Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes

DAPA-CKD Trial Committees and Investigators; Heerspink, Hiddo J L; Jongs, Niels; Chertow, Glenn M; Langkilde, Anna Maria; McMurray, John J V; Correa-Rotter, Ricardo; Rossing, Peter; Sjöström, C David; Stefansson, Bergur V

Published in:
Lancet Diabetes & Endocrinology

DOI:
10.1016/S2213-8587(21)00242-4

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Takedown policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial

Hiddo J L Heerspink, Niels Jongs, Glenn M Chertow, Anna Maria Langkilde, John J V McMurray, Ricardo Correa-Rotter, Peter Rossing, C David Sjöström, Bergur V Stefansson, Robert D Toto, David C Wheeler, Tom Greene for the DAPA-CKD Trial Committees and Investigators

Summary
Background Dapagliflozin reduced the risk of kidney failure in patients with chronic kidney disease with and without type 2 diabetes in the DAPA-CKD trial. In this pre-specified analysis, we assessed the effect of dapagliflozin on the rate of change in estimated glomerular filtration rate (eGFR)—ie, the eGFR slope.

Methods DAPA-CKD was a randomised controlled trial that enrolled participants aged 18 years or older, with or without type 2 diabetes, with a urinary albumin-to-creatinine ratio (UACR) of 200–5000 mg/g, and an eGFR of 25–75 mL/min per 1.73 m². Participants were randomly assigned (1:1) to oral dapagliflozin 10 mg once daily or placebo, added to standard care. In this pre-specified analysis, we analysed eGFR slope using mixed-effect models with different slopes from baseline to week 2 (acute eGFR decline), week 2 to end of treatment (chronic eGFR slope), and baseline to end of treatment (total eGFR slope). DAPA-CKD is registered with ClinicalTrials.gov, NCT03036150, and is now complete.

Findings Between Feb 2, 2017, and April 3, 2020, 4304 participants were recruited, of whom 2152 (50%) were assigned to dapagliflozin and 2152 (50%) were assigned to placebo. At baseline, the mean age was 62 years (SD 12), 1425 (33.1%) participants were women, 2906 (67.5%) participants had type 2 diabetes. The median on-treatment follow-up was 2.3 years (IQR 1.8–2.6). From baseline to end of treatment, dapagliflozin compared with placebo slowed eGFR decline by 0.95 mL/min per 1.73 m² per year (95% CI 0.63 to 1.27) in the overall cohort. Between baseline and week 2, dapagliflozin compared with placebo resulted in an acute eGFR decline of 2.61 mL/min per 1.73 m² (2.16 to 3.06) in patients with type 2 diabetes and -0.01 mL/min per 1.73 m² (-1.36 to 2.66) in those without type 2 diabetes. Between week 2 and end of treatment, dapagliflozin compared with placebo reduced the mean rate of eGFR decline by a greater amount in patients with type 2 diabetes (mean difference in chronic eGFR slope 2.26 mL/min per 1.73 m² (2.16 to 3.06) in patients with type 2 diabetes and 2.01 mL/min per 1.73 m² (1.36 to 2.66) in those without type 2 diabetes). Between week 2 and end of treatment, dapagliflozin compared with placebo reduced the mean rate of eGFR decline by a greater amount in patients with type 2 diabetes (mean difference in chronic eGFR slope 2.26 mL/min per 1.73 m² (2.16 to 3.06) in patients with type 2 diabetes and 2.01 mL/min per 1.73 m² (1.36 to 2.66) in those without type 2 diabetes). Between week 2 and end of treatment, dapagliflozin compared with placebo reduced the mean rate of eGFR decline by a greater amount in patients with type 2 diabetes (mean difference in chronic eGFR slope 2.26 mL/min per 1.73 m² (2.16 to 3.06) in patients with type 2 diabetes and 2.01 mL/min per 1.73 m² (1.36 to 2.66) in those without type 2 diabetes). Between week 2 and end of treatment, dapagliflozin compared with placebo reduced the mean rate of eGFR decline by a greater amount in patients with type 2 diabetes (mean difference in chronic eGFR slope 2.26 mL/min per 1.73 m² (2.16 to 3.06) in patients with type 2 diabetes and 2.01 mL/min per 1.73 m² (1.36 to 2.66) in those without type 2 diabetes). Between week 2 and end of treatment, dapagliflozin compared with placebo reduced the mean rate of eGFR decline by a greater amount in patients with type 2 diabetes (mean difference in chronic eGFR slope 2.26 mL/min per 1.73 m² (2.16 to 3.06) in patients with type 2 diabetes and 2.01 mL/min per 1.73 m² (1.36 to 2.66) in those without type 2 diabetes). Between week 2 and end of treatment, dapagliflozin compared with placebo reduced the mean rate of eGFR decline by a greater amount in patients with type 2 diabetes (mean difference in chronic eGFR slope 2.26 mL/min per 1.73 m² (2.16 to 3.06) in patients with type 2 diabetes and 2.01 mL/min per 1.73 m² (1.36 to 2.66) in those without type 2 diabetes). Between week 2 and end of treatment, dapagliflozin compared with placebo reduced the mean rate of eGFR decline by a greater amount in patients with type 2 diabetes (mean difference in chronic eGFR slope 2.26 mL/min per 1.73 m² (2.16 to 3.06) in patients with type 2 diabetes and 2.01 mL/min per 1.73 m² (1.36 to 2.66) in those without type 2 diabetes).

Interpretation Dapagliflozin significantly slowed long-term eGFR decline in patients with chronic kidney disease compared with placebo. The mean difference in eGFR slope between patients treated with dapagliflozin versus placebo was greater in patients with type 2 diabetes, higher HbA₁c, and higher UACR.

Funding AstraZeneca.

Copyright © 2021 Elsevier Ltd. All rights reserved.

Introduction
The DAPA-CKD trial showed that the sodium-glucose co-transporter-2 (SGLT2) inhibitor dapagliflozin reduced the relative risk of kidney failure in a broad population of patients with chronic kidney disease with and without type 2 diabetes. Drug efficacy estimations using a clinical dichotomous outcome, such as kidney failure, are primarily sensitive to the treatment effect in patients who are more likely to reach the outcome. The decline in kidney function over time (glomerular filtration rate [GFR] slope) is on the causal pathway to kidney failure. Emerging evidence supports the estimated GFR (eGFR) slope as a viable surrogate for kidney failure in clinical trials of progression of chronic kidney disease. By contrast with event-driven analyses in which the treatment effect primarily depends on the subgroup with sufficiently fast progression to reach events, drug efficacy estimates based on eGFR slope are more
sensitive to the treatment effect in all patients, including those with slower rates of progression. Thus, estimating the effect of dapagliflozin on eGFR slope provides a comprehensive picture of the drug’s effect in all patients.

However, there are separate challenges to interpreting the effects of SGLT2 inhibitors on eGFR slope. SGLT2 inhibitors induce an acute, reversible reduction in eGFR. Early eGFR decline is reversible after drug discontinuation which indicates that SGLT2 inhibitors exert a favourably haemodynamic effect associated with preservation of kidney function during maintenance treatment. The total eGFR slope over the full follow-up period of a study incorporates both acute and chronic elements; thus, the effects of therapeutic agents on long-term kidney function might be diluted by the acute (ie, early), reversible haemodynamic effect.

Another factor that can complicate interpretation of a treatment effect on GFR slope is the possibility that the effect of some treatments on the slope might be increased if patients with faster underlying rates of disease progression. If the effects of dapagliflozin were increased in patients with faster disease progression, we would expect more pronounced effects in patients with more rapid progression before trial participation (ie, those with higher baseline levels of albuminuria or systolic blood pressure, or both). Greater treatment effects on eGFR slope for patients with faster disease progression than for those with slower disease progression have been observed with some interventions used in patients with chronic kidney disease such as dietary protein intake and angiotensin receptor blockers.

In this prespecified analysis of the DAPA-CKD trial, we performed an in-depth assessment of the effect of dapagliflozin on eGFR slope by establishing the effect of dapagliflozin on changes in eGFR during the acute phase (ie, the first 2 weeks of treatment) and during the subsequent maintenance phase after 2 weeks. In the full cohort, dapagliflozin compared with placebo reduced the rate of eGFR decline from baseline to end of treatment by 0.95 mL/min per 1.73 m². This effect was more pronounced in patients with than in those without type 2 diabetes. The eGFR slope was steeper in patients with higher baseline HbA₁c, and urinary albumin-to-creatinine ratio (UACR); the effect of dapagliflozin on eGFR slope was also more pronounced in patients with higher baseline HbA₁c, and UACR. The effect of dapagliflozin on eGFR decline was consistent irrespective of baseline eGFR. This pattern suggests that dapagliflozin exerted a slightly greater treatment effect on eGFR slope in faster progressors than in slower progressors.

Implications of all the available evidence
Although benefits of dapagliflozin on kidney outcomes in slower progressors would require a longer treatment duration, the benefit of dapagliflozin on hospitalisation due to heart failure or cardiovascular death and mortality were observed during the trial, supporting the use of dapagliflozin in slow and fast progressors.

Methods
Study design and participants
DAPA-CKD was a double-blind, randomised, placebo-controlled, trial conducted at 386 sites in 21 countries (Argentina, Brazil, Canada, China, Denmark, Germany, Hungary, India, Japan, Mexico, Peru, Philippines, Poland, Russia, South Korea, Spain, Sweden, UK, Ukraine, USA, and Vietnam). The study design and primary results have been published previously. Briefly, eligible participants were aged 18 years or older with a diagnosis of chronic kidney disease, defined as an eGFR of 25–75 mL/min per 1.73 m² and a urinary albumin-to-creatinine ratio (UACR) of 200–5000 mg/g. Patients with and without type 2 diabetes were eligible for participation. Patients with type 1 diabetes, lupus nephritis, polycystic kidney disease, or anti-neutrophil cytoplasmic antibody (ANCA)-associated
vasculitis and those receiving immunotherapy for primary or secondary kidney disease within 6 months before enrolment were excluded. All participants were receiving treatment with a stable maximum labelled or maximum tolerated dose of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for 4 weeks or longer before random assignment to treatment, unless they had a documented intolerance to these agents.

The trial protocol was approved by a central or local ethics committee at each trial site. All participants provided written informed consent before any trial-specific procedure.

**Randomisation and masking**

Eligible participants were randomly assigned (1:1) to either dapagliflozin or matched placebo. Randomisation was done via an interactive voice-response or web-response system, stratified by diagnosis of type 2 diabetes and UACR (≤1000 mg/g or >1000 mg/g). Participants and all trial personnel were masked to group assignment.

**Procedures**

Participants assigned to dapagliflozin were given 10 mg orally once daily, in addition to standard care. Participants in the placebo group received matched placebo in addition to standard care. Study treatment was to be continued until the occurrence of diabetic ketoacidosis, pregnancy, or study completion. After randomisation, we performed in-person study visits after 2 weeks; after 2, 4, and 8 months; and at 4 month intervals thereafter. At each follow-up visit, we recorded vital signs and collected blood and urine samples for laboratory assessment, and information on potential study endpoints, adverse events, concomitant therapies, and study drug adherence.

**Outcomes**

The primary outcome of the DAPA-CKD trial was the first occurrence of any of the following: a decline in eGFR of at least 50% (confirmed by a second serum creatinine measurement ≥28 days), end-stage kidney disease, or death from a kidney or cardiovascular cause. The primary prespecified outcome of the current analysis was the rate of change in eGFR from baseline to the end of treatment. Serum creatinine was measured at baseline and at each follow-up visit during the trial. We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and incorporated results from the equation as originally defined, including a term for investigator-reported race (Black vs non-Black). We also assessed the acute change in eGFR, which was defined as the change from baseline to the first on-treatment study visit 2 weeks after randomisation. The rate of change in eGFR during the maintenance phase of the trial (ie, chronic slope) was defined as being from 2 weeks until the end of treatment.

Secondary outcomes from the original study that were prespecified for analysis here by acute, chronic and total eGFR slope period were time to: the composite kidney endpoint of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from a kidney cause; a composite cardiovascular endpoint defined as hospitalisation for heart failure or cardiovascular death; and death from any cause.

**Statistical analysis**

We summarised baseline characteristics by baseline eGFR (<45 vs ≥45 mL/min per 1.73 m²). We report continuous variables as mean (SD) or as median (IQR). We report categorical variables as n (%).

We analysed 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 14 days) with correlated random intercepts and slopes for each participant over time (ie, unstructured). eGFR measurements after treatment discontinuation were excluded from slope analyses to avoid biasing slope estimates from haemodynamic changes in eGFR after discontinuation of dapagliflozin. For the overall population, the model included fixed effects for treatment, the randomisation stratification factors (diabetes status and UACR), a two-slope linear spline in follow-up time as a continuous variable, and the interactions of treatment with the two-slope linear spline terms.

We also estimated the effect of dapagliflozin compared with placebo on the rate of eGFR decline in prespecified subgroups defined by type 2 diabetes status, underlying chronic kidney disease aetiology, age, sex, baseline eGFR, UACR, HbA₁c, and systolic blood pressure and in post-hoc subgroups defined by history of heart failure, and diuretic use. For each subgroup factor, we added to the model all possible two-way and three-way interactions between the randomised treatment, subgroup factor, and two-slope linear spline in follow-up time to account for differences between subgroups in the effect of the treatment on the mean eGFR trajectories. We avoided including redundant terms for the randomisation strata and subgroup factors when the two coincided. We calculated the acute slope as the mean change in eGFR from baseline to week 2 and the chronic eGFR slope as the mean rate of change after week 2 until last on-treatment visit per year. We defined the total slope as the weighted combination of the acute and chronic slopes, which reflects the mean rate of eGFR decline from randomisation until end of study drug treatment, with a median on treatment period of 2·3 years.

To visualise trajectories in mean eGFR over time without assuming a linear decline, we fitted a separate set of longitudinal models in which follow-up time was represented by visit as a categorical variable. These models included fixed effects for treatment, visit (as a categorical factor), the treatment-by-visit interaction, and baseline eGFR (as a continuous factor). To assess the effect of dapagliflozin relative to placebo on eGFR slope in the prespecified subgroups, we added a categorical three-way
interaction term between the subgroup factor, study visit, and treatment assignment. We used an unstructured variance-covariance matrix—i.e., a data-dependent model that allows for a general pattern of SDs and correlations for the eGFR measurements at different timepoints. In an additional prespecified analysis, we examined the effect of treatment on eGFR according to continuous baseline UACR, eGFR, and Hba$_A$% by replacing the categorical subgroup factors in the interaction terms with the cubic splines (with three percentile-based knots) in these continuous baseline markers.

We graphically displayed estimates of the full slope distribution in each randomised treatment group by providing kernel density curves for the best linear unbiased predictions for the acute and chronic eGFR slope for the individual study participants under the two-slope mixed-effects model. Additionally, we performed within-individual regression to obtain least square estimates of the chronic eGFR slopes for participants with at least four measurements after randomisation. We compared the SDs of the estimated eGFR slopes between participants randomly assigned to dapagliflozin and placebo with Levene’s test. We did these comparisons in the overall cohort and in patients with and without type 2 diabetes separately.

We analysed the effect of dapagliflozin on systolic and diastolic blood pressure by fitting repeated measures models using restricted maximum likelihood. These models included categorical fixed effects for treatment, visit, the treatment-by-visit interactions, continuous fixed-effect covariates for baseline systolic or diastolic blood pressure, and the interaction of baseline systolic or diastolic blood pressure with visit. To assess the effect of dapagliflozin relative to placebo on blood pressure, we used the average coefficient of treatment to estimate the effect of dapagliflozin on the mean systolic and diastolic blood pressure across follow-up assessments. We used Pearson’s correlation to assess the association between changes from baseline in systolic blood pressure and eGFR at week 2.

A sensitivity analysis was performed using log-transformed eGFR values to assess distributions and shifts in eGFR during dapagliflozin or placebo treatment. Finally, we compared the number of clinical endpoints in post-hoc defined subgroups defined by the total eGFR slope (decline in eGFR of >5 mL/min per 1·73 m$^2$ per year [fast progressors], >1 to 5 mL/min per 1·73 m$^2$ per year [moderate progressors], and ≤1 mL/min per 1·73 m$^2$ per year [slow progressors]) as described in the methods section.

Results

Between Feb 2, 2017, and April 3, 2020, 4304 participants were enrolled and randomly assigned to dapagliflozin 10 mg once daily (2152 [50%]) or placebo (2152 [50%]). The median on-treatment follow-up was 2·3 years (IQR 1·8–2·6), and the trial was stopped (April 3, 2020) because the primary endpoint was met following a regular review meeting of the Independent Data Monitoring Committee. At baseline, the mean age was 62 years (SD 12), 1425 (33·1%) participants were women, 2906 (67·5%) participants had type 2 diabetes mellitus, and 2152 (50%) participants had type 2 diabetes mellitus. The median on-treatment follow-up was 2·3 years (IQR 1·8–2·6), and the trial was stopped (April 3, 2020) because the primary endpoint was met following a regular review meeting of the Independent Data Monitoring Committee. At baseline, the mean age was 62 years (SD 12), 1425 (33·1%) participants were women, 2906 (67·5%) participants had type 2 diabetes mellitus, mean eGFR was 43 mL/min per 1·73 m$^2$ (SD 12), and the median UACR was 949 mg/g (IQR 477–1885; 107 mg/mmol [53·9–213]). There were 2522 participants (58·6%) with a baseline eGFR of less than 45 mL/min
per 1·73 m² and 1782 (41·4%) with a baseline eGFR of
45 mL/min per 1·73 m² or higher. Participants with a
baseline eGFR of less than 45 mL/min per 1·73 m²
were less likely to have type 2 diabetes, had a lower
HbA₁c and haemoglobin, and higher UACR and
potassium, and were more likely to receive diuretics
than those with an eGFR of 45 mL/min per 1·73 m² or
higher (table 1).

The mean eGFR slope from baseline to 2·3 years
(end of treatment) in the dapagliflozin group was
−2·88 mL/min per 1·73 m² per year (SE 0·11) and in the
placebo group was −3·83 mL/min per 1·73 m² per year
(SE 0·12), resulting in a between-group difference of
0·95 mL/min per 1·73 m² per year (95% CI 0·63 to 1·27),
or a 24·8% slower decline in the dapagliflozin group
than with placebo. In patients with and without type 2
diabetes, dapagliflozin led to a significant mean acute
decline in eGFR at week 2, although this early decline
was slightly attenuated in patients without type 2 diabetes
(figure 1, 2). The difference between dapagliflozin and
placebo in the acute eGFR decline was 2·61 mL/min
per 1·73 m² (95% CI 2·16 to 3·06) in patients with type 2
diabetes and 2·01 mL/min per 1·73 m² (1·36 to 2·66) in
patients without type 2 diabetes (data not otherwise
shown). Thereafter, eGFR decreased in the placebo group
by 3·84 mL/min per 1·73 m² per year (SD 0·14) in
patients with type 2 diabetes and by 3·18 mL/min per 1·73 m²
(1·36 to 2·66) in patients without type 2 diabetes. In the dapagliflozin group, eGFR decreased by
1·58 mL/min per 1·73 m² per year (SD 0·14) in patients
with diabetes and by 1·90 mL/min per 1·73 m² per year
(SD 0·20) in those without diabetes (figure 1, 2).

Figure 1: Change from baseline in eGFR in the dapagliflozin and placebo groups in patients with type 2 diabetes (A) and without type 2 diabetes (B)
Data are least square mean change, with error bars indicating SEs. eGFR=estimated glomerular filtration rate.
Dapagliflozin compared with placebo led to a slower decrease in the chronic eGFR slope with a larger effect in patients with type 2 diabetes (difference between dapagliflozin and placebo 2·26 mL/min per 1·73 m² per year [95% CI 1·88 to 2·64]) versus patients without type 2 diabetes (1·29 mL/min per 1·73 m² per year [0·73 to 1·85]; pinteraction=0·0049; figure 2A). Compared with placebo, dapagliflozin attenuated the loss of kidney function (the combined effect of the acute eGFR change and change during the chronic phase of the trial—ie, total slope), by 1·18 mL/min per 1·73 m² per year (95% CI 0·46 to 1·90; p=0·005) in patients with type 2 diabetes (29·2% slower decline than with placebo) and by 0·79 to 1·56; p<0·0001) in patients without type 2 diabetes (12·6% slower decline than with placebo; p interaction=0·040; figure 2B). When we assessed the effect of dapagliflozin on total and chronic eGFR slopes by subcategories of baseline HbA1c, we observed that in the placebo group eGFR decline was more pronounced among patients with higher baseline HbA1c (figure 2B). Moreover, the effect of dapagliflozin on eGFR decline (assessed by the total and chronic eGFR slopes) was more pronounced in higher HbA1c subgroups (pinteraction=0·028 for total slope and pinteraction=0·070 for chronic slope). An additional prespecified analysis incorporating baseline HbA1c as a continuous variable showed a significantly more pronounced effect of dapagliflozin on total eGFR slope at higher baseline HbA1c than at lower baseline HbA1c (figure 3A).

Exploring the effect of dapagliflozin by the underlying cause of chronic kidney disease, treatment with dapagliflozin consistently led to greater mean acute eGFR declines than did placebo across different chronic kidney disease aetiologies (figure 2). Dapagliflozin attenuated

### Table

<table>
<thead>
<tr>
<th>A</th>
<th>Acute effect (2 weeks)</th>
<th>Chronic slope (per year)</th>
<th>Difference (95% CI)</th>
<th>Pinteraction</th>
<th>Percentage change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>eGFR decline, mL/min per 1·73 m² per 2 weeks</strong></td>
<td><strong>eGFR decline, mL/min per 1·73 m² per year</strong></td>
<td><strong>eGFR decline, mL/min per 1·73 m² per year</strong></td>
<td><strong>eGFR decline, mL/min per 1·73 m² per year</strong></td>
<td><strong>eGFR decline, mL/min per 1·73 m² per year</strong></td>
<td><strong>eGFR decline, mL/min per 1·73 m² per year</strong></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>-2·7 (0·2)</td>
<td>-0·6 (0·2)</td>
<td>-1·98 (0·15)</td>
<td>-3·91 (0·15)</td>
<td>0·876</td>
</tr>
<tr>
<td>&gt;65</td>
<td>-3·5 (0·2)</td>
<td>-0·7 (0·2)</td>
<td>-2·07 (0·17)</td>
<td>-3·24 (0·18)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·320</td>
</tr>
<tr>
<td>Male</td>
<td>-3·2 (0·2)</td>
<td>-0·5 (0·2)</td>
<td>-1·66 (0·14)</td>
<td>-3·72 (0·14)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>-2·9 (0·2)</td>
<td>-0·9 (0·2)</td>
<td>-1·72 (0·20)</td>
<td>-3·45 (0·20)</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·005</td>
</tr>
<tr>
<td>Yes</td>
<td>-3·2 (0·2)</td>
<td>-0·6 (0·2)</td>
<td>-1·58 (0·14)</td>
<td>-3·84 (0·14)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>-2·8 (0·2)</td>
<td>-0·8 (0·2)</td>
<td>-1·90 (0·20)</td>
<td>-3·18 (0·20)</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·070</td>
</tr>
<tr>
<td>Normoglycaemia</td>
<td>-2·6 (0·3)</td>
<td>-0·6 (0·3)</td>
<td>-2·06 (0·28)</td>
<td>-3·14 (0·28)</td>
<td></td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>-3·0 (0·3)</td>
<td>-0·9 (0·3)</td>
<td>-1·72 (0·29)</td>
<td>-3·29 (0·29)</td>
<td></td>
</tr>
<tr>
<td>≥8% 5%</td>
<td>-3·6 (0·2)</td>
<td>-0·8 (0·2)</td>
<td>-1·46 (0·16)</td>
<td>-3·50 (0·16)</td>
<td></td>
</tr>
<tr>
<td>&gt;8% 5%</td>
<td>-1·9 (0·3)</td>
<td>0·0 (0·3)</td>
<td>-1·94 (0·26)</td>
<td>-4·86 (0·27)</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease aetiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·810</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>-3·2 (0·2)</td>
<td>-0·6 (0·2)</td>
<td>-1·62 (0·14)</td>
<td>-3·97 (0·15)</td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>-3·1 (0·3)</td>
<td>-0·7 (0·3)</td>
<td>-2·31 (0·29)</td>
<td>-3·75 (0·28)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>-3·1 (0·3)</td>
<td>-0·7 (0·3)</td>
<td>-1·50 (0·29)</td>
<td>-3·12 (0·27)</td>
<td></td>
</tr>
<tr>
<td>Other or unknown</td>
<td>-2·3 (0·4)</td>
<td>-0·9 (0·4)</td>
<td>-1·32 (0·37)</td>
<td>-2·22 (0·38)</td>
<td></td>
</tr>
<tr>
<td>UACR, mg/g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·016</td>
</tr>
<tr>
<td>&lt;500</td>
<td>-2·7 (0·3)</td>
<td>0·2 (0·3)</td>
<td>-0·62 (0·20)</td>
<td>-1·97 (0·21)</td>
<td></td>
</tr>
<tr>
<td>500 to &lt;1000</td>
<td>-2·7 (0·3)</td>
<td>-0·3 (0·3)</td>
<td>-0·56 (0·22)</td>
<td>-2·71 (0·23)</td>
<td></td>
</tr>
<tr>
<td>1000 to &lt;2000</td>
<td>-3·4 (0·3)</td>
<td>-0·6 (0·3)</td>
<td>-2·00 (0·21)</td>
<td>-3·98 (0·21)</td>
<td></td>
</tr>
<tr>
<td>≥2000</td>
<td>-3·5 (0·3)</td>
<td>-2·0 (0·3)</td>
<td>-3·86 (0·23)</td>
<td>-6·50 (0·24)</td>
<td></td>
</tr>
<tr>
<td>eGFR, mL/min/1·73 m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·343</td>
</tr>
<tr>
<td>&lt;45</td>
<td>-2·6 (0·2)</td>
<td>-0·4 (0·2)</td>
<td>-1·48 (0·15)</td>
<td>-3·22 (0·15)</td>
<td></td>
</tr>
<tr>
<td>≥45</td>
<td>-3·7 (0·2)</td>
<td>-1·0 (0·2)</td>
<td>-1·99 (0·17)</td>
<td>-4·13 (0·17)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·343</td>
</tr>
<tr>
<td>&lt;130</td>
<td>-2·7 (0·2)</td>
<td>-0·2 (0·2)</td>
<td>-1·28 (0·19)</td>
<td>-3·43 (0·19)</td>
<td></td>
</tr>
<tr>
<td>≥130</td>
<td>-3·2 (0·2)</td>
<td>-0·9 (0·2)</td>
<td>-1·91 (0·14)</td>
<td>-3·74 (0·14)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>-3·1 (0·1)</td>
<td>-0·6 (0·1)</td>
<td>-1·68 (0·11)</td>
<td>-3·61 (0·11)</td>
<td></td>
</tr>
</tbody>
</table>

(Figure 2 continues on next page)
the decline in eGFR (assessed by total or chronic slope) irrespective of the underlying cause of chronic kidney disease, although the effect was relatively larger in patients with diabetic nephropathy than in those with other causes of chronic kidney disease (figure 2).

A similar pattern of changes in eGFR during the acute and chronic phases of the trial was observed in subgroups by baseline age, sex, eGFR, and systolic blood pressure, (figure 2), and in the post-hoc subgroups defined by history of heart failure and diuretic use (data not shown).

In each of these subgroups, dapagliflozin led to an acute decline in eGFR during the first 2 weeks followed by relative preservation of kidney function during the chronic phase with no evidence that the effect varied between subgroups (figure 2A). A notable exception were subgroups defined by baseline UACR. Treatment with dapagliflozin resulted in an acute decline in eGFR in each category of baseline UACR (figure 2). The rate of chronic eGFR decline during placebo treatment was progressively more rapid in higher UACR subgroups. Dapagliflozin attenuated the chronic eGFR slope with a significantly larger effect in the two highest UACR subgroups than in the two lowest UACR subgroups (across all UACR subgroups pinteraction=0·016). In our analysis of the total slope, the point estimates favoured dapagliflozin over placebo in each UACR subgroup, although the benefit was progressively larger in higher UACR subgroups (pinteraction<0·0001; figure 2B). Similar findings were observed when the effect of dapagliflozin was modelled across the spectrum of baseline UACR values (figure 3B).
We compared the distribution of eGFR changes in patients assigned to dapagliflozin and placebo during the acute and chronic phases. During the first 2 weeks, the dapagliflozin group showed a uniformly larger reduction in eGFR than did the placebo group, with a shift in eGFR changes towards the negative without a change in the variability (SDs of acute eGFR slopes was 3·0 mL/min per 1·73 m² per 2 weeks in the dapagliflozin group vs 3·1 mL/min per 1·73 m² per 2 weeks in the placebo group; ratio 0·962; figure 4A). During the chronic phase, eGFR declined more slowly in the dapagliflozin group than in the placebo group, and the variability of eGFR decline was somewhat reduced, as indicated by the contraction of the lowest end of the distribution of eGFR decline (SDs of the slopes determined by best linear unbiased predictions in the dapagliflozin and placebo groups 7·2 mL/min per 1·73 m² from week 2 until the end of treatment in the dapagliflozin group vs 7·6 mL/min per 1·73 m² from week 2 until end of treatment in the placebo group; ratio 0·938; figure 4B). Calculation of the chronic eGFR slopes using
within-individual linear regression provided similar results (SDs of chronic eGFR slopes were 13·9 mL/min per 1·73 m² from week 2 until end of treatment in the dapagliflozin group and 16·0 mL/min per 1·73 m² from week 2 until end of treatment in the placebo group; ratio 0·866; Levene’s test p=0·015; appendix p 2). These patterns of shifts in eGFR trajectory in the overall population were, however, different in patients with and without type 2 diabetes. In patients with type 2 diabetes, a uniform shift in the distribution of the chronic eGFR slope was observed with no indication that the SD was different between the dapagliflozin and placebo groups (15·3 mL/min per 1·73 m² from week 2 until end of treatment vs 18·4 mL/min per 1·73 m² from week 2 until end of treatment; ratio 1·04; Levene’s test p=0·53; appendix p 3). By contrast, in patients without type 2 diabetes, mean eGFR decline and the variability in chronic eGFR decline was reduced, as indicated by a contraction of the lowest end of the distribution suggesting a somewhat larger effect of dapagliflozin in fast progressors (SD 9·9 mL/min per 1·73 m² from week 2 until end of treatment in the dapagliflozin group vs 12·5 mL/min per 1·73 m² from week 2 until end of treatment in the placebo group; ratio 0·78; Levene’s test p<0·0001; appendix p 3). Results from the sensitivity analyses using log-transformed eGFR values provided similar results (data not shown).

Compared with placebo, dapagliflozin reduced systolic blood pressure by 2·9 mm Hg (95% CI 2·3–3·6; p<0·0001) and diastolic blood pressure by 1·0 mm Hg (0·6–1·4; p<0·0001) over the course of the study period (appendix p 4). As described in our companion paper, this effect of dapagliflozin did not differ between patients with and without type 2 diabetes.11 A weak correlation was observed between changes in systolic blood pressure and eGFR at week 2 in the dapagliflozin group (Pearson correlation 0·126) and placebo group (Pearson correlation 0·141; data not otherwise shown).

Of all 385 composite kidney endpoint events, 368 (96%) occurred in patients with eGFR decline of more than 5 mL/min per 1·73 m² per year (ie, fast progressors; table 2). The occurrence of the composite hospitalisation due to heart failure or cardiovascular death and all-cause mortality endpoints was more equally distributed between subgroups of patients with or without fast progression (table 2).

**Discussion**

We found dapagliflozin to reduce the risk of kidney failure in patients with chronic kidney disease with and without type 2 diabetes.1 In this prespecified analysis, we provide additional insight into the effects of dapagliflozin on eGFR slope. We found that dapagliflozin caused an acute decline in eGFR but slowed the subsequent rate of eGFR decline in patients with and without type 2 diabetes, with more pronounced attenuation of chronic decline in eGFR in patients with type 2 diabetes. We also found that the effect of dapagliflozin on the rate of eGFR decline over time was slightly larger compared with the effect of placebo in patients with more extensive albuminuria or poorer glycaemic control.

The DAPA-CKD trial showed that dapagliflozin reduced the risk of kidney failure in patients with chronic kidney disease with consistent effects in patients with (hazard ratio [HR] 0·64 [95% CI 0·52–0·79]) and without (0·50 [0·35–0·72]) type 2 diabetes.12 Because the rate of change in eGFR is strongly associated with kidney failure, our finding that the effects of dapagliflozin on the rate of eGFR decline varied significantly among patients with and without type 2 diabetes is surprising. One possible explanation for this dichotomy is that treatment effects in analyses of time to kidney failure are based on
Number of patients in each total eGFR slope change category and secondary endpoint events

Table 2: Number of patients in each total eGFR slope change category and secondary endpoint events

<table>
<thead>
<tr>
<th>Composite kidney endpoint (sustained eGFR decline of ≥50%, end-stage kidney disease, or death from kidney causes)</th>
<th>Dapagliflozin group (n=2152)</th>
<th>Placebo group (n=2152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decline of ≥5 mL/min per 1·73 m² per year</td>
<td>99/871 (11·4%)</td>
<td>162/940 (17·2%)</td>
</tr>
<tr>
<td>Decline of &gt;1 to 5 mL/min per 1·73 m² per year</td>
<td>3/242 (1·2%)</td>
<td>8/225 (3·6%)</td>
</tr>
<tr>
<td>Decline of ≤1 mL/min per 1·73 m² per year</td>
<td>1/342 (0·3%)</td>
<td>3/286 (1·0%)</td>
</tr>
<tr>
<td>Without type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decline of ≥5 mL/min per 1·73 m² per year</td>
<td>37/418 (8·9%)</td>
<td>70/441 (15·9%)</td>
</tr>
<tr>
<td>Decline of &gt;1 to 5 mL/min per 1·73 m² per year</td>
<td>2/146 (0·7%)</td>
<td>0/123</td>
</tr>
<tr>
<td>Decline of ≤1 mL/min per 1·73 m² per year</td>
<td>2/133 (0·8%)</td>
<td>0/137</td>
</tr>
<tr>
<td>Hospitalisation due to heart failure or cardiovascular death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decline of ≥5 mL/min per 1·73 m² per year</td>
<td>59/871 (6·8%)</td>
<td>87/940 (9·3%)</td>
</tr>
<tr>
<td>Decline of &gt;1 to 5 mL/min per 1·73 m² per year</td>
<td>11/242 (4·5%)</td>
<td>14/225 (6·2%)</td>
</tr>
<tr>
<td>Decline of ≤1 mL/min per 1·73 m² per year</td>
<td>15/342 (4·4%)</td>
<td>18/286 (6·3%)</td>
</tr>
<tr>
<td>Without type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decline of ≥5 mL/min per 1·73 m² per year</td>
<td>12/418 (2·9%)</td>
<td>13/441 (2·9%)</td>
</tr>
<tr>
<td>Decline of &gt;1 to 5 mL/min per 1·73 m² per year</td>
<td>1/146 (0·7%)</td>
<td>3/123 (2·4%)</td>
</tr>
<tr>
<td>Decline of ≤1 mL/min per 1·73 m² per year</td>
<td>2/133 (1·5%)</td>
<td>3/137 (2·2%)</td>
</tr>
<tr>
<td>All-cause death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decline of ≥5 mL/min per 1·73 m² per year</td>
<td>59/871 (6·8%)</td>
<td>82/940 (8·7%)</td>
</tr>
<tr>
<td>Decline of &gt;1 to 5 mL/min per 1·73 m² per year</td>
<td>11/242 (4·5%)</td>
<td>16/225 (7·1%)</td>
</tr>
<tr>
<td>Decline of ≤1 mL/min per 1·73 m² per year</td>
<td>14/342 (4·1%)</td>
<td>15/286 (5·2%)</td>
</tr>
<tr>
<td>Without type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decline of ≥5 mL/min per 1·73 m² per year</td>
<td>13/418 (3·1%)</td>
<td>27/441 (6·1%)</td>
</tr>
<tr>
<td>Decline of &gt;1 to 5 mL/min per 1·73 m² per year</td>
<td>1/146 (0·7%)</td>
<td>4/123 (3·3%)</td>
</tr>
<tr>
<td>Decline of ≤1 mL/min per 1·73 m² per year</td>
<td>3/133 (2·3%)</td>
<td>2/137 (1·5%)</td>
</tr>
</tbody>
</table>

Data are number of events/number of participants with % in parentheses. In total, 385 composite kidney endpoint events, 238 heart failure hospitalisation or cardiovascular death events, and 247 all-cause death events occurred during the trial. eGFR=estimated glomerular filtration rate.

Comparisons of the rates at which patients reach the kidney failure endpoint in the dapagliflozin and placebo groups, and thus depend primarily on faster progressors who have the potential to reach the endpoint during the study’s follow-up period. By contrast, the estimated treatment effects in our analyses of mean slope are averaged across all patients randomly assigned to treatment, including fast and slow progressors.1 Dapagliflozin seems to exert a slightly greater treatment effect in faster progressors than in slower progressors, as illustrated by a significant contraction of the lowest end of the distribution of eGFR slopes. This pattern appears to have been more pronounced in patients without type 2 diabetes than those with type 2 diabetes. Thus, the averaged eGFR slope over all patients might have been diluted by smaller effects in slower progressors to a greater extent in patients without type 2 diabetes than in those with type 2 diabetes. Differences in the underlying pathophysiology or drug mechanism of action between patients with and without type 2 diabetes might also explain the different treatment effects on eGFR slope, although such differences would also likely lead to different treatment effects on clinical outcomes.

Not only did dapagliflozin reduce the risk of kidney failure in patients with chronic kidney disease but it also reduced the risk of hospitalisation due to heart failure and cardiovascular death as well as all-cause mortality, with consistent benefits in patients with and without type 2 diabetes.1 Importantly, these benefits of dapagliflozin on kidney failure, heart failure, and mortality were also consistent across a broad range of other subgroups including patients with different aetiologies of chronic kidney disease.12,13 In the current study, we found that patients benefit from treatment with dapagliflozin, even if their absolute risk of kidney failure within the relatively short timeframe of the trial is relatively small. In other words, while the effect of dapagliflozin on attenuating eGFR decline was more pronounced in patients with higher albuminuria and poorer glycaemic control, who had a more rapid decline in kidney function, those who progress more slowly also derive cardiovascular and other benefits including favourable effects on risk markers of chronic kidney disease progression.14,15 The relatively short timeframe of the study precludes assessment of kidney benefits over an extended period and this hypothesis will require further analysis in future studies.

Previous trials have assessed effects of SGLT2 inhibitors on the rate of eGFR decline. The effect of canagliflozin in reducing the risk of kidney outcomes in the CREDENCE trial was similar across the spectrum of baseline HbA1c values including patients with near normal glycaemic control (HbA1c between 6·5% [48 mmol/mol] and 7·0% [53 mmol/mol]).16 However, similar to our findings with dapagliflozin, the effect of canagliflozin in attenuating eGFR decline was significantly less in patients with near normal glycaemia than in patients with higher HbA1c values.17 Furthermore, the effect of dapagliflozin on the rate of kidney function decline in patients with heart failure and reduced ejection fraction was also larger in patients with type 2 diabetes than in those without type 2 diabetes.18 Finally, an analysis from the EMPAREG-OUTCOME trial reported the effects of empagliflozin on eGFR trajectories in patients with type 2 diabetes and established cardiovascular disease.19 Similar to our findings in patients with type 2 diabetes, the EMPAREG-OUTCOME trial found no clear evidence that empagliflozin exerted a proportional treatment effect, although the effect of empagliflozin on the annual rate of decline in eGFR was larger in patients with more extensive albuminuria, like in our study.

The acute decline in eGFR was relatively larger in patients with type 2 diabetes than in those without type 2 diabetes suggesting a larger reduction in intraglomerular pressure. A modelling and simulation study comparing patients with and without type 2 diabetes with impaired
kidney function found attenuated diuretic effects and an attenuated reduction in intraglomerular pressure in patients without type 2 diabetes compared with those with type 2 diabetes resulting in less albuminuria reduction. This finding is in accord with our companion paper describing the effect of dapagliflozin on albuminuria in the DAPA-CKD trial. In those analyses, we showed that the acute change in eGFR correlated directly with changes in albuminuria. Moreover, we found an attenuation of the albuminuria lowering effect of dapagliflozin in patients without type 2 diabetes.

We recognise limitations to our study, of which the first is the absence of eGFR data after dapagliflozin discontinuation to assess the reversibility of the acute decline in eGFR, as shown in previous trials. Additionally, early termination of the trial resulted in a relatively short follow-up. We also did not adjust for multiple comparisons. Finally, our findings apply to patients with chronic kidney disease and substantial albuminuria and cannot be generalised to patients with chronic kidney disease without albuminuria, although the concordance of the results with eGFR slope analyses from the DECLARE trial, in which the majority of participants had little or no albuminuria, is reassuring.

In summary, our analyses of DAPA-CKD trial data show that dapagliflozin significantly slowed the rate of eGFR decline in participants with chronic kidney disease. The effect of dapagliflozin on eGFR slope was more pronounced in patients with a faster rate of progression, including patients with type 2 diabetes, and among those with more extensive albuminuria or higher HbA1c, than in those with less pronounced albuminuria or lower HbA1c.

Contributors
HJLLH was involved in the study design, conduct of the study, data collection and interpretation, and wrote the first draft of the manuscript. NJ did the data analyses. DCW, GMC, JJVM, RDT, TG, PR, and RC-R are members of the executive committee of the DAPA-CKD study and were involved in the study design and data collection, analysis, and interpretation. AMI, CDS, and BVS were involved in the study design, conduct of the study, and data collection, and interpretation. HJLLH and NJ verified and had full access to all data and had the final responsibility to submit for publication. All authors reviewed the manuscript drafts, provided approval of the final version for submission, and take responsibility for the accuracy and integrity of the data.

Declaration of Interests
HJLLH is consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Gilead, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe, Novo Nordisk, and Travere, and has received research support from Abbvie, AstraZeneca, Boehringer Ingelheim, and Janssen. GMC has received fees from AstraZeneca for the DAPA-CKD trial steering committee; has received research grants from the US National Institute of Diabetes and Digestive and Kidney Diseases, and Amgen; is on the board of directors for Satellite Healthcare; has received fees for advisory boards from Baxter, Cricket, DiaMedica, and Reata; holds stock options for Ardelyx, CloudCath, Durect, DiaNow, and Outset; has received fees from Akebia, Sanofi, and Vertex for trial steering committees; and has received fees for Data Safety and Monitoring Board service from Angion, Bayer, and ReCor. TG has received grants for statistical consulting from AstraZeneca, CSL-pharma, and Boehringer Ingelheim and has received personal fees from Janssen Pharmaceuticals, DURECT Corporation, and Pfizer for statistical consulting. JJVM’s employer, Glasgow University, has received payments for his work on clinical trials, consulting, and is on the advisory board of Alnylam, Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cardurion, Cytokinetiks, DAICor, GSK, Ionis Pharmaceuticals, KBP Biosciences, Novartis, and Theracos; and has received personal lecture fees from Abbott, Alkermes, Eris Lifesciences, Hikma, Lupin, Sun Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, and the Corpus. RC-R has received consulting fees from Boehringer Ingelheim, and Chinook; lecture fees from Amgen, Boehringer Ingelheim, and Janssen; honoraria for advisory boards from Boehringer Ingelheim and Novo Nordisk; and research support from GSK, Novo Nordisk and AstraZeneca. RDT has received consulting fees from Boehringer Ingelheim, Reata Pharma, and Chinook Pharma; received speakers fees from Medscape; participated in advisory boards for Bayer and Vifor; and participated in data monitoring committees for Akebia and Otsuka.

PR has received honoraria to Steno Diabetes Center Copenhagen for lecture fees, steering group participation, and advisory board participation from AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, Novo Nordisk, Sanofi, and Eli Lilly, and research support from AstraZeneca. DCW provides ongoing consultancy services to AstraZeneca and has received honoraria or consultancy fees from Amgen, AstraZeneca, Astellas, Boehringer Ingelheim, Bayer, GSK, Janssen, Napp, Mundipharma, Tricida, and Vifor Fresenius. BVS, CDS, and AML are employees and stockholders of AstraZeneca. NJ declares no competing interests.

Data sharing
Data underlying the findings described in this Article can be obtained in accordance with AstraZeneca’s data sharing policy described online.

Acknowledgments
We thank all investigators, trial teams, and patients for their participation in the trial. We also thank Parita Sheth, from inScience Communications, London, UK, for assistance in editing and preparation of figures; this support was funded by AstraZeneca.

References


