

Effect of Dapagliflozin on Total Heart Failure Events in Patients With Heart Failure With Mildly Reduced or Preserved Ejection Fraction

A Prespecified Analysis of the DELIVER Trial

Pardeep S. Jhund, MBChB, MSc, PhD; Brian L. Claggett, PhD; Atefeh Talebi, PhD; Jawad H. Butt, MD; Samvel B. Gasparyan, PhD; Lee-Jen Wei, PhD; Zachary R. McCaw, PhD; Ulrica Wilderäng, PhD; Olof Bengtsson, PhD; Akshay S. Desai, MD, MPH; Magnus Petersson, MD, PhD; Anna Maria Langkilde, MD, PhD; Rudolf A. de Boer, MD, PhD; Adrian F. Hernandez, MD; Silvio E. Inzucchi, MD; Mikhail N. Kosiborod, MD; Carolyn S. P. Lam, MD; Felipe A. Martinez, MD; Sanjiv J. Shah, MD; Muthiah Vaduganathan, MD, MPH; Scott D. Solomon, MD; John J. V. McMurray, MD

 Supplemental content

IMPORTANCE In the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial, dapagliflozin reduced the risk of time to first worsening heart failure (HF) event or cardiovascular death in patients with HF with mildly reduced or preserved ejection fraction (EF).

OBJECTIVE To evaluate the effect of dapagliflozin on total (ie, first and recurrent) HF events and cardiovascular death in this population.

DESIGN, SETTING, AND PARTICIPANTS In this prespecified analysis of the DELIVER trial, the proportional rates approach of Lin, Wei, Yang, and Ying (LWYY) and a joint frailty model were used to examine the effect of dapagliflozin on total HF events and cardiovascular death. Several subgroups were examined to test for heterogeneity in the effect of dapagliflozin, including left ventricular EF. Participants were enrolled from August 2018 to December 2020, and data were analyzed from August to October 2022.

INTERVENTIONS Dapagliflozin, 10 mg, once daily or matching placebo.

MAIN OUTCOMES AND MEASURES The outcome was total episodes of worsening HF (hospitalization for HF or urgent HF visit requiring intravenous HF therapies) and cardiovascular death.

RESULTS Of 6263 included patients, 2747 (43.9%) were women, and the mean (SD) age was 71.7 (9.6) years. There were 1057 HF events and cardiovascular deaths in the placebo group compared with 815 in the dapagliflozin group. Patients with more HF events had features of more severe HF, such as higher N-terminal pro-B-type natriuretic peptide level, worse kidney function, more prior HF hospitalizations, and longer duration of HF, although EF was similar to those with no HF events. In the LWYY model, the rate ratio for total HF events and cardiovascular death for dapagliflozin compared with placebo was 0.77 (95% CI, 0.67-0.89; $P < .001$) compared with a hazard ratio of 0.82 (95% CI, 0.73-0.92; $P < .001$) in a traditional time to first event analysis. In the joint frailty model, the rate ratio was 0.72 (95% CI, 0.65-0.81; $P < .001$) for total HF events and 0.87 (95% CI, 0.72-1.05; $P = .14$) for cardiovascular death. The results were similar for total HF hospitalizations (without urgent HF visits) and cardiovascular death and in all subgroups, including those defined by EF.

CONCLUSIONS AND RELEVANCE In the DELIVER trial, dapagliflozin reduced the rate of total HF events (first and subsequent HF hospitalizations and urgent HF visits) and cardiovascular death regardless of patient characteristics, including EF.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: John J. V. McMurray, MD, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Pl, Glasgow G12 8TA, United Kingdom (john.mcmurray@glasgow.ac.uk).

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Patients with heart failure (HF) are frequently hospitalized for decompensation of HF. While the risk of death declines as ejection fraction (EF) increases, the risk of hospitalization for HF remains relatively static across the spectrum of EF.¹ Therefore, repeated hospitalizations account for a greater proportion of the burden of disease in patients with HF with mildly reduced EF (HFmrEF) or HF with preserved EF (HFpEF) compared with HF with reduced EF (HFrEF). These repeated hospitalizations are the major driver of the burden of HF on patients and health care systems. In HFmrEF and HFpEF, as with HFrEF, these repeated hospitalizations are also associated with a higher subsequent risk of death.² The gradient of risk is linear; as the number of repeated hospitalizations increases, the subsequent risk of both cardiovascular and all-cause mortality also increases.³

Recognizing the importance of repeated hospitalizations in patients with HF, analysis of repeated or total hospitalizations for HF was the primary outcome in a trial of sacubitril/valsartan in patients with HFmrEF or HFpEF.⁴ More recently, there has also been a recognition that urgent visits for treatment for HF are associated with worse outcomes, and these events have been incorporated into time to first event composites along with HF hospitalizations.⁵⁻⁷ Trials of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin were designed with a primary outcome of time to first worsening HF event (first hospitalization for HF or urgent HF visit) or cardiovascular death, in recognition of the prognostic impact of both of these nonfatal events.^{8,9} However, to our knowledge, the trials of SGLT2 inhibitors in HF still only examine the total number of hospitalizations for HF as a secondary outcome^{7,10-12} and not the effect of treatment on the total burden of this condition reflected by the full spectrum of HF events from urgent visits through to cardiovascular death. In this prespecified analysis, we describe in detail the efficacy of dapagliflozin on total HF events, ie, first and subsequent HF hospitalizations or urgent visits for HF and cardiovascular deaths, in the population with HFmrEF or HFpEF enrolled in the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial.¹⁰

Methods

In the DELIVER trial, patients with HFmrEF or HFpEF, defined as HF with New York Heart Association (NYHA) functional class II to IV and an EF greater than 40%, were randomized to the SGLT2 inhibitor dapagliflozin, 10 mg, once daily or matching placebo in a double-blind, event-driven randomized clinical trial. The design, baseline characteristics, and primary results have been published previously.^{8,10,13} The trial protocol can be found in [Supplement 1](#), and the statistical analysis plan can be found in [Supplement 2](#). The ethics committees of all participating sites approved the protocol, and all patients gave written informed consent.

Study Patients

Patients were enrolled if they had HF with a left ventricular EF (LVEF) greater than 40%, 40 years or older, HF of NYHA

Key Points

Question Does dapagliflozin reduce the risk of total episodes of worsening heart failure (HF; defined as hospitalization for HF or urgent HF visit requiring intravenous HF therapies) and cardiovascular death in patients with mildly reduced or preserved ejection fraction heart failure?

Findings In this prespecified analysis of the DELIVER trial including 6263 patients, dapagliflozin reduced the risk of total HF events and cardiovascular death by 23%, and this was consistent across a range of subgroups, including across the spectrum of ejection fraction.

Meaning In this study, dapagliflozin demonstrated no reduction in efficacy in reducing second or subsequent HF events.

class II to IV, had an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of 300 pg/mL or greater (greater than 600 pg/mL if atrial fibrillation was present on electrocardiography at enrollment), and who were receiving usual therapy. Patients who were hospitalized or were within 30 days of hospitalization for HF and patients ambulant in the community were eligible for enrollment. In addition, patients with a previous measure of LVEF of 40% or less were eligible for enrollment. The main exclusions to enrollment were a history of type 1 diabetes, symptomatic hypotension or systolic blood pressure less than 95 mm Hg, and estimated glomerular filtration rate (eGFR) less than 25 mL/min/1.73 m². The complete list of exclusion criteria has been published.⁸ Patients were assigned a race subgroup on the case report form based on their self-identification. The prespecified groups were American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or other race, in accordance with US Food and Drug Administration guidance.

HF Events

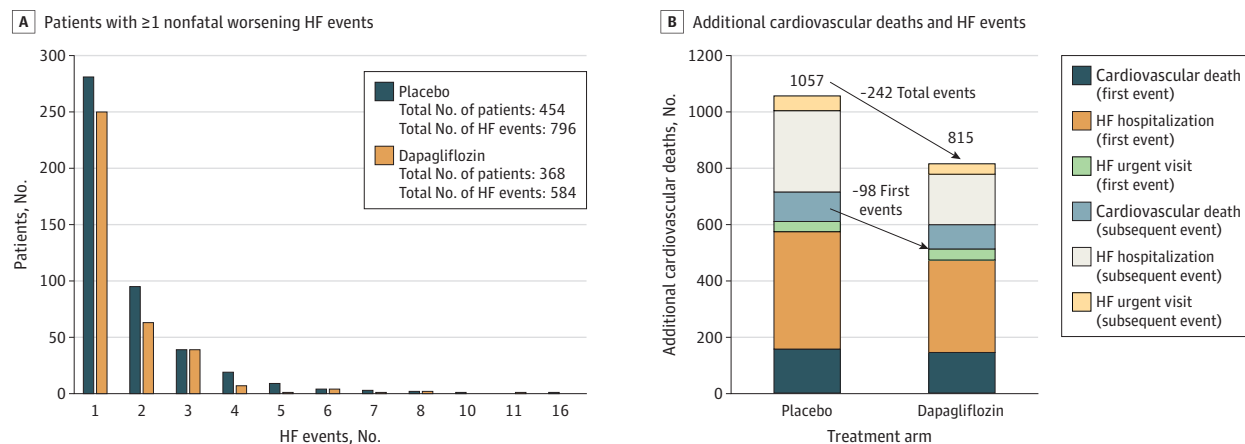
The primary outcome of the DELIVER trial was the composite of worsening HF (HF hospitalization or urgent visit for HF requiring intravenous therapy) or cardiovascular death, whichever occurred first. In the present analyses, we explored the predefined secondary end point of total (first and repeated) worsening episodes of HF and cardiovascular deaths. Hospitalizations or urgent visits occurring on the day of death were not counted in this analysis.

Statistical Analysis

We summarized baseline characteristics with means and SDs, medians and IQRs, or counts and percentages. Total HF events were examined using 2 methods that were prespecified in the statistical analysis plan, with the analyses stratified by baseline diabetes status.

The first prespecified method used was the semiparametric proportional-rates model described by Lin, Wei, Yang, and Ying (LWYY).¹⁴ This is an extension of the proportional hazards model. The LWYY model uses a robust SE estimator to account for the interdependence of events within an individual. We specified in the statistical analysis plan that the 2

Figure 1. Total Number of Heart Failure (HF) Events and Cardiovascular Deaths



A, Patients with 1 or more worsening HF event (defined as urgent visits or hospital admissions for HF). B, Additional cardiovascular deaths and HF events added to first events in the dapagliflozin and placebo groups.

components in the composite end point (total number of HF events and cardiovascular deaths) would be analyzed separately to quantify the respective treatment effects and check the consistency between the composite and the components. Subgroup estimates, using the subgroups predefined for the primary efficacy analysis of the trial, were also calculated using the LWYY method and the interaction term tested. EF was examined using prespecified categories and as a continuous variable. EF was modeled as a restricted cubic spline with 3 knots based on the best-fitting spline according to the Akaike information criterion. The knots were placed at EF of 45%, 54%, and 70%.

The second statistical method for the analysis of total HF events prespecified in the statistical analysis plan was the joint frailty model.¹⁵ This method accounts for the association between HF events and subsequent mortality and the competing risk of mortality on HF events. The advantage of the joint frailty model is that it allows a distinct treatment effect to be estimated for each of the individual outcomes (HF events and cardiovascular death) while taking account of the association between the 2 through a common frailty term. The frailty is a random term specific to a participant that accounts for some patients being at higher risk (having large frailty) than others (who have smaller frailty). Rate ratios for the effect of dapagliflozin on HF events and cardiovascular death are provided separately for the joint model. Total hospitalizations were plotted using nonparametric estimates of the marginal mean of the cumulative number of HF hospitalization rates over time, allowing for cardiovascular death as the terminal event following the approach of Ghosh and Lin.¹⁶ Finally, in a post hoc exploratory analysis, we used a model-free area under the receiver operator characteristic curve (AUC) approach to describe the efficacy of the randomized therapy.¹⁷ This AUC-based approach does not rely on any of the assumptions of the model-based methods, such as the LWYY or joint frailty models described above. In this method, the Ghosh-Lin cumulative event curves were constructed using HF events and cardiovascular

death as events of interest and noncardiovascular death as competing risk.¹⁶ The integrated AUC for each treatment arm was used to measure the cumulative morbidity and mortality experienced by each randomized group. The absolute difference and relative ratio of the resulting AUCs were then estimated.

All analyses were conducted using Stata version 16.1 (StataCorp) and SAS version 9.4 (SAS Institute). Our exploratory analyses of AUC were conducted using R version 4.2.1 (The R Foundation). *P* values less than .05 were considered statistically significant, and all *P* values were 2-tailed. Continuous variables were compared across groups using analysis of variance and categorical variables using χ^2 tests.

Results

Of 6263 included patients, 2747 (43.9%) were women, and the mean (SD) age was 71.7 (9.6) years. Among 6263 patients randomized in the DELIVER trial, during a median (IQR) follow-up of 2.3 (1.7-2.8) years, a total of 1380 nonfatal worsening HF events (urgent visits or hospital admissions) occurred in 822 patients (Figure 1). Most patients had 1 or 2 worsening events during follow-up (median [IQR] number of worsening HF events in both groups was 1 [1-2]), with a maximum of 16 events. The additional nonfatal HF events and cardiovascular deaths occurring after a first HF event are shown in Figure 1. There were an additional 447 events in the placebo groups and an additional 303 events in the dapagliflozin group. There were 212 fewer total worsening HF events (199 fewer total HF hospitalizations and 13 fewer urgent visits for HF) and 30 fewer total cardiovascular deaths in the dapagliflozin group compared with the placebo group (Figure 1).

Baseline Characteristics

Of the patients who had a nonfatal worsening HF event, the patients with 1 or more total events were older and more likely

to be men (Table). They were also more likely to be from Asia and North America but less likely to be from Latin America. Participants with 2 or more HF events had higher heart rates, body mass index, and NT-proBNP and hemoglobin A_{1c} levels. They also had worse kidney function, with higher creatinine levels and lower eGFR, and a larger proportion had an eGFR less than 60 mL/min/1.73 m². With regards to HF characteristics, patients with multiple HF events were more likely to be in a higher NYHA class, had slightly longer duration of HF, greater prevalence of prior hospitalization for HF, or had been randomized in the hospital or within 30 days of hospitalization. They also had worse Kansas City Cardiomyopathy Questionnaire total symptom, clinical summary, and overall summary scores. EF was similar in the patients with and without multiple HF events, and the proportion with a previous measurement of EF less than 40% was not different. Patients with multiple HF events also had a higher prevalence of comorbidities, with higher rates of atrial fibrillation, stroke, type 2 diabetes, and chronic obstructive pulmonary disease. Patients with multiple HF events were more likely to be treated with diuretics and less likely to be receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers but more likely to be receiving an oral anticoagulant or have an implanted cardiac device.

Effect of Dapagliflozin on Total HF Events and Cardiovascular Deaths

The rate of total (first and repeated) HF events and cardiovascular death was 15.3 per 100 patient-years in the placebo group and 11.8 per 100 patient-years in the dapagliflozin group, a reduction of 3.5 events per 100 patient-years of follow-up. The cumulative rate of total HF events with cardiovascular death as a competing risk was lower in the dapagliflozin group compared with the placebo group when plotted according to the method of Ghosh and Lin (Figure 2).¹⁶ The rate ratio from the LWYY model for total HF events and cardiovascular death was 0.77 (95% CI, 0.67-0.89; $P < .001$) compared with a hazard ratio of 0.82 (95% CI, 0.73-0.92; $P < .001$) for the traditional time to first event composite of worsening HF event or cardiovascular death (Figure 3). When the constituents of the total worsening HF events and cardiovascular deaths composite were examined, there was a reduction in total HF events, with a rate ratio of 0.73 (95% CI, 0.62-0.87; $P < .001$) but not in cardiovascular death (hazard ratio, 0.88; 95% CI, 0.74-1.05; $P = .17$). In the joint frailty model, the rate ratio was 0.72 (95% CI, 0.65-0.81; $P < .001$) for HF events and 0.87 (95% CI, 0.72-1.05; $P = .14$) for cardiovascular death (Figure 3). As a sensitivity analysis, we examined the effect of dapagliflozin on total HF events and all deaths using the LWYY method, which found a similar result (rate ratio, 0.81; 95% CI, 0.72-0.92), as well as using the joint frailty model, which was also similar (total HF events: rate ratio, 0.72; 95% CI, 0.65-0.81; all-cause death: rate ratio, 0.93; 95% CI, 0.81-1.06).

In a post hoc analysis, compared with patients with no HF event (HF hospitalization or urgent HF visit), the hazard of subsequent death was 1.67 (95% CI, 0.90-3.12) in those whose first event was an urgent HF visit and 5.70 (95% CI, 4.95-6.56) in those whose first event was an HF hospitalization. Compared

with patients who had an HF hospitalization as their first event, the risk of death in patients where the first event was an urgent visit for HF was 0.30 (95% CI, 0.16-0.57). Therefore, the risk of death in a patient whose first event was an urgent HF visit was higher than patients who experienced no events but lower than that of patients whose first event was an HF hospitalization.

To allow comparison with prior trials of SGLT2 inhibitors in HF, we also examined the outcome of total HF hospitalizations, ie, without urgent visits for HF. There were 508 HF hospitalizations in total in the dapagliflozin group and 707 in the placebo group. When a composite of total HF hospitalizations and cardiovascular deaths was examined using the LWYY approach (rate ratio, 0.76; 95% CI, 0.66-0.88; $P < .001$) and in a joint frailty model (rate ratio, 0.71; 95% CI, 0.63-0.80; $P < .001$), the findings were similar to the analysis of total HF events.

The 2 analytic procedures are valid when their model assumptions are met. For example, the LWYY assumes that the 2 curves in Figure 2A would be proportional over the entire study period. To relax those model constraints, we conducted a robust, model assumption-free analysis for the multiple outcomes. Specifically, we used the mean cumulative count AUC in Figure 2B as a summary measure as a total disease burden, which is the total event-free time lost to HF and cardiovascular death. The larger the AUC, the worse the treatment. In this exploratory post hoc analysis, with 36 months of follow-up, the AUC was 5.7 months for the dapagliflozin group and 7.8 months in the placebo group ($P < .001$) (Figure 2). This corresponds to an absolute increase of 2.2 months (95% CI, 1.2-3.2) and a rate ratio of 0.72 (95% CI, 0.63-0.84) for dapagliflozin compared with placebo, a 28% reduction in the cumulative burden of HF events and cardiovascular death over time, favoring dapagliflozin. These results support those by the prespecified procedures.

Efficacy of Dapagliflozin on Total HF Events by Subgroups

The effect of dapagliflozin on total HF events and cardiovascular deaths did not differ across any of the predefined subgroups (Figure 4). There was no evidence of treatment heterogeneity in those with and without an improved EF or according to whether they were randomized within 30 days of hospitalization. In particular, there was no evidence of treatment heterogeneity by LVEF at baseline. When the interaction was modeled with EF as a continuous variable, using a restricted cubic spline, the rate ratio remained less than 1, in favor of dapagliflozin, across the entire EF spectrum when analyzed using the LWYY model (eFigure in Supplement 3).

Discussion

In patients with HFmrEF or HFpEF, dapagliflozin reduced the risk of total HF events, ie, repeated in addition to first events. This benefit was observed in all the prespecified DELIVER subgroups and across the spectrum of EF. The characteristics associated with multiple HF events in this population with HFmrEF or HFpEF were similar to those in patients with HFrEF experiencing multiple hospitalizations.¹⁸

Table. Baseline Characteristics by Number of Heart Failure (HF) Events

Characteristic	HF events, No. (%)			P value
	None (n = 5441)	1 (n = 531)	≥2 (n = 291)	
Age, mean (SD), y	71.6 (9.5)	71.5 (9.6)	72.9 (10.1)	.06
Gender				
Women	2416 (44.4)	216 (40.7)	115 (39.5)	.08
Men	3025 (55.6)	315 (59.3)	176 (60.5)	
Race ^a				
Asian	1105 (20.3)	102 (19.2)	67 (23.0)	<.001
Black or African American	130 (2.4)	15 (2.8)	14 (4.8)	
White	3829 (70.4)	402 (75.7)	208 (71.5)	
Other race	377 (6.9)	12 (2.3)	2 (0.7)	
Geographic region				
Europe and Saudi Arabia	2595 (47.7)	266 (50.1)	144 (49.5)	<.001
Asia	1064 (19.6)	98 (18.5)	64 (22.0)	
Latin America	1099 (20.2)	66 (12.4)	16 (5.5)	
North America	683 (12.6)	101 (19.0)	67 (23.0)	
Physiological measures				
Systolic blood pressure, mean (SD), mm Hg	128.2 (15.2)	127.8 (15.8)	128.8 (17.3)	.66
Heart rate, mean (SD), beats per minute	71.2 (11.7)	73.1 (11.8)	73.3 (12.2)	<.001
Body mass index, mean (SD) ^b	29.7 (6.0)	30.3 (6.5)	31.2 (6.4)	<.001
NT-proBNP, median (IQR), pg/mL	961 (602-1644)	1433 (800-2695)	1500 (839-2618)	<.001
Hemoglobin A _{1c} , mean (SD), %	6.6 (1.4)	6.7 (1.5)	6.9 (1.6)	<.001
Creatinine, mean (SD), mg/dL	101.0 (30.2)	109.4 (34.2)	116.5 (35.5)	<.001
eGFR, mL/min/1.73 m ²				
Mean (SD)	61.7 (19.0)	57.9 (20.0)	53.6 (18.9)	<.001
<60	2586 (47.5)	296 (55.7)	188 (64.6)	<.001
≥60	2854 (52.5)	235 (44.3)	103 (35.4)	
HF-related characteristics				
Prior LVEF measurement ≤40%	990 (18.2)	107 (20.2)	54 (18.6)	.54
Randomized during or within 30 d of a HF hospitalization	497 (9.1)	96 (18.1)	61 (21.0)	<.001
Duration of HF				
0-3 mo	497 (9.1)	51 (9.6)	20 (6.9)	.02
>3-6 mo	536 (9.9)	40 (7.5)	16 (5.5)	
>6-12 mo	747 (13.7)	58 (10.9)	37 (12.7)	
>1-2 y	859 (15.8)	80 (15.1)	56 (19.2)	
>2-5 y	1363 (25.1)	132 (24.9)	74 (25.4)	
>5 y	1434 (26.4)	170 (32.0)	88 (30.2)	
LVEF, mean (SD), %	54.2 (8.8)	53.9 (8.7)	53.5 (8.4)	.26
LVE, %				
≤49	1822 (33.5)	189 (35.6)	105 (36.1)	.65
50-59	1965 (36.1)	184 (34.7)	107 (36.8)	
≥60	1654 (30.4)	158 (29.8)	79 (27.1)	
NYHA class				
I, II	4169 (76.6)	355 (66.8)	190 (65.3)	<.001
III, IV	1272 (23.4)	176 (33.2)	101 (34.7)	
KCCQ, median (IQR)				
Total symptom score	72.9 (56.3-88.5)	67.7 (50.0-83.3)	66.7 (46.9-83.3)	<.001
Clinical summary score	71.1 (55.6-85.4)	65.3 (47.9-80.0)	65.3 (47.2-79.9)	<.001
Overall summary score	69.2 (53.8-83.3)	63.8 (47.1-77.9)	62.5 (45.0-80.0)	<.001
Medical history				
Hospitalization for HF	2071 (38.1)	289 (54.4)	179 (61.5)	<.001
Atrial fibrillation/flutter	3023 (55.6)	339 (63.8)	190 (65.3)	<.001

(continued)

Table. Baseline Characteristics by Number of Heart Failure (HF) Events (continued)

Characteristic	HF events, No. (%)			P value
	None (n = 5441)	1 (n = 531)	≥2 (n = 291)	
Stroke	497 (9.1)	60 (11.3)	40 (13.7)	.01
Angina	1302 (23.9)	126 (23.7)	69 (23.7)	.99
Myocardial infarction	1416 (26.0)	142 (26.7)	81 (27.8)	.75
Hypertension	4813 (88.5)	476 (89.6)	264 (90.7)	.38
Type 2 diabetes	2370 (43.6)	276 (52.0)	160 (55.0)	<.001
Chronic obstructive pulmonary disease	554 (10.2)	96 (18.1)	42 (14.4)	<.001
Treatment				
Loop diuretic	4086 (75.1)	466 (87.8)	259 (89.3)	<.001
Other diuretic (excluding loop and MRA)	1212 (22.3)	77 (14.5)	54 (18.6)	<.001
ACEI/ARB	3976 (73.1)	380 (71.6)	187 (64.5)	.005
ARNI	250 (4.6)	29 (5.5)	22 (7.6)	.05
β-Blocker	4521 (83.1)	421 (79.3)	235 (81.0)	.06
MRA	2321 (42.7)	232 (43.7)	114 (39.3)	.46
Digoxin	252 (4.6)	28 (5.3)	16 (5.5)	.65
Antiplatelet	2310 (42.5)	194 (36.5)	126 (43.4)	.03
Anticoagulant	2881 (53.0)	325 (61.2)	176 (60.7)	<.001
Pacemaker	554 (10.2)	57 (10.7)	51 (17.5)	<.001
CRT-P/CRT-D	84 (1.5)	6 (1.1)	10 (3.4)	.03
ICD/CRT-D	136 (2.5)	21 (4.0)	11 (3.8)	.07

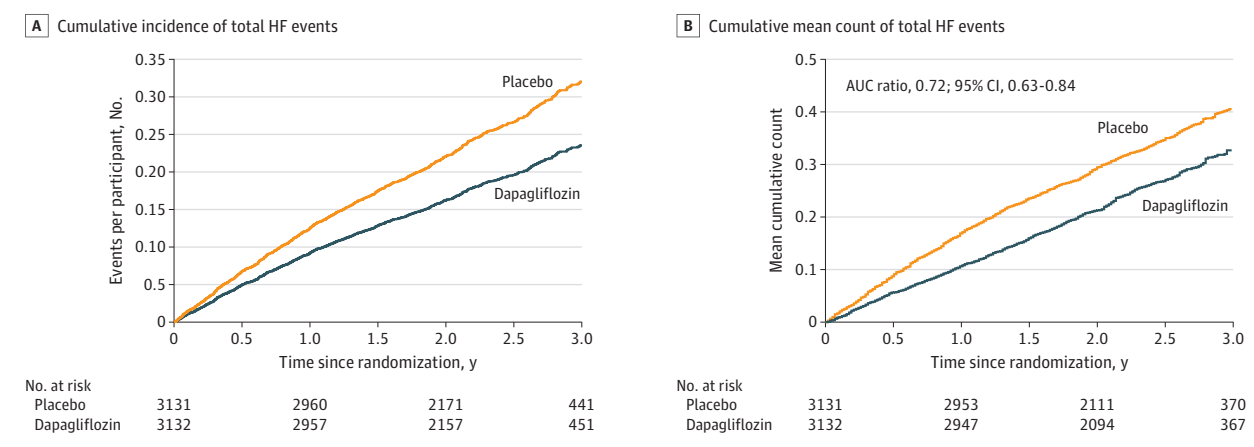
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CRT-D, cardiac resynchronisation therapy–defibrillator; CRT-P, cardiac resynchronisation therapy–pacemaker; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide level; NYHA, New York Heart Association.

SI conversion factor: To convert creatinine to μmol/L, multiply by 88.4.

^a Patients were assigned a race subgroup on the case report form based on their self-identification. The prespecified groups were American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or other race, in accordance with US Food and Drug Administration guidance.

^b Calculated as weight in kilograms divided by height in meters squared.

Figure 2. Cumulative Incidence and Mean Count of Total Heart Failure (HF) Events



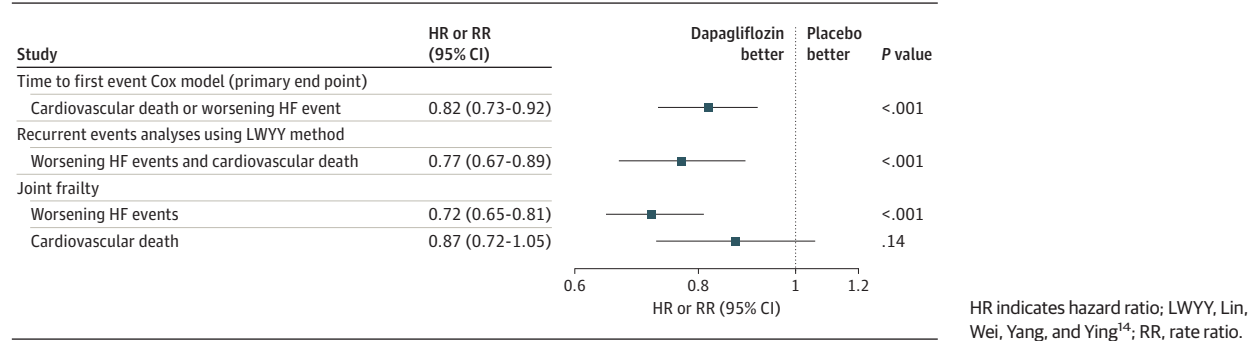
A, Cumulative incidence of total HF events with cardiovascular death as a competing risk, plotted using the method of Ghosh and Lin.¹⁶ B, Cumulative mean count of total HF events and cardiovascular deaths with

noncardiovascular deaths as a competing risk. AUC indicates area under the receiver operator characteristic curve.

The reduction in burden of total HF events with dapagliflozin was evident regardless of the method used to analyze the total events and whether we examined total HF events including urgent HF visits or HF hospitalizations without urgent visits. The point estimates were more favorable to that

obtained in the time to first event analysis, which was the primary outcome of the DELIVER trial,¹⁰ ie, dapagliflozin demonstrated no reduction in efficacy in reducing second or subsequent events. The estimates were also consistent with other trials of SGLT2 inhibitors in patients with HFmrEF HFpEF. In

Figure 3. Effect of Dapagliflozin vs Placebo on First Heart Failure (HF) Events or Cardiovascular Death



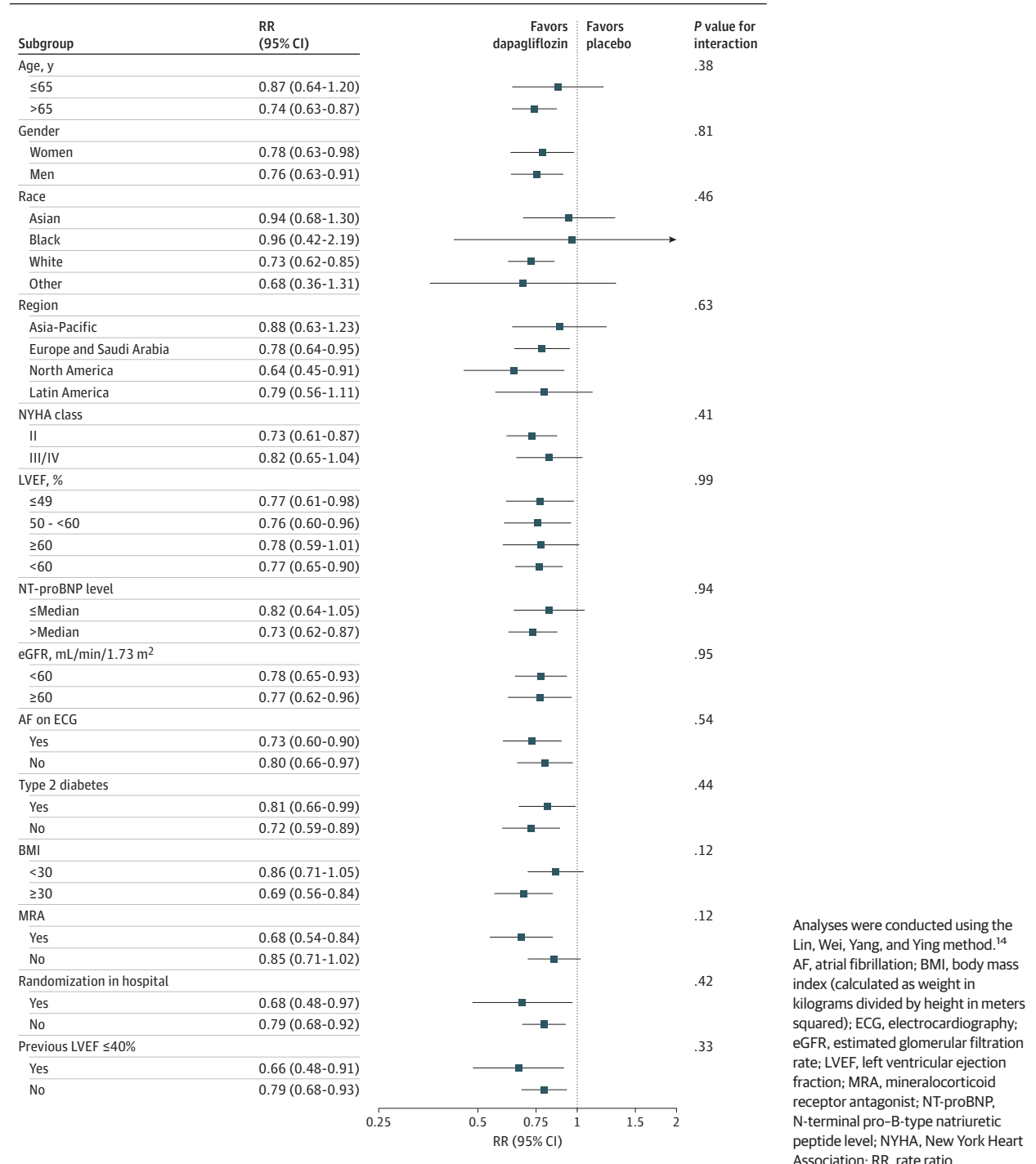
the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial,¹² the SGLT2 inhibitor empagliflozin reduced the rate of total HF hospitalizations by 27% (rate ratio, 0.73; 95% CI, 0.61-0.88; $P < .001$) using the joint frailty approach (compared with 0.71 [95% CI, 0.63-0.80; $P < .001$] using the same outcome and model in the DELIVER trial).¹⁰ In a separate analysis of the DELIVER trial, we also examined if this reduction in total HF events was also observed for all-cause hospitalizations and found that there was a similar but smaller relative risk reduction of 11%.¹⁹ The observation that the benefits of dapagliflozin were consistent across the range of EF is important, as an earlier pooled analysis of total HF hospitalizations in the EMPEROR-Reduced and EMPEROR-Preserved trials reported that the effect of empagliflozin on total HF hospitalizations appeared to diminish at higher EFs.²⁰ We did not see any evidence of an attenuation of the benefit of dapagliflozin on total HF events at higher EFs in this analysis or for total HF hospitalizations in our pooled analysis.²¹ We also found that the elevated risk for subsequent death in a patient whose first event was an urgent HF visit, compared with a patient who did not have any worsening HF event, was elevated, in keeping with reports from HFrEF trials.^{5,22} Furthermore, we found that although urgent HF visits were associated with a higher risk of death, the excess risk was not as high as in patients in whom the first event experienced during follow-up was an HF hospitalization, in keeping with the findings of a similar analysis in the Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF) trial.⁶

As most prior trials enrolling patients with an EF greater than 40% have been neutral, there are few data with which to compare the relative efficacy of SGLT2 inhibitors in reducing total HF events. A post hoc analysis of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity-Preserved (CHARM-Preserved) trial, which enrolled patients with an EF greater than 40%, suggested that candesartan reduced total HF hospitalizations and cardiovascular death using a negative binomial model.²³ In that analysis, candesartan reduced total HF hospitalizations by 25%, ie, the rate ratio for total HF hospitalizations and cardiovascular death was 0.75 (95% CI, 0.62-0.91; $P = .003$). This post hoc analysis appeared to provide enough power to detect a treatment effect that was not evident in a time to first event analysis. In theory,

total events should require a smaller sample size to demonstrate a treatment effect, as not only are subsequent nonfatal HF events counted but cardiovascular deaths that occur after these events are also counted (whereas both are ignored after a first HF event in a traditional time to first event analysis). In our trial, these repeated events contributed a further 193 deaths and 557 HF events that would otherwise have been ignored. Consequently, power calculations in the setting of total events are more complex, and factors such as heterogeneity of patient risk have to be incorporated, which is not currently part of routine sample size estimation strategies.²⁴ However, use of total HF events as a primary outcome may result in a smaller sample size than is needed for a time to first event primary end point (or provide more power for secondary total events end points in trials powered for a time to first event primary outcome).

One attraction of recurrent or total events analysis is that they describe the full burden of disease and are potentially more meaningful to patients, representing the full disease experience. Therefore, describing reductions in total events may be helpful to explain treatment effects to patients. Explaining treatment efficacy is difficult in a clinical setting, and it is well known that relative risks are poorly understood by patients and by some clinicians. Other methods of expressing treatment benefits, such as the number needed to treat, are equally, if not more difficult, in the setting of total events.²⁵ We reported that the AUC ratio for dapagliflozin vs placebo was 0.72, not dissimilar to the estimates from the conventional model-based approaches that we had prespecified. Although the relative risk reduction can be described as a ratio, perhaps more usefully the absolute risk reduction of 2.2 months over a 3-year period is easily explained to clinicians and patients, ie, a gain of 2.2 months of event-free survival. This absolute risk reduction with the accompanying time scale is a directly interpretable into clinically relevant terms for the patient. Simulation studies of power calculations using this approach suggest that sample sizes based on time to first events may be 20% larger than samples based on an AUC.¹⁷ The results that we observed using the AUC method (which is an extension of the restricted mean survival time used in multiple disease areas²⁶⁻²⁹) were consistent with the more traditional model-based approaches to analyzing total events. The technique may be useful in situations where model assumptions are not met, as the approach does not require a statistical model to be

Figure 4. Effect of Dapagliflozin vs Placebo on Total Heart Failure Events and Cardiovascular Deaths in the Prespecified Subgroups



Analyses were conducted using the Lin, Wei, Yang, and Ying method.¹⁴ AF, atrial fibrillation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ECG, electrocardiography; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide level; NYHA, New York Heart Association; RR, rate ratio.

constructed and could be used in addition to other metrics, such as days alive and out of hospital.³⁰

Limitations

This study has limitations. As with any clinical trial, follow-up was limited. Therefore, we do not know what the full lifetime burden of HF events or deaths was in each treatment group and how this may affect the treatment

benefit in the longer term. Patients were selected according to specific inclusion and exclusion criteria, and our findings may not apply to all patients with HFmrEF or HFpEF in the broader population. Hospitalization rates vary widely by country and health care system, and patients were enrolled in 20 countries; however, there was no heterogeneity of treatment effect according to geographic region in the subgroup analysis.

Conclusions

In summary, among patients with HFmrEF or HFpEF, dapagliflozin reduced the risk of total (first and recurrent) HF

events or cardiovascular deaths compared with placebo. HF events are common and preventable, and the efficacy of dapagliflozin in reducing the number of these events is consistent across a broad range of subgroups and across the spectrum of EF.

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Author Affiliations: British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (Jhund, Talebi, Butt, McMurray); Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts (Claggett, Desai, Vaduganathan, Solomon); Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden (Gasparyan, Wilderäng, Bengtsson, Petersson, Langkilde); Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Wei); Insitro, South San Francisco, California (McCaw); Erasmus Medical Center, Rotterdam, the Netherlands (de Boer); Duke University Medical Center, Durham, North Carolina (Hernandez); Associate Editor, *JAMA Cardiology* (Hernandez); Yale School of Medicine, New Haven, Connecticut (Inzucchi); Saint Luke's Mid America Heart Institute, University of Missouri–Kansas City (Kosiborod); National Heart Centre Singapore and Duke-National University of Singapore, Singapore (Lam); University of Cordoba, Cordoba, Argentina (Martinez); Northwestern University Feinberg School of Medicine, Chicago, Illinois (Shah).

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Study concept and design: Jhund, Claggett, Butt, Gasparyan, Wei, Langkilde, Inzucchi, Lam, Shah, Solomon.

Acquisition, analysis, or interpretation of data: Jhund, Claggett, Talebi, Butt, Gasparyan, McCaw, Wilderäng, Bengtsson, Desai, Petersson, Langkilde, de Boer, Hernandez, Inzucchi, Kosiborod, Martinez, Vaduganathan, McMurray.

Drafting of the manuscript: Jhund, Talebi.

Critical revision of the manuscript for important intellectual content: Claggett, Butt, Gasparyan, Wei, McCaw, Wilderäng, Bengtsson, Desai, Petersson, Langkilde, de Boer, Hernandez, Inzucchi, Kosiborod, Lam, Martinez, Shah, Vaduganathan, Solomon, McMurray.

Statistical analysis: Jhund, Claggett, Talebi, Butt, Gasparyan, Wei, McCaw, Wilderäng, Bengtsson, Petersson.

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Data Sharing Statement: See [Supplement 4](#).

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