

RESEARCH LETTER

Effect of sotagliflozin on albuminuria in patients with type 2 diabetes and chronic kidney disease

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1 | BACKGROUND

Albuminuria in patients with/without diabetes is associated with risk for adverse renal and cardiovascular (CV) outcomes. Sodium-glucose cotransporter (SGLT)2 inhibitors reduce albuminuria and risk of CV and kidney-related outcomes. In the SCORED trial, the dual SGLT1 and SGLT2 inhibitor, sotagliflozin, significantly reduced risk of CV outcomes in high-risk patients with type 2 diabetes (T2D) and chronic kidney disease (CKD).¹ This treatment was associated with a non-significant reduction (hazard ratio [HR] = 0.71; 95% confidence interval [CI]: 0.46, 1.08) in the prespecified kidney-related composite endpoint, probably attributable to the small event numbers during the abbreviated follow-up period.¹ The effect of sotagliflozin on albuminuria has not been assessed in SCORED. In post hoc analyses, the aim was to determine the effect of sotagliflozin on urine albumin-to-creatinine ratio (UACR) and UACR-related outcomes in patients with T2D and CKD.

glomerular filtration rate [eGFR] 25–60 ml/min/1.73 m² regardless of UACR), and increased CV risk. Patients were randomized to sotagliflozin (200 mg/day uptitrated to 400 mg/day) versus placebo ([clinicaltrials.gov](https://clinicaltrials.gov/NCT03315143) NCT03315143). The primary endpoint was total CV death, hospitalization for heart failure, or urgent visit for heart failure.¹ UACR was assessed with spot urines collected at baseline and post-randomization clinical visits scheduled at weeks 4, 8 and 26, and every 6 months thereafter. For these analyses, the last available spot urine collected from the screening to randomization visits was used for baseline UACR. Percentage treatment difference was estimated with geometric mean ratio overall and by baseline UACR, eGFR and HbA1c subgroups using a repeated-measures mixed effects model. Progression and regression of UACR categories were assessed as described previously.² HR, 95% CI and *p*-values were estimated with a Cox proportional hazards model.

2 | METHODS

SCORED was a randomized, double-blind study of 10 584 patients with T2D [glycated haemoglobin (HbA1c) ≥7%], CKD (estimated

3 | RESULTS

Baseline characteristics for the trial have been reported previously.¹ For kidney measures, baseline mean eGFR was 45 ml/min/1.73 m², with 8% of patients with an eGFR <30 ml/min/1.73 m² and baseline

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median (Q1, Q3) UACR was 75 mg/g (17, 481), with 35%, 34% and 31% categorized with normoalbuminuria (defined as UACR <30 mg/g), microalbuminuria (UACR 30 to <300 mg/g), and macroalbuminuria (UACR ≥300 mg/g), respectively. At baseline, patients were treated with renin-angiotensin-aldosterone system inhibitors (89%), beta-blockers (63%) and loop (35%) or another diuretic (30%). Most patients (>95%) used ≥1 antihyperglycaemic medication, including biguanides (55%), insulin and/or insulin analogues (64%), sulphonylureas (27%), dipeptidyl peptidase-4 inhibitors (20%) and/or glucagon-like peptide-1 receptor agonists (6%).

Sotagliflozin significantly reduced UACR compared with placebo overall [−21.6% (95% CI: −23.8, −19.3); $p < .0001$]. Reductions in UACR with sotagliflozin were observed with normoalbuminuria [−6.5% (95% CI: −10.6, −2.3); $p = .003$], microalbuminuria [−27.3% (−30.9, −23.6); $p < .0001$] and macroalbuminuria [−30.0% (−33.5, −26.3); $p < .0001$]. In patients with baseline UACR within the upper range of 'normoalbuminuria' (UACR ≥15 to <30 mg/g), the geometric mean UACR was lower [−12.2% (95% CI: −18.2, −5.8); $p = .0003$] during follow-up with sotagliflozin versus placebo. The change in

UACR was not associated with change in HbA1c with sotagliflozin (Spearman correlation coefficient = 0.03, $p > .05$). A reduction with sotagliflozin relative to placebo was observed as early as 1 month and persisted throughout the follow-up period for the overall cohort and the micro- and macroalbuminuria subgroups (Figure 1). The curves within the normoalbuminuria subgroup appeared to diverge between treatments at 2 months.

The UACR reduction with sotagliflozin relative to placebo was consistent across baseline eGFR subgroups: <30 [−26.5% (95% CI: −33.6, −18.7)], eGFR 30 to <45 [−20.4% (−23.8, −16.9)] and eGFR ≥45 ml/min/1.73 m² [−22.0% (−25.1, −18.7)]. Change in UACR with sotagliflozin relative to placebo was also similar across baseline HbA1c subgroups: <8% [−17.2% (95% CI: −20.9, −13.4)], 8–8.9% [−24.8% (−28.6, −20.8)] and ≥9% [−23.3% (−27.1, −19.3)].

Sotagliflozin was associated with a 26% relative risk reduction for the progression of albuminuria from a lower albuminuria category [HR = 0.74 (95% CI: 0.68, 0.81); $p < .0001$] and a 34% relative increase in regression from a higher albuminuria category [HR = 1.34 (1.21, 1.48); $p < .0001$] (Figure 2).

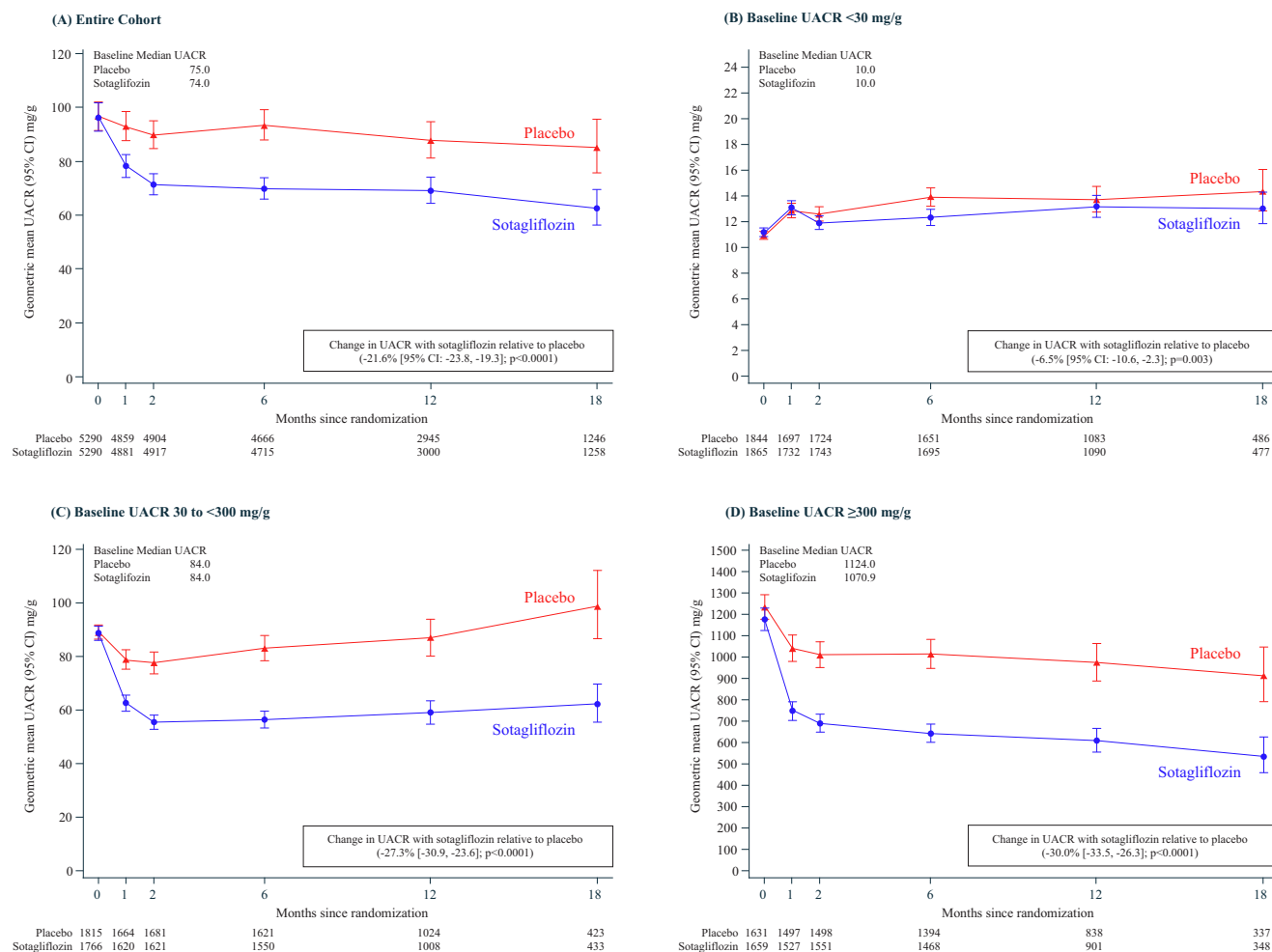
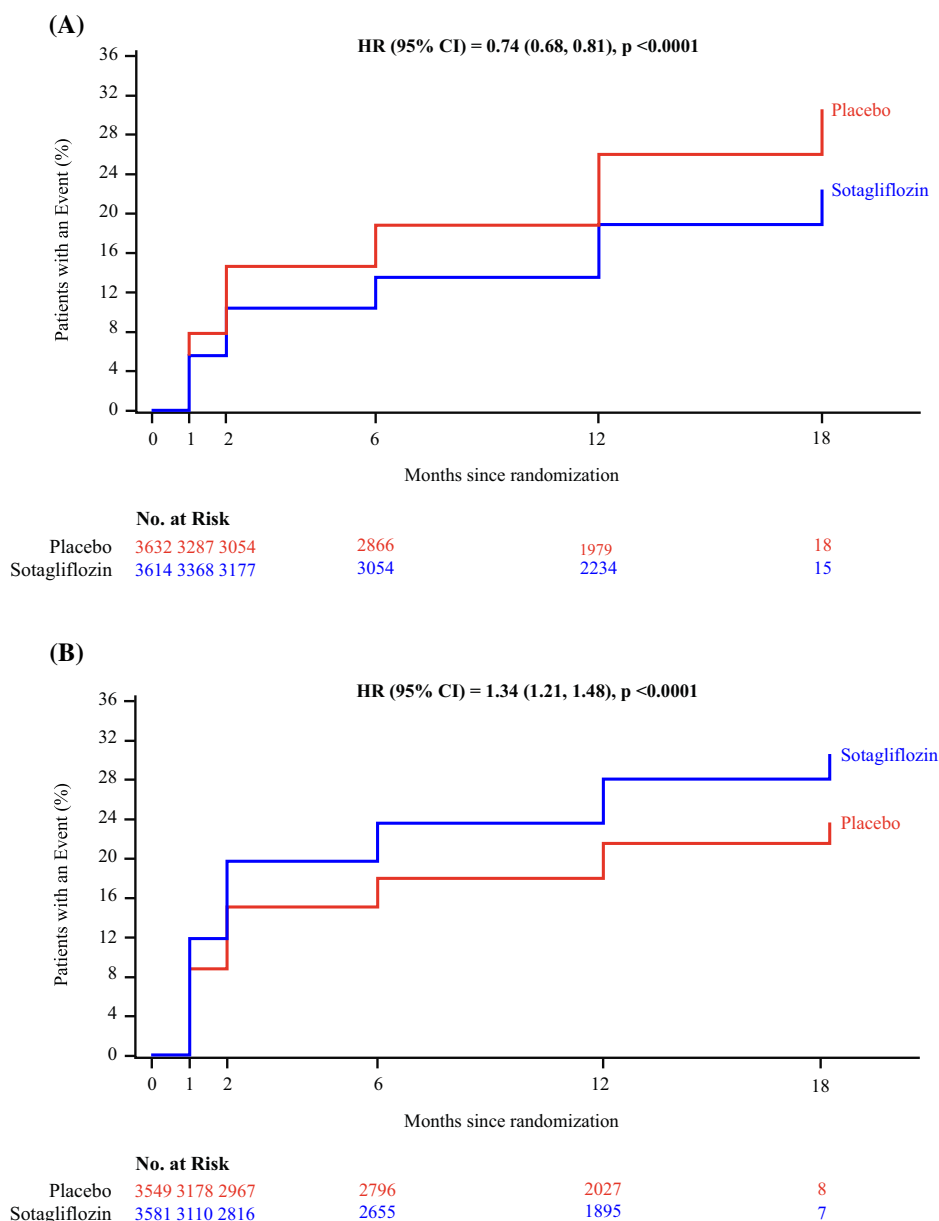


FIGURE 1 Effects of sotagliflozin and placebo on UACR over time in the (A) entire cohort and by UACR subgroups: (B) <30 mg/g, (C) 30 to <300 mg/g and (D) ≥300 mg/g. CI, confidence interval; UACR, urine albumin-to-creatinine ratio.

FIGURE 2 Effect of sotagliflozin vs placebo on urine albumin-to-creatinine ratio in (A) progression of albuminuria and (B) regression of albuminuria. CI, confidence interval; HR, hazard ratio.



4 | CONCLUSION

SGLT2 inhibition reduces CKD progression risk in patients with/without diabetes and reduces UACR, a clinical marker of long-term cardiorenal risk.³ While mechanisms responsible for end-organ protection and UACR lowering with SGLT2 inhibitors remain incompletely understood, the effects on haemodynamics, inflammation and hypoxia-related pathways are probably involved. Beyond association between UACR levels and risk, declines in UACR levels are linked with longer-term kidney and CV protection. Accordingly, ADA Standards of Practice Guidelines include UACR lowering as a clinical goal of pharmacotherapy in people with diabetes and CKD, with a recommended UACR-lowering target of $\geq 30\%$. In previous trials, SGLT2 inhibitors reduced UACR by 25%–40%. In this SCORED analysis, sotagliflozin significantly reduced UACR and favourably affected UACR progression/regression in patients with

T2D and CKD. Sotagliflozin significantly reduced albuminuria across the UACR spectrum, an effect that may be based on both SGLT2 and SGLT1 inhibition-derived physiological effects.⁴ While the impact on UACR as a marker of kidney protection was consistent across the spectrum of baseline eGFR, HbA1c and UACR in SCORED, previous CV outcome trials demonstrated benefits across baseline kidney risk.⁵ To date, only SCORED and EMPA-Kidney⁶ specifically enrolled patients based on having CKD, regardless UACR level. Sotagliflozin was also well tolerated in patients with T2D and CKD, with a safety profile consistent with other SGLT inhibitors and a small increase in diarrhoea consistent with its partial inhibition of SGLT1 in the gut.¹

Sotagliflozin improved UACR and rates of UACR progression/regression across a range of patients with T2D and CKD who are followed clinically by CV, kidney and endocrine specialists, as well as primary care.

AUTHOR CONTRIBUTIONS

DZIC wrote the first draft of the manuscript. All authors contributed to discussion, reviewed and edited the manuscript, and approved the final version.

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PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15203>.

DATA AVAILABILITY STATEMENT

Data may be made available upon reasonable request to the corresponding author.

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