Title: **Effects of dapagliflozin according to a score integrating classes and doses of guideline-directed medical therapies in patients with heart failure and reduced ejection fraction: Insights from DAPA-HF**

Running title: *Dapagliflozin and evidence-based therapy in HFrEF*

Authors:
Jawad H Butt MD*[a,b]
Pooja Dewan MBBS*[a]
Ersilia M DeFilippis MD[c]
Tor Biering-Sørensen MD PhD MPH[d]
Kieran F Docherty MBChB[a]
Pardeep S Jhund MBChB MSc PhD[a]
Mikhail N Kosiborod MD[e]
Felipe A Martinez MD[f]
Olof Bengtsson Ph Lic[g]
Niklas Dyrby Johansen MD[d]
Anna Maria Langkilde MD PhD[g]
Mikaela Sjöstrand MD PhD[g]
Muthiah Vaduganathan MD MPH[h]
Scott D Solomon MD[h]
Marc S Sabatine MD MPH[h,i]
Lars Køber MD DMS[b]
Mona Fiuzat PharmD[j]
John JV McMurray MD[a]

*Both authors contributed equally

Affiliations:
[a]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [b]Department of Cardiology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark; [c]Columbia University Irving Medical Center, New York, NY, USA; [d]Department of Cardiology, Copenhagen University Hospital - Herlev and Gentofte, Hellerup, Denmark; [e]Saint Luke's Mid America Heart Institute, University of Missouri, Kansas City; The George Institute for Global Health, University of New South Wales, Sydney, Australia; [f]Universidad Nacional de Córdoba, Córdoba, Argentina; [g]Late Stage Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [h]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; [i]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; [j]Division of Cardiology, Duke University School of Medicine, Durham, NC, USA.

Funding: The DAPA-HF trial was funded by AstraZeneca. Prof. McMurray is supported by British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217.

Disclosures: The corresponding author need to consult the co-authors about potential conflicts of interest and will provide details for inclusion in the Conflicts of Interest section of the manuscript.

Word count: 4,856

Address for Correspondence:
Professor John J.V. McMurray
British Heart Foundation Cardiovascular Research Centre
University of Glasgow
126 University Place, Glasgow, G12 8TA, United Kingdom
Tel: +44 141 330 3479
Fax: +44 141 330 6955
Email: john.mcmurray@glasgow.ac.uk

ABSTRACT

Objectives: We investigated the efficacy of dapagliflozin according to a modified Heart Failure Collaboratory (HFC) score in DAPA-HF.

Background: The HFC has developed a score integrating classes and doses of guideline-directed medical therapies (GDMT) prescribed for patients with heart failure (HF) and reduced ejection fraction (HFrEF). One potential use of this score is to test whether new treatments demonstrate incremental benefits, even in patients receiving comprehensive GDMT.

Methods: In DAPA-HF, 4,744 HFrEF patients were randomized to dapagliflozin or placebo. The modified HFC score accounted for race and ECG rhythm and rate, with a maximum possible score of 100%. The primary outcome was the composite of worsening HF or cardiovascular death.

Results: The median modified HFC score was 50% (interquartile range, 27.5-62.5%; range 0-100%). Compared with the lowest tertile, the highest tertile of the treatment score was associated with a lower risk of worsening HF or cardiovascular death (tertile 1, reference; tertile 2, hazard ratio 0.97 [95%CI, 0.82-1.14]; tertile 3, 0.83 [0.70-0.99]). Dapagliflozin reduced the risk of worsening HF or cardiovascular death, irrespective of treatment score – the hazard ratios for dapagliflozin versus placebo from tertile 1 to 3 were: 0.76[0.61-0.94], 0.76[0.60-0.97], and 0.71[0.55-0.90]), respectively; $P_{interaction}$=0.89. Consistent benefits were observed for HF hospitalization, cardiovascular death, all-cause mortality, and improvement in the Kansas City Cardiomyopathy Questionnaire total symptom score.

Conclusions: Dapagliflozin, compared with placebo, improved all outcomes examined, regardless of the modified HFC score. This score can be easily calculated in clinical trials and used to evaluate the incremental effects of new treatments.

Key words: Heart failure, dapagliflozin, clinical trial, Heart Failure Collaboratory.

ABBREVIATION LIST

AF: Atrial fibrillation

AFL: Atrial flutter

BB: Beta-blocker

CHAMP-HF: Change the Management of Patients with Heart Failure

DAPA-HF: Dapagliflozin And Prevention of Adverse outcomes in Heart Failure

ECG: Electrocardiogram

eGFR: Estimated glomerular filtration rate

HF: Heart failure

HFC: Heart Failure Collaboratory

HFrEF: Heart failure with reduced ejection fraction

HR: Hazard ratio

KCCQ-TTS: Kansas City Cardiomyopathy Questionnaire Total Symptom Score

LVEF: Left ventricular ejection fraction

MAHLER: Medical Management of Chronic Heart Failure in Europe and Its Related Costs

MRA: Mineralocorticoid-receptor antagonist

NYHA: New York Heart Association

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

RAS: Renin-angiotensin-system

SD: Standard deviation

SGLT2: sodium-glucose cotransporter 2

INTRODUCTION

During the past decade, the treatment landscape for heart failure (HF) with reduced ejection fraction (HFrEF) has evolved substantially. Evidence-based pharmacological therapy for patients with HFrEF now includes a neprilysin inhibitor, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and, in selected patients, hydralazine, ivabradine, and vericiguat, in addition to the original cornerstones of a beta-blocker (BB), renin-angiotensin-system (RAS) inhibitor, and mineralocorticoid-receptor antagonist (MRA).(1) With these expanding treatment options, it is ever more important to investigate whether the effects of a new therapy are truly additive to the benefits of established treatments. This question is not just about the number of background treatments but also their doses, i.e. the completeness or "quality" of background therapy. The latter is particularly important because there is evidence for a dose-response effect for some conventional therapies, e.g. RAS inhibitors,(2,3) and the incremental benefit of new treatments may theoretically be less if the dosing of evidence-based therapies is optimized. This raises the difficult issue of how to summarise the "quality" of medical therapy in HFrEF with the complex therapeutic landscape of multiple drugs and doses.

To address this issue, the Heart Failure Collaboratory (HFC) developed a score integrating classes and doses of guideline-directed medical therapies and providing a summary measure of treatment quality.(4–6) It is hoped that this score will standardize the quantification of evidence-based medical therapy in epidemiological studies, registries, and clinical trials. In clinical trials, this score may help in determining the additive effects of new drug and device treatments in HFrEF.(5,6)

Therefore, in a *post hoc* analysis of the Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF) trial, we evaluated the effect of the SGLT2 inhibitor, dapagliflozin, versus placebo, according to a modified HFC (mHFC) score. This refinement of the HFC score accounts for the two active components of sacubitril-valsartan (and dose of each of these), treatment with ivabradine (for patients in sinus rhythm with a heart rate >70 beats/minute) and dose of MRA and

hydralazine. Previous analyses of the original score included very few patients treated with sacubitril-valsartan or ivabradine, and DAPA-HF represents the first opportunity to test the incremental benefit of a novel therapy using this score.

METHODS

DAPA-HF was a randomized, double-blind, placebo-controlled trial in patients with HFrEF, evaluating the efficacy and safety of dapagliflozin 10 mg once daily compared with matching placebo, added to standard care. The design, baseline characteristics, and primary results of DAPA-HF are published.(7–9) The Ethics Committee of each of the 410 participating institutions in 20 countries approved the protocol, and all patients gave written informed consent.

Study patients

Key inclusion criteria included a diagnosis of HF for at least 2 months, New York Heart Association (NYHA) functional class II-IV, a left ventricular ejection fraction (LVEF) of ≤40%, optimal treatment with pharmacological and device therapy (unless contraindicated or not tolerated), and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥600 pg/mL (≥400 pg/mL if hospitalized for HF within the previous 12 months; ≥900 pg/mL if atrial fibrillation (AF) or atrial flutter (AFL) on the electrocardiogram (ECG) at enrollment, 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 complete list of exclusion criteria is provided in the design paper.(7) After randomization, follow-up visits were scheduled at 14, 60, and 120 days and then every four months thereafter.

The Heart Failure Collaboratory score

The integrated summary score for guideline-directed medical therapy created by the HFC was developed based on the strength of evidence, literature review, and data regarding dose effects from

clinical HFrEF trials.(4–6) Patients are assigned a score for each drug class, and the sum of these is the total score. For beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, patients are assigned 0 (no treatment), 1 (<50% target daily dose), or 2 points (≥50% target daily dose) for each therapy. For MRA, sacubitril-valsartan, and hydralazine (only scored in Black patients), patients are assigned 0 (no treatment) or 1 point (any dose) [2 points for sacubitril-valsartan] for each therapy.

In the present analysis, the mHFC treatment score used also accounted for 1) treatment with ivabradine (only scored in patients with a sinus rhythm rate ≥70), 2) the target daily dose for sacubitril-valsartan, MRA, and hydralazine (the target daily dose for these therapies was not considered in the original score), and 3) both the valsartan and sacubitril components of sacubitril-valsartan separately, as illustrated in Table 1. The total possible score for each patient accounted for the eligibility of treatment with hydralazine and ivabradine (i.e., the total possible score for a patient with an indication for both, one, and neither of these drugs was 12, 10, and 8 respectively). For each patient, the total score (the sum of the scores for each drug class) was divided with the total possible score expressed as a percentage, with a maximum mHFC treatment score of 100%.

For example, the total possible score for a non-black patient (not eligible for treatment with hydralazine) in sinus rhythm with a heart rate of 80 bpm (eligible for treatment with ivabradine) would be 10. If this patient was treated with a beta-blocker ≥50% target daily dose (2 points), sacubitril/valsartan ≥50% target daily dose (2 points for the ACE-I/ARB part and 2 points for the sacubitril part), MRA ≥50% target daily dose (2 points), and ivabradine ≥50% target daily dose (2 points), the total score would be 10, and the mHFC score would be 100% (i.e., (10/10)*100). However, if the patient was treated with a beta-blocker <50% target daily dose (1 point), ARB ≥50% target daily dose (2 points for the ACE-I/ARB part and 0 points for the sacubitril part), MRA ≥50%

target daily dose (2 points), and ivabradine <50% target daily dose (1 point), the total score would be 6 and the mHFC score 60% (i.e., (6/10)*100).

Trial outcomes

The primary outcome in DAPA-HF was the composite of worsening HF (HF hospitalization or an urgent visit for worsening HF and administration of intravenous therapy) or cardiovascular death. The secondary outcomes in the trial were 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 worsening renal function endpoint (this endpoint was not examined in the present analysis due to the small number of these events overall), and death from any cause. In this analysis, we also examined the change from baseline to 8 months in NYHA functional class. Prespecified safety analyses included serious adverse events, adverse events leading to discontinuation of trial treatment and adverse events of interest, including volume depletion (e.g., dehydration, hypovolemia, or hypotension), renal adverse events, bone fracture, amputation, major hypoglycemia, and diabetic ketoacidosis. Safety analyses were only performed in patients who had undergone enrollment and received at least one dose of either dapagliflozin or placebo; a total of eight randomized patients were excluded from the safety analysis.

Statistical analyses

In the present analysis, patients were divided into three subgroups, based on the tertiles of baseline mHFC treatment score. Baseline characteristics were summarized as frequencies with percentages, means with standard deviation (SD), or medians with interquartile ranges. Differences in baseline characteristics were tested using the Cochran-Armitage trend test for binary variables, the Cochran-

Mantel-Haenszel test for categorical variables, and the Jonckheere-Terpstra test and linear regression for non-normal and normally distributed continuous variables, respectively. Time-to-event data, regardless of treatment allocation, were evaluated using the Kaplan-Meier estimator (all-cause death), the Aalen-Johansen estimator (taken the competing risk of death into account for all outcomes except all-cause death), 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) with 95% CIs. In addition, HRs stratified according to diabetes mellitus status and adjusted for a history of HF hospitalization, treatment-group assignment, age, sex, geographical region, heart rate, systolic blood pressure, body mass index, HF etiology, LVEF, NYHA functional class, log of NT-proBNP, eGFR, hypertension, and a history of AF/AFL were reported. The models for all-cause death did not include an adjustment for a history of HF hospitalization. The relationship between the mHFC score as a continuous variable and the incidence rate of the primary endpoint was examined in restricted cubic spline analyses based on Poisson regression models.

To compare the effects of dapagliflozin versus placebo, time-to-event data were evaluated with 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 model for all-cause death was not adjusted for a history of HF hospitalization). The effect of dapagliflozin was also examined according to continuous mHFC treatment score as a fractional polynomial. Total, including recurrent events, were evaluated with semiparametric proportional-rates models.(10) The difference between treatment groups in the change in KCCQ-TSS from baseline to 8 months in surviving patients was analysed using a two-sample T-test. Responder analyses examining proportions of patients with a deterioration (decrease of ≥5 points) and a clinically important improvement (an increase of ≥5 points) in KCCQ-TSS at 8 months were performed with the treatment effect expressed as an odds

ratio with 95% CI using methods previously described.(11) The change in NYHA functional class (i.e., no deterioration) at 8 months was analyzed using logistic regression.

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

RESULTS

Patient characteristics

Overall, 93.6%, 96.1%, and 71.0% of patients were treated with a RAS inhibitor/ARNI, a BB, or an MRA, respectively, and 65.2% were treated with "triple therapy". The dosing of guideline-recommended pharmacological therapies, overall and according to treatment assignment, at baseline are shown in **Table 1**. Among patients prescribed a RAS inhibitor/ARNI, BB, or MRA, 41.0%, 51.5%, and 87.6% were treated with $\geq$50% of the target daily dose, respectively. There was no difference in the use of these therapies between the dapagliflozin and placebo groups.

The median treatment score was 50% (interquartile range, 27.5-62.5%; total range 0-100%). The three groups defined by treatment score tertiles were <41, 41-60, and >60%. Baseline characteristics according to baseline mHFC treatment score tertiles are presented in **Table 2**. There were no meaningful differences in age or sex across tertiles. However, compared to those with lower scores, individuals with higher scores were more often White and more likely to have AF (both as a history and on ECG) and a history of hypertension. Patients with higher treatment scores had a lower mean heart rate and systolic blood pressure, but higher body mass index and higher NT-proBNP levels (in those without AF/AFL on their ECG). They also had worse NYHA functional class, lower KCCQ-TSS (i.e., more symptoms), and longer duration of HF than those with lower treatment scores. Patients with higher treatment scores were more likely to have a defibrillating device.

Outcomes according to baseline mHFC treatment score

The distribution of baseline mHFC treatment score and the adjusted incidence rate of the primary endpoint according to continuous mHFC treatment score is displayed in **Figure 1**. The cumulative incidence and HRs for outcomes according to baseline mHFC treatment score tertiles are shown in **Supplementary Figure 1** and **Table 3**, respectively.

Compared with the lowest tertile, patients in the highest tertile of mHFC treatment score had a lower risk of worsening HF or cardiovascular death, even after adjustment for prognostic variables (first tertile, reference; second tertile, adjusted HR 0.97 [95% CI, 0.82-1.14]; third tertile, adjusted HR 0.83 [95% CI, 0.70-0.99]) **[Table 3].** There was no statistically significant difference between groups for the other outcomes after adjustment for prognostic variables, although there was a trend towards a lower risk among participants with a higher mHFC treatment score **(Table 3)**.

Effects of dapagliflozin on clinical outcomes according to baseline mHFC treatment score

Primary composite outcome

Compared with placebo, dapagliflozin reduced the risk of worsening HF or cardiovascular death across baseline mHFC treatment score – the HRs from lowest to highest tertile were: 0.76 [95% CI, 0.61-0.94], 0.76 [95% CI, 0.60-0.97], and 0.71 [95% CI, 0.55-0.90]), respectively, with no interaction between mHFC treatment score and the effect of treatment (P for interaction=0.89) **[Table 4]**. The effect of dapagliflozin on worsening HF or cardiovascular death was also consistent across the baseline mHFC treatment score examined as a continuous variable **(Figure 2A)**.

Secondary outcomes

HRs, rate ratios, and ORs for the effect of dapagliflozin, compared with placebo, on the secondary endpoints are shown in **Table 4**. The effect of dapagliflozin was consistent across baseline mHFC treatment score tertiles for HF hospitalization or cardiovascular death (P for interaction=0.91), HF hospitalization (P for interaction=0.28), cardiovascular death (P for interaction=0.24), all-cause death (P for interaction=0.61), and recurrent HF hospitalization or cardiovascular death (P for interaction=0.78). The effect of dapagliflozin on HF hospitalization, cardiovascular death, and all-

cause death was also consistent across baseline mHFC treatment score examined as a continuous variable **(Figure 2B-2D)**.

The mean increase in KCCQ-TSS from baseline to 8 months was significantly greater with dapagliflozin across baseline mHFC treatment score tertiles (P for interaction=0.76). The proportion of patients with an increase in KCCQ-TSS of ≥5 points was greater with dapagliflozin, compared with placebo, irrespective of baseline mHFC treatment score tertile (P for interaction=0.93). 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 mHFC treatment score tertiles (P for interaction=0.52) **[Table 4].**

The effect of dapagliflozin on the change in NYHA functional class was consistent across baseline mHFC treatment score tertiles i.e., the proportion of patients without deterioration in the placebo and dapagliflozin groups were: 87.0% versus 90.2%, 90.8% versus 90.3%, and 88.6 versus 89.7%, respectively, across HFC categories; the corresponding odds ratios were 1.38 (1.02-1.86), 0.95 (0.67-1.35) and 1.11 (0.81-1.53), respectively (P for interaction=0.89).

Safety analyses

The proportions of patients who discontinued trial treatment or experienced adverse events according to treatment assignment were similar across baseline mHFC treatment score, except for volume depletion. In the highest tertile, more patients experienced volume depletion with dapagliflozin than with placebo, whereas in the middle tertile, fewer patients in the dapagliflozin group (compared with the placebo group) experienced this adverse event (P for interaction=0.007) **(Supplementary Table 1)**.

DISCUSSION

In DAPA-HF, a summary score integrating the use and dosing of guideline-directed medical therapy was easy to calculate and a higher score (i.e. indicating more optimal therapy) was associated with better outcomes. In addition, dapagliflozin, compared with placebo, reduced the risk of worsening HF events, cardiovascular death, and all-cause death, and improved symptoms, across the range of baseline mHFC treatment scores, with no indication of lower efficacy in patients receiving better background therapy.

Medical treatment scores

Standardizing the quantification of evidence-based medical therapy in HFrEF is important for several reasons. First, standardization facilitates the comparison of treatments across different populations in epidemiological studies, registries, and clinical trials. Second, such standardization provides a simple summary measure of the quality of care. Third, this approach allows the examination of temporal trends in treatment, e.g. to document improvements in care over time in population studies. Fourth, standardization may help in determining the incremental effect of a new drug or device treatment and this was the focus of the present study. Previous attempts have been made to evaluate evidence-based medical therapy in HFrEF, for example in the Medical Management of Chronic Heart Failure in Europe and Its Related Costs (MAHLER) survey (12) and the quality of adherence to guideline recommendations for life-saving treatment in heart failure: an international survey (QUALIFY).(13) However, the former score did not account for evidence-based target doses, and the latter score did not include treatment with hydralazine or sacubitril-valsartan. In the present study, we used a mHFC score, which also accounted for treatment with ivabradine in eligible patients; both the valsartan and sacubitril components of sacubitril-valsartan separately (two distinct drugs with different mechanisms of action); and target daily dose for sacubitril-valsartan, MRA, and hydralazine (given the evidence

for a dose-response with some drugs e.g. RAS inhibitors).(2,3) Therefore, these modifications may provide a more precise quantification of evidence-based medical therapy in patients with HFrEF.

Outcomes according to the mHFC treatment score

A high proportion of patients enrolled in DAPA-HF received conventional guideline-recommended therapies for HFrEF. However, ivabradine and hydralazine remained underutilized. Among those with an apparent indication for ivabradine (sinus rhythm ≥70 bpm) and hydralazine (Black patients), only 6.9% and 22.1%, respectively, were treated with these beneficial (and in the case of hydralazine lifesaving) therapies. As a result of the latter, Black patients had a disproportionately low score compared to other patients.

Similarly, dosing of each medication type was frequently below guideline targets, with only approximately 40% and 50% treated with ≥50% of the target daily dose of a RAS inhibitor/ARNI and BB, respectively. However, "real-world" registry-based studies have consistently shown much greater underutilization of evidence-based treatment in clinical practice, even in patients with no contraindications, and that target doses are infrequently achieved.(14–16) For example, among more than 150,000 hospitalized patients with HFrEF in the Get With The Guidelines-Heart Failure Registry, only 23% were treated with triple therapy with a RAS inhibitor/ARNI, a BB, and an MRA.(15) Similarly, in an analysis of the Change the Management of Patients with Heart Failure (CHAMP-HF) Registry, which included 3,518 outpatients with HFrEF, 73.4%, 67.0%, and 33.4% of patients without any documented contraindications were treated with a RAS inhibitor/ARNI, a BB, and an MRA, respectively, and only 22.1% were treated with triple therapy.(16)

Importantly, and in line with previous studies,(12,13,17,18) we found that patients in the highest tertile of baseline treatment score (i.e. most complete therapy) had a significantly lower risk of the composite of worsening HF or cardiovascular death compared with those in the lowest tertile, even

after adjustment for known prognostic variables including NT-proBNP. Although this association in an observational analysis does not prove cause and effect, it does highlight the potential consequences of the substantial underutilization of guideline-recommended pharmacological therapies in contemporary clinical practice and underline the importance of achieving optimal medical therapy in the absence of contraindications. A recent network meta-analysis of pharmacological treatment of HFrEF also demonstrated that the estimated aggregate benefit was greatest for a combination of BB, ARNI, MRA, and SGLT2 inhibitor.(19) Taken together, these findings underline the urgent need for effective strategies to improve use and target dosing of life-saving medical therapies.

Efficacy and safety of dapagliflozin according to the mHFC treatment score

With the expanding treatment landscape in HFrEF, it becomes ever more important to be able to demonstrate that the effects of a new therapy are truly incremental and therefore a worthwhile addition to multiple existing treatments. We have previously demonstrated that the benefit of dapagliflozin in DAPA-HF was consistent regardless of background drug and device therapy.(20) However, the incremental value of a new treatment may depend on both the number of background therapies used and the doses of evidence-based therapies prescribed. Therefore, in the present report, we examined the effects of dapagliflozin according to a mHFC summary score that integrates both. We found that the efficacy of dapagliflozin was not modified by the baseline treatment score. Specifically, dapagliflozin, compared with placebo, reduced the risk of worsening HF or cardiovascular death across the range of treatment score, and the benefits of dapagliflozin on HF hospitalization (both first and recurrent), cardiovascular death, and all-cause death were also entirely consistent, irrespective of treatment score, with no evidence of attenuation of efficacy in patients receiving optimal background therapy. In addition, dapagliflozin increased the proportion of patients with a clinically meaningful improvement, and reduced the proportion with a deterioration, in

symptoms (≥5 point change in KCCQ-TSS), irrespective of baseline treatment score. Collectively, these findings suggest that the substantial effects of dapagliflozin are incremental, and complementary, to the benefits of conventional therapies for HFrEF, even in patients achieving guideline-recommended doses of background medical therapy.

In this exemplar study, the mHFC score appears to be a simple and useful tool for evaluating the incremental effects of new HFrEF treatments. This may assist regulators, payers, prescribers, and patients in quantifying the clinical value of using an additional therapy. This is an increasingly important consideration in an era of an expanding multi-drug regimen in HFrEF. However, further work is warranted to refine the score, determine the score distribution in other clinical trials and in routine clinical practice, and determine appropriate cut-points in relation to outcomes.(6)

With respect to safety and tolerability, study drug discontinuation and serious adverse events were not more frequently reported in the dapagliflozin group than in the placebo group across baseline HFC treatment score tertiles. However, in the highest tertile, more patients experienced volume depletion with dapagliflozin than with placebo, whereas in the middle tertile, fewer patients in the dapagliflozin group compared with the placebo group experienced this adverse event. While the explanations for this finding are not clear, it is likely that it may have resulted from the play of chance. Importantly, study drug discontinuation for any reason or due to adverse events was not more common in the dapagliflozin group than in the placebo in the highest treatment score tertile.

Limitations

The findings of this study should be viewed in the context of potential limitations. First, the analyses were not prespecified. Second, the pre-specified inclusion and exclusion criteria precluded the enrolment of very high-risk patients and patients with very low mHFC treatment scores, which might affect the generalizability of our results.

Conclusions

Using a summary score integrating drugs and doses of GDMT, we found that dapagliflozin, compared with placebo, reduced the risk of worsening HF events, cardiovascular death, and all-cause death, and improved symptoms, across the range of scores at baseline. The mHFC treatment score can be easily calculated in clinical trials and used to evaluate the incremental effects of new treatments.

CLINICAL PERSPECTIVES

Competencies in Medical Knowledge

In this *post hoc* analysis of the DAPA-HF trial, which included 4,744 patients with heart failure (HF) with reduced ejection fraction, dapagliflozin reduced the risk of worsening HF or cardiovascular death across the range of a modified treatment score, integrating classes and doses of guideline-directed medical therapy, developed by the Heart Failure Collaboratory. Consistent benefits were observed for HF hospitalization, cardiovascular death, all-cause mortality, and improvement in the Kansas City Cardiomyopathy Questionnaire total symptom score across the range of treatment scores.

Translational Outlook

The modified Heart Failure Collaboratory treatment score can be easily calculated in clinical trials and used to evaluate the incremental effects of new treatments. Further examination of this score in registries and trials would be useful.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep;42(36):3599–726.
2. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation. 1999 Dec;100(23):2312–8.
3. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet. 2009 Nov;374(9704):1840–8.
4. Abraham WT, Psotka MA, Fiuzat M, Filippatos G, Lindenfeld J, Mehran R, et al. Standardized Definitions for Evaluation of Heart Failure Therapies: Scientific Expert Panel From the Heart Failure Collaboratory and Academic Research Consortium. JACC Heart Fail. 2020 Dec;8(12):961–72.
5. DeFilippis EM, Fiuzat M. Putting the "Optimal" in Optimal Medical Therapy. JACC Hear Fail. 2021 Jan;9(1):39–41.
6. Fiuzat M, Hamo CE, Butler J, Abraham WT, DeFilippis EM, Fonarow GC, et al. Optimal Background Pharmacological Therapy for Heart Failure Patients in Clinical Trials: JACC Review Topic of the Week. J Am Coll Cardiol. 2022 Feb;79(5):504–10.
7. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, et al. A trial to evaluate the effect of the sodium–glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). Eur J Heart Fail. 2019;21(5):665–75.

8. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, et al. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. Eur J Heart Fail. 2019;21(11):1402–11.
9. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995–2008.
10. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. J R Stat Soc Ser B Stat Methodol. 2000;62(4):711–30.
11. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, et al. Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients with Heart Failure and Reduced Ejection Fraction: Results from the DAPA-HF Trial. Circulation. 2020;141(2):90–9.
12. Komajda M, Lapuerta P, Hermans N, Gonzalez-Juanatey JR, van Veldhuisen DJ, Erdmann E, et al. Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey. Eur Heart J. 2005 Aug;26(16):1653–9.
13. Komajda M, Schöpe J, Wagenpfeil S, Tavazzi L, Böhm M, Ponikowski P, et al. Physicians' guideline adherence is associated with long-term heart failure mortality in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. Eur J Heart Fail. 2019 Jul;21(7):921–9.
14. Brunner-La Rocca H-P, Linssen GC, Smeele FJ, van Drimmelen AA, Schaafsma H-J, Westendorp PH, et al. Contemporary Drug Treatment of Chronic Heart Failure With Reduced Ejection Fraction: The CHECK-HF Registry. JACC Hear Fail. 2019 Jan;7(1):13–21.
15. Patel RB, Fonarow GC, Greene SJ, Zhang S, Alhanti B, DeVore AD, et al. Kidney Function

and Outcomes in Patients Hospitalized With Heart Failure. J Am Coll Cardiol. 2021;78(4):330–43.

16. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. J Am Coll Cardiol. 2018 Jul;72(4):351–66.

17. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. Eur Heart J. 2017 Jun;38(24):1883–90.

18. Poelzl G, Altenberger J, Pacher R, Ebner CH, Wieser M, Winter A, et al. Dose matters! Optimisation of guideline adherence is associated with lower mortality in stable patients with chronic heart failure. Int J Cardiol. 2014 Jul;175(1):83–9.

19. Tromp J, Ouwerkerk W, van Veldhuisen DJ, Hillege HL, Richards AM, van der Meer P, et al. A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction. JACC Hear Fail. 2022 Feb;10(2):73–84.

20. Docherty KF, Jhund PS, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. Eur Heart J. 2020 Jul;41(25):2379–92.

Table 1. Calculation of modified HFC treatment score and use of guideline-recommended pharmacological therapies according to treatment assignment

Therapy	Score	Overall N=4,744	Placebo N=2,371	Dapagliflozin N=2,373
Beta-blocker				
<50% of target daily dose	1	2,209 (46.6)	1,110 (46.8)	1,099 (46.3)
≥50% of target daily dose	2	2,349 (49.5)	1,170 (49.3)	1,179 (49.7)
ACEI/ARB/ARNI (valsartan part)				
<50% of target daily dose	1	2,621 (55.2)	1,330 (56.1)	1,291 (54.4)
≥50% of target daily dose	2	1,820 (38.4)	877 (37.0)	943 (39.7)
ARNI (sacubitril part)				
<50% of target daily dose	1	200 (4.2)	104 (4.4)	96 (4.0)
≥50% of target daily dose	2	308 (6.5)	154 (6.5)	154 (6.5)
Mineralocorticoid-receptor antagonist				
<50% of target daily dose	1	417 (8.8)	201 (8.5)	216 (9.1)
≥50% of target daily dose	2	2,953 (62.2)	1,473 (62.1)	1,480 (62.4)
Ivabradine*				
<50% of target daily dose	1	23/1,366 (1.7)	12/679 (1.8)	11/687 (1.6)
≥50% of target daily dose	2	71/1,366 (5.2)	36/679 (5.3)	35/687 (5.1)
Hydralazine**				
<50% of target daily dose	1	31/226 (13.7)	16/104 (15.4)	15/122 (12.3)
≥50% of target daily dose	2	19/226 (8.4)	8/104 (7.7)	11/122 (9.0)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor.

**Only scored in patients with sinus rhythm ≥70 bpm. The denominator is the number of patients with sinus rhythm ≥70 bpm.*

***Only scored in Black patients. The denominator is the number of Black patients.*

The modified HFC treatment score is calculated as the total score (the sum of the scores for each drug class) divided by the total possible score, with a maximum treatment score of 1 (or 100%).

The total possible score for non-black patients not in sinus rhythm or sinus rhythm <70 bpm, 8 points; non-black patients with sinus rhythm ≥70 bpm, 10 points; black patients not in sinus rhythm or sinus rhythm <70 bpm, 10 points; black patients with sinus rhythm ≥70 bpm, 12 points.

Target daily doses for beta-blockers were carvedilol 50 mg, bisoprolol 10 mg, metoprolol succinate 200 mg, metoprolol tartrate 200 mg, and nebivolol 10 mg; patients taking other beta-blockers were classified as taking <50% target dose.

Target daily doses for ACEI and ARB were captopril 150 mg, enalapril 40 mg, fosinopril 40 mg, lisinopril 35 mg, perindopril 16 mg, quinapril 40 mg, ramipril 10 mg, trandolapril 4 mg, candesartan 32 mg, losartan 150 mg, valsartan 320 mg, and irbesartan 300 mg; patients taking other ACEI/ARBs were classified as taking <50% target dose.

The target daily dose for the valsartan and sacubitril part of ARNI was 206 mg and 194 mg, respectively.

Target daily doses for mineralocorticoid-receptor antagonists were 50 mg spironolactone or 50 mg eplerenone.

The target daily dose for ivabradine was 15 mg.

The target daily dose for hydralazine was 225 mg.

Table 2. Baseline characteristics of the study population according to tertiles of a modified HFC treatment score

	Overall N=4,744	<41 N=1,733	41-60 N=1,463	>60 N=1,548	P-value
Age (years), mean (SD)	66.3 (10.9)	67.1 (11.0)	65.3 (11.3)	66.4 (10.2)	0.047
Sex, N (%)					0.78
Female	1,109 (23.4)	392 (22.6)	375 (25.6)	342 (22.1)	
Male	3,635 (76.6)	1,341 (77.4)	1,088 (74.4)	1,206 (77.9)	
Race, N (%)					<0.001
Asian	1,116 (23.5)	686 (39.6)	314 (21.5)	116 (7.5)	
Black	226 (4.8)	84 (4.8)	116 (7.9)	26 (1.7)	
White	3,333 (70.3)	950 (54.8)	1,003 (68.6)	1,380 (89.1)	
Other	69 (1.5)	13 (0.8)	30 (2.1)	26 (1.7)	
Geographic region, N (%)					<0.001
Asia/Pacific	1,096 (23.1)	679 (39.2)	310 (21.2)	107 (6.9)	
Europe	2,154 (45.4)	566 (32.7)	678 (46.3)	910 (58.8)	
North America	677 (14.3)	296 (17.1)	167 (11.4)	214 (13.8)	
South America	817 (17.2)	192 (11.1)	308 (21.1)	317 (20.5)	
Physiologic measures					
Systolic blood pressure (mmHg), mean (SD)	121.8 (16.3)	122.5 (18.9)	122.1 (16.1)	120.8 (15.9)	0.004
Heart rate (bpm), mean (SD)	71.5 (11.7)	73.8 (11.8)	71.5 (11.5)	69.0 (11.3)	<0.001
BMI (kg/m^2), mean (SD)	28.1 (6.0)	26.9 (5.5)	28.4 (6.0)	29.4 (6.0)	<0.001
Creatinine (μmol/L), mean (SD)	104.4 (30.4)	104.6 (30.7)	103.3 (30.9)	105.3 (29.5)	0.57
Glycated hemoglobin, median (IQR)	6.1 (5.7-6.9)	6.1 (5.7-6.8)	6.2 (5.7-6.9)	6.1 (5.7-6.8)	0.69
eGFR ($mL/min/1.73m^2$), mean (SD)	65.8 (19.4)	65.4 (19.8)	67.3 (20.2)	64.7 (18.1)	0.35
eGFR ($mL/min/1.73m^2$), N (%)					0.91
< 60	1,926 (40.6)	719 (41.5)	560 (38.3)	647 (41.8)	

≥ 60	2,816 (59.4)	1,014 (58.5)	901 (61.7)	901 (58.2)	
NT-proBNP, median (IQR)					
Atrial fibrillation/flutter on ECG at enrolment	1,948 (1,265-3,204)	1,953 (1,279-3,131)	1,931 (1,243-3,108)	1,983 (1,258-3,209)	0.76
No atrial fibrillation/flutter on ECG at enrolment	1,290 (772-2,415)	1,382 (836-2,647)	1,258 (727-2,352)	1,212 (739-2,244)	<0.001
Main cause of HF, N (%)					0.001
Ischemic	2,674 (56.4)	986 (56.9)	804 (55.0)	884 (57.1)	
Non-ischemic	1,687 (35.6)	574 (33.1)	552 (37.7)	561 (36.2)	
Unknown	383 (8.1)	173 (10.0)	107 (7.3)	103 (6.7)	
Duration of HF, N (%)					<0.001
0-3 months	150 (3.2)	59 (3.4)	45 (3.1)	46 (3.0)	
3-6 months	393 (8.3)	149 (8.6)	139 (9.5)	105 (6.8)	
6-12 months	555 (11.7)	236 (13.6)	178 (12.2)	141 (9.1)	
1-2 years	686 (14.5)	243 (14.0)	218 (14.9)	225 (14.5)	
2-5 years	1,105 (23.3)	406 (23.4)	335 (22.9)	364 (23.5)	
>5 years	1,855 (39.1)	640 (36.9)	548 (37.5)	667 (43.1)	
LVEF, mean (SD)	31.1 (6.8)	31.3 (6.7)	30.7 (6.9)	31.1 (6.8)	0.26
NYHA class, N (%)					<0.001
II	3,203 (67.5)	1,222 (70.5)	992 (67.8)	989 (63.9)	
III	1,498 (31.6)	489 (28.2)	454 (31.0)	555 (35.9)	
IV	43 (0.9)	22 (1.3)	17 (1.2)	4 (0.3)	
KCCQ-TSS, mean (SD)	73.6 (21.8)	75.6 (21.2)	73.2 (22.1)	71.9 (22.0)	<0.001
Medical history, N (%)					
History of atrial fibrillation/flutter	1,885 (39.7)	616 (35.5)	525 (35.9)	744 (48.1)	<0.001
Atrial fibrillation/flutter on ECG at enrolment	1,128 (23.8)	316 (18.2)	311 (21.3)	501 (32.4)	<0.001
Hospitalization for HF	2,251 (47.4)	852 (49.2)	690 (47.2)	709 (45.8)	0.05
Hypertension	3,523 (74.3)	1,236 (71.3)	1,075 (73.5)	1,212 (78.3)	<0.001
Type 2 diabetes	2,139 (45.1)	771 (44.5)	680 (46.5)	688 (44.4)	0.99

Chronic obstructive pulmonary disease	585 (12.3)	236 (13.6)	160 (10.9)	189 (12.2)	0.20
Previous MI	2,092 (44.1)	767 (44.3)	637 (43.5)	688 (44.4)	0.93
Treatment, N (%)					
ACEI/ARB	3,952 (83.3)	1,420 (81.9)	1,328 (90.8)	1,204 (77.8)	0.004
ARNI	508 (10.7)	58 (3.3)	100 (6.8)	350 (22.6)	<0.001
ACEI/ARB/ARNI	4,442 (93.6)	1,473 (85.0)	1,421 (97.1)	1,548 (100.0)	<0.001
Beta-blocker	4,558 (96.1)	1,578 (91.1)	1,438 (98.3)	1,542 (99.6)	<0.001
Mineralocorticoid-receptor antagonist	3,370 (71.0)	655 (37.8)	1,232 (84.2)	1,483 (95.8)	<0.001
Triple therapy*	3,091 (65.2)	448 (25.9)	1,166 (79.7)	1,477 (95.4)	<0.001
Quadruple therapy**	332 (7.0)	4 (0.2)	49 (3.3)	279 (18.0)	<0.001
Ivabradine (sinus rhythm ≥70 bpm)	94 (6.9)	20 (2.6)	37 (7.3)	37 (47.4)	<0.001
Ivabradine (no sinus rhythm/sinus rhythm <70 bpm)	134 (4.0)	34 (3.6)	42 (4.4)	58 (3.9)	0.71
Hydralazine (Black patients)	50 (22.1)	16 (19.0)	22 (19.0)	12 (46.2)	0.03
Hydralazine (non-Black patients)	82 (1.8)	32 (1.9)	17 (1.3)	33 (2.2)	0.66
Digoxin	887 (18.7)	295 (17.0)	276 (18.8)	316 (20.4)	0.01
Amiodarone	569 (12.0)	188 (10.8)	179 (12.2)	202 (13.0)	0.05
Oral anticoagulant***					
History of atrial fibrillation/flutter	1,582 (83.9)	479 (77.8)	438 (83.4)	665 (89.4)	<0.001
No history of atrial fibrillation/flutter	387 (13.5)	133 (11.9)	113 (12.0)	141 (17.5)	<0.001
Antiplatelet****	2,592 (54.6)	1,041 (60.1)	817 (55.8)	734 (47.4)	<0.001
CRT-P/CRT-D	354 (7.5)	105 (6.1)	95 (6.5)	154 (9.9)	<0.001
ICD/CRT-D	1,242 (26.2)	355 (20.5)	341 (23.3)	547 (35.3)	<0.001

ACE angiotensin-converting enzyme; 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; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ-TTS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

**ACEI/ARB/ARNI + beta-blocker + mineralocorticoid-receptor antagonist.*

***ARNI + beta-blocker + mineralocorticoid-receptor antagonist.*

****Vitamin K antagonists (warfarin/coumadin) and "direct" oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban).*

*****Aspirin, ADP-receptor inhibitors (clopidogrel, ticagrelor, prasugrel), and adenosine reuptake inhibitors (dipyridamole).*

Table 3. Outcomes according to tertiles of a modified HFC treatment score

	<41 N=1,733	41-60 N=1,463	>60 N=1,548
Worsening HF event or cardiovascular death			
N (%)	344 (19.8)	276 (18.9)	268 (17.3)
Event rate per 100 person-years (95% CI)	14.8 (13.3-16.5)	13.5 (12.0-15.2)	12.2 (10.8-13.8)
HR (95% CI)*	Reference	0.91 (0.78-1.07)	0.83 (0.71-0.97)
HR (95% CI)**	Reference	0.97 (0.82-1.14)	0.83 (0.70-0.99)
HF hospitalization or cardiovascular death			
N (%)	338 (19.5)	273 (18.7)	266 (17.2)
Event rate per 100 person-years (95% CI)	14.5 (13.1-16.2)	13.3 (11.8-15.0)	12.1 (10.7-13.6)
HR (95% CI)*	Reference	0.92 (0.78-1.08)	0.84 (0.71-0.98)
HR (95% CI)**	Reference	0.98 (0.83-1.15)	0.84 (0.70-1.00)
HF hospitalization			
N (%)	213 (12.3)	168 (11.5)	168 (10.9)
Event rate per 100 person-years (95% CI)	9.2 (8.0-10.5)	8.2 (7.0-9.5)	7.6 (6.6-8.9)
HR (95% CI)*	Reference	0.90 (0.73-1.10)	0.85 (0.69-1.04)
HR (95% CI)**	Reference	0.97 (0.78-1.19)	0.83 (0.67-1.03)
Cardiovascular death			
N (%)	196 (11.3)	154 (10.5)	150 (9.7)
Event rate per 100 person-years (95% CI)	7.9 (6.9-9.1)	7.1 (6.1-8.3)	6.5 (5.5-7.6)
HR (95% CI)*	Reference	0.88 (0.72-1.09)	0.82 (0.66-1.01)
HR (95% CI)**	Reference	0.91 (0.73-1.14)	0.80 (0.63-1.00)
All-cause death			
N (%)	234 (13.5)	180 (12.3)	191 (12.3)
Event rate per 100 person-years (95% CI)	9.5 (8.3-10.8)	8.3 (7.2-9.6)	8.3 (7.2-9.5)

HR (95% CI)*	Reference	0.87 (0.71-1.05)	0.87 (0.72-1.05)
HR (95% CI)**	Reference	0.91 (0.74-1.11)	0.85 (0.69-1.05)

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

***Stratified according to diabetes mellitus status and adjusted for a history of HF hospitalization, randomized treatment allocation, age, sex, geographical region, heart rate, systolic blood pressure, body mass index, HF etiology, left ventricular ejection fraction, NYHA functional class, log of NT-proBNP, estimated glomerular filtration rate, hypertension, and a history of atrial fibrillation/flutter.*

Table 4. Effects of dapagliflozin compared with placebo on clinical events across tertiles of a modified HFC treatment score

Tertile	<41 N=1,733		41-60 N=1,463		>60 N=1,548		P-value for interaction
Outcome	Placebo N=884	Dapagliflozin N=849	Placebo N=703	Dapagliflozin N=760	Placebo N=784	Dapagliflozin N=764	
Worsening HF event or cardiovascular death							0.89
N (%)	196 (22.2)	148 (17.4)	149 (21.2)	127 (16.7)	157 (20.0)	111 (14.5)	
Event rate per 100 person-years (95% CI)	16.9 (14.7-19.4)	12.8 (10.9-15.0)	15.4 (13.1-18.1)	11.8 (9.9-14.0)	14.3 (12.2-16.7)	10.1 (8.4-12.2)	
HR (95% CI)*	0.76 (0.61-0.94)		0.76 (0.60-0.97)		0.71 (0.55-0.90)		
HF hospitalization or cardiovascular death							0.91
N (%)	193 (21.8)	145 (17.1)	147 (20.9)	126 (16.6)	155 (19.8)	111 (14.5)	
Event rate per 100 person-years (95% CI)	16.5 (14.4-19.0)	12.5 (10.6-14.7)	15.2 (12.9-17.8)	11.7 (9.8-13.9)	14.1 (12.1-16.5)	10.1 (8.4-12.1)	
HR (95% CI)*	0.76 (0.61-0.94)		0.77 (0.60-0.97)		0.72 (0.56-0.91)		
HF hospitalization							0.28
N (%)	132 (14.9)	81 (9.5)	86 (12.2)	82 (10.8)	100 (12.8)	68 (8.9)	
Event rate per 100 person-years (95% CI)	11.3 (9.5-13.4)	7.0 (5.6-8.7)	8.9 (7.2-11.0)	7.6 (6.1-9.4)	9.1 (7.5-11.1)	6.2 (4.9-7.8)	
HR (95% CI)*	0.61 (0.47-0.81)		0.85 (0.63-1.15)		0.68 (0.50-0.92)		
Cardiovascular death							0.24
N (%)	101 (11.4)	95 (11.2)	83 (11.8)	71 (9.3)	89 (11.4)	61 (8.0)	
Event rate per 100 person-years (95% CI)	8.0 (6.6-9.7)	7.9 (6.4-9.6)	8.0 (6.5-10.0)	6.2 (5.0-7.9)	7.7 (6.2-9.5)	5.3 (4.1-6.8)	
HR (95% CI)*	0.99 (0.75-1.32)		0.77 (0.56-1.06)		0.70 (0.50-0.97)		
All-cause death							0.61
N (%)	125 (14.1)	109 (12.8)	95 (13.5)	85 (11.2)	109 (13.9)	82 (10.7)	
Event rate per 100 person-years (95% CI)	9.9 (8.3-11.8)	9.0 (7.5-10.9)	9.2 (7.5-11.3)	7.5 (6.0-9.2)	9.4 (7.8-11.3)	7.1 (5.8-8.9)	
HR (95% CI)*	0.92 (0.71-1.19)		0.81 (0.60-1.08)		0.76 (0.57-1.02)		
Recurrent HF hospitalization or cardiovascular death							0.78
No. of events	296	217	217	193	229	157	

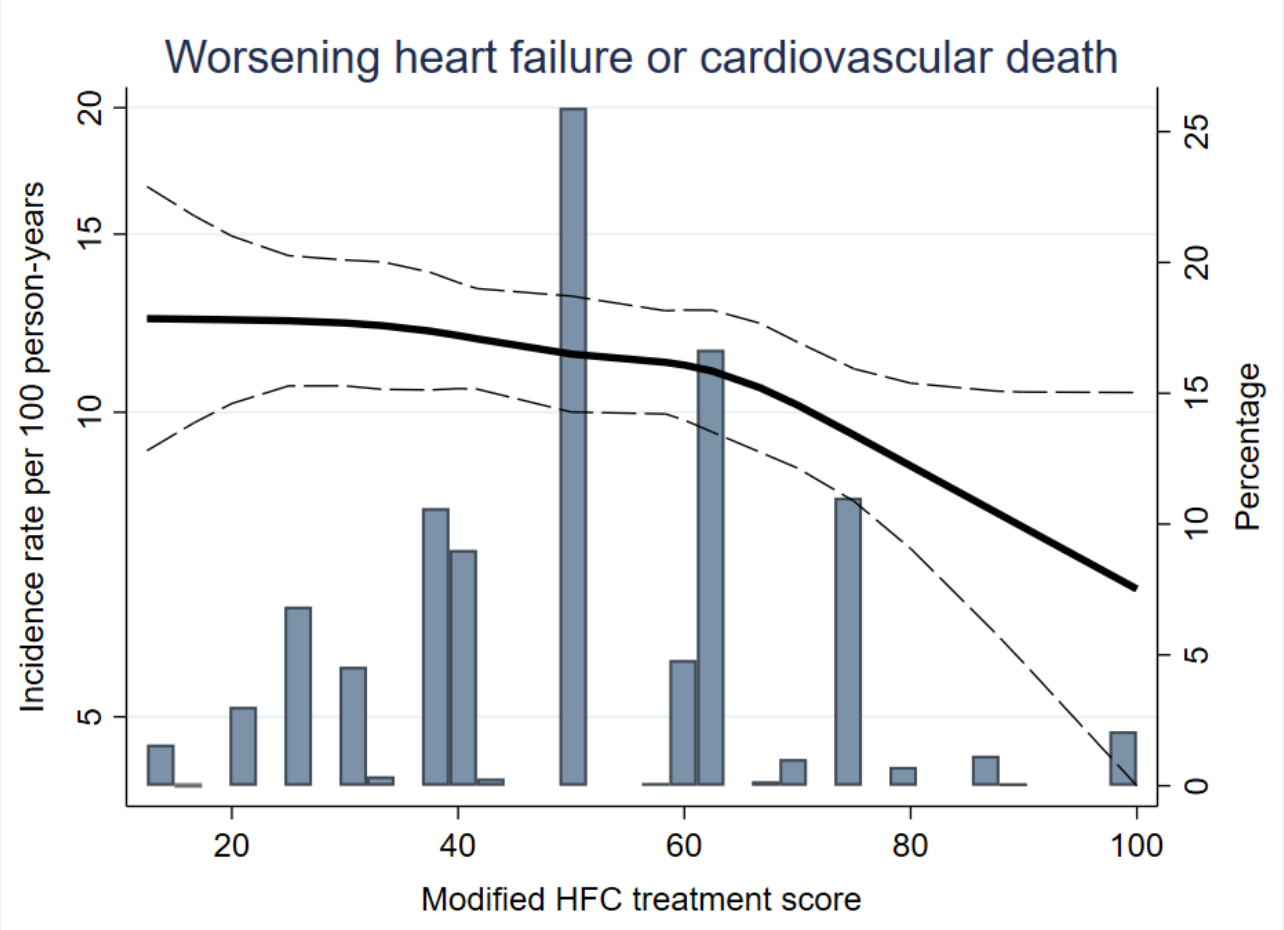
RR (95% CI)*	0.76 (0.60-0.97)		0.80 (0.61-1.04)		0.70 (0.54-0.92)		
KCCQ-TSS							
Change in KCCQ-TSS score at 8 months	3.0 (1.6-4.4)	5.8 (4.4-7.2)	3.7 (2.2-5.3)	5.9 (4.4-7.3)	3.3 (1.7-4.8)	6.7 (5.2-8.1)	0.76
≥5-point improvement in KCCQ-TSS at 8 months							0.93
Proportion of patients	51.1	58.6	51.2	57.9	50.6	58.4	
OR (95% CI)	1.16 (1.05-1.29)		1.13 (1.02-1.27)		1.16 (1.04-1.29)		
≥5-point decrease in KCCQ-TSS at 8 months							0.52
Proportion of patients	32.3	25.7	31.9	26.1	34.3	24.1	
OR (95% CI)**	0.85 (0.76-0.95)		0.88 (0.78-0.99)		0.78 (0.70-0.88)		

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

***Adjusted for baseline value and diabetes status.*

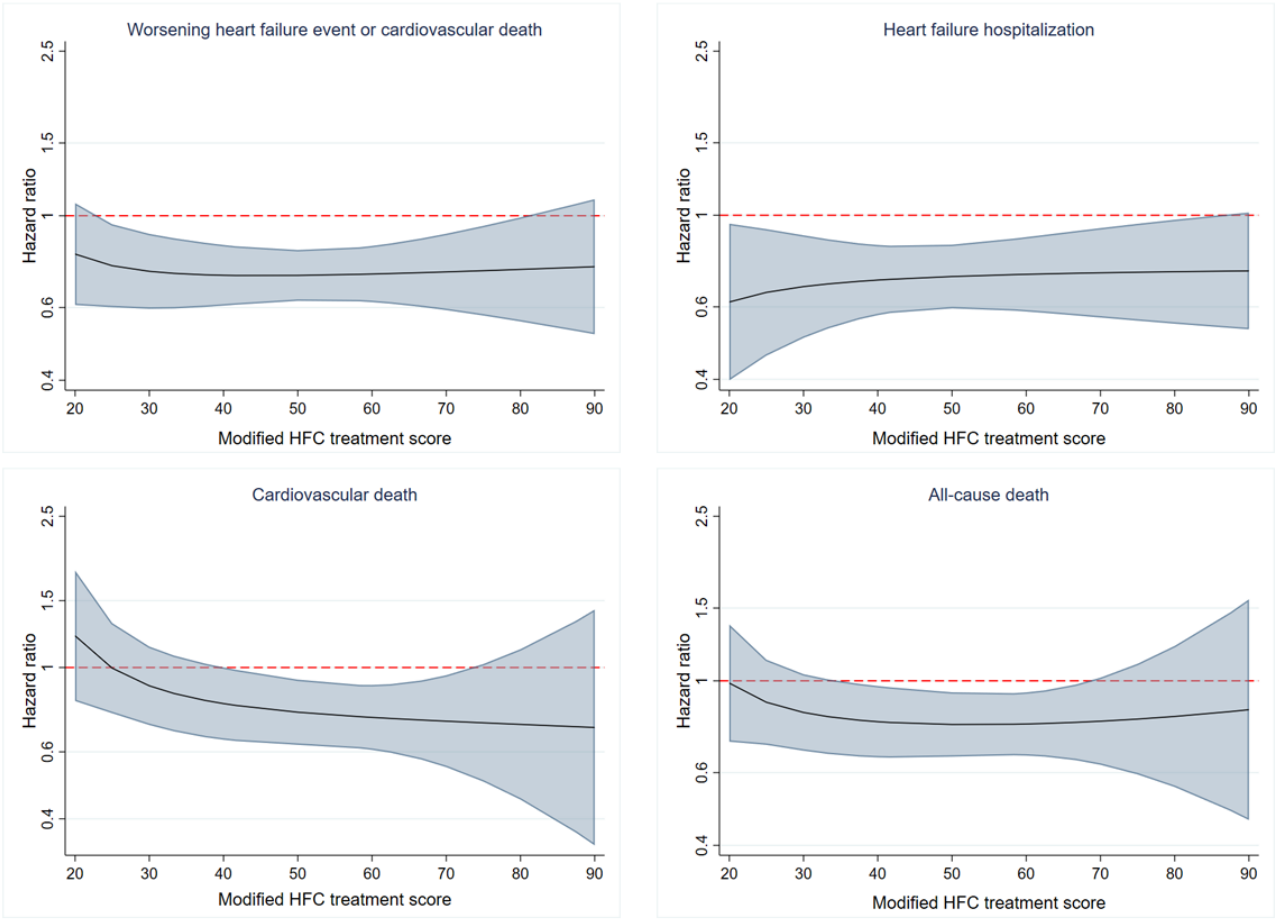
Figure 1. The incidence rate for worsening heart failure or cardiovascular death according to a modified HFC treatment score



Restricted cubic spline analysis showing the incidence rate of worsening heart failure or cardiovascular death per 100 person-years according to a modified HFC treatment score. The results are derived from models based on the entire spectrum of a modified HFC treatment score, except scores<10 (given the small number of patients).

Poisson regression model adjusted for a history of HF hospitalization, diabetes mellitus status, randomized treatment allocation, age, sex, geographical region, heart rate, systolic blood pressure, body mass index, HF etiology, left ventricular ejection fraction, NYHA functional class, log of NT-proBNP, estimated glomerular filtration rate, hypertension, and a history of atrial fibrillation/flutter.

Figure 2. Effect of dapagliflozin compared with placebo according to a modified HFC treatment score



Fractional polynomial analyses showing the effect of dapagliflozin on outcomes across the range of a modified HFC treatment score.

Figures have been restricted to a modified HFC treatment score between 20-90, but the results are derived from models based on the entire spectrum of a modified HFC treatment score, except scores<10 (given the small number of patients).

P-values for interaction: worsening heart failure event or cardiovascular death, 0.58; heart failure hospitalization, 0.78; cardiovascular death, 0.06; and all-cause death 0.36.

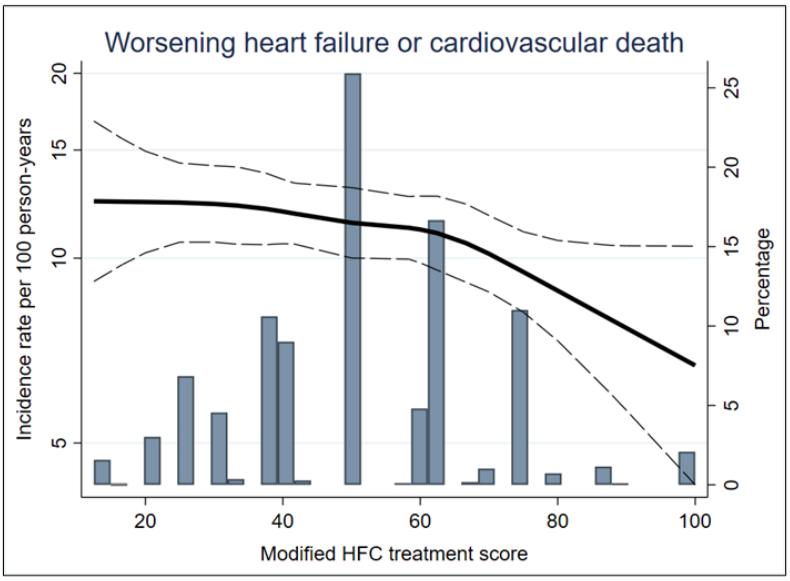
CENTRAL ILLUSTRATION. Components of the modified HFC treatment score and effect of dapagliflozin according to a modified HFC treatment score

Components of the modified HFC treatment score

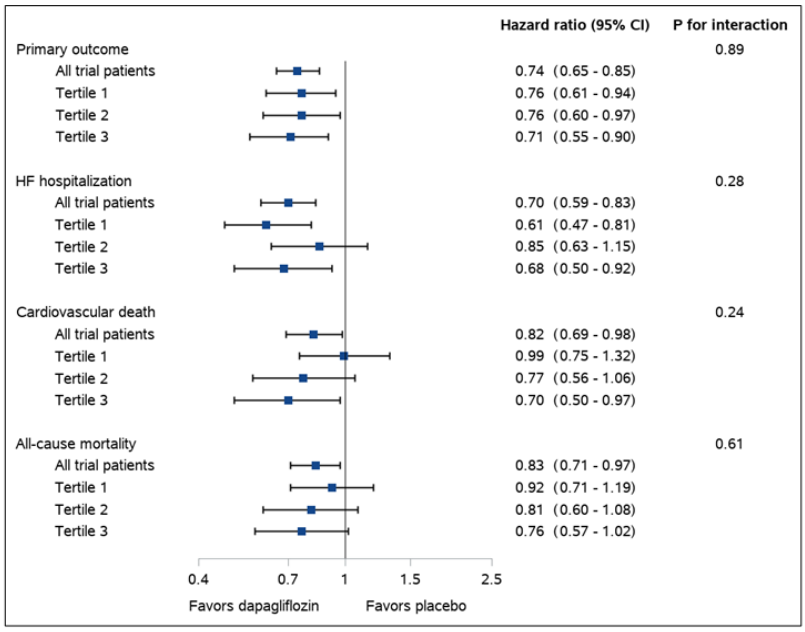
$$\text{Modified HFC score} = \frac{\text{Total score}}{\text{Total possible score}} * 100$$

Therapy	Score
Beta-blocker	
<50% of target daily dose	1
≥50% of target daily dose	2
ACEI/ARB/ARNI (valsartan part)	
<50% of target daily dose	1
≥50% of target daily dose	2
ARNI (sacubitril part)	
<50% of target daily dose	1
≥50% of target daily dose	2
Mineralocorticoid-receptor antagonist	
<50% of target daily dose	1
≥50% of target daily dose	2
Ivabradine*	
<50% of target daily dose	1
≥50% of target daily dose	2
Hydralazine**	
<50% of target daily dose	1
≥50% of target daily dose	2

A higher modified HFC treatment score (indicating more optimal therapy) was associated with a lower risk of adverse outcomes



Dapagliflozin reduced the risk of adverse outcomes across the range of the modified HFC treatment score



**Only scored in patients with sinus rhythm >70 bpm. **Only scored in Black patients.*

The total possible score for non-black patients not in sinus rhythm or sinus rhythm <70 bpm, 8 points; non-black patients with sinus rhythm >70 bpm, 10 points; black patients not in sinus rhythm or sinus rhythm <70 bpm, 10 points; black patients with sinus rhythm >70 bpm, 12 points.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor.