Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Efficacy and Safety of Luseogliflozin in Patients with Type 2 Diabetes Mellitus: An Umbrella Review of Systematic Reviews

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Abstract: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder with rising global prevalence, requiring effective management to prevent complications. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, including luseogliflozin, are a novel class of drugs that provide benefits beyond glycemic control. This umbrella review synthesized evidence from multiple systematic reviews and meta-analyses to evaluate the efficacy and safety of luseogliflozin in T2DM patients. Following Joanna Briggs Institute (JBI) guidelines and PRISMA standards, eligible studies included systematic reviews and meta-analyses of randomized controlled trials (RCTs) and observational studies involving adult T2DM patients treated with luseogliflozin. A comprehensive literature search was performed in PubMed, EMBASE, and Web of Science up to June 10, 2024. Data extraction and quality assessment were independently conducted by two reviewers, and statistical analyses were performed using R software version 4.3. Fourteen systematic reviews were included, showing that luseogliflozin significantly reduced HbA1c levels (pooled mean difference −1.784, 95% CI: −3.99 to −0.431), fasting plasma glucose (FPG) levels (−3.165, 95% CI: −4.046 to −2.284), and postprandial glucose (PPG) levels (−37.148, 95% CI: −65.361 to −8.935) compared with placebo. Additional benefits included significant reductions in body weight (−1.322 kg, 95% CI: −1.58 to −1.056), triglycerides (−13.891, 95% CI: −26.539 to −1.243), uric acid (−0.350, 95% CI: −0.524 to −0.176), and alanine aminotransferase (ALT) levels (−7.345, 95% CI: −5.845 to −1.463). No significant increase in hypoglycemia risk was observed (pooled risk ratio 1.305, 95% CI: 0.692 to 2.459). These findings suggest that luseogliflozin is an effective and safe treatment for T2DM, offering substantial benefits in glycemic control, weight management, blood pressure lowering, and metabolic parameters, with a favorable safety profile regarding hypoglycemia. Further long-term studies are warranted to establish its definitive role in clinical practice and support broader regulatory approvals.

Keywords: luseogliflozin, umbrella review, type 2 diabetes mellitus, fasting plasma glucose

Introduction

Type 2 diabetes mellitus (T2DM) is a long-term metabolic condition marked by insulin resistance and the gradual decline of pancreatic β-cell function, resulting in elevated blood glucose levels.[1,2] The global prevalence of T2DM is escalating, posing substantial health, economic, and social burdens.[3] Effective management of T2DM is crucial for preventing complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy.[4–7] The therapeutic landscape for T2DM has evolved significantly, with the introduction of various classes of drugs aimed at improving glycemic control[8] and reducing the risk of diabetes-related complications.[9–11] Among these, sodium-glucose cotransporter 2 (SGLT2) inhibitors represent a novel class

Received: 14 August 2025
Accepted: 25 November 2025
Published: 2 December 2025

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that offers benefits beyond glycemic control, including weight reduction, blood pressure lowering, and potentially cardio-renal protective effects.[12–14]

Luseogliflozin, a member of the SGLT2 inhibitor class, has garnered attention due to its unique mechanisms of action.[15] By inhibiting SGLT2 in the proximal renal tubules, luseogliflozin prevents glucose reabsorption, thereby promoting glucosuria and reducing plasma glucose levels.[16,17] This mechanism not only addresses hyperglycemia but does so in a way that is independent of insulin, which is particularly advantageous in patients with insulin resistance or β-cell dysfunction.[13,18] Furthermore, the osmotic diuresis induced by glucosuria leads to a reduction in blood pressure and a modest decrease in body weight, which are beneficial in the context of the obesity often associated with T2DM.[19]

Despite the growing body of research supporting the efficacy and safety of luseogliflozin, the landscape of evidence is complex due to the diversity of study designs, populations, and outcomes assessed. To address this complexity, umbrella reviews, which synthesize information from multiple systematic reviews and meta-analyses, provide a higher order of evidence that can inform clinical guidelines and policy decisions.[20,21] They offer a comprehensive overview of the evidence, quantifying the degree of risk and benefit, and identifying gaps in current research.

The rationale for conducting an umbrella review on luseogliflozin centers on several key points. While individual studies and systematic reviews have reported on the efficacy and safety of luseogliflozin, an aggregate view of all available reviews can provide a clearer picture of its position within the therapeutic landscape of T2DM. By examining disparate data sources, we can assess the consistency of findings across various patient demographics, including age, duration of diabetes, baseline body mass index (BMI), and presence of comorbidities. An umbrella review allows for the examination of a broad spectrum of outcomes, from primary metrics such as HbA1c reduction and fasting plasma glucose levels to secondary outcomes including impacts on renal function, cardiovascular health, and adverse events. Such comprehensive analysis is crucial, as it aids in defining the precise clinical scenarios where luseogliflozin may offer the most benefit or pose risks.

While previous umbrella reviews have evaluated the SGLT2 inhibitor class as a whole.[22,23] The efficacy and safety profile can vary between individual agents due to differences in selectivity, pharmacokinetics, and approved dosages. Luseogliflozin, for instance, is available at the lowest dosage among its class and may have a distinct adverse event profile. Therefore, this umbrella review aims to provide a focused synthesis of evidence specifically for luseogliflozin to inform clinicians about its unique position within the therapeutic arsenal for T2DM.

This umbrella review seeks to provide a thorough, evidence-based assessment of the efficacy and safety of luseogliflozin in patients with T2DM. By integrating data from multiple systematic reviews and meta-analyses, it aims to offer insights that are both comprehensive and nuanced, thereby guiding clinicians in optimizing diabetes care with an evidence-informed approach.

Methods

This umbrella review was carried out following the guidelines suggested by the Joanna Briggs Institute (JBI).[21] During this review, we complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Table S1).[24] A checklist based on PRISMA was completed and can be found in Table S1. Additionally, the protocol for this umbrella review was registered with PROSPERO.

Eligibility Criteria

The eligibility criteria were designed to encompass systematic reviews and meta-analyses evaluating the efficacy and safety of luseogliflozin in adult patients with T2DM. Included studies needed to compile outcomes from randomized controlled trials (RCTs) and observational studies, focusing on luseogliflozin used alone or in combination with other antidiabetic medications. Comparative studies against placebo, no treatment, or other antidiabetic agents were also considered. The outcomes of interest were changes in glycemic control markers such as HbA1c and fasting plasma glucose (FPG), body weight, blood pressure, hypoglycemia, and uric acid. We included studies published in any language, provided they had English abstracts.

Exclusion criteria ruled out narrative reviews, editorials, commentaries, letters without systematic data analysis, studies focused solely on populations under 18 years of age or those with type 1 diabetes mellitus or gestational diabetes. Reviews concentrating exclusively on pharmacokinetic data or preclinical studies, as well as those lacking a rigorous risk

of bias assessment, were also excluded. This approach ensured the inclusion of high-quality, relevant studies capable of providing robust evidence on the therapeutic value and safety of luseogliflozin for managing T2DM.

Literature Search

The literature search for this umbrella review was conducted meticulously across multiple electronic databases including EMBASE, PubMed, and Web of Science up to June 10, 2024. To ensure a comprehensive retrieval of relevant studies assessing the efficacy and safety of luseogliflozin in treating T2DM, the search strategy was crafted with the assistance of a medical librarian. This strategy employed a combination of MeSH terms and free text keywords such as "luseogliflozin", "SGLT2 inhibitors", "type 2 diabetes mellitus", "T2DM", "systematic review", and "meta-analysis", tailored to each database's specific syntax. Although searches were not restricted by language, only articles with English abstracts were considered.

The complete search strategy for all databases, including all search terms and filters, is provided in Table S2 The screening process was managed using Nested-Knowledge software, which facilitated independent screening by two reviewers and flagged discrepancies for consensus discussion. No automated decision-making functions were used, thus avoiding automation bias. Grey literature, preprints, and unpublished data were not included in this review. As an umbrella review of systematic reviews, our unit of analysis was the review itself and its pooled estimate; while we acknowledged potential overlap of primary studies across reviews, we did not assess this quantitatively as our focus was on synthesized evidence rather than primary studies.

Screening

Search results were documented and managed using reference management software, with duplicates removed. Screening for eligibility was conducted independently by two reviewers at the title and abstract level, followed by full-text assessments. Differences among reviewers were settled through discussion or by seeking the input of a third reviewer, ensuring a rigorous and comprehensive approach to study selection. Nested-Knowledge software was used for screening.

Data Extraction

For this umbrella review, a structured data extraction process was implemented, engaging two independent reviewers to ensure accuracy and consistency. The reviewers utilized a standardized data extraction form, which was initially tested on a select few studies to refine the criteria and ensure comprehensive coverage of all relevant data points. This form captured essential details such as bibliographic information (authors, publication year, journal, country), study characteristics, number of included studies, risk of bias, intervention specifics (luseogliflozin dosage, administration frequency, combination therapies), comparators (other medications, placebo, or no treatment), and outcomes (efficacy and safety metrics, statistical results, effect sizes).

Statistical Analysis

The primary objective was to quantify the overall effect of luseogliflozin on efficacy and safety outcomes in patients with T2DM. We utilized random-effects models to conduct meta-analyses, acknowledging potential heterogeneity among the included studies in terms of study design, populations, and outcomes. This model provides an appropriate method for pooling data under the assumption that the studies estimate different, yet related, effect sizes. The effect sizes were expressed as mean differences for continuous outcomes (eg, changes in HbA1c levels, FPG) and as risk ratios for dichotomous outcomes such as hypoglycemia. Confidence intervals (CI) were set at 95%, providing a range within which the true effect is likely to lie with a high degree of certainty. The heterogeneity across studies was measured using the I^2 statistic, which calculates the proportion of overall variation across studies that stems from heterogeneity instead of chance. An I^2 value above 50% indicated significant heterogeneity. All statistical evaluations were carried out using R software version 4.3. Effect estimates (Mean Differences and Risk Ratios) and their 95% confidence intervals were directly extracted from the included meta-analyses; we did not recalculate pooled estimates from primary study data. Subgroup analysis was done based on study duration where data permitted.

Results

Literature Search

A total of 349 records were initially identified from various databases including PubMed (133), Cochrane Library (6), Embase (129), and Web of Science (81). From these, 143 duplicate records were removed, leaving 206 records for screening. After the screening process, 164 records were excluded for various reasons, and the remaining 42 records were retrieved and assessed in full for eligibility. Of these, 28 full-text articles were excluded due to reasons such as irrelevance (26 records), issues with the study protocol (1 record), and clinical trials (1 record). Ultimately, 14 systematic reviews were included in the final analysis (Figure 1).[15,25–37]

Characteristics of Included Studies

The important characteristics of the included systematic reviews are summarized in Table 1 and detail information in Table S4. The systematic literature reviews were predominantly published between 2017 and 2024, with a notable concentration of research emerging around 2023. All reviews included in this analysis focus on RCTs, reflecting a strong preference for high-quality evidence. The primary area of study across these reviews is T2DM, indicating a sustained research interest in this significant global health issue. Common outcomes studied include metabolic parameters like HbA1c, fasting plasma glucose, body weight, serum uric acid, and renal outcomes, emphasizing the multifaceted impact of SGLT2 inhibitors. The reviews encompass studies from various global contexts, suggesting the widespread relevance and applicability of the findings. Concerning study quality, the reviews generally report a low to moderate risk of bias within included studies, lending credibility to their conclusions. While a few reviews noted significant publication bias, the majority highlighted low or no publication bias. The quality assessment of the reviews is presented in Table S3.

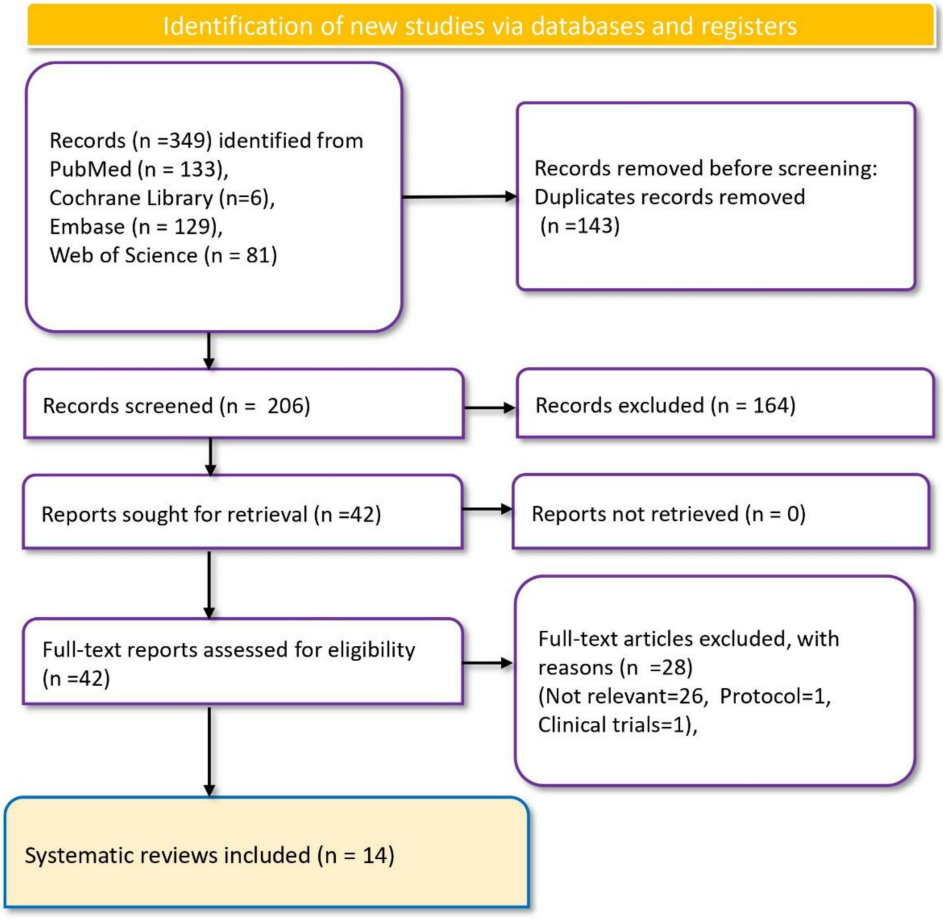

Figure 1 PRISMA flowchart depicting screening and study selection process.

Table 1 Summary of Included Systematic Reviews

Study ID	Number of Included Studies	Type of Studies	Outcomes	Risk of Bias of Included Studies
Akbari A 2022[25]	55	RCT	FPG, body weight, and HbA1c, SUA	9 low, 46 Moderate
Cai X 2018[26]	55	RCT	Body weight	Low
Dutta 2023[27]	10	RCT	HbA1c, fasting glucose, systolic blood pressure, body weight, triglycerides PCG, uric acid, alanine aminotransferase	Most of the studies have low risk of bias
Galigutta RR 2024[15]	8	RCT	HbA1c, FPG, PPG body weight	3 high risk, 2 low risk, and 3 raised some concerns
Hegde 2023[28]	45	RCT	e GFR, albumin creatinine ratio	2 high risk, 10 some concern, 33 low risk
Hu 2022[29]	19	RCT	Serum Uric acid	Included RCTs were of high quality with a low risk of bias
Kullari 2021[30]	22	RCT, Observational studies	Renal outcome	NA
Li 2023[31]	113	RCTs	RTI, pollakiuria, SUCRA, PSRF	NA
Lin 2022[32]	15	RCT	e GFR	4 RCTs -unknown risks. 6-unclear risks, 1 high risk,4 Low risk
Malik 2020[33]	7	RCT	MI, Stroke, Heart failure	NA
Monami 2017[34]	8	RCT	DKA	NA
Saad 2017[35]	8	RCT	All-cause mortality, cardiovascular mortality	NA
Shyangdan 2016[36]	13	RCT	HBA1c, SBP, Weight	Low ROB
Zhao 2017[37]	62	RCT	Serum Uric acid	Low ROB

Note: Detailed characteristics and key findings of included studies are available in Table S4.
Abbreviations: DKA, Diabetic ketoacidosis; DM, Diabetes mellitus; FPG, Fasting plasma glucose; GFR, Glomerular filtration rate; PPG, Postprandial glucose; PSRF, Potential scale reduction factor; RCT, Randomized controlled trial; RTI, Reproductive tract infections; SBP, Systolic blood pressure; SGLT2, Sodium–glucose cotransporter-2; SUCRA, Surface under the cumulative ranking scores.

Cardiovascular and Renal Outcomes

Our synthesis of the included systematic reviews did not identify pooled data on cardiovascular or renal outcomes specifically for luseogliflozin. While some reviews[27,28] reported that SGLT2 inhibitors as a class demonstrated benefits for cardiovascular outcomes and renal protection in patients with T2DM, these findings were not disaggregated for individual agents. Therefore, specific efficacy data for luseogliflozin on hard endpoints such as hospitalization for heart failure or progression of renal disease remain unavailable in the current systematic review literature.

HbA1c

When compared to placebo, Luseogliflozin showed a significant reduction in HbA1c levels across multiple studies. The pooled mean difference for the placebo-controlled studies was −1.784 (95% CI: −3.99 to −0.431), indicating a consistent and significant effect of Luseogliflozin in lowering HbA1c levels. This demonstrates the efficacy of Luseogliflozin in reducing HbA1c levels in diabetic patients compared to a placebo, with high heterogeneity (I^2 = 100%). When compared to DPP4i inhibitors from three studies, Luseogliflozin did not show any significant difference (MD = 0.00, 95% CI: −0.004 to 0.004), with low heterogeneity (I^2 = 8%) (Figure 2).

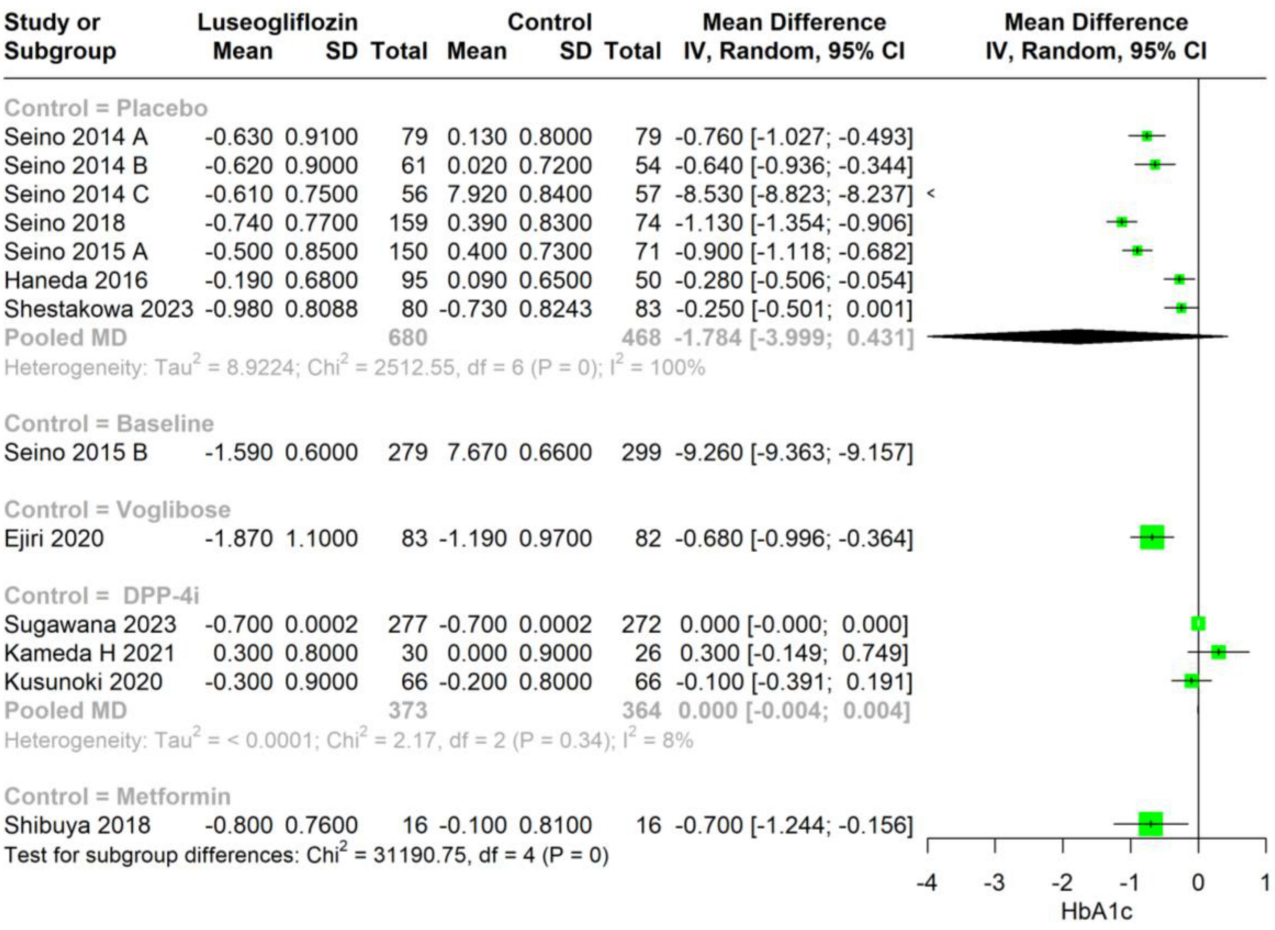

Figure 2 Effect of Luseogliflozin on HbA1c.
Abbreviations: IV, inverse variance; MD, Mean difference; SD, Standard deviation.

FPG

When compared to placebo, Luseogliflozin showed a significant reduction in fasting plasma glucose (FPG) levels across multiple studies. The pooled mean difference for the placebo-controlled studies was −3.165 (95% CI: −4.046 to −2.284), indicating a consistent and significant effect of Luseogliflozin in lowering FPG levels. This demonstrates the efficacy of Luseogliflozin in reducing FPG levels in diabetic patients compared to a placebo, with high heterogeneity (I^2 = 70%).

Subgroup analysis based on study duration also yielded significant results. For studies with a duration of 24 weeks, Seino 2014 A reported a mean difference of −3.330 (95% CI: −4.391 to −2.269). For studies with a duration of 12 weeks, the pooled mean difference was −2.840 (95% CI: −3.787 to −1.971). For studies with a duration of 52 weeks, the pooled mean difference was −3.414 (95% CI: −4.551 to −0.872), showing a significant difference (Figure 3).

PPG

When compared to placebo, Luseogliflozin showed a significant reduction in postprandial glucose (PPG) levels across multiple studies. The pooled mean difference for the placebo-controlled studies was −37.148 (95% CI: −65.361 to −8.935), indicating a consistent and significant effect of Luseogliflozin in lowering PPG levels (Figure 4). This demonstrates the efficacy of Luseogliflozin in reducing PPG levels in diabetic patients compared to a placebo, with high heterogeneity (I^2 = 96%).

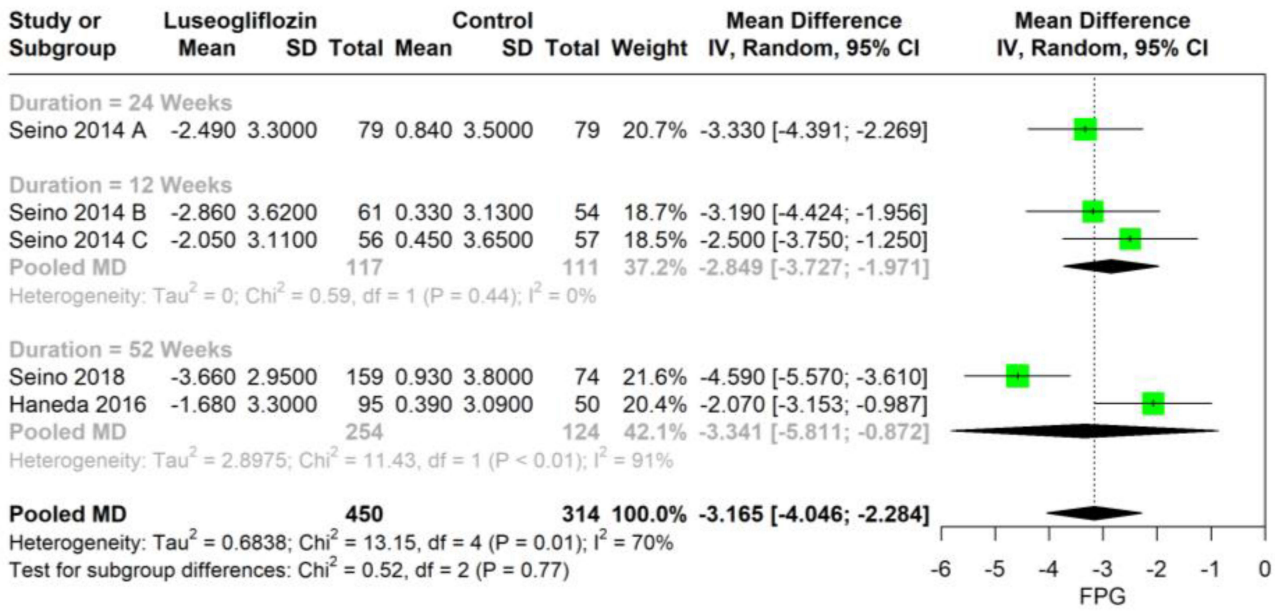

Figure 3 Effect of Luseogliflozin on FPG.
Abbreviations: IV, inverse variance; MD, Mean difference; SD, Standard deviation.

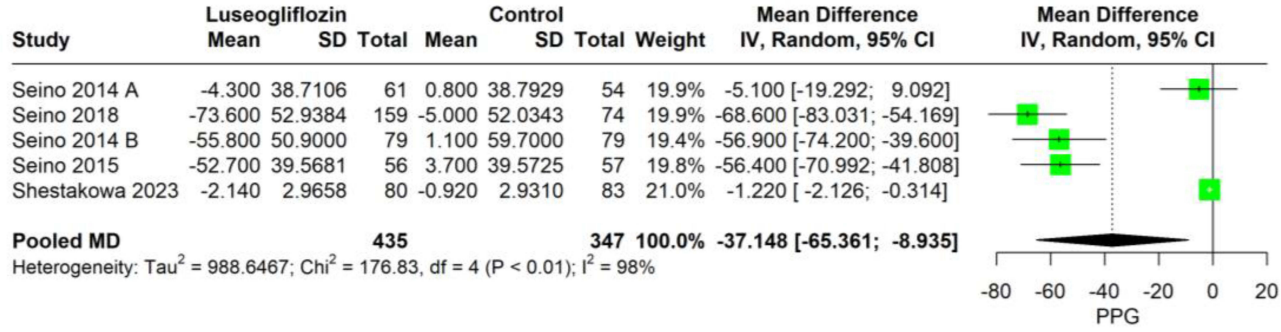

Figure 4 Effect of Luseogliflozin on PPG.
Abbreviations: IV, inverse variance; MD, Mean difference; SD, Standard deviation.

Alanine Transferase

When compared to placebo, Luseogliflozin showed a significant reduction in alanine aminotransferase (ALT) levels across multiple studies. The pooled mean difference for the placebo-controlled studies was −7.345 (95% CI: −5.845 to −1.463), indicating a consistent and significant effect of Luseogliflozin in lowering ALT levels. This demonstrates the efficacy of Luseogliflozin in reducing ALT levels in diabetic patients compared to a placebo, with no significant heterogeneity ($I^2 = 0\%$). When compared to DPP4i inhibitors from two studies, Luseogliflozin did not show a significant difference. The pooled mean difference was −5.300 (95% CI: −8.485 to 2.685). When compared to Metformin, the single study (Shibuya 2018) reported a mean difference of 4.500 (95% CI: −11.792 to 2.792) (Figure 5).

Glycosylated Albumin

Luseogliflozin showed a significant reduction in glycosylated albumin levels across multiple studies compared to placebo. The pooled mean difference for the placebo-controlled studies was −3.322 (95% CI: −5.187 to −1.056), indicating a consistent and significant effect of Luseogliflozin in lowering glycosylated albumin levels. This demonstrates the efficacy of Luseogliflozin in reducing glycosylated albumin levels in diabetic patients compared to a placebo, with high heterogeneity ($I^2 = 89\%$). When compared to DPP4 inhibitors from three studies, Luseogliflozin showed a significant reduction with a pooled mean difference of

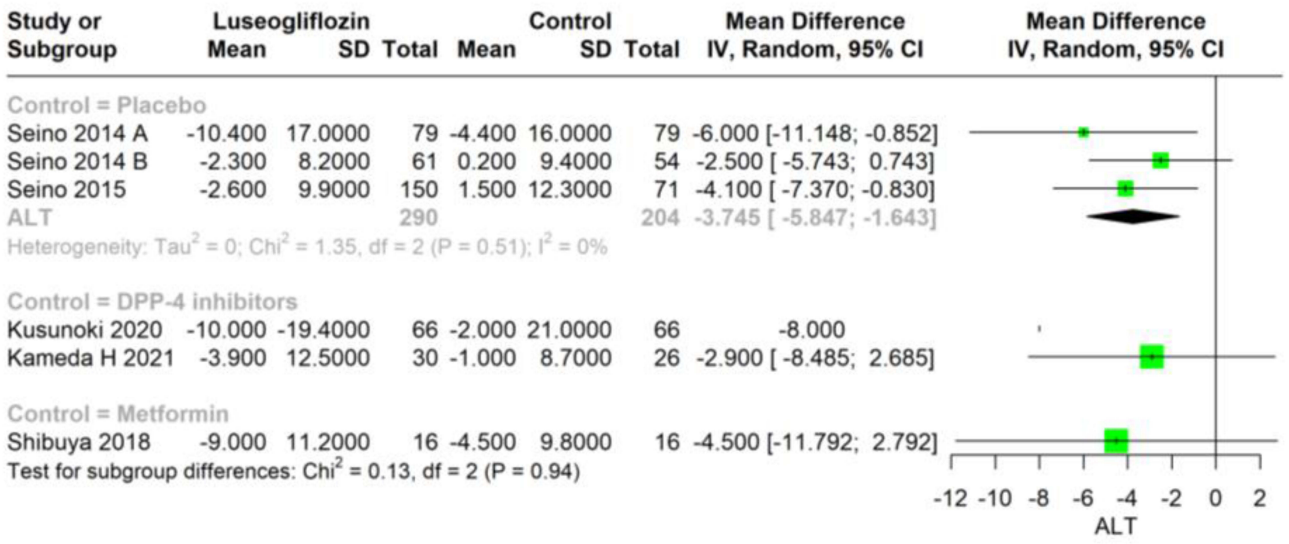

Figure 5 Effect of Luseogliflozin on ALT.
Abbreviations: IV, inverse variance; MD, Mean difference; SD, Standard deviation.

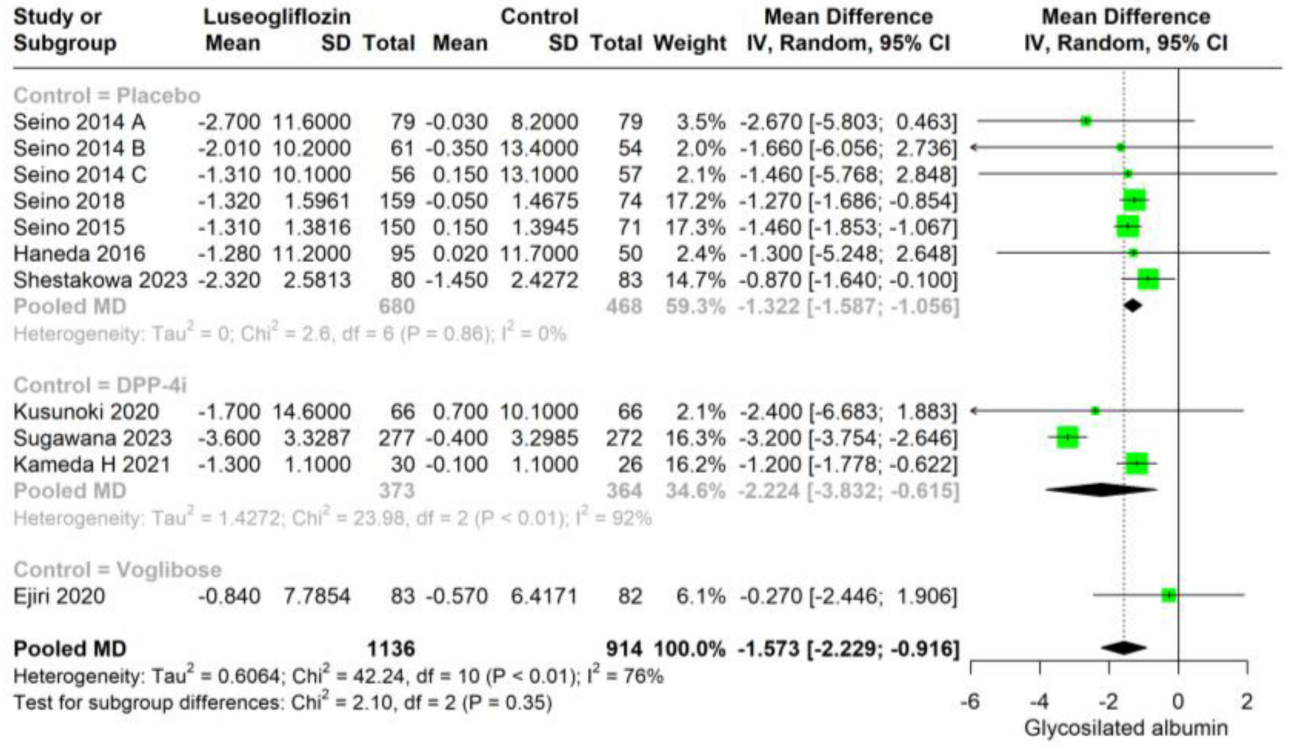

Figure 6 Effect of Luseogliflozin on glycosylated albumin.
Abbreviations: IV, inverse variance; MD, Mean difference; SD, Standard deviation.

−3.224 (95% CI: −4.382 to −0.615). When compared to Voglibose, the single study (Eiji 2020) reported a mean difference of −0.270 (95% CI: −2.446 to 1.906) (Figure 6).

Triglycerides

Compared to placebo, Luseogliflozin showed a significant reduction in triglyceride levels across multiple studies. The pooled mean difference for the placebo-controlled studies was −13.891 (95% CI: −26.539 to −1.243), indicating

a consistent and significant effect of Luseogliflozin in lowering triglyceride levels. This demonstrates the efficacy of Luseogliflozin in reducing triglyceride levels in diabetic patients compared to a placebo, with no significant heterogeneity (I^2 = 0%). Compared to DPP4 inhibitors from two studies, Luseogliflozin did not show a significant reduction with a pooled mean difference of −10.929 (95% CI: −33.116 to 11.257) (Figure 7).

Body Weight

Compared to placebo, Luseogliflozin showed a significant reduction in body weight across multiple studies. The pooled mean difference for the placebo-controlled studies was −1.322 kg (95% CI: −1.58 to −1.056), indicating a consistent and significant effect of useogliflozin in lowering body weight. This demonstrates the efficacy of Luseogliflozin in reducing body weight in diabetic patients compared to a placebo, with low heterogeneity (I^2 = 0%). Compared to DPP4 inhibitors from three studies, Luseogliflozin showed a significant reduction in body weight with a pooled mean difference of −2.224 (95% CI: −3.832 to −0.615). When compared to Voglibose, the single study (Eiji 2020) reported a mean difference of −0.270 (95% CI: −2.446 to 1.906) (Figure 8).

Uric Acid

Compared to placebo, Luseogliflozin showed a significant reduction in uric acid levels across multiple studies. The pooled mean difference for the placebo-controlled studies was −0.350 (95% CI: −0.524 to −0.176), indicating a consistent and significant effect of Luseogliflozin in lowering uric acid levels. This demonstrates the efficacy of Luseogliflozin in reducing uric acid levels in diabetic patients compared to a placebo, with no significant heterogeneity (I^2 = 0%). When compared to DPP4 inhibitors, the single study (Kusunoki 2020) reported a mean difference of −0.900 (95% CI: −1.361 to −0.439) (Figure 9).

Systolic Blood Pressure

When compared to placebo, Luseogliflozin showed a significant reduction in systolic blood pressure (SBP) across multiple studies. The pooled mean difference for the placebo-controlled studies was −3.561 (95% CI: −7.516 to 0.394), indicating a consistent and significant effect of Luseogliflozin in lowering SBP levels. This demonstrates the efficacy of Luseogliflozin in reducing SBP in diabetic patients compared to a placebo, with high heterogeneity (I^2 = 73%) (Figure 10).

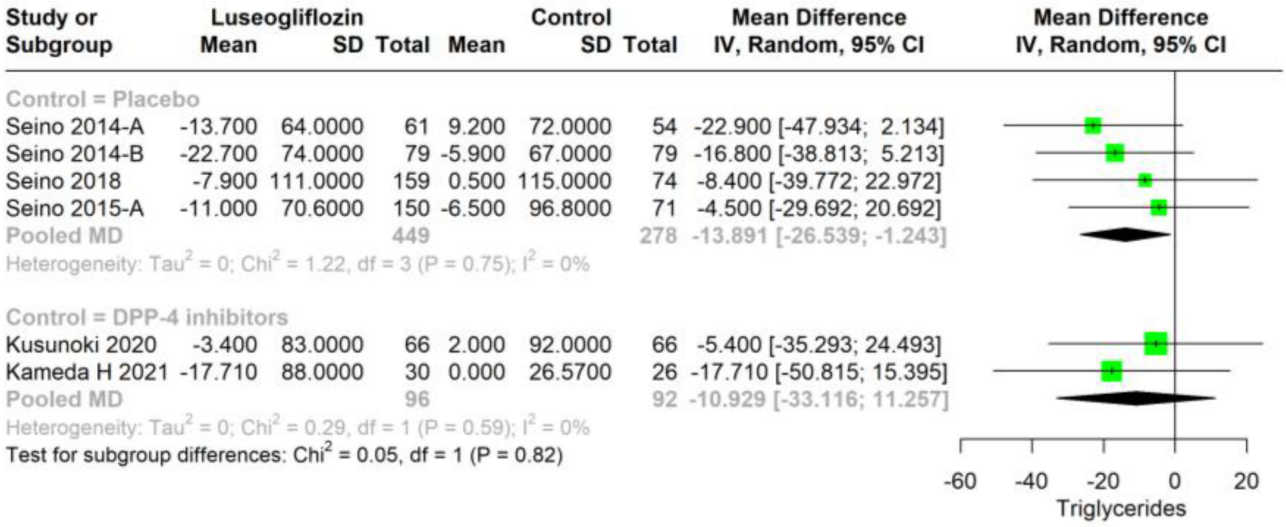

Figure 7 Effect of Luseogliflozin on triglycerides.
Abbreviations: IV, inverse variance; MD, Mean difference; SD, Standard deviation.

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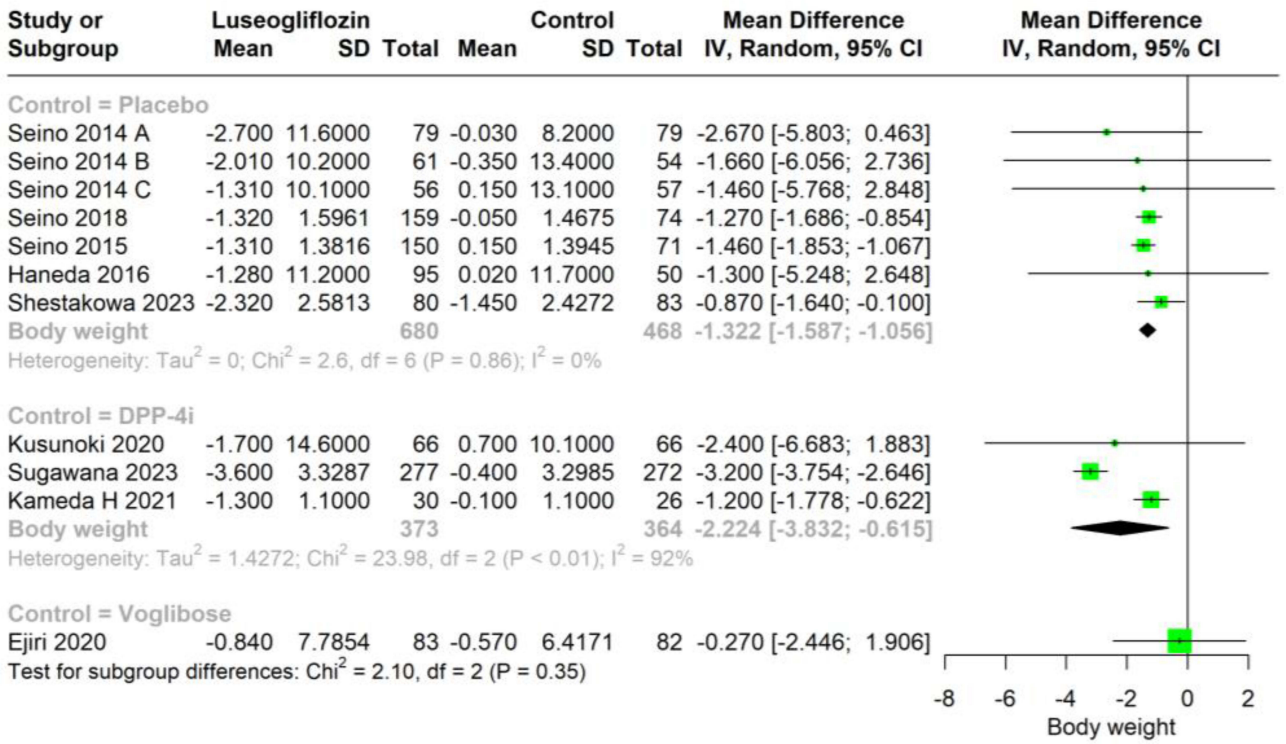

Figure 8 Effect of Luseogliflozin on body weight.
Abbreviations: IV, inverse variance; MD, Mean difference; SD, Standard deviation.

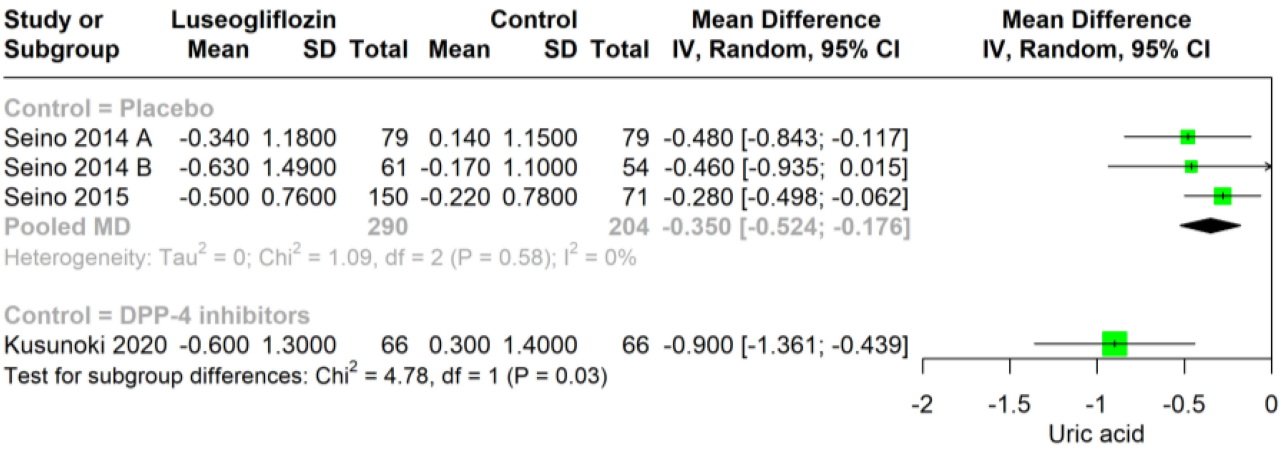

Figure 9 Effect of Luseogliflozin on uric acid.
Abbreviations: IV, inverse variance; MD, Mean difference; SD, Standard deviation.

Hypoglycemia

The incidence of hypoglycemia events with Luseogliflozin compared to placebo was evaluated across multiple studies. The pooled RR for the placebo-controlled studies was 1.305 (95% CI: 0.692 to 2.459), indicating no significant difference in the risk of hypoglycemia between Luseogliflozin and placebo groups. This suggests that Luseogliflozin does not significantly increase the risk of hypoglycemia in diabetic patients compared to a placebo, with no significant heterogeneity ($I^2 = 0\%$) (Figure 11).

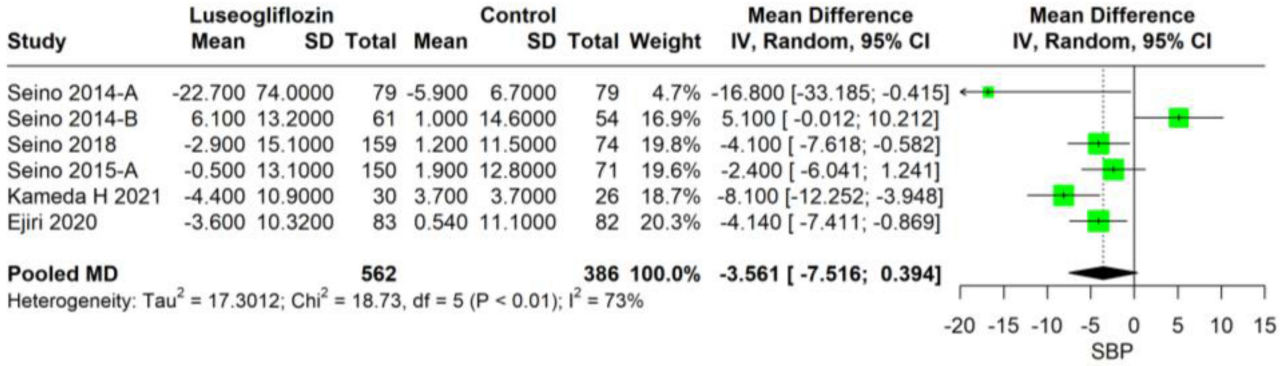

Figure 10 Effect of Luseogliflozin on SBP.
Abbreviations: IV, inverse variance; MD, Mean difference; SD, Standard deviation.

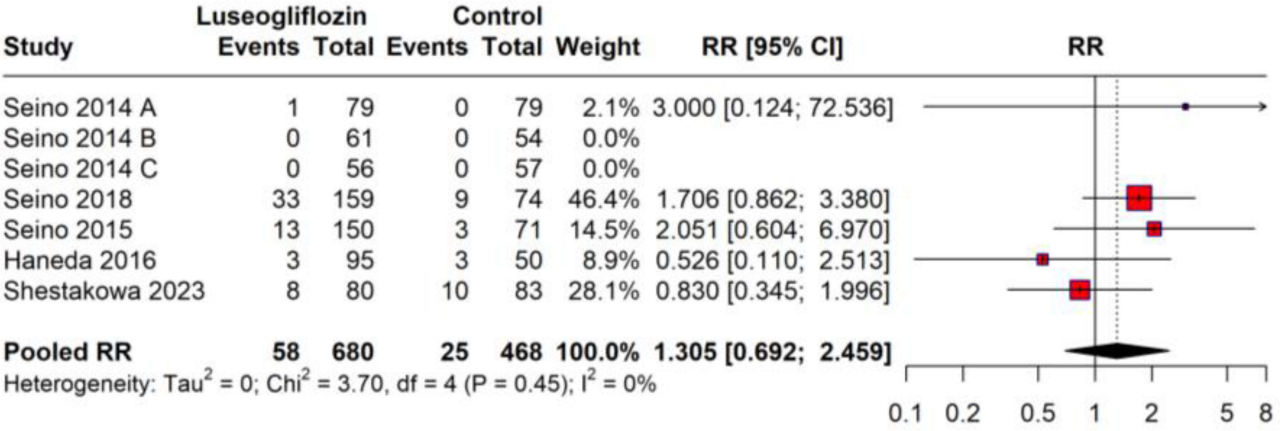

Figure 11 Effect of Luseogliflozin on incidence hypoglycemia.
Abbreviations: IV, inverse variance; MD, Mean difference; SD, Standard deviation.

Discussion

This umbrella review provides a comprehensive synthesis of the efficacy and safety of Luseogliflozin in patients with T2DM, integrating findings from multiple systematic reviews and meta-analyses. Our findings confirm the significant benefits of Luseogliflozin in managing various aspects of T2DM, highlighting its potential role in optimizing diabetes care.

When compared to other SGLT2 inhibitors, luseogliflozin demonstrates comparable efficacy in glycemic control with some potential distinctions. While the reduction in HbA1c levels is similar to that observed with canagliflozin, dapagliflozin, and empagliflozin, luseogliflozin is available at the lowest dosage among its class and may offer a favorable safety profile with a lower incidence of certain adverse events.[38,39] However, unlike dapagliflozin and empagliflozin which have proven benefits in large cardiovascular outcome trials, the evidence base for luseogliflozin's effects on hard cardio-renal endpoints remains limited.

Luseogliflozin demonstrated substantial efficacy in improving glycemic control, evidenced by significant reductions in HbA1c, FPG, and PPG levels. These glycemic benefits align with the known mechanism of action of SGLT2 inhibitors, which promote glucose excretion via urine. One of the notable benefits of Luseogliflozin is its impact on body weight, which can be attributed to the caloric loss associated with glucosuria and osmotic diuresis.[40] Furthermore, Luseogliflozin significantly reduced triglyceride levels, indicating a beneficial effect on lipid metabolism, although no significant reduction was observed when compared to DPP4 inhibitors. The reduction in ALT levels indicates potential hepatoprotective effects of Luseogliflozin. The exact mechanisms remain to be fully elucidated but may involve improvements in insulin sensitivity and reductions in hepatic fat content.[41] Additionally, the significant reduction in uric acid levels aligns with the observed metabolic benefits and may confer additional advantages in patients with hyperuricemia. The risk of hypoglycemia with Luseogliflozin was not

significantly different from placebo, suggesting a favorable safety profile. This is an important consideration, as hypoglycemia is a major concern in diabetes management, particularly with agents that directly increase insulin secretion. The comparable incidence of hypoglycemia events highlights the advantage of Luseogliflozin in minimizing this risk while providing effective glycemic control.[42] When compared to other antidiabetic agents, particularly DPP4 inhibitors, Luseogliflozin did not show significant differences in glycemic control but demonstrated advantages in weight reduction and uric acid lowering. These findings show the role of Luseogliflozin as a multifaceted therapeutic option that offers additional metabolic benefits beyond glycemic control.[40,43,44]

A previous umbrella review assessed the effectiveness of combining Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), dipeptidyl peptidase-4 inhibitors (DPP-4i), and SGLT-2i for treating T2DM showing limited response to standard insulin and metformin/sulfonylurea therapies.[45,46] This combination was found to significantly improve HbA1c and fasting plasma glucose levels in patients with T2DM who do not adequately respond to basic insulin and metformin/sulfonylurea treatment. In comparison to placebo, GLP-1 RAs notably decrease both body weight and the required doses of basic insulin. Additionally, DPP-4i and SGLT-2i are associated with a reduced risk of hypoglycemia. A comprehensive synthesis from another umbrella review demonstrated that SGLT-2 inhibitors markedly decrease the risk of hospitalization due to heart failure, cardiovascular death, overall mortality, and serious adverse events, while also enhancing quality of life. These inhibitors appear to be safe and effective for managing patients with heart failure, particularly regarding their immediate health outcomes.[47]

Luseogliflozin has demonstrated good tolerability across various treatment groups. Developed by Taisho Pharmaceutical Co., Ltd., it was first approved in Japan in 2013[35] but has not received FDA approval in the US, highlighting the need for further multicenter trials to establish its global regulatory status.

Meanwhile, other SGLT2 inhibitors like canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin have been FDA-approved to help manage blood sugar levels in adult T2DM patients as part of a comprehensive treatment plan including diet and exercise.[48] Studies currently suggest that SGLT2 inhibitors significantly improve cardio-renal outcomes in T2DM patients.[48–50] The reduction in HbA1c levels by luseogliflozin is similar to those seen with canagliflozin, dapagliflozin, and empagliflozin.[27,51,52] Additionally, luseogliflozin has shown a lower incidence of adverse events compared to other SGLT2 inhibitors and is available at the lowest dosage among them.[53,54]

Our study has some limitations. Firstly, we only included articles written in English, potentially excluding relevant studies published in other languages. Secondly, the number of studies was limited for certain outcomes, which may affect the robustness of our conclusions. The review relies on the quality and accuracy of the original studies, and any inherent biases or limitations within those studies that could impact our findings.

The absence of specific cardio-renal outcome data for luseogliflozin in our synthesis represents an important evidence gap. While SGLT2 inhibitors as a class have demonstrated significant improvements in cardio-renal outcomes in T2DM patients, it remains unclear whether these class effects extend uniformly to luseogliflozin. Future cardiovascular outcome trials focusing specifically on luseogliflozin are essential to determine if it shares the established cardio-renal benefits of other SGLT2 inhibitors.

Conclusion

Luseogliflozin appears to be a highly effective and safe option for managing T2DM, offering significant benefits in glycemic control, weight reduction, blood pressure lowering, and metabolic effects. Its favorable safety profile, particularly regarding hypoglycemia risk, makes it a valuable addition to the therapeutic arsenal for T2DM.

Future research should focus on long-term outcomes, particularly cardiovascular and renal endpoints, through dedicated outcome trials to further establish luseogliflozin's role in clinical practice and support broader regulatory approvals.

Data Sharing Statement

The data is with the authors and available on request. Corresponding Author Wahby Mohammed Babaresh will provide data upon request.

Acknowledgments

We acknowledge the Nested-Knowledge, MN, USA for providing the access to the software.

Author Contributions

MS: Supervision, Writing – Review & Editing, Formal Analysis, Methodology; MK: Investigation, Data Curation, Writing – Original Draft; AU, HS and AU: Validation, Investigation, Writing – Review & Editing; AV: Supervision, Visualization, Writing – Review & Editing; RS: Visualization, Writing – Original Draft; RM and WMB: Project Administration, Supervision, Writing Original DraftFormal Analysis, Methodology, Investigation.

All authors have agreed on the journal to which the article will be submitted.; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage and agree to take responsibility and be accountable for the contents of the article.

Funding

This study received no funding.

Disclosure

The authors report no conflict of interest.

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