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Patient Characteristics, Outcomes, and Effects of Dapagliflozin According to the Duration of Heart Failure: A Prespecified Analysis of the DELIVER Trial

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BACKGROUND: How patient characteristics and outcomes vary according to the duration of heart failure (HF) is unknown in individuals with mildly reduced or preserved ejection fraction. We compared these, and the efficacy and safety of dapagliflozin, according to the time from diagnosis of HF in a prespecified analysis of the DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure).

METHODS: HF duration was categorized as ≤6 months, >6 to 12 months, >1 to 2 years, >2 to 5 years, or >5 years. The primary outcome was the composite of worsening HF or cardiovascular death. The effect of treatment was examined by HF duration category.

RESULTS: The number of patients in each category was as follows: 1160 (≤6 months), 842 (>6 to 12 months), 995 (>1 to 2 years), 1569 (>2 to 5 years), and 1692 (>5 years). Patients with longer-duration HF were older and had more comorbidities with worse symptoms. The rate of the primary outcome (per 100 person-years) increased with HF duration: ≤6 months, 7.3 (95% CI, 6.3 to 8.4); >6 to 12 months, 7.1 (6.0 to 8.5); >1 to 2 years, 8.4 (7.2 to 9.7); >2 to 5 years, 8.9 (7.9 to 9.9); and >5 years, 10.6 (9.5 to 11.7). Similar trends were seen for other outcomes. The benefit of dapagliflozin was consistent across HF duration category: the hazard ratio for the primary outcome in the ≤6-month group was 0.67 (95% CI, 0.50 to 0.91); >6 to 12 months, 0.78 (0.55 to 1.12); >1 to 2 years, 0.81 (0.60 to 1.09); >2 to 5 years, 0.97 (0.77 to 1.22); and >5 years, 0.78 (0.64 to 0.96; $P_{interaction}$=0.41). The absolute benefit was greatest in longest-duration HF; the number needed to treat for HF >5 years was 24 versus 32 for ≤6 months.

CONCLUSIONS: Patients with longer-duration HF were older, had more comorbidities and symptoms, and had higher rates of worsening HF and death. The benefits of dapagliflozin were consistent across HF duration. Even patients with long-standing HF and generally mild symptoms are not stable, and it is not too late for such patients to benefit from a sodium–glucose cotransporter 2 inhibitor.

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Key Words: clinical trial ■ heart failure ■ therapeutics

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Clinical Perspective

What Is New?

- Whether the efficacy and safety of sodium–glucose cotransporter 2 inhibitor therapy are maintained with increasing duration of heart failure with mildly reduced ejection fraction or heart failure with preserved ejection fraction is unknown. In a prespecified analysis of DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure), longer heart failure duration was associated with worse clinical outcomes.
- The benefit of dapagliflozin, compared with placebo, on clinical outcomes and health status was consistent regardless of the duration of heart failure.
- Adverse events were not more common in patients randomized to receive dapagliflozin, compared with placebo, irrespective of the duration of heart failure.

What Are the Clinical Implications?

- The risk/benefit balance associated with the duration of heart failure in patients with heart failure and mildly reduced or preserved ejection fraction was favorable for dapagliflozin.
- Even patients with long-standing heart failure and generally mild symptoms are not "stable," and it is not too late for such patients to benefit from a sodium–glucose cotransporter 2 inhibitor.

Nonstandard Abbreviations and Acronyms

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
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire Total Symptom Score
LVEF	left ventricular ejection fraction
NNT	number needed to treat
NT-proBNP	N-terminal pro–B-type natriuretic peptide
NYHA	New York Heart Association
PARADIGM-HF	Prospective Comparison of ARNI With an ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure
RR	rate ratio
SGLT2	sodium–glucose cotransporter 2
SHIFT	Systolic Heart Failure Treatment With the If Inhibitor Ivabradine

As is the case for heart failure (HF) with reduced ejection fraction (HFrEF), there are now 2 large randomized morbidity–mortality trials with sodium–glucose cotransporter 2 (SGLT2) inhibitors demonstrating substantial and consistent reductions in the composite outcome of hospitalization for worsening HF or death from cardiovascular causes in patients with HF with mildly reduced ejection fraction (HFmrEF) and patients with HF with preserved ejection fraction (HFpEF).[1–5] The evidence for the benefit of SGLT2 inhibitors is stronger than for any other treatment in these patients.

It is important to understand how the effects of any new treatment vary by the duration of HF. On the one hand, physicians may think that a patient who has longer-standing HF represents a "stable" survivor, for whom a new treatment is unnecessary.[6–8] On the other hand, the view has been expressed that patients with long-standing HF may have more advanced disease, and there may come a point when they no longer respond to or tolerate the addition of new therapies, particularly because of hypotension, kidney dysfunction, or electrolyte abnormality.[6–8] However, few studies have described such analyses, and, to date, in ambulatory populations, all have been performed in HFrEF trials.[6–8] Therefore, we investigated these questions further in a prespecified analysis of the DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure), in which dapagliflozin was compared with placebo in 6263 patients with HFmrEF or HFpEF.[4,9,10] We compared patient demographics, HF characteristics, comorbidities, and background therapy according to the duration of HF, as well as the key trial outcomes related to time from diagnosis of HF. We also analyzed the efficacy and safety of dapagliflozin, compared with a placebo, according to the duration of HF.

METHODS

DELIVER is a prospective, double-blind, randomized, controlled trial in patients with HFmrEF or HFpEF that compared the efficacy and safety of dapagliflozin (10 mg once daily) with a matching placebo added to standard care. The design, baseline characteristics, and primary results of DELIVER have been published.[4,9,10] The trial protocol was approved by the ethics committee at all participating centers, and all patients provided

written informed consent. The corresponding author had full access to all the trial data and takes responsibility for its integrity and the data analysis.

Data underlying the findings described in this article can be obtained following the AstraZeneca data sharing policy, described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Study Patients

Key inclusion criteria were ≥40 years of age, HF diagnosis ≥6 weeks, with at least intermittent use of diuretic treatment, New York Heart Association (NYHA) functional class II through IV, a left ventricular ejection fraction (LVEF) >40%, evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy), and an NT-proBNP (N-terminal pro–B-type natriuretic peptide) concentration ≥300 pg/mL (≥600 pg/mL if atrial fibrillation or flutter was present on ECG at enrollment). Key exclusion criteria included type 1 diabetes, estimated glomerular filtration rate (eGFR) <25 mL/min per 1.73 m^2, or systolic blood pressure <95 mm Hg. A complete list of inclusion and exclusion criteria are provided in the design article.[9]

Duration of HF (Time From Diagnosis)

Time from diagnosis of HF was collected in the following categories: ≤3 months, >3 to 6 months, >6 to 12 months, >1 to 2 years, >2 to 5 years, and >5 years. Five patients whose information on time from diagnosis of HF was missing were excluded from the analysis. In the main analysis, we combined the first 2 categories to form a group with a duration of HF ≤6 months to ensure adequate numbers for analysis in each category. However, all predefined categories were used in the threshold analysis (see below).

Trial Outcomes

The primary outcome in DELIVER was the composite of worsening HF (HF hospitalization or urgent HF visit) or cardiovascular death, analyzed as the time to first event. The secondary outcomes in the trial were a worsening HF event, cardiovascular death, all-cause death, the composite of total (first and repeat) worsening HF events and cardiovascular deaths, and change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS).

Prespecified safety analyses included serious adverse events, adverse events leading to discontinuation or interruption of trial treatment, and selected adverse events, including amputation, diabetic ketoacidosis, major hypoglycemia, and serious adverse events and adverse events leading to discontinuation of randomized treatment related to volume depletion or renal dysfunction. Fournier gangrene was not reported, as there were no cases in either treatment group.

Statistical Analyses

Baseline characteristics were summarized as frequencies with percentages, means with standard deviation, or medians with interquartile ranges. Differences in baseline characteristics were tested using the Cochran-Armitage trend test for binary variables, the Cochran-Mantel-Haenszel test for categorical variables, and the Jonckheere Terpstra test for continuous variables, respectively.

Regardless of treatment assignment, time-to-event data were evaluated using the Kaplan-Meier estimator and Cox proportional hazards models, adjusted for treatment assignment, and hazard ratios (HRs) with 95% CIs were reported for the duration of HF (with HF ≤6 months as the reference). Total (first and recurrent) events were evaluated with semiparametric proportional-rates models, adjusted for treatment assignment, and rate ratios (RRs) with 95% CIs were reported. In addition, HRs and RRs were adjusted for treatment assignment, age, sex, race, region, heart rate, systolic blood pressure, creatinine, previous LVEF ≤40%, history of HF hospitalization, NYHA class, LVEF, type 2 diabetes, atrial fibrillation, hypertension, myocardial infarction, coronary artery bypass graft, stroke, and NT-proBNP (log-transformed).

To compare the effects of dapagliflozin with placebo, times to first event were evaluated with Cox proportional hazards models, and HRs with 95% CIs were reported for the duration of HF. Total (first and recurrent) HF worsening events and cardiovascular deaths were evaluated with semiparametric proportional-rates models, and RRs with 95% CIs were reported. These models were stratified according to diabetes status, as prespecified.[11] The presence of an interaction between the duration of HF and the effect of treatment on the occurrence of each outcome was examined using a likelihood ratio test. The difference between treatment groups in the change in KCCQ-TSS from baseline to 8 months was analyzed using mixed-effect models for repeated measurements, adjusted for baseline value, follow-up visits (months 1, 4, and 8), treatment assignment, and interaction of treatment and visit. The least-squares mean differences with 95% CI between treatment groups were reported. Numbers needed to treat (NNTs) were calculated by applying the overall HR to the event rates in the placebo group of each duration category. We also performed a post hoc threshold analysis in which the treatment effect of dapagliflozin, compared with placebo, on the primary composite outcome was calculated for each threshold value for HF duration (>0, >3, and >6 months, and >1, >2, >5 years) using a Cox model adjusted for prognostic variables described previously.[6–8]

All analyses were conducted using STATA version 17.0 (College Station, TX).

RESULTS

Among the 6258 patients in DELIVER with data on the duration of HF, the number in each duration category was 568 (9.1%) ≤3 months, 592 (9.5%) >3 to 6 months, 1160 (18.5%) ≤6 months, 842 (13.5%) >6 to 12 months, 995 (15.9%) >1 to 2 years, 1569 (25.1%) >2 to 5 years, and 1692 (27.0%) >5 years.

Patient Characteristics

Many baseline characteristics, including demographics, comorbidities, and functional status, differed according to the duration of HF (Table 1). Patients with longer-duration HF were slightly older (mean, 72.7 years in the HF >5-year group versus 71.0 years in the ≤6-month group) and had more comorbidities, with higher prevalence of

Table 1. Baseline Characteristics According to Duration of Heart Failure

Characteristics	HF ≤6 months (n=1160)	HF >6 to 12 months (n=842)	HF >1 to 2 years (n=995)	HF >2 to 5 years (n=1569)	HF >5 years (n=1692)	P_{trend}
Age, y	71.0±10.3	71.3±9.4	70.8±9.8	71.8±9.5	72.7±8.9	<0.001
Female sex	502 (43.3)	362 (43.0)	454 (45.6)	716 (45.6)	712 (42.1)	0.84
Race						<0.001
White	776 (66.9)	607 (72.1)	723 (72.7)	1136 (72.4)	1197 (70.7)	
Asian	302 (26.0)	174 (20.7)	171 (17.2)	287 (18.3)	335 (19.8)	
Black or African American	20 (1.7)	11 (1.3)	29 (2.9)	46 (2.9)	53 (3.1)	
Other	62 (5.3)	50 (5.9)	72 (7.2)	100 (6.4)	107 (6.3)	
Geographic region						<0.001
Europe or Saudi Arabia	568 (49.0)	418 (49.6)	472 (47.4)	779 (49.6)	768 (45.4)	
Asia	290 (25.0)	169 (20.1)	164 (16.5)	276 (17.6)	322 (19.0)	
Latin America	147 (12.7)	177 (21.0)	208 (20.9)	294 (18.7)	355 (21.0)	
North America	155 (13.4)	78 (9.3)	151 (15.2)	220 (14.0)	247 (14.6)	
Body mass index, kg/m^2	29.3±6.0	29.4±6.0	30.2±6.2	30.1±6.1	30.0±6.1	<0.001
Body mass index group, kg/m^2						0.005
<18.5 (Underweight)	10 (0.9)	8 (1.0)	7 (0.7)	13 (0.8)	16 (0.9)	
18.5 to 24.9 (Normal weight)	273 (23.5)	201 (23.9)	196 (19.7)	328 (20.9)	343 (20.3)	
25.0 to 29.9 (Overweight)	431 (37.2)	287 (34.1)	314 (31.6)	491 (31.4)	547 (32.4)	
30.0 to 34.9 (class I obesity)	254 (21.9)	200 (23.8)	276 (27.7)	405 (25.9)	439 (26.0)	
35.0 to 39.9 (class II obesity)	117 (10.1)	93 (11.0)	129 (13.0)	228 (14.6)	231 (13.7)	
≥40 (class III obesity)	75 (6.5)	53 (6.3)	73 (7.3)	101 (6.4)	113 (6.7)	
Vital signs						
Pulse, beats/min	72.2±12.7	70.8±11.1	71.4±12.0	71.4±11.4	71.5±11.5	0.47
SBP, mm Hg	128.1±15.6	128.6±15.1	127.9±15.4	128.4±15.2	128.2±15.4	0.97
DBP, mm Hg	74.3±10.6	74.3±9.9	74.5±10.4	73.9±10.4	73.2±10.4	0.002
Laboratory values						
HbA1c, %	6.1 (5.7–6.9)	6.1 (5.7–6.8)	6.1 (5.7–7.0)	6.2 (5.8–7.0)	6.2 (5.7–7.0)	0.048
Creatinine, μmol/L	101.0±30.1	100.4±29.3	102.3±32.5	103.0±30.9	104.2±31.9	0.002
eGFR, mL/min per 1.73 m^2	62.3±19.5	62.3±19.0	61.7±20.1	60.3±18.7	59.8±18.7	<0.001
eGFR <60, mL/min per 1.73 m^2	556 (47.9)	395 (47.0)	485 (48.7)	781 (49.8)	853 (50.4)	0.081
NT-proBNP, ng/L	1005.0 (623.0–1710.0)	1026.5 (601.0–1797.0)	980.0 (601.0–1709.0)	1032.0 (637.0–1802.0)	1011.5 (633.0–1747.0)	0.35
NT-proBNP if baseline ECG in AF or flutter, ng/L	1339.0 (938.0–2119.0)	1454.0 (1017.0–2400.0)	1474.0 (970.0–2192.0)	1431.5 (974.0–2311.0)	1371.0 (933.0–2149.0)	0.63
NT-proBNP if baseline ECG not in AF or flutter, ng/L	734.0 (472.5–1332.5)	724.0 (477.0–1456.0)	685.5 (461.5–1171.0)	721.5 (456.0–1287.0)	700.0 (469.0–1239.0)	0.24
Heart failure characteristics						
Previous LVEF ≤40%	131 (11.3)	114 (13.5)	149 (15.0)	350 (22.3)	407 (24.1)	<0.001
Previous HF hospitalization	478 (41.2)	310 (36.8)	364 (36.6)	658 (41.9)	725 (42.8)	0.040
Recent HF hospitalization*	171 (14.7)	71 (8.4)	99 (9.9)	166 (10.6)	146 (8.6)	<0.001
NYHA functional class						<0.001
II	913 (78.7)	657 (78.0)	750 (75.4)	1151 (73.4)	1237 (73.1)	
III or IV	247 (21.3)	185 (22.0)	245 (24.6)	417 (26.6)	455 (26.9)	
KCCQ-TSS	75.0 (57.3–89.6)	75.0 (58.3–89.6)	72.9 (54.2–87.5)	71.9 (54.2–87.5)	70.8 (54.2–87.5)	<0.001
Baseline LVEF, %	55.0 (48.0–60.0)	53.5 (47.0–60.0)	55.0 (47.0–60.0)	54.0 (46.0–60.0)	53.0 (46.0–60.0)	0.001
Clinical history						
Type 2 diabetes	502 (43.3)	344 (40.9)	443 (44.5)	712 (45.4)	805 (47.6)	0.003

(*Continued*)

Table 1. Continued

Characteristics	HF ≤6 months (n=1160)	HF >6 to 12 months (n=842)	HF >1 to 2 years (n=995)	HF >2 to 5 years (n=1569)	HF >5 years (n=1692)	P_{trend}
AF	603 (52.0)	431 (51.2)	537 (54.0)	894 (57.0)	999 (59.0)	<0.001
Hypertension	1010 (87.1)	742 (88.1)	883 (88.7)	1418 (90.4)	1497 (88.5)	0.092
Myocardial infarction	273 (23.5)	204 (24.2)	241 (24.2)	412 (26.3)	507 (30.0)	<0.001
CABG	103 (8.9)	62 (7.4)	110 (11.1)	205 (13.1)	297 (17.6)	<0.001
Stroke	96 (8.3)	77 (9.1)	86 (8.6)	145 (9.2)	193 (11.4)	0.007
COPD	109 (9.4)	72 (8.6)	99 (9.9)	190 (12.1)	222 (13.1)	<0.001
Treatment						
Beta-blocker	925 (79.7)	696 (82.7)	828 (83.2)	1320 (84.1)	1404 (83.0)	0.020
Calcium channel blocker	367 (31.6)	241 (28.6)	291 (29.2)	471 (30.0)	545 (32.2)	0.48
ACEi, ARB, or ARNI	853 (73.5)	664 (78.9)	767 (77.1)	1247 (79.5)	1297 (76.7)	0.065
MRA	463 (39.9)	401 (47.6)	421 (42.3)	653 (41.6)	727 (43.0)	0.76
Loop diuretics	868 (74.8)	610 (72.4)	763 (76.7)	1220 (77.8)	1346 (79.6)	<0.001
Other (nonloop) diuretics	271 (23.4)	193 (22.9)	208 (20.9)	325 (20.7)	345 (20.4)	0.028
ICD/CRT-D	12 (1.0)	13 (1.5)	22 (2.2)	47 (3.0)	74 (4.4)	<0.001
CRT-P/CRT-D	8 (0.7)	6 (0.7)	3 (0.3)	25 (1.6)	58 (3.4)	<0.001

Data are presented as mean±SD or median (interquartile range) for continuous variables and n (%) for categorical variables. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; ICD, implantable cardioverter defibrillator; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire–Total Symptom Score; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; and SBP, systolic blood pressure.

*Randomized during heart failure (HF) hospitalization or within 30 days of discharge.

type 2 diabetes, atrial fibrillation, myocardial infarction, stroke, and chronic obstructive pulmonary disease, and had a slightly higher body mass index.

Regarding HF characteristics, more patients (14.7%) with a recent diagnosis of HF (≤6 months) were enrolled during or shortly after HF hospitalization compared with the patients with longest duration of HF (8.6%). Despite this, patients with shorter-duration HF had a better NYHA class profile and higher (better) KCCQ-TSS score. A greater proportion of patients with longer-duration HF had a previous LVEF ≤40%. LVEF and eGFR tended to be lower in patients with longer-duration HF but systolic blood pressure did not differ by the duration of HF.

Within subgroups defined by HF duration, baseline characteristics among those assigned to placebo versus dapagliflozin were well balanced (Table S1).

Treatments at Baseline

Loop diuretic, beta-blocker, implantable cardioverter defibrillator, and cardiac resynchronization therapy were used slightly but significantly more frequently among patients with longer-standing HF.

Primary and Secondary Outcomes According to the Duration of HF

The rate (per 100 patient-years) of the primary composite outcome of worsening HF or cardiovascular death increased with the duration of HF: ≤6 months, 7.3 (95% CI, 6.3 to 8.4); >6 to 12 months, 7.1 (6.0 to 8.5); >1 to 2 years, 8.4 (7.2 to 9.7); >2 to 5 years, 8.9 (7.9 to 9.9); and >5 years, 10.6 (9.5 to 11.7). The HRs adjusted for prognostic variables, using the HF ≤6-month group as the reference, were: 1.04 (0.82 to 1.31); 1.21 (0.98 to 1.49); 1.20 (0.99 to 1.45); and 1.38 (1.15 to 1.67), respectively, for HF >6 to 12 months, >1 to 2 years, >2 to 5 years, and >5-year duration (Table 2 and Figure 1). Similar trends were seen for the components of the composite outcome and all-cause mortality.

Effects of Dapagliflozin on Outcomes According to Duration of HF

The benefit of dapagliflozin was consistent across the spectrum of HF duration for all outcomes examined (Table 3 and Figure 2). The overall HR for the primary composite outcome was 0.82 (95% CI, 0.73 to 0.92); in the ≤6-month group, it was 0.67 (0.50 to 0.91); in the >6 to 12–month group, 0.78 (0.55 to 1.12); in the >1 to 2–year group, 0.81 (0.60 to 1.09); in the >2 to 5–year group, 0.97 (0.77 to 1.22); and in the >5-year group, 0.78 (0.64 to 0.96; $P_{interaction}$=0.41). The effects of dapagliflozin on the primary outcome, according to the duration of HF, in men versus women, and in patients with and without type 2 diabetes, are shown in Table S2.

Because the absolute risk was highest in patients with the longest-duration HF, the absolute benefit

Table 2. Outcomes According to Duration of Heart Failure Category

Outcomes	HF ≤6 months (n=1160)	HF >6 to 12 months (n=842)	HF >1 to 2 years (n=995)	HF >2 to 5 years (n=1569)	HF >5 years (n=1692)
Primary outcome					
N (%)	175 (15.1)	123 (14.6)	172 (17.3)	290 (18.5)	362 (21.4)
Rate (95% CI)	7.3 (6.3–8.4)	7.1 (6.0–8.5)	8.4 (7.2–9.7)	8.9 (7.9–9.9)	10.6 (9.5–11.7)
Unadjusted HR (95% CI)*	REF	0.98 (0.78–1.23)	1.16 (0.94–1.43)	1.22 (1.01–1.47)	1.46 (1.22–1.74)
Adjusted HR (95% CI)†	REF	1.04 (0.82–1.31)	1.21 (0.98–1.49)	1.20 (0.99–1.45)	1.38 (1.15–1.67)
Worsening HF event					
N (%)	127 (11.0)	95 (11.3)	137 (13.8)	206 (13.1)	258 (15.3)
Rate (95% CI)	5.3 (4.4–6.3)	5.5 (4.5–6.7)	6.7 (5.6–7.9)	6.3 (5.5–7.2)	7.5 (6.7–8.5)
Unadjusted HR (95% CI)*	REF	1.04 (0.80–1.36)	1.27 (1.00–1.62)	1.19 (0.96–1.49)	1.43 (1.16–1.77)
Additional adjustment (95% CI)†	REF	1.14 (0.87–1.49)	1.34 (1.05–1.71)	1.17 (0.93–1.46)	1.35 (1.09–1.68)
Cardiovascular death					
N (%)	77 (6.6)	53 (6.3)	66 (6.6)	128 (8.2)	168 (9.9)
Rate (95% CI)	3.0 (2.4–3.8)	2.9 (2.2–3.8)	3.0 (2.3–3.8)	3.6 (3.0–4.3)	4.5 (3.9–5.3)
Unadjusted HR (95% CI)*	REF	0.95 (0.67–1.35)	0.99 (0.71–1.37)	1.19 (0.90–1.58)	1.50 (1.15–1.96)
Adjusted HR (95% CI)†	REF	0.94 (0.66–1.34)	1.02 (0.73–1.42)	1.15 (0.87–1.54)	1.43 (1.08–1.88)
All-cause death					
N (%)	161 (13.9)	120 (14.3)	149 (15.0)	266 (17.0)	326 (19.3)
Rate (95% CI)	6.3 (5.4–7.4)	6.5 (5.4–7.8)	6.7 (5.7–7.9)	7.5 (6.7–8.5)	8.8 (7.9–9.8)
Unadjusted HR (95% CI)*	REF	1.03 (0.81–1.31)	1.07 (0.85–1.33)	1.18 (0.97–1.43)	1.39 (1.15–1.68)
Adjusted HR (95% CI)†	REF	1.01 (0.79–1.28)	1.06 (0.85–1.33)	1.11 (0.91–1.36)	1.26 (1.03–1.52)
Total number of worsening HF events and cardiovascular deaths					
N (%)	271	215	317	472	597
Rate (95% CI)	10.7 (9.0–12.8)	11.7 (9.6–14.5)	14.4 (12.0–17.4)	13.4 (11.7–15.4)	16.1 (14.2–18.4)
Unadjusted HR (95% CI)*	REF	1.10 (0.84–1.43)	1.35 (1.05–1.74)	1.25 (1.00–1.57)	1.52 (1.22–1.89)
Adjusted HR (95% CI)†	REF	1.18 (0.90–1.54)	1.39 (1.08–1.79)	1.21 (0.96–1.52)	1.41 (1.12–1.77)

Event rates (per 100 patient-years) and risk of study end points according to the duration of heart failure (HF; ≤6 months as reference). Rates are given per 100 patient-years. HR indicates hazard ratio.

*Baseline model adjusted for randomized treatment.

†Adjusted for randomized treatment, age, sex, race, region, heart rate, systolic blood pressure, creatinine, previous left ventricular ejection fraction ≤40%, history of heart failure hospitalization, New York Heart Association class, left ventricular ejection fraction, type 2 diabetes, atrial fibrillation, hypertension, myocardial infarction, coronary artery bypass graft, stroke, and NT-proBNP (N-terminal pro–B-type natriuretic peptide; log-transformed).

was also greatest in those patients, assuming a constant treatment effect size across HF duration categories. On this basis, for the primary outcome, the NNT over the median duration of the trial (2.3 years) was 24 for patients with HF >5 years, compared with an NNT of 32 for patients with HF of ≤6-month duration.

The improvement in KCCQ-TSS between baseline and month 8 with dapagliflozin, compared with placebo, tended to be smaller in patients with longer-standing HF, although there was no statistically significant interaction between the duration of HF and the effect of dapagliflozin.

Threshold Analysis

The threshold analysis showed a consistent benefit of dapagliflozin, compared with placebo, on the primary end point, regardless of the threshold value for HF duration (Figure 3). The adjusted HR for the primary end point was 0.81 (95% CI, 0.72 to 0.92) for patients with HF duration >3 months, 0.82 (0.72 to 0.93) for HF duration >6 months, 0.83 (0.73 to 0.96) for HF duration >1 year, 0.85 (0.73 to 0.99) for HF duration >2 years, and 0.75 (0.61 to 0.93) for HF duration >5 years.

Tolerability and Safety of Dapagliflozin Versus Placebo

Irrespective of treatment assignment, rates of adverse events did not vary significantly across subgroups defined by HF duration. The frequency of the prespecified adverse events and discontinuation of randomized therapy associated with dapagliflozin versus placebo generally did not differ according to the duration of HF, other than discontinuation of randomized therapy

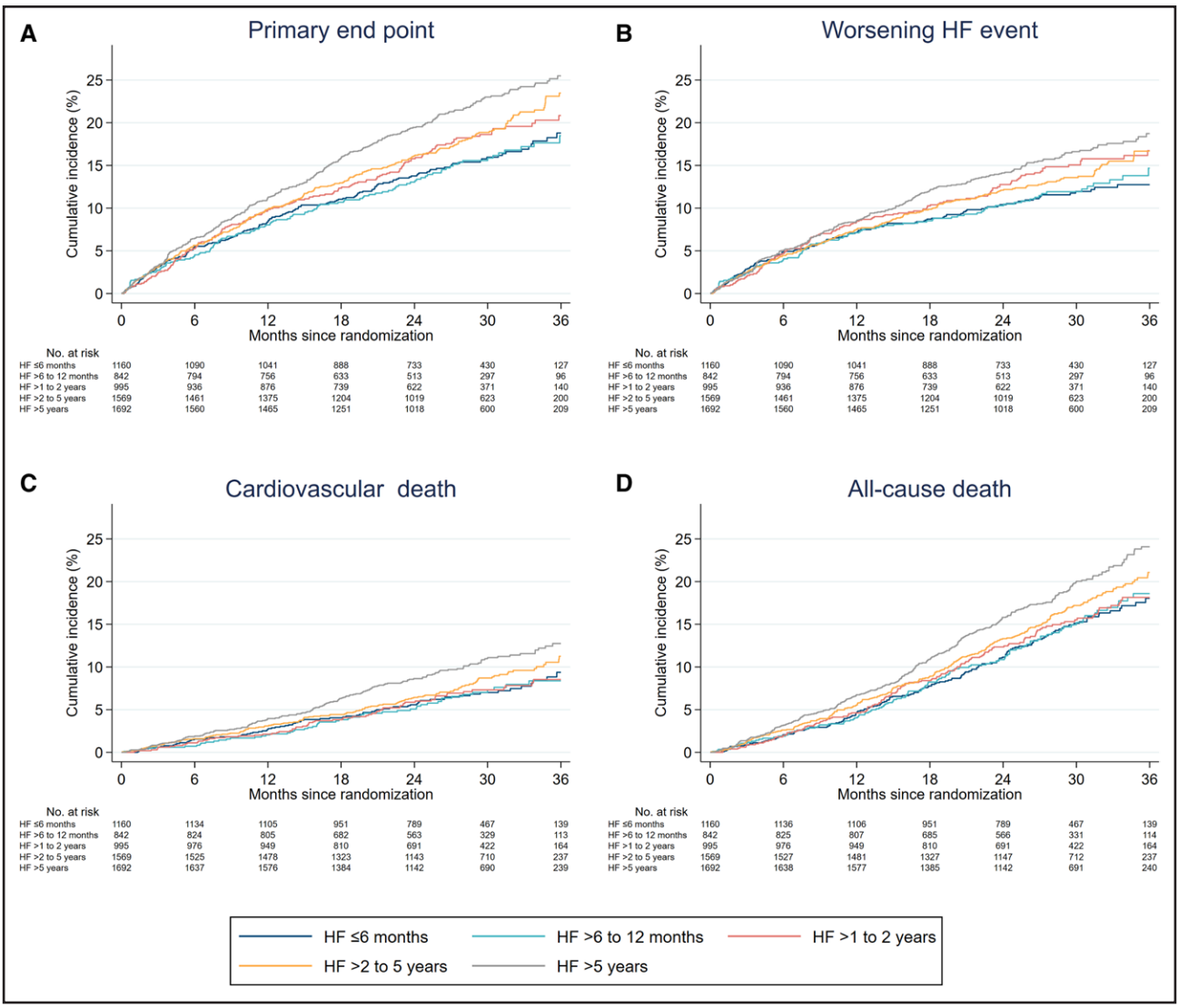

Figure 1. Kaplan-Meier curves for key trial outcomes, according to heart failure duration.
Cumulative event curves for the primary composite outcome (worsening heart failure [HF] or death from cardiovascular causes [**A**]), worsening HF (**B**), death from cardiovascular causes (**C**), and death from any cause (**D**).

resulting from volume depletion, during which patients with longer-duration HF were less likely to experience volume depletion than those with shorter-duration HF (P=0.042; Table 4).

DISCUSSION

In this prespecified analysis of DELIVER, we showed that demographic characteristics, comorbidities, HF status (including the proportion of participants with a previously reduced LVEF), and treatments varied according to time from diagnosis in patients with HFmrEF or HFpEF; we showed that the rate of clinical outcomes increased with increasing duration of HF; and we found that the benefits of treatment with dapagliflozin were not modified by the duration of HF, with substantial absolute risk reductions in patients with longer-standing HF.

The few studies that have described variation in the characteristics of ambulant patients and their outcomes according to the duration of HF were performed in HFrEF data sets.[6–8,12–15] These include an original report from SHIFT (Systolic Heart Failure Treatment With the If Inhibitor Ivabradine), a follow-up report from PARADIGM-HF (Prospective Comparison of ARNI With an ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure), and, recently, an analysis of DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure).[6–8] In all 3 studies, patients with longer-duration HF were older, had a greater prevalence of comorbidities, and were more likely to have an ischemic pathogenesis. The findings in the current analysis of DELIVER were broadly consistent, including the higher prevalence of coronary artery disease.

Table 3. Effect of Randomized Treatment on Outcomes According to Duration of Heart Failure Category

Outcome	HF ≤6 months		HF >6 to 12 months		HF >1 to 2 years		HF >2 to 5 years		HF >5 years		$P_{interaction}$
	Placebo (n=586)	Dapagliflozin (n=574)	Placebo (n=427)	Dapagliflozin (n=415)	Placebo (n=488)	Dapagliflozin (n=507)	Placebo (n=800)	Dapagliflozin (n=769)	Placebo (n=829)	Dapagliflozin (n=863)	
Primary end point											
N (%)	104 (17.8)	71 (12.4)	69 (16.2)	54 (13.0)	92 (18.9)	80 (15.8)	149 (18.6)	141 (18.3)	196 (23.6)	166 (19.2)	
Rate (95% CI)	8.7 (7.2–10.5)	5.9 (4.7–7.4)	8.0 (6.3–10.2)	6.3 (4.8–8.2)	9.3 (7.6–11.4)	7.5 (6.0–9.4)	8.9 (7.6–10.5)	8.8 (7.4–10.4)	12.0 (10.4–13.7)	9.3 (8.0–10.8)	
HR	0.67 (0.50–0.91)		0.78 (0.55–1.12)		0.81 (0.60–1.09)		0.97 (0.77–1.22)		0.78 (0.64–0.96)		0.41
Worsening HF event											
No (%)	81 (13.8)	46 (8.0)	51 (11.9)	44 (10.6)	71 (14.6)	66 (13.0)	107 (13.4)	99 (12.9)	145 (17.5)	113 (13.1)	
Rate (95% CI)	6.8 (5.4–8.4)	3.8 (2.9–5.1)	5.9 (4.5–7.8)	5.1 (3.8–6.8)	7.2 (5.7–9.1)	6.2 (4.9–7.9)	6.4 (5.3–7.8)	6.2 (5.1–7.5)	8.8 (7.5–10.4)	6.3 (5.3–7.6)	
HR	0.56 (0.39–0.80)		0.86 (0.57–1.29)		0.87 (0.62–1.21)		0.95 (0.72–1.24)		0.72 (0.57–0.93)		0.18
Cardiovascular death											
No (%)	44 (7.5)	33 (5.8)	30 (7.0)	23 (5.5)	39 (8.0)	27 (5.3)	60 (7.5)	68 (8.8)	88 (10.6)	80 (9.3)	
Rate (95% CI)	3.4 (2.5–4.6)	2.6 (1.9–3.7)	3.2 (2.3–4.6)	2.5 (1.7–3.8)	3.6 (2.7–5.0)	2.4 (1.6-3.5)	3.3 (2.6-4.3)	3.9 (3.1-5.0)	4.9 (3.9-6.0)	4.2 (3.4–5.3)	
HR	0.76 (0.49–1.20)		0.79 (0.46–1.36)		0.65 (0.40–1.06)		1.18 (0.83–1.67)		0.86 (0.64–1.17)		0.30
All-cause death											
No (%)	84 (14.3)	77 (13.4)	68 (15.9)	52 (12.5)	83 (17.0)	66 (13.0)	129 (16.1)	137 (17.8)	161 (19.4)	165 (19.1)	
Rate (95% CI)	6.5 (5.3–8.1)	6.1 (4.9–7.6)	7.3 (5.8–9.3)	5.7 (4.3–7.5)	7.7 (6.2–9.6)	5.8 (4.6–7.4)	7.1(6.0–8.4)	7.9 (6.7–9.4)	8.9 (7.6–10.4)	8.7 (7.5–10.1)	
HR	0.93 (0.68–1.27)		0.78 (0.55–1.12)		0.75 (0.54–1.03)		1.11 (0.88–1.42)		0.98 (0.79–1.21)		0.28
Total number of worsening HF events and cardiovascular deaths											
No (%)	171	100	117	98	175	142	237	235	357	240	
Rate (95% CI)	13.4 (10.7–16.9)	7.9 (6.0–10.7)	12.6 (9.8–16.6)	10.8 (7.9–15.1)	16.3 (12.6–21.4)	12.5 (9.7-16.4)	13.1 (10.8-16.0)	13.7 (11.3–16.8)	19.7 (16.6-23.8)	12.7 (10.7–15.2)	
Rate ratio	0.59 (0.41–0.84)		0.86 (0.57–1.30)		0.76 (0.53–1.09)		1.04 (0.79–1.36)		0.64 (0.50–0.83)		0.067
KCCQ-TSS											
Mean change in KCCQ at 8m (95% CI)	4.4 (2.9–6.0)	8.8 (7.2–10.3)	5.2 (3.3–7.0)	7.7 (5.8–9.6)	6.2 (4.5–7.9)	8.2 (6.5–9.9)	5.4 (4.0–6.9)	8.0 (6.5–9.4)	6.2 (4.8–7.6)	7.2 (5.8–8.5)	
Placebo-corrected change at 8m (95% CI)*	4.3 (2.1–6.5)		2.5 (−0.1 to 5.2)		2.0 (−0.4 to 4.4)		2.5 (0.5–4.5)		0.9 (−1.0 to 2.9)		0.28

Treatment effect according to the duration of heart failure (HF; dapagliflozin vs placebo hazard ratio [HR] or difference and 95% CI). Rates are given per 100 patient-years. KCCQ-TSS indicates Kansas City Cardiomyopathy Questionnaire–Total Symptom Score.

*Mixed-effect models for repeated measurements adjusted for baseline value, visit (months 1, 4, and 8), randomized treatment, and interaction of treatment and visit.

We previously questioned whether the older age and greater prevalence of noncardiovascular and cardiovascular comorbidities in patients with a longer history of HF might lead to worse treatment tolerability and greater treatment discontinuation.[8] This issue was not addressed in SHIFT, and the design of PARADIGM-HF precluded straightforward analysis (because of the 2 active run-in periods excluding some susceptible patients before randomization).[6,7] In DAPA-HF, adverse effects were more common with increasing duration of HF, as was the discontinuation of randomized treatment, but neither was more common with dapagliflozin compared with placebo.[8] No such trend to more adverse events or greater discontinuation was observed in DELIVER, with consistent tolerability and adherence across the range of HF durations examined, even though DELIVER was larger and had a longer median follow-up.

In terms of clinical outcomes, we observed worse outcomes in patients with longer-duration HF compared with those with shorter-duration HF. This was observed for the primary outcome and worsening HF in patients with HF for more than a year, and for mortality, the increment in event rate was most apparent after 2 years. The elevated risk associated with a

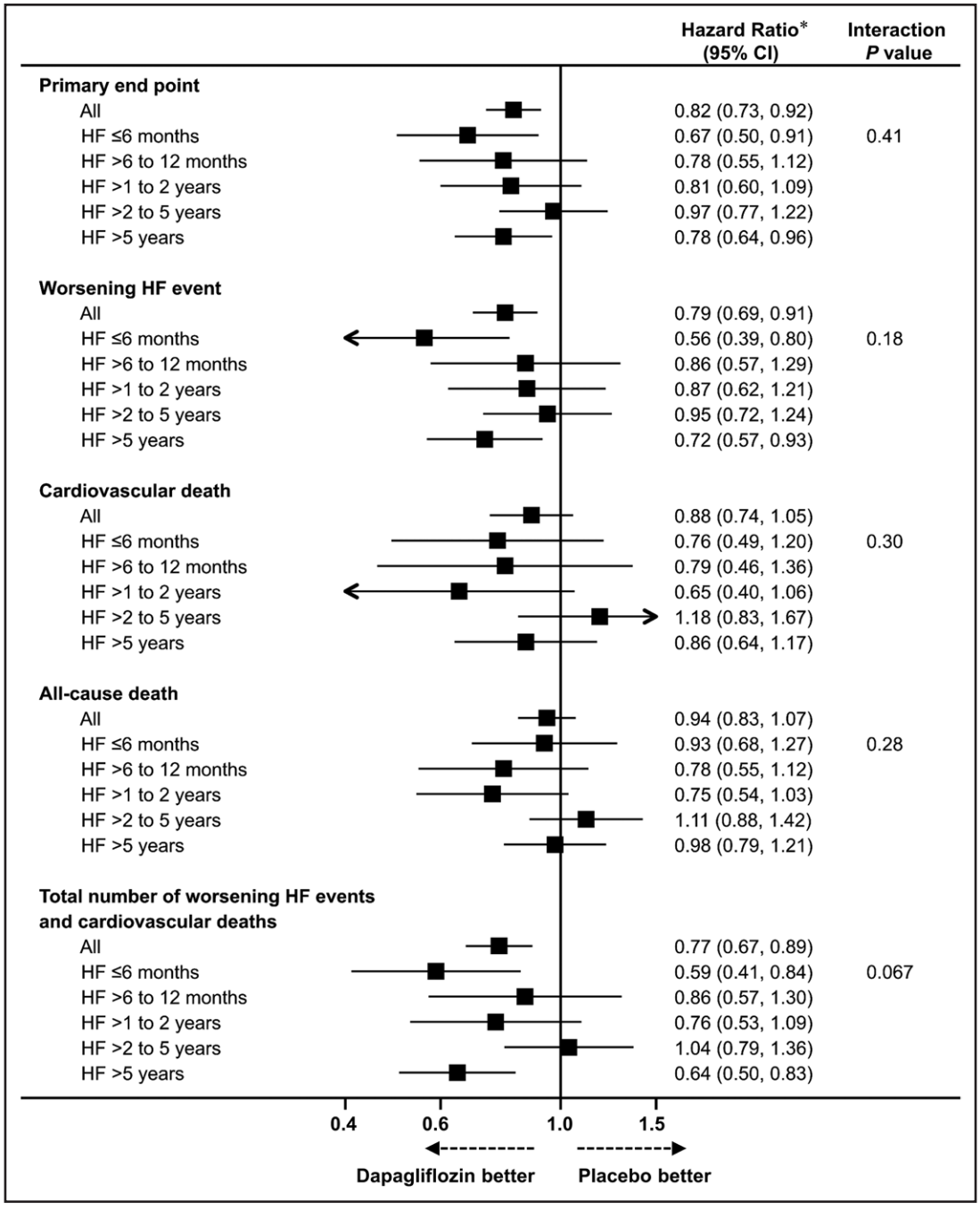

Figure 2. Effect of dapagliflozin on outcomes according to duration of heart failure category.
*Rate ratio is shown for total heart failure (HF) hospitalizations and cardiovascular death.

longer duration of HF persisted after extensive adjustment for prognostic variables, although this was only statistically significant for participants with a diagnosis of HF for >5 years. As in HFrEF, this suggests that the excess risk related to longer-duration HF is not wholly explained by conventional prognostic variables including age, demographics, and comorbidities and raises interesting questions about what might underlie such residual risk (eg, right ventricular dysfunction, inflammation, and insulin resistance).[8]

The final but most important observation in the current study was the finding that the benefit of dapagliflozin, compared with placebo, was entirely consistent across the range of HF duration categories examined, as well as using a threshold analysis. These observations complement the findings that SGLT2 inhibitors have a rapid onset of action and are beneficial in acute, subacute, and chronic settings.[16–20] This means that it is never too early or too late to start treatment in patients who have had a diagnosis of HF for some time and who may (mistakenly)

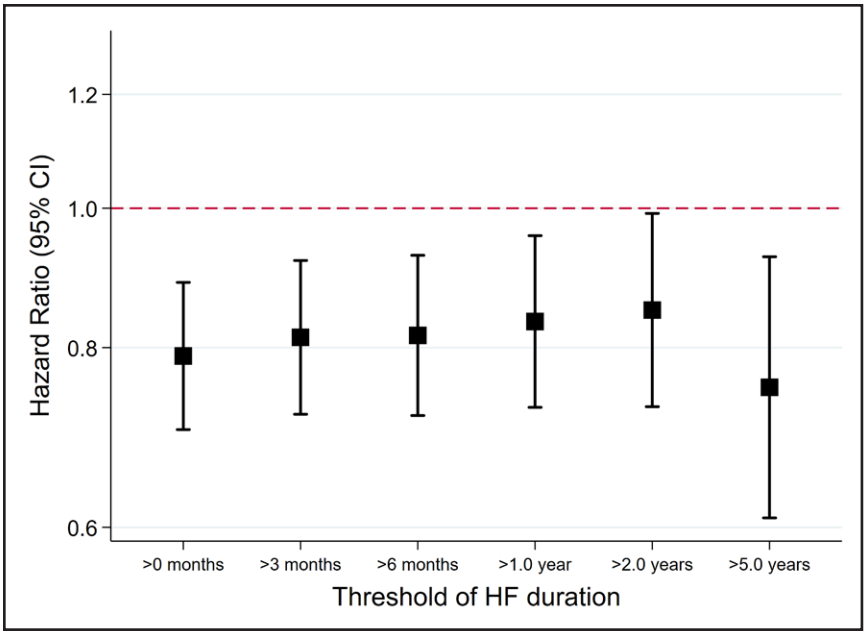

Figure 3. Treatment effect of dapagliflozin on the primary composite outcome (cardiovascular death or worsening heart failure) according to threshold duration of heart failure.
Treatment effect for the primary composite outcome using a Cox model adjusted for prognostic variables as per Table 2, according to threshold duration of heart failure. HF indicates heart failure.

be considered "stable" survivors. This is clearly not the case. In fact, because patients with long-standing HF have a substantially higher absolute risk of events, with a consistent relative benefit of dapagliflozin across the range of HF duration, they have a larger absolute risk reduction than patients with shorter-duration HF (NNT, 24 for patients with HF >5 years, compared with an NNT of 32 for patients with HF for ≤6 months). This greater benefit may also reflect the various mechanisms of action of SGLT2 inhibitors on associated comorbidities (eg, worse kidney function).

Patients with longer-duration HF are a group for whom the safety profile of SGLT2 inhibitors may be of concern, as these patients are older and have more frailty.[21,22] However, we found that patients with longer-duration HF did not experience more adverse effects with dapagliflozin compared with placebo (and volume depletion was less common), in keeping with what we found in analyses of safety and efficacy of dapagliflozin according to age and frailty in patients in DELIVER.[21,22]

Study Limitations

There are limitations to all studies like this one. Patients enrolled in a clinical trial are selected according to specific inclusion and exclusion criteria, and our results

Table 4. Adverse Events According to Duration of Heart Failure Category

	HF ≤6 months		HF >6-12 months		HF >1-2 years		HF >2-5 years		HF >5 years		
Adverse events	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	$P_{interaction}$
N	586	573	426	415	488	507	800	767	825	861	
Any SAE	264 (45.1)	243 (42.4)	180 (42.3)	171 (41.2)	239 (49.0)	226 (44.6)	394 (49.3)	365 (47.6)	430 (52.1)	449 (52.1)	0.85
Any AE that led to discontinuation of randomized treatment	45 (7.7)	40 (7.0)	24 (5.6)	22 (5.3)	19 (3.9)	27 (5.3)	41 (5.1)	39 (5.1)	51 (6.2)	55 (6.4)	0.84
Any AE that led to the interruption of randomized treatment	84 (14.3)	69 (12.0)	53 (12.4)	53 (12.8)	85 (17.4)	69 (13.6)	134 (16.8)	109 (14.2)	137 (16.6)	136 (15.8)	0.73
Any amputation	7 (1.2)	5 (0.9)	1 (0.2)	2 (0.5)	8 (1.6)	5 (1.0)	7 (0.9)	3 (0.4)	3 (0.4)	4 (0.5)	0.76
Any definite or probable diabetic ketoacidosis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	NA
Any major hypoglycemic event	2 (0.3)	1 (0.2)	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.4)	3 (0.4)	0 (0.0)	2 (0.2)	3 (0.3)	NA
Any SAE or DAE related to volume depletion	2 (0.3)	11 (1.9)	3 (0.7)	6 (1.4)	6 (1.2)	10 (2.0)	15 (1.9)	6 (0.8)	11 (1.3)	16 (1.9)	0.042
Any renal SAE or DAE	17 (2.9)	19 (3.3)	8 (1.9)	8 (1.9)	18 (3.7)	18 (3.6)	22 (2.8)	12 (1.6)	26 (3.2)	27 (3.1)	0.66

Prespecified adverse effects and study drug discontinuation according to the duration of heart failure (HF). A total of 10 randomized patients were excluded from the safety analysis because this was performed in patients who had undergone randomization and received at least 1 dose of dapagliflozin or placebo. AE indicates adverse event; DAE, adverse event leading to discontinuation of randomized treatment; and SAE, serious adverse event.

may not be generalizable to all patients with HFmrEF or HFpEF in the general population. The entry criteria in DELIVER did not match those comprising the H_2FPEF score or the HFA–PEFF diagnostic algorithm and thus will have excluded some patients with HFpEF with elevated rest or exercise left ventricular filling pressures but an NT-proBNP level below the inclusion threshold of ≥300 pg/mL (≥600 pg/mL for patients with atrial fibrillation or flutter).[23,24] As in most global trials, Black patients were poorly represented, and we do not know for certain that our findings apply to non-White patients. The duration of HF was obtained from investigators on the basis of predefined time ranges. By definition, patients with longer-standing HF are selected as survivors. Only patients with ≥6 weeks of symptoms were eligible, and patients with newly diagnosed HF were therefore not included; thus, we could not address the efficacy and safety of dapagliflozin in patients with recently diagnosed HF.

Conclusions

Patients with longer-duration HF were older and had more comorbidities. Patients with longer-duration HF had worse symptoms and higher rates of worsening HF and death. Dapagliflozin was as well tolerated as a placebo in patients with longer-duration HF, and the benefits of dapagliflozin were consistent regardless of the duration of HF, with greater absolute benefits in patients with longer-duration HF. Even patients with long-standing HF and generally mild symptoms are not "stable," and it is not too late for such patients to benefit from an SGLT2 inhibitor.

ARTICLE INFORMATION

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Supplemental Material

Tables S1 and S2

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