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

Brief Title: Dapagliflozin by NT-proBNP in HFmrEF or HFpEF

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STRUCTURED ABSTRACT

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

**Objectives:** To assess the treatment effect of dapagliflozin across baseline levels of NT-proBNP among patients with HF with mildly reduced or preserved EF.

**Methods:** This was a post hoc analysis from DELIVER, a randomized, placebo-controlled trial of dapagliflozin in patients with HF with mildly reduced or preserved EF. Elevated NT-proBNP was part of the inclusion criteria (≥300 ng/L for non-atrial fibrillation/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 (Q1-Q3) baseline concentration of NT-proBNP was 716 [469-1280] ng/L and 1399 [962-2212] 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 log₂NTproBNP was 1.53 (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-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 HF with mildly reduced or preserved EF, with the greatest absolute benefit likely seen in patients with higher NT-proBNP concentrations.

**Clinical Trial Registration:** DELIVER; NCT03619213

**Key Words:** Dapagliflozin, SGLT2 inhibitors, NT-proBNP, HFpEF, HFmrEF, clinical trial
CONDENSED ABSTRACT

In this post hoc analysis of the DELIVER trial, we demonstrate that baseline levels of NT-proBNP are strongly and linearly associated with the risk of cardiovascular events in patients with heart failure with mildly reduced or preserved ejection fraction. Dapagliflozin reduced the risk of cardiovascular death or worsening HF events, irrespective of baseline NT-proBNP. The effect on health status and the safety profile of the drug was also consistent across a range of NT-proBNP. As patients with higher baseline NT-proBNP levels experienced heightened risk of clinical events, the absolute risk reduction from dapagliflozin was greatest in these patients.
ABBREVIATIONS AND ACRONYMS

AFF = atrial fibrillation or flutter
CI = confidence interval
CV = cardiovascular
DELIVER = Dapagliflozin Evaluation to Improve the LlVEs of Patients With PReserved Ejection Fraction Heart Failure
eGFR = estimated glomerular filtration rate
HR = hazard ratio
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
LVEF = left ventricular ejection fraction
NT-proBNP = N-terminal pro-B-type natriuretic peptide
SGLT2 = sodium glucose cotransporter-2
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 1A recommendation in current guidelines (1). However, patients with HF with preserved ejection fraction (HFP EF) typically have lower levels than patients with HF 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 HFP EF, such as atrial fibrillation or flutter (AFF) and chronic kidney disease, are associated with higher levels of NT-proBNP (3).

Diagnostic algorithms for HFP EF are less dependent on NT-proBNP (4), and clinical trials typically use lower NT-proBNP thresholds as inclusion criteria in HFP EF compared to 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.

Several clinical trials in heart failure, both in HFrEF and HFP EF, 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 SGLT-2 inhibition in HF with EF>40% is less certain. The DELIVER trial randomized patients with heart failure and mildly reduced (HFrEF; 41-49%) or preserved (≥50%) ejection fraction to dapagliflozin 10 mg daily or placebo, and showed that dapagliflozin reduced the composite of cardiovascular death or worsening heart
failure 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 Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER; NCT03619213) trial was a multicenter, randomized, double-blind trial in patients with chronic heart failure and left ventricular ejection fraction (LVEF) >40%, comparing the effect of dapagliflozin 10 mg daily versus matching placebo (10,11). Ambulatory or hospitalized patients ≥40 years old with signs and symptoms of HF (New York Heart Association [NYHA] functional class II-IV) were eligible for enrollment. Patients with and without type 2 diabetes mellitus (T2DM) 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 atrial fibrillation or flutter (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 mmHg), severe hypertension, type 1 diabetes mellitus or estimated glomerular filtration rate (eGFR) <25 mL/min/1.73m². 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 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, Penzberg, Germany) 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 ANOVA tests. NT-proBNP levels were non-normally distributed (assessed by visual inspection of the distribution) and are presented as median (and interquartile range, Q1-Q3). The other continuous variables are presented as mean±standard deviation. 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 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, in order 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 versus 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 log2-transformed NT-proBNP. To compare the effects of dapagliflozin versus 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 (i.e. difference in each score between patients randomized to dapagliflozin and placebo, adjusted for baseline values). Statistical analyses were performed using STATA 17.1 (College Station, TX, USA).

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 (Q1-Q3) concentration of NT-proBNP was 1011 (623-1751) 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 (Suppl. Figure 1). Higher concentrations of NT-proBNP were associated with older age, White race, lower BMI, lower blood pressure, and lower eGFR (Table 1). Patients with higher NT-proBNP had a lower prevalence of T2DM or prior myocardial infarction, and a higher prevalence of prior HF hospitalization, NYHA class III/IV functional class, and lower ejection fractions. NT-proBNP was higher in patients with AFF (1399 [962-2212] ng/L) compared to SR (716 [469-1280] ng/L; p<0.001) and only 2% of patients had AFF in the lowest quartile of NT-proBNP compared to 45%, 59% and 62% in quartile 2,3 and 4, respectively.

Associations between baseline NT-proBNP levels and outcomes

The median (Q1-Q3) follow-up time was 2.3 (1.7-2.8) years. The incidence rate (per 100 patient-years) of the primary composite outcome increased linearly (p for non-linearity=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, BMI, 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 (Suppl. 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-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 (Suppl. Table 2.)

Treatment effect of dapagliflozin according to baseline NT-proBNP

Dapagliflozin reduced the 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 (Suppl. 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-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 trial of patients with HF with mildly reduced or preserved ejection fraction. 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 to 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 HF with mildly reduced or preserved ejection fraction. 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 300 ng/L in DELIVER and EMPEROR-Preserved. As AFF directly increases NT-proBNP, the threshold was higher for patients with AFF at the baseline ECG (600 ng/L in DELIVER and 900 ng/L in EMPEROR-Preserved). Levels 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 to 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 (i.e. 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 out of 1570 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 AF 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 (14), supporting the consistent effect of SGLT2 inhibition across the range of baseline NT-proBNP.

Prior trials of HF with mildly reduced or preserved ejection fraction have suggested potentially greater treatment response in those with lower natriuretic peptide levels, however, these observations were based on small sample sizes and with nominal interaction terms (7,8). In DELIVER, to date the largest trial in HF with mildly reduced or preserved ejection fraction, with over 1,500 patients with NT-proBNP levels in the lowest quartile (~300-600ng/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 SGLT2i, DECLARE-TIMI 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 to 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 to 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.

Limitations
This study has 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 EF spectrum of HF have demonstrated modest reductions in NT-proBNP with SGLT2 inhibitors (5-10%) (13,17), which is less pronounced than other HF drugs (18). While 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. Due to 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 (19), this may have influenced their level, particularly in patients who were enrolled during or shortly after hospitalization.

CONCLUSIONS
In HF with mildly reduced or preserved ejection fraction, higher NT-proBNP concentrations were consistently and linearly associated with a higher risk of cardiovascular events. Dapagliflozin was safe, well-tolerated, and reduced the relative risk of cardiovascular events across the range of NT-proBNP studied (300 to 31,290 ng/L). While these data suggest that
patients with HF with mildly reduced or preserved ejection fraction 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.
CLINICAL PERSPECTIVES

Competency in Medical Knowledge:

Dapagliflozin reduces cardiovascular events irrespective of baseline NT-proBNP concentrations in patients with HF and mildly reduced or preserved ejection fraction.

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 HF with mildly reduced or preserved ejection fraction; 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 HF with mildly reduced or preserved ejection fraction.
REFERENCES


FIGURE LEGENDS

Figure 1. Association between baseline concentrations of NT-proBNP and cardiovascular events.
The figures represent fitted cubic splines using 3 knots for the association between log$_2$-transformed 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 ECG.

Figure 2. Association between baseline NT-proBNP levels and incidence of the primary outcome in patients with and without atrial fibrillation or flutter (AFF) at baseline
The figures represent fitted cubic splines using 3 knots for the association between log$_2$-transformed baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and the composite primary outcome.

Figure 3. Treatment effect of dapagliflozin versus placebo by baseline concentrations of NT-proBNP
N-terminal pro-B-type natriuretic peptide (NT-proBNP) was log$_2$-transformed and the panels represent the association with A) the primary composite outcome, B) heart failure (HF) hospitalization, C) cardiovascular (CV) death; and D) all-cause death using restricted cubic splines.

Central Illustration. NT-proBNP levels, clinical outcomes and response to dapagliflozin in the DELIVER trial
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).
Table 1 Baseline characteristics according to quartiles of NT-proBNP

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<th></th>
<th>NT-proBNP Q1 (300-623 ng/L)</th>
<th>NT-proBNP Q2 (624-1010 ng/L)</th>
<th>NT-proBNP Q3 (1011-1751 ng/L)</th>
<th>NT-proBNP Q4 (1752-31,290 ng/L)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1570</td>
<td>1563</td>
<td>1565</td>
<td>1564</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>70.0 ± 9.7</td>
<td>70.7 ± 9.4</td>
<td>72.6 ± 9.1</td>
<td>73.4 ± 9.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>845 (53.8%)</td>
<td>897 (57.4%)</td>
<td>881 (56.3%)</td>
<td>893 (57.1%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>1095 (69.7%)</td>
<td>1112 (71.1%)</td>
<td>1116 (71.3%)</td>
<td>1115 (71.3%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>293 (18.7%)</td>
<td>339 (21.7%)</td>
<td>323 (20.6%)</td>
<td>319 (20.4%)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>57 (3.6 %)</td>
<td>35 (2.2 %)</td>
<td>29 (1.9 %)</td>
<td>38 (2.4 %)</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>69 (4.4 %)</td>
<td>40 (2.6 %)</td>
<td>41 (2.6 %)</td>
<td>39 (2.5 %)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>56 (3.6 %)</td>
<td>37 (2.4 %)</td>
<td>56 (3.6 %)</td>
<td>53 (3.4 %)</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>30.3 ± 6.2</td>
<td>30.5 ± 6.3</td>
<td>29.8 ± 6.1</td>
<td>28.7 ± 5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New York Heart Association Class III/IV</td>
<td>259 (16.5%)</td>
<td>346 (22.1%)</td>
<td>375 (23.9%)</td>
<td>568 (36.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>55.1 ± 9.0</td>
<td>54.7 ± 8.7</td>
<td>54.3 ± 8.6</td>
<td>52.5 ± 8.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>130.2 ± 15.7</td>
<td>128.4 ± 15.4</td>
<td>127.6 ± 15.0</td>
<td>126.6 ± 15.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (mL/min/1.73m²)</td>
<td>64.6 ± 19.7</td>
<td>64.6 ± 18.4</td>
<td>60.8 ± 18.4</td>
<td>54.2 ± 18.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Geographic Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Europe and Saudi Arabia</td>
<td>720 (45.9%)</td>
<td>760 (48.6%)</td>
<td>772 (49.3%)</td>
<td>752 (48.1%)</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>283 (18.0%)</td>
<td>328 (21.0%)</td>
<td>312 (19.9%)</td>
<td>303 (19.4%)</td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>370 (23.6%)</td>
<td>279 (17.9%)</td>
<td>262 (16.7%)</td>
<td>270 (17.3%)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>197 (12.5%)</td>
<td>196 (12.5%)</td>
<td>219 (14.0%)</td>
<td>239 (15.3%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus</td>
<td>769 (49.0%)</td>
<td>748 (47.9%)</td>
<td>665 (42.5%)</td>
<td>623 (39.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>522 (33.2%)</td>
<td>377 (24.1%)</td>
<td>364 (23.3%)</td>
<td>376 (24.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1401 (89.2%)</td>
<td>1396 (89.3%)</td>
<td>1393 (89.0%)</td>
<td>1362 (87.1%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Prior HF Hospitalization</td>
<td>539 (34.3%)</td>
<td>588 (37.6%)</td>
<td>633 (40.4%)</td>
<td>778 (49.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Condition</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>Group 4</td>
<td>p-value</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>918 (58.5%)</td>
<td>771 (49.3%)</td>
<td>737 (47.1%)</td>
<td>737 (47.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial Fibrillation/Flutter at baseline ECG</td>
<td>35 (2.2%)</td>
<td>708 (45.3%)</td>
<td>925 (59.1%)</td>
<td>975 (62.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>158 (10.1%)</td>
<td>156 (10.0%)</td>
<td>175 (11.2%)</td>
<td>203 (13.0%)</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>Baseline Medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>1089 (69.5%)</td>
<td>1152 (73.7%)</td>
<td>1236 (79.0%)</td>
<td>1333 (85.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
<td>586 (37.4%)</td>
<td>568 (36.3%)</td>
<td>582 (37.2%)</td>
<td>559 (35.7%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>616 (39.3%)</td>
<td>586 (37.5%)</td>
<td>550 (35.1%)</td>
<td>519 (33.2%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Angiotensin receptor neprilysin inhibitor</td>
<td>73 (4.7%)</td>
<td>82 (5.2%)</td>
<td>59 (3.8%)</td>
<td>87 (5.6%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>1275 (81.3%)</td>
<td>1274 (81.5%)</td>
<td>1303 (83.3%)</td>
<td>1324 (84.7%)</td>
<td>0.043</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonist</td>
<td>614 (39.2%)</td>
<td>681 (43.6%)</td>
<td>677 (43.3%)</td>
<td>694 (44.4%)</td>
<td>0.015</td>
</tr>
</tbody>
</table>
Table 2 Incidence of study outcomes by baseline NT-proBNP quartiles and continuously (log₂-transformed). The associations are adjusted for age, sex, race, geographic region, body mass index, systolic blood pressure, left ventricular ejection fraction, atrial fibrillation/flutter on ECG, chronic obstructive pulmonary disease, mineralocorticoid receptor antagonist use, angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor use and estimated glomerular filtration rate.

<table>
<thead>
<tr>
<th></th>
<th>NT-proBNP Q1 (300-623 ng/L)</th>
<th>NT-proBNP Q2 (624-1010 ng/L)</th>
<th>NT-proBNP Q3 (1011-1751 ng/L)</th>
<th>NT-proBNP Q4 (1752-31,290 ng/L)</th>
<th>P for trend</th>
<th>Log₂ NT-proBNP continuously</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite</strong></td>
<td>171 events [5.0 / 100py] [REF]</td>
<td>210 events [6.3 / 100py] [REF]</td>
<td>281 events [8.6 / 100py] [REF]</td>
<td>460 events [16.1 / 100py] [REF]</td>
<td>HR 1.38 (1.12, 1.70)</td>
<td>HR 1.92 (1.57, 2.36)</td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td>74 events [2.1 / 100py] [REF]</td>
<td>88 events [2.5 / 100py] [REF]</td>
<td>110 events [3.1 / 100py] [REF]</td>
<td>220 events [6.8 / 100py] [REF]</td>
<td>HR 1.31 (0.96, 1.81)</td>
<td>HR 1.61 (1.17, 2.20)</td>
</tr>
<tr>
<td><strong>HF Hospitalization</strong></td>
<td>104 events [3.0 / 100py] [REF]</td>
<td>137 events [4.1 / 100py] [REF]</td>
<td>190 events [5.8 / 100py] [REF]</td>
<td>316 events [10.9 / 100py] [REF]</td>
<td>HR 1.45 (1.12, 1.89)</td>
<td>HR 2.08 (1.61, 2.69)</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>173 events [4.9 / 100py] [REF]</td>
<td>191 events [5.4 / 100py] [REF]</td>
<td>251 events [7.1 / 100py] [REF]</td>
<td>408 events [12.7 / 100py] [REF]</td>
<td>HR 1.22 (0.98, 1.50)</td>
<td>HR 1.53 (1.24, 1.88)</td>
</tr>
</tbody>
</table>

Abbreviations: NT-proBNP = N-terminal pro B-type natriuretic peptide; CV = cardiovascular; HF = heart failure; HR = hazard ratio; Q = quartile; REF = reference
Table 3: Treatment effect of dapagliflozin versus placebo on study outcomes by quartiles of baseline concentrations of NT-proBNP

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>NT-proBNP Q1 (300-623 ng/L)</th>
<th>NT-proBNP Q2 (624-1010 ng/L)</th>
<th>NT-proBNP Q3 (1011-1751 ng/L)</th>
<th>NT-proBNP Q4 (1752-31,290 ng/L)</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite</strong></td>
<td>HR 0.82 (0.73-0.92)</td>
<td>HR 0.99 (0.74, 1.34)</td>
<td>HR 0.72 (0.55, 0.95)</td>
<td>HR 0.74 (0.58, 0.94)</td>
<td>HR 0.82 (0.68, 0.98)</td>
<td>P=0.40</td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td>HR 0.88 (0.74-1.05)</td>
<td>HR 1.29 (0.81, 2.04)</td>
<td>HR 0.88 (0.58, 1.34)</td>
<td>HR 0.79 (0.54, 1.15)</td>
<td>HR 0.80 (0.61, 1.04)</td>
<td>P=0.33</td>
</tr>
<tr>
<td><strong>HF Hospitalization</strong></td>
<td>HR 0.77 (0.67-0.89)</td>
<td>HR 0.88 (0.60, 1.30)</td>
<td>HR 0.72 (0.52, 1.02)</td>
<td>HR 0.75 (0.57, 1.00)</td>
<td>HR 0.73 (0.58, 0.91)</td>
<td>P=0.86</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>HR 0.94 (0.83-1.07)</td>
<td>HR 1.07 (0.79, 1.44)</td>
<td>HR 0.84 (0.63, 1.12)</td>
<td>HR 0.87 (0.68, 1.12)</td>
<td>HR 0.96 (0.79, 1.17)</td>
<td>P=0.64</td>
</tr>
</tbody>
</table>

Abbreviations: NT-proBNP = N-terminal pro B-type natriuretic peptide; CV = cardiovascular; HF = heart failure; HR = Hazard ratio; Q = quartile
Table 4  Changes in Kansas City Cardiomyopathy Questionnaire Scores from baseline to the 8 month visit in patients randomized to dapagliflozin and placebo by quartiles of baseline NT-proBNP. Presented is the difference in each score between patients randomized to dapagliflozin and placebo, adjusted for baseline values, the associated 95% confidence interval and the p for interaction by quartiles of baseline NT-proBNP.

<table>
<thead>
<tr>
<th></th>
<th>NT-proBNP Q1</th>
<th>NT-proBNP Q2</th>
<th>NT-proBNP Q3</th>
<th>NT-proBNP Q4</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Symptom Score</td>
<td>1.2 (-0.8, 3.2)</td>
<td>3.2 (1.3, 5.1)</td>
<td>3.1 (1.3, 5.0)</td>
<td>2.1 (0.0, 4.3)</td>
<td>0.44</td>
</tr>
<tr>
<td>Clinical Summary Score</td>
<td>1.7 (-0.1, 3.5)</td>
<td>2.8 (1.1, 4.6)</td>
<td>2.9 (1.2, 4.6)</td>
<td>1.8 (-0.1, 3.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>Overall Summary Score</td>
<td>1.2 (-0.8, 3.2)</td>
<td>3.3 (1.3, 5.2)</td>
<td>3.4 (1.5, 5.3)</td>
<td>2.1 (0.0, 4.2)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Abbreviations: NT-proBNP = N-terminal pro B-type natriuretic peptide; Q = quartile
Table 5  Adverse events in patients treated with dapagliflozin and placebo, stratified by quartiles of baseline NT-proBNP

<table>
<thead>
<tr>
<th></th>
<th>NT-proBNP Q1</th>
<th>NT-proBNP Q2</th>
<th>NT-proBNP Q3</th>
<th>NT-proBNP Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Dapa</td>
<td>Placebo</td>
<td>Dapa</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>leading to death</td>
<td>67 (8.5 %)</td>
<td>74 (9.5 %)</td>
<td>82 (10.4 %)</td>
<td>69 (8.9 %)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(all)</td>
<td>306 (38.8 %)</td>
<td>329 (42.4 %)</td>
<td>351 (44.7 %)</td>
<td>291 (37.5 %)</td>
</tr>
<tr>
<td>Discontinuation of study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>drug due to adverse event</td>
<td>37 (4.7 %)</td>
<td>46 (5.9 %)</td>
<td>31 (3.9 %)</td>
<td>37 (4.8 %)</td>
</tr>
<tr>
<td>Interruption of study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>drug due to adverse event</td>
<td>104 (13.2 %)</td>
<td>96 (12.4 %)</td>
<td>130 (16.6 %)</td>
<td>102 (13.1 %)</td>
</tr>
</tbody>
</table>

Abbreviations: NT-proBNP = N-terminal pro B-type natriuretic peptide; Q = quartile
Figure 1

(A) Primary composite
Adjusted
overall p < 0.001
p for non-linearity 0.743

(B) HF Hospitalization
Adjusted
overall p < 0.001
p for non-linearity < 0.001

(C) CV death
Adjusted
overall p < 0.001
p for non-linearity 0.147

(D) All-cause death
Adjusted
overall p < 0.001
p for non-linearity < 0.001
Figure 3
Central Illustration

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

**Consistent relative benefits with dapagliflozin irrespective of NT-proBNP levels**

**Greater absolute benefits with dapagliflozin among patients with higher NT-proBNP levels**

Primary Endpoint

HR (95% CI)

Overall (n=6,262)

Q1 (300-623 ng/L)

Q2 (624-1010 ng/L)

Q3 (1011-1751 ng/L)

Q4 (1752-31,290 ng/L)

$P_{interaction} = 0.40$

Favors dapagliflozin   Favors placebo

Primary Endpoint

Rate Difference (per 100py)

Baseline NT-proBNP (ng/L)

500   1000   2000   5000   10000