Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a pre-specified analysis from the DAPA-CKD trial

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Abstract (407 words)

Background: Dapagliflozin reduces the risk of kidney failure and heart failure in patients with chronic kidney disease (CKD). We examined the effects of dapagliflozin on kidney, cardiovascular, and mortality endpoints according to presence or absence of type 2 diabetes and according to underlying cause of CKD, reported as diabetic nephropathy, chronic glomerulonephritides, ischaemic/hypertensive CKD, or CKD of other/unknown cause.

Methods: DAPA-CKD (NCT03036150) was a randomised controlled trial, which enrolled 4304 participants with urinary albumin to creatinine ratio (UACR) ≥200 mg/g and estimated glomerular filtration rate (eGFR) 25–75 mL/min/1·73m^2, randomised to dapagliflozin 10 mg once-daily or placebo, as adjunct to standard care, and followed for median 2·4 years. The primary endpoint was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or kidney or cardiovascular death. Key secondary endpoints included the kidney composite (as primary endpoint, without cardiovascular death), a composite of cardiovascular death or hospitalisation for heart failure, and all-cause mortality.

Findings: Overall, 2906/4304 participants (68%) had a diagnosis of type 2 diabetes, of whom 396 (14%) had CKD ascribed to causes other than diabetic nephropathy. The relative risk reduction for the primary composite outcome with dapagliflozin was consistent in participants with type 2 diabetes (HR, 0·64; 95%CI, 0·52-0·79) and those without diabetes (HR, 0·50; 95%CI, 0·35-0·72; p-interaction, 0·24), as reported previously. Similar findings were reported for the secondary outcomes, including cardiovascular death or hospitalisation for heart failure (HR, 0·70, 95%CI 0·53-0·92 and 0·79; 95%CI, 0·40-1·55, respectively; p-interaction, 0·78) and all-cause mortality (HR, 0·74; 95%CI, 0·56-0·98 and 0·52; 95%CI, 0·29-0·93, respectively; p-interaction, 0·25). The effect of dapagliflozin on the primary outcome was also consistent among patients with diabetic nephropathy (n=2510; HR 0·63, 95%CI 0·51-0·78), chronic glomerulonephritides (n=695; HR 0·43, 95%CI 0·26-0·71), ischaemic/hypertensive CKD (n=687; HR 0·75, 95%CI 0·44-1·26), and CKD of other/unknown cause (n=412; HR 0·58, 95%CI 0·29-1·19; p-interaction 0·53). Reduction in cardiovascular death or hospitalisation for heart failure was consistent across kidney disease aetiologies (p-interaction 0.24), as was reduction in all-cause mortality (p-interaction 0.55). The proportion of patients who experienced serious adverse events or discontinued study drug due to adverse events did not vary in patients with or without type 2 diabetes nor across CKD aetiologies. There were few serious adverse events and few discontinuations due to adverse events of urinary tract infections or genital infections.

Interpretation: Dapagliflozin reduces the risks of major adverse kidney and cardiovascular events and all-cause mortality in patients with diabetic and non-diabetic CKD.

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Research in context

Evidence before this study

Search criteria: We searched PubMed from January 1, 1990, to September 1, 2020 for all publications with the search terms ‘SGLT2’, ‘SGLT2 inhibitor’, Chronic Kidney Disease, Diabetic Neprohopathy, Glomerulonephritides, ‘Hypertensive Kidney Disease and Randomised Controlled Clinical Trial.

In large cardiovascular outcome trials of patients with type 2 diabetes, sodium-glucose cotransporter-2 (SGLT2) inhibitors have demonstrated beneficial effects on cardiovascular outcomes and slowed the progression of kidney function decline. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial demonstrated that the SGLT2 inhibitor canagliflozin reduced the risk of kidney failure and cardiovascular outcomes in patients with type 2 diabetes and stages 2 and 3 chronic kidney disease (CKD) who were already receiving an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. The Dapagliflozin and Prevention of Adverse Outcome in CKD (DAPA-CKD) trial extended these findings to a broader group of patients with CKD, 33% of whom did not have type 2 diabetes at the time of recruitment and 42% of whom had CKD due to causes other than diabetic nephropathy.

Added value of this study

The benefits of dapagliflozin on clinical outcomes (which include reductions in risk of kidney failure, cardiovascular death, and hospitalisation for heart failure, as well as reductions in all-cause mortality) were consistent whether or not patients had type 2 diabetes at the time of recruitment into the DAPA-CKD study. These benefits also extend to patients with a broad range of underlying causes of CKD other than diabetic nephropathy, including those with primary glomerulonephritides and ischaemic/hypertensive kidney disease. Dapagliflozin was shown to be well tolerated in patients with CKD with and without type 2 diabetes.

Implications of all the available evidence

The DAPA-CKD trial indicates that dapagliflozin could impart substantial cardio-renal benefit to a broad range of patients with impaired kidney function and proteinuria, including those with non-diabetic CKD.

Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors were developed for the treatment of type 2 diabetes. By reducing glucose reabsorption in the proximal convoluted tubule and thereby enhancing urinary glucose excretion, these agents reduce blood glucose concentrations. In large cardiovascular safety trials involving participants with type 2 diabetes, the majority of whom did not have chronic kidney disease (CKD), SGLT2 inhibitors slowed the rate of decline of estimated glomerular filtration rate (eGFR) and reduced albuminuria. The first SGLT2 inhibitor trial dedicated to patients with CKD and type 2 diabetes, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), demonstrated substantial benefits in kidney and cardiovascular outcomes.[1]

In clinical studies in type 1 and type 2 diabetes, an early reduction in eGFR is observed on initiation of SGLT2 inhibitors, even in participants with good glycaemic control.[2,3] The same is seen in patients with proteinuric CKD but without diabetes.[4] These observations, along with strong experimental data, supports a favourable glomerular haemodynamic effect, leading to speculation that SGLT2 inhibitors have renoprotective actions that are independent of blood glucose concentrations.[5,6] It follows that, like angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs),[7-10] SGLT2 inhibitors may have beneficial effects on kidney outcomes in patients with aetiologies of CKD other than type 2 diabetes. The Dapagliflozin And Prevention of Adverse outcomes in CKD trial (DAPA-CKD) tested the hypothesis that, compared with placebo, dapagliflozin is superior in reducing the risk of major adverse kidney and cardiovascular events as well as prolonging overall survival in a broad group of individuals with CKD.[11,12] Crucially, and unlike CREDENCE, DAPA-CKD included over one-third of participants without type 2 diabetes. Moreover, not all participants with type 2 diabetes at the time of recruitment had a diagnosis of diabetic nephropathy, with some having specific alternative aetiologies of CKD, often supported by a prior kidney biopsy.[13]

In the DAPA-CKD trial, dapagliflozin reduced the risk of kidney failure, death from cardiovascular causes or hospitalisation for heart failure, and death from any cause.[11] In this pre-specified analysis of DAPA-CKD, we examined whether the presence or absence of type 2 diabetes at baseline and the underlying aetiology of kidney disease modified the effects of dapagliflozin on these clinical outcomes.

Methods:

Trial design and study participants

DAPA-CKD was a multicentre, double-blind, placebo-controlled, randomised trial conducted at 386 study sites in 21 countries. The trial was designed to assess the effects of dapagliflozin on kidney and cardiovascular outcomes in patients with CKD, with or without type 2 diabetes. DAPA-CKD was registered with ClinicalTrials.gov as NCT03036150. The trial was approved by Ethics Committees at each participating centre. All participants provided written informed consent before commencement of any study specific procedure. An independent Data Monitoring Committee provided trial oversight. The study protocol, including a detailed description of the trial design, statistical analysis plan, and patient eligibility criteria has been published previously.[11,12]

Briefly, patients were eligible if they had CKD, defined as eGFR between 25 and ≤75 mL/min/1·73m^2, and urinary albumin-to-creatinine ratio (UACR) between 200 and ≤5000 mg/g (22·6 to ≤565·6 mg/mmol). All participants were required to be receiving a stable dose of an ACEi or ARB for at least 4 weeks before enrolment into the trial, unless contraindicated. Main exclusion criteria included a diagnosis of type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis. Participants receiving immunotherapy for primary or secondary kidney disease within the 6 months prior to enrolment were also excluded.

Baseline categorisation of diabetes status and cause of kidney disease

At Visit 1 (screening visit), investigators recorded whether the participant had a diagnosis of type 2 diabetes. Glycated haemoglobin (HbA1c) levels were measured in a central laboratory at Visit 1 and Visit 2 (randomisation visit). For this pre-specified analysis, patients were categorised as having type 2 diabetes if they had a documented diagnosis or if their HbA1c was ≥6·5% (48 mmol/mol) at both Visits 1 and 2.

At the screening visit, investigators also recorded the diagnosis of kidney disease. This could be based on prior kidney biopsy where this information was available, but a biopsy-confirmed diagnosis was not mandatory. The following prespecified categories of causes of kidney were defined: ‘diabetic nephropathy’, ‘glomerulonephritides’, ‘ischaemic or hypertensive CKD’, and ‘other or unknown causes of CKD’. Patients with type 2 diabetes who had a reported cause of kidney disease other than diabetic nephropathy were analysed accordingly to the investigator reported underlying aetiology. Among participants with glomerulonephritides, immunoglobulin A (IgA) nephropathy comprised the largest subgroup and was analysed separately.[13]

Randomisation and study procedures

As described previously,[11,12] participants were randomly assigned to dapagliflozin 10 mg once-daily or matching placebo, in accordance with the sequestered, fixed randomisation schedule, using balanced blocks to ensure an approximate 1:1 ratio of the two regimens. Randomisation was conducted using an interactive voice- or web-based system and stratified on the diagnosis of type 2 diabetes and UACR (≤1000 mg/g or >1000 mg/g). Study personnel (except the Independent Data Monitoring Committee) and participants were blinded to the treatment allocation. Drug and placebo were identically packaged, with uniform tablet appearance, labelling, and administration schedule. After randomisation, study visits occurred at 2 weeks, at 2, 4, and 8 months, and at 4-month intervals thereafter. At each visit, blood and urine samples were sent for laboratory assessment, vital signs assessed and information on potential study endpoints, adverse events, concomitant therapies, and study drug adherence recorded.

Outcomes

The primary outcome of the trial was a composite endpoint of sustained ≥50% decline in eGFR (confirmed by a second serum creatinine after at least 28 days), onset of end-stage kidney disease (defined as maintenance dialysis for more than 28 days, kidney transplantation, or eGFR <15 mL/min/1·73 m^2 confirmed by a second measurement after at least 28 days), or death from kidney or cardiovascular cause. The secondary outcomes were, in hierarchical order: a kidney-specific outcome defined in the same way as the primary outcome, but excluding cardiovascular death; a composite endpoint of cardiovascular death or hospitalisation for heart failure; and all-cause mortality. An independent event adjudication committee adjudicated all clinical endpoints using rigorous pre-specified endpoint definitions.

Statistical analysis

We pre-specified analysis of the effects of dapagliflozin on the primary and secondary efficacy endpoints in participants with and without type 2 diabetes, and according to the underlying cause of kidney disease (Supplementary Appendix). The statistical assumptions of the DAPA-CKD trial have been published previously,[11,12] and are available in the Supplementary Appendix. We included data from all randomised patients according to the intention-to-treat principle. We summarized baseline characteristics by diabetes status and cause of CKD using mean (standard deviations), median (25^{th}, 75^{th} percentile range), or proportion.

We fitted a Cox proportional hazards regression model, stratified by type 2 diabetes and UACR and adjusted for baseline eGFR to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for dapagliflozin compared with placebo in participants with or without type 2 diabetes, and within each pre-specified subgroup reporting cause of CKD. We tested for heterogeneity by adding interaction terms between type 2 diabetes or cause of kidney disease and randomised treatment assignment to the relevant Cox models. We calculated annualised incidence rates, expressed as number of events per 100 patient-years follow-up. We calculated absolute risk reductions by subtracting the annualised incidence rate in the dapagliflozin group from the placebo group. We estimated heterogeneity in absolute treatment effects using fixed effects meta-analysis. No multiplicity adjustment was made.

Finally, we summarized safety data according to type 2 diabetes and cause of CKD, by treatment group, amongst all participants who were randomised to and received at least one dose of dapagliflozin or placebo. Logistic regression was used to estimate the odds ratio and 95% CI for dapagliflozin compared with placebo in participants with and without type 2 diabetes. Test for interactions were performed by adding an interaction term between type 2 diabetes or cause of kidney disease and randomised treatment assignment to the relevant logistic regression models.

We performed all analyses with SAS version 9.4 (SAS Institute) or R version 4.0.2 (R-Foundation).

Role of funding source

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. The corresponding author (DCW) and last author (HJLH) had full access to all of the data and had the final responsibility to submit for publication.

Results:

The DAPA-CKD trial randomised 4304 participants (mean age, 62 years; 1425/4304 [33%] female; mean eGFR, 43 mL/min/1·73m^2, median UACR, 949·3 mg/g [107 mg/mmol]), who were followed for a median of 2·4 (interquartile range, 2·0 to 2·7) years. The Independent Data Monitoring Committee undertook an analysis during routine assessment at a pre-planned meeting, and not at the request of the trial sponsor or the trial's executive committee. Based on the results of this independent analysis, it was recommended that the trial be stopped early because of clear efficacy.[11]

The number of participants randomised with and without type 2 diabetes was 2906 and 1398, respectively. Participants without type 2 diabetes were younger, had a lower body mass index, eGFR and UACR (Table 1). As expected, cardiovascular disease history was less common in participants without diabetes. The proportion of patients with stage 4 CKD was similar between patients with (13·8%) and without type 2 diabetes (16·0%). In total, 873 (20·3%) participants had a prior kidney biopsy.[13] Baseline characteristics were well balanced between the dapagliflozin and placebo groups in participants with and without type 2 diabetes (Table 1).

Diabetic nephropathy was the most frequently reported cause of CKD (2510/4304 [58·3%]), followed by glomerulonephritis (695/4304 [16·1%]), ischaemic or hypertensive CKD (687/4304 [16·0%]), and CKD of other or uncertain cause (412/4304 [9·5%]). In 396 participants with type 2 diabetes, investigators reported that CKD was not attributed to diabetic nephropathy. Participants with glomerulonephritides were younger, had a lower body weight and systolic blood pressure, and were less likely to have heart failure compared with participants with diabetic nephropathy or ischaemic or hypertensive CKD. Haemoglobin levels were lower in participants with diabetic nephropathy (Supplementary Table 1).

During follow-up, in participants with type 2 diabetes, the event rate for the primary outcome was lower in the dapagliflozin group (5·2 events per 100 patient-years) compared with the placebo group (8·0 events per 100 patient-years); the hazard ratio (HR) was 0·64 (95% CI, 0·52-0·79).[11] Amongst participants without diabetes, the event rate for the primary outcome was also lower in the dapagliflozin group (3·4 events per 100 patient-years) compared with the placebo group (6·3 events per 100 patient-years); the HR was 0·50 (95% CI, 0·35-0·72), with an interaction p-value of 0·24.[11] Additionally, the Kaplan-Meier curves started to diverge early in the trial, after approximately 4 to 8 months, and continued to diverge throughout the remainder of the follow-up (Figure 1). The point estimates for each component of the

composite outcome favoured dapagliflozin in participants with and without type 2 diabetes (Figure 2).

The effect of dapagliflozin on the secondary kidney composite outcome (sustained eGFR decline ≥50%, end-stage kidney disease, or renal death) was consistent in participants with type 2 diabetes (HR, 0·57; 95% CI, 0·45-0·73) and those without diabetes (HR, 0·51; 95% CI, 0·34-0·75; interaction p-value, 0·57; Figure 3). Event rates for the composite outcome of cardiovascular death or hospitalisation for heart failure were higher in participants with type 2 diabetes compared to those without, but the relative benefit of dapagliflozin was similar (corresponding HR, 0·70, 95%CI 0·53-0·92 and 0·79; 95% CI, 0·40-1·55, respectively; interaction p-value, 0·78). Finally, all-cause mortality was reduced with dapagliflozin in participants with and without type 2 diabetes (HR, 0·74; 95% CI, 0·56-0·98 and HR, 0·52; 95% CI, 0·29-0·93, respectively; interaction p-value, 0·25).

Exploring outcomes by the underlying cause of CKD, the effect of dapagliflozin on the primary composite endpoint was consistent in participants with diabetic nephropathy (HR, 0·63; 95% CI, 0·51-0·78), glomerulonephritides (HR, 0·43; 95% CI, 0·26-0·71), ischaemic or hypertensive CKD (HR, 0·75; 95% CI, 0·44-1·26), and CKD of other or unknown cause (HR, 0·58; 95% CI, 0·29-1·19) (p-interaction 0·53; Figure 4). Likewise, the underlying cause of CKD did not modify the beneficial effect of dapagliflozin on the secondary endpoints including all-cause mortality (Figure 4). In participants with glomerulonephritides, IgA nephropathy was the most frequently reported cause of kidney disease. Among 270 participants with IgA nephropathy, dapagliflozin reduced the risk of the primary endpoint compared with placebo (HR, 0·29; 95% CI, 0·12-0·73; Supplementary Figure 1).

Absolute risk reductions were generally consistent among participants with and without type 2 diabetes, except for the composite endpoint of cardiovascular death or hospitalisation for heart failure, where there was evidence that the absolute benefits were greater in participants with type 2 diabetes compared with those without diabetes (Figure 2). Absolute risk reduction for the primary and kidney-specific endpoints varied according to cause of kidney disease, wherein the greatest absolute benefit was seen in participants with glomerulonephritides (Figure 3). There was no evidence that the absolute benefits on survival differed according to the presence of diabetes or cause of kidney disease.

The proportion of participants who experienced serious adverse events or discontinued study drug due to adverse events did not vary by diabetes status (p-interaction, 0·48 and

0·20, respectively) or underlying cause of CKD (p-interaction, 0·14 and 0·04, respectively) (Table 2; Supplementary Table 2). Overall, there were very few serious adverse events of urinary tract infections or genital infections, or discontinuations due to adverse events of urinary tract infections or genital infections. There were numerically more events in patients with type 2 diabetes than those without diabetes, as well as generally more events with dapagliflozin than placebo (Supplementary Table 3).

Discussion

By including patients with and without type 2 diabetes in the DAPA-CKD trial, we were able to explore the effects of SGLT2 inhibitors in patients with CKD due to a range of underlying causes, including chronic glomerulonephritides, ischaemia or hypertensive CKD, and other or unknown causes. This pre-specified analysis demonstrated that dapagliflozin reduced major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic kidney disease.

Participants enrolled in DAPA-CKD were required to receive either an ACEi or ARB unless not tolerated. This is because of the known benefits of these drugs in patients with CKD and elevated levels of urinary protein excretion, demonstrated in trials completed more than 20 years ago. These prior trials recruited individuals with type 2 diabetes and CKD[10] and those with CKD but without diabetes.[7-9] One of these trials, assessing the effect of ramipril in patients with glomerular disease and overt proteinuria but without diabetes, led to the license for this drug.[7] The effect of dapagliflozin on the primary and kidney specific outcomes highlights the potential of this drug to improve the management of patients with CKD with and without type 2 diabetes. No other class of medication has been specifically proven to slow progression of CKD in patients with and without diabetes and no drug to date has improved survival in patients with CKD.

Our findings in the non-diabetic CKD aetiological subgroups were consistent with findings from other small, mechanistic trials of SGLT2 inhibitors in non-diabetic individuals. In a small, cross-over study including patients with proteinuric CKD, but without diabetes, dapagliflozin 10 mg led to an acute but reversible reduction in GFR, indicating that dapagliflozin reduces intraglomerular pressure consistent with observations in patients with diabetes.[4] Additionally, the study showed that dapagliflozin reduced body weight and increased haematocrit, suggesting enhanced glycosuria and natriuresis. These physiological changes are believed to preserve long-term kidney function both in patients with and without type 2 diabetes, as was observed in the current study. In addition to this haemodynamic-mediated pathway, recent studies suggest that metabolic alterations due to enhanced glycosuria in diabetic and non-diabetic settings stimulate a diverse range of molecular changes that result in activation of factors sirtuin-1 and its downstream activators peroxisome proliferator-activated receptor γ coactivator 1α and fibroblast growth factor 21. Activation of these mediators enhances gluconeogenesis, ketogenesis and fatty acid oxidation and promotes autophagy, a process that cleanses cells from dysfunctional organelles. Collectively these effects ameliorate oxidative stress and inflammation and may

result in long-term preservation of kidney function.[14] Another hypothesized metabolic pathway includes fuel switches that exploit amino acids from muscles to generate glucose and fatty acids.[15] Additional proposed pathways of kidney protection include suppression of inflammation and fibrosis, possibly through inhibition of the renin-angiotensin-aldosterone-system, and reducing ischaemia in the kidney.[16,17]

In DAPA-CKD, dapagliflozin significantly reduced the composite endpoint of cardiovascular death or hospitalisation for heart failure. The magnitude of the relative effect did not vary among participants with or without type 2 diabetes. These findings are in keeping with results from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF trial), which showed that dapagliflozin reduced a composite endpoint of worsening of heart failure or cardiovascular death in patients with heart failure and reduced ejection fraction with consistent effects in those with and without type 2 diabetes.[18,19] In DAPA-HF, the composite renal outcome (≥50% sustained decline eGFR, end stage kidney disease or renal death) was not different between those randomised to dapagliflozin versus placebo,[11] but the rate of decline in eGFR was less with dapagliflozin, a response observed in those with and without type 2 diabetes at baseline.[20] Data from the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) demonstrated that empagliflozin improved clinical outcomes in patients with heart failure and reduced ejection fraction, again with and without type 2 diabetes, suggesting similar effects of different SGLT2 inhibitors in reducing the risk of heart failure in patients regardless of diabetes status.[21] The ongoing EMPA-KIDNEY study (Study of Heart and Kidney Protection With Empagliflozin; NCT03594110) is investigating the effect of empagliflozin on kidney disease progression and cardiovascular death in patients with CKD. This trial allows inclusion of patients with an eGFR of 25-45 mL/min/1·73m^2 who do not have albuminuria. Results from the EMPA-KIDNEY trial may shed light on the effects of SGLT2 inhibitors in patients with reduced eGFR, but normoalbuminuria.[22]

Our findings have wide ranging clinical implications. First, clinicians who consider treatment for kidney or cardiovascular protection in patients who share clinical characteristics of the participants of this trial may do so regardless of the presence of type 2 diabetes and can expect protection even in those without type 2 diabetes. The absolute risk reductions for the primary outcome in participants with and without type 2 diabetes translated in a number needed to be treated to prevent a major kidney outcome or cardiovascular death of 19 participants with type 2 diabetes, and 19 for participants without diabetes. Second, in

contrast to the earlier large outcome trials, about 1 in 7 participants in the DAPA-CKD study had stage 4 CKD, with a similar proportion among participants with and without diabetes.[13] The positive benefit-risk ratio support initiation of dapagliflozin in patients with eGFR as low as 25 mL/min/1·73m^2.

Dapagliflozin was well tolerated in this population, confirming its established beneficial safety profile. Overall, the proportion of participants with serious adverse events was higher amongst participants with type 2 diabetes compared to those without type 2 diabetes. It is reassuring to note that there were no cases of diabetic ketoacidosis or hypoglycaemia in participants receiving dapagliflozin who did not have type 2 diabetes.

The DAPA-CKD trial has limitations. The diagnosis of type 2 diabetes was based on investigator-reported diagnosis or HbA1c values at screening and randomisation visits and not on more conventional tests such as oral glucose tolerance testing or fasting glucose measurement. However, our approach was compatible with recommendations of the World Health Organization for the diagnosis of type 2 diabetes.[23] In addition, the cause of kidney disease was based on clinical judgement (investigator reports), which may have led to misclassifications. A biopsy confirmation of the cause of the kidney disease was not a requirement for enrolment in this study, but was available for one in five trial participants. In the absence of kidney biopsy for many patients, 'diabetic kidney disease' may be considered more appropriate terminology for the diagnoses classified as 'diabetic nephropathy'; however, within these analyses we retained the pre-specified diagnosis categories to be consistent with the investigator-reported diagnosis. A further limitation is that, while the Independent Data Monitoring Committee recommended termination of the trial because of overwhelming efficacy, it did so well before an anticipated number of events had accrued. Thus, while treatment with dapagliflozin resulted in fewer major adverse kidney and cardiovascular events compared with placebo, the precision of the effect estimates was lower than it would have been had the trial been allowed to extend to planned completion. It should also be noted that the DAPA-CKD trial enrolled patients with increased albuminuria, and the results cannot be generalized to patients with impaired kidney function and normoalbuminuria. Finally, in this study, eGFR data were not collected after the discontinuation of the study drug. Consequentially, we are unable to ascertain whether the initial reduction in eGFR is reversible after discontinuation of dapagliflozin, a phenomenon which has been shown in several other studies in patients with CKD, both with type 2 diabetes[24,25] and without diabetes.[4]

In conclusion, this pre-specified analysis of the DAPA-CKD study demonstrates that when added to ACEi/ARB therapy, dapagliflozin reduces the risk of a number of clinical endpoints including kidney failure, hospitalisation for heart failure and all-cause mortality in patients with CKD. These benefits are observed irrespective of diabetic status and the underlying cause of kidney disease.

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Author Contribution

DCW was involved in the study design, conduct of the study, data collection, interpretation of the data, co-wrote the first draft of the manuscript and participated in critical revision of all drafts of the manuscript.

HJLH was involved in the study design, conduct of the study, data analysis, interpretation of the data and co-wrote the first draft of the manuscript and participated in critical revision of all drafts of the manuscript.

GMC, JMcM, TG, FFH, RC-R, PR and RDT are members of the study's executive committee and were involved in the study design, data collection, analysis or interpretation of the data.

NJ performed the data analyses.

AML, CDS and BVS were involved in the study design and interpretation of data.

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 interest

DCW has received honoraria and/or consultancy fees from Amgen, AstraZeneca, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Janssen, Napp, Mundipharma, Medscape, Merck Sharp and Dohme, Pharmacosmos, Reata, Takeda, and Vifor Fresenius.

NJ has nothing to declare.

GMC has received fees from AstraZeneca for the DAPA-CKD trial steering committee, research grants from NIDDK, and Amgen; he is on the board of directors for Satellite

Healthcare, has received fees for advisory boards for Baxter, Cricket, DiaMedica, and Reata; and holds stock options for Ardelyx, CloudCath, Durect, DxNow, and Outset; has received fees from Akebia, Sanifit and Vertex for Trial steering committees; and has received fees for DSMB service from Angion, Bayer and ReCor.

TG has received grants for statistical consulting from AstraZeneca, CSL, Vertex and Boehringer-Ingelheim; has received personal fees from Janssen Pharmaceuticals, DURECT Corporation and Pfizer for statistical consulting.

FFH has received honoraria from AbbVie and AstraZeneca.

JMcM Payments to my employer, Glasgow University, for my work on clinical trials, consulting and other activities: Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardurion, Cyclerion, Cytokinetics, DalCor, GSK, Merck, Novartis, Pfizer, Servier, Theracos. Personal lecture fees: Abbott, Hickma, Sun Pharmaceuticals.

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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.

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Table 1: Baseline characteristics of participants stratified by diabetes status at baseline (all randomised participants)

	Type 2 diabetes		Without diabetes	
Characteristic	**Dapagliflozin**	**Placebo**	**Dapagliflozin**	**Placebo**
	(N=1455)	(N=1451)	(N=697)	(N=701)
Age (years), mean (SD)	64·1 (9·8)	64·7 (9.5)	56·9 (14·6)	56·0 (14·6)
Female sex, n (%)	494 (34·0)	471 (32·5)	215 (30·8)	245 (35·0)
Race,[†] n (%)				
White	751 (51·6)	790 (54·4)	373 (53·5)	376 (53·6)
Black or African American	76 (5·2)	61 (4·2)	28 (4·0)	26 (3·7)
Asian	481 (33·1)	451 (31·1)	268 (38·5)	267 (38·1)
Other	147 (10·1)	149 (10·3)	28 (4·0)	32 (4·6)
Weight (kg), mean (SD)	83·2 (20·9)	83·8 (21·2)	77·9 (17·8)	78·3 (19·9)
Current Smoker, n (%)	195 (13·4)	200 (13·8)	88 (12·6)	101 (14·4)
Blood Pressure (mmHg), mean (SD)				
Systolic	138·8 (17·6)	139·6 (17·1)	132·3 (16·4)	132·9 (16·9)
Diastolic	76·5 (10·4)	76·5 (9·9)	79·6 (10·9)	79·6 (10·8)
Estimate GFR (mL/min/1 ·73 m^2)	44·0 (12·6)	43·6 (12·6)	41·7 (11·5)	41·8 (11·9)
Estimated GFR ≥60 mL/min/1·73 m^2, n (%)	179 (12·3)	169 (11·6)	55 (7·9)	51 (7·3)
Estimated GFR 45 to <60 mL/min/1·73 m^2, n (%)	450 (30·9)	468 (32·3)	196 (28·1)	214 (30·5)
Estimated GFR 30 to <45 mL/min/1·73 m^2, n (%)	636 (43·7)	603 (41·6)	343 (49·2)	316 (45·1)
Estimated GFR <30 mL/min/1·73 m^2, n (%)	190 (13·1)	211 (14·5)	103 (14·8)	120 (17·1)
Haemoglobin (g/L), mean (SD)	126·3 (17·8)	125·6 (18·0)	133·4 (17·9)	132·7 (17·2)
Serum potassium (mmol/L), mean (SD)	4·7 (0·6)	4·7 (0·6)	4·6 (0·5)	4·6 (0·5)
UACR (mg/g), median (IQR)	1024·5	1004·5	870·5	841·5

	(472·5-2111·0)	(493·3-2017·0)	(472·0-1533·5)	(458·5-1554·5)
UACR >1000 mg/g, n (%)	741 (50·9)	732 (50·4)	307 (44·0)	299 (42·7)
Type 2 diabetes, n (%)	1455 (100·0)	1451 (100·0)	-	-
HbA1c (%), mean (SD)	7·8 (1·7)	7·8 (1·6)	5·6 (0·4)	5·6 (0·4)
HbA1c (mmol/mol), mean (SD)	62 (18·6)	62 (17·5)	38 (4·4)	38 (4·4)
Heart failure, n (%)	177 (12·2)	184 (12·7)	58 (8·3)	49 (7·0)
Prior Medication, n (%)				
ACE inhibitor	451 (31·0)	443 (30·5)	222 (31·9)	238 (34·0)
ARB	984 (67·8)	974 (67·1)	460 (66·0)	452 (64·5)
Diuretic	718 (49·3)	747 (51·5)	210 (30·1)	207 (29·5)
Statin	1039 (71·4)	1043 (71·9)	356 (51 ·1)	356 (50.8)
Metformin (biguanides)*	629 (43·6)	613 (42·5)	··	··
SU derivative*	389 (26·9)	385 (26·7)	··	··
DPP4 inhibitor*	364 (25·2)	378 (26·2)	··	··
GLP-1 analogue*	63 (4·4)	59 (4·1)	··	··
Insulin*	814 (56·4)	784 (54·4)	··	··

*Dapagliflozin N=1444; placebo N=1442.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; DPP4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; IQR, inter quartile range; UACR, urinary albumin-to-creatinine ratio

Table 2: Adverse events by diabetes status (safety analysis set)

Outcome, n (%)	Dapagliflozin (N=2149)	Placebo (N=2149)	Odds ratio (95% CI)	P-value interaction
Without diabetes	696	699		
Type 2 diabetes	1453	1450		
Discontinuation due to adverse event				
Without diabetes	36 (5·2)	29 (4·1)	1·26 (0·77, 2·09)	0·20
Type 2 diabetes	82 (5·6)	94 (6·5)	0·86 (0·63, 1·17)	
Any serious adverse event[a]				
Without diabetes	150 (21·6)	167 (23·9)	0·88 (0·68, 1·12)	0·48
Type 2 diabetes	483 (33·2)	562 (38·8)	0·79 (0·68, 0·92)	
Adverse events of interest				
Amputation[b]				
Without diabetes	0 (0·0)	1 (0·1)	NA	0·26
Type 2 diabetes	35 (2·4)	38 (2·6)	0·92 (0·57, 1·46)	
Any definite or probable diabetic ketoacidosis				
Without diabetes	..	..	..	
Type 2 diabetes	0 (0·0)	2 (0·1)	NA	NA
Fracture[c]				
Without diabetes	20 (2·9)	18 (2·6)	1·12 (0·59, 2·15)	0·72
Type 2 diabetes	65 (4·5)	51 (3·5)	1·28 (0·89, 1·87)	
Renal related adverse event[c]				
Without diabetes	34 (4·9)	40 (5·7)	0·85 (0·53, 1·35)	0·83
Type 2 diabetes	121 (8·3)	148 (10·2)	0·80 (0·62, 1·03)	

Major hypoglycaemia[d]				
Without diabetes	..	..	..	1·00
Type 2 diabetes	14 (1·0)	28 (1·9)	0·49 (0·25, 0·93)	
Volume depletion[c]				
Without diabetes	35 (5·0)	19 (2·7)	1·90 (1·09, 3·41)	0·27
Type 2 diabetes	92 (6·3)	71 (4·9)	1·31 (0·96, 1·81)	

[a]Includes death.

[b]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma.

[c]Based on pre-defined list of preferred terms.

[d]Adverse event with the following criteria confirmed by the investigator: i) Symptoms of severe impairment in consciousness or behaviour, ii) need of external assistance, iii) intervention to treat hypoglycaemia, iv) prompt recovery of acute symptoms following the intervention.

NA, not applicable.

Figure 1: Kaplan-Meier curve of the primary outcome in participants (A) with type 2 diabetes and (B) without type 2 diabetes, and kidney-specific secondary outcome in participants (C) with type 2 diabetes and (D) without type 2 diabetes.

Primary outcome number needed to treat in participants with type 2 diabetes = 19; primary outcome number needed to treat in participants without type 2 diabetes = 19.

Figure 2: Forest plot of the components of the primary endpoint in participants (A) with type 2 diabetes and (B) without type 2 diabetes.

Primary composite outcome p-interaction = 0·24; ≥50% estimated GFR decline p-interaction = 0·68; end-stage kidney disease p-interaction = 0·40; cardiovascular death p-interaction = 0·52.
In participants with type 2 diabetes, the composite endpoint of chronic dialysis and kidney transplant HR (95% CI) was 0·68 (0·47, 0·99); in participants without type 2 diabetes, the composite endpoint of chronic dialysis and kidney transplant HR (95% CI) was 0·63 (0·36, 1·09).
GFR, glomerular filtration rate.

Figure 3: Forest plot of primary and secondary endpoints in participants with and without type 2 diabetes.

Figure 4: Forest plot of primary and secondary endpoints according to kidney disease diagnosis at baseline.

Patients with type 2 diabetes who had a reported cause of kidney disease other than diabetic nephropathy were analysed accordingly to the investigator reported underlying aetiology.