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Heart Failure, Investigator-Reported Sleep Apnea and Dapagliflozin: A Patient-Level Pooled Meta-Analysis of DAPA-HF and DELIVER

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ABSTRACT

Background: Sleep apnea is more common in patients with heart failure (HF) than in the general population, but little is known about its association with clinical outcomes in various HF phenotypes or how it might modify the effect of HF therapy.

Objectives: To examine the prevalence of sleep apnea, its association with outcomes and the effects of dapagliflozin in patients with HF with and without sleep apnea in a pooled analysis of 2 trials comparing dapagliflozin to placebo in HFrEF (DAPA-HF trial) and HFmrEF/HFpEF (DELIVER trial).

Methods: A history of sleep apnea was investigator-reported. The primary outcome was a composite of worsening HF or cardiovascular death.

Results: The prevalence of sleep apnea was 5.7% and 7.8% in patients with HFrEF and HFmrEF/HFpEF, respectively. The primary outcome occurred at a rate of 16.0 in participants with sleep apnea compared to 10.6 per 100 person-years in those without (adjusted HR 1.29 [95%CI, 1.10–1.52]). Compared with placebo, dapagliflozin reduced the risk of the primary endpoint to the same extent in patients with (HR 0.78 [95% CI, 0.59–1.03]) and without sleep apnea (HR 0.79 [0.72–0.87]) [$P_{interaction}$ = 0.93]. The beneficial effects of dapagliflozin on other clinical outcomes and symptom burden, physical function, and quality of life were consistent in participants with and without sleep apnea.

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Conclusions: In DAPA-HF and DELIVER, the true prevalence of sleep apnea was likely underestimated. An investigator-reported history of sleep apnea was associated with higher rates of worsening HF events. The benefits of dapagliflozin on clinical outcomes were consistent in patients with and without sleep apnea.

Clinical trial registration: Unique identifiers: NCT01920711

Condensed Abstract: In a pooled analysis of the DAPA-HF and DELIVER trials of more than 11,000 patients with heart failure (HF) across the range of ejection fractions, an investigator-reported history of sleep apnea was associated with higher rates of worsening HF events but not mortality. The beneficial effects of dapagliflozin on clinical outcomes were consistent in patients with and without sleep apnea. These findings provide further evidence for dapagliflozin as a new treatment option for patients with heart failure across the range of ejection fractions. (*J Cardiac Fail 2023;00:1–13*)

Key Words: Heart failure, sleep apnea, dapagliflozin, clinical trial, outcomes.

Sleep-disordered breathing is a spectrum of sleep-related conditions; the 2 major types are obstructive sleep apnea and central sleep apnea.[1–4] The former is characterized by a partial or complete obstruction of the upper airway during sleep and the latter by abnormalities in the brainstem respiratory centers, with a periodic reduction or cessation of respiratory effort without prominent airway collapse.[1–4] Although central sleep apnea is rare in the general population, obstructive sleep apnea may afflict as many as 1 in 7 individuals in the world, although it is largely undiagnosed.[5,6] Pathophysiological abnormalities related to these disorders include intrathoracic pressure swings, intermittent hypoxia, sleep reduction and fragmentation, sympathetic nervous system activation, and endothelial dysfunction, all of which are associated with increased risk of cardiovascular diseases, including incident heart failure (HF).[1–4] In patients with established HF, sleep-disordered breathing is thought to be more common than in the general population,[2,7,8–17] and it is associated with poor quality of life and higher crude rates of hospitalization and death than in patients without sleep-disordered breathing.[17–22] However, few of these studies examining the association between sleep apnea and outcomes in HF were rigorously adjusted for known prognostic variables, and none have included measurement of natriuretic peptides, the single most powerful predictor of outcome in HF.[23–26] In addition, little is known about the relationship between sleep apnea and outcomes in patients with HF with preserved ejection fraction (HFpEF).[16] To address these outstanding questions, we have examined the investigator-reported prevalence of sleep apnea at baseline, the association between sleep apnea and clinical outcomes, and the effects of dapagliflozin in patients with and without sleep apnea in each of the major HF phenotypes (reduced or preserved ejection fraction). We did this in 2 recent clinical trials in HF, both of which randomized participants to treatment with dapagliflozin or placebo and which were pooled for analysis across the range of left ventricular ejection fraction (LVEF).[27–29]

Methods

DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) were event-driven, randomized, double-blind, controlled trials in patients with symptomatic HF and elevated natriuretic peptides, comparing the efficacy and safety of dapagliflozin 10 mg once daily with a matching placebo. The main difference between the 2 trials was that DAPA-HF enrolled patients with a LVEF of $\leq$ 40%, and DELIVER enrolled with a LVEF $>$ 40%. The design, baseline characteristics and primary results of both trials have been published.[27,28,30–33] The trial protocols were approved by the ethics committees at all participating institutions, and all patients provided written informed consent.

Trial Patients

Ambulant patients in New York Heart Association (NYHA) functional class II–IV, with a LVEF of $\leq$ 40% and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were eligible for DAPA-HF.[30] Participants were also required to receive guideline-recommended treatments for HF with reduced EF (HFrEF). The main exclusion criteria were a history of type 1 diabetes mellitus, symptomatic hypotension or systolic blood pressure $<$ 95 mmHg, and an estimated glomerular filtration rate (eGFR) $<$ 30 mL/min/1.73m^2.[30]

Ambulatory and hospitalized patients in NYHA functional class II–IV, with a LVEF $>$ 40% and elevated NT-proBNP levels were eligible for DELIVER.[32] Participants were also required to have evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy). All patients had to be receiving at least intermittent diuretic therapy. Key exclusion criteria were similar to those in DAPA-HF, although the eGFR threshold was lower in DELIVER (25 mL/min/1.73m^2).[32]

Both trials randomized patients with and without type 2 diabetes, and randomization was stratified by type 2 diabetes status.

History of Sleep Apnea

In DAPA-HF and DELIVER, data concerning medical conditions at baseline, including a history of sleep apnea, were investigator-reported and retrieved from the trials' case report forms.

Trial Outcomes

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

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

Statistical Analyses

Baseline characteristics were summarized as frequencies with percentages, means with standard deviation or medians with interquartile ranges. Differences in baseline characteristics were tested using the χ^2 test for binary or categorical variables and the Wilcoxon test and 2-sample *t* test for non-normal and normally distributed continuous variables, respectively.

Following the prespecified statistical analysis plan, time-to-event data were evaluated using Cox proportional-hazards models, stratified according to diabetes mellitus status and trial and adjusted for treatment assignment and history of HF hospitalization (except in the analysis of all-cause death), and hazard ratios (HRs) with 95% CIs were reported. 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. Interaction with clinically important variables, including age and sex, were tested for and found not significant. Total (first and recurrent) events were evaluated with semiparametric proportional-rates models,[34] stratified according to diabetes mellitus status and trial and adjusted for treatment assignment and history of HF hospitalization, and rate ratios (RR) with 95% CIs were reported. In addition, HRs and RRs, stratified according to diabetes mellitus status and adjusted for treatment assignment, history of HF hospitalization, age, sex, geographical region, systolic blood pressure, heart rate, body mass index, log of NT-proBNP, eGFR, LVEF, NYHA functional class, history of myocardial infarction, atrial fibrillation, and hypertension were reported.

The incidence rate of the primary outcome and each of its components, according to continuous LVEF in patients with and without a history of sleep apnea, respectively, was estimated with Poisson regression models, with LVEF included as a restricted cubic spline.

The effect of dapagliflozin on the primary outcome and each of its components was also examined according to continuous LVEF as a fractional polynomial in patients with and without a history of sleep apnea, respectively. The number of patients needed to treat with dapagliflozin to prevent 1 event over the median follow-up was calculated by applying the overall relative risk reduction to the placebo group's event rate. The differences between treatment groups in the change in KCCQ score from baseline to 8 months were analyzed using mixed-effect models for repeated measurements, adjusted for baseline value, visit (months 4 and 8), treatment assignment, the interaction between treatment and visit, and trial. The least-squares mean differences with 95% CI between treatment groups were reported. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and STATA version 17.0 (College Station, TX).

Results

Of the 11,007 patients randomized in DAPA-HF and DELIVER, 2 were excluded due to missing a history of sleep apnea at baseline. Of the 11,005 patients included in this analysis, 755 (6.7%) had a history of sleep apnea at baseline. The prevalence of sleep apnea was 5.7% and 7.8% in patients with a LVEF $\leq$ 40% and $>$ 40%, respectively. The prevalence was 7.8% in men vs 5.1% in women.

Patient Characteristics

The baseline characteristics of patients according to histories of sleep apnea are shown in Table 1. Patients with a history of sleep apnea were more commonly men and White or Black (and less often Asian), and they had lower systolic blood pressure, heart rate, NT-proBNP and eGFR levels compared with individuals without a history of sleep apnea. They had higher body mass index and were more likely to be obese (obesity classes II–III; 43.1% vs 15.1%) and to be former smokers. Patients with a history of sleep apnea were more likely to have a history of hypertension (88.1% vs 82.0%), atrial fibrillation (58.9% vs 47.2%) and

Table 1 Baseline characteristics according to a history of sleep apnea

	No Sleep Apnea n = 10250	Sleep Apnea n = 755	*P* value
Age (years), mean (SD)	69.4±10.5	69.3±9.8	0.84
Sex, n (%)			<0.001
Women	3661 (35.7)	195 (25.8)	
Men	6589 (64.3)	560 (74.2)	
Race, n (%)			<0.001
White	7206 (70.3)	564 (74.7)	
Asian	2288 (22.3)	102 (13.5)	
Black or African American	305 (3.0)	80 (10.6)	
Other	451 (4.4)	9 (1.2)	
Geographic region, n (%)			<0.001
Europe and Saudi Arabia	4970 (48.5)	187 (24.8)	
North America	1083 (10.6)	445 (58.9)	
South America	1966 (19.2)	32 (4.2)	
Asia/Pacific	2231 (21.8)	91 (12.1)	
Physiological measures			
Systolic blood pressure (mmHg), mean (SD)	125.6±16.0	123.9±17.2	0.004
Diastolic blood pressure (mmHg), mean (SD)	73.9±10.3	71.9±11.2	<0.001
Heart rate (bpm), mean (SD)	71.6±11.7	70.3±11.4	0.004
Body mass index, mean (SD)	28.8±5.9	33.9±7.0	<0.001
Body mass index, N (%)			<0.001
<18.5	140 (1.4)	1 (0.1)	
18.5−24.9	2541 (24.8)	63 (8.4)	
25.0−29.9	3639 (35.5)	155 (20.6)	
30−34.9	2376 (23.2)	210 (27.9)	
≥35.0	1547 (15.1)	325 (43.1)	
NT-proBNP (pg/mL), median (IQR)	1184 (704−2142)	1103 (680−1879)	0.02
Atrial fibrillation/flutter on ECG	1570 (1046−2528)	1361 (876−2089)	<0.001
No atrial fibrillation/flutter on ECG	967 (565−1846)	916 (565−1789)	0.42
Hemoglobin A1C (%), mean (SD)	6.5±1.4	6.6±1.3	0.04
Creatinine (μmol/L), mean (SD)	102.6±30.5	113.5±33.4	<0.001
eGFR (mL/min/1.73m^2), mean (SD)	63.4±19.4	59.0±19.3	<0.001
Smoking status, n (%)			<0.001
Current	1100 (10.7)	77 (10.2)	
Former	3947 (38.5)	405 (53.6)	
Never	5203 (50.8)	273 (36.2)	
Duration of HF, N (%)			<0.001
0−3 months	680 (6.6)	38 (5.0)	
>3−6 months	944 (9.2)	41 (5.4)	
>6−12 months	1327 (13.0)	68 (9.0)	
>1−2 years	1581 (15.4)	100 (13.2)	
>2−5 years	2494 (24.3)	180 (23.8)	
>5 years	3219 (31.4)	328 (43.4)	
LVEF (%), mean (SD)	44.0±13.8	46.4±15.2	<0.001
LVEF (%), n (%)			<0.001
≤40	4477 (43.7)	270 (35.8)	
41−49	1983 (19.3)	130 (17.2)	
≥50	3790 (37.0)	355 (47.0)	
NYHA class, n (%)			<0.001
II	7413 (72.3)*	502 (66.5)	
III/IV	2837 (27.7)	253 (33.5)	
KCCQ-TSS, mean (SD)	72.2±21.8	63.8±24.0	<0.001
KCCQ-CSS, mean (SD)	70.1±20.5	62.3±22.5	<0.001
KCCQ-OSS, mean (SD)	67.8±20.3	61.0±22.0	<0.001
Medical history, N (%)			
Hospitalization for HF	4454 (43.5)	335 (44.4)	0.62
Time from last HF hospitalization, n (%)			0.005
No prior HF hospitalization	5797 (56.6)	420 (55.6)	
0−3 months	1289 (12.6)	81 (10.7)	
3−6 months	673 (6.6)	44 (5.8)	
6−12 months	799 (7.8)	48 (6.4)	
>1 year	1692 (16.5)	162 (21.5)	

(*Continued*)

Table 1. (*Continued*)

	No Sleep Apnea n = 10250	Sleep Apnea n = 755	*P* value
Atrial fibrillation	4838 (47.2)	445 (58.9)	<0.001
Stroke	982 (9.6)	81 (10.7)	0.30
Myocardial infarction	3513 (34.3)	218 (28.9)	0.002
PCI or CABG	3897 (38.0)	293 (38.8)	0.67
Hypertension	8409 (82.0)	665 (88.1)	<0.001
Type 2 diabetes mellitus	4387 (42.8)	402 (53.2)	<0.001
Treatment, N (%)			
ACEi/ARB	8001 (78.1)	492 (65.2)	<0.001
ARNI	705 (6.9)	104 (13.8)	<0.001
Beta-blocker	9084 (88.6)	650 (86.1)	0.036
MRA	5684 (55.5)	352 (46.6)	<0.001
Loop diuretic	7974 (77.8)	660 (87.4)	<0.001
Digoxin	1123 (11.0)	60 (7.9)	0.01
Statin	6682 (65.2)	533 (70.6)	0.003
Antiplatelet	4868 (47.5)	354 (46.9)	0.75
Anticoagulant	4901 (47.8)	450 (59.6)	<0.001
CRT-P/CRT-D	392 (3.8)	62 (8.2)	<0.001
ICD/CRT-D	1240 (12.1)	170 (22.5)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CABG, coronary artery bypass graft surgery; CRT, cardiac resynchronization therapy; CSS, clinical summary score; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid-receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OSS, overall summary score; PCI, percutaneous coronary intervention; SD, standard deviation; TSS, total symptom score.

*1 additional patient was NYHA class I.

type 2 diabetes (53.2% vs 42.8%), but they were less likely to have a history of myocardial infarction. They also had higher LVEF, longer duration of HF, more advanced NYHA functional class, and worse KCCQ scores (eg, mean KCCQ-TSS 63.8 vs 72.2 points, respectively).

Regarding pharmacological therapy, patients with a history of sleep apnea were more commonly treated with an angiotensin receptor-neprilysin inhibitor, loop diuretic, statin, and anticoagulant, but they were less commonly treated with a beta-blocker, mineralocorticoid-receptor antagonist and digoxin, compared with individuals without a history of sleep apnea.

Baseline characteristics of patients according to a history of sleep apnea and LVEF $\leq$ and $>$ 40%, respectively, are shown in Supplementary Table 1.

Outcomes According to a History of Sleep Apnea

Patients with a history of sleep apnea had significantly higher risks of worsening HF or cardiovascular death, worsening HF and total HF hospitalizations and cardiovascular death, but not cardiovascular death or all-cause death, compared to individuals without a history of sleep apnea (Table 2). These associations persisted after adjustment for prognostic variables, including NT-proBNP levels (Table 2).

The crude event rates of worsening HF or cardiovascular death and each of its components, according to continuous LVEF in patients with and without a history of sleep apnea, are shown in Fig. 1. Overall, patients with a history of sleep apnea had higher rates of worsening HF or cardiovascular death and worsening HF than those without, and this association was not modified by LVEF ($P_{interaction} \geq 0.67$). The rate of cardiovascular death was similar in patients with and without a history of sleep apnea, and this association was also not modified by LVEF ($P_{interaction} = 0.36$). Analysis by LVEF category gave similar findings (Supplementary Table 2).

Examination of outcomes related to a history of sleep apnea according to sex suggested that sleep apnea may be associated with greater risk in women compared to men (Supplementary Table 3).

Effects of Dapagliflozin on Clinical Outcomes According to a History of Sleep Apnea

Compared with placebo, dapagliflozin reduced the risk of worsening HF or cardiovascular death to the same extent in patients with (HR 0.78 [95% CI, 0.59−1.03]) and without a history of sleep apnea (HR 0.79 [0.72−0.87]), with no interaction between sleep apnea and effect of treatment ($P_{interaction} = 0.93$). The number of patients needed to treat with dapagliflozin to prevent 1 event over the median follow-up of 22 months was 16 [95% CI, 13−24] and 23 [18−35] in patients with and without a history of sleep apnea, respectively. The effect of dapagliflozin was also consistent for all secondary clinical outcomes, including the components of the primary outcome, HF hospitalizations, all-cause death and total HF hospitalizations or cardiovascular death, regardless of a history of sleep apnea (Table 3). The mean increase in KCCQ scores from

Table 2 Outcomes according to histories of sleep apnea

	No Sleep Apnea n=10250	Sleep Apnea n=755
Worsening HF or cardiovascular death		
No. of events (%)	1918 (18.7)	202 (26.8)
Event rate per 100 person-years (95% CI)	10.6 (10.1–11.1)	16.0 (14.0–18.4)
HR (95% CI)*	Reference	1.50 (1.30–1.74)
HR (95% CI)†	Reference	1.29 (1.10–1.52)
HR (95% CI)‡	Reference	1.29 (1.10–1.52)
Worsening HF		
No. of events (%)	1217 (11.9)	168 (22.3)
Event rate per 100 person-years (95% CI)	6.7 (6.4–7.1)	13.3 (11.5–15.5)
HR (95% CI)*	Reference	1.94 (1.65–2.28)
HR (95% CI)†	Reference	1.43 (1.19–1.72)
HR (95% CI)‡	Reference	1.44 (1.20–1.73)
HF hospitalization		
No. of events (%)	1134 (11.1)	162 (21.5)
Event rate per 100 person-years (95% CI)	6.2 (5.9–6.6)	12.7 (10.9–14.9)
HR (95% CI)*	Reference	2.02 (1.71–2.38)
HR (95% CI)†	Reference	1.51 (1.25–1.82)
HR (95% CI)‡	Reference	1.52 (1.26–1.83)
Cardiovascular death		
No. of events (%)	1057 (10.3)	75 (9.9)
Event rate per 100 person-years (95% CI)	5.5 (5.2–5.8)	5.2 (4.2–6.6)
HR (95% CI)*	Reference	0.97 (0.77–1.22)
HR (95% CI)†	Reference	1.02 (0.79–1.32)
HR (95% CI)‡	Reference	1.03 (0.80–1.32)
All-cause death		
No. of events (%)	1510 (14.7)	118 (15.6)
Event rate per 100 person-years (95% CI)	7.8 (7.4–8.2)	8.2 (6.8–9.8)
HR (95% CI)*	Reference	1.05 (0.87–1.26)
HR (95% CI)†	Reference	1.08 (0.88–1.33)
HR (95% CI)‡	Reference	1.09 (0.89–1.34)
Total HF hospitalizations and cardiovascular death		
No. of events	2802	354
RR (95% CI)*	Reference	1.70 (1.43–2.02)
RR (95% CI)†	Reference	1.34 (1.11–1.61)
RR (95% CI)‡	Reference	1.35 (1.11–1.63)

CI, confidence interval; HF, heart failure; HR, hazard ratio; RR, rate ratio.

*Models were stratified by diabetes status and trial and adjusted for treatment assignment and heart failure hospitalization (except in the analysis of all-cause death).

†Models were stratified by diabetes status and trial and adjusted for treatment assignment, a history of heart failure hospitalization (except in the analysis of all-cause death), age, sex, geographical region, systolic blood pressure, heart rate, body mass index, estimated glomerular filtration rate, left ventricular ejection fraction, New York Heart Association, a history of myocardial infarction, atrial fibrillation, and hypertension.

‡As above and log of N-terminal pro-B-type natriuretic peptide.

baseline to 8 months was greater with dapagliflozin compared with placebo in patients with and without a history of sleep apnea ($P_{interaction} \geq 0.55$).

The effects of dapagliflozin, compared with placebo, on the primary outcome and each of its components, according to continuous LVEF in patients with and without a history of sleep apnea, respectively, are displayed in Fig. 2. The beneficial effect of dapagliflozin was consistent across the range of LVEF in patients with ($P_{interaction} \geq 0.43$) and without a history of sleep apnea ($P_{interaction} \geq 0.58$).

The proportions of patients who discontinued trial treatment or experienced adverse events according to treatment assignment were similar, regardless of a history of sleep apnea (Table 4).

Discussion

In a pooled analysis of DAPA-HF and DELIVER, including more than 11,000 patients with HF across the range of LVEFs, an investigator-reported history of sleep apnea was associated with higher rates of worsening HF events but not cardiovascular death or death from any cause. The beneficial effects of dapagliflozin on clinical events were not modified by sleep apnea.

Prevalence and Characteristics of Sleep Apnea

In this pooled analysis of 2 recent and large HF trials, 755 participants (~ 7%) had a history of sleep apnea, as reported by the investigators. Although this is a substantially lower prevalence than that reported in dedicated sleep apnea studies, it is consistent with another recent trial, PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction), where the investigator-reported prevalence of sleep apnea was 7.6% in patients with HFpEF.[2,8–17] It is difficult to gauge the exact prevalence of sleep-disordered breathing in patients with HF, because most prior studies enrolled small numbers of patients who were often included because of features suggesting higher risks of sleep apnea, and participants were systematically screened using polysomnography or other diagnostic devices.[2,7–17] Therefore, the striking difference in the prevalence of sleep apnea between the present and previous studies likely reflects not just low awareness but also the absence of routine screening for sleep-disordered breathing in routine clinical practice. The true prevalence of sleep apnea is certainly greater than that found in either of our recent trials, because it is undoubtedly underrecognized and underdiagnosed in middle-aged and older adults in the general population and in patients with HF.[5,6,35] Population-based studies of HF confirm the low recognition of sleep-disordered breathing. For example, in the European Society of Cardiology Heart Failure Long-Term Registry (2011–2016), among 8310 outpatients with HF, only 5.7% were reported to have sleep apnea.[36] Even in countries with higher levels of awareness and investigation such as the United States, sleep-disordered breathing is underdiagnosed; in a recent report on hospitalizations due to HF in the U.S. between 2008 and 2018, obstructive sleep apnea as a comorbidity was reported to have increased from only 6.0%–16.0% over the period studied.[37] Similarly, in the ARIC (Atherosclerosis Risk in

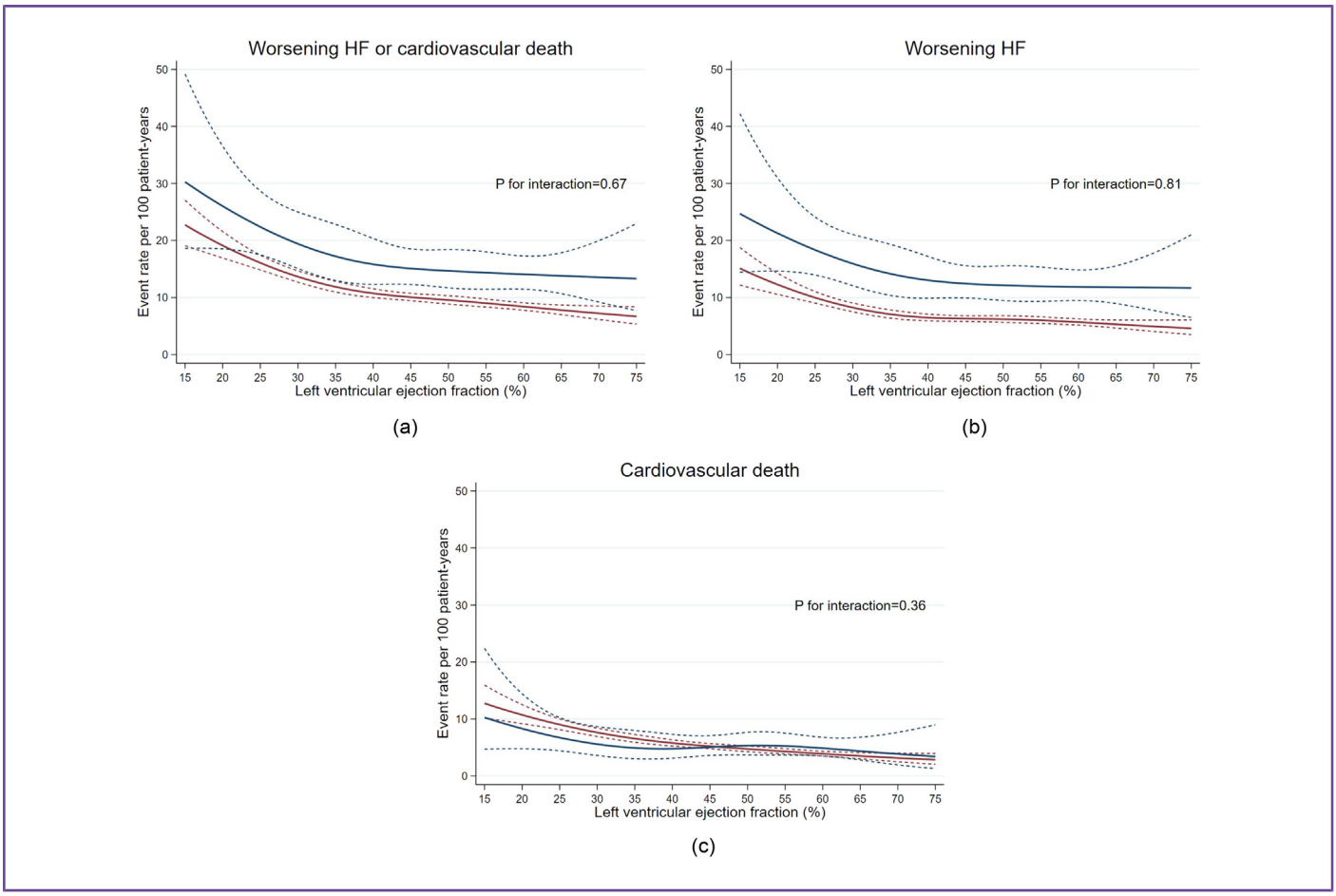


Fig. 1. Incidence rates of outcomes according to a history of sleep apnea across the range of LVEF at baseline. Patients with a history of sleep apnea (blue) had higher rates of worsening HF or cardiovascular death and worsening HF than those without a history (red), and this association was not modified by LVEF ($P_{interaction} \geq 0.67$). The rate of cardiovascular death was similar in patients with and without a history of sleep apnea, and this association was also not modified by LVEF ($P_{interaction} = 0.36$). HF, heart failure; LVEF, left ventricular ejection fraction.

Communities) study, the reported prevalence of sleep apnea increased from 7.6% in 2005 to 14.6% in 2014 in patients hospitalized with acute decompensated HF.[38] In 2 other relevant trials, EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and VERTIS-CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes) obstructive sleep apnea was reported to be present at baseline in 391 of 7020 participants (5.6%) and in 549 of 8246 patients (6.7%), respectively, with type 2 diabetes and cardiovascular disease.[39,40]

As expected, sleep apnea was more prevalent in men than in women, given that men have longer pharynxes and more upper-airway fat deposition and anatomic narrowing than women in the presence of obesity.[1] The prevalence of sleep apnea was also slightly higher in patients with preserved or mildly reduced ejection fraction (7.8%) than in those with reduced ejection fraction (5.7%). Compared with patients with HFrEF, those with HFpEF are typically older, more obese and more commonly have atrial fibrillation,[27,28,41,42] all of which are strongly associated with sleep-disordered breathing.[9] In population-based studies, where the age differences between patients with HFrEF and HFpEF were relatively small, there were no notable differences in the prevalence of noncardiac comorbidities.[43] Therefore, it is very likely that the age difference between patients with HFpEF and HFrEF observed in our study may contribute to the higher prevalence of sleep apnea in the former group. The higher prevalence of sleep apnea in those with HFpEF is also interesting, given that male sex is a risk factor for sleep-disordered breathing,[9] and men are more likely to develop HFrEF and less likely to develop HFpEF than are women.

Although advanced age is strongly associated with sleep-disordered breathing, there was no difference in age between patients with and without an investigator-reported history of sleep apnea in the present study, possibly reflecting even greater underdiagnosis in older individuals.

We did not have data on the type of apnea, but the finding that more than 40% of patients with a history of sleep apnea had class II or III obesity (vs 15% of those

Table 3 Effects of dapagliflozin compared with placebo on outcomes according to a history of sleep apnea

	No sleep apnea n=10250		Sleep apnea n=755		*P* value for interaction
	Placebo n=5126	Dapagliflozin n=5124	Placebo n=376	Dapagliflozin n=379	
Worsening HF or cardiovascular death					0.93
No. of events (%)	1056 (20.6)	862 (16.8)	110 (29.3)	92 (24.3)	
Event rate per 100 person-years (95% CI)	11.8 (11.1–12.6)	9.4 (8.8–10.0)	18.1 (15.0–21.8)	14.1 (11.5–17.3)	
HR (95% CI)*	0.79 (0.72–0.87)		0.78 (0.59–1.03)		
Worsening HF					0.72
No. of events (%)	689 (13.4)	528 (10.3)	91 (24.2)	77 (20.3)	
Event rate per 100 person-years (95% CI)	7.7 (7.2–8.3)	5.8 (5.3–6.3)	15.0 (12.2–18.4)	11.8 (9.4–14.8)	
HR (95% CI)*	0.74 (0.66-0.83)		0.79 (0.58-1.07)		
HF hospitalization					0.69
No. of events (%)	648 (12.6)	486 (9.5)	88 (23.4)	74 (19.5)	
Event rate per 100 person-years (95% CI)	7.2 (6.7–7.8)	5.3 (4.8–5.8)	14.4 (11.7–17.7)	11.2 (8.9–14.1)	
HR (95% CI)*	0.73 (0.65–0.82)		0.77 (0.57–1.05)		
Cardiovascular death					0.18
No. of events (%)	562 (11.0)	495 (9.7)	45 (12.0)	30 (7.9)	
Event rate per 100 person-years (95% CI)	5.8 (5.4–6.3)	5.1 (4.7–5.6)	6.4 (4.8–8.6)	4.1 (2.9–5.8)	
HR (95% CI)*	0.88 (0.78–0.99)		0.63 (0.39–0.99)		
All-cause death					0.07
No. of events (%)	785 (15.3)	725 (14.1)	70 (18.6)	48 (12.7)	
Event rate per 100 person-years (95% CI)	8.1 (7.6–8.7)	7.5 (7.0–8.1)	10.0-7.9–12.6)	6.5 (4.9–8.6)	
HR (95% CI)*	0.92 (0.83–1.02)		0.65 (0.45–0.95)		
Total HF hospitalizations and cardiovascular death					0.58
No. of events	1579	1223	204	150	
RR (95% CI)*	0.77 (0.69–0.86)		0.70 (0.50–0.97)		
KCCQ-TSS					0.77
Change from baseline to 8 months (95% CI)†	4.7 (4.1–5.2)	7.0 (6.5–7.5)	3.5 (1.4–5.6)	7.9 (5.7–10.2)	
Placebo-corrected change at months (95% CI)†	2.3 (1.6–3.0)		4.4 (1.4–7.5)		
KCCQ-OSS					0.55
Change from baseline to 8 months (95% CI)†	4.6 (4.1–5.0)	6.6 (6.1–7.0)	3.3 (1.3–5.3)	7.2 (5.2–9.2)	
Placebo-corrected change at months (95% CI)†	2.0 (1.3–2.7)		3.9 (1.1–6.7)		
KCCQ-CSS					0.84
Change from baseline to 8 months (95% CI)†	3.9 (3.5–4.4)	6.2 (5.7–6.7)	3.1 (1.2–5.1)	6.9 (4.9–9.0)	
Placebo-corrected change at months (95% CI)†	2.2 (1.6–2.9)		3.8 (0.9–6.6)		

CI, confidence interval; HF, heart failure; HR, hazard ratio; RR, rate ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; TSS, Total Symptom Score; OSS, Overall Summary Score; CSS, Clinical Summary Score.

*Models were stratified by diabetes status and trial and adjusted for a history of HF hospitalization (except in the analysis of all-cause death).

†Mixed-effect models for repeated measurements adjusted for baseline value, visit (months 4 and 8), randomized treatment, the interaction between treatment and visit, and trial. Cardiovascular death includes undetermined deaths.

without) suggests that most patients had obstructive, rather than central, sleep apnea. However, because patients with HF can have both types, we cannot rule out that some patients may also have central, in addition to obstructive, sleep apnea.[1,2] Other studies have found central sleep apnea to be more common than obstructive sleep apnea in HFrEF, whereas the opposite appears to be true in HFpEF, but there is considerable variation in the reported prevalence of these 2 forms of sleep apnea.[2,7,12,13,15–17]

Outcomes Related to a History of Sleep Apnea

Sleep apnea has been consistently associated with worse outcomes in patients with HFrEF.[17–22] However, previous reports did not take into account other prognostic variables, particularly natriuretic peptides, the single most powerful predictor of outcome in HF.[23–26] In addition, remarkably little is known about the association between sleep apnea and adverse outcomes in HFpEF, despite a high prevalence of sleep apnea in these patients.[16] In the present study of more than 11,000 patients with HFrEF and HFpEF, we found that an investigator-reported history of sleep apnea was associated with substantially higher rates of the primary composite outcome, a worsening HF event and the composite of total HF hospitalizations and cardiovascular death, but not cardiovascular death or death from any cause. These associations persisted after comprehensive adjustment for prognostic variables, including LVEF and NT-proBNP levels, and this was evident in patients with HFrEF and HFmrEF/HFpEF. Although the explanation for the dissociation between fatal and nonfatal events is not clear, patients participating in clinical trials may receive better care than the population at large, and the follow-up might have been too short to show a difference in mortality rates.

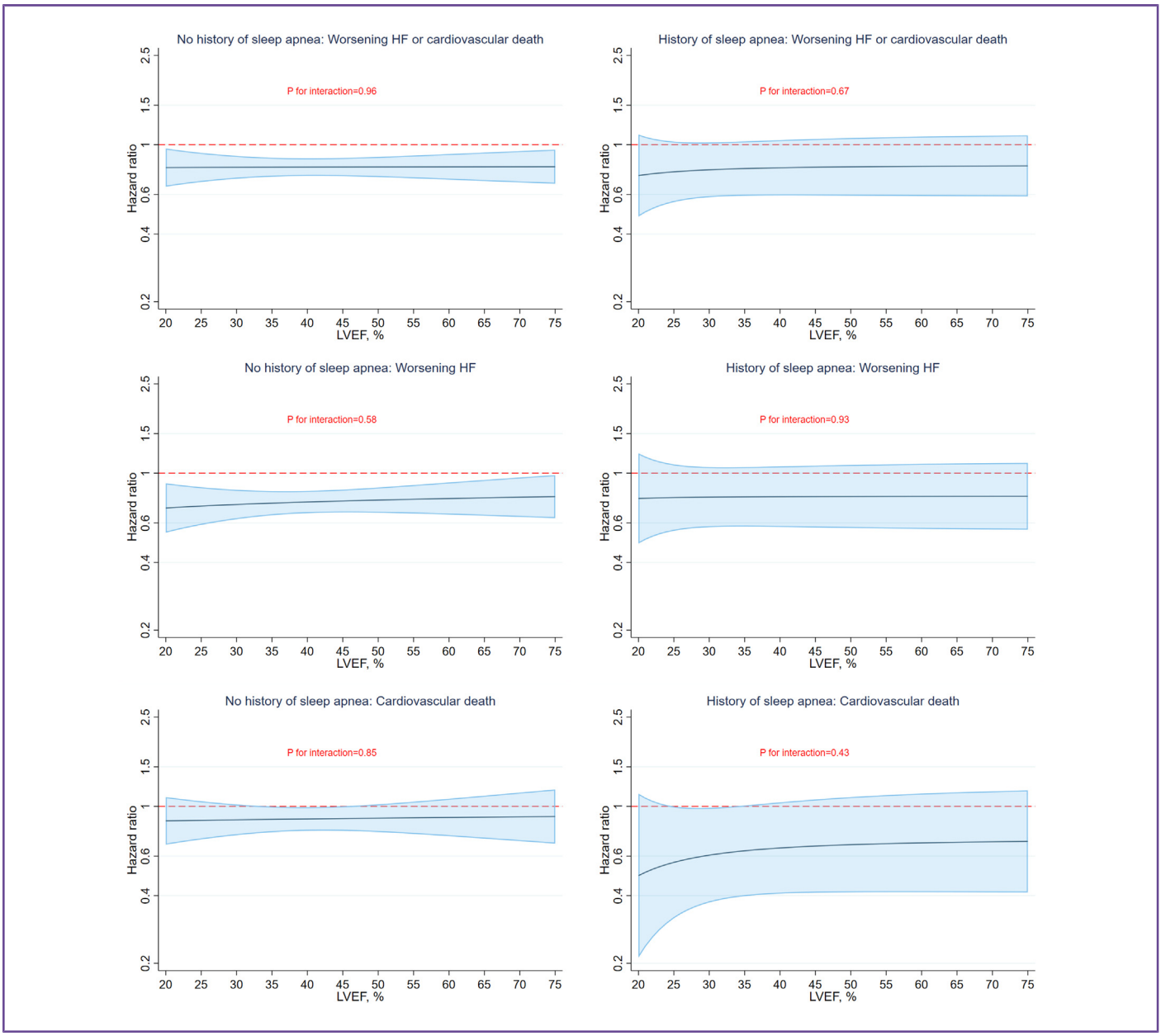


Fig. 2. Effects of dapagliflozin compared with placebo on outcomes across the range of LVEF at baseline in patients with and without a history of sleep apnea. Models were stratified by diabetes status and trial and adjusted for a history of HF hospitalization. The beneficial effect of dapagliflozin on worsening HF or cardiovascular death and all of the components of the primary outcome, were consistent across the range of LVEF in both patients with ($P_{interaction} \geq 0.43$) and without a history sleep apnea ($P_{interaction} \geq 0.58$). HF, heart failure; LVEF, left ventricular ejection fraction.

Unfortunately, the few randomized controlled trials conducted in patients with HFrEF with either of the subtypes of sleep apnea have either not investigated or have failed to demonstrate any benefit of positive airway pressure therapy, adaptive servo-ventilation or phrenic nerve stimulation, among other interventions, on cardiovascular outcomes,[1,2,4,44–49] and the effects of these therapies are largely unknown in individuals with HFpEF. Although some of these therapies improve sleep quality and nocturnal oxygenation, effective treatments that improve "hard" outcomes in patients with HF and sleep apnea are warranted.

Effects of Dapagliflozin on Clinical Outcomes According to a History of Sleep Apnea

Despite the substantial differences in the characteristics and outcomes of patients with and without a history of sleep apnea, the beneficial effects of dapagliflozin were entirely consistent for all clinical outcomes examined, whether or not patients had a history of sleep apnea. Specifically, dapagliflozin, compared with placebo, reduced the risk of the primary composite outcome of worsening HF or cardiovascular death, its components, first and total HF hospitalizations, and all-cause death, regardless of a

Table 4 Adverse events in patients assigned to dapagliflozin or placebo according to a history of sleep apnea

	No Sleep Apnea n=10233		Sleep Apnea n=754		*P* value for interaction
	Placebo n=5119	Dapagliflozin n=5114	Placebo n=375	Dapagliflozin n=379	
Discontinuation of study drug for any reason, n (%)	627 (12.2)	619 (12.1)	72 (19.2)	74 (19.5)	0.86
Discontinuation of study drug due to an adverse event, n (%)	259 (5.1)	269 (5.3)	37 (9.9)	25 (6.6)	0.09
Volume depletion,* n (%)	169 (3.3)	201 (3.9)	30 (8.0)	26 (6.9)	0.24
Renal adverse event,† n (%)	226 (4.4)	207 (4.0)	35 (9.3)	30 (7.9)	0.74
Amputation, n (%)	34 (0.7)	29 (0.6)	4 (1.1)	3 (0.8)	0.86
Major hypoglycemia, n (%)	11 (0.2)	9 (0.2)	0 (0.0)	3 (0.8)	N/A
Diabetic ketoacidosis, n (%)	0 (0.0)	4 (0.1)	0 (0.0)	1 (0.3)	N/A

N/A, not applicable.

A total of 18 randomized patients were excluded from the safety analysis, because these were performed in patients who had undergone randomization and received at least 1 dose of dapagliflozin or placebo.

*As per the prespecified collection of adverse events in each of the trials, this included any serious adverse events or adverse events that led to discontinuation of dapagliflozin or placebo that were suggestive of volume depletion in DELIVER and all adverse events that were suggestive of volume depletion in DAPA-HF.

†As per the prespecified collection of adverse events in each of the trials, this included any renal serious adverse events or adverse events that led to discontinuation of dapagliflozin or placebo in DELIVER and all renal adverse events in DAPA-HF.

history of sleep apnea. Reflecting their higher risk at baseline, patients with a history of sleep apnea had larger absolute risk reductions in the primary outcome with dapagliflozin, with the number of patients needed to treat to prevent 1 event being 16 for individuals with and 23 for those without a history of sleep apnea. In addition, though dapagliflozin increased (improved) the mean KCCQ scores from baseline to 8 months, regardless of a history of sleep apnea, the placebo-corrected mean increase was numerically twice as large in patients with a history of sleep apnea than in those without such history, although this difference was not statistically significant. This finding is particularly important, because patients with a history of sleep apnea had substantially greater symptom burden and worse physical functioning and quality of life at baseline than those without. Reassuringly, adverse events and discontinuation of randomized treatment were not significantly more common in the dapagliflozin group compared with the placebo group, irrespective of sleep apnea status.

Our data also support the finding that empagliflozin reduced the risk of all outcomes in EMPA-REG OUTCOME, regardless of obstructive sleep apnea status, although EMPA-REG OUTCOME enrolled only 391 patients with obstructive sleep apnea, and only 24 patients were hospitalized with HF in the empagliflozin group.[39] Interestingly, using adverse events reported according to the Medical Dictionary for Regulatory Activities, the EMPAREG-OUTCOME investigators also suggested that empagliflozin might reduce the incidence of new obstructive sleep apnea. A similar observation was made with ertugliflozin in VERTIS-CV.[40]

The exact mechanisms by which sodium-glucose cotransporter-2 inhibitors exert their beneficial cardiovascular effects are uncertain, but these agents have a broad range of actions that include a diuretic effect, decreased cardiac filling pressures, favorable cardiac remodeling, increased renal erythropoietin secretion and anemic correction, preservation of kidney function and, possibly, improvement in myocardial metabolism, reduction of cardiac fibrosis, inhibition of cardiac sodium-hydrogen exchange, and alterations in adipokines, cytokine production, and epicardial adipose tissue mass, among others.[50–52]

Limitations

This study has some limitations. First, the analyses were not prespecified. Second, the prespecified inclusion and exclusion criteria in DAPA-HF and DELIVER precluded the enrolment of very high-risk patients, which may affect the generalizability of our results. Third, a history of sleep apnea was reported by the investigators, and because sleep apnea is underdiagnosed in the general population, the true prevalence of this condition has likely been underestimated in the present study. Fourth, the type of sleep apnea patients had was not reported, and data on the management of sleep apnea (eg, with continuous positive airway pressure or other treatments) were not available. Fifth, given the observational nature of the analyses of the association between sleep apnea status and clinical outcomes, the possibility of residual confounding cannot be fully excluded despite adjustment for measured, known confounders. Finally, although it would have been interesting to examine the effects of dapagliflozin on incident sleep apnea, these data were not collected systematically in either trial.

Conclusions

In DAPA-HF and DELIVER, the true prevalence of sleep apnea was likely underestimated. An investigator-

reported history of sleep apnea was associated with higher rates of worsening HF events but not mortality. The beneficial effects of dapagliflozin on clinical outcomes were consistent in patients with and without sleep apnea.

JAWAD H. BUTT

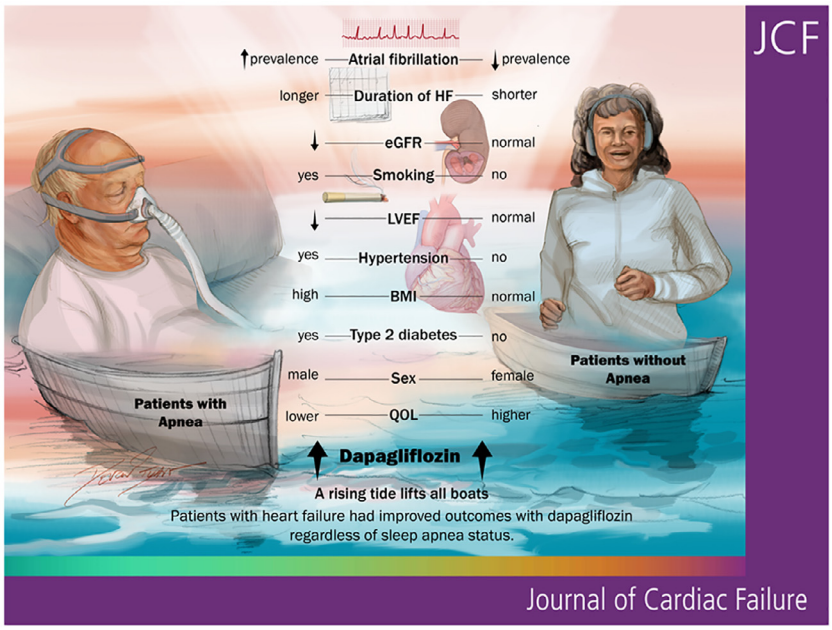
Lay Summary

Sleep apnea is a common disorder in patients with heart failure (HF). Whether dapagliflozin, a guideline-recommended treatment for HF, is effective in patients with and without sleep apnea is not known. In a large analysis of 2 randomized controlled trials, a history of sleep apnea increased the risk of worsening HF events. Treatment with dapagliflozin reduced the risk of clinical outcomes and improved health-related quality of life, and these benefits were observed in patients with and without sleep apnea. These important data provide further support for the efficacy and safety of dapagliflozin in patients with HF.

Visual Take-Home Figure. The effect of dapagliflozin on clinical outcomes according to a history of sleep apnea. Dapagliflozin, compared with placebo, significantly reduced the risk of worsening HF or cardiovascular death, of each of the components of this composite outcome, and of all-cause death to a similar extent in patients with and without a history of sleep apnea.

Disclosures

JHB reports advisory board honoraria from AstraZeneca and Bayer, consultant honoraria from Novartis and AstraZeneca and travel grants from AstraZeneca. RADB has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals, Ionis Pharmaceuticals, Novo Nordisk, and Roche and has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Roche. BLC has received consulting fees from Boehringer Ingelheim. ASD has received grants and personal fees from AstraZeneca during the conduct of the study, personal fees from Abbott, Biofourmis, Boston Scientific, Boehringer Ingelheim, Corvidia, DalCor Pharma, Relypsa, Regeneron, and Merck, grants and personal fees from Alnylam and Novartis, and personal fees from Amgen, outside the submitted work. AFH has received research support from American Regent, AstraZeneca, Boehringer Ingelheim, Merck, Novartis, and Verily and has served as a consultant or on the advisory boards of Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Myokardia, Merck, Novartis, and Vifor. SEI 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 Astra-Zeneca and Boehringer Ingelheim. PSJ's employer, the University of Glasgow, has been remunerated by Astrazeneca for working on the DAPA-HF and DELIVER trials, and he has received personal fees from Novartis and Cytokinetics and grants from Boehringer Ingelheim. LK reports compensation from Novartis, Novo Nordisk and AstraZeneca for other services. MNK has received research grant support from AstraZeneca and Boehringer Ingelheim, has served as a consultant or on an



advisory board for Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Esperion Therapeutics, Janssen, Merck (Diabetes and Cardiovascular), Novo Nordisk, Sanofi, and Vifor Pharma and has received other research support from AstraZeneca and honoraria from AstraZeneca, Boehringer Ingelheim and Novo Nordisk. CSPL is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore, has received research support from AstraZeneca, Bayer, Boston Scientific, and Roche Diagnostics, has served as a consultant or on the advisory board/steering committee/executive committee for Actelion, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma, Us2.ai, Janssen Research & Development, Medscape, Merck, Novartis, Novo Nordisk, Radcliffe Group, Roche Diagnostics, Sanofi, and WebMD Global and serves as the cofounder and nonexecutive director of Us2.ai. FAM has received personal fees from AstraZeneca. PP reports compensation from AstraZeneca, Boehringer Ingelheim, and Servier for consultant services, compensation from AstraZeneca and Pfizer for other services, compensation from Amgen and Vifor Pharma for consultant services; compensation from Novartis and Abbott Vascular for other services. MSS reports research grant support through Brigham and Women's Hospital from Abbott, Amgen, Anthos Therapeutics, AstraZeneca, Bayer, Daiichi-Sankyo, Eisai, Intarcia, IONIS, Medicines Company, MedImmune, Merck, Novartis, Pfizer, and Quark Pharmaceuticals and consulting fees from Althera, Amgen, Anthos Therapeutics, AstraZeneca, Bristol-Myers Squibb, CVS Caremark, DalCor, Dr. Reddy's Laboratories, Fibrogen, IFM Therapeutics, Intarcia, MedImmune, Merck, Moderna, and Novo Nordisk. SJS has received either personal or institutional research support for DELIVER from AstraZeneca. MV has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, and Relypsa, has had speaker engagements with Novartis and Roche Diagnostics and participates on clinical endpoint committees for studies sponsored by Galmed and Novartis. AML, OB, MP, MS, and UWkilde are employees of and shareholders in AstraZeneca. SDS has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/NHLBI, Neurotronik, Novartis, Novo-Nordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellPro-Thera, Moderna, American Regent, and Sarepta. JJVM has received payments through Glasgow University for work on clinical trials, consulting and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, DalCor, GSK, Ionis, KBP Biosciences, Novartis, Pfizer, Theracos and lecture fees: the Corpus, Abbott, Hikma, Sun Pharmaceuticals, Medscape/Heart.Org, Radcliffe Cardiology, Servier Director, Global Clinical Trial Partners.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2023.08.027.

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