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Effects of Dapagliflozin in Patients With Kidney Disease, With and Without Heart Failure

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ABSTRACT

OBJECTIVES The purpose of this paper was to investigate the effects of dapagliflozin in chronic kidney disease (CKD) patients, with and without heart failure (HF).

BACKGROUND Patients with CKD, with and without type 2 diabetes, were enrolled in the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial. Some patients had HF at baseline.

METHODS A total of 4,304 participants were randomized to dapagliflozin 10 mg daily or placebo. The primary composite endpoint was ≥50% decline in estimated glomerular filtration rate, end-stage kidney disease, or kidney/cardiovascular death. Secondary endpoints were a kidney composite (primary endpoint minus cardiovascular death), the composite of cardiovascular death/HF hospitalization, and all-cause death. Analysis of outcomes according to HF history was prespecified.

RESULTS HF patients (n = 468; 11%) were older and had more coronary disease, atrial fibrillation, and type 2 diabetes. Mean estimated glomerular filtration rate was similar in patients with and without HF. Rates of HF hospitalization/cardiovascular death and death from any cause were higher in HF patients, but the secondary kidney failure outcome occurred at the same rate in people with and without HF. Dapagliflozin reduced the risk of the primary outcome equally in patients with HF (HR: 0.58 [95% CI: 0.37-0.91]) and without HF (HR: 0.62 [95% CI: 0.51-0.75]) (*P* interaction = 0.59). The proportional risk-reductions were similar in patients with and without HF for the cardiovascular death/HF hospitalization composite (HR: 0.68 [95% CI: 0.44-1.05] vs HR: 0.70 [95% CI: 0.51-0.97], respectively; *P* interaction = 0.90), and all-cause death (HR: 0.56 [95% CI: 0.34-0.93] vs HR: 0.73 [95% CI: 0.54-0.97], respectively; *P* interaction = 0.39), although absolute risk reductions were larger in HF patients. Adverse event rates were low and did not differ among patients with or without HF.

CONCLUSIONS Dapagliflozin reduced the risk of kidney failure and cardiovascular death/HF hospitalization and prolonged survival in CKD patients with or without type 2 diabetes, independently of history of HF. (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease [DAPA-CKD]; NCT03036150) (J Am Coll Cardiol HF 2021;9:807–820) © 2021 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

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HF = heart failure

SGLT2 = sodium glucose cotransporter 2

UACR = urinary albumin-to-creatinine ratio

Heart failure (HF) is common in patients with chronic kidney disease (CKD), reflecting the high prevalence of hypertension and diabetes in these individuals. These, along with premature and extensive atherosclerotic disease, impaired sodium and water homeostasis, and anemia, cause or aggravate cardiac and vascular hypertrophy and fibrosis as well as myocardial ischemia, leading to left ventricular diastolic and systolic dysfunction. HF is an important cause of hospitalization and a powerful and independent predictor of death in this population (1-7). In the ARIC (Atherosclerosis Risk In Communities) study, the adjusted incidence of HF was 3-fold higher in people with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 compared with those with eGFR >90 mL/ min/1.73 m^2 (1,4). Additional epidemiological studies confirmed these findings, showing that the magnitude of risk of HF in people with CKD was as high as that for coronary disease and higher than that for stroke (1-7). The incidence and prevalence of HF is higher in patients with more severe CKD; recent reports from the US Renal Data System suggest that up to 30% of patients with CKD have concomitant HF, a much higher prevalence than in the general population (6,7). HF is associated with a particularly poor survival in patients with CKD. Consequently, both prevention and treatment of HF in patients with CKD is a priority.

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A series of large randomized controlled trials have demonstrated that sodium glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of HF hospitalization in patients with type 2 diabetes mellitus, including those with CKD (8-12). More recently, this benefit of SGLT2 inhibitors was expanded to patients with CKD without type 2 diabetes in the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial (13). Whereas the SGLT2 inhibitor trials in patients with type 2 diabetes largely described prevention of incident HF, the effect of SGLT2 inhibitors in patients with CKD, diabetes, and prevalent HF was reported in the CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) trial (12,14). Here we extend these findings to patients with CKD and HF, with and without type 2 diabetes, reporting the effects of dapagliflozin on HF hospitalization, kidney outcomes, and mortality in patients with HF at baseline in DAPA-CKD (13,15). This analysis is clinically relevant, given the suggestion that development of HF may accelerate the rate of decline in glomerular filtration rate, leading to a vicious circle whereby one condition exacerbates the other (1-7). In addition, the greater concomitant use of diuretic therapy in patients with HF is also relevant here, given that these drugs can also worsen kidney function and that their action might be augmented by the diuresis caused by SGLT2 inhibitors.

METHODS

DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter trial, and the protocol and primary results are published (13). The study was registered at clinicaltrials.gov (NCT03036150). All participants provided written informed consent, and the trial was approved by an ethics committee at each site. Data supporting the findings described in this paper may be obtained in accordance with AstraZeneca's data sharing policy.

PATIENTS. Adults with or without type 2 diabetes, an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1.73 m^2, and a urinary albumin-to-creatinine ratio (UACR) between 200 and 5,000 mg/g were eligible. Unless intolerant, participants were required to be prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in a stable dose for at least 4 weeks before screening. The full inclusion and exclusion criteria are described elsewhere (13). Participants were randomized to dapagliflozin 10 mg once daily or placebo, with stratification by diagnosis of type 2 diabetes and UACR (≤1,000 or >1,000 mg/g). The median follow-up was 2.4 years (25th, 75th percentile range 2.0-2.7 years).

BASELINE HF AND HF HOSPITALIZATION. Investigators reported history of HF at baseline using a check box on the electronic case report form. No specific diagnostic criteria were provided, and left ventricular ejection fraction was not recorded. We collected

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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information on pharmacological therapy and cardiac devices, ie, use of cardiac resynchronization therapy or an implantable cardioverter-defibrillator.

HF hospitalization was a prespecified outcome. Hospital admissions potentially caused by HF were adjudicated by a blinded independent committee, which also reviewed events in DAPA-HF. The criteria used to confirm a HF hospitalization are provided in the Supplemental Appendix.

PRESPECIFIED TRIAL OUTCOMES. The primary composite outcome was the time to the first occurrence of any of the following: ≥50% decline in eGFR (confirmed by a second serum creatinine measurement after at least 28 days), onset of end-stage kidney disease (defined as maintenance dialysis for more than 28 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 confirmed by a second measurement after at least 28 days), or death from kidney or cardiovascular cause.

Prespecified secondary outcomes were as follows, in hierarchal order: 1) a kidney composite outcome identical to the primary endpoint, but excluding death from cardiovascular causes; 2) a cardiovascular composite outcome consisting of HF hospitalization or death from cardiovascular causes; and 3) death from any cause. All primary and secondary outcomes were formally adjudicated except for changes in eGFR, which were calculated from central laboratory measurements. Deaths with an undetermined cause were assumed to be cardiovascular.

We also examined the prespecified exploratory outcome of time-to-first HF hospitalization and total number of HF hospitalizations.

Additional prespecified exploratory endpoints included rate of decline in eGFR over time and doubling of serum creatinine concentration (measured locally or centrally) since the most recent central laboratory measurement.

As in prior dapagliflozin outcome trials, we collected only selected adverse event data, including serious adverse events, adverse events resulting in the discontinuation of trial treatment, and "adverse events of interest" described in the primary results paper (13).

STATISTICAL ANALYSIS. The efficacy analyses included all randomized participants and were conducted according to the intention-to-treat principle. We prespecified an analysis of trial results according to history of HF. We calculated HRs (95% CIs) for the effect of dapagliflozin 10 mg, compared with placebo, separately for the HF and no HF subgroups using Cox proportional hazards regression models including a factor for treatment group, stratified by randomization stratification factors (type 2 diabetes, UACR), and adjusting for baseline eGFR. We calculated interaction *P* values based on likelihood ratio tests comparing full factorial models against reduced models with main effects only. Treatment effects were not estimated for variables with <15 events in total (both arms combined). Time-to-event data are illustrated using Kaplan-Meier curves.

The method used to analyze eGFR slopes is described in the Supplemental Appendix.

Rate ratios and HRs for recurrent HF hospitalizations and time to death were obtained by using a semiparametric regression model. Standard errors were obtained through bootstrapping (200 bootstrap samples). The effect of dapagliflozin vs placebo is presented as a rate ratio (95% CI) for the recurrent event process and as a HR (95% CI) for the failure process. Safety data are reported by treatment group in all patients who received at least 1 dose of randomized treatment. We conducted all analyses using R version 4.02 (R Foundation for Statistical Computing).

RESULTS

Of the 4,304 patients randomized, 468 (10.9%) had a diagnosis of HF at baseline and 3,836 (89.1%) participants did not have a history of HF.

BASELINE CHARACTERISTICS ACCORDING TO HISTORY OF HF. Baseline characteristics of patients with and without HF are shown in Table 1. Patients with HF were older (65.3 years vs 61.4 years), more often white (80.1% vs 49.9%), had a higher body mass index (31.7 kg/m^2 vs 29.2 kg/m^2), and were more likely to have obesity (defined as body mass index ≥30 kg/m^2) (57.5% vs 43.0%) and diabetes (77.1% vs 66.3%) than those without a history of HF. Mean eGFR and median UACR were similar in patients with and without HF.

Among patients with HF, 26.7% had a history of myocardial infarction, 12.2% stroke, 15.8% peripheral artery disease, and 19.0% atrial fibrillation/flutter; all of these were one-third to one-half as common in patients without HF. Almost all patients (>95%) with or without HF had a history of hypertension.

Use of diuretic agents, beta-blockers, hydralazine, and digoxin was more common in patients with HF compared with those without HF (Table 1). Mineralocorticoid receptor antagonists were used in 17.3% of patients with HF, compared with 3.9% of patients without. Use of devices was very low overall. Nearly all patients with and without HF were receiving an angiotensin-converting enzyme

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TABLE 1 Characteristics of Patients at Baseline, According to History of Heart Failure at Baseline

	No Heart Failure (n = 3,836)	Heart Failure (n = 468)	*P* Value
Age, y	61.4 (12.3)	65.3 (12.1)	<0.001
Male	2,580 (67.3)	299 (63.9)	0.146
Race			<0.001
White	1,915 (49.9)	375 (80.1)	
Black or African American	163 (4.2)	28 (6.0)	
Asian	1,419 (37.0)	48 (10.3)	
Other	339 (8.8)	17 (3.6)	
Region			<0.001
Europe	945 (24.6)	288 (61.5)	
Asia/Pacific	1,303 (34.0)	43 (9.2)	
South America	855 (22.3)	57 (12.2)	
North America	733 (19.1)	80 (17.1)	0.001
Heart rate, beats/min = pulse	73.1 ± 11.7	71.3 ± 9.7	0.017
Systolic blood pressure, mm Hg	136.9 ± 17.6	138.9 ± 15.9	<0.001
HbA1c, %	7.0 ± 1.7	7.4 ± 1.7	0.037
Hemoglobin, g/dL	128.0 ± 17.9	129.9 ± 19.5	0.165
Current smoker	535 (13.9)	49 (10.5)	<0.001
Body mass index, kg/m^2	29.2 ± 6	31.7 ± 6.8	<0.001
Obese (body mass index ≥30 kg/m^2)	1,648 (43.0)	269 (57.5)	<0.001
Medical history			
Hypertension	3,658 (95.4)	463 (98.9)	<0.001
Atrial fibrillation or flutter	138 (3.6)	89 (19.0)	<0.001
Angina	211 (5.5)	194 (41.5)	<0.001
Myocardial infarction	267 (7.0)	125 (26.7)	<0.001
Coronary artery bypass grafting	121 (3.2)	55 (11.8)	<0.001
Percutaneous coronary intervention	227 (5.9)	67 (14.3)	<0.001
Stroke	241 (6.3)	57 (12.2)	<0.001
Transient ischemic attack	65 (1.7)	14 (3.0)	0.067
Peripheral artery disease	251 (6.5)	74 (15.8)	<0.001
Amputation	154 (4.0)	27 (5.8)	0.088
Type 2 diabetes	2,545 (66.3)	361 (77.1)	<0.001
Estimated GFR, mL/min/1.73 m^2	43.1 ± 12.3	43.2 ± 12.4	0.83
Estimated GFR category			0.927
≥60 mL/min/1.73 m^2	403 (10.5)	51 (10.9)	
45-59 mL/min/1.73 m^2	1,187 (30.9)	141 (30.1)	
30-44 mL/min/1.73 m^2	1,694 (44.2)	204 (43.6)	
<30 mL/min/1.73 m^2	552 (14.4)	72 (15.4)	
UACR, mg/g	949.8 (480.4-1,890)	940 (455.6-1,846.9)	0.803
Device therapy			
Implantable cardioverter-defibrillator	3 (0.1)	11 (2.4)	<0.001
Cardiac resynchronization therapy	1 (0.0)	5 (1.1)	<0.001
Pacemaker	34 (0.9)	21 (4.5)	<0.001
Cardiovascular and renal medication			
Beta-blocker	1,355 (35.3)	325 (69.4)	<0.001
Diuretic	1,579 (41.2)	303 (64.7)	<0.001
Loop diuretic	835 (21.8)	221 (47.2)	<0.001
Thiazide diuretic	804 (21.0)	102 (21.8)	0.677
Mineralocorticoid receptor antagonist	148 (3.9)	81 (17.3)	<0.001
ACE inhibitor, ARB, or other RAS blocker	3,716 (96.9)	458 (97.9)	<0.001
Digitalis glycoside	14 (0.4)	15 (3.2)	<0.001
Hydralazine	78 (2.0)	24 (5.1)	<0.001
Calcium channel blocker	1,943 (50.7)	240 (51.3)	0.797
Antiplatelet	1,573 (41.0)	307 (65.6)	<0.001
Statin	2,460 (64.1)	334 (71.4)	0.002
Other lipid-lowering therapy	598 (15.6)	47 (10.0)	0.001

Continued on the next page

TABLE 1 Continued

	No Heart Failure (n = 3,836)	Heart Failure (n = 468)	*P* Value
Glucose-lowering medication			
Biguanide	1,081 (28.2)	169 (36.1)	<0.001
Sulfonylurea	672 (17.5)	104 (22.2)	0.015
DPP-4 inhibitor	680 (17.7)	62 (13.2)	0.013
GLP-1 receptor agonist	110 (2.9)	12 (2.6)	0.705
Insulin	1,402 (36.5)	196 (41.9)	0.025

Values are n (%), mean ± SD, or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; DPP-4 = dipeptidyl peptidase; GFR = glomerular filtration rate; GLP = glucagon-like peptide; HbA1c = hemoglobin A1c (glycated hemoglobin); RAS = renin-angiotensin system; UACR = urinary albumin-to-creatinine ratio.

inhibitor or angiotensin receptor blocker, as required by protocol.

Of patients without a history of HF taking a diuretic agent, 53% were taking a loop diuretic and 51% a thiazide diuretic, whereas among patients with a history of HF, 73% were prescribed a loop diuretic and 34% a thiazide diuretic.

PRIMARY OUTCOME AND KIDNEY OUTCOMES ACCORDING TO BASELINE HISTORY OF HF. Comparing all trial participants, irrespective of randomized treatment assignment, the primary composite outcome of sustained decline in eGFR of at least 50%, end-stage kidney disease or death from cardiovascular disease or kidney failure, occurred at a rate of 8.7 (95% CI: 6.9-10.8) per 100 person-years in the patients with a history of HF, compared with a rate of 5.7 (95% CI: 5.1-6.2) per 100 person-years in patients without a history of HF (HR: 1.48; 95% CI: 1.17-1.88; $P = 0.0019$) (**Central Illustration**). The higher rate of the primary outcome in patients with HF was largely caused by a higher rate of cardiovascular death in these participants: 4.3 (95% CI: 3.1-5.7) per 100 person-years compared with 1.2 (95% CI: 1.0-1.5) per 100 person years in people without HF (HR: 3.31; 95% CI: 2.32-4.73; $P < 0.0001$). The rate of the key secondary, kidney-specific composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from kidney cause was similar in these 2 patient groups: 4.2 (95% CI: 3.0-5.8) per 100 person-years in the patients with a history of HF compared with a rate of 4.6 (95% CI: 4.1-5.1) per 100 person-years in those without HF (HR: 0.90; 95% CI: 0.65-1.25; $P = 0.53$).

CARDIOVASCULAR OUTCOMES AND ALL-CAUSE MORTALITY ACCORDING TO BASELINE HISTORY OF HF. The key secondary composite outcome of cardiovascular death or hospitalization for HF occurred at a more than 4-fold higher rate in patients with a history of HF compared with those without: 8.5 (95% CI: 6.8-10.5) per 100 person-years in those with HF at baseline compared with 1.9 (95% CI: 1.6-2.2) per 100 person-years in patients without HF (HR: 4.31; 95% CI: 3.30-5.63; $P < 0.0001$). Death from any cause also occurred more frequently in patients with a history of HF compared with those without, although the difference between groups was not as large as for the composite of death or HF hospitalization: 6.2 (95% CI: 4.8-7.9) per 100 person-years in individuals with HF compared with 2.2 (95% CI: 1.9-2.6) per 100 person-years in those without (HR: 2.70; 95% CI: 2.03-3.60; $P < 0.0001$).

EFFECT OF DAPAGLIFLOZIN ON THE PRIMARY OUTCOME AND SECONDARY RENAL OUTCOME ACCORDING TO BASELINE HISTORY OF HF. Among patients with HF, the primary composite outcome occurred in 31 (13.2%) participants in the dapagliflozin group and 51 (21.9%) participants in the placebo group (HR: 0.58; 95% CI: 0.37-0.91); the corresponding numbers were 166 (8.7%) and 261 (13.6%) in participants without a history of HF (HR: 0.62; 95% CI: 0.51-0.75; P interaction = 0.59) (**Table 2, Figure 1, Central Illustration**). Event rates for all components of the primary outcome favored dapagliflozin, irrespective of whether patients had HF or not.

The kidney-specific secondary endpoint was also reduced significantly by dapagliflozin in patients with and without a history of HF (**Table 2**).

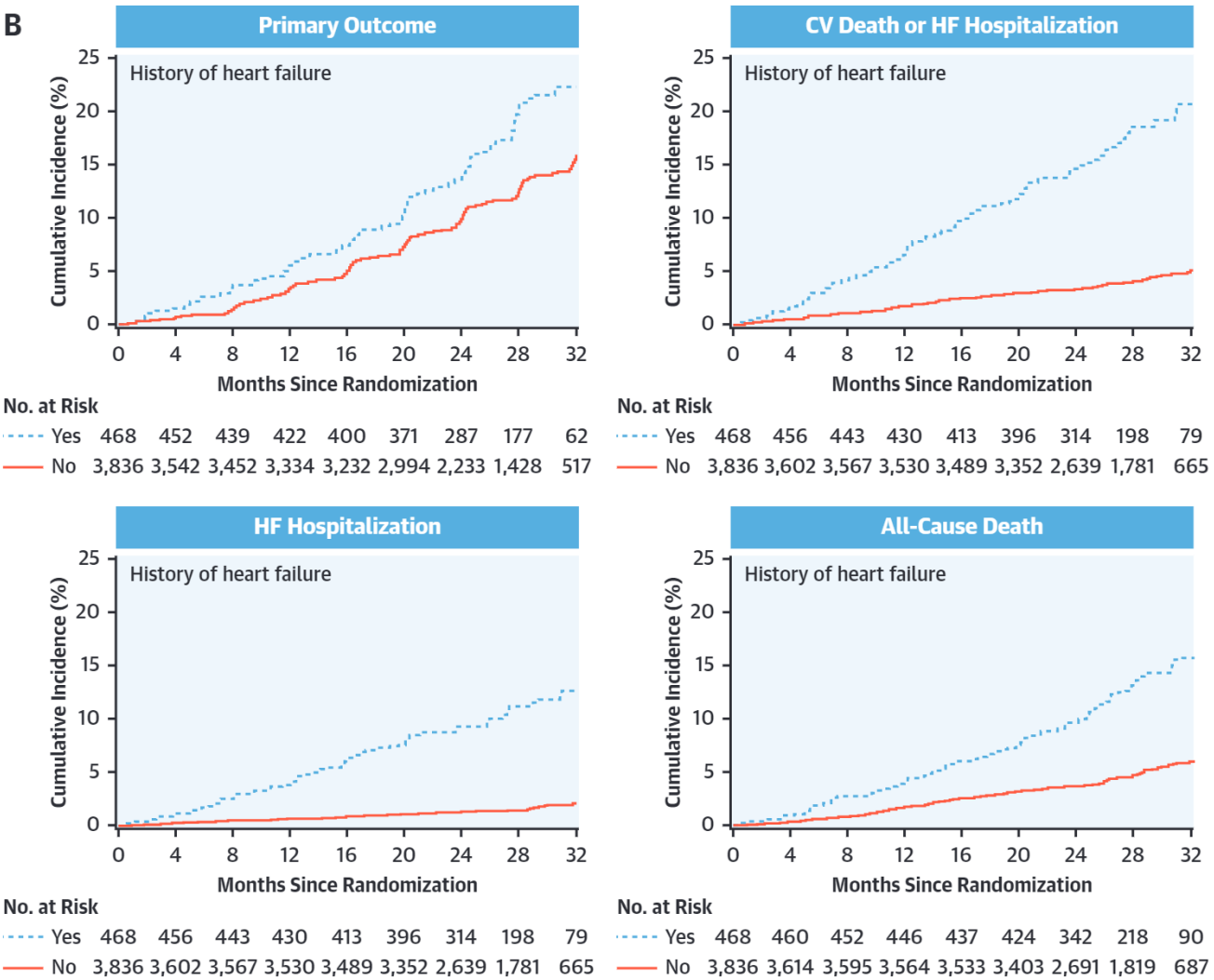
EFFECT OF DAPAGLIFLOZIN ON CARDIOVASCULAR DEATH OR HF HOSPITALIZATION AND ALL-CAUSE MORTALITY ACCORDING TO BASELINE HISTORY OF HF. Among patients with a history of HF, the key secondary composite outcome of cardiovascular death or hospitalization for HF occurred in 36 (15.3%) participants in the dapagliflozin group and 48 (20.6%) participants in the placebo group (HR: 0.68; 95% CI: 0.44-1.05); corresponding numbers were 64 (3.3%) and 90 (4.7%) in participants without HF (HR: 0.70; 95% CI: 0.51-0.97; P interaction = 0.90) (**Table 2,**

CENTRAL ILLUSTRATION Patients With and Without Heart Failure at Baseline in DAPA-CKD

A

	No Heart Failure	Heart Failure
Mean age, years	61.4	65.3
Female, %	32.7	36.1
Prior myocardial infarction, %	7.0	26.7
Type 2 diabetes, %	66.3	77.1
Atrial fibrillation, %	3.6	19.0
Mean eGFR, ml/min/1.73m^2	43.1	43.2

B



McMurray, J.J.V. et al. J Am Coll Cardiol HF. 2021;9(11):807–820.

(A) Key differences in baseline characteristics, **(B)** outcomes, and **(C)** consistency of effect of dapagliflozin, all according to baseline heart failure status.
CV = cardiovascular; DAPA-CKD = Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; HF = heart failure

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CENTRAL ILLUSTRATION Continued

C **Effect of Dapagliflozin, Compared With Placebo, in DAPA-CKD Overall and According to Baseline Heart Failure Status**

	Dapagliflozin n/N	Placebo n/N	Dapagliflozin Events/100 Patient-Years	Placebo Events/100 Patient-Years	HR (95% CI)	*P* Value for Interaction
Primary outcome: *eGFR decline ≥50%, ESKD, or kidney or CV death*						
Overall	197/2,152	312/2,152	4.6	7.5	0.61 (0.51–0.72)	
HF at baseline	31/235	51/233	6.5	11.0	0.58 (0.37–0.91)	0.59
No HF at baseline	166/1,917	261/1,919	4.4	7.0	0.62 (0.51–0.75)	
Secondary outcome: *eGFR decline ≥50%, ESKD, or kidney death*						
Overall	142/2,152	243/2,152	3.3	5.8	0.56 (0.45–0.68)	
HF at baseline	13/235	27/233	2.7	5.8	0.45 (0.23–0.87)	0.36
No HF at baseline	129/1,917	216/1,919	3.4	5.8	0.57 (0.46–0.71)	
Secondary outcome: *CV death or heart failure hospitalization*						
Overall	100/2,152	138/2,152	2.2	3.0	0.71 (0.55–0.92)	
HF at baseline	36/235	48/233	7.1	10.1	0.68 (0.44–1.05)	0.90
No HF at baseline	64/1,917	90/1,919	1.6	2.2	0.70 (0.51–0.97)	
Secondary outcome: *All-cause death*						
Overall	101/2,152	146/2,152	2.2	3.1	0.69 (0.53–0.88)	
HF at baseline	24/235	40/233	4.6	7.9	0.56 (0.34–0.93)	0.39
No HF at baseline	77/1,917	106/1,919	1.9	2.6	0.73 (0.54–0.97)	
Exploratory outcome: *Heart failure hospitalization*						
Overall	37/2,152	71/2,152	0.8	1.6	0.51 (0.34–0.76)	
HF at baseline	20/235	29/233	3.9	6.1	0.62 (0.35–1.10)	0.28
No HF at baseline	17/1,917	42/1,919	0.4	1.0	0.40 (0.23–0.70)	

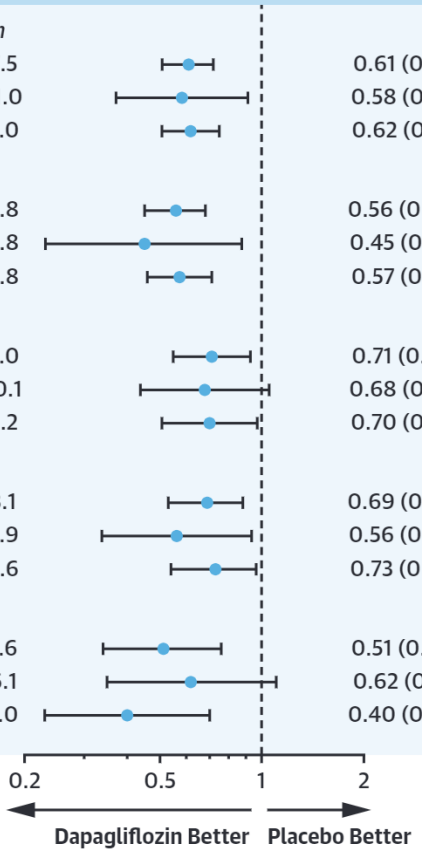

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Figure 1, **Central Illustration**). The reduction in risk was largely driven by HF hospitalization, which occurred in 20 (8.5%) participants in the dapagliflozin group and 29 (12.4%) participants in the placebo group with a history of HF (HR: 0.62; 95% CI: 0.35-1.10); corresponding numbers in participants without HF were 17 (0.9%) and 42 (2.2%) (HR: 0.40; 95% CI: 0.23-0.70); *P* interaction = 0.28. The reduction in cardiovascular death (alone) with dapagliflozin was not statistically significant, but all-cause mortality was reduced significantly overall and in the HF and no HF subgroups (Table 2).

EFFECT OF DAPAGLIFLOZIN ON TOTAL (FIRST AND REPEAT) HOSPITALIZATIONS FOR HF. Among patients with a history of HF, in the placebo group (n = 204), 22 patients had 1 hospitalization for HF and 7 patients had ≥2 admissions (total hospitalizations = 39); corresponding numbers in the dapagliflozin group (n = 215) were 16 with 1 admission and 4 patients with ≥2 admissions (total hospitalizations = 26). Among patients without a history of HF, in the placebo group (n = 1,877), 33 patients had 1 hospitalization for HF and 9 patients had ≥2 admissions (total hospitalizations = 54); the corresponding numbers in the dapagliflozin group were 14 with 1 admission and 3 patients with ≥2 admissions (total hospitalizations = 23). The rate ratio for total hospitalizations for HF in the whole trial population was 0.52 (95% CI: 0.32-0.82), 0.40 (95% CI: 0.17-0.96) in patients with HF, and 0.57 (95% CI: 0.33-0.97) in patients without HF.

EFFECT OF DAPAGLIFLOZIN ON EXPLORATORY KIDNEY OUTCOMES. Doubling of serum creatinine. Among patients with a history of HF assigned to

TABLE 2 Primary, Secondary, and Exploratory Endpoints According to Baseline History of Heart Failure and Randomized Treatment Assignment

	Dapagliflozin (n = 2,152)		Placebo (n = 2,152)				
	No Heart Failure (n = 1,917) Heart Failure (n = 235)		No Heart Failure (n = 1,919) Heart Failure (n = 233)				
		Participants With Event/100 Patient-Years		Participants With Event/100 Patient-Years	Absolute Risk Difference (95% CI)	Hazard Ratio (95% CI)	Interaction *P* Value
Primary composite outcome and individual components							
eGFR decline ≥50%, end-stage kidney disease, or kidney or cardiovascular death[a]							
All patients	197 (9.2)	4.6	312 (14.5)	7.5	−5.3 (−7.3 to −3.4)	0.61 (0.51 to 0.72)	
No heart failure	166 (8.7)	4.4	261 (13.6)	7.0	−4.9 (−6.9 to −3.0)	0.62 (0.51 to 0.75)	0.59
Heart failure	31 (13.2)	6.5	51 (21.9)	11.0	−8.7 (−15.5 to −1.8)	0.58 (0.37 to 0.91)	
≥50% estimated GFR decline							
All patients	112 (5.2)	2.6	201 (9.3)	4.8	−4.1 (−5.7 to −2.6)	0.53 (0.42 to 0.67)	
No heart failure	99 (5.2)	2.6	176 (9.2)	4.7	−4.0 (−5.6 to −2.4)	0.54 (0.43 to 0.70)	0.59
Heart failure	13 (5.5)	2.7	25 (10.7)	5.4	−5.2 (−10.1 to −0.3)	0.49 (0.25 to 0.95)	
End-stage kidney disease							
All patients	109 (5.1)	2.5	161 (7.5)	3.8	−2.4 (−3.9 to −1.0)	0.64 (0.50 to 0.82)	
No heart failure	100 (5.2)	2.6	145 (7.6)	3.8	−2.3 (−3.9 to −0.8)	0.66 (0.51 to 0.86)	0.46
Heart failure	9 (3.8)	1.8	16 (6.9)	3.4	−3.0 (−7.1 to 1.0)	0.53 (0.23 to 1.21)	
Kidney death							
All patients	2 (0.1)	0.0	6 (0.3)	0.1	—	—	
No heart failure	2 (0.1)	0.0	4 (0.2)	0.1	—	—	-
Heart failure	0 (0.0)	0.0	2 (0.9)	0.4	—	—	
Cardiovascular death							
All patients	65 (3.0)	1.4	80 (3.7)	1.7	−0.7 (−1.8 to 0.4)	0.81 (0.58 to 1.12)	
No heart failure	47 (2.5)	1.1	54 (2.8)	1.3	−0.4 (−1.4 to 0.7)	0.87 (0.59 to 1.29)	0.40
Heart failure	18 (7.7)	3.4	26 (11.2)	5.1	−3.5 (−8.8 to 1.8)	0.65 (0.36 to 1.20)	
Secondary outcomes							
eGFR decline ≥50%, end-stage kidney disease or kidney death							
All patients	142 (6.6)	3.3	243 (11.3)	5.8	−4.7 (−6.4 to −3.0)	0.56 (0.45 to 0.68)	
No heart failure	129 (6.7)	3.4	216 (11.3)	5.8	−4.5 (−6.3 to −2.7)	0.57 (0.46 to 0.71)	0.36
Heart failure	13 (5.5)	2.7	27 (11.6)	5.8	−6.1 (−11.1 to −1.0)	0.45 (0.23 to 0.87)	
Cardiovascular death or hospitalization for heart failure							
All patients	100 (4.6)	2.2	138 (6.4)	3.0	−1.8 (−3.1 to −0.4)	0.71 (0.55 to 0.92)	
No heart failure	64 (3.3)	1.6	90 (4.7)	2.2	−1.4 (−2.6 to −0.1)	0.70 (0.51 to 0.97)	0.90
Heart failure	36 (15.3)	7.1	48 (20.6)	10.1	−5.3 (−12.2 to 1.7)	0.68 (0.44 to 1.05)	
All-cause death							
All patients	101 (4.7)	2.2	146 (6.8)	3.1	−2.1 (−3.5 to −0.7)	0.69 (0.53 to 0.88)	
No heart failure	77 (4.0)	1.9	106 (5.5)	2.6	−1.5 (−2.9 to −0.2)	0.73 (0.54 to 0.97)	0.39
Heart failure	24 (10.2)	4.6	40 (17.2)	7.9	−7.0 (−13.2 to -0.8)	0.56 (0.34 to 0.93)	
Prespecified exploratory cardiovascular outcome							
First heart failure hospitalization							
All patients	37 (1.7)	0.8	71 (3.3)	1.6	−1.6 (−2.5 to −0.6)	0.51 (0.34 to 0.76)	
No heart failure	17 (0.9)	0.4	42 (2.2)	1.0	−1.3 (−2.1 to −0.5)	0.40 (0.23 to 0.70)	0.28
Heart failure	20 (8.5)	3.9	29 (12.4)	6.1	−3.9 (−9.5 to 1.6)	0.62 (0.35 to 1.10)	

Values are n (%), unless otherwise indicated. [a]End-stage kidney disease = eGFR <15 mL/min/1.73 m^2, long-term dialysis, or kidney transplantation.
CV = cardiovascular; eGFR = estimated glomerular filtration rate.

dapagliflozin, 17 (7.2%) experienced a doubling in serum creatinine concentration, compared with 21 (9.0%) in the placebo group; HR: 0.77 (95% CI: 0.41-1.47); the corresponding Figures in patients without HF were 46 (2.4%) and 70 (3.6%); HR: 0.65 (95% CI: 0.45-0.95); *P* interaction = 0.71.

eGFR slopes in patients with and without HF. The change in eGFR over time, according to randomized treatment assignment, is shown in Figure 2 for patients with and without HF. In the placebo group, the overall rate of decline in eGFR ("total slope") was −2.74 ± 0.35 mL/min/1.73 m^2 per year among patients with a history of HF, compared with −3.96 ± 0.12 mL/min/1.73 m^2 per year in people without HF. The total eGFR slope was attenuated by dapagliflozin, similarly in patients with and without

HF: the rate of decline in eGFR was 1.03 ± 0.49 mL/min/1.73 m^2 per year slower, with dapagliflozin compared with placebo, in patients with HF and 0.93 ± 0.17 mL/min/1.73 m^2 per year slower in patients without HF (*P* interaction = 0.85).

The initial transient "dip" in eGFR with dapagliflozin was 2.32 ± 0.57 mL/min/1.73 m^2 in patients with and 2.42 ± 0.20 mL/min/1.73 m^2 in those without HF (p interaction = 0.85). The subsequent rate of decline in eGFR was attenuated by dapagliflozin, compared with placebo, to a similar extent in patients with HF (rate of decline 1.99 mL/min/1.73 m^2 per year less) and without HF (1.94 mL/min/1.73 m^2 per year less) (*P* interaction = 0.92).

SAFETY OUTCOMES AND ADVERSE EVENTS. Rates of all prespecified adverse events of interest were low overall and were generally similar in the HF and no HF subgroups (Table 3). Adverse event rates were similar, overall, in patients assigned to dapagliflozin and placebo, irrespective of history of HF (Table 3). In patients with HF, serious adverse events attributed to acute kidney injury were reported in 8 (3.4%) patients assigned to dapagliflozin and 10 (4.3%) assigned to placebo; HR: 0.72 (95% CI: 0.28-1.82). The corresponding figures in patients without HF were 46 (2.4%) and 59 (3.1%); HR: 0.78 (95% CI: 0.53-1.14), (*P* interaction = 0.87).

DISCUSSION

Among participants with CKD with and without type 2 diabetes, in DAPA-CKD, 11% had a history of HF. Although the risk of HF hospitalization or cardiovascular death and all-cause death differed markedly according to history of HF, risk of progressive kidney disease did not. Dapagliflozin was equally efficacious in reducing the risk of kidney failure, the composite outcome of hospitalization for HF or cardiovascular death, and death from any cause, irrespective of history of HF at baseline. These findings highlight the crucial value of SGLT2 inhibitors in the primary and secondary prevention of HF in patients with CKD, irrespective of history of diabetes (and the value of this class of therapy in slowing progression of CKD, irrespective of history of HF).

PRIMARY PREVENTION OF HF. While the rate of the kidney-specific endpoint was similar in participants with or without a history of HF, the rate of hospitalization for HF was 6× higher in those with a history of HF. The prevention of HF is a priority in patients with CKD, as highlighted in recent epidemiological and registry studies (1-7). In addition to contributing to a huge burden of symptoms, resource utilization, and costs, prior studies have reported that development of HF is associated with a high rate of premature mortality (1-7). In keeping with this, we found that in patients with stages 2-4 albuminuric CKD of diverse etiology, the risk of both cardiovascular death and all-cause death was approximately 3× as high in patients with HF at baseline, relative to patients with no history of HF.

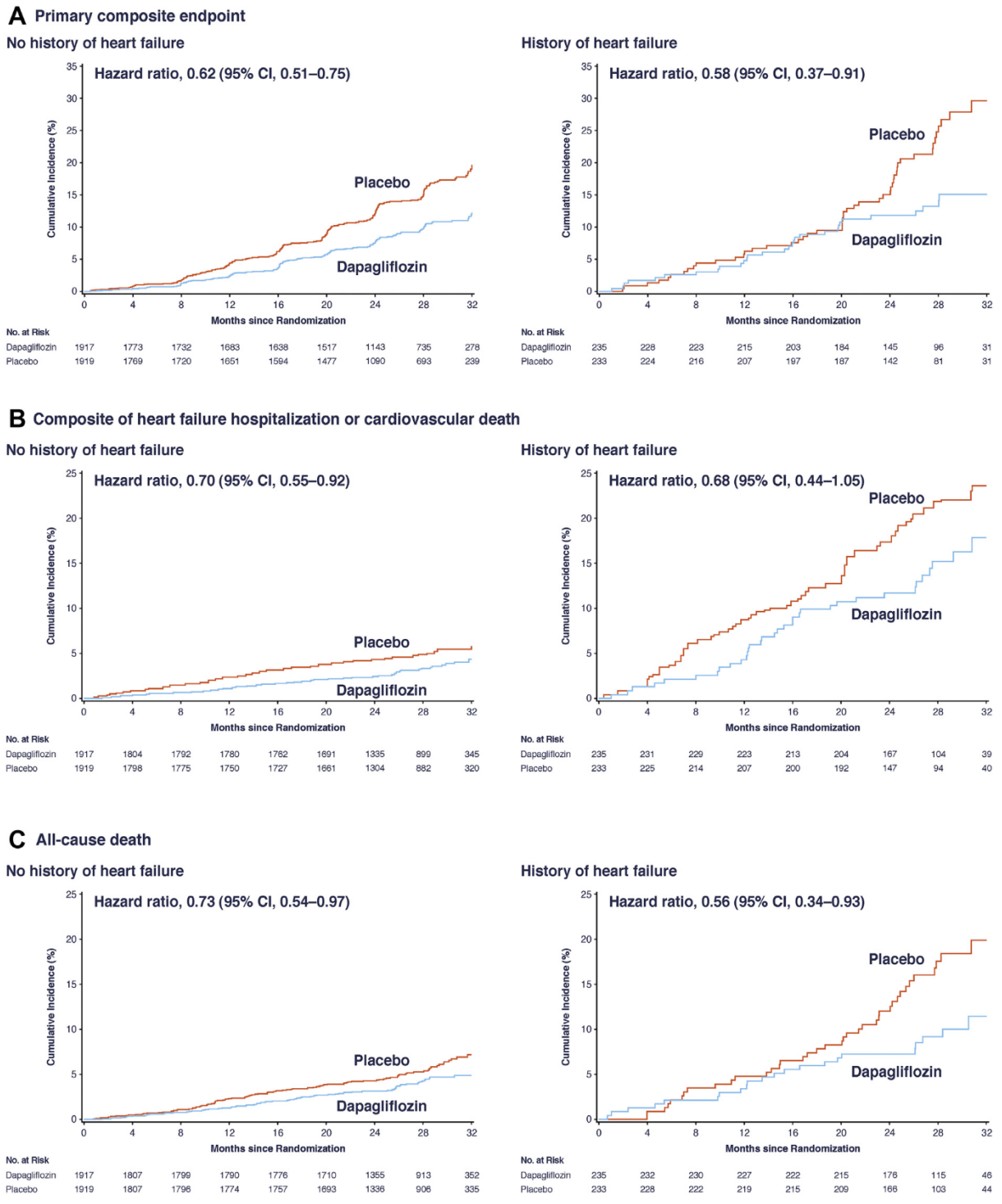
Dapagliflozin reduced the risk of incident HF hospitalization (and the composite of HF hospitalization or cardiovascular death) substantially. Specifically, the relative risk reduction in HF hospitalization was estimated at 60% (30%-77%), highlighting the benefit of dapagliflozin in HF in patients with stage 2-4 CKD, including those without type 2 diabetes (12,14).

SECONDARY PREVENTION OF HF. In patients who already had HF, dapagliflozin was as effective at secondary prevention as at primary prevention. In patients with a history of HF, the proportional reduction in the risk of the composite of HF hospitalization or cardiovascular death was similar to that observed in patients without HF. However, the absolute risk reduction (ARR) was much larger (ARR 5.3% vs 1.4% in patients without HF). A further problem once HF is established is that patients often experience recurrent admissions with worsening of their condition, and these events constitute a major health care and economic burden (1-7). Dapagliflozin was effective at reducing repeat as well as first hospitalizations. Specifically, in a recurrent events analysis, dapagliflozin reduced the total number (ie, first and repeat) of hospitalizations for HF by 60% (95% CI: 4%-83%).

Dapagliflozin was also as effective at reducing mortality in patients with a history of HF as in those with no history of HF. Because patients with HF had a much higher risk of premature death, the absolute all-cause mortality reduction was also large, at around 7% (compared with 1.5% in individuals without HF at baseline).

PREVENTION OF KIDNEY FAILURE. We found that the rate of the rate of the kidney-specific endpoint was the same in participants regardless of history of HF. This is of interest, given previous suggestions that development of HF might accelerate decline in kidney function in patients with existing CKD (7). Moreover, the rate of decline in eGFR over time was not steeper in patients with HF compared with those without HF. Although these findings do not support the hypothesis that HF accelerates decline in kidney function, longer-term follow-up is required to make a robust assessment of the impact of HF on future risk of end-stage kidney disease.

FIGURE 1 The Effect of Dapagliflozin, Compared With Placebo, on the Primary, Secondary, and Exploratory Outcomes



(A) Primary composite outcome; **(B)** composite of hospitalization for heart failure or death from cardiovascular causes and **(C)** all-cause death (prespecified secondary outcomes); and **(D)** the exploratory outcome of hospitalization for heart failure. The primary composite outcome was time to the first occurrence of any of the following: ≥50% decline in eGFR (confirmed by a second serum creatinine measurement after at least 28 days), onset of end-stage kidney disease (defined as maintenance dialysis for more than 28 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 confirmed by a second measurement after at least 28 days), or death from kidney or cardiovascular cause, according to history of heart failure at baseline. One prespecified secondary outcome is not shown and was a kidney composite outcome identical to the primary endpoint, excepting death from cardiovascular causes. CV = cardiovascular.

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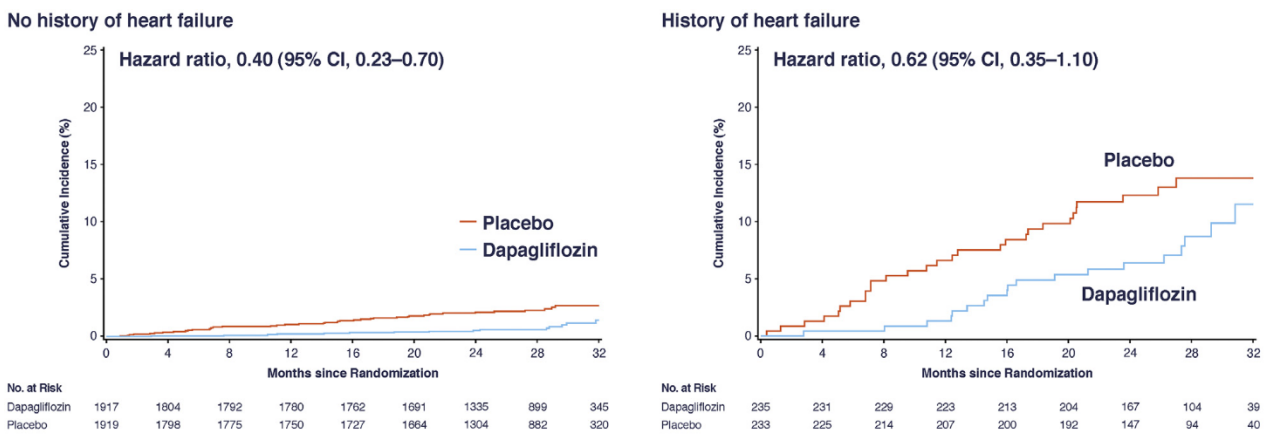
FIGURE 1 Continued



Importantly, dapagliflozin was equally effective in reducing the risk of the kidney-specific endpoint, irrespective of history of HF. Specifically, the relative risk reduction was 50%-60%, with an ARR of around 5% in each subgroup.

Two other trials have reported the effect of agents that inhibit SGLT2 on HF hospitalization in patients with CKD (12,14,16). One of these, CREDENCE, has described the findings related to HF in detail (12,14). There was a much greater differential risk among patients with and without HF in DAPA-CKD compared with CREDENCE. Patients with HF in DAPA-CKD had around a 6-fold higher rate of HF hospitalization (and 4-fold higher rate of HF hospitalization or cardiovascular death) compared with patients without HF, whereas the difference in risk in CREDENCE was around 2-fold for each of these outcomes. The differential was caused by a much lower event rate among patients *without* HF in DAPA-CKD compared with those *without* HF in CREDENCE (by contrast, the event rates were similar in each trial among patients *with* a history of HF) (14). The most likely explanation for this difference was the requirement for all participants in CREDENCE to have type 2 diabetes, whereas only 66% of patients in DAPA-CKD without HF had diabetes, a condition that substantially augments risk of HF (17,18). The same consideration applies to the difference in all-cause mortality between the 2 trials. Another difference between the 2 trials was the reduction in death from any cause in DAPA-CKD, which was not observed in CREDENCE. The reason for this difference is unknown. In DAPA-CKD, the effect of dapagliflozin on all-cause mortality was similar in patients with and without a history of HF, which was consistent with the findings of DAPA-HF (19).

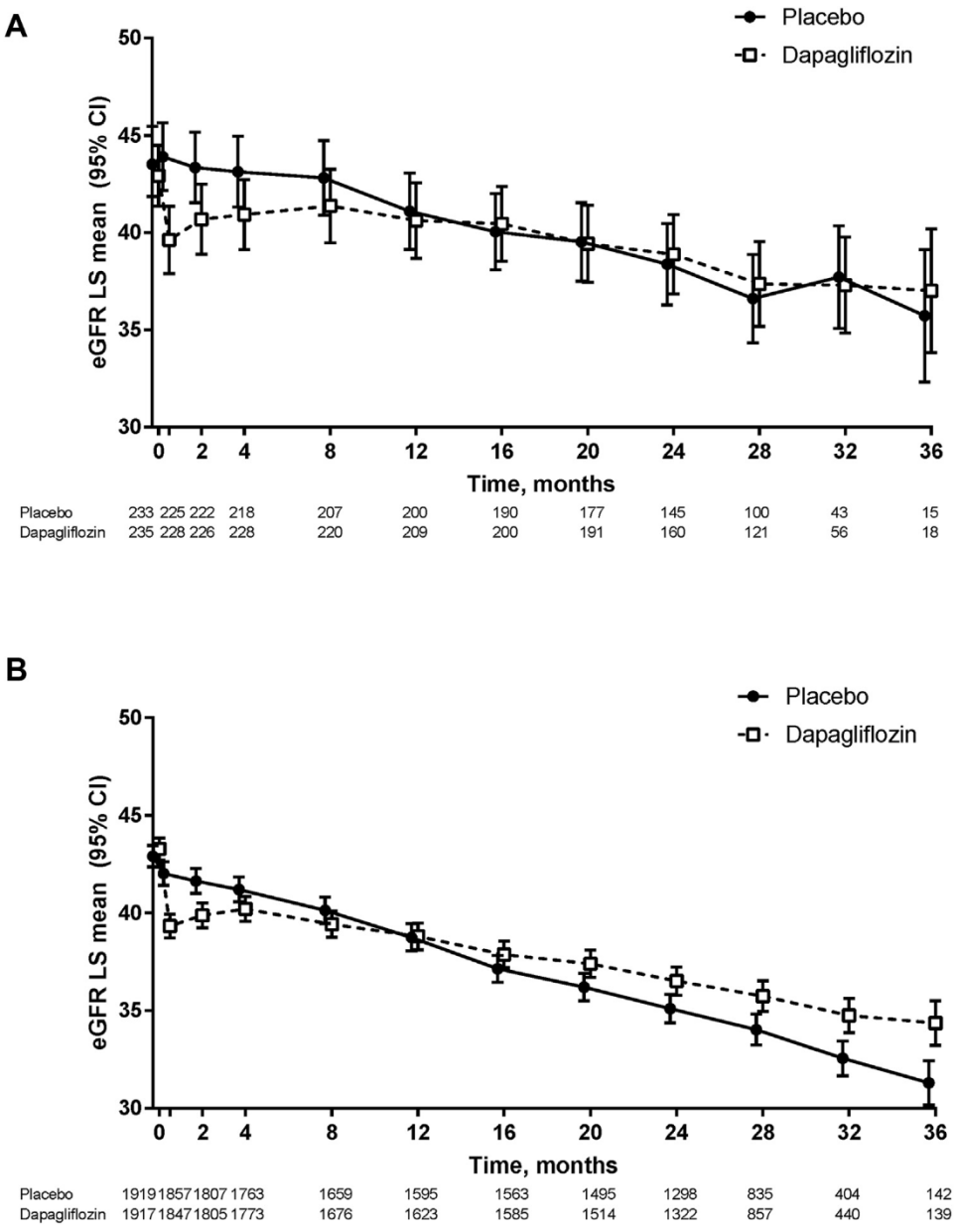
TABLE 3 Prespecified AEs and Study Drug Discontinuation Because of AEs, According to History of Heart Failure at Baseline

	Dapagliflozin		Placebo		
	No Heart Failure (n = 1,914)	Heart Failure (n = 235)	No Heart Failure (n = 1,916)	Heart Failure (n = 233)	*P* Value for Interaction
Any serious AE	503 (26.3)	130 (55.3)	607 (31.7)	122 (52.4)	0.055
AE leading to study drug discontinuation	106 (5.5)	12 (5.1)	113 (5.9)	10 (4.3)	0.588
Amputation	30 (1.6)	5 (2.1)	34 (1.8)	5 (2.1)	0.864
Fracture	75 (3.9)	10 (4.3)	64 (3.3)	5 (2.1)	0.343
Renal AE	133 (6.9)	22 (9.4)	157 (8.2)	31 (13.3)	0.495
Major hypoglycemia[a]	12 (0.6)	2 (0.9)	22 (1.1)	6 (2.6)	0.556
Volume depletion	106 (5.5)	21 (8.9)	78 (4.1)	12 (5.2)	0.503

Values are n (%). [a]The following criteria were confirmed by the investigator: symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention. Definite or probable ketoacidosis occurred in 2 patients without heart failure randomly allocated to placebo; there were no cases of ketoacidosis in the dapagliflozin group.

AE = adverse event; CV = cardiovascular.

FIGURE 2 eGFR Over Time, According to History of Heart Failure at Baseline and Randomized Treatment Assignment



Estimated glomerular filtration rate (eGFR), over time, according to history of heart failure at baseline and randomized treatment assignment (**[A]** history of heart failure at baseline; **[B]** no history of heart failure at baseline).

STUDY LIMITATIONS. Our patients were enrolled in a clinical trial and, therefore, were selected by virtue of the inclusion and exclusion criteria and other factors that influence participation in trials. We did not have a measurement of left ventricular ejection fraction and do not, therefore, know whether patients had HF with reduced or preserved ejection fraction. Because of this, we also do not know whether patients with HF were treated as well as they should be with evidence-based therapy. Some of the analyses were not prespecified and had limited statistical power because of the relatively small size of the subgroup of patients with HF.

CONCLUSIONS

Dapagliflozin reduced the risk of kidney failure, death from cardiovascular causes, or HF hospitalization, and prolonged survival in people with CKD, with or without type 2 diabetes, independently of history of HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The effect of SGLT2 inhibitors on the primary and secondary prevention of HF in CKD patients both with and without type 2 diabetes had not been studied previously. Dapagliflozin was equally effective in preventing incident HF hospitalization in patients with no history of HF and HF hospitalization in patients with a prior diagnosis of HF. Dapagliflozin was also equally effective in preventing kidney failure and all-cause death in both patient groups. Dapagliflozin improves both HF and kidney outcomes in CKD patients, with or without type 2 diabetes, independently of history of HF.

TRANSLATIONAL OUTLOOK: Further research is needed to elucidate the mechanisms underlying the cardiac and kidney benefits of SGLT-2 inhibitors and whether they are the same or different for each type of organ protection.

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KEY WORDS cardiovascular disease, chronic kidney disease, dapagliflozin, heart failure, SGLT2 inhibitor

APPENDIX For an expanded Methods section, please see the online version of this paper.