Circulation

ORIGINAL RESEARCH ARTICLE

Effect of Dapagliflozin on Clinical Outcomes in Patients With Chronic Kidney Disease, With and Without Cardiovascular Disease

BACKGROUND: Dapagliflozin reduces the risk of end-stage renal disease in patients with chronic kidney disease. We examined the relative risk of cardiovascular and renal events in these patients and the effect of dapagliflozin on either type of event, taking account of history of cardiovascular disease.

METHODS: In the DAPA-CKD trial (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease), 4304 participants with chronic kidney disease were randomly assigned to dapagliflozin 10 mg once daily or placebo. The primary end point was a composite of sustained decline in estimated glomerular filtration rate ≥50%, end-stage kidney disease, or kidney or cardiovascular death. The secondary end points were a kidney composite outcome (primary end point, minus cardiovascular death), the composite of hospitalization for heart failure or cardiovascular death, and all-cause death. In a prespecified subgroup analysis, we divided patients into primary and secondary prevention subgroups according to history of cardiovascular disease.

RESULTS: Secondary prevention patients (n=1610; 37.4%) were older, were more often male, had a higher blood pressure and body mass index, and were more likely to have diabetes. Mean estimated glomerular filtration rate and median urinary albumin-to-creatinine ratio were similar in the primary and secondary prevention groups. The rates of adverse cardiovascular outcomes were higher in the secondary prevention group, but kidney failure occurred at the same rate in the primary and secondary prevention groups. Dapagliflozin reduced the risk of the primary composite outcome to a similar extent in both the primary (hazard ratio, 0.61 [95% CI, 0.48–0.78]) and secondary (0.61 [0.47–0.79]) prevention groups (*P*-interaction=0.90). This was also true for the composite of heart failure hospitalization or cardiovascular death (0.67 [0.40–1.13] versus 0.70 [0.52–0.94], respectively; *P*-interaction=0.88), and all-cause mortality (0.63 [0.41–0.98] versus 0.70 [0.51–0.95], respectively; *P*-interaction=0.71). Rates of adverse events were low overall and did not differ between patients with and without cardiovascular disease.

CONCLUSIONS: Dapagliflozin reduced the risk of kidney failure, death from cardiovascular causes or hospitalization for heart failure, and prolonged survival in people with chronic kidney disease, with or without type 2 diabetes, independently of the presence of concomitant cardiovascular disease.

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John J.V. McMurray, MD
David C. Wheeler, MD
Bergur V. Stefánsson, MD
Niels Jongs, MSc
Douwe Postmus, PhD
Ricardo Correa-Rotter, MD
Glenn M. Chertow, MD
Tom Greene, PhD
Claes Held, MD, PhD
Fan-Fan Hou, MD
Johannes F.E. Mann, MD
Peter Rossing, MD
C. David Sjöström, MD
Roberto D. Toto, MD
Anna Maria Langkilde, MD
Hiddo J.L. Heerspink, PhD
For the DAPA-CKD Trial Committees and Investigators

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Clinical Perspective

What Is New?

- The primary and secondary preventive effects of sodium glucose cotransporter 2 inhibitors on cardiovascular outcomes have not been studied in patients with chronic kidney disease, with and without type 2 diabetes.
- Dapagliflozin reduced the risk of the primary composite outcome to a similar extent in the primary and secondary prevention groups. This was also true for the composite of heart failure hospitalization or cardiovascular death (and all-cause mortality).

What Are the Clinical Implications?

- The combined cardiorenal benefits of sodium glucose cotransporter 2 inhibitors in patients with chronic kidney disease, with and without type 2 diabetes, are substantial, regardless of a history of cardiovascular disease.

A series of large randomized controlled trials have shown that sodium glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiovascular events in people with type 2 diabetes.[1–3] Overall, these trials showed consistent, sizeable reductions in heart failure hospitalization with SGLT2 inhibitors, whereas the benefit on atherothrombotic events such as myocardial infarction and stroke was modest and, in meta-analyses, appeared confined to patients with known cardiovascular disease.[4,5] In contradistinction, reduction in heart failure hospitalization was seen in people with and without a history of cardiovascular disease.[1–5]

The CREDENCE trial (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) extended these findings to patients with type 2 diabetes and chronic kidney disease, who are at exceptionally high risk of adverse cardiovascular outcomes.[6] In CREDENCE, canagliflozin reduced the risk of the primary composite renal end point, and the key secondary composite outcomes of cardiovascular death or hospitalization for heart failure and cardiovascular death, myocardial infarction, or stroke. These benefits of canagliflozin were consistent in participants with and without a history of cardiovascular disease.[7]

However, diabetes is not the only cause of chronic kidney disease, and people with chronic kidney disease attributable to other causes are also at heightened risk of adverse cardiovascular outcomes, even if they do not have preexisting cardiovascular disease.[8–11] Consequently, treatments that are both effective and safe are needed for the primary and secondary prevention of cardiovascular events in the broad spectrum of patients with chronic kidney disease, regardless of concomitant type 2 diabetes.

Here, we report the effects of dapagliflozin on the prespecified kidney and cardiovascular outcomes in patients with chronic kidney disease with and without type 2 diabetes, according to history of cardiovascular disease, in the DAPA-CKD trial (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease).[12–14]

METHODS

DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter trial; and the design, baseline findings, and primary results have been published.[12–14] The study was registered at https://www.clinicaltrials.gov (Unique identifier: 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 article may be obtained in accordance with AstraZeneca's data sharing policy (https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure).

Patients

Adults with or without type 2 diabetes, an estimated glomerular filtration rate (eGFR) between 25 and 75 mL·min^{-1}·1.73 m^{-2}, and a urinary albumin-to-creatinine ratio between 200 and 5000 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. Key exclusion criteria included the following: type 1 diabetes, polycystic kidney disease, lupus nephritis, antineutrophil cytoplasmic antibody–associated vasculitis, and patients receiving immunotherapy for primary or secondary renal disease within 6 months before enrollment. The full inclusion and exclusion criteria are described elsewhere.[12]

Treatment and Follow-Up

Participants were randomly assigned to dapagliflozin 10 mg once daily or placebo, with stratification by diagnosis of type 2 diabetes and urinary albumin-to-creatinine ratio (≤1000 mg/g or >1000 mg/g). Randomization was monitored to ensure that at least 30% of the patients had type 2 diabetes and at least 30% did not. After randomization, study visits were planned at 2 weeks; 2, 4, and 8 months; and at 4-month intervals thereafter. A recommendation by the Independent Data Monitoring Committee on March 26, 2020, that the trial be discontinued early for overwhelming efficacy was accepted and the trial closed out, with April 3, 2020, chosen as the cutoff date for all efficacy analyses. The resultant median follow-up was 2.4 years (interquartile range, 2.0–2.7 years).

Definition of Baseline Cardiovascular Disease

We prespecified that we would examine the effect of dapagliflozin in patients according to history of cardiovascular disease. For this analysis, we divided participants into those with and without baseline cardiovascular disease. Cardiovascular

disease was defined as any of the following: coronary heart disease (angina pectoris, myocardial infarction, coronary artery stenosis, percutaneous coronary intervention, coronary artery bypass surgery); cerebrovascular disease (ischemic stroke, hemorrhagic stroke, carotid artery stenosis, transient ischemic attack); peripheral artery disease (peripheral arterial occlusive disease, aneurysm of the abdominal aorta, noncoronary revascularization, vascular stent); heart failure (heart failure, cardiac resynchronization therapy); valvular heart disease; atrial fibrillation or atrial flutter; ventricular arrhythmia; pulmonary embolism; and cardiac devices other than cardiac resynchronization therapy (cardiac pacemaker, implantable cardioverter defibrillator).

Prespecified and Post Hoc 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 >28 days, kidney transplantation, or eGFR <15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ confirmed by a second measurement after at least 28 days), or death from renal or cardiovascular causes.

Prespecified secondary outcomes were, in hierarchal order: (1) a kidney composite outcome identical to the primary end point, with the exception of death from cardiovascular causes; (2) a cardiovascular composite outcome consisting of hospitalization for heart failure or death from cardiovascular causes; and (3) death from any cause. A blinded independent committee adjudicated all components of the primary and secondary outcomes except for changes in eGFR that were calculated from central laboratory measurements. Deaths with an undetermined cause were assumed to be cardiovascular.

In this study, we also examined 2 prespecified exploratory outcomes: (1) a cardiovascular composite outcome of time to first occurrence of myocardial infarction, stroke, or death from cardiovascular causes; and (2) time to first heart failure hospitalization.

Last, we examined 2 post hoc composite outcomes (analyzed as time to first event): (1) myocardial infarction, stroke, heart failure hospitalization, or death from cardiovascular causes (to examine all major adverse cardiovascular events); and (2) myocardial infarction, stroke, heart failure hospitalization, end-stage kidney disease, or death from any cause (to examine all the major nonfatal and fatal adverse outcomes that patients with chronic kidney disease face).

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 that included symptoms of volume depletion, renal events, major hypoglycemia, bone fractures, amputations, and diabetic ketoacidosis (potential diabetic ketoacidosis events were adjudicated by an independent committee).[3,12]

Statistical Analysis

The efficacy analyses included all randomly assigned participants and were conducted according to the intention-to-treat principle. Cox proportional hazard regression models including the stratification variables and adjusted for baseline eGFR were used to estimate the hazard ratio (HR) and 95% CIs for dapagliflozin in comparison with placebo for the primary and secondary study outcomes. HRs (95% CIs) for the effect of dapagliflozin 10 mg, in comparison with placebo, were obtained separately for the cardiovascular disease and no cardiovascular disease subgroups using Cox proportional hazards models with a factor for treatment group, stratified by randomization stratification factors (type 2 diabetes, urinary albumin-to-creatinine ratio), and adjusting for baseline eGFR. Interaction *P* values were based on likelihood ratio tests comparing full factorial models against reduced models with main effects only (again stratified by randomization stratification factors and adjusted for baseline eGFR). Treatment effects are not presented for variables with <15 events in total (both arms combined). Time-to-event data are illustrated by using Kaplan-Meier curves.

Safety data are reported by treatment group in all patients who received at least 1 dose of randomized treatment.

All analyses were performed with R (version 4.02).

RESULTS

Of the 4304 patients randomly assigned, 1610 (37.4%) had a diagnosis of cardiovascular disease at baseline (secondary prevention patients) and 2694 (62.6%) participants did not have a history of cardiovascular disease (primary prevention patients).

Baseline Characteristics

The baseline characteristics of patients with and without cardiovascular disease are shown in Table 1. Patients with cardiovascular disease were older (66.3 versus 59.2 years), more often male (70.5% versus 64.7%), and smokers (52.6% versus 43.2% current or prior smokers). They had a higher mean systolic blood pressure (139.2 versus 135.8 mm Hg) and higher body mass index (30.6 versus 28.9 kg/m^2), and they were more likely to have diabetes (79.6% versus 60.3%) than those without a history of cardiovascular disease. Mean eGFR and median urinary albumin-to-creatinine ratio were similar in patients with and without cardiovascular disease.

Among patients in the secondary prevention group, 56% had coronary artery disease, 29% had cerebrovascular disease, 26% had peripheral artery disease, 29% had heart failure, and 14% had atrial fibrillation/flutter. Almost all patients in each of the primary and secondary prevention groups had hypertension. Overall use of cardiovascular pharmacological therapy was greater in secondary prevention patients than in primary prevention patients (Table 1).

Primary Outcome and Kidney Outcomes According to Baseline History of Cardiovascular Disease

In a comparison of all trial participants, irrespective of randomized treatment assignment, the primary

Table 1. Patient Characteristics, by Baseline Cardiovascular Disease and Randomized Treatment Assignment

Characteristics	Baseline cardiovascular disease (n=1610)		No baseline cardiovascular disease (n=2694)	
	Dapagliflozin	Placebo	Dapagliflozin	Placebo
	n=813	n=797	n333=1339	n=1355
Age, y	66.5 (9.7)	66.2 (9.3)	59 (12.5)	59.4 (12.9)
Male sex, n (%)	587 (72.2)	548 (68.8)	856 (63.9)	888 (65.5)
Race, n (%)				
White	539 (66.3)	523 (65.6)	585 (43.7)	643 (47.5)
Black or African American	37 (4.6)	43 (5.4)	67 (5)	44 (3.2)
Asian	180 (22.1)	173 (21.7)	569 (42.5)	545 (40.2)
Other	57 (7.0)	58 (7.3)	118 (8.8)	123 (9.1)
Region, n (%)				
Europe	307 (37.8)	288 (36.1)	303 (22.6)	335 (24.7)
Asia/Pacific	165 (20.3)	157 (19.7)	527 (39.4)	497 (36.7)
South America	167 (20.5)	173 (21.7)	282 (21.1)	290 (21.4)
North America	174 (21.4)	179 (22.5)	227 (17.0)	233 (17.2)
Heart rate – beats/min = pulse	71.6 (11.4)	70.7 (11.3)	73.7 (11.4)	74.1 (11.6)
Systolic blood pressure, mm Hg	138.8 (17.6)	139.7 (17.6)	135.5 (17.3)	136.1 (17.0)
Hemoglobin A1c (glycohemoglobin), %	7.4 (1.7)	7.4 (1.7)	6.9 (1.7)	6.8 (1.7)
Hemoglobin, g/dL	130.1 (17.9)	127.9 (18.4)	127.7 (18.2)	127.9 (17.8)
Current smoker, n (%)	97 (11.9)	117 (14.7)	186 (13.9)	184 (13.6)
Body mass index, kg/m^2	30.3 (6.2)	30.9 (6.5)	28.8 (5.9)	28.9 (6.0)
Obese (body mass index ≥30 kg/m^2), n (%)	415 (51.0)	435 (54.6)	526 (39.3)	541 (39.9)
Medical history, n (%)				
Any atherosclerotic cardiovascular disease	663 (81.5)	666 (83.6)	–	–
Hypertension	803 (98.8)	788 (98.9)	1262 (94.2)	1268 (93.6)
Heart failure	235 (28.9)	233 (29.2)	–	–
Atrial fibrillation or flutter	115 (14.1)	112 (14.1)	–	–
Angina	201 (24.7)	204 (25.6)	–	–
Myocardial infarction	185 (22.8)	207 (26.0)	–	–
Coronary artery bypass grafting	74 (9.1)	102 (12.8)	–	–
Percutaneous coronary intervention	145 (17.8)	149 (18.7)	–	–
Stroke	144 (17.7)	154 (19.3)	–	–
Transient ischemic attack	41 (5.0)	38 (4.8)	–	–
Peripheral artery disease	154 (18.9)	171 (21.5)	–	–
Amputation	59 (7.3)	50 (6.3)	36 (2.7)	36 (2.7)
Type 2 diabetes	640 (78.7)	641 (80.4)	815 (60.9)	810 (59.8)
Estimated glomerular filtration rate, mL·min^{-1}·1.73 m^{-2} of body surface area	43.3 (12.0)	43.0 (12.6)	43.2 (12.5)	42.9 (12.3)
Estimated glomerular filtration rate category, n (%)				
≥60 mL·min^{-1}·1.73 m^{-2}	94 (11.6)	88 (11.0)	140 (10.5)	132 (9.7)
45–59 mL·min^{-1}·1.73 m^{-2}	233 (28.7)	254 (31.9)	413 (30.8)	428 (31.6)
30–44 mL·min^{-1}·1.73 m^{-2}	388 (47.7)	322 (40.4)	591 (44.1)	597 (44.1)
<30 mL·min^{-1}·1.73 m^{-2}	98 (12.1)	133 (16.7)	195 (14.6)	198 (14.6)
Median urinary albumin-to-creatinine ratio (interquartile range), mg/g	1012 (446–1956)	944 (473–1825)	937 (487–1856)	933 (488–1911)
Device therapy, n (%)				
Implantable cardioverter-defibrillator	8 (1.0)	6 (0.8)	–	–

(*Continued*)

Table 1. Continued

Characteristics	Baseline cardiovascular disease (n=1610)		No baseline cardiovascular disease (n=2694)	
	Dapagliflozin	Placebo	Dapagliflozin	Placebo
	n=813	n=797	n333=1339	n=1355
Cardiac resynchronization therapy	2 (0.2)	4 (0.5)	–	–
Pacemaker	27 (3.3)	28 (3.5)	–	–
Cardiovascular and renal medication, n (%)				
β-Blocker	495 (60.9)	474 (59.5)	351 (26.2)	360 (26.6)
Diuretic	437 (53.8)	443 (55.6)	491 (36.7)	511 (37.7)
Mineralocorticoid receptor antagonist	65 (8.0)	74 (9.3)	44 (3.3)	46 (3.4)
Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or other renin-angiotensin system blocker	798 (98.2)	761 (95.5)	1296 (96.8)	1319 (97.3)
Antiplatelet	577 (71.0)	547 (68.6)	375 (28.0)	381 (28.1)
Statin	622 (76.5)	609 (76.4)	773 (57.7)	790 (58.3)
Other lipid-lowering therapy	132 (16.2)	115 (14.4)	188 (14.0)	210 (15.5)
Glucose-lowering medication, n (%)				
Biguanide	272 (33.5)	274 (34.4)	362 (27.0)	342 (25.2)
Sulfonylurea	158 (19.4)	156 (19.6)	232 (17.3)	230 (17.0)
Dipeptidyl peptidase inhibitor	133 (16.4)	145 (18.2)	231 (17.3)	233 (17.2)
Glucagon-like peptide 1 receptor agonist	30 (3.7)	23 (2.9)	33 (2.5)	36 (2.7)
Insulin	382 (47.0)	367 (46)	432 (32.3)	417 (30.8)

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 7.0 (95% CI, 6.2–8.0) per 100 person-years in the patients with a history of cardiovascular disease, in comparison with a rate of 5.4 (95% CI, 4.8–6.0) per 100 person-years in patients without a history of cardiovascular disease (HR, 1.24 [95% CI, 1.04–1.48]; *P*=0.02). The higher rate of the primary outcome in the secondary prevention patients was attributable to a higher rate of cardiovascular death in these participants: 2.9 (95% CI, 2.3–3.5) per 100 person-years in comparison with 0.8 (95% CI, 0.6–1.0) per 100 person years in the primary prevention patients. 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 a renal cause was similar in these 2 patient groups: 4.3 (95% CI, 3.6–5.0) per 100 person-years in the patients with a history of cardiovascular disease, in comparison with a rate of 4.7 (95% CI, 4.2–5.4) per 100 person-years in the primary prevention group (HR, 0.87 [95% CI, 0.70–1.07]; *P*=0.18).

Cardiovascular Outcomes and All-Cause Mortality According to Baseline History of Cardiovascular Disease

The key secondary composite outcome of cardiovascular death or hospitalization for heart failure occurred at a >4-fold higher rate in secondary prevention patients than in primary prevention patients: 5.2 (95% CI, 4.4–6.0) per 100 person-years in the secondary prevention group in comparison with 1.0 (95% CI, 0.83–1.3) per 100 person-years in the primary prevention group (HR, 4.52 [95% CI 3.36–6.07]; *P*<0.001). Likewise, the rate of the prespecified composite of cardiovascular death, myocardial infarction, or stroke occurred at a higher rate in patients with a history of cardiovascular disease than in those without a history of cardiovascular disease: 5.4 (95% CI, 4.6–6.2) per 100 person-years in the secondary prevention group in comparison with 1.6 (95% CI, 1.3–2.0) per 100 person-years in the primary prevention group (HR, 3.10 [95% CI, 2.41–4.00]; *P*<0.001). Death from any cause also occurred more frequently in patients with a history of cardiovascular disease than in those without, although the difference between groups was not as large as for the aforementioned end points: 4.6 (95% CI, 3.9–5.3) per 100 person-years in the secondary prevention group in comparison with 1.5 (95% CI, 1.2–1.8) per 100 person-years in the primary prevention group (HR, 2.90 [95% CI, 2.22–3.78]; *P*<0.001).

Effect of Dapagliflozin on Prespecified Clinical Outcomes According to Baseline History of Cardiovascular Disease

Among patients with cardiovascular disease, the primary composite outcome occurred in 91 (11.2%) participants

in the dapagliflozin group and 137 (17.2%) participants in the placebo group (HR, 0.61 [95% CI, 0.47–0.79]); the corresponding numbers were 106 (7.9%) and 175 (12.9%) in participants without cardiovascular disease (HR, 0.61 [0.48–0.78]; *P*-interaction=0.90 (Table 2 and Figures 1 and 2). In both the primary and secondary prevention patients, the event rates favored dapagliflozin for all components of the primary outcome and for the key, kidney-specific, secondary end point, although the reduction in cardiovascular death was not statistically significant (Table 2).

Among patients with cardiovascular disease, the key secondary composite outcome of cardiovascular death or hospitalization for heart failure occurred in 76 (9.3%) participants in the dapagliflozin group and 102 (12.8%) participants in the placebo group (HR, 0.70 [0.52–0.94]); the corresponding numbers were 24 (1.8%) and 36 (2.7%) in participants without cardiovascular disease (HR, 0.67 [0.40–1.13]; *P*-interaction=0.88; Table 2 and Figures 1 and 2). The reduction in risk was driven by heart failure hospitalization, which occurred in 33 (4.1%) participants in the dapagliflozin group and 58 (7.3%) participants in the placebo group with cardiovascular disease (HR, 0.54 [0.35–0.82]); the corresponding numbers in participants without cardiovascular disease were 4 (0.3%) and 13 (1.0%) (HR, 0.31 [0.10–0.94]; *P*-interaction=0.35.

Dapagliflozin did not decrease the risk of the prespecified composite of cardiovascular death, myocardial infarction, or stroke significantly in either the secondary or the primary prevention group (Table 2).

Effect of Dapagliflozin on Post Hoc Cardiovascular and Cardiorenal Composite Outcomes According to Baseline History of Cardiovascular Disease

Among patients with cardiovascular disease, the expanded cardiovascular composite outcome (death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure) occurred in 114 (14.0%) participants in the dapagliflozin group and 135 (16.9%) participants in the placebo group (HR, 0.80 [0.62–1.03]); the corresponding numbers were 44 (3.3%) and 60 (4.4%) in participants without cardiovascular disease (HR, 0.73 [0.50–1.08]; *P*-interaction=0.72 (Table 2).

Among patients with cardiovascular disease, the cardiorenal composite outcome (death from any cause, myocardial infarction, stroke, heart failure hospitalization, or end-stage kidney disease) occurred in 156 (19.2%) participants in the dapagliflozin group and 199 (25.0%) participants in the placebo group (HR, 0.72 [0.58–0.89]); the corresponding numbers were 118 (8.8%) and 177 (13.1%) in participants without cardiovascular disease (HR, 0.68 [0.54–0.85]; *P*-interaction=0.77 (Table 2). The number of patients needed to treat over the duration of the trial to prevent 1 patient from experiencing this broad composite end point was 21 (95% CI, 15–38) in the overall population; in primary prevention patients, the number needed to treat was 24 (15–53), and, in secondary prevention patients, the number of patients needed to treat was 17 (10–58).

Safety Outcomes and Adverse Events

The rates of all prespecified adverse events of interest were low overall and, in general, similar in the primary and secondary prevention subgroups, with the exception of amputation, which occurred more often in participants with a history of cardiovascular disease (Table 3). Adverse event rates, including for amputation, were similar overall in patients assigned to dapagliflozin and placebo, irrespective of history of cardiovascular disease (Table 3).

DISCUSSION

In DAPA-CKD, among participants with chronic kidney disease, with and without type 2 diabetes, over one-third had a history of cardiovascular disease.[12–14] Although the cardiovascular risk of participants differed markedly in relation to baseline cardiovascular disease status, renal risk did not. Dapagliflozin was similarly efficacious in reducing the risk of adverse kidney outcomes, the composite outcome of cardiovascular death or hospitalization for heart failure, and death from any cause, irrespective of history of cardiovascular disease at baseline.

The dichotomy in rates of the prespecified renal and cardiovascular end points in the primary and secondary prevention patient subgroups was striking. Although the rate of the kidney-specific end point was the same in participants regardless of history of cardiovascular disease, the rate of the composite of cardiovascular death or hospitalization for heart failure was 5 times higher in those with known cardiovascular disease (secondary prevention group) than in participants with no history of cardiovascular disease (primary prevention group). Likewise, the rate of the prespecified exploratory composite of cardiovascular death, myocardial infarction, or stroke was similarly elevated in secondary prevention, in comparison with primary prevention participants. As a result, the rate of cardiovascular events, and death, was considerably higher than the rate of adverse kidney outcomes in patients with a history of cardiovascular disease, whereas the reverse was true in the primary prevention participants, although the differential risk was not as marked.

Table 2. Primary, Secondary, and Exploratory End Points According to Baseline Cardiovascular Disease Status

End points	Dapagliflozin (n=2152)*		Placebo (n=2152)†		Absolute risk difference (95% CI)	Hazard ratio (95% CI)	Interaction *P* value
	n (%)	Participants with event/100 patient-years	n (%)	Participants with event/100 patient-years			
Primary composite outcome and individual components							
Estimated glomerular filtration rate decline ≥50%, end-stage kidney disease, or kidney or cardiovascular death‡							
No cardiovascular disease	106 (7.9)	4.0	175 (12.9)	6.7	–5.0% (–7.3 to –2.7)	0.61 (0.48 to 0.78)	0.90
Cardiovascular disease	91 (11.2)	5.5	137 (17.2)	8.7	–6.0% (–9.4 to –2.6)	0.61 (0.47 to 0.79)	
≥50% estimated glomerular filtration rate decline							
No cardiovascular disease	71 (5.3)	2.7	127 (9.4)	4.9	–4.1% (–6.0 to –2.1)	0.57 (0.42 to 0.76)	0.54
Cardiovascular disease	41 (5.0)	2.5	74 (9.3)	4.7	–4.2% (–6.8 to –1.7)	0.50 (0.34 to 0.73)	
End-stage kidney disease							
No cardiovascular disease	72 (5.4)	2.7	106 (7.8)	4.0	–2.4% (–4.3 to –0.6)	0.69 (0.51 to 0.93)	0.50
Cardiovascular disease	37 (4.6)	2.2	55 (6.9)	3.4	–2.3% (–4.6 to –0.1)	0.59 (0.39 to 0.91)	
Kidney death							
No cardiovascular disease	1 (0.1)	0.0	2 (0.1)	0.1	–	–	–
Cardiovascular disease	1 (0.1)	0.1	4 (0.5)	0.2	–	–	–
Cardiovascular death							
No cardiovascular disease	20 (1.5)	0.7	24 (1.8)	0.8	–0.3% (–1.2 to 0.7)	0.85 (0.47 to 1.54)	0.80
Cardiovascular disease	45 (5.5)	2.5	56 (7.0)	3.2	–1.5% (–3.9 to 0.9)	0.77 (0.52 to 1.14)	
Secondary outcomes							
Estimated glomerular filtration rate decline ≥50%, end-stage kidney disease or kidney death							
No cardiovascular disease	93 (6.9)	3.6	154 (11.4)	5.9	–4.4% (–6.6 to –2.2)	0.61 (0.47 to 0.79)	0.29
Cardiovascular disease	49 (6.0)	2.9	89 (11.2)	5.6	–5.1% (–7.9 to –2.4)	0.49 (0.34 to 0.69)	
Cardiovascular death or hospitalization for heart failure							
No cardiovascular disease	24 (1.8)	0.8	36 (2.7)	1.3	–0.9% (–2.0 to 0.2)	0.67 (0.40 to 1.13)	0.88
Cardiovascular disease	76 (9.3)	4.3	102 (12.8)	6.1	–3.4% (–6.5 to –0.4)	0.70 (0.52 to 0.94)	
All-cause death							
No cardiovascular disease	33 (2.5)	1.1	53 (3.9)	1.8	–1.4% (–2.8 to –0.1)	0.63 (0.41 to 0.98)	0.71
Cardiovascular disease	68 (8.4)	3.8	93 (11.7)	5.4	–3.3% (–6.2 to –0.4)	0.70 (0.51 to 0.95)	
Prespecified exploratory cardiovascular outcomes							
Cardiovascular death, myocardial infarction or stroke							
No cardiovascular disease	41 (3.1)	1.4	50 (3.7)	1.7	–0.6% (–2.0 to 0.7)	0.83 (0.55 to 1.25)	0.61
Cardiovascular disease	91 (11.2)	5.2	93 (11.7)	5.5	–0.5% (–3.6 to 2.6)	0.94 (0.71 to 1.26)	
First heart failure hospitalization							
No cardiovascular disease	4 (0.3)	0.1	13 (1.0)	0.5	–0.7% (–1.3 to –0.1)	0.31 (0.10 to 0.94)	0.35
Cardiovascular disease	33 (4.1)	1.9	58 (7.3)	3.5	–3.2% (–5.5 to –1.0)	0.54 (0.35 to 0.82)	
Post hoc exploratory cardiovascular/cardiorenal outcomes							
Cardiovascular death, myocardial infarction, stroke, or heart failure hospitalization							
No cardiovascular disease	44 (3.3)	1.5	60 (4.4)	2.1	–1.1% (–2.6 to 0.3)	0.73 (0.50 to 1.08)	0.72
Cardiovascular disease	114 (14.0)	6.6	135 (16.9)	8.3	–2.9% (–6.4 to 0.6)	0.80 (0.62 to 1.03)	
All-cause death, myocardial infarction, stroke, heart failure hospitalization, or end-stage kidney disease							
No cardiovascular disease	118 (8.8)	4.5	177 (13.1)	6.8	–4.3% (–6.6 to –1.9)	0.68 (0.54 to 0.85)	0.77
Cardiovascular disease	156 (19.2)	9.6	199 (25.0)	13.1	–5.8% (–9.8 to –1.7)	0.72 (0.58 to 0.89)	

*In the dapagliflozin group, the number of patients without cardiovascular disease was 1339 and with cardiovascular disease was 813.
†In the placebo group, the number of patients without cardiovascular disease was 1355 and with cardiovascular disease was 797.
‡End-stage kidney disease=estimated glomerular filtration rate <15 mL·min^{-1}·1.73 m^{-2}, long-term dialysis, or kidney transplantation.

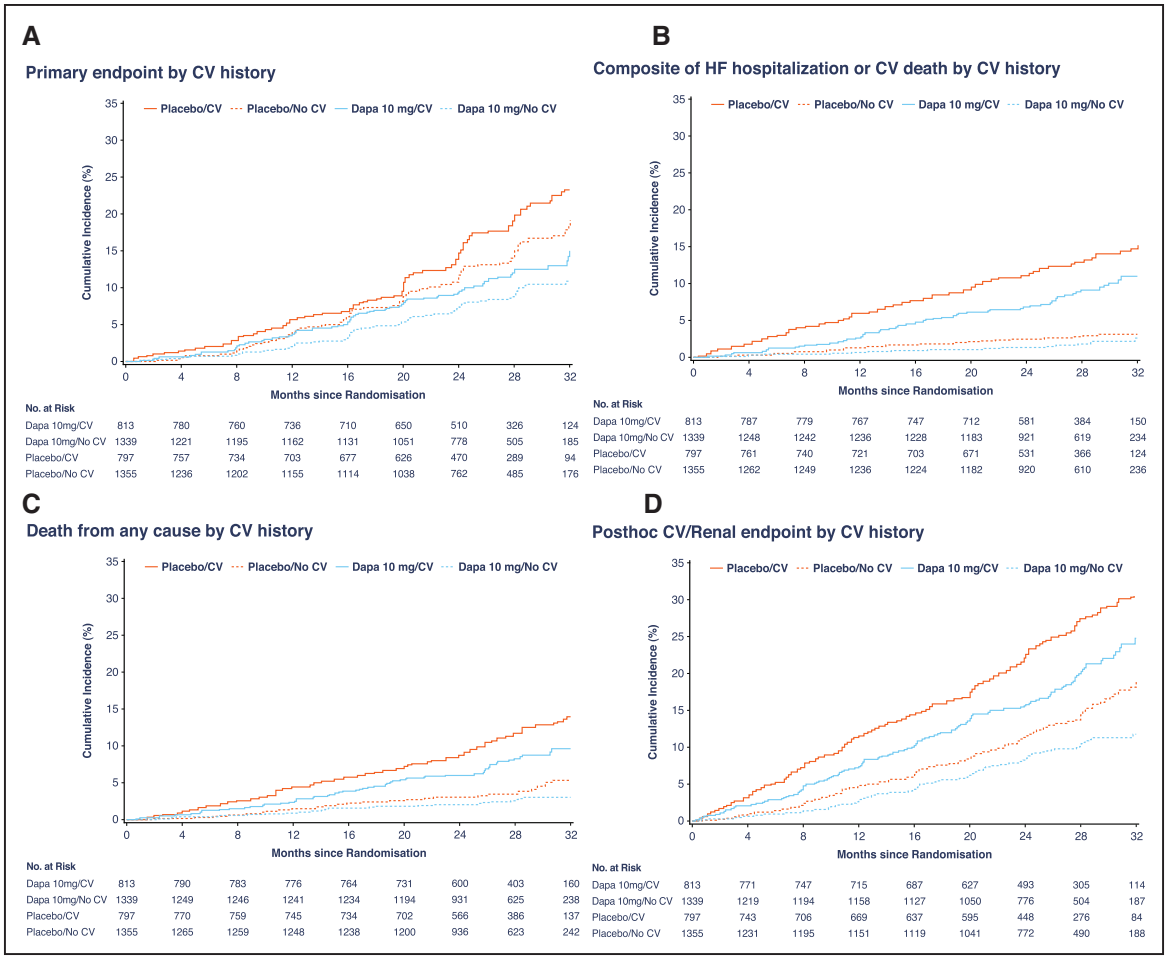

Figure 1. The effect of dapagliflozin in comparison with placebo.
Effects on primary composite outcome (**A**); composite of hospitalization for heart failure or death from cardiovascular causes (**B**) and death from any cause (prespecified secondary outcome) (**C**); and the exploratory composite of myocardial infarction, stroke, heart failure hospitalization, end-stage kidney disease, or death from any cause (**D**). 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 >28 days, kidney transplantation, or eGFR <15 mL·min^{-1}·1.73 m^{-2} confirmed by a second measurement after at least 28 days), or death from renal or cardiovascular cause, according to history of cardiovascular disease at baseline. One prespecified secondary outcome is not shown and was a kidney composite outcome identical to the primary end point, with the exception of death from cardiovascular causes. CV indicates cardiovascular; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; and HF, heart failure.

Our finding of a heightened risk of cardiovascular events in the secondary prevention patients, in comparison with primary prevention patients, is not unexpected and is consistent with the findings of CREDENCE.[7] However, the much greater differential risk between the primary and secondary prevention populations in DAPA-CKD in comparison with CREDENCE is more notable, likely reflecting differences in trial design, participants, and definitions of cardiovascular disease. The secondary prevention patients in CREDENCE had ≈2-fold higher rate of adverse cardiovascular outcomes than the primary prevention patients, whereas this risk difference was 3- to 5-fold in DAPA-CKD. As a result, although the rates of the prespecified cardiovascular outcomes were similar in secondary prevention patients in CREDENCE and DAPA-CKD, the rates of these outcomes in primary prevention patients were much lower in DAPA-CKD than in CREDENCE.[6,7] One probable explanation for this difference was the requirement for all participants in CREDENCE to have type 2 diabetes, whereas only 60% of patients in the DAPA-CKD primary prevention subgroup had diabetes, a condition that substantially augments cardiovascular risk.[6,7] Baseline cardiovascular disease was also defined differently in the 2 trials; heart failure was not included as cardiovascular disease in CREDENCE.[6,7]

It is more important that dapagliflozin reduced the risk of adverse kidney outcomes irrespective of baseline cardiovascular disease status, and this was also true for the main secondary cardiovascular composite outcome, which was the composite of heart failure hospitalization or cardiovascular death, although there were relatively few of the latter events in the primary prevention group. However, dapagliflozin did not reduce the prespecified exploratory composite of cardiovascular death, myocardial infarction, or stroke overall, or in the secondary prevention subgroup.

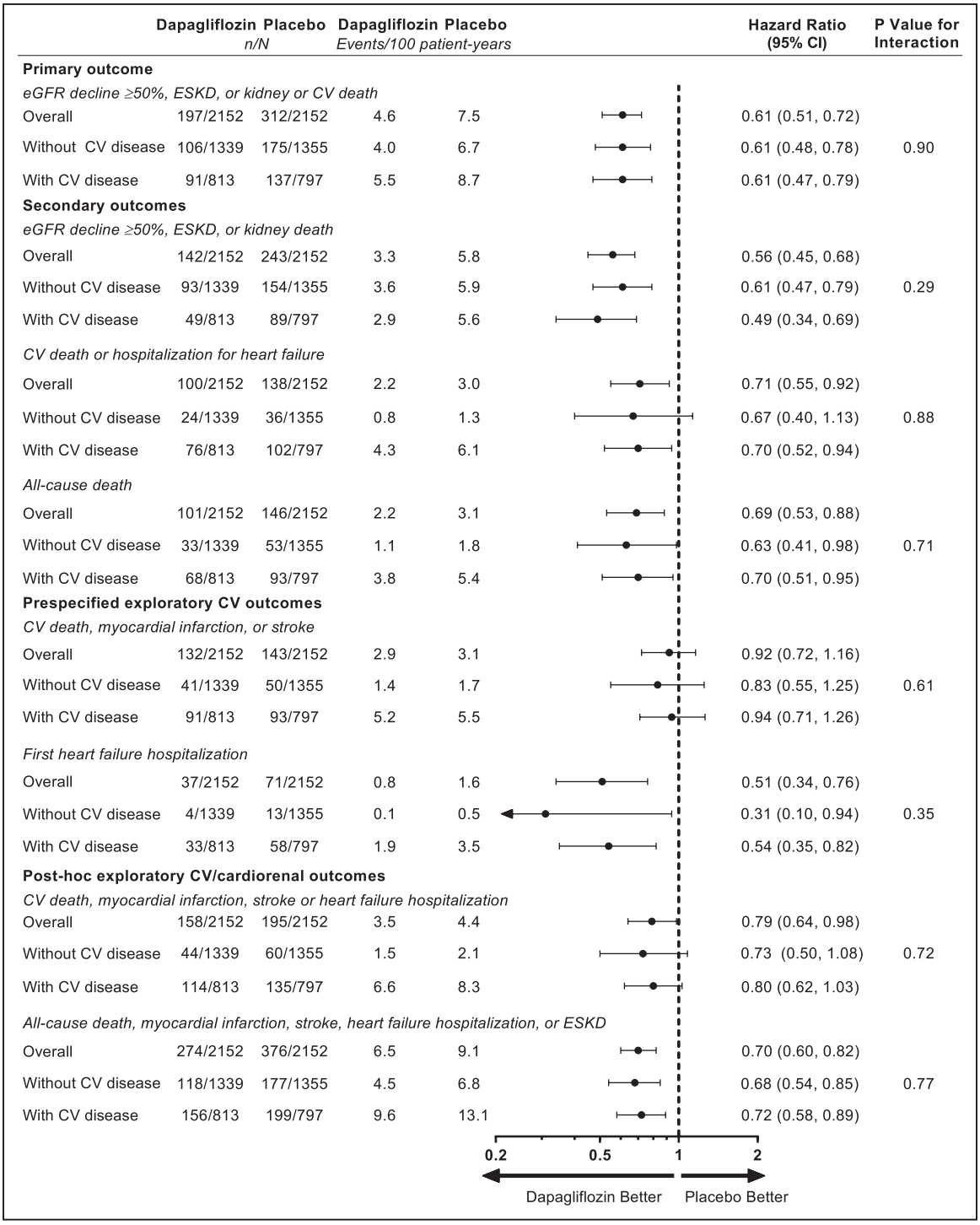

Figure 2. Prespecified and post hoc outcomes overall and according to history of cardiovascular disease at baseline.
CV indicates cardiovascular; eGFR, estimated glomerular filtration rate; and ESKD, end-stage kidney disease.

In focusing on the cardiovascular outcomes, SGLT2 inhibitors clearly reduce heart failure hospitalization, and the treatment effect size in DAPA-CKD was particularly large with an approximate halving of the risk of this outcome, with a consistent proportional risk reduction in primary and secondary prevention patients. This finding is important in 2 respects. First, it cements the evidence that the benefit of SGLT2 inhibitors on heart failure is independent of background atherosclerotic disease and is not mediated through the prevention of atherosclerotic events.[1–7] Second, it extends the evidence that SGLT2 inhibitors prevent a common, disabling, and deadly cardiovascular complication in patients with chronic kidney disease overall, that is, heart failure, to people without diabetes, and without known cardiovascular disease, as well (although the risk

Table 3. Prespecified Adverse Events and Study Drug Discontinuation Because of Adverse Events

Adverse event	Dapagliflozin		Placebo		*P* value for interaction
	No cardiovascular disease (n=1337)	Cardiovascular disease (n=812)	No cardiovascular disease (n=1352)	Cardiovascular disease (n=797)	
Any serious adverse event	287 (21.5)	346 (42.6)	371 (27.4)	358 (44.9)	0.09
Adverse event leading to study drug discontinuation	73 (5.5)	45 (5.5)	70 (5.2)	53 (6.6)	0.36
Amputation	10 (0.7)	25 (3.1)	15 (1.1)	24 (3.0)	0.40
Fracture	44 (3.3)	41 (5.0)	44 (3.3)	25 (3.1)	0.15
Renal adverse event	76 (5.7)	79 (9.7)	99 (7.3)	89 (11.2)	0.61
Volume depletion	75 (5.6)	52 (6.4)	46 (3.4)	44 (5.5)	0.20
Major hypoglycemia*	3 (0.2)	11 (1.4)	13 (1.0)	15 (1.9)	0.12

Values are n (%). Definite or probable ketoacidosis occurred in 2 patients without cardiovascular disease randomly allocated to placebo; there were no cases of ketoacidosis in the dapagliflozin group.

*The investigator confirmed the following criteria: 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.

of heart failure was relatively low in the latter patients during the relatively short- to medium-term follow-up in DAPA-CKD).[10,15,16]

The composite of cardiovascular death, myocardial infarction, or stroke was not reduced in DAPA-CKD, unlike in CREDENCE.[6,7] The likely explanation for this difference is the lack of statistical power, because approximately twice as many patients in CREDENCE experienced at least one of these events, in comparison with DAPA-CKD, reflecting the higher proportion of patients with baseline cardiovascular disease (50.4% versus 37.4%) and diabetes (100% versus 60.3%) in CREDENCE.

Another difference between the 2 trials was the reduction in death from any cause in DAPA-CKD, which was not observed in CREDENCE. This effect in DAPA-CKD was consistent in patients with and without a history of cardiovascular disease, extending another critically important clinical benefit to people with chronic kidney disease without diabetes and to those patients without cardiovascular disease. The mortality benefit also supports the findings of the DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure).[17]

Last, although not prespecified, we examined a cardiorenal composite outcome reflecting the overall disease burden faced by patients with chronic kidney disease and the full spectrum of events, each of which an ideal treatment would reduce (death from any cause, myocardial infarction, stroke, heart failure hospitalization, or end-stage kidney disease). Dapagliflozin led to an ≈30% relative risk reduction in this outcome, and this effect was consistent in the primary and secondary prevention subgroups. The absolute risk reductions of 4% to 6% were also substantial, irrespective of history of cardiovascular disease. The resultant number needed to treat ranged from 24 in the primary prevention subgroup to 17 in the secondary prevention participants to prevent 1 patient from experiencing a major fatal or nonfatal adverse renal or cardiovascular outcome over a median of 2.3 years.

As with any study of this type, there are certain 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. Some of the analyses were not prespecified. Certain events were infrequent (eg, death from renal causes) and the effect of treatment on these could not be assessed reliably.

In summary, dapagliflozin reduced the risk of kidney failure, death from cardiovascular causes or hospitalization for heart failure, and prolonged survival in people with chronic kidney disease, independently of the presence of concomitant cardiovascular disease.

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Correspondence

John J.V. McMurray, MD, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, Scotland, United Kingdom. Email john.mcmurray@glasgow.ac.uk

Affiliations

Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom (J.J.V.M.). Department of Renal Medicine, University College London, United Kingdom (D.C.W.). The George Institute for Global Health, Sydney, Australia (D.C.W., H.J.L.H.). Late-Stage Development, Cardiovascular, Renal and Metabolism (CVRM), Biopharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden (B.V.S., C.D.S., A.M.L.). Department Clinical Pharmacy and Pharmacology (N.J., H.J.L.H.), Department of Epidemiology (D.P.), University of Groningen, University Medical Center Groningen, Netherlands. National Medical Science and Nutrition Institute Salvador Zubirán, Mexico City, Mexico (R.C.-R.). Departments of Medicine and Epidemiology and Population Health, Stanford University School of Medicine, CA (G.M.C.). Study Design and Biostatistics Center,

University of Utah Health Sciences, Salt Lake City (T.G.). Department of Medical Sciences, Cardiology, Uppsala Clinical Research Center, Uppsala University, Sweden (C.H.). Division of Nephrology, Nanfang Hospital, Southern Medical University, National Clinical Research Center for Kidney Disease, Guangzhou, China (F.F.H.). KfH Kidney Center Munich, and Department of Medicine 4, University of Erlangen-Nürnberg, Germany (J.F.E.M.). Steno Diabetes Center Copenhagen, Gentofte, Denmark (P.R.). Department of Clinical Medicine, University of Copenhagen, Denmark (P.R.). Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas (R.D.T.).

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