Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease

DAPA-CKD Trial Committees and Investigators; Wheeler, David C; Stefánsson, Bergur V; Jongs, Niels; Chertow, Glenn M; Greene, Tom; Hou, Fan Fan; McMurray, John J V; Correa-Rotter, Ricardo; Rossing, Peter

Published in:
Lancet Diabetes & Endocrinology

DOI:
10.1016/S2213-8587(20)30369-7

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

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

Lancet Diabetes Endocrinol 2021; 9: 22–31

See **Comment** page 3

*Members listed in appendix 1

Department of Renal Medicine, University College London, London, UK (Prof D C Wheeler MD); The George Institute for Global Health, Sydney, NSW, Australia (Prof D C Wheeler, Prof H J L Heerspink PhD); Late-Stage Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden (B V Stefánsson MD, C D Sjöström MD, A M Langkilde MD); Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands (N Jongs MSc, Prof H J L Heerspink); Departments of Medicine and Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA, USA (Prof G M Chertow MD); Study Design and Biostatistics Center, University of Utah Health Sciences, Salt Lake City, UT, USA (Prof T Greene PhD); Division of Nephrology, Nanfang Hospital, Southern Medical University, National Clinical Research Center for Kidney Disease, Guangzhou, China (Prof F F Hou PhD); Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK (Prof J J V McMurray MD); National Medical Science and Nutrition Institute Salvador Zubirán, Mexico City, Mexico (Prof R Correa-Rotter MD); Steno Diabetes Center Copenhagen, Gentofte, Denmark (Prof P Rossing MD); Department of Clinical Medicine, University of Copenhagen, Copenhagen,

Summary

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

Methods DAPA-CKD was a multicentre, double-blind, placebo-controlled, randomised trial done at 386 study sites in 21 countries, in which participants with a urinary albumin-to-creatinine ratio of 200–5000 mg/g and an estimated glomerular filtration rate (eGFR) of 25–75 mL/min per 1·73m² were randomly assigned (1:1) to dapagliflozin 10 mg once daily or matching placebo, as an adjunct to standard care. The primary outcome was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or kidney-related or cardiovascular death. Secondary efficacy outcomes were a kidney-specific composite (the same as the primary outcome but excluding cardiovascular death), a composite of cardiovascular death or hospital admission for heart failure, and all-cause mortality. In this study, we conducted a prespecified subgroup analysis of the DAPA-CKD primary and secondary endpoints by presence or absence of type 2 diabetes and by aetiology of chronic kidney disease. DAPA-CKD is registered with ClinicalTrials.gov, NCT03036150.

Findings The study took place between Feb 2, 2017, and June 12, 2020. 4304 participants were randomly assigned (2152 to dapagliflozin and 2152 to placebo) and were followed up for a median of 2·4 years (IQR 2·0–2·7). Overall, 2906 (68%) participants had a diagnosis of type 2 diabetes, of whom 396 (14%) had chronic kidney disease ascribed to causes other than diabetic nephropathy. The relative risk reduction for the primary composite outcome with dapagliflozin was consistent in participants with type 2 diabetes (hazard ratio [HR] 0·64, 95% CI 0·52–0·79) and those without diabetes (0·50, 0·35–0·72; $p_{interaction}$=0·24). Similar findings were seen for the secondary outcomes: kidney-specific composite outcome (0·57 [0·45–0·73] *vs* 0·51 [0·34–0·75]; $p_{interaction}$=0·57), cardiovascular death or hospital admission for heart failure (0·70 [0·53–0·92] *vs* 0·79 [0·40–1·55]; $p_{interaction}$=0·78), and all-cause mortality (0·74 [0·56–0·98] *vs* 0·52 [0·29–0·93]; $p_{interaction}$=0·25). The effect of dapagliflozin on the primary outcome was also consistent among patients with diabetic nephropathy (n=2510; HR 0·63, 95% CI 0·51–0·78), glomerulonephritides (n=695; 0·43, 0·26–0·71), ischaemic or hypertensive chronic kidney disease (n=687; 0·75, 0·44–1·26), and chronic kidney disease of other or unknown cause (n=412; 0·58, 0·29–1·19; $p_{interaction}$=0·53), with similar consistency seen across the secondary outcomes. The proportions of participants in the dapagliflozin and placebo groups who had serious adverse events or discontinued study drug due to adverse events did not vary between those with and those without type 2 diabetes.

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

Funding AstraZeneca.

Introduction

SGLT2 inhibitors were developed for the treatment of type 2 diabetes. By reducing glucose reabsorption in the proximal convoluted tubule and thereby enhancing urinary glucose excretion, these drugs reduce blood glucose concentrations. In large cardiovascular safety trials done in participants with type 2 diabetes, the majority of whom did not have chronic kidney disease, SGLT2 inhibitors slowed the rate of decline of estimated glomerular filtration rate (eGFR) and reduced

Research in context

Evidence before this study

We searched PubMed for publications in English from between Jan 1, 1990, and Sept 1, 2020, using the search terms "SGLT2", "SGLT2 inhibitor", "chronic kidney disease", "diabetic nephropathy", "glomerulonephritides", "hypertensive kidney disease", and "randomised controlled clinical trial". In large cardiovascular outcome trials in patients with type 2 diabetes, SGLT2 inhibitors have been shown to have beneficial effects on cardiovascular outcomes and to slow the progression of kidney function decline. The CREDENCE trial showed that the SGLT2 inhibitor canagliflozin reduced the risk of kidney failure and cardiovascular outcomes in patients with type 2 diabetes and stages 2 or 3 chronic kidney disease who were already receiving an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. The DAPA-CKD trial extended these findings to a broader group of patients with chronic kidney disease, a third of whom did not have type 2 diabetes at the time of recruitment and 42% of whom had chronic kidney disease due to causes other than diabetic nephropathy.

Added value of this study

Our results show that the benefits of dapagliflozin on clinical kidney, cardiovascular, and heart failure outcomes, as well as all-cause mortality, were consistent whether or not patients had type 2 diabetes at the time of recruitment into the DAPA-CKD trial. These benefits also extend to patients with a broad range of underlying causes of chronic kidney disease other than diabetic nephropathy, including those with primary glomerulonephritides and ischaemic or hypertensive kidney disease. Dapagliflozin was well tolerated in patients with chronic kidney disease with and without type 2 diabetes.

Implications of all the available evidence

Dapagliflozin could impart substantial cardiorenal benefit to a broad range of patients with impaired kidney function and proteinuria, including patients with non-diabetic chronic kidney disease.

Denmark (Prof P Rossing); **and Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA** (Prof R D Toto MD)

Correspondence to:
Prof David C Wheeler, Department of Renal Medicine, University College London, Royal Free Campus, Rowland Hill Street, London NW3 2NB, UK
d.wheeler@ucl.ac.uk

See **Online** for appendix 1

albuminuria.[1] The results of the first dedicated SGLT2 inhibitor outcome trial in patients with chronic kidney disease and type 2 diabetes, CREDENCE, showed substantial benefits of canagliflozin on kidney and cardiovascular outcomes.[2]

In clinical studies in type 1 and type 2 diabetes, an early reduction in eGFR is seen on initiation of SGLT2 inhibitor treatment, even in participants with good glycaemic control.[3,4] The same effect is seen in patients with proteinuric chronic kidney disease but without diabetes.[5] These observations, along with strong experimental data, support a favourable glomerular haemodynamic effect, leading to speculation that SGLT2 inhibitors have renoprotective actions that are independent of their effects on blood glucose concentrations.[6,7] As such, like angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs),[8–11] SGLT2 inhibitors might have beneficial effects on kidney outcomes in patients with aetiologies of chronic kidney disease other than type 2 diabetes. The DAPA-CKD (Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease) trial tested the hypothesis that, compared with placebo, dapagliflozin is superior in reducing the risk of major adverse kidney and cardiovascular events as well as prolonging overall survival in a broad group of individuals with chronic kidney disease.[12,13] Crucially, and unlike CREDENCE,[2] DAPA-CKD included many participants without type 2 diabetes (a third of the study population). Moreover, not all participants with type 2 diabetes at the time of recruitment had a diagnosis of diabetic nephropathy, with some having specific alternative aetiologies of chronic kidney disease, often supported by a previous kidney biopsy.[14]

In DAPA-CKD, dapagliflozin reduced the risk of kidney failure, death from cardiovascular causes or hospital admission for heart failure, and death from any cause.[12] In this prespecified analysis of DAPA-CKD, we aimed to investigate whether the presence or absence of type 2 diabetes at baseline and the underlying aetiology of kidney disease modified the effects of dapagliflozin on these clinical outcomes.

Methods

Study design and participants

DAPA-CKD was a multicentre, double-blind, placebo-controlled, randomised trial done at 386 study 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 was designed to assess the effects of dapagliflozin on kidney and cardiovascular outcomes in patients with chronic kidney disease, with or without type 2 diabetes. The study protocol,[13] including a detailed description of the trial design, statistical analysis plan, and patient eligibility criteria, and the primary results of the trial,[12] have been published previously.[13] In this study, we conducted a prespecified subgroup analysis of the DAPA-CKD primary and secondary endpoints by presence or absence of type 2 diabetes and by aetiology of chronic kidney disease. The full study protocol and the academic statistical analysis plan used for the present analysis are provided in appendix 2.

See **Online** for appendix 2

Briefly, patients were eligible for the trial if they had chronic kidney disease, defined as an 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). All participants were required to be receiving a stable dose of an ACE inhibitor or ARB for at least 4 weeks before enrolment into the trial, unless contraindicated. Main exclusion criteria included a diagnosis of type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis. Participants receiving immunotherapy for primary or secondary kidney disease within the 6 months before enrolment were also excluded. A full list of inclusion and exclusion criteria is provided in the study protocol (appendix 2).

The trial was approved by ethics committees at all participating centres and all participants provided written informed consent before commencement of any study-specific procedure. An independent data monitoring committee provided trial oversight.

Randomisation and masking

As described previously,[12,13] participants were randomly assigned to dapagliflozin 10 mg (AstraZeneca, Gothenburg, Sweden) once daily or matching placebo, as adjunct to standard care, in accordance with the sequestered, fixed randomisation schedule, with balanced blocks to ensure an approximate 1:1 ratio. Randomisation was done via an interactive voice-based or web-based system and stratified on the 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 schedule.

Procedures

At visit 1 (screening visit), investigators recorded whether the participant had a diagnosis of type 2 diabetes. HbA_{1c} was measured in a central laboratory at visit 1 and visit 2 (randomisation visit). For this prespecified analysis, patients were categorised as having type 2 diabetes if they had a documented diagnosis or if their HbA_{1c} was 6·5% (48 mmol/mol) or higher at both visits 1 and 2.

At the screening visit, investigators also recorded the diagnosis of kidney disease. This diagnosis could be based on previous kidney biopsy where this information was available, but a biopsy-confirmed diagnosis was not mandatory. The following prespecified categories of causes of kidney disease were defined: diabetic nephropathy, chronic glomerulonephritides, ischaemic or hypertensive chronic kidney disease, and other or unknown causes of chronic kidney disease. Patients with type 2 diabetes who had a reported cause of kidney disease other than diabetic nephropathy were analysed according to the investigator-reported underlying aetiology. Among participants with glomerulonephritides, IgA nephropathy comprised the largest subgroup[14] and was analysed separately.

Throughout the study, efforts were made to maintain participants on their stable optimised dose of ACE inhibitors or ARBs. Management of blood pressure, lipids, and glucose and the use of other essential therapies was left to the discretion of the investigators, in keeping with local clinical practice and guidelines.

After randomisation, study visits occurred at 2 weeks, at 2, 4, and 8 months, and at 4-month intervals thereafter. At each visit, blood and urine samples were sent for laboratory assessment, vital signs were assessed, and information on potential study outcome events, adverse events, concomitant therapies, and study drug adherence was recorded.

Outcomes

The primary outcome of the trial was a composite 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. The secondary outcomes were, in hierarchical order: a kidney-specific composite outcome defined in the same way as the primary outcome but excluding cardiovascular death; a composite outcome of cardiovascular death or hospital admission for heart failure; and all-cause mortality. An independent event adjudication committee adjudicated all clinical outcome events using rigorous prespecified endpoint definitions. We also assessed the individual components of the primary composite outcome and a prespecified composite outcome of chronic dialysis, kidney transplantation, and death from kidney-related causes.

Data for adverse events are reported by diabetes status at baseline, and by diagnosis of chronic kidney disease. These data included all serious adverse events, all adverse events leading to discontinuation, and specified adverse events of interest (amputations, potential diabetic ketoacidosis, bone fractures, kidney-related adverse events, major hypoglycaemia, and symptoms of volume depletion). Events of potential diabetic ketoacidosis were adjudicated by an independent adjudication committee. Serious adverse events and discontinuations related to urinary tract infections and genital infections are also reported by diabetes status at baseline.

Statistical analysis

We prespecified analysis of the effects of dapagliflozin on the primary and secondary efficacy outcomes in participants with and without type 2 diabetes, and according to the underlying cause of kidney disease (appendix 2). The statistical assumptions of the DAPA-CKD trial have been published previously[12,13] and are available in the study protocol (appendix 2). For analysis of all efficacy outcomes, we included data from all randomly assigned patients in accordance with the

intention-to-treat principle. We summarised baseline characteristics by diabetes status and cause of chronic kidney disease using means (SDs), medians (IQRs), or proportions.

We fitted a Cox proportional-hazards regression model, stratified by type 2 diabetes and UACR and adjusted for baseline eGFR, to estimate the hazard ratio (HR) and 95% CIs for dapagliflozin compared with placebo in participants with or without type 2 diabetes, and within each prespecified subgroup based on reported cause of chronic kidney disease. We tested for heterogeneity by adding interaction terms between type 2 diabetes status or cause of kidney disease and randomised treatment assignment to the relevant Cox models. We calculated annualised incidence rates, expressed as number of events per 100 patient-years of follow-up. We calculated absolute risk reductions by subtracting the annualised incidence rate in the dapagliflozin group from the placebo group. In a post-hoc calculation, we determined the number needed to treat to prevent one primary outcome event from the reciprocal of the absolute risk difference at the median follow-up, using the Kaplan-Meier curve for the primary outcome by diabetes status. We estimated heterogeneity in absolute treatment effects using fixed-effects meta-analysis. No multiplicity adjustment was made.

Finally, we summarised safety data according to type 2 diabetes status and cause of chronic kidney disease, by treatment group, among all participants who were randomly assigned to and received at least one dose of dapagliflozin or placebo (safety analysis set). Logistic regression was used to estimate the odds ratio and 95% CI for dapagliflozin compared with placebo in participants with and without type 2 diabetes. Tests for interactions were done by adding an interaction term between type 2 diabetes status or cause of kidney disease and treatment assignment to the relevant logistic regression models.

All analyses were done with SAS version 9.4 or R version 4.0.2.

DAPA-CKD is registered with ClinicalTrials.gov, NCT03036150.

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit for publication. All authors had full access to all the data in the study. DCW and HJLH had final responsibility for the decision to submit for publication.

	Type 2 diabetes		Without diabetes	
	Dapagliflozin (n=1455)	Placebo (n=1451)	Dapagliflozin (n=697)	Placebo (n=701)
Age (years)	64·1 (9·8)	64·7 (9·5)	56·9 (14·6)	56·0 (14·6)
Sex				
Female	494 (34%)	471 (32%)	215 (31%)	245 (35%)
Male	961 (66%)	980 (68%)	482 (69%)	456 (65%)
Race				
White	751 (52%)	790 (54%)	373 (54%)	376 (54%)
Black or African American	76 (5%)	61 (4%)	28 (4%)	26 (4%)
Asian	481 (33%)	451 (31%)	268 (38%)	267 (38%)
Other	147 (10%)	149 (10%)	28 (4%)	32 (5%)
Bodyweight (kg)	83·2 (20·9)	83·8 (21·2)	77·9 (17·8)	78·3 (19·9)
Current smoker	195 (13%)	200 (14%)	88 (13%)	101 (14%)
Blood pressure (mm Hg)				
Systolic	138·8 (17·6)	139·6 (17·1)	132·3 (16·4)	132·9 (16·9)
Diastolic	76·5 (10·4)	76·5 (9·9)	79·6 (10·9)	79·6 (10·8)
eGFR (mL/min per 1·73 m^2)	44·0 (12·6)	43·6 (12·6)	41·7 (11·5)	41·8 (11·9)
≥60	179 (12%)	169 (12%)	55 (8%)	51 (7%)
45 to <60	450 (31%)	468 (32%)	196 (28%)	214 (31%)
30 to <45	636 (44%)	603 (42%)	343 (49%)	316 (45%)
<30	190 (13%)	211 (15%)	103 (15%)	120 (17%)
Haemoglobin (g/L)	126·3 (17·8)	125·6 (18·0)	133·4 (17·9)	132·7 (17·2)
Serum potassium (mmol/L)	4·7 (0·6)	4·7 (0·6)	4·6 (0·5)	4·6 (0·5)
Median UACR (mg/g)	1024·5 (472·5–2111·0)	1004·5 (493·3–2017·0)	870·5 (472·0–1533·5)	841·5 (458·5–1554·5)
UACR >1000 mg/g	741 (51%)	732 (50%)	307 (44%)	299 (43%)
HbA_{1c} (%)	7·8 (1·7)	7·8 (1·6)	5·6 (0·4)	5·6 (0·4)
HbA_{1c} (mmol/mol)	62 (18·6)	62 (17·5)	38 (4·4)	38 (4·4)
History of heart failure	177 (12%)	184 (13%)	58 (8%)	49 (7%)
Baseline medication				
ACE inhibitor	451 (31%)	443 (31%)	222 (32%)	238 (34%)
ARB	984 (68%)	974 (67%)	460 (66%)	452 (64%)
Diuretic	718 (49%)	747 (51%)	210 (30%)	207 (30%)
Statin	1039 (71%)	1043 (72%)	356 (51%)	356 (51%)
Metformin (biguanides)*	629 (44%)	613 (43%)	..	..
Sulfonylurea derivative*	389 (27%)	385 (27%)	..	..
DPP-4 inhibitor*	364 (25%)	378 (26%)	..	..
GLP-1 analogue*	63 (4%)	59 (4%)	..	..
Insulin*	814 (56%)	784 (54%)	..	..

Data are mean (SD), n (%), or median (IQR). Table shows data for all randomly assigned participants. eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. *Data for glucose-lowering drug use at baseline among participants with type 2 diabetes were missing for 11 participants in the dapagliflozin group and nine participants in the placebo group; as such, the denominators used for percentage calculations for use of these drugs are 1444 for the dapagliflozin group and 1442 for the placebo group.

Table 1: **Baseline characteristics, stratified by diabetes status at baseline**

Results

The study took place between Feb 2, 2017, and June 12, 2020. 4304 participants were randomly assigned (2152 to dapagliflozin and 2152 to placebo) and were followed up for a median of 2·4 years (IQR 2·0–2·7). The mean age of participants was 62 years (SD 12·1), 1425 (33%) were female, the mean eGFR was 43 mL/min per 1·73 m² (SD 12·4), and the median UACR was 949 mg/g (IQR 477–1885; 107 mg/mmol [IQR 54–213]). The independent data monitoring committee undertook an analysis during routine assessment at a preplanned meeting on March 26, 2020 (with no involvement from the trial funder or the trial executive committee). Following the recommendation of the independent data

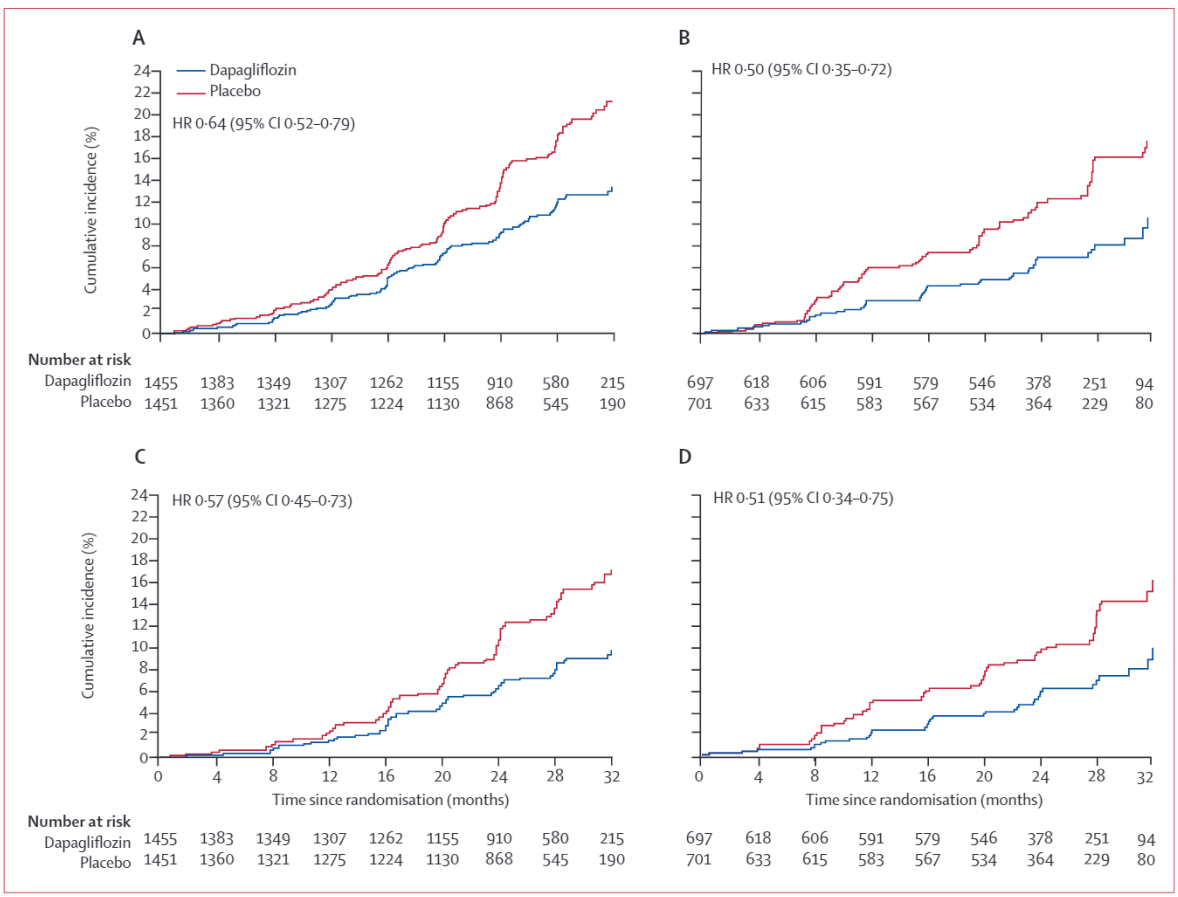

Figure 1: **Kaplan-Meier curves of the primary composite outcome in participants (A) with type 2 diabetes and (B) without diabetes and the kidney-specific composite secondary outcome in participants (C) with type 2 diabetes and (D) without diabetes**
HR=hazard ratio.

monitoring committee and based on the results of this independent analysis, the trial was stopped early because of clear efficacy.[12]

2906 (68%) participants had type 2 diabetes and 1398 (32%) did not. Generally, compared with participants with type 2 diabetes, participants without diabetes were younger, had lower bodyweight, lower eGFR, and lower UACR (table 1). As expected, cardiovascular disease history was less common in participants without diabetes. The proportion of patients with stage 4 chronic kidney disease was similar between patients with (13·8%) and without type 2 diabetes (16·0%). In total, 873 (20·3%) participants had a previous kidney biopsy.[14] Baseline characteristics were well balanced between the dapagliflozin and placebo groups in participants with and without type 2 diabetes (table 1).

Diabetic nephropathy was the most frequently reported cause of chronic kidney disease (2510 [58%]), followed by glomerulonephritis (695 [16%]), ischaemic or hypertensive chronic kidney disease (687 [16%]), and chronic kidney disease of other or uncertain cause (412 [10%]). For 396 participants with type 2 diabetes, investigators reported that chronic kidney disease was attributed to causes other than diabetic nephropathy (200 had ischaemic or hypertensive chronic kidney disease, 97 had glomerulonephritides, and 99 had chronic kidney disease of other or unknown causes).[14] Compared with participants with diabetic nephropathy or ischaemic or hypertensive chronic kidney disease, those with glomerulonephritides were generally younger, had lower bodyweight and lower systolic blood pressure, and were less likely to have heart failure. Haemoglobin levels were lower in participants with diabetic nephropathy than in those with other diagnoses (appendix 1 p 7).

During follow-up, in participants with type 2 diabetes, the event rate for the primary composite outcome was lower in the dapagliflozin group (5·2 events per 100 patient-years) than in the placebo group (8·0 events per 100 patient-years); as reported previously,[12] the HR was 0·64 (95% CI 0·52–0·79). Among participants without diabetes, the event rate for the primary outcome was also lower in the dapagliflozin group (3·4 events per 100 patient-years) than in the placebo group (6·3 events per 100 patient-years); as reported previously,[12] the HR was 0·50 (0·35–0·72). There was no significant interaction of the effect by diabetes status ($p_{interaction}$=0·24). Additionally,

the Kaplan-Meier curves both for participants with and those without type 2 diabetes started to diverge early in the trial, after about 4–8 months, and continued to diverge throughout the remainder of the follow-up (figure 1). We calculated a number needed to treat of 19 to prevent one primary outcome event, for both participants with type 2 diabetes and those without diabetes, over the median follow-up of 2·4 years. The point estimates for each component of the composite outcome favoured dapagliflozin in participants with and those without type 2 diabetes and interaction testing suggested no differences in the effects on the components of the composite primary outcome by diabetes status (figure 2). For the prespecified composite outcome of chronic dialysis, kidney transplantation, and kidney-related death, the HRs were 0·70 (95% CI 0·48–1·00) in participants with type 2 diabetes and 0·59 (0·34–1·02) in those without diabetes ($p_{interaction}$=0·63).

The effect of dapagliflozin on the secondary kidney-specific composite outcome (sustained eGFR decline ≥50%, end-stage kidney disease, or kidney-related death) was consistent in participants with and without type 2 diabetes (figure 3). The Kaplan-Meier curves for participants with diabetes and those without diabetes started to diverge early in the trial and continued to diverge throughout the follow-up (figure 1). Event rates for the composite outcome of cardiovascular death or hospital admission for heart failure were higher in participants with type 2 diabetes than in those without diabetes, but the point estimates for the relative benefit of dapagliflozin were similar, with interaction testing suggesting no effect modification by diabetes status. Finally, all-cause mortality was reduced with dapagliflozin in participants with and without type 2 diabetes, with interaction testing suggesting no difference in effect by diabetes status.

Exploring outcomes by the underlying cause of chronic kidney disease, the effect of dapagliflozin on the primary composite outcome was consistent in participants with diabetic nephropathy, glomerulonephritides, ischaemic or hypertensive chronic kidney disease, and chronic kidney disease of other or unknown cause (figure 4). Likewise, the underlying cause of chronic kidney disease did not modify the beneficial effect of dapagliflozin on the secondary outcomes, including all-cause mortality (figure 4). In participants with glomerulonephritides, IgA nephropathy was the most frequently reported cause of kidney disease. Among 270 participants with IgA nephropathy, dapagliflozin reduced the risk of the primary outcome compared with placebo (HR 0·29, 95% CI 0·12–0·73; appendix 1 p 10).

Absolute risk reductions were generally consistent among participants with and without type 2 diabetes (figure 3). Absolute risk reduction for the primary and kidney-specific outcomes appeared to vary according to cause of kidney disease, with the greatest absolute benefit in participants with glomerulonephritides, but interaction testing suggested no heterogeneity (figure 4). There was

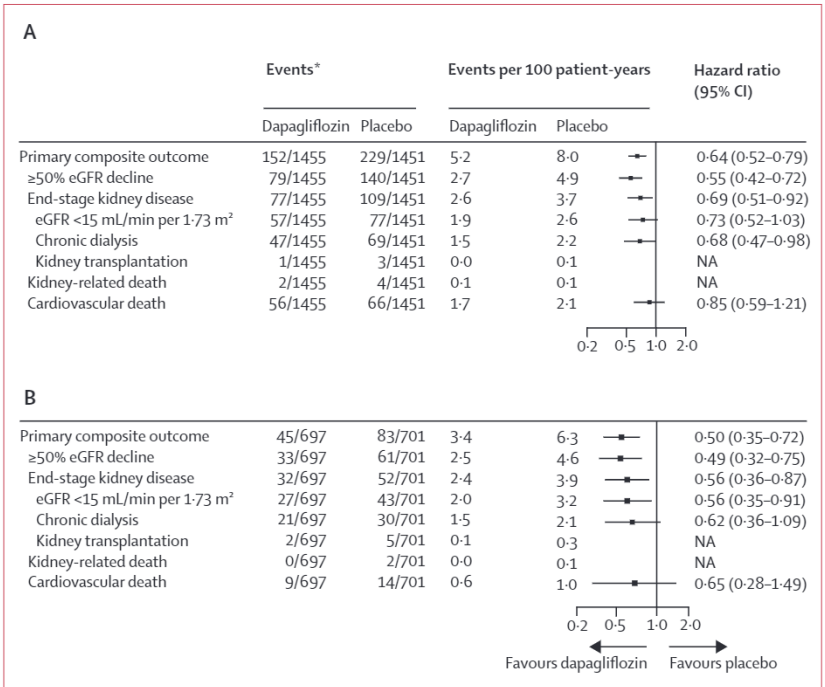

Figure 2: **Forest plot of the components of the primary outcome in (A) participants with type 2 diabetes and (B) participants without diabetes**

Primary composite outcome $p_{interaction}$=0·24. ≥50% eGFR decline $p_{interaction}$=0·68. End-stage kidney disease $p_{interaction}$=0·40. Kidney-related death $p_{interaction}$=NA (not calculable). Cardiovascular death $p_{interaction}$=0·52. eGFR=estimated glomerular filtration rate. NA=not available. *Event data are numbers of participants with an outcome event/total participants.

no evidence that the absolute benefits with respect to all-cause mortality differed according to the presence of diabetes or the cause of kidney disease (figures 3, 4).

The proportions of participants in the dapagliflozin and placebo groups who had serious adverse events or discontinued their assigned study drug because of adverse events did not vary by diabetes status (table 2). Proportions with serious adverse events did not vary by underlying cause of chronic kidney disease, but proportions who discontinued because of adverse events did appear to vary by aetiological subgroup (appendix 1 p 8). There were very few serious adverse events of urinary tract infections or genital infections and very few discontinuations because of adverse events of urinary tract infections or genital infections, with numerically more events in patients with type 2 diabetes than in those without diabetes, and generally more events with dapagliflozin than with placebo (appendix 1 p 9).

Discussion

By including patients with and without type 2 diabetes in the DAPA-CKD trial, we were able to explore the effects of SGLT2 inhibitors in patients with chronic kidney disease due to a range of underlying causes, including chronic glomerulonephritides, ischaemia or hypertensive chronic kidney disease, and other or unknown causes. The results of this prespecified analysis show that

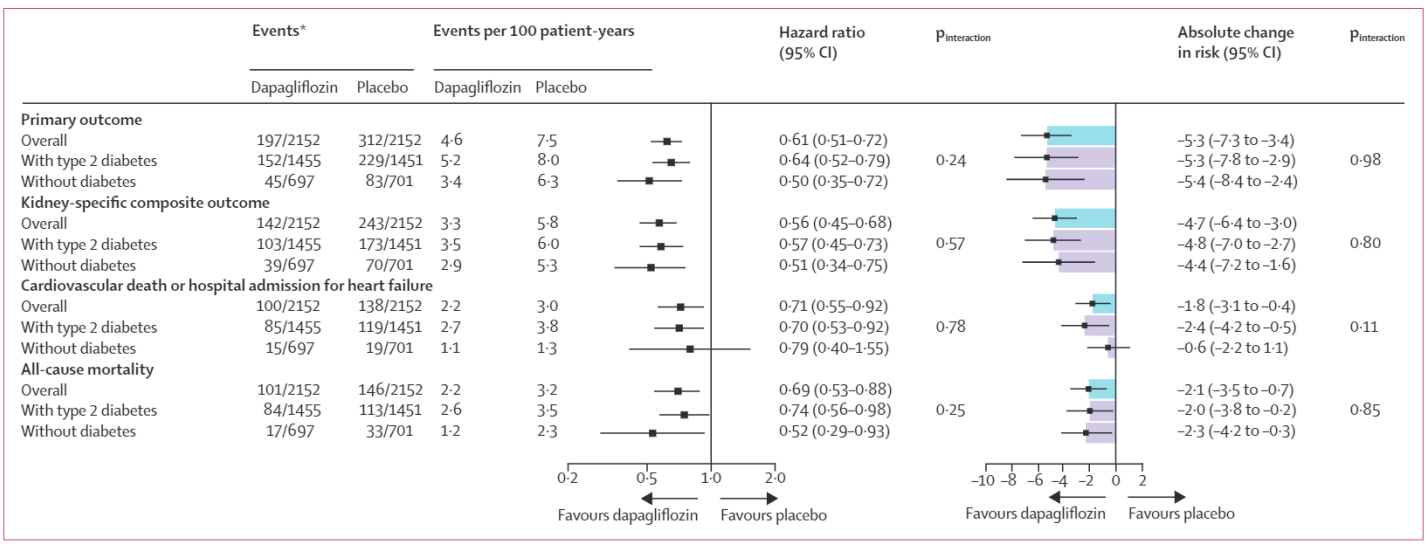

Figure 3: **Forest plot of primary and secondary outcomes in participants with and without diabetes**
*Event data are numbers of participants with an outcome event/total participants.

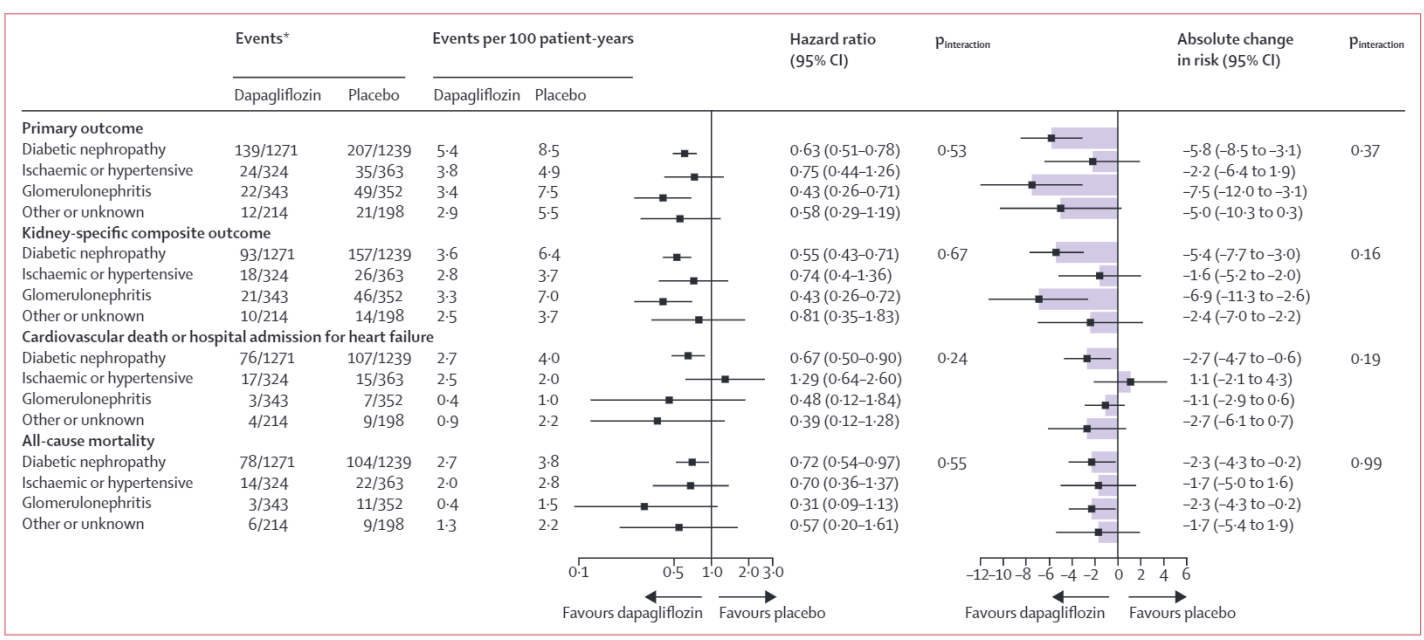

Figure 4: **Forest plot of primary and secondary outcomes by kidney disease diagnosis at baseline**
Participants with type 2 diabetes who had a reported cause of kidney disease other than diabetic nephropathy were analysed on the basis of the investigator-reported underlying aetiology. *Event data are numbers of participants with an outcome event/total participants.

dapagliflozin reduced major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic kidney disease.

Participants enrolled in DAPA-CKD were required to be receiving either an ACE inhibitor or an ARB unless not tolerated. This requirement is because of the known benefits of these drugs in patients with chronic kidney disease and increased urinary protein excretion, as shown in trials completed more than 20 years ago. These previous trials recruited individuals with type 2 diabetes and chronic kidney disease[11] and those with chronic kidney disease but without diabetes.[8–10] One of these trials, which assessed the effect of ramipril in patients with glomerular disease and overt proteinuria but without diabetes, led to the granting of the licence for this drug in non-diabetic chronic kidney disease.[8] The effects of dapagliflozin on the primary and kidney-specific secondary outcomes show its potential to improve the management of patients with chronic kidney disease with and without type 2 diabetes. Apart from

ACE inhibitors and ARBs, no other class of medication has been specifically proven to slow progression of chronic kidney disease in patients with and without diabetes, and no drug to date has improved survival in patients with chronic kidney disease.

Our findings in the non-diabetic chronic kidney disease aetiological subgroups were consistent with findings from other small, mechanistic trials of SGLT2 inhibitors in people without diabetes. In a crossover trial in patients with proteinuric chronic kidney disease but without diabetes, dapagliflozin (10 mg per day) led to an acute but reversible reduction in GFR, suggesting that dapagliflozin reduces intraglomerular pressure, consistent with observations in patients with diabetes.[5] Additionally, the study showed that dapagliflozin reduced bodyweight and increased haematocrit, suggesting enhanced glycosuria and natriuresis. These physiological changes are believed to preserve long-term kidney function both in patients with and without type 2 diabetes, as was apparent in DAPA-CKD. In addition to this haemodynamic-mediated pathway, findings from other studies suggest that metabolic alterations due to enhanced glycosuria in diabetic and non-diabetic settings stimulate a diverse range of molecular changes that result in activation of sirtuin 1 and its downstream activators peroxisome proliferator-activated receptor-γ, coactivator 1α and fibroblast growth factor 21.[15] Activation of these mediators enhances gluconeogenesis, ketogenesis, and fatty acid oxidation and promotes autophagy, a process that cleanses cells of dysfunctional organelles. Collectively these effects ameliorate oxidative stress and inflammation and might result in long-term preservation of kidney function.[15] Another hypothesised metabolic pathway involves fuel switches that exploit amino acids from muscles to generate glucose and fatty acids.[16] Additional proposed pathways of kidney protection include suppression of inflammation and fibrosis, possibly through inhibition of the renin–angiotensin–aldosterone system, and reduction of ischaemia in the kidney.[17,18]

In DAPA-CKD, dapagliflozin significantly reduced the composite outcome of cardiovascular death or hospital admission for heart failure.[12] In the present analysis, based on interaction testing, the relative effect did not differ between participants with and without type 2 diabetes. These findings are in keeping with results from the DAPA-HF trial,[19] which showed that dapagliflozin reduced a composite endpoint of worsening of heart failure or cardiovascular death in patients with heart failure and reduced ejection fraction, with consistent effects in those with and without type 2 diabetes.[20] In DAPA-HF, the composite kidney outcome (≥50% sustained decline eGFR, end-stage kidney disease, or kidney-related death) did not differ between dapagliflozin and placebo,[19] but the rate of decline in eGFR was less with dapagliflozin, a response seen in those with and those without type 2 diabetes at baseline.[21] Results from the EMPEROR-Reduced trial showed that empagliflozin improved clinical outcomes in patients with heart failure and reduced ejection fraction, again both with and without type 2 diabetes, suggesting similar effects of different SGLT2 inhibitors in reducing the risk of heart failure in patients irrespective of diabetes status.[22] The ongoing EMPA-KIDNEY trial (NCT03594110) is being done to investigate the effect of empagliflozin on kidney disease progression and cardiovascular death in patients with chronic kidney disease. As EMPA-KIDNEY allows the inclusion of patients with an eGFR of 25–45 mL/min per 1·73m² who do not have albuminuria, findings from the study might allow us to understand the effects of SGLT2 inhibitors in patients with reduced eGFR with but normoalbuminuria.[23]

	Dapagliflozin (n=2149*)	Placebo (n=2149*)	Odds ratio (95% CI)	$p_{interaction}$
Discontinuations and serious adverse events				
Discontinuation due to adverse event				0·20
Without diabetes	36 (5%)	29 (4%)	1·26 (0·77–2·09)	..
Type 2 diabetes	82 (6%)	94 (6%)	0·86 (0·63–1·17)	..
Any serious adverse event†				0·48
Without diabetes	150 (22%)	167 (24%)	0·88 (0·68–1·12)	..
Type 2 diabetes	483 (33%)	562 (39%)	0·79 (0·68–0·92)	..
Adverse events of special interest				
Amputation‡				0·26
Without diabetes	0	1 (<1%)	NA	..
Type 2 diabetes	35 (2%)	38 (3%)	0·92 (0·57–1·46)	..
Any definite or probable diabetic ketoacidosis				NA
Without diabetes	..	..	..	..
Type 2 diabetes	0	2 (<1%)	NA	..
Fracture§				0·72
Without diabetes	20 (3%)	18 (3%)	1·12 (0·59–2·15)	..
Type 2 diabetes	65 (4%)	51 (4%)	1·28 (0·89–1·87)	..
Kidney-related adverse event§				0·83
Without diabetes	34 (5%)	40 (6%)	0·85 (0·53–1·35)	..
Type 2 diabetes	121 (8%)	148 (10%)	0·80 (0·62–1·03)	..
Major hypoglycaemia¶				1·00
Without diabetes	..	..	..	..
Type 2 diabetes	14 (1%)	28 (2%)	0·49 (0·25–0·93)	..
Volume depletion§				0·27
Without diabetes	35 (5%)	19 (3%)	1·90 (1·09–3·41)	..
Type 2 diabetes	92 (6%)	71 (5%)	1·31 (0·96–1·81)	..

Data are the number (%) of participants with at least one occurrence of an event in the specified adverse event category. Adverse events were assessed in the safety analysis set, which consists of all participants who were randomly assigned to and received at least one dose of dapagliflozin or placebo. NA=not available. *In the dapagliflozin group there were 696 participants without diabetes and 1453 participants with type 2 diabetes and in the placebo group there were 699 participants without diabetes and 1450 participants with type 2 diabetes (used as denominators for percentage calculations). †Includes deaths (in the dapagliflozin group there were 84 deaths in participants with type 2 diabetes and 17 deaths in those without diabetes; in the placebo group there were 113 deaths in those with type 2 diabetes and 33 deaths in those without diabetes). ‡Surgical or spontaneous or non-surgical amputation, excluding amputation resulting from trauma. §Based on a predefined list of preferred terms. ¶Adverse event with the following criteria, confirmed by the investigator: symptoms of severe impairment in consciousness or behaviour, need for external assistance, use of an intervention to treat hypoglycaemia, and prompt recovery of acute symptoms following the intervention.

Table 2: **Adverse events by diabetes status at baseline**

Our findings have wide-ranging clinical implications. First, clinicians who consider treatment with dapagliflozin for kidney or cardiovascular protection in patients who share the clinical characteristics of the participants of this trial might do so irrespective of the presence of type 2 diabetes and can expect protection even in those without type 2 diabetes. The absolute risk reductions for the primary outcome in participants with and without type 2 diabetes translated to a number needed to treat to prevent a major kidney outcome or cardiovascular death of 19, both for patients with type 2 diabetes and for those without diabetes. Second, by contrast with the earlier large outcome trials, about one in seven participants in DAPA-CKD had stage 4 chronic kidney disease, with a similar proportion among participants with and without diabetes.[14] The positive benefit-to-risk ratio in patients with and without type 2 diabetes suggests that initiation of dapagliflozin could be appropriate in patients with an eGFR as low as 25 mL/min per 1·73m².

Dapagliflozin was well tolerated in the study population, confirming its established beneficial safety profile. Overall, the proportion of participants with serious adverse events was higher among participants with type 2 diabetes than among those without type 2 diabetes. It is reassuring to note that there were no cases of diabetic ketoacidosis or hypoglycaemia in participants receiving dapagliflozin who did not have type 2 diabetes. Safety findings were generally consistent across subgroups defined by underlying cause of chronic kidney disease; although interaction testing suggested a difference in the proportions of participants who discontinued assigned treatment because of adverse events, this could be a chance finding due to the number of interaction tests done.

This study has some limitations. The diagnosis of type 2 diabetes was based on investigator-reported diagnosis or HbA_{1c} values at screening and randomisation visits and not on more conventional tests such as oral glucose tolerance testing or fasting glucose measurement. However, our approach was compatible with recommendations from WHO for the diagnosis of type 2 diabetes.[24] Additionally, the cause of kidney disease was based on clinical judgement (investigator reports), which might have led to misclassifications. A biopsy confirmation of the cause of the kidney disease was not a requirement for enrolment in the study but was available for one in five trial participants. In the absence of kidney biopsy for many patients, diabetic kidney disease might be considered a more appropriate term for the diagnoses classified as diabetic nephropathy; however, within the reporting of these analyses we have retained the prespecified diagnosis categories to be consistent with the investigator-reported diagnoses. A further limitation is that, although the independent data monitoring committee recommended termination of the trial because of overwhelming efficacy, it did so well before the anticipated number of outcome events had accrued. Thus, although treatment with dapagliflozin resulted in fewer major adverse kidney and cardiovascular events compared with placebo, the precision of the effect estimates was lower than it would have been had the trial been allowed to extend to planned completion. Notably, DAPA-CKD enrolled patients with increased albuminuria and the results cannot be generalised to patients with impaired kidney function and normoalbuminuria. Finally, in this study, eGFR data were not collected after the discontinuation of the study drug. Consequently, we were unable to ascertain whether the initial reduction in eGFR was reversible after discontinuation of dapagliflozin, a phenomenon that has been shown in several other studies in patients with chronic kidney disease, both with type 2 diabetes[25,26] and without diabetes.[5]

In conclusion, the findings of this prespecified analysis of the DAPA-CKD trial show that, when added to ACE inhibitor or ARB therapy, dapagliflozin reduces the risk of several important clinical outcomes in patients with chronic kidney disease, with these benefits apparent irrespective of diabetes status and the underlying cause of kidney disease.

Contributors

DCW was involved in the study design, study conduct, data collection, and data interpretation; he co-wrote the first draft of the report and participated in critical revision of all drafts of the report. HJLH was involved in the study design, study conduct, data analysis, and data interpretation; he co-wrote the first draft of the report and participated in critical revision of all drafts of the report. GMC, JJVM, TG, FFH, RC-R, PR, and RDT are members of the study's executive committee and were involved in the study design and interpretation of the data. HJLH led and NJ performed the data analysis; TG also contributed to the data analysis. AML, CDS, and BVS were involved in the study design, study conduct, data collection, and data interpretation. HJLH, DCW, and NJ had full access to and verified the data in the study. All authors reviewed the drafts of the report, approved the final version for submission, and take responsibility for the accuracy and integrity of the data.

Declaration of interests

DCW provides ongoing consultancy services to AstraZeneca and has received honoraria for participation in advisory boards and other activities, consultancy fees, or both from Amgen, AstraZeneca, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Janssen, Napp, Mundipharma, Medscape, Merck Sharp & Dohme, Pharmacosmos, Reata, Takeda, and Vifor Fresenius. GMC has received fees from AstraZeneca for participation in the DAPA-CKD trial executive committee. He has received research grants from the US National Institute of Diabetes and Digestive and Kidney Diseases and Amgen; is on the board of directors for Satellite Healthcare; has received fees for participation in advisory boards for Ardelyx, Baxter, CloudCath, Cricket, DiaMedica, Durect, DxNow, Outset, and Reata; and holds stock options for Ardelyx, CloudCath, Durect, DxNow, and Outset. He has also received fees from Akebia, Gilead, Sanifit, and Vertex for participation in trial steering committees and from Angion, Bayer, and ReCor for service on data and safety monitoring boards. TG has received grants for statistical consulting from AstraZeneca, CSL, Vertex, and Boehringer Ingelheim and has received personal fees for statistical consulting from Janssen, Durect, and Pfizer. FFH has received fees from AstraZeneca for participation in the DAPA-CKD trial executive committee and from AbbVie for participation in the SONAR trial executive committee. JJVM has received payments to his employer (University of Glasgow) for his work on clinical trials, consulting, and other activities from Amgen, AstraZeneca, Cytokinetics, and Servier. RC-R has received fees for participation in the DAPA-CKD trial executive committee; speaker fees from Boehringer Ingelheim, Amgen, and Janssen; personal fees for

advisory events from Novo Nordisk, Medtronic, and Boehringer Ingelheim; and research support from GlaxoSmithKline and Novo Nordisk. PR has received honoraria (paid to his employer [Steno Diabetes Center Copenhagen]) for participation on steering groups from AstraZeneca, Novo Nordisk, Gilead, and Bayer; for participation in advisory boards from Sanofi Aventis and Boehringer Ingelheim; and for lecture fees from Lilly. RDT has received fees from AstraZeneca for participation in the DAPA-CKD trial executive committee; fees for participation in advisory boards from Bayer and Relypsa; fees for participation on data monitoring committees from Reata and Bayer; consultancy fees from Boehringer Ingelheim; and is a faculty associate for Quest Diagnostics. BVS, CDS, and AML are employees and stockholders of AstraZeneca. HJLH has received honoraria (paid to his institution [University Medical Center Groningen]) for participation in steering committees from AstraZeneca, Janssen, Gilead, Bayer, Chinook, and CSL Pharma; honoraria for participation in advisory boards from Merck, Mitsubishi Tanabe, Janssen, and Mundipharma; fees for consultancy from AstraZeneca, AbbVie, Retrophin, Boehringer Ingelheim, and Novo Nordisk; and research grant support from AstraZeneca, AbbVie, Janssen, and Boehringer Ingelheim. NJ declares no competing interests.

Data sharing

The data underlying the findings in this report may be obtained in accordance with AstraZeneca's data sharing policy.

Acknowledgments

The trial was funded by AstraZeneca. The authors thank all investigators, trial teams, and patients for their participation in the trial. We also acknowledge Parita Sheth and Nicola Truss (inScience Communications, London, UK) for assistance with the editing of the draft report and preparation of the figures (support funded by AstraZeneca).

References

1 Wheeler DC, James J, Patel D, et al. SGLT2 inhibitors: slowing of chronic kidney disease progression in type 2 diabetes. *Diabetes Ther* 2020; **11**: 2757–74.

2 Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377**: 644–57.

3 Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; **375**: 323–34.

4 Cherney DZI, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014; **129**: 587–97.

5 Cherney DZI, Dekkers CCJ, Barbour SJ, et al. Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. *Lancet Diabetes Endocrinol* 2020; **8**: 582–93.

6 Heerspink HJL, Perkins BA, Fitchett DH et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation* 2016; **134**: 752–72.

7 van Bommel EJM, Muskiet MHA, van Baar MJB, et al. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. *Kidney Int* 2020; **97**: 202–12.

8 The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997; **349**: 1857–63.

9 Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996; **334**: 939–45.

10 Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006; **354**: 131–40.

11 Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**: 861–69.

12 Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020 **383**: 1436–46.

13 Heerspink HJL, Stefansson BV, Chertow GM, et al. Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. *Nephrol Dial Transplant* 2020; **35**: 274–82.

14 Wheeler DC, Stefansson B.V, Batiushin M, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. *Nephrol Dial Transplant* 2020; **35**: 1700–11.

15 Packer M. Cardioprotective effects of sirtuin-1 and its downstream effectors potential role in mediating the heart failure benefits of SGLT2 (sodium-glucose cotransporter 2) inhibitors. *Circ Heart Fail* 2020; published online Sept 8. https://dx.doi.org/10.1161/CIRCHEARTFAILURE.120.007197.

16 Marton A, Kaneko T, Kovalik J-P, et al. Organ protection by SGLT2 inhibitors: role of metabolic energy and water conservation. *Nat Rev Nephrol* 2020; published online Oct 1. https://dx.doi.org/10.1038/s41581-020-00350-x.

17 Dekkers CCJ, Petrykiv S, Laverman GD, Cherney DZ, Gansevoort RT, Heerspink HJL. Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers. *Diabetes Obes Metab* 2018; **20**: 1988–93.

18 Woods TC, Satou R, Miyata K, et al. Canagliflozin prevents intrarenal angiotensinogen augmentation and mitigates kidney injury and hypertension in mouse model of type 2 diabetes mellitus. *Am J Nephrol* 2019; **49**: 331–42.

19 McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381**: 1995–2008.

20 Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA* 2020; **323**: 1353–68.

21 Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. *Circulation* 2020; published online Oct 12. https://dx.doi.org/10.1161/CIRCULATIONAHA.120.050391.

22 Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; **383**: 1413–24.

23 Herrington WG, Preiss D, Haynes R, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clin Kidney J* 2018; **11**: 749–61.

24 WHO. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. Geneva: World Health Organization, 2011.

25 Fioretto P, Del Prato S, Buse JB, et al. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): the DERIVE study. *Diabetes Obes Metab* 2018; **20**: 2532–40.

26 Pollock C, Stefánsson B, Reyner D, et al. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019; **7**: 429–41.

For **AstraZeneca's data sharing policy** see https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure