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Contemporary Use and Implications of Beta-Blockers in Patients With HFmrEF or HFpEF

The DELIVER Trial

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ABSTRACT

BACKGROUND Although beta-blockers are not recommended for the treatment of heart failure with preserved ejection fraction (HFpEF) according to the latest European Society of Cardiology and American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines, these therapies remain commonly used for comorbidity management. There has been concern that beta-blockers may adversely influence clinical outcomes by limiting chronotropic response in HFpEF.

OBJECTIVES This study sought to examine the contemporary use and implications of beta-blockers in patients with heart failure with mildly reduced ejection fraction (HFmrEF) or HFpEF.

METHODS In the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trial, a total of 6,263 patients with symptomatic heart failure (HF) with a left ventricular ejection fraction (LVEF) >40% were randomized to dapagliflozin or placebo across 20 countries. In this prespecified analysis, efficacy and safety outcomes were examined according to beta-blocker use at randomization. The primary outcome was cardiovascular death or worsening HF.

RESULTS Overall, beta-blockers were used in 5,177 patients (83%), with wide variation by geographic region. Beta-blocker use was associated with a lower risk of the primary outcome in covariate-adjusted models (HR: 0.70; 95% CI: 0.60-0.83). Dapagliflozin consistently reduced the risk of the primary outcome in patients taking beta-blockers (HR: 0.82; 95% CI: 0.72-0.94) and in patients not taking beta-blockers (HR: 0.79; 95% CI: 0.61-1.03; $P_{interaction} = 0.85$), with similar findings for key secondary endpoints. Adverse events were balanced between patients randomized to dapagliflozin and placebo, regardless of background beta-blocker use.

CONCLUSIONS In patients with HFmrEF or HFpEF who were enrolled in DELIVER, 4 out of 5 participants were treated with a beta-blocker. Beta-blocker use was not associated with a higher risk of worsening HF or cardiovascular death. Dapagliflozin consistently and safely reduced clinical events, irrespective of background beta-blocker use. (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure [DELIVER]; NCT03619213) (J Am Coll Cardiol HF 2023;■:■-■) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

AE = adverse event

AFF = atrial fibrillation or flutter

CAD = coronary artery disease

eGFR = estimated glomerular filtration rate

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

LVEF = left ventricular ejection fraction

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

SGLT2 = sodium-glucose cotransporter-2

Beta-blockers are cornerstone therapeutic agents for the management of heart failure with reduced ejection fraction (HFrEF). Conversely, high-quality randomized trial data on beta-blocker use among patients with heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) remain sparse. Although a meta-analysis of 11 randomized trials suggested that the benefits of beta-blockers extend to patients with HFmrEF, data on beta-blockers in HFpEF remain limited to observational studies and a small number of older, less well phenotyped trials with inconclusive results.[1-3] Given the limited evidence from randomized trials, the latest European Society of Cardiology and American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) guidelines do not recommend the use of beta-blockers for the treatment of HFpEF. However, these therapies remain widely used in these patients for management of comorbidities, including hypertension, ischemic heart disease, and atrial fibrillation.[4-8] Concurrently, data from TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) and a recent analysis of the U.S. National Cardiovascular Data Registry PINNACLE (Practice Innovation and Clinical Excellence) Registry suggested that beta-blocker use may be associated with a potentially increased risk of hospitalizations for heart failure (HF) in patients with HFpEF.[9,10] Similarly, the PRESERVE-HR (beta-blockers Withdrawal in Patients With HFpEF and Chronotropic Incompetence: Effect on Functional Capacity) trial showed that the withdrawal of beta-blockers may improve functional capacity in patients with HFpEF and chronotropic incompetence.[11]

Although sodium-glucose cotransporter-2 (SGLT2) inhibitors were demonstrated to reduce worsening HF events or cardiovascular death across the spectrum of HF, it is unknown whether combined therapy with beta-blockers may attenuate these benefits.[12] The DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; NCT03619213) trial is the largest randomized trial conducted to date in heart failure (HF) patients with LVEF >40%, with two-thirds of participants having LVEF ≥50%, and a substantial proportion (>80%) taking a beta-blocker. In this *prespecified* analysis of the DELIVER trial, we examine the implications of beta-blocker use in patients with HFmrEF or HFpEF.

METHODS

TRIAL DESIGN AND PATIENTS. The design, baseline characteristics, and primary results of the DELIVER trial have been reported previously.[13-15] Briefly, DELIVER was an international, randomized, double-blind trial comparing dapagliflozin, 10 mg once daily, with a matching placebo in patients with HFmrEF or HFpEF. The study enrolled ambulatory and hospitalized patients 40 years of age or older, with NYHA functional class II to IV, LVEF >40%, elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (≥300 pg/mL in sinus rhythm or ≥600 pg/mL in patients in atrial fibrillation or flutter [AFF]), and evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy). Patients with SGLT2 inhibitor treatment within 4 weeks of randomization, intolerance to SGLT2 inhibitors, type 1 diabetes mellitus, estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2, systolic blood pressure ≥160 mm Hg if not using ≥3 antihypertensive medications or ≥180 mm Hg regardless of number of medications, or alternative diagnoses potentially accounting for the patients' HF symptoms were excluded. The study protocol was approved by the Institutional Review Board or ethics committee at each participating site, and each patient provided written informed consent.

BETA-BLOCKER USE AND INDICATIONS. Data on medication at enrollment were collected by case

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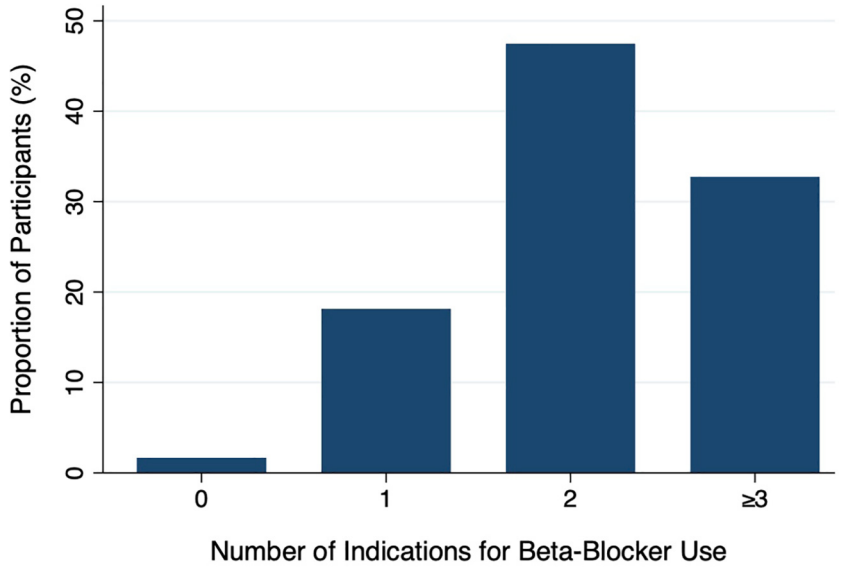
FIGURE 1 Potential Indications for Concomitant Beta-Blocker Use



Distribution of potential indications for beta-blocker use at randomization across all participants.

report forms, with beta-blocker use categorized using Anatomical Therapeutic Chemical classification codes. Potential non-HF indications for beta-blocker treatment (defined as either hypertension, AFF, coronary artery disease [CAD], or previous LVEF≤40%) were assessed on the basis of the participant's medical history examined through case report forms. Beta-blocker doses were standardized according to carvedilol equivalents (Supplemental Methods). Target doses for evidence-based beta-blockers for the treatment of HFrEF or HFmrEF (carvedilol, metoprolol succinate, and bisoprolol) were defined according to the latest AHA/ACC/HFSA guidelines.

STUDY OUTCOMES. The primary outcome of DELIVER was the composite of worsening HF events (unplanned hospitalization for HF or urgent HF visit requiring intravenous therapy) or cardiovascular death. Secondary outcomes included the total number of HF events and cardiovascular death, cardiovascular death, death from any cause, and change in the Kansas City Cardiomyopathy Questionnaire (KCCQ)-Total Symptom Score (TSS) between baseline and 8 months. Additional analyses examined change from baseline to 8 months in KCCQ-Clinical Summary Score (CSS) and KCCQ-Overall Summary Score (OSS). Safety outcomes included serious adverse events (AEs), AEs leading to study treatment discontinuation, and selected AEs, including amputation, major hypoglycemic events, diabetic ketoacidosis, volume depletion, renal events, hypotension, dizziness, presyncope, and bradycardia.

STATISTICAL ANALYSIS. Baseline characteristics were summarized as mean ± SD, median (quartile 1-quartile 3), or frequencies (%). Differences in baseline characteristics between patients who were and those who were not taking a beta-blocker were compared by Student's *t*-test for continuous variables and by the chi-square test or Fisher exact test for categorical variables. Associations between beta-blocker use and clinical events were examined using Cox proportional hazards models with and without stratification by site and adjustment for age, sex, race, AFF, type 2 diabetes mellitus, any CAD, hypertension, previous HF hospitalization, improved LVEF (previous LVEF ≤40%) status, baseline body mass index, baseline NYHA functional class, baseline LVEF, log-transformed baseline NT-proBNP levels, baseline heart rate, baseline systolic blood pressure, and baseline eGFR. For sensitivity, additional models were stratified by deciles of a propensity score on the basis of a multivariate logistic regression model including all baseline covariates. Additional sensitivity analyses were based on competing risk models accounting for all-cause mortality. Moreover, models with interaction terms analyzed the modification of the association between beta-blocker use and clinical

TABLE 1 Baseline Characteristics According to Beta-Blocker Use

	Overall Population	No Beta-Blocker Use (n = 1,086)	Beta-Blocker Use (n = 5,177)	*P* Value
Randomized to dapagliflozin	3,131 (50.0)	539 (49.6)	2,592 (50.1)	0.79
Age, y	71.7 ± 9.6	73.5 ± 10.0	71.3 ± 9.4	<0.001
Male	3,516 (56.1)	596 (54.9)	2,920 (56.4)	0.36
Race				<0.001
White	4,439 (70.9)	643 (59.2)	3,796 (73.3)	
Asian	1,274 (20.3)	298 (27.4)	976 (18.9)	
Black or African American	159 (2.5)	23 (2.1)	136 (2.6)	
American Indian or Alaska Native	189 (3.0)	67 (6.2)	122 (2.4)	
Other	202 (3.2)	55 (5.1)	147 (2.8)	
Geographic region				<0.001
Europe and Saudi Arabia	3,005 (48.0)	385 (35.5)	2,620 (50.6)	
Asia	1,226 (19.6)	292 (26.9)	934 (18.0)	
Latin America	1,181 (18.9)	244 (22.5)	937 (18.1)	
North America	851 (13.6)	165 (15.2)	686 (13.3)	
Medical history				
Atrial fibrillation/flutter	3,552 (56.7)	583 (53.7)	2,969 (57.3)	0.027
Stroke	597 (9.5)	114 (10.5)	483 (9.3)	0.23
Type 2 diabetes mellitus	2,806 (44.8)	457 (42.1)	2,349 (45.4)	0.047
Noncoronary revascularization	140 (2.2)	17 (1.6)	123 (2.4)	0.10
Myocardial infarction	1,639 (26.2)	222 (20.4)	1,417 (27.4)	<0.001
Hypertension	5,553 (88.7)	930 (85.6)	4,623 (89.3)	<0.001
Any coronary artery disease	3,218 (51.4)	474 (43.6)	2,744 (53.0)	<0.001
Previous HF hospitalization	2,539 (40.5)	384 (35.4)	2,155 (41.6)	<0.001
Previous LVEF ≤40%	1,151 (18.4)	160 (14.7)	991 (19.1)	<0.001
Physiologic measures				
Body mass index, kg/m^2	29.8 ± 6.1	28.7 ± 6.1	30.1 ± 6.1	<0.001
Systolic blood pressure, mm Hg	128.2 ± 15.3	129.7 ± 15.3	127.9 ± 15.4	<0.001
Diastolic blood pressure, mm Hg	73.9 ± 10.4	72.8 ± 10.5	74.2 ± 10.3	<0.001
Pulse, beats/min	71.5 ± 11.7	71.0 ± 11.6	71.6 ± 11.8	0.14
Atrial fibrillation/flutter (ECG)	2,644 (42.2)	418 (38.5)	2,226 (43.0)	0.006
Time from diagnosis of HF to baseline				0.06
0-3 mo	568 (9.1)	121 (11.2)	447 (8.6)	
>3-6 mo	592 (9.5)	114 (10.5)	478 (9.2)	
>6-12 mo	842 (13.5)	146 (13.5)	696 (13.5)	
>1-2 y	995 (15.9)	167 (15.4)	828 (16.0)	
>2-5 y	1,569 (25.1)	249 (22.9)	1,320 (25.5)	
>5 y	1,692 (27.0)	288 (26.5)	1,404 (27.1)	
NYHA functional class at baseline				0.031
I	1 (0.0)	0 (0.0)	1 (0.0)	
II	4,713 (75.3)	855 (78.7)	3,858 (74.5)	
III	1,531 (24.4)	229 (21.1)	1,302 (25.1)	
IV	18 (0.3)	2 (0.2)	16 (0.3)	
LVEF, %	54.2 ± 8.8	56.0 ± 9.2	53.8 ± 8.6	<0.001
KCCQ-TSS	70.0 ± 22.2	70.5 ± 23.3	69.9 ± 21.9	0.51
KCCQ-CSS	68.3 ± 20.7	69.1 ± 21.7	68.2 ± 20.5	0.21
KCCQ-OSS	66.6 ± 20.2	67.2 ± 21.0	66.5 ± 20.1	0.35
NT-proBNP in AFF (ECG)	1,399 [962-2,212]	1,256 [880-2,082]	1,420 [979-2,249]	0.002
NT-proBNP when no AFF (ECG)	716 [469-1,280]	707 [458-1,244]	717 [472-1,292]	0.34
Creatinine, μmol/L	102.5 ± 31.1	103.1 ± 31.6	102.3 ± 31.0	0.43
Baseline eGFR, mL/min/1.73 m^2	61.0 ± 19.1	59.6 ± 18.9	61.3 ± 19.2	0.008
HbA_{1c}, %	6.6 ± 1.4	6.5 ± 1.4	6.6 ± 1.4	0.14

Continued on the next page

TABLE 1 Continued

	Overall Population	No Beta-Blocker Use (n = 1,086)	Beta-Blocker Use (n = 5,177)	*P* Value
Treatment				
Loop diuretic agents	4,811 (76.8)	796 (73.3)	4,015 (77.6)	0.003
ACEI/ARB	4,543 (72.5)	727 (66.9)	3,816 (73.7)	<0.001
ARNI	301 (4.8)	48 (4.4)	253 (4.9)	0.51
MRA	2,667 (42.6)	377 (34.7)	2,290 (44.2)	<0.001
Pacemaker	662 (10.6)	143 (13.2)	519 (10.0)	0.002
ICD	113 (1.8)	9 (0.8)	104 (2.0)	0.008

Values are n (%), mean ± SD, or median [quartile 1-quartile 3]. *P*-values are reported for differences between participants with and without background beta-blocker therapy.

ACEI = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; AFF = atrial fibrillation or flutter; ARB = angiotensin receptor blocker; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; HF = heart failure; ICD = implantable cardioverter-defibrillator; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; 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.

events by baseline LVEF group (LVEF ≤49% vs ≥50%). The modification of the association between beta-blocker use and clinical events as a continuous function of LVEF was further examined by crude and adjusted Poisson regression models, with baseline LVEF expressed by restricted cubic splines with 3 knots. The effects of dapagliflozin compared with placebo were assessed by Cox proportional hazards models stratified by type 2 diabetes status at baseline with interaction terms for effect modification by beta-blocker use. Changes in KCCQ scores between baseline and 8 months according to beta-blocker use were examined by linear regression models adjusted for each score's respective baseline value. Differences in change in KCCQ scores from baseline to 8 months by randomized treatment were assessed by linear regression models adjusted for each score's respective baseline value and interaction terms for randomized treatment and beta-blocker use. Responder analyses examined the proportions of patients with clinically meaningful improvement (≥5-point increase) and deterioration (≥5-point decrease) in KCCQ scores by logistic regression models. Total events were analyzed on the basis of the semiparametric method of Lin et al.[16] Safety outcomes by beta-blocker use were examined using logistic regression models with interaction terms. Statistical analyses were performed using Stata software version 16.1 (StataCorp). Values of $P < 0.05$ were considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS. Of the 6,263 randomized patients, a total of 5,177 (83%) were taking beta-blockers at baseline, and 4,534 (88%) of these patients were prescribed a drug indicated for the treatment of HF (Supplemental Table 1). Although the median daily carvedilol dose equivalent among patients receiving evidence-based beta-blockers was 25 mg, more than one-half of these patients achieved ≥50% of the guideline-recommended target dose (n = 2,488 [55%]). Beta-blocker use varied widely by country, ranging from 60% (Mexico) to 94% (Hungary) (Supplemental Figure 1). Almost all patients taking beta-blockers had at least 1 potential non-HF indication (n = 5,106 [99%]), such as hypertension (n = 4,623 [89%]), AFF (n = 2,969 [57%]), CAD (n = 2,744 [53%]), or previous LVEF ≤40% that has since improved (n = 991 [19%]) (**Figure 1**).

Those patients taking beta-blockers were younger, were more likely White and enrolled in Europe, had a higher body mass index, had lower systolic blood pressure, had higher diastolic blood pressure, presented more frequently in AFF at enrollment, had higher eGFR, lower LVEF, worse NYHA functional class, and higher NT-proBNP levels when in AFF (**Table 1**). A history of AFF, diabetes, hypertension, previous HF hospitalization, previous LVEF ≤40%, CAD, and myocardial infarction were more common in patients taking beta-blockers. Patients taking beta-blockers were more frequently treated with loop diuretic agents, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and mineralocorticoid receptor antagonists, were less likely to have pacemakers, but were more likely to have received implantable cardioverter-defibrillator therapy. Randomized treatment, sex, heart rate, duration of HF, glycated hemoglobin levels, NT-proBNP levels in patients without AFF, baseline KCCQ scores, history of stroke, and sacubitril/valsartan use were similar in patients with and without beta-blocker use.

OUTCOMES BY BETA-BLOCKER USE. Beta-blocker use was associated with a lower risk for the primary composite of worsening HF events or cardiovascular

TABLE 2 Primary Composite Outcome and Key Secondary Outcomes by Beta-Blocker Use

Outcome	No Beta-Blocker Use (n = 1,086)	Beta-Blocker Use (n = 5,177)	*P* Value
Primary composite			
Events	227 (21)	895 (17)	0.002
Rate, per 100 pt-y	10.6	8.3	
HR (95% CI)	Ref.	0.79 (0.68-0.92)	
Adjusted HR (95% CI)	Ref.	0.70 (0.60-0.83)	<0.001
HF Event			
Events	166 (15)	657 (13)	0.009
Rate, per 100 pt-y	7.8	6.1	
HR (95% CI)	Ref.	0.80 (0.67-0.95)	
Adjusted HR (95% CI)	Ref.	0.69 (0.57-0.84)	<0.001
CV death			
Events	107 (10)	385 (7)	0.003
Rate, per 100 pt-y	4.6	3.3	
HR (95% CI)	Ref.	0.72 (0.58-0.89)	
Adjusted HR (95% CI)	Ref.	0.66 (0.52-0.84)	0.001
All-cause death			
Events	193 (18)	830 (16)	0.052
Rate, per 100 pt-y	8.3	7.2	
HR (95% CI)	Ref.	0.86 (0.73-1.00)	
Adjusted HR (95% CI)	Ref.	0.83 (0.70-0.99)	0.044
Total HF events and CV death			
Events	371	1501	0.025
Rate, per 100 pt-y	16.1	13.1	
RR (95% CI)	Ref.	0.81 (0.68-0.97)	
Adjusted RR (95% CI)	Ref.	0.74 (0.62-0.90)	0.002
KCCQ-TSS			
Mean change at 8 mo	7.2 ± 20.4	6.7 ± 20.2	0.50
Proportion with increase ≥5 in score at 8 mo	359 (49.3)	1,829 (49.7)	0.86
OR (95% CI)	Ref.	1.01 (0.86-1.19)	
Adjusted OR (95% CI)	Ref.	0.93 (0.79-1.10)	0.41
Proportion with decrease ≥5 in score at 8 mo	168 (23.1)	883 (24.0)	0.60
OR (95% CI)	Ref.	1.05 (0.87-1.27)	
Adjusted OR (95% CI)	Ref.	1.06 (0.88-1.29)	0.52
KCCQ-CSS			
Mean change at 8 mo	6.3 ± 17.9	5.8 ± 18.0	0.54
Proportion with increase ≥5 in score at 8 months	350 (48.1)	1,806 (49.0)	0.64
OR (95% CI)	Ref.	1.04 (0.89-1.22)	
Adjusted OR (95% CI)	Ref.	0.96 (0.82, 1.14)	0.66
Proportion with decrease ≥5 in score at 8 months	155 (21.3)	877 (23.8)	0.14
OR (95% CI)	Ref.	1.16 (0.95-1.40)	
Adjusted OR (95% CI)	Ref.	1.16 (0.95-1.42)	0.14
KCCQ-OSS			
Mean change at 8 mo	6.8 ± 17.3	6.0 ± 17.4	0.28
Proportion with increase ≥5 in score at 8 mo	369 (50.7)	1,871 (50.8)	0.96
OR (95% CI)	Ref.	1.00 (0.86-1.18)	
Adjusted OR (95% CI)	Ref.	0.92 (0.78-1.09)	0.33
Proportion with decrease ≥5 in score at 8 mo	158 (21.7)	844 (22.9)	0.48
OR (95% CI)	Ref.	1.07 (0.88-1.30)	
Adjusted OR (95% CI)	Ref.	1.09 (0.89-1.33)	0.40

Values are n, n (%), n/100 pt-y, mean ± SD, HR (95% CI), RR (95% CI), or OR (95% CI). Multivariable models were stratified by site and adjusted for age, sex, race, atrial fibrillation/flutter, type 2 diabetes mellitus, any coronary artery disease, hypertension, prior heart failure hospitalization, improved ejection (previous ejection ≤40%) status, baseline body mass index, baseline NYHA functional class, baseline left ventricular ejection fraction, log-transformed baseline N-terminal pro-B-type natriuretic peptide levels, baseline heart rate, baseline systolic blood pressure, and baseline estimated glomerular filtration rate. *P* values are reported for differences between participants with- and without background beta-blocker therapy.

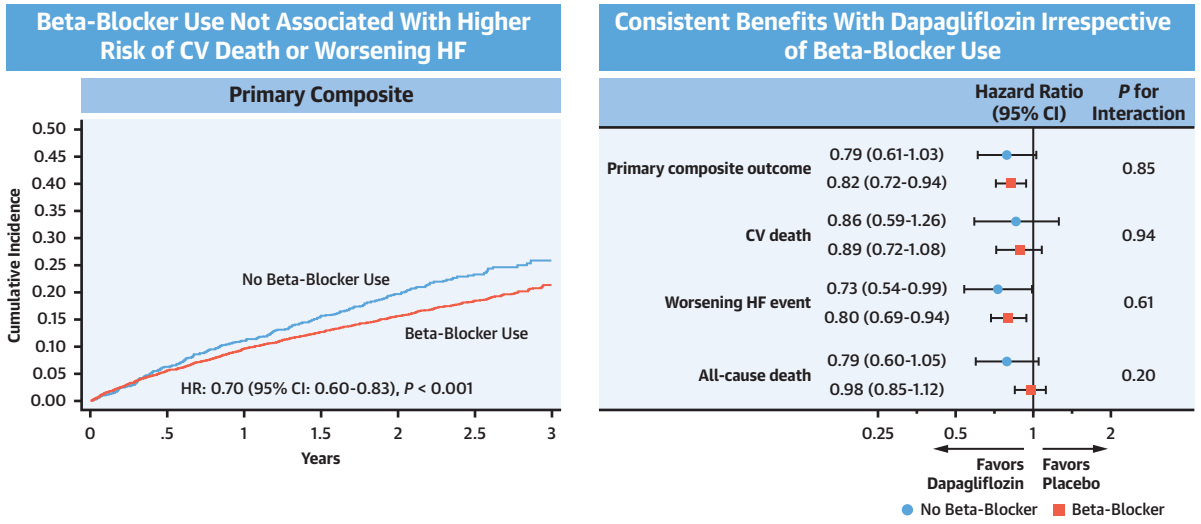
CV = cardiovascular; pt-y = patient-years; Ref = reference; RR = rate ratio; other abbreviations as in Table 1.

death (HR: 0.79; 95% CI: 0.68-0.92), with consistent results after adjustment for baseline demographics and prognostic variables (HR: 0.70; 95% CI: 0.60-0.83) and in propensity score- (HR: 0.76; 95% CI: 0.65-0.90) as well as competing risk model-based sensitivity analyses (HR: 0.68; 95% CI: 0.58-0.79) (**Table 2**, **Central Illustration**, Supplemental Tables 2 and 3). Similarly, patients taking a beta-blocker had a lower risk for HF events, cardiovascular death, and total HF events and cardiovascular death in crude, covariate-adjusted, and propensity score-based models (**Table 2**, **Figure 2**, Supplemental Table 2). Event rates for the primary and key secondary outcomes according to beta-blocker by geographic region use are shown in Supplemental Table 4. Deteriorations in KCCQ-TSS, KCCQ-CSS, and KCCQ-OSS were similar between those patients taking vs not taking beta-blockers, and these findings remained consistent following covariate adjustment and in propensity score-based models (**Table 2**, Supplemental Table 2). The associations between beta-blocker use and clinical outcomes were not modified by LVEF according to categorical (LVEF ≤49% vs ≥50%) ($P_{interaction} > 0.47$ for all) and continuous ($P_{interaction} > 0.63$ for all) assessments (**Figure 3**).

EFFECT OF DAPAGLIFLOZIN ON CLINICAL OUTCOMES ACCORDING TO BETA-BLOCKER USE. The treatment effect of dapagliflozin on the primary composite was similar in patients taking beta-blockers (HR 0.82: 95% CI: 0.72- 0.94) and those not taking beta-blockers (HR: 0.79; 95% CI: 0.61-1.03; $P_{interaction} = 0.85$) (**Table 3**, **Central Illustration**). Similarly, the benefits of dapagliflozin on worsening HF events, cardiovascular death, all-cause mortality, and total HF events and cardiovascular death did not differ by beta-blocker use ($P_{interaction} > 0.20$ for all) (**Table 3**, **Figure 4**). Moreover, improvements in KCCQ-TSS, KCCQ-CSS, and KCCQ-OSS with dapagliflozin were consistent among those patients taking and not taking beta-blockers ($P_{interaction} > 0.12$ for all) (**Table 3**). The achievement of ≥50% of the guideline-recommended beta-blocker target dose did not influence the treatment effect of dapagliflozin on clinical outcomes and KCCQ scores. ($P_{interaction} > 0.13$ for all) (Supplemental Table 5).

SAFETY OUTCOMES. Discontinuation of the study treatment for any reason or because of an AE did not occur more frequently with dapagliflozin regardless of beta-blocker use, with no differences in the frequency of serious AEs, diabetic ketoacidosis, hypoglycemic events, volume depletion, renal events, hypotension, dizziness, presyncope, and bradycardia (**Table 4**).

CENTRAL ILLUSTRATION **Beta-Blocker Use, Clinical Outcomes, and Treatment Response to Dapagliflozin**



In the DELIVER trial of 6,263 participants with HF with LVEF >40%:
- 83% were treated with beta-blockers, with the vast majority having one or more potential indications such as hypertension, atrial fibrillation/flutter, previous LVEF ≤40%, and CAD.
- Beta-blocker use was not associated with adverse HF outcomes and mortality.
- Dapagliflozin consistently reduced CV death or worsening HF events, regardless of baseline beta-blocker use.

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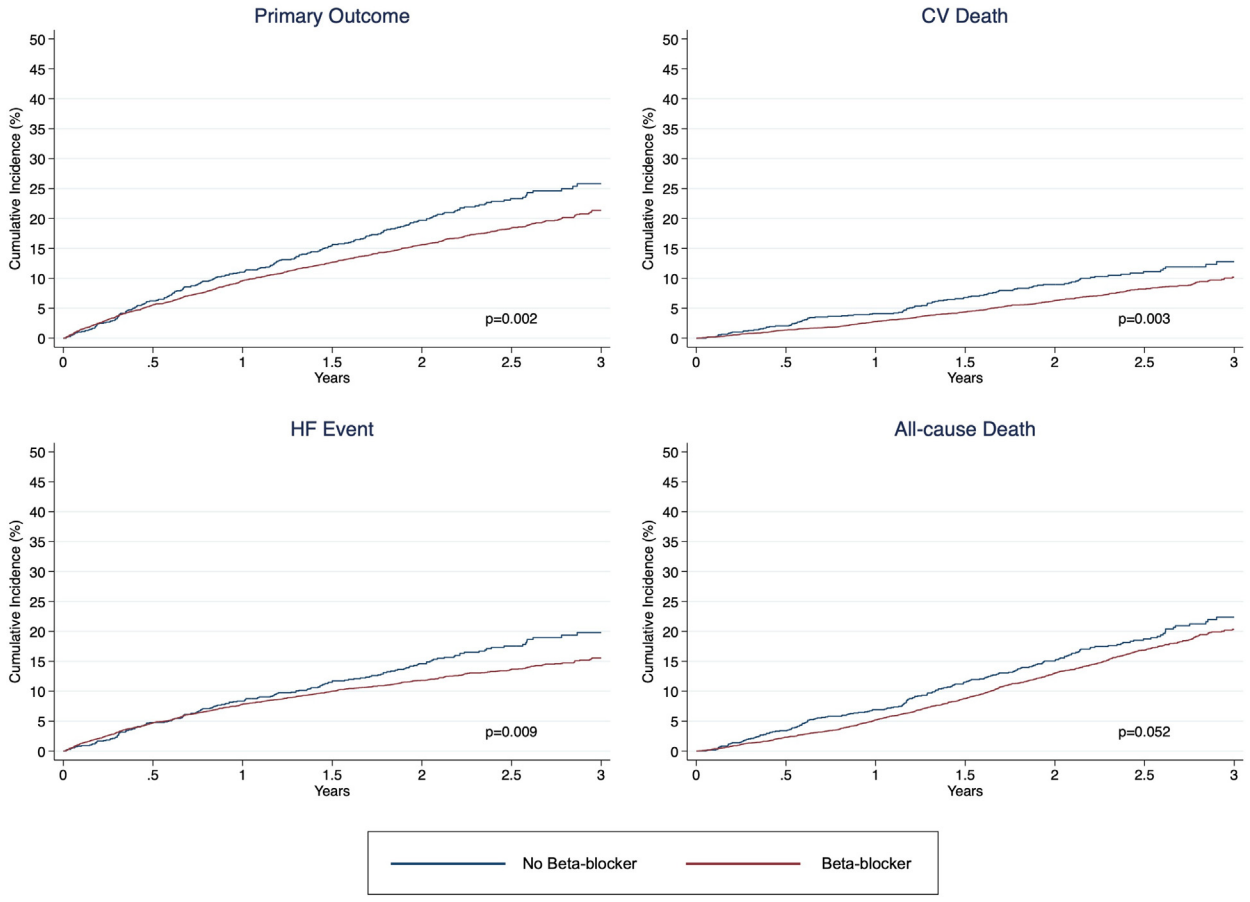
Cumulative incidence of the primary composite outcome and treatment effect of dapagliflozin compared with placebo on the primary composite outcome and key secondary outcomes according to beta-blocker use, on the basis of Cox proportional hazards models. CAD = coronary artery disease; CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction.

DISCUSSION

In this prespecified analysis of DELIVER trial of patients with HFmrEF and HFpEF, more than 4 out of 5 participants were treated with a beta-blocker, and beta-blocker use was associated with a lower risk of worsening HF or cardiovascular death. The benefits of dapagliflozin on symptoms and clinical events did not differ in patients who were or were not taking a beta-blocker at baseline, with a consistent safety profile in both groups.

Despite the lack of recommendation in recent guidelines for the specific use of beta-blockers for the treatment of HFpEF, the high prevalence of 83% taking a beta-blocker in DELIVER is consistent with observations from previous randomized trials in patients with HFpEF.[6,7,17] Given the considerable variation in beta-blockers by country ranging from 60% in Mexico to 94% in Hungary, prescription patterns likely mirror heterogeneity in global comorbidity burden, HF origin, and disease management patterns.[18] Whereas specific beta-blocker indications were not prospectively ascertained, nearly all patients had at least 1 condition potentially recommending beta-blocker use, such as AFF, hypertension, coronary artery disease, or improved LVEF. Although recommendations for some of these conditions have weakened over time, more recent survey data suggest that a substantial proportion of physicians may use beta-blockers in patients with HFpEF without evidence-based indications.[8,19,20] It is notable that a vast majority of 88% of those taking a beta-blocker in DELIVER received a therapy that is evidence based for the management of HFrEF or HFmrEF, including bisoprolol, carvedilol, and metoprolol succinate. Similar to previous observational studies in patients with HFrEF, slightly more than one-half of the patients taking evidence-based beta-blockers achieved ≥50% of the guideline-recommended dosing targets.[21] Although there is no previous evidence on the efficacy of bisoprolol and metoprolol succinate in HFpEF from randomized

FIGURE 2 Cumulative Incidence of Key Outcomes by Beta-Blocker Use

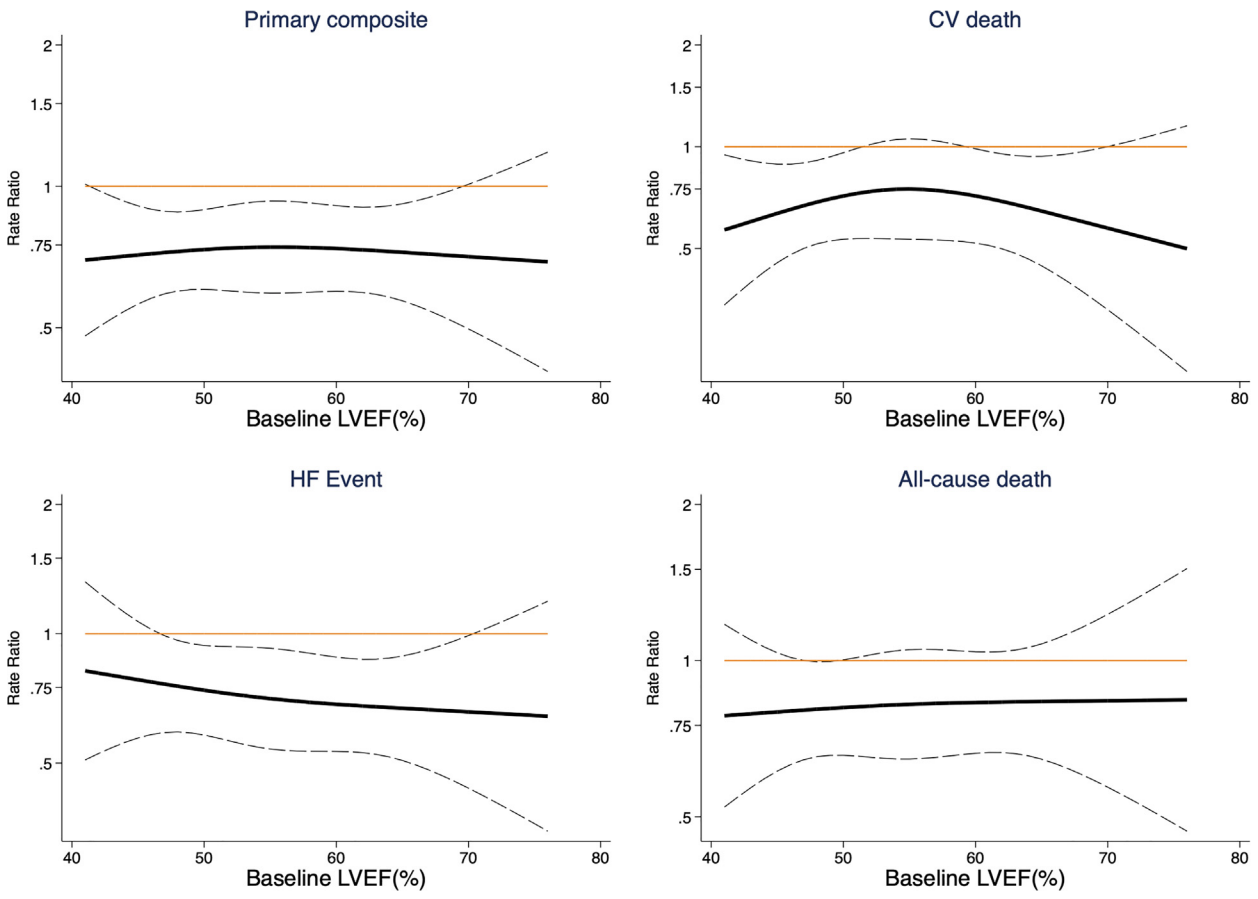


Cumulative incidence of the primary composite outcome (first occurrence of cardiovascular [CV] death, heart failure [HF] hospitalization, or urgent heart failure visit), cardiovascular death, worsening heart failure events (heart failure hospitalization and urgent heart failure visit), and all-cause death according to beta-blocker use.

trials, carvedilol appeared to have neutral effects on cardiovascular death and HF hospitalizations in the randomized open-label Japanese Diastolic Heart Failure Study (J-DHF) of patients with an LVEF >40%.[22] Concurrently, the SENIORS (Randomized Trial to Determine the Effect of Nebivolol on Mortality and Cardiovascular Hospital Admission in Elderly Patients With Heart Failure) trial suggested potential benefits on all-cause mortality and cardiovascular hospitalizations in the subgroup of participants with LVEF of 40% with nebivolol, which was the fourth most common beta-blocker in DELIVER.[3]

Although beta-blockers may be associated with a lower risk of clinical events in DELIVER, which comprised patients with HFmrEF and HFpEF, previous studies supported potential benefits of beta-blockers in patients with HFmrEF or HF with improved ejection fraction, and effects among those patients with HFpEF remain inconsistent.[1,9,22,23] For instance, in the TOPCAT trial and the U.S.-based National Cardiovascular Data Registry PINNACLE registry, beta-blocker use was associated with an increased risk of HF hospitalizations in patients with HF and LVEF of 50% or greater, whereas the associations between beta-blocker use and clinical events in DELIVER were not influenced by LVEF.[9,10] It is possible that the broader international population, younger age, higher prevalence of comorbidities such as AFF, hypertension, diabetes, or previous MI, and the enrollment of patients with improved LVEF in DELIVER may have contributed to the discrepancies compared with previous studies.[24] Indeed, because inhibition of adrenergic activity can alter multiple distinct pathways in addition to its direct influence

FIGURE 3 Association Between Beta-Blocker Use and Key Outcomes by LVEF as a Continuous Measure



Association between beta-blocker use and the primary composite outcome (first occurrence of cardiovascular [CV] death, heart failure [HF] hospitalization, or urgent heart failure visit), cardiovascular death, worsening heart failure events (heart failure hospitalization and urgent heart failure visit), and all-cause death according to baseline left ventricular ejection fraction (LVEF), obtained from Poisson regression models with baseline left ventricular ejection fraction expressed through restricted cubic spline. Models were adjusted for country, age, sex, race, atrial fibrillation/flutter, type 2 diabetes mellitus, any coronary artery disease, hypertension, previous heart failure hospitalization, improved ejection fraction (previous ejection fraction ≤40%) status, baseline body mass index, baseline NYHA functional class, log-transformed baseline N-terminal pro-B-type natriuretic peptide levels, baseline heart rate, baseline systolic blood pressure, and baseline estimated glomerular filtration rate.

on the myocardium, the role of beta-blockers in these patients may ultimately vary depending on cause, ventricular phenotype, and comorbidity burden.[25] In addition, although natriuretic peptides are important prognostic markers in HF, the foregoing analyses in TOPCAT and PINNACLE were not adjusted for NT-proBNP.[26,27] Moreover, despite apprehensions that negative chronotropic effects of beta-blockers may adversely affect outcomes and symptoms in HFpEF, we observed similar heart rates at baseline in patients who were or were not taking a beta-blocker, but we were not able to capture heart rate response at peak or submaximal exercise performance.[12,28,29] We further found that baseline KCCQ scores did not differ regardless of beta-blocker use, with no increased risk of worsening at 8 months in patients taking a beta-blocker. These observations appear to diverge from those that resulted from a specific subset with coexisting chronotropic incompetence.[11] Notably, although the observed lower point estimates could raise the possibility of a potential benefit of beta-blockers on clinical outcomes, it is important to note that these findings are confounded by the non-randomized use of beta-blockers and should be interpreted with caution. Nevertheless, these data contribute to the so far sparse evidence from randomized clinical trials and suggest, at the very least, no increased risk of adverse clinical outcomes with

TABLE 3 Treatment Effect According to Beta-Blocker Use

Outcome	No Beta-Blocker Use		Beta-Blocker Use		$P_{interaction}$[a]
	Dapagliflozin (n = 539)	Placebo (n = 547)	Dapagliflozin (n = 2,592)	Placebo (n = 2,585)	
Primary composite					
Events	102 (19)	125 (23)	410 (16)	485 (19)	0.85
Rate, per 100 pt-y	9.4	11.9	7.5	9.1	
HR (95% CI)	0.79 (0.61-1.03)		0.82 (0.72-0.94)		
HF event					
Events	71 (13)	95 (17)	297 (11)	360 (14)	0.61
Rate, per 100 pt-y	6.5	9.0	5.5	6.8	
HR (95% CI)	0.73 (0.54- 0.99)		0.80 (0.69- 0.94)		
CV death					
Events	50 (9)	57 (10)	181 (7)	204 (8)	0.94
Rate, per 100 pt-y	4.3	4.9	3.1	3.5	
HR (95% CI)	0.86 (0.59-1.26)		0.89 (0.72-1.08)		
All-cause death					
Events	86 (16)	107 (20)	411/2,592 (16)	419/2,585 (16)	0.20
Rate, per 100 pt-y	7.4	9.3	7.1	7.3	
HR (95% CI)	0.79 (0.60-1.05)		0.98 (0.85-1.12)		
Total HF events and CV death					
Events	57	64	428	489	0.26
Rate, per 100 pt-y	8.9	10.5	10.2	11.7	
RR (95% CI)	0.65 (0.48-0.88)		0.80 (0.68-0.94)		
KCCQ-TSS					
Mean change at 8 mo	8.0 ± 19.3	6.3 ± 21.5	8.0 ± 19.8	5.4 ± 20.6	0.59
Proportion with increase ≥5 in score at 8 mo	187 (49.7)	172 (48.9)	948 (51.8)	881 (47.6)	0.41
OR (95% CI)	1.04 (0.77-1.38)		1.18 (1.04-1.35)		
Proportion with decrease ≥5 in score at 8 mo	70 (18.6)	98 (27.8)	402 (22.0)	481 (26.0)	0.12
OR (95% CI)	0.59 (0.42-0.84)		0.80 (0.69-0.93)		
KCCQ-CSS					
Mean change at 8 mo	7.2 ± 17.3	5.3 ± 18.4	7.1 ± 17.9	4.6 ± 18.1	0.64
Proportion with increase ≥5 in score at 8 mo	182 (48.4)	168 (47.7)	939 (51.3)	867 (46.8)	0.35
OR (95% CI)	1.03 (0.77-1.37)		1.20 (1.05-1.36)		
Proportion with decrease ≥5 in score at 8 mo	65 (17.3)	90 (25.6)	395 (21.6)	482 (26.0)	0.21
OR (95% CI)	0.61 (0.42-0.87)		0.78 (0.67-0.91)		
KCCQ-OSS					
Mean change at 8 mo	7.6 ± 17.1	5.9 ± 17.5	7.2 ± 17.7	4.9 ± 17.1	0.63
Proportion with increase ≥5 in score at 8 mo	187 (49.7)	182 (51.7)	964 (52.6)	907 (49.0)	0.16
OR (95% CI)	0.92 (0.69-1.24)		1.16 (1.02-1.32)		
Proportion with decrease ≥5 in score at 8 mo	71 (18.9)	87 (24.7)	383 (20.9)	461 (24.9)	0.55
OR (95% CI)	0.71 (0.50-1.01)		0.80 (0.68-0.93)		

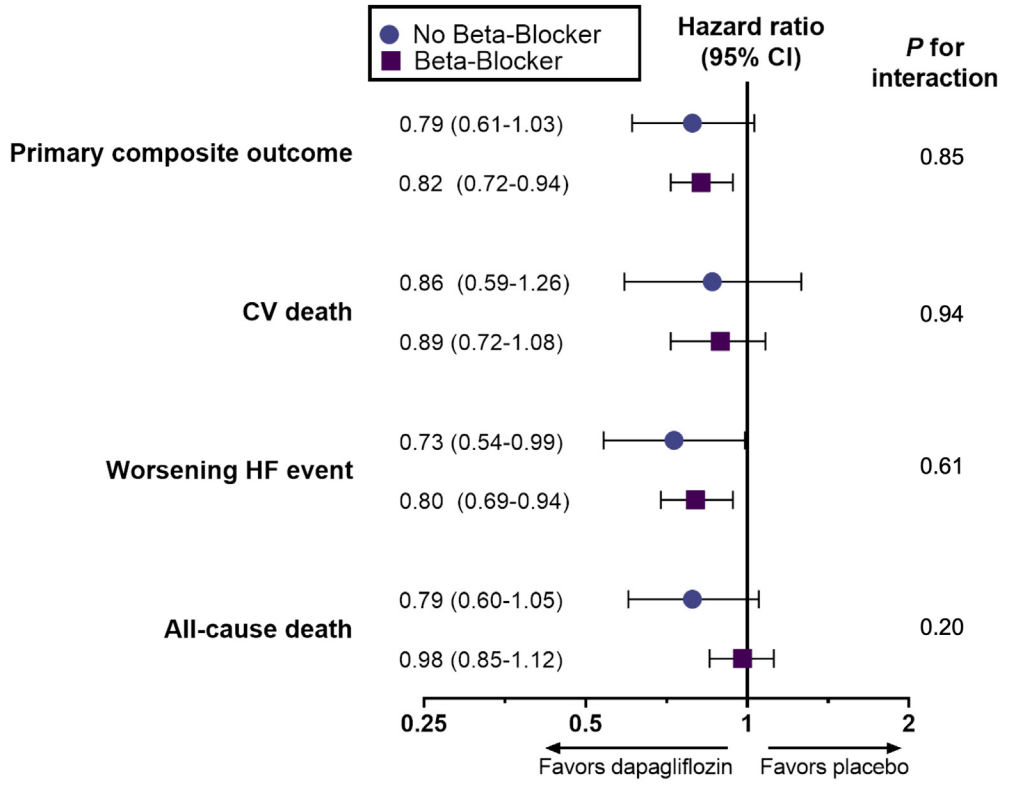
Values are n, n (%), n/N (%), n/100 pt-y, mean ± SD, HR (95% CI), RR (95% CI), or OR (95% CI). [a]$P_{interaction}$ values are reported for interaction between treatment effect and beta-blocker use.

Abbreviations as in Tables 1 and 2.

background beta-blocker therapy in patients with HFmrEF or HFpEF.

Although the mechanisms of SGLT2 inhibitors and beta-blockers are thought to be distinct, given the current concerns and sparse evidence regarding beta-blocker use in HFpEF, it remained uncertain whether combined therapy can alter the treatment benefits of SGLT2 inhibitors.[30] In DELIVER, the benefits of dapagliflozin on clinical events were consistent in patients who were and were not taking a beta-blocker, with no treatment effect modification by beta-blocker use for any outcome. Despite objections that beta-blockers may worsen functional capacity in HFpEF, dapagliflozin therapy similarly led to improved KCCQ scores, regardless of beta-blocker use.[11,31] Although differences in background therapy dosing may affect clinical outcomes and health-related quality of life, the achievement of beta-blocker target dosing did not influence the treatment effect of dapagliflozin.[32] Importantly, patients taking a beta-blocker also did not experience higher rates of treatment discontinuation and AEs,

FIGURE 4 Effect of Dapagliflozin According to Beta-Blocker Use



Treatment effect of dapagliflozin, compared with placebo, on the primary composite outcome (first occurrence of cardiovascular [CV] death, heart failure [HF] hospitalization, or urgent heart failure visit), cardiovascular death, worsening heart failure events (heart failure hospitalization and urgent heart failure visit), and all-cause death according to beta-blocker use, obtained from Cox proportional hazards models.

TABLE 4 Occurrence of Adverse Events According to Beta-Blocker Use

	No Beta-Blocker Use		Beta-Blocker Use		
	Dapagliflozin (n = 539)	Placebo (n = 546)	Dapagliflozin (n = 2,587)	Placebo (n = 2,581)	$P_{interaction}$[a]
Any serious AE (including death)	254 (47.1)	268 (49.1)	1,107 (42.8)	1,155 (44.8)	0.99
Treatment discontinuation for any reason	93 (17.0)	84 (15.6)	349 (13.5)	360 (13.9)	0.45
Treatment discontinuation for any AE	34 (6.3)	48 (8.8)	148 (5.7)	133 (5.2)	0.07
Any amputation	2 (0.4)	6 (1.1)	17 (0.7)	19 (0.7)	0.27
Any potential risk factor AE for amputation affecting lower limbs	39 (7.2)	32 (5.9)	149 (5.8)	167 (6.5)	0.20
Any definite or probable diabetic ketoacidosis	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	NA
Any major hypoglycemic event	0 (0.0)	0 (0.0	6 (0.2)	7 (0.3)	NA
Any serious AE or DAE suggestive of volume depletion	7 (1.3)	7 (1.3)	35 (1.4)	25 (1.0)	0.59
Any renal serious AE or DAE	14 (2.6)	13 (2.4)	59 (2.3)	66 (2.6)	0.63
Any serious hypotension AE	2 (0.4)	1 (0.2)	9 (0.3)	3 (0.1)	0.33
Any serious AE related to dizziness	2 (0.4)	0 (0.0)	3 (0.1)	3 (0.1)	NA
Any serious AE related to presyncope	1 (0.2)	0 (0.0)	1 (0.0)	3 (0.1)	NA
Any serious bradycardia AE	3 (0.6)	2 (0.4)	12 (0.5)	8 (0.3)	0.52

Values are n (%). [a]$P_{interaction}$ values are reported for interaction between treatment effect and beta blocker use. Safety analyses were performed in randomized participants who received at least 1 dose of study medication, with a total of 10 participants excluded.

AE = adverse event; DAE = adverse events leading to treatment discontinuation; NA = not applicable.

with a balanced safety profile between dapagliflozin and placebo, irrespective of beta-blocker use. In addition to beta-blockers, patients with HFmrEF or HFpEF are frequently treated with other HF medical therapies. Previous DELIVER analyses have demonstrated consistent benefits of SGLT2 inhibitors with background use of a mineralocorticoid receptor antagonist and an angiotensin receptor-neprilysin inhibitor and with the total of concomitant medications in DELIVER.[33,34] The current analysis from DELIVER extends these findings to support consistency of treatment efficacy and safety, irrespective of beta-blocker use or dosing.

STUDY LIMITATIONS. Although the number of participants not taking a beta-blocker was relatively small, there was wide variation in its use by geographic region and country. Data on medication use were based on case report forms and were not cross-validated against additional sources such as pharmacy fill data. In addition, measures of adherence were not collected in DELIVER, with potential differences in adherence rates between this trial and routine clinical practice, which could in turn affect the generalizability of our results. Despite accounting for confounding by a covariate-adjusted and propensity score–based models, imbalances in patient characteristics stemming from the nonrandomized use of beta-blockers may have influenced the results of this study. Finally, although conditions potentially recommending beta-blocker use were assessed on the basis of the patient's medical history, DELIVER did not capture specific clinical indications for background therapies.

CONCLUSIONS

In DELIVER, most participants were treated with a beta-blocker, whereas most of these patients had at least 1 potential indication for use. Beta-blocker use was not associated with a higher risk of worsening HF events or cardiovascular death and deteriorations of health-related quality of life. The benefits of dapagliflozin on clinical events were consistent among patients taking or not taking a beta-blocker, with a similar safety profile. These data provide reassurance for background beta-blocker treatment in HFmrEF or HFpEF and complement previous evidence supporting SGLT2 inhibitors as therapeutic options in these patients irrespective of background medical therapy.

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The DELIVER trial was funded by AstraZeneca. Dr Peikert has received a research grant from the German Research Foundation. Dr Bart has received research grant support (paid to institution) from AstraZeneca, Cardurion, and Daxor; and has participated in clinical trial committees for studies sponsored by Daxor and Nuwellis. Dr Vaduganathan has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Chiesi, Cytokinetics, Lexicon Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; and has participated on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. Dr Claggett has received consulting fees from Alnylam, Cardurion, Corvia, Cytokinetics, Intellia, and Rocket. Dr Kosiborod has received research grant support from AstraZeneca, Boehringer Ingelheim, and Pfizer; has served as a consultant or on an advisory board for 35 Pharma, Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics, Imbria Pharmaceuticals, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Pfizer, scPharmaceuticals Structure Therapeutics, Vifor Pharma, and Youngene Therapeutics; has received other research support from AstraZeneca; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. Dr Desai has received institutional research grants from Abbott, AstraZeneca, Alnylam, Bayer, Novartis, and Pfizer; and has received personal consulting fees from Abbott, AstraZeneca, Alnylam, Avidity, Axon Therapeutics, Bayer, Biofourmis, GlaxoSmithKline, Medpace, Merck, Novartis, Parexel, Regeneron, River2Renal, Veristat, Verily, and Zydus. Dr Jhund has received speaker fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals; has received advisory board fees from AstraZeneca, Boehringer Ingelheim, Novartis; has received research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc; has received personal fees from Roche and Intas Pharma; has served as Director of Global Clinical Trial Partners (GCTP); and his employer, the University of Glasgow, has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis, and Novo Nordisk. Dr Lam has received supported from a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the advisory board/steering committee/executive committee for Actelion, Alleviant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc, EchoNous, Eli Lilly, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research and Development, Medscape/WebMD Global, Merck, Novartis, Novo Nordisk, Prosciento, Radcliffe Group, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and us2.ai; and has served as cofounder and nonexecutive director of us2.ai. Dr Inzucchi has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lexicon, Merck, Pfizer, vTv Therapeutics, Abbott, and Esperion; and has given lectures sponsored by AstraZeneca and Boehringer Ingelheim. Dr Martinez has received personal fees from AstraZeneca. 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. Dr Hernandez has received research grants from American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Somologic and Verily; and has served as a consultant or on the advisory board for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cytokinetics, Eidos, Intercept, Merck, and Novartis. Dr Shah has received research grants from the National Institutes of Health (U54 HL160273, R01 HL107577, R01 HL127028, R01 HL140731, and R01 HL149423), Actelion, AstraZeneca, Corvia, Novartis, and Pfizer; and has received consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardiora, Coridea, CVRx, Cyclerion,

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with HFmrEF or HFpEF, beta-blocker use was not associated with a higher risk of worsening HF or cardiovascular death and did not modify the benefits with dapagliflozin on symptoms and clinical events, with a similar safety profile.

TRANSLATIONAL OUTLOOK: These data further emphasize the considerable benefits and the favorable safety profile of dapagliflozin in HF, regardless of background beta-blocker use. Although this study does not indicate an increased risk of adverse clinical outcomes with beta-blocker treatment in patients with HFmrEF or HFpEF, future randomized trials are needed to validate this study's findings.

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APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.