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ORIGINAL INVESTIGATIONS

Atrial Fibrillation and Dapagliflozin Efficacy in Patients With Preserved or Mildly Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Atrial fibrillation (AF) is common in heart failure (HF), is associated with worse outcomes compared with sinus rhythm, and may modify the effects of therapy.

OBJECTIVES This study examined the effects of dapagliflozin according to the presence or not of AF in the DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) trial.

METHODS A total of 6,263 patients with HF with New York Heart Association functional class II-IV, left ventricular ejection fraction >40%, evidence of structural heart disease, and elevated N-terminal pro-B-type natriuretic peptide levels were randomized to dapagliflozin or placebo. Clinical outcomes and the effect of dapagliflozin, according to AF status, were examined. The primary outcome was a composite of cardiovascular death or worsening HF.

RESULTS Of the 6,261 patients with data on baseline AF, 43.3% had no AF, 18.0% had paroxysmal AF, and 38.7% had persistent/permanent AF. The risk of the primary endpoint was higher in patients with AF, especially paroxysmal AF, driven by a higher rate of HF hospitalization: no AF, HF hospitalization rate per 100 person-years (4.5 [95% CI: 4.0-5.1]), paroxysmal AF (7.5 [95% CI: 6.4-8.7]), and persistent/permanent AF (6.4 [95% CI: 5.7-7.1]) ($P < 0.001$). The benefit of dapagliflozin on the primary outcome was consistent across AF types: no AF, HR: 0.89 (95% CI: 0.74-1.08); paroxysmal AF, HR: 0.75 (95% CI: 0.58-0.97); persistent/permanent AF, HR: 0.79 (95% CI: 0.66-0.95) ($P_{interaction} = 0.49$). Consistent effects were observed for HF hospitalization, cardiovascular death, all-cause mortality, and improvement in the KCCQ-TSS.

CONCLUSIONS In DELIVER, the beneficial effects of dapagliflozin compared with placebo on clinical events and symptoms were consistent, irrespective of type of AF at baseline. (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure. [DELIVER]; NCT03619213) (J Am Coll Cardiol 2022;80:1705-1717) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ECG = electrocardiogram

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

KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score

LVEF = left ventricular ejection fraction

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

NYHA = New York Heart Association

RR = rate ratio

SGLT2 = sodium-glucose cotransporter-2

Atrial fibrillation (AF) is common in patients with heart failure and preserved ejection fraction (HFpEF), with a reported prevalence of up to 65%.[1-3] Patients with AF have worse outcomes than those with sinus rhythm, and notably, the elevated risk related to AF is greater in patients with HFpEF than in those with heart failure and reduced ejection fraction (HFrEF).[2,4] Therefore, the identification of effective therapies for patients with both HFpEF and AF is very important. However, not all treatments for HF are effective in patients with concomitant AF. For example, ivabradine is not indicated for patients with AF, and in clinical trials of HFrEF, the effectiveness of beta-blockers, cardiac resynchronization therapy, and most recently, omecamtiv mecarbil was attenuated in the presence of AF.[5-9] Conversely, AF did not seem to modify the effects of other therapies in HFrEF, including sodium-glucose cotransporter-2 (SGLT2) inhibitors. The picture in HFpEF is less clear as, until recently, no treatment had been shown, definitively, to reduce risk in these patients, although AF did not appear to modify the effects of spironolactone or sacubitril/valsartan in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) and PARAGON-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), respectively.[10,11] The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) and DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) trials have now shown a clear and unequivocal benefit of SGLT2 inhibitors in patients with heart failure and mildly reduced ejection fraction (HFmrEF) and HFpEF.[12,13]

SEE PAGE 1718

The subgroup analyses published in the main results papers for both of these trials demonstrated a consistent benefit of SGLT2 inhibition on the primary outcome. Here, we provide a detailed report of the effect of dapagliflozin on all of the prespecified outcomes in DELIVER, along with a description of safety and tolerability, in patients with and without AF, including subtypes of AF. We also addressed the longstanding question of whether AF is associated with worse outcomes just because it is a marker of more severe HF or if it is an independent predictor of poor prognosis. Although this question has now been studied extensively in HFrEF, it has not in HFpEF.[2,4,10,11,14-23] In addition, we investigated whether paroxysmal AF is associated with greater risk than persistent/permanent AF, as has been shown recently in HFrEF.[19]

METHODS

DELIVER was an event-driven, randomized, double-blind, controlled trial in patients with heart failure (HF) and mildly reduced and preserved left ventricular ejection fraction (LVEF) that compared the efficacy and safety of dapagliflozin 10 mg once daily compared with matching placebo. The design, baseline characteristics, and primary results of DELIVER are published.[13,24-26] The trial protocol was approved by the Ethics Committee at all participating institutions, and all patients provided written informed consent.

STUDY PATIENTS. Key inclusion criteria were age ≥40 years, a diagnosis of HF for ≥6 weeks and at least intermittent use of a diuretic agent, New York Heart Association (NYHA) functional class II-IV, LVEF >40%, evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy), and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥300 pg/mL (≥600 pg/mL if AF on the electrocardiogram [ECG] at enrollment). Both ambulatory and hospitalized patients were eligible for enrollment. Key exclusion criteria were treatment of type 1 diabetes, estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2, and systolic

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blood pressure <95 mm Hg. A complete list of exclusion criteria is provided in the design paper.[24]

ATRIAL FIBRILLATION. Data on history of AF were collected on the trial case report forms, investigators were first asked whether patients had a history of AF any time before enrollment and then to specify the type of AF according to the following options: paroxysmal (intermittent [lasting at least 30 seconds], self-terminating AF, lasting for a maximum of 1 week), persistent (non-self-terminating AF with a duration of >1 week and/or required cardioversion), and permanent (non-self-terminating, long-standing AF in which cardioversion has failed or not attempted). Data on heart rhythm on the ECG at enrollment were also collected on the case report forms, and investigators were asked to specify the heart rhythm from the following options: normal sinus rhythm, atrial fibrillation, atrial flutter, paced rhythm, and other (specify).

As in previous studies, "atrial fibrillation" included atrial fibrillation or flutter. Based on AF status, we made the following comparisons: 1) patients without any AF (no history of AF and no AF on enrollment ECG) vs any AF (a history of AF or AF on enrollment ECG); 2) patients without any AF (no history of AF and no AF on enrollment ECG) vs AF on enrollment ECG (irrespective of history of AF); and 3) patients without any AF (no history of AF and no AF on enrollment ECG) vs paroxysmal AF (history of paroxysmal AF or AF on enrollment ECG without a history of AF) vs persistent/permanent AF (history of persistent/permanent AF).

Patients were included in the present study if they had available data on a history of AF and enrollment ECG.

TRIAL OUTCOMES. The primary outcome in DELIVER was the composite of worsening HF (HF hospitalization or urgent HF visit) or cardiovascular death. The secondary outcomes were total HF events (first and repeat HF hospitalizations) and cardiovascular death, change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS), death from cardiovascular causes, and death from any cause. In the present analysis, we also examined worsening HF and HF hospitalization as components of the primary composite outcome, sudden cardiac death, and pump failure death.

Prespecified safety analyses included serious adverse events, adverse events leading to discontinuation of trial treatment, and selected adverse events, including volume depletion, renal adverse events, amputation, major hypoglycemia, and diabetic ketoacidosis for consistency across reporting in trials. Safety analyses were only performed in patients who had undergone enrollment and received at least 1 dose of either dapagliflozin or placebo; a total of 10 randomized patients were excluded from the safety analysis.

STATISTICAL ANALYSES. Baseline characteristics were summarized as frequencies (%), mean ± SD, or median (IQR). Differences in baseline characteristics were tested using the chi-square test for binary or categorical variables and the Wilcoxon test and 2-sample Student's *t*-test for nonnormal 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 (all outcomes except all-cause death), and Cox proportional hazards models; stratified according to diabetes mellitus status; and adjusted for treatment assignment. HRs with 95% CIs were reported (for AF category vs no AF as reference). Total (first and recurrent) events were evaluated with semiparametric proportional-rates models, stratified according to diabetes mellitus status, and adjusted for treatment assignment, and rate ratios (RRs) with 95% CIs were reported.[27] In addition, HRs and RRs, stratified according to diabetes mellitus status and adjusted for treatment assignment, sex, geographical region, systolic blood pressure, heart rate, body mass index, estimated glomerular filtration rate, HF duration, a history of HF hospitalization, LVEF, NYHA functional class, history of any coronary artery disease, hypertension, chronic obstructive pulmonary disease, and stroke/transient ischemic attack were reported. Finally, HRs and RRs, additionally adjusted for log of NT-proBNP, were also reported. Given that patients with AF on the enrollment ECG were required to have an NT-proBNP ≥600 pg/mL (whereas those without were eligible if the NT-proBNP level was ≥300 pg/mL), sensitivity analyses were conducted, in which the association between AF status and outcomes were examined in patients with a NT-proBNP level ≥600 pg/mL. The proportional hazards assumption was examined with log(-log[survival]) curves and scaled Schoenfeld residuals, and the assumption was not violated for any of the models.

To compare the effects of dapagliflozin vs placebo, 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 diabetes mellitus status. The difference between treatment groups in the change in

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NOVEMBER 1, 2022:1705–1717

TABLE 1 Baseline Characteristics According to AF (History or on Enrollment Electrocardiogram)

	No AF (n = 2,709)	Any AF (n = 3,552)	*P* Value
Age, y	69.4 ± 10.4	73.4 ± 8.5	<0.001
≤65	907 (33.5)	597 (16.8)	
66-75	984 (36.3)	1,428 (40.2)	
≥76	818 (30.2)	1,527 (43.0)	
Sex			0.89
Women	1,186 (43.8)	1,561 (43.9)	
Men	1,523 (56.2)	1,991 (56.1)	
Race			<0.001
White	1,822 (67.3)	2,615 (73.6)	
Black or African American	110 (4.1)	49 (1.4)	
Asian	534 (19.7)	740 (20.8)	
Other	243 (9.0)	148 (4.2)	
Geographic region			<0.001
Europe and Saudi Arabia	1,130 (41.7)	1,873 (52.7)	
Asia	503 (18.6)	723 (20.4)	
Latin America	763 (28.2)	418 (11.8)	
North America	313 (11.6)	538 (15.1)	
Physiological measures			
Systolic blood pressure, mm Hg	129.7 ± 15.7	127.1 ± 15.0	<0.001
Diastolic blood pressure, mm Hg	72.9 ± 10.3	74.7 ± 10.3	<0.001
Heart rate, beats/min	69.1 ± 10.1	73.3 ± 12.6	<0.001
Body mass index, kg/m^2	29.5 ± 6.1	30.1 ± 6.2	<0.001
NT-proBNP, pg/mL	701 (460-1,271)	1,242 (826-2,043)	<0.001
Hemoglobin A1c, %	6.8 ± 1.6	6.4 ± 1.2	<0.001
Creatinine, μmol/L	102.1 ± 33.2	102.7 ± 29.4	0.47
eGFR, mL/min/1.73 m^2	63.0 ± 20.5	59.5 ± 17.9	<0.001
<60	1,226 (45.3)	1,844 (51.9)	
≥60	1,483 (54.7)	1,707 (48.1)	
Smoking status			<0.001
Current	257 (9.5)	227 (6.4)	
Former	968 (35.7)	1,293 (36.4)	
Never	1,484 (54.8)	2,032 (57.2)	
Duration of HF			<0.001
0-3 mo	240 (8.9)	328 (9.2)	
>3-6 mo	298 (11.0)	294 (8.3)	
>6-12 mo	400 (14.8)	442 (12.4)	
>1-2 y	447 (16.5)	548 (15.4)	
>2-5 y	653 (24.1)	915 (25.8)	
>5 y	667 (24.7)	1,024 (28.8)	
Left ventricular ejection fraction, %	53.4 ± 9.1	54.8 ± 8.5	<0.001
≤49	1,072 (39.6)	1,043 (29.4)	
50-59	885 (32.7)	1,370 (38.6)	
≥60	752 (27.8)	1,139 (32.1)	
Left atrial diameter, cm	4.5 ± 0.5	4.8 ± 0.8	<0.001
Left atrial area, cm^2	25.1 ± 6.2	29.5 ± 8.3	<0.001
Left atrial volume, mL	81.4 ± 78.3	100.1 ± 50.9	<0.001
Left atrial volume index, mL/m^2	44.3 ± 25.8	55.7 ± 36.8	<0.001
NYHA functional class			<0.001
I	0 (0.0)	1 (0.0)	
II	2,139 (79.0)	2,572 (72.4)	
III	562 (20.7)	969 (27.3)	
IV	8 (0.3)	10 (0.3)	
KCCQ-TSS	70.5 ± 22.1	69.7 ± 22.2	0.16
KCCQ-CSS	68.9 ± 20.9	67.9 ± 20.5	0.083
KCCQ-OSS	66.8 ± 20.3	66.5 ± 20.2	0.56

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KCCQ-TSS from baseline to 8 months was analyzed using mixed-effect models for repeated measurements adjusted for baseline value, visit (month 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.

All analyses were conducted using SAS version 9.4 (SAS Institute) and STATA version 17.0 (StataCorp).

RESULTS

Of the 6,263 patients randomized, 2 were excluded because of a lack of ECG data at baseline.

PATIENT CHARACTERISTICS. Any AF (history or enrollment ECG). A total of 3,552 (56.7%) patients had any AF (ie, a history of AF or AF on enrollment ECG) at enrollment. Baseline characteristics of these patients compared with those without any AF are shown in Table 1. Compared with patients without AF, those with AF were older and more often White, and they had a higher heart rate and body mass index, but lower systolic blood and eGFR. Patients with AF were more likely to have a prior stroke and chronic obstructive pulmonary disease, but were less likely to have type 2 diabetes (40.6% of patients with AF vs 50.3% in those without). Patients with AF were much less likely to have a history of myocardial infarction (17.5% vs 37.5%) and other evidence of coronary artery disease.

Patients with AF had a longer duration of HF, a higher rate of prior HF hospitalization, higher NT-proBNP, and worse NYHA functional class but higher mean LVEF.

Regarding pharmacological therapy, patients with AF were less frequently treated with a renin-angiotensin-system inhibitor (69.3% of patients with AF vs 76.8% in those without) or sacubitril/valsartan (4.4% vs 5.3%) but were more often prescribed a beta-blocker (83.6% vs 81.5%). There was a larger difference in the use of loop diuretic agents (82% vs 70%). Patients with AF were also more likely to have a pacemaker. Overall, 88.5% of patients with AF were treated with an oral anticoagulant, 7.7% with digoxin, and 10.2% with amiodarone (compared with 8.8%, 0.8%, and 3.4%, respectively, among patients without AF).

AF on enrollment ECG. A total of 2,644 (42.2%) patients had AF on their ECG at enrollment (irrespective of history of AF). Baseline characteristics of these patients compared with those without any AF are presented in Supplemental Table 1. Overall, the differences were similar to those described in the previous text and in Table 1.

Type of AF. Baseline characteristics according to the type of AF are presented in Supplemental Table 2. Compared with patients with paroxysmal AF, those with persistent/permanent AF were more often men and less often White, and they had a higher heart rate, eGFR, and NT-proBNP (median 1,385 pg/mL [IQR: 952-2,196 pg/mL] vs 908 pg/mL [IQR: 573-1,607 pg/mL]), but lower systolic blood pressure. Patients with persistent/permanent AF were more likely to have a prior stroke (11.5% of patients with persistent/permanent AF vs 8.7% in those with paroxysmal AF), but were less likely to have type 2 diabetes, history of myocardial infarction (15.3% vs 22.1%), and other evidence of coronary artery disease. They also had a longer duration of HF and were in a worse NYHA functional class. Patients with persistent/permanent AF were more frequently treated with a mineralocorticoid-receptor antagonist (45.0% of patients with persistent/permanent AF vs 36.4% in those with paroxysmal AF), digoxin (9.5% vs 3.8%), and oral anticoagulants (91.6% vs 81.8%), but less often with amiodarone (5.2% vs 20.9%). There was no substantial difference in the use of beta-blockers. Patients with persistent/permanent AF were less likely to have a pacemaker.

OUTCOMES ACCORDING TO AF STATUS. Any AF (history or on enrollment ECG). Patients with AF had a higher risk of all clinical outcomes except for cardiovascular death, sudden cardiac death, and all-cause death compared with individuals without AF (**Table 2**). After adjustment for prognostic variables (excluding NT-proBNP), the risk of all the clinical outcomes examined no longer differed significantly between patients with and without AF. After further adjustment for NT-proBNP, the risk of the primary outcome, cardiovascular death, sudden cardiac death, all-cause death, and total HF hospitalizations and cardiovascular death were significantly lower in patients with AF, compared with those without (**Table 2**).

AF on enrollment ECG. After adjustment for prognostic variables, except NT-proBNP, patients with AF on their enrollment ECG had a similar risk of all clinical outcomes compared with individuals without AF (Supplemental Table 3). However, after further adjustment for NT-proBNP, the risk of each clinical outcome, except for pump failure death, was lower in patients with AF on their enrollment ECG than in those without AF (Supplemental Table 3).

Type of AF. Both patients with paroxysmal and persistent/permanent AF had a higher unadjusted risk of all clinical outcomes, except cardiovascular death, sudden cardiac death, and all-cause death, compared with individuals without AF (**Figure 1,**

TABLE 1 Continued

	No AF (n = 2,709)	Any AF (n = 3,552)	*P* Value
Medical history			
History of AF	0 (0.0)	3,551 (100.0)	NA
Type of AF			NA
No history	2,709 (100.0)	1 (0.0)	
Paroxysmal	0 (0.0)	1,126 (31.7)	
Persistent	0 (0.0)	762 (21.5)	
Permanent	0 (0.0)	1,663 (46.8)	
AF on enrollment ECG	0 (0.0)	2,644 (74.4)	NA
Hospitalization for HF	942 (34.8)	1,596 (44.9)	<0.001
Time from last HF hospitalization			<0.001
No prior HF hospitalization	1,768 (65.3)	1,956 (55.1)	
Randomized in hospital	23 (0.8)	67 (1.9)	
1-7 d	39 (1.4)	108 (3.0)	
8-30 d	156 (5.8)	261 (7.3)	
>1-3 mo	124 (4.6)	224 (6.3)	
>3-12 mo	262 (9.7)	369 (10.4)	
>1 y	337 (12.4)	567 (16.0)	
Stroke	220 (8.1)	377 (10.6)	<0.001
Stroke/TIA	277 (10.2)	495 (13.9)	<0.001
Angina	754 (27.8)	742 (20.9)	<0.001
Myocardial infarction	1,017 (37.5)	621 (17.5)	<0.001
PCI or CABG	1,205 (44.5)	944 (26.6)	<0.001
Any coronary artery disease	1,664 (61.4)	1,499 (42.2)	<0.001
Pulmonary embolism	38 (1.4)	68 (1.9)	0.12
Hypertension	2,412 (89.0)	3,140 (88.4)	0.43
Type 2 diabetes mellitus	1,362 (50.3)	1,443 (40.6)	<0.001
Chronic obstructive pulmonary disease	242 (8.9)	450 (12.7)	<0.001
Treatment			
Loop diuretic	1,896 (70.0)	2,913 (82.0)	<0.001
Other diuretic, excluding loop and MRA	665 (24.6)	678 (19.1)	<0.001
ACE inhibitor	1,051 (38.8)	1,242 (35.0)	0.002
ARB	1,040 (38.4)	1,232 (34.7)	0.002
ACE inhibitor/ARB	2,078 (76.8)	2,463 (69.3)	<0.001
ARNI	149 (5.5)	152 (4.3)	0.025
Beta-blocker	2,206 (81.5)	2,969 (83.6)	0.030
MRA	1,165 (43.0)	1,502 (42.3)	0.55
Digoxin	23 (0.8)	273 (7.7)	<0.001
Amiodarone	91 (3.4)	362 (10.2)	<0.001
Lipid-lowering medication	1,999 (73.8)	2,157 (60.7)	<0.001
Antiplatelet	1,915 (70.7)	714 (20.1)	<0.001
Anticoagulant	238 (8.8)	3,143 (88.5)	<0.001
Pacemaker	179 (6.6)	483 (13.6)	<0.001
CRT-P/CRT-D	33 (1.2)	67 (1.9)	0.036
ICD	53 (2.0)	60 (1.7)	0.43
ICD/CRT-D	72 (2.7)	96 (2.7)	0.91
CHA_2DS_2-VASc score	4.6 ± 1.4	4.7 ± 1.4	0.054
CHA_2DS_2-VASc score ≥2	2,684 (99.2)	3,530 (99.4)	0.29

Values are mean ± SD, n (%), or median (IQR). CHA_2DS_2-VASc is a stroke risk score for patients with atrial fibrillation (AF), and a higher score indicates a higher stroke risk. Congestive heart failure/left ventricular dysfunction, 1 point; hypertension, 1 point; age ≥75 years, 2 points; diabetes, 1 point; stroke/transient ischemic attack (TIA), 2 points; vascular disease (defined in the present study as a history of myocardial infarction, percutaneous coronary intervention (PCI)/coronary artery bypass graft surgery (CABG), peripheral arterial occlusive disease, renal artery stenosis, aneurysm of abdominal aorta, or non-coronary revascularization), 1 point; age 65-74 years, 1 point; female sex, 1 point.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CABG = coronary artery bypass graft surgery; CSS = clinical summary score; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; MRA = mineralocorticoid-receptor antagonist; NA = not applicable; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OSS = overall summary score; PCI = percutaneous coronary intervention; TSS = total symptom score.

TABLE 2 Outcomes According to AF (History or on Enrollment Electrocardiogram)

	No AF (n = 2,709)	Any AF (n = 3,552)
Primary composite outcome		
No. of events	429 (15.8)	693 (19.5)
Event rate per 100 person-y (95% CI)	7.6 (6.9-8.4)	9.5 (8.9-10.3)
HR (95% CI)[a]	Reference	1.28 (1.14-1.45)
HR (95% CI)[b]	Reference	1.04 (0.91-1.19)
HR (95% CI)[c]	Reference	0.84 (0.73-0.96)
HR (95% CI)[d]	Reference	0.99 (0.88-1.12)
Worsening HF		
No. of events	294 (10.9)	529 (14.9)
Event rate per 100 person-y (95% CI)	5.2 (4.7-5.9)	7.3 (6.7-7.9)
HR (95% CI)[a]	Reference	1.43 (1.24-1.65)
HR (95% CI)[b]	Reference	1.11 (0.95-1.30)
HR (95% CI)[c]	Reference	0.89 (0.75-1.04)
HR (95% CI)[d]	Reference	1.10 (0.95-1.27)
HF hospitalization		
No. of events	256 (9.4)	491 (13.8)
Event rate per 100 person-y (95% CI)	4.5 (4.0-5.1)	6.7 (6.1-7.3)
HR (95% CI)[a]	Reference	1.52 (1.31-1.77)
HR (95% CI)[b]	Reference	1.18 (1.00-1.39)
HR (95% CI)[c]	Reference	0.96 (0.81-1.13)
HR (95% CI)[d]	Reference	1.18 (1.01-1.37)
Cardiovascular death		
No. of events	200 (7.4)	292 (8.2)
Event rate per 100 person-y (95% CI)	3.4 (2.9-3.9)	3.7 (3.3-4.1)
HR (95% CI)[a]	Reference	1.11 (0.93-1.33)
HR (95% CI)[b]	Reference	0.97 (0.80-1.19)
HR (95% CI)[c]	Reference	0.79 (0.64-0.97)
HR (95% CI)[d]	Reference	0.84 (0.70-1.01)
All-cause death		
No. of events	414 (15.3)	609 (17.1)
Event rate per 100 person-y (95% CI)	7.0 (6.3-7.7)	7.7 (7.1-8.3)
HR (95% CI)[a]	Reference	1.12 (0.99-1.27)
HR (95% CI)[b]	Reference	0.98 (0.85-1.13)
HR (95% CI)[c]	Reference	0.82 (0.71-0.95)
HR (95% CI)[d]	Reference	0.88 (0.77-1.00)
Sudden cardiac death		
No. of events	105 (3.9)	130 (3.7)
Event rate per 100 person-y (95% CI)	1.8 (1.5-2.1)	1.6 (1.4-2.0)
HR (95% CI)[a]	Reference	0.95 (0.74-1.23)
HR (95% CI)[b]	Reference	0.89 (0.66-1.18)
HR (95% CI)[c]	Reference	0.72 (0.54-0.97)
HR (95% CI)[d]	Reference	0.74 (0.57-0.96)

Continued on the next page

Supplemental Table 4). After adjustment for prognostic variables, except NT-proBNP, patients with paroxysmal AF had a higher risk of worsening HF and HF hospitalization, whereas those with persistent/permanent AF had a similar risk of all clinical outcomes compared with patients with no AF. After further adjustment for NT-proBNP, patients with paroxysmal AF continued to have a higher risk of HF hospitalization than individuals without AF. By contrast, after additional adjustment for NT-proBNP, those with persistent/permanent AF had a lower risk of all clinical outcomes, except pump failure death, compared with patients with no AF (Supplemental Table 4).

In unadjusted analyses, patients with paroxysmal AF did not have significantly worse outcomes than those with persistent/permanent AF. However, in the adjusted analyses including NT-proBNP, patients with paroxysmal AF had a significantly higher risk of the primary outcome and worsening HF, but not of death (Supplemental Table 5).

SENSITIVITY ANALYSES. The analyses on the association between AF status and outcomes were also conducted in patients with a NT-proBNP level ≥600 pg/mL at baseline. Overall, findings were similar to those from the main analyses (Supplemental Tables 6 to 9).

EFFECTS OF DAPAGLIFLOZIN ACCORDING TO AF STATUS. Any AF (history or on enrollment ECG). Dapagliflozin, compared with placebo, reduced the risk of worsening HF or cardiovascular death to the same extent in patients with (HR: 0.78; 95% CI: 0.67-0.90) and without AF (HR: 0.89; 95% CI: 0.74-1.08), with no interaction between AF status and effect of treatment ($P_{interaction}$ = 0.26). The effect of dapagliflozin was also consistent in patients with and without AF for all secondary clinical outcomes (**Table 3**). The mean increase in KCCQ-TSS from baseline to 8 months was significantly greater with dapagliflozin to a similar extent in patients with and without AF ($P_{interaction}$ = 0.80).

The proportions of patients who discontinued trial treatment or experienced adverse events according to treatment assignment were similar, irrespective of AF status (**Table 4**).

AF on enrollment ECG. The effect of dapagliflozin in patients with AF on their enrollment ECG compared with those without any AF was also consistent for the primary and secondary endpoints (Supplemental Table 10). Rates of treatment discontinuation and adverse events in the dapagliflozin and placebo groups were similar in patients with and without AF on their enrollment ECG (Supplemental Table 11).

Type of AF. The effect of dapagliflozin was consistent for the primary and secondary endpoints according to the type of AF (**Central Illustration**, Supplemental Table 12). For the primary outcome, the HRs for the effect of dapagliflozin were: no AF, HR: 0.89 (95% CI: 0.74-1.08); paroxysmal AF, HR: 0.75 (95% CI: 0.58-0.97); persistent/permanent AF, HR: 0.79 (95% CI: 0.66-0.95) ($P_{interaction}$ = 0.49). The proportions of patients who discontinued trial treatment or experienced adverse events according to treatment assignment were similar, irrespective of the type of AF (Supplemental Table 13).

DISCUSSION

In the DELIVER trial, AF was common, and patients with AF had a higher unadjusted risk of worsening HF events and HF hospitalization, compared with individuals without AF. This excess risk was greatest in those with paroxysmal AF, rather than persistent/permanent AF. The risk of HF hospitalization in participants with paroxysmal AF remained elevated after extensive adjustment for other prognostic variables including NT-proBNP. Importantly, the beneficial effects of dapagliflozin, compared with placebo, on clinical events and symptoms were not modified by AF at baseline, irrespective of definition or type (Central Illustration).

BASELINE CHARACTERISTICS AND OUTCOMES ACCORDING TO AF STATUS AT BASELINE. Although AF is associated with worse outcomes in patients with HF, this has not been a consistent finding after adjustment for prognostic variables, and it remains uncertain whether AF is an independent predictor of adverse outcomes or simply a marker of more advanced HF.[2,4,10,11,14-23] In addition, data on the association between type of AF (ie, paroxysmal, persistent, or permanent) and subsequent outcomes in HF are sparse and conflicting.[19,20] Although AF was associated with worse outcomes in TOPCAT and PARAGON-HF, these analyses were not adjusted for NT-proBNP, the single strongest predictor of adverse outcomes in HF, and the association between the type of AF and outcome was not examined.[28-31] Therefore, the present analyses of DELIVER add considerably to these prior reports, especially because DELIVER enrolled a larger and broader HFmrEF/HFpEF population, including patients with improved LVEF, and some with very recent hospitalization, than any prior trial. The key findings were as follows. First, although AF was associated with a higher crude rate of worsening HF events and HF hospitalization, irrespective of definition and type, it was not associated with a higher risk of cardiovascular death or all-cause death. This was despite the requirement that patients with AF on enrollment ECG have a higher NT-proBNP compared with those in sinus rhythm (as in PARAGON-HF). Although the latter observations related to mortality in DELIVER do not support the view that AF is a marker of more advanced HF, the median follow-up of 2.3 years in the trial might have been too short to detect a mortality difference. Second, only paroxysmal AF (and not persistent/permanent AF) was associated with a greater risk of HF hospitalization after adjustment for prognostic variables (including NT-proBNP), consistent with recent findings in HFrEF.[19] One potential explanation for this observation is that the occurrence of paroxysms of AF may simply reflect deterioration in HF more generally, eg, increases in atrial pressure precipitate both episodes of AF and decompensation leading to hospital admission.[19] Alternatively, primary electrical instability, causing a paroxysm of AF and leading to a sudden increase in ventricular rate, may be the direct cause of decompensation. If the latter is true, prevention of paroxysms of AF by catheter ablation might reduce the risk of decompensation.[32-35] Notably, amiodarone was used in a much higher proportion (21%) of patients with paroxysmal AF, compared with persistent/permanent AF (5%), presumably with this therapeutic goal in mind. A third clinically relevant finding was that although the use of anticoagulants was high in DELIVER, in contrast to prior reports, these agents still appeared to be underutilized in patients with paroxysmal AF compared with persistent/permanent AF.

EFFECTS OF DAPAGLIFLOZIN ACCORDING TO AF STATUS AT BASELINE. The beneficial effects of certain HFrEF therapies may be modified by the presence of AF, as has been shown in clinical trials of beta-blockers, cardiac resynchronization therapy, and omecamtiv mecarbil,[7-9] highlighting the importance of assessing the efficacy and safety of new therapies in patients with and without AF. In EMPEROR-Preserved, the subgroup forest plot in the main results paper showed that empagliflozin reduced the

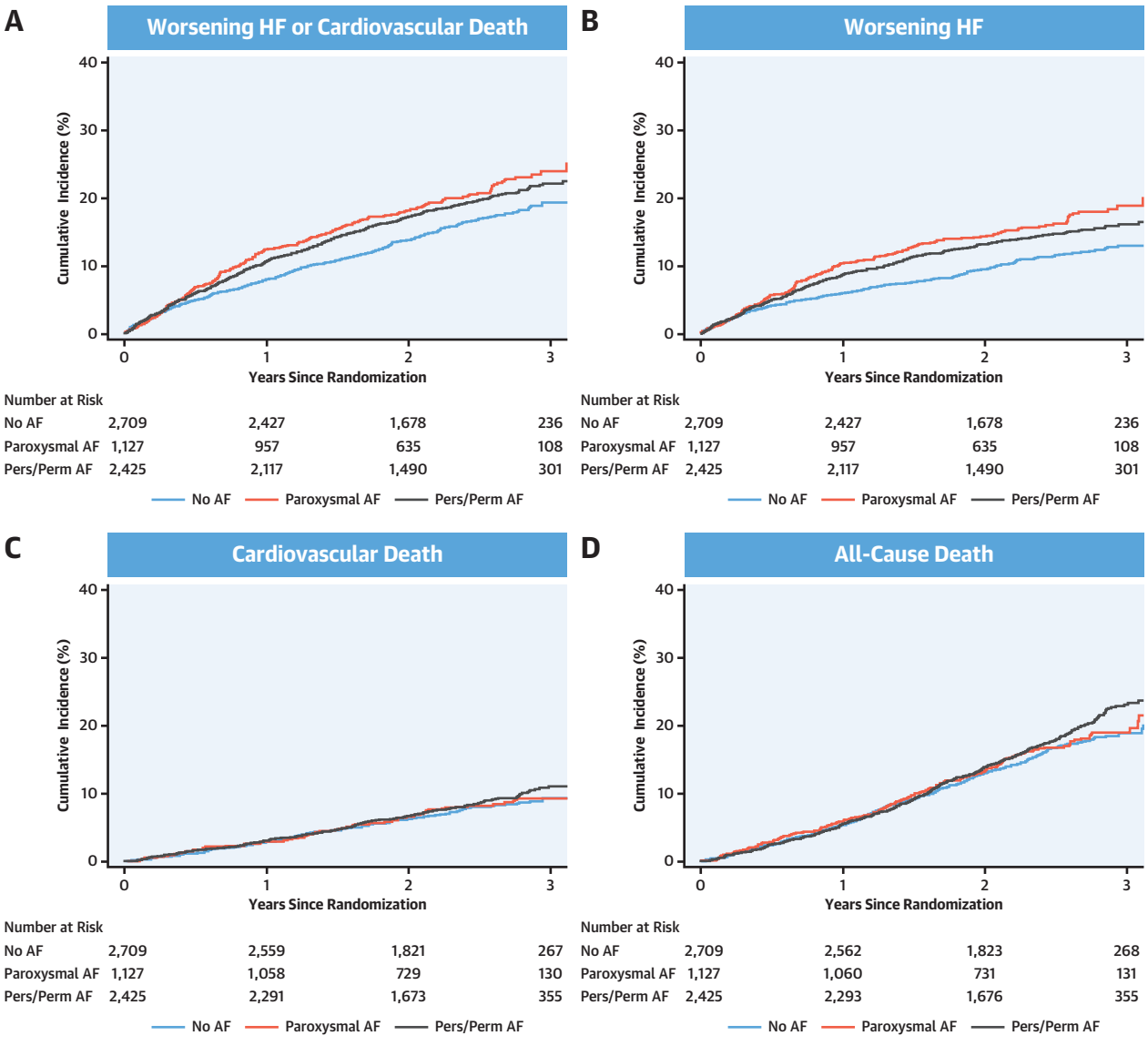
TABLE 2 Continued

	No AF (n = 2,709)	Any AF (n = 3,552)
Pump failure death		
No. of events	56 (2.1)	108 (3.0)
Event rate per 100 person-y (95% CI)	0.9 (0.7-1.2)	1.4 (1.1-1.7)
HR (95% CI)[a]	Reference	1.44 (1.04-1.99)
HR (95% CI)[b]	Reference	1.09 (0.77-1.56)
HR (95% CI)[c]	Reference	0.87 (0.61-1.25)
HR (95% CI)[d]	Reference	1.04 (0.75-1.44)
Total HF events or cardiovascular death		
No. of events	698	1,174
RR (95% CI)[a]	Reference	1.30 (1.12-1.51)
RR (95% CI)[b]	Reference	1.02 (0.87-1.20)
RR (95% CI)[c]	Reference	0.83 (0.71-0.98)
RR (95% CI)[d]	Reference	1.00 (0.86-1.16)

Values are n (%) unless otherwise indicated. [a]Stratified by diabetes status and adjusted for treatment assignment. [b]Stratified by diabetes status and adjusted for treatment assignment, age, sex, geographical region, systolic blood pressure, heart rate, body mass index, estimated glomerular filtration rate, HF duration, a history of HF hospitalization, left ventricular ejection fraction (LVEF), New York Heart Association, any coronary artery disease, hypertension, chronic obstructive pulmonary disease, and stroke/transient ischemic attack. [c]Stratified as in b and adjusted for log of N-terminal pro-B-type natriuretic peptide. [d]Stratified by diabetes status and adjusted for treatment assignment and log of N-terminal pro-B-type natriuretic peptide.

RR = rate ratio; other abbreviations as in Table 1.

FIGURE 1 **Cumulative Incidence of Outcomes According to Type of AF**



This figure shows the cumulative incidence of worsening heart failure (HF) or cardiovascular death **(A)**, worsening HF **(B)**, cardiovascular death **(C)**, and all-cause death **(D)** according to type of atrial fibrillation (AF) at baseline (no AF, paroxysmal AF, and persistent/permanent AF). Compared with patients without AF, those with paroxysmal and persistent/permanent AF have a higher cumulative incidence of worsening HF or cardiovascular death and worsening HF, but not cardiovascular death or all-cause death.

risk of the primary endpoint to a similar extent in patients with and without a "history of atrial fibrillation or atrial flutter" (no further details available).[12] In the present report, we demonstrated that the efficacy of dapagliflozin on a range of clinical outcomes was not modified by AF, irrespective of the definition or type of AF. Specifically, dapagliflozin reduced the risk of the primary composite outcome of worsening HF or cardiovascular death, as well as worsening HF events and HF hospitalization (both first and recurrent), to a similar extent in patients with and without AF at baseline, without any suggestion of attenuation of benefit regardless of definition and type of AF. Of course, because of the higher risk experienced by patients with AF, the absolute risk reduction was greater in these patients.

Reducing the symptom burden and improving physical function and quality of life are also key goals

TABLE 3 Effects of Dapagliflozin Compared With Placebo on Outcomes According to AF (History or on Enrollment Electrocardiogram)

	No AF (n = 2,709)		Any AF (n = 3,552)		
	Placebo (n = 1,337)	Dapagliflozin (n = 1,372)	Placebo (n = 1,794)	Dapagliflozin (n = 1,758)	$P_{interaction}$
Primary composite outcome					0.26
No. of events	222 (16.6)	207 (15.1)	388 (21.6)	305 (17.3)	
Event rate per 100 person-years (95% CI)	8.1 (7.1-9.2)	7.2 (6.3-8.3)	10.8 (9.8-11.9)	8.3 (7.4-9.3)	
HR (95% CI)[a]	0.89 (0.74-1.08)		0.78 (0.67-0.90)		
Worsening HF					0.24
No. of events	153 (11.4)	141 (10.3)	302 (16.8)	227 (12.9)	
Event rate per 100 person-years (95% CI)	5.6 (4.7-6.5)	4.9 (4.2-5.8)	8.4 (7.5-9.4)	6.2 (5.4-7.1)	
HR (95% CI)[a]	0.88 (0.70-1.11)		0.74 (0.63-0.88)		
HF hospitalization					0.28
No. of events	135 (10.1)	121 (8.8)	283 (15.8)	208 (11.8)	
Event rate per 100 person-years (95% CI)	4.8 (4.1-5.7)	4.2 (3.5-5.0)	7.8 (6.9-8.7)	5.6 (4.9-6.4)	
HR (95% CI)[a]	0.86 (0.67-1.10)		0.73 (0.61-0.87)		
Cardiovascular death					0.44
No. of events	101 (7.6)	99 (7.2)	160 (8.9)	132 (7.5)	
Event rate per 100 person-years (95% CI)	3.4 (2.8-4.2)	3.3 (2.7-4.0)	4.0 (3.4-4.7)	3.4 (2.8-4.0)	
HR (95% CI)[a]	0.96 (0.73-1.27)		0.83 (0.66-1.05)		
All-cause death					0.80
No. of events	209 (15.6)	205 (14.9)	317 (17.7)	292 (16.6)	
Event rate per 100 person-years (95% CI)	7.1 (6.2-8.1)	6.8 (5.9-7.8)	8.0 (7.1-8.9)	7.4 (6.6-8.3)	
HR (95% CI)[a]	0.96 (0.79-1.16)		0.93 (0.79-1.09)		
Sudden cardiac death					0.62
No. of events	54 (4.0)	51 (3.7)	72 (4.0)	58 (3.3)	
Event rate per 100 person-years (95% CI)	1.8 (1.4-2.4)	1.7 (1.3-2.2)	1.8 (1.4-2.3)	1.5 (1.1-1.9)	
HR (95% CI)[a]	0.93 (0.63-1.36)		0.81 (0.58-1.15)		
Pump failure death					0.12
No. of events	24 (1.8)	32 (2.3)	61 (3.4)	47 (2.7)	
Event rate per 100 person-years (95% CI)	0.8 (0.5-1.2)	1.1 (0.8-1.5)	1.5 (1.2-2.0)	1.2 (0.9-1.6)	
HR (95% CI)[a]	1.30 (0.77-2.21)		0.78 (0.53-1.14)		
Total HF events or cardiovascular death					0.12
No. of events	365	333	692	482	
RR (95% CI)[a]	0.89 (0.70-1.13)		0.70 (0.59-0.84)		
KCCQ-TSS					0.80
Change from baseline to 8 mo (95% CI)[b]	5.6 (4.5-6.6)	8.5 (7.5-9.6)	5.5 (4.6-6.5)	7.5 (6.5-8.4)	
Placebo-corrected change at 8 mo (95% CI)[b]	2.9 (1.4-4.4)		1.9 (0.6-3.3)		

Values are n (%) unless otherwise indicated. [a]Stratified by diabetes status. [b]Mixed-effect models for repeated measurements adjusted for baseline value, visit (months 1, 4, and 8), randomized treatment, and interaction of treatment and visit.

KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Summary Score; other abbreviations as in Tables 1 and 2.

TABLE 4 Adverse Events of Dapagliflozin Compared With Placebo According to AF (History or on Enrollment Electrocardiogram)

	No AF (n = 2,703)		Any AF (n = 3,548)		
	Placebo (n = 1,332)	Dapagliflozin (n = 1,371)	Placebo (n = 1,794)	Dapagliflozin (n = 1,754)	$P_{interaction}$
Discontinuation of study drug for any reason	178 (13.4)	168 (12.3)	264 (14.7)	276 (15.7)	0.23
Discontinuation of study drug because of adverse event	73 (5.5)	68 (5.0)	108 (6.0)	115 (6.6)	0.38
Volume depletion SAE/DAE	10 (0.8)	17 (1.2)	27 (1.5)	32 (1.8)	0.51
Renal SAE/DAE	36 (2.7)	38 (3.8)	55 (3.1)	46 (2.6)	0.55
Amputation	16 (1.2)	13 (0.9)	10 (0.6)	6 (0.3)	0.69
Major hypoglycemia	4 (0.3)	4 (0.3)	3 (0.2)	4 (0.2)	NA
Diabetic ketoacidosis[a]	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	NA

Values are n (%). A total of 10 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]Confirmed by independent adjudication committee.

AF = atrial fibrillation; DAE = adverse event leading to treatment discontinuation; SAE = serious adverse event.

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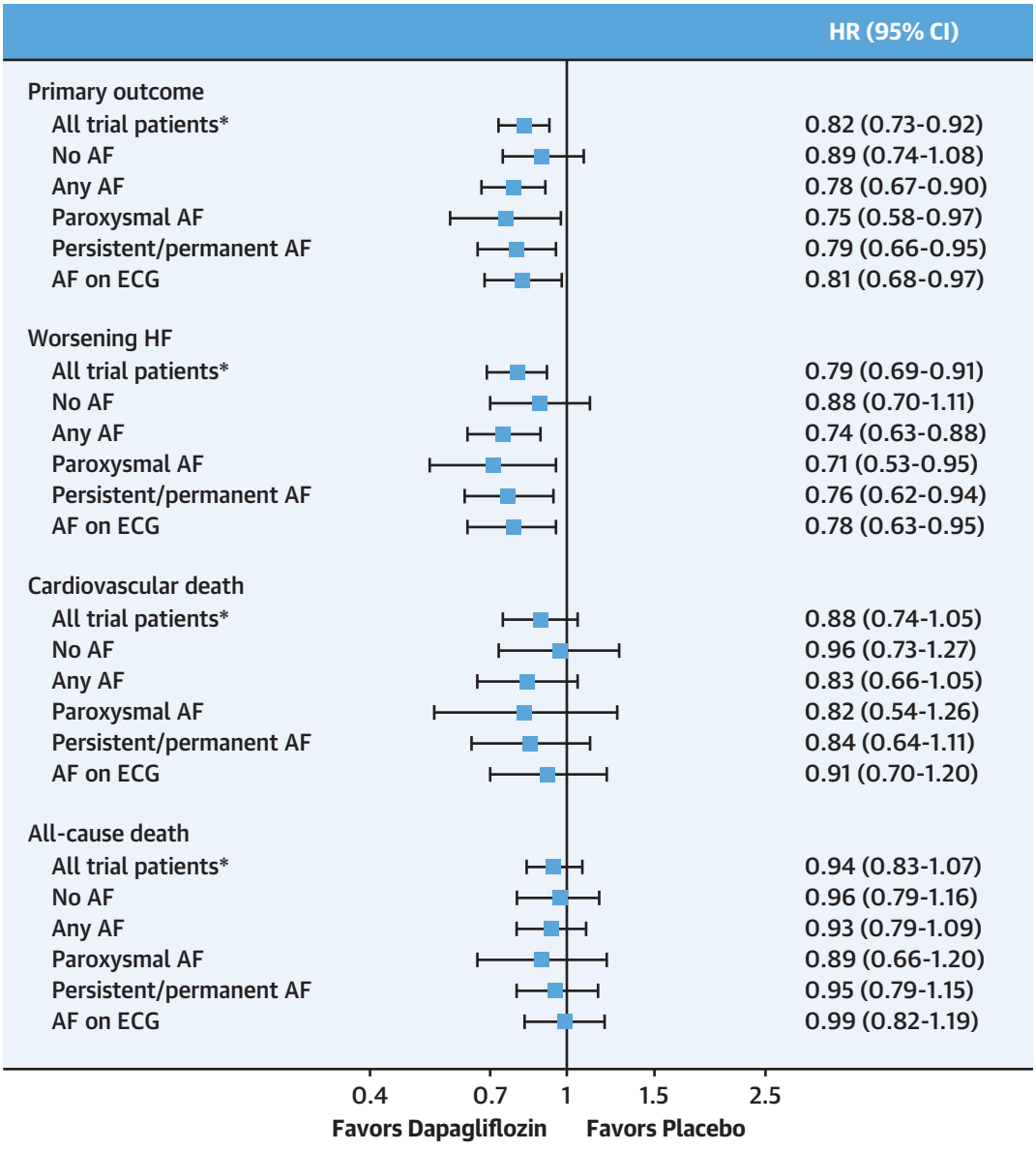
NOVEMBER 1, 2022:1705–1717

CENTRAL ILLUSTRATION **Effects of Dapagliflozin vs Placebo on Outcomes According to Atrial Fibrillation Status**



Butt JH, et al. J Am Coll Cardiol. 2022;80(18):1705–1717.

This figure shows the effects of dapagliflozin, compared with placebo, on clinical outcomes (worsening heart failure [HF] or cardiovascular death [primary outcome]; worsening HF; cardiovascular death; and all-cause death), overall in the trial and according to atrial fibrillation (AF) status at baseline. The effects of dapagliflozin on all outcomes are consistent regardless of the definition or type of AF. All HRs are stratified by diabetes status. *All 6,263 patients, including the 2 patients with missing data on AF at baseline. ECG = electrocardiogram.

in the management of patients with HF,[5,6] and for some patients, improving HF-related health status may be as important as extending life.[36] Dapagliflozin, compared with placebo, increased the mean KSSQ-TSS after 8 months of treatment, irrespective of AF status.

Collectively, these data underline the substantial, and clinically meaningful, benefits of dapagliflozin in HFmrEF/HFpEF, regardless of AF status, and provide further evidence for dapagliflozin as a new treatment option for patients with HF across the range of LVEF.

Regarding safety and tolerability, patients with AF were, overall, more likely to discontinue treatment and experience adverse events than those without, although neither was common. Importantly, study drug discontinuation and adverse events were not reported more frequently in the dapagliflozin group than in the placebo group in patients with or without AF. These reassuring data highlight the safety and tolerability of dapagliflozin in patients with HFmrEF/HFpEF, irrespective of AF status.

STUDY LIMITATIONS. The findings of this study should be viewed in the context of potential limitations. Atrial fibrillation was a predefined subgroup analysis, but the assessment of secondary and exploratory outcomes by AF status was done post hoc. The prespecified inclusion and exclusion criteria in DELIVER precluded the enrollment of very high-risk patients, which may affect the generalizability of our results. Paroxysmal AF may have been undiagnosed in some patients. Patients with AF on enrollment ECG were required to have a higher NT-proBNP level for inclusion in DELIVER, as in most other trials in HF. Finally, given the observational nature of the analyses on the association between AF and clinical outcomes, the possibility of residual confounding cannot be fully excluded despite adjustment for measured, known confounders in our analyses and collider bias may also exist.

CONCLUSIONS

In DELIVER, the beneficial effects of dapagliflozin, compared with placebo, on clinical events and symptoms were not modified by AF at baseline, irrespective of definition or type of AF. These findings provide further evidence for dapagliflozin as a new treatment option for patients with HFmrEF/HFpEF.

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The DELIVER trial was funded by AstraZeneca. Dr Butt has received advisory board honoraria from Bayer. Dr Kondo has received speaker fees from Abbott, Ono Pharma, Otsuka Pharma, Novartis, AstraZeneca, Bristol Myers Squibb, and Abiomed. Dr Jhund's employer has been remunerated for his work on the DELIVER and DAPA-HF trials by AstraZeneca; has received consulting and speaker fees from Novartis, AstraZeneca, and Boehringer Ingelheim; has received research funding from AstraZeneca and Boehringer Ingelheim; and has received remuneration for clinical trial work from Novo Nordisk and Bayer. Profs Jhund and McMurray are supported by a British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217. 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Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellPro-Thera, Moderna, American Regent, and Sarepta. Dr McMurray has received payments through Glasgow University from work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardurion, Cytokinetics, Dal-Cor, GlaxoSmithKline, Ionis, KBP Biosciences, Novartis, Pfizer, and Theracos; and has received personal lecture fees from the Corpus, Abbott, Hikma, Sun Pharmaceuticals, Medscape/Heart.Org, Radcliffe Cardiology, Servier Director, and Global Clinical Trial Partners (GCTP).

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with heart failure and preserved or mildly reduced ejection fraction, the benefit of dapagliflozin on symptoms and clinical events was not modified by baseline atrial fibrillation.

TRANSLATIONAL OUTLOOK: Additional prospective studies could improve understanding of the effects of diastolic ventricular function and atrial arrhythmias on the clinical response to SGLT-2 inhibition in patients with heart failure or various etiologies.

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