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

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Summary

Background Reductions in albuminuria are associated with a subsequent lower risk of kidney failure in patients with chronic kidney disease. The SGLT2 inhibitor dapagliflozin significantly reduced albuminuria in patients with type 2 diabetes and normal or near-normal kidney function. Whether this effect persists in patients with chronic kidney disease with and without type 2 diabetes is unknown. We assessed the effects of dapagliflozin on albuminuria in patients with chronic kidney disease with and without type 2 diabetes in the dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial.

Methods DAPA-CKD was a multicentre, double-blind, placebo-controlled, randomised trial done at 386 sites in 21 countries. Patients were eligible for the trial if they had chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) between 25 mL/min per 1·73 m² and 75 mL/min per 1·73 m² and a urinary albumin-to-creatinine ratio (UACR) between 200 mg/g and 5000 mg/g (22·6 to 565·6 mg/mmol). Participants were randomly assigned to dapagliflozin 10 mg (AstraZeneca; Gothenburg, Sweden) once daily or matching placebo, in accordance with the sequestered, fixed randomisation schedule, using balanced blocks to ensure an approximate 1:1 ratio. Change in albuminuria was a pre-specified exploratory outcome of DAPA-CKD. Regression in UACR stage, defined as a transition from macroalbuminuria (≥300 mg/g) to microalbuminuria or normoalbuminuria (<300 mg/g), and progression in UACR stage, defined as a transition from less than 3000 mg/g to 3000 mg/g or greater, were additional discrete endpoints. The trial is registered with ClinicalTrials.gov, NCT03036150.

Findings Between Feb 2, 2017, and April 3, 2020, 4304 patients were recruited and randomly assigned to either dapagliflozin (n=2152) or placebo (n=2152). Median UACR was 949 mg/g (IQR 477 to 1885). Overall, compared with placebo, dapagliflozin reduced geometric mean UACR by 29·3% (95% CI −33·1 to −25·2; p<0·0001); relative to placebo, treatment with dapagliflozin resulted in a geometric mean percentage change of −35·1% (95% CI −39·4 to −30·6; p<0·0001) in patients with type 2 diabetes and −14·8% (−22·9 to −5·9; p=0·0016) in patients without type 2 diabetes over the follow-up visits ($p_{interaction}$<0·0001) Among 3860 patients with UACR of 300 mg/g or greater at baseline, dapagliflozin increased the likelihood of regression in UACR stage (hazard ratio 1·81, 95% CI 1·60 to 2·05). Among 3820 patients with UACR less than 3000 mg/g at baseline, dapagliflozin decreased the risk of progression in UACR stage (0·41, 0·32 to 0·52). Larger reductions in UACR at day 14 during dapagliflozin treatment were significantly associated with attenuated eGFR decline during subsequent follow-up (β per log unit UACR change −3·06, 95% CI −5·20 to −0·90; p=0·0056).

Interpretation In patients with chronic kidney disease 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 effect of dapagliflozin in patients with chronic kidney disease might be mediated through pathways unrelated to reduction in albuminuria.

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Introduction

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

SGLT2 inhibitors slow progression and reduce the risk of kidney failure in patients with and without chronic

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Research in context

Evidence before this study

We searched PubMed between Jan 1, 2000, and April 2, 2021, for trials published in English, 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. Previous clinical trials have shown that sodium-glucose co-transporter 2 (SGLT2) inhibitors reduce albuminuria in patients with type 2 diabetes and chronic kidney disease. For example, in the DELIGHT study, the SGLT2 inhibitor dapagliflozin reduced the urinary albumin-to-creatinine ratio (UACR) by 28% at 4 weeks compared with placebo in patients with chronic kidney disease and type 2 diabetes. Two small clinical studies in patients with chronic kidney disease without diabetes reported that the albuminuria-lowering effect of dapagliflozin was diminished compared with patients with diabetes. Because these studies were relatively small and of short duration, no definitive conclusions could be drawn over whether the different effects of dapagliflozin on albuminuria between patients with and without diabetes were an actual or chance finding.

The DAPA-CKD trial was a large international clinical trial to assess the effects of dapagliflozin on clinical outcomes in patients with chronic kidney disease with and without type 2 diabetes. The results of the trial showed that dapagliflozin compared with placebo significantly decreased the relative risks of kidney failure, cardiovascular death or heart failure hospitalisation, and all-cause mortality. In this prespecified 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

The acute decline in estimated glomerular filtration rate (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 prespecified analysis of the DAPA-CKD trial, we showed that dapagliflozin reduced albuminuria in patients with chronic kidney disease 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 reduces the risk of clinical outcomes in patients with and without type 2 diabetes, suggest that the protective effects of dapagliflozin in patients with chronic kidney disease are likely to be mediated in part through pathways related, and in part through pathways unrelated, to reduction in albuminuria. The association between an early reduction in albuminuria with attenuated longer-term eGFR decline highlights the importance of monitoring albuminuria as a marker to guide patient management.

kidney disease. SGLT2 inhibitors were initially developed as oral glucose-lowering drugs for patients with type 2 diabetes and were not recommended for patients with chronic kidney disease because of lower glycaemic efficacy in patients with lower estimated glomerular filtration rate (eGFR). However, clinical trials showed that SGLT2 inhibitors reduce albuminuria in patients with type 2 diabetes and chronic kidney disease.[6,7] These findings raised interest in studying the effect of SGLT2 inhibitors on long-term kidney outcomes. The CREDENCE trial[8] showed that canagliflozin reduced the risk of clinically important kidney and cardiovascular endpoints in patients with type 2 diabetes and chronic kidney disease.[8] The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial extended these findings to patients with chronic kidney disease with and without type 2 diabetes, showing significantly lower rates of progressive chronic kidney disease, cardiovascular death or heart failure hospitalisation, and all-cause mortality.[9] In this prespecified 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

Study design and participants

DAPA-CKD was a multicentre, double-blind, placebo-controlled, randomised trial done 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 trial protocol, statistical analysis plan, and study design have been published previously.[9,10] The trial protocol was approved by a central or local ethics committee at each trial site. In brief, the primary outcome of the original trial was to determine whether dapagliflozin reduces the incidence of kidney and cardiovascular events in patients with chronic kidney disease with or without type 2 diabetes, with a composite endpoint of a sustained decline of 50% or more 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 per 1·73 m² confirmed by a second measurement after at least 28 days), or death from kidney or cardiovascular

causes. Patients were eligible for the trial if they had chronic kidney disease, defined as an eGFR between 25 mL/min per 1·73 m² and 75 mL/min per 1·73 m² and a urinary albumin-to-creatinine ratio (UACR) between 200 mg/g and 5000 mg/g (22·6 to 565·6 mg/mmol). All participants were required to be receiving a stable dose of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least 4 weeks before enrolment on the trial, 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 masking

Participants were randomly assigned to dapagliflozin (AstraZeneca; Gothenburg, Sweden) once daily or matching placebo, in accordance with the sequestered, fixed randomisation schedule, using balanced blocks to ensure an approximate 1:1 ratio. Randomisation was done via an interactive voice-based or web-based system and stratified by diagnosis of type 2 diabetes and UACR (≤1000 mg/g or >1000 mg/g). Study personnel (apart from the independent data monitoring committee) and participants were masked to treatment allocation. Drug and placebo were identically packaged, with uniform tablet appearance, labelling, and administration schedules.

Procedures

Participants received oral dapagliflozin 10 mg once daily or placebo, in addition to standard care. Study drug 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, as well as information on potential study endpoints, adverse events, concomitant therapies, and study drug adherence. We defined UACR at baseline as the mean of the UACR values from samples collected at the screening and randomisation visit measured in a central laboratory. UACR at baseline and each follow-up visit was measured in a single first morning void urine sample and analysed in a central laboratory.

Outcomes

The mean change in log-transformed UACR from baseline to the end of the study was prespecified 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% 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 microalbuminuria 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 prespecified 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 mg/g *vs* >1000 mg/g). We reported continuous variables as means and SDs for variables with approximate symmetric distributions. Variables with skewed distributions were reported as median (IQR) or as geometric means and categorical variables were reported as n (%).

We analysed the effect of dapagliflozin on UACR by fitting repeated measures models using restricted maximum likelihood. To visually depict the percentage 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, and 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 (eg, 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 randomly assigned treatment on geometric mean UACR across the follow-up assessments for the different levels of the subgroup factor. For all models, we used an unstructured variance–covariance matrix to allow for general patterns of SDs and correlations across the repeated outcome measurements. We fit all models using log-transformed ($\ln[UACR_{visit} \div UACR_{baseline}]$) ratios of follow-up versus 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 HbA_{1c} 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. In this model we replaced baseline log UACR with baseline systolic or diastolic blood pressure and replaced log UACR with systolic or diastolic blood pressure 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 (HRs) and 95% CIs (dapagliflozin *vs* placebo) for UACR progression and regression outcomes. In these models, the baseline hazard function was stratified by type 2 diabetes and UACR category (≤1000 mg/g *vs* >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 a 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 generalised linear regression of the scaled Schoenfeld residuals on follow-up time.

We fit a generalised linear model to assess the association between the change in log transformed albuminuria from baseline to 14 days (visit 2) after random allocation with short-term change in eGFR by randomised 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

	UACR ≤1000 mg/g			UACR >1000 mg/g		
	Dapagliflozin (n=1104)	Placebo (n=1121)	Total (n=2225)	Dapagliflozin (n=1048)	Placebo (n=1031)	Total (n=2079)
Age, years	62·6 (12·3)	62·8 (12·1)	62·7 (12·2)	61·0 (11·8)	60·8 (12·2)	60·9 (12·0)
Sex						
Female	351 (31·8%)	372 (33·2%)	723 (32·5%)	358 (34·2%)	344 (33·4%)	702 (33·8%)
Male	753 (68·2%)	749 (66·8%)	1502 (67·5%)	690 (65·8%)	687 (66·6%)	1377 (66·%)
Race						
White	602 (54·5%)	636 (56·7%)	1238 (55·6%)	522 (49·8%)	530 (51·4%)	1052 (50·6%)
Black or African American	55 (5·0%)	49 (4·4%)	104 (4·7%)	49 (4·7%)	38 (3·7%)	87 (4·2%)
Asian	383 (34·7%)	377 (33·6%)	760 (34·2%)	366 (34·9%)	341 (33·1%)	707 (34·0%)
Other*	64 (5·8%)	59 (5·3%)	123 (5·5%)	111 (10·6%)	122 (11·8%)	233 (11·2%)
Weight, kg	81·8 (20·1)	82·2 (20·8)	82·0 (20·5)	81·1 (20·1)	81·8 (21·0)	81·5 (20·6)
BMI, kg/m²	29·4 (6·0)	29·6 (6·2)	29·5 (6·1)	29·4 (6·0)	29·7 (6·3)	29·6 (6·2)
Blood pressure, mm Hg						
Systolic	133·9 (16·6)	134·6 (16·6)	134·2 (16·6)	139·8 (17·8)	140·5 (17·6)	140·1 (17·7)
Diastolic	76·3 (10·6)	76·4 (10·1)	76·4 (10·4)	78·7 (10·6)	78·7 (10·3)	78·7 (10·4)
HbA_{1c}, %	7·0 (1·7)	6·9 (1·6)	7·0 (1·7)	7·1 (1·7)	7·2 (1·8)	7·2 (1·7)
eGFR, mL/min per 1·73 m²	44·2 (12·1)	43·7 (12·4)	44·0 (12·2)	42·2 (12·5)	42·2 (12·4)	42·2 (12·4)
Haemoglobin, g/L	129·9 (17·2)	129·8 (17·4)	129·8 (17·3)	127·3 (19·0)	125·9 (18·5)	126·6 (18·8)
Serum potassium, mEq/L	4·6 (0·5)	4·6 (0·6)	4·6 (0·5)	4·7 (0·6)	4·7 (0·6)	4·7 (0·6)
UACR, mg/g	480 (318–692)	495 (337–703)	488 (326–698)	1933 (1373–2907)	1931 (1380–2920)	1931 (1377–2910)
Type 2 diabetes	714 (64·7%)	719 (64·1%)	1433 (64·4%)	741 (70·7%)	732 (71·0%)	1473 (70·9%)
Cardiovascular disease	401 (36·3%)	414 (36·9%)	815 (36·6%)	412 (39·3%)	383 (37·1%)	795 (38·2%)
Heart failure	110 (10·0%)	127 (11·3%)	237 (10·7%)	125 (11·9%)	106 (10·3%)	231 (11·1%)
Previous medication						
ACE inhibitor	362 (32·8%)	362 (32·3%)	724 (32·5%)	311 (29·7%)	319 (30·9%)	630 (30·3%)
ARB	720 (65·2%)	737 (65·7%)	1457 (65·5%)	724 (69·1%)	689 (66·8%)	1413 (68·0%)
Diuretic	459 (41·6%)	483 (43·1%)	942 (42·3%)	469 (44·8%)	471 (45·7%)	940 (45·2%)
Statin	692 (62·7%)	715 (63·8%)	1407 (63·2%)	703 (67·1%)	684 (66·3%)	1387 (66·7%)

Data are mean (SD), n (%), or median (IQR). ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio. *Includes Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other.

Table: **Baseline characteristics by baseline UACR subgroups**

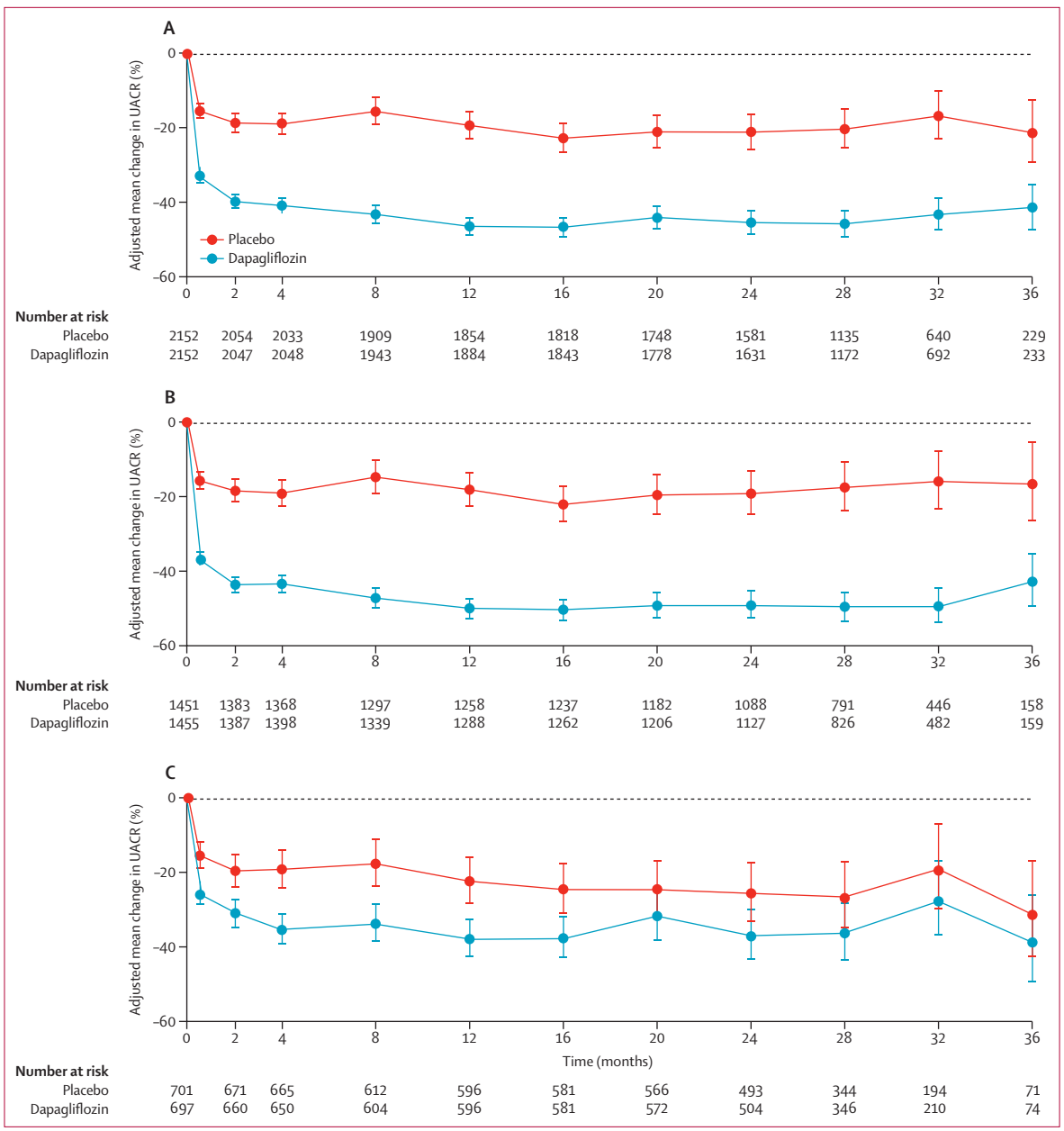

Figure 1: **Change from baseline in urinary albumin-to-creatinine ratio in the dapagliflozin and placebo groups in all participants (A), in patients with type 2 diabetes (B), and patients without type 2 diabetes (C)**
Error bars show 95% CIs. UACR=urinary albumin-to-creatinine ratio.

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 association 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.

We used a two-slope random effects model 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 blood pressure, change from baseline in systolic blood pressure at week 2, baseline HbA_{1c}, baseline haemoglobin, smoking status, and cardiovascular disease history. This analysis was repeated with change in log

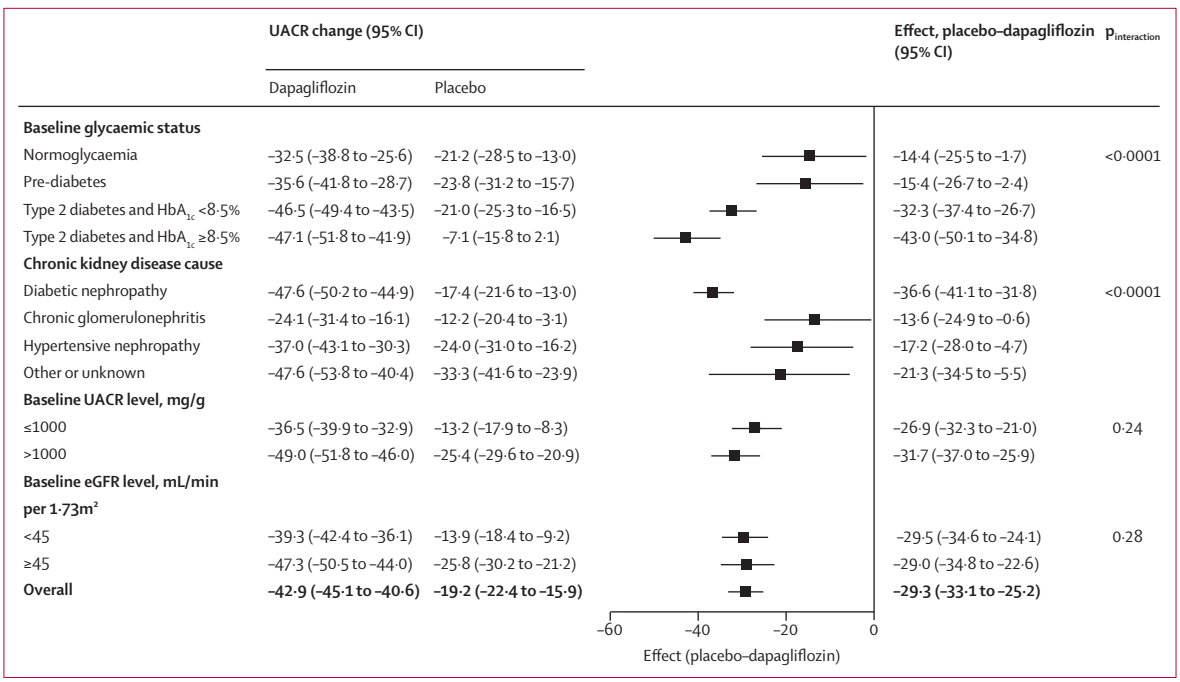

Figure 2: **Effects of dapagliflozin versus placebo on UACR in patient subgroups defined by baseline characteristics**
eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio.

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

We used R version 4.1.1 for statistical analyses. The trial is registered with ClinicalTrials.gov, NCT03036150.

Role of the funding source

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

Results

In the DAPA-CKD trial, between Feb 2, 2017, and April 3, 2020, 4304 patients were recruited and randomly assigned to either dapagliflozin (n=2152) or placebo (n=2152). These participants were followed up for a median of 2·4 years (IQR 2·0–2·7). Overall, participants had a median UACR of 949 mg/g (IQR 477–1885; 107 mg/mmol, IQR 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. 2079 (48%) of 4304 patients had a baseline UACR greater than 1000 mg/g. Compared with 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 higher blood pressure, lower eGFR, and lower haemoglobin. Baseline characteristics were similar between the dapagliflozin group and the placebo group within each UACR subgroup (table).

Compared with placebo, the geometric mean percentage change in UACR was −26·5% (95% CI −22·1 to −30·9; p<0·0001) 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<0·0001) relative to placebo (figure 1A).

The median UACR was 1017 mg/g and 861 mg/g in patients with and without type 2 diabetes, respectively (p<0·0001). Relative to placebo, treatment with dapagliflozin resulted in a geometric mean percentage change of −35·1% (95% CI −39·4 to −30·6; p<0·0001; figure 1B) in patients with type 2 diabetes and −14·8% (−22·9 to −5·9; p=0·0016; figure 1C) in patients without type 2 diabetes over the follow-up visits ($p_{interaction}$<0·0001). Effects of dapagliflozin compared with placebo on UACR were larger in patients with diabetic nephropathy compared with other causes of chronic kidney disease (figure 2). Analysis by categories of glycaemic control (ie, normoglycaemic, pre-diabetes, type 2 diabetes with HbA_{1c} ≥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 using baseline HbA_{1c} as a continuous variable showed a more pronounced effect of dapagliflozin at higher baseline HbA_{1c} (figure 3). The relative effects of dapagliflozin on UACR in patients with type 2 diabetes versus without type 2 diabetes were not accounted for by differences

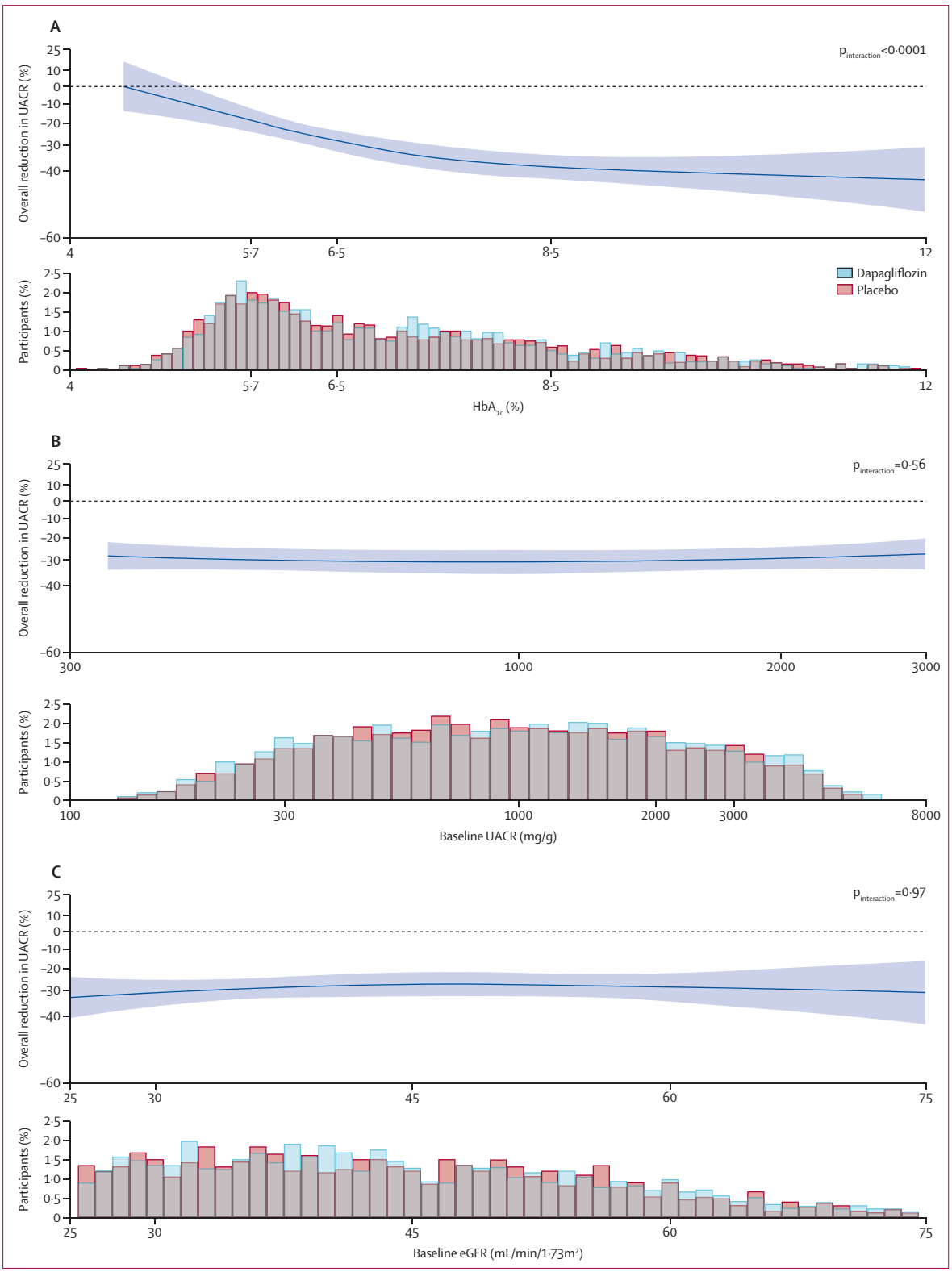

Figure 3: **Albuminuria-lowering effect of dapagliflozin compared with placebo based on baseline HbA_{1c} (A), urinary albumin-to-creatinine ratio (B), and eGFR (C)**
The solid line represents the geometric mean percentage difference in follow-up UACR between dapagliflozin and placebo. The horizontal dashed line represents no effect (0% difference). The shaded area represents the pointwise 95% CI. The distribution of baseline HbA_{1c}, UACR, and eGFR in the dapagliflozin and placebo groups is shown in the histograms. eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio.

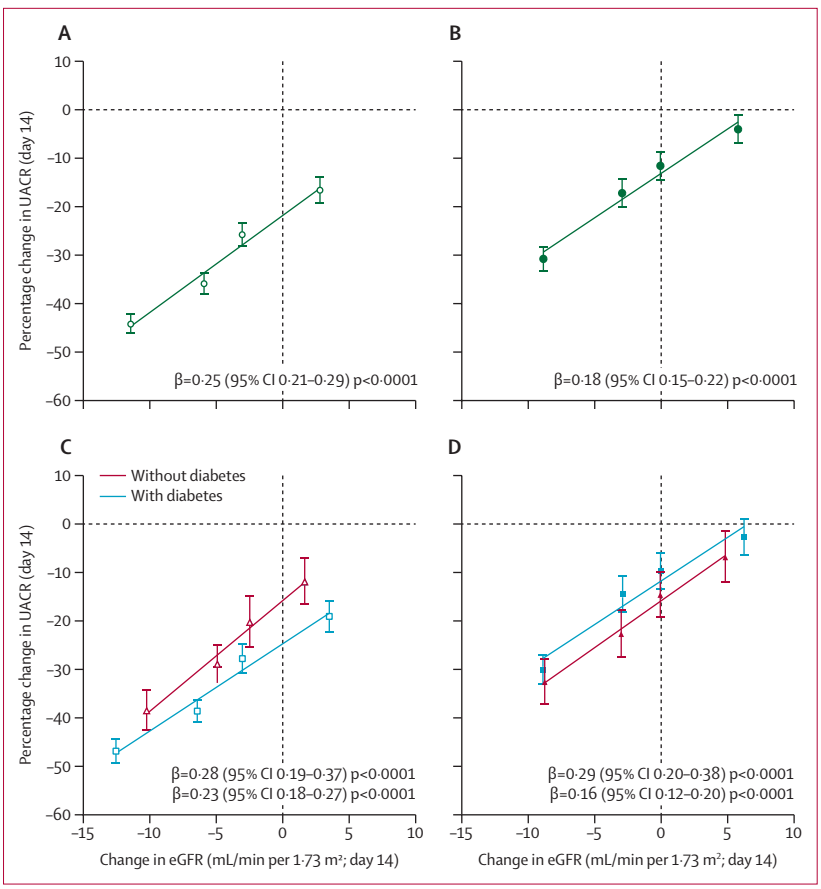

Figure 4: **Associations between changes from baseline to day 14 in eGFR and UACR in the dapagliflozin (A) and placebo (B) groups, and associations between changes in eGFR and UACR in patients with and without type 2 diabetes separately in the dapagliflozin (C) and placebo (D) group**
Error bars indicate 95% CIs. eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio.

in baseline UACR between the two subgroups (appendix pp 2–3). The effects of dapagliflozin on UACR were consistent across the spectrum of baseline eGFR (<45 mL/min per 1·73 m² and ≥45 mL/min per 1·73 m²) and UACR (≤1000 mg/g and >1000 mg/g; figures 2, 3).

Treatment with dapagliflozin significantly increased the likelihood of regression in UACR stage. Among 3860 patients with baseline UACR of 300 mg/g or greater, 638 randomly assigned to dapagliflozin had regression in albuminuria compared with 424 assigned to placebo (HR 1·81, 95% CI 1·60–2·05; appendix pp 5–6). Treatment with dapagliflozin significantly increased the likelihood of regression in UACR in patients with type 2 diabetes (2·06, 1·78–2·39) and without type 2 diabetes (1·33, 1·07–1·66); the effect was significantly more pronounced in patients with type 2 diabetes (baseline diabetes treatment interaction p=0·0011). In parallel, treatment with dapagliflozin significantly reduced the likelihood of progression in UACR stage. Among 3820 patients with UACR less than 3000 mg/g at baseline, 95 allocated to dapagliflozin had progression in albuminuria to nephrotic range of 3000 mg/g or greater compared with 215 patients allocated to placebo (0·41, 0·32–0·52; appendix p 6). The effects of dapagliflozin on progression of albuminuria did not differ significantly among patients with type 2 diabetes (0·39, 0·29–0·51) and without type 2 diabetes (0·50, 0·30–0·82; $p_{intereaction}$=0·40; appendix p 6).

In the placebo group, systolic and diastolic blood pressure remained stable over time (appendix p 7). In the dapagliflozin group, systolic and diastolic blood pressure fell after 2 weeks and this reduction was sustained throughout follow-up (appendix p 7). Compared with placebo, dapagliflozin reduced systolic and diastolic blood pressure by 2·9 mmHg (95% CI 2·3–3·6; p<0·0001) and 1·0 mmHg (0·6–1·4; p<0·0001). We found no evidence that the reduction in systolic and diastolic blood pressure with dapagliflozin compared with placebo was different in patients with type 2 diabetes (3·2 mmHg, 95% CI 2·5–4·0 and 0·8 mmHg, 0·4–1·3], respectively) compared with patients without type 2 diabetes (2·3 mmHg, 1·2–3·4 and 1·4 mmHg, 0·7–2·1, respectively; $p_{interaction}$=0·17 for systolic blood pressure and 0·15 for diastolic blood pressure). The change from baseline in systolic blood pressure at week 2 weakly correlated with 2-week changes in UACR in the dapagliflozin and placebo groups (Pearson correlation coefficients 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 random assignment were significantly associated with a larger reduction in UACR at day 14 (β=0·25; p<0·0001; figure 4A). This effect was also present in the placebo group (β=0·18; p<0·0001; $p_{interaction}$=0·0094; 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 ($p_{interaction}$=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 ($p_{interaction}$=0·011; figure 4D).

When examining the change from baseline in UACR over the first 2 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=0·0056; figure 5A). Subgroup analysis revealed that this correlation was present in patients with and without type 2 diabetes (β=–2·78; p<0·0001 and β=–3·35; p<0·0001, respectively; 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 randomly assigned to placebo but the strength of the association was weaker when compared with patients randomly assigned

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to dapagliflozin ($p_{interaction}$<0·0001; figure 5B, D). Results were essentially similar when the analyses were repeated using change in UACR from baseline to month 4 (appendix p 8).

Discussion

SGLT-2 inhibitors reduce albuminuria in patients with type 2 diabetes.[11] Herein, we extend these findings by showing that dapagliflozin reduced albuminuria in patients with chronic kidney disease 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 normoalbuminuria or microalbuminuria and reduced the likelihood of progression to more severe degrees of albuminuria. Furthermore, we showed that the early decline in eGFR after initiation of dapagliflozin was associated with an early reduction in albuminuria. Finally, an early reduction in albuminuria was associated with attenuated longer-term eGFR decline, particularly among patients treated with dapagliflozin. Taken together, these findings support the albuminuria-lowering properties of dapagliflozin in patients with chronic kidney disease 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 around 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 chronic kidney disease and type 2 diabetes was consistent with previously published results. For example, among patients with chronic kidney disease and type 2 diabetes enrolled in the DELIGHT trial, dapagliflozin reduced albuminuria by 28% compared with 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 chronic kidney disease and type 2 diabetes in the CREDENCE trial.[8] To our knowledge, only two studies have assessed effects of dapagliflozin on albuminuria in patients with chronic kidney disease without type 2 diabetes.[12,13] A randomised open-label pilot study reported a 10% reduction in proteinuria in ten patients with focal segmental glomerulosclerosis.[12] Another study in 53 patients with chronic kidney disease without type 2 diabetes compared dapagliflozin with placebo in a double blind crossover trial, and showed a geometric mean reduction in albuminuria of 17%.[13] However, the relatively small sample size and large CI did not exclude the possibility of a larger effect on albuminuria. In the larger subgroup of patients without type 2 diabetes in the DAPA-CKD trial, we found with more precision the albuminuria-lowering effects of dapagliflozin in patients with chronic kidney disease without type 2 diabetes, although the magnitude of the albuminuria-lowering effect was diminished relative to that observed in patients with type 2 diabetes.

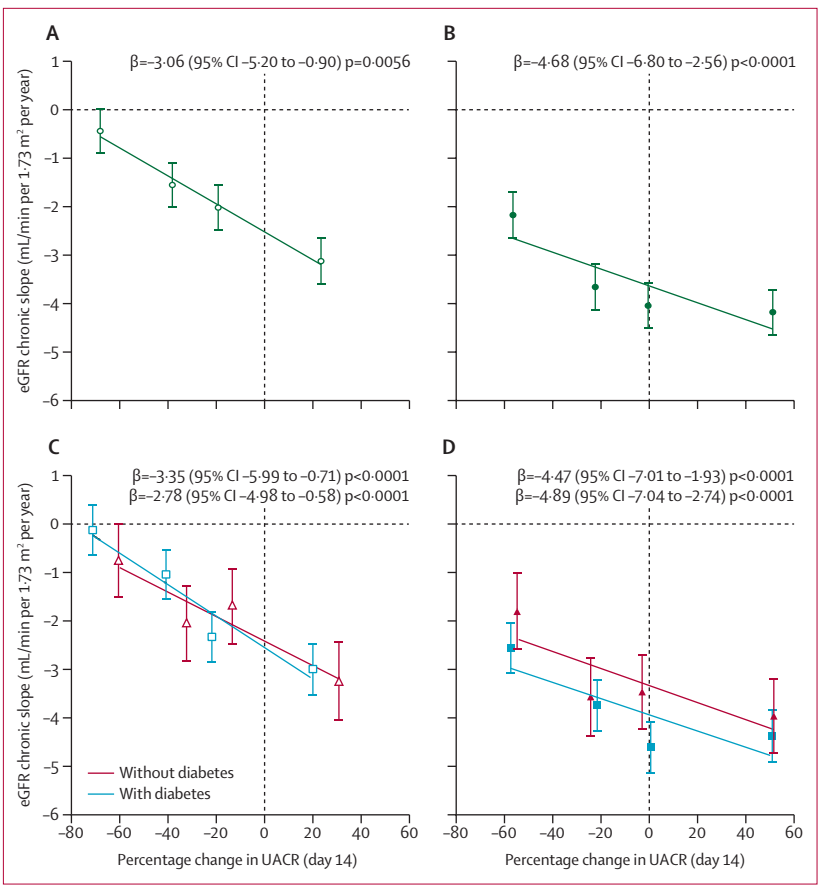

Figure 5: **Associations between changes from baseline to day 14 in geometric mean UACR with eGFR slope from day 14 through to the end-of-treatment in the dapagliflozin (A) and placebo (B) groups, and the same associations in patients with and without type 2 diabetes separately in the dapagliflozin (C) and placebo (D) groups**

Error bars represent 95% CIs. eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio.

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 20–30%.[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 might 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 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 chronic kidney disease 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 could explain the long-term kidney protective effects of dapagliflozin in patients without type 2 diabetes, although most of these effects have been described in pre-clinical studies.[17–19] Indeed, these effects might also be responsible in part for benefits observed in patients with type 2 diabetes.

The larger albuminuria-lowering effect observed in patients with type 2 diabetes could be 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 and ARBs, which also reduce albuminuria.[22,23] The acute decline in eGFR correlated directly with the reduction in albuminuria in DAPA-CKD participants.[24] Interestingly, as shown in the accompanying paper,[24] 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 showed that a larger reduction in albuminuria during the first 2 weeks of treatment with dapagliflozin was associated with a lower rate of subsequent kidney function decline. This association was consistent among patients with and without type 2 diabetes, and indicates that, although a larger reduction in albuminuria was observed in patients with type 2 diabetes compared with those without type 2 diabetes, an individual patient with a given albuminuria reduction might have the same rate of eGFR decline, irrespective of diabetes status. Previous 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.[25,26] In this study, we extend these findings to a large contemporary population treated with SGLT2 inhibitors. Our findings suggest that the larger reduction in albuminuria in patients with type 2 diabetes could explain the larger effect of dapagliflozin on the rate of eGFR decline in these patients.[24] These findings suggest that the larger reduction in albuminuria might explain the larger effect of dapagliflozin on the rate of eGFR decline.[24]

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

Our results should be interpreted with limitations in mind. First, albuminuria was measured in single spot urine samples. Within-person day-to-day variation in spot urine samples is high, which could 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. We acknowledge that among patients with chronic glomerulonephritides the albuminuria lowering effect of dapagliflozin might vary depending on the specific underlying cause of kidney disease. For example, in patients with IgA nephropathy, the reduction in albuminuria with dapagliflozin was shown to be of similar magnitude to that observed in patients with type 2 diabetes.[29] Other subgroups of patients with chronic glomerulonephritides were too small for meaningful analyses. The associations between early change in albuminuria and subsequent eGFR decline were 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 chronic kidney disease 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 (chronic kidney disease 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 chronic kidney disease could be mediated in part through pathways related, and in part through pathways unrelated, to reduction in albuminuria.

Contributors

NJ and HJLH had full access to all data and had final responsibility for the decision 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 the data in the study, reviewed the manuscript drafts, provided approval for the final version for submission, and take responsibility for the accuracy and integrity of the data. HJLH and NJ verified the data.

Declaration of interests

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. GMC has received fees from AstraZeneca for the DAPA-CKD trial steering committee, 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, DxNow, and Outset, has received fees from Akebia, Sanifit and Vertex for trial steering committees, and has received fees for data safety and monitoring board service from Angion, Bayer, and ReCor. 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, Cytokinetics, DAICor, GSK, Ionis Pharmaceuticals, KBP Biosciences, Novartis, and Theracos; and had received personal lecture fees from Abbott, Alkem Metabolics, Eris Lifesciences, Hikma, Lupin, Sun Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, and the Corpus. AML, CDS, and BVS are employees and stockholders of AstraZeneca. 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. 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. RDT is a consultant for AstraZeneca, Amgen, Bayer, Boehringer-Ingelheim, Medscape, Otsuka, Reata, and Relypsa. DCW provides ongoing consultancy services to AstraZeneca and has received honoraria or consultancy fees from Amgen, AstraZeneca, Astellas, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Janssen, Napp, Mundipharma, Tricida, and Vifor Fresenius. HJLH 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. 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.

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