A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy

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Immunoglobulin A (IgA) nephropathy is a common form of glomerulonephritis, which despite use of renin-angiotensin-aldosterone-system blockers and immunosuppressants, often progresses to kidney failure. In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial, dapagliflozin reduced the risk of kidney failure and prolonged survival in participants with chronic kidney disease with and without type 2 diabetes, including those with IgA nephropathy. Participants with estimated glomerular filtration rate (eGFR) 25-75 mL/min/1.73m^2 and urinary albumin-to-creatinine ratio 200-5000 mg/g (22.6-565 mg/mol) were randomized to dapagliflozin 10mg or placebo, as adjunct to standard care. The primary composite endpoint was a sustained decline in eGFR of 50% or more, end-stage kidney disease, or death from a kidney disease-related or cardiovascular cause. Of 270 participants with IgA nephropathy (254 [94%] confirmed by previous biopsy), 137 were randomized to dapagliflozin and 133 to placebo, and followed for median 2.1 years. Overall, mean age was 51.2 years; mean eGFR, 43.8 mL/min/1.73m^2; and median urinary albumin-to-creatinine ratio, 900 mg/g. The primary outcome occurred in six (4%) participants on dapagliflozin and 20 (15%) on placebo (hazard ratio, 0.29; 95% confidence interval, 0.12, 0.73). Mean rates of eGFR decline with dapagliflozin and placebo were −3.5 and −4.7 mL/min/1.73m^2/year, respectively. Dapagliflozin reduced the urinary albumin-to-creatinine ratio by 26% relative to placebo. Adverse events leading to study drug discontinuation were similar with dapagliflozin and placebo. There were fewer serious adverse events with dapagliflozin, and no new safety findings in this population. Thus, in participants with IgA nephropathy, dapagliflozin reduced the risk of chronic kidney disease progression with a favorable safety profile.

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Editor's Note

The Editors would like to call your attention to the commentary regarding this paper.

IgA nephropathy is the most common primary glomerular disease worldwide.[1] Despite advances in our understanding of its pathogenesis, treatment strategies have changed little over the last 2 or 3 decades.[2] Over a period of 4 to 15 years (mean, 6.1 years), approximately 30% of patients with IgA nephropathy progress to kidney failure, and risk factors for deterioration of kidney function include decreased estimated glomerular filtration rate (eGFR), persistent proteinuria, and hypertension.[3]

There are no commercially available disease-specific therapies for IgA nephropathy,[4] in part because no large-scale, randomized clinical trials have demonstrated a reduction in mortality or in major adverse kidney or cardiovascular events with any therapeutic intervention. The established treatment approach for most patients with IgA nephropathy is to apply supportive measures that include the use of renin-angiotensin-aldosterone system blockade,[5] which is recommended for patients with at least moderate proteinuria (>1 g/d) in global clinical practice guidelines (Kidney Disease: Improving Global Outcomes [KDIGO] Glomerular Disease Work Group, personal communication, 2021). Fish oil is also a treatment option suggested for IgA nephropathy based on mixed data from largely underpowered clinical trials and a favorable safety profile.[6] Although IgA nephropathy is an immune-mediated disease, with mucosal-derived IgA forming circulating immune complexes that deposit in the mesangium,[1] the role of immunosuppressive therapy remains controversial and is usually reserved for patients who do not respond to supportive measures. Many patients are offered corticosteroid therapy, or other immunosuppressive agents, such as azathioprine, mycophenolate mofetil, cyclophosphamide, or rituximab, despite a lack of consensus on whether the benefits of these therapies outweigh the risks.[2,4]

Dapagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor that reduces glucose reabsorption in the proximal convoluted tubule of the kidney, thereby enhancing urinary glucose excretion.[7] Because they improve glycemic control, SGLT2 inhibitors were initially developed for the treatment of type 2 diabetes. Subsequently, in large cardiovascular outcome trials involving participants with type 2 diabetes, empagliflozin, canagliflozin, and dapagliflozin slowed the rate of decline of eGFR and reduced albuminuria, with a similar eGFR trend observed for ertugliflozin.[8–11] In type 1 and type 2 diabetes, clinical studies have shown that early and reversible reductions in eGFR occurred on initiation of SGLT2 inhibitor therapy, including in those participants with good glycemic control,[12–14] suggesting that SGLT2 inhibitors reduce intraglomerular pressure, which may preserve long-term kidney function. This same effect was also observed in patients with proteinuric chronic kidney disease (CKD) without diabetes,[15] providing a rationale for the use of these agents as renoprotective therapies in patients with CKD due to causes other than diabetes.

The Dapagliflozin and Prevention of Adverse Outcomes in CKD Trial (DAPA-CKD) tested the hypothesis that dapagliflozin was superior to placebo in reducing the risk of major adverse kidney and cardiovascular events as well as prolonging overall survival in a broad group of individuals with proteinuric CKD.[16] The primary results showed that in patients with CKD, regardless of the presence or absence of type 2 diabetes and regardless of CKD etiology, dapagliflozin significantly reduced the risk of the primary composite outcome and the secondary outcomes, including all-cause mortality, compared with placebo.[17] As previously reported, the DAPA-CKD study included 270 participants with a diagnosis of IgA nephropathy.[18] In this prespecified analysis, we investigated the effects of dapagliflozin on progression of CKD and other major adverse kidney and cardiovascular events in patients with IgA nephropathy.

METHODS

Trial design and study participants

DAPA-CKD was a multicenter, double-blind, placebo-controlled, randomized 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, and was registered with ClinicalTrials.gov as NCT03036150. The trial was approved by Ethics Committees at each participating center. All participants provided written informed consent before commencement of any study-specific procedure. An independent Data Monitoring Committee provided oversight. The study protocol, statistical analysis plan, and patient eligibility criteria have been previously published, as have articles describing trial design, baseline characteristics, primary results, and results stratified by diabetes status and history of cardiovascular disease.[16–20]

Briefly, eligible participants had an eGFR between 25 and 75 ml/min per 1.73 m^2 and urinary albumin-to-creatinine ratio (UACR) between 200 and ≤5000 mg/g (22.6–≤565.6 mg/mmol) and were receiving a stable dose of an angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) for at least 4 weeks before enrollment into the trial, unless contraindicated. Exclusion criteria included patients receiving immunotherapy for primary or secondary kidney disease within the previous 6 months before trial enrollment.[16,17]

Baseline categorization of cause of kidney disease

At the screening visit, investigators recorded the diagnosis of kidney disease and were asked to indicate whether this diagnosis was based on information obtained from a prior kidney biopsy. IgA nephropathy was included as a prespecified category among participants with glomerulonephritis.

Randomization and study procedures

As described previously,[16,17] participants were randomly assigned to dapagliflozin, 10 mg once daily, or matching placebo, in accordance with the sequestered, fixed randomization schedule, using balanced blocks to ensure an approximate 1:1 ratio of the 2 regimens. Randomization was conducted using an interactive voice- or web-based system and stratified on the diagnosis of type 2 diabetes and UACR (≤1000 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, labeling, and administration schedule. After randomization, study visits occurred at 2 weeks, at 2, 4, and 8 months, and at 4-month intervals thereafter. At

Table 1 | Baseline characteristics

Characteristic	Dapagliflozin (n = 137)	Placebo (n = 133)	Total (n = 270)
Age, mean (SD), yr	52.2 (13.1)	50.1 (13.1)	51.2 (13.1)
Female sex, n (%)	44 (32.1)	44 (33.1)	88 (32.6)
Race, n (%)			
White	54 (39.4)	54 (40.6)	108 (40.0)
Black	0 (0)	1 (0.8)	1 (0.4)
Asian	82 (59.9)	77 (57.9)	159 (58.9)
Other	1 (0.7)	1 (0.8)	2 (0.7)
Weight, mean (SD), kg	75.1 (15.4)	78.7 (20.2)	76.8 (18.0)
BMI, mean (SD), kg/m^2	26.3 (4.2)	27.6 (6.1)	27.0 (5.3)
Current smoker, n (%)	13 (9.5)	20 (15.0)	33 (12.2)
Blood pressure, mean (SD), mm Hg			
Systolic	127.7 (16.2)	127.0 (13.9)	127.4 (15.1)
Diastolic	78.7 (11.8)	79.5 (10.1)	79.1 (11.0)
HbA1c, mean (SD), %	5.7 (0.7)	5.6 (0.5)	5.6 (0.6)
Hemoglobin, mean (SD), g/l	133.7 (18.7)	131.3 (15.4)	132.5 (17.2)
Potassium, mean (SD), mmol/l	4.6 (0.5)	4.6 (0.5)	4.6 (0.5)
eGFR, mean (SD), ml/min per 1.73 m^2	44.3 (12.4)	43.2 (12.0)	43.8 (12.2)
Urinary albumin-to-creatinine ratio, median (Q1–Q3), mg/g	889.5 (557.5–1472.0)	902.5 (500.5–1633.0)	900 (539.6–1515.0)
Type 2 diabetes diagnosis, n (%)	24 (17.5)	14 (10.5)	38 (14.1)
History of heart failure, n (%)	4 (2.9)	2 (1.5)	6 (2.2)
Baseline medication, n (%)			
ACE inhibitor	44 (32.1)	41 (30.8)	85 (31.5)
ARB	89 (65.0)	96 (72.2)	185 (68.5)
Diuretic	29 (21.2)	36 (27.1)	65 (24.1)
Statin	68 (49.6)	67 (50.4)	135 (50.0)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; Q1, quartile 1; Q3, quartile 3.

each visit, blood and urine samples were collected for laboratory assessment, vital signs were recorded, and information was gathered on potential study endpoints, adverse events, concomitant therapies, and study drug adherence. The study was stopped early because of clear efficacy following a recommendation by the Independent Data Monitoring Committee.

Safety analyses included all the participants who had undergone randomization and received at least one dose of study drug. Selected adverse event data were collected during the trial. These included serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of interest, including major hypoglycemia and potential diabetic ketoacidosis. Major hypoglycemia was defined by the following criteria, confirmed by the investigator: symptoms of severe impairment in consciousness or behaviour, need for external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention.

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 (ESKD; defined as maintenance dialysis for at least 28 days, kidney transplantation, or eGFR <15 ml/min per 1.73 m^2 confirmed by a second measurement after at least 28 days), or death from a kidney disease–related or cardiovascular cause. The secondary outcomes, in hierarchical order, were a kidney-specific outcome, similar to the primary outcome but excluding cardiovascular death; a composite endpoint of cardiovascular death or hospitalization for heart failure; and all-cause mortality. An independent event adjudication committee assessed all clinical endpoints using these prespecified endpoint definitions.

Statistical analysis

We prespecified analyses of the effects of dapagliflozin on the primary and secondary efficacy endpoints in participants according to the etiology of kidney disease, with the glomerulonephritis category further subcategorized by underlying cause, including IgA nephropathy. We included data from all randomized patients according to the intention-to-treat principle. Study data in tables and text are presented as mean ± SD (or mean ± SE for slope data), or as median with 25th and 75th percentile range.

We fitted a series of Cox proportional hazards regression models, stratified by type 2 diabetes and UACR and adjusted for baseline eGFR to estimate the hazard ratio (HR) and 95% confidence intervals (CIs; dapagliflozin versus placebo) for the primary composite endpoint, secondary endpoints, and prespecified exploratory endpoints. We also assessed the effects of dapagliflozin versus placebo in subgroups by baseline eGFR and UACR. Testing for heterogeneity was done by adding interaction terms between eGFR or UACR, fitted as continuous variables, and randomizing treatment assignment to the relevant Cox model. Sensitivity analysis was restricted to participants with biopsy-proven IgA nephropathy.

The effects of dapagliflozin on the mean on-treatment eGFR slope were analyzed by fitting a 2-slope mixed effects linear spline model (with a knot at week 2) to eGFR values, with random intercept and random slopes for treatment. The variance-covariance matrix was assumed to be unstructured (i.e., purely data dependent). The mean total slope was computed as a weighted combination of the short- and long-term slopes to reflect the mean rate of eGFR change to last on-treatment visit. We also visually presented the pattern of change in mean eGFR using a restricted maximum likelihood repeated measures approach. This analysis included the fixed, categoric effects of treatment, visit, and treatment-by-visit

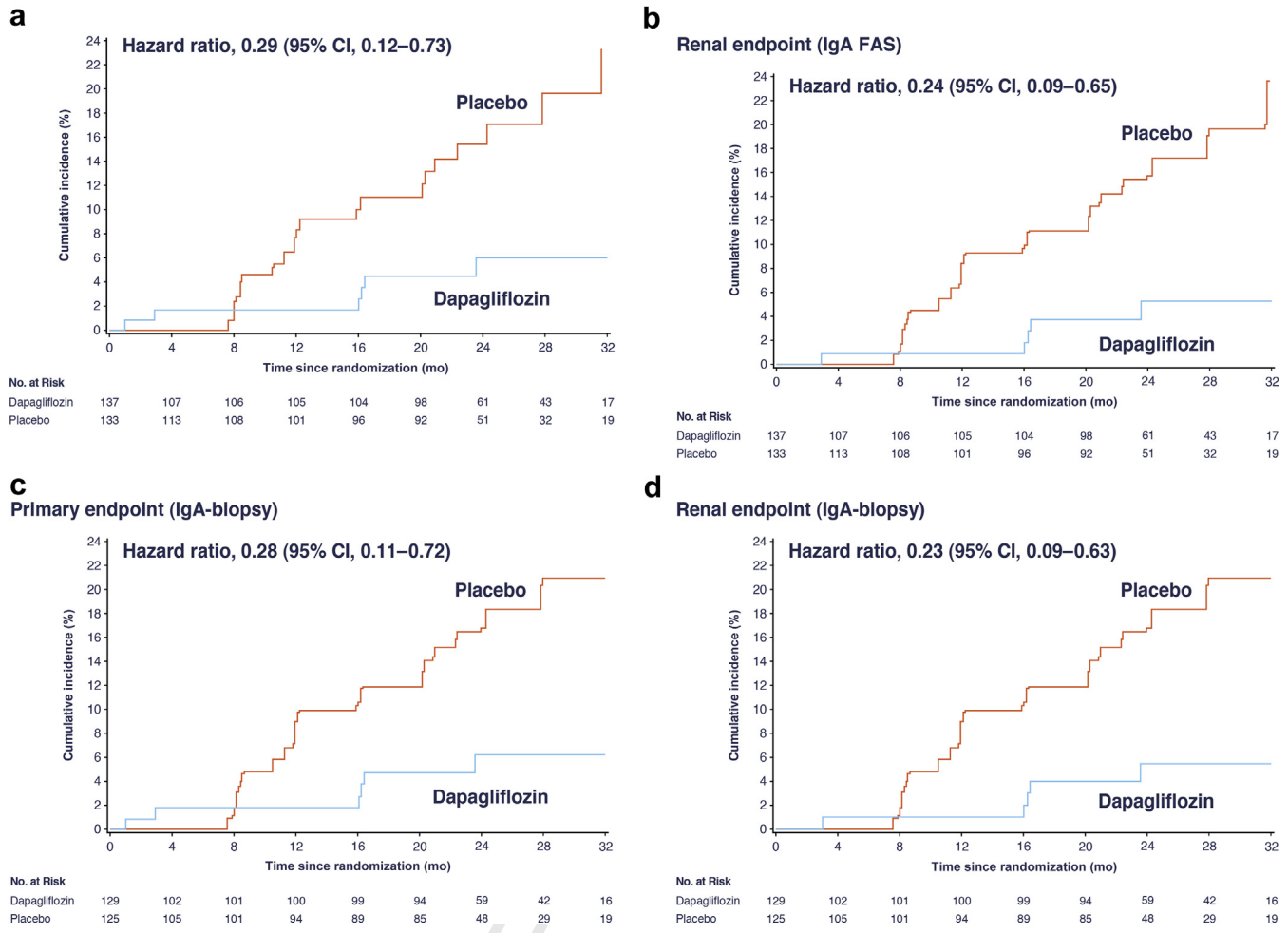

Figure 1 | Cumulative incidence curves in IgA nephropathy for the (a) primary composite endpoint, (b) kidney-specific secondary composite endpoint, (c) primary composite outcome in patients with IgA nephropathy confirmed by a biopsy, and (d) kidney-specific secondary composite outcome in the patients with IgA nephropathy confirmed by a biopsy. CI, confidence interval; FAS, xxx. Q21

interaction as well as the continuous, fixed covariates of baseline eGFR and baseline eGFR-by-visit interaction. The same repeated measures approach was used to fit the change in systolic blood pressure and UACR over time.

All analyses were performed using 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 article for publication.

RESULTS

The trial included 270 participants with investigator-reported IgA nephropathy, of whom 254 (94%) had a kidney biopsy to substantiate this diagnosis. Of these 270 participants, 137 were randomized to dapagliflozin and 133 to placebo. Participants assigned to dapagliflozin or placebo had similar baseline characteristics (Table 1). Overall, the mean age was 51.2 years, 67.4% were male, 58.9% were Asian, and 14.1% had type 2 diabetes. Mean eGFR (SD) was 43.8 (12.2) ml/min per 1.73 m^2 and median UACR (25th–75th percentile range) was 900 mg/g (540–1515 mg/g). Mean overall systolic and diastolic blood pressures were 127 (15) and 79 (11) mm Hg, respectively. The median follow-up was 2.1 years (minimum–maximum, 0.025–3.2 years).

Effects of dapagliflozin on the primary composite and other endpoints

The primary composite outcome occurred in 6 (4%) participants in the dapagliflozin group and 20 (15%) participants in the placebo group (HR, 0.29 [95% CI, 0.12–0.73]; $P = 0.005$; Figures 1a and 2). Absolute risk difference was −10.7% [95% CI, −17.6% to −3.7%]). We observed similar results for the secondary kidney-specific outcome (HR, 0.24 [95% CI, 0.09–0.65; $P = 0.002$]; Figures 1b and 2). Five participants (4%) in the dapagliflozin group and 16 (12%) in the placebo group developed ESKD during the trial (HR, 0.30 [95% CI, 0.11–0.83]; $P = 0.014$; Figure 2).

There was no evidence that the effect of dapagliflozin on the primary composite endpoint differed across subgroups defined by prespecified baseline eGFR and UACR categories (Figure 3). Compared with participants with eGFR ≥45 ml/min per

Variable	Dapagliflozin No. of participants/total no.	Placebo No. of participants/total no.	Dapagliflozin Events/100 patient-years	Placebo Events/100 patient-years	Hazard ratio (95%CI)	*P* Value
Composite primary endpoint (≥50 eGFR decline/ESKD/CV death/renal death)	6/137	20/133	2.5	8.8	0.29 (0.12, 0.73)	0.005
Composite of renal endpoint (≥50 eGFR decline/ESKD/renal death)	5/137	20/133	2.1	8.8	0.24 (0.09, 0.65)	0.002
Composite of ESKD (sustained eGFR <15/chronic dialysis/ renal transplant)	5/137	16/133	2.1	6.9	0.30 (0.11, 0.83)	0.014
Composite endpoint of chronic dialysis, renal transplant, and renal death	2/137	10/133	0.8	4.0	0.23 (0.05, 1.04)	NC

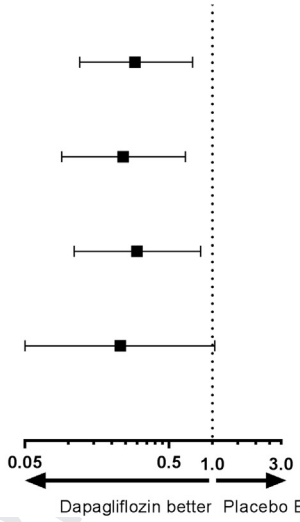

Figure 2 | Forest plot of the key endpoints. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; NC, not calculable.

1.73 m^2 or UACR <1000 mg/g, the incidence of the primary composite outcome was 3.5-fold higher in participants with baseline eGFR <45 ml/min per 1.73 m^2 or UACR >1000 mg/g. In these high-risk subgroups, the HR for the primary composite outcome was 0.41 (95% CI, 0.15–1.14) and 0.27 (95% CI, 0.09–0.82). The absolute risk differences for the primary composite outcome in participants with baseline eGFR <45 ml/min per 1.73 m^2 or UACR >1000 mg/g were −9.2% (95% CI, −20.0% to 1.5) and −18.3% (95% CI, −31.0% to −5.7%).

Sensitivity analyses for the primary endpoint

The effects of dapagliflozin among participants with biopsy-proven IgA nephropathy were consistent with the overall analyses; HR for the primary composite endpoint was 0.28 (95% CI, 0.11–0.72; $P = 0.005$) and for the secondary kidney-specific endpoint was 0.23 (95% CI, 0.09–0.63; $P = 0.002$; Figure 1c and d).

When the effect of dapagliflozin on the primary composite endpoint was investigated in participants with IgA nephropathy based on their diabetes status at baseline, there was a consistent effect in those without diabetes (HR [95% CI], 0.32 [0.13–0.82]; $P = 0.013$). In the 38 participants with IgA nephropathy and type 2 diabetes at baseline, there was only one event (in a participant randomized to placebo) and therefore more detailed analysis could not be performed.

Effects of dapagliflozin on continuous outcomes

The least mean squares eGFR slopes from baseline to end of treatment in the dapagliflozin and placebo groups were −3.5 (SE, 0.5) and −4.7 (SE, 0.5) ml/min per 1.73 m^2 per year, respectively, resulting in a between-group difference of 1.2 ml/min per 1.73 m^2 per year (95% CI, −0.12 to 2.51 ml/min per 1.73 m^2 per year; Figure 4a). During the first 2 weeks, the eGFR reduction was larger in the dapagliflozin than placebo group (−3.4 [±0.4] vs. −0.5 [0.4] ml/min per 1.73 m^2). Thereafter, annual mean eGFR change was smaller with dapagliflozin compared with placebo (−2.2 [0.5] and −4.6 [0.47], respectively), resulting in a between-group difference of 2.4 ml/min per 1.73 m^2 per year (95% CI, 1.08–3.71 ml/min per 1.73 m^2 per year).

At baseline, median UACR (25th–75th percentile range) in the dapagliflozin and placebo groups were 890 (558–1472) mg/g and 903 (501–1633) mg/g, respectively. The mean percentage difference in UACR between dapagliflozin and placebo at month 4 was −35.0% (95% CI, −51.0% to −18.9%; $P < 0.001$). This difference in UACR was sustained throughout follow-up, resulting in a least squares mean difference in change from baseline in UACR between dapagliflozin and placebo during follow-up of −26% (95% CI, −37.0% to −14.0%; $P < 0.001$; Figure 4b).

At baseline, mean systolic and diastolic blood pressure levels in the dapagliflozin and placebo groups were 127.7 mm Hg and 127.0 mm Hg, and 78.7 mm Hg and 79.5 mm Hg, respectively. During follow-up, blood pressures were lower in patients randomized to dapagliflozin. The mean difference in systolic and diastolic blood pressure between the dapagliflozin and placebo groups was 3.5 (95% CI, 5.7−1.3; $P = 0.002$) and 2.2 (95% CI, 3.7−0.8; $P = 0.003$) mm Hg, respectively (Figure 4c and d).

Safety

Overall, adverse events leading to discontinuation of study drug were similar in the dapagliflozin and placebo groups. There were fewer serious adverse events with dapagliflozin versus placebo (Table 2). None of the participants developed major hypoglycemia. There were no events of diabetic ketoacidosis.

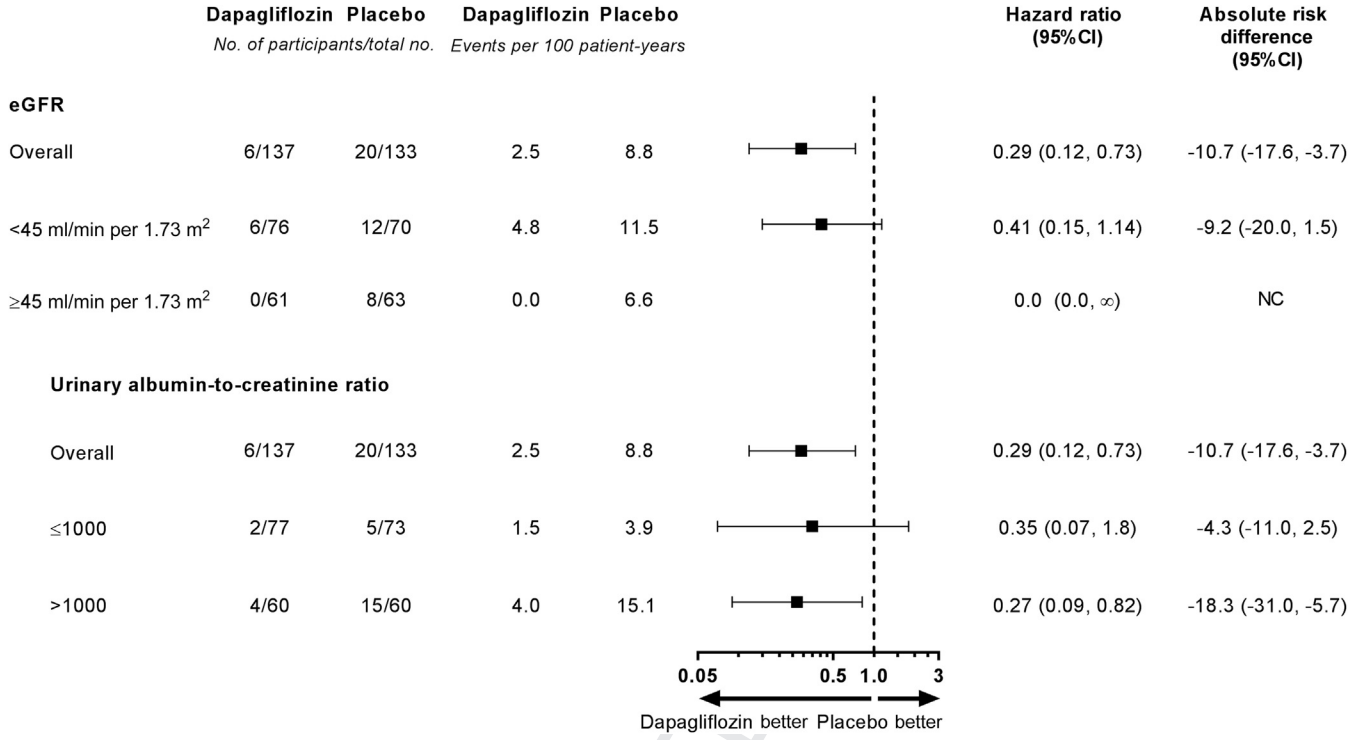

Figure 3 | Forest plot of the effect on the primary composite endpoint by prespecified baseline estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR) subgroups. *P* values for the interaction between baseline UACR and eGFR and treatment effects in participants with IgA > 0.2 for both. CI, confidence interval; NC, not calculable. Q23

DISCUSSION

The DAPA-CKD study assessed the effect of dapagliflozin, 10 mg, in patients with CKD due to several different underlying etiologies, all of whom had albuminuria. Investigator-reported causes of CKD were collected at the time of participant enrollment. After diabetic nephropathy and ischemic/hypertensive nephropathy, participants with IgA nephropathy (n = 270) comprised the third largest group with a single specific kidney disease.[18] The diagnosis of IgA nephropathy was based on a kidney biopsy in 94% of these participants. In this prespecified analysis, we demonstrate that, among participants with IgA nephropathy, dapagliflozin reduced the risk of the primary composite outcome by 71% and the secondary kidney-specific outcome by 75%. Accepting that this study included a small subgroup of DAPA-CKD participants and that the number of events was also small, no prior trial of any therapeutic agent in IgA nephropathy has demonstrated an effect of this magnitude.

The inclusion criteria for DAPA-CKD required participants to be receiving a stable dose of an ACEi or ARB for at least 4 weeks before study enrollment, unless these drugs were contraindicated. Current international guidelines recommend the use of ACEi/ARBs in patients with IgA nephropathy and proteinuria (>1 g/d) with up-titration depending on blood pressure (Kidney Disease: Improving Global Outcomes [KDIGO] Glomerular Disease Work Group, personal communication, 2021). Evidence for use of ACEi/ARB therapy in IgA nephropathy is based largely on small trials of short duration demonstrating favorable changes in biochemical parameters, with no study demonstrating a reduction in progression to kidney failure.[21–23] The benefits of ACEi/ARB therapy are also supported by data extrapolated from larger studies that have included a broader range of patients with nondiabetic kidney disease and albuminuria.[24,25] Given the paucity of event-driven trials in IgA nephropathy, clinicians and patients are likely to welcome a novel therapeutic approach that can be used as an adjunct to ACEi/ARB treatment (or where ACEi/ARB treatment is contraindicated).

The DAPA-CKD study excluded participants receiving immunotherapy for primary or secondary kidney disease within the 6 months before enrollment. Several clinical trials in IgA nephropathy have assessed immunosuppressive regimens. A meta-analysis published in 2012 suggested that there were benefits resulting from the use of corticosteroid therapy, but it was noted that trials included in the meta-analysis were small and of poor quality, with adverse outcomes not fully reported.[26] Since then, larger clinical trials have addressed the role of steroids in the management of IgA nephropathy. The TESTING trial recruited 262 participants with an eGFR of 20 to 120 ml/min per 1.73 m^2 and proteinuria randomized to oral methylprednisolone (0.6–0.8 mg/kg per day) or matching placebo for 2 months, before weaning over 4 to 6 months.[27] The primary composite endpoint was ESKD or a 40% decrease in eGFR, which could not be fully assessed because the trial was terminated early due to an excess of serious

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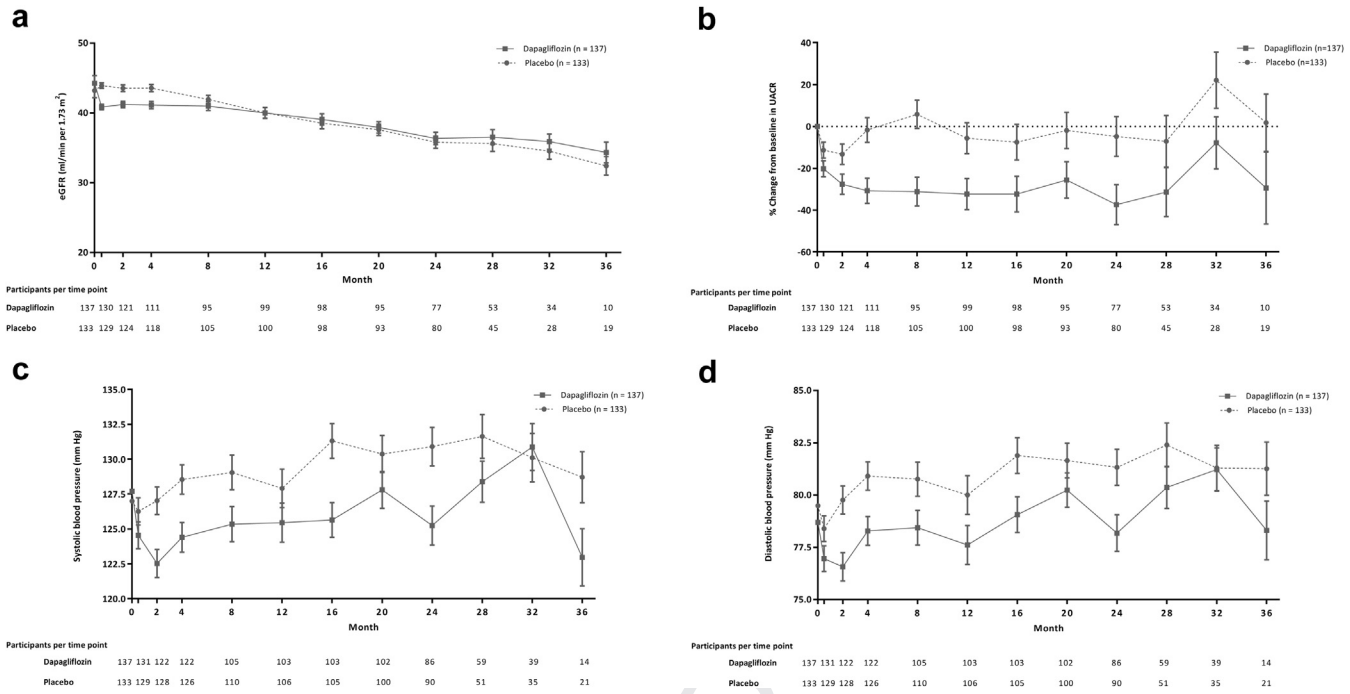

Figure 4 | Changes over time in (a) estimated glomerular filtration rate (eGFR) trajectory, (b) urinary albumin-to-creatinine ratio (UACR), (c) systolic blood pressure, and (d) diastolic blood pressure with dapagliflozin and placebo. Error bars represent SE.

adverse events occurring in participants randomized to methylprednisolone. Recruitment has since restarted with a modified steroid regimen (ClinicalTrials.gov NCT01560052).

Q14 The STOP-IgA nephropathy trial recruited patients with proteinuria ranging from 0.75 to 3.5 g/d and eGFR >30 ml/min per 1.73 m^2 and randomized those who did not "respond" to a 6-month run-in period of supportive care to continued supportive care or to receive additional immunosuppressive therapy. The latter comprised steroids (in patients with an eGFR >60 ml/min per 1.73 m^2) or steroids plus either azathioprine or cyclophosphamide. Analysis of the pooled data showed no benefits of immunosuppression on proteinuria, eGFR decline, or development of ESKD after 3 years[28] and no benefit on the long-term primary composite endpoint (all-cause mortality, ESKD, and decline in eGFR >40%) after up to 10 years of follow-up.[29]

An alternative approach to immunosuppression is the use a formulation of the glucocorticoid budesonide that targets mucosal-associated lymphoid tissues in the gut. In a phase 2b

Q15 trial that enrolled 150 patients, the NEFIGAN study, budesonide reduced urinary protein-to-creatinine ratio and stabilized eGFR decline compared with placebo in patients already receiving ACEi/ARBs.[30] The drug is now being assessed in an ongoing phase 3 trial (NEFIGARD) (ClinicalTrials.gov Identifier: NCT03643965).[31] Other potential therapeutic approaches, some of which are being assessed in ongoing trials, include inhibition of endothelin-1 (NCT04663204 and NCT04573478), inhibition of complement activation, and proteasome inhibitors.[4]

Our findings in the IgA nephropathy subgroup of DAPA-CKD are consistent with findings from other smaller, mechanistic trials of SGLT2 inhibitors in patients without diabetes.[15] In a small, crossover study including patients with proteinuric CKD but without diabetes, of whom nearly 50% had IgA nephropathy, dapagliflozin, 10 mg, led to a short-term but reversible reduction in measured glomerular filtration rate, suggesting that dapagliflozin reduces intraglomerular pressure consistent with observations in patients with diabetes. In addition, the study showed that dapagliflozin reduced body weight and increased hematocrit, suggesting enhanced glycosuria and natriuresis.[15] These physiological changes are believed to preserve long-term kidney function in patients with and without type 2 diabetes, as was observed in the current study. Although the mechanisms by which SGLT2 inhibitors protect kidney function are not fully understood, other proposed pathways include suppression of inflammation and fibrosis, possibly through inhibition of the renin-angiotensin-aldosterone system, and reductions in ischemia in the kidney.[32,33]

Our findings have clinical implications for the management of patients with IgA nephropathy who share the clinical

Table 2 | Safety

Characteristic	Dapagliflozin (n = 137)	Placebo (n = 133)
Adverse events leading to discontinuation of study drug	6 (4.4)	7 (5.3)
Serious adverse events[a]	22 (16.1)	34 (25.6)

Values are n (%).
[a]Including death.

characteristics of the trial participants and who are already on renin-angiotensin-aldosterone system blocking therapy. DAPA-CKD is the first event-driven trial of an SGLT2 inhibitor to include patients with CKD due to a range of underlying etiologies, including patients with IgA nephropathy, and to demonstrate a beneficial effect on major adverse kidney events. We demonstrated a significant absolute risk difference in the primary composite outcome of the trial, which extended to those with lower baseline eGFR and higher baseline albuminuria. Dapagliflozin was well tolerated in the IgA nephropathy population, confirming its established safety profile. Clinicians will be reassured by the fact that there were no cases of diabetic ketoacidosis or major hypoglycemia in participants with IgA nephropathy receiving dapagliflozin. Although these results are encouraging, the ongoing EMPA-KIDNEY trial (ClinicalTrials.gov Identifier: NCT03594110) has recruited a larger population of CKD patients and is likely to shed more light on the safety of SGLT2 inhibitors in patients with IgA nephropathy.

With respect to limitations, the DAPA-CKD study was not specifically designed to test our hypothesis in patients with IgA nephropathy (e.g., we did not have available data on MEST-C score), and the relatively small sample size in this subgroup limited the precision of estimates of treatment effects on the study endpoints. However, the analysis presented herein was included in the original study design, without knowing *a priori* how many participants with IgA nephropathy would ultimately be enrolled. We only learnt after recruitment was complete that the largest number of participants with glomerular disease had a diagnosis of IgA nephropathy. Another limitation is that 6% (16) of IgA nephropathy participants had not undergone a kidney biopsy. The diagnosis of IgA nephropathy in these participants was based on the clinical acumen of the investigator, and it is possible that some or all had another glomerular or kidney disease. Excluding these 16 patients did not alter our conclusions. Furthermore, although we would have liked to have assessed mortality and cardiovascular endpoints in participants with IgA nephropathy, only 3 participants died (2 of cardiovascular disease) and only 1 participant was hospitalized for heart failure. Thus, the small number of events precluded our ability to assess the effect of dapagliflozin on these endpoints in the IgA nephropathy subgroup. Another limitation was that eGFR data were not collected after discontinuation of study drug. We were therefore unable to determine whether initial reductions in eGFR were reversible after discontinuation of dapagliflozin. Finally, although the findings in this particular subgroup of participants with IgA nephropathy are robust, we did not investigate the effects of dapagliflozin in patients with normoalbuminuria or normal glomerular filtration rate, and hence the applicability of the current data to a broader population may be limited.

In conclusion, this prespecified analysis of the DAPA-CKD study demonstrates that in patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduces the risk of CKD progression with a favorable safety profile.

DISCLOSURE

DCW provides ongoing consultancy services to AstraZeneca and 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. RDT is a consultant for AstraZeneca, Amgen, Bayer, Boehringer-Ingelheim, Medscape, Otsuka, Reata, and Relypsa. BVS, CDS, and AML are employees and stockholders of AstraZeneca. GMC has received fees from AstraZeneca for the Dapagliflozin and Prevention of Adverse Outcomes in CKD Trial (DAPA-CKD) trial steering committee, research grants from the National Institute of Diabetes and Digestive and Kidney Diseases, 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. TG has received grants for statistical consulting from AstraZeneca, CSL, and Boehringer-Ingelheim; and has received personal fees from Janssen Pharmaceuticals, DURECT Corporation, and Pfizer for statistical consulting. FFH has received honoraria from AbbVie and AstraZeneca. Payments were made to the employer of JJVM, Glasgow University, for their work on clinical trials, consulting, and other activities: Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardurion, Cytokinetics, GSK, Novartis, Pfizer, Theracos; personal lecture fees: the Corpus, Abbott, Hickma, Sun Pharmaceuticals, Medsca. RP-F received research grants from Fresenius Medical Care, National Council for Scientific and Technological Development, and honoraria (paid to employer) from AstraZeneca, Boehringer-Lilly, Novo Nordisk, Akebia, and Bayer for participation in advisory boards and educational activities. RC-R has received honoraria from AbbVie, AstraZeneca, GlaxoSmithKline, Medtronic, and Boehringer Ingelheim; has lectured for Amgen, Janssen, Takeda, AstraZeneca, and Boehringer Ingelheim; and has received research support from GlaxoSmithKline, Novo Nordisk, and AstraZeneca. PR has received honoraria to Steno Diabetes Center Copenhagen for consultancy from AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, Gilead, Novo Nordisk, Merck, Mundipharma, Sanofi, Vifor; and research support from Astra Zeneca and Novo Nordisk. KU has received research funding and consulting fees from AstraZeneca and has also received consulting fees from NovoNordisk. HJLH is a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Gilead, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe, Novo Nordisk, and Retrophin and received research support from Abbvie, AstraZeneca, Boehringer Ingelheim, and Janssen. All the other authors declared no competing interests.

DATA STATEMENT

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

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AUTHOR CONTRIBUTIONS

DCW was involved in the study design, conduct of the study, data collection and interpretation, and wrote the first draft of the manuscript. HJLH and RDT were involved in the study design, data collection, conduct of the study, data analysis and interpretation, and critical revision of all drafts of the manuscript. GMC, JJVM, TG, FFH, PR, and RC-R are members of the executive committee of the Dapagliflozin and Prevention of Adverse Outcomes in CKD Trial (DAPA-CKD) study and were involved in the study design and data collection, analysis, and interpretation. NJ performed the data analyses. RP-F and KU were national lead investigators and were involved in the data collection and interpretation. AML, CDW, and BVS were involved in the study design, conduct of the study, and data collection and interpretation. DCW and HJLH had full access to all data and had the final responsibility to submit for publication. All authors reviewed the manuscript drafts, provided approval of the final version for submission, and take responsibility for the accuracy and integrity of the data.

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