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Published in:
Lancet Diabetes & Endocrinology

DOI:
[10.1016/S2213-8587\(20\)30162-5](https://doi.org/10.1016/S2213-8587(20)30162-5)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

DIAMOND investigators, Cherney, D. Z. I., Dekkers, C. C. J., Barbour, S. J., Cattran, D., Abdul Gafor, A. H., Greasley, P. J., Laverman, G. D., Lim, S. K., Di Tanna, G. L., Reich, H. N., Vervloet, M. G., Wong, M. G., Gansevoort, R. T., & Heerspink, H. J. L. (2020). 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 & Endocrinology*, 8(7), 582-593. [https://doi.org/10.1016/S2213-8587\(20\)30162-5](https://doi.org/10.1016/S2213-8587(20)30162-5)

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Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial

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Summary

Background SGLT2 inhibition decreases albuminuria and reduces the risk of kidney disease progression in patients with type 2 diabetes. These benefits are unlikely to be mediated by improvements in glycaemic control alone. Therefore, we aimed to examine the kidney effects of the SGLT2 inhibitor dapagliflozin in patients with proteinuric kidney disease without diabetes.

Methods DIAMOND was a randomised, double-blind, placebo-controlled crossover trial done at six hospitals in Canada, Malaysia, and the Netherlands. Eligible participants were adult patients (aged 18–75 years) with chronic kidney disease, without a diagnosis of diabetes, with a 24-h urinary protein excretion greater than 500 mg and less than or equal to 3500 mg and an estimated glomerular filtration rate (eGFR) of at least 25 mL/min per 1.73 m², and who were on stable renin–angiotensin system blockade. Participants were randomly assigned (1:1) to receive placebo and then dapagliflozin 10 mg per day or vice versa. Each treatment period lasted 6 weeks with a 6-week washout period in between. Participants, investigators, and study personnel were masked to assignment throughout the trial and analysis. The primary outcome was percentage change from baseline in 24-h proteinuria during dapagliflozin treatment relative to placebo. Secondary outcomes were changes in measured GFR (mGFR; via iothexol clearance), bodyweight, blood pressure, and concentrations of neurohormonal biomarkers. Analyses were done in accordance with the intention-to-treat principle. This study is registered with ClinicalTrials.gov, NCT03190694.

Findings Between Nov 22, 2017, and April 5, 2019, 58 patients were screened, of whom 53 (mean age 51 years [SD 13]; 32% women) were randomly assigned (27 received dapagliflozin then placebo and 26 received placebo then dapagliflozin). One patient discontinued during the first treatment period. All patients were included in the analysis. Mean baseline mGFR was 58.3 mL/min per 1.73 m² (SD 23), median proteinuria was 1110 mg per 24 h (IQR 730–1560), and mean HbA_{1c} was 5.6% (SD 0.4). The difference in mean proteinuria change from baseline between dapagliflozin and placebo was 0.9% (95% CI –16.6 to 22.1; p=0.93). Compared with placebo, mGFR was changed with dapagliflozin treatment by –6.6 mL/min per 1.73 m² (–9.0 to –4.2; p<0.0001) at week 6. This reduction was fully reversible within 6 weeks after dapagliflozin discontinuation. Compared with placebo, bodyweight was reduced by 1.5 kg (0.03 to 3.0; p=0.046) with dapagliflozin; changes in systolic and diastolic blood pressure and concentrations of neurohormonal biomarkers did not differ significantly between dapagliflozin and placebo treatment. The numbers of patients who had one or more adverse events during dapagliflozin treatment (17 [32%] of 53) and during placebo treatment (13 [25%] of 52) were similar. No hypoglycaemic events were reported and no deaths occurred.

Interpretation 6-week treatment with dapagliflozin did not affect proteinuria in patients with chronic kidney disease without diabetes, but did induce an acute and reversible decline in mGFR and a reduction in bodyweight. Long-term clinical trials are underway to determine whether SGLT2 inhibitors can safely reduce the rate of major clinical kidney outcomes in patients with chronic kidney disease with and without diabetes.

Funding AstraZeneca.

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Introduction

Inhibition of proximal tubular SGLT2 reduces plasma glucose and HbA_{1c} in patients with type 2 diabetes by augmenting glucosuria. SGLT2 inhibitors were therefore originally developed as glucose-lowering drugs, but have subsequently been shown to have broader applications

as cardiovascular and kidney protective therapies independent of glucose lowering in large cardiovascular and kidney outcome trials.^{1–4} Post-hoc analyses and meta-analyses of these trials have shown that favourable effects of SGLT2 inhibitors on cardiorenal outcomes are consistent across baseline estimated glomerular filtration

Lancet Diabetes Endocrinol
2020; 8: 582–93

This online publication has been corrected. The corrected version first appeared at thelancet.com/diabetes-endocrinology on June 25, 2020

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Research in context

Evidence before this study

We searched PubMed for publications in English from Jan 1, 1990, to Jan 31, 2020, using the search terms “SGLT2”, “SGLT2 inhibitor”, “albuminuria”, “proteinuria”, “kidney disease”, “nephropathy”, and “HbA_{1c}”. SGLT2 inhibitors have cardiovascular and kidney benefits in people with type 2 diabetes, as shown in large cardiovascular and kidney outcome trials and analyses of data from clinical practice registries. Analyses from these studies suggest that the benefits of SGLT2 inhibitors on kidney function are largely independent of their glucose-lowering effects. In the CREDENCE trial, the SGLT2 inhibitor canagliflozin was shown to reduce the risk for cardiorenal outcomes in people with type 2 diabetes and chronic kidney disease irrespective of baseline HbA_{1c}. Whether kidney protection with SGLT2 inhibitors can similarly be achieved in non-diabetic proteinuric kidney disease is unknown.

Added value of this study

To our knowledge, this is the first randomised, placebo-controlled, multicentre study examining the effects of an SGLT2 inhibitor on proteinuria in patients with non-diabetic chronic kidney disease and residual proteinuria. 6 weeks of treatment with dapagliflozin did not reduce proteinuria compared with placebo. Dapagliflozin treatment caused an anticipated acute dip in iothexol-measured glomerular filtration rate (mGFR),

which was completely reversible after drug discontinuation. Furthermore, dapagliflozin decreased bodyweight and increased haematocrit and haemoglobin (suggesting haemoconcentration); although systolic and diastolic blood pressure were not significantly different between dapagliflozin and placebo treatment, they were numerically lower with dapagliflozin treatment. Dapagliflozin did not reduce HbA_{1c} or fasting plasma glucose in these patients without diabetes and did not affect urine adenosine or other vasoactive mediators, which are factors that have been linked with changes in kidney haemodynamics in previous SGLT2 inhibitor studies in patients with diabetes.

Implications of all the available evidence

Dapagliflozin treatment affects mGFR, bodyweight, and markers of haemoconcentration in patients with and without diabetes, suggesting ubiquitous effects on kidney function irrespective of glycaemic effects. The absence of an effect on proteinuria during 6 weeks of treatment suggests that reduced glomerular pressure via SGLT2 inhibition does not affect proteinuria in this short timeframe in patients without diabetes. The effects of long-term treatment with dapagliflozin on clinical kidney outcomes in patients with chronic kidney disease with and without diabetes are being evaluated in the ongoing DAPA-CKD and EMPA-KIDNEY trials.

rate (eGFR) and HbA_{1c} subgroups, as well as in patients with and without albuminuria.^{5–7} Specifically, in the CREDENCE trial, canagliflozin reduced the risk for the major kidney composite outcome by about a third in participants with type 2 diabetes and chronic kidney disease.⁴ This reduction was also apparent in subgroups of patients in whom diabetes was well controlled, suggesting that the effect of SGLT2 inhibitors on kidney function is unlikely to be mediated by further improvement of glycaemic effects.⁸

Although the mechanisms of kidney protection by SGLT2 inhibitors are not yet fully understood, kidney benefits might be mediated by natriuresis, leading to systemic and intrarenal haemodynamic changes. Specifically, SGLT2 inhibition increases distal tubular sodium and chloride delivery to the macula densa, which augments tubuloglomerular feedback, causing afferent arteriolar vasoconstriction. As a result, SGLT2 inhibitors cause an acute decrease in intraglomerular pressure and GFR in hyperfiltering animals and humans, and also acutely lower GFR in non-hyperfiltering patients with type 2 diabetes.^{9,10} This reduction in intraglomerular pressure could lead to protection against loss of kidney function in patients with various causes of chronic kidney disease, but has so far been studied mainly in the setting of diabetic kidney disease.

In view of the potential role of hyperglycaemia-independent kidney protective pathways, we hypothesised that kidney protection with SGLT2 inhibitors can be similarly applied to other causes of non-diabetic

proteinuric kidney disease that are characterised by single-nephron hyperfiltration, such as obesity-induced chronic kidney disease, focal segmental glomerular sclerosis, and IgA nephropathy.¹¹ The few existing preclinical and clinical pilot studies of SGLT2 inhibitors in non-diabetic chronic kidney disease were non-randomised and did not include control groups, and results have been inconsistent.^{12–15} Therefore, in the DIAMOND study, we aimed to examine the effects of an SGLT2 inhibitor on surrogate measures of kidney protection, such as proteinuria and measured GFR (mGFR), in an exclusively non-diabetic population at risk of progressive kidney function loss.

Methods

Study design and participants

DIAMOND was an investigator-initiated, prospective, randomised, double-blind, placebo-controlled crossover trial done at six hospitals in Canada (University Health Network Toronto, Toronto, and University of British Columbia, Vancouver), Malaysia (Hospital Canselor Tuanku Muhriz and University of Malaya, Kuala Lumpur), and the Netherlands (University Medical Centre Groningen, Groningen, and Amsterdam University Medical Center, Amsterdam).

Adult patients (aged 18–75 years) with chronic kidney disease, with a 24-h urinary protein excretion greater than 500 mg and less than or equal to 3500 mg and an eGFR of at least 25 mL/min per 1.73 m², and who had used a stable

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dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers for at least 4 weeks before randomisation were recruited from the outpatient clinics of the participating hospitals. The main exclusion criteria were a diagnosis of type 1 or type 2 diabetes; a diagnosis of chronic kidney diseases considered unresponsive to SGLT2 inhibition, such as autosomal dominant or recessive polycystic kidney disease, lupus nephritis, or antineutrophil cytoplasmic antibody-associated vasculitis; an indication for immunosuppressants or previous use of immunosuppressants for kidney disease within 6 months before enrolment; peripheral vascular disease; or being at risk of dehydration or volume depletion. A full list of the inclusion and exclusion criteria is provided in the appendix (pp 55–56).

See Online for appendix

The study was approved by the medical ethics committees of each centre. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and in line with the study protocol and statistical analysis plan (appendix pp 1–54). Written informed consent was provided by all participants before any study-specific procedures were initiated.

Randomisation and masking

Participants were randomly assigned (1:1) to one of two treatment groups, in which patients either first received placebo then received dapagliflozin 10 mg per day, or vice versa. Randomisation was done via an interactive web response system (IBM Clinical Development Merge)

with block size of four. The randomisation codes were provided by an unmasked pharmacist employed by the study sponsor (University Medical Centre Groningen, Groningen, Netherlands). The study medication was labelled on the basis of the generated codes. The generated codes were used by the unmasked data manager to set up the randomisation module. The investigational drug or placebo was dispensed by local pharmacists, who were masked to treatment group assignment, on the basis of the randomisation number generated in the interactive web response system. Study medication was dispensed at the beginning of the two treatment periods. Patients, investigators, and all study personnel were masked to treatment group assignment throughout the trial and analysis. There were no medical emergencies that required activation of the unblinding procedure. The dapagliflozin and placebo tablets appeared identical and were supplied in identical bottles.

Procedures

Patients that met the inclusion criteria and received a maximum tolerable stable dose of an ACE inhibitor or angiotensin receptor blocker for at least 4 weeks proceeded directly to the randomisation visit. Participants for whom ACE inhibitor or angiotensin receptor blocker medication was changed during the preceding 4 weeks of the screening visit entered a run-in phase during which the type and dose of these drugs were stabilised. Thereafter, all patients were randomly assigned to one of the two consecutive double-blind treatment periods in which they were first treated with placebo and then with dapagliflozin 10 mg per day or vice versa. Dapagliflozin and placebo tablets were supplied by AstraZeneca (Gothenburg, Sweden). Each treatment period lasted 6 weeks with a 6-week washout period in between to avoid carryover effects. Both treatment periods consisted of three study visits to the outpatient clinic at the start, week 3, and week 6 of each period. A telephone call was made to participants 1 week after the start of each treatment period to assess tolerability. A follow-up visit was scheduled 6 weeks after the last treatment period to assess off-treatment effects. Participants were instructed to take their study medication in the morning; on study visit days, medication was taken after the visit.

At each study visit, a physical examination was done and the patient's bodyweight, heart rate, and blood pressure were measured. Blood pressure (systolic and diastolic) was measured three times with at least 1 min between measurements. The mean of the three measurements was used in the analysis. 24-h urine samples were collected and blood samples were taken in fasted condition for measurement of a clinical chemistry panel and biomarkers related to kidney function changes. eGFR was calculated with the CKD-EPI equation.¹⁶ During the first and last visit of each treatment period and at the last follow-up visit, GFR was

Figure 1: Trial profile

measured by plasma disappearance of iothexol (mGFR). After a 5 mL bolus infusion of iothexol (300 mg iodine per mL), blood samples were taken at 120 min, 150 min, 180 min, 210 min, and 240 min. Iothexol was measured in a central laboratory by use of a high-performance liquid chromatography tandem mass spectrometry technique with an intraassay and interassay coefficient of variation of less than 15%. Iothexol clearance was calculated from the total injected dose of iothexol and the estimated area under the curve by use of a one-compartment model to obtain GFR, after correction for the early part of the plasma concentration-time curve according to Bröchner-Mortensen and body surface area.^{17,18} During the last visit of each treatment period, blood samples were taken for assessment of treatment adherence. Additionally, treatment adherence was assessed via a pill count done by the researcher and later by the independent study monitor.

Outcomes

The primary outcome was the percentage change from baseline in 24-h proteinuria during dapagliflozin treatment relative to placebo. Secondary outcomes were changes in mGFR, bodyweight, systolic and diastolic blood pressure, and neurohormonal biomarkers (N-terminal pro B-type natriuretic peptide and prostaglandin markers).

Prespecified exploratory outcomes were 24-h albuminuria, 24-h protein-to-creatinine ratio, and 24-h albumin-to-creatinine ratio. Post-hoc exploratory outcomes were changes in fasting plasma glucose, HbA_{1c}, haemoglobin, haematocrit, potassium, calcium, phosphate, total protein, and HDL and LDL cholesterol. The numbers of adverse events of special interest (including hypoglycaemia [determined by clinical judgment], acute kidney injury, lower-limb amputation, and fractures) and serious adverse events were also recorded and compared between dapagliflozin and placebo treatments.

Statistical analysis

We calculated that 50 patients completing the study would provide 80% power (at $\alpha=0.05$) to detect a 25% reduction in proteinuria between dapagliflozin and placebo, assuming an SD of 0.7 in log-transformed proteinuria (within-subject SD of 0.475). To account for early treatment discontinuation and early study discontinuations, we enrolled 53 participants.

Descriptive statistics were used for baseline characteristics, which were summarised as means and SDs or medians and IQRs. The analysis was performed according to the intention-to-treat principle, including all available proteinuria measurements. A mixed-effects linear regression model was used to analyse repeated measures and estimate mean differences between dapagliflozin and placebo. The same model was used for the primary, secondary, and exploratory outcomes. The model included treatment and categorical time period as

fixed factors and patients as a random factor. Period-specific treatment effects were also explored by adding the interaction between treatment and period covariates in the model.

Furthermore, in a prespecified analysis, the effects of dapagliflozin on the primary outcome of geometric mean

	Overall (n=53)	Placebo then dapagliflozin (n=26)	Dapagliflozin then placebo (n=27)
Age, years	51 (13)	51 (16)	52 (10)
Sex			
Female	17 (32%)	8 (31%)	9 (33%)
Male	36 (68%)	18 (69%)	18 (67%)
Ethnic origin			
Asian	17 (32%)	6 (23%)	11 (41%)
Hispanic	2 (4%)	0	2 (7%)
White	29 (55%)	17 (65%)	12 (44%)
Other	5 (9%)	3 (12%)	2 (7%)
Chronic kidney disease diagnosis			
IgA nephropathy	25 (47%)	14 (54%)	11 (41%)
FSGS	11 (21%)	3 (12%)	8 (30%)
Hypertensive nephropathy	7 (13%)	4 (15%)	3 (11%)
Other*	10 (19%)	5 (19%)	5 (19%)
Bodyweight, kg	83.0 (20.3)	79.6 (15.5)	86.2 (24.0)
BMI, kg/m ²	28.0 (5.1)	27.2 (4.1)	28.8 (5.8)
Heart rate, beats per min	68.5 (13.7)	69.0 (15.6)	68.0 (12.0)
Systolic blood pressure, mm Hg	126.0 (14.8)	124.6 (13.1)	127.4 (16.4)
Diastolic blood pressure, mm Hg	76.2 (8.2)	75.2 (7.8)	77.2 (8.7)
HbA _{1c} , %	5.6 (0.4)	5.6 (0.4)	5.6 (0.5)
HbA _{1c} , mmol/mol	37.6 (4.7)	37.7 (4.3)	37.4 (5.1)
HDL cholesterol, mmol/L	1.3 (0.5)	1.2 (0.3)	1.4 (0.7)
LDL cholesterol, mmol/L	2.8 (0.9)	2.7 (1.0)	2.8 (0.8)
Haemoglobin, g/L	134.6 (20.4)	134.4 (20.8)	134.8 (20.4)
mGFR, mL/min per 1.73 m ² †			
≤60	58.3 (23.0)	57.8 (25.5)	58.9 (20.7)
>60	33 (62%)	17 (65%)	16 (59%)
>60	20 (38%)	9 (35%)	11 (41%)
Proteinuria, mg per 24 h†			
1110.0	1110.0	1105.0	1170.0
(730.0–1560.0)	(730.0–1560.0)	(720.0–1530.0)	(730.0–1690.0)
<1000	20 (38%)	11 (42%)	9 (33%)
≥1000	33 (62%)	15 (58%)	18 (67%)
Albuminuria, mg per 24 h	856.5	844.0	891.0
(559.5–1225.0)	(559.5–1225.0)	(538.0–1142.0)	(599.0–1338.0)
Medication use			
ACE inhibitor	31 (58%)	16 (62%)	15 (56%)
Angiotensin receptor blocker	22 (42%)	10 (38%)	12 (44%)
Diuretic	14 (26%)	8 (31%)	6 (22%)
NSAID	2 (4%)	1 (4%)	1 (4%)
Vitamin D analogue	12 (23%)	9 (35%)	3 (11%)
Corticosteroids	4 (8%)	2 (8%)	2 (7%)

Data are n (%), mean (SD), or median (IQR). FSGS=focal segmental glomerulosclerosis. mGFR=measured glomerular filtration rate. ACE=angiotensin-converting enzyme. NSAID=non-steroidal anti-inflammatory drug. *Other diagnoses were Alport syndrome (n=2), VATER syndrome (n=1), membranous nephropathy (n=1), collagen 4 mutation (n=1), and unknown (n=6). †Further categories of mGFR and proteinuria are presented in the appendix (p 58).

Table 1: Baseline characteristics

Figure 2: Changes in 24-h proteinuria (A), 24-h albuminuria (B), protein-to-creatinine ratio (C), and albumin-to-creatinine ratio (D) during dapagliflozin and placebo treatment
Absolute values are geometric means. Error bars are 95% CIs. Data are from a total of 53 participants, 27 of whom received dapagliflozin then placebo and 26 of whom received placebo then dapagliflozin.

change in proteinuria and the key secondary outcome of mean change in mGFR were further assessed in various subgroups, including subgroups defined by sex, region (Europe, North America, or Asia), baseline kidney diagnosis, proteinuria level, mGFR, systolic blood pressure, BMI, and diuretic use. The subgroup analyses were done in two stages, first for each subgroup separately and then comparing the estimated treatment effects and their SEs within each group by a χ^2 test with degrees of freedom equal to the number of subgroups being compared minus one.

Prespecified sensitivity analyses were done to account for changes in medication use during the study that could affect proteinuria. Prespecified sensitivity analyses were also done to examine potential differences in the primary outcome when proteinuria data collected at week 3 of each treatment period was included, when the average of proteinuria at screening and at randomisation was used as baseline proteinuria, and when proteinuria was indexed for mGFR.

No formal adjustments for multiplicity were done; a nominal (two-sided) level α was set at 0.05. All statistical analyses were done with SAS version 9.4.

This trial is registered with ClinicalTrials.gov, NCT03190694.

Role of the funding source

The funder of the study had no role in the data collection or data analysis. The funder reviewed the study protocol and a coauthor employed by the funder (PJG) was involved in the data interpretation and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

58 patients were screened between Nov 22, 2017, and April 5, 2019, of whom 53 were enrolled and randomly assigned to receive placebo for 6 weeks then dapagliflozin 10 mg per day for 6 weeks (n=26) or vice versa

Figure 3: Changes in iohexol mGFR (A), systolic blood pressure (B), bodyweight (C), and HbA_{1c} (D) during dapagliflozin and placebo treatment

Absolute values are means. Error bars are 95% CIs. Data are from a total of 53 participants, 27 of whom received dapagliflozin then placebo and 26 of whom received placebo then dapagliflozin. mGFR=measured glomerular filtration rate.

(n=27; figure 1). All participants except one completed both treatment periods; one participant discontinued during the first treatment period (in which the treatment was dapagliflozin) and did not cross over to the second treatment period. Two participants discontinued during the wash-out after period 2 (in which they received placebo), and had no follow-up visit 6 weeks after the period 2. Baseline data and results from at least one proteinuria assessment during the treatment period were recorded for all randomly assigned participants, so all randomly assigned participants were included in the efficacy analyses. Baseline demographic, clinical, and biochemical characteristics are shown in table 1. The most common kidney disease diagnoses among participants were IgA nephropathy (n=25), focal segmental glomerulosclerosis (n=11), and hypertensive nephropathy (n=7); baseline characteristics for these subgroups are provided in the appendix (p 57). Treatment adherence,

defined as proportion of patients who used between 80% and 120% of their medication (based on pill counts) was excellent. 52 (98%) of 53 patients were adherent to study medication in period 1 (one patient taking dapagliflozin was non-adherent) and 52 (100%) of 52 were adherent in period 2.

Geometric mean 24-h proteinuria at the start of placebo treatment was 1088.1 mg per 24 h (95% CI 904.6–1308.6), which decreased by 15.8% (3.5 to 26.4) after 6 weeks. At the start of dapagliflozin treatment, geometric mean 24-h proteinuria was 1029.8 mg per 24 h (866.1–1224.3), which decreased by 15.0% (2.8 to 25.7) after 6 weeks. Accordingly, the difference in mean percentage change in 24-h proteinuria from baseline between dapagliflozin and placebo treatment was 0.9% (-16.6 to 22.1; p=0.93; figure 2A). The difference in mean percentage change in 24-h albuminuria between dapagliflozin and placebo treatment was -11.8% (-30.4 to 12.0; p=0.30; figure 2B).

	Placebo	Dapagliflozin
NT-proBNP		
n	50	52
Baseline mean (SD), ng/L	125.0 (161.1)	118.8 (151.2)
Week 6 mean (SD), ng/L	152.6 (277.7)	108.7 (148.7)
Adjusted mean change from baseline (95% CI), %*	1.1% (-13.3 to 17.9)	-14.9% (-26.9 to -1.0)
Difference in mean change vs placebo (95% CI; p value), %*	..	-15.8% (-32.2 to 4.5; p=0.18)
Urine adenosine†		
n	50	51
Baseline mean (SD), µmol/mmol	0.19 (0.15)	0.20 (0.16)
Week 6 mean (SD), µmol/mmol	0.24 (0.25)	0.22 (0.17)
Adjusted mean change from baseline (95% CI), µmol/mmol	0.04 (-0.02 to 0.10)	0.02 (-0.04 to 0.08)
Difference in adjusted mean change vs placebo (95% CI; p value), µmol/mmol	..	-0.02 (-0.11 to 0.06; p=0.57)
Urine thromboxane B2†		
n	50	51
Baseline mean (SD), pg/mmol	0.096 (0.047)	0.092 (0.057)
Week 6 mean (SD), pg/mmol	0.093 (0.050)	0.106 (0.101)
Adjusted mean change from baseline (95% CI), pg/mmol	-0.003 (-0.023 to 0.018)	0.015 (-0.006 to 0.035)
Difference in adjusted mean change vs placebo (95% CI; p value), pg/mmol	..	0.017 (-0.012 to 0.047; p=0.24)
Urine 6-keto prostaglandin F1α†		
n	50	51
Baseline mean (SD), pg/mmol	0.117 (0.040)	0.117 (0.042)
Week 6 mean (SD), pg/mmol	0.120 (0.055)	0.128 (0.045)
Adjusted mean change from baseline (95% CI), pg/mmol	0.005 (-0.007 to 0.017)	0.011 (-0.001 to 0.023)
Difference in adjusted mean change vs placebo (95% CI; p value), pg/mmol	..	0.006 (-0.011 to 0.023; p=0.50)
Urine prostaglandin E2†		
n	50	51
Baseline mean (SD), pg/mmol	0.098 (0.103)	0.113 (0.150)
Week 6 mean (SD), pg/mmol	0.095 (0.143)	0.170 (0.266)
Adjusted mean change from baseline (95% CI), pg/mmol	-0.002 (-0.051 to 0.047)	0.057 (0.008 to 0.105)
Difference in adjusted mean change vs placebo (95% CI; p value), pg/mmol	..	0.059 (-0.010 to 0.128; p=0.092)
Urine PGEM†		
n	50	51
Baseline mean (SD), pg/mmol	0.095 (0.055)	0.100 (0.056)
Week 6 mean (SD), pg/mmol	0.096 (0.057)	0.097 (0.054)
Adjusted mean change from baseline (95% CI), pg/mmol	0.002 (-0.006 to 0.011)	-0.002 (-0.010 to 0.007)
Difference in adjusted mean change vs placebo (95% CI; p value), pg/mmol	..	-0.004 (-0.016 to 0.008; p=0.50)

n is the number with data available. NT-proBNP=N-terminal pro B-type natriuretic peptide. PGEM=prostaglandin E2 metabolite. *Log-transformed data were back-transformed using the formula: 1-exponent(log value) × 100.
†Biomarkers were corrected for urine creatinine.

Table 2: Changes in neurohormonal biomarkers during placebo and dapagliflozin treatment at 6 weeks

The difference in mean percentage change in protein-to-creatinine ratio between dapagliflozin and placebo treatment was -6.1% (-21.7 to 12.5; p=0.49; figure 2C).

The difference in mean percentage change in albumin-to-creatinine ratio between dapagliflozin and placebo treatment was -17.0% (-33.2 to 3.4; p=0.095; figure 2D).

Mean mGFR was 58.0 mL/min per 1.73 m² (SD 23.6) at the start of placebo treatment and 59.3 mL/min per 1.73 m² (23.8) at the start of dapagliflozin treatment. mGFR increased during placebo treatment by 0.3 mL/min per 1.73 m² (95% CI -1.4 to 2.0) and decreased by 6.3 mL/min per 1.73 m² (4.6 to 8.0) during dapagliflozin treatment. After 6 weeks, the difference in mean mGFR change from baseline for dapagliflozin versus placebo was -6.6 mL/min per 1.73 m² (-9.0 to -4.2; p<0.0001; figure 3A). The reduction in mGFR with dapagliflozin was completely reversible within 6 weeks after discontinuation, with mGFR values in the dapagliflozin period showing no difference from placebo or from their respective baseline values (figure 3A).

Dapagliflozin treatment for 6 weeks resulted in a significant placebo-corrected change in mean bodyweight of -1.5 kg (95% CI -3.0 to -0.03; p=0.046; figure 3C). There were no changes from baseline in systolic blood pressure and HbA_{1c} with dapagliflozin treatment compared with placebo (figure 3B, 3D). There was also no change in heart rate (-0.13 beats per min [-3.1 to 2.8; p=0.93]) or diastolic blood pressure (-1.38 mm Hg [-4.1 to 1.3; p=0.31]) during dapagliflozin treatment compared with placebo. Additionally, plasma concentrations of biomarkers, including N-terminal pro B-type natriuretic peptide, and prostaglandin markers were unchanged after dapagliflozin treatment (table 2).

Overall, dapagliflozin was well tolerated in these patients with chronic kidney disease without diabetes. 30 patients had one or more adverse events; 17 (32%) of 53 participants had one or more adverse events during dapagliflozin treatment and 13 (25%) of 52 had one or more adverse events during placebo treatment (table 3). Adverse events of special interest were uncommon, with two occurring during placebo treatment and four during dapagliflozin treatment. No participants had a hypoglycaemic event during the study. One participant had a kidney-related adverse event (acute kidney injury) during dapagliflozin treatment. Urinary tract infections and genital infections occurred in one patient each during dapagliflozin treatment. There were two serious adverse events, with one (cellulitis) occurring during placebo treatment and the other (colon cancer) during dapagliflozin treatment.

Post-hoc analysis of exploratory biochemical parameters showed a significant increase in haemoglobin (increase of 5.3 g/L [95% CI 2.7 to 7.9; p<0.0001]) and haematocrit (increase of 0.02 L/L [0.01 to 0.03; p<0.0001]) with dapagliflozin treatment versus placebo (table 4). Other exploratory biochemical parameters, including fasting plasma glucose, potassium, calcium, and phosphate, were unchanged during dapagliflozin treatment.

The effects of dapagliflozin on 24-h proteinuria were consistent in subgroups defined by sex, region, kidney diagnosis, proteinuria level, systolic blood pressure, BMI,

and diuretic use. However, the effect of dapagliflozin on 24-h proteinuria was modified by baseline mGFR, with a significant between-group difference in proteinuria in those with an mGFR of more than 60 mL/min per 1.73 m² (−27.2% [95% CI −44.6 to −4.2; *p*=0.0040]; figure 4). The effect of dapagliflozin on mGFR was generally consistent across the examined subgroups, apart from in the subgroup by age (appendix p 60).

Prespecified sensitivity analyses were done to assess the robustness of the results for the primary outcome of proteinuria. The results did not change when proteinuria data collected at week 3 of each treatment period were included in the analysis (percentage difference between dapagliflozin and placebo 2.5% [95% CI −12.3 to 19.7; *p*=0.76]; appendix p 59). There was also no difference in 24-h proteinuria between dapagliflozin and placebo when we indexed proteinuria for mGFR (data not shown). Additionally, similar results were obtained when eight patients in whom treatments that could modify proteinuria were changed during the trial were excluded from the analysis (difference between dapagliflozin and placebo in 24-h proteinuria −2.5% [95% CI −20.9 to 20.3; *p*=0.81]) or when the average of screening and randomisation proteinuria was used as baseline (1.2% [95% CI −16.4 to 22.6; *p*=0.90]; appendix p 59).

Discussion

In this first-in-human randomised crossover trial involving patients with proteinuric chronic kidney disease without diabetes, proteinuria did not decrease over a 6-week treatment period with dapagliflozin compared with placebo.

The beneficial effects of SGLT2 inhibitors on kidney function are potentially mediated through non-glycaemic pathways, suggesting that these drugs might also confer clinical benefits in patients without diabetes. The findings of this trial were consistent with the concept that SGLT2 inhibitors exert haemodynamic effects in normoglycaemic individuals, because mGFR decreased acutely and returned rapidly back to baseline after treatment discontinuation, consistent with a reversible decrease in intraglomerular hypertension. Moreover, haemoconcentration occurred (ie, haematocrit and haemoglobin increased), with significant decreases in bodyweight, suggesting a significant natriuretic response occurred even in the absence of ambient hyperglycaemia. Despite these physiological changes that are considered to confer kidney and cardiovascular protection, proteinuria did not decrease significantly.

Previous studies have shown that in patients with type 2 diabetes and microalbuminuria or macroalbuminuria, SGLT2 inhibition reduces albuminuria by 30–50% after 4–8 weeks of treatment.^{6,19–21} Furthermore, these studies showed that the antiproteinuric effects are completely reversible after cessation of treatment, suggesting that they have a haemodynamic basis. The results of the DIAMOND trial suggest that, although 6-week SGLT2 inhibition does

	Placebo (n=52)*	Dapagliflozin (n=53)
Any adverse event	13 (25%)	17 (32%)
Adverse event leading to study drug discontinuation†	0	1 (2%)
Any serious adverse event‡	1 (2%)	1 (2%)
Serious adverse event leading to study drug discontinuation	1 (2%)	0
Death	0	0
Adverse event of special interest		
Kidney-related adverse event§	0	1 (2%)
Urinary tract infection	0	1 (2%)
Genital infection	0	1 (2%)
Volume depletion		
Hypotension	1 (2%)	0
Dizziness	1 (2%)	0
Amputations	0	0
Fractures	0	1 (2%)
Diabetic ketoacidosis	0	0
Hypoglycaemia	0	0

Data are number of patients (%) with one or more adverse event of the specified type. *One patient discontinued the study during the first treatment period with dapagliflozin; this patient did not start the placebo treatment period and was therefore not included in the safety assessments for the placebo group. †The adverse event leading to discontinuation was swelling of the left foot. ‡The two serious adverse events were cellulitis (during placebo treatment) and colon cancer (during dapagliflozin treatment). §The kidney-related adverse event was investigator-reported acute kidney injury.

Table 3: Adverse events

exert haemodynamic effects in individuals without diabetes, as reflected by changes in mGFR, significant proteinuria lowering does not occur. However, these findings do not rule out the possibility of longer-term kidney protection. The DAPA-CKD trial,^{22,23} which assessed the long-term effects of dapagliflozin on major kidney outcomes in patients with chronic kidney disease, was stopped early due to overwhelming efficacy in March, 2020. Although the detailed results are not yet available, the early trial termination suggests that dapagliflozin reduces the risks of clinical outcomes in a cohort of patients with kidney disease of diverse causes, including the causes of non-diabetic chronic kidney disease of the patients enrolled in the DIAMOND trial.²²

The reason why proteinuria was unaffected by dapagliflozin, despite a dip in mGFR suggesting reduced intraglomerular pressure, is not known. One possibility is that the treatment period was too short to observe significant changes in proteinuria, although the duration was expected to be sufficient on the basis of studies in people with type 2 diabetes. By contrast with previous studies that included only individuals with diabetic kidney disease, our study included a broader chronic kidney disease population without diabetes. Although most patients had one of three types of non-diabetic kidney disease (IgA nephropathy, focal segmental

	Placebo	Dapagliflozin
Fasting plasma glucose		
n	52	52
Baseline mean (SD), mmol/L	5.5 (0.7)	5.6 (1.2)
Week 6 mean (SD), mmol/L	5.4 (0.7)	5.3 (0.7)
Adjusted mean change from baseline (95% CI), mmol/L	-0.1 (-0.3 to 0.1)	-0.3 (-0.5 to -0.1)
Difference in adjusted mean change vs placebo (95% CI; p value), mmol/L	..	-0.2 (-0.5 to 0.1; p=0.16)
Haemoglobin		
n	51	53
Baseline mean (SD), g/L	134.5 (20.2)	133.3 (19.4)
Week 6 mean (SD), g/L	131.8 (21.0)	136.7 (18.2)
Adjusted mean change from baseline (95% CI), g/L	-2.3 (-4.1 to -0.4)	3.0 (1.2 to 4.8)
Difference in adjusted mean change vs placebo (95% CI; p value), g/L	..	5.3 (2.7 to 7.9; p<0.0001)
Haematocrit		
n	52	53
Baseline mean (SD), L/L	0.40 (0.05)	0.40 (0.06)
Week 6 mean (SD), L/L	0.39 (0.06)	0.41 (0.05)
Adjusted mean change from baseline (95% CI), L/L	-0.01 (-0.01 to -0.002)	0.01 (0.01 to 0.02)
Difference in adjusted mean change vs placebo (95% CI; p value), L/L	..	0.02 (0.01 to 0.03; p<0.0001)
Estimated glomerular filtration rate		
n	52	52
Baseline mean (SD), mL/min per 1.73 m ²	59.9 (28.0)	57.4 (26.7)
Week 6 mean (SD), mL/min per 1.73 m ²	59.2 (28.8)	57.2 (27.9)
Adjusted mean change from baseline (95% CI), mL/min per 1.73 m ²	-0.8 (-2.5 to 0.9)	-1.8 (-3.5 to -0.1)
Difference in adjusted mean change vs placebo (95% CI; p value), mL/min per 1.73 m ²	..	-1.0 (-3.4 to 1.4; p=0.42)
Potassium		
n	52	53
Baseline mean (SD), mmol/L	4.2 (0.4)	4.1 (0.4)
Week 6 mean (SD), mmol/L	4.2 (0.4)	4.1 (0.4)
Adjusted mean change from baseline (95% CI), mmol/L	0.02 (-0.06 to 0.10)	0.00 (-0.08 to 0.08)
Difference in adjusted mean change vs placebo (95% CI; p value), mmol/L	..	-0.02 (-0.13 to 0.10; p=0.78)
Calcium		
n	52	52
Baseline mean (SD), mmol/L	2.3 (0.1)	2.3 (0.1)
Week 6 mean (SD), mmol/L	2.3 (0.1)	2.3 (0.1)
Adjusted mean change from baseline (95% CI), mmol/L	-0.01 (-0.03 to 0.02)	0.01 (-0.02 to 0.03)
Difference in adjusted mean change vs placebo (95% CI; p value), mmol/L	..	0.01 (-0.02 to 0.04; p=0.55)

(Table 4 continues in next column)

	Placebo	Dapagliflozin
(Continued from previous column)		
Phosphate		
n	51	51
Baseline mean (SD), mmol/L	1.0 (0.2)	1.0 (0.2)
Week 6 mean (SD), mmol/L	1.1 (0.2)	1.1 (0.2)
Adjusted mean change from baseline (95% CI), mmol/L	0.01 (-0.04 to 0.06)	0.05 (-0.002 to 0.09)
Difference in adjusted mean change vs placebo (95% CI; p value), mmol/L	..	0.03 (-0.03 to 0.01; p=0.30)
Total protein		
n	49	51
Baseline mean (SD), g/L	68.7 (5.7)	68.8 (5.5)
Week 6 mean (SD), g/L	68.9 (6.0)	70.3 (6.2)
Adjusted mean change from baseline (95% CI), g/L	0.05 (-0.98 to 1.09)	1.13 (0.12 to 2.14)
Difference in adjusted mean change vs placebo (95% CI; p value), g/L	..	1.08 (-0.37 to 2.53; p=0.14)
HDL cholesterol		
n	52	53
Baseline mean (SD), mmol/L	1.3 (0.3)	1.3 (0.5)
Week 6 mean (SD), mmol/L	1.2 (0.3)	1.2 (0.3)
Adjusted mean change from baseline (95% CI), mmol/L	-0.03 (-0.13 to 0.08)	-0.10 (-0.20 to 0.00)
Difference in adjusted mean change vs placebo (95% CI; p value), mmol/L	..	-0.07 (-0.22 to 0.07; p=0.31)
LDL cholesterol		
n	52	53
Baseline mean (SD), mmol/L	2.7 (0.9)	2.6 (0.8)
Week 6 mean (SD), mmol/L	2.7 (0.9)	2.6 (0.8)
Adjusted mean change from baseline (95% CI), mmol/L	-0.07 (-0.21 to 0.07)	-0.06 (-0.20 to 0.08)
Difference in adjusted mean change vs placebo (95% CI; p value), mmol/L	..	0.02 (-0.18 to 0.21; p=0.88)

n is the number of patients with available measurements.

Table 4: Changes in exploratory biochemical parameters during placebo and dapagliflozin treatment at 6 weeks

glomerulosclerosis, and hypertensive nephropathy), and the effects on proteinuria and mGFR were consistent in all subgroups, differences in underlying disease pathophysiology could have contributed to the inability to detect an antiproteinuric response. For example, patients in our cohort might have had a significant tubulointerstitial source of proteinuria that is less responsive to changes in glomerular pressure. Finally, SGLT2 inhibitors might simply not reduce proteinuria in the absence of diabetes, although mathematical modelling simulations of SGLT2 blockade in a non-diabetic kidney predicted an attenuated response rather than an absence of response.²⁴ Although proteinuria did not change in our overall study population, it decreased significantly in the

Figure 4: Effects of dapagliflozin on 24-h proteinuria in patient subgroups defined by baseline characteristics
CKD=chronic kidney disease. FSGS=focal segmental glomerulosclerosis. mGFR=measured glomerular filtration rate.

subgroup of patients with mGFR greater than 60 mL/min per 1.73 m². We must be cautious in interpreting this finding due to the small sample size; however, if a decrease in proteinuria only occurs in the setting of non-diabetic chronic kidney disease in patients with higher kidney function, this would suggest that a sufficient increase in solute delivery to the macula densa in normoglycaemic patients occurs only with higher levels of GFR. By contrast, in patients without diabetes, whose glucose filtration is already lower compared with those with diabetes, a reduction in GFR leads to a further lowering of glucose and sodium delivery to the macula densa. Hence, tubuloglomerular feedback and other autoregulatory systems might not be sufficiently activated by SGLT2 inhibition to reduce proteinuria in individuals without diabetes and with a GFR of less than 60 mL/min per 1.73 m². Finally, we identified slightly larger effects when the 24-h protein and albumin excretion rates were indexed for 24-h creatinine excretion, suggesting that urine collection errors were made during the 24-h

collection period. Nevertheless, despite the potential collection errors, the study was well powered to detect a 25% reduction in proteinuria because the observed variability in 24-h proteinuria was 0.68, consistent with our sample size assumption.

Although dapagliflozin did not reduce proteinuria, mGFR dipped significantly. The mechanisms responsible for changes in GFR and kidney haemodynamics are not yet firmly established, although both afferent and efferent kidney arteriolar pathways have been suggested.^{9,10} Irrespective of the mechanisms involved, GFR decreases acutely in response to SGLT2 inhibition in patients with type 2 diabetes and, as shown in this study, similar effects occur in patients with non-diabetic proteinuric kidney disease and mean mGFR in the chronic kidney disease stage 3 range. Notably, in our previous pilot study with dapagliflozin in patients with proteinuria caused by focal segmental glomerulosclerosis, inulin-measured GFR tended to decrease by a similar magnitude to that seen in the present study, although the

changes in the pilot study were not statistically significant.¹² These acute, reversible changes in kidney function have been closely linked with reduced intraglomerular pressure and might thereby reduce clinical kidney risk over time.¹² None of the secondary biomarkers associated with control of kidney haemodynamics, such as adenosine and prostaglandin markers, changed in response to dapagliflozin in the DIAMOND trial, emphasising the importance of completing ongoing mechanistic and outcome trials with SGLT2 inhibitors to better understand the relevance of these drugs in normoglycaemic individuals.^{9,10} Moreover, our results suggest that other vasoactive mediators linked with SGLT2 inhibition-related vascular function effects could be involved as regulators of GFR in individuals without diabetes, including endothelin, nitric oxide, and oxidative stress pathways. These possibilities merit dedicated mechanistic investigations.^{25,26}

In people with type 2 diabetes, SGLT2 inhibitors reduce systolic blood pressure by 3–5 mm Hg and diastolic blood pressure by 1–2 mm Hg.²⁷ Although blood pressure changes in our cohort were not significant, the magnitude of the change was similar. Additionally, SGLT2 inhibitors reduce bodyweight in people with type 2 diabetes by 1–3 kg, which is thought to mostly occur via reducing body fat and water.²⁷ In our non-diabetic cohort, bodyweight changed by a similar, statistically significant amount. Furthermore, haematocrit and haemoglobin increased significantly, which could reflect natriuresis and effective circulating volume contraction, although we cannot exclude potential effects of erythropoietin production. This haemoconcentration might be of additional importance beyond natriuresis, because it has been linked with improved cardiovascular prognosis in cardiovascular outcome trials involving SGLT2 inhibitors for patients with type 2 diabetes with established cardiovascular disease.²⁸ Changes in haemoconcentration are aligned with anticipated effects in patients with type 2 diabetes and could suggest that these drugs have broader cardiovascular benefits outside of known indications.

Our study was initiated on the basis of growing evidence suggesting that the effect of SGLT2 inhibition on kidney protection is independent of glucose lowering, raising the possibility of benefit of these drugs in patients without diabetes. First, in patients with type 2 diabetes, SGLT2 inhibitors reduce blood pressure in patients who have stage 3 chronic kidney disease, even though HbA_{1c} levels remain unaffected at this level of kidney impairment due to diminished urinary glucose excretion.²⁹ Second, in the CREDENCE trial,⁸ canagliflozin significantly reduced the rate of eGFR decline and reduced the risks of major kidney and cardiovascular outcomes, even in patients with near-normal HbA_{1c} values. Finally, in the DAPA-HF trial,³⁰ which included patients with and without type 2 diabetes, benefits on heart failure and kidney outcomes were consistent in patients irrespective of their diabetes status. Despite these compelling lines of evidence, 24-h

proteinuria did not decrease in our study. Nevertheless, the overall haemodynamic profile of dapagliflozin was consistent with effects in people with type 2 diabetes: mGFR dipped acutely and in a reversible manner, bodyweight decreased, and haematocrit increased. Additionally, systolic blood pressure and urinary albumin-to-creatinine ratio tended to numerically decrease, although these latter changes were not statistically significant. In this study, we included patients with proteinuric chronic kidney diseases without diabetes. Similar patients (ie, patients with chronic kidney disease without diabetes) are now included in the ongoing EMPA-KIDNEY (NCT03594110; empagliflozin) and DAPA-CKD (NCT03036150; dapagliflozin)²² clinical outcome trials. The overall pattern of physiological effects in the DIAMOND trial emphasises the importance of kidney protection trials involving patients with chronic kidney disease with and without diabetes to provide more detailed insight into the long-term kidney protective effects of SGLT2 inhibitors in a broader cohort of patients.

The strengths of our study include carefully controlled study procedures, such as precise methods to capture kidney function and the use of 24-h urine samples rather than spot urine collections. However, the study also had some limitations. First, the sample size was small and the primary outcome was based on single 24-h urine collections. Second, the study follow-up was too short to fully characterise the safety of dapagliflozin in this patient population, although the number of adverse events was small and serious adverse events were rare, which is consistent with the good tolerability and safety record of dapagliflozin in patients with type 2 diabetes. Finally, we recognise that our primary outcome, proteinuria, does not necessarily reflect whether or not dapagliflozin has kidney-protective effects in patients with non-diabetic kidney disease. Similarly, we recognise that the reductions in mGFR identified in the DIAMOND trial, as a reflection of reduced glomerular hypertension, might take longer to translate to antiproteinuric effects in patients with proteinuria without diabetes. Hence, longer-term kidney outcome trials are needed to better characterise long-term efficacy and safety.

Contributors

DZIC and HJLH designed the study. DZIC, CCJD, SJB, DC, AHAG, GDL, SKL, HNR, MGW, RTG, and HJLH were involved in data collection. GLDT analysed the data. DZIC, CCJD, and HJLH led the writing of the first draft of the report. All authors were involved in data interpretation and in drafting and critically revising the report for important intellectual content. All authors reviewed and approved the final submitted version of the report.

Declaration of interests

DZIC has received honoraria for speaking and consulting from Boehringer Ingelheim–Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, AbbVie, Janssen, Bayer, Prometic, BMS, and Novo Nordisk, and operational funding for clinical trials from Boehringer Ingelheim–Lilly, Merck, Janssen, Sanofi, AstraZeneca, and Novo Nordisk. PJG is employed by and owns shares in AstraZeneca. GDL has received research grants and consulting fees from Sanofi and AstraZeneca, and research grants from Novo Nordisk. SKL has received consulting fees or speaking honoraria from AstraZeneca, Boehringer Ingelheim, Novo Nordisk,

Fresenius Kabi, Baxter, and Sanofi. GLDT has received consulting fees from Amgen. HNR has received consulting fees from Omeros and was involved in clinical trials supported by Omeros and Calliditas. MGW has received consulting fees from Amgen, Vifor Fresenius Medical Care Renal Pharma, Medice, Cablon Medical, Otsuka, and Kyowa Kirin. MGW has received honoraria for scientific lectures from AstraZeneca, Retrophin, Amgen, and Baxter; his employer, the George Institute for Global Health, holds research contracts for trials in cardiovascular disease or kidney disease with several commercial organisations. RTG has consulting agreements with AstraZeneca, Bayer, Sanofi–Genzyme, and Mundi Pharma; all fees are paid to his institution. HJLH has consulting relationships with AbbVie, AstraZeneca, Boehringer Ingelheim, CSL Pharma, Fresenius, Gilead, Janssen, Merck, Mitsubishi–Tanabe, Mundi Pharma, and Retrophin. All other authors declare no competing interests.

Data sharing

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement by the corresponding author. Data requests can be submitted by email from 12 months after publication of this report and data will be made accessible for 12 months, with possible extensions considered.

Acknowledgments

We thank all investigators, trial teams, and patients for their participation in the trial. We acknowledge Jasper Stevens, Jan Roggevel, and Bettine Haandrikman (University of Groningen, Groningen, Netherlands) for their contributions to iohexol analysis and glomerular filtration rate calculations. MGW is supported by the Diabetes Australian Research Trust Millennium Grant.

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