Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: new insights from the DAPA-CKD trial

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Abstract (346/300 words)

Background: Reductions in albuminuria are associated with a subsequent lower risk of kidney failure in patients with chronic kidney disease (CKD). The sodium-glucose co-transporter 2 inhibitor dapagliflozin significantly reduced albuminuria in patients with type 2 diabetes and normal/near-normal kidney function. Whether this effect persists in patients with CKD with and without diabetes is unknown. We assessed the effects of dapagliflozin on albuminuria in patients with CKD with and without type 2 diabetes from the DAPA-CKD trial (NCT03036150).

Methods: We randomised 4304 patients with estimated glomerular filtration rate 25-75 mL/min/1·73m^2 and urinary albumin-to-creatinine ratio (UACR) 200-5000 mg/g to dapagliflozin (10 mg) or placebo. Change in albuminuria was a pre-specified exploratory outcome. Regression in UACR stage, defined as a transition from macroalbuminuria (≥300 mg/g) to micro- or normoalbuminuria (<300 mg/g), and progression in UACR stage, defined as a transition from <3000 mg/g to ≥3000 mg/g, were additional discrete endpoints.

Findings: Median (25th-75th percentile) UACR was 949 (477-1885) mg/g. Overall, dapagliflozin, compared to placebo, reduced geometric mean UACR by 29·3% (95% confidence interval [CI], 25·2–33·1; p<0·001); 35·1% (95% CI, 30·6–39·4) and 14·8% (95% CI, 5·9–22·9) in patients with and without type 2 diabetes, respectively (interaction p<0·001). Among the 3860 patients with UACR ≥300 mg/g at baseline, dapagliflozin increased the likelihood of regression in UACR stage (hazard ratio [HR] 1·81; 95% CI, 1·60–2·05). Among the 3820 patients with UACR <3000 mg/g at baseline, dapagliflozin decreased the risk of progression in UACR stage (HR 0·41; 95% CI, 0·32, 0·52). Larger reductions in UACR at day 14 were significantly

associated with attenuated eGFR decline during subsequent follow-up (β per log unit UACR change -1·15; 95% CI -1·81, -0·49; p<0·001).

Interpretation: In patients with CKD with and without type 2 diabetes, dapagliflozin significantly reduced albuminuria, with a larger relative reduction in patients with type 2 diabetes. The similar effects of dapagliflozin on clinical outcomes in patients with or without type 2 diabetes, but different effects on UACR suggest that part of the protective effects of dapagliflozin in patients with CKD may be mediated through pathways unrelated, to reduction in albuminuria.

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Research in Context

Evidence before this study

PubMed was searched from January 1, 2000 to April 2, 2021 using the search terms 'SGLT2', 'SGLT2 inhibitor', 'Chronic Kidney Disease', 'Albuminuria', 'UACR' and 'Randomised Controlled Clinical Trial'. Albuminuria is an established risk marker for progression of chronic kidney disease (CKD). Prior clinical trials have shown that sodium-glucose co-transporter 2 (SGLT2) inhibitors reduce albuminuria in patients with type 2 diabetes and CKD. For example, in the DELIGHT study the SGLT2 inhibitor dapagliflozin reduced the urinary albumin-to-creatinine ratio (UACR) by 28% at 4 weeks compared to placebo in patients with CKD *and* type 2 diabetes. Two small clinical studies in patients with CKD *without* diabetes reported that the albuminuria-lowering effect of dapagliflozin was diminished when compared to patients *with* diabetes. Because these studies were relatively small and of short duration, no definitive conclusions could be drawn whether the different effects of dapagliflozin on albuminuria between patients with and without diabetes were real or a chance finding.

The DAPA-CKD trial was a large international clinical trial to assess the effects of dapagliflozin on clinical outcomes in patients with CKD with and without type 2 diabetes. The results of the trial showed that dapagliflozin compared to placebo significantly decreased the relative risks of kidney failure, cardiovascular death or heart failure hospitalization, and all-cause mortality. In this pre-specified analyses of the DAPA-CKD trial we assessed the effect of dapagliflozin on albuminuria, investigated the consistency of these effects in patients with and without type 2 diabetes, and explored the association between early changes in albuminuria and subsequent longer-term changes in kidney function.

Added value of this study

Dapagliflozin, compared to placebo, changed geometric mean UACR by –29·3% (95% confidence interval [CI] –33.1 to –25·2; p<0·001) from baseline. Treatment with dapagliflozin resulted in a percentage change of −35·1% (95% CI −39·4 to −30·6; p<0·001) in patients with type 2 diabetes and −14·8% (95% CI −22·9 to −5·9; p<0·001) in patients without type 2 diabetes over time (p for interaction p<0·001). The acute decline in eGFR after 2 weeks treatment with dapagliflozin correlated with

the reduction in UACR at Week 2. This association was present in patients with and without type 2 diabetes. The reduction in UACR after 2 weeks was associated with a lower rate of decline in eGFR during the trial both in patients with and without type 2 diabetes.

Implications of all the available evidence

In this pre-specified analysis of the DAPA-CKD trial we demonstrated that dapagliflozin reduced albuminuria in patients with CKD with and without type 2 diabetes, with a larger reduction in patients with type 2 diabetes. These data, in combination with the available evidence that dapagliflozin consistently reduced clinical outcomes in patients with and without type 2 diabetes, suggest that the protective effects of dapagliflozin in patients with CKD are likely to be mediated in part through pathways related, and in part through pathways unrelated, to reduction in albuminuria. The association between the early reduction in albuminuria with attenuated longer-term eGFR decline highlight the importance of monitoring albuminuria as a marker to guide patient management.

Introduction

Albuminuria is a well-established risk marker for kidney failure and cardiovascular events in patients with chronic kidney disease (CKD).[1,2] Various pharmacologic interventions including renin-angiotensin-system inhibitors, sodium-glucose co-transporter 2 (SGLT2) inhibitors, and glucagon-like peptide 1 receptor agonists reduce albuminuria.[3,4] Meta-analyses of clinical trials showed that the early reduction in albuminuria is associated with a lower risk for kidney failure, supporting the use of albuminuria as a surrogate for kidney failure.[5]

SGLT2 inhibitors slow progression of CKD and reduce the risk of kidney failure in patients with and without CKD. SGLT2 inhibitors were initially developed as oral glucose-lowering drugs for patients with type 2 diabetes and were not recommended for patients with CKD due to lower glycaemic efficacy in patients with lower eGFR. However, clinical trials demonstrated that SGLT2 inhibitors reduce albuminuria in patients with type 2 diabetes and CKD.[6,7] These findings raised interest in studying the effect of SGLT2 inhibitors on long-term kidney outcomes. The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial showed that canagliflozin reduced the risk of clinically important kidney and cardiovascular endpoints in patients with type 2 diabetes and CKD.[8] The DAPA-CKD (Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease) trial extended these findings to patients with CKD with and without type 2 diabetes, demonstrating significantly lower rates of progressive CKD, cardiovascular death or heart failure hospitalisation, and all-cause mortality.[9] In this pre-specified analysis of the DAPA-CKD trial, we assessed the effects of dapagliflozin on albuminuria, investigated the consistency of these effects in patients with and without

type 2 diabetes, and explored the association between early changes in albuminuria and subsequent longer-term changes in kidney function.

Methods

Trial Design and Participants

DAPA-CKD was a randomised, placebo-controlled, double-blind trial in which patients were recruited at 386 sites in 21 countries. The trial was registered with clinicaltrials.gov (NCT03036150), and the trial protocol together with the trial design and statistical analysis plan have been published previously.[9,10] In short, the primary objective of the trial was to determine whether dapagliflozin reduces the incidence of kidney and cardiovascular events in patients with CKD with or without type 2 diabetes. Eligible participants were adult patients with CKD with an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1·73 m² and a urinary albumin-to creatinine ratio (UACR) between 200 and 5000 mg/g (22·6 to 565·6 mg/mmol). Participants had to receive a stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) for at least 4 weeks prior to trial enrollment, unless contraindicated. Patients were excluded from the trial if they had type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis. A detailed overview of inclusion and exclusion criteria has been published previously.[10]

Randomisation and Procedures

Participants were randomly assigned in a 1:1 ratio to either dapagliflozin (10 mg once daily) or placebo. Randomisation was stratified by diagnosis of type 2 diabetes and UACR ≤1000 mg/g or >1000 mg/g. UACR at baseline was defined as the mean

of the UACR values from samples collected at the screening and randomisation visit measured in a central laboratory. After randomisation, in-person follow-up visits were conducted after 2 weeks, 2, 4 and 8 months and continued at 4-month intervals. UACR at baseline and each follow-up visit was measured in a single first morning void urine sample and measured in a central laboratory.

Outcomes

The mean change in log-transformed UACR from baseline to the end of study was pre-specified as an exploratory outcome. We calculated least squares mean log-transformed UACRs to determine the treatment effect and subsequently back-transformed values to obtain geometric mean percentage changes and 95% confidence intervals (CIs). We also established the effect of dapagliflozin on the likelihood of achieving progression or regression in UACR stage. For this discrete post-hoc analysis, progression in UACR stage was defined as the initial development of nephrotic range albuminuria (UACR ≥3000 mg/g). We defined regression in UACR stage as the initial transition from macroalbuminuria (UACR ≥300 mg/g) to micro- or normoalbuminuria (UACR <300 mg/g). To account for within-person day-to-day variation in UACR measurements, the UACR progression and regression outcomes had to be confirmed by a second measurement at the subsequent follow-up visit. The annual rate of eGFR decline from Week 2 until the last on-treatment study visit was also pre-specified as an exploratory outcome. We determined the association between change in UACR from baseline to Week 2 with the subsequent rate of eGFR decline in patients randomised to dapagliflozin versus placebo, with and without type 2 diabetes.

Statistical Analysis

All analyses presented here followed the intention-to-treat principle. We summarised baseline characteristics by baseline UACR (≤1000 vs >1000 mg/g). We reported continuous variables as means and standard deviations for variables with approximate symmetric distributions. Variables with skewed distributions were reported as medians (25^{th}, 75^{th} percentile) or as geometric means and categorical variables were reported as counts and proportions.

We analysed the effect of dapagliflozin on UACR by fitting repeated measures models using restricted maximum likelihood. To visually depict the percent changes in geometric mean UACR by treatment group over the follow-up period, we used a longitudinal model with categorical fixed effects for treatment, visit, the treatment-by-visit interaction as well as continuous fixed effect covariates for baseline log UACR and the interaction of baseline log UACR with visit. To assess the effect of dapagliflozin relative to placebo on UACR in the full cohort, we used the average coefficient of treatment to estimate the effect of dapagliflozin on the geometric mean UACR across the follow-up assessments. For different categorical subgroup factors of interest (e.g. patients with or without type 2 diabetes), we expanded this model by the addition of main effect for the subgroup and separate three-way interaction terms between the subgroup factor with the treatment and with follow-up visit. We used linear contrasts to estimate and compare the effects of the randomized treatment on geometric mean UACR across the follow-up assessments for the different levels of the subgroup factor. For all models, we utilised an unstructured variance-covariance matrix to allow for general patterns of standard deviations and correlations across the repeated outcome measurements. We fit all models using log-transformed

(ln[$UACR_{visit}$ / $UACR_{baseline}$]) ratios of follow-up vs. baseline UACR levels as the dependent variable. In companion analyses, we estimated the effect of treatment on UACR according to continuous baseline log UACR, eGFR and HbA1c by replacing the categorical subgroups in the subgroup by treatment interaction terms with continuous baseline markers using a restricted cubic spline (defined using three percentile-based knots). We used the same repeated measures model to estimate the effect of dapagliflozin relative to placebo on systolic and diastolic blood pressure (BP). In this model we replaced baseline log UACR with baseline systolic or diastolic BP and replaced log UACR with systolic or diastolic BP in the interaction term with visit. We used Pearson correlation to assess the association between changes from baseline in systolic blood pressure and log UACR at week 2.

We used Cox proportional hazards regression models to calculate the hazard ratios (HR) and 95% CI (dapagliflozin versus placebo) for UACR progression and regression outcomes. In these models the baseline hazard function was stratified by type 2 diabetes and UACR category (≤ or > 1000 mg/g), and baseline eGFR was included as a covariate. We also estimated the effect of dapagliflozin on these endpoints by baseline type 2 diabetes status. For these analyses, we removed type 2 diabetes as stratification factor from the model. We tested for heterogeneity in the dapagliflozin treatment effect in patients with and without type 2 diabetes by adding a multiplicative interaction term to the model. We used Kaplan-Meier curves to visualize the UACR progression and regression outcomes by treatment group. Data were censored on the date of last central laboratory assessment. We confirmed the proportional hazard assumption by visual inspection of the Schoenfeld

Residuals and by performing a generalized linear regression of the scaled Schoenfeld residuals on follow-up time.

We fit a generalised linear model (GLM) to assess the association between the change in log transformed albuminuria from baseline to 14 days (Visit 2) after randomisation with short-term change in eGFR by randomized treatment group and diabetes status. This model included fixed effects for baseline eGFR and appropriate interaction terms to fit different outcome means for all combinations of the quartiles for the change in eGFR from baseline to Visit 2, treatment and type 2 diabetes status. This analysis was repeated with change in eGFR coded as a continuous variable (instead of categorical quartiles) to estimate the coefficients that describe the relation between change in albuminuria from baseline to 14 days (Visit 2) and short-term eGFR changes by treatment group for patients with and without type 2 diabetes. We inspected the distribution of residuals to assess approximate consistency with normality.

A two-slope random effects model was used to assess the association of the change in albuminuria from baseline to 2 weeks after randomisation with longer-term eGFR slope after 2 weeks, often referred to as the “chronic slope”. This model included appropriate main effect and interaction terms to estimate the mean longer-term eGFR slope separately for each quartile for the change in UACR to Visit 2 by treatment group and by type 2 diabetes status. The model also included covariates for log transformed baseline UACR, age, sex, race, baseline systolic BP, change from baseline in systolic BP at week 2, baseline HbA1c, baseline haemoglobin, smoking status and cardiovascular disease history. This analysis was repeated with

change in log UACR to Visit 2 coded as a continuous variable (instead of categorical quartiles). We used restricted maximum likelihood (REML) for estimation of statistical inference, and the intercept and short and long-term slopes were included as random effects.

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 (HJLH) and first author (NJ) had full access to all of the data, verified the data, and had the final responsibility to submit for publication.

Results

In the DAPA-CKD trial, 4304 patients were randomly assigned to either dapagliflozin (n=2152) or placebo (n=2152). These participants were followed for a median of 2·4 years (25^{th}, 75^{th} percentile: 2·0–2·7). Overall, participants had a median UACR of 949 mg/g (477–1885) (107 mg/mmol [53·9–213]) at baseline. Median UACR at baseline was 965 mg/g (472–1903) in the dapagliflozin group and 934 mg/g (482–1868) in the placebo group. Approximately half (48%) had a baseline UACR >1000 mg/g. Compared to participants with a lower UACR, those with a higher baseline UACR were younger, and were more likely to have type 2 diabetes. The higher UACR subgroup also had a higher BP, lower eGFR, and lower haemoglobin. Baseline characteristics were balanced between dapagliflozin- and placebo-assigned patients within each UACR subgroup (Table 1).

Compared with placebo, the geometric mean percentage change in UACR was −26·5% (95% CI −22·1 to −30·9; p<0·001) with dapagliflozin at Week 2. This reduction in UACR was sustained through to the end of follow-up. Taking all follow-up UACR measurements into account, the geometric mean percentage change in UACR during follow-up was −29·3% (95% CI −33·1 to −25·2; p<0·001) relative to placebo (Figure 1A).

Median UACR was 1017 mg/g and 861 mg/g in patients with and without type 2 diabetes, respectively (P<0.001). Relative to placebo, treatment with dapagliflozin resulted in a geometric mean percentage change of −35·1% (95% CI −39·4 to −30·6; p<0·001; Figure 1B) in patients with type 2 diabetes and −14·8% (95% CI −22·9 to −5·9; p=0·001; Figure 1C) in patients without type 2 diabetes over the follow-up visits (p for interaction p<0·001). Effects of dapagliflozin compared to placebo on UACR were larger in patients with diabetic nephropathy compared to other aetiologies of CKD (Figure 2). Analysis by categories of glycaemic control (i.e., normoglycaemic, pre-diabetic, type 2 diabetes with HbA_{1c} of ≥6·5% to <8·5% and type 2 diabetes with HbA_{1c} >8·5%) showed that the effect of dapagliflozin on UACR was more pronounced in patients with poorer glycaemic control (Figure 2). An additional analysis that used baseline HbA1c as a continuous variable demonstrated a more pronounced effect of dapagliflozin at higher baseline HbA1c (Figure 3). The relative effects of dapagliflozin on UACR in patients with versus without type 2 diabetes were not accounted for by differences in baseline UACR between the two subgroups (Supplement 1 and Supplemental Figure 1). The effects of dapagliflozin on UACR were consistent across the spectrum of baseline eGFR (<45 and ≥45 ml/min/1·73 m^2) and UACR (≤1000 and >1000 mg/g; Figure 2 and Figure 3).

Treatment with dapagliflozin significantly increased the likelihood of regression in UACR stage. Among 3860 patients with baseline UACR ≥300 mg/g, 638 patients randomised to dapagliflozin experienced regression in albuminuria compared with 424 patients randomised to placebo (HR 1·81, 95% CI 1·60 to 2·05; Supplemental Figures 2 and 3). Treatment with dapagliflozin significantly increased the likelihood of regression in UACR in patients with (HR 2·06, 95% CI 1·78 to 2·39) and without (HR 1·33, 95% CI 1·07 to 1·66) type 2 diabetes; the effect was significantly more pronounced in patients with type 2 diabetes (baseline diabetes * treatment interaction p=0·001). In parallel, treatment with dapagliflozin significantly reduced the likelihood of progression in UACR stage. Among 3820 patients with UACR <3000 mg/g at baseline, 95 patients randomised to dapagliflozin experienced progression in albuminuria to nephrotic range ≥3000 mg/g compared with 215 patients randomised to placebo (HR 0·41, 95% CI 0·32 to 0·52; Supplemental Figure 2). The effects of dapagliflozin on progression of albuminuria did not differ significantly among patients with (HR 0.39, 95% CI 0·29 to 0·51) and without (HR 0·50, 95% CI 0·30 to 0·82) type 2 diabetes (interaction p=0·40).

In the placebo group, systolic and diastolic BP remained fairly stable over time (Supplemental Figure 4). In the dapagliflozin group, systolic and diastolic BP fell after two weeks and this reduction was sustained throughout follow-up (Supplemental Figure 4). Compared with placebo, dapagliflozin reduced systolic and diastolic BP by 2·9 mmHg (95% CI 2·3 to 3·6; p<0·001) and 1·0 mmHg (95% CI 0·6 to 1·4; p<0·001). There was no evidence that the reduction in systolic and diastolic BP with dapagliflozin compared to placebo was different in patients with type 2 diabetes (3·2

mmHg (95% CI 2·5 to 4·0) and 0·8 mmHg [95% CI 0·4 to 1·3], respectively) versus patients without type 2 diabetes (2·3 mmHg [95% CI 1·2 to 3·4] and 1·4 mmHg [95% CI 0·7 to 2·1], respectively; p for interaction systolic and diastolic BP 0·167 and 0·152). The change from baseline in systolic BP at week 2 weakly correlated with 2-week changes in UACR in the dapagliflozin and placebo groups (Pearson correlation 0·167 and 0·133, respectively).

In exploring the association between changes in UACR and eGFR, we observed that larger acute declines in eGFR 2 weeks after randomisation were significantly associated with a larger reduction in UACR at Day 14 (β = 0·25; p<0·001, Figure 4A). This effect was also present in the placebo arm (β = 0·18; p<0·001; interaction p=0·008, Figure 4B). Within the dapagliflozin group this association was similar in patients with and without type 2 diabetes although the distribution was shifted to the right because of the larger decline in eGFR in patients with type 2 diabetes (interaction p=0·32, Figure 4C). In the placebo group the association was also consistent in patients with and without type 2 diabetes, although the left shift in distribution of the correlation in type 2 diabetes was not present (interaction p=0·011, Figure 4D).

When examining the change from baseline in UACR over the first two study weeks with the subsequent rate of eGFR decline during maintenance treatment with dapagliflozin, we observed an inverse correlation such that larger reductions in UACR at Week 2 were associated with less steep declines in eGFR over time (β = –3·06; p=0·006, Figure 5A). Subgroup analysis revealed that this correlation was present in patients with and without type 2 diabetes (β = –2·78; p<0·001 and β = –3·35; p<0·001, Figure 5C) although the UACR change was shifted to the left in

patients with type 2 diabetes as a result of the larger reduction in UACR at Week 2. The association between early change in UACR and longer-term eGFR decline was also evident in patients randomised to placebo but the strength of the association was weaker when compared to patients randomised to dapagliflozin (interaction p<0·001, Figures 5B and 5D). Results were not materially different when the analyses were repeated using change in UACR from baseline to month 4 (Supplement Figure 5).

Discussion

SGLT-2 inhibitors reduce albuminuria in patients with type 2 diabetes. Herein we extend these findings by demonstrating that dapagliflozin reduced albuminuria in patients with CKD with and without type 2 diabetes, with a larger reduction in patients with type 2 diabetes. Consistent with these findings, dapagliflozin significantly increased the likelihood of regression to normo- or microalbuminuria and reduced the likelihood of progression to more severe degrees of albuminuria. Furthermore, we demonstrated that the early decline in eGFR after initiation of dapagliflozin is associated with the early reduction in albuminuria. Finally, the early reduction in albuminuria was associated with attenuated longer-term eGFR decline, particularly among patients treated with dapagliflozin. Taken together, these findings confirm the albuminuria-lowering properties of dapagliflozin in patients with CKD and highlight the importance of monitoring albuminuria after initiation of dapagliflozin as a prognostic marker of sustained kidney health and to guide patient management.

We determined that the approximately 30% reduction in albuminuria observed in dapagliflozin-treated patients was achieved by 2 weeks after starting therapy and

was sustained over time. The change in albuminuria was more pronounced in patients with type 2 diabetes. The magnitude of dapagliflozin-induced reduction in albuminuria in patients with CKD and type 2 diabetes is consistent with previously published results. For example, among patients with CKD and type 2 diabetes enrolled in the DELIGHT trial, dapagliflozin reduced albuminuria by 28% compared to placebo after 4 weeks and the effect was sustained throughout 24-weeks of follow-up.[11] Similarly, canagliflozin reduced albuminuria by 31% on average during follow-up in patients with CKD and type 2 diabetes in the CREDENCE trial.[8] Only two studies have assessed effects of dapagliflozin on albuminuria in patients with CKD without type 2 diabetes.[12,13] The first randomised open-label pilot study reported a 10% reduction in proteinuria in 10 patients with focal segmental glomerulosclerosis.[12] Another study in 53 patients with CKD without type 2 diabetes compared dapagliflozin with placebo in a double blind cross-over trial, and showed a geometric mean reduction in albuminuria of 17%.[13] However, the relatively small sample size and large confidence interval did not exclude the possibility of a larger effect on albuminuria. In the much larger subgroup of patients without type 2 diabetes in the DAPA-CKD trial, we confirm with more precision the albuminuria-lowering effects of dapagliflozin in patients with CKD without type 2 diabetes, although the magnitude of the albuminuria-lowering effect was diminished relative to that observed in patients with type 2 diabetes.

The minimal threshold for an albuminuria-lowering effect to have a high probability of providing a clinical benefit on kidney outcomes has been estimated to be 20% to 30%.[5] Dapagliflozin reduced albuminuria by 35% in patients with type 2 diabetes and reduced the risk of the kidney composite endpoint by 36% in these patients.[14] These

findings are consistent with the proposed albuminuria thresholds to infer clinical benefit. These findings also suggest that the early reduction in albuminuria after initiation of SGLT2 inhibitors may explain a substantial proportion of the long-term kidney protective treatment effect in accordance with previous studies with SGLT2 inhibitors.[15,16] Based on data from other clinical studies, we might not have expected as profound a clinical benefit in patients without type 2 diabetes if benefits were largely mediated through the albuminuria-lowering effect of dapagliflozin. However, dapagliflozin significantly reduced the risk of the kidney composite outcome by 50% and prolonged survival in patients with CKD without type 2 diabetes.[14] Other potential mechanisms mediated through non-albuminuric pathways, such as reductions in tubular workload and hypoxia, increased oxygen delivery capacity, increased urea driven osmolyte production resulting in enhanced ketogenesis and more efficient energy transfer to the kidney, metabolic effects resulting in increased autophagy, and possibly anti-inflammatory and fibrotic effects may explain the long-term kidney protective effects of dapagliflozin in patients without type 2 diabetes, although most of these effects are described in pre-clinical studies.[17-19] Indeed, these effects may be responsible in part for benefits observed in patients with type 2 diabetes as well.

The larger albuminuria-lowering effect observed in patients with type 2 diabetes is likely explained by a larger reduction in intra-glomerular pressure. SGLT2 inhibitors increase glucose-induced osmotic diuresis and natriuresis and induce an acute, reversible reduction in glomerular filtration which is often referred to as the GFR "dip".[20,21] This response pattern suggests that these agents reduce glomerular hypertension – an effect reminiscent of ACE inhibitors/ARBs which also reduce

albuminuria.[22,23] The acute decline in eGFR correlated directly with the reduction in albuminuria in DAPA-CKD participants. Interestingly, as shown in the accompanying paper, the acute reduction in eGFR was nominally larger in patients with type 2 diabetes suggesting a larger reduction in intra-glomerular pressure and resulting in a larger reduction in albuminuria as shown here.

In the DAPA-CKD trial we also demonstrated that a larger reduction in albuminuria during the first two weeks of treatment with dapagliflozin was associated with a lower rate of subsequent kidney function decline. The association was consistent among patients with and without type 2 diabetes. This finding indicates that, although a larger reduction in albuminuria was observed in patients with compared to those without type 2 diabetes, an individual patient with a given albuminuria reduction may experience the same rate of eGFR decline irrespective of diabetes status. Prior studies with renin–angiotensin–aldosterone system inhibitors have shown that early changes in albuminuria correlate with eGFR decline and explain a substantial fraction of the long-term protective effect on kidney outcomes.[24,25] Here we confirm and extend these findings to a large contemporary population treated with SGLT2 inhibitors. These findings suggest that the larger reduction in albuminuria in patients with type 2 diabetes may explain the larger effect of dapagliflozin on the rate of eGFR decline in these patients, as described in the accompanying paper.[26] These findings suggest that the larger reduction in albuminuria may explain the larger effect of dapagliflozin on the rate of eGFR decline as described in the accompanying paper.

Dapagliflozin reduced systolic and diastolic BP compared to placebo. The magnitude of this effect did not differ between patients with and without type 2 diabetes and was consistent with prior dapagliflozin studies in patients with CKD.[11,13,27] The weak correlation between changes in UACR and BP suggests that the modest reduction in BP is not responsible for the sizeable UACR lowering effect of dapagliflozin.

The results of this study should be interpreted with the limitations in mind. First, albuminuria was measured in single spot urine samples. It is known that the within-person day-to-day variation in spot urine samples is high, which may have influenced the precision of our effect estimates.[28] However, the large sample size and results that were consistent with previously published data suggest that our findings are robust, even with extensive variation. We acknowledge that among patients with chronic glomerulonephridites the albuminuria lowering effect of dapagliflozin may vary depending on the specific underlying aetiology of kidney disease. For example, in patients with IgA nephropathy the reduction in albuminuria with dapagliflozin were shown to be of similar magnitude as those observed in patients with type 2 diabetes.[29] Other subgroups of patients with chronic glomerulnonephridites were too small for meaningful analyses. It should also be noted that the associations between early change in albuminuria and subsequent eGFR decline were derived post-hoc and despite adjustment for multiple confounders, residual confounding cannot be excluded. These analyses cannot determine whether patients without a reduction in albuminuria still derive benefit because the subgroups were defined based on a post-randomisation variable.

In conclusion, among patients with CKD with and without type 2 diabetes, dapagliflozin significantly reduced albuminuria and the effect was more pronounced in patients with type 2 diabetes. The similar effects of dapagliflozin on clinical endpoints (CKD progression, cardiovascular death or heart failure hospitalisation, and all-cause mortality) in patients with or without type 2 diabetes, with differential effects on albuminuria suggest that the protective effects of dapagliflozin in patients with CKD are probably mediated in part through pathways related, and in part through pathways unrelated, to reduction in albuminuria.

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Author Contribution

NJ and HJLH had full access to all data and had the final responsibility to submit for publication. NJ and HJLH analysed the data and wrote the first draft of the manuscript. All authors had full access to all of the data, reviewed the manuscript drafts, provided approval of the final version for submission, and take responsibility for the accuracy and integrity of the data.

Data sharing statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Declaration of interests

NJ has nothing to declare.

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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; 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.

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Figure Legends

***Figure 1*: Change from baseline in urinary albumin-to-creatinine ratio in the dapagliflozin and placebo groups in all participants (Panel A), in patients with type 2 diabetes (Panel B) and patients without type 2 diabetes (Panel C)**

***Figure 2*: Effects of dapagliflozin versus placebo on urinary albumin-to-creatinine ratio in patient subgroups defined by baseline characteristics**

***Figure 3*: Albuminuria-lowering effect of dapagliflozin compared to placebo based on baseline HbA1c (Panel A), urinary albumin-to-creatinine ratio (Panel B) and eGFR (Panel C). The solid line represents the geometric mean percentage difference in follow-up UACR between dapagliflozin and placebo. The horizontal dotted line represents no effect (0% difference). The shaded area represents the 95% pointwise confidence interval. The distribution of baseline HbA1c, UACR and eGFR in the dapagliflozin and placebo group is shown in the histograms.**

***Figure 4*: Associations between changes from baseline to Day 14 in estimated GFR and urinary albumin-to-creatinine ratio in the dapagliflozin (Panel A) and placebo (Panel B) groups. The associations between changes in estimated GFR and urinary albumin-to-creatinine ratio in patients with and without type 2 diabetes separately are shown in the dapagliflozin (Panel C) and placebo (Panel D) group**

***Figure 5*: Associations between changes from Baseline to Day 14 in geometric mean UACR with estimated GFR slope from Day 14 through the end-of-treatment in dapagliflozin (Panel A) and placebo (Panel B) groups. The same associations in patients with and without type 2 diabetes separately are shown in the dapagliflozin (Panel C) and placebo (Panel D) groups.**