

# Efficacy and Safety of Dapagliflozin in Patients with Chronic Kidney Disease across the Spectrum of Frailty

Priya Vart, PhD;<sup>1,2\*</sup> Jawad H. Butt, MD;<sup>3,4\*</sup> Niels Jongs,<sup>1</sup> PhD; Meir Schechter, MD;<sup>1,5,6</sup> Glenn M. Chertow, MD;<sup>7,8</sup> David C. Wheeler, MD;<sup>9</sup> Roberto Pecoits-Filho, PhD;<sup>10,11</sup> Anna Maria Langkilde, MD;<sup>12</sup> Ricardo Correa-Rotter, MD;<sup>13</sup> Peter Rossing, MD;<sup>14,15</sup> John J. V. McMurray, MD;<sup>3</sup> Hidde J. L. Heerspink, PhD<sup>1,16</sup>

<sup>1</sup>Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

<sup>2</sup>Department of Internal Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

<sup>3</sup>Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK.

<sup>4</sup>Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark.

<sup>5</sup>Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel.

<sup>6</sup>Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel.

<sup>7</sup>Department of Medicine, Stanford University School of Medicine, Stanford, California, USA.

<sup>8</sup>Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, California, USA.

<sup>9</sup>Department of Renal Medicine, University College London, London, UK.

<sup>10</sup>Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA.

<sup>11</sup>School of Medicine, Pontificia Universidade Catolica do Parana, Curitiba, Brazil.

<sup>12</sup>BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden.

<sup>13</sup>The National Medical Science and Nutrition Institute Salvador Zubiran, Mexico City, Mexico.

<sup>14</sup>Steno Diabetes Center Copenhagen, Gentofte, Denmark.

<sup>15</sup>Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.

<sup>16</sup>The George Institute for Global Health, Sydney, New South Wales, Australia.

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\*Equally contributed

*Corresponding author*

Priya Vart

Department of Clinical Pharmacy and Pharmacology;

University Medical Center Groningen;

Hanzeplein 1;

PO Box 30 000;

9700 AD Groningen;

Tel: +31 69 881 8463

E-mail: p.vart@umcg.nl

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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 estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m<sup>2</sup> and urinary albumin-to-creatinine ratio 200–5000 mg/g were randomized to dapagliflozin (10 mg/day) or placebo. The primary endpoint was composite of sustained  $\geq 50\%$  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 4303/4304 (99.9%) patients: 1162 (27.0%) in not-to-mildly frail (FI  $\leq 0.210$ ), 1642 (38.2%) in moderately frail (FI 0.211–0.310), and 1499 (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% 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  $\geq 50\%$  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  $p = 0.42$ ). Results were consistent when using FI as a continuous variable. Occurrence of serious adverse events was numerically lower in patients receiving dapagliflozin vs. 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:** SGLT2 inhibitors, cardiovascular disease, diabetes

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## INTRODUCTION:

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, cardiovascular disease, and death at all stages of CKD compared with non-frail 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 non-frail 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.

## **METHODS:**

### *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.<sup>(8-11)</sup> Briefly, participants aged 18 years or older with CKD, with or without type 2 diabetes, and with estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m<sup>2</sup> and urinary albumin-to-creatinine ratio (UACR) 200–5000 mg/g were included in the trial. Excluded patients comprised those with a history of type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-nuclear 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  $\geq 4$  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 a matching placebo once daily according to the fixed randomization schedule. Randomization was stratified by diabetes status and UACR ( $\leq 1000$  or  $>1000$  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, concomitant therapies, and study drug adherence were collected.

### *Frailty index*

A 32-item frailty index was constructed using the Rockwood cumulative deficit approach.<sup>(12)</sup> In summary, at least 30 items covering a range of body systems are required to create frailty index 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; **eTable 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 cut-offs, where possible. We calculated the frailty index 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 non-missing items only. Patients with  $\geq 20\%$  missing items ( $n=1$ ,  $<0.01\%$ ) were excluded. In the present analysis, patients were divided into 3 subgroups: frailty index  $\leq 0.210$  (not-to-mildly frail), frailty index  $0.211-0.310$  (moderately frail), and frailty index  $\geq 0.311$  (severely frail). These cut-offs have been used in several previous studies.<sup>(13-15)</sup>

### *Study Endpoints*

The primary endpoint was a composite of sustained  $\geq 50\%$  decline in eGFR (confirmed by a second serum creatinine after at least 28 days), the onset of end-stage kidney disease (defined as maintenance dialysis for more than 28 days, kidney transplantation, or eGFR  $<15$

mL/min/1.73m<sup>2</sup> 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  $\geq 50\%$  sustained eGFR decline, end-stage kidney disease, 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 adverse events (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 among the frailty index 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 frailty index 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 three groups described above). We conducted companion analyses considering the frailty index as a continuous variable, structured as a fractional polynomial. We assessed for non-uniformity of 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 < 0.05 to indicate statistical significance. We performed all analyses with Stata version 14.2 (Stata Corp).

## **RESULTS:**

### *Patient characteristics*

Of the 4,304 patients randomized in the DAPA-CKD trial, frailty index was assessable for 4,303 (99.9%) patients. The numbers of patients with missing data for cumulative and individual components of the frailty index are shown in **eTables 2** and **3**, respectively.

Distribution of frailty index is shown in **eFigure 1**. Mean frailty index was 0.273 (SD, 0.091).

A total of 1,162 (27.0%) patients were in not-to-mildly frail category (frailty index <0.210;),

1,642 (38.2%) in moderately frail category (frailty index 0.211–0.310;), and 1,499 (34.8%) in severely frail category (frailty index >0.311;).

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

#### *Association of frailty index with clinical endpoints*

Kaplan-Meier curves for the cumulative incidence of the primary composite endpoint by frailty index category are presented in **eFigure 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 [eTable 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 frailty index with hazard ratios (HR) 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 = 0.67) [Table 2, Figure 1]. Non-heterogeneity was also demonstrated when evaluating effects of dapagliflozin across the entire range of frailty index ( $P$ -interaction = 0.84) [Figure 2]. Absolute risk reductions with dapagliflozin treatment were also similar across the frailty index 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 of 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 = 0.58).

#### *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 frailty index categories [Table 2, Figure 1]. For all secondary outcomes, there was no heterogeneity of benefit on relative reduction by frailty index category, or by frailty index as a continuous variable [Figure 2]. When considering absolute risk reductions, there was no heterogeneity of the dapagliflozin effect by frailty index category for the kidney composite endpoint ( $P$ -interaction = 0.59), although absolute risk reductions for the cardiovascular composite endpoint and all-cause mortality were more pronounced along with spectrum of increasing frailty ( $P$ -interaction = 0.02 for both endpoints).

### *Hospitalization and eGFR change over time*

Effect of dapagliflozin on time to the first hospitalization was consistent across frailty index categories [eTable 6]. Compared with placebo, dapagliflozin reduced the risk of first hospitalization across all categories of frailty index, 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 = 0.92). Similarly, the effect of dapagliflozin on eGFR slope was consistent across frailty index categories. In frailty index 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/1.73m<sup>2</sup> per year, respectively ( $P$ -interaction = 0.47). 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/1.73m<sup>2</sup> per year in favor of dapagliflozin;  $P$ -interaction = 0.44) 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/1.73m<sup>2</sup> per year in favor of dapagliflozin ( $P$ -interaction = 0.68), 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 patient on dapagliflozin compared to placebo in any of the frailty index categories. The occurrence of SAEs was numerically lower with no increased likelihood of SAEs among patients randomized to dapagliflozin versus placebo in all examined frailty index 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 placebo group across frailty index 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 efficacy of commonly prescribed pharmacological agents by frailty status in patients with CKD. However, some studies in other patient populations that investigated 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 non-frail patients (*P*-interaction = 0.02).(19) Relative effects on blood pressure of perindopril and indapamide were similar among frail and non-frail 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 non-significant 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)

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 SGLT-2 inhibitors use 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 frailty index was similar to another study with a comparable patient age and kidney function (mean frailty index 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 frailty index 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 (e.g., 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 (e.g., 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 [eTable 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 frailty index 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 (NYHA) class IV congestive heart failure, or active malignancy. As it is 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 adverse events may differ from that of similar patients in routine clinical practice. Finally, in the examination of the association of frailty index 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.



### **Conflict of Interest:**

PV report travel grants from AstraZeneca.

NJ report travel grants from AstraZeneca.

JHB reports receiving payment/honoraria from AstraZeneca, Bayer, and Novartis. He has served on a Data Safety Monitoring/Advisory Board for Bayer.

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## **Author Contributions:**

PV, JHB, JJVM, and HJLH conceptualized and designed the study. PV wrote the original manuscript draft. PV and NJ performed statistical analysis. All authors contributed to interpretation of results and critical revision of the manuscript. JJVM and HJLH provided supervision.

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## **Data sharing statement**

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](http://www.vivli.org).

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## Tables

**Table 1** Baseline characteristics of the study population by level of frailty index

Characteristic	FI $\leq$ 0.210 (Not-to-mildly frail) n=1162	FI 0.211-0.310 (Moderately Frail) n=1642	FI $\geq$ 0.311 (Severely Frail) n=1499	P-value
Age (years), mean (SD)	53.9 (13.5)	63.3 (10.8)	66.4 (9.0)	<0.001
Sex (female), n (%)	388 (33.4)	540 (32.9)	497 (33.2)	0.96
Race and Ethnicity, n (%)				<0.001
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 (%)				<0.001
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)	<0.001
Systolic blood pressure (mmHg),	127.8	137.1 (16.4)	144.3	<0.001

mean (SD)	(14.1)		(17.4)	
Diastolic blood pressure (mmHg), mean (SD)	79.0 (10.2)	77.6 (10.7)	76.3 (10.3)	<0.001
Body mass index (kg/m <sup>2</sup> ), mean (SD)	26.8 (5.0)	29.3 (5.8)	31.9 (6.4)	<0.001
Pulse pressure (mmHg), mean (SD)	48.8 (10.9)	59.5 (14.4)	68.0 (16.3)	<0.001
Heart rate (bpm), mean (SD)	74.0 (11.0)	73.3 (11.5)	71.6 (11.8)	<0.001
Glycated hemoglobin (%), mean (SD)	6.2 (1.4)	7.2 (1.7)	7.6 (1.7)	<0.001
Estimated glomerular filtration rate (mL/min/1.73m <sup>2</sup> ), mean (SD)	44.4 (12.1)	43.6 (12.8)	41.6 (11.9)	<0.001
Estimated glomerular filtration rate <60 mL/min/1.73m <sup>2</sup> , n (%)	1031 (88.7)	1441 (87.8)	1377 (91.9)	0.001
Urinary albumin-to-creatinine ratio (mg/g), median (IQR)	796 (434, 1528)	965 (476, 1871)	1090 (506, 2169)	<0.001
Sodium (mmol/L), mean (SD)	139.9 (2.4)	139.5 (2.9)	139.1 (3.6)	<0.001
Potassium (mmol/L), mean (SD)	4.6 (0.5)	4.6 (0.6)	4.7 (0.6)	0.004
Hemoglobin (g/L), mean (SD)	133.2 (17.0)	128.8 (18.0)	123.8 (17.9)	<0.001
Alanine aminotransferase (U/L), mean (SD)	19.8 (10.9)	20.5 (11.3)	20.3 (11.7)	0.29
Phosphate (mg/dL), mean (SD)	3.5 (0.6)	3.6 (0.6)	3.7 (0.7)	<0.001
Diabetes (yes), n (%)	364 (31.3)	1180 (71.9)	1361 (90.8)	<0.001
Diabetes duration (years),	10.0	12.8	15.8	<0.001

median (IQR)	(5.2, 18.0)	(6.5, 19.8)	(9.2, 22.3)	
Hypertension (yes), n (%)	1011 (87.0)	1613 (98.2)	1496 (99.8)	<0.001
Cardiovascular disease (yes), n (%)	92 (7.9)	497 (30.3)	1021 (68.1)	<0.001
Heart failure (yes), n (%)	16 (1.4)	113 (6.9)	339 (22.6)	<0.001
Ischemic heart disease (yes), n (%)	30 (2.6)	179 (10.9)	507 (33.8)	<0.001
Non-coronary arterial disease (yes), n (%)	18 (1.5)	175 (10.7)	597 (39.8)	<0.001
Atrial fibrillation/flutter (yes), n (%)	5 (0.4)	57 (3.5)	165 (11.0)	<0.001
Chronic obstructive pulmonary disease (yes), n (%)	8 (0.7)	43 (2.6)	145 (9.7)	<0.001
Stroke (yes), n (%)	21 (1.8)	111 (6.8)	233 (15.5)	<0.001
Dyslipidemia (yes), n (%)	401 (34.5)	1223 (74.5)	1363 (90.9)	<0.001
Gout (yes), n (%)	140 (12.0)	271 (16.5)	360 (24.0)	<0.001
Cancer (yes), n (%)	14 (1.2)	42 (2.6)	84 (5.6)	<0.001
Syncope (yes), n (%)	5 (0.4)	14 (0.8)	33 (2.2)	<0.001
Sleep apnea (yes), n (%)	10 (0.9)	66 (4.0)	219 (14.6)	<0.001
Neuropathy (yes), n (%)	24 (2.1)	277 (16.9)	651 (43.4)	<0.001
Osteoporosis (yes), n (%)	401 (34.5)	1223 (74.5)	1363 (90.9)	<0.001
ACE inhibitor/ARB (yes), n (%)	1128 (97.1)	1592 (96.9)	1453 (96.9)	0.975
Diuretics (yes), n (%)	258 (22.2)	702 (42.7)	921 (61.4)	<0.001

Insulin (yes), n (%) <sup>a</sup>	144 (39.6)	604 (51.2)	849 (62.4)	<0.001
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*Note:* ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; IQR: interquartile range; SD: standard deviation; <sup>a</sup>In those with diabetes

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**Table 2** Effects of dapagliflozin compared with placebo on clinical events by frailty index

	<b>Dapagliflozin</b> (n=2151)	<b>Placebo</b> (n=2152)	<b>Absolute Risk</b>		<b>Hazard Ratio</b>	
			<b>Difference %</b> <b>(95% CI)</b>	<b>P-int</b>	<b>(95% CI)</b>	<b>P-int</b>
	FI ≤0.210 (n=593)	FI ≤0.210 (n=569)				
	FI 0.211-0.310 (n=816)	FI 0.211-0.310 (n=826)				
	FI ≥311 (n=742)	FI ≥311 (n=757)				
	n (%)	n (%)				
<b>Primary composite outcome</b>						
<i>eGFR decline ≥50%, end-stage kidney disease, or kidney or cardiovascular death</i>						
				0.581		0.667
Not-to-mildly frail (n=1162)	35 (5.9)	63 (11.1)	5.2 (2.0, 8.4)		0.50 (0.33, 0.76) <i>P</i> = 0.001	
Moderately frail (n=1642)	64 (7.8)	99 (12.0)	4.1 (1.3, 7.0)		0.62 (0.45, 0.85) <i>P</i> = 0.003	
Severely frail (n=1499)	98 (13.2)	150 (19.8)	6.6 (2.9, 10.3)		0.64 (0.49, 0.83) <i>P</i> = 0.001	
<b>Secondary outcomes</b>						
<i>Kidney composite outcome: eGFR decline ≥50%, end-stage kidney disease or kidney death</i>						
				0.585		0.437
Not-to-mildly frail (n=1162)	27 (4.5)	57 (10.0)	5.5 (2.5, 8.4)		0.42 (0.27, 0.67)	

				<i>P</i> < 0.001
Moderately frail				0.62
(n=1642)	55 (6.7)	85 (10.3)	3.5 (0.9, 6.2)	(0.44, 0.87) <i>P</i> = 0.006
Severely frail				0.57
(n=1499)	60 (8.1)	101 (13.3)	5.3 (2.1, 8.4)	(0.41, 0.9), <i>P</i> = 0.001
<i>Cardiovascular outcome: Hospitalization for heart failure or cardiovascular death</i>				
				0.019
Not-to-mildly frail				0.627
(n=1162)	11 (1.8)	10 (1.8)	-0.1 (-1.6, 1.4)	1.02 (0.43, 2.41) <i>P</i> = 0.964
Moderately frail				0.70
(n=1642)	21 (2.6)	29 (3.5)	0.9 (-0.7, 2.6)	(0.40, 1.24) <i>P</i> = 0.222
Severely frail				0.67
(n=1499)	68 (9.2)	99 (13.1)	3.9% (0.7, 7.1)	(0.49, 0.92) <i>P</i> = 0.012
<i>All-cause mortality</i>				
				0.021
Not-to-mildly frail				0.417
(n=1162)	12 (2.0)	11 (1.9)	-0.1 (-1.7, 1.5)	1.03 (0.45, 2.34) <i>P</i> = 0.941
Moderately frail				0.56
(n=1642)	26 (3.2)	46 (5.6)	2.4 (0.4, 4.4)	(0.34, 0.90) <i>P</i> = 0.018

Severely frail				0.69
(n=1499)	63 (8.5)	89 (11.8)	3.3 (0.2, 6.3)	(0.50, 0.96) <i>P</i> = 0.027

*Note:* eGFR: estimated glomerular filtration rate; FI: frailty index *P*-int: *P*-interaction  
 Not-to-mildly frail: FI ≤0.210; Moderately frail: FI 0.211-0.310; Severely frail: FI ≥0.311

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**Table 3** Safety by level of frailty index

<b>Outcome, n (%)</b>	<b>Dapagliflozin (n=2148)</b>	<b>Placebo (n=2149)</b>	<b>Odds ratio (95% CI)</b>	<b>P-interaction</b>
<b>Discontinuation due to adverse event</b>				<b>0.374</b>
Not-to-mildly frail (n=1160)	18 (3.0)	23 (4.0)	0.76 (0.40, 1.42)	
Moderately frail (n=1639)	52 (6.4)	44 (5.3)	1.21 (0.80, 1.83)	
Severely frail (n=1498)	48 (6.5)	56 (7.4)	0.88 (0.59, 1.31)	
<b>Any serious adverse event<sup>a</sup></b>				<b>0.988</b>
Not-to-mildly frail (n=1160)	100 (16.9)	114 (20.1)	0.81 (0.60, 1.09)	
Moderately frail (n=1639)	214 (26.3)	253 (30.7)	0.80 (0.65, 1.00)	
Severely frail (n=1498)	318 (42.9)	362 (47.8)	0.82 (0.67, 1.01)	
<b>Adverse events of interest</b>				
<b>Amputation<sup>b</sup></b>				<b>0.876</b>
Not-to-mildly frail (n=1160)	0	3 (0.5)	-	
Moderately frail (n=1639)	10 (1.2)	11 (1.3)	0.94 (0.40, 2.24)	
Severely frail (n=1498)	25 (3.4)	25 (3.3)	1.02 (0.58, 1.79)	
<b>Any definite or probable diabetic ketoacidosis</b>				
Not-to-mildly frail (n=1160)	0	0	-	
Moderately frail (n=1639)	0	1 (0.1)	-	
Severely frail (n=1498)	0	1 (0.1)	-	
<b>Fracture<sup>c</sup></b>				<b>0.256</b>
Not-to-mildly frail (n=1160)	13 (2.2)	16 (2.8)	0.79 (0.37, 1.65)	



Moderately frail (n=1639)	30 (3.7)	26 (3.2)	1.17 (0.69, 2.00)	
Severely frail (n=1498)	42 (5.7)	27 (3.6)	1.63 (0.99, 2.68)	
Renal related adverse event <sup>c</sup>				0.868
Not-to-mildly frail (n=1160)	18 (3.0)	26 (4.6)	0.66 (0.36, 1.21)	
Moderately frail (n=1639)	44 (5.4)	65 (7.9)	0.66 (0.45, 0.99)	
Severely frail (n=1498)	93 (12.5)	97 (12.8)	0.99 (0.73, 1.34)	
Major hypoglycemia <sup>d</sup>				0.727
Not-to-mildly frail (n=1160)	1 (0.2)	4 (0.7)	0.23 (0.02, 2.12)	
Moderately frail (n=1639)	4 (0.5)	6 (0.7)	0.67 (0.19, 2.39)	
Severely frail (n=1498)	9 (1.2)	18 (2.4)	0.51 (0.23, 1.14)	
Volume depletion <sup>c</sup>				0.406
Not-to-mildly frail (n=1160)	27 (4.6)	12 (2.1)	2.22 (1.11, 4.42)	
Moderately frail (n=1639)	45 (5.5)	34 (4.1)	1.36 (0.86, 2.14)	
Severely frail (n=1498)	55 (7.4)	44 (5.8)	1.29 (0.86, 1.95)	

*Note:* <sup>a</sup>Includes death; <sup>b</sup>Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; <sup>c</sup>Based on pre-defined list of preferred terms; <sup>d</sup>Adverse event with the following criteria confirmed by the investigator: i) Symptoms of severe impairment in consciousness or behaviour, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention.

## Figure Legends

**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

**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

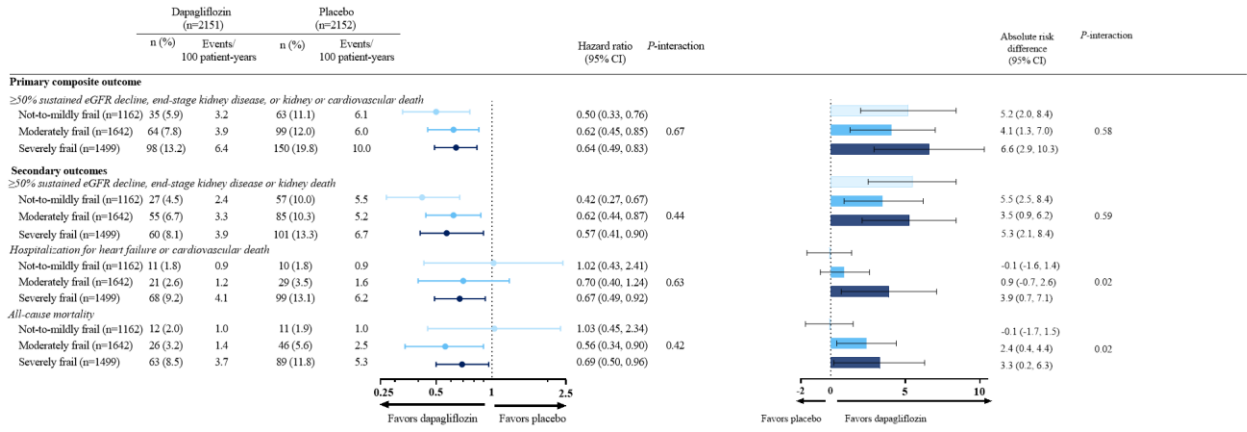
## Table Legends

**Table 1** Baseline characteristics of the study population by levels of frailty index

**Table 2** Effects of dapagliflozin compared with placebo on clinical events by frailty index

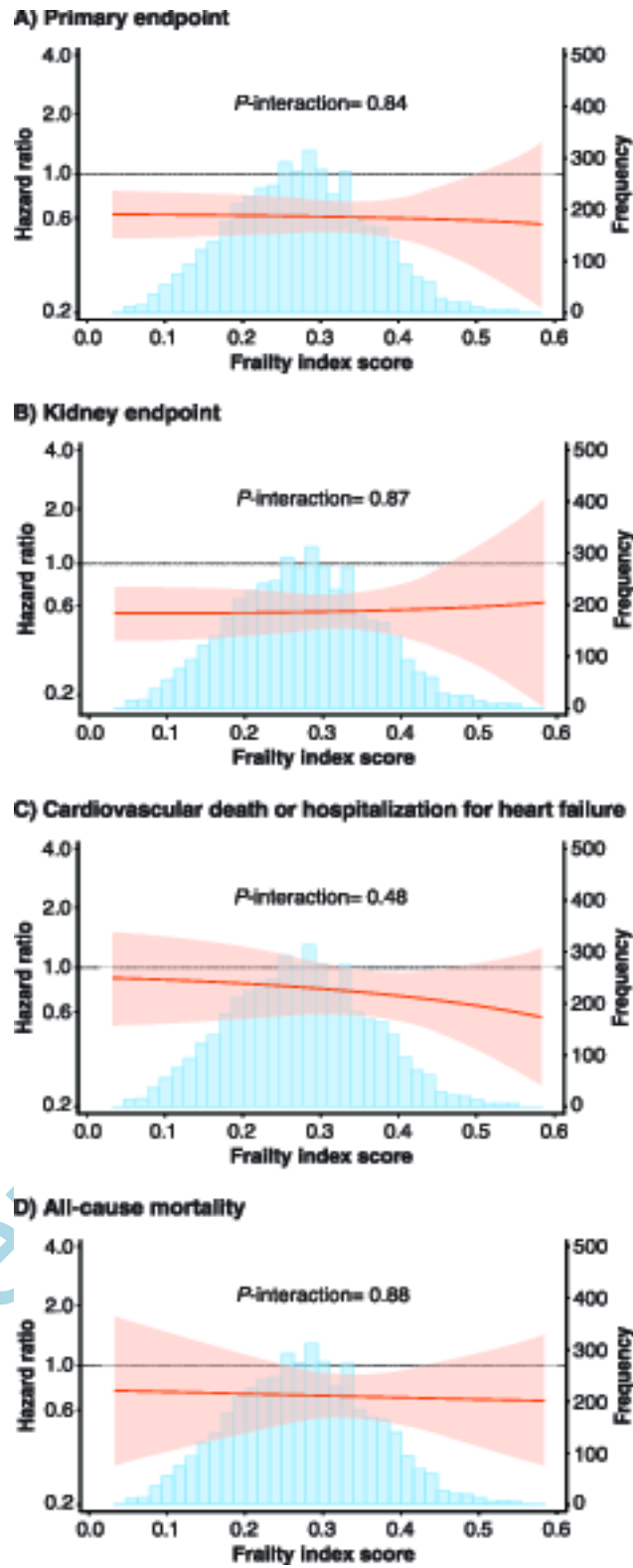
**Table 3** Safety by level of frailty index

Figure 1



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Figure 2



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