Chertow Glenn M (Orcid ID: 0000-0002-7599-0534)
Mcmurray John (Orcid ID: 0000-0002-6317-3975)
Heerspink Hiddo L (Orcid ID: 0000-0002-3126-3730)

Quételet (Body Mass) Index and Effects of Dapagliflozin in CKD

Glenn M. Chertow[1], Priya Vart[2], Niels Jongs[2], Anna Maria Langkilde[3], John J. V. McMurray[4], Ricardo Correa-Rotter[5], Peter Rossing[6,7], C. David Sjöström[3], Bergur V. Stefansson[3], Robert D. Toto[8], David C. Wheeler[9], Hiddo J. L. Heerspink[2,10]

1. Departments of Medicine and Epidemiology and Population Health, Stanford University School of Medicine, Stanford, USA
2. Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
3. Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden
4. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
5. The National Medical Science and Nutrition Institute Salvador Zubiran, Mexico City, Mexico
6. Steno Diabetes Center Copenhagen, Gentofte, Denmark
7. Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
8. Department of Internal Medicine, UT Southwestern Medical Center, Dallas, USA
9. Department of Renal Medicine, University College London, London, UK
10. The George Institute for Global Health, Sydney, Australia

Correspondence to:
Glenn M. Chertow, MD, MPH
Departments of Medicine and Epidemiology and Population Health
Stanford University School of Medicine
1070 Arastradero Road, Suite 311
Palo Alto, CA 94304
email: gchertow@stanford.edu
telephone: (650) 725-4738
fax: (650) 721-1443
Twitter: @gchertow

Running title: BMI in DAPA-CKD
Word count: 3535 (with headings and subheadings)
Abstract word count: 252
References: 40
Tables: 2
Figures: 3
Supplementary Tables: 5
Supplementary Figures: 5

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.14641

ABSTRACT (max allowed: 250 words; current: 252)

Aims. This post-hoc analysis of DAPA-CKD (NCT03036150) assessed the effects of dapagliflozin in patients with chronic kidney disease (CKD) and albuminuria, with and without type 2 diabetes, stratified by the Quételet (body mass) index (BMI).

Methods. We randomized 4304 adult patients with estimated glomerular filtration rate (eGFR) of 25-75 mL/min/1.73m^2 and urinary albumin-to-creatinine ratio of 200-5000 mg/g to dapagliflozin 10 mg/day or placebo. The primary outcome was a composite of sustained decline in eGFR of ≥50%, kidney failure, or death from kidney or cardiovascular causes. Secondary outcomes included kidney composite endpoint (primary composite endpoint without cardiovascular death), cardiovascular composite endpoint (hospitalized heart failure/ cardiovascular death), and all-cause mortality. We categorized participants according to World Health Organization BMI criteria: lean/ideal (<25 kg/m^2), overweight (25-<30 kg/m^2), grade 1 obesity (30-<35 kg/m^2) and grade 2/3 obesity (≥35 kg/m^2).

Results. Of 4296 (99.8%) randomized participants, 888 (20.7%), 1491 (34.7%), 1136 (26.4%), and 781 (18.2%) were categorized as lean/ideal, overweight, grade 1 obesity, and grade 2/3 obesity, respectively. Median follow-up was 2.4 years. Benefits of dapagliflozin were observed independent of baseline BMI for primary and secondary endpoints. Hazard ratios (95% CI) for dapagliflozin versus placebo for the primary composite endpoint were 0.60 (0.43, 0.85), 0.55 (0.40, 0.75), 0.71 (0.49, 1.04), and 0.57 (0.37, 0.87), among participants in the lean/ideal, overweight, grade 1 obesity, and grade 2/3 obesity groups (interaction p=0.72).

Conclusion. Among participants with CKD and albuminuria, with or without type 2 diabetes, kidney and cardiovascular benefits of dapagliflozin were evident and consistent across the BMI spectrum.

Key words: Quételet index; body mass index; obesity; dapagliflozin; chronic kidney disease; clinical trial

INTRODUCTION

The prevalence of overweight and obesity in developed and developing countries is high and rising rapidly [1-5]. Obesity is associated with impaired glucose tolerance, type 2 diabetes, obstructive sleep apnea, hypertension, heart failure, atrial fibrillation, proteinuria, impaired kidney function, and cardiovascular and sudden death [6-9]. The prevalence of obesity in patients with chronic kidney disease (CKD) (conventionally defined as Quételet (body mass) index (BMI) ≥30 kg/m^2), has been reported to range from 12-38% [10-13].

Sodium–glucose co-transporter 2 (SGLT2) inhibitors were initially developed for the treatment of type 2 diabetes. These agents improve glycemic control by inhibiting proximal tubule glucose reabsorption; as a result, glucose is wasted in the urine, resulting in loss of ingested calories and modest weight loss. Over the past several years, large cardiovascular outcomes trials (initially designed to meet regulatory requirements for ensuring cardiovascular safety) have demonstrated that SGLT2 inhibitors reduce cardiovascular and kidney events and prolong survival in patients with type 2 diabetes [14-18]; more recently, evidence of benefits of the SGLT2 inhibitor dapagliflozin have also been extended to patients with heart failure and CKD with albuminuria without type 2 diabetes [14].

Given the high prevalence of obesity in patients with CKD, and favorable metabolic effects of dapagliflozin in patients with obesity and insulin resistance, we hypothesized that the benefits of dapagliflozin on kidney and cardiovascular outcomes would be accentuated in obese patients with CKD and albuminuria relative to non-obese patients. To explore this hypothesis, we conducted a series of secondary analyses from the DAPA-CKD trial presented herein.

METHODS

DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter clinical trial; manuscripts describing trial design, baseline characteristics, primary results, and results stratified by diabetes status and history of cardiovascular disease have been previously published [14,19-21]. The trial was sponsored by AstraZeneca and conducted at 386 sites in 21 countries from February 2017 through June 2020 and registered at clinicaltrials.gov (NCT03036150). All participants provided written informed consent before any study specific procedure commenced. The safety of participants in the trial was overseen by an independent data and safety monitoring committee.

Participants

Adults with or without type 2 diabetes, estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m^2 and urinary albumin-to-creatinine ratio (UACR) 200–5000 mg/g were eligible for participation. We required patients to be treated with a stable maximally-tolerated dose of renin-angiotensin-aldosterone-system (RAAS) inhibitor for ≥4 weeks unless medically contraindicated. Key exclusion criteria included documented diagnosis of type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis. A complete list of inclusion and exclusion criteria and the trial protocol have been previously published [19].

Procedures

Participants were randomly assigned to dapagliflozin 10 mg once daily or matching placebo, in accordance with the sequestered, fixed-randomization schedule, with the use of

balanced blocks to ensure an approximate 1:1 ratio of the two regimens. Randomization was stratified by diabetes status and UACR (≤ or >1000 mg/g). We categorized participants according to World Health Organization (WHO) BMI criteria: lean or ideal (<25 kg/m^2), overweight (25 to <30 kg/m^2), grade 1 obesity (30 to <35 kg/m^2) and grade 2/3 obesity (≥35 kg/m^2). We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and incorporated results from the equation as originally defined, including a term for self-reported race (Black versus non-Black). Recruitment of patients with eGFR 60-75 mL/min/1.73m^2 was limited to no more than 10% of trial participants. Participants and all study personnel (except the Independent Data Monitoring Committee) were masked to treatment allocation.

After randomization, in-person study visits were performed after 2 weeks, 2, 4, and 8 months and at 4-month intervals thereafter. At each follow-up visit, study personnel recorded vital signs, obtained blood and urine samples, and recorded information on potential study endpoints, adverse events, concomitant therapies, and study drug adherence.

Endpoints

The primary composite endpoint was time to 50% decline in eGFR (confirmed by a second serum creatinine measurement after at least 28 days), onset of kidney failure (defined as maintenance dialysis for at least 28 days, kidney transplantation, or eGFR <15 mL/min/1.73m^2 confirmed by a second measurement after at least 28 days), or death from a kidney or cardiovascular cause. Secondary endpoints were time to: 1) a composite kidney endpoint of ≥50% sustained decline in eGFR, kidney failure or death from kidney disease; 2) a composite cardiovascular endpoint defined as hospitalization for heart failure or cardiovascular death; and

3) death from any cause. We also prespecified change in eGFR slope as an exploratory efficacy endpoint. All efficacy endpoints were adjudicated by a masked, independent Clinical Events Committee, except for the quantitative assessments of eGFR which were obtained from our central laboratory.

For the purpose of the current analysis, we also examined the effect of dapagliflozin on body weight across BMI categories.

Safety

Given extensive prior experience with dapagliflozin, we limited our ascertainment of adverse events (AEs) to serious adverse events (SAEs), AEs resulting in the discontinuation of 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, power calculation, and pre-specified statistical analysis plan have been previously published [22,23]. All analyses presented here followed the intention-to-treat principle. Briefly, we conducted time-to-event analyses using a proportional hazards (Cox) regression stratified by randomization factors (diabetes status and UACR), adjusting for baseline eGFR, yielding hazard ratios (HR) and 95% confidence intervals (95% CI) from model parameter coefficients and standard errors (SE). For the purpose of the current analysis, we evaluated the primary, secondary, and other pre-specified efficacy endpoints in participants stratified by WHO BMI categories, collapsing the "lean" (<18.5 kg/m^2) and "ideal" (18.5 to <25

kg/m^2) categories owing to the small proportion of DAPA-CKD participants (n=27, 0.6%) in the former. We compared results across the spectrum of body size/composition by including a multiplicative interaction term between randomized treatment group and BMI category. For time to event analyses, we assessed for non-uniformity of HRs with the Akaike's information criterion. We considered p-values <0.05 to be statistically significant.

We analyzed the effects of dapagliflozin on the mean on-treatment eGFR slope by fitting a two-slope mixed effects linear spline model (with a knot at week 2) with a random intercept and random slopes for treatment. The model included fixed effects for treatment, BMI category, stratification factors (diabetes status and UACR) and a continuous, fixed covariate for time-to-visit. To determine eGFR slopes for the BMI categories, we added to the model all possible interaction terms for treatment effect, BMI categories, and time-to-visit, assuming an unstructured variance-covariance matrix. We computed the mean total slope as a weighted combination of the acute and chronic slopes to reflect the mean rate of eGFR change to until the last on-treatment visit. We also presented the pattern of change in mean eGFR using a restricted maximum likelihood repeated measures approach. This latter analysis included fixed effects of treatment, visit, treatment-by-visit interaction, and treatment-by-BMI category interaction. We added interaction terms between BMI category, visit, and treatment assignment to assess the change in eGFR within BMI subgroups.

Given differences in the validity of BMI as a proxy for obesity in men and women, we performed exploratory analyses stratified by sex. We also performed exploratory analyses stratified by type 2 diabetes status. We conducted companion analyses in which we categorized patients of Asian race using modified WHO categories for lean or ideal (<23 kg/m^2), overweight (23 to <25 kg/m^2), grade 1 obesity (25 to <30 kg/m^2), and grade 2/3 obesity (≥30 kg/m^2).

We analyzed the effect of dapagliflozin on body weight by fitting repeated measures models using restricted maximum likelihood. This model included categorical fixed effects for treatment, visit, and a three-way interaction term between BMI category, visit, and treatment. We utilized an unstructured variance-covariance matrix i.e., a data-dependent model that allows for a general pattern of standard deviations and correlations for the body weight measurements at different time points. Two-tailed p-values <0.05 were considered to be statistically significant. We performed all analyses with SAS version 9.4 (SAS Institute) or R version 4.0.2 (R Foundation).

RESULTS

Of the 4296 (99.8%) participants randomized with data on height and body weight, 888 (20.7%), 1491 (34.7%), 1136 (26.4%), and 781 (18.2%) were categorized as lean or ideal, overweight, grade 1 obesity, and grade 2/3 obesity, respectively. **Supplementary Figure S1** shows the CONSORT diagram for participants enrolled in DAPA-CKD randomized by BMI categories.

Table 1 shows baseline characteristics of randomized participants stratified by BMI categories. The mean age was slightly lower among participants in the lean or ideal BMI category, and similar across the overweight and obese categories. The distribution of participants by investigator-reported race differed substantially across BMI categories. Asian participants were more likely to be in the lower BMI categories, whereas white and Black participants were more likely to be in the higher BMI categories. Baseline eGFR and UACR were similar across BMI categories. The proportion of participants with type 2 diabetes and the baseline hemoglobin A1c were directly correlated with BMI. The proportion of participants with overt cardiovascular disease was higher in obese participants than among those who were lean or ideal or overweight, as was the use of diuretics.

Effects of dapagliflozin on discrete events

Fifty-seven (12.6%), 59 (7.8%), 48 (8.3%), and 33 (9.1%) participants randomized to dapagliflozin and 79 (18.1%), 104 (14.2%), 66 (11.8%), and 61 (18.6%) participants randomized to placebo in the lean or ideal, overweight, grade 1 obesity, and grade 2/3 obesity, experienced a primary composite endpoint. Median follow-up was 2.4 years. **Figure 1, panels A-D** shows the cumulative incidence of the primary composite endpoint in participants categorized as lean or

ideal, overweight, grade 1 obesity and grade 2/3 obesity in both randomized groups. **Supplementary Figure 2, panels A-D; Supplementary Figure 3, panels A-D;** and **Supplementary Figure 4, panels A-D** show the cumulative incidence of the kidney composite endpoint, the cardiovascular composite endpoint, and all-cause mortality in corresponding BMI groups. **Figure 2** summarizes event rates in participants randomized to dapagliflozin or placebo (per 100 patient-years), along with differences in absolute and relative risks (with 95% CI) and interaction p-values (tests of heterogeneity for the dapagliflozin versus placebo comparison) for the primary composite and three secondary endpoints stratified by BMI category. Beneficial effects of dapagliflozin were evident across BMI categories. Rates of the primary composite and kidney composite endpoints were highest in participants categorized as lean or ideal while rates of the cardiovascular composite endpoint were highest in participants with grade 2/3 obesity. There was no effect modification on the primary outcome by sex (randomized treatment × BMI × sex; interaction p=0.47) or diabetes status (randomized treatment × BMI × diabetes; interaction p=0.40). Beneficial effects of dapagliflozin on other exploratory endpoints were also evident across BMI categories (**Supplementary Table S1**).

Effects of dapagliflozin on eGFR slope

Figure 3, panels A-D show least squares mean change in eGFR slope (±SE) in the dapagliflozin and placebo groups within each of the four BMI subgroups. **Supplementary Table S2** shows the acute (baseline to 2 weeks), chronic (Week 2 to end-of-treatment) and total eGFR slopes within BMI categories. The dapagliflozin-induced acute decline in eGFR was more pronounced in participants with higher BMI; mean relative effects were −1.26, −2.52, −2.60, and −3.07 mL/min/1.73m^2 in the lean or ideal, overweight, grade 1 obesity, and grade 2/3 obesity

groups, respectively, (interaction p=0.03) suggesting differential acute effects. The beneficial effects of dapagliflozin on chronic and total eGFR slopes were present in all BMI groups, with no evidence of heterogeneity (interaction p=0.97 and 0.32, respectively).

Companion analyses using different BMI cutoffs for Asian participants

The WHO has recommended the use of different BMI cutoffs when considering designations of ideal, overweight, and obesity for certain persons of Asian race. Given the relatively high proportion of Asian participants in DAPA-CKD, we conducted companion analyses using the following WHO-recommended categories to represent lean or ideal, overweight, grade 1 obesity and grade 2/3 obesity: <23, 23 to <25, 25 to <30, and ≥30 kg/m^2, respectively. **Supplementary Tables S3** and **S4** show baseline characteristics of the 1467 Asian participants, categorized using the conventional and modified BMI groups, respectively. **Supplementary Table S5** shows event rates, absolute risk differences, hazard ratios, and tests of interaction (treatment × BMI category) for the primary composite endpoint and secondary endpoints when re-classifying Asian participants. Results were similar to the original analyses, showing benefits of dapagliflozin across categories of BMI.

Effects of dapagliflozin on body weight

The effects of dapagliflozin on body weight were modest (**Supplementary Figure S5, panels A-D**); overall, body weight integrated over time was 0.85 (95% CI 0.62 to 1.08) kg lower in participants randomized to dapagliflozin relative to placebo (p<0.001), but with no significant differences by BMI category (interaction p=0.31).

Serious Adverse Events

Table 2 shows a summary of SAEs and AEs of special interest observed in participants stratified by treatment group and BMI subgroup. Obese participants in both groups were more likely to experience one or more SAEs than did lean or ideal or overweight participants. SAEs were numerically less frequent in participants randomized to dapagliflozin (compared with placebo) within each BMI category (interaction p=0.46).

DISCUSSION

In the current secondary analysis of DAPA-CKD, we demonstrate that the beneficial effects of dapagliflozin on the primary composite endpoint, a sustained decline in eGFR of ≥50%, kidney failure, or death from a kidney or cardiovascular cause, and on the kidney composite endpoint, cardiovascular composite endpoint, and all-cause mortality were similar across the range of body composition, as assessed by the Quételet index or BMI. Effects of dapagliflozin on the total and chronic eGFR slopes were also similar across the spectrum of BMI. In other words, in patients with CKD and albuminuria, with or without type 2 diabetes, dapagliflozin yields kidney and cardiovascular benefits "through thick and thin".

Owing to the glucose-lowering effects of dapagliflozin [24,25], its effects on body weight [26,27], and the previously observed association between obesity and CKD [28,29], we had hypothesized that the beneficial effects of dapagliflozin might be more pronounced in patients at higher versus lower baseline BMI. In fact, rates of the primary composite and kidney composite endpoints were highest in participants categorized as lean or ideal; in contrast, rates of the cardiovascular composite endpoint were highest in participants with grade 2/3 obesity. Relative benefits of dapagliflozin were observed across the spectrum of BMI, and within BMI strata, among women and men and participants with and without diabetes. Absolute benefits of dapagliflozin on the composite cardiovascular endpoint were highest in participants with grade 2/3 obesity, confirming findings recently published by Oyama et al. from the DECLARE-TIMI 58 trial [30]. We observed similar results across other, exploratory composite endpoints including the traditional major adverse cardiovascular event (MACE) endpoint of cardiovascular death or non-fatal myocardial infarction or stroke. Serious adverse events were seen more frequently

among obese participants although rates were numerically lower in participants randomized to dapagliflozin within each BMI category.

Obesity has been blamed (in part) for the plateau and decline in life expectancy in the United States over the past decade [31]. Obesity contributes to degenerative diseases within nearly all organ systems [32], driven in part by an inflammatory milieu induced by adipocytes [33]. Associations between obesity and cardiovascular events have been well described over decades; heightened risks of stroke, heart failure and arrhythmia, including atrial fibrillation and sudden cardiac death, are particularly noteworthy [7,33,34]. However, the link between obesity and progressive kidney disease is less well described. In a seminal report by Hsu et al. [35], 320,252 adult members of an integrated healthcare delivery system were screened between 1964 and 1985 and data were linked with the United States Renal Data System (USRDS), a registry of nearly all patients treated with maintenance dialysis in the United States since 1988; 1487 cases of treated end-stage kidney disease (ESKD) were identified over 8,347,955 person-years of follow-up. Relative to persons with "ideal" body composition (BMI 18.5 to <25 kg/m^2), risks of treated end-stage kidney disease, adjusted for age, sex, self-reported race, and baseline diabetes, blood pressure, serum creatinine, serum cholesterol, and dipstick hematuria and proteinuria, in persons with BMI 25 to <30 kg/m^2 ("overweight"), 30 to <35 kg/m^2, 35 to <40 kg/m^2, and ≥40 kg/m^2 ("grades 1, 2, and 3 obesity") were 1.87-, 3.57-, 6.12-, and 7.07-fold higher. A more recent report from the Atherosclerosis Risk in Communities (ARIC) study incorporating data from 13,496 participants with midlife assessments of obesity over 30 years of follow-up, reported that one standard deviation higher BMI, adjusted for age, center, smoking, and coronary heart disease, was associated with 26% (–2% to 62%), 51% (14 to 101%), 75% (29 to 136%),

and 68% (33 to 113%) higher risks of treated ESKD in white men, white women, Black men, and Black women, respectively [36].

In view of these two population-based studies showing higher rates of kidney failure among more obese persons in the general population, we were surprised to observe that DAPA-CKD participants categorized as overweight or obese were not more likely to experience the kidney composite endpoint or more rapid decline in eGFR. Examining data from a contemporary, well-characterized cohort of patients with CKD of multiple etiologies – the Chronic Renal Insufficiency Cohort (CRIC) study – Ricardo et al. showed that relative to patients with BMI 20 to <25 kg/m^2, overweight (BMI 25 to <30 kg/m^2) and obese (BMI ≥30 kg/m^2) patients experienced 34% (95% CI 17 to 48%) and 43% (95% CI 29 to 54%) *lower* relative risks of progressive CKD, defined as 50% or more decline in eGFR or the provision of maintenance dialysis or kidney transplantation; mortality rates were virtually identical, suggesting that competing risks were not responsible for these findings [34]. Nevertheless, the current analyses provide compelling evidence that dapagliflozin yields sizeable reductions in risk irrespective of BMI and the underlying rate of CKD progression.

Previous studies using other SGLT2 inhibitors have explored effects on cardiovascular and kidney endpoints stratified by BMI. Okhuma et al. examined the effects of canagliflozin and placebo in 10,128 Canagliflozin Cardiovascular Assessment Program (CANVAS) participants stratified by the following BMI categories: <25, 25 to <30, and ≥30 kg/m^2 [37]. Canagliflozin significantly reduced the risk of the primary composite endpoint (cardiovascular death or non-fatal myocardial infarction or stroke); the relative hazard was numerically lowest in the obese group, but there was no statistical evidence of heterogeneity. Absolute effects on body weight were modest, but more pronounced in obese participants; relative effects on body weight were

similar across BMI categories. Ji et al. conducted a similar analysis from the EMPA-REG OUTCOME trial [38]. Empagliflozin reduced the risks of all-cause mortality, hospitalized heart failure or cardiovascular death, and "worsening nephropathy" (a composite of progression to macroalbuminuria, doubling of serum creatinine to an eGFR ≤45 mL/min/1.73m^2, provision of dialysis or death due to kidney disease) by 32%, 34%, and 39%, respectively; there was no heterogeneity by BMI category. More recently, Adamson et al. showed similar relative benefits of dapagliflozin across the spectrum of BMI on cardiovascular death or heart failure exacerbation and other cardiovascular endpoints in patients with heart failure with reduced ejection fraction enrolled in the DAPA-HF trial [39]. Our results extend those of Okhuma et al., Ji et al., and Adamson et al. by examining patients with CKD and kidney as well as cardiovascular endpoints.

There are several strengths to this analysis. Data were derived from a randomized trial and major kidney and cardiovascular events were adjudicated by an independent panel. Trial participants were diverse by age, sex, country of origin, and primary cause of kidney disease. The majority of participants were on guideline-recommended therapies at baseline; nearly all participants were treated with RAAS inhibitors and other agents proven to reduce rates of cardiovascular disease. Effects of dapagliflozin were consistent whether considering risks of discrete events (which are generally observed among "rapid progressors") as well as eGFR slope. There are also several limitations. Despite its widespread use in population-based studies, the Quételet index (BMI) is an imperfect proxy for obesity. The BMI fails to distinguish body weight related to intracellular water (largely housed in the skeletal muscle), extracellular water (which tends to accumulate in advanced CKD) and adipose tissue. Moreover, the simplification of the height correction to the second power more thoroughly reduces the correlation between the

index and height in men versus women (hence, the reason to explore effect modification by sex) [40]. The DAPA-CKD trial was stopped early following a recommendation from the Independent Data Monitoring Committee. As a result, the trial accrued fewer than 75% of its anticipated number of events, and the precision of our estimated treatment effects within the BMI subgroups was diminished. Moreover, foreshortening of the trial may have reduced the likelihood of identifying clinically meaningful effect modification. We did not collect eGFR after the completion of the trial, which might have increased the observed difference in eGFR slope between groups if a fraction of the initial decline observed in treated participants were reversible. Finally, body weight was not a pre-specified endpoint in the DAPA-CKD trial, and measures to ensure accurate and precise determination of changes in body weight over time were not in place.

In conclusion, among patients with CKD and albuminuria, with or without type 2 diabetes, kidney and cardiovascular benefits of dapagliflozin were evident and consistent across the spectrum of BMI.

AUTHOR CONTRIBUTIONS

GMC, JJVM, RC-R, PR, RDT, DCW and HJLH are members of the study's executive committee and were involved in the study design, data collection, and analysis/interpretation of the data. NJ and PV performed the data analyses. BVS, CDS and AML were involved in the study design, conduct of the study, and interpretation of data. GMC wrote the first draft of the manuscript. All authors reviewed the manuscript drafts for important intellectual content, provided approval of the final version for submission and take responsibility for the accuracy and integrity of the data including ensuring that any questions are appropriately investigated and resolved. GMC is the guarantor and corresponding author, and as such accepts full responsibility for the overall content of the work and conduct of the study, had access to the data, and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. GMC had the final responsibility to submit for publication.

AUTHOR DISCLOSURES

GMC has received fees from AstraZeneca for the DAPA-CKD trial steering committee, research grants from NIDDK, support for research staff attending meetings from Amgen, participated in data safety monitoring boards for Bayer and Recor, is on the board of directors for Satellite Healthcare and on trial steering committees for Akebia, Gilead, Sanifit and Vertez, and holds stock options or stock options with Ardelyx, CloudCath, Durect, DxNow, Miromatrix, Outset and Unicycive.

PV and NJ have nothing to declare.

AML, BVS, CDS, are employees and stockholders of AstraZeneca.

JJVM has received payments to his employer, Glasgow University, 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, Cardurion and Alnylam, and has received personal lecture fees from Abbott, Alkem Metabolics, Eris Life Sciences, Hickma, Lupin, Sun Pharmaceuticals, Medscape/Heart.org, ProAdWise Communications, Radcliffe Cardiology, Servier and the Corpus.

RC-R is a member of the Executive Committee of the DAPA-CKD study, has received grants/contracts from GlaxoSmithKline and Novo Nordisk, consulting fees from Boehringer Ingelheim and Chinook, and payment/honoraria as a speaker or advisor from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Janssen and Novo Nordisk.

PR has received honoraria to Steno Diabetes Center Copenhagen for: steering group membership and/or lectures and advice from AstraZeneca, Novo Nordisk, Bayer and Eli Lilly; advisory board participation from Sanofi Aventis and Boehringer ingelheim; steering group participation from Gilead.

RDT is a consultant for AstraZeneca, Amgen, Bayer, Boehringer-Ingelheim, Medscape, Otsuka, Reata and Relypsa.

DCW provides ongoing consultancy services to AstraZeneca and personal fees from Bayer, Boehringer Ingelheim, Astellas, GlaxoSmithKline, Janssen, Napp, Mundipharma, Reata, Vifor Fresenius and Tricida.

HJLH has received funding/honoraria and consulting fees to his institution for Steering Committee membership and/or advisory board participation from AstraZeneca (DAPA-CKD study), Abbvie, Travere Pharmaceuticals, Janssen, Gilead, Bayer, Chinook, Merck, CSL Pharma,

consulting fees from Boehringer Ingelheim and Novo Nordisk, honoraria for lectures from AstraZeneca and participated in advisory boards for Mitsubishi Tanabe and Mundipharma.

ACKNOWLEDGMENTS

The authors thank all investigators, trial teams, and patients for their participation in the trial. The authors would also like to acknowledge Parita Sheth and Nicola Truss, inScience Communications, London, UK, for assistance in editing and preparation of figures. This support was funded by AstraZeneca.

FUNDING

This work was supported by AstraZeneca.

The sponsor of the study was involved in the study design, analysis, interpretation of data, writing of the report and the decision to submit the paper for publication.

DATA SHARING

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.

References

1. Blüher M. Obesity: global epidemiology and pathogenesis. *Nature Reviews Endocrinology.* 2019;15(5):288-298.
2. Development OfEC-oa. Organisation for Economic Co-operation and Development - Obesity update 2017 2017; https://www.oecd.org/els/health-systems/Obesity-Update-2017.pdf.
3. Federation WO. World Obesity Federation - Prevalence of Obesity https://www.worldobesity.org/about/about-obesity/prevalence-of-obesity.
4. OECD, Organization WH. *Overweight and obesity.* 2020.
5. Wong MCS, Huang J, Wang J, et al. Global, regional and time-trend prevalence of central obesity: a systematic review and meta-analysis of 13.2 million subjects. *European journal of epidemiology.* 2020;35(7):673-683.
6. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health.* 2009;9(1):88.
7. Aune D, Schlesinger S, Norat T, Riboli E. Body mass index, abdominal fatness, and the risk of sudden cardiac death: a systematic review and dose–response meta-analysis of prospective studies. *European journal of epidemiology.* 2018;33(8):711-722.
8. Pouwels S, Topal B, Knook MT, et al. Interaction of obesity and atrial fibrillation: an overview of pathophysiology and clinical management. *Expert review of cardiovascular therapy.* 2019;17(3):209-223.
9. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: a systematic review and meta-analysis. *Kidney international.* 2008;73(1):19-33.
10. Evangelista LS, Cho WK, Kim Y. Obesity and chronic kidney disease: A population-based study among South Koreans. *PloS one.* 2018;13(2):e0193559.
11. Friedman AN, Miskulin DC, Rosenberg IH, Levey AS. Demographics and trends in overweight and obesity in patients at time of kidney transplantation. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2003;41(2):480-487.
12. Wang Z, Zhang J, Chan S, et al. BMI and its association with death and the initiation of renal replacement therapy (RRT) in a cohort of patients with chronic kidney disease (CKD). *BMC Nephrology.* 2019;20(1):329.
13. Zou CY, Liu XK, Sang YQ, Wang B, Liang J. Effects of SGLT2 inhibitors on cardiovascular outcomes and mortality in type 2 diabetes: A meta-analysis. *Medicine.* 2019;98(49):e18245.
14. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *The New England journal of medicine.* 2020;383(15):1436-1446.
15. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *The New England journal of medicine.* 2015;373(22):2117-2128.
16. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *The New England journal of medicine.* 2019;380(24):2295-2306.

17. Wanner C, Lachin JM, Inzucchi SE, et al. Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. *Circulation.* 2018;137(2):119-129.
18. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *The lancet Diabetes & endocrinology.* 2019;7(8):606-617.
19. Wheeler DC, Stefansson BV, Batiushin M, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2020;35(10):1700-1711.
20. McMurray JJV, Wheeler DC, Stefánsson BV, et al. Effect of Dapagliflozin on Clinical Outcomes in Patients With Chronic Kidney Disease, With and Without Cardiovascular Disease. *Circulation.* 2021;143(5):438-448.
21. Wheeler DC, Stefánsson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *The lancet Diabetes & endocrinology.* 2021;9(1):22-31.
22. Heerspink HJL, Stefansson BV, Chertow GM, et al. Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. *Nephrol Dial Transplant.* 2020;35(2):274-282.
23. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020;383(15):1436-1446.
24. Wilding JP, Woo V, Rohwedder K, Sugg J, Parikh S. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. *Diabetes, obesity & metabolism.* 2014;16(2):124-136.
25. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes care.* 2010;33(10):2217-2224.
26. Bolinder J, Ljunggren Ö, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *The Journal of clinical endocrinology and metabolism.* 2012;97(3):1020-1031.
27. Bolinder J, Ljunggren Ö, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes, obesity & metabolism.* 2014;16(2):159-169.
28. Gelber RP, Kurth T, Kausz AT, et al. Association between body mass index and CKD in apparently healthy men. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2005;46(5):871-880.
29. Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. *Epidemiology (Cambridge, Mass).* 2003;14(4):479-487.
30. Oyama K, Raz I, Cahn A, et al. Obesity and effects of dapagliflozin on cardiovascular and renal outcomes in patients with type 2 diabetes mellitus in the DECLARE-TIMI 58 trial. *European heart journal.* 2021.

31. Preston SH, Vierboom YC, Stokes A. The role of obesity in exceptionally slow US mortality improvement. *Proceedings of the National Academy of Sciences of the United States of America.* 2018;115(5):957-961.
32. Uranga RM, Keller JN. The Complex Interactions Between Obesity, Metabolism and the Brain. *Frontiers in neuroscience.* 2019;13:513.
33. Fuster JJ, Ouchi N, Gokce N, Walsh K. Obesity-Induced Changes in Adipose Tissue Microenvironment and Their Impact on Cardiovascular Disease. *Circulation research.* 2016;118(11):1786-1807.
34. Ricardo AC, Anderson CA, Yang W, et al. Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2015;65(3):412-424.
35. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. *Annals of internal medicine.* 2006;144(1):21-28.
36. Yu Z, Grams ME, Ndumele CE, et al. Association Between Midlife Obesity and Kidney Function Trajectories: The Atherosclerosis Risk in Communities (ARIC) Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2021;77(3):376-385.
37. Ohkuma T, Van Gaal L, Shaw W, et al. Clinical outcomes with canagliflozin according to baseline body mass index: results from post hoc analyses of the CANVAS Program. *Diabetes, obesity & metabolism.* 2020;22(4):530-539.
38. Ji Q, Ji L, Mu Y, et al. Effect of empagliflozin on cardiorenal outcomes and mortality according to body mass index: A subgroup analysis of the EMPA-REG OUTCOME trial with a focus on Asia. *Diabetes, obesity & metabolism.* 2021;23(8):1886-1891.
39. Adamson C, Jhund PS, Docherty KF, et al. Efficacy of dapagliflozin in heart failure with reduced ejection fraction according to body mass index. *European journal of heart failure.* 2021.
40. Sperrin M, Marshall AD, Higgins V, Renehan AG, Buchan IE. Body mass index relates weight to height differently in women and older adults: serial cross-sectional surveys in England (1992-2011). *Journal of public health (Oxford, England).* 2016;38(3):607-613.

Table 1: Baseline characteristics in patients with chronic kidney disease based on BMI categories[a]

	Lean or Ideal (n=888)		Overweight (n=1491)		Grade 1 obesity (n=1136)		Grade 2/3 obesity (n=781)	
	Dapagliflozin n=451	Placebo n=437	Dapagliflozin n=757	Placebo n=734	Dapagliflozin n=579	Placebo n=557	Dapagliflozin n=362	Placebo n=419
Age, years, mean (±SD)	58.6±14.4	59.3±14.6	62.4±11.8	62.6±12.1	62.9±11.0	63.2±10.6	62.7±10.4	61.7±11.0
Female sex, n (%)	173 (38.4)	164 (37.5)	210 (27.7)	218 (29.7)	190 (32.8)	174 (31.2)	136 (37.6)	158 (37.7)
Race[b], n (%)								
Asian	292 (64.7)	302 (69.1)	333 (44.0)	289 (39.4)	98 (16.9)	108 (19.4)	26 (7.2)	19 (4.5)
Black or African American	9 (2.0)	5 (1.1)	24 (3.2)	21 (2.9)	32 (5.5)	28 (5.0)	39 (10.8)	32 (7.6)
White	119 (26.4)	93 (21.3)	332 (43.9)	363 (49.5)	392 (67.7)	362 (65.0)	280 (77.3)	345 (82.3)
Other	31 (6.9)	37 (8.5)	68 (9.0)	61 (8.3)	57 (9.8)	59 (10.6)	17 (4.7)	23 (5.5)
BMI, kg/m^2, mean (±SD)	22.3±1.6	22.1±1.8	27.0±1.4	27.0±1.4	31.7±1.4	31.7±1.4	39.4±4.8	39.4±4.5
Current smoker, n (%)	60 (13.3)	79 (18.1)	117 (15.5)	105 (14.3)	61 (10.5)	74 (13.3)	44 (12.1)	43 (10.3)
Blood pressure, mmHg, mean (±SD)								
Systolic	132.2±17.5	134.1±18.4	135.4±17.1	136.6±17.2	139.8±16.8	138.5±16.6	140.4±17.6	140.9±16.6
Diastolic	76.1±10.9	77.5±10.7	77.0±10.5	76.9±10.4	78.6±10.5	77.6±9.8	78.5±10.8	78.4±10.1
eGFR, mL/min/1.73m^2, mean (±SD)	42.6±12.3	41.7±11.8	43.2±12.0	43.0±12.4	44.2±12.6	43.2±12.7	42.5±12.4	44.0±12.5
Median UACR (Q1–Q3)	975 (472–1986)	949 (461–2069)	949 (494–1854)	875 (448–1789)	987 (462–1913)	994 (514–1824)	901 (414–1882)	950 (505–1946)
UACR >1000 mg/g, n (%)	221 (49.0)	211 (48.3)	366 (48.3)	334 (45.5)	288 (49.7)	278 (49.9)	171 (47.2)	206 (49.2)
HbA1c, %, mean (±SD)	6.6±1.5	6.7±1.8	7.0±1.7	7.0±1.7	7.3±1.8	7.2±1.7	7.6±1.7	7.3±1.7
Type 2 diabetes, n (%)	253 (56.1)	246 (56.3)	483 (63.8)	480 (65.4)	417 (72.0)	399 (71.6)	300 (82.9)	321 (76.6)
Median duration of diabetes, years (Q1–Q3)	11.6 (6.3–19.3)	13.4 (6.8–20.6)	13.2 (7.3–21.0)	14.3 (7.2–21.0)	15.0 (7.1–20.6)	13.6 (7.4–20.2)	15.1 (7.5–20.8)	15.2 (8.7–20.6)
Cardiovascular disease[c], n (%)	131 (29.0)	118 (27.0)	266 (35.1)	242 (33.0)	257 (44.4)	244 (43.8)	158 (43.6)	191 (45.6)
Prior medication, n (%)								
ACE inhibitor/ARB	441 (97.8)	419 (95.9)	746 (98.6)	723 (98.5)	569 (98.3)	541 (97.1)	353 (97.5)	409 (97.6)
Diuretic	121 (26.8)	106 (24.3)	280 (37.0)	275 (37.5)	294 (50.8)	288 (51.7)	232 (64.1)	280 (66.8)
Insulin	116 (25.7)	112 (25.6)	256 (33.8)	231 (31.5)	242 (41.8)	225 (40.4)	199 (55.0)	213 (50.8)

[a]Lean or ideal: <25 kg/m^2; Overweight: 25–<30 kg/m^2; Grade 1 obesity: 30–<35 kg/m^2; Grade 2/3 obesity: ≥35 kg/m^2

[b]As reported by the investigator; 'other' includes Native Hawaiian or other Pacific Islander; American Indian or Alaska Native and Other.

[c]Included participants with a history of peripheral artery disease, angina pectoris, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, heart failure, valvular heart disease, abdominal aorta aneurysm, atrial fibrillation, atrial flutter, ischemic stroke, transient ischemic attack, hemorrhagic stroke, carotid artery stenosis, cardiac pacemaker insertion, vascular stent, coronary artery stenosis, ventricular arrhythmia, implantable cardioverter-defibrillator, non-coronary revascularization or surgical amputation.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio

Table 2: Safety of dapagliflozin in patients with chronic kidney disease based on BMI categories[a]

		Dapagliflozin (n=2146)	Placebo (n=2144)
Discontinuation due to adverse event, n (%)	Lean or ideal	30 (6.7)	37 (8.5)
	Overweight	36 (4.8)	40 (5.5)
	Grade 1 obesity	34 (5.9)	27 (4.8)
	Grade 2/3 obesity	18 (5.0)	19 (4.5)
Any serious adverse event[b], n (%)	Lean or ideal	126 (28.0)	126 (28.8)
	Overweight	197 (26.1)	232 (31.7)
	Grade 1 obesity	181 (31.3)	190 (34.1)
	Grade 2/3 obesity	128 (35.4)	177 (42.2)
Adverse events of interest, n (%)			
Amputation[c]	Lean or ideal	2 (0.4)	6 (1.4)
	Overweight	17 (2.2)	13 (1.8)
	Grade 1 obesity	10 (1.7)	13 (2.3)
	Grade 2/3 obesity	6 (1.7)	5 (1.2)
Any definite or probable diabetic ketoacidosis	Lean or ideal	0	0
	Overweight	0	1 (0.1)
	Grade 1 obesity	0	0
	Grade 2/3 obesity	0	0
Fracture[c]	Lean or ideal	12 (2.7)	15 (3.4)
	Overweight	32 (4.2)	27 (3.7)
	Grade 1 obesity	26 (4.5)	19 (3.4)
	Grade 2/3 obesity	15 (4.1)	8 (1.9)
Renal related adverse event[d]	Lean or ideal	32 (7.1)	38 (8.7)
	Overweight	46 (6.1)	62 (8.5)
	Grade 1 obesity	34 (5.9)	41 (7.4)
	Grade 2/3 obesity	43 (11.9)	45 (10.7)
Major hypoglycemia[e]	Lean or ideal	1 (0.2)	8 (1.8)
	Overweight	4 (0.5)	7 (1.0)
	Grade 1 obesity	6 (1.0)	6 (1.1)
	Grade 2/3 obesity	3 (0.8)	7 (1.7)
Volume depletion[d]	Lean or ideal	26 (5.8)	13 (3.0)
	Overweight	43 (5.7)	30 (4.1)
	Grade 1 obesity	28 (4.8)	23 (4.1)
	Grade 2/3 obesity	30 (8.3)	23 (5.5)

[a]Lean or ideal: <25 kg/m^2, (n: dapagliflozin=450; placebo=437); Overweight: 25–<30 kg/m^2, (n: dapagliflozin=756; placebo=731); Grade 1 obesity: 30–<35 kg/m^2, (n: dapagliflozin=578; placebo=557); Grade 2/3 obesity: ≥35 kg/m^2, (n: dapagliflozin=362; placebo=419).
[b]Includes death.
[c]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma.
[d]Based on pre-defined list of preferred terms.
[e]Adverse event confirmed by the investigator based on 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

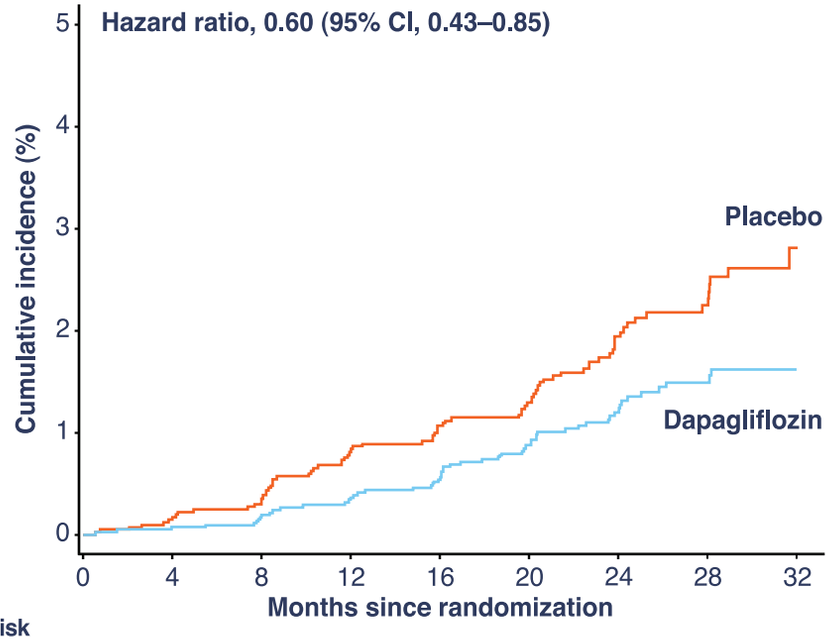
Figure Legends

Figure 1: Primary endpoint in patients with chronic kidney disease based on BMI categories: (A) Lean or ideal <25 kg/m^2, (B) Overweight 25–<30 kg/m^2, (C) Grade 1 obesity 30–<35 kg/m^2, (D) Grade 2/3 obesity ≥35 kg/m^2

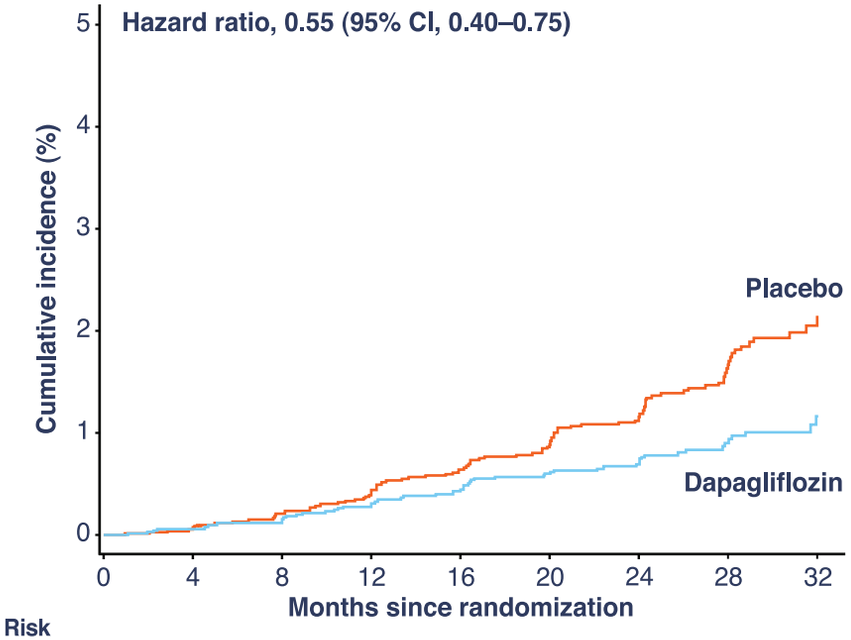
Figure 2: Primary and secondary outcomes in patients with chronic kidney disease based on BMI categories

Lean or ideal: <25 kg/m^2; Overweight: 25–<30 kg/m^2; Grade 1 obesity: 30–<35 kg/m^2; Grade 2/3 obesity: ≥35 kg/m^2

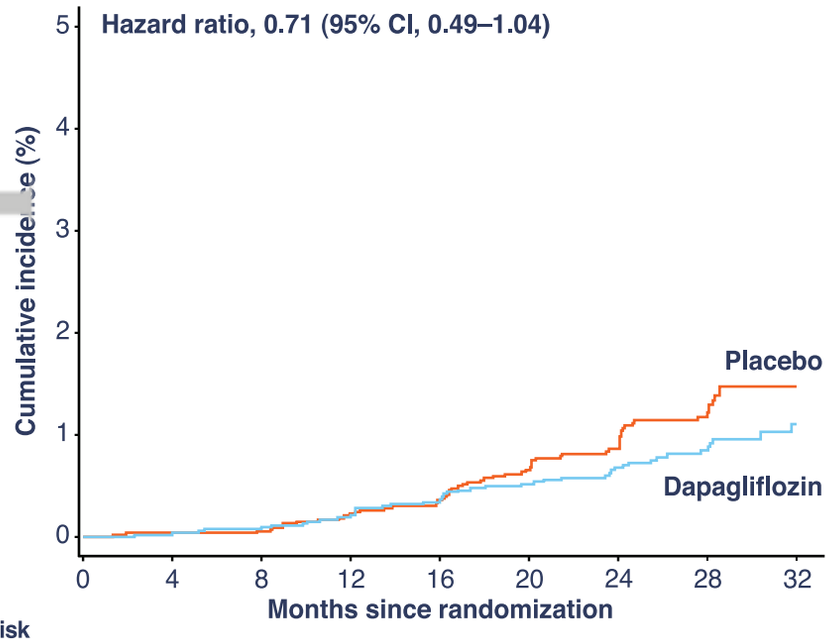
Figure 3: eGFR slopes in patients with chronic kidney disease based on BMI categories: (A) Lean or ideal <25 kg/m^2, (B) Overweight 25–<30 kg/m^2, (C) Grade 1 obesity 30–<35 kg/m^2, (D) Grade 2/3 obesity ≥35 kg/m^2



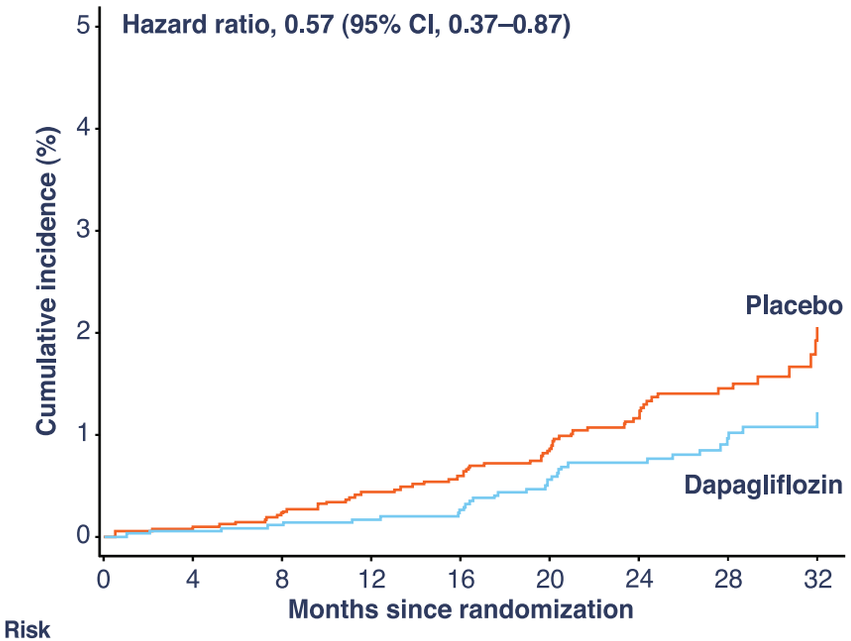
No. at Risk									
Dapagliflozin	451	411	398	386	371	346	243	139	40
Placebo	437	376	362	337	320	300	186	116	33



No. at Risk									
Dapagliflozin	757	677	662	639	616	572	412	282	106
Placebo	734	667	642	617	594	557	412	260	97



No. at Risk									
Dapagliflozin	579	558	547	530	519	479	382	249	97
Placebo	557	534	528	515	499	464	361	228	78



No. at Risk									
Dapagliflozin	362	352	345	340	332	301	249	160	66
Placebo	419	411	399	384	373	339	270	168	61

	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	*P* Value for Interaction	Absolute Risk Difference, % (95% CI)
	n/N		*Events/100 patient-years*				
Primary outcome: eGFR decline ≥50%, ESKD, or kidney or cardiovascular death							
Lean or ideal	57/451	79/437	6.7	10.6	0.60 (0.43, 0.85)	0.72	5.4 (0.7, 10.2)
Overweight	59/757	104/734	4.1	7.4	0.55 (0.40, 0.75)		6.4 (3.2, 9.5)
Grade 1 obesity	48/579	66/557	4.0	5.7	0.71 (0.49, 1.04)		3.6 (0.1, 7.1)
Grade 2/3 obesity	33/362	61/419	4.3	7.0	0.57 (0.37, 0.87)		5.4 (0.9, 9.9)
Secondary outcome: eGFR decline ≥50%, ESKD or kidney death							
Lean or ideal	47/451	70/437	5.6	9.4	0.55 (0.38, 0.80)	0.98	5.6 (1.1, 10.0)
Overweight	44/757	79/734	3.0	5.6	0.54 (0.37, 0.78)		4.9 (2.2, 7.7)
Grade 1 obesity	26/579	49/557	2.1	4.2	0.51 (0.32, 0.83)		4.3 (1.4, 7.2)
Grade 2/3 obesity	25/362	43/419	3.2	5.0	0.60 (0.36, 0.98)		3.4 (-0.6, 7.3)
Secondary outcome: Hospitalization for heart failure or cardiovascular death							
Lean or ideal	16/451	17/437	1.7	2.0	0.88 (0.44, 1.74)	0.21	0.3 (-2.1, 2.8)
Overweight	27/757	36/734	1.7	2.3	0.72 (0.44, 1.19)		1.3 (-0.7, 3.4)
Grade 1 obesity	37/579	39/557	2.9	3.2	0.94 (0.60, 1.48)		0.6 (-2.3, 3.5)
Grade 2/3 obesity	20/362	45/419	2.4	4.9	0.46 (0.27, 0.77)		5.2 (1.4, 9.0)
Secondary outcome: All-cause mortality							
Lean or ideal	21/451	25/437	2.2	2.9	0.78 (0.44, 1.40)	0.27	1.1 (-1.9, 4.0)
Overweight	31/757	60/734	2.0	3.8	0.51 (0.33, 0.79)		4.1 (1.6, 6.5)
Grade 1 obesity	31/579	31/557	2.4	2.5	0.98 (0.60, 1.62)		0.2 (-2.4, 2.9)
Grade 2/3 obesity	18/362	30/419	2.1	3.2	0.65 (0.36, 1.18)		2.2 (-1.1, 5.5)