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Efficacy and safety of luseogliflozin in improving glycaemic and non-glycaemic outcomes in type-2 diabetes: A meta-analysis

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ABSTRACT

Background & aims: No meta-analysis is available analysing the role of luseogliflozin in type-2 diabetes. We undertook this meta-analysis to address this knowledge-gap.
Methods: Electronic databases were searched for RCTs involving diabetes patients receiving luseogliflozin in intervention arm, and placebo/active comparator in control arm. Primary outcome was to evaluate changes in HbA1c. Secondary outcomes were to evaluate alterations in glucose, blood pressure, weight, lipids, and adverse events.
Results: From initially screened 151 articles, data from 10 RCTs involving 1304 patients was analysed. Individuals receiving luseogliflozin 2.5 mg/d had a significantly lower HbA1c [MD -0.76% (95% CI: 1.01 to −0.51); $P < 0.01$; $I^2 = 83\%$], fasting glucose [MD -26.69 mg/dl (95% CI: 35.41 to −17.96); $P < 0.01$; $I^2 = 80\%$], systolic blood pressure [MD -4.19 mm Hg (95% CI: 6.31 to −2.07); $P < 0.01$; $I^2 = 0\%$], body-weight [MD -1.61 kg (95% CI: 3.14 to −0.08); $P = 0.04$; $I^2 = 0\%$], triglycerides PCG [MD -12.60 mg/dl (95% CI: 24.25 to −0.95); $P = 0.03$; $I^2 = 0\%$], uric acid [MD -0.48 mg/dl (95% CI: 0.73 to −0.23); $P < 0.01$; $I^2 = 49\%$] and alanine aminotransferase [MD -4.11 IU/L (95% CI: 6.12 to −2.10); $P < 0.01$; $I^2 = 0\%$] compared to placebo. Occurrence of treatment-emergent adverse-events [RR 0.93 (95% CI: 0.72−1.20); $P = 0.58$; $I^2 = 0\%$], severe adverse-events [RR 1.19 (95% CI: 0.40−3.55); $P = 0.76$; $I^2 = 0\%$], hypoglycaemia [RR 1.56 (95% CI: 0.85−2.85); $P = 0.15$; $I^2 = 0\%$] and genital infections [RR 1.42 (95% CI: 0.48−4.18); $P = 0.53$; $I^2 = 0\%$] were not increased with luseogliflozin. Cardiovascular outcome trials are lacking and are urgently required.
Conclusion: Luseogliflozin has good glycaemic and non-glycaemic benefits similar to other SGLT2 inhibitors and is well tolerated.

1. Introduction

Luseogliflozin is a selective sodium-glucose cotransporter-2 (SGLT2) inhibitor, approved and available for clinical use for managing type-2 diabetes (T2DM) in Japan Since 2014 [1]. Luseogliflozin has 1650-fold greater selectivity for SGLT2 over SGLT1. It has a mean time to maximum plasma concentration ranged from 0.67 to 2.25 h and mean half-life of 9.2−13.8 h [2]. The recommended starting dose for luseogliflozin is 2.5 mg once daily which may later be increased to 5 mg/day in case adequate glycaemic control is not achieved [1,3]. Studies have shown that the $AUC_{0-\infty}$ after administration of a single 5 mg oral dose of luseogliflozin was similar in patients of T2DM with normal or mild, moderate or severe, renal function [1,4]. In a study evaluating pharmacodynamic effects of single dose of 5 mg luseogliflozin across the spectrum of renal function viz. the normal (estimated glomerular filtration rate (GFR) 90 ml/min/1.73 m^2 or above), mildly (60−89 ml/min/1.73 m^2), mild-to-moderately (45−59 ml/min/1.73 m^2), moderate-to

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severely (30–44 ml/min/1.73 m^2) and severely (15–29 ml/min/1.73 m2) impaired renal function; the mean 24-h urine glucose excretion across the groups were significantly increased from baseline by 88.3, 69.7, 57.3, 35.3 and 21.8 g respectively [4]. Hence it was apparent that the quantum of 24-h urine glucose excretion increase was significantly reduced in people with GFR <30 ml/min/1.73 m^2. Several randomized controlled trials (RCTs) have been published evaluating the efficacy of luseogliflozin alone or in combination with other medication in T2DM focussing on glycaemic outcomes, fatty liver disease and heart failure outcomes [5–7]. However, till data no meta-analysis has been published holistically evaluating the clinical outcomes with luseogliflozin. Hence this meta-analysis aimed to evaluate the impact of luseogliflozin on glycaemic, hepatic, metabolic and cardiovascular outcomes in people with T2DM.

2. Methods

The meta-analysis was done as per the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), with the predefined protocol registered with PROSPEFO having registration number of CRD42022389863 [8]. PICOS criteria was used to select studies for the meta-analysis. All randomized controlled trials (RCTs) published till December 2022 were considered. Case reports, conference abstracts, case series and posters were excluded. Only patients with T2DM were considered. Patients with other forms of diabetes were excluded. Studies having one arm of patients with T2DM on luseogliflozin and the other arm receiving either placebo or any other diabetes medication in place of luseogliflozin were considered. Studies with at least 12 weeks (3 months) follow-up were included in this meta-analysis, as that is the minimum follow-up mandated to detect meaningful changes in the primary outcome of this meta-analysis viz. HbA1c. The primary outcome was changes in HbA1c. Secondary outcomes were alterations in fasting glucose (FPG), 2-h post-prandial glucose (PPG), weight, systolic blood pressure, diastolic blood pressure, adverse events, hypoglycaemia, lipid parameters, insulin resistance parameters, inflammatory markers, and glycaemic variability parameters. Studies evaluating either the primary outcome or at least 2 secondary outcomes were included in the meta-analysis. Analysis of the outcomes was done based on whether the control group received an active comparator diabetes medication – labelled as active control group (ACG) or placebo – labelled as passive control Group (PCG).

We systematically searched Embase database, Cochrane library, Medline (PubMed), clinicaltrials.gov, ctri.nic.in, global health and Google scholar using Boolean search strategy: (luseogliflozin) [MESH] AND (diabetes).

Data extraction with regards to all the primary and secondary outcomes stated above was carried out independently by two authors. Multiple publications from the same group on the same cohort of patients were pooled together and considered as a single study for the purpose of meta-analysis. Details have been elaborated in previous meta-analysis published by our group [9]. The risk of bias assessment was done by 3 authors using the risk of bias assessment tool in Review Manager (Revman) Version 5.4 software. The different types of bias looked for have been elaborated in previous metanalyses by our group [9].

The international system of units (SI units) was used for all the analysis done. Continuous variable outcomes were presented as mean differences (MD). For dichotomous variables, outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI) and as hazard ratios (HR) for adverse events. RevMan 5.4 was used for doing all the statistical analysis and generation of Forest plots in this meta-analysis. Random effect model for analysis expressed as 95% confidence intervals (95%CI). The forest plot generated for all the different outcomes was used to assess the heterogeneity. We specifically used Chi^2 test on N-1° of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test [10]. The details of heterogeneity analysis have been elaborated elsewhere [9].

Grading of results is an important as it helps us to understand the quality of the results generated in a meta-analysis. After all any meta-analysis can be as good as the quality of RCTs used in the analysis. The grading/certainty of the evidence of some of the major outcomes in this meta-analysis was done using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach [11]. The details have been elaborated elsewhere [9]. Publication bias was assessed by plotting the Funnel Plot [11]. The details of how the Funnel plots were plotted have been elaborated elsewhere [9]. The funnel plots of the key outcomes of this study have been elaborated in Supplementary Fig. 2. Table-1 was generated using the GRADE software (https://gdt.gradepro.org/app/) which highlights the grading of key outcomes.

3. Results

A total of 151 articles were found after the initial search (Figure-1). Following the screening of the titles, abstracts, followed by full-texts, the search was reduced down to 31 studies which were evaluated in detail for inclusion in this meta-analysis (Figure-1). Data from 10 RCTs with 1304 people with T2DM which fulfilled all criteria were analysed in this meta-analysis [5–7,12–18]. The study by Nakashima et al. [19] and Ejiri (2022) et al. [20] were an extension of the study by Ejiri (2020) et al. [7]. Hence the results of all the 3 studies have been presented here together under Ejiri (2020) et al. [7]. The studies by Nishimura (2015) et al. [21], Nishimura (2015a) et al. [22], Yabe et al. [23]. Jinnouchi et al. [24], Samukawa (2016) et al. [25], Sasaki et al. [26], Samukawa (2017) et al. [27] were excluded as they were either short term continuous glucose monitoring (CGM) studies of few days to weeks duration or were pharmacokinetic studies.

Of the 10 RCTs included in this meta-analysis, 6 RCTs (Haneda et al. [18], Seino 2014a et al. [12], Seino 2014b et al. [13], Seino 2014c et al. [14], Seino 2015 et al. [15], Seino 2018 et al. [5]) had placebo as controls, and hence the outcomes of those studies have been analysed under the placebo control group (PCG); and 4 RCTs (Ejiri et al. [7], Hashimoto-Kameda et al. [17], Kusunoki et al. [16] and Shibuya et al. [6]) had anti-diabetes medications as controls and hence the outcomes of those studies have been analysed under the active control group (ACG). The active controls in the studies by Ejiri et al. [7], Hashimoto-Kameda et al. [17], Kusunoki et al. [16] and Shibuya et al. [6] were voglibose 0.2 mg thrice daily, dipeptidyl-peptidase-4 inhibitors (DPP4i) (either vildagliptin, teneligliptin, sitagliptin, linagliptin, alogliptin, anagliptin or saxagliptin), DPP4i (either sitagliptin, vildagliptin, alogliptin, anagliptin, or linagliptin), and metformin 1500 mg/d respectively. The details of the studies included in this meta-analysis have been elaborated in Supplementary Table-1.

The summaries of risk of bias of the 10 studies included in the meta-analysis have been elaborated in Supplementary Figs. 1a and 1b. Attrition bias and, reporting bias were judged to be at low risk of bias in all the 10 studies (100%). Random sequence generation bias was low risk in 9 out of 10 studies (90%). Allocation concealment bias was low risk in 7 out of 10 studies (70%). Performance bias and detection bias was low risk in 6 out of 10 studies (60%). Origin of funding, especially pharmaceutical organizations, authors from the pharmaceutical organizations and conflict of interests were looked into the “other bias” section. Other bias was judged to be at low risk in only 2 out of 10 studies (20%) (Supplementary table-2).

Table 1
Summary of findings of key outcomes of meta-analysis comparing luseogliflozin 2.5 mg/day as compared to placebo in type-2 diabetes.

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE) [11]
	Risk with Control	Risk with Luseogliflozin 2.5 mg/d			
HbA1c	The mean HbA1c in PCG was 7.77%	MD 0.76% lower (1.01 lower to 0.51 lower)	–	985 (6 RCTs)	⨁⨁⨁◯ Moderate[a]
Fasting Glucose	The mean fasting Glucose in PCG was 157.57 mg/dl	MD 26.69 mg/dl lower (35.41 lower to 17.96 lower)	–	995 (6 RCTs)	⨁⨁◯◯ Low[a,b]
Body Weight	The mean body-weight in PCG was 69.60 kg	MD 1.61 kg lower (3.14 lower to 0.08 lower)	–	906 (6 RCTs)	⨁⨁⨁⨁ High
Systolic blood pressure (SBP)	The mean SBP in PCG was 130.48 mm Hg	MD 4.19 mm Hg lower (6.31 lower to 2.07 lower)	–	625 (4 RCTs)	⨁⨁⨁⨁ High
Diastolic blood pressure (DBP)	The mean DBP in PCG was 75.58 mm Hg	MD 2.7 mm Hg lower (4.36 lower to 1.03 lower)	–	625 (4 RCTs)	⨁⨁⨁⨁ High
Uric Acid	The mean uric acid in PCG was 5.12 mg/dl	MD 0.48 mg/dl lower (0.73 lower to 0.23 lower)	–	626 (4 RCTs)	⨁⨁⨁⨁ High
Alanine aminotransferase (ALT)	The mean ALT in PCG was 29.28 IU/L	MD 4.11 IU/L lower (6.12 lower to 2.1 lower)	–	626 (4 RCTs)	⨁⨁⨁◯ Moderate[b]
Triglycerides	The mean triglycerides PCG (12–24 weeks) was 151.36 mg/dl	MD 12.6 mg/dl lower (24.25 lower to 0.95 lower)	–	859 (5 RCTs)	⨁⨁⨁⨁ High
Treatment-emergent Adverse Events	484 per 1,000	466 per 1,000 (403–529)	OR 0.93 (0.72 –1.20)	1150 (7 RCTs)	⨁⨁⨁⨁ High
Hypoglycaemia	34 per 1,000	52 per 1,000 (29–92)	OR 1.56 (0.85 –2.85)	1150 (7 RCTs)	⨁⨁⨁⨁ High
Genital Infections	9 per 1,000	12 per 1,000 (4–35)	OR 1.42 (0.48 –4.18)	1150 (7 RCTs)	⨁⨁⨁⨁ High

CI: confidence interval; MD: mean difference; OR: odds ratio; PCG: placebo control group.
[a] Due to large variation in effect, the confidence intervals do not overlap, the P-value for heterogeneity is < 0.05, and I^2 is >60%.
[b] Funnel plot is suggestive of presence of most of the studies outside the plot, hence it is likely that significant publication bias is present (Supplementary figure-2).

4. Effect of luseogliflozin 2.5 mg/d on primary outcomes

Data from 6 studies (985 people) and 4 studies (385 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on HbA1c after 12–24 weeks of treatment as compared to placebo (PCG) and active controls (ACG) respectively. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of HbA1c as compared to placebo [MD -0.76% (95% CI: 1.01 to −0.51); P < 0.01; I^2 = 83% (moderate heterogeneity); figure-2a], but comparable lowering of HbA1c as compared to active controls [MD -0.29% (95% CI: 0.74 − 0.16); P = 0.2; I^2 = 82% (moderate heterogeneity); figure-2b].

5. Effect of luseogliflozin 2.5 mg/d on secondary outcomes

Data from 6 studies (995 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on fasting glucose after 12–24 weeks of treatment as compared to PCG. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of fasting glucose as compared to placebo [MD -26.69 mg/dl (95% CI: 35.41 to −17.96); P < 0.01; I^2 = 80% (moderate heterogeneity); figure-2c].

Data from 4 studies (619 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on 2-hPPG after 12–24 weeks of treatment as compared to PCG. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of 2 h-PPG as compared to placebo [MD -57.73 mg/dl (95% CI: 67.93 to −47.52); P < 0.01; I^2 = 19% (low heterogeneity); figure-2d].

Data from 4 studies (625 people) and 2 studies (221 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on systolic blood pressure (SBP) after 12–24 weeks of treatment as compared to PCG and ACG respectively. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of SBP as compared to PCG [MD -4.19 mm Hg (95% CI: 6.31 to −2.07); P < 0.01; I^2 = 0% (low heterogeneity); figure-2e] as well as ACG [MD -4.46 mm Hg (95% CI: 7.38 to −1.54); P < 0.01; I^2 = 0% (low heterogeneity); figure-2f].

Data from 4 studies (625 people) and 1 study (56 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on diastolic blood pressure (DBP) after 12–24 weeks of treatment as compared to PCG and ACG respectively. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of DBP as compared to PCG [MD -2.70 mm Hg (95% CI: 4.36 to −1.03); P < 0.01; I^2 = 17% (low heterogeneity); figure-3a], but not ACG [MD -2.80 mm Hg (95% CI: 6.63 − 1.03); P = 0.15; Hashimoto-Kameda et al.].

Data from 6 studies (906 people) and 2 studies (221 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on body weight after 12–24 weeks of treatment as compared to PCG and ACG respectively. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of body weight as compared to PCG [MD -1.61 kg (95% CI: 3.14 to −0.08); P = 0.04; I^2 = 0% (low heterogeneity); figure-3b], but not ACG [MD -0.70 mm Hg (95% CI: 1.61 − 0.21); P = 0.13; I^2 = 88% (considerable heterogeneity); figure-3c].

Data from 5 studies (859 people) and 2 studies (213 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on serum triglycerides after 12–24 weeks of treatment as compared to PCG and ACG respectively. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of triglycerides as compared to PCG [MD -12.60 mg/dl (95% CI: 24.25 to −0.95); P = 0.03; I^2 = 0% (low heterogeneity); figure-3d], but not ACG [MD -11.65 mg/dl (95% CI: 23.54 − 0.24); P = 0.05; I^2 = 0% (low heterogeneity); figure-3e].

Data from 4 studies (626 people) and 1 study (56 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on serum uric acid after 12–24 weeks of treatment as compared to PCG and ACG respectively. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of serum uric acid as compared to PCG [MD -0.48 mg/dl (95% CI: 0.73 to −0.23); P < 0.01; I^2 = 49% (moderate heterogeneity); figure-3f], as well as ACG [MD

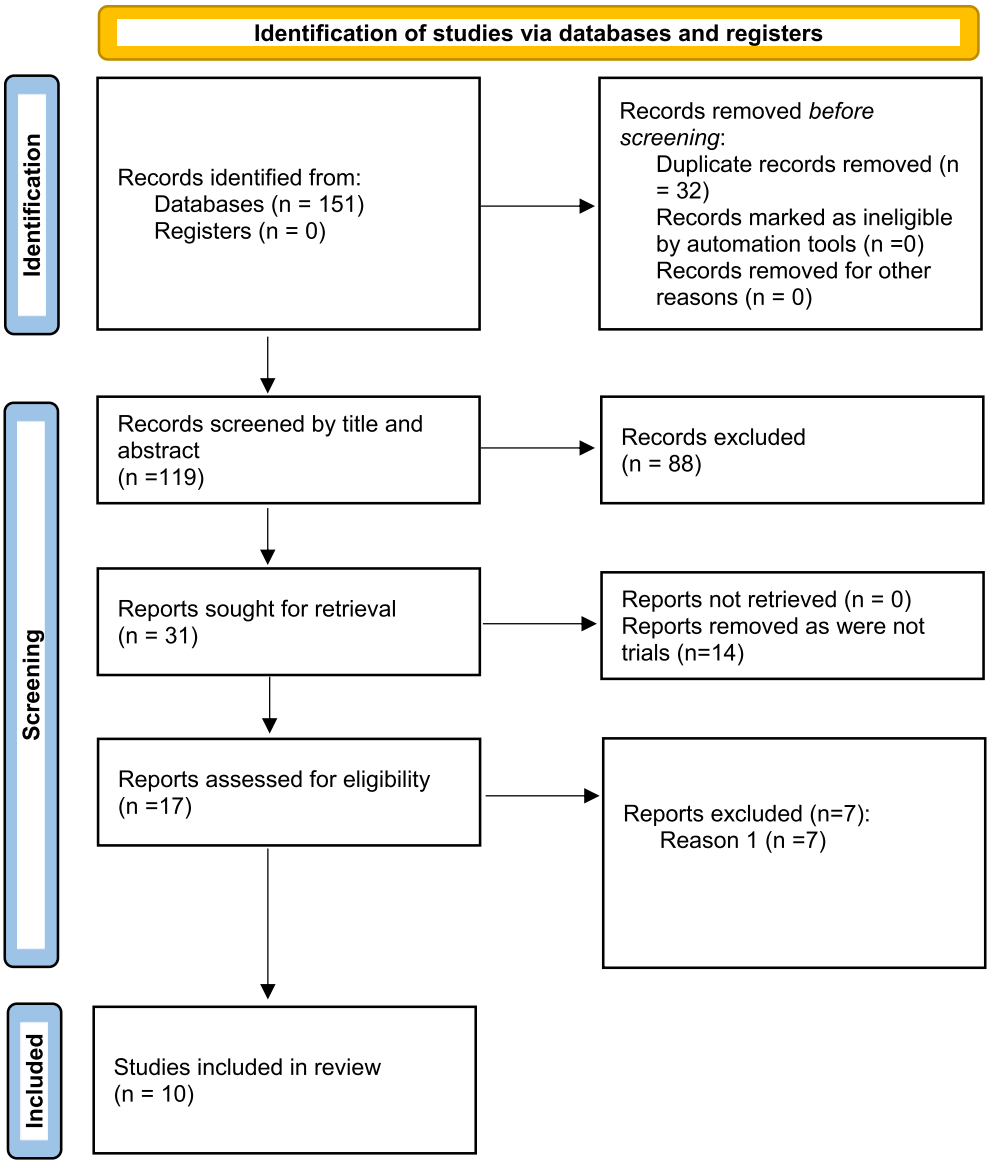

Fig. 1. Flowchart elaborating on study retrieval and inclusion in the meta-analysis
Reason-1: Research papers were excluded as they were either short term continuous glucose monitoring (CGM) studies of few days to weeks duration or were pharmacokinetic studies; RCT: randomized controlled trial.

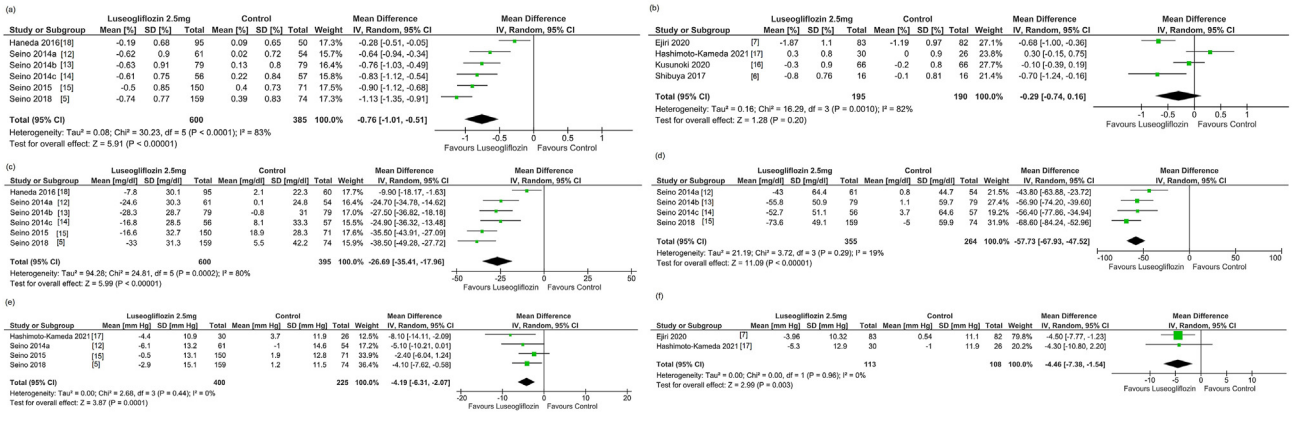

Fig. 2. Forest plot highlighting the impact of luseogliflozin 2.5 mg/d over 12–24 weeks of therapy on (a) HbA1c as compared to placebo; (b) HbA1c as compared to active controls; (c) Fasting glucose as compared to placebo; (d) 2-h post-prandial glucose as compared to placebo; (e): Systolic blood pressure (SBP) as compared to placebo; (f): SBP as compared to active controls.

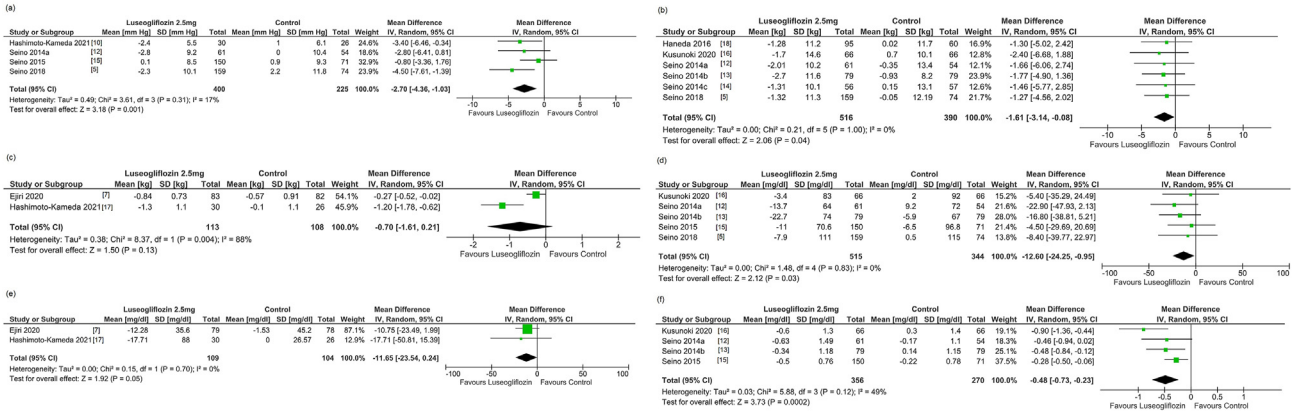

Fig. 3. Forest plot highlighting the impact of luseogliflozin 2.5 mg/d over 12−24 weeks of therapy on (a) Diastolic blood pressure as compared to placebo; (b) body-weight as compared to placebo; (c) body weight as compared to active controls; (d) Serum triglycerides as compared to placebo; (e): Serum triglycerides as compared to active controls; (f): Serum uric acid as compared to placebo.

-0.50 mg/dl (95% CI: 0.96 to −0.04); P = 0.03; Hashimoto-Kameda et al.].

Data from 5 studies (774 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on glycosylated albumin after 12−24 weeks of treatment as compared to PCG. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of glycosylated albumin as compared to PCG [MD -3.16% (95% CI: 4.07 to −2.24); P < 0.01; I^2 = 71% (moderate heterogeneity); figure-4a].

Data from 3 studies (386 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on homeostatic model for insulin resistance (HOMA-IR) after 12−24 weeks of treatment as compared to PCG. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of HOMA-IR as compared to PCG [MD -0.73 (95% CI: 1.25 to −0.20); P < 0.01; I^2 = 2% (low heterogeneity); figure-4b].

Data from 4 studies (626 people) and 2 studies (88 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on serum alanine aminotransferase (ALT) after 12−24 weeks of treatment as compared to PCG and ACG respectively. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater lowering of ALT as compared to PCG [MD -4.11 IU/L (95% CI: 6.12 to −2.10); P < 0.01; I^2 = 0% (low heterogeneity); figure-4c], but not ACG [MD -3.49 IU/L (95% CI: 7.93 − 0.94); P = 0.12; I^2 = 0% (low heterogeneity); figure-4d].

Data from 3 studies (386 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on urine glucose excretion after 12−24 weeks of treatment as compared to PCG. Individuals receiving luseogliflozin 2.5 mg/d had a significantly greater urine glucose excretion as compared to PCG [MD 7.95 gm/2 h (95% CI: 7.25−8.65); P < 0.01; I^2 = 0% (low heterogeneity); figure-4e].

Data from 2 studies (321 people) and 1 study (56 people) with T2DM was analysed to find out the impact of luseogliflozin 2.5 mg/d on abdominal circumference after 12−24 weeks of treatment as compared to PCG and ACG respectively. Individuals receiving luseogliflozin 2.5 mg/d had no significant change in abdominal circumference as compared to PCG [MD -1.22 cm (95% CI: 3.04 − 0.61); P = 0.19; I^2 = 0% (low heterogeneity); figure-4f], but had significant reduction in abdominal circumference as compared to ACG [MD -1.90 cm (95% CI: 3.57 to −0.23); P = 0.03; Hashimoto-Kameda et al.].

Data from 165 patients was analysed by Ejiri et al. [7] to evaluate percent change in B-type natriuretic peptide (BNP%) and estimated plasma volume (ePV%) with the use of luseogliflozin 2.5 mg/d as compared to voglibose in people with heart failure with preserved ejection fraction (HFpEF). Individuals received luseogliflozin had a significantly greater reduction in BNP% [MD -14.3% (95% CI: 18.21 to −10.39); P < 0.01] and ePV% [MD -12.3% (95% CI: 13.05 to −11.55); P < 0.01] as compared to voglibose.

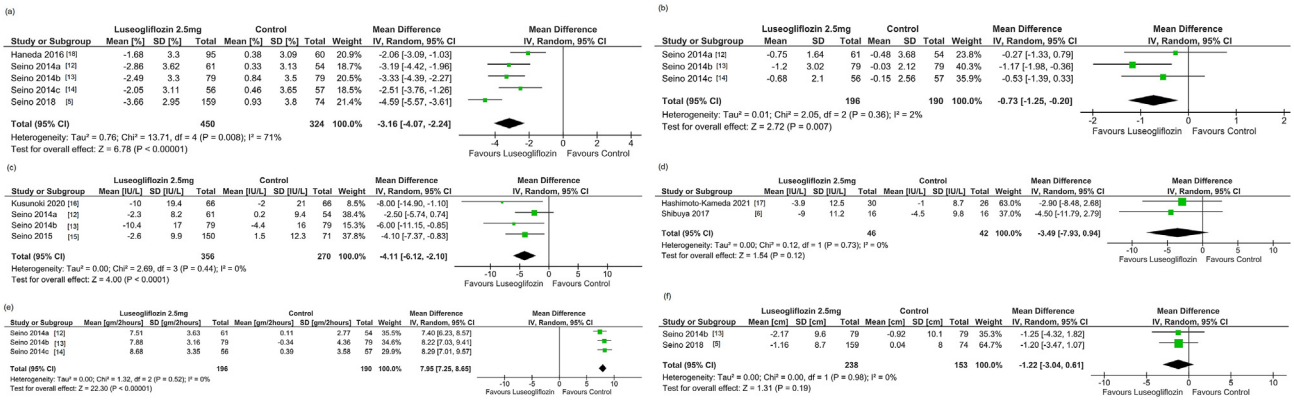

Fig. 4. Forest plot highlighting the impact of luseogliflozin 2.5 mg/d over 12−24 weeks of therapy on (a): Glycosylated albumin as compared to placebo; (b): Homeostatic model of insulin resistance (HOMA-IR) as compared to placebo; (c): Alanine aminotransferase as compared to placebo; (d): Alanine aminotransferase as compared to active controls; (e): Urine glucose excretion over 2 h of tablet intake as compared to placebo; (f): Change in abdominal circumference as compared to placebo.

6. Safety

Data from 7 studies (1150 patients) was analysed to evaluate the impact of luseogliflozin 2.5 mg/d on the occurrence of adverse events [(treatment-emergent adverse events (TAEs) and severe adverse events (SAEs)], hypoglycaemia, genital infections over 12–24 weeks of treatment. The side effects which were predominantly noted in the study and control groups in different studies were polyuria, headache, nasopharyngitis, upper respiratory infections, diarrhoea, hypoglycaemia, increased C-reactive protein, ketonuria and urogenital infections. The 3 SAEs noted in the study by Seino 2014c et al. were 2 patients with Prinzmetal angina and one with laryngeal carcinoma [14]. In the study by Seino 2015 et al., there were 3 events of myocardial infarction, 1 patient with prostatitis and 1 patient with drug eruption noted in the study and the control groups [15]. The occurrence of TAEs [Risk ratio (RR) 0.93 (95% CI: 0.72–1.20); P = 0.58; I^2 = 0% (low heterogeneity); figure-5a], SAEs [RR 1.19 (95% CI: 0.40–3.55); P = 0.76; I^2 = 0% (low heterogeneity); figure-5b], hypoglycaemia [RR 1.56 (95% CI: 0.85–2.85); P = 0.15; I^2 = 0% (low heterogeneity); figure-5c], genital infections [RR 1.42 (95% CI: 0.48–4.18); P = 0.53; I^2 = 0% (low heterogeneity); figure-5d], urinary tract infections [RR 1.34 (95% CI: 0.22–8.02); P = 0.75; I^2 = 0% (low heterogeneity); figure-5e] were not statistically different in patients receiving luseogliflozin 2.5 mg/d as compared to the controls.

Data from 3 studies (386 patients) was analysed to evaluate the impact of luseogliflozin 2.5 mg/d on the occurrence of ketone bodies in urine over 12–24 weeks of treatment. The occurrence of ketone bodies in urine [RR 2.82 (95% CI: 0.42–18.88); P = 0.29; I^2 = 0% (low heterogeneity); figure-5f] was not statistically different in patients receiving luseogliflozin 2.5 mg/d as compared to the controls. Data from 2 studies (378 patients; Haneda et al., Seino 2018 et al.) was analysed to evaluate the impact of luseogliflozin 2.5 mg/d on the occurrence of volume depletion (thirst/dehydration) over 12–24 weeks of treatment. The occurrence of volume depletion (thirst/dehydration) [RR 0.70 (95% CI: 0.02–21.24); P = 0.84; I^2 = 71% (moderate heterogeneity)] was not statistically different in patients receiving luseogliflozin 2.5 mg/d as compared to the controls.

7. Effect of luseogliflozin 5 mg/d on primary and secondary outcomes

Data from 2 studies (226 patients; Seino 2014a et al. and Seino 2014c et al.) was analysed to evaluate the impact of luseogliflozin 5 mg/d on primary and secondary outcomes over 12 weeks of clinical use. As compared to placebo, patients receiving luseogliflozin 5 mg/d had a significantly greater lowering of HbA1c [MD -0.74% (95% CI: 0.95 to −0.53); P < 0.01; I^2 = 0% (low heterogeneity)], fasting glucose [MD -28.08 mg/dl (95% CI: 35.69 to −20.47); P < 0.01; I^2 = 0% (low heterogeneity)], 2-hPPG [MD -59.49 mg/dl (95% CI: 73.78 to −45.19); P < 0.01; I^2 = 0% (low heterogeneity)], glycosylated albumin [MD -3.43% (95% CI: 4.32 to −2.54); P < 0.01; I^2 = 0% (low heterogeneity)], SBP [MD -5.20 mm Hg (95% CI: 8.92 to −1.47); P < 0.01; I^2 = 0% (low heterogeneity)], DBP [MD -2.79 mm Hg (95% CI: 5.41 to −0.16); P = 0.04; I^2 = 0% (low heterogeneity)], ALT [MD -3.85 IU/L (95% CI: 7.56 to −0.14); P = 0.04; I^2 = 0% (low heterogeneity)],triglycerides [MD -31.83 mg/dl (95% CI: 54.57 to −9.09); P < 0.01; I^2 = 0% (low heterogeneity)], uric acid [MD -0.35 mg/dl (95% CI: 0.66 to −0.04); P = 0.03; I^2 = 0% (low heterogeneity)] and urine glucose excretion [MD 9.39 gm/2 h (95% CI: 7.71–11.08); P < 0.01; I^2 = 83% (considerable heterogeneity)].

As compared to placebo, patients receiving luseogliflozin 5 mg/d did not have any statistically significant change with regards to HOMA-IR [MD -0.55 (95% CI: 1.21 − 0.11); P = 0.10; I^2 = 0% (low heterogeneity)], creatinine [MD 0.02 mg/dl (95% CI: 0.02 − 0.05); P = 0.35; I^2 = 0% (low heterogeneity)], TAEs [RR 0.85 (95% CI: 0.38–1.89); P = 0.69; I^2 = 56% (moderate heterogeneity)], SAEs [RR 1.06 (95% CI: 0.06–17.33); P = 0.97], hypoglycaemia [RR 3.22 (95% CI: 0.13–80.87); P = 0.48], genital infections [RR 0.97 (95% CI: 0.10–9.43); P = 0.98; I^2 = 0% (low heterogeneity)] and ketone bodies in urine [RR 1.06 (95% CI: 0.06–17.33); P = 0.97]. Analysis could not be done for urinary tract infection as there were zero events in both the study and the control group.

The summary of findings of the key outcomes of this meta-analysis comparing luseogliflozin 2.5 mg/day to placebo has been elaborated in table-1.

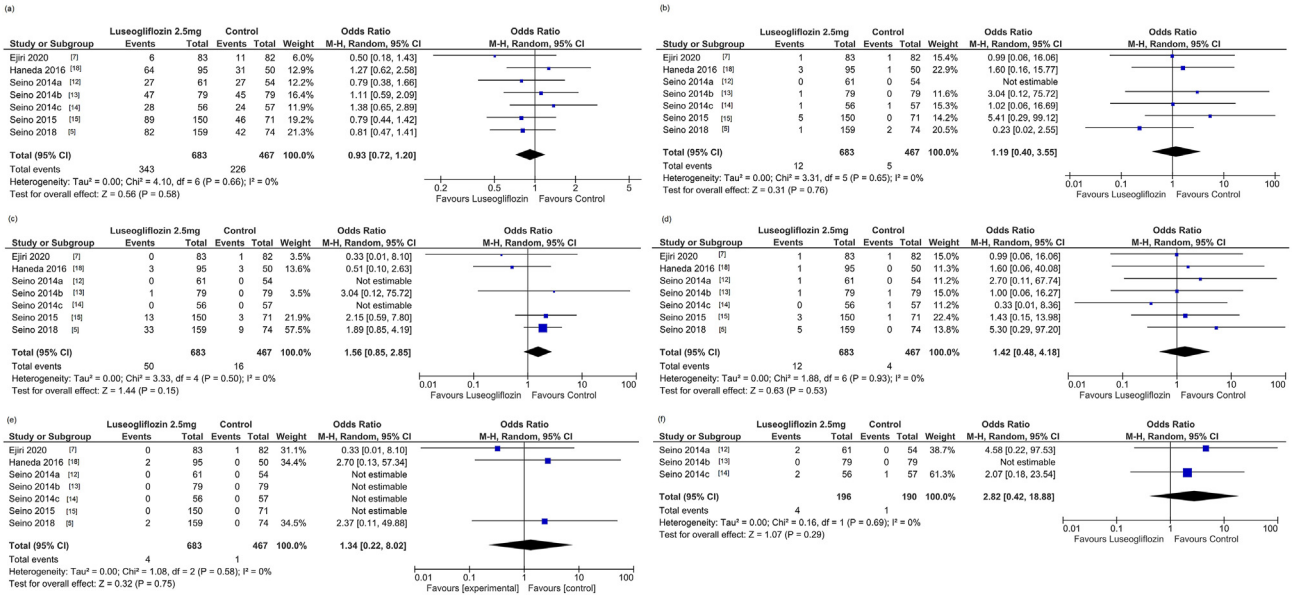

Fig. 5. Forest plot highlighting the impact of luseogliflozin 2.5 mg/d over 12–24 weeks of therapy on (a): Treatment-emergent adverse events (TAEs); (b): Severe adverse events (SAEs); (c): Hypoglycaemia; (d) Genital infections; (e): Urinary infections; (f): Urine ketonuria.

8. Discussion

A review of the National Database of Health Insurance Claims and Specific Health Check-ups of Japan, for the years 2016 and 2017 revealed luseogliflozin along with ipragliflozin, dapagliflozin, empagliflozin and canagliflozin to be the top 5 prescribed SGLT2i across Japan with the increment for the annual volume of tablets claimed for each SGLT2 inhibitor from 2016 to 2017 being 24.1% for ipragliflozin, 50.9% for dapagliflozin, 52.3% for luseogliflozin, 64.3% for canagliflozin, and 133.4% for empagliflozin [28]. Hence in spite of being a popular SGLT2i in clinical practice, no meta-analysis was ever done prior to this holistically evaluating the clinical outcomes with luseogliflozin.

Over 3–6 months of clinical use, this meta-analysis highlights the good glycaemic efficacy of luseogliflozin 2.5 mg/d as evidenced by mean HbA1c, FPG and 2hPPG reduction of −0.76%, −26.69 mg/dl, and −57.73 mg/dl respectively, as compared to placebo. It must be realised that majority of the RCTs have been done with luseogliflozin 2.5 mg/d, with data from higher dose of luseogliflozin 5 mg/d coming from only those patients not having adequate glycaemic control with luseogliflozin 2.5 mg/d, during the open labelled single arm phase of the study, and hence could not be included in the meta-analysis. Only 2 small studies directly evaluated luseogliflozin 5 mg/d as compared to placebo and the glycaemic and the non-glycaemic benefits noted appeared similar to marginally better to that of luseogliflozin 2.5 mg/d. The mean HbA1c reduction with dapagliflozin 10 mg/d, empagliflozin 25 mg/d and canagliflozin 100 mg/d noted in different meta-analysis have been −0.52 to −0.67% [29], −0.92-1.06% [30], and −0.49 to −0.77% [31] respectively.

Real world studies have documented good glycaemic and weight loss durability of luseogliflozin. Luseogliflozin monotherapy in a single arm uncontrolled study involving 279 patients documented significant reduction in HbA1c (−0.50%), fasting glucose (−16.3 mg/dL) and body weight (−2.68 kg, P < 0.001) after 52 weeks therapy as compared to baseline [32]. In another single arm uncontrolled study involving 62 patients, luseogliflozin when added to the treatment regimen of liraglutide monotherapy, resulted in an additional significant reduction in HbA1c (0.68%), fasting glucose (−32.1 mg/dL) and body weight (−2.71 kg), after 52 weeks therapy as compared to baseline [33].

Non-glycaemic benefits with luseogliflozin 2.5 mg/d noted in this meta-analysis included a mild but significant reduction in body weight (−1.61 kg), significant reduction in SBP (−4.19 mm Hg), DBP (−2.7 mm Hg), triglycerides (−12.6 mg/dl), uric acid levels (−0.48 mg/dl) and liver enzyme ALT (−4.11 IU/L), highlighting the beneficial impact of luseogliflozin in different aspects of metabolic syndrome like hypertension, dyslipidemia, hyperuricemia and fatty liver disease. In an uncontrolled study, 24 weeks luseogliflozin therapy in 37 patients documented a significant reduction in total body fat [−1.97 kg (95% CI: 2.66 to −1.28)], with a non-significant minor change in skeletal muscle mass index and no change in bone mineral content, highlighting a favourable impact on body composition parameters [34]. Epicardial fat volume (EFV) has been established as a reliable predictor of cardiovascular events. Significant reduction in EPV (assessed using magnetic resonance imaging) was noted with 12 weeks therapy of luseogliflozin in 19 patients with T2DM [35].

These non-glycaemic benefits have now been largely determined to be class effects and has already been documented with dapagliflozin, empagliflozin and canagliflozin [29–31]. Luseogliflozin was well tolerated with no increase in occurrence of TAEs, SAEs, hypoglycaemia, genital infection and urinary tract infection. Limitations of this meta-analysis include the short duration of all the RCTs evaluated. All the RCTs had study duration of 3–6 months. Lack of availability of long-term cardiovascular outcome trials (CVOTs) is also a limitation with luseogliflozin, when we compare it with dapagliflozin, empagliflozin or canagliflozin. Hence longer RCTs of >52 weeks duration evaluating CVOTs are urgently warranted. However Ejiri et al. [7] has demonstrated encouraging data of significant reduction in BNP% and ePV% with luseogliflozin in people with HFpEF. Currently a clinical trial is on evaluating the impact of combining luseogliflozin 2.5 mg/d to injectable semaglutide 0.5 mg once weekly in improving hepatic outcomes in people with metabolic-dysfunction associated fatty liver disease in T2DM, the results of which are expected by 2025 [36].

To conclude, it may be said that this meta-analysis provides with reassuring data on the glycaemic efficacy and safety of luseogliflozin in managing T2DM, which appears to be similar to other popular SGLT2i like dapagliflozin, empagliflozin and canagliflozin.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2023.102742.

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