

ORIGINAL ARTICLE

The albuminuria-lowering response to dapagliflozin is variable and reproducible among individual patients

Sergei I. Petrykiv MD¹ | Gozewijn D. Laverman MD, PhD² | Dick de Zeeuw MD, PhD¹ | Hiddo J. L. Heerspink PhD¹ 

¹Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

²Department of Nephrology, Ziekenhuisgroep Twente, Almelo and Hengelo, the Netherlands

Correspondence

Hiddo J. L. Heerspink PhD, Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Hanzeplein 1EB71, PO Box 30.001, 9700 RB Groningen, the Netherlands.
Email: h.j.lambers.heerspink@umcg.nl

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Aims: Albuminuria reduction is essential for renal and cardiovascular protection. We characterized the efficacy of dapagliflozin, a sodium-glucose co-transporter 2 inhibitor, on albuminuria. Secondly, we assessed whether the albuminuria-lowering effect varies among patients, and whether this variability in response is reproducible.

Material and methods: A double-blind, randomized, placebo controlled crossover trial was conducted. Patients with type 2 diabetes and albumin:creatinine ratio > 100 mg/g on a stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) were enrolled. Patients were assigned to 6-week treatment periods with dapagliflozin 10 mg/d or placebo in random order, separated by 6-weeks wash-out periods. After the 2 treatment periods, half of the patients were re-exposed for 6 weeks to dapagliflozin 10 mg/d. Primary outcome was change in 24-hour urinary albumin excretion rate (24 h UAE). To assess reproducibility in individual albuminuria response, responses from the first and second exposure to dapagliflozin were correlated.

Results: A total of 33 patients (age, 61 years; female gender, 24.2%; median 24 h UAE, 470 mg/24 h) completed the study. Dapagliflozin, as compared to placebo, reduced 24 h UAE by 36.2% (95% CI, 22.9-47.2; $P < .001$). Systolic blood pressure fell by 5.2 mm Hg (95% CI, 0.5-10.0) and eGFR by 5.3 (95% CI, 2.7-8.0). All effects were reversible directly after treatment discontinuation. In a subgroup of 15 patients who were exposed twice to dapagliflozin, 24 h UAE responses showed a large variation among individuals: first exposure (range, -76% to +52%) and second exposure (-90% to +95%) and first and second individual response were significantly correlated ($r = 0.69$ [95% CI, 0.27-0.89]; $P < .004$).

Conclusion: Dapagliflozin significantly reduces albuminuria when given as adjunct to ACEi or ARB. The albuminuria response to dapagliflozin markedly varies among patients. This variation is not a random phenomenon, but is reproducible upon re-exposure. These data support personalized therapy approaches to optimize diabetic kidney disease.

KEYWORDS

albuminuria, dapagliflozin, response variability, SGLT2, type 2 diabetes

1 | INTRODUCTION

The sodium glucose co-transporter 2 (SGLT2), located in the proximal tubule of the kidney, is an effective transporter system that is responsible for reabsorption of glucose and sodium. Dapagliflozin is an SGLT2 inhibitor that reversely inhibits the SGLT-2 transporter.

This leads to enhanced glucose and sodium excretion and reductions in HbA1c, plasma volume, body weight and blood pressure.¹⁻³

Post-hoc analyses from various clinical trials have suggested that SGLT2-inhibitors decrease albuminuria.⁴⁻⁷ Long-term renoprotective effects have also been suggested, based on secondary outcomes from large clinical trials.⁸ Potential renoprotective effects are thought to

involve various pathways including natriuretic and diuretic effects, as well as restoration of tubulo-glomerular feedback and correction of glomerular hyperfiltration.^{9,10} However, dedicated prospective randomized trials characterizing the albuminuria-lowering and renoprotective effects of SGLT2-inhibitors are lacking.

Previous studies have shown that individual patients show wide variability in albuminuria response to many drugs.¹¹ As it is also known that albuminuria fluctuates from day to day,^{11,12} the among individual-drug response variability could reflect true variation in drug response or random fluctuations in albuminuria. Prospective clinical trials to address this issue are lacking.

We conducted a randomized controlled cross-over study to, firstly, determine prospectively the albuminuria-lowering effects of the SGLT2 inhibitor dapagliflozin. Secondly, we assessed among-patient variability in albuminuria response during dapagliflozin, and assessed whether the individual albuminuria response to dapagliflozin is reproducible at second exposure.

2 | MATERIAL AND METHODS

2.1 | Trial design

We conducted a prospective, randomized, double-blind, placebo-controlled cross-over clinical trial. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen, the Netherlands (METc 2014/111). The study was registered with the Netherlands Trial Register (NTR 4439) and complied with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent before any specific study procedure commenced.

2.2 | Study population

Patients aged between 18 and 75 years with a first morning void albumin:creatinine ratio (U_{ACR}) ≥ 100 mg/g and <3500 mg/g, eGFR ≥ 45 mL/min/1.73 m², HbA1c between 55 and 100 mmol/mol (7.2% and 11.3%) and who were receiving stable doses of angiotensin-converting-enzyme inhibitors (ACEi) or Angiotensin Receptor Blockers (ARB) for more than 4 weeks were recruited from the outpatient clinic of the Department of Internal Medicine Ziekenhuis-Groep Twente, Almelo/Hengelo, the Netherlands. Key exclusion criteria were systolic/diastolic blood pressure $>180/110$ mm Hg, a cardiovascular event during the past 6 months and current use of pioglitazone, GLP-1 analogues, DDP-IV-inhibitors or SGLT-2 inhibitors.

2.3 | Intervention and randomization

Patients were randomly allocated to 1 of the 2 treatment orders generated by an independent pharmacist using a computer software tool prior to the inclusion of the first patient. The study employed a double-blind design. There was no difference in appearance between medications for each sequence/treatment group. In each phase, medication for each treatment group was supplied in identical bottles that were labelled appropriately to maintain blindness. All study personnel and patients remained blinded to the sequence allocation.

2.4 | Procedures

The study consisted of a screening visit and a run-in period of 4 weeks for those subjects who were not receiving a stable dose of ACEi or ARB or of glucose-lowering medication. Eligible patients then proceeded to the randomization visit. The study comprised 3 consecutive cross-over treatment periods of 6 weeks each, in which patients were treated with dapagliflozin 10 mg per day or placebo, with wash-out periods of 6 weeks in between. Accordingly, 15 randomly selected patients were exposed to dapagliflozin 10 mg per day during 2 treatment periods. Study medication was dispensed at the beginning of each treatment period. Patients were instructed to take the tablet in the morning. All efforts were done to keep the use and dosage of all concomitant medication stable during follow-up.

2.5 | Measurements

Patients collected 24-hour urine samples at the beginning and end of each treatment period to assess urinary albumin concentration. In addition, 3 consecutive first morning void urine samples were collected at the beginning and end of each treatment period to determine the urinary albumin to creatinine ratio. Blood samples were taken in fasting condition at the beginning and end of each treatment to assess glucose, HbA1c and lipid profile. eGFR was calculated from the MDRD equation using serum creatinine concentration measured at the beginning and end of each treatment period.¹³ Systolic and diastolic blood pressure was recorded as the mean of 3 consecutive blood-pressure readings. Blood-pressure measurements were performed with a calibrated sphygmomanometer in a seated position after at least 10 minutes of rest, with a time interval of 2 minutes between readings.

2.6 | Endpoints

The primary endpoint was the percentage change in 24-hour urinary albumin excretion (24 h UAE). Secondary endpoints included correlation between the 24 h UAE response to dapagliflozin during the first and second treatment period. Additional secondary endpoints included change from baseline in first morning void U_{ACR} of 3 consecutive first morning void urine samples, plasma glucose, HbA1c, body weight, systolic blood pressure and eGFR. Data on reported adverse events and serious adverse events were collected during the trial.

A sample size of 32 patients completing the protocol was estimated to provide 80% power to detect a 25% reduction in 24 h UAE between the dapagliflozin and placebo groups, assuming a standard deviation of 0.7 in log transformed 24 h UAE. To account for potential loss to follow-up, we enrolled 34 patients. Efficacy analyses were conducted on the modified intention-to-treat population, comprising all individuals who completed the study. The primary analysis was a mixed effects repeated measures analysis. The model included sequence, period, treatment and subject as factors and baseline 24 h UAE as a covariate. Albuminuria was log transformed before entering data in the repeated measures model. The between-group geometric mean change in 24 h UAE was derived by $100 \times (\exp[\text{least square mean change}] - 1)$, and the same transformation was applied to the 95% confidence limits. For secondary end point analyses, we used

the same repeated measures model that was used for the primary analysis, with the exception that baseline 24 h UAE was removed as covariate and the analyses were adjusted for the baseline parameter of interest. Comparisons of changes in 24 h UAE between the first and second exposure to dapagliflozin were performed using Deming linear regression, which accounts for errors in observation in both the x-value and y-value. A Fisher's z' transformation was performed to calculate the 95% confidence interval of the correlation. Exposing 15 patients twice to dapagliflozin provided 80% power to detect a correlation between first and second exposure of 0.65. All statistical analyses were performed with SAS software version 8.2 (SAS Institute, Inc., Cary, NC, USA). All statistical tests were 2-sided, with a statistical significance level of 5%.

3 | RESULTS

Between September 2014 and February 2016, 46 patients were screened, of whom 34 were randomized. One patient was hospitalized during the study; this patient discontinued study medication and was excluded from the primary analysis (Figure 1). Baseline demographics and clinical and biochemical characteristics of the 33 patients comprising the efficacy population are shown in Table 1. Adherence to study medication was excellent, with 97.5% (standard deviation 5.0) of all doses being taken. Adherence was more than 90% in all patients.

3.1 | Effects on albuminuria

Patients had a geometric mean 24 h UAE of 470 (95% CI, 334-662) mg/24 h at baseline, which was reduced to 331 (95% CI, 303-362) mg/24 h after 6 weeks of treatment with dapagliflozin. During 6 weeks of treatment with placebo, albuminuria increased to 519 mg/g (95% CI, 475-567). Accordingly, the repeated measures model showed that dapagliflozin, as compared to placebo,

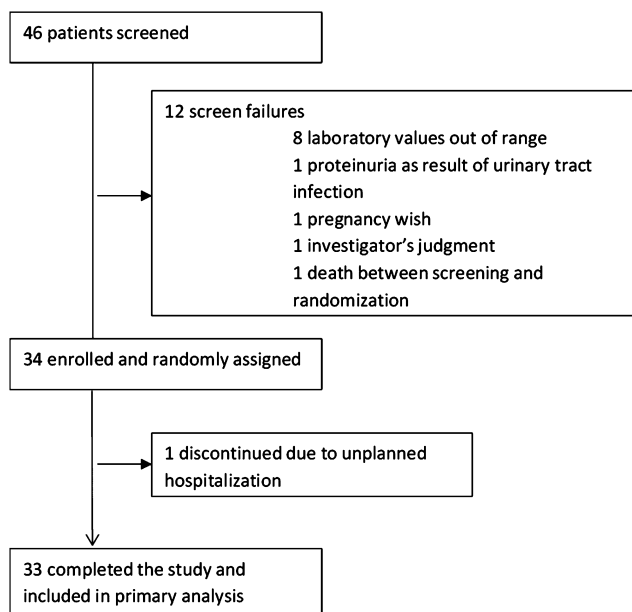


FIGURE 1 Trial profile

TABLE 1 Baseline characteristics

Characteristic	Total (N=33)
Age (years)	61 (9)
Sex (female/male) (n)	8/25
Caucasian (n, %)	30 (91)
Smoking status (n, %)	9 (27.3)
HbA1c (mmol/mol)	57 (9.5)
Diabetes duration (years)	10 (7)
Systolic blood pressure	142 (15)
Diastolic blood pressure	77 (5.9)
Weight (kg)	96 (22)
BMI (kg/m ²)	31 (5.5)
Estimated GFR (mL/min/1.73 m ²)	72 (21)
Cardiovascular disease history (n, %) ^a	10 (30.3)
UAER (mg/24 h)	470 [191-997]
U _{ACR} * (mg/mmol)	31 [13-68]
<i>Medication</i>	
Metformin, n (%)	30 (90.9)
Sulfonylurea, n (%)	9 (27.3)
Insulin, n (%)	21 (63.6)
Antihypertensive medication, n (%)	33 (100)
ACEi	16 (48.5)
ARB	16 (48.5)
B-blocker	16 (48.5)
Ca - channel blockers	14 (42.4)
Diuretics	26 (78.8)

Data are given as mean (SD) and *geometric mean (25th to 75th percentile).

^a Cardiovascular disease history defined as history of coronary artery disease or peripheral vascular disease.

significantly decreased albuminuria by 36.2% (95% CI, 22.9-47.2) [Figure 2A] $P < .001$. The individual albuminuria response to dapagliflozin varied markedly among individuals (range, -84% to +94%). During dapagliflozin treatment vs placebo, 84% and 65% of patients, respectively, achieved a $\geq 0\%$ and $\geq 30\%$ reduction in 24 h UAE (both $P < .01$). Dapagliflozin decreased first morning void U_{ACR} by 29.7% (95% CI, 16.8%-40.7%) (Figure 2B) as compared to placebo ($P < .001$). Six weeks after discontinuation of the dapagliflozin treatment period, the change in 24 h UAE from baseline was 0.5% (95% CI, -20.4 to 26.8), indicating that the anti-albuminuric response was completely reversible 6 weeks after discontinuation of dapagliflozin.

3.2 | Effects on eGFR, HbA1c, blood pressure and body weight

Baseline eGFR was 72 mL/min/1.73 m². eGFR fell during dapagliflozin treatment by 4.8 mL/min/1.73 m² (95% CI, -6.7 to -3.0) and increased by 0.9 mL/min/1.73 m² (95% CI, -1.5 to 3.3) during placebo treatment ($P < .001$ vs dapagliflozin) (Figure 2F). Change in eGFR 6 weeks after discontinuation of dapagliflozin was -1.3 mL/min/1.73 m² (95% CI, -4.6 to +1.5), indicating that eGFR returned to baseline values. After 6 weeks of dapagliflozin treatment, changes in HbA1c and SBP relative to placebo were -2.5 mmol/mol (95% CI,

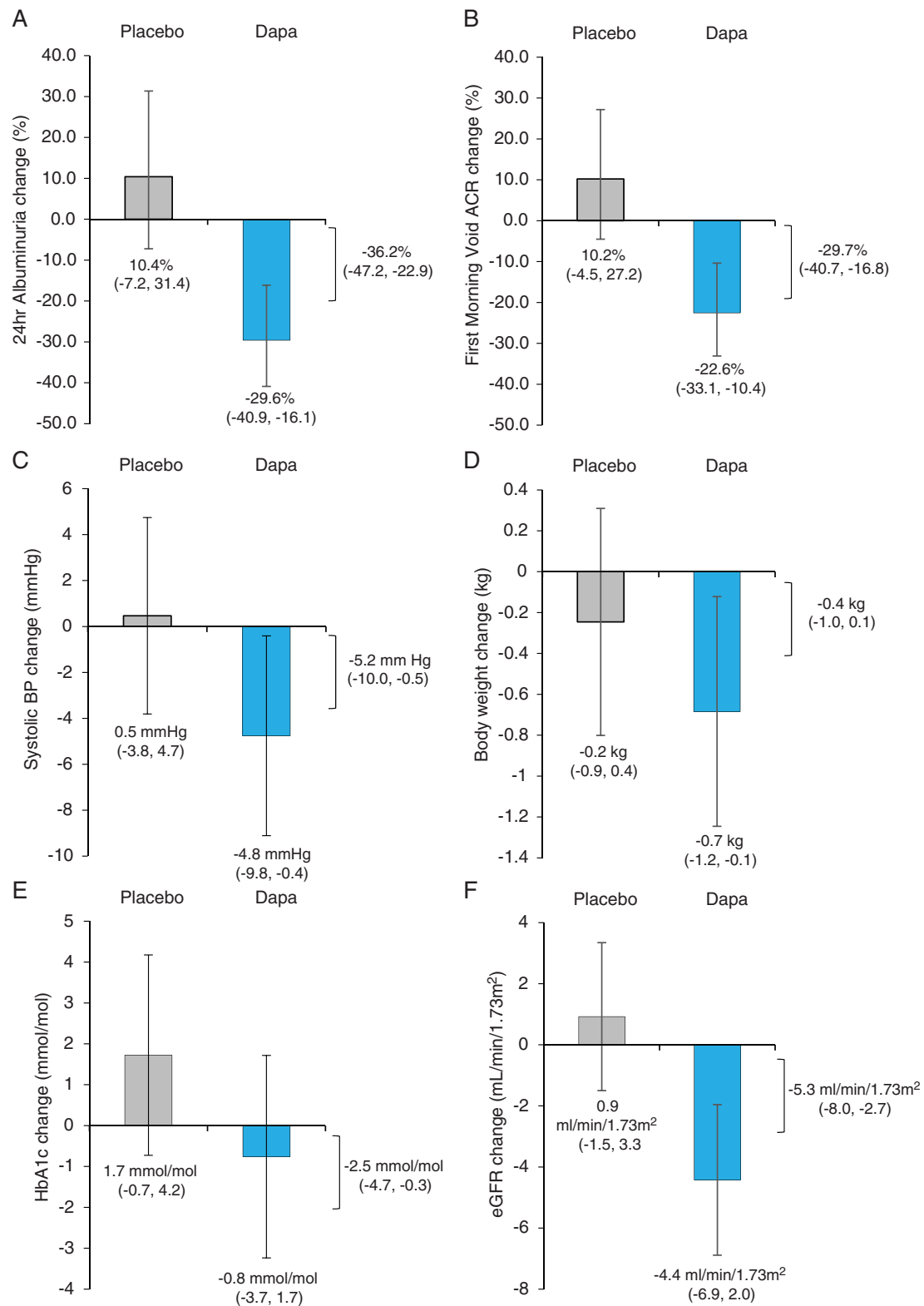


FIGURE 2 A, Primary endpoint: percentage change in 24-hour urinary albumin excretion rate from baseline. B to F, Secondary endpoints: B, percentage change in first morning void albumin:creatinine ratio from baseline; C, change in systolic blood pressure; D, change in body weight; E, change in HbA1c; F, change in eGFR

-4.7 to -0.3; $P = .026$) and -5.2 mm Hg (95% CI, -10.0 to -0.5; $P = .032$), respectively (Figure 2C and E). The corresponding change in body weight was -0.4 kg (95% CI, -1.0 to 0.1; $P = .095$; Figure 2D).

3.3 | Albuminuria response after re-exposure

To assess whether the individual response to dapagliflozin is reproducible upon re-exposure we exposed 15 patients twice to 6 weeks of dapagliflozin 10 mg. Baseline characteristics of these 15 patients

are shown online in Table S1. In this subgroup, the change in 24 h UAE during the first exposure was -41% (range, -76 to $+52$) and during the second exposure was -27% (range -90 to $+95$; $P = .18$ vs first period) (Figure 3). A statistically significant correlation was observed in the UAER response during the first and second exposure ($r = 0.69$; [95% CI, 0.27–0.89] $P = .004$), indicating that 48% of the among-individual variance in UAER response during the second exposure could be explained by the first exposure (Figure 3). Adjustment of changes in 24-hour sodium, potassium and phosphate excretion (as proxies for changes in dietary intake) between the first and second treatments increased the explained variance (R^2) of the 24 h UAE response during the second exposure to 69%. One patient used a non-steroidal anti-inflammatory drug during the first treatment period. Excluding this patient from the analysis did not change the result. Significant correlations in response between the first and second exposure were also observed for systolic blood pressure ($r = 0.67$; $R^2 = 0.45$ [95% CI, 0.24–0.88]; $P = .006$).

3.4 | Predictors of individual albuminuria response

Various baseline parameters were analysed to assess if these predict the individual response to dapagliflozin. The placebo-corrected reduction in 24 h UAE was consistent in patients with microalbuminuria, 46.3% (95% CI, 26.4–60.8), and macroalbuminuria, 29.9% (11.4–44.6; P for interaction = .173). Similarly, 24 h UAE response was consistent in patients with $eGFR < 60$ mL/min/1.73 m², 36.6% (15.1–52.6), and ≥ 60 mL/min/1.73 m², 36.0% (17.9–50.1; P for interaction = .961). The albuminuria response also was not determined by baseline age, gender, HbA1c, systolic blood pressure or 24-h sodium or potassium excretion. The change in systolic blood pressure, HbA1c and fasting plasma glucose did not correlate with the change in 24 h UAE during dapagliflozin treatment, except for the change in eGFR which showed a modest association with the change in 24 h UAE ($r = 0.34$; $P = .06$).

3.5 | Safety

Overall, dapagliflozin was well tolerated. Three patients experienced a urinary tract infection during dapagliflozin treatment vs 1 patient

during placebo treatment. Hypoglycaemia was reported by 2 patients during dapagliflozin treatment. Both patients also used insulin. None of the adverse events led to drug discontinuation. Serious adverse events occurred in 4 patients. Two of these events occurred during dapagliflozin treatment (1 fracture and 1 hospitalization because of general malaise) and 2 events occurred during placebo treatment (1 fracture and 1 hospitalization because of fever and diarrhea). None of these events was thought by the treating physician to be related to study medication.

4 | DISCUSSION

In this prospective randomized controlled trial, the albuminuria-lowering effect of the SGLT2 inhibitor dapagliflozin was assessed in patients with type 2 diabetes and residual albuminuria. Dapagliflozin 10 mg/d lowered 24-hour urinary albumin excretion by 36%, on average, with a large variation among individuals. The individual albuminuria-lowering response was reproducible when patients were re-exposed to dapagliflozin 10 mg/d, supporting the notion that the individual anti-albuminuric response is a true response to dapagliflozin and can be adequately quantified in a clinical trial setting.

Previous *post-hoc* analyses of clinical trials have indicated that SGLT2 inhibitors appear to decrease albuminuria. All these trials were designed primarily to assess effects of SGLT2 inhibitors on HbA1c or blood pressure.^{4–7} To the best of our knowledge this is the first dedicated prospective randomized controlled trial that demonstrates and confirms the albuminuria-lowering efficacy of the SGLT2 inhibitor dapagliflozin. In this trial both 24-hour urine samples and 3 consecutive first morning void urine samples were collected to characterize precisely the albuminuria-lowering effect of dapagliflozin, whereas previous trials used only single random urine samples, a less precise measure to assess albuminuria-lowering effects.¹² The magnitude of the albuminuria-lowering effect was similar to that previously described in *post-hoc* analyses. For example, in patients with type 2 diabetes and micro- or

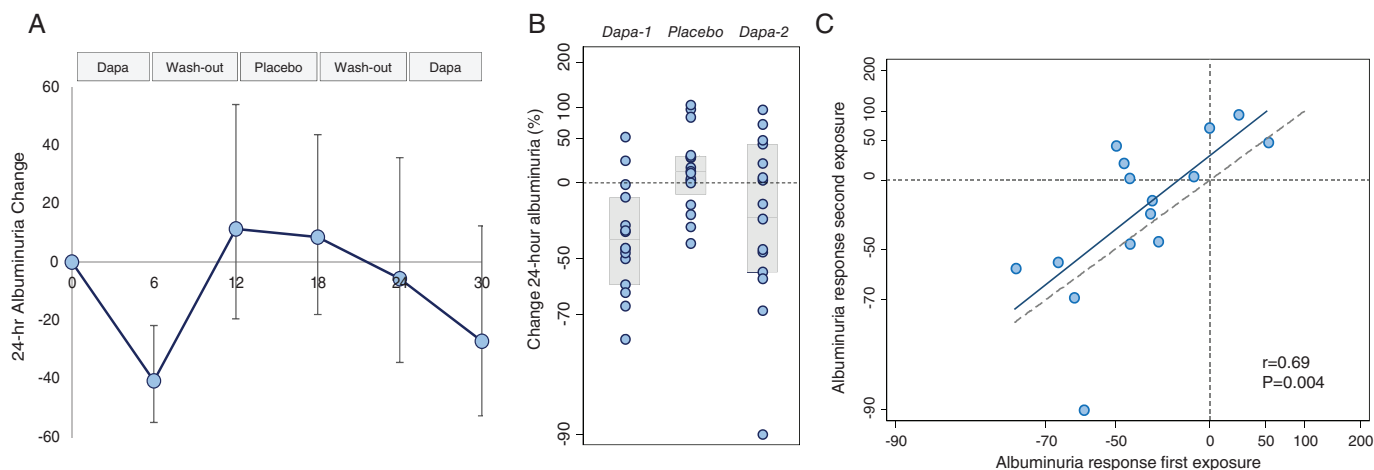


FIGURE 3 A, Change in 24-hour urinary albumin excretion over time during dapagliflozin and placebo treatment among 15 patients who received dapagliflozin during 2 treatment periods; B, individual changes in albuminuria during dapagliflozin and placebo treatment; C, correlation between changes in albuminuria during the first and second dapagliflozin treatment periods

macroalbuminuria, dapagliflozin and empagliflozin decreased the albumin:creatinine ratio by approximately 30%.^{4,6} Similar magnitudes of effect were reported with canagliflozin in a subgroup of patients with type 2 diabetes and micro- or macroalbuminuria.¹⁴

A large among-individual variability in changes in 24 h UAE was observed after exposure to dapagliflozin for 6 weeks. The finding that the individual response at re-exposure was reproducible for the individual indicates that the large among-patient heterogeneity in albuminuria response is a true pharmacological variation in response to dapagliflozin and can be adequately quantified in a clinical trial setting. A recent study with the glucagon-like peptide-1 agonist liraglutide also showed that the individual drug response is reproducible after second exposure, although this study was not designed primarily to address this topic.¹⁵ Given that the change in albuminuria is a strong predictor of changes in future risk of renal and cardiovascular disease, these data suggest that some patients benefit significantly while others, with no reduction in albuminuria, comprising approximately 20% to 30% of the population, are less likely to benefit. We explored several physical and biochemical parameters as predictors of response but could not identify any. Future analyses are required to identify biomarkers of response to dapagliflozin to tailor and optimize therapy.

We had not expected that the individual 24 h UAE response to dapagliflozin at second exposure would completely reproduce the first dapagliflozin response as it is known that the biological day-to-day variation in albuminuria is high.¹² In addition, many factors, which could be different during the first and second periods, may have influenced reproducibility in response to dapagliflozin, including variation in dietary patterns, differences in disease activity or changes in concomitant medication. Indeed, when we adjusted the analyses for differences in sodium, potassium and phosphate excretion, as proxy for differences in dietary intake, the albuminuria correlation between first and second exposure increased. This suggests that, despite the careful provision of dietary advice, changes in dietary patterns have influenced reproducibility in response. We also explored changes in concomitant medication during the first and second dapagliflozin periods as a potential explanation for the incomplete correlation, but these were markedly stable throughout the study.

Changes in metabolic parameters including HbA1c, fasting plasma glucose and body weight were not the primary focus of this study. In particular, in line with the duration of the active treatment period, there was only a modest, but statistically significant, reduction in HbA1c. Interestingly, despite the small reduction in HbA1c, a large reduction in albuminuria was present, indicating that reduction in albuminuria is independent of glycaemic control. This finding is in accordance with a previous *post-hoc* analysis from a large randomized controlled trial demonstrating that long-term effects of the SGLT2 inhibitor canagliflozin on renal function are independent of its glycaemic effects.¹⁴

What could be the mechanism of the albuminuria-lowering effect? As observed in the current study, previous trials have shown acute but modest decline in eGFR within 3 to 6 weeks of treatment initiation. The acute decline in eGFR is followed by a period of

stable renal function, and is reversible after drug discontinuation. This pattern is reminiscent of ACEi and ARBs and suggests a reduction in glomerular pressure and renal hyperfiltration which is associated with long-term renoprotection.¹⁶ Such a mechanism could also explain the reduction in albuminuria independent of changes in metabolic control, and the association we found between changes in eGFR and 24 h UAE during dapagliflozin. The difference between SGLT2 inhibitors and ACEi or ARBs is that the reduction in intraglomerular pressure induced by ACEi and ARBs is mediated through efferent vasodilation, whereas SGLT2 inhibitors are thought to induce afferent vasoconstriction.¹⁰ The hypothesis that SGLT2 inhibition reduces intraglomerular pressure is supported by data in patients with type 1 diabetes, demonstrating that the SGLT2 inhibitor empagliflozin reduces calculated glomerular pressure and afferent arterial tone.¹⁷

An alternative mechanism that may contribute to the albuminuria-lowering effects may be related to decreases in circulating volume and natriuretic effects. Dapagliflozin has been shown to decrease plasma volume and to increase hematocrit to an extent similar to that of hydrochlorothiazide.³ Previous studies have shown that optimizing extracellular volume through dietary sodium restriction or diuretic use decreases albuminuria, allegedly through potentiating the effects of ACEi or ARBs.¹⁸ As patients in the current study were already receiving ACEi and ARBs, a sustained reduction in effective circulating volume induced by dapagliflozin may have potentiated ACEi and ARBs effects. In support of this proposed mechanism is the finding from the EMPAREG trial demonstrating that the renoprotective effects of the SGLT2 inhibitor empagliflozin tended to be larger among patients already using ACEi or ARBs.⁸

Finally, it may be possible that SGLT2 inhibitors influence pro-inflammatory pathways. Inflammatory pathways are often activated in patients with diabetic nephropathy and may initiate and sustain disease progression.¹⁹ Experimental studies have reported that SGLT2 inhibitors reduce markers of inflammation.^{20,21} Further studies are required to characterize the anti-inflammatory properties of SGLT2 inhibitors.

This study has limitations. First, the study used a surrogate outcome measure as primary outcome and additional studies are required to characterize the renoprotective effects of dapagliflozin on hard renal end points. In addition, the study follow-up period was only 6 weeks. Whether reductions in 24 h UAE persist over longer time periods could not be investigated. A *post-hoc* analysis from the EMPAREG trial suggested that the SGLT2i empagliflozin instantaneously reduces albuminuria and the effect persisted throughout the 4-year follow-up period.²² That trial also reported that empagliflozin reduces renal risk, but the number of hard renal end points was small. The renoprotective effects of SGLT2 inhibitors in patients with type 2 diabetes will be definitively tested in the CREDENCE trial (ClinicalTrials.gov identifier NCT02065791). Secondly, we used dapagliflozin at 10 mg per day, which is the dose used clinically. This dose is selected, however, based on dose-response studies using HbA1c as the primary efficacy parameter. Whether the dose-response curve for albuminuria is similar to that of HbA1c is unknown. In addition, whether patients not responding

to dapagliflozin 10 mg/d would respond to a higher dose was not assessed. Finally, despite strict dietary advice, not all patients adhered to a stable dietary pattern, which has probably led to an underestimation of reproducibility in individual responses during the 2 exposure periods to dapagliflozin.

In conclusion, dapagliflozin therapy markedly reduces 24-hour urinary albumin excretion in patients with type 2 diabetes with micro- or macroalbuminuria who are already undergoing ACEi or ARB therapy. The reduction in albuminuria, however, varies to a significant degree among individual patients. Although albuminuria fluctuates within an individual over time, the variation in albuminuria response to dapagliflozin is reproducible upon re-exposure. These data support implementation of personalized medicine approaches in clinical practice to optimally tailor therapy and maximize diabetic kidney disease care.

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Conflict of interest

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Author contributions

All authors were involved in the design of the study. S. P. was responsible for data collection, data analysis, interpretation of the results and wrote the first draft of the manuscript. D. dZ. assisted in data interpretation and contributed to critical revision of the manuscript. G. L. contributed to data collection and critical revision of the manuscript. H. J. L. H. was responsible for data analysis, data interpretation and final review of the manuscript. All authors read and approved the final manuscript. H. J. L. H. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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