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Dapagliflozin in Patients Recently Hospitalized With Heart Failure and Mildly Reduced or Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Patients recently hospitalized for heart failure (HF) are at high risk for rehospitalization and death.

OBJECTIVES The purpose of this study was to investigate clinical outcomes and response to dapagliflozin in patients with HF with mildly reduced or preserved left ventricular ejection fraction (LVEF) who were enrolled during or following hospitalization.

METHODS The DELIVER (Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure) trial randomized patients with HF and LVEF >40% to dapagliflozin or placebo. DELIVER permitted randomization during or shortly after hospitalization for HF in clinically stable patients off intravenous HF therapies. This prespecified analysis investigated whether recent HF hospitalization modified risk of clinical events or response to dapagliflozin. The primary outcome was worsening HF event or cardiovascular death.

RESULTS Of 6,263 patients in DELIVER, 654 (10.4%) were randomized during HF hospitalization or within 30 days of discharge. Recent HF hospitalization was associated with greater risk of the primary outcome after multivariable adjustment (HR: 1.88; 95% CI: 1.60-2.21; $P < 0.001$). Dapagliflozin reduced the primary outcome by 22% in recently hospitalized patients (HR: 0.78; 95% CI: 0.60-1.03) and 18% in patients without recent hospitalization (HR: 0.82; 95% CI: 0.72-0.94; $P_{interaction} = 0.71$). Rates of adverse events, including volume depletion, diabetic ketoacidosis, or renal events, were similar with dapagliflozin and placebo in recently hospitalized patients.

CONCLUSIONS Dapagliflozin safely reduced risk of worsening HF or cardiovascular death similarly in patients with and without history of recent HF hospitalization. Starting dapagliflozin during or shortly after HF hospitalization in patients with mildly reduced or preserved LVEF appears safe and effective. (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure [DELIVER]; NCT03619213) (J Am Coll Cardiol 2022;80:1302–1310)

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Hospitalizations for heart failure (HF) are common, costly, and associated with high risk for subsequent rehospitalization and death.[1] Initiating effective HF therapies during or shortly after hospitalization is now supported as a Class I recommendation in clinical practice guidelines for patients with HF and reduced left ventricular ejection fraction (LVEF),[2] and may attenuate disease progression and increase rates of long-term guideline-directed medical therapy implementation.[3-5] However, positive results from clinical trials enrolling primarily outpatients with chronic HF may not generalize to this vulnerable period, in which patients may have unstable volume status, renal function, and blood pressure and other HF therapies may require adjustment. Thus, there is a need to evaluate evidence-based HF therapies specifically in hospitalized or recently discharged patients.

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Sodium-glucose co-transporter-2 (SGLT2) inhibitors have been shown to reduce HF hospitalization and cardiovascular death across the LVEF spectrum, including among those with HF with mildly reduced or preserved LVEF in the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure with Preserved Ejection Fraction) and DELIVER (Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure) trials.[6-10] There is little data about initiation of evidence-based therapies in hospitalized or recently discharged patients with preserved LVEF. Studies of SGLT2 inhibitors in this subacute patient population have enrolled primarily patients with reduced LVEF.[8,11] As for patients with HF and preserved ejection fraction, the EMPEROR-Preserved trial excluded patients with acute decompensated HF within 1 week of screening or during the screening period before randomization.

The DELIVER trial compared dapagliflozin to placebo in 6,263 patients with HF with mildly reduced or preserved LVEF, including 654 who were randomized while hospitalized for HF or within 30 days of hospital discharge. We conducted a prespecified analysis of DELIVER to evaluate the baseline characteristics, risk for clinical events, and response to dapagliflozin in patients recently hospitalized for HF.

METHODS

STUDY DESIGN AND PROCEDURES. The design and primary results of the DELIVER trial have been previously described.[10,12,13] DELIVER was a multicenter, double-blind, randomized clinical trial comparing dapagliflozin 10 mg daily to placebo in patients with HF with mildly reduced, preserved, or improved LVEF. Eligible patients included those with and without type 2 diabetes age 40 years or older, with signs and symptoms of HF (New York Heart Association [NYHA] functional class II-IV), LVEF >40%, elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and echocardiographic left atrial dilation or left ventricular hypertrophy.

DELIVER permitted randomization during or shortly after hospitalization for HF, as long as patients had been clinically stable and off intravenous HF therapies for at least 12 hours before enrollment and 24 hours before randomization. As prespecified in the DELIVER regulatory statistical analysis plan defined before study unblinding, this subgroup analysis compared baseline characteristics and clinical outcomes of patients who were or were not randomized while hospitalized for HF or within 30 days of discharge from a hospitalization for HF.

The primary outcome for this study and for the main trial was a composite of cardiovascular death or worsening HF event, the latter defined as either HF hospitalization or urgent HF visit. Key additional endpoints included worsening HF event, hospitalization for HF, cardiovascular death, all-cause death, total (first and recurrent) HF events and cardiovascular deaths, and change in HF symptoms at 32 weeks as measured using the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS). A blinded Clinical Events Committee at Brigham & Women's Hospital (Boston, Massachusetts, USA) and University of Glasgow (Glasgow, United Kingdom) adjudicated these endpoints except for KCCQ-TSS. All participants in DELIVER provided written informed consent. Local ethics committees and Institutional Review Boards at each participating site approved the study protocols.

STATISTICAL ANALYSIS. Baseline characteristics of patients with and without recent HF hospitalization were described using proportions for categorical variables, mean ± SD for normally distributed continuous variables, and medians and IQRs for skewed continuous variables, and compared using Pearson chi-square test, Student's *t*-test, and Wilcoxon rank sum test, respectively. Associations between recent hospitalization and incident cardiovascular outcomes were analyzed using Cox proportional hazards regression with and without adjustment for 14 clinical covariates (selected a priori) that have been shown to predict HF and death events in other studies: age, sex, geographic region,

ABBREVIATIONS AND ACRONYMS

HF = heart failure

KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score

LVEF = left ventricular ejection fraction

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

NYHA = New York Heart Association

SGLT2 = sodium-glucose co-transporter-2

TABLE 1 Baseline Characteristics of Patients With or Without History of Hospitalization for HF

	No Recent HF Hospitalization (n = 5,609)	Recent HF Hospitalization (n = 654)	*P* Value
Age	71.6 ± 9.6	71.9 ± 9.1	0.48
Age group			0.09
≤65	1,364 (24.3)	140 (21.4)	
>75	2,109 (37.6)	238 (36.4)	
>65-75	2,136 (38.1)	276 (42.2)	
Men	3,178 (56.7)	338 (51.7)	0.02
Race			<0.001
White	3,914 (69.8)	525 (80.3)	
Asian	1,168 (20.8)	106 (16.2)	
Black or African American	144 (2.6)	15 (2.3)	
American Indian or Alaska Native	184 (3.3)	5 (0.8)	
Other	199 (3.5)	3 (0.5)	
Geographic region			<0.001
Europe and Middle East	2,561 (45.7)	444 (67.9)	
Asia	1,121 (20.0)	105 (16.1)	
Latin America	1,104 (19.7)	77 (11.8)	
North America	823 (14.7)	28 (4.3)	
History of atrial fibrillation or flutter	3,116 (55.6)	436 (66.7)	<0.001
History of stroke	505 (9.0)	92 (14.1)	<0.001
History of hypertension	4,945 (88.2)	608 (93.0)	<0.001
History of type 2 diabetes mellitus	2,487 (44.3)	319 (48.8)	0.03
History of chronic obstructive pulmonary disease	603 (10.8)	89 (13.6)	0.03
History of noncoronary revascularization	123 (2.2)	17 (2.6)	0.51
History of sleep apnea	453 (8.1)	32 (4.9)	0.004
Prior myocardial infarction	1,465 (26.1)	174 (26.6)	0.79
Coronary artery disease	2,810 (50.1)	354 (54.1)	0.05
Atherosclerotic cardiovascular disease	3,156 (56.3)	396 (60.6)	0.04
Smoking status			<0.001
Current	438 (7.8)	46 (7.0)	
Former	2,080 (37.1)	181 (27.7)	
Never	3,091 (55.1)	427 (65.3)	

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history of atrial fibrillation or flutter, stroke, type 2 diabetes, chronic obstructive pulmonary disease, coronary artery disease, smoking status (current or former), NYHA functional class III or IV compared with II, LVEF, systolic blood pressure, estimated glomerular filtration rate, and log-transformed NT-proBNP. Interaction testing was performed to investigate whether recent HF hospitalization modified the relative treatment effects of dapagliflozin compared with placebo on clinical outcomes, without adjustments. The endpoint of total (first and recurrent) worsening HF events and cardiovascular death was similarly analyzed using the recurrent events regression method of Lin et al.[14] The treatment effect on KCCQ-TSS was analyzed using a linear mixed effects model incorporating data from the baseline, 4-, 16-, and 32-week study visits, with random patient-level intercept terms. All analyses were performed in the intent-to-treat population. Statistical analysis was performed in STATA v16. A 2-sided *P* value <0.05 was considered significant.

RESULTS

BASELINE CHARACTERISTICS. Among 6,263 total patients in DELIVER, 654 (10.4%) were randomized during hospitalization for HF or within 30 days of hospital discharge. Of these, 90 were randomized in the hospital, 147 were randomized 1 to 7 days after hospital discharge, and 417 were randomized 8 to 30 days after discharge. The baseline characteristics of patients with and without recent HF hospitalization are presented in Table 1. Recently hospitalized patients were more likely to be women (48% vs 43%), White (80% vs 70%), and enrolled in Europe or the Middle East (68% vs 46%). Recently hospitalized patients had a greater burden of cardiovascular comorbidities including type 2 diabetes (49% vs 44%), prior stroke (14% vs 9%), and chronic obstructive pulmonary disease (14% vs 11%), and were more likely to have NYHA functional class III or IV symptoms (49% vs 22%). Baseline NT-proBNP was higher in recently hospitalized patients (median: 1,284 vs 988 pg/mL), and LVEF was slightly lower (mean: 52.5% vs 54.3%). Age, history of myocardial infarction, body mass index, and systolic blood pressure were similar between patients with and without recent hospitalization. Baseline medication use was similar except that recently hospitalized patients were more likely to use mineralocorticoid receptor antagonists (52% vs 42%). Among recently hospitalized patients, baseline characteristics of the dapagliflozin and placebo groups were balanced (Supplemental Tables 1 and 2).

CLINICAL OUTCOMES. The primary outcome of worsening HF event or cardiovascular death occurred in 206 of 654 patients with recent HF hospitalization (event rate: 17.5 events per 100 patient-years) compared with 916 of 5,609 patients without recent HF hospitalization (7.8 events per 100 patient-years) (HR: 2.21; 95% CI: 1.90-2.57; $P < 0.001$). Recent HF hospitalization was also associated with greater risk of cardiovascular death (HR: 2.11; 95% CI: 1.68-2.65; $P < 0.001$), worsening HF event (HR: 2.30; 95% CI: 1.93-2.73; $P < 0.001$), HF hospitalization (HR: 2.42; 95% CI: 2.02-2.90; $P < 0.001$), all-cause death (HR: 1.68; 95% CI: 1.42-1.99; $P < 0.001$), and total (first and recurrent) worsening HF events and cardiovascular death (rate ratio: 2.44; 95% CI: 2.01-2.97; $P < 0.001$). The greater risk associated with all these outcomes persisted after multivariable adjustment for clinical covariates including NT-proBNP (primary outcome adjusted HR: 1.88; 95% CI: 1.60-2.21; $P < 0.001$) (Supplemental Table 3).

EFFICACY AND SAFETY OF DAPAGLIFLOZIN. Relative reductions in the primary outcome of worsening HF event or cardiovascular death with dapagliflozin were consistent in patients with and without history of recent HF hospitalization. Dapagliflozin reduced the primary outcome by 22% in recently hospitalized patients (HR: 0.78; 95% CI: 0.60-1.03) and 18% in patients without recent hospitalization (HR: 0.82; 95% CI: 0.72-0.94; $P_{interaction} = 0.71$) (**Central Illustration**). There was no significant evidence of effect modification by LVEF within the recently hospitalized population ($P_{interaction} = 0.60$). Absolute reduction in primary outcome event rate with dapagliflozin compared with placebo was 4.4 events per 100 patient-years in recently hospitalized patients and 1.5 events per 100 patient-years in patients who were not recently hospitalized. The number needed to treat with dapagliflozin to prevent 1 primary outcome event was 28 patient-years in recently hospitalized patients and 65 patient-years in patients not recently hospitalized.

The effect of dapagliflozin on additional endpoints was also consistent regardless of recent HF hospitalization. No significant treatment interaction was observed for HF hospitalization (HR: 0.76; 95% CI: 0.60-1.04 in recently hospitalized and 0.77; 95% CI: 0.66-0.90 without recent hospitalization; $P_{interaction} = 0.90$), cardiovascular death (HR: 0.85; 95% CI: 0.56-1.29 in recently hospitalized and 0.89; 95% CI: 0.73-1.09 without recent hospitalization; $P_{interaction} = 0.77$), all-cause death (HR: 0.96; 95% CI: 0.70-1.31 in recently hospitalized and 0.94; 95% CI: 0.82-1.07 without recent hospitalization; $P_{interaction} = 0.95$), or total (ie, first and recurrent) worsening HF events and cardiovascular death (rate ratio: 0.69; 95% CI: 0.49-0.98 in recently hospitalized and 0.79; 95% CI: 0.68-0.92 without recent hospitalization; $P_{interaction} = 0.46$) (**Figure 1**). Dapagliflozin compared with placebo improved KCCQ-TSS both in patients with recent HF hospitalization (treatment effect +3.5 points; 95% CI: 0.2-6.8 points) and in patients without recent HF hospitalization (treatment effect +2.3 points; 95% CI: 1.4-3.3 points; $P_{interaction} = 0.59$) (**Figure 2**).

Serious adverse events were more common in recently hospitalized patients compared with patients who were not recently hospitalized (52% vs 44%; $P < 0.001$). In patients with recent HF hospitalization, rates of serious adverse events were similar between treatment groups (49% in dapagliflozin group; 54% in the placebo group; $P = 0.18$), including for volume depletion, diabetic ketoacidosis, and renal events, as well as adverse events leading to study drug discontinuation (**Table 2**). Dapagliflozin modestly reduced blood pressure at the 4-week follow-up visit similarly regardless of recent HF hospitalization ($P_{interaction} = 0.64$).

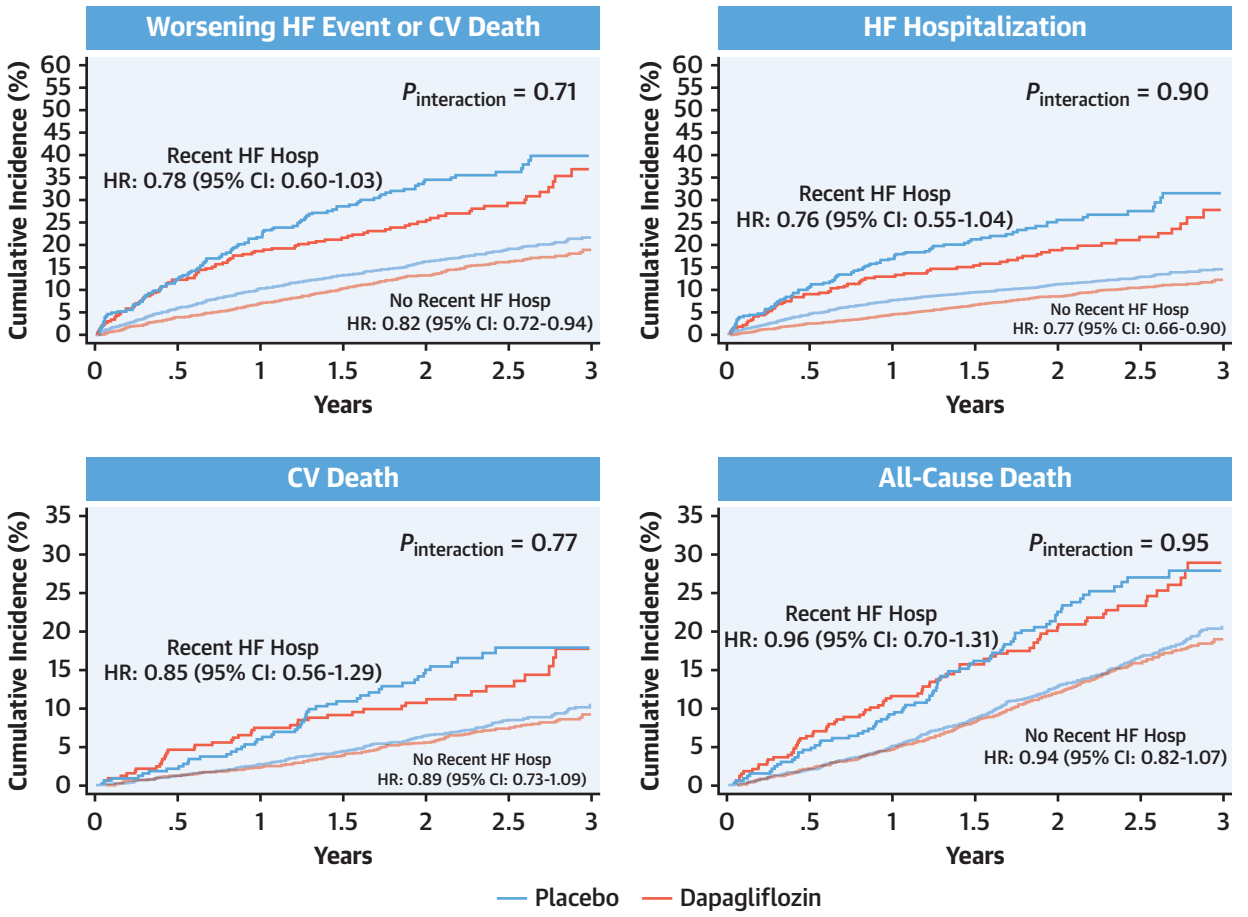
TABLE 1 Continued

	No Recent HF Hospitalization (n = 5,609)	Recent HF Hospitalization (n = 654)	*P* Value
Body mass index, kg/m^2	29.9 ± 6.1	29.8 ± 6.1	0.93
Body mass index group, kg/m^2			0.25
<18.5 (underweight)	49 (0.9)	5 (0.8)	
18.5-24.9 (normal weight)	1,189 (21.2)	154 (23.6)	
25.0-29.9 (overweight)	1,879 (33.5)	194 (29.7)	
30.0-34.9 (class I obesity)	1,393 (24.9)	181 (27.7)	
35.0-39.9 (class II obesity)	719 (12.8)	79 (12.1)	
≥40 (class III obesity)	375 (6.7)	40 (6.1)	
Time from diagnosis of HF to baseline			<0.001
0-3 mo	454 (8.1)	114 (17.5)	
>3-6 mo	535 (9.5)	57 (8.7)	
>6-12 mo	771 (13.8)	71 (10.9)	
>1-2 y	896 (16.0)	99 (15.2)	
>2-5 y	1,403 (25.0)	166 (25.4)	
>5 y	1,546 (27.6)	146 (22.4)	
NYHA class at baseline			<0.001
I	1 (0.0)	0 (0.0)	
II	4,376 (78.0)	337 (51.5)	
III	1,221 (21.8)	310 (47.4)	
IV	11 (0.2)	7 (1.1)	
LVEF, %	54.3 ± 8.8	52.5 ± 8.2	<0.001
Pooled LVEF group			<0.001
≤49%	1,857 (33.1)	259 (39.6)	
50%-59%	2,007 (35.8)	249 (38.1)	
≥60%	1,745 (31.1)	146 (22.3)	
Baseline NT-proBNP, pg/mL	988 (610, 1,689)	1,284 (748, 2,414)	<0.001
NT-proBNP in AFF (ECG)	1,377 (953, 2,149)	1,647 (1,040, 2,629)	<0.001
NT-proBNP when no AFF (ECG)	704 (462, 1,232)	857 (531, 1,920)	<0.001
Baseline ECG atrial fibrillation/flutter	2,322 (41.4)	322 (49.2)	<0.001
Baseline systolic blood pressure, mm Hg	128.4 ± 15.4	127.2 ± 15.0	0.06
Baseline diastolic blood pressure, mm Hg	73.8 ± 10.4	74.7 ± 9.8	0.05
Baseline HbA1c, %	6.6 ± 1.4	6.7 ± 1.4	0.02
Baseline heart rate, beats/min	71.3 ± 11.7	73.4 ± 12.3	<0.001
Baseline creatinine, μmol/L	102.0 ± 30.9	106.4 ± 32.2	<0.001
Baseline eGFR, mL/min/1.73 m^2	61.4 ± 19.2	57.7 ± 18.8	<0.001
eGFR ≥60 mL/min/1.73 m^2	2,916 (52.0)	27 (42.2)	<0.001
Loop diuretics	4,250 (75.8)	561(85.9)	<0.001
ACE inhibitor	2,059 (36.7)	236 (36.1)	0.77
ARB	2,049 (36.5)	223 (34.2)	0.23
ARNI	272 (4.9)	29 (4.4)	0.64
Beta-blocker	4,635 (82.6)	542 (83.0)	0.82
MRA	2,325 (41.5)	342 (52.4)	<0.001
Pacemaker	580 (10.3)	82 (12.5)	0.08
ICD	105 (1.9)	8 (1.2)	0.24

Values are mean ± SD, n (%), or median (IQR).

ACE = angiotensin-converting enzyme; AFF = atrial fibrillation or flutter; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; Hba1c = hemoglobin a1c; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

CENTRAL ILLUSTRATION **Efficacy of Dapagliflozin in Patients With and Without Recent Hospitalization**



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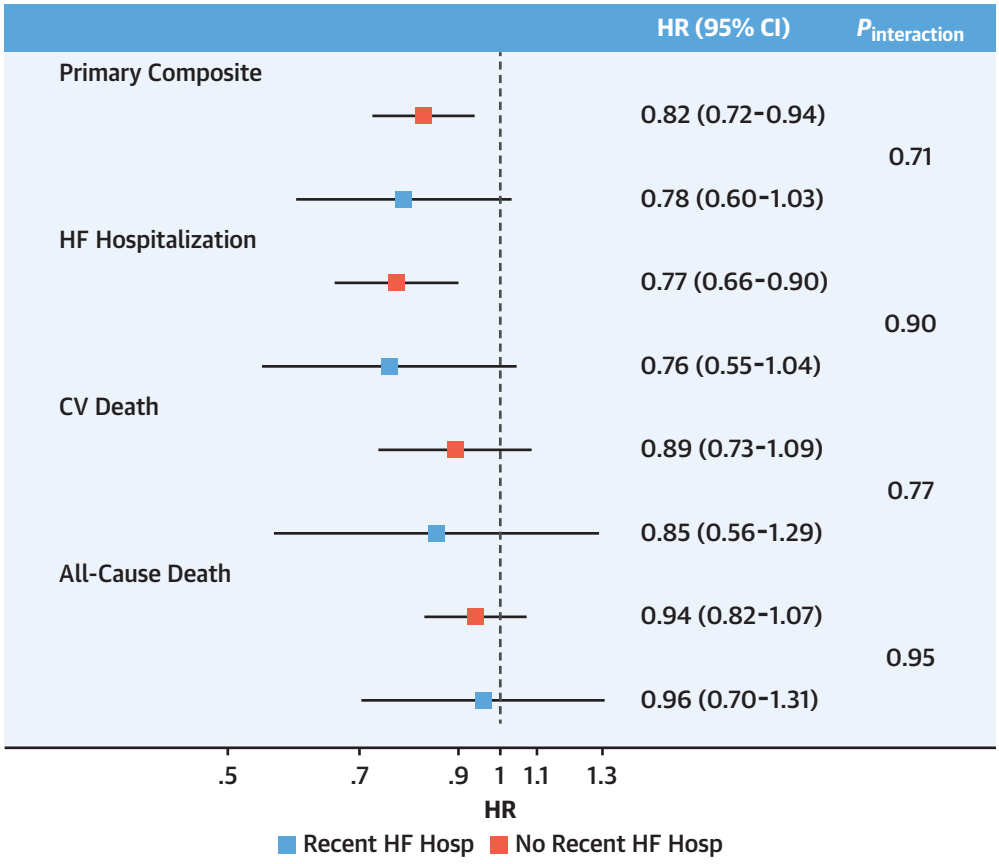
The recent HF hospitalization group was defined by randomization either during hospitalization or within 30 days after discharge. HRs with 95% CIs compare rates of the indicated endpoint between the dapagliflozin and placebo groups, without adjustment. **Solid lines** represent patients with recent HF hospitalization and **faded lines** represent patients without recent HF hospitalization. CV = cardiovascular; HF = heart failure.

DISCUSSION

In the DELIVER trial evaluating dapagliflozin in patients with HF with mildly reduced or preserved LVEF, the 10% of patients who were randomized during hospitalization for HF or within 30 days of discharge experienced high rates of rehospitalization and death. The relative reduction in the primary outcome of worsening HF event or cardiovascular death with dapagliflozin was consistent regardless of recent HF hospitalization. Rates of adverse events were balanced between dapagliflozin and placebo, including among the higher risk recently hospitalized cohort. These results suggest that starting dapagliflozin during or shortly after hospitalization for HF in patients with mildly reduced or preserved LVEF is safe and effective.

COMPARISON WITH PREVIOUS TRIALS. Previous clinical trials in HF with preserved LVEF have enrolled few patients who were recently hospitalized for HF. The PARAGON-HF (Efficacy and Safety of LCZC696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction) trial of sacubitril/valsartan did allow screening, but not randomization, during hospitalization; given the run-in period, no patients were randomized within 30 days of discharge.[15] An ongoing trial of 800 patients is evaluating whether sacubitril/valsartan reduces NT-proBNP in hospitalized or recently discharged patients with HF and mildly

FIGURE 1 Treatment Effect on Clinical Outcomes by Recent HF Hospitalization Group



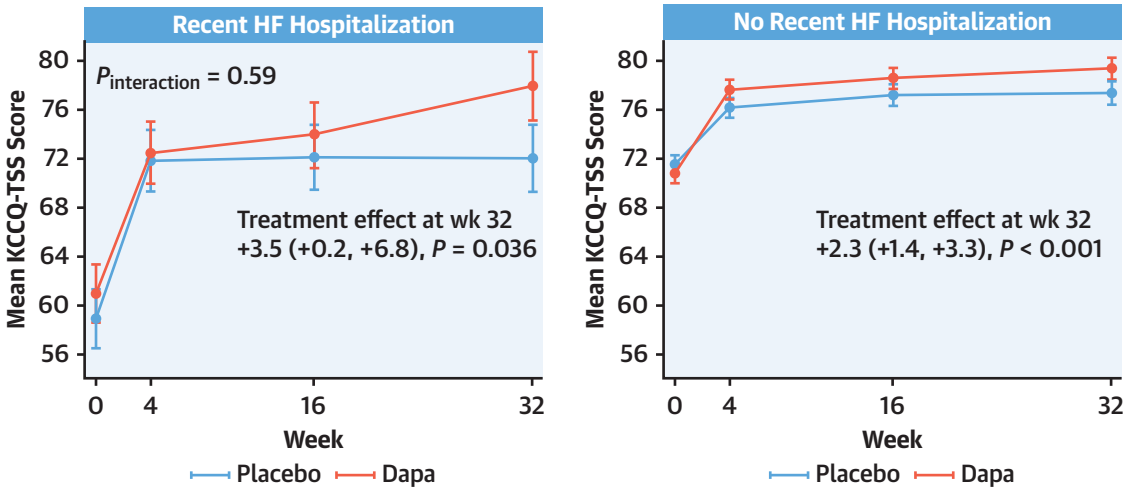
The primary composite outcome of DELIVER was worsening HF event or CV death. CV = cardiovascular; DELIVER = Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure; HF = heart failure.

reduced or preserved LVEF (NCT03988634). The EMPEROR-Preserved trial of empagliflozin excluded patients with acute decompensated HF within 1 week of screening or during the screening period before randomization.[9]

Our results complement 3 trials of SGLT2 inhibitors that enrolled patients during or shortly after hospitalization for HF regardless of LVEF. In 530 hospitalized patients, empagliflozin led to short-term clinical benefit measured by win ratio driven predominantly by improvements in KCCQ-TSS, without an increase in adverse events, in EMPULSE (A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure). Treatment benefit was consistent regardless of LVEF, but only 169 patients (32%) had LVEF >40%.[11] In the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial, the combination SGLT1/2 inhibitor sotagliflozin reduced total HF events and cardiovascular death in patients with type 2 diabetes and HF when started during hospitalization or immediately after discharge. Although just 255 patients with preserved LVEF were enrolled due to early trial termination, the trial demonstrated a statistically significant 52% reduction in clinical events even within the preserved LVEF subgroup.[8] A third study with 79 patients hospitalized for HF (fewer than one-half with LVEF >40%) found that empagliflozin reduced in-hospital worsening HF, rehospitalization for HF, or death at 60 days.[16]

SAFETY PROFILE. The safety of dapagliflozin in recently hospitalized patients is as important as the efficacy. Because many clinical trials evaluating HF drugs have excluded recently hospitalized patients, physicians may hesitate to start new therapies in this vulnerable phase. In this study, adverse events were balanced between the treatment groups even in recently hospitalized patients. Balanced rates of

FIGURE 2 KCCQ-TSS Trajectory by Treatment Arm and Recent HF Hospitalization



Mean and 95% CI Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) are shown for each time point, treatment group, and recent hospitalization subgroup. The treatment effect on KCCQ-TSS was analyzed using a linear mixed effects model incorporating data from the baseline, 4-, 16-, and 32-week study visits, with random patient-level intercept terms. Abbreviations as in Figure 1.

adverse events that led to study drug discontinuation indicate dapagliflozin was well-tolerated. SGLT2 inhibitors have demonstrated excellent safety profile across multiple populations of patients with type 2 diabetes, HF, and renal disease.[6,7,9,17,18] The findings of this study are consistent with the SOLOIST-WHF and EMPULSE trials in patients with worsening HF, and collectively should reassure clinicians regarding initiation of SGLT2 inhibitors regardless of the clinical setting (in-hospital, shortly after discharge, or in the outpatient setting).[8,11]

TABLE 2 Adverse Events in Patient With Recent Hospitalization for HF

	Placebo (n = 326)	Dapagliflozin (n = 328)
Any serious adverse event	177 (54.3)	161 (49.1)
Any adverse event that led to discontinuation of study drug	25 (7.7)	16 (4.9)
Any adverse event that led to interruption of study drug	57 (17.5)	46 (14.0)
Any amputation	3 (0.9)	2 (0.6)
Any adverse event that potentially placed a patient at risk for a lower-limb amputation	18 (5.5)	18 (5.5)
Any definite or probable diabetic ketoacidosis	0 (0.0)	1 (0.3)
Any major hypoglycemic event	0 (0.0)	1 (0.3)
Any serious adverse event or adverse event that led to discontinuation of study drug that was suggestive of volume depletion	3 (0.9)	4 (1.2)
Any renal serious adverse event or adverse event that led to discontinuation of the study drug	11 (3.4)	10 (3.0)

Values are n (%).
Abbreviation as in Table 1.

IMPLICATIONS FOR CLINICAL IMPLEMENTATION. Initiating SGLT2 inhibitors during HF hospitalization or on discharge may help to overcome therapeutic inertia and improve uptake of this effective drug class. Implementation studies of guideline-directed medical therapy for HF with reduced LVEF have found low uptake in real-world practice despite strong evidentiary support for efficacy and safety.[19,20] Medications started during inpatient hospitalization are more likely to be used months later.[21] Hospitalization is a convenient setting for scalable implementation science interventions to optimize long-term medications and inpatient treatment optimization is now guideline-supported for patients with HF with reduced LVEF.[2,5] Implementation programs developed for HF with reduced LVEF should now be extended to improve uptake of SGLT2 inhibitors in patients with mildly reduced or preserved LVEF.

STUDY STRENGTHS AND LIMITATIONS. Strengths of the present analysis included randomized treatment assignment, larger sample size of hospitalized or recently discharged patients compared with previous trials, centrally adjudicated clinical outcomes, and examination of a prespecified subgroup. However, findings should be considered in light of several limitations. DELIVER was not designed to evaluate for effect modification by recent HF hospitalization, so analyses of treatment interaction are underpowered. Treating physicians or site investigators may

have preferentially enrolled a subset of recently hospitalized patients whom they felt were most stable. Because only 90 patients in our study were randomized during hospitalization, we did not have sufficient sample size to analyze this population separately and the current findings are based primarily on recently discharged patients; 2 ongoing clinical trials (NCT04363697 and NCT04298229) are evaluating in-hospital initiation of dapagliflozin across the LVEF spectrum. Finally, we did not consider the cost effectiveness of dapagliflozin.

CONCLUSIONS

The DELIVER trial showed that dapagliflozin reduced worsening HF events or cardiovascular death in patients with HF with mildly reduced or preserved LVEF. Those patients randomized into DELIVER during HF hospitalization or within 30 days of discharge experienced high rates of clinical events. The benefit of dapagliflozin was consistent regardless of recent hospitalization, and there was no indication of excess adverse events (including those related to volume depletion or renal dysfunction) with dapagliflozin in these patients. These results suggest that starting dapagliflozin during or shortly after hospitalization for HF in patients with mildly reduced or preserved LVEF is safe and effective.

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Dr Desai has received grant support from Abbott, Alnylam, AstraZeneca, Bayer, and Novartis; and has received consulting fees from Abbott, Alnylam, AstraZeneca, Avidity, Axon Therapeutics, Bayer, Biofourmis, Boston Scientific, Cytokinetics, GlaxoSmithKline, Merck, Novartis, Parxel, Regeneron, Roche, and Verily. Dr Jhund's employer has been remunerated for his work on the DELIVER and DAPA-HF trials by AstraZeneca; has received consulting and speaker fees from Novartis, AstraZeneca, and Boehringer Ingelheim; has received research funding from Boehringer Ingelheim; and has received remuneration for clinical trial work from Novo Nordisk and Bayer. Dr de Boer has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Ionis Pharmaceuticals, Novo Nordisk, and Roche; and has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Roche. 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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The efficacy and safety of dapagliflozin in patients with mildly reduced or preserved left ventricular ejection fraction was maintained in patients who were hospitalized with heart failure within 30 days.

TRANSLATIONAL OUTLOOK: Ongoing studies are evaluating in-hospital initiation of dapagliflozin in patients with heart failure with preserved ejection fraction.

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KEY WORDS heart failure, hospitalization, preserved ejection fraction, sodium-glucose co-transporter-2 inhibitor

APPENDIX For supplemental tables, please see the online version of this paper.