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Research Article

Efficacy and Safety of Dapagliflozin in Patients With Chronic Kidney Disease Across the Spectrum of Frailty

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Abstract

Background: A sizeable proportion of patients with chronic kidney disease (CKD) are reported to be frail. Here we examined the safety and efficacy of dapagliflozin in patients with CKD by frailty level.

Methods: Adults with CKD, with/without type 2 diabetes, with an estimated glomerular filtration rate (eGFR) of 25–75 mL/min/1.73 m^2, and urinary albumin-to-creatinine ratio 200–5 000 mg/g were randomized to dapagliflozin (10 mg/day) or placebo. The primary endpoint was a composite of sustained ≥50% eGFR decline, end-stage kidney disease (ESKD), or death from kidney or cardiovascular (CV) causes.

Results: Frailty index (FI), assessed by Rockwood cumulative deficit approach, was calculable in 4 303/4 304 (99.9%) patients: 1 162 (27.0%) in not-to-mildly frail (FI ≤0.210), 1 642 (38.2%) in moderately frail (FI 0.211–0.310), and 1 499 (34.8%) in severely frail categories (FI >0.311). Dapagliflozin reduced the risk of the primary composite endpoint across all FI categories (hazard ratios [95% confidence interval {CI}]: 0.50 [0.33–0.76], 0.62 [0.45–0.85], and 0.64 [0.49—0.83], respectively; *p*-interaction = 0.67). Results were similar for secondary outcomes including kidney composite outcome (sustained ≥50% eGFR decline, ESKD or death from kidney cause; *p*-interaction = 0.44), CV endpoint (heart failure hospitalization or CV death; *p*-interaction = 0.63), and all-cause mortality (*p*-interaction *p* = .42). Results were consistent when using FI as a continuous variable. Occurrence of serious adverse events was numerically lower in patients receiving dapagliflozin versus placebo in all FI categories (16.9% vs 20.1%, 26.3% vs 30.7%, and 42.9% vs 47.8%, in not-to-mildly, moderately, and severely frail categories, respectively).

Conclusions: The relative benefit of dapagliflozin for all outcomes was consistent across all frailty categories, with no difference in associated safety.

Keywords: Cardiovascular disease, Diabetes, SGLT-2 inhibitors

Frailty, a state of increased vulnerability to physical stressors owing to a progressive and sustained degeneration in multiple physiological systems, is becoming increasingly common (1,2). About 10% of patients with chronic kidney disease (CKD) stages G1–G4 are reported to be frail (3), and the prevalence of frailty can reach more than 70% in older patients with advanced stages of CKD (4). Frail patients with CKD have an increased risk of progressive kidney disease,

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cardiovascular disease, and death at all stages of CKD compared with nonfrail patients (4,5).

Common chronic conditions other than CKD, including obesity, diabetes, heart failure, atherosclerotic vascular disease, and atrial fibrillation, frequently accompany CKD and contribute to frailty. Frail patients are commonly prescribed multiple medications, which makes them prone to more frequent adverse drug reactions and poorer adherence compared with nonfrail patients (6). As a consequence, clinicians may be reluctant to initiate new therapies in frail patients due to doubts about the balance of risks and benefits and concerns about predisposing frail patients to additional adverse drug effects (7). Moreover, some clinicians exhibit therapeutic nihilism, believing that therapeutic interventions are not "worth it" in such patients, even if there is indisputable, high-quality evidence in favor of the intervention.

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial showed that relative to placebo, dapagliflozin prolonged survival and reduced the risks of CKD progression and hospitalization for heart failure or cardiovascular death when taken with standard-of-care treatment and maximally tolerated doses of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (8). Here we aimed to determine whether the effects of dapagliflozin were modified by the presence and/or severity of frailty.

Method

Study Design and Participants

We used data from the DAPA-CKD trial, a randomized, double-blind, placebo-controlled multicenter trial conducted at 386 study sites in 21 countries from February 2017 until June 2020. Details of the study design and primary results have been published previously (8–11). Briefly, participants aged 18 years or older with CKD, with or without type 2 diabetes, and with estimated glomerular filtration rate (eGFR) of 25–75 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio (UACR) 200–5 000 mg/g were included in the trial. Excluded patients comprised those with a history of type 1 diabetes, polycystic kidney disease, lupus nephritis, or antinuclear cytoplasmic antibody (ANCA)-associated vasculitis, as well as those receiving immunotherapy for primary or secondary kidney disease within 6 months before enrollment. All eligible patients were required to be treated with a stable maximally tolerated dose of an ACE inhibitor or ARB for ≥4 weeks before randomization, unless there was documented intolerance to these drugs. All participants provided signed informed consent. The trial was sponsored by AstraZeneca, and the trial protocol was approved by a central or local ethics committee at each trial site. The trial was registered at ClinicalTrials.gov (NCT03036150).

Procedures

Eligible participants were randomly assigned to receive dapagliflozin 10 mg or matching placebo once daily according to the fixed randomization schedule. Randomization was stratified by diabetes status and UACR (≤1 000 or >1 000 mg/g) at baseline. Randomization was monitored to ensure that a minimum of 30% of the participants were recruited to either the population with type 2 diabetes or the population without diabetes. After randomization, in-person study visits were conducted after 2 weeks, 2, 4, and 8 months, and at 4-month intervals thereafter. At each follow-up visit, information on vital signs was recorded, blood and urine samples were obtained, and information on potential study endpoints, adverse events (AEs), concomitant therapies, and study drug adherence was collected.

Frailty Index

A 32-item frailty index (FI) was constructed using the Rockwood cumulative deficit approach (12). In summary, at least 30 items covering a range of body systems are required to create FI using this approach. These items are required to be associated with health and not be a part of normal aging, though the constructed index should generally increase with age. We extracted items from medical history, vital signs, laboratory data, and the EuroQoL-5 Domain (EQ-5D) questionnaire (quality-of-life measures, including functional status; Supplementary Table 1). Binary items were scored 0/1 (absent/present), ordinal variables were scored from 0 to 1 (1 indicating the greatest severity), and continuous variables were categorized and scored as 0/1 (normal/abnormal). Items on a continuous scale were categorized using conventional clinical cutoffs, where possible. We calculated the FI for each patient by summing their score and dividing by the total number of available items in that patient. Higher scores indicated more pronounced frailty. Scores were assigned for nonmissing items only. Patients with ≥20% missing items (n = 1, <0.01%) were excluded. In the present analysis, patients were divided into 3 subgroups: FI ≤0.210 (not-to-mildly frail), FI 0.211–0.310 (moderately frail), and FI ≥0.311 (severely frail). These cutoffs have been used in several previous studies (13–15).

Study Endpoints

The primary endpoint was a composite of sustained ≥50% decline in eGFR (confirmed by a second serum creatinine after at least 28 days), the onset of end-stage kidney disease (ESKD; 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 causes. Secondary endpoints were, in hierarchical order: composite kidney endpoint of ≥50% sustained eGFR decline, ESKD, or death from kidney cause; composite cardiovascular endpoint of hospitalization for heart failure or cardiovascular death; and all-cause mortality. All efficacy endpoints were adjudicated by an independent event adjudication committee using rigorous pre-specified endpoint definitions. As additional analyses, we investigated the effect of treatment on hospitalization and change in eGFR by frailty status.

Safety

Given the extensive prior experience with dapagliflozin, ascertainment of AEs was limited to serious adverse events (SAEs), AEs resulting in the discontinuation of the study drug, and AEs of special interest (symptoms of volume depletion, kidney disease events, major hypoglycemia, bone fractures, amputations, potential diabetic ketoacidosis). Potential diabetic ketoacidosis events were adjudicated by an independent adjudication committee.

Statistical Analysis

The overall analytic approach and pre-specified statistical analysis plan for DAPA-CKD have been previously

published (8,9). Briefly, all analyses presented here followed the intention-to-treat principle. Baseline characteristics of the study population were summarized as frequencies with percentages, means with standard deviation (*SD*), or medians with 25%, 75% range. We performed all time-to-event analyses using a proportional hazards (Cox) regression, stratified by randomization factors (diabetes status and UACR) and adjusting for baseline eGFR. In time-to-event analysis, first, we investigated the relations between the FI and efficacy endpoints while adjusting for treatment assignment. This model was additionally adjusted for age, sex, race and ethnicity, and region. Variables used in the calculation of FI were not included in the model. Second, we investigated the effects of dapagliflozin versus placebo on efficacy outcomes by frailty status. To evaluate effect modification by frailty status, we included a multiplicative interaction term between randomized treatment and frailty status (using the 3 groups described earlier). We conducted companion analyses considering the FI as a continuous variable, structured as a fractional polynomial. We assessed for nonuniformity of hazard ratios (HRs) with Akaike's information criterion.

To investigate the effect of treatment on eGFR by frailty status, we used a mixed-effects regression model for the on-treatment analysis population. The model was adjusted for baseline eGFR, trial-group assignment, visit, and the interaction between trial-group assignment, visit, and frailty status. We analyzed the effect of dapagliflozin as compared with placebo on the rate of decline in GFR during the acute phase (baseline to Week 2), chronic phase (Week 2 until end of treatment), and total slope to Month 30 with a 2-slope model. We report the least-squares mean differences with 95% CI between treatment groups.

We considered 2-tailed p values <.05 to indicate statistical significance. We performed all analyses with Stata version 14.2 (StataCorp LLC, College Station, TX).

Results

Patient Characteristics

Of the 4 304 patients randomized in the DAPA-CKD trial, the FI was assessable for 4 303 (99.9%) patients. The numbers of patients with missing data for cumulative and individual components of the FI are shown in Supplementary Tables 2 and 3, respectively. The distribution of FI is shown in Supplementary Figure 1. Mean FI was 0.273 (*SD*, 0.091). A total of 1 162 (27.0%) patients were in not-to-mildly frail category (FI <0.210), 1 642 (38.2%) in moderately frail category (FI 0.211–0.310), and 1 499 (34.8%) in severely frail category (FI >0.311).

Baseline characteristics of the patient population according to FI category are presented in Table 1. Patients with higher FI were older, more often White, more likely to have cardiovascular and noncardiovascular comorbidities, and less often smokers compared to patients with lower FI. They also had higher systolic blood pressure, Quetelet (body mass index [BMI]), HbA1c, UACR, and lower eGFR and hemoglobin. Patients with higher FI were more likely to have a longer duration of diabetes. Baseline characteristics of patients by treatment allocation and frailty category demonstrated the balance in the patient characteristics between dapagliflozin and placebo groups (Supplementary Table 4).

Association of Frailty Index with Clinical Endpoints

Kaplan–Meier curves for the cumulative incidence of the primary composite endpoint by FI category are presented in Supplementary Figure 2. Compared to patients in the not-to-mildly frail category, patients in the severely frail category were at a higher risk of the primary composite endpoint, the kidney composite endpoint, the cardiovascular composite endpoint, and all-cause mortality in the fully adjusted model (Supplementary Table 5). Compared to patients in the not-to-mildly frail category, those in the moderately frail category also had a higher risk of primary composite and kidney composite endpoints, although the associations of moderately frail category with the cardiovascular composite endpoint and all-cause mortality were not statistically significant in the fully adjusted model.

Effects of Dapagliflozin on Primary Composite Endpoint According to Frailty Index Category

Median follow-up was 2.0 years in not-to-mildly frail category and 2.2 years in mildly and severely frail categories. Event rates (per 100 patient-years) for the primary composite endpoint were 3.2, 3.9, and 6.4 in patients randomized to dapagliflozin and 6.1, 6.0, and 10.0 in patients randomized to placebo in not-to-mildly, moderately, and severely frail categories, respectively. Compared with placebo, dapagliflozin reduced the risk of primary composite endpoint across all categories of FI with HRs of 0.50 (95% CI, 0.33–0.76), 0.62 (95% CI, 0.45–0.85), and 0.64 (95% CI, 0.49–0.83) in not-to-mildly, moderately, and severely frail categories, respectively. There was no evidence of heterogeneity of the dapagliflozin effect (p-interaction = .67; Table 2, Figure 1]). Non-heterogeneity was also demonstrated when evaluating the effects of dapagliflozin across the entire range of FI (p-interaction = .84; Figure 2). Absolute risk reductions with dapagliflozin treatment were also similar across the FI categories, with absolute risk reductions of 5.2% (95% CI, 2.0–8.4), 4.1% (95% CI, 1.3–7.0), and 6.6% (95% CI, 2.9–10.3) corresponding to numbers needed to treat 20 (95% CI, 12–50), 25 (95% CI, 15–77), and 16 (95% CI, 10–35) in not-to-mildly, moderately, and severely frail categories, respectively (p-interaction = .58).

Effects of Dapagliflozin on Secondary Outcomes According to Frailty Index Categories

Similar to the primary composite outcome, dapagliflozin reduced the incidence of the kidney composite endpoint, cardiovascular composite endpoint, and all-cause mortality across all FI categories (Table 2, Figure 1). For all secondary outcomes, there was no heterogeneity of benefit on relative reduction by FI category, or by FI as a continuous variable (Figure 2). When considering absolute risk reductions, there was no heterogeneity of the dapagliflozin effect by FI category for the kidney composite endpoint (p-interaction = .59), although absolute risk reductions for the cardiovascular composite endpoint and all-cause mortality were more pronounced along with a spectrum of increasing frailty (p-interaction = .02 for both endpoints).

Hospitalization and eGFR Change Over Time

Effect of dapagliflozin on time to the first hospitalization was consistent across FI categories (Supplementary Table 6). Compared with placebo, dapagliflozin reduced the risk of first

Table 1. Baseline Characteristics of the Study Population by Level of Frailty Index

Characteristic	FI ≤0.210 (Not-to-mildly Frail), *n* = 1 162	FI 0.211–0.310 (Moderately Frail), *n* = 1 642	FI ≥0.311 (Severely Frail), *n* = 1 499	*p* Value
Age (years), mean (*SD*)	53.9 (13.5)	63.3 (10.8)	66.4 (9.0)	<.001
Sex (female), *n* (%)	388 (33.4)	540 (32.9)	497 (33.2)	.96
Race and ethnicity, *n* (%)				<.001
White	481 (41.4)	815 (49.6)	993 (66.2)	
Black or African American	31 (2.7)	65 (4.0)	95 (6.3)	
Asian	601 (51.7)	604 (36.8)	262 (17.5)	
Others	49 (4.2)	158 (9.6)	149 (9.9)	
Geographic region, *n* (%)				<.001
Asia	572 (49.2)	553 (33.7)	221 (14.7)	
Europe	298 (25.6)	419 (25.5)	516 (34.4)	
North America	115 (9.9)	275 (16.7)	423 (28.2)	
Latin/South America	177 (15.2)	395 (24.1)	339 (22.6)	
Current smoking, *n* (%)	169 (14.6)	234 (14.3)	181 (12.1)	<.001
Systolic blood pressure (mmHg), mean (*SD*)	127.8 (14.1)	137.1 (16.4)	144.3 (17.4)	<.001
Diastolic blood pressure (mmHg), mean (*SD*)	79.0 (10.2)	77.6 (10.7)	76.3 (10.3)	<.001
Body mass index (kg/m^2), mean (*SD*)	26.8 (5.0)	29.3 (5.8)	31.9 (6.4)	<.001
Pulse pressure (mmHg), mean (*SD*)	48.8 (10.9)	59.5 (14.4)	68.0 (16.3)	<.001
Heart rate (bpm), mean (*SD*)	74.0 (11.0)	73.3 (11.5)	71.6 (11.8)	<.001
Glycated hemoglobin (%), mean (*SD*)	6.2 (1.4)	7.2 (1.7)	7.6 (1.7)	<.001
Estimated glomerular filtration rate (mL/min/1.73 m^2), mean (*SD*)	44.4 (12.1)	43.6 (12.8)	41.6 (11.9)	<.001
Estimated glomerular filtration rate <60 mL/min/1.73 m^2, *n* (%)	1 031 (88.7)	1 441 (87.8)	1 377 (91.9)	.001
Urinary albumin-to-creatinine ratio (mg/g), median (IQR)	796 (434, 1 528)	965 (476, 1 871)	1 090 (506, 2 169)	<.001
Sodium (mmol/L), mean (*SD*)	139.9 (2.4)	139.5 (2.9)	139.1 (3.6)	<.001
Potassium (mmol/L), mean (*SD*)	4.6 (0.5)	4.6 (0.6)	4.7 (0.6)	.004
Hemoglobin (g/L), mean (*SD*)	133.2 (17.0)	128.8 (18.0)	123.8 (17.9)	<.001
Alanine aminotransferase (U/L), mean (*SD*)	19.8 (10.9)	20.5 (11.3)	20.3 (11.7)	.29
Phosphate (mg/dL), mean (*SD*)	3.5 (0.6)	3.6 (0.6)	3.7 (0.7)	<.001
Diabetes (yes), *n* (%)	364 (31.3)	1 180 (71.9)	1 361 (90.8)	<.001
Diabetes duration (years), median (IQR)	10.0 (5.2, 18.0)	12.8 (6.5, 19.8)	15.8 (9.2, 22.3)	<.001
Hypertension (yes), *n* (%)	1 011 (87.0)	1 613 (98.2)	1 496 (99.8)	<.001
Cardiovascular disease (yes), n (%)	92 (7.9)	497 (30.3)	1 021 (68.1)	<.001
Heart failure (yes), *n* (%)	16 (1.4)	113 (6.9)	339 (22.6)	<.001
Ischemic heart disease (yes), *n* (%)	30 (2.6)	179 (10.9)	507 (33.8)	<.001
Non-coronary arterial disease (yes), *n* (%)	18 (1.5)	175 (10.7)	597 (39.8)	<.001
Atrial fibrillation/flutter (yes), *n* (%)	5 (0.4)	57 (3.5)	165 (11.0)	<.001
Chronic obstructive pulmonary disease (yes), *n* (%)	8 (0.7)	43 (2.6)	145 (9.7)	<.001
Stroke (yes), *n* (%)	21 (1.8)	111 (6.8)	233 (15.5)	<.001
Dyslipidemia (yes), *n* (%)	401 (34.5)	1 223 (74.5)	1 363 (90.9)	<.001
Gout (yes), *n* (%)	140 (12.0)	271 (16.5)	360 (24.0)	<.001
Cancer (yes), *n* (%)	14 (1.2)	42 (2.6)	84 (5.6)	<.001
Syncope (yes), *n* (%)	5 (0.4)	14 (0.8)	33 (2.2)	<.001
Sleep apnea (yes), *n* (%)	10 (0.9)	66 (4.0)	219 (14.6)	<.001

Table 1. Continued

Characteristic	FI ≤0.210 (Not-to-mildly Frail), *n* = 1 162	FI 0.211–0.310 (Moderately Frail), *n* = 1 642	FI ≥0.311 (Severely Frail), *n* = 1 499	*p* Value
Neuropathy (yes), *n* (%)	24 (2.1)	277 (16.9)	651 (43.4)	<.001
Osteoporosis (yes), *n* (%)	401 (34.5)	1 223 (74.5)	1 363 (90.9)	<.001
ACE inhibitor/ARB (yes), *n* (%)	1 128 (97.1)	1 592 (96.9)	1 453 (96.9)	.975
Diuretics (yes), *n* (%)	258 (22.2)	702 (42.7)	921 (61.4)	<.001
Insulin (yes), *n* (%)[a]	144 (39.6)	604 (51.2)	849 (62.4)	<.001

Notes: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; IQR = interquartile range; *SD* = standard deviation.
[a]In those with diabetes.

Table 2. Effects of Dapagliflozin Compared With Placebo on Clinical Events by Frailty Index

	Dapagliflozin (*n* = 2 151)	Placebo (*n* = 2 152)	Absolute Risk Difference % (95% CI)	*p*-interaction	Hazard Ratio (95% CI)	*p*-interaction
	FI ≤0.210 (*n* = 593) FI 0.211–0.310 (*n* = 816) FI ≥311 (*n* = 742)	FI ≤0.210 (*n* = 569) FI 0.211–0.310 (*n* = 826) FI ≥311 (*n*= 757)				
	n (%)	*n* (%)				
Primary composite outcome						
eGFR decline ≥ 50%, end-stage kidney disease, or kidney or cardiovascular death						
				0.581		0.667
Not-to-mildly frail (*n* = 1 162)	35 (5.9)	63 (11.1)	5.2 (2.0, 8.4)		0.50 (0.33, 0.76) *p* = .001	
Moderately frail (*n* = 1 642)	64 (7.8)	99 (12.0)	4.1 (1.3, 7.0)		0.62 (0.45, 0.85) *p* = .003	
Severely frail (*n* = 1 499)	98 (13.2)	150 (19.8)	6.6 (2.9, 10.3)		0.64 (0.49, 0.83) *p* = .001	
Secondary outcomes						
Kidney composite outcome: eGFR decline ≥ 50%, end-stage kidney disease or kidney death						
				0.585		0.437
Not-to-mildly frail (*n* = 1 162)	27 (4.5)	57 (10.0)	5.5 (2.5, 8.4)		0.42 (0.27, 0.67) *p* < .001	
Moderately frail (*n* = 1 642)	55 (6.7)	85 (10.3)	3.5 (0.9, 6.2)		0.62 (0.44, 0.87) *p* = .006	
Severely frail (*n* = 1 499)	60 (8.1)	101 (13.3)	5.3 (2.1, 8.4)		0.57 (0.41, 0.9), *p* = .001	
Cardiovascular outcome: Hospitalization for heart failure or cardiovascular death						
				0.019		0.627
Not-to-mildly frail (*n* = 1 162)	11 (1.8)	10 (1.8)	−0.1 (−1.6, 1.4)		1.02 (0.43, 2.41) *p* = .964	
Moderately frail (*n* = 1 642)	21 (2.6)	29 (3.5)	0.9 (−0.7, 2.6)		0.70 (0.40, 1.24) *p* = .222	
Severely frail (*n* = 1 499)	68 (9.2)	99 (13.1)	3.9 (0.7, 7.1)		0.67 (0.49, 0.92) *p* = .012	
All-cause mortality						
				0.021		0.417
Not-to-mildly frail (*n* = 1 162)	12 (2.0)	11 (1.9)	−0.1 (−1.7, 1.5)		1.03 (0.45, 2.34) *p* = .941	
Moderately frail (*n* = 1 642)	26 (3.2)	46 (5.6)	2.4 (0.4, 4.4)		0.56 (0.34, 0.90) *p* = .018	
Severely frail (*n* = 1 499)	63 (8.5)	89 (11.8)	3.3 (0.2, 6.3)		0.69 (0.50, 0.96) *p* = .027	

Notes: CI = confidence interval; eGFR = estimated glomerular filtration rate; FI = frailty index.
Not-to-mildly frail: FI ≤0.210; Moderately frail: FI 0.211–0.310; Severely frail: FI ≥0.311.

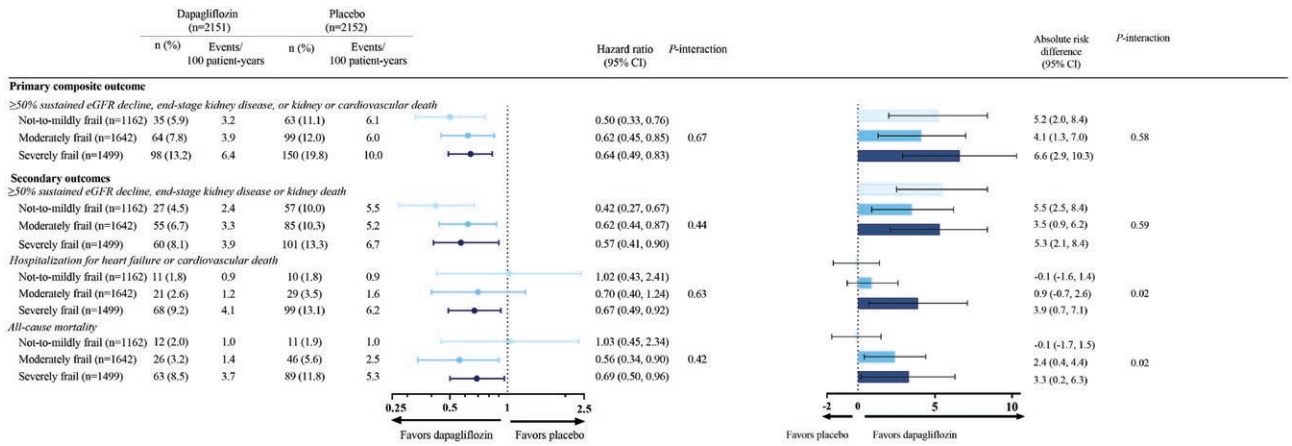

Figure 1. Forest plot demonstrating effects of dapagliflozin compared with placebo on clinical events by categories of frailty index. CI = confidence interval; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease.

hospitalization across all categories of FI, with HR of 0.87 (95% CI, 0.65–1.17), 0.82 (95% CI, 0.68–0.99), and 0.85 (95% CI, 0.73–1.00) in not-to-mildly, moderately, and severely frail categories, respectively (p-interaction = .92). Similarly, the effect of dapagliflozin on eGFR slope was consistent across FI categories. In FI categories from least severe to most severe, placebo-corrected differences in acute slope were −2.1 (95% CI, −2.8 to −1.4), −2.7 (95% CI −3.3 to −2.0), and −2.4 (95% CI −3.0 to −1.8) mL/min/1.73 m^2 per year, respectively (p-interaction = .47). Chronic slopes were 1.7 (95% CI, 1.1–2.3), 2.1 (95% CI, 1.6–2.6), and 2.0 (95% CI, 1.5–2.5) mL/min/1.73 m^2 per year in favor of dapagliflozin (p-interaction = .44) and total slopes were 0.8 (95% CI: 0.2–1.4), 1.0 (95% CI: 0.5–1.5) and 1.0 (95% CI: 0.5–1.5) mL/min/1.7 3m^2 per year in favor of dapagliflozin (p-interaction = .68), respectively.

Safety Analyses

Patients with more severe frailty at baseline were more likely to discontinue the study drug and experience SAEs. About 3% of the patients in the not-to-mildly frail category and 6.5% of the patients in severely frail category in dapagliflozin arm discontinued study drug due to AEs. In these frailty categories, the numbers were 4.0% and 7.4%, respectively, in the placebo arm. Of note, there was no increased likelihood of this event among patients on dapagliflozin compared to placebo in any of the FI categories. The occurrence of SAEs was numerically lower with no increased likelihood of SAEs among patients randomized to dapagliflozin versus placebo in all examined FI categories (16.9% vs 20.1%, 26.3% vs 30.7%, and 42.9% vs 47.8%, in not-to-mildly, moderately, and severely frail categories, respectively). Results were largely similar for the likelihood of other examined AEs in dapagliflozin compared with the placebo group across FI categories (Table 3).

Discussion

The majority of patients enrolled in the DAPA-CKD trial were classified as frail. A higher level of frailty was associated with an increased risk of clinical endpoints including the primary composite endpoint, the kidney and cardiovascular composite endpoints, and all-cause mortality. The relative benefit of dapagliflozin in lowering the risk of clinical outcomes compared to placebo was consistent across all frailty categories. Although patients with more severe frailty at baseline experienced more SAEs, these SAEs were less frequent in patients randomized to dapagliflozin compared with placebo.

There are concerns about unfavorable benefit/risk ratio of treatment with pharmacological agents in frail patients (16–18). Unfortunately, data are limited on the efficacy of commonly prescribed pharmacological agents by frailty status in patients with CKD. However, some studies in other patient populations that investigated the efficacy of agents commonly prescribed in patients with CKD have reported effect modification by frailty status. For example, in a high-risk population of patients with type 2 diabetes, HR for the effect of intensive glucose control with gliclazide on combined microvascular and macrovascular endpoints was 1.03 (95% CI, 0.90–1.19) in frail and 0.84 (95% CI, 0.74–0.94) in nonfrail patients (p-interaction = .02) (19). Relative effects on blood pressure of perindopril and indapamide were similar among frail and nonfrail patients. Similarly, cholesterol-lowering medications in older patients, a large fraction of whom are also frail, have shown diminished efficacy. For instance, in an analysis of patients older than 75 years in PROSPER, JUPITER, and HOPE-3 clinical trials, the benefits of statin therapy on composite cardiovascular outcomes were modest and nonsignificant on all-cause mortality (20).

The increased frequency of AEs in frail patients has influenced the real and/or perceived benefit/risk ratio of several pharmacological agents (16–18). In our study, although the occurrence of AEs and discontinuation of allocated treatment were more frequent in patients with more severe frailty at baseline, SAEs were less frequent among patients randomized to dapagliflozin compared with placebo across the frailty spectrum. Hospitalization, one of the most frequently reported adverse outcomes related to pharmacological treatment in frail patients (21,22), was significantly lower in patients randomized to dapagliflozin compared to placebo, including in severely frail patients. These findings demonstrate a favorable benefit/risk ratio for dapagliflozin in patients with CKD and frailty. A similar favorable benefit/risk ratio has been previously demonstrated for dapagliflozin in randomized clinical trials enrolling patients with frailty and heart failure with reduced ejection fraction (DAPA-HF) and heart failure with mildly reduced or preserved ejection fraction (DELIVER) (14,15).

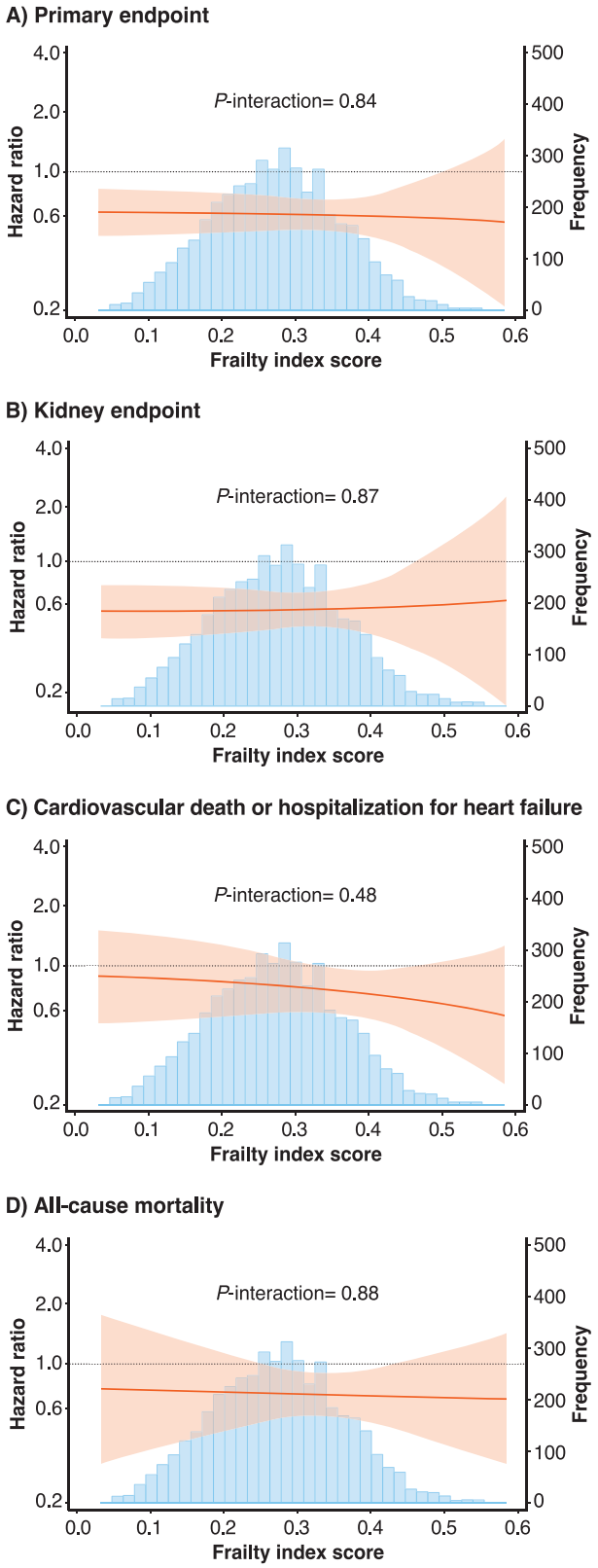

Figure 2. Effect of dapagliflozin on clinical endpoints across the spectrum of frailty index. (A) Primary endpoint; (B) Kidney endpoint; (C) Cardiovascular death or hospitalization for heart failure; (D) All-cause mortality. The solid line represents the hazard ratio for the primary outcome, the horizontal dotted line represents no effect, and the shaded area represents the 95% pointwise confidence interval.

As expected, the likelihood of fracture was higher among more severely frail patients; however, unlike other AEs of special interest, there were numerically more events in dapagliflozin-treated compared with placebo-treated patients despite fewer reported episodes of volume depletion. These results should be interpreted with caution, given the low number and non-adjudication of events. Additionally, several previous studies have reported no association between the use of SGLT-2 inhibitors and risk of fractures, including in frail patients (23,24). Similar results have been recently reported for volume depletion in elderly patients (25).

Several methods have been proposed for assessing frailty in patients with CKD, and the prevalence of frailty varies, among others, by the method used and the underlying study population (26). The cumulative deficit approach is one of the commonly used methods for evaluating frailty which assesses cumulative declines across multiple physiological systems (26). Compared to other study populations, such as those with heart failure, frailty was more frequent in DAPA-CKD. In the DAPA-HF and DELIVER studies, 50%–63% of the patients were classified as frail, respectively. It is noteworthy that in DAPA-CKD, the prevalence of several comorbid conditions, including diabetes, hypertension, osteoporosis, neuropathy, and gout was higher than in DAPA-HF or DELIVER. In DAPA-CKD, the mean FI was similar to another study with a comparable patient age and kidney function (mean FI in other study = 0.25 [range 0.02–0.61]) (27). Moreover, in a study of almost 150 000 patients with CKD from primary-care setting with a similar mean eGFR, the prevalence of frailty based on the FI was almost 75% (4). Irrespective of the method used, the prevalence and burden of frailty are considerable in this population, especially those with more advanced (eg, Stage 4) CKD, and is strongly associated with poor clinical outcomes.

The main strength of our study is the randomized and double-blind design of the trial. The study design prevented the patient's underlying health condition (eg, frailty) from influencing treatment allocation and thereby allowed a comparison between dapagliflozin and placebo without selection bias or confounding by indication. Additionally, the trial was relatively large, and participants were diverse by age, sex, designated race or ethnicity, underlying etiology of CKD, and well balanced by key determinants of progression, including baseline eGFR, UACR, and blood pressure. Results from this study also corroborated that frailty is related to, but distinct from, aging, and has clinical consequences independent of age (Supplementary Table 5). This study has several limitations. First, due to the lack of tests of muscle strength and functional capacity in DAPA-CKD, we were not able to assess results when using other methods of frailty assessment. The Rockwood cumulative deficit is another commonly used approach for assessing frailty and has the advantage of incorporating health deficits across several domains, including cognition, activities of daily living, social relations or support, comorbid diseases, and abnormal laboratory results. The FI has shown good concordance with other types of frailty scores (28,29). Although we also assessed frailty using the Rockwood cumulative deficit, we lacked data on cognition and activities of daily living. Second, by design, DAPA-CKD did not include patients with CKD plus other life-threatening conditions, including the New York Heart Association class IV congestive heart failure, or active malignancy. As it is

Table 3. Safety by Level Of Frailty Index

Outcome, *n* (%)	Dapagliflozin (*n* = 2 148)	Placebo (*n* = 2 149)	Odds ratio (95% CI)	*p*-interaction
Discontinuation due to adverse event				0.374
Not-to-mildly frail (*n* = 1 160)	18 (3.0)	23 (4.0)	0.76 (0.40, 1.42)	
Moderately frail (*n* = 1 639)	52 (6.4)	44 (5.3)	1.21 (0.80, 1.83)	
Severely frail (*n* = 1 498)	48 (6.5)	56 (7.4)	0.88 (0.59, 1.31)	
Any serious adverse event[a]				0.988
Not-to-mildly frail (*n* = 1 160)	100 (16.9)	114 (20.1)	0.81 (0.60, 1.09)	
Moderately frail (*n* = 1 639)	214 (26.3)	253 (30.7)	0.80 (0.65, 1.00)	
Severely frail (*n* = 1 498)	318 (42.9)	362 (47.8)	0.82 (0.67, 1.01)	
Adverse events of interest				
Amputation[b]				0.876
Not-to-mildly frail (*n* = 1 160)	0	3 (0.5)	—	
Moderately frail (*n* = 1 639)	10 (1.2)	11 (1.3)	0.94 (0.40, 2.24)	
Severely frail (*n* = 1 498)	25 (3.4)	25 (3.3)	1.02 (0.58, 1.79)	
Any definite or probable diabetic ketoacidosis				
Not-to-mildly frail (*n* = 1 160)	0	0	—	
Moderately frail (n = 1 639)	0	1 (0.1)	—	
Severely frail (*n* = 1 498)	0	1 (0.1)	—	
Fracture[c]				0.256
Not-to-mildly frail (*n* = 1 160)	13 (2.2)	16 (2.8)	0.79 (0.37, 1.65)	
Moderately frail (*n* = 1 639)	30 (3.7)	26 (3.2)	1.17 (0.69, 2.00)	
Severely frail (*n* = 1 498)	42 (5.7)	27 (3.6)	1.63 (0.99, 2.68)	
Renal-related adverse event[c]				0.868
Not-to-mildly frail (*n* = 1 160)	18 (3.0)	26 (4.6)	0.66 (0.36, 1.21)	
Moderately frail (*n* = 1 639)	44 (5.4)	65 (7.9)	0.66 (0.45, 0.99)	
Severely frail (*n* = 1 498)	93 (12.5)	97 (12.8)	0.99 (0.73, 1.34)	
Major hypoglycemia[d]				0.727
Not-to-mildly frail (*n* = 1 160)	1 (0.2)	4 (0.7)	0.23 (0.02, 2.12)	
Moderately frail (*n* = 1 639)	4 (0.5)	6 (0.7)	0.67 (0.19, 2.39)	
Severely frail (*n* = 1 498)	9 (1.2)	18 (2.4)	0.51 (0.23, 1.14)	
Volume depletion[c]				0.406
Not-to-mildly frail (*n* = 1 160)	27 (4.6)	12 (2.1)	2.22 (1.11, 4.42)	
Moderately frail (*n* = 1 639)	45 (5.5)	34 (4.1)	1.36 (0.86, 2.14)	
Severely frail (*n* = 1 498)	55 (7.4)	44 (5.8)	1.29 (0.86, 1.95)	

Notes: CI = confidence interval.
[a]Includes death.
[b]Surgical or spontaneous/nonsurgical amputation, excluding amputation due to trauma.
[c]Based on predefined list of preferred terms.
[d]Adverse event with the following criteria confirmed by the investigator: (i) symptoms of severe impairment in consciousness or behavior, (ii) need of external assistance, (iii) intervention to treat hypoglycemia, (iv) prompt recovery of acute symptoms following the intervention.

generally with randomized controlled trials, patients enrolled in a randomized clinical trial may not be representative of patients seen in routine care, especially severely frail patients. Moreover, due to trial procedures, the reporting of AEs may differ from that of similar patients in routine clinical practice. Finally, in the examination of the association of FI with clinical endpoints, despite the adjustment for several known confounders, the possibility of a meaningful degree of residual confounding cannot be fully excluded.

In conclusion, in patients with CKD with and without type 2 diabetes, treatment with dapagliflozin reduced the relative risks of kidney and cardiovascular disease events and all-cause mortality across the spectrum of frailty, with no evidence of heterogeneity; absolute benefits were similar, or of larger magnitude, for frail patients. Moreover, the frequency of SAEs was lower in patients randomized to dapagliflozin compared with placebo across the spectrum of frailty, yielding a strongly favorable benefit/risk ratio for dapagliflozin in patients with CKD and frailty.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

P.V. report travel grants from AstraZeneca. N.J. report travel grants from AstraZeneca. J.H.B. reports receiving payment/honoraria from AstraZeneca, Bayer, and Novartis. He has served on a Data Safety Monitoring/Advisory Board for Bayer. M.S. reports receiving a grant for this manuscript, paid to his institution from AstraZeneca. He has also received travel grants from AstraZeneca and Novo Nordisk. G.M.C. has received fees from AstraZeneca for the DAPA-CKD trial steering committee. He serves on the Board of Directors for Satellite Healthcare, a nonprofit dialysis provider. He has received research grants from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases, and CSL Behring. He has served on trial steering committees with Akebia, AstraZeneca, Gilead, Sanifit, and Vertex. He has served as an advisor to Ardelyx, CloudCath, Durect, Miromatrix, Outset, Renibus, Reata, Sanifit, Unicycive, and Vertex. He has served on DSMBs for NIDDK, Bayer, Mineralys, and ReCor. D.C.W. has received consultancy fees and payment for travel and accommodation from AstraZeneca for this manuscript. He has received consultancy fees from Astellas, Boehringer Ingelheim, George Clinical, GlaxoSmithKline, Gilead, Merck Sharp and Dohme, ProKidney, Tricida, and Vifor. He also reports receiving payment/honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, Intas, and Vifor. He had received a grant from the NIHR HTA program for the EVOLVE study and has received support for a leadership/fiduciary role from NIHR National specialty Lead for Renal Disorders (UK). R.P.-F. has received research grants from Fresenius Medical Care, National Council for Scientific and Technological Development, grants (paid to employer) from AstraZeneca, Boehringer-Lilly, Novo Nordisk, Akebia, Bayer for participation in advisory Boards and educational activities. R.P.-F. is employed by Arbor Research Collaborative for health, who runs the DOPPS studies. A.M.L. is an employee and stockholder of AstraZeneca. R.C.-R. has support from AstraZeneca for this manuscript as being a member for the DAPA-CKD steering committee. He has received grants from AstraZeneca, GlaxoSmithKline, and Novo Nordisk; and honoraria as a speaker fees from fromAstraZeneca, Bayer, Boehringer Ingelheim, Amgen, and Janssen. He has received support for a leadership/fiduciary role from the Latin American Society of Nephrology as a member of the Diabetes Committee. P.R. has received honoraria to Steno Diabetes Center Copenhagen for steering group participation from AstraZeneca for this manuscript. He has received grants from AstraZeneca, Novo Nordisk, and Bayer; and consulting fees from Astellas, Astra Zeneca, Boehringer Ingelheim, Bayer, Gilead, Novo Nordisk, Merck, and Sanofi. He has also received honoraria/payment from EliLilly as speaker fees. J.J.V.M. has received payments from his employer, Glasgow University, as support on the current manuscript from AstraZeneca. He has received payment/honoraria for lecture fees from Abbott, Alkem Metabolics, Eris Lifesciences, Hikma, Lupin, Sun Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, the Corpus. His institution has also received fees for his work on clinical trials, consulting and other activities from AstraZeneca, Cytokinetics, KBP Biosciences, Amgen, Bayer, Theracos, Ionis Pharmaceuticals, Dalcor Pharmaceuticals, Novartis, GlaxoSmithKline, Bristol-Myers Squibb, Boehringer Ingelheim, and Bayer. H.J.L.H. has received grants (paid to his institution [University Medical Center Groningen]) from AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk. He has received consulting fees from AstraZeneca, Abbvie, Boehringer Ingelheim, CSL Behring, Bayer, Chinook, Dimerix, EliLilly, Gilead, Goldfinch, Merck, Novartis, NovoNordisk, Janssen, Travere Pharmaceuticals. He has received payment/honoraria from AstraZeneca and Novo Nordisk and travel grant from EliLilly.

Data Availability

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/

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Author Contributions

P.V., J.H.B., J.J.V.M., and H.J.L.H. conceptualized and designed the study. P.V. wrote the original manuscript draft. P.V. and N.J. performed statistical analysis. All authors contributed to interpretation of results and critical revision of the manuscript. J.J.V.M. and H.J.L.H. provided supervision.

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