ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

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ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure and cardiovascular death among patients with chronic heart failure and a left ventricular ejection fraction of 40% or less. Whether SGLT2 inhibitors are effective in patients with a higher left ventricular ejection fraction remains less certain.

METHODS

We randomly assigned 6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death, as assessed in a time-to-event analysis.

RESULTS

Over a median of 2.3 years, the primary outcome occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05). Total events and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with or without diabetes. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, NCT03619213.)

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*A complete list of the DELIVER trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors, which were originally developed as glucose-lowering agents for the treatment of type 2 diabetes mellitus, reduce the risk of death and other adverse outcomes among patients with chronic heart failure and a reduced ejection fraction (i.e., a left ventricular ejection fraction of ≤40%) and in those with chronic kidney disease, regardless of the presence or absence of type 2 diabetes mellitus.[1-3] Current clinical guidelines strongly recommend the use of SGLT2 inhibitors in patients with chronic heart failure and a reduced ejection fraction.[4]

Few pharmacologic treatment options exist for patients with heart failure and a mildly reduced or preserved left ventricular ejection fraction.[5,6] Recently, treatment with the SGLT2 inhibitor empagliflozin was shown to reduce the combined risk of hospitalization for heart failure or cardiovascular death among patients with heart failure and a left ventricular ejection fraction of more than 40%, a finding that suggests that the benefits of SGLT2 inhibition may extend to all patients with heart failure, regardless of the left ventricular ejection fraction.[7] The benefit, which was driven by a reduction in hospitalization for heart failure, appeared to be attenuated in patients with ejection fractions in the highest part (≥65%) of the range.[8]

Several gaps in evidence remain regarding the benefits of SGLT2 inhibitors in patients with heart failure, including whether these benefits are conserved in patients with an ejection fraction at the highest end of the ejection fraction spectrum, in patients who start the treatment during or soon after hospitalization, and in patients with a previously reduced ejection fraction that has since improved to more than 40%. We designed the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial to test the hypothesis that the SGLT2 inhibitor dapagliflozin would reduce the risk of worsening heart failure or cardiovascular death among patients with a mildly reduced or preserved ejection fraction.

Methods

Trial Design and Oversight

The DELIVER trial was a phase 3, international, multicenter, parallel-group, event-driven, double-blind, randomized, controlled trial in which patients with chronic heart failure and a left ventricular ejection fraction of more than 40% received dapagliflozin or matching placebo, in addition to their usual therapy. The steering committee designed and oversaw the conduct of the trial and the analysis of the data in collaboration with the sponsor (AstraZeneca). The trial protocol was approved by a local or central institutional review board at each trial center. The authors who had access to the data vouch for the accuracy and completeness of the data, and all the authors vouch for the fidelity of the trial to the protocol. Details regarding the design of the trial are provided in the protocol and in the Supplementary Appendix, both of which are available with the full text of this article at NEJM.org.

Trial Patients

Patients were eligible for enrollment if they were at least 40 years of age; had stabilized heart failure, with or without type 2 diabetes mellitus; had a left ventricular ejection fraction of more than 40%; had evidence of structural heart disease; and had an elevated natriuretic peptide level. Patients who had had a previous left ventricular ejection fraction of 40% or less were eligible provided that they had an ejection fraction of more than 40% at the time of enrollment. Patients could have been enrolled either as outpatients or during hospitalization for heart failure. Detailed inclusion and exclusion criteria have been published previously[9] and are provided in Table S1 in the Supplementary Appendix.

Trial Procedures and Outcomes

All the patients provided written informed consent. Those who met the inclusion and exclusion criteria were randomly assigned to receive dapagliflozin at a dose of 10 mg once daily or matching placebo, in addition to their usual therapy.

The primary outcome was a composite of worsening heart failure, which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure, or cardiovascular death. Secondary outcomes were the total number of worsening heart failure events and cardiovascular deaths, the change from baseline in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) at month 8, cardiovascular death,

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and death from any cause. All potential worsening heart failure events and all deaths were adjudicated according to prespecified criteria[10] by an independent clinical events committee whose members were unaware of the trial-group assignments. In light of the extensive data on the safety of dapagliflozin, only data on serious adverse events, adverse events that led to discontinuation of dapagliflozin or placebo, and select other adverse events were collected.

STATISTICAL ANALYSIS

The primary outcome, the occurrence of worsening heart failure or cardiovascular death, was assessed in a time-to-event analysis with the use of a Cox proportional-hazards model, stratified according to diabetes status. This analysis was performed concurrently in the overall population and in patients with a left ventricular ejection fraction of less than 60%, with an alpha level of 0.024 used in the former analysis and an alpha level of 0.038 used in the latter analysis (see the Supplementary Methods section and Fig. S1 and Table S2). We estimated that enrollment of 6100 patients followed for at least 13.5 months (and up to 39 months) would result in the occurrence of at least 1117 events and would provide the trial with 93% power to detect a hazard ratio of 0.80 for the comparison of dapagliflozin and placebo with respect to the primary outcome in the overall population, at a two-sided alpha level of 0.024. All the analyses were performed according to the intention-to-treat principle. Secondary analyses were performed with the use of a closed-testing procedure that included a prespecified hierarchical ordering of the primary and secondary outcomes; these outcomes included (in hierarchical order) the total number of worsening heart failure events and cardiovascular deaths, a decrease in symptom burden as measured by an increase in the KCCQ total symptom score, and cardiovascular death and death from any cause (both of which were assessed in a time-to-event analysis). We analyzed the KCCQ total symptom score as a composite outcome based on the rank of the change in score from baseline to month 8, with a corresponding win ratio used to estimate the magnitude of the treatment effect.[11-13] We assessed the consistency of the treatment effect on the primary outcome in prespecified subgroups. In separate sensitivity analyses, patient data were censored at the time of coronavirus disease 2019 (Covid-19) diagnosis, and death from noncardiovascular causes was taken into account as a competing risk.[14]

RESULTS

PATIENTS

Between August 27, 2018, and December 30, 2020, a total of 10,418 patients were screened at 353 centers in 20 countries; of these patients, 6263 were randomly assigned to receive dapagliflozin or matching placebo (Fig. S2). The reasons for exclusion from randomization are provided in Table S3. The demographic and clinical characteristics of the two groups were well balanced at baseline (Table 1 and Table S4). Dapagliflozin was discontinued for reasons other than death in 444 patients (14.2%), and placebo was discontinued for reasons other than death in 442 patients (14.1%). The vital status was known at the end of the trial in all but 2 patients in the dapagliflozin group and 2 patients in the placebo group. The median duration of follow-up was 2.3 years (interquartile range, 1.7 to 2.8).

EFFICACY

In the overall population, the primary outcome occurred in 512 patients (16.4%) in the dapagliflozin group and in 610 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001) (Table 2 and Fig. 1A). The results of the analysis of the primary outcome in the patients with a left ventricular ejection fraction of less than 60% were similar to those of the overall population (hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.009) (Table S5).

The number of cardiovascular deaths and first and recurrent worsening heart failure events was lower in the dapagliflozin group than in the placebo group in the overall population (rate ratio, 0.77; 95% CI, 0.67 to 0.89; P<0.001) and among the patients with a left ventricular ejection fraction of less than 60% (rate ratio, 0.77; 95% CI, 0.65 to 0.90; P=0.002). The incidence of the components of the primary outcome favored the dapagliflozin group both in the overall population and among those with a left ventricular ejection fraction of less than 60%, including worsening heart failure (hazard ratio in the overall population, 0.79; 95% CI, 0.69 to 0.91) and cardiovascular death (hazard ratio, 0.88; 95% CI, 0.74 to 1.05) (Fig. 1B and 1C), as well as

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dapagliflozin (N=3131)	Placebo (N=3132)
Age — yr	71.8±9.6	71.5±9.5
Female sex — no. (%)	1364 (43.6)	1383 (44.2)
Race — no. (%)†		
Asian	630 (20.1)	644 (20.6)
Black	81 (2.6)	78 (2.5)
White	2214 (70.7)	2225 (71.0)
Other	206 (6.6)	185 (5.9)
Geographic region — no. (%)		
North America	428 (13.7)	423 (13.5)
Latin America	602 (19.2)	579 (18.5)
Europe or Saudi Arabia	1494 (47.7)	1511 (48.2)
Asia	607 (19.4)	619 (19.8)
NYHA class — no. (%)‡		
II	2314 (73.9)	2399 (76.6)
III	807 (25.8)	724 (23.1)
IV	10 (0.3)	8 (0.3)
Left ventricular ejection fraction		
Mean — %	54.0±8.6	54.3±8.9
Distribution — no. (%)		
≤49%	1067 (34.1)	1049 (33.5)
50–59%	1133 (36.2)	1123 (35.9)
≥60%	931 (29.7)	960 (30.7)
Medical history — no. (%)		
Type 2 diabetes mellitus	1401 (44.7)	1405 (44.9)
Hypertension	2755 (88.0)	2798 (89.3)
Previous left ventricular ejection fraction ≤40%	572 (18.3)	579 (18.5)
Estimated GFR — ml/min/1.73 m^2	61±19	61±19

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. GFR denotes glomerular filtration rate.
† Race was reported by the investigators.
‡ One patient in the placebo group who had New York Heart Association (NYHA) class I disease at baseline was not included in the analysis of this variable.

death from any cause (hazard ratio, 0.94; 95% CI, 0.83 to 1.07) (Fig. 1D). The change from baseline to month 8 in the KCCQ total symptom score indicated a benefit with dapagliflozin as compared with placebo with respect to symptoms of heart failure (win ratio, 1.11; 95% CI, 1.03 to 1.21; P=0.009; mean placebo-corrected difference between baseline and month 8 among survivors, 2.4 points; 95% CI, 1.5 to 3.4).

The effect of dapagliflozin on the primary outcome was consistent across all prespecified subgroups. These included the subgroups that were defined according to the presence or absence of type 2 diabetes mellitus; enrollment that occurred during or within 30 days after hospitalization for heart failure or enrollment that did not occur during or within 30 days after hospitalization for heart failure; and the presence or absence of a previous left ventricular ejection fraction of 40% or less that improved to more than 40% by the time of enrollment (Fig. 2). A prespecified Covid-19 sensitivity analysis in which

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Table 2. Primary and Secondary Cardiovascular Outcomes and Safety Outcomes in the Overall Population.*

Variable	Dapagliflozin (N=3131)		Placebo (N=3132)		Hazard or Rate Ratio or Win Ratio (95% CI)	P Value
	values	*events/ 100 patient-yr*	*values*	*events/ 100 patient-yr*		
Efficacy outcomes						
Primary composite outcome — no. (%)	512 (16.4)	7.8	610 (19.5)	9.6	0.82 (0.73–0.92)	<0.001
Hospitalization for heart failure or an urgent visit for heart failure	368 (11.8)	5.6	455 (14.5)	7.2	0.79 (0.69–0.91)	NA
Hospitalization for heart failure	329 (10.5)	5.0	418 (13.3)	6.5	0.77 (0.67–0.89)	NA
Urgent visit for heart failure	60 (1.9)	0.9	78 (2.5)	1.1	0.76 (0.55–1.07)	NA
Cardiovascular death†	231 (7.4)	3.3	261 (8.3)	3.8	0.88 (0.74–1.05)	NA
Secondary outcomes						
Total no. of worsening heart failure events and cardiovascular deaths‡	815	11.8	1057	15.3	0.77 (0.67–0.89)	<0.001
Change in KCCQ total symptom score at mo 8§	—	—	—	—	1.11 (1.03–1.21)	0.009
Mean change in KCCQ total symptom score at mo 8 among survivors	—	—	—	—	2.4 (1.5–3.4)	NA
Death from any cause — no. (%)	497 (15.9)	7.2	526 (16.8)	7.6	0.94 (0.83–1.07)	NA
Safety outcomes — no./total no. (%)¶						
Any serious adverse event	1361/3126 (43.5)	—	1423/3127 (45.5)	—	—	—
Any adverse event that led to discontinuation of dapagliflozin or placebo	182/3126 (5.8)	—	181/3127 (5.8)	—	—	—
Any adverse event that led to interruption of dapagliflozin or placebo	436/3126 (13.9)	—	494/3127 (15.8)	—	—	—
Any amputation	19/3126 (0.6)	—	25/3127 (0.8)	—	—	—
Any adverse event that potentially placed a patient at risk for a lower-limb amputation	188/3126 (6.0)	—	199/3127 (6.4)	—	—	—
Any definite or probable diabetic ketoacidosis	2/3126 (0.1)	—	0	—	—	—
Any major hypoglycemic event‖	6/3126 (0.2)	—	7/3127 (0.2)	—	—	—
Any serious adverse event or adverse event that led to discontinuation of dapagliflozin or placebo that was suggestive of volume depletion	42/3126 (1.3)	—	32/3127 (1.0)	—	—	—
Any renal serious adverse event or adverse event that led to discontinuation of dapagliflozin or placebo	73/3126 (2.3)	—	79/3127 (2.5)	—	—	—
Fournier's gangrene	0	—	0	—	—	—

* All treatment effects are shown as hazard ratios, except for the total number of hospitalizations for heart failure and cardiovascular deaths, which is reported as a rate ratio, and the change in Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score at month 8, which is reported as a win ratio. The total symptom scores on the KCCQ range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations. NA denotes not applicable because P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical-testing strategy.

† Cardiovascular death was also a prespecified secondary outcome.

‡ Worsening heart failure events were defined as hospitalization for heart failure or an urgent visit for heart failure. The total number of worsening heart failure events included first and recurrent events.

§ The results of the assessment of the KCCQ total symptom score in a sensitivity analysis in which data were not censored after March 11, 2020, were similar to those shown (win ratio, 1.11; 95% CI, 1.05 to 1.18).

¶ A total of 10 patients (5 in the dapagliflozin group and 5 in the placebo group) were excluded from the safety analyses because they did not receive any dose of dapagliflozin or placebo. Safety outcomes were events with an onset date on or after the date of the first dose and up to and including 30 days after the last dose of dapagliflozin or placebo.

‖ Major hypoglycemic events are defined in the Supplementary Methods section in the Supplementary Appendix.

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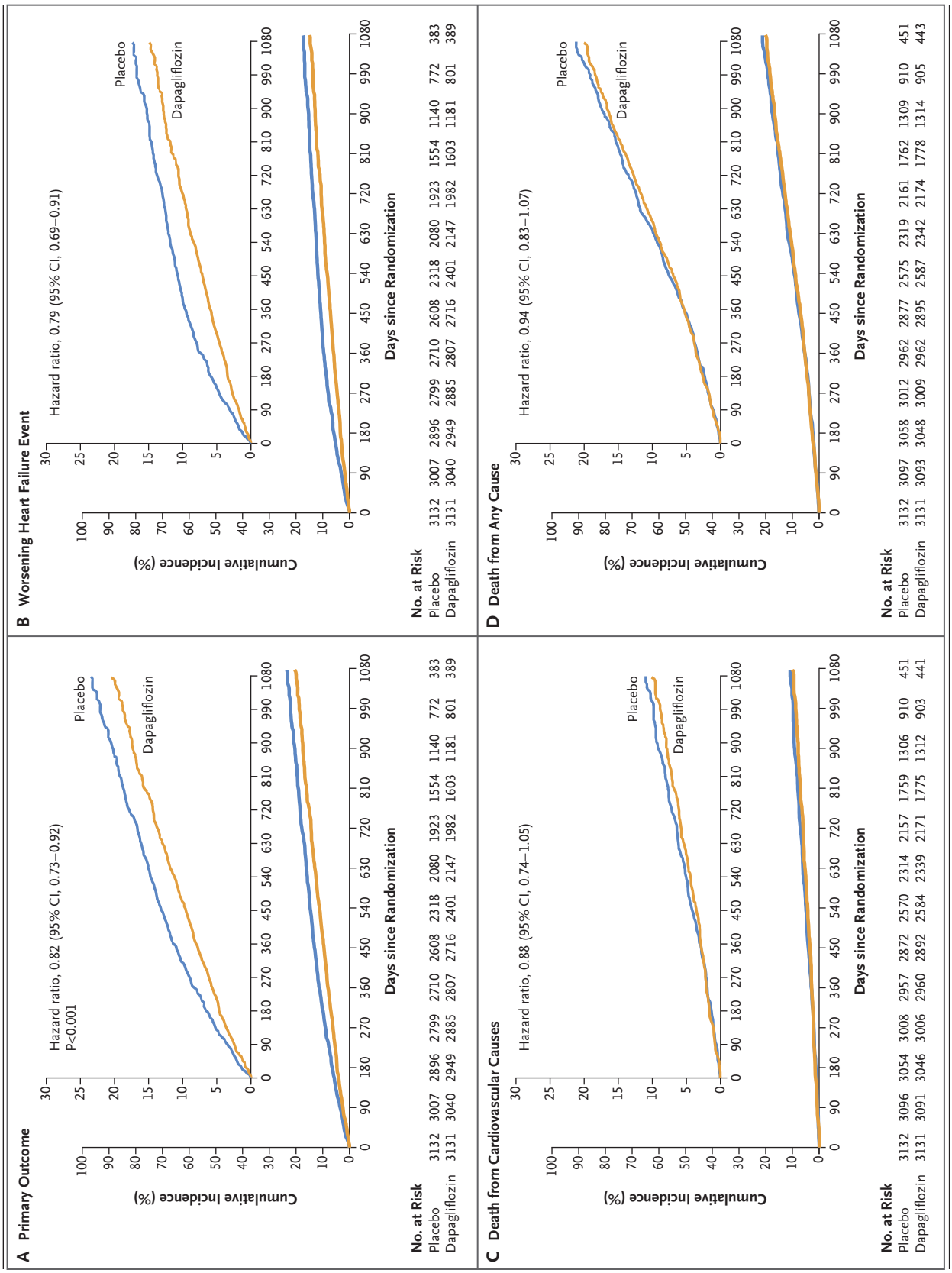

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Figure 1 (facing page). Efficacy Outcomes in the Overall Population.

Shown are time-to-event curves for the primary outcome (Panel A), individual components of the primary outcome (worsening heart failure [Panel B] and cardiovascular death [Panel C]), and death from any cause (Panel D). The insets show the same data on an expanded y axis.

patient data were censored at the time of Covid-19 diagnosis showed similar results (Table S6). Overall results were similar when death from noncardiovascular causes was taken into account as a competing risk (subdistribution hazard ratio, 0.82; 95% CI, 0.73 to 0.92). The results of the assessment of the proportional-hazards assumption are provided in the Supplementary Appendix.

SAFETY

Overall, serious adverse events, including death, were reported in 1361 patients (43.5%) in the dapagliflozin group and in 1423 patients (45.5%) in the placebo group (Table 2). Adverse events that led to discontinuation of dapagliflozin or placebo were reported in 182 patients (5.8%) in the dapagliflozin group and in 181 patients (5.8%) in the placebo group (Table S7).

DISCUSSION

In this randomized, placebo-controlled trial involving patients with heart failure and a mildly reduced or preserved ejection fraction, dapagliflozin resulted in a lower risk of the primary composite outcome, worsening heart failure or cardiovascular death, than placebo, with no appreciable difference in benefit among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, or in other subgroups. Each of the three components of this composite outcome was less common in the dapagliflozin group than in the placebo group. In addition, dapagliflozin resulted in fewer total worsening heart failure events and cardiovascular deaths and a lower symptom burden than placebo. The incidence of adverse events was similar to that in the placebo group.

In a previous trial (DAPA-HF; Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), dapagliflozin reduced the risk of worsening heart failure or cardiovascular death among patients with heart failure and a left ventricular ejection fraction of 40% or less.[1] The results of the DELIVER trial extend those of the DAPA-HF trial to patients with heart failure and a left ventricular ejection fraction of more than 40% and are consistent with the overall results of the EMPEROR-Preserved trial (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction), which assessed the effects of empagliflozin in patients with a left ventricular ejection fraction of more than 40%.[10] The rationale for the dual primary analyses in our trial (i.e., evaluation of the primary outcome in patients with a left ventricular ejection fraction of less than 60% in addition to the overall patient population) was based on concern about a potential declining benefit in patients with an ejection fraction in the normal range that had been observed in several previous trials of neurohormonal modulators.[6,15] Although the EMPEROR-Preserved trial suggested some potential attenuation of benefit in the highest part of the range of ejection fraction,[8] we observed no evidence of heterogeneity with respect to left ventricular ejection fraction in the DELIVER trial, with similar overall treatment effects among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%. This finding suggests that the benefit of SGLT2 inhibition is likely to extend throughout the full range of ejection fraction.

The DELIVER trial was designed with broader inclusion criteria than those used in previous trials involving similar populations in that we enrolled patients who were hospitalized or recently hospitalized, for whom evidence-based therapy is limited, as well as those with heart failure and a left ventricular ejection fraction that had improved to more than 40% at the time of enrollment.[4] Our data suggest that these understudied groups also benefit from dapagliflozin.

The most recent guidelines of the American Heart Association, American College of Cardiology, and Heart Failure Society of America designated SGLT2 inhibitors as class IIA, level B, for the treatment of heart failure with a mildly reduced or preserved left ventricular ejection fraction.[4] The results of the DELIVER trial may inform future guidelines and provide further guidance for their broader use in clinical practice. Although the risk of cardiovascular death

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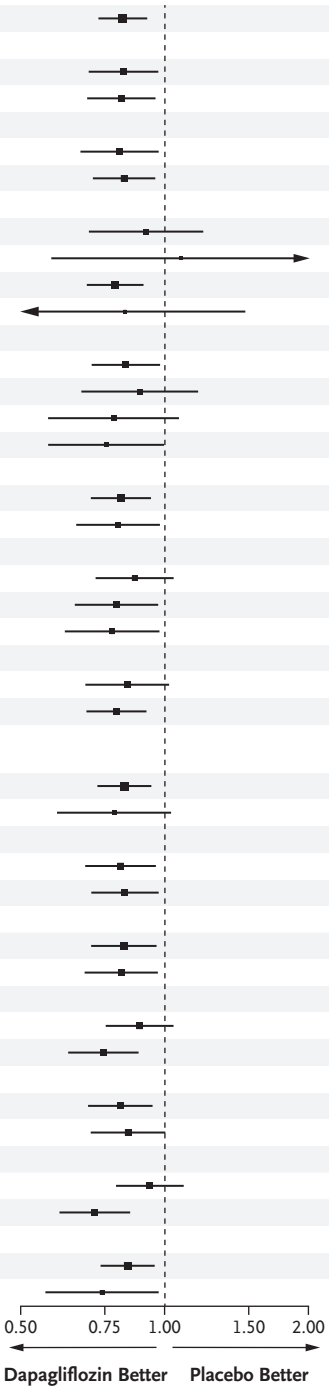
Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
All patients	512/3131	610/3132	0.82 (0.73–0.92)
Age			
≤72 yr	247/1545	306/1604	0.82 (0.69–0.97)
>72 yr	265/1586	304/1528	0.81 (0.69–0.96)
Sex			
Female	195/1364	243/1383	0.81 (0.67–0.97)
Male	317/1767	367/1749	0.82 (0.71–0.96)
Race			
Asian	97/630	106/644	0.91 (0.69–1.21)
Black	21/81	19/78	1.08 (0.58–2.01)
White	372/2214	461/2225	0.79 (0.69–0.90)
Other	22/206	24/185	0.83 (0.46–1.48)
Geographic region			
Europe or Saudi Arabia	261/1494	309/1511	0.83 (0.70–0.98)
Asia	92/607	103/619	0.89 (0.67–1.18)
Latin America	70/602	87/579	0.78 (0.57–1.07)
North America	89/428	111/423	0.75 (0.57–1.00)
NYHA class at enrollment			
II	331/2314	411/2399	0.81 (0.70–0.94)
III or IV	181/817	198/732	0.80 (0.65–0.98)
LVEF at enrollment			
≤49%	207/1067	229/1049	0.87 (0.72–1.04)
50–59%	174/1133	211/1123	0.79 (0.65–0.97)
≥60%	131/931	170/960	0.78 (0.62–0.98)
NT-proBNP at enrollment			
≤1011 pg/ml	173/1555	208/1578	0.84 (0.68–1.02)
>1011 pg/ml	339/1576	402/1553	0.79 (0.69–0.92)
Enrollment during or within 30 days after hospitalization for heart failure			
No	419/2803	497/2806	0.82 (0.72–0.94)
Yes	93/328	113/326	0.78 (0.60–1.03)
Type 2 diabetes mellitus at enrollment			
No	242/1730	293/1727	0.81 (0.68–0.96)
Yes	270/1401	317/1405	0.83 (0.70–0.97)
Atrial fibrillation or flutter at enrollment ECG			
No	285/1803	339/1814	0.82 (0.70–0.96)
Yes	227/1327	271/1317	0.81 (0.68–0.97)
Body-mass index at enrollment			
<30	275/1734	302/1736	0.89 (0.75–1.04)
≥30	236/1395	308/1392	0.74 (0.63–0.88)
Estimated GFR at enrollment			
<60 ml/min/1.73 m^2	289/1516	355/1554	0.81 (0.69–0.94)
≥60 ml/min/1.73 m^2	223/1615	255/1577	0.84 (0.70–1.00)
Systolic blood pressure at randomization			
≤128 mm Hg	280/1568	300/1590	0.93 (0.79–1.10)
>128 mm Hg	232/1563	310/1542	0.71 (0.60–0.85)
Previous LVEF ≤40%			
No	420/2559	491/2553	0.84 (0.73–0.95)
Yes	92/572	119/579	0.74 (0.56–0.97)



was not significantly lower with dapagliflozin than with placebo, the rate of cardiovascular death among patients who received placebo was substantially lower among patients with a left ventricular ejection fraction of more than 40% than among those in the DAPA-HF trial with a reduced ejection fraction (3.8 events per 100 patient-years in DELIVER vs. 7.9 events per 100

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Figure 2 (facing page). Primary Outcome in Prespecified Subgroups.

The primary outcome was a composite of worsening heart failure, which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure, or cardiovascular death. Race was reported by the investigators. The body-mass index is the weight in kilograms divided by the square of the height in meters. The size of the boxes is proportional to the number of patients in the subgroup, and arrows on the confidence interval bars indicate that the upper or lower boundary of the confidence interval is off the scale. One patient in the placebo group who had New York Heart Association (NYHA) class I disease at baseline was not included in the analysis of NYHA class at enrollment. ECG denotes electrocardiography, GFR glomerular filtration rate, LVEF left ventricular ejection fraction, and NT-proBNP N-terminal pro–B-type natriuretic peptide.

patient-years in DAPA-HF), and DELIVER was not powered to assess the effect of dapagliflozin on cardiovascular death alone. Trials in higher-risk populations, or of longer duration, or pooled analyses of several trials would be needed for robust evaluation of benefits with respect to mortality.

This trial has some limitations. The use of specific inclusion and exclusion criteria may have limited the generalizability of our findings. Less than 5% of the patients enrolled were Black, although this percentage was proportional to the population percentage on a regional basis (Table S8). Owing to the Covid-19 pandemic, assessment of symptom burden was limited to patients for whom an 8-month assessment was planned or performed before March 11, 2020, although results were similar in all patients for whom data were available. Because all the subgroups in the DELIVER trial were underpowered, within-subgroup results should be interpreted cautiously.

Among patients with heart failure and a mildly reduced or preserved ejection fraction, dapagliflozin resulted in a lower risk of the primary composite outcome (worsening heart failure or cardiovascular death), in fewer worsening heart failure events and cardiovascular deaths, and in a lower symptom burden, with no excess of adverse events. Findings were consistent across prespecified subgroups, including those defined according to left ventricular ejection fraction. These data provide further evidence to support the use of an SGLT2 inhibitor as essential therapy in patients with heart failure, regardless of the presence or absence of type 2 diabetes mellitus or left ventricular ejection fraction.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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