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Effect of the dual sodium-glucose co-transporter-1 and -2 inhibitor sotagliflozin on renal outcomes in type 1 diabetes and type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Aim: To investigate the renal safety profile of sotagliflozin, a novel sodium-glucose co-transporter-1 and -2 inhibitor, in patients with type 1 diabetes and type 2 diabetes, with or without renal impairment, as well as its efficacy in decreasing the risk of further renal events, with an emphasis on those with previous renal impairment.

Methods: Embase, Medline, CENTRAL and Scopus were searched from their inception until 24 April 2023 for randomized controlled trials that reported estimated glomerular filtration rate (eGFR), urinary albumin excretion or composite renal events (CRE). The Cochrane risk of bias 2 tool was used. Mean difference, relative risk (RR) and 95% confidence intervals were estimated (PROSPERO: CRD42023425583).

Results: Fourteen studies were included in this review ($n = 17\,574$ participants; intervention $n = 9312$, control $n = 8262$). The median follow-up was 24.5 (Q1 = 15.25, Q3 = 28) months. Four studies recruited participants with renal impairment; baseline eGFR ranged from 23.8 to 50.5 mL/min/1.73m^2. The change in eGFR for studies ($n = 6$) with a follow-up of 52 weeks or longer was −1.23 (−1.45, −1.01) mL/min/1.73m^2. Sotagliflozin did not significantly alter urinary albumin excretion. No change was observed in the risk of CRE ($n = 6$ studies; RR = 0.82 [0.61, 1.12]), including in participants with renal impairment. High risk of bias was a limitation of this review.

Conclusions: Sotagliflozin did not adversely affect renal function or change the risk of key renal outcomes, including for participants with pre-existing renal impairment. Therefore, sotagliflozin was safe; however, further research is needed to determine its efficacy in reducing the risk of diabetic kidney disease.

Panagiotis Sardellis and Rosa Thuemmler contributed equally.

KEYWORDS
diabetes, meta-analysis, renal, sodium-glucose co-transporter-1, sodium-glucose co-transporter-2, sotagliflozin

1 | INTRODUCTION

Diabetes is a chronic metabolic disorder[1] affecting approximately 463 million adults worldwide, a number which is expected to increase to 700 million by 2045. Diabetic kidney disease, a complication of diabetes, is the primary cause of end-stage renal disease (ESRD).[2,3] Hyperglycaemia-induced endothelial dysfunction and hyperfiltration contribute to the development and progression of ESRD.[4]

Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of cardiovascular and renal events,[5,6] such as acute kidney injury (AKI),[7] in patients with type 1 diabetes (T1D)[8,9] and type 2 diabetes (T2D).[5,10,11] SGLT2 inhibitors block glucose reabsorption in the kidney's proximal tubules, increasing urinary glucose excretion and improving glycaemic control.[12,13] They have renoprotective effects, including a reduction in albuminuria, urinary albumin-to-creatinine ratio (uACR), and delaying the progression of chronic kidney disease (CKD) in patients with diabetes.[14] The CREDENCE and DAPA-CKD trials have shown significant renal benefits with SGLT2 inhibitors by assessing estimated glomerular filtration rate (eGFR),[5] albuminuria[5] and composite renal events (CRE)[5,15] in patients with CKD, independent of their glycaemic effects.

Nephroprotective effects have been identified with sodium-glucose co-transporter-1 (SGLT1) inhibitors, despite their primary target being intestinal glucose absorption.[16] The mechanism underlying these renoprotective effects may involve improved renal haemodynamics, reduced intraglomerular pressure and decreased inflammation.[17] Sotagliflozin, a sodium-glucose co-transporter-1 and -2 (SGLT1/2) inhibitor, increases renal glucose excretion through SGLT2 inhibition and inhibits intestinal glucose absorption by acting on the SGLT1 transporter, leading to additional glucose-lowering effects.[18] It significantly reduced HbA1c, body weight, systolic blood pressure and the incidence of myocardial infarction and heart failure (HF) compared with placebo.[19] However, the renal safety profile of sotagliflozin in patients with diabetes and efficacy in those with renal impairment have not been investigated sufficiently.

This systematic review aimed to establish the renal safety profile of sotagliflozin by evaluating its effect on kidney outcomes in patients with T1D and T2D with or without pre-existing renal impairment. The primary outcome was to establish whether sotagliflozin exhibited non-inferiority[20] compared with control, defined as (1) the absence of a clinically significant decline in renal function (measured with eGFR and urinary albumin excretion); and (2) the absence of a statistically significant increase in renal adverse events, with sotagliflozin compared with control. These objectives reflected the safety profile of sotagliflozin. Superiority[20] was also explored as a secondary outcome, defined as a statistically significant reduction in renal adverse events with sotagliflozin compared with control, reflecting the efficacy of sotagliflozin in reducing the risk for diabetic kidney disease.

2 | METHODS

2.1 | Data source and search strategy

This review was undertaken according to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) statement.[21] This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42023425583). The databases Medline, Embase, Scopus and CENTRAL were searched from their inception until 24 April 2023 to identify relevant literature. The search strategy was verified by a medical librarian (Appendix S1).

2.2 | Eligibility criteria

This review assessed records that fulfilled the eligibility criteria: (1) phase II or III randomized controlled trials (RCTs) in participants with T1D or T2D with or without pre-existing renal impairment; (2) the intervention was sotagliflozin or LX4211 and the comparator was either placebo or active comparator; (3) the RCTs reported on renal outcomes; and (4) the records were written in the English language. Single-arm treatment RCTs, RCTs that recruited participants aged younger than 18 years or under the legal age of majority (whichever was greater) and RCTs that either did not report on renal outcomes or from which it was not possible to extract renal data, were excluded. Reviews, animal, in vitro studies and conference abstracts were also excluded.

2.3 | Data screening and extraction

Two independent reviewers screened the identified reports, first by title and abstract and then by full text, using the research collaboration platform Rayyan.[22] Disagreements were resolved by a third reviewer. Data extraction was undertaken from the peer-reviewed published report and supplemented with data from the clinical trials registry only if data were unavailable from the publication. If data were not provided by the publication or registry, they were annotated as not available. If there were discrepancies between the published report and registry, data were extracted from the peer-reviewed published record. Data were extracted in duplicate using a pilot-tested extraction form.

2.4 | Risk of bias and certainty of evidence

The quality of evidence was assessed using the Cochrane risk of bias 2 (ROB2) tool,[23] by two reviewers independently and adjudicated by a third reviewer. Risk of bias plots were produced using the RobVis tool.[24] The certainty of evidence was evaluated independently by two reviewers following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach,[25] using the GRADE profiler (GRADEpro, version 3.6).[26] Discrepancies were resolved by a third reviewer. RCTs without important limitations were of 'high quality' and downgraded or upgraded by one or two levels, according to the scoring rubric developed (Appendix S2).[25]

2.5 | Data analysis

The primary objectives were change in the eGFR, urinary albumin excretion and risk of adverse renal events. Change in eGFR was defined by change from baseline and reported as the least squares mean (LSM) change in mL/min/1.73m^2. Change in urinary albumin excretion was reported from baseline and encompassed the endpoints of 24-hour albuminuria (LSM in mg) and uACR (as percentage change from placebo for participants with uACR > 3.39 mg/mmol).

The assessment of adverse renal events involved two approaches, because of variations in data availability from the included studies. First, we analysed the CRE, for the RCTs that presented adverse renal events as a pre-estimated composite (trial-reported CRE). This composite was either a preidentified list of renal events[27–29] or 'a sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of <15 ml/min/1.73 m^2 for ≥30 days'.[30–32]

Additionally, a second approach was used for the trials that reported adverse renal events using individual definitions. These individual definitions were consolidated into a single outcome referred to as 'Expanded version CRE'. This method aimed to investigate whether a different risk pattern would emerge when examining renal adverse events using a broader and less stringent composite definition compared with the definitions used for the trial-reported CRE outcome. The components of the expanded version CRE encompassed renal failure, renal impairment, AKI, CKD, ESRD and need for dialysis events. AKI and ESRD were also analysed as separate endpoints. The version of the Medical Dictionary for Regulatory Activities Preferred Term used by the individual studies for these renal adverse event definitions is presented in Appendix S3. Changes in HbA1c (LSM in percentage), systolic and diastolic blood pressure (LSM in mmHg), weight (LSM in kg) and risk of cardiovascular outcomes were also evaluated.

2.6 | Data synthesis and statistical analysis

Meta-analyses were undertaken in R project version 4.1.1[33] using the package 'meta'. The Knapp–Hartung adjustment was applied to reduce uncertainty associated with sparse data. If data from the same study were available for different doses or durations of treatment, data reflecting the longest duration or highest dose were used in the analysis. Analyses were performed based on treatment duration (≥ 52 or < 52 weeks), to establish variations between long- and short-term effects and renal impairment status, to determine if sotagliflozin was effective in reducing the renal adverse events in participants with pre-existing renal impairment. If a study did not report baseline eGFR or if a study did not report that they recruited participants with pre-existing kidney disease, it was assumed that the average eGFR of participants from these studies was 60 mL/min/1.73m^2 or higher.

The mean difference (MD) with inverse variance weighting for pooling and 95% confidence intervals assuming a standard normal distribution were calculated for all continuous outcomes. For the outcome of uACR, pooling was performed using the precalculated percent difference from placebo because of limited data. The τ^2 estimator applied was the DerSimonian–Laird method. The Mantel and Haenszel method was used to estimate the incidence risk ratio (IRR) or relative risk (RR) and 95% confidence intervals for binary outcomes. The τ^2 estimator employed was the Paule–Mandel method. A random-effects model was employed. The χ^2 test on Cochrane's Q statistic and I^2 were estimated as a measure for heterogeneity. An I^2 of 0%-25% was classified as insignificant heterogeneity, 25%-50% as low, 50%-75% as moderate and more than 75% as high heterogeneity.[25] Funnel plots were generated to detect publication bias. A *P* value of .05 or less was considered statistically significant.

2.7 | Deviations from protocol

Data for IRR estimation were only available for trial-reported CRE. Therefore, RR was used as a pooled effect measure instead. One study[34] used active comparator, with the remainder using placebo, thus making a subgroup analysis according to comparator unattainable. This study was excluded from all meta-analyses. The included studies reported the continuous outcomes using standardized units and, as such, the MD instead of the standardised MD was used, to improve ease of interpretation. Egger's test was not used as the number of studies was less than 10 for all outcomes.

3 | RESULTS

In total, 860 records were identified from the search after record deduplication, of which 750 reports were excluded at the abstract-screening stage. From the remaining 110 reports, 76 full texts were reviewed, 14 of which fulfilled the eligibility criteria and were included in this systematic review (Figure 1).

3.1 | Study characteristics

All the studies were double-blinded RCTs (Table 1); 10[27–32,35–38] (71%) were phase 3 trials, and the others were phase 2 trials[34,39–41] (29%);

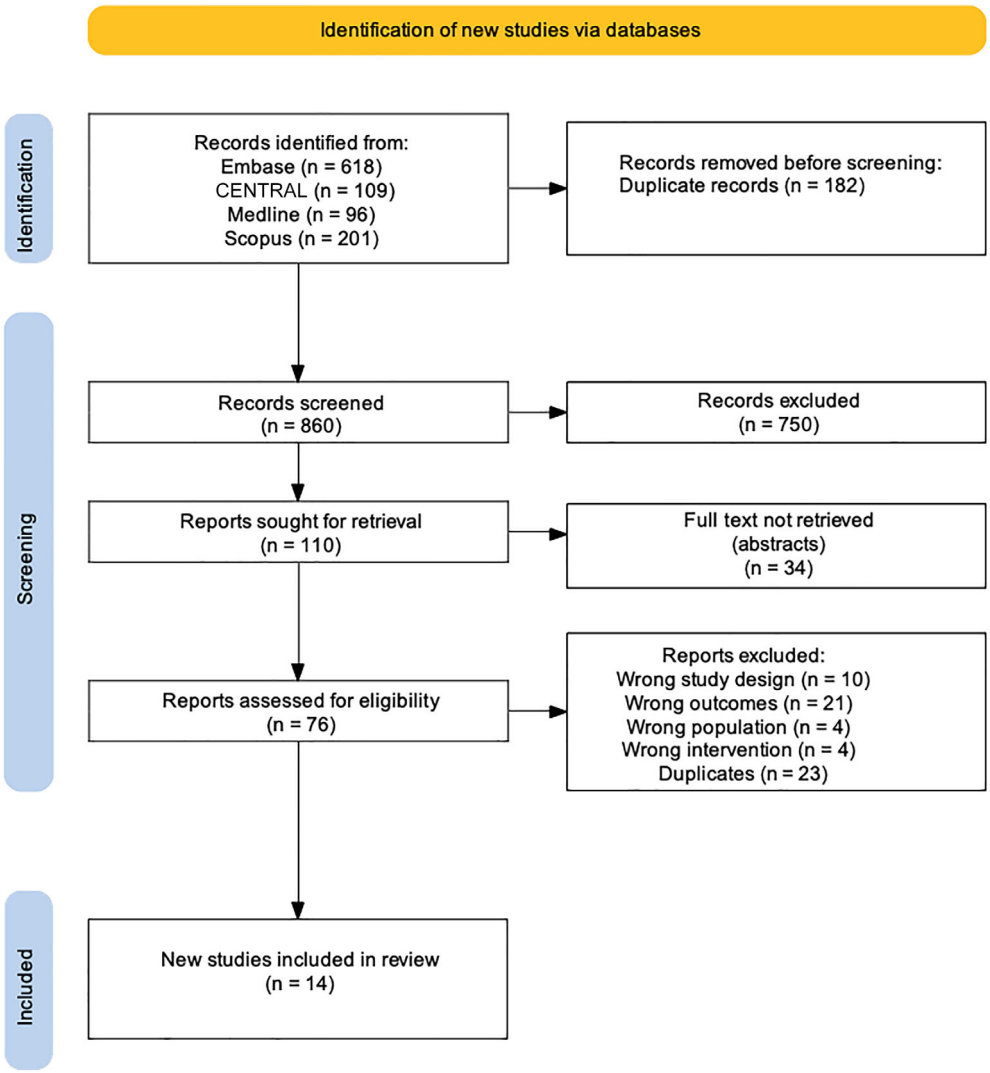

FIGURE 1 PRISMA flowchart indicating the study selection process. Full texts not retrieved because of availability of the records being in abstract format only. PRISMA, Preferred Reporting Items for Systematic review and Meta-Analyses.

13 (94%) studies were placebo controlled; and one study assessed empagliflozin[34] as an active comparator. Nine (64%) RCTs[30–32,34–39] recruited participants with T2D ($n = 13\,897$) and five[27–29,40,41] recruited participants with T1D ($n = 2449$). Two (14.3%) were single-centre studies and 12 (86%) were multicentre international studies. The number of countries where the sites were located ranged from 19 to 44. The location sites included Europe ($n = 9$), Asia ($n = 5$), North America ($n = 12$), South America ($n = 4$), Africa ($n = 2$) and Oceania ($n = 2$) (Appendix S4). The duration, defined as the duration of time during which the outcome was assessed, ranged from 1[39] to 31[32] months, with the median follow-up being 24.50 (Q1 to Q3; 15.25-28) months. Five RCTs[28,30–32,35] evaluated the 200- and 400-mg doses, one[40] the 7-, 200- and 400-mg doses and one[39] the 150- and 300-mg doses.

3.2 | Population characteristics

\The pooled sample size was 17 574 participants: 9312 (53%) in the sotagliflozin cohort and 8262 (47%) in the comparator cohort. The two cohorts had similar characteristics at baseline (Appendix S5). The baseline HbA1c level for the intervention and control groups ranged from 7.1% to 8.3% and from 7.2% to 9.7%, respectively. Four[29–31,33] of the assessed RCTs recruited participants with kidney impairment at baseline, ranging from 23.8 to 50.5 mL/min/1.73m^2. Six[28,29,34,39–41] of the RCTs recruited patients with an eGFR of more than 60 mL/min/1.73m^2, ranging from 88.6 to 139 mL/min/1.73m^2. Four[27,36–38] of the RCTs did not report baseline eGFR. The lowest baseline eGFR was reported by Cherney et al.[31] as 23.8 ± 4.8 mL/min/1.73m^2, and the highest by Zambrowicz et al.[39] as 139 ± 36 mL/min/1.73m^2. Average baseline values for systolic and diastolic blood pressures were comparable between the intervention and control groups.

3.3 | Risk of bias

The risk of bias assessments are presented in Appendix S6. Risk of bias arising from the randomization process was low in nine studies (64%),[27–31,35,40,41] raised some concerns in four studies (29%)[34,35,37,39] and was high in one study (7%).[36] The nine studies with low risk used a central Interactive Response Technology system for randomization, which was considered adequate. The remaining five studies reported randomization without specification and were assessed as having

TABLE 1 Study characteristics of the included RCTs.

Study ID	Follow-up duration (mo)	Therapeutic regimen			Sample size (patients)	
		Intervention	Dose (mg)	Placebo	Intervention	Control
Bhatt et al., 2021 (a)[32]	31	Sotagliflozin	200/400	Placebo	5292	5292
Bhatt et al., 2021 (b)[35]	24	Sotagliflozin	200/400	Placebo	608	614
Cherney et al., 2021[31]	28	Sotagliflozin	200/400	Placebo	92; 92	93
Posch et al., 2022[34]	13	Sotagliflozin	400	Empagliflozin	20	21
NCT02926950, 2020[36]	28	Sotagliflozin + MTF	400	Placebo + MTF	259	259
NCT03066830, 2020[37]	26	Sotagliflozin + MTF + SU	400	Placebo+ MTF + SU	253	254
Cherney et al., 2023[30]	26	Sotagliflozin	200/400	Placebo	263; 264	260
Garg et al., 2017[29]	18	Sotagliflozin	400	Placebo	699	703
Buse et al., 2018[28]	23	Sotagliflozin	200/400	Placebo	263; 262	268
Danne et al., 2018[27]	25	Sotagliflozin	400	Placebo	261; 263	258
Baker et al., 2019[40]	13	Sotagliflozin	75/200/400	Placebo	35; 35; 35	36
Bode et al., 2021[41]	17	Sotagliflozin	400	Placebo	43	42
Zambrowicz et al., 2012[39]	1	LX4211	150/300	Placebo	12; 12	12
NCT02926937, 2021[38]	30	Sotagliflozin	400	Placebo	107; 142	150

Note: Duration = maximum timeframe including follow-up.
Abbreviations: MTF, metformin, RCT, randomized controlled trial; SU, sulphonylurea.

some concerns. Seven studies (50%)[27,28,30,31,36,37,41] were at high risk of bias because of more than 5% missingness of data. Three studies (21%)[31,36,37] imputed missing data as placebo, which was regarded as introducing bias because the original treatment assignment may not have been preserved. Four studies (29%)[27–29,40] imputed missing outcomes as no response, which was considered adequate. One study (7%)[41] offered no information regarding missing data handling. Two studies (14%)[32,35] provided a missingness table and conducted sensitivity analyses or discussed the impact of imputation on their findings.

3.4 | GRADE assessment

Change in eGFR was assessed to be a moderate certainty outcome, while trial-reported CRE and urinary albumin excretion were very low certainty outcomes (Table 2). Expanded version CRE was of low certainty, and AKI and ESRD were of very low certainty (Appendix S7). The results of meta-analyses can be found in Appendix S8, with the corresponding forest plots in Appendices S9 and S10. Subgroup analyses are summarized in Appendix S11. No publication bias was detected (Appendix S12).

3.5 | Renal outcomes

3.5.1 | Change in eGFR

Eleven RCTs ($n = 15\,034$)[27–32,34,35,39–41] (79%) assessed eGFR. Nine RCTs,[27–32,35,40,41] involving a total of 14 957 participants, 7481 in the intervention cohort and 7476 in the comparator cohort, reported changes in eGFR from baseline to week 130,[32] week 95,[35] week 52,[27,28,30,31] week 24[29] and week 12.[40,41] The pooled MD was −1.2 (−1.42, −0.98) mL/min/1.73m^2 (Appendix S9). No heterogeneity was identified ($I^2 = 0\%$, $P = .81$).

A sensitivity analysis was undertaken (Figure 2) for studies ($n = 6$)[27,28,30–32,35] with a duration of 52 weeks or longer. The pooled sample size for the intervention cohort was 6707 participants, while for the control cohort it was 6702 participants. The MD was −1.23 (−1.45, −1.01) mL/min/1.73m^2. No heterogeneity was identified ($I^2 = 0\%$, $P = .83$). Subgroup analyses (Appendix S9) did not identify significant differences for eGFR according to the duration of treatment (duration ≥ 52 weeks, MD = −1.23 [−1.45, −1.01] mL/min/1.73m^2; duration < 52 weeks, MD = −1.03 [−1.87, −0.19] mL/min/1.73m^2; $P = .58$).

Further subgroup analyses (Appendix S9) for studies ($n = 6$)[27,28,30–32,35] with a duration of 52 weeks or longer did not identify significant differences for eGFR according to dose (dose = 200 mg, MD = −1.19 [−2.42, 0.03] mL/min/1.73m^2; dose = 400 mg, MD = −1.03 [−2.18, 0.12] mL/min/1.73m^2; $P = .76$) and pre-existing renal impairment (eGFR < 60 mL/min/1.73m^2, MD = −1.24 [−1.57, −0.91] mL/min/1.73m^2; eGFR ≥ 60 mL/min/1.73m^2, MD = −0.90 [−3.63, 1.82]; $P = .16$). Additionally, no differences were found according to risk of bias (ROB = low, MD = −1.24 [−2.24, −0.25] mL/min/1.73 m^2; ROB = high, MD = −1.03 [−2.18, 0.12] mL/min/1.73m^2; $P = .56$) and diabetes type (T2D, MD = −1.24 [−1.57, −0.91] mL/min/1.73m^2; T1D, MD = −0.90 [−3.63, 1.82] mL/min/1.73m^2; $P = .16$).

One (7%) RCT ($n = 41$)[34] reported eGFR as standard error of the mean from day 0 to day 70 against an active comparator (empagliflozin); no clinically significant differences were identified. One (7%) RCT ($n = 36$)[39] reported decreased eGFR from day 1 to day 28 as an arithmetic mean.

TABLE 2 Summary of findings for the primary outcomes of eGFR, urine albumin excretion and composite renal events.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with comparator	Risk with sotagliflozin				
Change in eGFR for studies with a duration of ≥ 52 wk assessed with: mL/min/1.73m^2	MD 1.23 mL/min/1.73m^2 lower (1.45 lower to 1.01 lower) with sotagliflozin		-	13 409 (6 RCTs)	⊕⊕⊕◯ Moderate[a,b]	Sotagliflozin probably results in a slight reduction in eGFR when therapy is continued for ≥ 52 wk
Change in urine albumin excretion assessed with: 24-h urine collection (mg/g) or uACR (mg/mmol percentage change from placebo)	Albuminuria[34]: Sotagliflozin baseline = 18 ± 55, change: −1.0 ± 1.7; Empagliflozin baseline = 13 ± 20, change: −5.8 ± 1.6 LS mean difference = 4.8 mg (0.1 to 9.5); P = .0476 uACR for participants with uACR > 3.39 mg/mmol at baseline[30,31]: Pooled percentage change from placebo = −24.7% (−163.15, 113.18)		-	485 (3 RCT)	⊕◯◯◯ Very low[c,d,e]	Sotagliflozin probably results in little to no difference in albuminuria or uACR for patients with baseline uACR > 3.39 mg/mmol
Trial-reported CRE assessed with: number of events	11 per 1000[f]	9 per 1000[f] (7 to 12)	RR 0.82 (0.61 to 1.12)	13 740 (6 RCTs)	⊕◯◯◯ Very low[c,g,h]	Sotagliflozin probably results in little to no difference in trial-reported CRE

Note: *The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence: ⊕⊕⊕⊕ = High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. ⊕⊕⊕◯ = Moderate certainty: we are moderately confident in the effect estimate: the true effect is probably close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕◯◯ = Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. ⊕◯◯◯ = Very low certainty: we have very little confidence in the effect estimate: the true effect is probably substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; CRE, composite renal events; eGFR, estimated glomerular filtration rate; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; LS, least squares; MD, mean difference; RCT, randomized controlled trial; RR, relative risk; uACR, urine albumin-creatinine ratio.

[a]> 50% of trials received a 'high' or 'some concern' risk of bias rating.

[b]Surrogate outcome of renal impairment; eGFR was expected to decrease because of the pharmacology of the drug.

[c]> 50% of trials received a 'high' risk of bias rating.

[d]Lack of coherence of evidence (uACR, albuminuria).

[e]The 95% CI crosses the line of no effect and there is clinical significant benefit or harm if the true effect of the intervention were to lie in the upper versus lower boundary of the CI.

[f]In the comparator cohort there were 11 instances of a trial-reported composite renal event per 1000 participants, whereas in the sotagliflozin cohort there were nine instances of a trial-reported composite renal event per 1000 participants.

[g]Difference between measured outcomes between RCTs: extensive renal events, sustained decrease of ≥ 50% in the eGFR from baseline for ≥ 30 days, long-term dialysis, renal transplantation or sustained eGFR of < 15 mL/min/1.73m^2 for ≥ 30 days.

[h]The 95% CI crosses the line of no effect.

3.5.2 | Urinary albumin excretion

One (7%) RCT[34] (n = 41; intervention n = 20, comparator n = 21) reported on 24-hour urinary albumin excretion. For the sotagliflozin group, the change in albuminuria from baseline (18 mg ± 55) was −1.0 ± 1.7 compared with empagliflozin, which was −5.8 ± 1.6 from baseline (13 mg ± 20). The between-group difference was 4.8 (0.1, 9.5) mg (P = .0476). This suggests that sotagliflozin was not as effective as empagliflozin. Five[27–31] (36%) studies reported on the change in uACR, of which two[30,31] evaluated the change for participants with uACR of more than 3.39 mg/mmol at baseline. The pooled percentage difference for the 400-mg group (n = 219 participants) from placebo (n = 225 participants) at week 52 was −24.7% (−163.2%, 113.8%) (Appendix S9).

3.5.3 | Composite renal events

Six[27,28,30–32,35] (49%) RCTs (intervention n = 6866; control n = 6874) presented adverse renal events as a pre-estimated composite (trial-

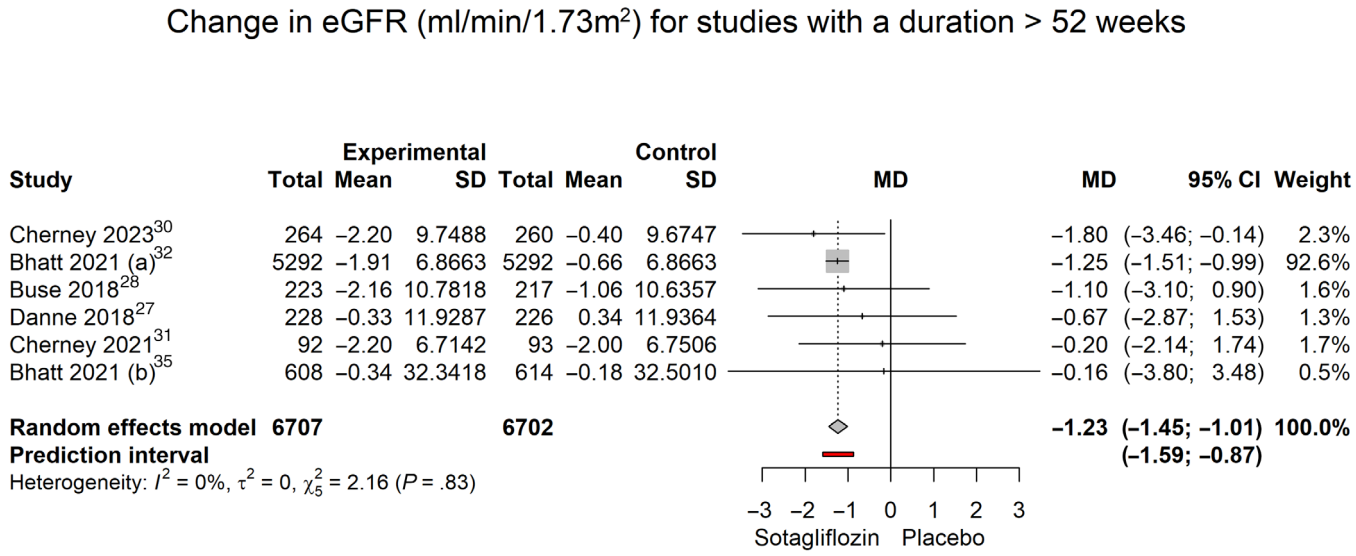

FIGURE 2 Forest plot for change in the eGFR (reported as LSM in mL/min/1.73m^2) of participants treated with sotagliflozin compared with placebo, for studies with a duration of 52 weeks or longer. CI, confidence interval; eGFR, estimated glomerular filtration rate; LSM, least squares mean; MD, mean difference; *P*, *p*-value; SD, standard deviation.

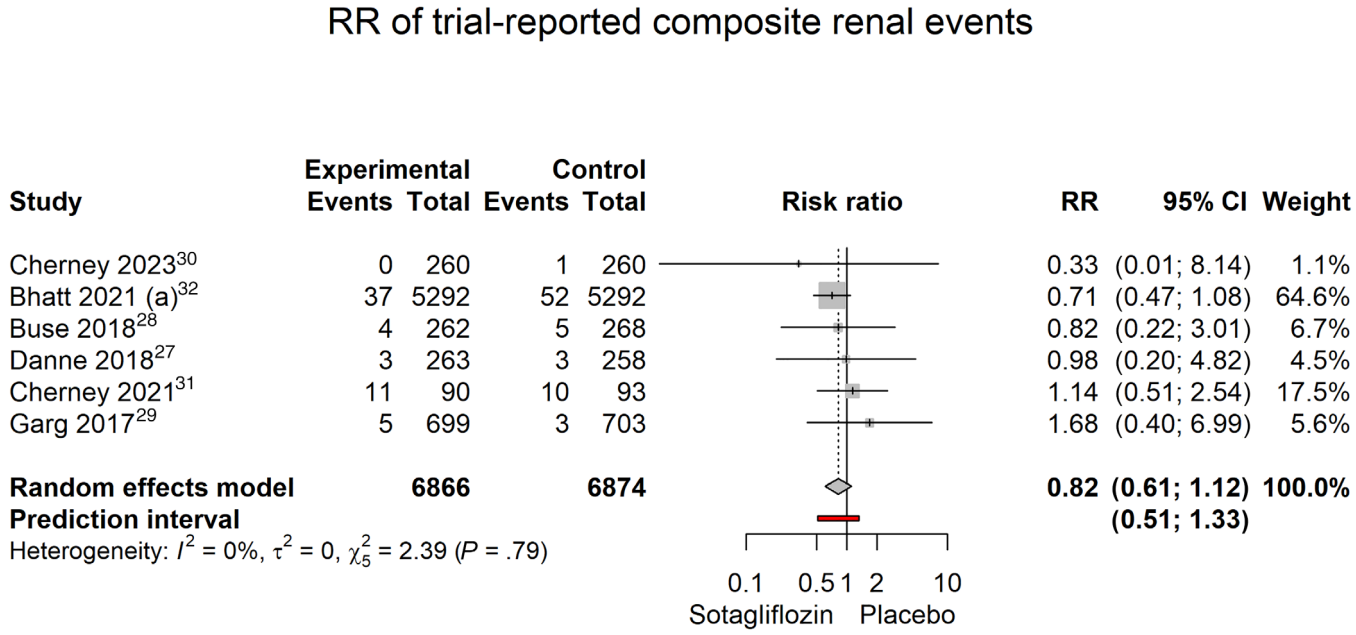

FIGURE 3 Forest plot for risk of trial-reported composite renal events with sotagliflozin compared with control. CI, confidence interval; *P*, *p*-value; RR, relative risk.

reported CRE); 60 (0.9%) and 74 (1.1%) trial-reported CRE occurred in the intervention and control cohort, respectively. The pooled RR was 0.82 (0.61, 1.12) (Figure 3). The IRR meta-analysis can be found in Appendix S13. No heterogeneity was identified (I^2 = 0%, *P* = .82). No significant reduction in trial-reported CRE was observed for participants with pre-existing renal impairment (*n* = 3 studies)[30–32] (RR = 0.78 [0.40, 1.49]). No differences were found according to the duration or dose (Appendix S9). Additionally, no differences were identified according to risk of bias [ROB = low, RR = 0.82 [0.01, 49.15]; ROB = high, RR = 0.99 [0.62, 1.57]; *P* = .61) or diabetes type (T1D, RR = 1.09 [0.42, 2.82]; T2D, RR = 0.78 [0.40, 1.49]; *P* = .21).

The expanded version CRE analysis (*n* = 9 studies[28–32,35–38]; RR = 0.92 [0.81, 1.06]) did not reveal any new insights or deviate from the results of the trial-reported CRE analysis. A comprehensive analysis of the expanded version CRE, as well as a breakdown of the number of events and sample size for each individual renal adverse event definition, can be found in Appendix S10.

3.5.4 | Acute kidney injury

Eight[27,28,30–32,35–37] (57%) RCTs ($n = 15\,453$; intervention = 7720, control = 7733) assessed AKI; 60 (1.17%) and 86 (1.11%) events occurred in the intervention and control groups, respectively. The pooled RR was 1.08 (0.75, 1.56). No heterogeneity was identified ($I^2 = 0\%$, $P = .43$). No significant reduction in the risk of AKI was noted according to pre-existing renal impairment (RR = 0.92 [0.14, 5.85]). Stratification by risk of bias, dose, duration or diabetes type revealed no significant difference (Appendix S10).

3.5.5 | End-stage renal disease

Three[30–32] (21%) RCTs ($n = 11\,280$; intervention = 5641, control = 5639), all of which recruited participants with renal impairment and T2D, assessed ESRD. Three (0.053%) events occurred in each group. The pooled RR of ESRD was 1.02 (0.03, 30.49). No heterogeneity was identified ($I^2 = 0\%$, $P = .80$) (Appendix S10).

3.6 | Adverse events, glycaemic and cardiovascular outcomes

3.6.1 | Adverse events

Thirteen RCTs[27–32,35–41] (93%) reported serious and non-serious adverse events; 1779 participants (19%) experienced a serious adverse event in the intervention group and 1766 (21%) in the control group. Also, 1716 (18%) participants experienced a non-serious event in the intervention group and 1321 (16%) in the control group. Five studies[32,34,35,39,41] reported treatment emergent adverse events; 4354 (66%) participants experienced at least one treatment emergent adverse event in the intervention and 4271 (64.4%) in the comparator group (Appendix S14).

3.6.2 | Glycaemic control and cardiovascular outcomes

Sotagliflozin was effective in reducing HbA1c (MD = −0.42% [−0.53, −0.31]) and body weight (MD = −2.07 [−2.97, 1.17] kg) in studies with a duration of 3 months or longer. Statistically significant reductions in systolic blood pressure (MD = −2.72 mmHg [−3.63, −1.80]) and HF events (RR = 0.67 [0.64, 0.70]) were also noted. More detailed analysis of the glycaemic and cardiovascular outcomes can be found in Appendix S10.

4 | DISCUSSION

This review assessed the effect of sotagliflozin on renal function and renal outcomes. While sotagliflozin reduced eGFR, this was not clinically significant. Likewise, no significant change in urinary albumin excretion and the risk of developing adverse renal events was observed. Although studies recruiting T1D participants were limited, the renal safety profile of sotagliflozin in this population was encouraging; no significant changes in eGFR or risk of adverse renal events were noted. The use of sotagliflozin in kidney disease was shown; no significant changes in the risk of renal adverse events were identified in participants with pre-existing renal impairment. These findings align with outcomes from trials of SGLT2 inhibitors, CREDENCE,[42] EMPEROR-Preserved[43] and DAPA-CKD.[15]

However, renal benefits have been established with SGLT2 inhibitors; one meta-analysis[44] estimated the pooled RR of CRE to be 0.64 (0.48, 0.85), while another[45] reported that SGLT2 inhibitors were associated with a 38% reduction in kidney disease progression. The inhibition of SGLT1 in the intestines with sotagliflozin is believed to provide additional benefits over selective SGLT2 inhibition; specifically, an incremental increase in the secretion of intestinal hormones, improved insulin sensitivity, reduced tubular glucose load and urinary glucose excretion.[46] Nevertheless, in our meta-analysis, no significant reductions in renal adverse events were found. This may be attributed to the limited number of studies that enrolled participants with renal impairment or the fact that studies included in this review were not specifically designed to investigate renal outcomes. Thus, future research should explore the utility of sotagliflozin in kidney disease, in a similar capacity to SGLT2 inhibitors.[47]

Furthermore, initial 'dips' in eGFR, a well-known characteristic of SGLT2 inhibitors,[48] were reported in four of the sotagliflozin RCTs[27,32,34,35] at the 4-week period. EGFR is influenced by changes in intraglomerular pressure. SGLT2 inhibition has been stipulated to decrease interglomerular pressure by attenuating glomerular hyperfiltration. This reduction in hyperfiltration is driven by the inhibition of sodium and glucose reabsorption in the proximal tubule, resulting in increased sodium delivery to the distal nephron, including the macula densa, leading to natriuresis and vasoconstriction of the renal afferent arteriole.[49]

Inhibition of SGLT1 has its own distinct and complementary effects on reducing glomerular hyperfiltration compared with inhibition of SGLT2. SGLT1 is located in the nephron in segments downstream of SGLT2, such as the late proximal tubule and thick ascending limb of the loop of Henle. It has the capacity to reabsorb glucose that has not been reabsorbed upstream. It is believed to reduce hyperfiltration, both by inhibiting SGLT1-mediated glucose sensing by the macula densa, and also by delivery of an overall lower glucose load to the kidney tubules.[50] With SGLT2 inhibitors the decrease in eGFR has been shown to stabilize with treatment continuation or reverse upon cessation of therapy.[46] Indeed, a review of long-term eGFR projections and renal safety profiles for SGLT2 inhibitors has revealed that these agents are nephroprotective, despite the initial eGFR dip they induce.[48] It is reasonable to expect comparable outcomes with dual SGLT1 and 2 inhibitors, although long-term studies to confirm this are warranted.

Moreover, sotagliflozin was effective in reducing the risk of HF, in line with findings from a previous review,[19] and similar to SGLT2

inhibitors.[51] Further work is needed to ascertain if, like the SGLT2 inhibitors,[52] sotagliflozin can be integrated into clinical practice for the management of HF.

This systematic review has limitations. Only English language papers were included, leading to the potential omission of other pertinent papers. A further limitation is the exclusive inclusion of RCTs, which could have led to the oversight of observational studies. Furthermore, only one study contributed to the outcome of albuminuria, and two to the outcome of uACR, limiting the generalizability of these findings. Retaining ESRD and AKI as distinct endpoints in this study potentially introduced a methodological limitation, as variations in the definitions used were not explored, impacting the meaningfulness of these individual analyses. Lack of comparison of sotagliflozin with an active comparator further limits the applicability of our findings. Other limitations were introduced by the study population; four studies recruited participants with renal impairment,[30–32,35] which may have introduced outcome bias.

In conclusion, to the best of the authors' knowledge, this is the first systematic review and meta-analysis to assess the effect of sotagliflozin on renal function and renal outcomes. Sotagliflozin had a favourable renal safety profile in both T1D and T2D participants, with or without pre-existing renal impairment. However, we did not show a significant reduction in renal adverse events when compared with placebo in those with pre-existing renal impairment. Therefore, sotagliflozin may not be a suitable treatment choice for individuals with diabetic kidney disease. Nonetheless, additional research exploring the effects of sotagliflozin on renal events is warranted, involving targeted recruitment of participants with diabetic kidney disease and selecting renal endpoints as the primary outcomes. In summary, sotagliflozin use did not adversely affect renal function or increase the risk of renal adverse events; however, further research is needed to determine its efficacy in reducing the risk of diabetic kidney disease.

AUTHOR CONTRIBUTIONS

MAB: conceptualization, methodology, validation, software, formal analysis, data curation and writing the original draft, review and editing; PS: conceptualization, methodology, validation, data curation, writing the original draft, review and editing, and visualization; RT: conceptualization, methodology, validation, data curation, writing the original draft, review and editing, and visualization; JK: conceptualization, methodology, validation, data curation, writing the original draft, review and editing, and visualization. DBB: conceptualization, methodology, data curation, writing the original draft, review and editing, and visualization; RM: conceptualization, methodology, data curation, writing the original draft, review and editing, and visualization. JP: conceptualization, methodology, writing the original draft, review and editing, and visualization. SP: conceptualization, methodology, writing the review and editing, and supervision.

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CONFLICT OF INTEREST STATEMENT

MAB, JP, PS, RT, DBB, JK and RM have no relevant financial or non-financial interests to disclose. SP declares the following activities/interests, which may be considered as potentially competing: AstraZeneca lecture fees, Napp Pharmaceuticals lecture fees.

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CONSENT FOR PUBLICATION

All authors have read and approved the final version to be submitted for publication.

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