Pharma; has received other research support from AstraZeneca; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. Dr Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the advisory board/steering committee/executive committee for Actelion, Alleviant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim,

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Dapagliflozin reduces cardiovascular events irrespective of baseline NT-proBNP concentrations in patients with HFmrEF or HFpEF.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: NT-proBNP is strongly and linearly associated with the risk of HF events and death among patients with HFmrEF or HFpEF; however, many patients with relatively lower NT-proBNP still experience a high burden of clinical events.

TRANSLATIONAL OUTLOOK: SGLT2 inhibition improves outcome across a wide range of NT-proBNP levels in patients with HFmrEF or HFpEF.

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