Efficacy and Safety of Dapagliflozin in Heart Failure with Reduced Ejection Fraction According to N-Terminal Pro-B-Type Natriuretic Peptide: Insights from the DAPA-HF trial

Running title: *Dapagliflozin and NT-proBNP in HFrEF*

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ABSTRACT

Background: Effective therapies for HFrEF usually reduce N-terminal B type natriuretic peptide (NT-proBNP) levels, and it is important to establish whether new treatments are effective across the range of NT-proBNP.

Methods: We evaluated both these questions in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). Patients in New York Heart Association functional class II-IV with a left ventricular ejection fraction ≤40% and a NT-proBNP level ≥600 pg/mL [≥600 ng/L] (≥400 pg/mL if hospitalized for HF within the previous 12 months or ≥900 pg/mL if atrial fibrillation/flutter) were eligible. The primary outcome was the composite of an episode of worsening HF or cardiovascular death.

Results: Of the 4,744 randomized patients, 4,742 had an available baseline NT-proBNP measurement (median 1,437 pg/mL [IQR 857-2,650 pg/mL]). Compared with placebo, treatment with dapagliflozin significantly reduced NT-proBNP from baseline to 8 months (absolute least-squares mean reduction, -303 pg/mL [95% CI, -457 to -150 pg/mL]; geometric mean ratio 0.92 [95% CI, 0.88-0.96]). Dapagliflozin reduced the risk of worsening HF or cardiovascular death, irrespective of baseline NT-proBNP quartile; the hazard ratio for dapagliflozin versus placebo, from lowest to highest quartile, was: 0.43 [95% CI, 0.27-0.67], 0.77 [0.56-1.04], 0.78 [0.60-1.01], and 0.78 [0.64-0.95]; P for interaction=0.09). Consistent benefits were observed for all-cause mortality. Compared with placebo, dapagliflozin increased the proportion of patients with a meaningful improvement (≥5 points) in Kansas City Cardiomyopathy Questionnaire total symptom score (P for interaction=0.99) and decreased the proportion with a deterioration ≥5 points (P for interaction=0.87) across baseline NT-proBNP quartiles.

Conclusions: In patients with HFrEF, dapagliflozin reduced NT-proBNP by 300 pg/mL after 8 months of treatment compared with placebo. In addition, dapagliflozin reduced the risk of

worsening HF and death, and improved symptoms, across the spectrum of baseline NT-proBNP levels included in DAPA-HF.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov; Unique Identifier: NCT03036124.

ABBREVIATIONS

CARE-HF: Cardiac Resynchronization in Heart Failure study

DECLARE-TIMI 58: Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58

eGFR: Estimated glomerular filtration rate

EMPEROR-Reduced: Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction

GALACTIC-HF: Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure

HR: Hazard ratio

IQR: Interquartile range

KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire total symptom score

NT-proBNP: N-terminal B type natriuretic peptide

OR: Odds ratio

PARADIGM-HF: Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure

PIONEER-HF: Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode

SD: Standard deviation

SGLT2: Sodium-glucose cotransporter-2

VICTORIA: Clinical Outcome Predictions for the Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction

What is new?

- In DAPA-HF, dapagliflozin, compared with placebo, reduced N-terminal B type natriuretic peptide (NT-proBNP) levels by 300 pg/mL or 8% after 8 months of treatment in 4,744 patients with heart failure with reduced ejection fraction.
- Dapagliflozin reduced the risk of worsening heart failure events, cardiovascular death, and all-cause death, and improved symptoms, across the spectrum of baseline NT-proBNP levels included (58 to 46,832 pg/mL).

What are the clinical implications?

- The benefit of dapagliflozin was consistent across the spectrum of baseline NT-proBNP levels.
- Given that the mechanisms by which SGLT2 inhibitors exert their beneficial cardiovascular effects are largely unknown, the relatively modest reduction in NT-proBNP levels with dapagliflozin support the possibility of non-hemodynamic mechanisms of action.

INTRODUCTION

Natriuretic peptides are fundamental to our understanding of the pathophysiology of heart failure because they reflect left ventricular filling pressure and wall stress.[1–3] They have a confirmed role in diagnostic testing and, because they integrate age, kidney function, and heart rhythm, as well as hemodynamics, they are also powerful predictors of outcome.[4–10] Recently, natriuretic peptides have been used as an enrollment requirement in clinical trials of heart failure therapies, as they both enhance the certainty of diagnosis and ensure an adequate event rate.[11,12]

The effect of treatment in relation to natriuretic peptides is also of interest, from two perspectives. First is the effect of the investigational therapy on natriuretic peptide concentrations.[5,13,14] As expected from their hemodynamic action, drugs that act as vasodilators, such as renin-angiotensin system blockers and the combination of hydralazine and isosorbide nitrate, reduce natriuretic peptides.[15–17] Similarly, sacubitril/valsartan, a combination of a neprilysin and an angiotensin receptor blocker, reduces N-terminal B-type natriuretic peptide (NT-proBNP) but not B-type natriuretic peptide, as the latter is a substrate for neprilysin whereas the former is not and reflects a reduction in left ventricular wall stress.[18,19] The effect of beta-blockers is more complex and time-dependent, with an early increase in natriuretic peptide levels, probably due to an initial depression of contractility, followed by a later decrease, presumably as a result of longer-term favorable left ventricular remodeling and improved systolic function.[8,20] The potential effect of sodium-glucose cotransporter-2 (SGLT2) inhibitors is therefore of particular interest, given that they are not thought to have either a major vasodilator action or an effect on contractility. The second and more recent question about natriuretic peptides is whether their concentration may determine response to treatment. It has been suggested that very high natriuretic peptide levels might identify patients with heart failure so advanced that there is limited potential to modify the

course of disease with drug treatment. This concern was highlighted by the results of the Clinical Outcome Predictions for the Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTORIA) trial, where treatment with vericiguat appeared attenuated in patients with a NT-proBNP concentration >4,000 pg/mL [>4000 ng/L] and absent >8,000 pg/mL.[21] This observation raises another key question concerning SGLT2 inhibitor therapy in HFrEF.

Therefore, we investigated these two questions in the DAPA-HF trial, which included 4,744 patients with HFrEF and showed that treatment with the SGLT2 inhibitor dapagliflozin, compared to placebo, led to significant reductions in cardiovascular death and heart failure hospitalization. We examined the effect of dapagliflozin on NT-proBNP concentration and whether the effect of dapagliflozin varied according to baseline NT-proBNP level. To add more granularity to the prespecified analysis (NT-proBNP level ≤median versus >median), we examined NT-proBNP by quartile and as a continuous measure.

METHODS

DAPA-HF was a randomized, double-blind, placebo-controlled trial in patients with HFrEF, which evaluated the efficacy and safety of dapagliflozin 10 mg once daily compared with matching placebo, in addition to standard care. The Ethics Committee of each of the 410 participating institutions in 20 countries approved the protocol, and all patients gave written informed consent. The design, baseline characteristics, and primary results of the trial have been published.[22–24] The corresponding author had full access to all the trial data and takes responsibility for its integrity and the data analysis. The data that support the findings of this study are available from the corresponding author on reasonable request.

Study patients

Men and women aged 18 years or older with a diagnosis of HF for at least 2 months were eligible if they were in New York Heart Association functional class II-IV, had a left ventricular ejection fraction of ≤40%, and were optimally treated with pharmacological and device therapy for HF. Participants were also required to have an NT-proBNP concentration ≥600 pg/mL (≥400 pg/mL if hospitalized for HF within the previous 12 months). Patients with atrial fibrillation/flutter were required to have a NT-proBNP level ≥900 pg/mL, irrespective of history of HF hospitalization. Key exclusion criteria included symptoms of hypotension or systolic blood pressure <95 mmHg, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 or rapidly declining renal function, type 1 diabetes, and other conditions likely to prevent patient participation in the trial or greatly limit life expectancy. A full list of exclusion criteria is provided in the design paper.[22] After randomization, follow-up visits were scheduled at 14 and 60 days, and then at 120, 240, 360 days and every four months thereafter.

NT-proBNP assay

NT-proBNP was measured at baseline in all randomized patients and at 8 months in surviving patients. Plasma NT-proBNP was measured in a central laboratory (Covance) using the Roche Elecsys NT-proBNP two-site electrochemiluminescence immunoassay (ECLIA). Analysis of the effect of dapagliflozin according to baseline NT-proBNP (≤median, >median) was prespecified.

Clinical outcomes

The primary outcome in the trial was the composite of an episode of worsening HF (unplanned HF hospitalization or urgent visit for worsening HF with administration of intravenous treatment for HF) or cardiovascular death, whichever occurred first. The secondary outcomes in the trial were the occurrence of HF hospitalization or cardiovascular death (we also examined the components of this composite); total HF hospitalizations (first and repeat) or cardiovascular death; change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS); a composite of worsening renal function, which was defined as a sustained decline in the eGFR of 50% or greater, end-stage renal disease (defined as a sustained [≥28 days] eGFR of <15 ml per minute per 1.73 m2, sustained dialysis, or renal transplantation), or renal death; and all-cause death. Due to the small number of renal events overall, the composite of worsening renal function was not examined in the present analysis. All cardiovascular endpoints and deaths were adjudicated by an independent, blinded, committee.

Prespecified safety analyses included adverse events leading to discontinuation of trial treatment and adverse events of interest, including volume depletion, renal adverse events, bone fracture, amputation, major hyperglycemia, and diabetic ketoacidosis. Safety analyses were performed in patients who had undergone randomization and received at least

one dose of dapagliflozin or placebo; a total of eight randomized patients were excluded from these analyses.

Statistical analyses

In the present analysis, patients were divided into four subgroups, based on the quartiles of baseline NT-proBNP. Baseline characteristics were summarized as frequencies with percentages, means with standard deviation (SD), or medians with interquartile ranges (IQR). Differences in baseline characteristics were tested using the $\chi 2$ test for categorical variables and Cuzick test for trend for continuous and binary variables. Normal distribution was examined by graphical assessment (i.e. histogram, boxplot, and quantile-quantile plot) and the Shapiro-Wilk test for normality. Baseline characteristics associated with baseline NT-proBNP level above median were examined with a multiple logistic regression model, including age, sex, race, geographic region, systolic blood pressure, heart rate, body mass index, glycated hemoglobin, eGFR, HF etiology, left ventricular ejection fraction, NYHA functional class, KCCQ-TTS score, hypertension, type 2 diabetes, a history of atrial fibrillation, hospitalization for HF, and myocardial infarction.

Time-to-event data for the primary outcome and secondary clinical outcomes according to NT-proBNP quartiles, regardless of treatment allocation, were evaluated using the Kaplan-Meier estimator and Cox proportional-hazards models, stratified according to diabetes mellitus status, with a history of HF hospitalization and treatment-group assignment as fixed-effect factors to calculate hazard ratios (HR), 95% CIs, and two-sided P-values. The models for all-cause death did not include adjustment for a history of HF hospitalization. In addition, adjusted HRs from models including age, sex, heart rate, systolic blood pressure, body mass index, HF etiology, left ventricular ejection fraction, NYHA functional class, atrial fibrillation, ~~and~~ estimated glomerular filtration rate, and medical therapy (angiotensin-

converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor, beta-blocker, mineralocorticoid receptor antagonist, diuretic, digoxin, oral anticoagulant, antiplatelet, statin, and cardiac resynchronization therapy) were reported. The proportional hazards assumption was examined with scaled Schoenfeld residuals, and the assumption was not violated in any model. The relationship between NT-proBNP as a continuous variable and the risk of the primary endpoint was also examined in a restricted cubic spline analysis.

The difference between treatment groups in the change in NT-proBNP at 8 months in surviving patients was analyzed using an analysis of covariance model, with treatment-group assignment as a fixed-effect factor and baseline NT-proBNP as a covariate. The results of the analyses of covariance are presented as least-squares mean differences with corresponding 95% CIs. The difference between treatment groups in the change in NT-proBNP at 8 months are also presented as geometric mean ratios. As changes in eGFR influence NT-proBNP levels, we also analyzed the change in NT-proBNP at 8 months by adjusting for baseline eGFR and changes in eGFR at 8 months, in addition to baseline NT-proBNP.

To compare the effects of dapagliflozin versus placebo on the primary outcome and secondary clinical outcomes according to NT-proBNP quartiles, time-to-event data were evaluated with the Kaplan-Meier estimator and Cox proportional-hazards models, stratified according to diabetes mellitus status, with a history of HF hospitalization and treatment-group assignment as fixed-effect factors. The models for all-cause death were not adjusted for a history of HF hospitalization. The effect of dapagliflozin on the primary outcome was also examined according to continuous NT-proBNP as a fractional polynomial. Total, including recurrent events were evaluated with semiparametric proportional-rates models.[25] The difference between treatment groups in the change in KCCQ-scores from baseline to 8 months in surviving patients according to NT-proBNP quartiles was analyzed using two-sample T-test.

Responder analyses examining proportions of patients with a deterioration (decrease in KCCQ-TSS of ≥5 points) and clinically important improvement (increase in KCCQ-TSS of ≥5 points)[26] in symptoms at 8 months according to NT-proBNP quartiles were conducted with the treatment effect expressed as an odds ratio (OR), and missing KCCQ values were accounted for with multiple imputation using methods previously described.[27]

All analyses were conducted using STATA version 16.1 (College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC). A P-value of 0.05 was considered statistically significant.

RESULTS

Of the 4,744 patients randomized, 4,742 had an available NT-proBNP measurement at baseline. Although the protocol prespecified that NT-proBNP should be >600 pg/mL (≥400 if HF hospitalization within 12 months or ≥900 if atrial fibrillation), 32 patients (0.7%) were included in violation of this criterion, resulting in a NT-proBNP range of 58 to 46,832 pg/mL. The median NT-proBNP was 1,437 pg/mL with a Q1 of 857 and Q3 of 2,650 pg/mL. Therefore, the four groups defined by quartiles we examined were: 1) <857 pg/mL (median 618 [IQR 477-742] pg/mL), 2) 857-1,437 pg/mL (median 1,126 [IQR 992-1,276] pg/mL), 3) 1,438-2,650 pg/mL (median 1,907 [IQR 1,654-2,243] pg/mL), and 4) >2,650 pg/mL (median 4,228 [IQR 3,249-6,332] pg/mL).

Patient characteristics

Baseline characteristics according to baseline NT-proBNP quartiles are presented in **Table 1**. Compared with patients with lower NT-proBNP levels, those with higher levels were older, more often female, and more likely to have AF (both as a history and on ECG) and type 2 diabetes. Patients with higher NT-proBNP levels had a lower mean systolic blood pressure, eGFR, and body mass index. They were also less likely to have an ischemic etiology and prior myocardial infarction. Patients with higher NT-proBNP levels had a lower ejection fraction, worse NYHA functional class, a lower KCCQ-TSS (i.e., more symptoms) and more often had a previous HF hospitalization than those with lower NT-proBNP levels. With respect to background HF therapy, patients with higher NT-proBNP levels were less frequently treated with angiotensin receptor–neprilysin inhibitors and more often with diuretics and cardiac resynchronization therapy. In a multivariable logistic regression model, increasing age, a history of atrial fibrillation, and higher NYHA functional class were associated with a greater likelihood of baseline NT-proBNP level above median, whereas an increase in body mass

index, eGFR, LVEF, and KCCQ-TTS were associated with a lower likelihood of baseline NT-proBNP level above median (Supplemental Table I).

Outcomes according to baseline NT-proBNP

Patients with higher baseline NT-proBNP had a higher risk of the primary outcome of worsening HF or cardiovascular death (1st quartile, reference; 2nd quartile, adjusted HR 1.82 [95% CI, 1.40-2.35]; 3rd quartile, adjusted HR 2.48 [95% CI, 1.93-3.18]; 4th quartile, adjusted HR 4.39 [95% CI, 3.44-5.60]) **(Figure 1**). Similarly, patients with higher baseline NT-proBNP had a higher risk of HF hospitalization or cardiovascular death; HF hospitalization and cardiovascular death individually; and all-cause death, even after adjustment for prognostic variables (**Supplemental Table II**).

Effect of dapagliflozin on NT-proBNP

The median NT-proBNP at baseline was similar in the dapagliflozin and placebo group **(Table 2)**. The mean change in NT-proBNP from baseline to 8 months was 101 pg/mL (SD 2,944 pg/mL) and -196 pg/mL (SD 2,387 pg/mL) with placebo and dapagliflozin, respectively. Compared with placebo, treatment with dapagliflozin led to a statistically significant reduction in NT-proBNP from baseline to 8 months (absolute least-squares mean reduction, -303 pg/mL [95% CI, -457 to -150 pg/mL]; geometric mean ratio 0.92 [95% CI, 0.88-0.96]). A similar reduction in NT-proBNP was also observed when adjusting for baseline eGFR and changes in eGFR at 8 months, in addition to baseline NT-proBNP (Supplemental Table III). The effect of dapagliflozin on reducing NT-proBNP was consistent across baseline NT-proBNP quartiles (P for interaction=0.19) **[Table 2]**.

Effects of dapagliflozin on clinical outcomes according to baseline NT-proBNP

Primary composite outcome

Compared with placebo, dapagliflozin reduced the risk of worsening HF or cardiovascular death across NT-proBNP quartiles – the HRs from lowest to highest quartile were: 0.43 [95% CI, 0.27-0.67], 0.77 [95% CI, 0.56-1.04], 0.78 [95% CI, 0.60-1.01], and 0.78 [95% CI, 0.64-0.95]), respectively, with a non-significant interaction between NT-proBNP quartile and the effect of treatment (P for interaction=0.09) **[Table 3]**.

Figure 2 displays the effect of dapagliflozin on the primary outcome according to NT-proBNP examined as a continuous variable. Dapagliflozin significantly reduced the risk of worsening HF or cardiovascular death across the range of NT-proBNP, with the treatment effect appearing more pronounced at a low concentration of NT-proBNP (P for interaction=0.02, both when NT-proBNP was untransformed and log-transformed).

Secondary outcomes

HRs, rate ratios, and ORs for the effect of dapagliflozin, compared with placebo, on the secondary clinical endpoints are displayed in **Table 3**. The effect of dapagliflozin was consistent across baseline NT-proBNP quartiles for HF hospitalization or cardiovascular death (P for interaction=0.06), HF hospitalization (P for interaction=0.71), HF hospitalization or urgent HF visit (P for interaction=0.69), and recurrent HF hospitalization or cardiovascular death (P for interaction=0.19). There was a nominally significant interaction between the effect of treatment and baseline NT-proBNP quartile on cardiovascular death (P for interaction=0.03), but not for all-cause death (P for interaction=0.17) [**Figure 3** and **Table 3**].

The mean increase in KCCQ-TSS from baseline to 8 months was significantly greater with dapagliflozin across baseline NT-proBNP quartiles (P for interaction=0.69). The proportion of patients with an improvement of KCCQ-TSS of ≥5 points was greater with dapagliflozin, compared with placebo, irrespective of baseline NT-proBNP quartile (ORs from

lowest to highest, 1.14 [95% CI, 1.01-1.28], 1.16 [1.02-1.31], 1.16 [1.03-1.31], and 1.15 [1.02-1.30]; P for interaction=0.99). Conversely, the proportion of patients with a decrease in KCCQ-TSS of ≥5 points was smaller in those treated with dapagliflozin, compared with placebo across baseline NT-proBNP quartiles (ORs from lowest to highest, 0.83 [95% CI, 0.72-0.95], 0.82 [0.72-0.94], 0.84 [0.73-0.96], and 0.86 [0.76-0.98]; P for interaction=0.87) [**Table 3**].

Safety analyses

The prespecified adverse events with dapagliflozin and placebo according to NT-proBNP quartiles are shown in **Table 4**. In general, the proportions of patients who discontinued trial treatment or experienced adverse events according to treatment assignment were similar across NT-proBNP quartiles.

DISCUSSION

We found that dapagliflozin, compared with placebo, reduced NT-proBNP levels in patients with HFrEF. Dapagliflozin also reduced the risk of worsening HF events and cardiovascular death, and improved symptoms, across the spectrum of baseline NT-proBNP levels studied (58 to 46,832 pg/mL). We also confirmed the strong association between higher NT-proBNP levels and worse outcomes in HFrEF.

Effect of dapagliflozin on NT-proBNP levels

Although SGLT2 inhibitors did not consistently reduce NT-proBNP in prior small, short-term, studies of patients with HFrEF,[28–30] in the much larger DAPA-HF trial, dapagliflozin reduced NT-proBNP from a median level of 1,437 pg/mL by 300 pg/mL, as compared to placebo, after 8 months of treatment. This corresponded to a relatively modest reduction of 8% (as assessed by the ratio of geometric means), which was consistent across baseline NT-proBNP quartiles. Our findings are supported by the results of the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trial, which was designed to enroll more patients with a markedly elevated NT-proBNP level (the baseline median NT-proBNP was 1,926 pg/mL). In that trial, the estimated 13% reduction in NT-proBNP after one year of treatment was also modest (geometric mean ratio, 0.87 [95% CI, 0.82-0.93]).[31] This decrease in NT-proBNP concentration is consistent with the reduction in left ventricular filling pressure and favorable effects on cardiac remodeling, recently reported with SGLT2 inhibitors.[30,32–34] Although the former effect might be explained by a diuretic action SGLT2 inhibitors, such an action is unlikely to lead to cardiac remodeling, especially as any diuresis seems to be short-lived.[35,36] We have previously demonstrated that dapagliflozin also slows the rate of decline in eGFR in patients with HFrEF,[37] and this favorable effect may also, in part, explain some of the observed decrease in NT-proBNP levels. However, we found

a similar reduction in NT-proBNP even after adjustment for baseline eGFR and changes in eGFR at 8 months.

Relatively few mortality and morbidity ("Phase III") trials have reported the effect on NT-proBNP of adding a novel treatment to conventional therapy with a renin-angiotensin system blocker, beta-blocker, and mineralocorticoid receptor antagonist in patients with HFrEF. In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, baseline NT-proBNP was slightly higher (median 1,608 pg/mL) than in DAPA-HF. Sacubitril/valsartan reduced median NT-proBNP by 28% after 8-10 weeks of treatment,[18] and this rapid and substantial effect on NT-proBNP was supported by the Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial, which enrolled patients hospitalized with HFrEF.[38] Although this may indicate greater hemodynamic effects of sacubitril/valsartan, compared with an SGLT2 inhibitor, neprilysin inhibition may also have a very specific effect through negative feedback mediated by elevation of BNP levels, leading to inhibition of pro-BNP secretion (and resultant reduction in NT-proBNP).[39]

Other therapies have less marked effects on NT-proBNP. In the VICTORIA trial, the soluble guanylate cyclase stimulator, vericiguat, which is also a vasodilator, reduced NT-proBNP by 10% at 32 weeks compared with placebo (geometric mean ratio, 0.90 [95% CI, 0.86-0.94]) in HFrEF patients with a very high baseline NT-proBNP level (median 3,377 pg/mL).[40] In the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial, in which baseline NT-proBNP level was also high (median 1,971 pg/mL), the selective cardiac myosin activator, omecamtiv mecarbil lowered NT-proBNP level with 10%, as compared with placebo, by 24 weeks (geometric mean ratio, 0.90 [95% CI, 0.86-0.94]).[41]

It is therefore of interest that despite similar, modest, proportional reductions in NT-proBNP levels, the effects of vericiguat and omecamtiv mecarbil, as assessed by the hazard ratio for the primary endpoint, were smaller than for dapagliflozin or empagliflozin.[24,31,40,41] We have previously reported that there is a correlation between reduction in natriuretic peptides and the effect of drug and device therapy in heart failure, with a stronger relationship for reduction in hospitalization than in death.[13] Whereas the effects of vericiguat and omecamtiv mecarbil (and sacubitril/valsartan) are in keeping with these prior findings, the effect of SGLT2 inhibitors on heart failure hospitalization appear to be larger than expected. This is of interest, given that we do not yet know the mechanisms by which SGLT2 inhibitors exert their beneficial cardiovascular effects, and the present findings may indirectly support the possibility of non-hemodynamic mechanisms of action including improvement in myocardial metabolism, reduction of cardiac fibrosis, inhibition of cardiac sodium-hydrogen exchange, and alterations in adipokines, cytokine production, and epicardial adipose tissue mass, among others.[42–48]

Efficacy and safety of dapagliflozin according to baseline NT-proBNP levels

Recently, there has also been interest in whether the effect of treatment might vary according to natriuretic peptide levels, reflecting severity on heart failure. This was particularly highlighted by the VICTORIA trial, in which there was highly significant interaction between baseline NT-proBNP level and the effect of vericiguat.[21] Baseline NT-proBNP concentration modified the response to vericiguat, with a decreasing benefit with increasing NT-proBNP, especially with levels >8,000 pg/mL.[21] A qualitatively similar finding was reported with cardiac resynchronization therapy in the Cardiac Resynchronisation in Heart Failure study (CARE-HF), where the relative risk reduction in death with was greater in patients with a NT-proBNP level below the median concentration (1,814 pg/mL), compared to those at or above the median (52% vs. 31% reduction in mortality, respectively), although a formal interaction

test was not reported.[49] The benefit of sacubitril/valsartan in PARADIGM-HF also appeared most pronounced in patients with the lowest quarter of NT-proBNP concentrations, although there was no statistically significant interaction between NT-proBNP quartile and effect of therapy.[7] Our findings in DAPA-HF were qualitatively similar to those in PARADIGM-HF with the most marked benefit in patients with the lowest baseline NT-proBNP, and there was a nominally statistically significant interaction test for cardiovascular death. However, this was not seen for other outcomes, including all-cause mortality, and the benefit of dapagliflozin on the primary endpoint (which the trial was powered to examine) was entirely consistent across NT-proBNP quartiles 2 to 4 and with the overall treatment effect. This consistent benefit of dapagliflozin on the primary endpoint across the range of baseline NT-proBNP (58 to 46,832 pg/mL) is important because few patients with HFrEF have NT-proBNP levels higher than 46,800 pg/mL[9] and, although most patients in DAPA-HF had a baseline concentration >400 pg/mL, it is unlikely that dapagliflozin would cease to be effective below this level. Moreover, dapagliflozin reduced the risk of HF hospitalization or cardiovascular death in the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial where the median NT-proBNP concentration was only 75 pg/mL (IQR 35-165 pg/mL).[50,51]

The favorable, and clinically meaningful, improvements in symptoms with dapagliflozin are important to highlight in addition to effects on hospitalization and death. As expected, individuals with lower NT-proBNP levels at baseline had substantially better KCCQ-TSS scores (i.e., fewer symptoms) than those with the highest NT-proBNP levels. Dapagliflozin increased (improved) the mean KSSQ-TSS, increased the proportion of patients with a clinically meaningful improvement in symptoms (increase in KCCQ-TSS of ≥5 points), and decreased the proportion of patients with a deterioration in symptoms (decrease in KCCQ-TSS of ≥5 points) at 8 months, similarly across the spectrum of NT-proBNP levels included.

With respect to safety and tolerability, patients with higher baseline NT-proBNP levels overall were more likely to discontinue study treatment (including placebo) and report adverse events than those with lower NT-proBNP levels. Importantly, and reassuringly, study drug discontinuation and serious adverse events were not more frequently reported in the dapagliflozin group than in the placebo group across baseline NT-proBNP quartiles. These data further underline that dapagliflozin is a safe and well-tolerated treatment in patients with HFrEF, irrespective of baseline NT-proBNP.

Limitations

The findings of this study should be viewed in the context of potential limitations. Although NT-proBNP was a predefined subgroup analysis, the assessment of clinical outcomes by quartiles of baseline NT-proBNP was done *post-hoc*. The requirement for an elevated NT-proBNP at inclusion did not permit the assessment of the efficacy of dapagliflozin in patients with lower levels of NT-proBNP. The prespecified inclusion and exclusion criteria precluded the enrolment of hospitalized and other very high-risk patients. These limitations might affect the generalizability of our results.

Conclusions

In DAPA-HF, dapagliflozin, compared with placebo, reduced NT-proBNP levels by 300 pg/mL (8%) after 8 months of treatment. Dapagliflozin reduced the risk of worsening HF events, cardiovascular death, and all-cause death, and improved symptoms, across the spectrum of baseline NT-proBNP levels included (58 to 46,832 pg/mL).

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TABLE AND FIGURE LEGENDS

Table 1. Baseline characteristics of patients in DAPA-HF according to quartile of NT-proBNP concentration at baseline

Data are presented as mean±SD or median (IQR) for continuous measures, and N (%) for categorical measures. P-values for continuous and binary variables are corrected for trend across NT-proBNP quartiles.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CRT-D, cardiac resynchronization therapy–defibrillator; CRT-P, cardiac resynchronization therapy–pacemaker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

Table 2. NT-proBNP levels in randomized treatment groups at baseline and at 8 months and change in NT-proBNP from baseline to 8 months

P for interaction using the least-square means change: 0.19. P for interaction using the ratio of geometric means = 0.24.

Of the 4,742 patients with an available baseline NT-proBNP measurement, 4,222 patients had NT-proBNP measured at 8 months (225 missing NT-proBNP due to death, 295 missing for reasons other than death). The proportions of patients with missing NT-proBNP at 8 months for reasons other than death were similar in the dapagliflozin and placebo groups at 8 months (6.0% vs 7.1%, respectively).

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 3. Effects of dapagliflozin compared with placebo on clinical events across quartiles of NT-proBNP

CI, confidence interval; HF, heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; OR, odds ratio; RR, rate ratio.

**Adjusted for history of HF hospitalization (apart from all cause death) and stratified by diabetes status.*

Table 4. Adverse events in patients randomly assigned to dapagliflozin or placebo, across baseline NT-proBNP quartile.

A total of eight randomized patients were excluded from the safety analysis, as these were performed in patients who had undergone randomization and received at least one dose of dapagliflozin or placebo.

**Logistic regression with likelihood-ratio test to compare models with and without interaction between NT-proBNP quartile and treatment.*

Figure 1. Time to first event of cardiovascular death or worsening heart failure according to NT-proBNP at baseline

a) NT-proBNP quartiles

b) NT-proBNP as a continuous variable

Restricted cubic spline analysis showing the risk of cardiovascular death or worsening heart failure according to NT-proBNP levels at baseline (using log-transformed values). The reference is the log-transformed median NT-proBNP at baseline.

Figures have been restricted to 1st-99th percentile, but the results are derived from models based on the entire spectrum of NT-proBNP in DAPA-HF.

CI; confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Figure 2. Effect of dapagliflozin on worsening HF or cardiovascular death according to NT-proBNP

Fractional polynomial analyses showing the effect of dapagliflozin on the primary composite outcome across the range of NT-proBNP.

Figures have been restricted to 1st-99th percentile, but the results are derived from models based on the entire spectrum of NT-proBNP in DAPA-HF.

NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Figure 3. Effects of dapagliflozin compared with placebo on clinical events across quartiles of NT-proBNP

All hazard ratios are adjusted for history of HF hospitalization (apart from all cause death) and stratified by diabetes status.

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 1. Baseline characteristics of patients in DAPA-HF according to quartile of NT-proBNP concentration at baseline

	NT-proBNP quartile				P-value
	<857 pg/mL N=1,187	857-1,437 pg/mL N=1,185	1,438-2,650 pg/mL N=1,185	>2,650 pg/mL N=1,185	
Age (years), mean (SD)	63.4±11.3	66.3±10.4	67.6±10.6	68.1±10.6	<0.001
Sex, N (%)					0.009
Female	251 (21.1)	268 (22.6)	290 (24.5)	300 (25.3)	
Male	936 (78.9)	917 (77.4)	895 (75.5)	885 (74.7)	
Race, N (%)					0.11
Asian	303 (25.5)	286 (24.1)	279 (23.6)	248 (20.9)	
Black	50 (4.2)	48 (4.1)	58 (4.9)	70 (5.9)	
White	814 (68.6)	838 (70.7)	834 (70.4)	845 (71.4)	
Other	20 (1.7)	13 (1.1)	14 (1.1)	22 (1.8)	
Geographic region, N (%)					0.012
Asia/Pacific	301 (25.4)	276 (23.3)	274 (23.1)	245 (20.7)	
Europe	511 (43.0)	542 (45.7)	559 (47.2)	542 (45.7)	
North America	180 (15.2)	182 (15.4)	157 (13.2)	156 (13.2)	
South America	195 (16.4)	185 (15.6)	195 (16.5)	242 (20.4)	
Physiologic measures					
Systolic blood pressure (mmHg), mean (SD)	123.5±16.2	122.1±15.8	121.7±16.2	119.9±16.8	<0.001
Diastolic blood pressure (mmHg), mean (SD)	73.9±10.2	73.7±10.3	73.6±10.6	72.8±10.8	0.011
Heart rate (bpm), mean (SD)	69.4±10.6	71.1±11.2	71.7±11.7	73.9±12.7	<0.001
BMI (kg/m^2), mean (SD)	28.9±6.1	28.7±5.9	28.1±6.0	27.0±5.6	<0.001
Creatinine (μmol/L), mean (SD)	97.8±28.5	101.9±28.4	104.0±27.7	114.1±34.2	<0.001
Glycated hemoglobin (%), median (IQR)	6.0 (5.6-6.8)	6.1 (5.7-6.8)	6.1 (5.7-6.9)	6.2 (5.8-6.9)	<0.001
eGFR ($mL/min/1.73m^2$), mean (SD)	72.4±19.5	67.1±18.7	64.5±18.1	59.1±18.9	<0.001
NT-proBNP (pg/mL), median (IQR)	618.0 (477.0-741.6)	1125.5 (991.6-1276.3)	1907.1 (1653.5-2243.3)	4228.2 (3248.5-6332.3)	
Main cause of HF, N (%)					0.033
Ischemic	698 (58.8)	690 (58.2)	644 (54.3)	640 (54.0)	
Non-ischemic	391 (32.9)	394 (33.2)	455 (38.4)	447 (37.7)	
Unknown	98 (8.3)	101 (8.5)	86 (7.3)	98 (8.3)	
LVEF, mean (SD)	32.3±6.2	31.6±6.6	30.9±6.8	29.4±7.2	<0.001
NYHA class, N (%)					<0.001
II	880 (74.1)	834 (70.4)	828 (69.9)	659 (55.6)	
III	301 (25.4)	345 (29.1)	342 (28.9)	510 (43.0)	
IV	6 (0.5)	6 (0.5)	15 (1.3)	16 (1.4)	
KCCQ-TSS, mean (SD)	76.5±21.0	76.1±21.1	74.5±20.7	67.4±23.0	<0.001
Medical history, N (%)					
Hypertension	871 (73.4)	878 (74.1)	876 (73.9)	896 (75.6)	0.25
Type 2 diabetes (medical history)	459 (38.7)	520 (43.9)	473 (39.9)	531 (44.8)	0.024
Atrial fibrillation (history of)	259 (21.8)	456 (38.5)	549 (46.3)	554 (46.8)	<0.001
Atrial fibrillation/flutter (baseline ECG)	97 (8.2)	278 (23.5)	379 (32.0)	374 (31.6)	<0.001
Hospitalization for HF	557 (46.9)	528 (44.6)	553 (46.7)	611 (51.6)	0.014
Previous MI	561 (47.3)	550 (46.4)	492 (41.5)	488 (41.2)	<0.001
Treatment, N (%)					
ACEI	665 (56.0)	640 (54.0)	678 (57.2)	678 (57.2)	0.293

ARB	338 (28.5)	358 (30.2)	305 (25.7)	304 (25.7)	0.026
ARNI	138 (11.6)	140 (11.8)	126 (10.6)	104 (8.8)	0.015
Beta-blocker	1,135 (95.6)	1,143 (96.5)	1,139 (96.1)	1,139 (96.1)	0.645
Mineralocorticoid receptor antagonist	877 (73.9)	809 (68.3)	826 (69.7)	858 (72.4)	0.609
Diuretic	935 (78.8)	973 (82.1)	1,011 (85.3)	1,088 (91.8)	<0.001
Digoxin	154 (13.0)	220 (18.6)	239 (20.2)	274 (23.1)	<0.001
Oral anticoagulant	338 (28.5)	496 (41.9)	571 (48.2)	564 (47.6)	<0.001
Antiplatelet	737 (62.1)	683 (57.6)	566 (47.8)	604 (51.0)	<0.001
Statin	824 (69.4)	831 (70.1)	770 (65.0)	749 (63.2)	<0.001
ICD/CRT-D	287 (24.2)	327 (27.6)	325 (27.4)	302 (25.5)	0.510
CRT-P/CRT-D	67 (5.6)	82 (6.9)	100 (8.4)	105 (8.9)	0.001

Data are presented as mean±SD or median (IQR) for continuous measures, and N (%) for categorical measures.

P-values for continuous and binary variables are corrected for trend across NT-proBNP quartiles.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CRT-D, cardiac resynchronization therapy–defibrillator; CRT-P, cardiac resynchronization therapy–pacemaker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; myocardial infarction, MI; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

Table 2. NT-proBNP levels in randomized treatment groups at baseline and at 8 months and change in NT-proBNP from baseline to 8 months

	Baseline		8 months		Ratio: 8 months/baseline geometric mean (95% CI)	Ratio: Dapagliflozin/placebo at 8 months (95% CI)	Mean change at 8 months (SD)	Mean treatment difference at 8 months (95% CI)
	Geometric mean (95% CI)	Median (IQR)	Geometric mean (95% CI)	Median (IQR)				
All patients with baseline and 8-month NT-proBNP measure (N=4,222)								
Dapagliflozin	1487 (1436 – 1541)	1385 (839 – 2518)	1221 (1172 – 1272)	1173 (673 – 2243)	0.82 (0.80 – 0.85)	0.92 (0.88 – 0.96)	-196 ± 2387	-303 (-457, -150)
Placebo	1495 (1442 – 1549)	1391 (836-2469)	1334 (1276 – 1394)	1323 (710 – 2475)	0.89 (0.86 – 0.92)		101 ± 2944	
NT-proBNP quartile 1 (N= 1,100)								
Dapagliflozin	553 (536 – 572)	605 (465 – 741)	548 (515 – 583)	577 (352 – 846)	0.99 (0.93 – 1.05)	0.94 (0.86 – 1.02)	130 ± 604	-82 (-170, 7)
Placebo	569 (552 – 586)	627 (492 – 742)	596 (558 – 637)	622 (397 – 948)	1.05 (0.99 – 1.12)		212 ± 865	
NT-proBNP quartile 2 (N=1,086)								
Dapagliflozin	1122 (1108 – 1136)	1118 (992 – 1280)	970 (925 – 1017)	1034 (703 – 1370)	0.87 (0.83 – 0.91)	0.94 (0.87 – 1.01)	-4 ± 644	-232 (-357, -107)
Placebo	1123 (1108 – 1137)	1132 (985 -1275)	1038 (974 – 1106)	1073 (720 -1580)	0.92 (0.87 – 0.98)		228 ± 1350	
NT-proBNP quartile 3 (N=1,064)								
Dapagliflozin	1925 (1897 – 1954)	1911 (1643 – 2240)	1494 (1407 – 1586)	1578 (1027 – 2262)	0.78 (0.73 – 0.82)	0.85 (0.78 – 0.92)	-69 ±1466	-536 (-836, -237)
Placebo	1920 (1892 – 1949)	1902 (1652 – 2228)	1758 (1649 – 1874)	1723 (1198 – 2572)	0.92 (0.86 – 0.98)		468 ± 3190	
NT-proBNP quartile 4 (N=972)								
Dapagliflozin	4626 (4432 – 4829)	4069 (3205 – 5759)	3086 (2851 – 3341)	3165 (1985 – 5278)	0.67 (0.62 – 0.72)	0.96 (0.86 – 1.07)	-906 ± 4542	-395 (-945, 154)
Placebo	4752 (4539 – 4974)	4176 (3229 – 6362)	3280 (2998 – 3589)	3550 (2094 – 5944)	0.69 (0.63 – 0.75)		-584 ± 4816	

P for interaction using the least-square means change: 0.19. P for interaction using the ratio of geometric means = 0.24.

Of the 4,742 patients with an available baseline NT-proBNP measurement, 4,222 patients had NT-proBNP measured at 8 months (225 missing NT-proBNP due to death, 295 missing for reasons other than death). The proportions of patients with missing NT-proBNP at 8 months for reasons other than death were similar in the dapagliflozin and placebo groups at 8 months (6.0% vs 7.1%, respectively).
CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 3. Effects of dapagliflozin compared with placebo on clinical events across quartiles of NT-proBNP

Quartile	<857 pg/mL N=1,187		857-1,437 pg/mL N=1,185		1,438-2,650 pg/mL N=1,185		>2,650 pg/mL N=1,185		P-value for interaction
Outcome	Placebo N=594	Dapagliflozin N=593	Placebo N=585	Dapagliflozin N=600	Placebo N=601	Dapagliflozin N=584	Placebo N=590	Dapagliflozin N=595	
Worsening HF event or cardiovascular death									0.09
N (%)	62 (10.4)	27 (4.6)	93 (15.9)	73 (12.2)	127 (21.1)	98 (16.8)	220 (37.3)	188 (31.6)	
Event rate per 100 person-years (95% CI)	7.3 (5.7-9.4)	3.1 (2.1-4.5)	11.3 (9.2-13.8)	8.6 (6.8-10.8)	15.5 (13.0-18.5)	12.0 (9.9-14.6)	31.9 (28.0-36.4)	25.1 (21.7-28.9)	
HR (95% CI)*	0.43 (0.27-0.67)		0.77 (0.56-1.04)		0.78 (0.60-1.01)		0.78 (0.64-0.95)		
HF hospitalization or cardiovascular death									0.06
N (%)	60 (10.1)	25 (4.2)	93 (15.9)	72 (12.0)	126 (21.0)	97 (16.6)	216 (36.6)	188 (31.6)	
Event rate per 100 person-years (95% CI)	7.1 (5.5-9.1)	2.9 (1.9-4.2)	11.3 (9.2-13.8)	8.5 (6.7-10.7)	15.4 (12.9-18.3)	11.9 (9.7-14.5)	31.1 (27.2-35.5)	25.0 (21.6-28.8)	
HR (95% CI)*	0.41 (0.26-0.65)		0.76 (0.56-1.03)		0.77 (0.59-1.01)		0.80 (0.66-0.97)		
HF hospitalization									0.71
N (%)	30 (5.1)	16 (2.7)	52 (8.9)	42 (7.0)	91 (15.1)	67 (11.5)	145 (24.6)	106 (17.8)	
Event rate per 100 person-years (95% CI)	3.5 (2.5-5.1)	1.8 (1.1-3.0)	6.3 (4.8-8.3)	4.9 (3.7-6.7)	11.1 (9.0-13.6)	8.2 (6.5-10.4)	20.9 (17.7-24.6)	14.1 (11.6-17.0)	
HR (95% CI)*	0.53 (0.29-0.97)		0.79 (0.52-1.18)		0.74 (0.54-1.01)		0.67 (0.52-0.86)		
HF hospitalization or urgent HF visit									0.69
N (%)	32 (5.4)	18 (3.0)	52 (8.9)	43 (7.2)	92 (15.3)	68 (11.6)	150 (25.4)	108 (18.2)	
Event rate per 100 person-years (95% CI)	3.8 (2.7-5.3)	2.1 (1.3-3.3)	6.3 (4.8-8.3)	5.1 (3.8-6.8)	11.2 (9.2-13.8)	8.3 (6.6-10.6)	21.8 (18.5-25.5)	14.4 (11.9-17.4)	
HR (95% CI)*	0.56 (0.31-0.99)		0.80 (0.54-1.21)		0.74 (0.54-1.02)		0.66 (0.51-0.84)		
Cardiovascular death									0.03
N (%)	33 (5.6)	13 (2.2)	54 (9.2)	40 (6.7)	59 (9.8)	43 (7.4)	127 (21.5)	131 (22.0)	
Event rate per 100 person-years (95% CI)	3.8 (2.7-5.3)	1.5 (0.9-2.5)	6.3 (4.8-8.2)	4.5 (3.3-6.2)	6.7 (5.2-8.6)	5.0 (3.7-6.7)	16.0 (13.5-19.1)	16.2 (13.7-19.3)	
HR (95% CI)*	0.39 (0.20-0.73)		0.73 (0.49-1.10)		0.75 (0.51-1.12)		1.00 (0.78-1.28)		
All-cause death									0.17

N (%)	38 (6.4)	20 (3.4)	65 (11.1)	52 (8.7)	73 (12.1)	53 (9.1)	153 (25.9)	151 (25.4)	
Event rate per 100 person-years (95% CI)	4.4 (3.2-6.0)	2.3 (1.5-3.5)	7.6 (5.9-9.6)	5.9 (4.5-7.7)	8.3 (6.6-10.4)	6.1 (4.7-8.0)	19.3 (16.5-22.6)	18.7 (16.0-22.0)	
HR (95% CI)*	0.51 (0.30-0.88)		0.79 (0.55-1.14)		0.76 (0.53-1.08)		0.96 (0.77-1.20)		
Total number of hospitalizations for heart failure or cardiovascular death									0.19
No. of events	74	33	132	101	187	138	349	295	
RR (95% CI)*	0.45 (0.27-0.74)		0.75 (0.52-1.06)		0.76 (0.57-1.01)		0.81 (0.66-1.01)		
KCCQ-TSS									
Change in KCCQ-TSS score at 8 months	3.2 ± 16.9	5.0 ± 16.0	2.3 ± 18.0	5.7 ± 17.3	1.9 ± 20.6	5.7 ± 19.7	6.2 ± 21.3	8.3 ± 21.5	0.69
≥5-point improvement in KCCQ-TSS at 8 months									0.99
Proportion of patients (95% CI) (%)	54 (50-58)	60 (56-65)	52 (48-57)	60 (56-64)	48 (44-52)	56 (52-60)	50 (45-54)	57 (52-61)	
OR (95% CI)	1.14 (1.01-1.28)		1.16 (1.02-1.31)		1.16 (1.03-1.31)		1.15 (1.02-1.30)		
≥5-point decrease in KCCQ-TSS at 8 months									0.87
Proportion of patients (95% CI) (%)	29 (25-33)	22 (18-25)	32 (28-36)	24 (21-28)	34 (30-38)	26 (22-29)	37 (33-41)	30 (26-34)	
OR (95% CI)	0.83 (0.72-0.95)		0.82 (0.72-0.94)		0.84 (0.73-0.96)		0.86 (0.76-0.98)		

CI, confidence interval; HF, heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; OR, odds ratio; RR, rate ratio.

**Adjusted for history of HF hospitalization (apart from all cause death) and stratified by diabetes status.*

Table 4. Adverse events in patients randomly assigned to dapagliflozin or placebo, across baseline NT-proBNP quartile.

Quartile	<857 pg/mL N=1,186		857-1,437 pg/mL N=1,183		1,438-2,650 pg/mL N=1,183		>2,650 pg/mL N=1,182		P-value for interaction*
Adverse event	Placebo N=594	Dapagliflozin N=592	Placebo N=584	Dapagliflozin N=599	Placebo N=601	Dapagliflozin N=582	Placebo N=588	Dapagliflozin N=594	
Discontinuation of study drug due to adverse event	18 (3.0%)	23 (3.9%)	24 (4.1%)	17 (2.8%)	32 (5.3%)	36 (6.2%)	42 (7.1%)	35 (5.9%)	0.37
Volume depletion	37 (6.2%)	32 (5.4%)	33 (5.7%)	33 (5.5%)	43 (7.2%)	57 (9.8%)	49 (8.3%)	56 (9.4%)	0.45
Renal adverse event	27 (4.5%)	24 (4.1%)	29 (5.0%)	28 (4.7%)	50 (8.3%)	42 (7.2%)	64 (10.9%)	59 (9.9%)	0.99
Fracture	9 (1.5%)	6 (1.0%)	10 (1.7%)	17 (2.8%)	14 (2.3%)	10 (1.7%)	17 (2.9%)	16 (2.7%)	0.41
Amputation	1 (0.2%)	3 (0.5%)	1 (0.2%)	3 (0.5%)	3 (0.5%)	3 (0.5%)	7 (1.2%)	4 (0.7%)	0.41
Major hypoglycemia	1 (0.2%)	1 (0.2%)	2 (0.3%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	2 (0.3%)	N/A
Diabetic ketoacidosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	N/A

A total of eight randomized patients were excluded from the safety analysis, as these were performed in patients who had undergone randomization and received at least one dose of dapagliflozin or placebo.

**Logistic regression with likelihood-ratio test to compare models with and without interaction between NT-proBNP quartile and treatment.*