Effect of dual sodium-glucose cotransporter (SGLT)-1/2 inhibitor sotagliflozin on glycemic and nonglycemic outcomes and on hypoglycemia in type 1 diabetes. A meta-analysis of randomized trials

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RUNNING TITLE: meta-analysis of sotagliflozin in type 1 diabetes:

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KEY POINTS

QUESTION

- What is the efficacy and safety of the novel dual dual sodium glucose co-transport ½(SGLT1/2 inhibitor sotagliflozin in patients with type 1 diabetes mellitus (T1DM)?

FINDINGS

- The dual SGLT1/2 inhibitor sotagliflozin improves glycemic and nonglycemic outcomes and reduces the incidence of hypoglycemia and of severe hypoglycemia in T1DM.
- Diabetic ketoacidosis (DKA) is the main adverse event associated with sotagliflozin treatment. The risk of DKA varies depending on initial HbA1c levels and basal insulin dose reduction during treatment. An increased risk of genital tract infections and diarrhea, but not of urinary tract infections, is also associated with sotagliflozin.

MEANING

- Sotagliflozin has incremental benefit over other adjunctive therapies, including incretin analogues and SGLT2 inhibitors, seeking an indication as an adjunct therapy to insulin in T1D.
- Careful patient selection and insulin dose adjustment may help minimize the risk of DKA associated with sotagliflozin treatment

Abstract

Background. Patients with type 1 diabetes mellitus (T1DM) achieve target glycemic control in 30% of cases and are encumbered with hypoglycemia, the main factor limiting optimal glucose control and a strong predictor of adverse outcomes and death. Hence, these patients urgently need adjunctive therapies to insulin.

Purpose. To assess efficacy and safety of the first-in-class dual sodium glucose co-transport 1/2 inhibitor sotagliflozin in T1DM.

Data sources. MEDLINE, Cochrane Library, EMBASE, International meeting abstracts, international and national clinical trial registries, websites of US, European and Japanese regulatory authorities, through Jan 10th, 2019.

Study Selection: Randomized controlled trial s(RCTs) evaluating the effect of sotagliflozin vs. active comparison or placebo on glycemic and nonglycemic outcomes and on adverse events in T1DM .

Data Extraction. Three reviewers extracted data for study characteristics, outcomes of interest, and risk of bias and summarized strength of evidence using the Grading of Recommendations Assessment, Development and Evaluation approach. Main outcomes were pooled using random-effects model.

Data Synthesis. Among 739 records identified, 6 placebo-controlled RCTs (3238 participants, duration ranging 4-52 weeks) were included. Sotagliflozin reduced HbA1c (WMD:-0.34%[95%CI:-0.41,-0.27], $p<0.00001$), fasting (WMD:-16.5 mg/dL [-22.1,-10.9] and 2h-postprandial plasma glucose (WMD:-39.2 mg/dL [-50.7, -27.6], and daily total (WMD:-8.99% [-10.93, -7.05]), basal (WMD:-8.03% [-10.14, -5.93]) and bolus (WMD:-9.14%[-12.17, -6.12]) insulin dose. Sotagliflozin improved time-in-range (WMD:+9.73%[6.66, 12.81]) and other continuous glucose monitoring parameters, and reduced body

weight(WMD:-3.54% [-3.98,-3.09]), systolic BP(WMD:-3.85 mmHg[-4.76, -2.93]) and albuminuria (WMD:-14.65 mg/g [-26.72,-2.58]).

Notably, sotagliflozin reduced hypoglycaemia (WMD:-9.09 events per patient-year [-13.82, -4.36]), and severe hypoglycaemia (RR: 0.69[0.49, 0.98]) , but increased the risk of ketoacidosis (RR: 3.93[1.94, 7.96]), genital tract infections (RR: 3.12[2.14, 4.54]) diarrhea (RR: 1.50[1.08, 2.10]) and volume depletion events (RR: 2.19[1.10, 4.36]). Initial HbA1c and basal insulin dose adjustment were associated with the risk of DKA. Sotagliflozin 400 mg was more effective that the 200 mg dose for most glycemic and nonglycemic outcomes, but not for adverse events. The quality of evidence was high-to-moderate for most effect and safety outcomes, but low for major adverse cardiovascular events and all-cause death.

Limitations. The relatively short duration of RCTs prevented assessment of long-term outcomes.

Conclusions. Sotagliflozin provides substantial glycemic and nonglycemic benefits and reduces hypoglycemia in T1DM, Strategies to minimize to risk of DKA and long-term effect on hard outcomes in T1DM patients receiving sotagliflozin warrant future assessment.

KEY-WORDS: sodium glucose co-transport-1/2 (SGLT1/2) inhibitors, LX4211, diabetes treatment, SGLT1, DKA

ABBREVIATIONS

ADA: American Diabetes Association; BP: blood pressure; DKA: diabetic ketoacidosis; EASD: European Association for the Study of Diabetes; EOT: end of treatment; FPG: fasting plasma glucose; LDL: low density lipoprotein; HDL: high density lipoprotein; GTI: genital tract infection. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomized controlled trial; SGLT: sodium glucose co-transporter; T1D: type 1 diabetes mellitus; TID: daily total insulin dose; UTI: urinary tract infection; WMD: weighted mean difference

Introduction

Type 1 diabetes mellitus (T1DM) affects 1.5 million people in the U.S. alone and its prevalence is continuously rising, partly because over 10% of patients initially presumed to have type 2 diabetes (T2DM) at diagnosis subsequently show evidence of islet autoimmunity and progress to insulin dependence in the following years[1,2].

The achievement and maintenance of glycemic goals in T1DM proved both difficult and hazardous: in the T1DM Exchange clinic registry the average HbA1c was 8%, only 30% of T1D patients achieved a goal HbA1c of 7% and severe hypoglycemia occurred in up to 20% of patients per-year[3]; similarly, in the Diabetes Complications and Control Trial (DCCT), patients with T1DM with HbA1c levels within target showed a 2.9-fold increased cardiovascular mortality[4] and the T1DM patients in the intensive intervention group escalated back to an HbA1c of 8% in the post-trial years[5].

Insulin is the mainstay of T1DM treatment, but has unwanted effects, including hypoglycemia and weight gain[6]. Severe hypoglycemia in particular is the main factor limiting optimal glucose control in T1DM, is frequent, adds costs to diabetes management, and is a strong predictor of adverse vascular and nonvascular outcomes and death[7,7,8,9].

None of the adjunctive therapies approved (i.e., pramlintide) or recently proposed for T1DM [i.e., metformin, incretin analogues, sodium-glucose cotransporter (SGLT)2 inhibitors] has reduced the incidence of hypoglycemia and severe hypoglycemia, which remain the major unsolved issue in the management of these patients[10,11,12,13,14,15,16,17,18,19,20].

SGLT1 is responsible for glucose absorption in the proximal intestine and missense mutations in SGLT1 gene were associated with protection from glucose intolerance, obesity and cardiometabolic risk in population-based studies[21].

Sotagliflozin (LX4211, SAR439954) is a novel first-in-class dual inhibitor of sodium-glucose cotransporter (SGLT)1 and of SGLT2 (SGLT1/2 inhibitor): while SGLT2 inhibition reduces renal tubule glucose reabsorption, SGLT1 inhibition decreases intestinal glucose absorption. This peculiar dual

mechanism of action may offer incremental benefits over selective SGLT2 inhibitors[22] by blunting postprandial glycemic excursions and glycemic variability, lowering the need for bolus insulin correction doses, and eventually reducing hypoglycemic risk[23].

Furthermore, reduced glucose absorption in the proximal intestine increases glucose delivery to the distal intestine, stimulating incretin glucagon-like peptide 1 (GLP-1)[24]. In preclinical models, the increased incretin release enhanced weight loss and counteracted glucagon-induced ketogenesis[25], which may reduce the risk of diabetic ketoacidosis (DKA)[23,24,25].

Sotagliflozin has recently reached phase 3 development in T1D[26, 27,28, 29, 30,31] but RCTs evaluating this drug have not been systematically reviewed. To clarify the evidence base of this novel approach, we conducted a meta-analysis of randomized controlled trials (RCTs) evaluating the efficacy and safety of sotagliflozin in adults with T1D.

METHODS

Data Sources and Searches

We searched English and non-English language publications up to January 10th 2019 on the following databases and international and national clinical trial registries: Ovid MEDLINE, Ovid MEDLINE Epub Ahead of Print, Ovid MEDLINE In-Process, EMBASE, Cochrane Database of Systematic Reviews, Epistemonikos, ClinicalTrials.gov, Cochrane CENTRAL Register of Controlled Trials;, World Health Organization International Clinical Trials Registry Platform, European Union (EU) Clinical Trials Register, International Standard Randomised Controlled Trial Number (ISRCTN) registry, Australian New Zealand Clinical Trials Registry, and 19 national clinical trial registries (the full list of clinical trial registries is provided in **Supplementary text**). No language restrictions were applied. We also searched the US Food and Drug Administration[32], European Medicines Agency[33] and Japanese Pharmaceutical and Medical Devices Agency[34] sites and drug manifacturers' websites[35,36] for relevant documents, and the American Diabetes Association (ADA) and /European Association for the Study of Diabetes (EASD) meeting abstracts, which were subjected to the same assessment as regular articles.

We also contacted by e-mail authors of relevant papers to verify results and methodological quality of retrieved articles and drug manifacturers to inquire about further published and unpublished trials. Additionally, we manually scanned reference lists from trials, review articles and reports to identify any other relevant data.

Search terms: sodium glucose co-transport 1/2 inhibitors, dual sodium-glucose transport inhibitors, SGLT1/2 inhibitors, SGLT1 inhibitors, SGLT2 inhibitors, SGLT1/2 inhibitor, sotagliflozin, LX4211, LP802034, SAR439954, Zynquista, management, therapy, treatment, trial, diabetes, type 1 diabetes (examples of online strategy run are provided in **supplementary text**).

Study Selection

Inclusion criteria: English and non-English (French, Spanish, Portuguese, German, Chinese, Japanese, Korean) articles reporting RCTs with participants aged>18 yrs, of any sex or ethnic origin, comparing sotagliflozin with placebo or active comparators as adjunct therapy to insulin in T1DM.

Exclusion criteria were: non-human studies, non-randomized trials, letters/case reports, articles not reporting outcomes of interest or primary data (editorials, reviews).

Outcome measures

We grouped evaluated outcomes into three broad sets: glycemic efficacy outcomes, non-glycemic outcomes, and safety outcomes.

Glycemic efficacy outcomes were:

-hemoglobin A1c (HbA1c) changes from baseline (primary outcome)

-changes in fasting plasma glucose (FPG) levels.

-changes in 2-hour postprandial glycemia (2h-PPG) as measured during an Oral Glucose Tolerance Test (OGTT) or a standardized Mixed Meal Tolerance Test (MTT), as numerous studies link postprandial glucose excursions to the risk of cardiovascular disease (CVD) and report that targeting PPG rather than FPG lowers cardiovascular risk[37,38].

-changes in total, basal, and bolus insulin dose, expressed as % initial insulin dose

-urinary glucose excretion: we also assessed the effect of SGLT-1/2 inhibitors on daily urinary glucose excretion.

-continuous glucose monitoring (CGM) parameters: CGM monitoring provides additional information to HbA1c and has been recently recommended for all adult patients with T1D and approved by the Food and Drug Administration (FDA) Advisory Committee[39] We therefore assessed the following CGM metrics (described in **supplementary text**): time-in-range (%), average daily glucose, standard deviation (SD) around average daily glucose, mean amplitude of glucose excursion (MAGE)[40].

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Non-glycemic outcomes

Non-glycemic outcome measures evaluated were: changes in body weight, systolic and diastolic blood pressure (BP); renal outcomes, defined as changes in estimated glomerular filtration rate (eGFR) and in albuminuria (expressed as urinary albumin/creatinine ratio, ACR), or need for renal replacement therapy; and changes in plasma lipids [triglyceride, low density (LDL)- and high density m(HDL)-cholesterol].

Safety outcomes

Safety measures, were severe hypoglycaemia and any hypoglycaemia, diabetic ketoacidosis (DKA) (definitions provided in **supplementary text**), urinary tract infections (UTIs), genital tract infections (GTIs), other infections; gastrointestinal symptoms, major adverse cardiovascular events (MACE) (cardiovascular death, myocardial infarction, stroke, hospitalization due to heart failure or unstable angina, or coronary revascularization), cancer (overall and type-specific); amputation; bone fracture, volume depletion, renal events, acidosis-related events, drug-induced liver injury, venous thromboembolism, serious adverse events (AEs), AEs leading to treatment discontinuation, all-cause mortality.

Volume depletion, acidosis-related events, renal events and serious AEs were defined according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred items version 14.0[41](**supplementary text**).

For DKA, we planned to investigate whether the risk of DKA varied across different modes of insulin delivery, i.e. multiple daily injections (MDI) or continuous subcutaneous infusion (CSI).

All measures of dispersion were converted to standard deviations (SDs).

Data extraction and Risk-of-Bias assessment. Two reviewers (GM, RG) extracted data independently and in duplicate by using a predesigned data collection form, based on the Cochrane Handbook for Systematic Reviews of Intervention; discrepancies were arbitrated by a third reviewer and resolved by consensus. The agreement between the 2 reviewers for selection and validity assessment of trials was scored by Kappa coefficient.

The quality of RCTs was assessed by the Cochrane Collaboration Risk-of-Bias Tool[42]. We also assessed sponsorship bias, which we included in the Risk-of-Bias tool. The 2018 Agency for Healthcare Research and Quality (AHRQ) recommendations caution against equating industry sponsorship with high risk of bias and automatically downgrading the evidence for industry sponsorship[43]. Therefore, for all included trials we systematically assessed a pre-specified list of eight items in trial designing, conducting and reporting , which have been empirically linked to the risk of biased outcomes in industry-funded trials and are not captured by the six domains of the RoB tool[44,45,46,47,48,49,50] (**supplementary Table 1).**

Data Synthesis, Analysis and Grading of Evidence. The analysis was carried out in concordance with the Cochrane Handbook of Systematic Reviews of Interventions[42] using Stata, release 11.2 (StataCorp, College Station, Texas) and RevMan Version 5.3.5(Nordic Cochrane Center, Copenhagen, Denmark[51] and was reported according to PRISMA guidelines[52](see **supplementary Appendix)**. Treatments were evaluated on an intention-to-treat principle.

We calculated weighted mean differences (WMDs) and 95% CIs for continuous outcomes using an inverse variance random-effects model. For dichotomous outcomes, we calculated Risk Ratios (RRs) and 95% CIs by using the random-effects Mantel–Haenszel approach with significance set at P=0.05. We

conservatively used *a priori* a random-effects model assuming a susbtantial variability in treatment effect size across studies.

Statistical heterogeneity was assessed using the I^2 statistic: with I^2 values ≥50%, we planned to explore individual study characteristics and those of subgroups of the main body of evidence[53].

We planned to conduct sensitivity analyses by repeating the analysis with alternative effect measures (odds ratio vs. relative risk), pooling methods (Peto vs. Mantel-Hanszel[54]), statistical models (fixed vs. random effects), by excluding RCTs where we imputed values and RCTs at high risk of bias in any domains of the RoB tool.

We also planned *a priori* subgroup analysis to explore potential effects on outcome measures of the following conditions: treatment duration (≤12 vs. > 12 weeks), initial HbA1c levels (≥8% vs. < 8%), duration of diabetes (< 20 yr vs. ≥ 20 yr), background therapy (pre-treatment insulin optimization vs. stable insulin therapy), presence and severity of renal dysfunction.

We explored interactions between different sotagliflozin doses and all outcomes primarily by comparing high dose to low dose arms within head-to-head trials (within-trial approach); we planned to verify robustness of this approach in ruling out dose-response relationship by using also across-trial comparison and meta-regression. Although the "across-trial" approach has a higher risk of ecological bias, it has a higher power that the within-trial approach, thus allowing ruling out dose-response interactions with higher confidence[55].

When ≥8 comparisons were available, the effect of different doses of SGLT1/2 inhibitor, of baseline HbA1c, of treatment duration and of diabetes duration on each outcome were assessed by meta-regression analysis (random effects model, within-study variance estimated with the unrestricted maximum-likelihood method).

The dose variable in the regression equation was treated categorically, with the starting dose coded as the baseline amount and each doubling of a drug dose was a single increment increase.

Publication bias was examined using funnel plots and the Egger test.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the strength of evidence at outcome level and determine confidence in summary estimates for clinically relevant comparisons and outcomes[56,57]. Three reviewers graded inconsistency, risk of bias, indirectness, imprecision, and publication bias for evidence related to the following areas: glycemic efficacy (outcomes: HbA1c, FPG, 2h-PPG, time-in-range), nonglycemic efficacy (outcomes: body weight, sys BP, eGFR, albuminuria), and adverse events (outcomes: hypoglycemia, severe hypoglycemia, DKA, urinary and genital tract infections, diarrhea, MACE, serious AEs, AEs leading to discontinuation, mortality).

Management of missing data.

We planned to manage missing data by contacting via e-mail the corresponding authors. Where this was unsuccessful, we planned to follow the approach described in Cochrane Handbook of Systematic Reviews of Intervention (chapter 7.6-7.8 and 16.1.3)[42] (see **supplementary text**).

Role of the Funding Source

This study received no funding.

The protocol of the meta-analysis was submitted as a module assignement fo the Systematic Review module and internally peer-reviewed at HUMANITAS University Gradenigo Hospital Insitutional Review Board and is available at our Institution at request.

Patient involvement

No patients were involved in definition of the research question or the outcome measures, and interpretation or writing up of results. Data relating to the impact of the intervention on participants' quality of life were not extracted. Where possible, results of this meta-analysis will be disseminated to the patient community or individual patients and families through the investigators of this meta-analysis.

RESULTS

The flow of study selection is reported in **Figure 1**. At the end of selection, 6 placebo-controlled RCTs (duration ranging 4-52 weeks) enrolling 3238 T1DM participants were included in the meta-analysis[26,27,28,29,30,31,58,59](main characteristics reported in **supplementary Table 1**).

Twelve phase 1 RCTs conducted in nondiabetic individuals, 18 RCTs enrolling T2DM patients (4 completed, 14 active) and 1 RCT enrolling nondiabetic patients with congestive heart failure were excluded (main characteristics of excluded RCTs reported in **supplementary Table 2).**

All included RCTs compared sotagliflozin with placebo on background insulin treatment. Three RCTs[28,30,31] compared different sotagliflozin doses (75 mg, 200 mg or 400 mg) with placebo Overall, ten comparison were available for the meta-analysis.

Two RCTs adopted insulin dose optimization (target: FPG 80-130 mg/dL and 2hr-PPG>180 mg/dL) during the 6 weeks preceding randomization[30,31].

Two RCTs excluded patients with impaired renal function (eGFR<60 ml/min/1.73m2)[26,28], four RCTs excluded patients with moderate-to-severe (eGFR<45 ml/min/1.73m2) renal impairment[27,29,30,31].

Participants' baseline characteristics were equally balanced between the study arms and in all RCTs dropout rates were generally low and balanced across arms. No trial used the last-observation-carried-forward (LOCF) approach to impute missing observations, which were imputed as nonresponse for dichotomous outcomes; for continuous outcomes, mixed-effects model for repeated measures (MMRM) statistics based on the restricted maximum likelihood method for estimation was used.

Two RCTs were clearly funded by non-profit organizations[26,27], while a pharmaceutical company funded four RCTs: however, we did not find any evidence of high risk of biased outcomes in trial designing, conducting and reporting.

The overall quality was good for all included RCTs. The risk of bias summary for individual RCTs and the risk of bias graph for each item across included RCTs are detailed in **supplementary Table 1** and summarized in **supplementary Figure 1-2.**

The analysis of Funnel plots and the Egger test (p>0.67 for all outcomes) did not find any evidence of publication bias **(supplementary Figure 3 panel A-S).**

No values had to be imputed for the meta-analysis during data extraction.

The agreement between the 2 reviewers for study selection was 0.96 and for quality assessment of trials was 0.89.

Glycemic efficacy outcomes

HbA1c

Compared with placebo, sotagliflozin treatment was associated with a significant reduction in HbA1c levels (WMD -0.34%, 95%CI: -0.41 to -0.27%, p<0.00001, I^2=20%, N-comparisons=10, 3238 participants)(**Figure 2 panel A**). There was little heterogeneity in the meta-analysis, suggesting a consistent drug effect.

Subgroup and meta-regression analysis revealed the effect was independent of trial duration (β=0.110; p=0.28) and baseline HbA1c (β=0.119; p=0.384) (**Supplementary Table 3**).

HbA1c reduction with sotagliflozin 400 mg/d was higher than with 200 mg/d (**Supplementary Table 4**).

Fasting plasma glucose (FPG) and 2h-postprandial plasma glucose (2h-PPG)

Sotagliflozin significantly reduced FPG (WMD -16.98 mg/dL, 95%CI: -22.09 to -11.86 mg/dL, p<0.00001, I^2=6%, N-comparisons=10, 3238 participants) and 2h-PPG (WMD -39.24 mg/dL, 95%CI: -50.42 to -28.06 mg/dL, p<0.00001, I^2=20%, N-comparisons=9, 539 participants) (**Figure 2 panel B-C**).

There was little heterogeneity in the meta-analysis, suggesting a consistent drug effect. The effect was independent of trial duration and baseline HbA1c (**Supplementary Table 3**)..

Continuous Glucose Monitoring (CGM) parameters

Four RCTs evaluated CGM-derived parameters[26,27,30,31].

Compared with placebo, sotagliflozin significantly increased time-in-range (WMD +9.73%, 95%CI: 6.66 to 12.81%, p<0.00001, I^2=24%, N-comparisons=6, 398 participants) and reduced average daily glucose (WMD -15.09 mg/dL, 95%CI: -21.40 to -8.79 mg/dL, p<0.00001, I^2=28%, N-comparisons=5, 312 participants), SD around average daily glucose (WMD -6.68 mg/dL, 95%CI: -10.59 to -2.77 mg/dL, p=0.0008, I^2=0%, N-comparisons=5, 311 participants) and mean amplitude of glucose excursion (MAGE) (WMD -19.52 mg/dL, 95%CI: -28.91 to -10.54 mg/dL, p<0.0001, I^2=0%, N-comparisons=5, 311 participants) (**supplementary Figure 4 panel A-D**).

There was little heterogeneity in the meta-analysis, suggesting a consistent drug effect.

Sotagliflozin 400 mg/d was significantly more effective than 200 mg/d dose at improving time-in-range, average daily glucose and MAGE (**Supplementary Table 4**).

Daily Total, Basal and Bolus Insulin Dose

Compared with placebo, sotagliflozin reduced daily total (WMD -8.99%, 95%CI: -10.93 to -7.05%, p<0.00001, I^2=33%, N-comparisons=10, 3238 participants), basal (WMD -8.03%, 95%CI: -10.14 to -5.93%, p<0.00001, I^2=0%, N-comparisons=10, 3238 participants) and bolus (WMD -9.14%, 95%CI: -12.17 to -6.12%, p<0.00001, I^2=67%, N-comparisons=10, 3238 participants) insulin dose in T1DM patients (**supplementary Figure 5 panel A-C**).

Heterogeneity for bolus insulin dose was high, and was accounted for by significant subgroup differences between high-dose (400 mg/d) and low-dose (200 mg/d) sotagliflozin (**supplementary Table 4**).

Urinary glucose excretion

Pooled data from two RCTs[26,28] indicated daily UGE progressively increased with increasing sotagliflozin dose from 75 mg/d to 200 mg/d, but then UGE reached a plateau around 60 g/24 hr with either 200 mg/d and 400 mg/d sotagliflozin **(supplementary Figure 6; supplementary Table 4)**

Non-glycemic outcomes

Body weight

Compared with controls, sotagliflozin induced a significant weight reduction (WMD -3.54%, 95%CI : -3.98 to -3.09%, p<0.00001, I^2=18%, N comparisons=10, 3238 participants) (**Figure 3 panel A**).

On meta-regression analysis, weight change (%) correlated with the magnitude of total insulin dose reduction from baseline (β=0.213; p=0.001).

Blood pressure (BP)

Compared to placebo, sotagliflozin use was associated with a reduction in systolic BP (WMD -3.85 mmHg, 95%CI: -4.76 to -2.93, p<0.00001, I^2=0%) and in diastolic BP (WMD -1.43 mmHg, 95%CI: -1.98 to -0.89, p<0.00001, I_2=0%, N comparisons=10, 3238 participants) (**Figure 3 panel B-C**).

These effects were not associated with an increased incidence of ortostatic hypotension (not shown).

Renal effects: eGFR and urinary ACR

Compared with placebo, sotagliflozin treatment was associated with a slight reduction in eGFR as (WMD: -0.80, 95% CI: -1.42 to -0.18 ml/min/1.73 m^2, p=0.01, I^2=0%, N comparisons=10, 3238 participants)(**Figure 4 panel A**).

Urinary ACR was evaluated in 3 phase 3 RCTs (2977 participants, trial duration ranging 24-52 weeks, mean baseline ACR of participants of 52.6, 31.6, 54.3 mg/g, respectively [29,30,31]). Pooled analysis of these RCTs showed sotagliflozin was associated with a decrease in ACR (WMD: -14.65, 95% CI : -2.58 to -26.72 mg/g, p=0.02, I_2=0%, N comparisons=5 **(Figure 4 panel A-B).** Subgroup analysis revealed eGFR reduction with sotagliflozin occurred only in RCTs lasting ≤ 12 weeks, but not in RCTs of longer duration (**Supplementary Table 4**).

To gain further insight into the effect of time on renal function, we examined the effect of sotagliflozin on eGFR in the 2 RCTs of longest duration (52 weeks) during the initial 24 weeks and during the following 28 weeks. While sotagliflozin continued to reduce ACR throughout the treatment period, the difference in eGFR between sotagliflozin and placebo varied during follow-up: during the initial 24 weeks patients

receiving sotagliflozin experienced a decline in eGFR , while in the following 28 weeks sotagliflozin significantly slowed the eGFR decline as compared with placebo (**supplementary Figure 7 panel A-B**).

Plasma lipids

No RCT reported the effect of active treatment or placebo on LDL-C, HDL-C and triglyceride

Safety outcomes

Hypoglycemia and severe hypoglycaemia

The definition of hypoglycemia and severe hypoglycemia was consistent across all RCTs (see online Appendix). Compared with placebo, sotagliflozin treatment was associated with a lower rate of hypoglycemia events (WMD: -9.09 events per patient-year, 95% CI: -13.82 to -4.36 events per patient-year, p=0.0002, I_2=0%, N comparisons=10, 3238 participants) and with a 31% lower risk of severe hypoglycaemia (RR 0.69, 95%CI: 0.49-0.98, p=0.04; N comparisons=10, I^2=0%) (**Figure 5 panel A-B**).

Diabetic ketoacidosis (DKA)

Compared with placebo, sotagliflozin was associated with an increased risk of DKA (RR 3.93, 95%CI: 1.94-7.96, p=0.0001; N comparisons=10, I^2=0%, 3238 participants, trial duration ranging 4-52 weeks)**(Figure 5 panel C).** Forty-six (69 %) of all cases of DKA occurred at blood glucose>250 mg/dL, while the remaining 21 cases(31%) occurred with blood glucose values ranging 150-250 mg/dL (**supplementary Table 5**).

The risk for DKA was increased for patients on multiple daily injections (MDI) (RR 3.22, 95%CI: 1.24-9.09, p=0.01; N comparisons=10, I^2=0%, 2072 patients) as well as for patients on continuous subcutaneous infusion(CSI) (RR 6.40, 95%CI: 2.82-15.64, p<0.0001; N comparisons=10, I^2=0%, 1166 patients).

Subgroup analyses revealed the risk of DKA varied according to initial HbA1c of included RCTs: the risk of DKA was increased in RCTs with a mean initial HbA1c<8% (RR 6.62, 95%CI: 2.04-21.48), I^2=0%, p=0.002, N=3, 1608 participants), but not in RCTs with a mean HbA1c≥8% (RR 2.21, 95%CI: 0.43-11.42, I^2=0%, p=0.34, N =3, 1630 participants) (**supplementary Table 4**).

In a meta-regression model including sotagliflozin dose, trial duration, initial HbA1c, initial FPG, changes in HbA1c and FPG, total bolus and basal insulin doses (baseline, changes and end-of-treatment doses) fasting and postprandial glycemia, body weight changes, volume depletion events, the risk of DKA correlated inversely with initial HbA1c (ß=-0.331; p=0.009) and with the magnitude of basal insulin dose reduction (ß=-0.218; p=0.012) **(supplementary Figure 8).**

Urinary tract infections (UTIs) and genital tract infections (GTI)

Compared with placebo, sotagliflozin did not affect the risk of UTIs (RR 0.97, 95% CI: 0.71-1.33, p=0.84; N comparisons=10, I^2=0%, 3238 participants) but was associated with an increased risk of mycotic GTIs (RR 3.12, 95% CI: 2.14-4.54, p<0.00001; N comparisons=10, I^2=0%) (**Figure 6 panel A-B).**

In a meta-regression model, the risk of GTI was not related to sotagliflozin dose, urinary glucose excretion, initial HbA1c, initial FPG, changes in HbA1c and FPG (all p-values>0.5).

Gastrointestinal events

Compared with control, sotagliflozin was associated with an increased risk of diarrhea (RR 1.50, 95%CI: 1.08-2.10, p=0.02; N comparisons=10, I^2=0%, 3238 participants) (**Figure 6 panel D**), but not of other gastrointestinal symptoms(**supplementary Table 5).**

Other adverse events

Compared with control, sotagliflozin treatment was associated with an increased risk of acidosis-related AEs (RR: 3.85, 95%CI: 2.33-6.36, p<0.00001; N comparisons=10, I^2_2=0%) and of volume depletion

events (RR: 2.19, 95%CI: 1.10-4.36, p=0.03; N comparisons=10, I^2=0%) **(Figure 6 panel D; supplementary Table 5).** Subgroup analysis revealed the risk of volume depletion events was increased in the first 12 weeks of treatment, but then subsided (**supplementary Table 3**).

The most common AEs leading to treatment discontinuation were DKA (35.8 % of all patients experiencing DKA discontinued treatment), diarrhea (treatment discontinuation in 6.9% of patients), genital tract infections (treatment discontinuation in 6.3 % of patients), severe hypoglycaemia (treatment discontinuation in 5.6 % of patients), UTIs (treatment discontinuation in 4.4 % of patients) and volume depletion events ((treatment discontinuation in 4.3 % of patients).

Sotagliflozin did not affect the risk of MACE (RR 1.06, 95% CI: 0.40-2.82, p=0.91; N comparisons=10, I^2=6%), cancer (RR 0.86, 95% CI: 0.25-2.97, p=0.81; N comparisons=9, I^2=0%) or all-cause death (RR 0.35, 95% CI: 0.07-1.71, p=0.19; N comparisons=9, I^2=0%) (**supplementary Table 5, supplementary Figure 9 panel B**),

The effect of sotagliflozin on other AEs is summarized in **supplementary Table 4.**

Dose-response analysis

Three RCTs evaluated the effects of sotagliflozin 400 mg and 200 mg and one RCT assessed also the 75 mg dose-effect. The analysis of dose-response interactions within these 3 RCTs found that the 200 mg dose had a greater glycosuric effect than the 75 mg dose (UGE), but this effect did not increased further with the 400 mg dose.

Sotagliflozin 400 mg/d was associated with a greater improvement than sotagliflozin 200 mg/d in the following outcomes HbA1c, FPG, 2h-PPG, time-in-range, average daily glucose, daily total basal and bolus insulin dose, body weight, systolic BP, eGFR and ACR (**supplementary Table 5**). We didn't find any relationship between different sotagliflozin doses and adverse events. The results of the within-trial comparison were all confirmed by the across-trial approach.

Sensitivity analyses

Sensitivity analysis conducted using alternative pooling methods, including Peto's Odds Ratio (OR), which has a greater power at event rates below 1%[54], confirmed the results of the main analysis (**supplementary Table X**)

Grading of Evidence

Quality of evidence was downgraded to moderate for effect on time-in-range glucose as it was unclear whether the population undergoing CGM substudies was representative of the whole study population, and to low for MACE and all-cause mortality for imprecision (**Table 1-2**).

DISCUSSION

The main findings of our analysis are the following:

1. in T1DM patients, sotagliflozin as add-on therapy to insulin ameliorated glycemic efficacy outcomes and showed also nonglycemic benefits, including body weight, blood pressure and nephropathy marker reduction.
2. sotagliflozin treatment was associated with a significant reduction in the incidence of hypoglycaemia and severe hypoglycemia
3. DKA was the most serious and frequent adverse event associated with sotagliflozin treatment, which also increased the risk of GTIs, diarrhea, and volume depletion events, but not of UTIs.
4. The risk of DKA varied depending on initial HbA1c levels and basal insulin dose reduction.

T1DM patients achieve glycemic goals in 30% of cases, experience severe hypoglycemia in up to 20% of cases per year and are overweight in 40% of cases[3], hence urgently needing adjunctive therapeutic strategies to complement glucose-lowering effects of insulin and mitigate its unwanted effects. Hypoglycemia, which results from the total dependence of T1D patients on injected insulin therapy, is of particular concern and can be viewed at the basis of highest unmet need in this population[9,10], as it is the main factor limiting optimal glucose control; furthermore, severe hypoglycemia is a strong predictor

of adverse clinical outcomes and death in diabetic patients[7,8-18,60]. None of the drugs recently approved for T2DM and seeking an indication for T1DM, including incretin analogues and SGLT2 inhibitors, reduced hypoglycemic risk, which is either unaffected or increased by these therapies[22,66,61]. Several mechanisms may underlie the observed hypoglycemic risk reduction observed with sotagliflozin. The dual intestinal SGLT1 and renal SGLT2 inhibition blunts acute glucose fluctuations and reduces glycemic variability (**supplementary Figure 4C-D**), thereby limiting the need for bolus insulin correction doses and the attendant hypoglycemic risk (**supplementary Figure 5C**)[15,16,62]. The reduction in the rate of hypoglycemic events may have *per se* contributed to reduce severe hypoglycaemia: the recurrence of hypoglycemic episodes blunts autonomic and hormonal responses to subsequent hypoglycemia, impairs hypoglycemia awareness and glucose counterregulation and paves the way to severe hypoglycemia. This functional impairment in counterregolatory mechanisms is distinct from autonomic neuropathy, occurs in the short-term and can be rapidly reversed by reducing hypoglycemia recurrence[63].

The analysis of pooled results from phase 3 RCTs disclosed also potential renoprotection for sotagliflozin, which reduced microalbuminuria, a marker of early diabetic nephropathy and an independent cardiovascular risk factor[19]**(Figure 4 panel B) .** The transient eGFR decline observed in the initial 12 weeks of treatment is similar to that observed with other SGLT2 inhibitors[64] and is consistent with renoprotective mechanisms of SGLT2 inhibition, which enhance afferent arteriolar tone, reduce intraglomerular pressure and relieve glomerular hyperfiltration and barrier damage[65]. However, in patients receiving sotagliflozin the reduced glomerular perfusion may be aggravated by volume depletion favoured by concomitant osmotic glycosuria (due to renal SGLT2 inhibition) and diarrhea (induced by intestinal SGLT1 inhibition) (**Figure 6 panel D**). Hence it is important to avoid volume depletion in the early months of treatment with sotagliflozin..

Differently from SGLT2 inhibitors, sotagliflozin did not increase the risk of UTIs **(Figure 6 panel A**): the lower glycosuric effects of sotagliflozin as compared with SGLT2 inhibitors[66] may have limited the incidence of UTIs, while SGLT1-mediated intestinal glucose malabsorption may have increased diarrhea, usually mild, self-limiting and not inducing treatment discontinuation.

Further supporting the relevance of intestinal SGLT1 inhibition, a dose-response gradient for most glycemic outcomes was observed with increasing sotagliflozin dosage, not paralleled by an increase in glycosuria, which reached a plateau at 60 g/day, 40-50% lower than that reported with full-dose SGLT2 inhibitors[67,68](**supplementary Figure 6).** Whether sotagliflozin maintains unaltered glucose-lowering efficacy in the presence of moderate-to-severe renal failure will be assessed by ongoing trials in T2DM **(supplementary Table 2)**

DKA was the most common relevant adverse event, observed in 61 out of 1912 (3.1%) of sotagliflozin-treated patients and inducing treatment discontinuation in 38% of cases (**supplementary Table 5**). While SGLT2 inhibitor-associated DKA has been reported to occur often at uncharacteristically normal or mildly elevated (<250 mg/dL) blood glucose levels (euglycemic DKA)[69], over two thirds of cases of sotagliflozin-related DKA occurred at high blood glucose levels(**supplementary Table 5**). Notably, our data indicate a lower initial HbA1c and a greater basal insulin dose reduction during sotagliflozin treatment increase the risk for DKA (**supplementary Figure 8; supplementary Table 3**), possibly because patients with less deteriorated baseline glycemic control experienced a more rapid insulin dose down-titration with sotagliflozin. The extent of basal insulin down-titration seems central for DKA development by allowing unrestricted fasting-induced lipolysis and ketogenesis on a background of negative glucose balance[69]. Consistently, insulin dose reduction >20% has been found to increase ketone levels and diminish the glucose-lowering effect of SGLT2 inhibitors[70].

Clinical and policy implications

In conclusion, sotagliflozin for up to 52 weeks provided consistent glycemic and nonglycemic benefits in T1DM, including the reduction of unwanted effects of insulin therapy, i.e., weight gain and hypoglycemia. These effects make sotagliflozin an attractive adjunctine therapy to insulin in T1DM patients, which achieve target glycemic goals in 30% of cases, are overweight in 40 % of cases and experience severe hypoglycemia at a rate of up to 20% of patients per-year[3]. The clinical impact of these benefits may be more appreciable in patients at higher risk of severe hypoglycemia, like those with

recurrent hypoglycemia and hypoglycemia unawareness, who represent 17-36% of the general T1DM population[71].

Our analysis may also help minimize the risk of DKA in T1DM treated with sotagliflozin by appropriate patient selection and by defining appropriate protocols for basal insulin dose adjustment. Ketone testing should be performed after each basal insulin dose reduction, rather than relying solely on overt triggering conditions or symptoms of DKA[28,29,30,31], which often fail to recognize early DKA[72]. Future research should define safer protocols for basal insulin dose adjustment: as an example, in a recent phase 3 RCT with dapagliflozin reporting no increased risk of DKA, participants were instructed to reduce insulin doses by no more than 20% on treatment initiation, to measure ketonemia whenever glucose readings were consistently elevated , and then subsequently to up-titrate insulin doses back to baseline following positive ketone testing[73].

Strengths and limitations

Strengths and limitations of our analysis derive from the characteristics of included evidence: strengths include the thorough assessment of efficacy and safety outcomes, the direct impact of extracted evidence regarding relevant clinical outcomes, like hypoglycemia and DKA, on decision-making in T1DM management. Limitations are the relatively small number and short duration of included trials, not exceeding 52 weeks, which prevented robust assessment of long-term hard outcomes, like MACE and overall mortality. Furthermore, although all included RCTs had good methodological quality, 66% of them were industry-funded, which makes them liable to sponsorship bias[45]. Recent guidelines recommend against automatically downgrading industry-funded trials and we therefore address this issue by verifying a list of items empirically linked by recent literature to biased outcomes in industry-funded trials[43]

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. Giovanni Musso takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data sharing statement:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Role of each author:

Giovanni Musso: data collection and elaboration, statistical analysis, writing of the manuscript

Roberto Gambino: data collection and discussion, review of the manuscript, approval of manuscript

Maurizio Cassader: data collection and discussion, review of the manuscript, approval of manuscript

Elena Paschetta: data collection and discussion, writing of the manuscript, approval of manuscript

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Table 1. Quality of evidence for clinically relevant glycemic and nonglycemic effect outcomes: Summary of Findings Table according to the GRADE approach

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with sotagliflozin				
Sotagliflozin compared to placebo for type 1 diabetes: glycemic effect outcomes						
Mean change in HbA1c(%) follow up: range 4 weeks to 52 weeks	The mean change in HbA1c ranged from **-0.99 to +0.04** %	The mean change in HbA1c in the intervention group was 0,34 % lower (0,41 lower to 0,27 lower)	-	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	Large effect. Dose-response gradient across the 200-400 mg doses
Mean change in fasting plasma glucose (FPG)(mg/dL) follow up: range 4 weeks to 52 weeks	The mean change in FPG ranged from **-11 to +39** mg/dL	The mean change in FPG in the intervention group was 16,98 mg/dL lower (22,09 lower to 11,86 lower)	-	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	Large effect Dose-response gradient across the 200-400 mg doses
Mean change in 2hr-postprandial plasma glucose (2h-PPG)(mg/dL) follow up: range 4 weeks to 52 weeks	The mean change in 2h-PPG ranged from **-18.5 to +0** mg/dL	The mean change in 2h-PPG in the intervention group was 39,24 mg/dL lower (50,42 lower to 28,06 lower)	-	539 (5 RCTs)	⨁⨁⨁⨁ HIGH	Large effect. Dose-response gradient across the 200-400 mg doses
Mean change in % time-in-range (70-180 mg/dL) follow up: range 4 weeks to 52 weeks	The mean mean change in % time-in-range ranged from **-1.83 to -0.2** %	The mean change in % time-in-range in the intervention group was 9,73 % higher (6,66 higher to 12,81 higher)	-	398 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	Large effect. Dose-response gradient across the 200-400 mg doses
Sotagliflozin compared to placebo for type 1 diabetes: non-glycemic effect outcomes						
Mean change in body weight (%) follow up: range 4 weeks to 52 weeks	The mean change in body weight ranged from **-0.99 to +0.04** %	The mean change in body weight in the intervention group was 3,54 % lower (3,98 lower to 3,09 lower)	-	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	Dose-response gradient across the 200-400 mg doses
Mean change in systolic blood pressure (BP)(mmHg) follow up: range 4 weeks to 52 weeks	The mean change in systolic BP ranged from **-3.8 to 1.7** mmHg	The mean change in systolic blood pressure (BP) in the intervention group was 3,85 mmHg lower (4,76 lower to 2,93 lower)	-	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	Dose-response gradient across the 200-400 mg doses
Mean change in eGFR (ml/min/1.73 m^2) follow up: range 4 weeks to 52 weeks	The mean mean change in eGFR ranged from **-1.09 to 0.34** ml/min/1.73 m^2	The mean mean change in eGFR in the intervention group was 0,8 ml/min/1.73 m2 lower (1,42 lower to 0,18 lower)	-	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	Dose-response gradient across the 200-400 mg doses

Mean change in urinary albumin/creatinine ratio (ACR)(mg/g) follow up: range 24 weeks to 52 weeks	The mean mean change in urinary ACR ranged from **4.1 to 14.9** mg/g	The mean change in urinary ACR in the intervention group was 14,57 mg/g lower (26,87 lower to 2,28 lower)	-	2977 (3 RCTs)	⨁⨁⨁⨁ HIGH	Dose-response gradient across the 200-400 mg doses

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

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 likely to be 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 likely to be substantially different from the estimate of effect

Explanations

a. unclear if the population undergoing Continuous Glucose Monitoring substudies was representativ of the whole trial population in the inTandem1 and inTandel2 trials

Table 2. Quality of evidence for clinically relevant adverse events (AEs): Summary of Findings Table according to the GRADE approach

Sotagliflozin compared to placebo for type 1 diabetes: adverse events (AEs)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with sotagliflozin				
Mean change in hypoglycemia events(events per patient-year) follow up: range 4 weeks to 52 weeks	The mean change in hypoglycemia events ranged from **69 to 179** events/patient-year	The mean change in hypoglycemia events in the intervention group was 9,09 events/patient-year lower (13,82 lower to 4,36 lower)	-	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	
Incidence of severe hypoglycemia follow up: range 4 weeks to 52 weeks	43 per 1.000	**30 per 1.000** (21 to 42)	**RR 0.69** (0.49 to 0.98)	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	
Incidence of diabetic ketoacidosis (DKA) follow up: range 4 weeks to 52 weeks	5 per 1.000	**18 per 1.000** (9 to 36)	**RR 3.93** (1.94 to 7.96)	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	Large effect
Incidence of urinary tract infections(UTIs) follow up: range 4 weeks to 52 weeks	48 per 1.000	**46 per 1.000** (34 to 63)	**RR 0.97** (0.71 to 1.33)	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	
Incidence of genital tract infections(GTIs) follow up: range 4 weeks to 52 weeks	23 per 1.000	**73 per 1.000** (50 to 106)	**RR 3.12** (2.14 to 4.54)	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	Large effect
Incidence of diarrhea follow up: range 4 weeks to 52 weeks	35 per 1.000	**52 per 1.000** (37 to 73)	**RR 1.50** (1.08 to 2.10)	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	
Incidence of AEs leading to treatment discontinuation follow up: range 4 weeks to 52 weeks	23 per 1.000	**31 per 1.000** (18 to 54)	**RR 1.34** (0.78 to 2.30)	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	
Incidence of serious AEs follow up: range 4 weeks to 52 weeks	69 per 1.000	**76 per 1.000** (58 to 99)	**RR 1.11** (0.85 to 1.44)	3238 (6 RCTs)	⨁⨁⨁⨁ HIGH	
Incidence of major adverse cardiovascular events (MACE) follow up: range 4 weeks to 52 weeks	5 per 1.000	**6 per 1.000** (2 to 15)	**RR 1.06** (0.40 to 2.82)	3238 (6 RCTs)	⨁⨁◯◯ LOW [a]	Few events, OIS not reached
All-cause mortality follow up: range 4 weeks to 52 weeks	2 per 1.000	**1 per 1.000** (0 to 4)	**RR 0.34** (0.07 to 1.70)	3238 (6 RCTs)	⨁⨁◯◯ LOW [a]	Few events, OIS not reached

Table 2. Quality of evidence for clinically relevant adverse events (AEs): Summary of Findings Table according to the GRADE approach

Sotagliflozin compared to placebo for type 1 diabetes: adverse events (AEs)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with sotagliflozin				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **OIS**: optimal information size

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 likely to be 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 likely to be substantially different from the estimate of effect

Explanations

a. downgraded for imprecision

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Figure 1: evidence acquisition flow diagram

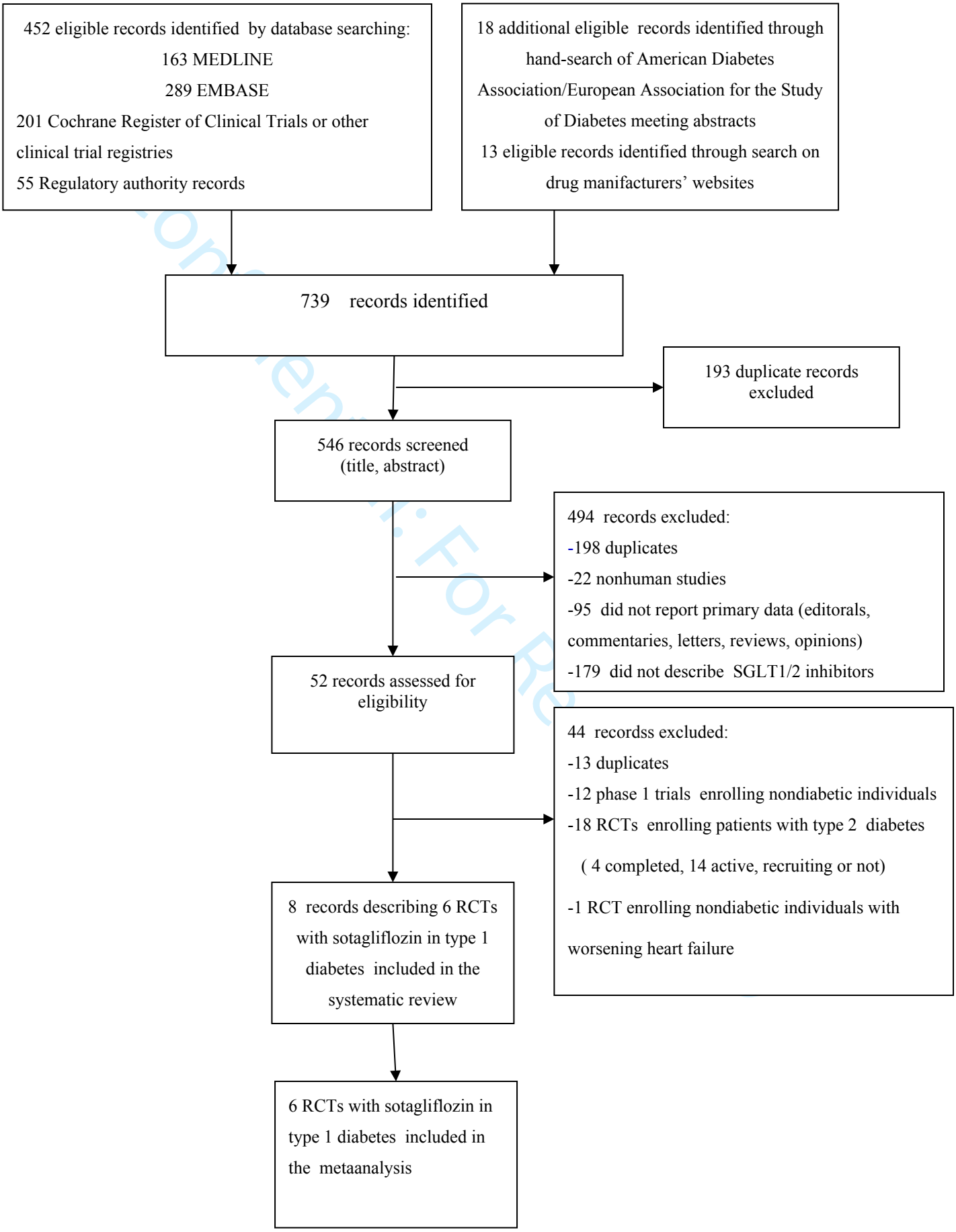
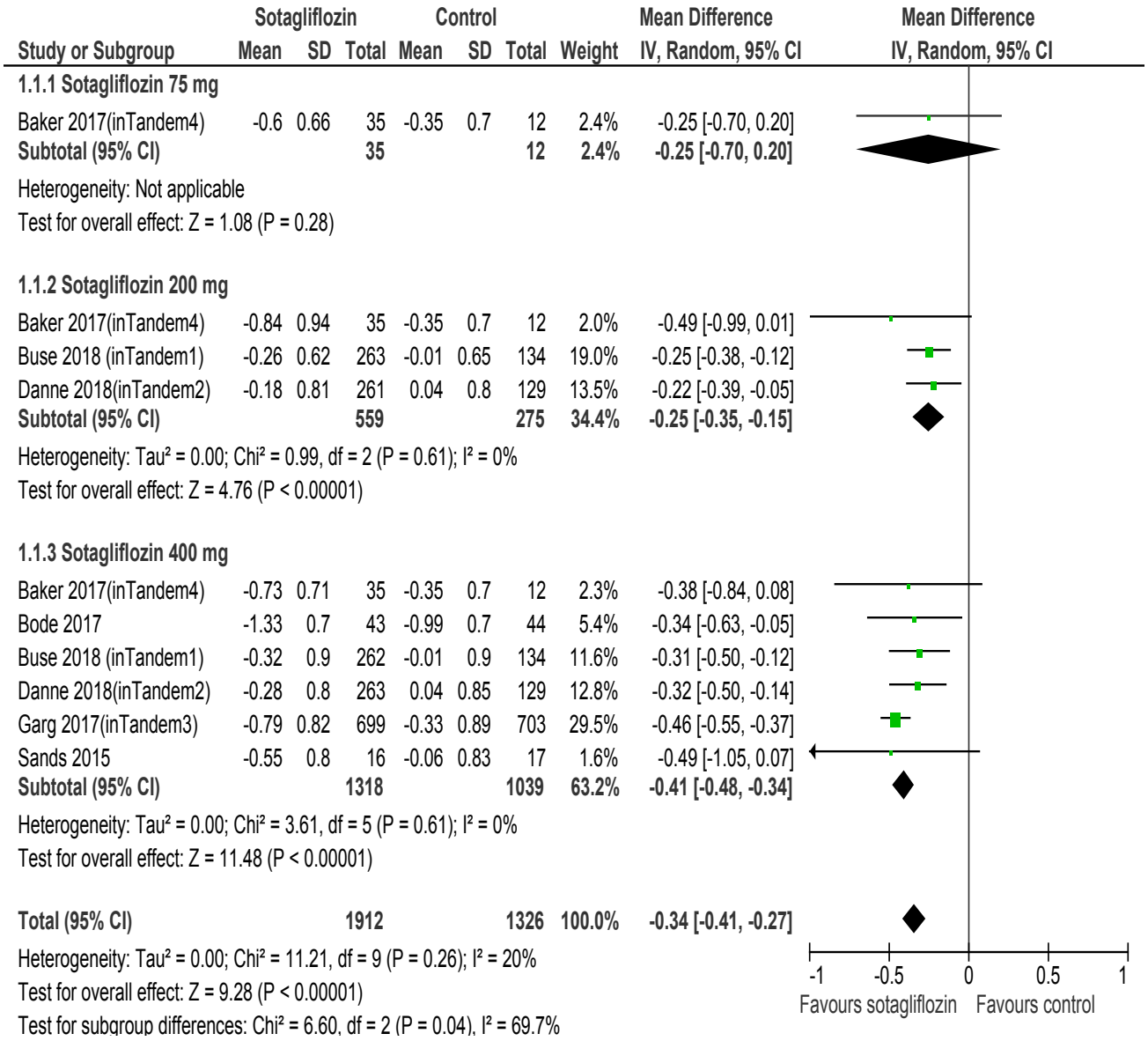
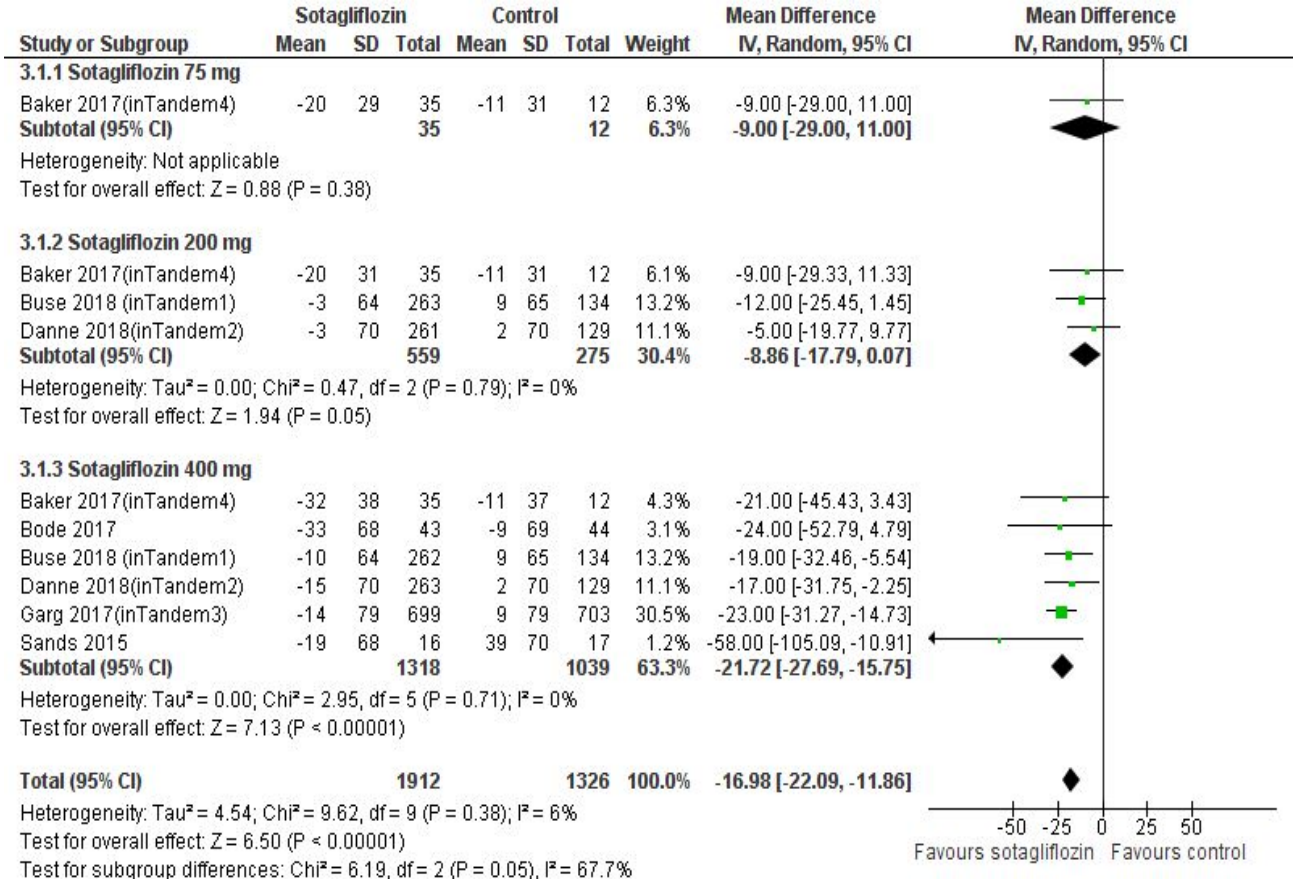


Figure 2. Forest plot of comparison: Sotagliflozin vs. placebo, outcome: HbA1c(%), Fasting Plasma Glucose (FPG) and 2 hour-Postprandial Plasma Glucose (2h-PPG).

Panel A: HbA1c(%) changes from baseline



Panel B: outcome: FPG changes from baseline (mg/dL)



Panel C: outcome: 2h-PPG changes from baseline (mg/dL)

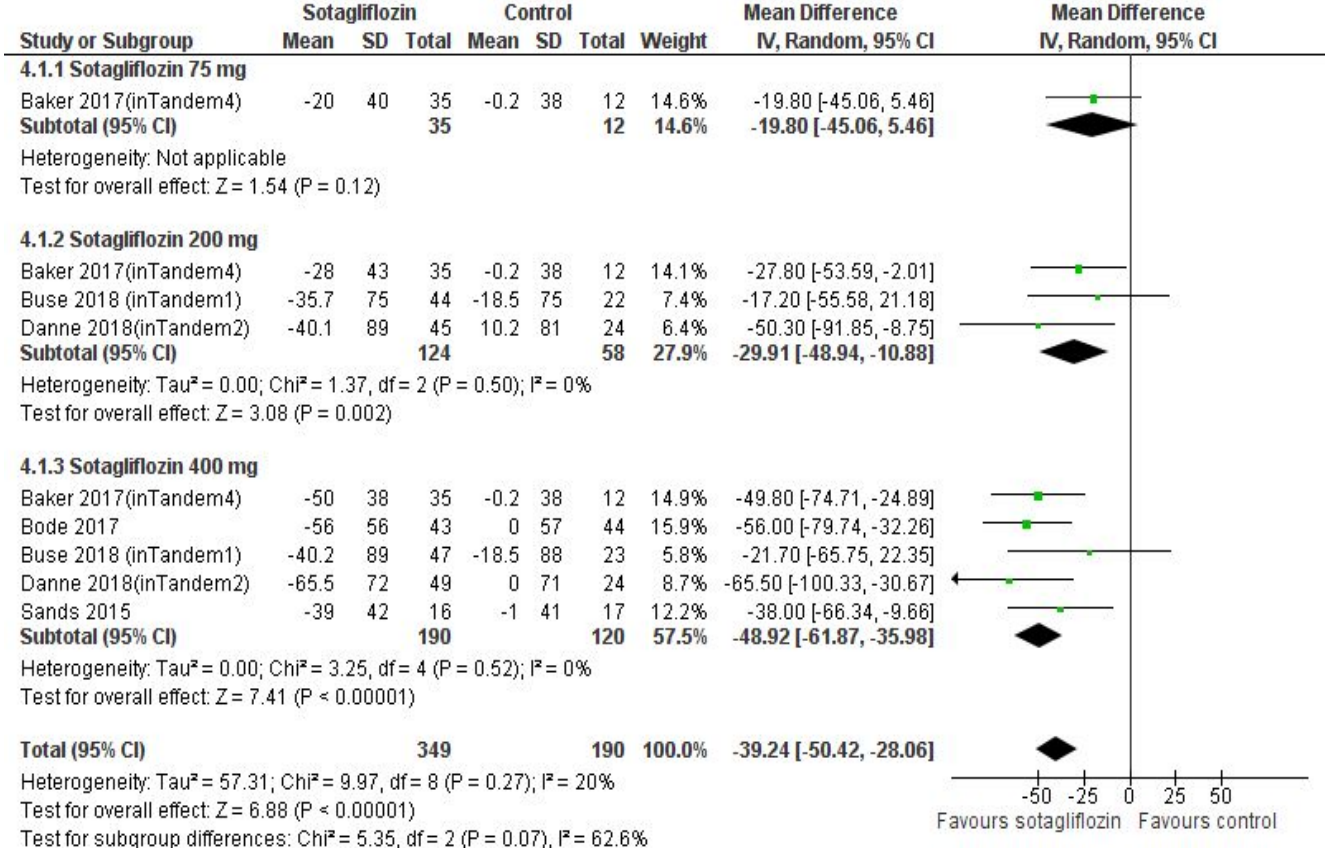
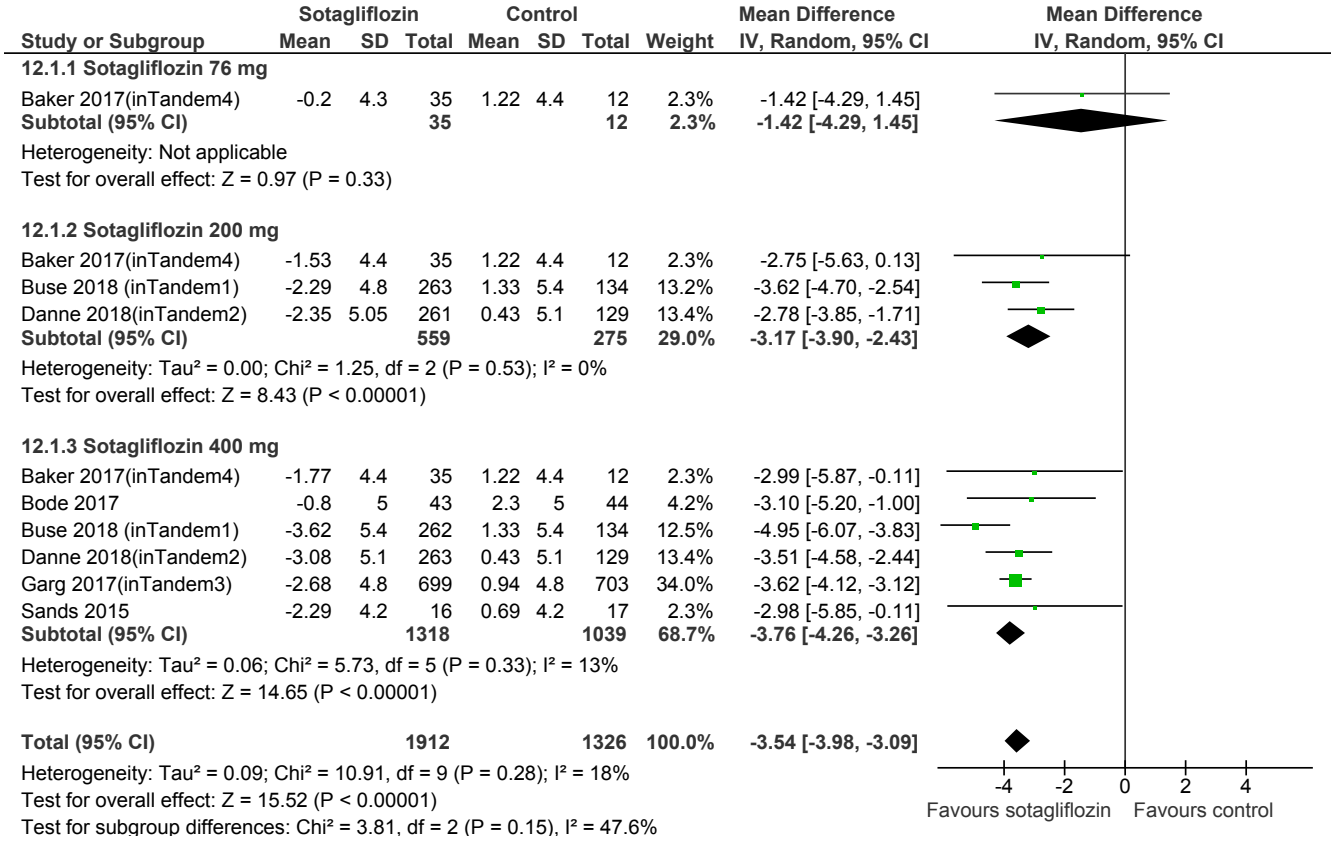
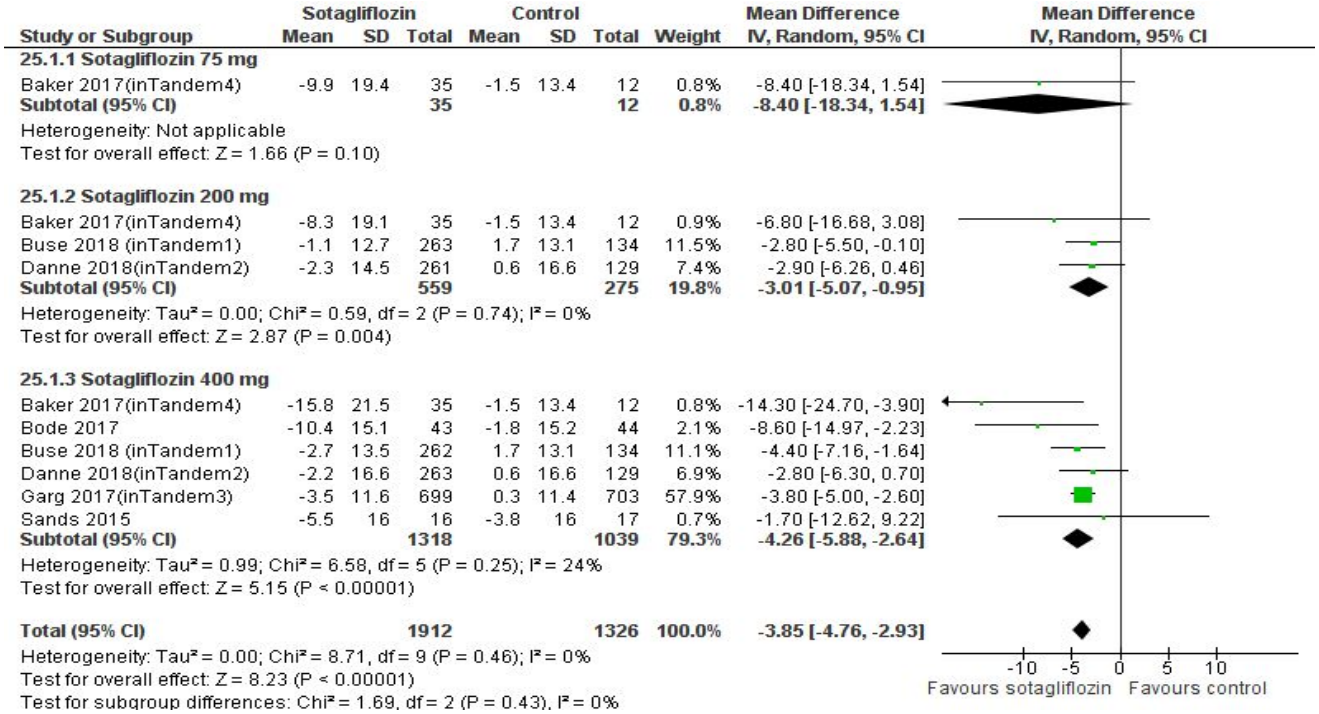


Figure 3. Forest plot of comparison: Sotagliflozin vs. placebo, outcomes: body weight, systolic BP (sysBP) and diastolic BP (diaBP).

Panel A: body weight changes from baseline (%)



Panel B: outcome: sysBP changes from baseline (mmHg)



Panel C: outcome: diaBP changes from baseline (mmHg)

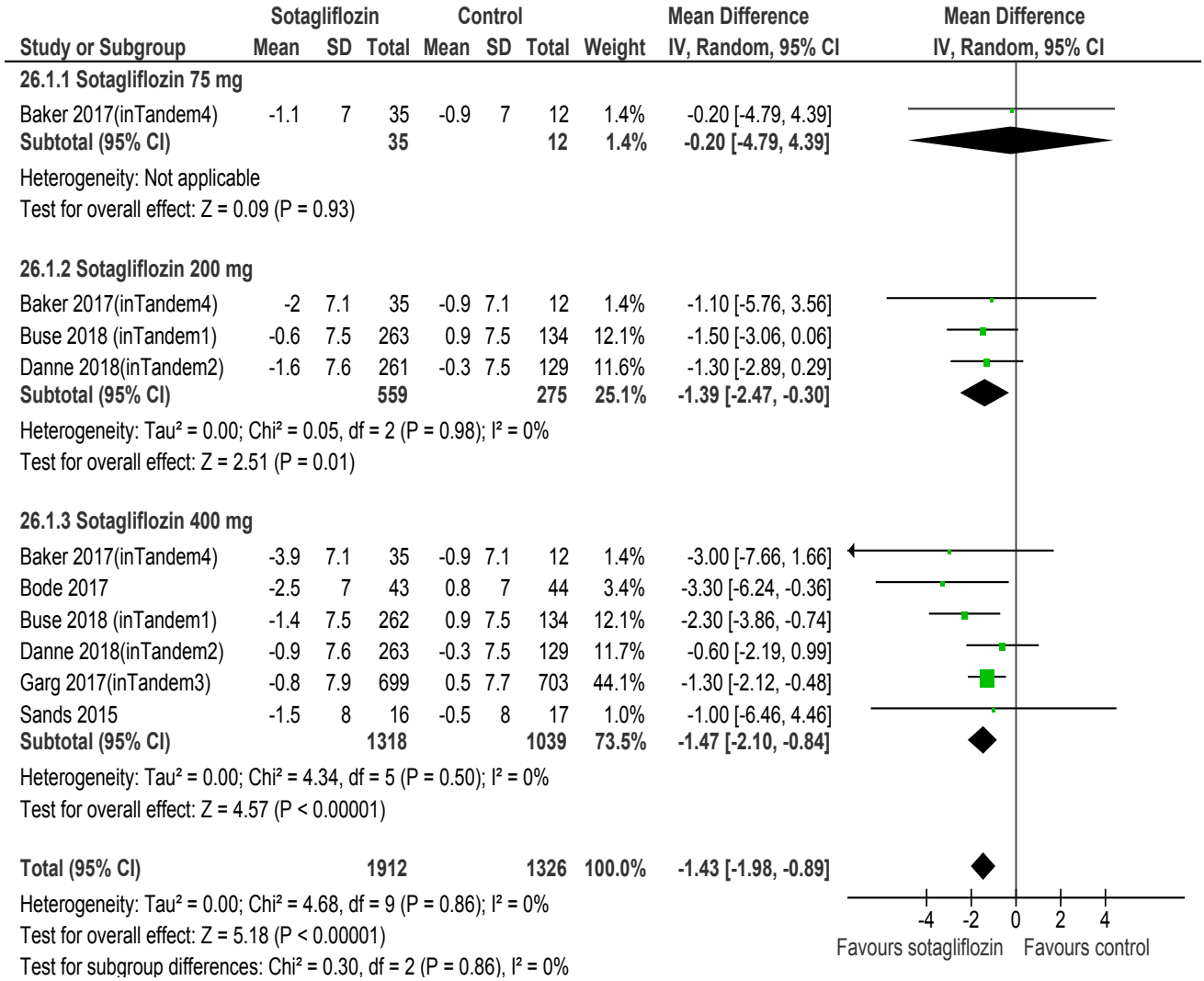
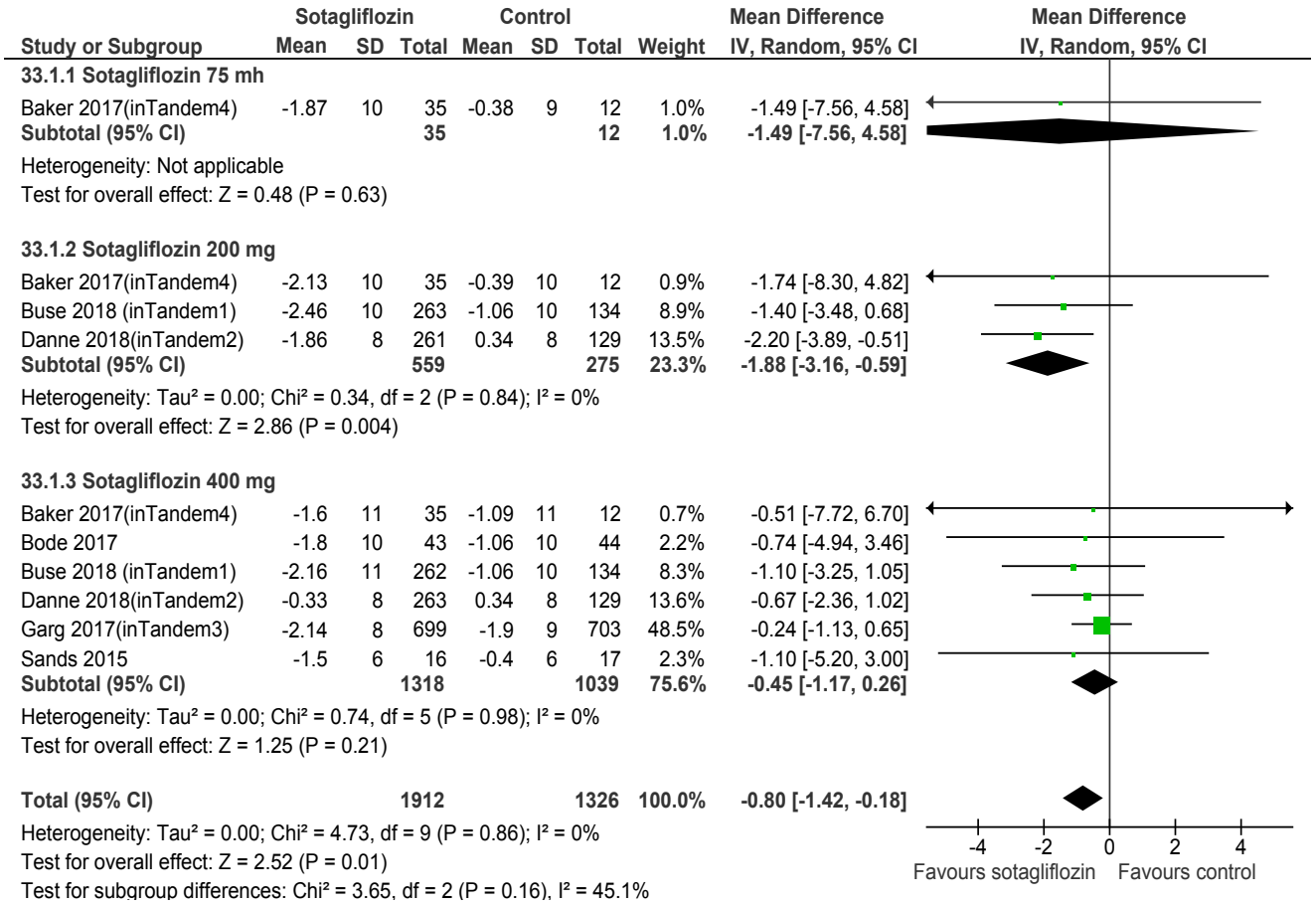


Figure 4. Forest plot of comparison: Sotagliflozin vs. placebo, outcomes: eGFR and urinary Albumin/Creatinine Ratio (ACR)

Panel A: outcome: eGFR changes from baseline (ml/min/1.73m²)



Panel B: outcome: ACR changes from baseline (mg/g)

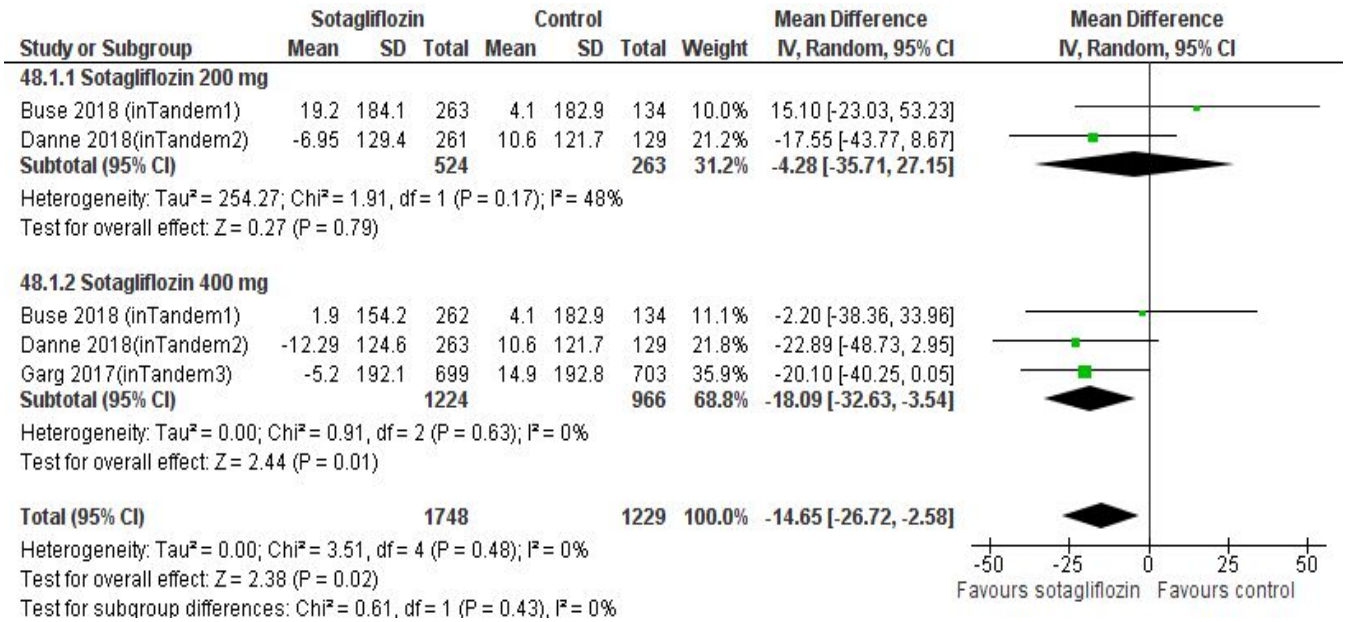
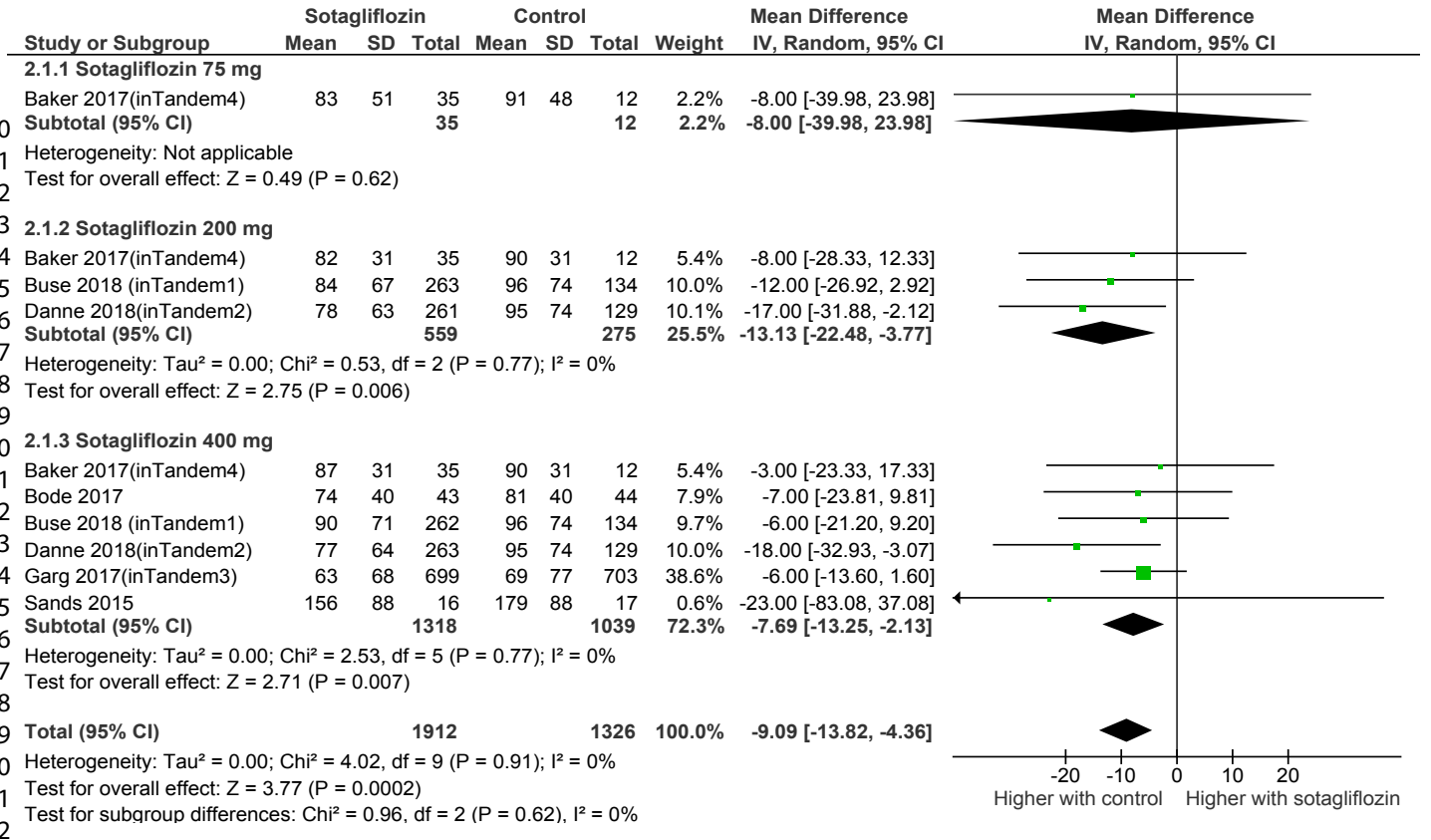
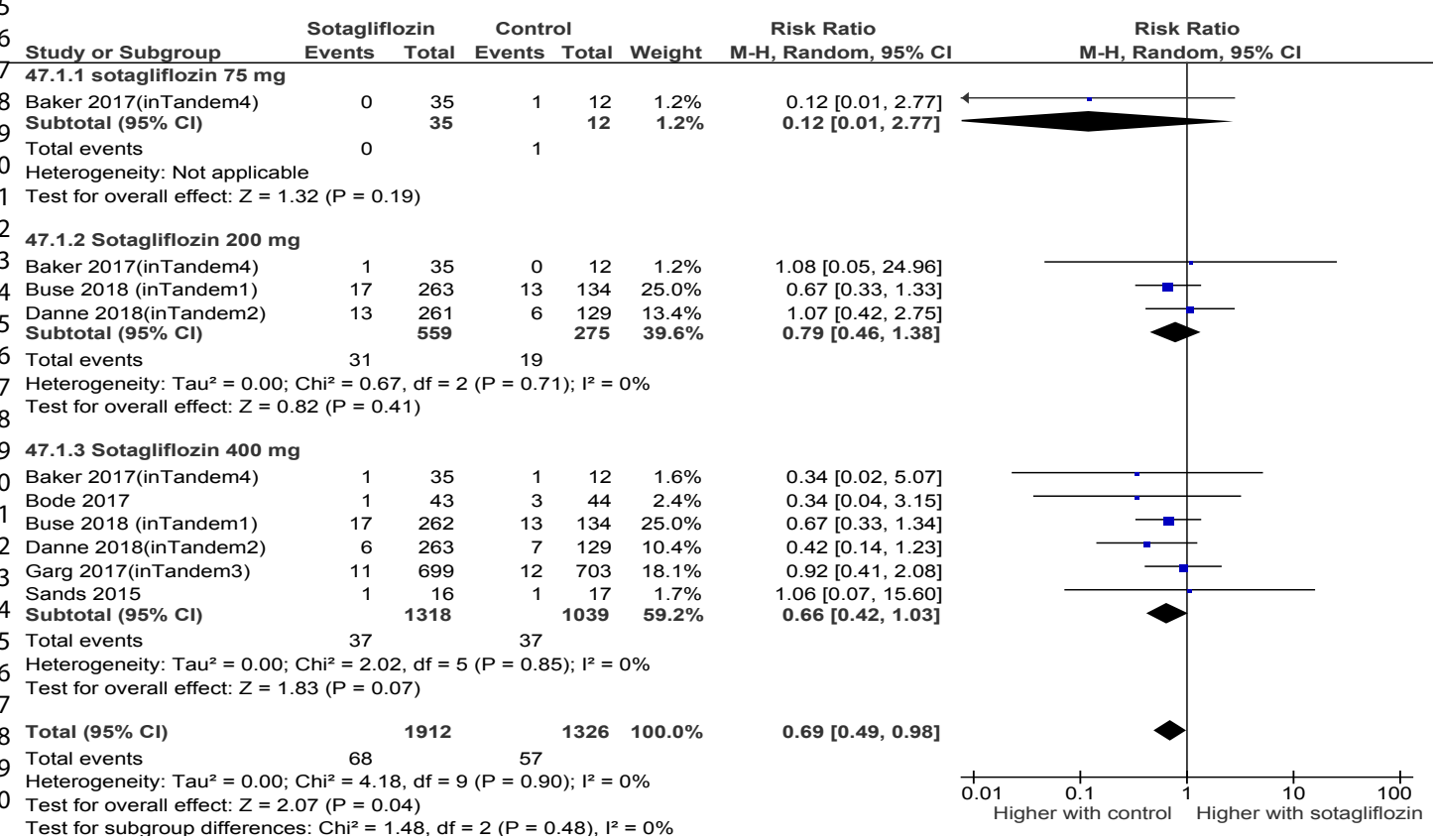


Figure 5. Forest plot of comparison: Sotagliflozin, outcomes: hypoglycemia, severe hypoglycaemia and diabetic ketoacidosis (DKA).

Panel A: outcome: hypoglycemia rate (events per patient-year)



Panel B: outcome: incident severe hypoglycemia



Panel C: outcome: incident DKA

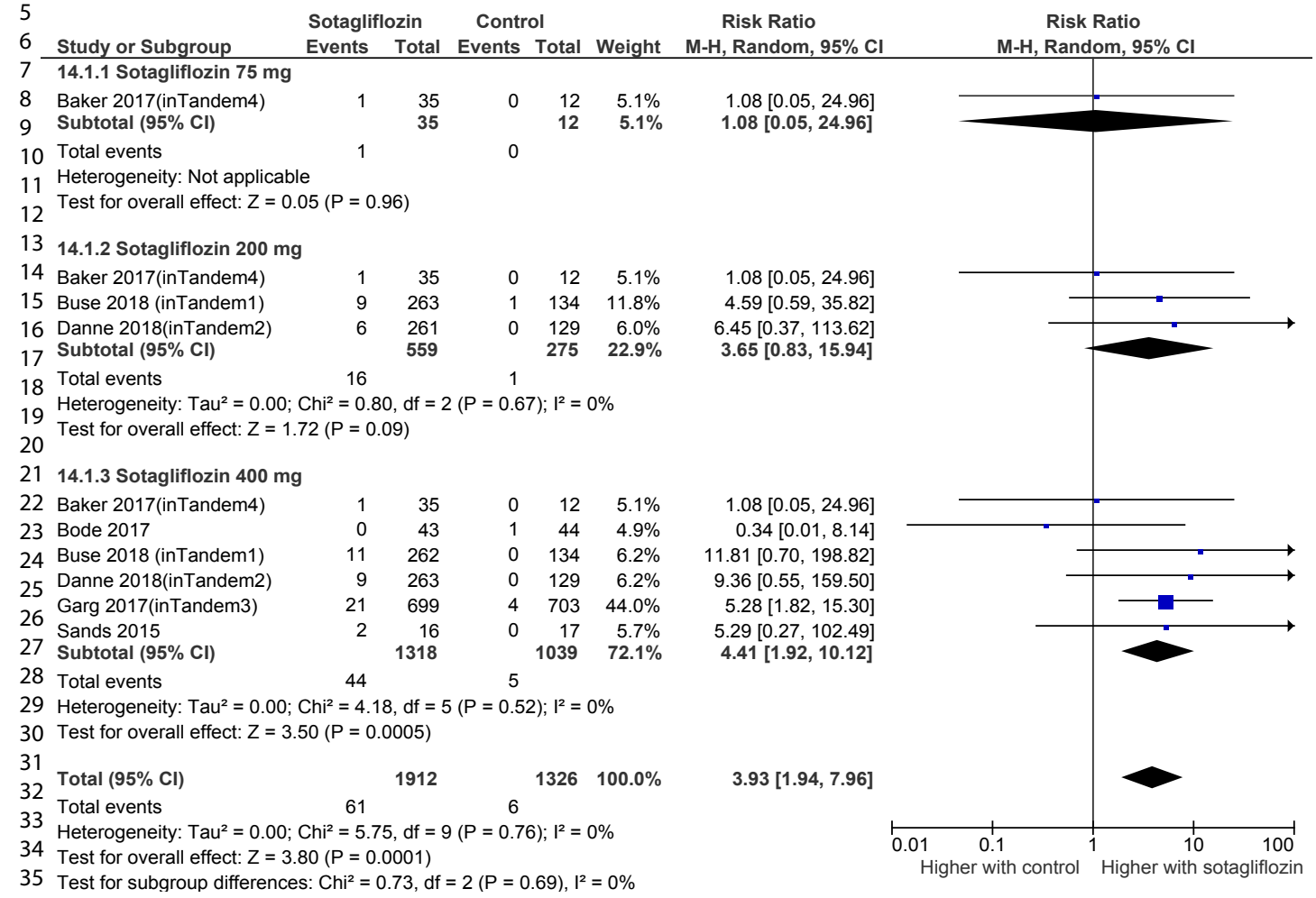
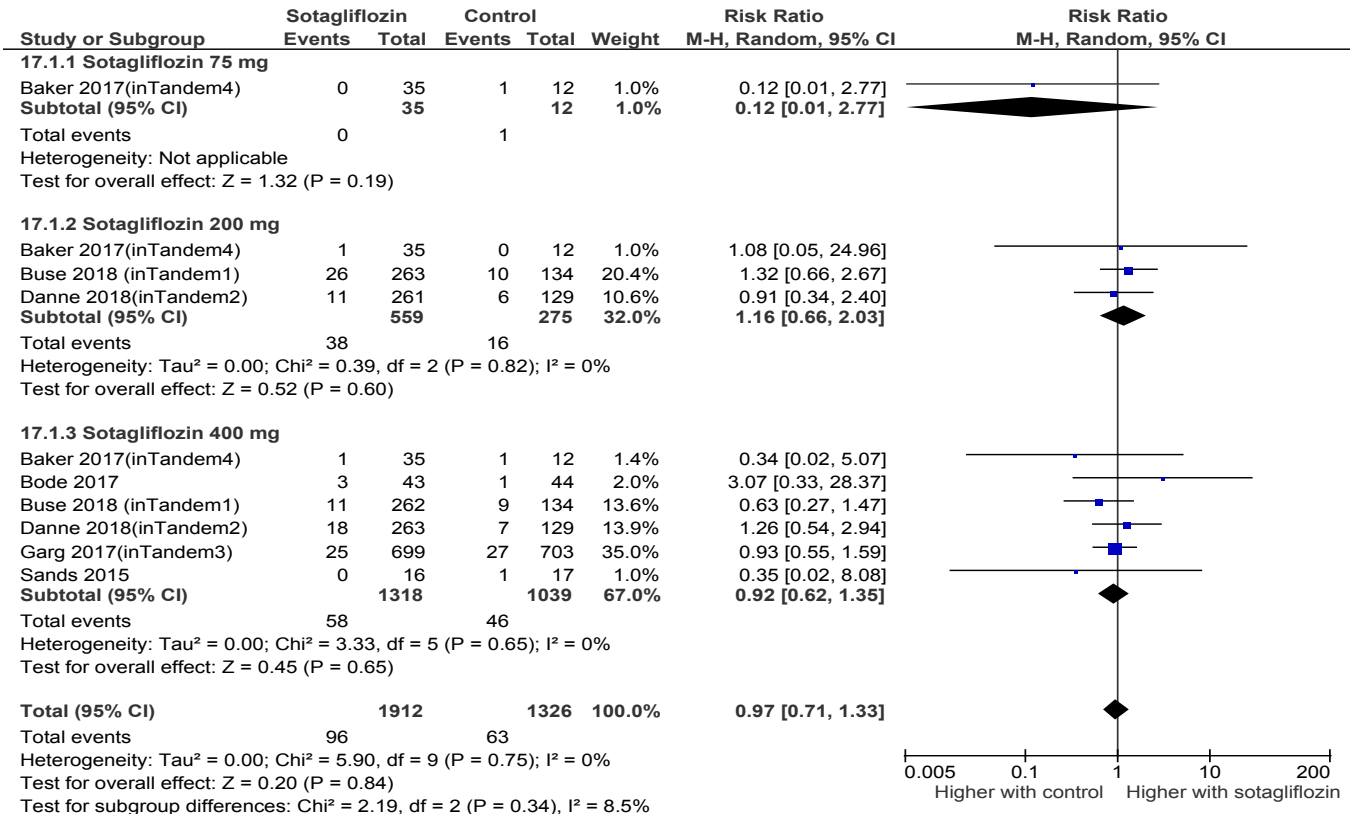
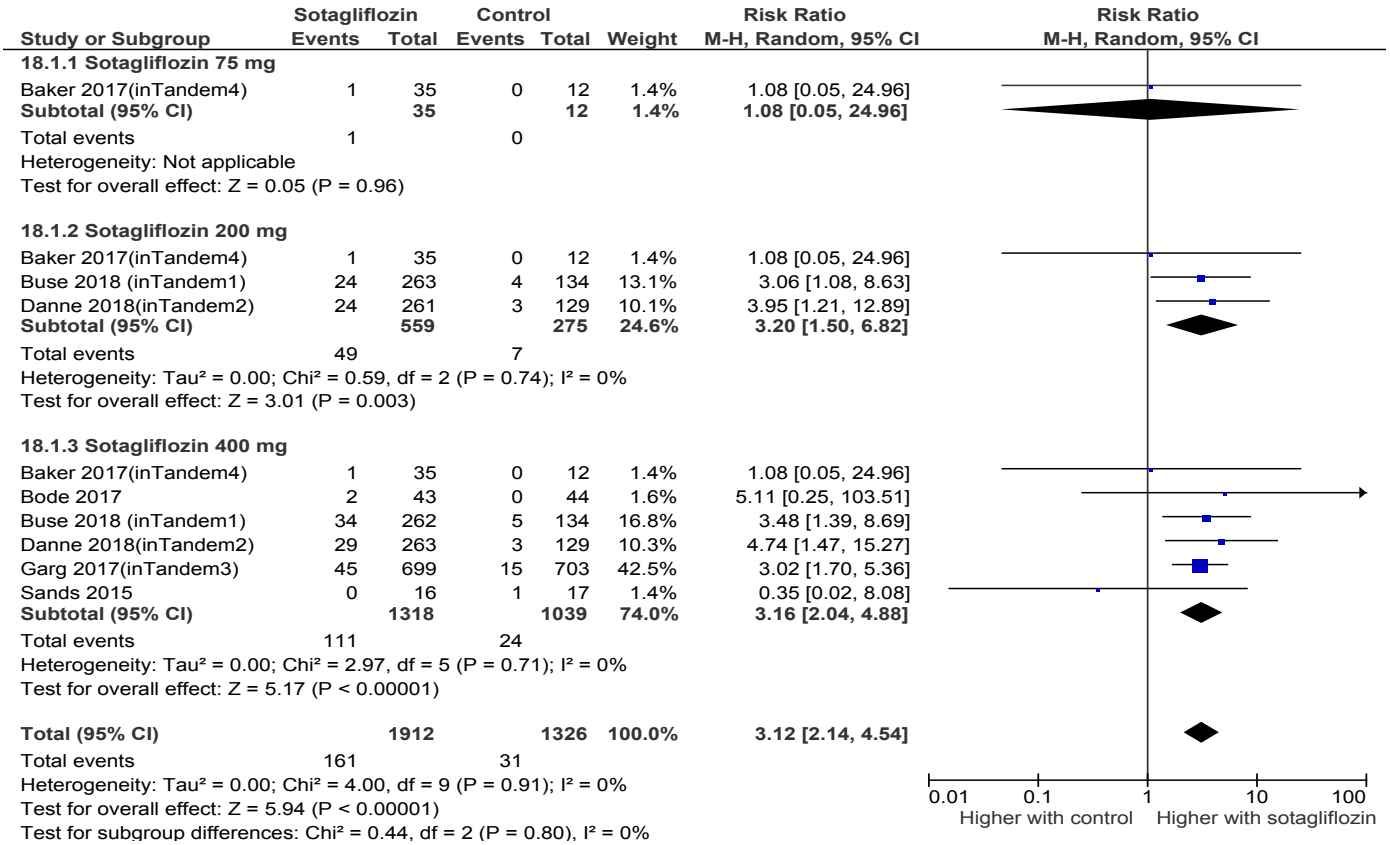


Figure 6. Forest plot of comparison: Sotagliflozin, outcome: Urinary Tract Infections (UTIs), Genital Tract Infections (GTIs), diarrhea and volume depletion events

Panel A: outcome: UTIs

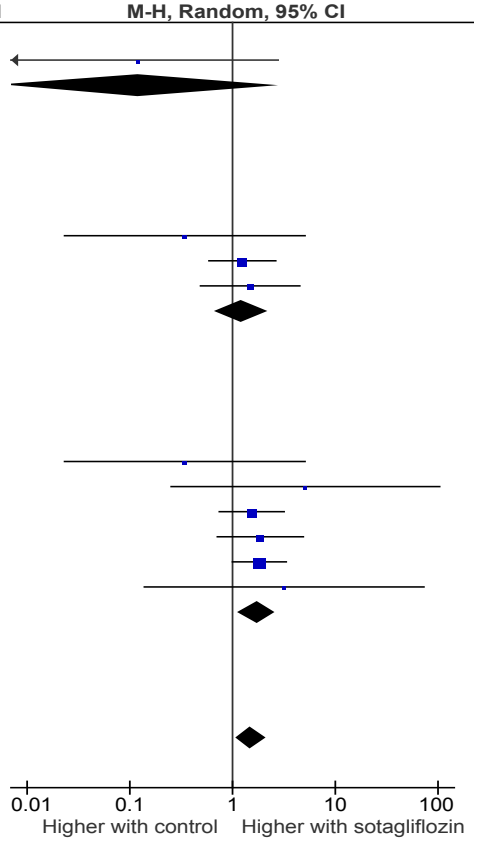


Panel B: outcome: GTIs



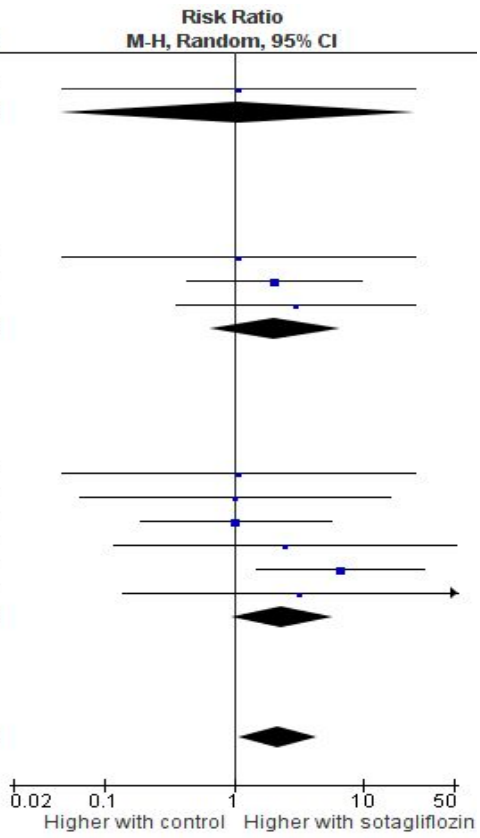
Panel C: outcome: diarrhea

Study or Subgroup	Sotagliflozin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
19.1.1 Sotagliflozin 75 mg						
Baker 2017(inTandem4)	0	35	1	12	1.1%	0.12 [0.01, 2.77]
Subtotal (95% CI)		**35**		**12**	**1.1%**	**0.12 [0.01, 2.77]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						
19.1.2 Sotagliflozin 200 mg						
Baker 2017(inTandem4)	1	35	1	12	1.5%	0.34 [0.02, 5.07]
Buse 2018 (inTandem1)	22	263	9	134	20.0%	1.25 [0.59, 2.63]
Danne 2018(inTandem2)	12	261	4	129	9.1%	1.48 [0.49, 4.51]
Subtotal (95% CI)		**559**		**275**	**30.6%**	**1.23 [0.67, 2.25]**
Total events	35		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
19.1.3 Sotagliflozin 400 mg						
Baker 2017(inTandem4)	1	35	1	12	1.5%	0.34 [0.02, 5.07]
Bode 2017	2	43	0	44	1.2%	5.11 [0.25, 103.51]
Buse 2018 (inTandem1)	27	262	9	134	21.3%	1.53 [0.74, 3.17]
Danne 2018(inTandem2)	19	263	5	129	12.1%	1.86 [0.71, 4.88]
Garg 2017(inTandem3)	29	699	16	703	30.9%	1.82 [1.00, 3.33]
Sands 2015	1	16	0	17	1.1%	3.18 [0.14, 72.75]
Subtotal (95% CI)		**1318**		**1039**	**68.2%**	**1.72 [1.15, 2.57]**
Total events	79		31			
Heterogeneity: Tau² = 0.00; Chi² = 2.19, df = 5 (P = 0.82); I² = 0%						
Test for overall effect: Z = 2.62 (P = 0.009)						
Total (95% CI)		**1912**		**1326**	**100.0%**	**1.50 [1.08, 2.10]**
Total events	114		46			
Heterogeneity: Tau² = 0.00; Chi² = 6.49, df = 9 (P = 0.69); I² = 0%						
Test for overall effect: Z = 2.39 (P = 0.02)						
Test for subgroup differences: Chi² = 3.33, df = 2 (P = 0.19), I² = 40.0%						



Panel D: outcome: volume depletion events

Study or Subgroup	Sotagliflozin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
44.1.1 Sotagliflozin 75 mg						
Baker 2017(inTandem4)	1	35	0	12	4.8%	1.08 [0.05, 24.96]
Subtotal (95% CI)		**35**		**12**	**4.8%**	**1.08 [0.05, 24.96]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
44.1.2 Sotagliflozin 200 mg						
Baker 2017(inTandem4)	1	35	0	12	4.8%	1.08 [0.05, 24.96]
Buse 2018 (inTandem1)	8	263	2	134	20.2%	2.04 [0.44, 9.46]
Danne 2018(inTandem2)	6	261	1	129	10.7%	2.97 [0.36, 24.37]
Subtotal (95% CI)		**559**		**275**	**35.7%**	**2.09 [0.66, 6.64]**
Total events	15		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 2 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
44.1.3 Sotagliflozin 400 mg						
Baker 2017(inTandem4)	1	35	0	12	4.8%	1.08 [0.05, 24.96]
Bode 2017	1	43	1	44	6.3%	1.02 [0.07, 15.84]
Buse 2018 (inTandem1)	4	262	2	134	16.7%	1.02 [0.19, 5.51]
Danne 2018(inTandem2)	2	263	0	129	5.2%	2.46 [0.12, 50.91]
Garg 2017(inTandem3)	13	699	2	703	21.5%	6.54 [1.48, 28.86]
Sands 2015	1	16	0	17	4.8%	3.18 [0.14, 72.75]
Subtotal (95% CI)		**1318**		**1039**	**59.5%**	**2.38 [0.97, 5.82]**
Total events	22		5			
Heterogeneity: Tau² = 0.00; Chi² = 3.49, df = 5 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.90 (P = 0.06)						
Total (95% CI)		**1912**		**1326**	**100.0%**	**2.19 [1.10, 4.36]**
Total events	38		8			
Heterogeneity: Tau² = 0.00; Chi² = 3.99, df = 9 (P = 0.91); I² = 0%						
Test for overall effect: Z = 2.23 (P = 0.03)						
Test for subgroup differences: Chi² = 0.23, df = 2 (P = 0.89), I² = 0%						



Supplementary text

Online Search strategies

Medline and Cochrane Central Register of Controlled Trials (Central):

1. randomized controlled trial.pt
2. controlled clinical trial.pt
3. randomized.tw
4. clinical trial/
5. randomly.ab
6. trial.ti
7. placebo.tw
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. sodium-glucose transporter 1/2/
10. sodium-glucose transporter 1/2.tw
11. SGLT1/2.tw
12. SGLT-1/2.tw
13. dual SGLT.tw
14. Sotagliflozin.tw OR LX4211.tw OR LP802034.tw OR SAR439954.tw OR Zynquista.tw
15. LX4211.tw
16. Sotagliflozin.tw
17. LP802034.tw
18. SAR439954.tw
19. Zynquista.tw
20. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. 8 and 20

EMBASE

1. 'randomized controlled trial'/exp OR 'randomized controlled trial'

2. 'sodium glucose cotransporter 1/2'/exp OR 'sodium glucose cotransporter 1/2'

3. 'sodium glucose cotransporter 1/2 inhibitor'/exp OR 'sodium glucose cotransporter 1/2 inhibitor'

4.'sotagliflozin'/exp OR 'sotagliflozin' OR 'LX4211' OR 'LP802034' OR 'SAR439954' OR 'Zynquista'

5. 2 OR 3 OR 4

22. 1 AND 5

CLINICALTRIALS.GOV

1. Sodium-GlucoseTransporter 1/2

2. SGLT-1/2

3. Sotagliflozin

4. LX4211

5 LP802034

6. SAR439954

7. Zynquista

US FDA, EMA, databases

1. Sodium-Glucose Transporter 1/2

2. SGLT-1/2

3. Sotagliflozin

4. LX4211

5. LP802034,

6. SAR439954

7. Zynquista

International and National Trial registries search results

-**World Health Organization-International Clinical Trials Registry Platform** (http://apps.who.int /trialsearch/): 82 records

-**ClinicalTrials.gov**(https://www.clinicaltrials.gov/ct2/home): 37 records

- **Cochrane CENTRAL Register of Controlled Trials** (https://www.cochranelibrary.com/central/about-central): 47 records

- **European Union(EU) Clinical Trials Register** (https://www.clinicaltrialsregister.eu/): 13 records

-**ISRCTN** (http://www.isrctn.com/): 0 results

-**Epistemonikos** *(*https://www.epistemonikos.org/*): 0 records*

-**Health Canada Clinical Trial Database** (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php): 11 records

-**German Clinical Trials Register** (https://drks-neu.uniklinik-freiburg.de/drks_web/): 0 results

-**Netherlands Trial Register (Dutch**) (http://www.trialregister.nl/trialreg/index.asp): 0 results

-**Swiss National Clinical Trials Portal** (http://www.kofam.ch/en/swiss -clinical-trials-portal.html) 6 results

-**Australian New Zealand Clinical Trials Registry** (http://www.anzctr.org.au/): 4 records

-**ChineseClinical Trial Register** (http://www.chictr.org.cn/enIndex.aspx): 0 records

-**Clinical Trials Registry–India**(http://ctri.nic.in/): 1 record

-**Iranian Registry of Clinical Trials** (http://www.irct.ir/): 0 records

-**Japan Primary Registries Network** (http://rctportal.niph.go.jp/): 0 records

-**ClinicalResearch Information Service, Republic of Korea** (https://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp): 0 records

-**Philippine Health Research Registry** (http://registry. healthresearch.ph/): 0 results

-**Sri Lanka Clinical Trials Registry** (http://www.slctr.lk/): 0 records

-**Thai Clinical Trials Registry** (http://www.clinicaltrials.in.th/): 0 records

-**Brazilian Clinical Trials Registry** (http://www.ensaiosclinicos.gov.br/): 0 records

-**Public Cuban Registry of Clinical Trials** (http://registroclinico.sld.cu/en/home): 0 records

-**Peruvian Registry of Clinical Trials** (http://www.ins.gob.pe/ ensayosclinicos/): 0 records

-**Pan AfricanClinical Trials Registry** (http://www.pactr.org/): 0 records

-**South African National Clinical Trials Register**: (http://www.sanctr.gov.za/): 0 records

-**Tanzania Clinical Trial Registry** (http://www.tzctr.or.tz/): 0 records

Regulatory Agencies sites search results

US Food and Drug Administration (FDA)

https://search.usa.gov/search?utf8=%E2%9C%93&affiliate=fda&query=sotagliflozin&commit=Search:

6 results

European Medicines Agency (EMA)

https://www.ema.europa.eu/en/search/search?search_api_views_fulltext=sotagliflozin): 49 results

Japanese Pharmaceutical and Medical Devices Agency(PMDA)

https://ss.pmda.go.jp/en_all/search.x?q=sotagliflozin&ie=UTF-8&page=1&x=30&y=11:

0 results

Definitions

Hypoglycemia: blood glucose levels ≤ 70 mg/dL documented on self-monitoring blood glucose, regardless of symptoms. We evaluated hypoglycaemia asnumber of hypoglycemic events per patient-year[1]

Severe hypoglycemia: an event consistent with hypoglycemia (regardless of whether biochemical documentation of a low glucose value was obtained) when any of the following three conditions occurred:

• the patient have an episode of suspected hypoglycemia treated with any form of carbohydrate or with glucagon that required the assistance of others to treat, because the neurologic impairment was severe enough to prevent self-treatment in the opinion of those providing assistance to treat.

• the patient lost consciousness during the episode

• the patient had a seizure during the episode

Diabetic ketoacidosis (DKA): DKA was diagnosed based on evidence of anion-gap metabolic acidosis related to excessive ketone production without a satisfactory alternative cause for anion-gap acidosis, as outlined in Kitabchi et al 2009[2].

Renal event: defined according to the following Medical Dictionary for Regulatory Activities preferred terms:

Acute prerenal failure; Anuria; Azotemia; Blood creatine abnormal; Blood creatine decreased; Blood creatine increased; Blood creatinine abnormal; Blood creatinine decreased; Blood creatinine increased Blood urea abnormal; Blood urea increased; Blood urea nitrogen/creatinine ratioincreased

Coma uremic; Computerized tomogram kidney abnormal; Creatine urine abnormal; Creatine urine decreased; Creatine urine increased; Creatinine renal clearance abnormal

Creatinine renal clearance decreased; Creatinine urine abnormal; Creatinine urine decreased

Creatinine urine increased; Cystatin C abnormal; Cystatin C increased, Diabetic end stage renal disease; Glomerular filtration rate abnormal; Glomerular filtration rate decreased;

Glomerular filtration rate increased; Hypercreatinemia; Hyperparathyroidism secondary

Inulin renal clearance abnormal; Inulin renal clearance decreased; Kidney fibrosis;
Nephrogenic anemia; Nitrogen balance negative; Edema due to renaldisease;
OliguriaPericarditis uremicPhenolsulfonphthalein test abnormal; Postoperative renal failure
Prerenal failure; Renal cortical necrosis; Renal disorder; Renal failure;
Renal failure acute;Renal failure chronic; Renal function test abnormal;Renal impairment;
Renal injury;Renalnecrosis;Renal papillary necrosis;Renal scan abnormal;Renal tubular acidosis;Renal tubular atrophy;Renal tubular disorder;Renal tubular necrosis;Ultrasound kidney abnormal;Uremicacidosis;Uremicencephalopathy;UremicgastropathyUremic neuropathy;
Uremic pruritus;Urea renal clearance;Urea renal clearance decreased;Urea renal clearance increased;Uridosis;Urine albumin/creatinine ratio abnormal;Urine albumin/creatinine ratio decreased;
Urine albumin/creatinine ratio increased;Urineoutput;Urine output decreased;Urine output increased;
Urine protein/creatinine ration abnormal;Urine protein/creatinine ratio decreased;
Urine protein/creatinine ratio increased.

Volume depletion event: defined according to the following Medical Dictionary for Regulatory Activities preferred terms:

Acute prerenal failure;Blood pressure abnormal;Blood pressure ambulatory abnormal;Blood pressure decreased;Blood pressure diastolic abnormal;Blood pressure diastolic decreased;Blood pressure fluctuation;Blood pressure immeasurable;Blood pressure inadequately controlled;Blood pressure orthostasisabnormal;Blood pressure orthostatic decreased;Blood pressure systolic abnormal;Blood pressure systolic decreased;Blood pressure systolic inspiratorydecreased;Brachial pulse abnormal;
Brachial pulse decreased;BUN/creatinine ratio increased;Capillary nail refill test abnormal;Cardiac index abnormal;Cardiac index decreased;Cardiac output decreased;Cardiovascularinsufficient;Carotid pulse abnormal;Carotid pulse decreased;Central venous pressure abnormal;Central venous pressure decreased;Circulatorycollapse;Decreasedventricularpreload;Dehydration;Diastolichypotension;Femoral

pulse abnormal;Femoral pulse decreased;Hemodynamic test abnormal;Heart rate abnormal;Heart rate decreased;

Heart rate increased;Hypoperfusion;Hypotension;Hypovolemia;Hypovolemic shock;

Labile blood pressure;Left ventricular end-diastolic pressuredecreased;Maximum heart rate decreased;

Mean arterial pressure decreased;Orthostatic heart rate response increased;Orthostatic hypotension;

Orthostatic intolerance;Pedal pulse abnormal;Pedal pulse decreased;Peripheral circulatory failure;Peripheral coldness;Peripheral pulse decreased;Popliteal pulse abnormal;Popliteal pulse decreased;

Prerenal failure;Presyncope;Pulseabnormal;Pulseabsent;Pulse pressure abnormal;Pulse pressure decreased;Pulse volume decreased;Pulse waveform abnormal;Radial pulse abnormal;Radial pulse decreased;Renalischemia;Schellingtest;Shock;Syncope;Thirst;Tilt table test positive;Urine albumin/creatinine ratio increased;Urine flow decreased;Urine output decreased;

Urine protein/creatinine ratio increased;Vascular test abnormal;Venous pressure abnormal;

Venous pressure decreased;Venous pressure jugular abnormal;Venous pressure jugular decreased;

Volume blood decreased.

Acidosis-related adverse event

Adverse events that satisfy the trigger terms for metabolic acidosis, which are the following Medical Dictionary for Regulatory Activities preferred terms: acetonemia, acidosis, acidosis hyperchloremic, blood ketone body, blood ketone body increased, blood ketone body present, DKA, diabetic hyperglycemia, coma, diabetic ketoacidotichyperglycemic diabetic metabolic decompensation, diabetic coma, hyperglycemic coma, hyperglycemic seizure, hyperglycemic unconsciousness, ketoacidosis, ketosis, lactic acidosis,metabolic acidosis, renaltubularacidosis,uremic acidosis, urine ketone body, and urine ketone body present.

Serious AEs

Serious adverse events were defined as serious if they resulted in death, a life-threaten, patient hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or if they required medical intervention to prevent one of the outcomes listed above. For this meta-analysis, serious AEs were defined as the number of participants experiencing death, cancer (all cancers, bladder cancer, breast cancer), MACE, severe hypoglycaemia, serious acidosis-related adverse events..

Management of missing data.

Missing data were managed by contacting via e-mail the corresponding authors of the RCTs. Where this was unsuccessful, we planned to calculate missing data from the raw numbers given in tables and/or estimated from bar charts. For missing standard deviations of mean change in parameters, and where the p value was provided for a comparison between treated and control groups, we planned to calculate the standard deviation by converting the p value into a t value with appropriate degrees of freedom, and then calculating standard error and standard deviation. If neither the standard deviations nor the p values were supplied, we planned to impute a standard deviation from studies with similar measurement methods, duration and measurement error was used if available1 and tested in a sensitivity analysis and reported if the estimate differed meaningfully from previous estimates. If no similar studies were available, a narrative approach would have been used to summarize the data

[1]Workgroup on Hypoglycemia, American Diabetes Association.Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28:1245-9

[2]Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemiccrises in adultpatients with diabetes.Diabetes Care. 2009;32:1335-43

Supplementary Tables

Supplementary Table 1 panel A. Characteristics of included randomized controlled trials

Author	N-participants	Study duration (week)	Study Arms	Age (yr)	Gender (%M)	Bodyweight (kg) / BMI (kg/m^2)	Initial HbA1c (%)	Diabetes duration (yr)	Background treatment / Daily TID (IU/kg)	Dropout rate(%)	Renal function
Sands 2015	33	4	Sota 400 mg	45	50	74.2 kg / 27.1 kg/m^2	7.94	18.5	Insulin 0.6 IU/kg	0%	eGFR≥60 ml/min/1.73 m^2
			placebo	44	47	72.7 kg / 26.2	7.98	16.8	Insulin 0.6 IU/kg	0%	
Bode 2017	87	12	Sota 400 mg	23	49	83.8 kg / 29.0	9.9	12	Insulin 0.8 IU/kg	0%	eGFR≥45 ml/min/1.73 m^2
			placebo	22	45	80.7 kg / 27.9	9.7	12	Insulin 0.8 IU/kg	4.8%	
Baker 2017	141	12	Sota 400 mg	45	57	84.1 kg / 29	8.1	24	Insulin 0.7 IU/kg	0%	eGFR≥60 ml/min/1.73 m^2
			Sota 200 mg	47	47	81.9 kg / 28	8.1	24	Insulin 0.7 IU/kg	0%	
			Sota 75 mg	42	40	78.1 kg / 27	8.0	23	Insulin 0.7 IU/kg	2.7%	
			placebo	48	42	89.6 kg /31	8.0	27	Insulin 0.7 IU/kg	2.7%	

Author	N-participants	Study duration (week)	Study Arms	Age (yr)	Gender (%M)	Bodyweight (kg) / BMI (kg/m^2)	Initial HbA1c (%)	Diabetes duration (yr)	Background treatment / Daily TID (IU/kg)	Dropout rate	Renal function
Garg 2017	1402	24	Sota 400 mg	43	51	82.4 kg/ 28.3	8.2	20	Insulin 0.7 IU/kg	13%	eGFR≥45 ml/min/1.73 m^2
			placebo	42	48	81.6/28.1	8.2	20	Insulin 0.7 IU/kg	11%	
Buse 2018	793	52	Sota 400 mg	46	46	86.5 kg/29.6	7.6	24	Insulin 0.7 IU/kg	10%	eGFR≥45 ml/min/1.73 m^2
			Sota 200 mg	47	48	86.9 kg/29.8	7.6	25	Insulin 0.7 IU/kg	9%	
			placebo	45	51	87.3 kg/29.6	7.5	24	Insulin 0.7 IU/kg	12%	
Danne 2018	782	52	Sota 400 mg	41	51	81.9 kg/ 27.9	7.7	19	Insulin 0.7 IU/kg	8%	eGFR≥45 ml/min/1.73 m^2
			Sota 200 mg	42	53	81.9 kg/ 27.9	7.7	18	Insulin 0.7 IU/kg	8%	
			placebo	40	52	81.1 kg/ 27.5	7.7	18	Insulin 0.7 IU/kg	8%	

Supplementary Table 1 panel B Risk of Bias of included randomized controlled trials

Author	Random sequence generation	Allocation concealment	Blinding of participants and èpersonnel	Blinding pf outcome assesment	Incomplete outcome data	Selective reporting	Other: sponsorship bias
Sands 2015	Low risk. Computer generated list	Low risk. Central allocation, web-based randomization	Low risk. Quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor)	Low risk. Quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessors)	Low risk. No patients dropped out	Low risk. Prespecified outcomes available on a clinical trial database and all reported in publication	Low risk. The Robert and Janice McNair Foundation funded the study
Bode 2017	Low risk. Computer generated list	Low risk. Central allocation, web-based randomization	Low risk. Quadruple masking	Low risk. Quadruple masking	Low risk. Low dropout rate:	Low risk. Prespecified outcomes available on a clinical trial database and all reported in publication	Low risk. JDRF funded the study
Baker 2017	Low risk. Computer generated list	Low risk. Central allocation, web-based randomization	Low risk. Quadruple masking	Low risk. Quadruple masking	Low risk. Low dropout rate:	Low risk. Prespecified outcomes available on a clinical trial database and all reported in publication	Low risk. Industry funded but no high risk of bias feature encountered*

Panel B(continued). Risk of Bias of included randomized controlled trials

Author	Random sequence generation	Allocation concealment	Blinding of participants and èpersonnel	Blinding pf outcome assesment	Incomplete outcome data	Selective reporting	Other: sponsorship bias
Garg 2017	Low risk. Computer generated list	Low risk Central allocation, web-based randomization	Low risk Quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor)	Low risk Quadruple masking	Low risk Low dropout rate: Missing observations at EOT imputed as nonresponse.	Low risk Prespecified outcomes available on a clinical trial database and all reported in publication	Low risk Industry funded but no high risk of bias feature encountered*
Buse 2018	Low risk. Computer generated list	Low risk Central allocation, web-based randomization	Low risk Quadruple Masking	Low risk Quadruple masking	Low risk Low dropout rate: Missing observations at EOT imputed as nonresponse.	Low risk Prespecified outcomes available on a clinical trial database and all	Low risk Industry funded but no high risk of bias feature encountered*
Danne 2018	Low risk. Computer generated list	Low risk Central allocation, web-based randomization	Low risk Quadruple Masking	Low risk Quadruple masking	Low risk Low dropout rate: Missing observations at EOT imputed as nonresponse.	Low risk Prespecified outcomes available on a clinical trial database and all	Low risk Industry funded but no high risk of bias feature encountered*

Abbreviations: eGFR: estimated glomerular filtration rate;JDRF: Juvenile Diabetes Research Foundation; Sota: sotagliflozin; TID: total insulin dose

[a]Insulin dose optimization during the 6 weeks preceding randomization(target: FPG 80-130 mg/dL and 2hr-PPG<180 mg/dL)

***Assessment of sponsorship bias**: in the presence of industry sponsorship, the following list of 8 items in trial designing, conducting or reporting, empirically linked by existing literature to biased outcomes in industry-funded trials and not captured by the Cochrane Risk of Bias domains, were assessed: if any one item was present, the trial was downgraded to "high risk of bias".

Item a: unclear clinical relevance of outcome measures: the clinical relevance of trial outcomes is not supported by international guidelines (American Association for the study of Diabetes-ADA or European Association for the Study of Diabetes-EASD guidelines).

Item b: if active comparator was used: inadequacy of doses timing or way of administration,

Item c: -deviations from study protocol or original protocol changes or amendments after trial initiation

Item d: post-hoc selection of the major findings and endpoints

Item e: use of last observation carried forward analysis to impute missing data

Item f:on-treatment outcome reporting /absence of data and safety monitoring board

Item g: absence of sponsor-independent statistician and data analysis

Item h: early trial termination before the endpoint recorded on clinical trial registries

Supplementary Table 2. Characteristics of randomized controlled trials(RTCs) with sotagliflozin excluded from this meta-analysis.

Phase 1 trials				
Official Title (author/ year of publication) ClinicalTrials.gov ID number	**Drug (dose)**	**N-participants (actual or anticipated)**	**Duration (week)**	**Year of registration Status**
Effect of Rifampicin on the Pharmacokinetics and Pharmacodynamics of Sotagliflozin NCT03063580	Sota 400 mg	16	7.5	2017 Completed
Oral Contraceptive DDI Study NCT02494609	Sota 400 mg	30	4	2015 Active, not recruiting
PK Study of Sotagliflozin in Subjects With Hepatic Impairment NCT02471274	Sota 400 mg	32	1	2015 Completed
Interaction study to evaluate the Effects of Mefenamic Acid on the Pharmacokinetics and Pharmacodynamics of Sotagliflozin in Healthy Male and Female Subjects. NCT03070678	Sota 400 mg	16	8	2017 Completed
A Drug to Drug Interaction Study of Sotagliflozin With Midazolam and Metoprolol. NCT02940379	Sota 200 mg or 400 mg	24	8	2016 Completed
Sotagliflozin Bioequivalence Study NCT03211195	Sota 200 mg	76	9	2017 Completed
A Study to Evaluate the Effect of Food on the Pharmacokinetics of Sotagliflozin and to Explore the Relative Bioavailability in Healthy Subjects. NCT03174548	Sota 200 mg	14	9	31/05/2017 Completed
A Drug to Drug Interaction Study of Sotagliflozin With Hydrochlorothiazide NCT03387657	Sota 200 mg	16	2	2018 Completed
Comparison of Sotagliflozin Prototype Tablets With	Sota	12	9	2017

Reference Tablet in Healthy Subjects NCT03310944	400 mg			Completed
A Bioequivalence Study Testing Two Formulations of Sotagliflozin in Healthy Male and Female Subjects Under Fasted Conditions NCT03776227	Sota 200 mg or 400 mg	58	14	2018 Active, not yet recruiting,
A Phase 1, Open-label, Parallel-group Study to Evaluate Sotagliflozin Safety and Pharmacokinetics in Subjects With Varying Degrees of Renal Function, NCT02647918	Sota 200 mg	44	1	2015 Active, Not recruiting
A Drug-Drug Interaction Study Between Sotagliflozin and Ramipril NCT03414723	Sota 400 mg	1	9	2018 Completed
Randomized trials in type 2 diabetes mellitus(T2DM)				
Official Title (author/ year of publication) ClinicalTrials.gov ID	**Sota dose**	**N-participants (actual or anticipated)**	**Duration (week)**	**Year of registration Status**
A Randomized, Open-Label, Three-Way Crossover Study of Two Oral Formulations of LX4211 in Subjects With Type 2 Diabetes Mellitus NCT01188863	Sota 150 mg or 300 mg	15	4	2012 Completed
A Study to Evaluate the Pharmacodynamic Effects of Single-Dose Co-Administration of LX4211 With Januvia® in Type 2 Diabetics NCT01441232	Sota 400 mg	18	3	2015 Completed
Pharmacodynamic and Pharmacokinetic Effects of LX4211 in Subjects With Type 2 Diabetes and Renal Impairment NCT01555008	Sota 400 mg	31	1	2015 Completed
Safety and Efficacy of LX4211 With Metformin in Type 2 Diabetes Patients With Inadequate Glycemic Control on Metformin NCT01376557	Sota 75 mg, 200 mg, 400 mg	299	12	2015 completed
Efficacy and Safety of Sotagliflozin Versus Placebo in Chinese Patients With Type 2 Diabetes Mellitus Not Adequately Controlled by Diet and Exercise NCT03760965	Sota 200 mg or 400 mg	369	24	29/11/2018 Recruiting,

Efficacy and Safety of Sotagliflozin Versus Placebo in Chinese Patients With Type 2 Diabetes Mellitus Not Adequately Controlled by Metformin With or Without Sulfonylurea NCT03761134	Sota 200 mg or 400 mg	369	24	Recruiting 29/11/2018
Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF Trial) NCT03521934	Sota 200 mg or 400 mg	4000	32	Recruiting30 /04/2018
Comparison of Pharmacodynamic Effects of Sotagliflozin and Empagliflozin in T2DM Patients With Mild to Moderate Hypertension NCT03462069	Sota 400 mg	40	8	Recruiting 06/03/2018
Efficacy and Bone Safety of Sotagliflozin Dose 1 and Dose 2 Versus Placebo in Subjects With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control. (SOTA-BONE Trial) NCT03386344	Sota 200 mg or 400 mg	360	24	Active, not recruiting 21/12/2017
Efficacy and Safety of Sotagliflozin Versus Glimepiride and Placebo in Subjects With Type 2 Diabetes Mellitus That Are Taking Metformin Monotherapy(SOTA-GLIM trial) NCT03332771	Sota 200 mg or 400 mg	930	52	Active, Not recruiting 02/11/2017
Efficacy and Safety of Sotagliflozin versus Placebo and Empagliflozin in Subjects with Type 2 Diabetes Mellitus who have Inadequate Glycemic Control while taking a DPP4 Inhibitor Alone or with Metformin(SOTA-EMPA trial) NCT03351478	Sota 400 mg	700	26	Active, not recruiting
Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk(SCORED trial) NCT03315143	Sota 200 mg vs. 400 mg	1500	5 years	Active, recruiting 04/10/2017
Efficacy and Safety of Sotagliflozin versus Placebo in Subjects with Type 2 Diabetes Mellitus who have inadequate glycemic control while Taking Insulin Alone or with Other Oral Antidiabetic Agents(SOTA-INS trial) NCT03285594	Sota 200 mg vs. sota 400 mg	560	96	Active, not recruiting 2017
Safety and Efficacy Study of Sotagliflozin on Glucose Control in Patients With Type 2 Diabetes, Moderate Impairment of Kidney Function, and Inadequate Blood Sugar Control (SOTA-CKD3 trial)	Sota 200 mg vs. sota 400 mg	780	52	Active, Not recruiting 03/08/2017

NCT03242252				
A Study to Evaluate Safety and Effects of Sotagliflozin Dose 1 and Dose 2 on Glucose Control in Patients With Type 2 Diabetes, Severe Impairment of Kidney Function and Inadequate Blood Sugar Control.(SOTA-CKD4 trial) NCT03242018	Sota 200 mg vs. sota 400 mg	276	52	Active, Not recruiting 03/08/2017
Efficacy and Safety of Sotagliflozin Versus Placebo in Patients With Type 2 Diabetes Mellitus on Background of Sulfonylurea Alone or With Metformin NCT03066830	Sota 400 mg	500	26	Active, Not recruiting 24/02/2017
Efficacy and Safety of Sotagliflozin Versus Placebo in Patients With Type 2 Diabetes Mellitus Not Currently Treated With Antidiabetic Therapy NCT02926937	Sota 400 mg	400	26	Active, Not recruiting 05/10/2016
Efficacy and Safety of Sotagliflozin Versus Placebo in Patients With Type 2 Diabetes Mellitus on Background of Metformin NCT02926950	Sota 200 mg vs. sota 400 mg	500	26	Active, Not recruiting 05/10/2016
Randomized trials in Congestive Heart Failure				
Official Title (author/ year of publication) ClinicalTrials.gov ID number	**Drug (dose)**	**N-participants (actual or anticipated)**	**Duration (week)**	**Year of registration Sstatus**
Safety, Tolerability and Pharmacodynamic Activity of Sotagliflozin in Hemodynamically Stable Patients With Worsening Heart Failure. NCT03292653	Sota 200 mg or 400 mg	81	5	Active, Recruiting 04/12/2017

Abbreviations: UGE: urinary glucose excretion; T2D: type 2 diabetes mellitus; OAD: Oral Antidiabetic Agents; Sota: sotagliflozin

Supplementary Table 3. Results of subgroup and sensitivity analysis.

Treatment duration		
Outcome	**treatment duration ≤12 weeks**	**treatment duration >12 weeks**
HbA1c (%)	-0.37 (-0.56, -0.18), I^2=0%, p=0.0001, N =5 comparisons, 261 participants	-0.36(-0.47, -0.26), I^2=12%, p<0.00001, N =5 comparisons, 2977 participants
FPG (mg/dL)	-16.74 (-28.49, -5.00), I^2=10%, p=0.005, N =5, 261 participants	-16.77 (-23.05, -10.49), I^2=25%, p<0.00001, N=5, 2977 participants
2h-PPG (mg/dL)	-38.72 (-52.27, -25.16), I^2=20%, p<0.00001, N=5, 261 participants	-40.10(-63.73, -16.47), I^2=30%, p=0.001, N=5, 278 participants
Total insulin dose (IU/d)	-9.51 (-17.91, -1.81), I^2=0%, p=0.009, N=5, 261 participants	-9.16 (-11.40, -6.92), I^2=36%, p<0.00001, N=3, 2977 participants
Basal insulin dose (IU/d)	-5.33 [-10.49,-1.49], I^2=0%, p=0.03, N=3, 261 participants	-8.89 (-11.16, -6.61) I^2=0%, p<0.00001, N=5, 2977 participants
Bolus insulin dose (IU/d)	-13.77 [-23.04, -3.50] I^2=34%, p=0.0004, N =5, 261 participants	-9.51 (-13.10, -5.92), I^2=24%, p<0.00001, N=5, 2977 participants
Time-in-Range (%)	11.31(6.75,15.87) I^2=0%, p<0.00001, N=2, 120 participants	8.88(4.25, 13.51) I^2=36%, p=0.0002, N=4, 278 participants
Body weight change (%)	-2.63(-4.09, -1.17), I^2=0%, p=0.0004, N=5, 261 participants	-3.67(-4.25, -3.10), I^2=0%, p<0.00001, N=5, 2977 participants
Systolic BP (mmHg)	-8.65(-12.49, -4.81), I^2=34%, p=0.0004, N=5, 285 participants	-3.61(-4.55, -2.66), I^2=0%, p<0.00001, N=5, 2977 participants
Diastolic BP (mmHg)	-2.13 (-4.00, -0.27), I^2=0%, p=0.02, N=3, 285 participants	-1.36 (-1.93, -0.80), I^2=0%, p<0.00001, N=3, 2977 participants
eGFR (ml/min/1.73 m^2)	-2.26(-4.41, -0.11), I^2=0%, p=0.04, N=5, 261 participants	-0.42(-1.15, 0.32), I^2=0%, p=0.26, N=5, 2977 participants
Albumin-creatinine ratio (ACR)(mg/g)	No studies	-14.57(-26.87, -2.28), I^2=0%, p=0.02, N=3, 2977 participants
Hypoglycemia (events per patient-year)	-9.82(-16.00, -1.48), I^2=0%, p=0.01, N=3, 261 participants	-9.71(-15.05, -4.38), I^2=0%, p<0.00001, N=3, 2977 participants
Severe hypoglycemia	0.41(0.13, 1.28), I^2=0%, p=0.12, N=5, 261 participants	0.72(0.51, 1.04), I^2=0%, p=0.08, N=5, 2977 participants
DKA	1.23(0.31, 4.94) I^2=0%, p=0.77, N=5, 261 participants	5.89(2.60, 13.36), I^2=0%, p<0.00001, N=5, 2977 participants
UTI	0.70(0.20, 2.42), I^2=0%, p=0.57, N=5, 261 participants	0.99(0.71, 1.37), I^2=0%, p<0.00001, N=5, 2977 participants

GTI	1.21(0.30, 4.86), I^2=0%, p=0.79, N=35 261 participants	3.36(2.27, 4.96), I^2=0%, p<0.00001, N=5, 2977 participants
Diarrhea	1.70(1.08, 2.77), I^2=0%, p=0.04, N=5, 261 participants	1.59(1.12, 2.24), I^2=0%, p=0.009, N=5, 2977 participants
Volume depletion events	2.62 (1.18, 5.82), I^2=3%, p=0.02, N=5, 261 participants	1.37 (0.30, 2.19), I^2=0%, p=0.68, N=5, 2977 participants
MACE	No events, N =5 comparisons, 261 participants	1.05(0.46, 2.43), I^2=0%, p=0.91, N=10, 2977 participants
Initial HbA1c levels		
Outcome	**initial HbA1c levels < 8%**	**initial HbA1c levels ≥8%**
HbA1c (%)	-0.27 (-0.35, -0.19), I^2=0%, p<0.00001, N =5 comparisons, 1608 participants	-0.44(-0.52, -0.36), I^2=0%, p<0.00001, N =5 comparisons, 1630 participants
FPG (mg/dL)	-14.77 [-23.25, -6.30], I^2=25%, p=0.0006, N =3, 1608 participants	-19.83 [-26.51, -13.15], I^2=0%, p<0.00001, N =3, 1630 participants
2h-PPG (mg/dL)	-39.82(-56.70, -22.94), I^2=8%, p<0.00001, N =5, 311 participants	-38.74 [-55.81, -21.67], I^2=4%, p<0.00001, N =4, 228 participants
Total insulin dose (IU/d)	-9.23 (-12.12, -6.33), I^2=39%, p<0.00001, N =5 comparisons, 1608 participants	-9.04(-11.48, -6.59), , I^2=0%, p<0.00001, N =5 comparisons, 1630 participants
Basal insulin dose (IU/d)	-8.19 (-10.84, -5.55), I^2=0%, p<0.00001, N =5 comparisons, 1608 participants	-7.76 (-11.23, -4.29), I^2=0%, p<0.00001, N =5 comparisons, 1630 participants
Bolus insulin dose (IU/d)	-9.94(-14.84, -5.05), I^2=32%, p<0.00001, N =5 comparisons, 1608 participants	-9.77(-14.01, -5.52), I^2=0%, p<0.00001, N =5 comparisons, 1630 participants
Time-in-Range (%)	8.88(4.25, 13.5), I^2=0%, p=0.0002, N =4, 278 participants	11.31(6.75, 15.87), I^2=0%, p<0.00001, N =2, 120 participants
Body weight change (%)	-3.66(-4.44, -2.87), I^2=30%, p<0.00001, N =5 comparisons, 1608 participants	-3.50(-3.96, -3.03), I^2=0%, p<0.00001, N =5 comparisons, 1630 participants
Systolic BP (mmHg)	-3.27 (-4.76, -1.78), I^2=0%, p<0.0001, N =5 comparisons, 1608 participants	-6.67(-10.38, -2.96), I^2=0%, p=0.0004, N =5 comparisons, 1630 participants
Diastolic BP (mmHg)	-1.42(-2.20, -0.65), I^2=0%, p=0.0003, N =5 comparisons, 1608 participants	-1.44(-2.20, -0.69), I^2=0%, p=0.0002, N =5 comparisons, 1630 participants
eGFR (ml/min/1.73 m^2)	-1.35 (-2.26, -0.44), I^2=0%, p=0.004, N =5, 1608 participants	-1.07 (-2.35, -0.29), I^2=0%, p=0.21, N =5, 1630 participants
Albumin-creatinine ratio (ACR)(mg/g)	-13.92(-27.36, -0.48), I^2=0%, p=0.04, N=4, 1608 participants	-20.10(-40.25, -0.63), I^2=NA, p=0.04, N =1, 1402 participants
Hypoglycemia	-13.47(-20.90, -6.03), I^2=0%, p=0.004,	-6.12(-10.96, -1.28), I^2=0%, p=0.01 N=5,

(events per patient-ear)	N=5, 1608 participants	1630 participants
Severe Hypoglycemia	0.69(0.46, 1.02), I^2=0%, p=0.07, N=5, 1608 participants	0.71(0.36, 1.43), I^2=0%, p=0.34, N =5, 1630 participants
DKA	6.62(2.04, 21.48), I^2=0%, p=0.002, N=5, 1608 participants	2.21(0.43, 11.42), I^2=0%, p=0.34, N =5, 1630 participants
UTI	0.86(0.48, 1.56), I^2=0%, p=0.62, N =3, 1608 participants	0.96(0.57, 1.59), I^2=0%, p=0.86, N =3, 1630 participants
GTI	3.39(1.53, 7.52), I^2=14%, p<0.003, N =5, 1608 participants	2.97(1.71, 5.19), I^2=0%, p=0.0001, N =5, 1630 participants
Diarrhea	1.50 (0.97, 2.29), I^2=0%, p=0.07, N =5, 1608 participants	0.98 (0.32, 3.01), I^2=0%, p=0.98, N =5, 1630 participants
Volume depletion Events	1.89 (0.76, 4.68), I^2=0%, p=0.17, N =5, 1608 participants	2.68 (0.93, 7.73), I^2=0%, p=0.0001, N =5, 1630 participants
MACE	0.89(0.33, 2.44), I^2=0%, p=0.82, N =5, 1608 participants	5.03(0.24, 104.55), I^2=0%, p=0.30, N =5, 1630 participants
Duration of diabetes		
Outcome	**duration of diabetes<20 yr**	**duration of diabetes≥20 yr**
HbA1c (%)	-0.33(-0.44, -0.22), I^2=0%, p<0.00001, N =4 comparisons, 902 participants	-0.36(-0.46, -0.25),, I^2=0%, p<0.00001, N =6, 2336 participants
FPG (mg/dL)	-17.18(-31.70, -2.66), I^2=0%, p=0.01, N =4 comparisons, 902 participants	-18.19(-23.76, -12.62), I^2=0%, p<0.00001, N =6, 2336 participants
2h-PPG (mg/dL)	-51.96(-67.00, -36.92), I^2=0%, p<0.00001, N =4 comparisons, 262 participants	-29.94(-42.98, -16.89), I^2=16%, p<0.00001, N =5, 277 participants
Total insulin dose (IU/d)	-7.16(-9.79, -4.53), I^2=0%, p<0.00001, N =4 comparisons, 902 participants	-9.75(-12.21, -7.28),, I^2=0%, p<0.00001, N =6, 2336 participants
Basal insulin dose (IU/d)	-5.83 (9.47, -2.19), I^2=0%, p=0.002, N =4 comparisons, 902 participants	-9.14(-11.72, -6.56),, I^2=0%, p<0.00001, N =6, 2336 participants
Bolus insulin dose (IU/d)	-9.42(-14.79, -4.04), I^2=0%, p=0.0006, N =4 comparisons, 902 participants	-9.18 (-13.47, -4.90),, I^2=20%, p<0.00001, N =6, 2336 participants
Time-in-Range (%)	11.53(8.21, 14.84), I^2=0%, p<0.00001, N =4 comparisons, 262 participants	7.69(1.52, 13.89), I^2=0%, p=0.02, N =2, 136 participants
Body weight change (%)	-3.13(-3.82, -2.44), I^2=0%, p<0.00001, N =4 comparisons, 902 participants	-3.13(-3.82, -2.44), I^2=0%, p<0.00001, N =6, 2336 participants
Systolic BP (mmHg)	-3.50(-5.72, -1.28), I^2=0%, p=0.0002, N =4 comparisons, 902 participants	-4.01(-5.33, -2.70), I^2=13%, p<0.00001, N =6, 2336 participants
Diastolic BP (mmHg)	-1.24(-2.27, -0.21), I^2=0%, p=0.02, N =4 comparisons, 902 participants	-1.51(-2.14, -0.87), I^2=0%, p<0.00001, N =6, 2336 participants
eGFR	-1.36(-2.47, -0.26), I^2=0%, p=0.02, N =4	-0.66(-1.36, -0.04), I^2=0%, p=0.04, N =6,

(ml/min/1.73 m²)	comparisons, 902 participants	2336 participants
Albumin-creatinine ratio (ACR)(mg/g)	-20.45(-33.12, -7.77), I^2=0%, p=0.002, N =2 comparisons, 782 participants	-15.71(-32.62, 1.21), I^2=0%, p=0.01, N =3, 1798 participants
Hypoglycemia (events per patient-year)	-13.68(-21.90, -5.46), I^2=0%, p=0.001, N =4 comparisons, 902 participants	-7.58(-11.24, -1.91), I^2=0%, p=0.006, N =6, 2336 participants
Severe Hypoglycemia	0.68(0.36, 1.31), I^2=0%, p=0.25, N =4 comparisons, 902 participants	0.70(0.47, 1.05), I^2=0%, p=0.08, N =6, 2336 participants
DKA	4.60(1.82, 15.73), I^2=0%, p=0.006, N =4 comparisons, 902 participants	4.30(1.98, 9.31), I^2=0%, p=0.0002, N =6, 2336 participants
UTI	1.13(0.62, 2.07), I^2=0%, p=0.69, N =4 comparisons, 902 participants	0.91(0.63, 1.32), I^2=0%, p=0.73, N =6, 2336 participants
GTI	3.76(1.73, 8.16), I^2=0%, p=0.0008, N =4 comparisons, 902 participants	2.95(1.92, 4.52), I^2=0%, p<0.00001, N =6, 2336 participants
Diarrhea	1.85 (0.93, 3.68), I^2=0%, p=0.08, N =4 comparisons, 902 participants	1.39 (0.92, 2.09), I^2=0%, p=0.12, N =6, 2336 participants
Volume depletion events	1.55 (0.63, 3.83), I^2=0%, p=0.34, N =4 comparisons, 902 participants	2.10 (0.92, 4.85) , I^2=0%, p=0.12, N =6, 2336 participants
MACE	2.02(0.34, 12.13), I^2=0%, p0.44, N =4 comparisons, 902 participants	0.82(0.17, 3.92), I^2=0%, p0.80, N =6, 2336 participants
Background therapy		
Outcome	**stable insulin therapy**	**pre-randomization insulin optimization**
HbA1c (5)	-0.44(-0.52, -0.36), I^2=0%, p<0.00001, N =6, 1663 participants	-0.37(-0.45, -0.29), I^2=0%, p<0.00001, N =4, 1575 participants
FPG (mg/dL)	-20.21(-27.60, -12.83), I^2=0%, p<0.00001, N =6, 1663 participants	-13.46(-20.49, -6.43), I^2=0%, p=0.0002, N =4, 1575 participants
2h-PPG (mg/dL)	-38.72(-52.27, -25.16), I^2=19%, p<0.00001, N =5, 261 participants	-40.10 (-63.73, -16.47), I^2=0%, p=0.0009, N =4, 278 participants
Total insulin dose (IU/d)	-9.26(-11.66, -6.87), I^2=0%, p<0.00001, N =6, 1663 participants	-8.94(-11.98, -5.89), I^2=0%, p<0.00001, N =4, 1575 participants
Basal insulin dose (IU/d)	-7.38(-10.71, -4.04), I^2=0%, p<0.00001, N =6, 1663 participants	-8.47(-11.18, -5.76), I^2=0%, p<0.00001, N =4, 1575 participants
Bolus insulin dose(IU/d)	-10.12(-15.07, -5.16), I^2=0%, p<0.0001, N =6, 1663 participants	-8.51(-12.57, -4.45), I^2=0%, p<0.0001, N =4, 1575 participants
Time-in-Range (%)	11.31(6.75, 15.87), I^2=0%, p<0.00001, N =6, 120 participants	9.35(5.50, 13.21), I^2=0%, p<0.00001, N =4, 311 participants
Body weight change (%)	-3.48(-3.95, -3.02), I^2=0%, p<0.00001, N =6, 1663 participants	-3.70(-4.58, -2.83), I^2=0%, p<0.00001, N =4, 1575 participants

Systolic BP (mmHg)	-6.67(-10.38, -2.96), I^2=0%, p=0.0004, N =6, 1663 participants	-3.27([-4.76, -1.78), I^2=0%, p<0.0001, N =4, 1575 participants
Diastolic BP (mmHg)	-1.43(-2.18, -0.69), I^2=0%, p=0.0002, N =6, 1663 participants	-1.43(-2.22, -0.65), I^2=0%, p=0.0004, N =4, 1575 participants
eGFR (ml/min/1.73 m^2)	-0.98(-1.70, -0.23), I^2=0%, p=0.03, N =6, 1663 participants	-1.37(-2.22, -0.52), I^2=0%, p=0.002, N =4, 1575 participants
Albumin-creatinine ratio (ACR)(mg/g)	-20.10(-39.57, -0.63), I^2=0%, p=0.04, N =1, 1402 participants	-13.92(-27.36, -0.48), I^2=0%, p=0.04, N =4, 1575 participants
Hypoglycemia (events per patient-year)	-7.23(-12.05, -2.40), I^2=0%, p=0.01, N =6, 1663 participants	-13.32(-20.81, -5.83), I^2=0%, p=0.0005, N =4, 1575 participants
Severe Hypoglycemia	0.70 (0.37, 1.04), I^2=0%, p=0.08, N =6, 1663 participants	0.68(0.46, 1.02), I^2=0%, p=0.06, N =4, 1575 participants
DKA	3.08(1.32, 7.17), I^2=0%, p=0.009, N =6, 1663 participants	6.90(1.91, 24.89), I^2=0%, p=0.003, N =4, 1575 participants
UTI	0.89 (0.54, 1.45), I^2=0%, p=0.64, N =6, 1663 participants	1.03(0.68, 1.55), I^2=0%, p0.90, N =4, 1575 participants
GTI	2.64(1.55, 4.49), I^2=0%, p=0.0003, N =6, 1663 participants	3.68(2.17, 6.24), I^2=0%, p<0.00001, N =4, 1575 participants
Diarrhea	1.59 (1.03, 2.46), I^2=0%, p=0.04, N =6, 1663 participants	1.51 (1.07, 2.26], I^2=0%, p=0.04, N =4, 1575 participants
Volume depletion events	2.23 [0.90, 7.44], I^2=0%, p=0.08, N =6, 1663 participants	1.80 (0.70, 4.65), I^2=0%, p=0.22, N =4, 1575 participants
MACE	0.89(0.33, 2.44), I^2=0%, p=0.82, N =6, 1663 participants	1.03 (0.24, 10.55) I^2=0%, p=0.78, N =4, 1575 participants
Renal function at baseline		
Outcome	**eGFR≥60 ml/min/1.73 m^2**	**eGFR≥45 ml/min/1.73m^2**
HbA1c (%)	-0.39 (-0.63, -0.14), I^2=0%, p=0.0002, N =4, 174 participants	-0.37 (-0.46, -0.27), I^2=0%, p<0.00001, N =6, 3064 participants
FPG (mg/dL)	-18.29 (-32.87, -3.71), I^2=28%, p=0.01, N =4, 174 participants	-17.46(-23.00, -11.92), I^2=6%, p<0.00001, N =6, 3064 participants
2h-PPG (mg/dL)	-33.81(-46.92, -20.69), I^2=2%, p<0.00001, N =4, 174 participants	-45.63(-63.51, -27.75), I^2=21%, p<0.00001, N =5, 365 participants
Total insulin dose (IU/d)	-8.46 (-15.13, -1.79), I^2=20%, p=0.01, N =4, 174 participants	-9.03(-11.14, -6.92), I^2=9%, p<0.00001, N =6, 3064 participants
Basal insulin dose (IU/d)	-8.51 [-15.60,- 0.59], I^2=8%, p=0.03, N =4, 174 participants	-8.57 (-10.77, -6.36), I^2=0%, p<0.00001, N =6, 3064 participants
Bolus insulin dose (IU/d)	-17.55 (-26.14, -8.96), I^2=0%, p=0.01, N =4, 174 participants	-9.04 (-12.21, -5.86), I^2=6%, p<0.00001, N =4, 3064 participants

Time-in-Range (%)	11.80 (3.50, 20.10), I^2=NA, p=0.005, N =1, 33 participants	9.44 (5.88, 12.99), I^2=17%, p<0.00001, N =5, 365 participants
Body weight change (%)	-2.98 (-5.02, -0.95), I^2=0%, p=0.0006, N =4, 174 participants	-3.64 (-4.16, -3.11), I^2=35%, p<0.00001, N =6, 3064 participants
Systolic BP (mmHg)	-7.93(-13.06, -2.80), I^2=0%, p=0.0002, N =4, 174 participants	-3.71(-4.64, -2.78), I^2=0%, p<0.00001, N =6, 3064 participants
Diastolic BP (mmHg)	-1.53(-2.59, -0.46), I^2=28%, p=0.005, N =4, 174 participants	-1.51(-2.33, -0.70), I^2=0%, p<0.00001, N =6, 3064 participants
eGFR (ml/min/1.73 m^2)	-1.21(-3.99, -0.57), I^2=0%, p=0.04, N =4, 174 participants	-0.78 [-1.42, -0.15], I^2=0%, p=0.02, N =6, 3064 participants
Albumin-creatinine ratio (ACR)(mg/g)	No study	-14.57(-26.87, -2.28), I^2=0%, p=0.02, N =5, 2977 participants
Hypoglycemia (events per patient-year)	-9.70 [-19.50, -3.11], I^2=0%, p=0.01, N =4, 174 participants	-9.47 (-14.55, -4.38), I^2=0%, p<0.00001, N =6, 3064 participants
Severe Hypoglycemia	0.49 (0.11, 2.06), I^2=0%, p=0.33, N =4, 174 participants	0.71 (0.50, 1.01), I^2=0%, p=0.06, N =6, 3064 participants
DKA	8.06(1.04, 22.25), I^2=0%, p=0.04, N =4, 174 participants	4.72 (1.99, 11.21), I^2=0%, p=0.0002, N =6, 3064 participants
UTI	0.35 (0.08, 1.59), I^2=0%, p=0.91, N =4, 174 participants	1.01 (0.73, 1.40), I^2=0%, p=0.76, N =6, 3064 participants
GTI	2.29 (1.07, 7.71), I^2=0%, p=0.04, N =4, 174 participants	3.38 (2.30, 4.98), I^2=0%, p<0.00001, N =6, 3064 participants
Diarrhea	1.50 [1.08, 3.10], I^2=0%, p=0.04, N =4, 174 participants	1.53 (1.09, 2.14), I^2=0%, p=0.03, N =6, 3064 participants
Volume depletion events	3.85 (0.89, 6.48), I^2=0%, p=0.13, N =4, 174 participants	2.23 (0.91, 4.60), I^2=0%, p=0.33, N =6, 3064 participants
MACE	No events, N =4, 174 participants	1.06 (0.40, 2.82), I^2=0%, p=0.91, N =6, 3064 participants

Sensitivity analysis: Peto Odds Ratio, fixed-effect model

Outcome	**OR(95%CI), I^2, statistical significance, N-comparisons, participants**
Severe Hypoglycemia	0.68(0.46, 0.98), I^2=0%, p=0.04,N=10, 3238 participants
DKA	3.92 (2.37, 6.47), I^2=0%, p<0.00001, N=10, 3238 participants
UTI	0.98(0.71, 1.37), I^2=0%, p=0.92, N=10, 3238 participants
GTI	2.85(2.10, 3.87), I^2=0%, p<0.00001, N=10, 3238 participants
Diarrhea	1.55 (1.11, 2.16), I^2=0%, p=0.01, N=10, 3238 participants

Nausea-vomiting	0.97(0.32, 2.96), I^2=0%, p=0.96, N=10, 3238 participants
Headache	1.69(0.26, 11.04), I^2=0%, p=0.58, N=10, 3238 participants
Sinusitis	1.07(0.06, 18.62), I^2=0%, p=0.91, N=10, 3238 participants
Nasopharyngitis	1.07(0.14, 8.39), I^2=0%, p=0.91, N=10, 3238 participants
Renal events	1.19(0.57, 2.45),I^2=0%, p=0.65, N=10, 3238 participants
Acidosis-related Events	3.70 (2.80, 4.90), I^2=0%, p<0.00001, N=10, 3238 participants
Volume depletion events	2.64 (1.44, 4.83), I^2=0%, p=0.01, N=10, 3238 participants
Bone fractures	0.70(0.39, 1.25), I^2=0%, p=0.23, N=10, 3238 participants
Amputation	3.40(0.26, 18.38)I^2=0%, p=0.38, N=10, 3238 participants
Suspected drug-duced liver injury	1.01(0.09, 11.13), I^2=0%, p=0.99, N=10, 3238 participants
Serious AEs	1.13(0.86, 1.48), I^2=0%, p=0.39, N=10, 3238 participants
AEs leading to Discontinuation	1.57 (1.06, 2.34), I^2=0%, p=0.02, N=10, 3238 participants
MACE	1.15(0.48, 2.80), I^2=0%, p=0.75, N=10, 3238 participants
Cancer	0.67(0.22, 2.11), I2=0%, p=0.75, N=10, 3238 participants
All-cause deaths	0.19 (0.03, 1.51), I^2=0%, p=0.12, N=10, 3238 participants

Abbreviations: AE: adverse events; FPG: fasting plasma glucose; MACE: major adverse cardiovascular outcomes DKA: diabetic ketoacidosis; GTI: genital tract infections; PPG: postprandial plasma glucose; UTI: urinary tract infections

Supplementary Table 4. Dose-response interactions: within-trial analysis of the pooled data from three RCTs (Baker et al; Buse et al; Danne et al.). Only statistically significant interactions between evaluated outcomes and sotagliflozin doses are reported.

Outcome	Sotagliflozin 200 mg vs. 75 mg	Sotagliflozin 400 mg vs. 200 mg
HbA1c (%)	-0.24 (-0.62, 0.14) I^2=NA, p=0.22, N =1, 70 participants	-0.22 (-0.28, -0.12) , I^2=0%, p=0.001, N =3, 1119 participants
FPG (mg/dL)	0.0 (-14.06, 14.06), I^2=NA, p=1.00, 1.0 N =1, 70 participants	-9.82 (-17.05, -2.58), I^2=0%, p=0.008, N =3, 1119 participants
2h-PPG (mg/dL)	-8.00(-27.46, 11.46), I^2=NA, p<0.00001, N =1, 70 participants	-20.51 (-33.98, -7.03), I^2=0%, p=0.003, N =3, 1119 participants
Total insulin dose (%)	2.60(-6.78, 11.98), I^2=0%, p=0.77, N =1, 70 participants	-5.25(-7.66, -2.84), I^2=0%, p<0.0001, N =3, 1119 participants
Basal insulin dose (%)	-0.10(-11.11, 10.91), I^2=0%, p=0.99, N =1, 70 participants	-4.64(-8.64, -0.64), I^2=0%, p=0.01, N =3, 1119 participants
Bolus insulin dose (%)	-2.80(-8.48, 14.08), I^2=0%, p=0.89, N =1, 70 participants	-7.85(-11.96, -3.75), I^2=0%, p=0.0002, N =3, 1119 participants
Time-in-range(%)	No study	6.48(2.97, 9.99), I^2=0%, p=0.0003, N =2, 185 participants
Average daily Glucose (mg/dL)	No study	-11.02(-17.70, -4.33), I^2=0%, p=0.001, N =2, 185 participants
Urinary glucose Excretion (g/24 hr)	16.00(3.06, 28.94), p=0.03, N =1, 70 participants	13.00(-1.78, 27.78), p=0.20, N =1, 70 participants
Body weight (%)	-1.33(-3.37, 0.71), p=0.20, N =1, 70 participants	-0.96 (-1.55, -0.37), I^2=0%, p=0.001, N =3, 1119 participants
Systolic BP(mmHg)	1.60(-7.42, 10.62), p=0.53, N =1, 70 participants	-2.51 (-3.83, -1.20), I^2=0%, p=0.0002, N =3, 1119 participants
eGFR (ml/min/1.73 m^2)	-0.26(-4.95, 4.43), p=0.91, N =1, 70 participants	1.05(0.11, 2.12], p=0.03, N =1, N =3, 1119 participants
Urinary albumin/creatinine ratio (ACR)(mg/g)	No study	-12.29 (-26.81, -1.23), I^2=0%, p=0.03, N =3, 1049 participants

Supplementary Table 5: Summary of main findings of meta-analysis for safety outcomes in included RCTs

Outcome	Studies (n)	Events/Participants (n/N)		Effect estimate [95%CI]	I^2 (%)
		Sotagliflozin	Control		
Hypoglicemia (events per patient-year)	**6**	**87/1912**	**98/1326**	**MD: -7.69 (-13.25, -2.13)**	**0**
Severe hypoglycemia	**6**	**68/1912**	**57/1326**	**RR: 0.69 (0.49, 0.98)**	**0**
Diabetic ketoacidosis (DKA)	**6**	**61/1912**	**6/1326**	**RR: 3.93 (1.94, 7.96)**	**0**
Occurring at blood glucose>250 mg/dL n(% total events)		42 (69%)	4 (67%)		
Occurring at blood glucose≥150-250 mg/dL n(% total events)		19(31%)	2(33%)		
Occurring at blood glucose<150-mg/dL n(% total events)		0 (0%)	0 (0%)		
Urinary tract infections (UTIs)	**6**	**96/1912**	**63/1326**	**RR: 0.97 (0.71, 1.33)**	**0**
Genital mycotic infections (GTIs)	**6**	**161/1912**	**31/1326**	**RR: 3.12 (2.14, 4.54)**	**0**
Diarrhea	**6**	**114/1912**	**46/1326**	**RR: 1.50 (1.08, 2.10)**	**0**
Nausea-vomiting	**6**	**8/ 1912**	**7/1326**	**RR: 0.60 (0.12, 2.94)**	**0**
Headache	**6**	**3/1912**	**2/1326**	**RR: 1.59 (0.30, 8.33]**	**0**
Sinusitis	**6**	**1/1912**	**1/1326**	**RR: 1.07 [0.06, 15.62)**	**0**
Nasopharingytis	**6**	**2/1912**	**2/1326**	**RR: 1.07 (0.13, 8.67)**	**0**
Renal events	**6**	**21/1912**	**11/1326**	**RR: 1.16 (0.56, 2.40)**	**0**
Acidosis-related events	**6**	**187/1912**	**32/1326**	**RR: 3.85 (2.33, 6.36)**	**23**
Volume depletion events	**6**	**38/1912**	**8/1326**	**RR: 2.19 (1.10, 4.36)**	**0**
Bone fractures	**6**	**29/1912**	**23/1326**	**RR: 0.71 (0.40, 1.24)**	**0**
Amputation	**6**	**2/1912**	**0/1326**	**RR: 3.02 (0.31, 29.09)**	**0**

Suspected drug-induced liver injury	**6**	**2/1912**	**1/1326**	**RR: 0.44 (0.07, 2.76)**	**0**
Venous thromboembolism	6	0/1877	0/1888	-	-
Serious AEs	**6**	**109/1912**	**143/1326**	**RR: 1.29 (0.89, 1.82)**	**0**
AEs leading to discontinuation	**6**	**81/1912**	**31/1326**	**RR: 1.34 (0.78, 2.30)**	**25**
Hypoglycemia		**1 (1%)***	**3(3%)***		
Severe hypoglycemia		**4(6%)***	**3(5%)***		
Diabetic ketoacidosis (DKA)		**23(38%)***	**1(17%)***		
Urinary tract infections (UTIs)		**3(3%)***	**4(6%)***		
Genital tract infections (GTIs)		**9(6%)***	**3(10%)***		
Diarrhea		**8(7%)***	**3(7%)***		
Volume depletion events		**1(4%)***	**1(12%)***		
Major adverse cardiovascular outcomes (MACE)	**6**	**15/1912**	**7/1326**	**RR: 1.06 (0.40, 2.82)**	**0**
AMI		8	3		
Stroke		1	2		
Hospitalization for HF/UA		0	0		
Coronary revascularization		6	2		
Cancer	**6**	**7/1912**	**4/1326**	**RR: 0.86 (0.25, 2.97)**	**0**
Breast		2	2		
Lung		3	2		
Thyroid		1	0		
Melanoma		1	0		
All-cause death	**6**	**1/1912**	**3/1326**	**RR: 0.35 (0.07, 1.70)**	**0**

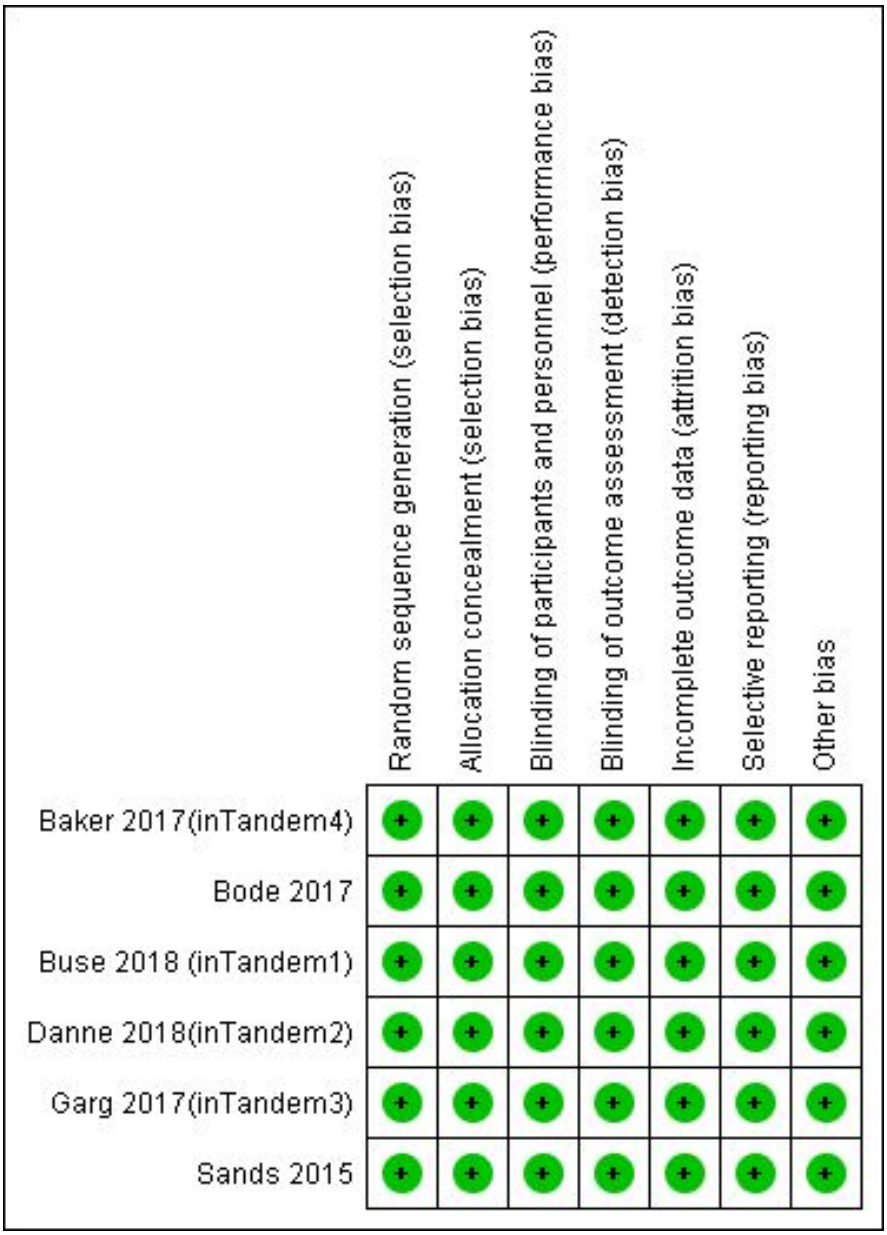
Abbreviations: AE : adverse events; VTE:Venousthromboembolism;Sota: sotagliflozin;TID: total daily insulin dose; plcb: placebo; HF: heart failure; UA: unstable angina.

*the percentage refers to the percentage of all patients experiencing that AE

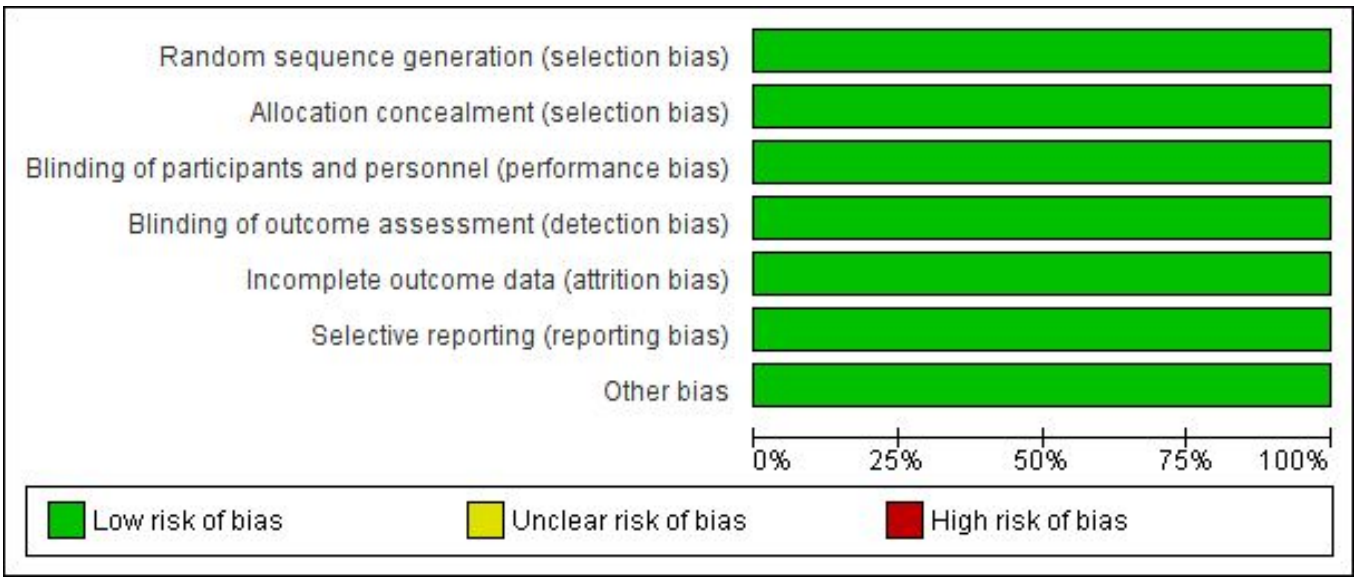
For all outcomes, the length of follow-up ranged 4 to 52 weeks

Supplementary Figures

Supplementary Figure 1. Risk of bias summary: risk of bias item for each included RCT according to Cochrane Risk-of-Bias Tool

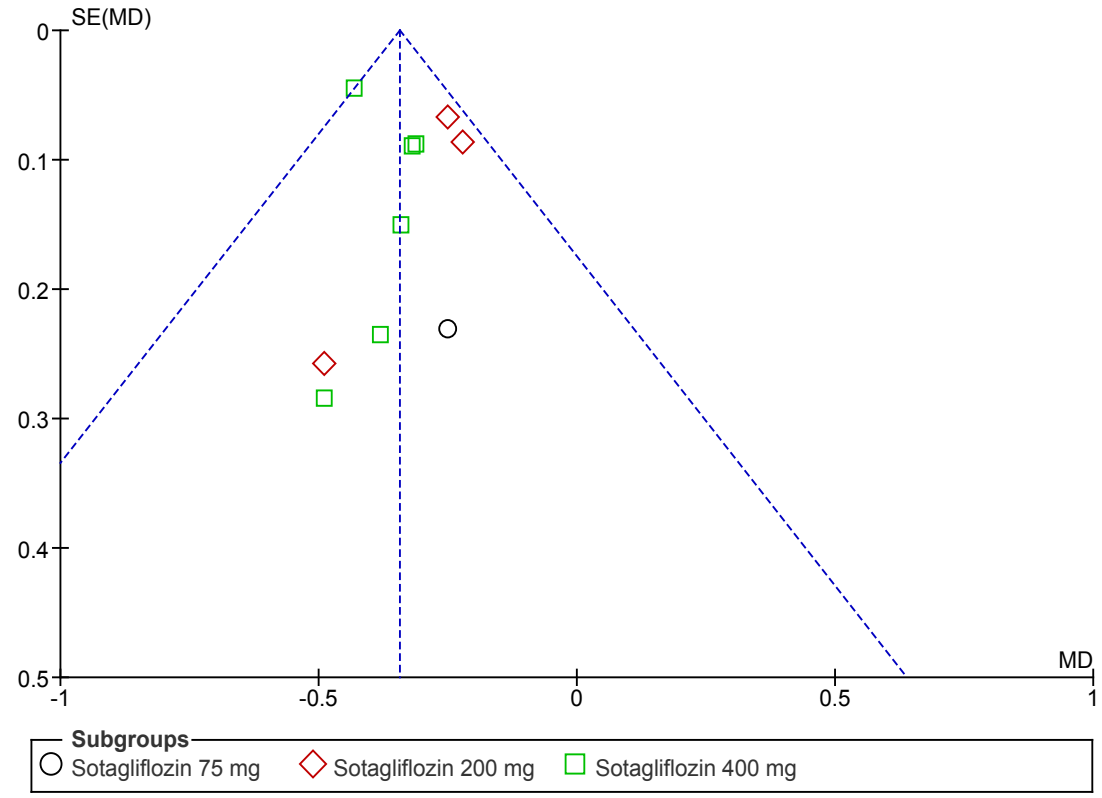


Supplementary Figure 2. Risk of bias graph: each risk of bias item is presented as percentages across all included RCTs.

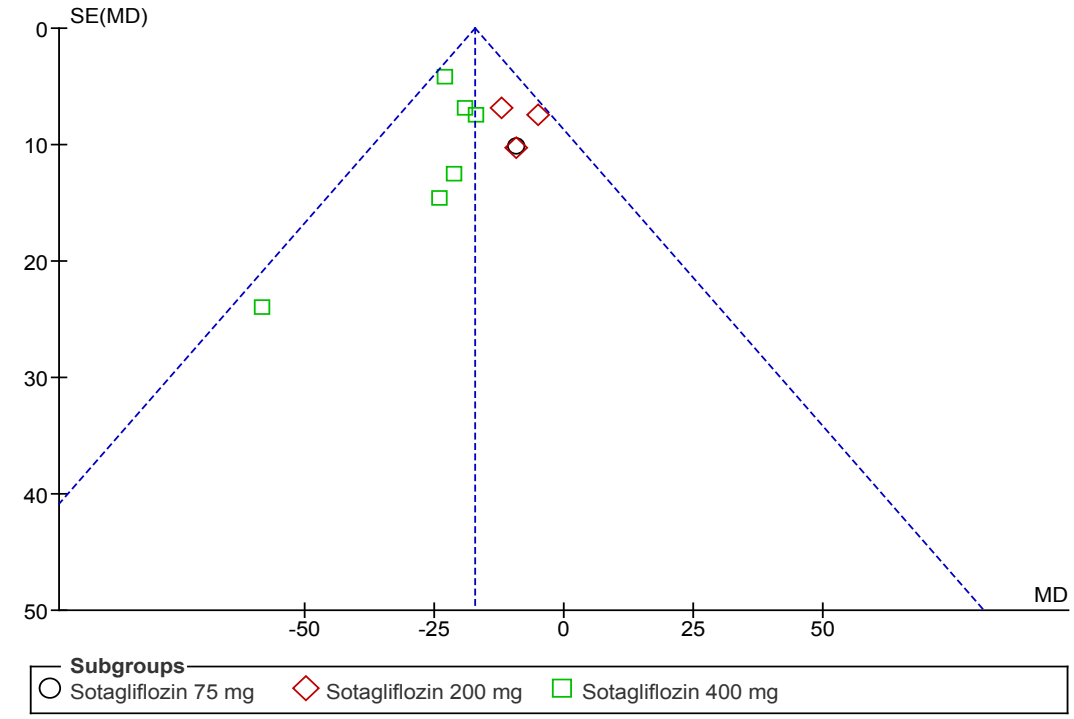


Supplementary Figure 3.

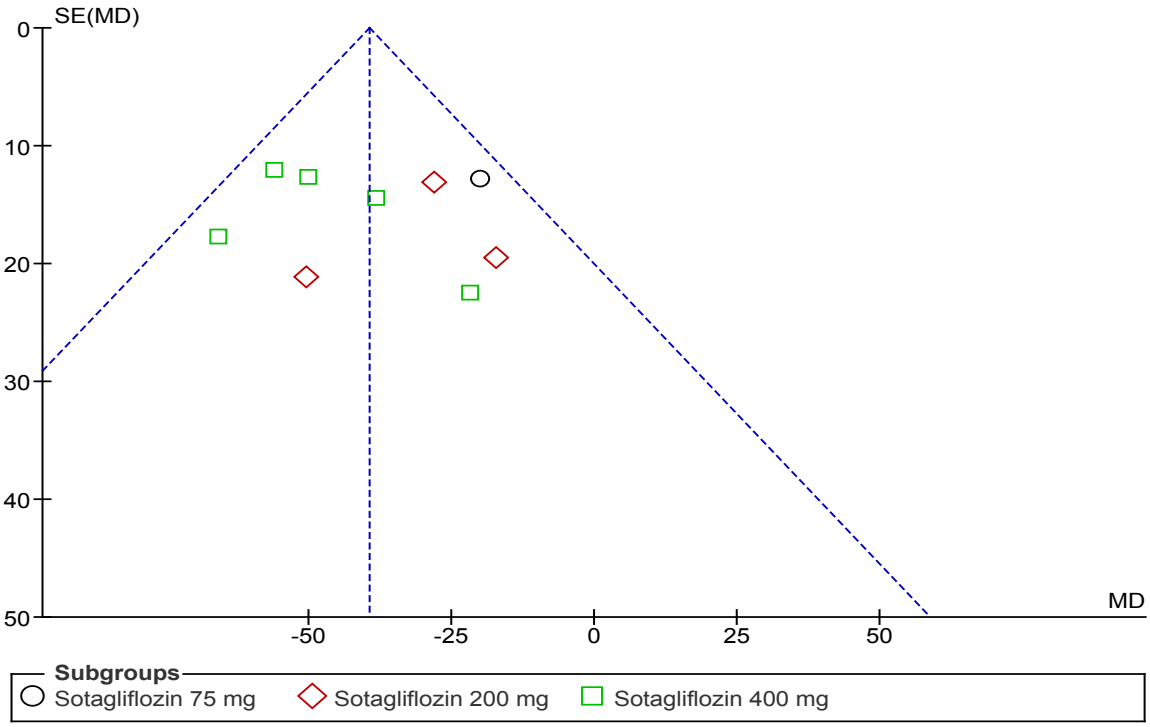
Panel A Funnel plot of comparison: HbA1c(%) outcome: HbA1c(%).



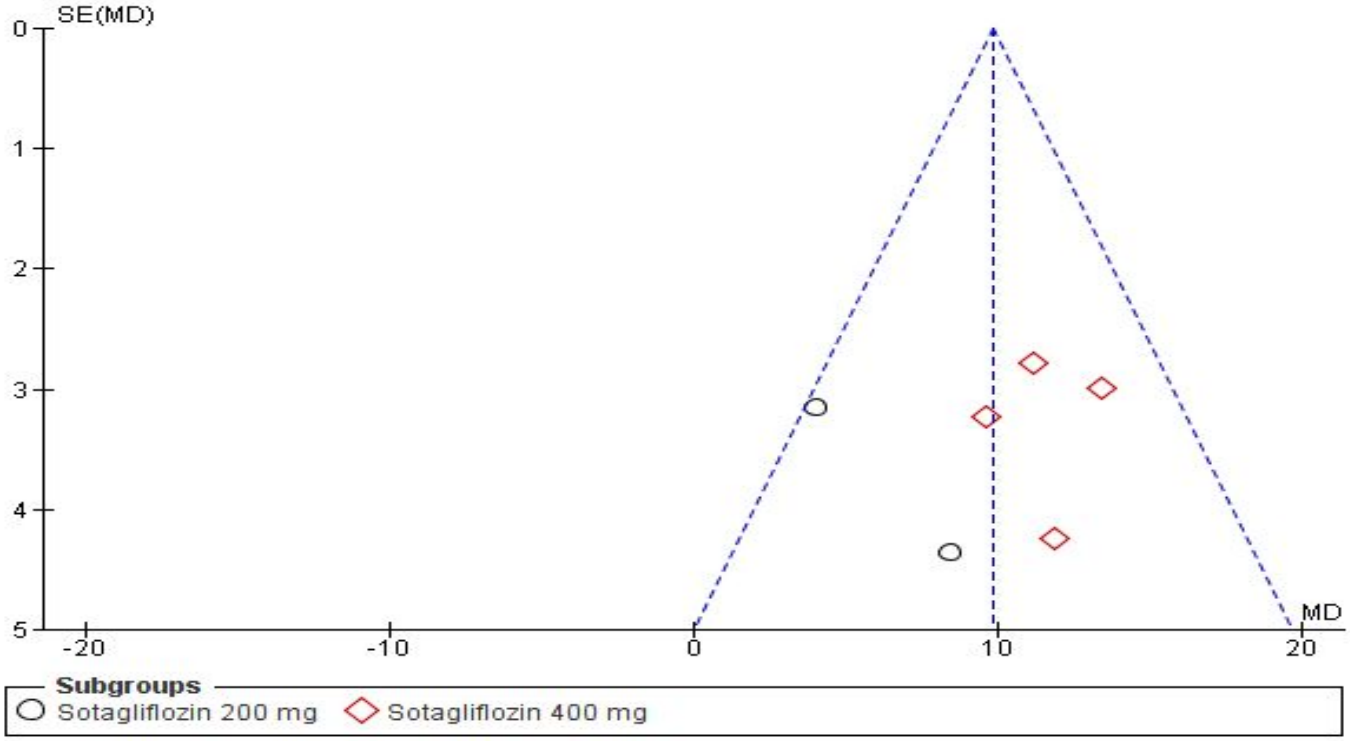
Panel B Funnel plot of comparison: Fasting plasma glucose (FPG; (mg/dL) outcome: FPG(mg/dL).



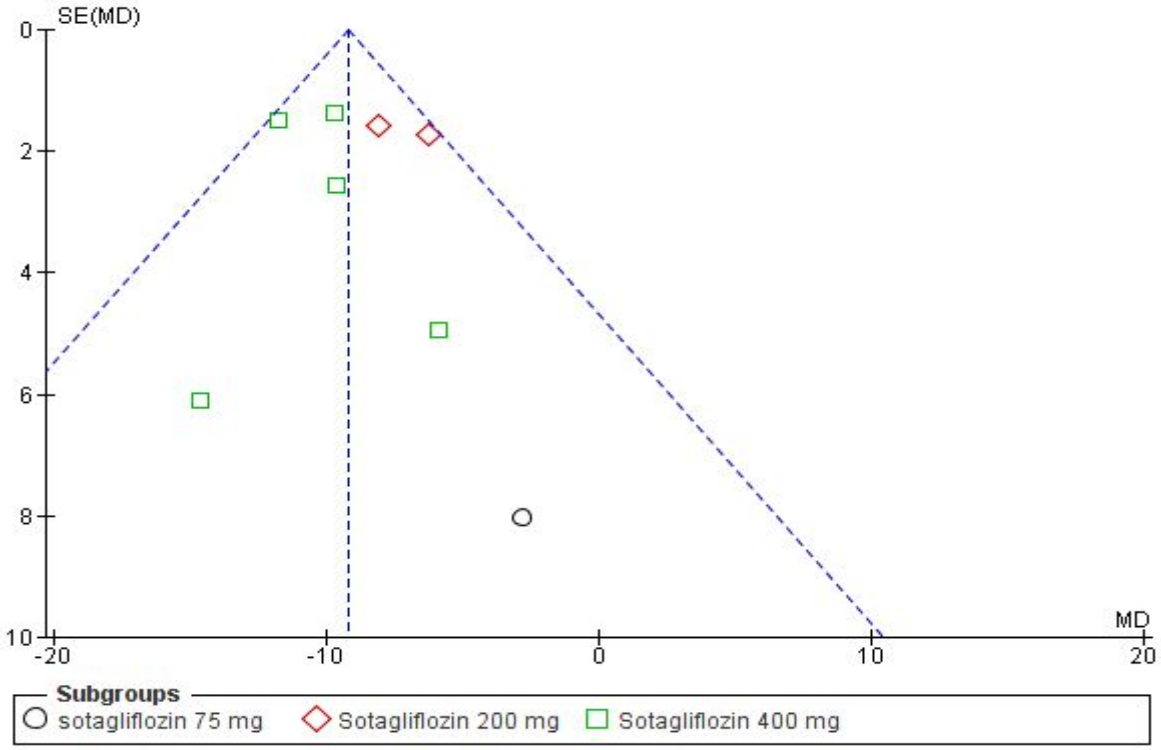
Panel C. Funnel plot of comparison: 2-hr postprandial plasma glucose(PPG) for outcome: 2hr-PPG.



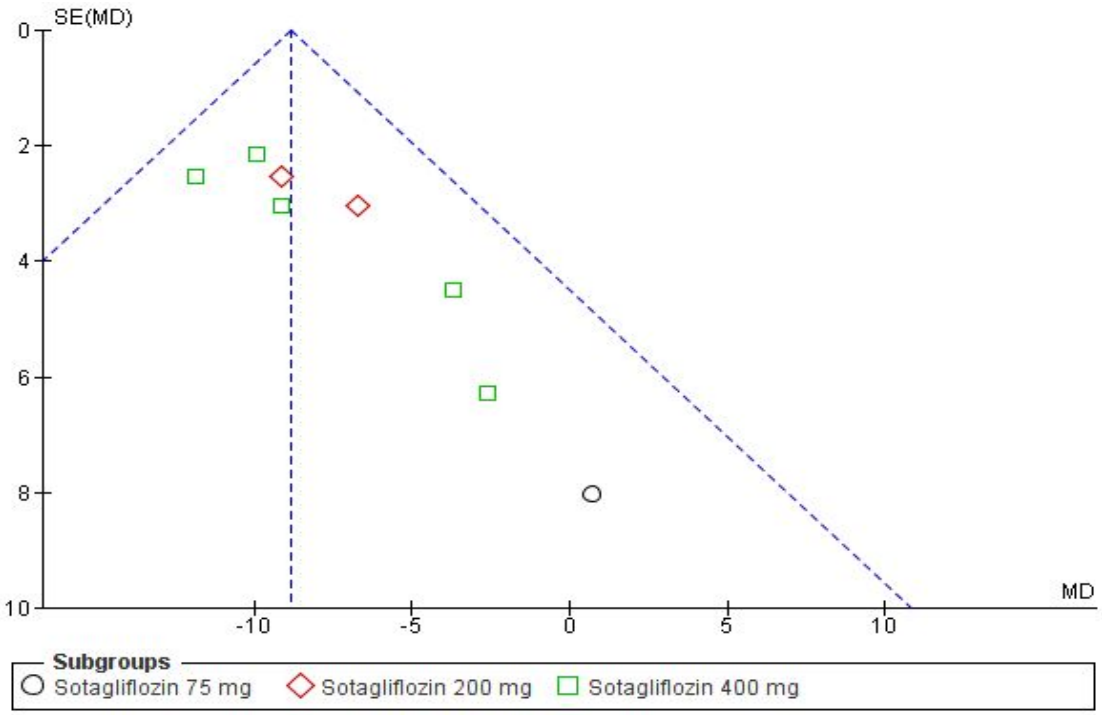
Panel D. Funnel plot of comparison: % time-in-range (70-180 mg/dL) for outcome: % time-in-range



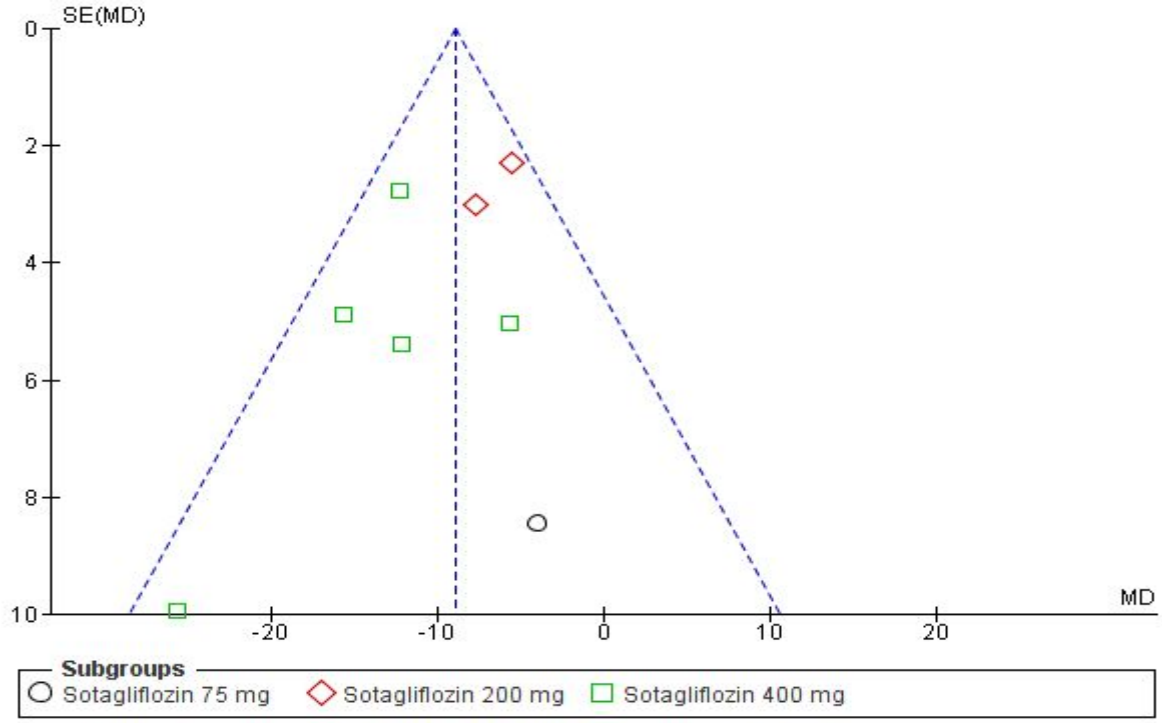
Panel E. Funnel plot of comparison: total daily insulin dose, outcome: total daily insulin dose(% change)



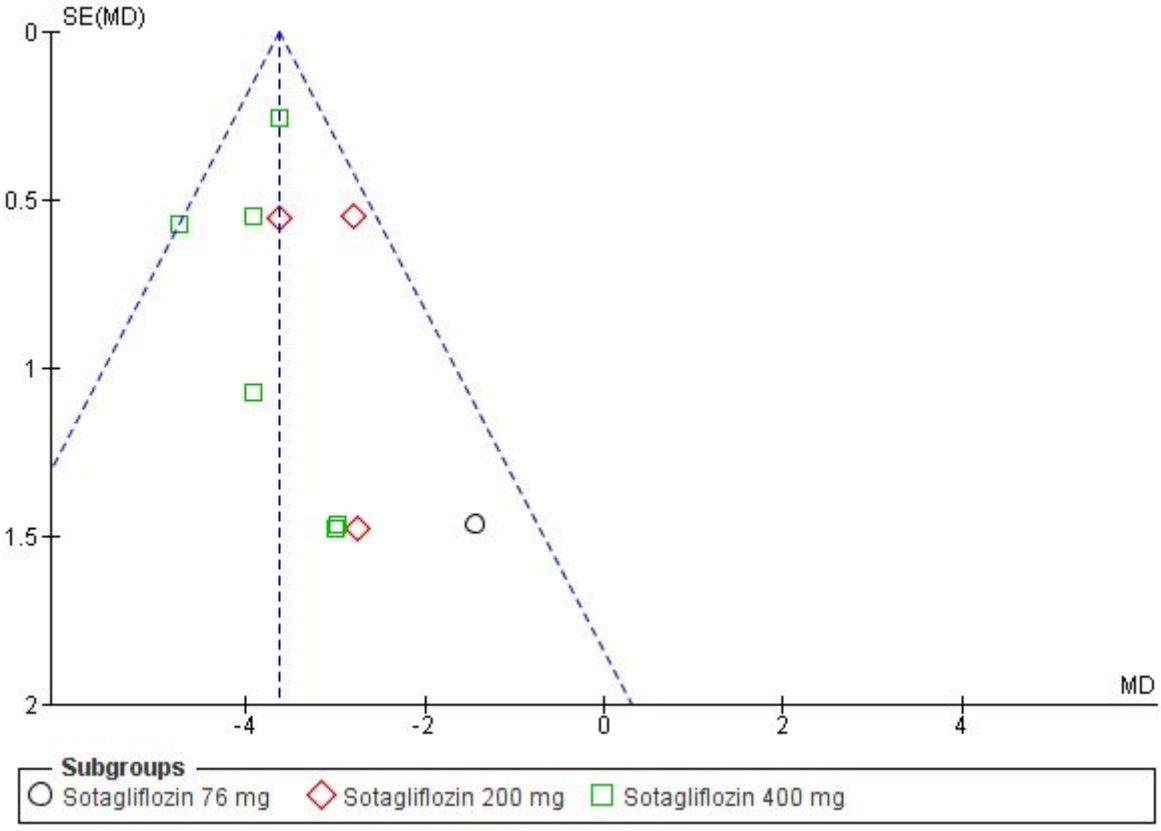
Panel F. Funnel plot of comparison: basal daily insulin dose, outcome: basal daily insulin dose(% change)



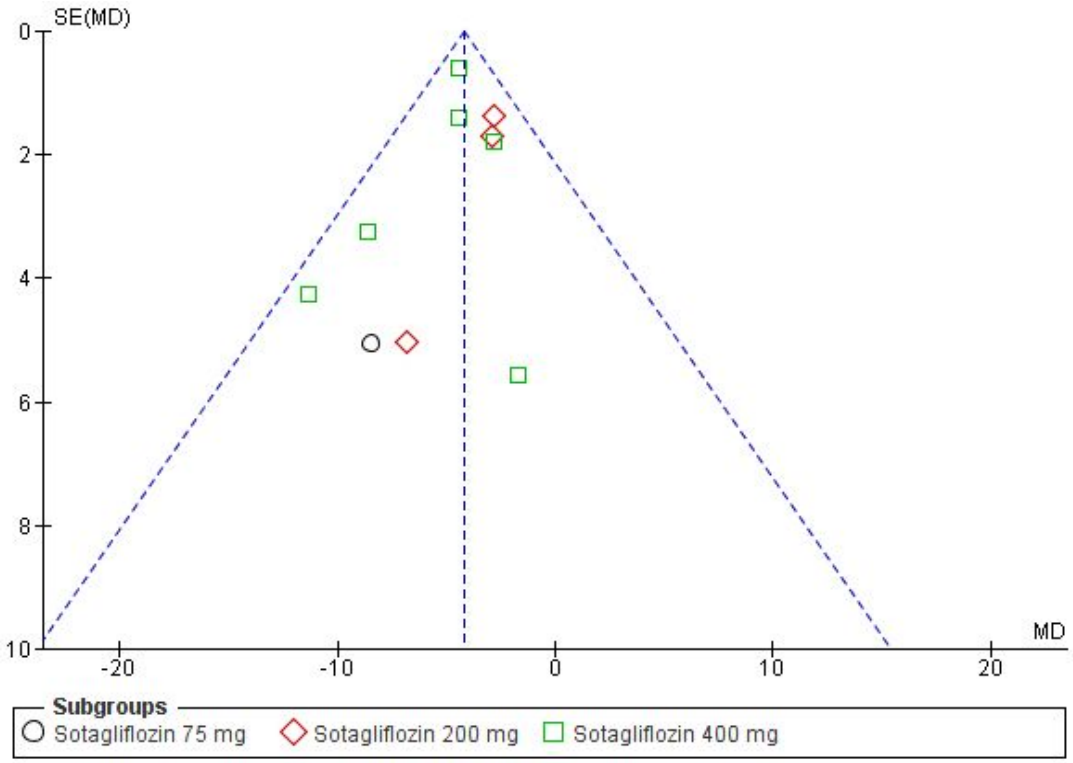
Panel G. Funnel plot of comparison: bolus daily insulin dose, outcome: bolus daily insulin dose(% change)



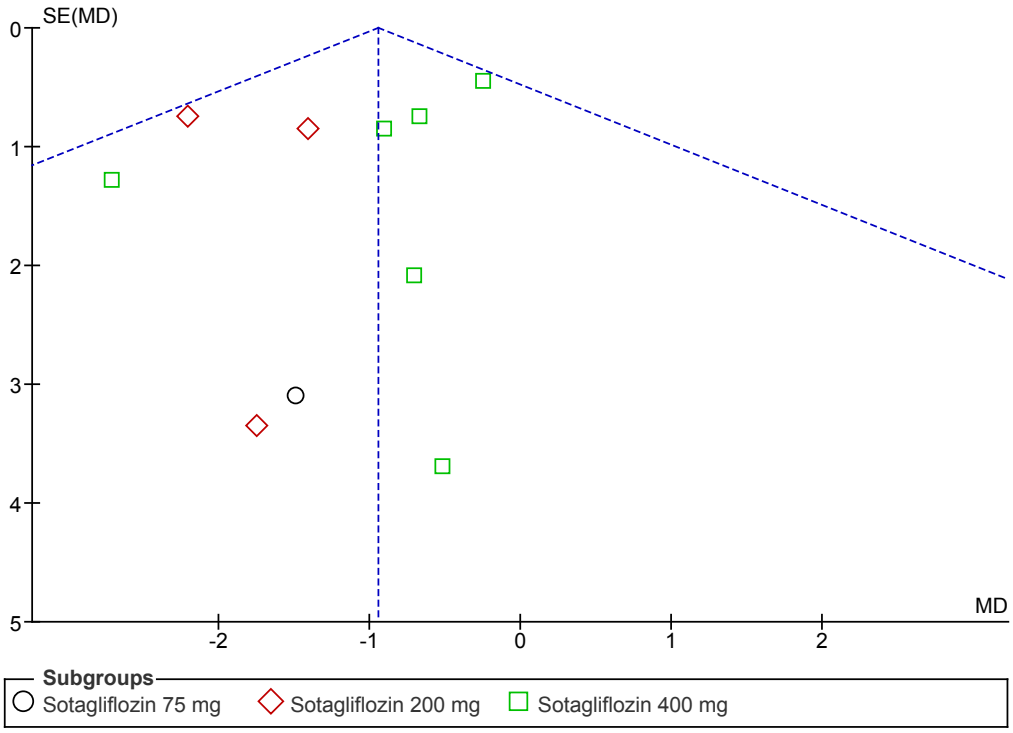
Panel H. Funnel plot of comparison: body weight changes, outcome: body weight changes(%)



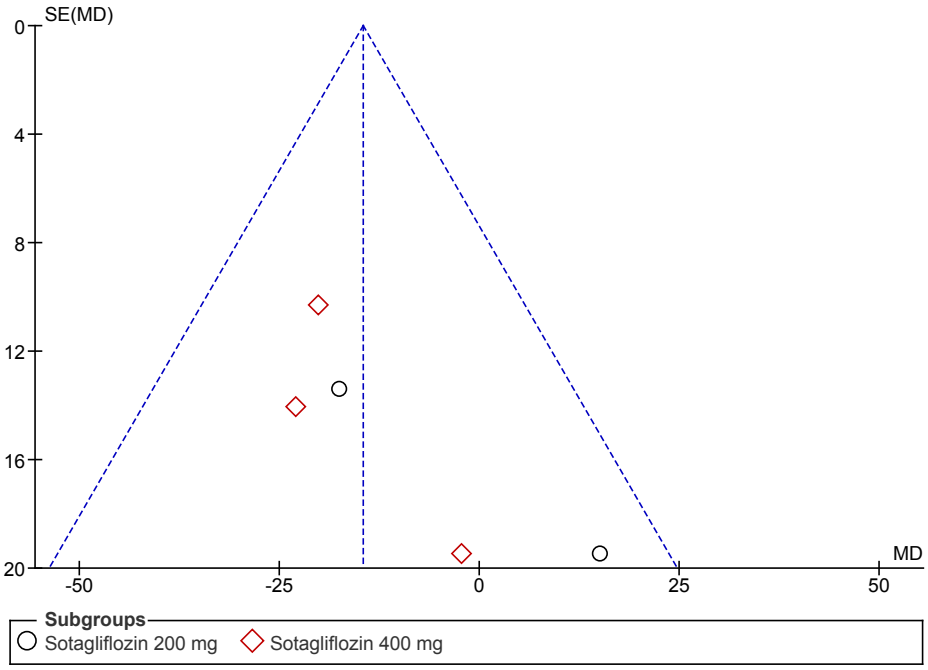
Panel I. Funnel plot of comparison: sys BP, outcome: sys BP(mmHg)



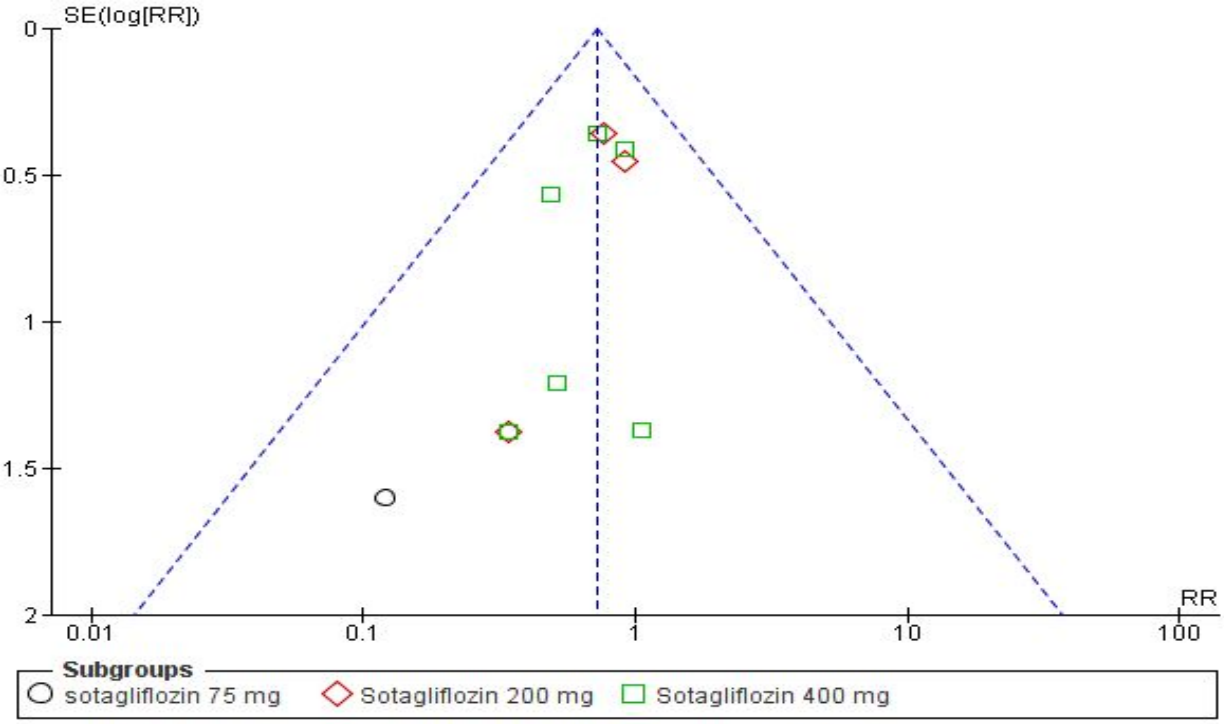
Panel L. Funnel plot of comparison: eGFR changes, outcome: eGFR changes(ml/min/1.73 m2)



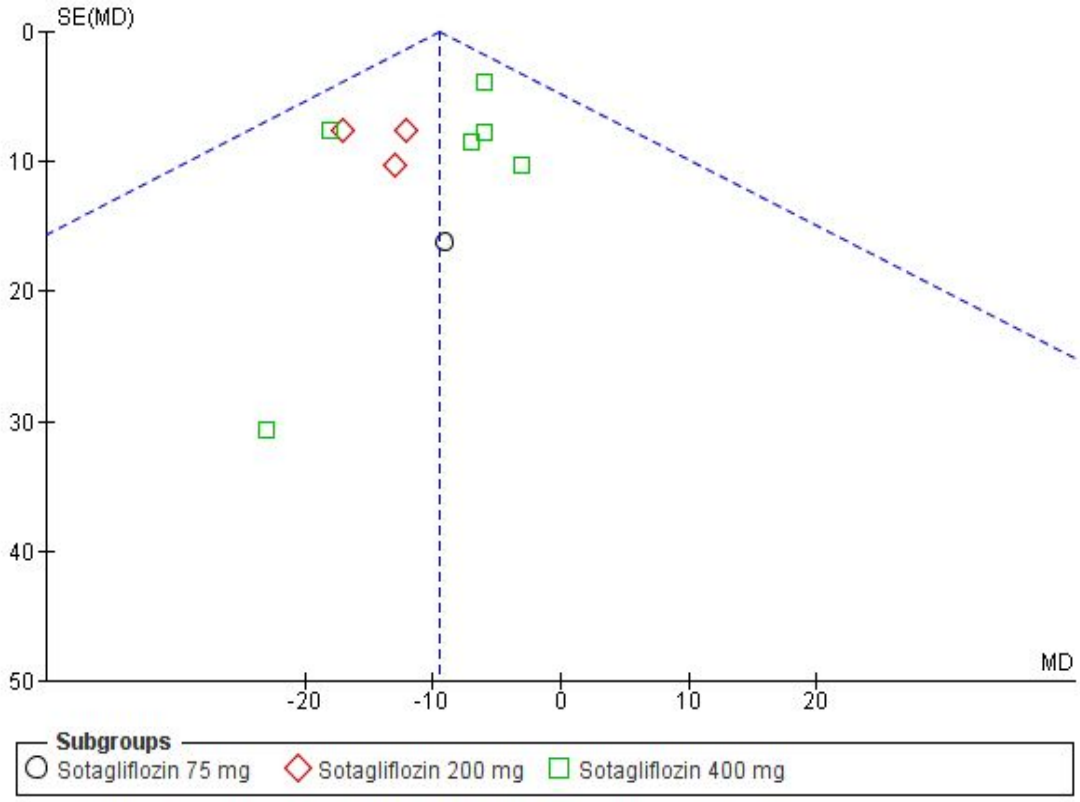
Panel M. Funnel plot of comparison: urinary A/C ratio, outcome: albumin/creatinine ratio(mg/g).



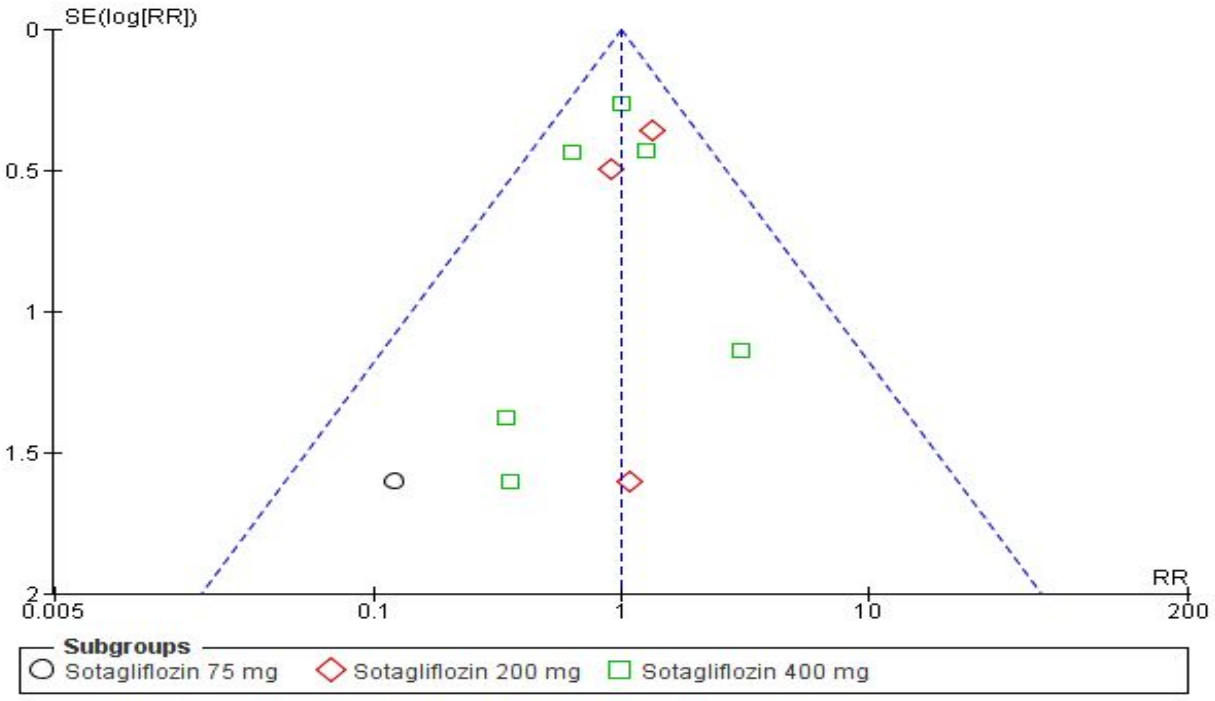
Panel N. Funnel plot of comparison: severe hypoglycemia, outcome: severe hypoglycemia.



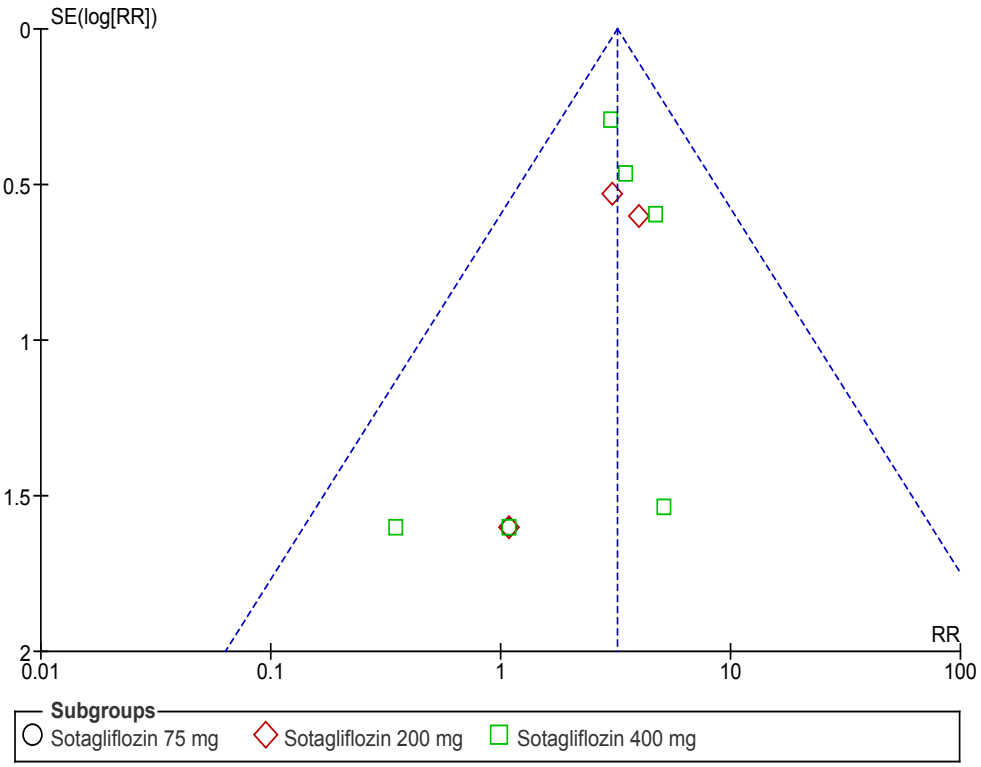
Panel O. Funnel plot of comparison: hypoglycemia, outcome: hypoglycemia (events per patient-year).



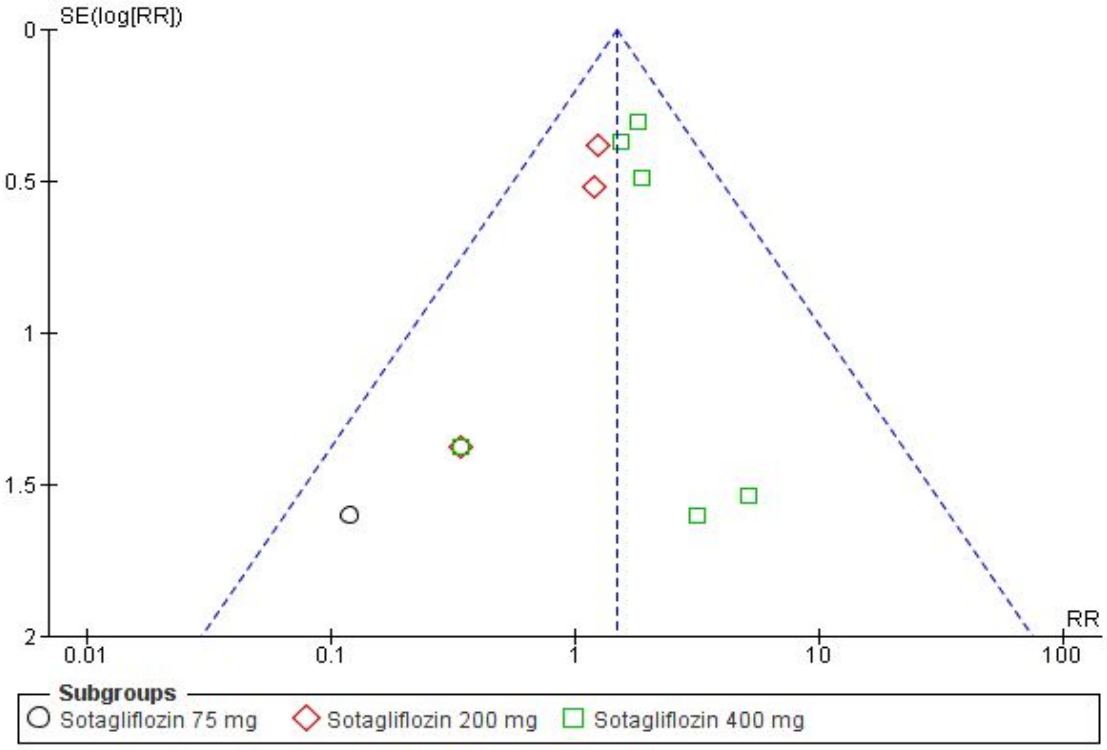
Panel P. Funnel plot of comparison: urinary tract infections, outcome: urinary tract infections.



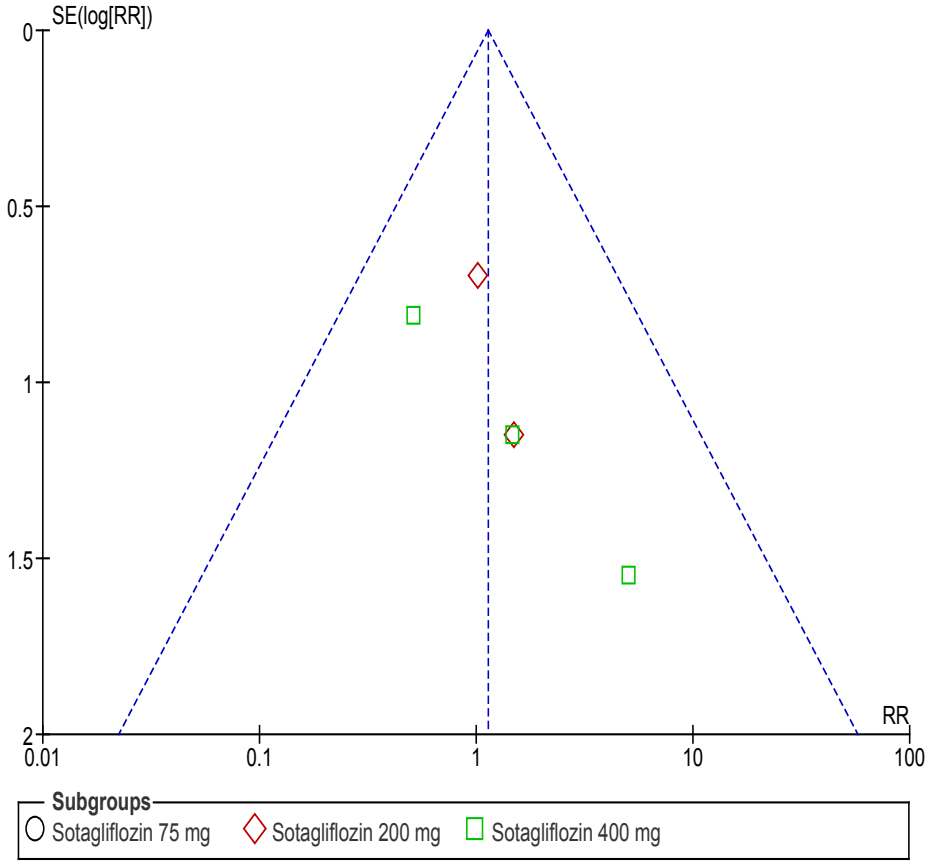
Panel Q. Funnel plot of comparison: genital tract infections, outcome: genital tract infections.



Panel R. Funnel plot of comparison: diarrhea, outcome: diarrhea

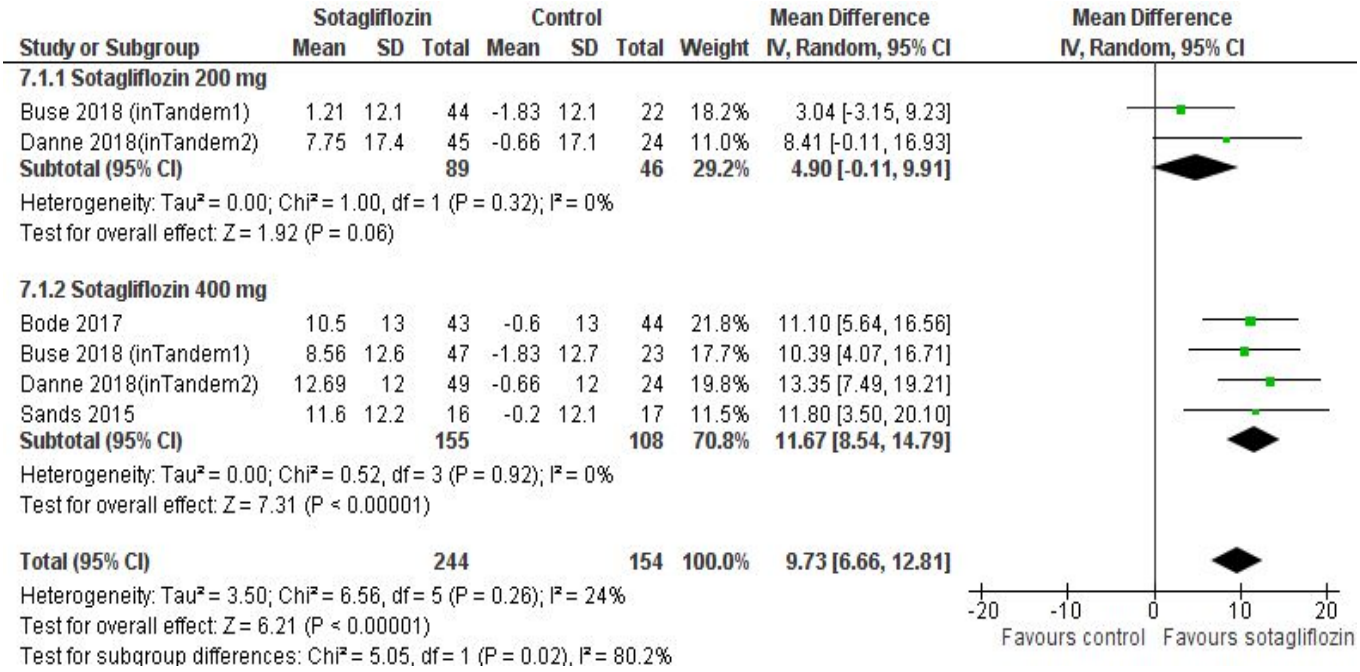


Panel S. Funnel plot of comparison: MACE, outcome: MACE

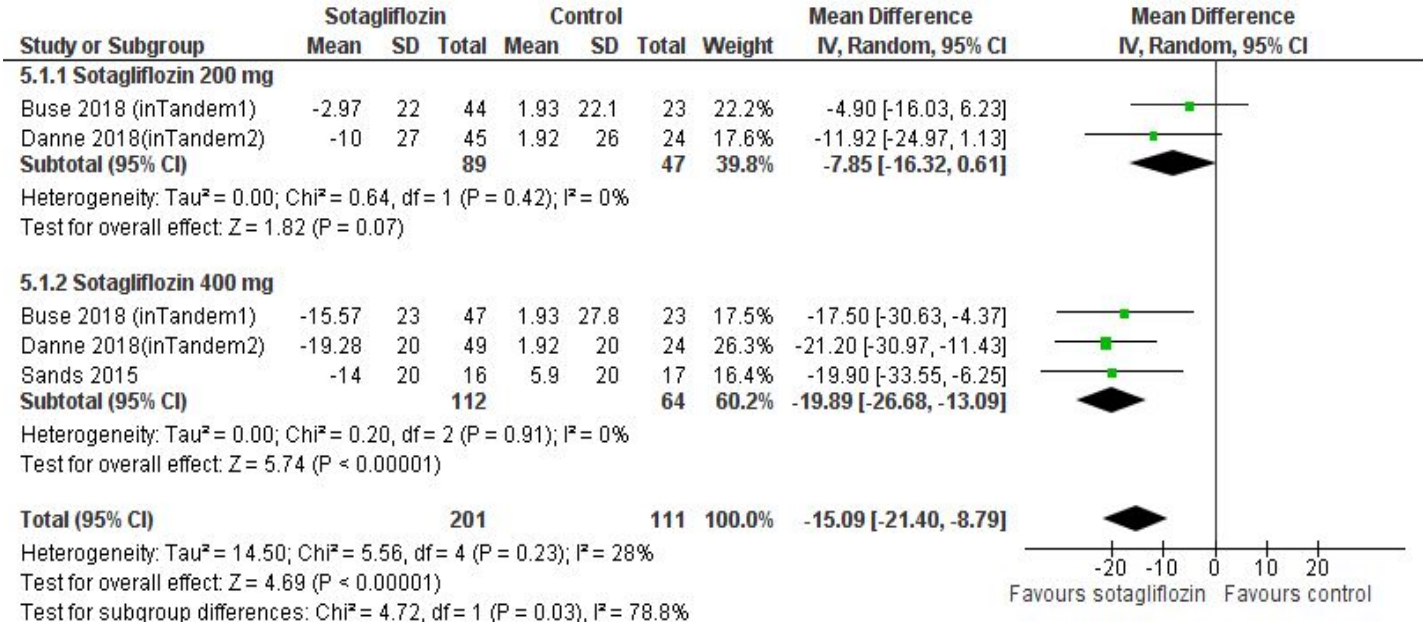


Supplementary Figure 4. Forest plot of comparison: Sotagliflozin, outcome: Continuous Glucose Monitoring (CGM) parameters.

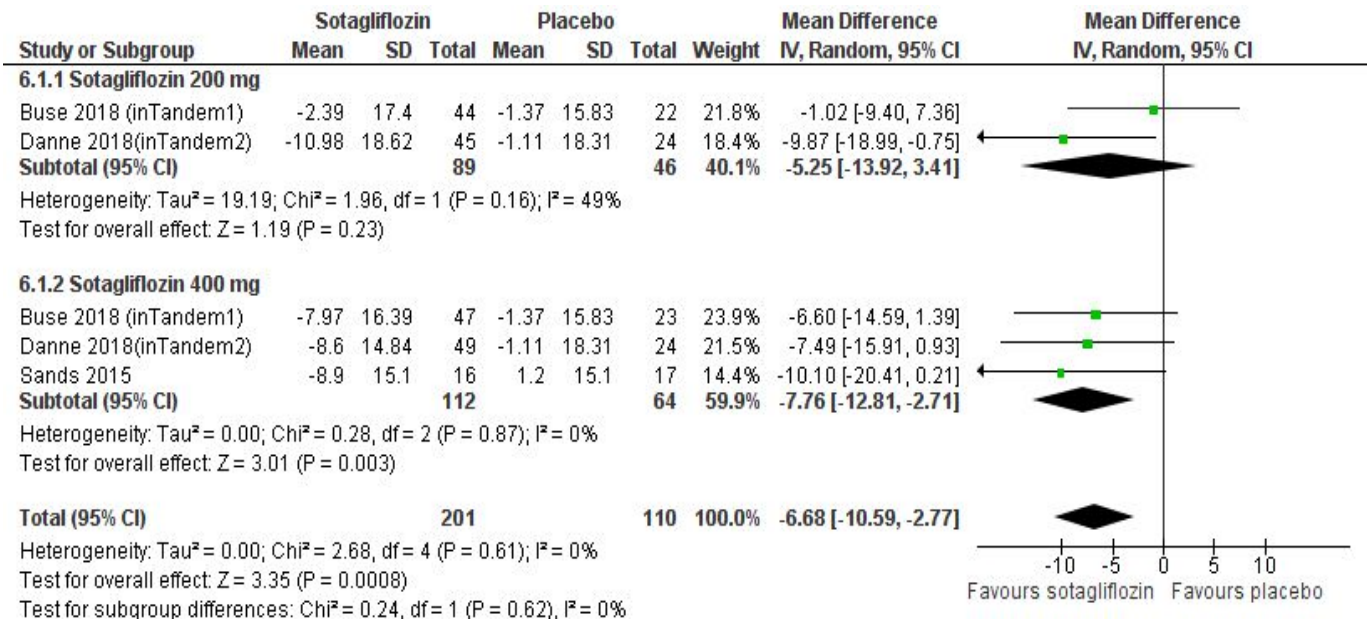
Panel A: outcome: time-in-range (%)



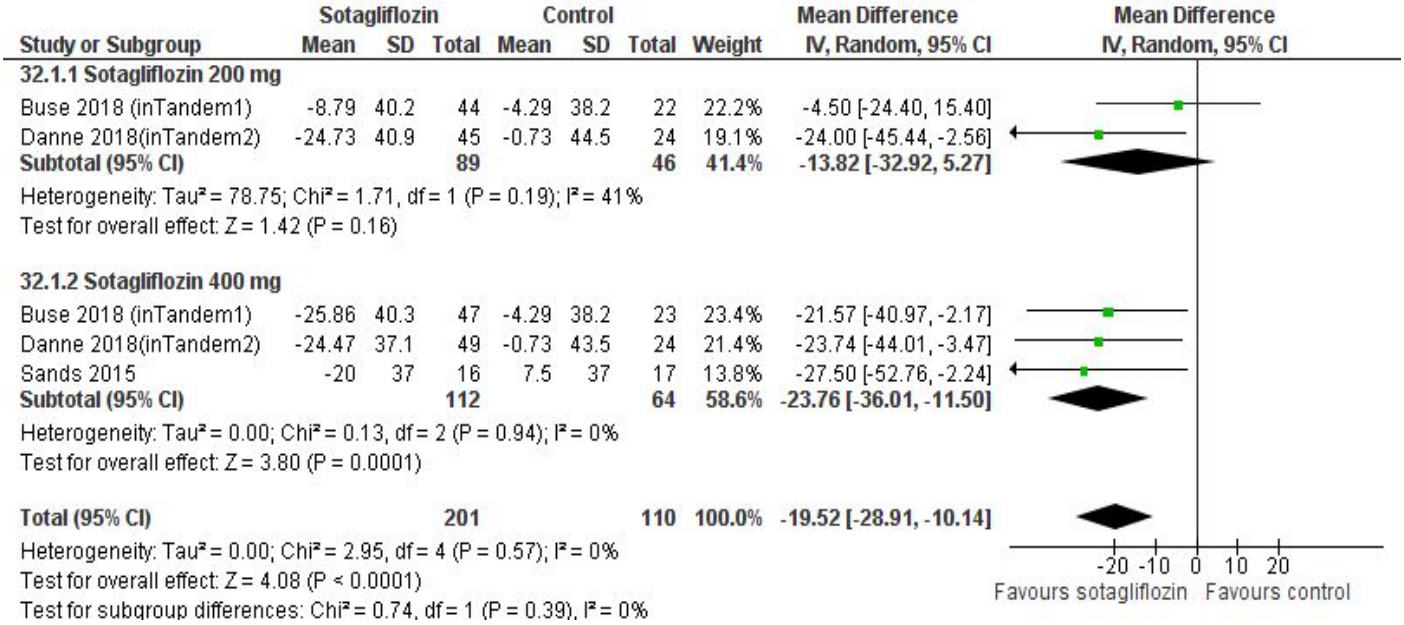
Panel B: outcome: average daily glucose (mg/dL)



Panel C: outcome: Standard Deviation (SD) around average daily glucose (mg/dL)

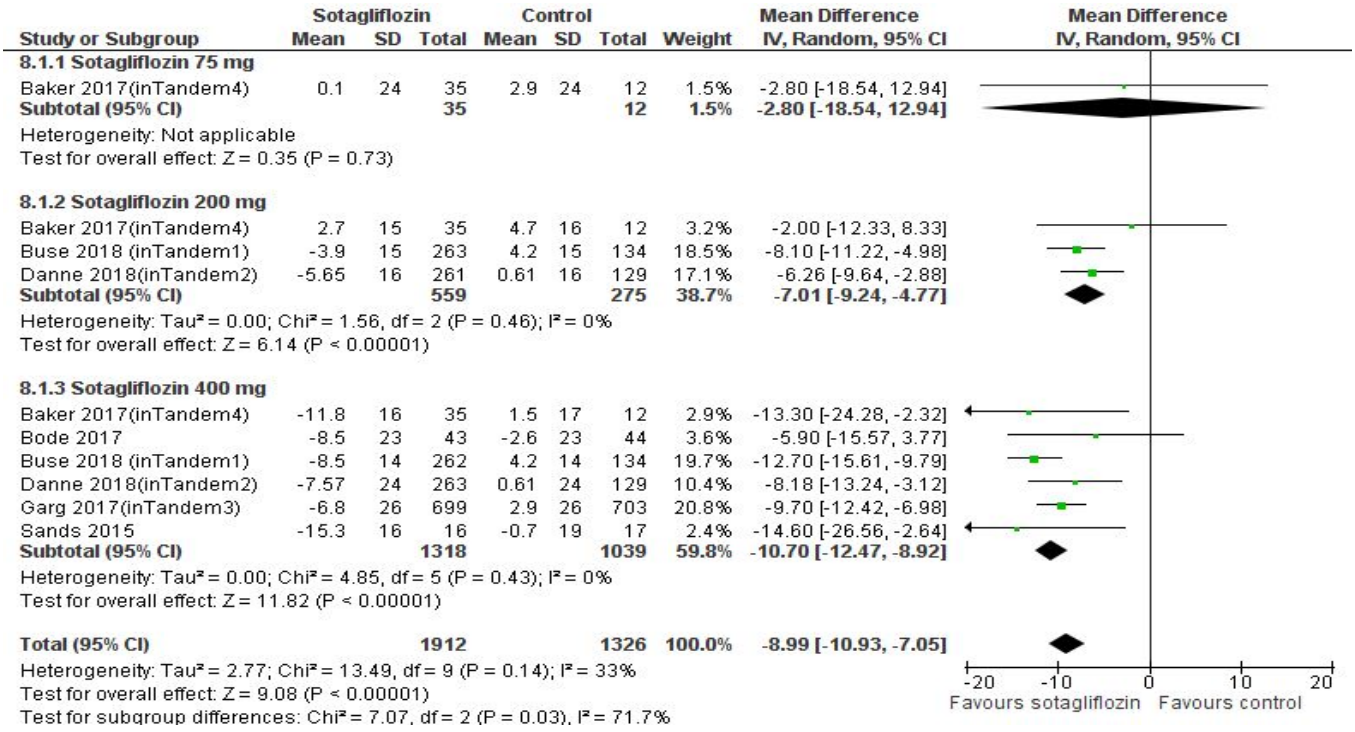


Panel D: outcome: mean amplitude of glucose excursion (MAGE) (mg/dL)

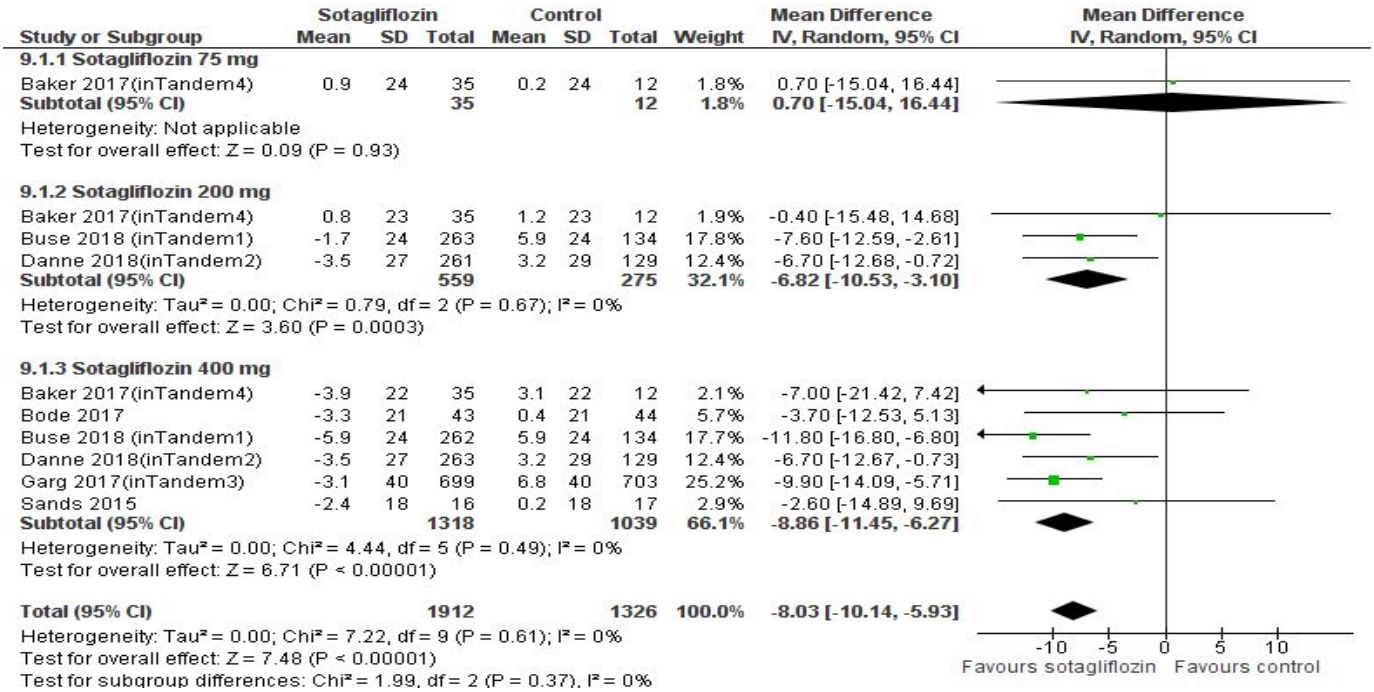


Supplementary Figure 5. Forest plot of comparison: Sotagliflozin, outcome: Daily total, basal and bolus insulin dose (%) changes from baseline.

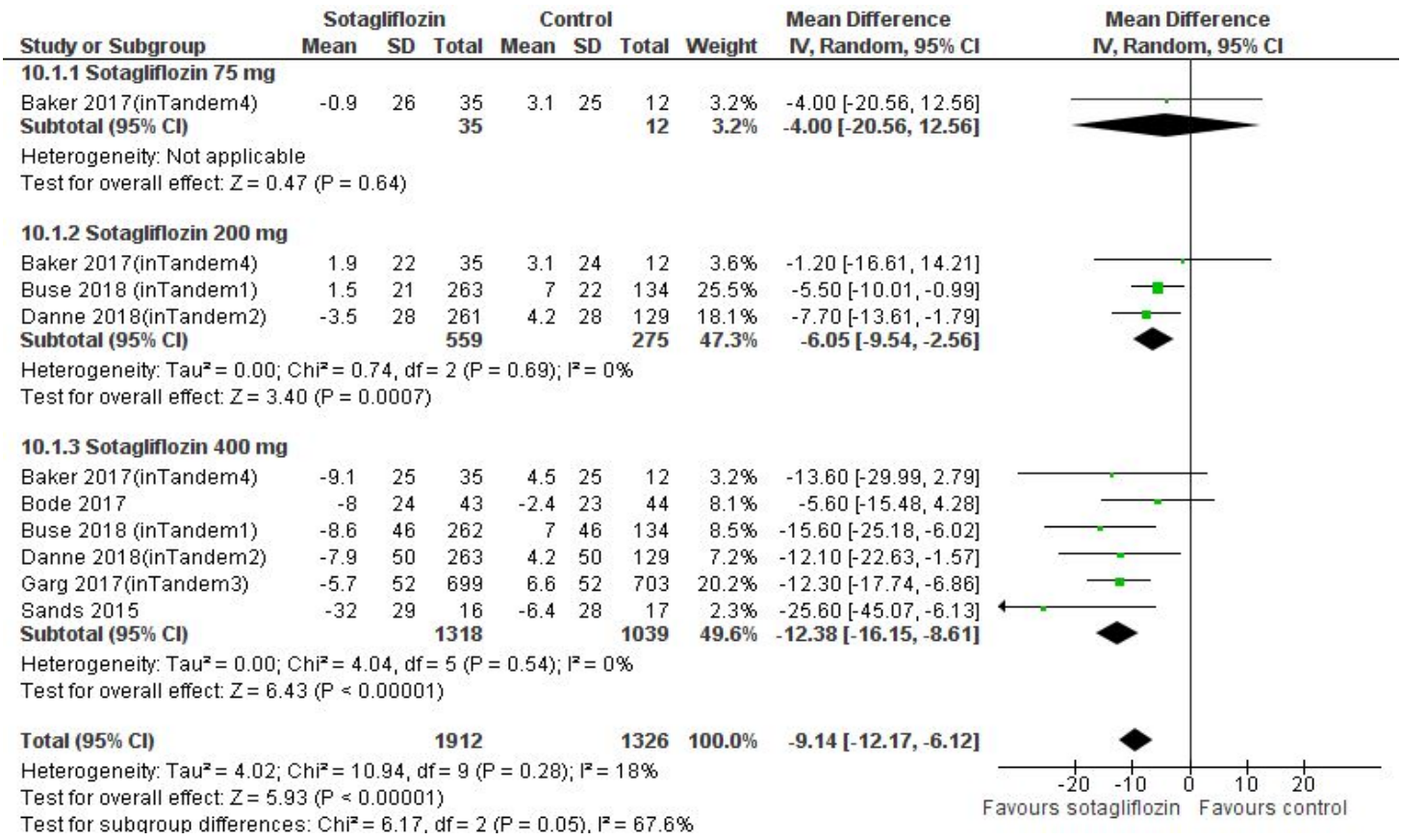
Panel A: outcome: daily total insulin dose (%)



Panel B: outcome: daily basal insulin dose (%)



Panel C: outcome: daily bolus insulin dose (%)



Supplementary Figure 6. Forest plot of comparison: Sotagliflozin, outcome: daily urinary glucose excretion (UGE) (g/24 hr)

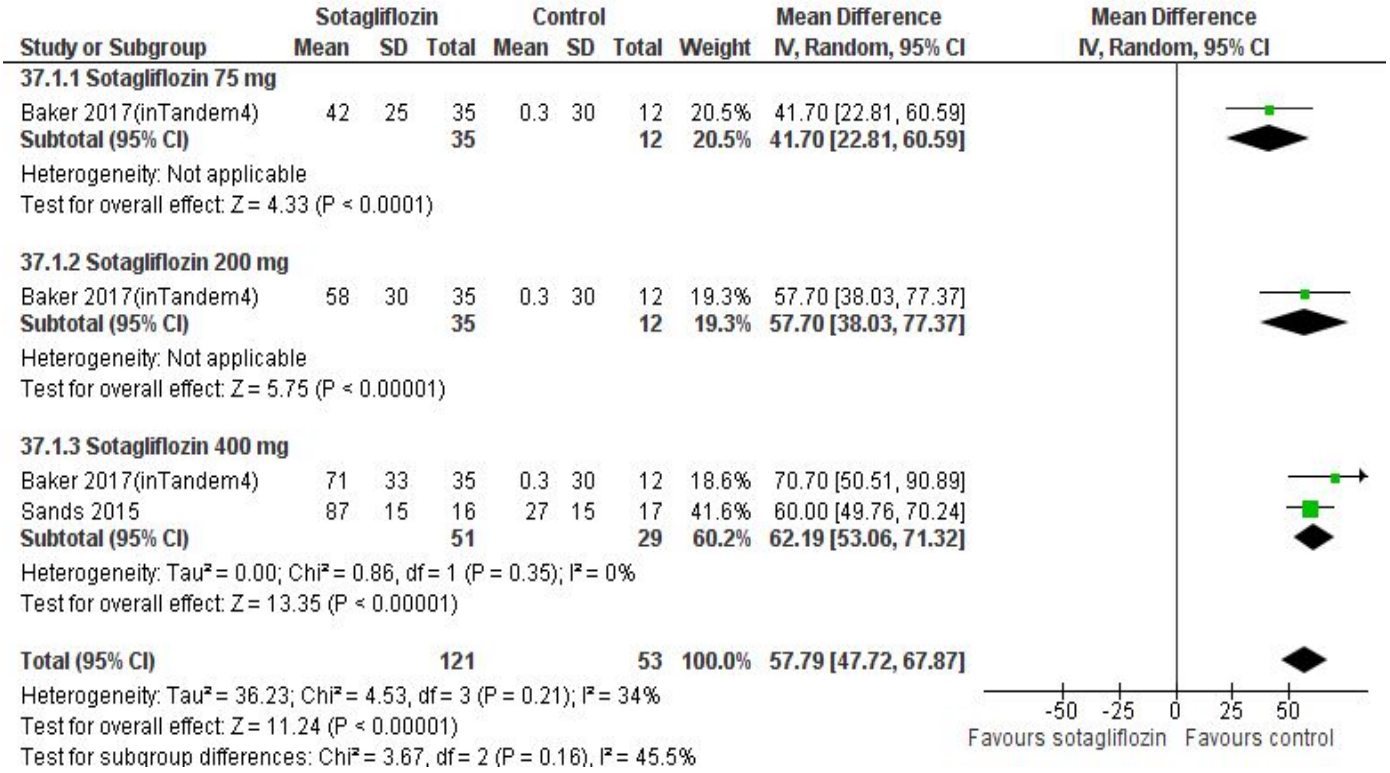
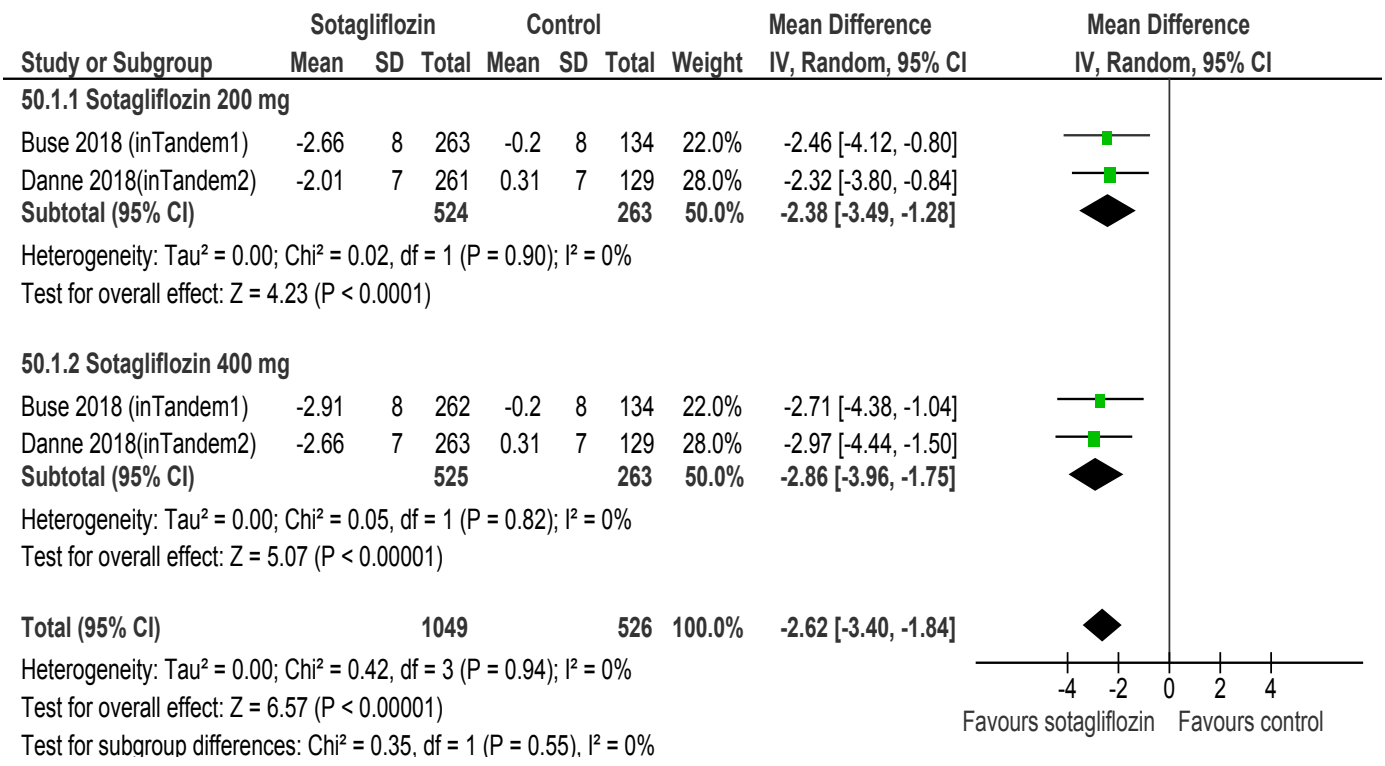
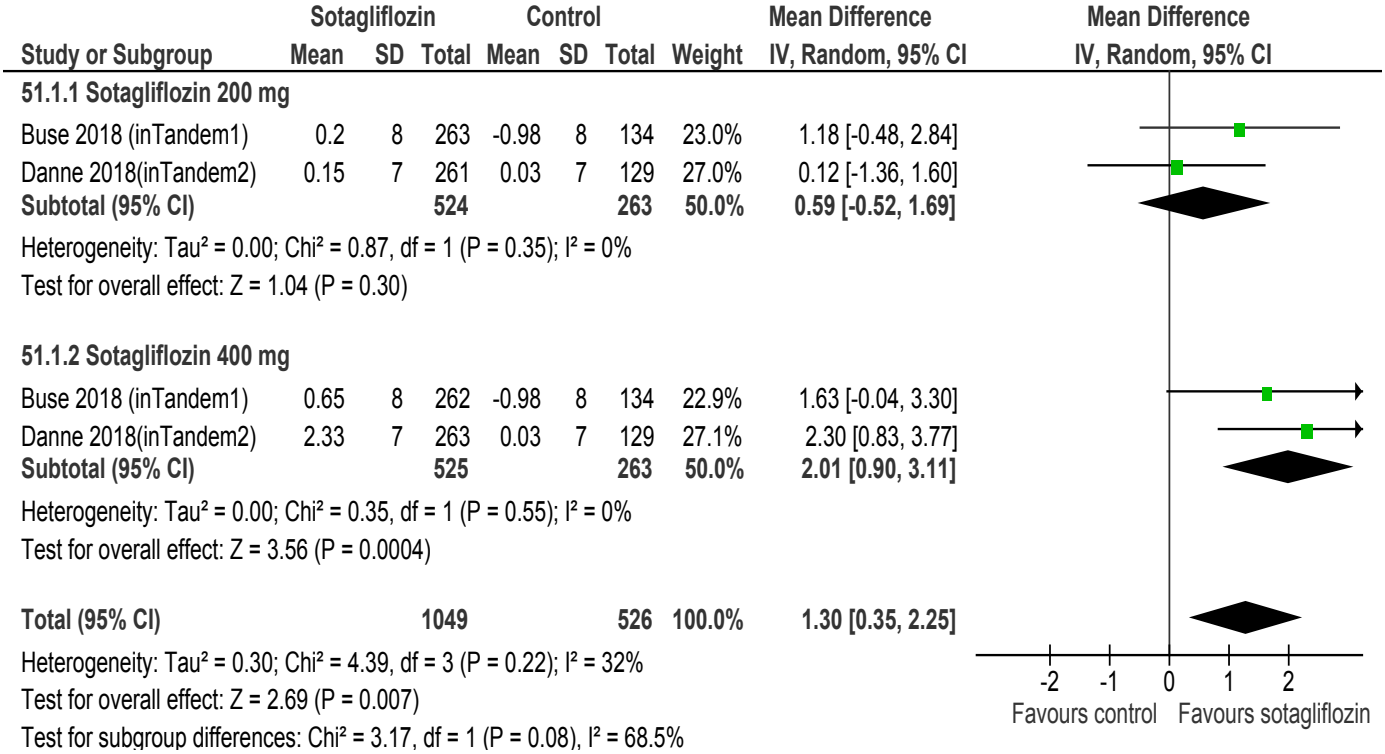


Figure 7. Forest plot of comparison: Sotagliflozin vs. placebo, outcomes: eGFR changes over week 0-52: pooled analysis of inTandem1 and inTandem2 trials

Panel A: outcome: eGFR changes from baseline during week 0-24 (ml/min/1.73m²)

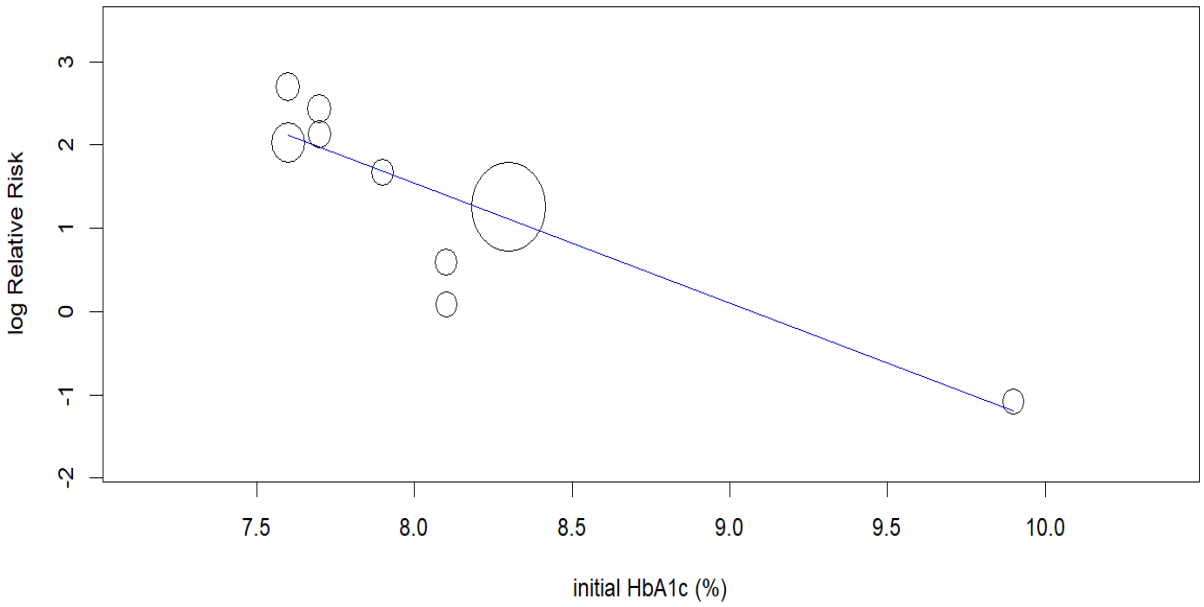


Panel B: outcome: eGFR changes from baseline during week 24-52 (ml/min/1.73m²)

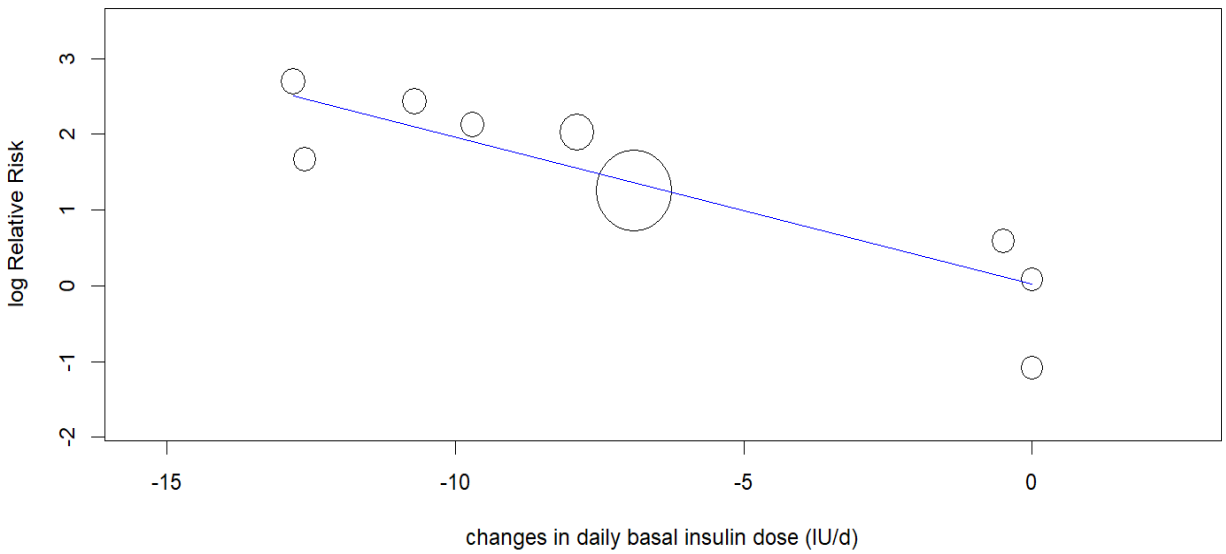


Supplementary Figure 8. Meta-regression analysis: regression plot of the effect of initial HbA1c(%) (**panel A**) and of changes in daily basal insulin dose(expressed as IU/d) from baseline (**panel B**) in relation to the risk (expressed as log risk ratio) of diabetic ketoacidosis (DKA). Each circle represents one comparison group, with the size of each circle representing the weight given to the group in meta-regression.

Panel A: effect of initial HbA1c (%) on the RR of DKA

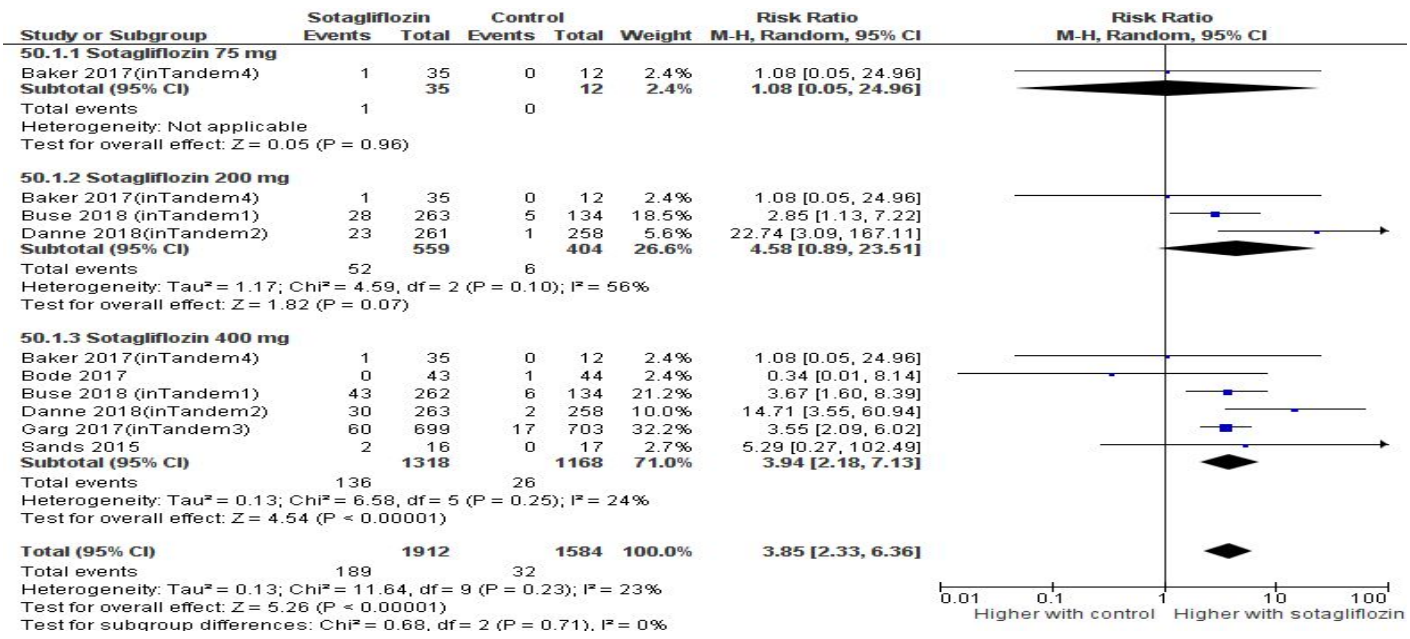


Panel B: effect of changes in daily basal insulin dose (IU/d) from baseline on the RR of DKA



Supplementary Figure 9. Forest plot of comparison: Sotagliflozin, outcome: incidence of acidosis-related and of major adverse cardiovascular events (MACE).

Panel A: outcome: acidosis-related adverse events



Panel B: outcome: major adverse cardiovascular events (MACE)