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Dapagliflozin and Timing of Prior Heart Failure Hospitalization

A Patient-Level Meta-Analysis of DAPA-HF and DELIVER

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ABSTRACT

BACKGROUND Patients recently hospitalized for heart failure (HF) are at a higher risk of adverse clinical outcomes, but they may experience a greater absolute and relative benefit from effective therapies than individuals who are considered more "stable."

OBJECTIVES The authors examined the effects of dapagliflozin according to the timing of prior HF hospitalization in a patient-level pooled analysis of DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure).

METHODS A total of 11,007 patients were randomized in DAPA-HF and DELIVER. The primary outcome was the composite of worsening HF or cardiovascular death.

RESULTS In total, 12.4% were hospitalized for HF within 3 months of randomization, 14.2% between 3 and 12 months, and 16.8% more than 1 year before randomization, whereas 56.5% had not been hospitalized. The risk of the primary endpoint was inversely associated with time from prior HF hospitalization, and patients with a recent HF hospitalization had the highest risk. Compared with placebo, dapagliflozin reduced the risk of the primary outcome across HF hospitalization category (0-3 months, HR: 0.66 [95% CI: 0.55-0.81]; 3-12 months, HR: 0.73 [95% CI: 0.59-0.90]; >1 year, HR: 0.91 [95% CI: 0.74-1.12]; and no prior hospitalization, HR: 0.83 [95% CI: 0.73-0.94]; $P_{interaction} = 0.09$). The number of patients needed to treat with dapagliflozin to prevent 1 event over the median follow-up of 22 months was 13, 20, 23, and 28, respectively. The beneficial effect was consistent across the range of LVEF regardless of HF hospitalization category.

CONCLUSIONS The relative benefits of dapagliflozin were consistent across the range of LVEF regardless of the timing of the most recent HF hospitalization with a greater absolute benefit in patients with recent hospitalization.
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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

NNT = number needed to treat

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

SGLT2i = sodium glucose co-transporter 2 inhibitor

Patients hospitalized for worsening heart failure (HF) experience high subsequent rates of readmission and death, especially in the vulnerable phase early after discharge.[1-5] The initiation of effective HF therapies during or shortly after hospitalization reduces these risks and attenuates disease progression, whereas if treatment is not started early, it may never be introduced.[6-10] Indeed, the 2023 focused update of the 2021 European Society of Cardiology guidelines for the management of HF recommends an intensive strategy of initiation and uptitration of evidence-based treatment before discharge and during follow-up in the first 6 weeks after HF hospitalization.[5] However, HF patients hospitalized, or recently discharged, may have unstable volume status, kidney function, and blood pressure. Therefore, it is important to evaluate the safety and efficacy of novel treatments in these high-risk patients.[8]

Sodium glucose co-transporter 2 inhibitors (SGLT2is) are the most recent class of drugs shown to decrease both morbidity and mortality in patients with chronic HF across the spectrum of left ventricular ejection fraction (LVEF).[11-16] These unequivocal benefits of SGLT2is have recently been extended to patients hospitalized, or recently discharged, for acute decompensated HF.[17,18] Here we provide a detailed report of the prognostic value of the timing of the most recent HF hospitalization and the effects of dapagliflozin on clinical outcomes according to the recency of HF hospitalization across the range of LVEF in a pooled analysis of DAPA-HF and DELIVER, both of which randomized patients with HF to treatment with dapagliflozin or placebo.[11,12]

METHODS

DAPA-HF and DELIVER were randomized, double-blind, controlled trials in patients with symptomatic HF and elevated natriuretic peptides comparing the efficacy and safety of dapagliflozin 10 mg once daily with a matching placebo. The main difference between the 2 trials was that DAPA-HF enrolled patients with LVEF ≤40% and DELIVER enrolled those with LVEF >40%. The design, baseline characteristics, and primary results of both trials were published previously.[11,12,16,19-22] The trial protocols were approved by the ethics committee at all participating institutions, and all patients provided written informed consent.

TRIAL PATIENTS. Ambulatory patients in NYHA functional class II to IV with LVEF ≤40% and an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level were eligible for DAPA-HF.[19] Patients were also required to receive guideline-recommended treatments for heart failure with reduced ejection fraction (HFrEF). The main exclusion criteria were a history of type 1 diabetes, symptomatic hypotension or a systolic blood pressure <95 mm Hg, an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, or hospitalization because of decompensated HF <4 weeks before enrollment.[19]

Ambulatory and hospitalized patients in NYHA functional class II to IV with LVEF >40% and an elevated NT-proBNP level were eligible for DELIVER.[21] Patients were also required to have evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy). All patients had to be receiving at least intermittent diuretic therapy. The key exclusion criteria were similar to those in DAPA-HF with 2 exceptions: 1) in DELIVER, the eGFR threshold was lower (25 mL/min/1.73 m^2), and 2) patients hospitalized with decompensated HF could be enrolled, although they had to be off intravenous HF therapy (including diuretics) for at least 12 hours before enrollment and 24 hours before randomization.[21]

TIME FROM LAST HF HOSPITALIZATION. In both trials, data on the timing of the most recent HF hospitalization were retrieved from the trial case report forms. Investigators were first asked if participants had been hospitalized for HF before randomization and then asked to specify the time from the following options: 0 to 3 months, >3 to 6 months, >6 to 12 months, >1 to 2 years, >2 to 5 years, and >5 years. In the present study, some of the prespecified categories were pooled to ensure a sufficient number of patients and events (and thereby increase power) in each category. Thus, patients were classified as having been hospitalized for HF within 3 months (including those randomized during hospitalization in DELIVER), between 3 and 12 months, >1 year before randomization, or never hospitalized before randomization.

TRIAL OUTCOMES. The primary outcome in both DAPA-HF and DELIVER was the composite of worsening HF (unplanned HF hospitalization or urgent visit for HF requiring administration of an intravenous diuretic) or cardiovascular death. In the present analysis, we also examined each of the components of the primary outcome; death from any cause; total (first and repeat) HF hospitalizations and cardiovascular death; and change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ)-Total Symptom Score (TSS).

In DAPA-HF, the definition of a cardiovascular death included deaths not adjudicated to have a noncardiovascular cause (ie, deaths for which the cause could not be determined were included). In DELIVER, deaths in which the cause could not be determined were excluded from the definition of death from cardiovascular causes. In the present study, the definition of death from cardiovascular causes included deaths of undetermined causes, following the prespecified statistical analysis plan for the pooled analyses.

STATISTICAL ANALYSES. Baseline characteristics were summarized as frequencies with percentages, means with SD, or medians with IQRs. Differences in baseline characteristics were tested using the chi-square test for binary or categoric variables and the Wilcoxon test and 2-sample Student's *t*-test for non-normal and normally distributed continuous variables, respectively.

Regardless of treatment allocation, time-to-event data were evaluated using the Kaplan-Meier estimator (all-cause death), the Aalen-Johansen estimator (taking the competing risk of death into account,[23] all outcomes except all-cause death), and Cox proportional hazards models stratified according to type 2 diabetes status and trial and adjusted for treatment assignment; HRs with 95% CIs were reported. The total (first and recurrent) events were evaluated with semiparametric proportional rates models[24] stratified according to type 2 diabetes status and trial and adjusted for treatment assignment; rate ratios with 95% CIs were reported. Noncardiovascular death was regarded as a censoring event in the analysis of total HF hospitalizations and cardiovascular death. In addition, HRs and rate ratios stratified according to type 2 diabetes status and trial and adjusted for treatment assignment, age, sex, geographic region, systolic blood pressure, heart rate, body mass index, log of NT-proBNP, eGFR, duration of HF, LVEF, NYHA functional class, a history of myocardial infarction, stroke, and atrial fibrillation were reported.

To compare the effects of dapagliflozin vs placebo on clinical outcomes, time-to-event data and total (first and recurrent) events were evaluated with Cox proportional hazards models and semiparametric proportional rates models, respectively, and these models were stratified according to type 2 diabetes status and trial. The number needed to treat (NNT) with dapagliflozin to prevent 1 event over the median follow-up was calculated by applying the overall relative risk reduction to the placebo group event rate. The effect of dapagliflozin on the primary outcome was also examined according to continuous LVEF as a fractional polynomial in each of the 4 hospitalization groups. The differences between treatment groups in the change in KCCQ-TSS from baseline to 8 months were analyzed using mixed-effects models for repeated measurements adjusted for baseline value, visit (months 4 and 8), treatment assignment, the interaction between treatment and visit, and trial. The least-squares mean differences with 95% CIs between treatment groups were reported.

The Wald test was used to test for interaction between the treatment effect of dapagliflozin and the timing of prior HF hospitalization (ie, the 4 categories defined previously) for all efficacy endpoints, and the respective models included treatment assignment, timing of prior HF hospitalization, and their interaction as covariates, in addition to those described previously. For the other safety outcomes, the Wald test was used to test for interaction between the treatment effect of dapagliflozin and the timing of prior HF hospitalization in a logistic regression model, which included treatment assignment, timing of prior HF hospitalization, and their interaction as covariates.

To examine whether the effect of dapagliflozin by the timing of HF hospitalization differed by LVEF, we tested a 3-way interaction term between LVEF as a binary variable (ie, above/below 40%), randomized treatment, and the timing of HF hospitalization. All analyses were conducted using SAS version 9.4 (SAS Institute) and STATA version 17.0 (StataCorp).

RESULTS

Of the 11,007 patients randomized in DAPA-HF and DELIVER, 6,218 (56.5%) did not have HF hospitalization before randomization. Among the 4,789 (43.5%) patients with prior HF hospitalization, 1,370 were hospitalized within 3 months (28.6% of patients with a hospitalization, 12.4% of all patients), 1,565 between 3 and 12 months (32.7% of patients with a hospitalization, 14.2% of all patients), and 1,854 more than 1 year before randomization (38.7% of patients with a hospitalization, 16.8% of all patients).

PATIENT CHARACTERISTICS. The baseline characteristics of patients according to the recency of HF hospitalization are shown in Table 1. Patients with a more recent HF hospitalization were older, more often women and White, and less often current or former smokers, and they had a higher heart rate, body mass index, and NT-proBNP but a lower eGFR. They were also more likely to have a history of atrial

TABLE 1 Baseline Characteristics According to Time From Last Heart Failure Hospitalization

	0-3 mo (n = 1,370)	3-12 mo (n = 1,565)	>1 y (n = 1,854)	No Hospitalization (n = 6,218)	*P* Value
Age, y	69.9 ± 10.6	67.4 ± 11.4	69.6 ± 10.2	69.7 ± 10.3	<0.001
Sex					<0.001
Women	532 (38.8)	494 (31.6)	588 (31.7)	2,242 (36.1)	
Men	838 (61.2)	1,071 (68.4)	1,266 (68.3)	3,976 (63.9)	
Race					<0.001
White	1,032 (75.3)	1,060 (67.7)	1,246 (67.2)	4,434 (71.3)	
Asian	265 (19.3)	409 (26.1)	496 (26.8)	1,220 (19.6)	
Black or African American	54 (3.9)	56 (3.6)	82 (4.4)	193 (3.1)	
Other	19 (1.4)	40 (2.6)	30 (1.6)	371 (6.0)	
Geographic region					<0.001
Europe and Saudi Arabia	812 (59.3)	747 (47.7)	859 (46.3)	2,741 (44.1)	
North America	127 (9.3)	171 (10.9)	284 (15.3)	946 (15.2)	
South America	171 (12.5)	243 (15.5)	225 (12.1)	1,359 (21.9)	
Asia/Pacific	260 (19.0)	404 (25.8)	486 (26.2)	1,172 (18.8)	
Physiological measures					
Systolic blood pressure, mm Hg	125.1 ± 15.5	124.7 ± 16.1	125.0 ± 16.5	125.9 ± 16.1	0.017
Heart rate, beats/min	72.9 ± 12.3	71.4 ± 11.7	71.9 ± 11.6	71.1 ± 11.6	<0.001
Body mass index	29.3 ± 6.1	28.6 ± 6.2	28.8 ± 6.1	29.3 ± 6.1	<0.001
Body mass index					0.027
<18.5	17 (1.2)	27 (1.7)	20 (1.1)	77 (1.2)	
18.5-24.9	336 (24.5)	398 (25.4)	469 (25.4)	1,401 (22.5)	
25.0-29.9	441 (32.2)	559 (35.7)	643 (34.8)	2,152 (34.6)	
30-34.9	325 (23.7)	343 (21.9)	419 (22.6)	1,500 (24.1)	
≥35.0	250 (18.3)	238 (15.2)	299 (16.2)	1,085 (17.5)	
NT-proBNP, pg/mL	1,394 (775-2,618)	1,246 (695-2,499)	1,242 (766-2,187)	1,108 (674-1,929)	<0.001
Atrial fibrillation/flutter on ECG	1,888 (1,143-2,986)	1,825 (1,201-3,035)	1,520 (1,062-2,466)	1,430 (973-2,247)	<0.001
No atrial fibrillation/flutter on ECG	1,017 (552-2,259)	1,020 (580-2,078)	1,072 (635-1,931)	916 (547-1,693)	<0.001
Hemoglobin A1c, %	6.7 ± 1.4	6.6 ± 1.5	6.5 ± 1.3	6.5 ± 1.4	0.003
Creatinine, μmol/L	106.6 ± 32.2	104.2 ± 30.9	106.4 ± 31.2	101.4 ± 30.2	<0.001
eGFR, mL/min/1.73 m^2	60.4 ± 20.0	64.0 ± 20.3	61.7 ± 19.0	63.9 ± 19.1	<0.001
Smoking status					<0.001
Current	123 (9.0)	213 (13.6)	209 (11.3)	632 (10.2)	
Former	455 (33.2)	628 (40.1)	829 (44.7)	2,441 (39.3)	
Never	792 (57.8)	724 (46.3)	816 (44.0)	3,145 (50.6)	
Duration of HF					<0.001
0-3 mo	270 (19.7)	28 (1.8)	9 (0.5)	411 (6.6)	
>3-6 mo	140 (10.2)	293 (18.7)	16 (0.9)	536 (8.6)	
>6-12 mo	137 (10.0)	430 (27.5)	33 (1.8)	797 (12.8)	
>1-2 y	184 (13.5)	192 (12.3)	312 (16.8)	993 (16.0)	
>2-5 y	304 (22.2)	242 (15.5)	615 (33.2)	1,513 (24.3)	
>5 y	333 (24.3)	379 (24.2)	868 (46.8)	1,967 (31.6)	
LVEF, %	46.8 ± 12.7	39.9 ± 13.2	41.6 ± 13.6	45.5 ± 14.1	<0.001
LVEF, %					<0.001
≤40	368 (26.9)	934 (59.7)	949 (51.2)	2,496 (40.1)	
41-49	384 (28.0)	253 (16.2)	351 (18.9)	1,125 (18.1)	
≥50	618 (45.1)	378 (24.2)	554 (29.9)	2,597 (41.8)	
NYHA functional class					<0.001
II	774 (56.5)	1,041 (66.5)	1,404 (75.7)	4,698 (75.6)[a]	
III/IV	596 (43.5)	524 (33.5)	450 (24.3)	1,520 (24.4)	
KCCQ-TSS	65.9 ± 23.1	72.7 ± 22.3	74.1 ± 21.3	71.8 ± 21.8	<0.001
KCCQ-CSS	64.3 ± 21.2	70.8 ± 21.0	71.9 ± 20.4	69.7 ± 20.5	<0.001

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TABLE 1 Continued

	0-3 mo (n = 1,370)	3-12 mo (n = 1,565)	>1 y (n = 1,854)	No Hospitalization (n = 6,218)	*P* Value
KCCQ-OSS	61.7 ± 20.7	67.6 ± 20.9	69.9 ± 20.0	67.7 ± 20.2	<0.001
Medical history					
Atrial fibrillation	803 (58.6)	700 (44.7)	951 (51.3)	2,829 (45.5)	<0.001
Stroke	153 (11.2)	137 (8.8)	212 (11.4)	561 (9.0)	0.002
Myocardial infarction	380 (27.7)	574 (36.7)	701 (37.8)	2,076 (33.4)	<0.001
PCI or CABG	427 (31.2)	635 (40.6)	817 (44.1)	2,311 (37.2)	<0.001
Angina	356 (26.0)	431 (27.5)	511 (27.6)	1,312 (21.1)	<0.001
Hypertension	1,187 (86.6)	1,241 (79.3)	1,539 (83.0)	5,109 (82.2)	<0.001
Type 2 diabetes mellitus	640 (46.7)	663 (42.4)	837 (45.1)	2,649 (42.6)	0.014
Treatment					
ACE inhibitor/ARB	1,014 (74.0)	1,215 (77.6)	1,407 (75.9)	4,859 (78.1)	0.005
ARNI	91 (6.6)	116 (7.4)	150 (8.1)	452 (7.3)	0.46
Beta-blocker	1,172 (85.5)	1,445 (92.3)	1,708 (92.1)	5,410 (87.0)	<0.001
MRA	787 (57.4)	1,000 (63.9)	1,029 (55.5)	3,221 (51.8)	<0.001
Loop diuretic	1,211 (88.4)	1,330 (85.0)	1,547 (83.4)	4,548 (73.1)	<0.001
Any diuretic	1,326 (96.8)	1,516 (96.9)	1,796 (96.9)	5,918 (95.2)	<0.001
Digoxin	143 (10.4)	221 (14.1)	246 (13.3)	573 (9.2)	<0.001
Statin	862 (62.9)	997 (63.7)	1,249 (67.4)	4,107 (66.1)	0.019
Antiplatelet	534 (39.0)	788 (50.4)	895 (48.3)	3,005 (48.3)	<0.001
Anticoagulant	761 (55.5)	726 (46.4)	1,008 (54.4)	2,856 (45.9)	<0.001
CRT-P/CRT-D	36 (2.6)	92 (5.9)	112 (6.0)	214 (3.4)	<0.001
ICD/CRT-D	92 (6.7)	211 (13.5)	332 (17.9)	775 (12.5)	<0.001

Values are mean ± SD, n (%), or median (Q1-Q3). [a]1 additional patient was NYHA functional class I.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CABG = coronary artery bypass graft surgery; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; CSS = Clinical Summary Score; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; 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; OSS = Overall Summary Score; PCI = percutaneous coronary intervention; TSS = Total Symptom Score.

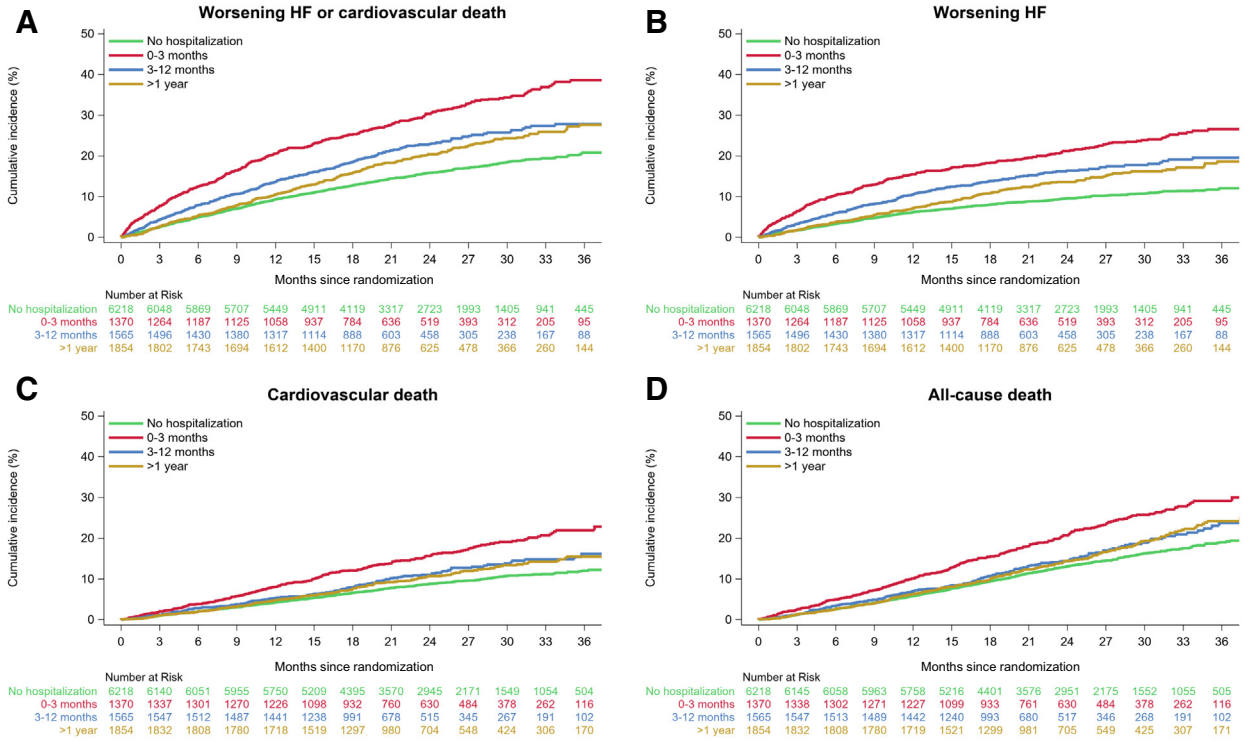
fibrillation, hypertension, and type 2 diabetes but less likely to have a history of myocardial infarction or coronary revascularization. Patients with a more recent HF hospitalization had a higher LVEF, a longer duration of HF, and worse NYHA functional class and KCCQ scores.

Regarding pharmacologic therapy, patients with a more recent HF hospitalization were more frequently treated with a loop diuretic and anticoagulant (consistent with the higher prevalence of atrial fibrillation) and less often with an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, angiotensin receptor neprilysin inhibitor, beta-blocker, statin, and antiplatelet (consistent with the lower prevalence of ischemic heart disease). They were also less likely to receive cardiac resynchronization therapy and a defibrillator (consistent with their higher LVEF).

OUTCOMES ACCORDING TO TIME FROM LAST HF HOSPITALIZATION. In both the full study population and the placebo group, patients without prior HF hospitalization had the lowest event rates for all outcomes, whereas those with HF hospitalization within 3 months had the highest rates (**Figure 1**, Supplemental Figure 1). In Cox regression models stratified by type 2 diabetes status and trial and adjusted for treatment assignment only, patients with prior HF hospitalization had a higher risk of worsening HF or cardiovascular death compared to those without, and there was a stepwise gradient in the risk of this outcome such that a more recent HF hospitalization was associated with a numerically higher risk of worsening HF or cardiovascular death (**Table 2**). A similar association was observed for worsening HF, HF hospitalization, and total HF hospitalizations and cardiovascular death. With respect to cardiovascular death and all-cause death, only patients with HF hospitalization within 3 months before randomization had a significantly higher risk of these outcomes compared to those without prior HF hospitalization (**Table 2**). After adjustment for prognostic variables, the associations between time from the last HF hospitalization and outcomes persisted but were attenuated.

The associations between the recency of HF hospitalization and outcomes were not significantly modified by LVEF group (≤40% vs >40%). However,

FIGURE 1 Cumulative Incidence of Outcomes According to Time From Last HF Hospitalization



This figure shows the cumulative incidence of outcomes according to the time from last heart failure (HF) hospitalization. (A) Worsening HF or cardiovascular death, (B) worsening HF, (C) cardiovascular death, and (D) all-cause death.

in patients with LVEF ≤40%, the magnitude of these associations was attenuated, and there was no significant association between the timing of the most recent HF hospitalization and cardiovascular death and all-cause death in these patients (Supplemental Tables 1 and 2).

EFFECTS OF DAPAGLIFLOZIN ON CLINICAL OUTCOMES ACCORDING TO TIME FROM LAST HF HOSPITALIZATION. Dapagliflozin compared with placebo reduced the relative risk of worsening HF or cardiovascular death by 33% in patients with HF hospitalization within 3 months before randomization (HR: 0.66; 95% CI: 0.55-0.81), 27% in those with hospitalization between 3 and 12 months before randomization (HR: 0.73; 95% CI: 0.59-0.90), 9% in those with hospitalization more than 1 year before randomization (HR: 0.91; 95% CI: 0.74-1.12), and 17% in individuals without prior hospitalization (HR: 0.83; 95% CI: 0.73-0.94), with no significant interaction between the timing of the most recent HF hospitalization and the effect of treatment ($P_{interaction}$ = 0.09). The NNT with dapagliflozin to prevent 1 event over the median follow-up of 22 months was 13 (95% CI: 10-20), 20 (95% CI: 15-29), 23 (95% CI: 18-34), and 28 (95% CI: 21-41), respectively.

The effects of dapagliflozin compared with placebo on the risk of worsening HF or cardiovascular death according to continuous LVEF in each of the 4 hospitalization groups are shown in Figure 2. The beneficial effect of dapagliflozin was consistent across the range of LVEF irrespective of the timing of the most recent HF hospitalization ($P_{interaction} \geq 0.20$).

The effect of dapagliflozin was also consistent for all secondary clinical outcomes, including the components of the primary outcome, HF hospitalization, all-cause death, and total HF hospitalizations and cardiovascular death, regardless of the timing of the most recent HF hospitalization (Table 3). The mean increase in the KCCQ-TSS score from baseline to 8 months was greater with dapagliflozin compared with placebo irrespective of the recency of HF hospitalization ($P_{interaction}$ = 0.88) (Table 3).

The effect of dapagliflozin was also consistent for all outcomes irrespective of the timing of the most

TABLE 2 Outcomes According to Time From Last HF Hospitalization

	0-3 mo (n = 1,370)	3-12 mo (n = 1,565)	>1 y (n = 1,854)	No Hospitalization (n = 6,218)
Worsening HF or cardiovascular death				
No. of events	428 (31.2)	335 (21.4)	370 (20.0)	998 (15.9)
Event rate per 100 person-years	18.9 (17.2-20.8)	13.2 (11.9-14.7)	11.5 (10.4-12.7)	8.7 (8.2-9.3)
HR[a]	2.22 (1.98-2.49)	1.40 (1.23-1.59)	1.25 (1.10-1.40)	Ref.
HR[b]	1.84 (1.64-2.08)	1.40 (1.24-1.60)	1.07 (0.95-1.21)	Ref.
Worsening HF				
No. of events	300 (21.9)	241 (15.4)	250 (13.5)	595 (9.6)
Event rate per 100 person-years	13.2 (11.8-14.8)	9.5 (8.4-10.8)	7.8 (6.9-8.8)	5.2 (4.8-5.7)
HR[a]	2.54 (2.21-2.92)	1.69 (1.45-1.96)	1.40 (1.21-1.63)	Ref.
HR[b]	2.11 (1.82-2.45)	1.71 (1.47-2.00)	1.15 (0.99-1.34)	Ref.
HF hospitalization				
No. of events	290 (21.2)	230 (14.7)	234 (12.6)	542 (8.7)
Event rate per 100 person-years	12.7 (11.3-14.2)	9.0 (7.9-10.3)	7.2 (6.4-8.2)	4.7 (4.4-5.2)
HR[a]	2.73 (2.36-3.15)	1.74 (1.49-2.03)	1.43 (1.23-1.67)	Ref.
HR[b]	2.27 (1.95-2.64)	1.78 (1.51-2.08)	1.17 (1.00-1.37)	Ref.
Cardiovascular death				
No. of events	228 (16.6)	162 (10.4)	194 (10.5)	548 (8.8)
Event rate per 100 person-years	8.8 (7.8-10.1)	5.9 (5.1-6.9)	5.6 (4.9-6.5)	4.6 (4.2-5.0)
HR[a]	2.04 (1.75-2.38)	1.16 (0.97-1.39)	1.15 (0.97-1.35)	Ref.
HR[b]	1.59 (1.35-1.87)	1.11 (0.93-1.33)	1.05 (0.88-1.24)	Ref.
All-cause death				
No. of events	301 (22.0)	221 (14.1)	278 (15.0)	828 (13.3)
Event rate per 100 person-years	11.7 (10.4-13.0)	8.1 (7.1-9.2)	8.0 (7.1-9.0)	6.9 (6.5-7.4)
HR[a]	1.72 (1.51-1.97)	1.12 (0.96-1.30)	1.12 (0.98-1.29)	Ref.
HR[b]	1.42 (1.23-1.63)	1.09 (0.94-1.28)	1.05 (0.91-1.21)	Ref.
Total HF hospitalizations and cardiovascular death				
No. of events	746	526	536	1,348
RR[a]	2.65 (2.31-3.04)	1.56 (1.35-1.81)	1.30 (1.13-1.49)	Ref.
RR[b]	2.18 (1.87-2.53)	1.53 (1.32-1.77)	1.10 (0.95-1.27)	Ref.

Values are n (%) or HR (95% CI). [a]Models were stratified by type 2 diabetes status and trial and adjusted for treatment assignment. [b]Models were stratified by type 2 diabetes status and trial and adjusted for treatment assignment, age, sex, geographic region, systolic blood pressure, heart rate, body mass index, log of NT-proBNP, eGFR, duration of HF, LVEF, NYHA functional class, a history or myocardial infarction, stroke, and atrial fibrillation.

HF = heart failure; Ref. = Reference; RR = rate ratio; other abbreviations as in Table 1.

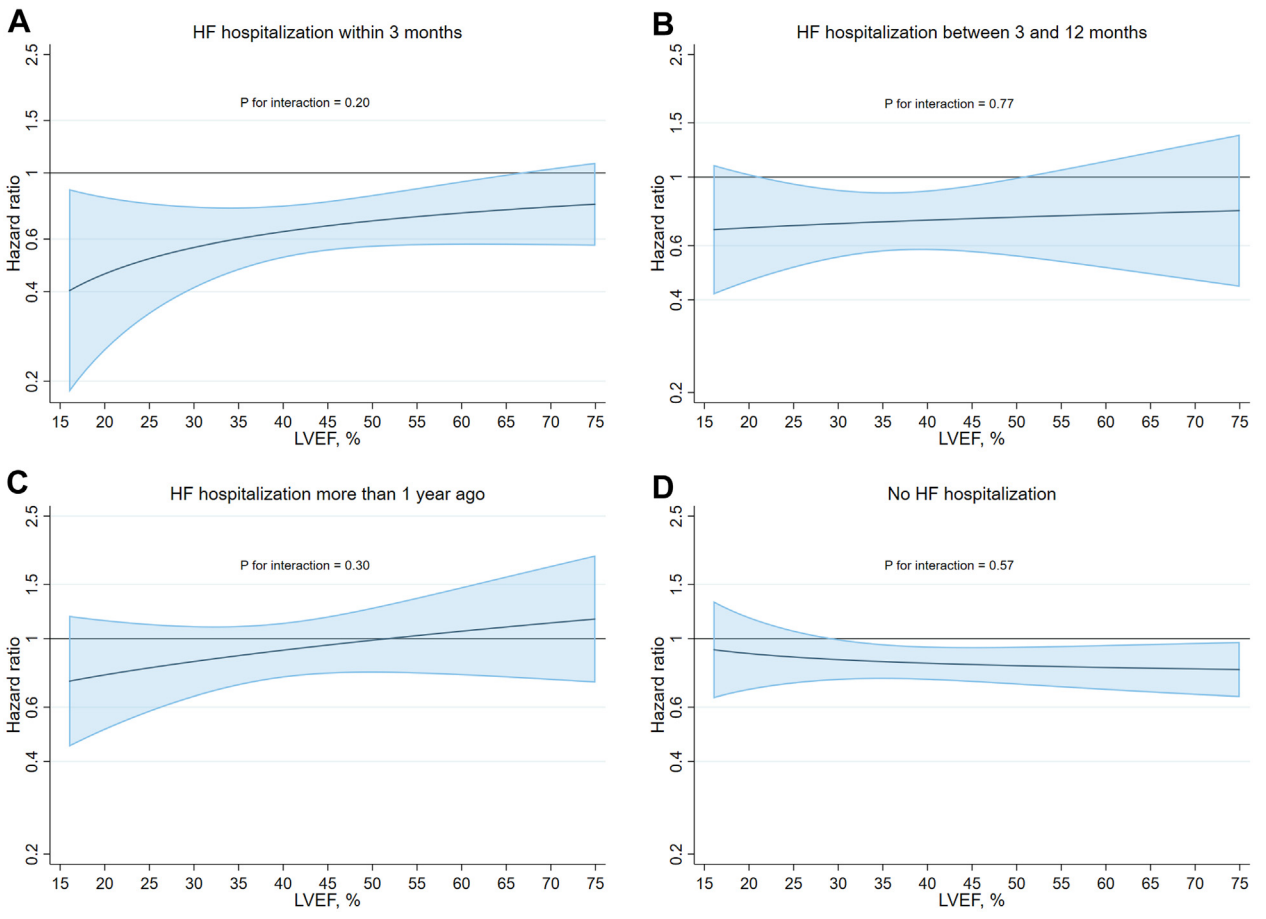
recent HF hospitalization in both patients with LVEF ≤40% and >40% (Supplemental Tables 3 and 4). Although there was a nominally significant interaction between the effect of dapagliflozin on the primary outcome and the recency of HF hospitalization ($P_{interaction} = 0.04$) in patients with LVEF ≤40%, when we formally tested the efficacy of dapagliflozin by the timing of HF hospitalization, it did not differ by LVEF for any of the outcomes (Supplemental Table 5). The proportions of patients who discontinued trial treatment or experienced adverse events according to treatment assignment were similar regardless of the timing of the last HF hospitalization (**Table 4**).

DISCUSSION

In this pooled analysis of DAPA-HF and DELIVER, the risk of adverse clinical outcomes was inversely associated with the timing from prior HF hospitalization, with patients with recent HF hospitalization (ie, in the 3 months before randomization) having the highest risk. Dapagliflozin decreased the relative risk of worsening HF events, cardiovascular death, and all-cause death and improved symptoms across the range of ejection fraction regardless of the timing of the most recent HF hospitalization. Because patients with recent HF hospitalization were at higher absolute risk, their absolute benefit with treatment was greater (**Central Illustration**).

Our finding that the risk of adverse clinical outcomes was inversely associated with the timing of prior HF hospitalization is consistent with previous reports.[8,9,25] Indeed, patients with HF hospitalization within 3 months before randomization had a 2- to 3-fold higher risk of worsening HF events, death, and other adverse outcomes compared with individuals who had never required HF hospitalization. Despite

FIGURE 2 **Effect of Dapagliflozin Compared With Placebo on the Risk of Worsening HF or Cardiovascular Death According to Timing From Prior HF Hospitalization**



This figure shows the effects of dapagliflozin compared with placebo on the risk worsening HF or cardiovascular death according to the timing from prior HF hospitalization. (A) HF hospitalization within 3 months, (B) HF hospitalization between 3 and 12 months, (C) HF hospitalization >1 year ago, and (D) no HF hospitalization. LVEF = left ventricular ejection fraction; other abbreviation as in Figure 1.

comprehensive adjustment for potential confounders, HF hospitalization within 3 months remained a strong independent predictor of all of the outcomes examined. Although HF hospitalization more than 3 months before randomization was also associated with a higher risk of most outcomes, the magnitude of these associations was lower than for more recent HF hospitalization. Perhaps more surprisingly, the magnitude of the elevation in the risk of outcomes related to the recency of HF hospitalization appeared to be greater in patients with HF with mildly reduced or preserved ejection fraction compared to those with HFrEF; this was because event rates were very low in the HF with mildly reduced or preserved ejection fraction group with no prior hospitalization compared to the equivalent patients with HFrEF (the no prior hospitalization group was the "reference group" for comparison with hospitalized patients in both cohorts).

Guidelines for the management of patients with HF recommend the initiation of effective HF therapies during or shortly after hospitalization for HF;[1,2,5] therefore, it is important to establish the safety and efficacy of novel therapies in these vulnerable high-risk patients. Two completed clinical trials specifically examined the effect of SGLT2is in hospitalized or recently discharged patients. The SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial included 1,222 patients with established HF and type 2 diabetes hospitalized for worsening HF, and patients were enrolled during

TABLE 3 Effects of Dapagliflozin Compared With Placebo on Outcomes According to Time From Last HF Hospitalization

	0-3 mo (n = 1,370)		3-12 mo (n = 1,565)		>1 y (n = 1,854)		No Hospitalization (n = 6,218)		
	Placebo (n = 667)	Dapagliflozin (n = 703)	Placebo (n = 801)	Dapagliflozin (n = 764)	Placebo (n = 927)	Dapagliflozin (n = 927)	Placebo (n = 3,108)	Dapagliflozin (n = 3,110)	*P* Value for Interaction
Worsening HF or cardiovascular death									0.09
No. of events	243 (36.4)	185 (26.3)	194 (24.2)	141 (18.5)	193 (20.8)	177 (19.1)	537 (17.3)	451 (14.5)	
Event rate per 100 person-years	23.0 (20.3-26.1)	15.3 (13.3-17.7)	15.5 (13.4-17.8)	11.0 (9.4-13.0)	12.0 (10.4-13.8)	11.0 (9.5-12.7)	9.6 (8.8-10.4)	7.9 (7.2-8.6)	
HR[a]	0.66 (0.55-0.81)		0.73 (0.59-0.90)		0.91 (0.74-1.12)		0.83 (0.73-0.94)		
Worsening HF									0.11
No. of events	175 (26.2)	125 (17.8)	142 (17.7)	99 (13.0)	129 (13.9)	121 (13.1)	335 (10.8)	260 (8.4)	
Event rate per 100 person-years	16.6 (14.3-19.2)	10.3 (8.7-12.3)	11.3 (9.6-13.3)	7.7 (6.4-9.4)	8.0 (6.7-9.5)	7.5 (6.3-9.0)	6.0 (5.4-6.6)	4.5 (4.0-5.1)	
HR[a]	0.63 (0.50-0.79)		0.70 (0.54-0.90)		0.93 (0.72-1.19)		0.76 (0.65-0.90)		
HF hospitalization									0.19
No. of events	170 (25.5)	120 (17.1)	135 (16.9)	95 (12.4)	123 (13.3)	111 (12.0)	308 (9.9)	234 (7.5)	
Event rate per 100 person-years	15.9 (13.7-18.5)	9.8 (8.2-11.8)	10.7 (9.0-12.6)	7.4 (6.1-9.1)	7.6 (6.4-9.1)	6.8 (5.7-8.3)	5.4 (4.9-6.1)	4.1 (3.6-4.6)	
HR[a]	0.62 (0.49-0.78)		0.71 (0.55-0.93)		0.89 (0.69-1.15)		0.75 (0.63-0.89)		
Cardiovascular death									0.63
No. of events	123 (18.4)	105 (14.9)	94 (11.7)	68 (8.9)	101 (10.9)	93 (10.0)	289 (9.3)	259 (8.3)	
Event rate per 100 person-years	9.8 (8.2-11.7)	7.9 (6.5-9.5)	6.8 (5.6-8.3)	5.0 (3.9-6.3)	5.8 (4.8-7.1)	5.4 (4.4-6.6)	4.8 (4.3-5.4)	4.3 (3.8-4.9)	
HR[a]	0.79 (0.61-1.02)		0.75 (0.55-1.02)		0.94 (0.71-1.24)		0.90 (0.76-1.06)		
All-cause death									0.42
No. of events	160 (24.0)	141 (20.1)	123 (15.4)	98 (12.8)	152 (16.4)	126 (13.6)	420 (13.5)	408 (13.1)	
Event rate per 100 person-years	12.8 (10.9-14.9)	10.6 (9.0-12.5)	8.9 (7.5-10.6)	7.2 (5.9-8.8)	8.7 (7.5-10.2)	7.3 (6.2-8.7)	7.0 (6.4-7.7)	6.8 (6.2-7.5)	
HR[a]	0.82 (0.65-1.03)		0.81 (0.62-1.06)		0.84 (0.66-1.07)		0.97 (0.85-1.11)		
Total HF hospitalizations and cardiovascular death									0.19
No. of events	443	303	310	216	287	249	743	605	
RR[a]	0.64 (0.51-0.80)		0.71 (0.55-0.92)		0.87 (0.69-1.10)		0.81 (0.70-0.94)		
KCCQ-TSS									0.88
Change from baseline to 8 mo[b]	6.9 (5.3-8.5)	10.4 (8.9-12.0)	5.2 (3.9-6.5)	6.9 (5.6-8.2)	2.8 (1.7-3.9)	6.0 (4.9-7.2)	4.4 (3.8-5.1)	6.7 (6.0-7.4)	
Placebo-corrected change at 8 mo[b]	3.6 (1.3-5.8)		1.7 (-0.2 to 3.5)		3.3 (1.7-4.8)		2.3 (1.3-3.2)		

Values are n (%) or HR (95% CI). Cardiovascular death includes undetermined deaths. [a]Models were stratified by type 2 diabetes status and trial. [b]Mixed-effects models for repeated measurements adjusted for baseline value, visit (months 4 and 8), randomized treatment, interaction of treatment and visit, and trial.

Abbreviations as in Tables 1 and 2.

admission or within 3 days after hospital discharge. Patients were randomized to the sodium glucose cotransporter 1 inhibitor/SGLT2i sotagliflozin or placebo; sotagliflozin reduced the risk of total worsening HF events and cardiovascular death by 33% (HR: 0.67 [95% CI: 0.52-0.85]; $P < 0.001$).[18] More recently, the EMPULSE (Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized) trial, which enrolled 530 patients with established or new-onset HF, without type 2 diabetes, and hospitalized for HF, demonstrated a greater clinical benefit (defined as a hierarchical composite of all-cause death, worsening HF events, and a change in KCCQ-TSS) at 90 days with empagliflozin compared to placebo.[17] A third trial, DAPA ACT HF-TIMI 68 (Dapagliflozin and Effect on Cardiovascular Event In Acute Heart Failure—Thrombolysis in Myocardial Infarction 68), is currently recruiting and is the largest SGLT2i trial in acute HF. This trial is testing the effects of early inpatient commencement of dapagliflozin compared with placebo on the risk of the composite of worsening HF events or cardiovascular death at 2 months in approximately 2,400 patients with established or new-onset HF, with or without type 2 diabetes, and hospitalized for HF.[26] All 3 trials have included patients with HF regardless of LVEF. In a post hoc analysis of EMPEROR-Pooled (EMPEROR-Reduced [Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction] and EMPEROR-Preserved [Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction] combined),

TABLE 4 Adverse Events of Dapagliflozin Compared With Placebo According to Time From Last Heart Failure Hospitalization

	0-3 mo (n = 1,370)		3-12 mo (n = 1,562)		>1 y (n = 1,852)		No Hospitalization (n = 6205)		
	Placebo (n = 667)	Dapagliflozin (n = 703)	Placebo (n = 800)	Dapagliflozin (n = 762)	Placebo (n = 926)	Dapagliflozin (n = 926)	Placebo (n = 3,102)	Dapagliflozin (n = 3,103)	*P* Value for Interaction
Discontinuation of study drug for any reason, %	17.1	15.8	11.9	13.4	13.2	13.6	11.9	11.4	0.66
Discontinuation of study drug because of an adverse event, %	7.8	5.3	4.3	4.9	6.2	6.5	5.0	5.2	0.25
Volume depletion,[a] %	2.1	3.6	4.0	5.6	4.0	5.6	3.7	3.4	0.11
Renal adverse event,[b] %	6.0	5.0	5.5	5.9	5.5	5.0	4.1	3.6	0.83
Amputation, %	0.7	0.6	0.1	0.4	0.8	0.3	0.8	0.7	0.45
Major hypoglycemia, %	0.1	0.3	0.3	0.3	0.3	0.4	0.2	0.1	NA
Diabetic ketoacidosis, %	0.0	0.3	0.0	0.3	0.0	0.1	0.0	0.0	NA

A total of 18 randomized patients were excluded from the safety analysis because these were performed in patients who had undergone randomization and received at least 1 dose of dapagliflozin or placebo. [a]Any serious adverse event or adverse event that led to the discontinuation of dapagliflozin or placebo that was suggestive of volume depletion in DELIVER. [b]Any renal serious adverse event or adverse event that led to the discontinuation of dapagliflozin or placebo in DELIVER.

NA = not applicable.

empagliflozin significantly reduced the risk of HF hospitalization or cardiovascular death in patients who were hospitalized for HF within 3 months before randomization, although only 275 participants had experienced hospitalization within 30 days before randomization, and none were randomized during hospitalization.[27]

In the present patient-level pooled meta-analysis of 11,007 patients with HF enrolled in DAPA-HF and DELIVER, more than 650 were randomized during hospitalization for HF or within 30 days after discharge. Our data complement and extend the previous findings described earlier by demonstrating a substantial clinical benefit of treatment with dapagliflozin in individuals recently hospitalized for HF. Specifically, dapagliflozin compared to placebo reduced the risk of the primary composite outcome of worsening HF or cardiovascular death, its components, first and total HF hospitalizations, and all-cause death in these high-risk patients. The relative risk reduction with dapagliflozin appeared greater in the most recently hospitalized patients with a *P* value for interaction for the primary outcome close to statistical significance (ie, 0.09). However, whether there is a gradient in relative risk reduction or not, according to the recency of hospital admission, all groups obtained benefit from dapagliflozin, including patients without prior HF hospitalization. The present study also complements and extends prior reports from DAPA-HF[9] and DELIVER[10] by using a more detailed breakdown of the timing of the most recent hospitalization and by examining the treatment effect according to the recency of HF hospitalization across the entire range of ejection fractions. Indeed, we found that the beneficial effect of dapagliflozin was entirely consistent across the range of LVEF irrespective of the timing of the most recent HF hospitalization.

Because patients with recent HF hospitalization were at higher absolute risk, their absolute benefit was greater, which was reflected in a smaller NNT for the primary outcome (13, 20, 23, and 28 in patients hospitalized for HF within 3 months, between 3 and 12 months, more than 1 year, and never before randomization, respectively), even when the NNT was calculated by applying the overall relative risk reduction to the placebo group event rate in each hospitalization subgroup.

Importantly, dapagliflozin improved the mean KCCQ-TSS score after 8 months of treatment irrespective of the timing of the most recent HF hospitalization. This finding is all the more important in patients with recent HF hospitalization who have a greater symptom burden and worse physical function and health-related quality of life than those without, as confirmed by the NYHA functional class and KCCQ findings in the present analysis.

Reassuringly, treatment with dapagliflozin was safe and well tolerated, and study drug discontinuation and serious adverse events were not more frequently reported in the dapagliflozin group than in the placebo group regardless of the timing of the most recent HF hospitalization. Taken together, these findings further emphasize the importance of initiating SGLT2is and other disease-modifying, lifesaving therapies during, or shortly after, hospitalization.

STUDY LIMITATIONS. The findings of this study should be viewed in the context of several limitations. The analysis was not prespecified, and the assessment of clinical outcomes according to the recency of HF hospitalization was performed post hoc. Therefore, the findings should be considered

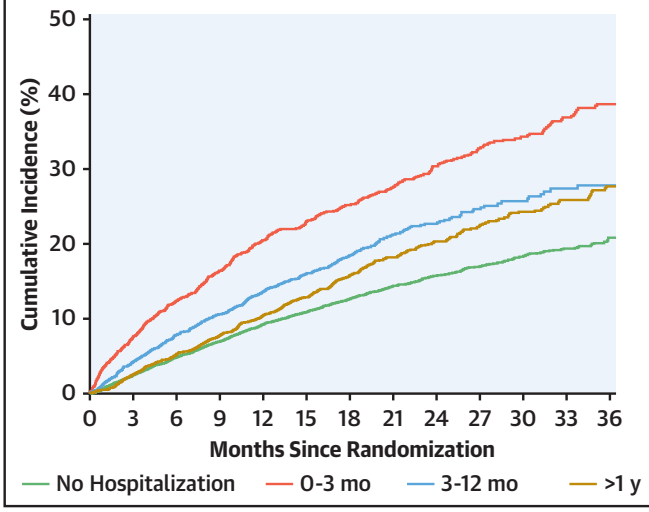
CENTRAL ILLUSTRATION Dapagliflozin, HF, and Timing From Prior HF Hospitalization

11,007 patients in DAPA-HF & DELIVER
HF hospitalization within 3 mo: 12.4%; HF hospitalization between 3 and 12 mo: 14.2%;
HF hospitalization more than 1 y ago: 16.8%; no HF hospitalization: 56.5%

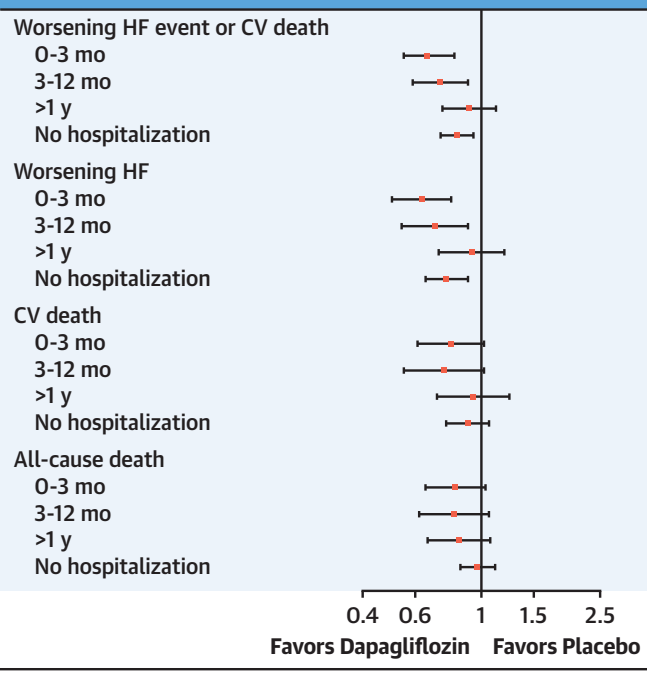
Characteristics of Patients With a More Recent HF Hospitalization

- ↑ Age
- ↑ Women
- ↓ Smokers
- ↑ BMI
- ↓ eGFR
- ↑ Atrial fibrillation
- ↑ Hypertension
- ↑ Type 2 diabetes
- ↓ MI/coronary revascularization
- ↑ NT-proBNP
- ↑ LVEF
- ↑ Duration of HF
- ↓ Health-related quality of life

Association Between Recency of HF Hospitalization and Worsening HF Event or CV Death



Effects of Dapagliflozin Compared With Placebo on Outcomes According to Recency of HF Hospitalization



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BMI = body mass index; CV = cardiovascular; DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER = Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

hypothesis generating. Patients enrolled in clinical trials are selected according to specific inclusion and exclusion criteria, and our results may not be generalizable to all patients with HF in the general population. Only 90 patients were randomized during hospitalization in DELIVER and none in DAPA-HF, and we did not have a sufficient sample size to analyze this population separately. Finally, data on the timing of the most recent HF hospitalization before randomization were categorized. Consequently, a more granular assessment of the clinical risk and the treatment effect as a function of proximity to prior HF hospitalization was not possible.

CONCLUSIONS

In patients with HF, recent HF hospitalization was a strong independent predictor of a higher risk of worsening HF events and death. The beneficial effects of dapagliflozin on the relative risk of clinical outcomes were consistent across the range of ejection fractions regardless of the timing of the most recent HF hospitalization, with a greater absolute benefit in patients with recent HF hospitalization because of their higher absolute risk. These findings further emphasize the importance of initiating SGLT2is and other disease-modifying, lifesaving therapies during, or shortly after, hospitalization.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a secondary analysis of the DAPA-HF and DELIVER trials, which included 11,007 patients with HF, the beneficial effects of dapagliflozin compared with placebo on clinical events and symptoms were consistent across the range of ejection fractions regardless of the timing of the most recent HF hospitalization, with a greater absolute benefit in patients with a recent HF hospitalization because of their higher absolute risk.

TRANSLATIONAL OUTLOOK: These findings provide further evidence for dapagliflozin as a new treatment option for patients with HF across the range of ejection fractions.

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KEY WORDS clinical trial, heart failure, outcomes

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