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BRIEF REPORT

Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers

Claire C. J. Dekkers MD¹  | Sergei Petrykiv MD² | Gozewijn D. Laverman MD³ | David Z. Cherney MD^{4,5} | Ron T. Gansevoort MD¹ | Hiddo J. L. Heerspink PhD¹ 

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

²Department of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

³Department of Nephrology, Ziekenhuisgroep Twente, Almelo and Hengelo, The Netherlands

⁴Department of Medicine, Division of Nephrology, Toronto General Hospital, University of Toronto, Toronto, Canada

⁵Department of Physiology and Banting and Best Diabetes Centre, University of Toronto, Toronto, Canada

Correspondence

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

The mechanisms by which SGLT-2 inhibitors lower albuminuria are incompletely understood. We assessed in a *post-hoc* analysis of a cross-over trial the effects of the SGLT2 inhibitor dapagliflozin on glomerular markers (IgG to IgG4 and IgG to albumin), tubular markers (urinary KIM-1, NGAL and LFABP) and inflammatory markers (urinary MCP-1 and IL-6) to provide more insight into kidney protective effects. Dapagliflozin decreased albuminuria by 43.9% (95% CI, 30.3%-54.8%) and eGFR by 5.1 (2.0-8.1) mL/min/1.73m² compared to placebo. Dapagliflozin did not change glomerular charge or size selectivity index compared to placebo. Dapagliflozin decreased urinary KIM-1 excretion by 22.6% (0.3%-39.8%; $P = .05$) and IL-6 excretion by 23.5% (1.4%-40.6%; $P = .04$) compared to placebo, whereas no changes in NGAL, LFABP and MCP-1 were observed. During dapagliflozin treatment, changes in albuminuria correlated with changes in eGFR ($r = 0.36$; $P = .05$) and KIM-1 ($r = 0.39$; $P = .05$). In conclusion, the albuminuria-lowering effect of 6 weeks of dapagliflozin therapy may be the result of decreased intraglomerular pressure or reduced tubular cell injury.

KEYWORDS

acute kidney injury, dapagliflozin, KIM-1, MCP-1, SGLT-2, type 2 diabetes

1 | INTRODUCTION

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors lower glycated haemoglobin (HbA1c), decrease blood pressure, body weight and albuminuria, and, in the long-term, SGLT-2 inhibitors appear to slow progression of kidney function decline.¹⁻³ The mechanisms responsible for the albuminuria-lowering effect are not yet completely understood. A reduction in glomerular hyperfiltration as a result of restoration of tubuloglomerular feedback may be 1 of the potential mechanisms.^{4,5} SGLT-2 inhibitors could also hypothetically lower albuminuria by restoring the charge and/or size selectivity of the glomerular basement membrane. Alternatively, improvement in tubular reabsorption of filtered albumin can potentially decrease albuminuria.⁶ SGLT-2 inhibition reduces the reabsorption of filtered sodium and glucose in the proximal tubule, and thereby reduces the oxygen-consuming transport workload. Less oxygen stress may help to improve tubular cell integrity and, potentially, tubular albumin reabsorption.^{7,8} As hyperglycaemia and albuminuria have proinflammatory

influences on renal tubules, reductions in these parameters could, hypothetically, reduce the generation of proinflammatory cytokines.⁹

Various biomarkers that are associated with glomerular and tubular structure and function are presently available. The aim of the current study was to characterize the effect of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury and inflammatory markers. Secondly, we assessed whether changes in albuminuria or eGFR during dapagliflozin therapy correlated with kidney injury markers to provide insight into the mechanisms responsible for the lowering of albuminuria with dapagliflozin.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a *post-hoc* analysis of a prospective, randomized, double-blind, placebo-controlled cross-over clinical trial. The study design,

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patient population and primary results have been described previously.¹⁰ In short, 33 patients with type 2 diabetes, aged between 18 and 75 years, with a first morning void albumin:creatinine ratio (U_{ACR}) ≥ 100 mg/g and < 3500 mg/g (11.3–395.5 mg/mmol) and an eGFR ≥ 45 mL/min/1.73m² were enrolled. Participants were required to have been using a maximum tolerated stable dose of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker for more than 4 weeks. Patients were randomly assigned to 2 consecutive treatment periods of 6 weeks, during which they received dapagliflozin 10 mg per day or placebo, with wash-out periods of 6 weeks in between. The primary outcome was change in 24-hour urinary albumin excretion rate (24 hour UAE). The study was registered with the Netherlands Trial Register (NTR 4439) and complied with the Declaration of Helsinki and Good Clinical Practice Guidelines.

2.2 | Measurements

Blood and urine samples were obtained at baseline, in the beginning and at the end of the 2 treatment periods, as well as at the end of the wash-out period. These urine and plasma samples were stored at -80 °C for no more than 24 months (range, 6–24 months). Blood and urine samples from 31 patients were available for this study.

Urinary IgG and IgG4 were measured as markers of glomerular damage. Urinary kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid-binding protein (LFABP) were measured as markers of tubular damage. Urinary monocyte chemoattractant protein-1 (MCP-1) and urinary interleukin-6 (IL-6) were measured as markers of inflammation.¹¹ To assess the effect of dapagliflozin on size-selectivity and charge-selectivity of the glomerular basement membrane, plasma IgG and IgG4 were also determined. The ratio of IgG to albumin clearance was calculated as an index of glomerular size selectivity.¹² Glomerular charge selectivity was calculated by the ratio of the clearance of the neutrally charged IgG to the clearance of the negatively charged IgG4.¹² For quantification of IgG4, KIM-1, NGAL, LFABP, MCP-1 and IL-6, direct sandwich-ELISAs were used according to the manufacturer's specifications (R&D systems, Minneapolis, Minnesota). IgG was quantified with nephelometry.

2.3 | Statistical analysis

The effect of dapagliflozin compared to placebo on the kidney injury markers was determined with a mixed effects repeated measures analysis. The model included sequence, period, treatment and subject as factors and baseline biomarker of interest as a covariate. All biomarkers were log transformed before entering data in the repeated measures model. The between-group geometric mean change in 24-hour excretion of the biomarker of interest was derived by $100 \times (\exp[\text{least square mean change}] - 1)$, and the same transformation was applied to the 95% confidence limits. Pearson's correlation coefficient was used to calculate correlations between eGFR, 24 hour UAE and kidney injury markers. All variables were log transformed before calculation of the Pearson's correlation coefficient. SAS software version 8.2 (SAS Institute, Inc., Cary, North Carolina) was used. All statistical tests were 2-sided, with a statistical significance level of P value $< .05$.

3 | RESULTS

Baseline characteristics of the 31 patients with available urine and plasma samples are reported online in Table S1. Dapagliflozin decreased 24 hour UAE by 42.5% (95% CI, 29.9%–52.9%; $P < .01$) and eGFR by 5.2 mL/min/1.73m² (2.5–7.8 mL/min/1.73m²; $P < .01$) (Figure 1A,B). The decrease in eGFR occurred within the first weeks of dapagliflozin therapy. Six weeks after dapagliflozin discontinuation the mean eGFR was 71 (SD, 19) mL/min/1.73m², indicating that the decline in eGFR was reversible after treatment discontinuation.

3.1 | Effect of dapagliflozin on glomerular, tubular and inflammatory markers

Dapagliflozin significantly reduced urinary glomerular damage markers compared to placebo. Compared to placebo, dapagliflozin decreased fractional clearance of IgG and IgG4 by 28.4% (95% CI, 7.2%–44.8%; $P = .01$) and 34.6% (3.0%–55.9%; $P = .04$), respectively. However, the IgG-to-IgG4 clearance ratio (marker of glomerular charge selectivity) and the IgG-to-albumin clearance ratio (marker of glomerular size selectivity) did not change significantly during dapagliflozin treatment compared to placebo (Table 1, Figure 1C,D).

At the tubular level, dapagliflozin, compared to placebo, reduced urinary KIM-1 excretion by 22.6% (0.3%–39.8%; $P = .05$) (Table 1 and Figure 1E), but did not change urinary excretion of NGAL (–13.4% [–35.6%–16.6%]; $P = 0.33$) (Table 1 and Figure 1F) or LFABP (0.9% [–13.2%–17.2%]; $P = .91$) (Table 1 and Figure 1G).

Changes in urinary excretion of inflammatory biomarkers with placebo and during dapagliflozin therapy are shown in Table 1 and Figure 1H,I. Dapagliflozin, compared to placebo, reduced urinary IL-6 excretion by 23.5% (1.4%–40.6%; $P = .04$) and urinary MCP-1 excretion by 14.1% (–32.2%–8.9%; $P = .20$).

3.2 | Correlations between 24 hour UAE, eGFR and kidney injury markers

At baseline, 24 hour UAE correlated with urinary NGAL, LFABP and IL-6 excretions (Table S2). During dapagliflozin treatment there was a significant correlation between 24 hour UAE change and eGFR change ($r = 0.36$; $P = .05$) (Figure S1A). Changes in 24 hour UAE did not correlate with changes in IgG to IgG4 clearance ratio ($r = -0.01$; $P = .97$) and IgG to albumin clearance ratio ($r = -0.36$; $P = .06$). Changes in KIM-1 excretion significantly correlated with changes in 24 hour UAE ($r = 0.39$; $P = .05$) (Figure S1D–F). There were no correlations between changes in the other tubular biomarkers and changes in 24 hour UAE. Both reductions in IL-6 and MCP-1 excretions correlated with reductions in 24 hour UAE ($r = 0.59$; $P < .01$ and $r = 0.44$; $P = .02$, respectively) (Figure S1G,H). Figure S2 shows that there were no correlations between eGFR changes and changes in any of the kidney injury markers during dapagliflozin therapy. Finally, after 6 weeks of dapagliflozin treatment, the residual 24 hour UAE level correlated with achieved urinary excretion of KIM-1, LFABP, NGAL, IL-6 and MCP-1 (Table S2).

TABLE 1 Mean percent changes from baseline in kidney injury markers

Injury markers	Baseline ^a	Mean % change from baseline, placebo (95% CI) ^b	P value	Mean % change from baseline, dapagliflozin (95% CI) ^b	P-value
Glomerular					
IgG	2269 [875-4600]	4.3 (-12.4, 24.2)	.64	-25.3 (-38.1, -9.9)	0.01
IgG4	4 [1-8]	3.6 (-21.0, 36.0)	.80	-32.2 (-49.1, -9.7)	0.01
IgG/IgG4	920 [396-1271]	-0.9 (-24.0, 29.2)	.95	16.7(-11.9, 54.5)	0.29
IgG/Albumin	0.2 [0.2-0.3]	10.9 (1.2, 21.6)	.04	18.2 (7.0, 30.4)	<0.01
Tubular					
KIM-1	1218 [597-2705]	-0.9 (-20.4, 23.4)	.94	-23.3 (-39.8, -2.2)	0.04
NGAL	23 [13-65]	9.3 (-9.7, 32.3)	.37	-5.3 (-22.5, 15.7)	0.60
LFABP	11 [8-17]	21.2 (6.0, 38.5)	.01	22.2 (6.4, 40.4)	0.01
Inflammatory					
IL-6	3 [2-5]	-0.7 (-18.1, 20.5)	.95	-24.0 (-37.9, -7.0)	0.01
MCP-1	268 [213-413]	5.6 (-11.1, 25.5)	.54	-9.3 (-24.3, 8.7)	0.30

^a Baseline data are given as median pg/24 h [25th to 75th percentile] for KIM-1, LFABP, IL-6 and MCP-1, and median ng/24 h for NGAL.

^b All biomarkers were log transformed. Mean change in 24-hour excretion of the individual biomarker was derived by $100 \times (\exp[\text{least square mean change}] - 1)$. The same transformation was applied to the 95% confidence limits.

4 | DISCUSSION

This study assessed the effects of dapagliflozin on glomerular, tubular and inflammatory biomarkers in patients with type 2 diabetes and albuminuria. Dapagliflozin decreased urinary KIM-1 and IL-6 excretion, suggesting that dapagliflozin may beneficially affect renal inflammation and reduces ischemic proximal tubular cell injury.

Reductions in urinary albumin excretion can be a consequence of changes in charge and/or size selectivity of the glomerular filtration barrier, decreased intraglomerular pressure or improved tubular reabsorptive capacity. The lack of effect on IgG-to-IgG4 clearance ratio and IgG-to-albumin clearance ratio suggests that changes in albuminuria in response to dapagliflozin treatment are not a result of effects on charge and size selectivity of the glomerular filtration barrier. Therefore, the observed reduction in albuminuria could still be explained by two other mechanisms: reduced intraglomerular pressure and improved tubular reabsorption processes.

The reduction in intraglomerular pressure, manifested by the reversible reduction in eGFR, may better explain the reduction in albuminuria as indicated by the positive correlation between eGFR and albuminuria changes. However, it is unlikely that the reduction in intraglomerular pressure completely explains albuminuria lowering with dapagliflozin as the time-course of effects on eGFR and albuminuria are different; eGFR changes occur rapidly, whereas effects on albuminuria probably take longer to be fully manifested. Nevertheless, acute hemodynamic effects may form the basis of gradual structural improvements in the glomerular filtration barrier. The albuminuria reduction observed in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUT-COME) was only partially reversed after treatment discontinuation, suggesting that SGLT-2 inhibitors induce structural improvements in the kidney over time.¹³

Dapagliflozin appeared to decrease urinary KIM-1 excretion, but there was no effect on urinary NGAL and LFABP excretion, compared to placebo. KIM-1 is a specific marker for hypoxic injury to proximal

tubular cells, which would suggest that dapagliflozin reduces proximal tubular cell injury.¹⁴ The reabsorption of electrolyte and organic solutes in the proximal tubule requires much energy.⁷ The proximal tubule therefore accounts for the largest amount of oxygen consumption in the kidney. SGLT-2 expression is increased in patients with diabetes.⁵ As a result, more glucose and sodium are reabsorbed, which increases the oxygen demand of tubular cells. This, in turn, renders the proximal tubule particularly susceptible to hypoxia in the setting of type 2 diabetes.^{7,8} Hypoxia appears to be one of the major drivers of kidney disease progression, especially in the diabetic kidney.^{8,15} SGLT-2 inhibition reduces sodium and glucose reabsorption in the proximal tubule, thereby reducing the workload for proximal tubular cells. Reduced workload may mitigate hypoxia-induced proximal tubular damage, which could lead to improved tubular cell structural integrity and, possibly, function.^{7,8} This notion is supported by a previous animal study showing that SGLT inhibition with phlorizin in diabetic rats improved renal cortical oxygen tension.¹⁶

We also observed a reduction in the inflammatory marker IL-6 during dapagliflozin treatment. IL-6 is an inflammatory cytokine and has been implicated in the progression of diabetic kidney disease.¹⁷ The presence of cytokines in the urine is thought to reflect local renal production of these cytokines.^{18,19} The decrease of IL-6 excretion observed in our study is in line with previous animal and in vitro studies.^{20,21} Previous studies showed that increased albumin leakage into the tubular compartment triggers an inflammatory response leading to MCP-1 and IL-6 release.²² The reduction in albumin leakage or tubular reabsorption may alleviate intra-renal inflammation and release of IL-6 and MCP-1. It is also possible that increasing urinary glucose excretion reduces intra-renal glucotoxicity and inflammation.⁹ Unfortunately, urinary glucose excretion was not measured in our study.

To the best of our knowledge, our study is the first to investigate the effect of SGLT-2 inhibition on tubular injury markers. Our data demonstrate that dapagliflozin does not increase tubular injury markers. In addition, the absence of correlation between changes in eGFR and changes in kidney injury markers indicates that 6-weeks

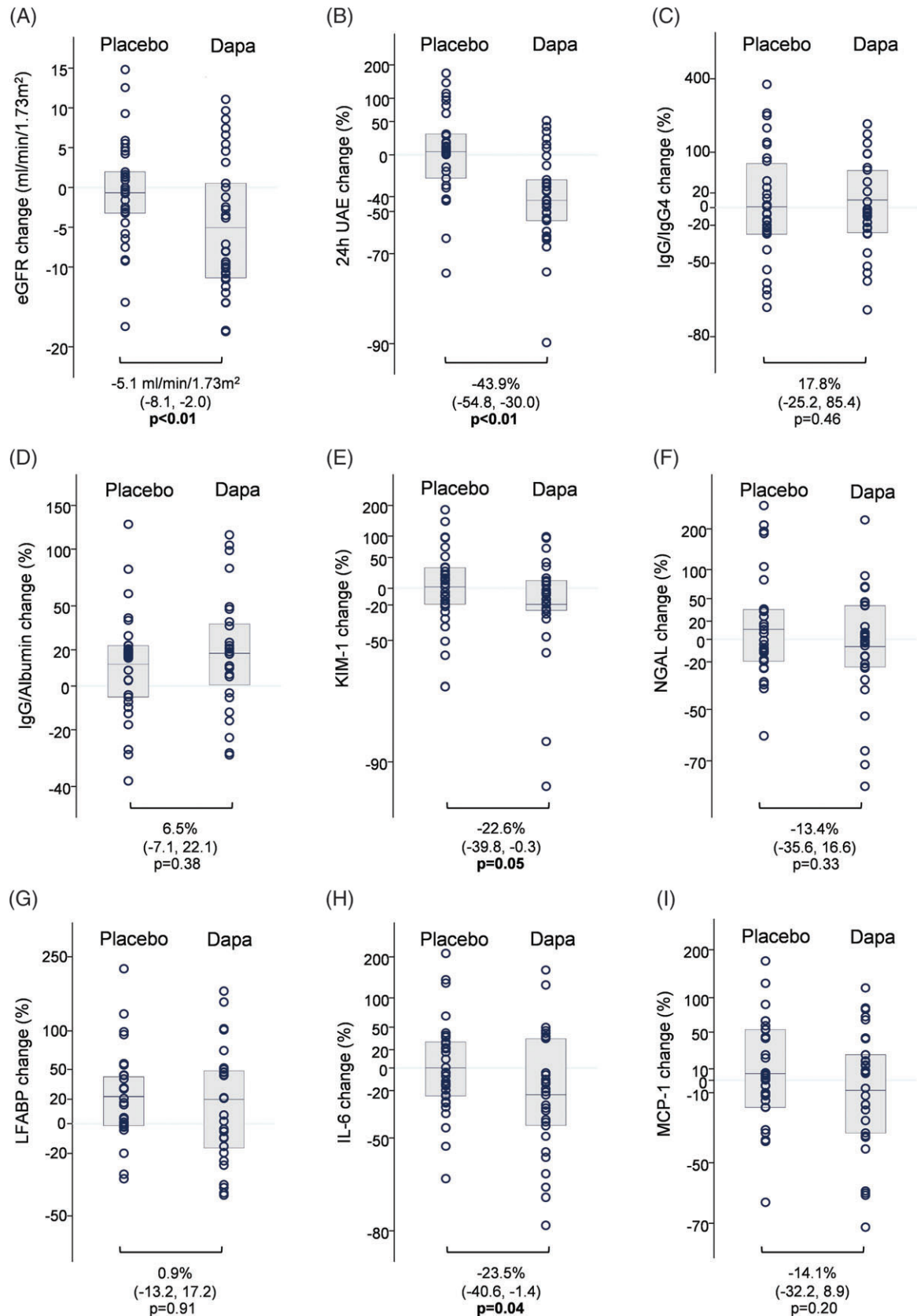


FIGURE 1 Change in eGFR (ml/min/1.73m²) A; percent change in 24 h UAE B; in IgG/IgG4 C; in IgG/Albumin D; in KIM-1 E; in NGAL F; in LFABP G; in IL-6 H; and in MCP-1 I during placebo and dapagliflozin treatment. Boxes show mean change within the 25th and 75th percentile. Mean differences and 95% confidence intervals of eGFR, 24 h UAE and kidney injury markers, compared to placebo, are shown under each sub-figure. One subject with an IgG/IgG4 change of 4860% is not shown in this figure C, and one subject with an LFABP change of 857% is not shown in this figure G

dapagliflozin therapy is not associated with tubular injury, although large studies, such as CREDENCE and DAPA-CKD, are required to confirm this finding.

This study has limitations. It was performed as a *post-hoc* analysis of a short-term study. As such, we were unable to investigate the long-term effects of SGLT-2 inhibition on glomerular, tubular and inflammatory biomarkers. It is not clear whether the results would apply to the sustained effects of dapagliflozin. In addition, because of the relatively small sample size, the power may have been too low to detect significant changes in, for example, the proxies for glomerular charge and size selectivity. These results should, thus, be regarded as hypothesis generating rather than hypothesis testing.

In conclusion, dapagliflozin therapy for 6 weeks decreases urinary excretion of proximal tubular marker KIM-1 and inflammatory marker IL-6. The observed reduction in albuminuria correlated positively with the decrease in eGFR, and also with the reduction in KIM-1 excretion. These findings support the hypothesis that the albuminuria-lowering effect of dapagliflozin could be the result of a reduction in glomerular pressure and improved proximal tubular cell integrity.

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Conflict of interest

C. C. J. D., S. P. and R. T. G. report no conflicts of interest. H. J. L. H. is a consultant for and has received honoraria from AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Janssen and Merck; he has a policy that all honoraria are paid to his employer. D. Z. I. C. has received speaker/consultant honoraria from Boehringer-Ingelheim, Eli Lilly, AstraZeneca, Sanofi, Merck, Mitsubishi-Tanabe and Janssen and has received operational funding for clinical trials from Boehringer Ingelheim, Merck and AstraZeneca. G. L. has received lecture fees from Sanofi, AstraZeneca and Jansen, and has served as a consultant for Abbvie, Sanofi, Novo Nordisk, AstraZeneca, Boehringer Ingelheim and MSD.

Author contributions

C. C. J. D., H. J. L. H. and R. T. G. designed the study and wrote the first draft of the manuscript. S. P. and G. L. contributed to data collection and to critical revisions of the manuscript. D. Z. I. C. contributed to critical revision of the 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 data analysis.

ORCID

Claire C. J. Dekkers  <http://orcid.org/0000-0002-5565-7240>

Hiddo J. L. Heerspink  <http://orcid.org/0000-0002-3126-3730>

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SUPPORTING INFORMATION

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