OPEN ACCESS

Check for updates

Efficacy and safety of dual SGLT 1/2 inhibitor sotagliflozin in type 1 diabetes: meta-analysis of randomised controlled trials

Giovanni Musso,[1] Roberto Gambino,[2] Maurizio Cassader,[2] Elena Paschetta[1]

[1]Humanitas University Gradenigo Hospital, 8 Corso Regina Margherita, 10132 Turin, Italy

[2]Laboratory of Diabetes and Metabolic Disorders, Department of Medical Sciences, University of Turin, Turin, Italy

Correspondence to: G Musso giovanni_musso@yahoo.it (ORCID 0000-0002-8569-2872)

Additional material is published online only. To view please visit the journal online.

ABSTRACT

OBJECTIVE
To assess the efficacy and safety of dual sodium glucose cotransporter (SGLT) 1/2 inhibitor sotagliflozin in type 1 diabetes mellitus.

DESIGN
Meta-analysis of randomised controlled trials.

DATA SOURCES
Medline; Cochrane Library; Embase; international meeting abstracts; international and national clinical trial registries; and websites of US, European, and Japanese regulatory authorities, up to 10 January 2019.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES
Randomised controlled trials evaluating the effect of sotagliflozin versus active comparators or placebo on glycaemic and non-glycaemic outcomes and on adverse events in type 1 diabetes in participants older than 18. Three reviewers extracted data for study characteristics, outcomes of interest, and risk of bias and summarised strength of evidence using the grading of recommendations assessment, development, and evaluation approach. Main outcomes were pooled using random effects models.

RESULTS
Of 739 records identified, six randomised placebo controlled trials (n=3238, duration 4-52 weeks) were included. Sotagliflozin reduced levels of glycated haemoglobin (HbA1c; weighted mean difference −0.34% (95% confidence interval −0.41% to −0.27%), P<0.001); fasting plasma glucose (−16.98 mg/dL, −22.1 to −11.9; 1 mg/dL=0.0555 mmol/L) and two hour-postprandial plasma glucose (−39.2 mg/dL, −50.4 to −28.1); and daily total, basal, and bolus insulin dose (−8.99%, −10.93% to −7.05%; −8.03%, −10.14% to −5.93%; −9.14%, −12.17% to −6.12%; respectively). Sotagliflozin improved time in range (weighted mean difference 9.73%, 6.66% to 12.81%) and other continuous glucose monitoring parameters, and reduced body weight (−3.54%, −3.98% to −3.09%), systolic blood pressure (−3.85 mm Hg, −4.76 to −2.93), and albuminuria (albumin:creatinine ratio −14.57 mg/g, −26.87 to −2.28). Sotagliflozin reduced hypoglycaemia (weighted mean difference −9.09 events per patient year, −13.82 to −4.36) and severe hypoglycaemia (relative risk 0.69, 0.49 to 0.98). However, the drug increased the risk of ketoacidosis (relative risk 3.93, 1.94 to 7.96), genital tract infections (3.12, 2.14 to 4.54), diarrhoea (1.50, 1.08 to 2.10), and volume depletion events (2.19, 1.10 to 4.36). Initial HbA1c and basal insulin dose adjustment were associated with the risk of diabetic ketoacidosis. A sotagliflozin dose of 400 mg/day was associated with a greater improvement in most glycaemic and non-glycaemic outcomes than the 200 mg/day dose, without increasing the risk of adverse events. The quality of evidence was high to moderate for most outcomes, but low for major adverse cardiovascular events and all cause death. The relatively short duration of trials prevented assessment of long term outcomes.

CONCLUSIONS
In type 1 diabetes, sotagliflozin improves glycaemic and non-glycaemic outcomes and reduces hypoglycaemia rate and severe hypoglycaemia. The risk of diabetic ketoacidosis could be minimised by appropriate patient selection and down-titration of the basal insulin dose.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In patients with type 1 diabetes mellitus, 30% achieve glycaemic targets and are encumbered by unwanted effects of insulin, namely hypoglycaemia and weight gain; severe hypoglycaemia, in particular, is the main factor limiting optimal glucose control and a risk factor for adverse events in diabetes

Sotagliflozin is a novel, dual sodium glucose co-transport (SGLT) 1/2 inhibitor that inhibits intestinal glucose absorption as well as renal glucose reabsorption; this mechanism of action could blunt postprandial glycaemic excursions and glycaemic variability, eventually reducing the need for bolus insulin corrections and hypoglycaemic risk

Sotagliflozin has completed phase III clinical development in type 1 diabetes, but the evidence regarding its efficacy and safety in this population has not been systematically reviewed

WHAT THIS STUDY ADDS

Compared with placebo, sotagliflozin improves glycaemic and non-glycaemic outcomes (including markers of diabetic nephropathy) and reduces the incidence of hypoglycaemia and of severe hypoglycaemia

Diabetic ketoacidosis (DKA) is the main adverse event associated with sotagliflozin treatment, and its risk depends on initial HbA1c levels in patients and reduction of the basal insulin dose during treatment; sotagliflozin is also associated with an increased risk of genital tract infections and diarrhoea, but not of urinary tract infections

Current evidence on long term outcomes is limited by the short duration of individual trials

Introduction

Type 1 diabetes mellitus affects 1.5 million people in the United States alone and its prevalence is continuously rising, partly because over 10% of patients initially presumed to have type 2 diabetes at diagnosis subsequently show evidence of islet autoimmunity and progress to insulin dependence later on.[1][2] The achievement and maintenance of glycaemic goals in type 1 diabetes has proven both difficult and hazardous. In the T1D Exchange clinic registry, the average level of glycated haemoglobin (HbA1c) was 8%, only 30% of patients with type 1 diabetes achieved an HbA1c goal of 7%, and severe

hypoglycaemia occurred in up to 20% of patients per year.[3] Similarly, in the Diabetes Complications and Control Trial, patients with type 1 diabetes with HbA1c levels within target showed a 2.9-fold increased cardiovascular mortality,[4] and patients in the intensive intervention group escalated back to an HbA1c of 8% in the years following the trial.[5]

Insulin is the mainstay of treatment for type 1 diabetes, but has unwanted effects, including hypoglycaemia and weight gain.[6] Severe hypoglycaemia in particular is the main factor limiting optimal glucose control in the disease; it is frequent, adds costs to diabetes management, and is a strong predictor of adverse vascular and non-vascular outcomes and death.[6-9] None of the adjunctive treatments approved (that is, pramlintide) or recently proposed for type 1 diabetes (that is, metformin, incretin analogues, and sodium glucose cotransporter (SGLT) 2 inhibitors) has reduced the incidence of hypoglycaemia and severe hypoglycaemia, which remain the major unresolved issue in the management of these patients.[10-20]

SGLT1 is responsible for glucose absorption in the proximal intestine, and missense mutations in SGLT1 gene have been 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 SGLT1 and SGLT2; while SGLT2 inhibition reduces glucose reabsorption in the renal tubule, SGLT1 inhibition decreases glucose absorption in the intestine. This dual mechanism of action could offer incremental benefits over selective SGLT2 inhibitors[22]

by blunting postprandial glycaemic excursions and glycaemic variability, lowering the need for bolus insulin correction doses, and eventually reducing hypoglycaemic 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 release of incretin has enhanced weight loss and counteracted glucagon induced ketogenesis,[25] which could reduce the risk of diabetic ketoacidosis.[23-25]

Sotagliflozin has recently reached phase III development in patients with type 1 diabetes[26-31] but randomised controlled trials evaluating this drug have not been systematically reviewed. To clarify the evidence base of this novel approach, we conducted a meta-analysis of randomised controlled trials evaluating the efficacy and safety of sotagliflozin in adults with type 1 diabetes.
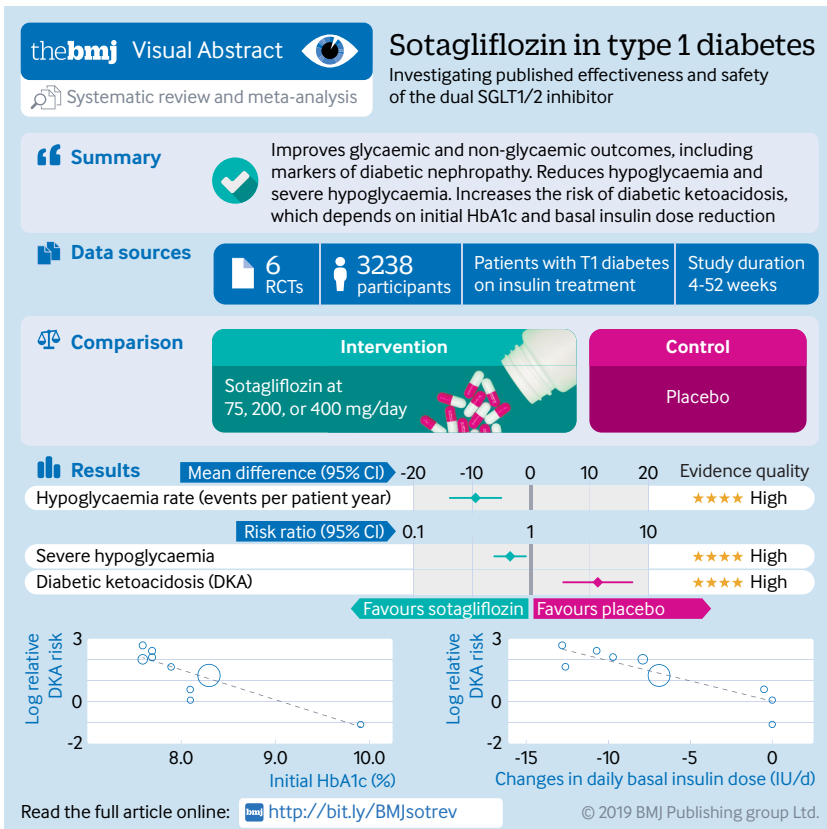
Methods
Data sources and searches
We searched English and non-English language publications up to 10 January 2019 on the following databases and international and national clinical trial registries: Ovid Medline, Ovid Medline Epub Ahead of Print, Ovid Medline In-Process, Embase, Cochrane Database of Systematic Reviews, Epistemonikos, ClinicalTrials.gov, Cochrane CENTRAL Register of Controlled Trials, World Health Organization International Clinical Trials Registry Platform, European Union Clinical Trials Register, International Standard Randomised Controlled Trial Number registry, Australian New Zealand Clinical Trials Registry, and 19 national clinical trial registries (full list of clinical trial registries 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] websites and drug manufacturers' websites[35 36] for relevant documents, and the American Diabetes Association and European Association for the Study of Diabetes meeting abstracts, which were subjected to the same assessment as regular articles.

Additionally, we emailed authors of relevant papers to verify results and methodological quality of retrieved articles, and drug manufacturers to inquire about further published and unpublished trials. We manually scanned reference lists from trials, review articles, and reports to identify any other relevant data. Search terms were "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," and "type 1 diabetes" (examples of online strategy run are provided in supplementary text).

Study selection
Inclusion criteria included English and non-English (French, Spanish, Portuguese, German, Chinese,

the**bmj** Visual Abstract

Systematic review and meta-analysis

Sotagliflozin in type 1 diabetes
Investigating published effectiveness and safety of the dual SGLT1/2 inhibitor

Summary — Improves glycaemic and non-glycaemic outcomes, including markers of diabetic nephropathy. Reduces hypoglycaemia and severe hypoglycaemia. Increases the risk of diabetic ketoacidosis, which depends on initial HbA1c and basal insulin dose reduction

Data sources — 6 RCTs | 3238 participants | Patients with T1 diabetes on insulin treatment | Study duration 4-52 weeks

Comparison
Intervention: Sotagliflozin at 75, 200, or 400 mg/day
Control: Placebo

Results

Mean difference (95% CI): -20, -10, 0, 10, 20 | Evidence quality
Hypoglycaemia rate (events per patient year) — ★★★★ High

Risk ratio (95% CI): 0.1, 1, 10
Severe hypoglycaemia — ★★★★ High
Diabetic ketoacidosis (DKA) — ★★★★ High

◄ Favours sotagliflozin | Favours placebo ►

Log relative DKA risk vs Initial HbA1c (%): 8.0, 9.0, 10.0
Log relative DKA risk vs Changes in daily basal insulin dose (IU/d): -15, -10, -5, 0

Read the full article online: http://bit.ly/BMJsotrev

© 2019 BMJ Publishing group Ltd.

Japanese, Korean) articles of randomised controlled trials. Trial participants were aged 18 and older of any sex or ethnic origin, and the trials compared sotagliflozin with placebo or active comparators as an adjunct treatment to insulin in type 1 diabetes. We excluded non-human studies, non-randomised trials, letters or case reports, and articles not reporting outcomes of interest or primary data (editorials, reviews).

Outcome measures

We grouped evaluated outcomes into three broad groups: glycaemic efficacy outcomes, non-glycaemic outcomes, and safety outcomes. Glycaemic efficacy outcomes were:

- Changes in glycated haemoglobin (HbA1c) from baseline (primary outcome)
- Changes in levels of fasting plasma glucose
- Changes in two hour postprandial glycaemia (2h-PPG), as measured during an oral glucose tolerance test or a standardised mixed meal tolerance test. Many studies have linked postprandial glucose excursions to the risk of cardiovascular disease and report that targeting postprandial glycaemia rather than fasting plasma glucose lowers cardiovascular risk[37 38]
- Changes in total, basal, and bolus insulin dose (expressed as % of the initial insulin dose)
- Effect of SGLT1/2 inhibitors on daily urinary glucose excretion
- Continuous glucose monitoring parameters. Continuous glucose monitoring provides additional information to HbA1c and has been recently recommended for all adults with type 1 diabetes and approved by the US Food and Drug Administration Advisory Committee.[39] We therefore assessed the following metrics of continuous glucose monitoring (described in the supplementary text): time in range (%), average daily glucose, standard deviation around average daily glucose, and mean amplitude of glucose excursion.[40]

Non-glycaemic outcome measures evaluated were changes in body weight, systolic and diastolic blood pressure; 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 lipoprotein-cholesterol, and high density lipoprotein-cholesterol).

Safety measures were severe hypoglycaemia and any hypoglycaemia, diabetic ketoacidosis (definitions provided in the supplementary text), urinary tract infections, genital tract infections, other infections, gastrointestinal symptoms, major adverse cardiovascular events (MACE; cardiovascular death, myocardial infarction, stroke, admission owing to heart failure or unstable angina, or coronary revascularisation), cancer (overall and type specific), amputation, bone fracture, volume depletion, renal events, acidosis related events, drug induced liver injury, venous thromboembolism, serious adverse events, adverse events leading to treatment discontinuation, and all cause mortality. Volume depletion, acidosis related events, renal events, and serious adverse events were defined according to the Medical Dictionary for Regulatory Activities preferred items version 14.0[41] (supplementary text). We also planned to investigate whether the risk of diabetic ketoacidosis varied across different modes of insulin delivery (that is, MDI or CSI). All measures of dispersion were converted to standard deviations.

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 two reviewers for selection and validity assessment of trials was scored by the κ coefficient.

The quality of randomised controlled trials 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 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 prespecified 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 risk of bias tool[44-50] (supplementary table 1).

Data synthesis, analysis, and grading of evidence

The analysis was carried out in accordance with the Cochrane handbook of systematic reviews of interventions[42] using Stata release 11.2 (StataCorp, College Station, TX, USA) and RevMan version 5.3.5 (Nordic Cochrane Center, Copenhagen, Denmark),[51] and was reported according to PRISMA guidelines[52] (preferred reporting items for systematic reviews and meta-analyses; see supplementary appendix). Treatments were evaluated on an intention-to-treat principle.

We calculated weighted mean differences and 95% confidence intervals for continuous outcomes using an inverse variance random effects model. For dichotomous outcomes, we calculated risk ratios and 95% confidence intervals 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 substantial variability in treatment effect size across studies. Statistical heterogeneity was assessed using the I^2 statistic: with I^2 values of 50% or over, we planned to explore individual study characteristics, and characteristics 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 v relative risk), pooling methods (Peto v Mantel-Hanszel[54]), and statistical models (fixed v random effects) by excluding randomised controlled trials where we imputed values and randomised controlled trials at high risk of bias in any domains of the risk of bias tool. We also planned a priori subgroup analyses to explore potential effects on outcome measures of the following conditions: treatment duration (≤12 v >12 weeks), initial HbA1c levels (≥8% v <8%), duration of diabetes (<20 v ≥20 years), background treatment (pretreatment insulin optimisation v stable insulin treatment), and presence and severity of renal dysfunction.

When trials evaluated different sotagliflozin doses, we planned to present data separately for each dose and to split sample size of the placebo group evenly among different dose comparisons.[42] We explored interactions between different sotagliflozin doses and all outcomes primarily by comparing different dose groups within head-to-head trials (within-trial approach); we planned to verify robustness of this approach by also using across-trial comparison and meta-regression. Although the across-trial approach has a higher risk of ecological bias, it has a higher power than the within-trial approach, thus allowing us to rule out dose-response interactions with higher confidence.[55]

When eight or more comparisons were available, the effect of different SGLT1/2 inhibitor doses, baseline HbA1c, treatment duration, and diabetes duration on each outcome were assessed by meta-regression analysis (random effects model, within-study variance estimated with the unrestricted maximum likelihood method). Furthermore, 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 considered to be a single increment increase. Publication bias was examined by funnel plots and the Egger test.

We used the grading of recommendations assessment, development, and evaluation (GRADE) approach to summarise 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: glycaemic efficacy (outcomes: HbA1c, fasting plasma glucose, 2h-PPG, time in range), non-glycaemic efficacy (outcomes: body weight, systemic blood pressure, eGFR, albuminuria), and adverse events (outcomes: hypoglycaemia, severe hypoglycaemia, diabetic ketoacidosis, urinary and genital tract infections, diarrhoea, MACE, serious adverse events, adverse events leading to discontinuation, and mortality). We planned to manage missing data by contacting via email the corresponding authors. Where this method 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).

Patient and public involvement

No patients were involved in the 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, six placebo controlled randomised trials (duration 4-52 weeks) enrolling 3238 participants with type 1 diabetes were included in the meta-analysis[26-31 58 59] (main characteristics reported in supplementary table 1). We excluded 12 phase I trials conducted in individuals without diabetes, 18 trials enrolling patients with type 2 diabetes (four completed, 14 active), and one trial enrolling patients without diabetes but with congestive heart failure (main characteristics of excluded trials reported in supplementary table 2). All included randomised controlled trials compared sotagliflozin with placebo on background insulin treatment. Three trials[28 30 31] compared different sotagliflozin doses (75, 200, or 400 mg/day) with placebo. Overall, 10 comparisons were available for the meta-analysis. Two trials adopted insulin dose optimisation (target: fasting plasma glucose 80-130 mg/dL and 2h-PPG >180 mg/dL; 1 mg/dL=0.0555 mmol/L) during the six weeks preceding randomisation.[30 31] Two trials excluded patients with impaired renal function (eGFR <60 mL/min/1.73 m^2),[26 28] and four trials excluded patients with moderate-to-severe renal impairment (eGFR <45 mL/min/1.73 m^2).[27 29 30 31]

Participants' baseline characteristics were equally balanced between the study arms; in all randomised controlled trials, dropout rates were generally low and balanced across arms. No trial used the last-observation-carried-forward approach to impute missing observations, which were imputed as non-response for dichotomous outcomes. For continuous outcomes, we used mixed effects model-for-repeated-measures statistics, based on the restricted maximum likelihood method for estimation. Two trials were partly funded by non-profit organisations,[26 27] while a pharmaceutical company entirely funded four trials. However, we did not find any evidence of high risk of biased outcomes in trial design, conduct, and reporting. The overall quality was good for all included trials. The risk of bias summary for individual trials and the risk of bias graph for each item across included trials are detailed in supplementary table 1 and summarised in supplementary figures 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). No values had to be imputed for the meta-analysis during data extraction. The agreement between the two reviewers was 0.96
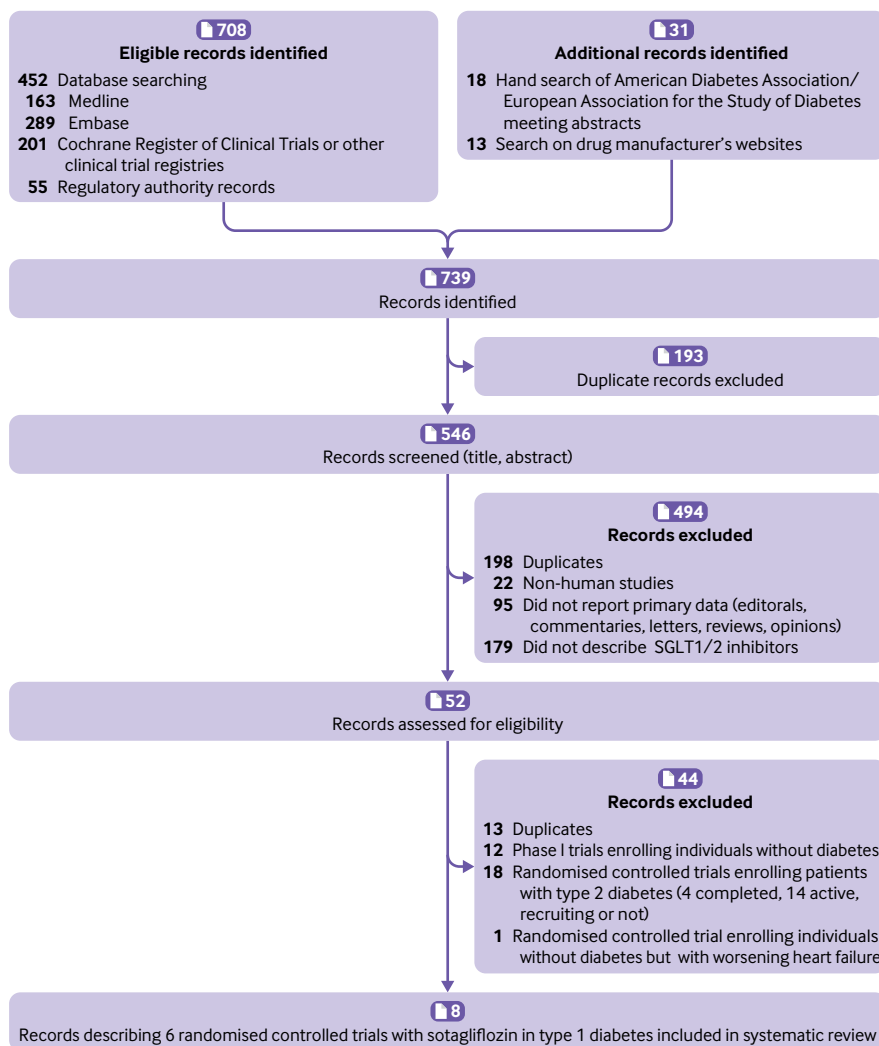
Fig 1 | Flow diagram of evidence acquisition during study

for study selection and 0.89 for quality assessment of trials.

Glycaemic efficacy outcomes

HbA1c

Compared with placebo, sotagliflozin treatment was associated with a significant reduction in HbA1c levels (weighted mean difference −0.34%, 95% confidence interval −0.41% to −0.27%, P<0.001, I^2=20%, 10 comparisons, 3238 participants; fig 2). We saw little heterogeneity in the meta-analysis, suggesting a consistent drug effect. Subgroup and meta-regression analysis showed that the effect was independent of trial duration (β=0.110, P=0.28) and baseline HbA1c (β=0.119, P=0.38; supplementary table 3). HbA1c reduction with sotagliflozin at 400 mg/day was higher than with 200 mg/day (supplementary table 4).

Fasting plasma glucose and two hour-postprandial plasma glucose

Sotagliflozin significantly reduced fasting plasma glucose (weighted mean difference −16.98 mg/dL, 95% confidence interval −22.09 to −11.86, P<0.001,

I^2=6%, 10 comparisons, 3238 participants) and 2h-PPG (−39.24 mg/dL, −50.42 to −28.06, P<0.001, I^2=20%, nine comparisons, 539 participants; fig 2). We saw 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 parameters

Four randomised controlled trials evaluated continuous glucose monitoring parameters.[26 27 30 31] Compared with placebo, sotagliflozin significantly increased time in range (weighted mean difference 9.73%, 95% confidence interval 6.66% to 12.81%, P<0.001, I^2=24%, six comparisons, 398 participants) and reduced average daily glucose (−15.09 mg/dL, −21.40 to −8.79, P<0.001, I^2=28%, five comparisons, 312 participants), standard deviation around average daily glucose (−6.68 mg/dL, −10.59 to −2.77, P<0.001, I^2=0%, five comparisons, 311 participants), and mean amplitude of glucose excursion (−19.52 mg/dL, −28.91 to −10.54, P<0.001, I^2=0%, five comparisons, 311 participants; supplementary figure 4). We saw little heterogeneity in

Study or subgroup	Mean difference IV random (95% CI)	Weight (%)	Mean difference IV random (95% CI)
HbA1c (%) changes from baseline			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		2.4	-0.25 (-0.70 to 0.20)
Subtotal		2.4	-0.25 (-0.70 to 0.20)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=1.08, P=0.28			
Sotagliflozin 200 mg/day			
Danne 2018 (inTandem2)		13.5	-0.22 (-0.39 to -0.05)
Buse 2018 (inTandem1)		19.0	-0.25 (-0.38 to -0.12)
Baker 2017 (inTandem4)		2.0	-0.49 (-0.99 to 0.01)
Subtotal		34.4	-0.25 (-0.35 to -0.15)
Test for heterogeneity: τ²=0.00; χ²=0.99, df=2, P=0.61; I²=0%			
Test for overall effect: Z=4.76, P<0.001			
Sotagliflozin 400 mg/day			
Sands 2015		1.6	-0.49 (-1.05 to 0.07)
Garg 2017 (inTandem3)		29.5	-0.46 (-0.55 to -0.37)
Danne 2018 (inTandem2)		12.8	-0.32 (-0.50 to -0.14)
Buse 2018 (inTandem1)		11.6	-0.31 (-0.50 to -0.12)
Bode 2017		5.4	-0.34 (-0.63 to -0.05)
Baker 2017 (inTandem4)		2.3	-0.38 (-0.84 to 0.08)
Subtotal		63.2	-0.41 (-0.48 to -0.34)
Test for heterogeneity: τ²=0.00; χ²=3.61, df=5, P=0.61; I²=0%			
Test for overall effect: Z=11.48, P<0.001			
Total (95% CI)		100.0	-0.34 (-0.41 to -0.27)
Test for heterogeneity: τ²=0.00; χ²=11.21, df=9, P=0.26; I²=20%			
Test for overall effect: Z=9.28, P<0.001			
Test for subgroup differences: χ²=6.60; df=2, P=0.04; I²=69.7%			

-1 -0.5 0 0.5 1
Favours sotagliflozin — Favours control

FPG changes from baseline (mg/dL)			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		6.3	-9.00 (-29.00 to 11.00)
Subtotal		6.3	-9.00 (-29.00 to 11.00)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=0.88, P=0.38			
Sotagliflozin 200 mg/day			
Baker 2017 (inTandem4)		6.1	-9.00 (-29.33 to 11.33)
Buse 2018 (inTandem1)		13.2	-12.00 (-25.45 to 1.45)
Danne 2018 (inTandem2)		11.1	-5.00 (-19.77 to 9.77)
Subtotal		30.4	-8.86 (-17.79 to 0.07)
Test for heterogeneity: τ²=0.00; χ²=0.47, df=2, P=0.79; I²=0%			
Test for overall effect: Z=1.94, P=0.05			
Sotagliflozin 400 mg/day			
Baker 2017 (inTandem4)		4.3	-21.00 (-45.43 to 3.43)
Bode 2017		3.1	-24.00 (-52.79 to 4.79)
Buse 2018 (inTandem1)		13.2	-19.00 (-32.46 to -5.54)
Danne 2018 (inTandem2)		11.1	-17.00 (-31.75 to -2.25)
Garg 2017 (inTandem3)		30.5	-23.00 (-31.27 to -14.73)
Sands 2015		1.2	-58.00 (-105.09 to -10.91)
Subtotal		63.3	-21.72 (-27.69 to -15.75)
Test for heterogeneity: τ²=0.00; χ²=2.95, df=5, P=0.71; I²=0%			
Test for overall effect: Z=7.13, P<0.001			
Total (95% CI)		100.0	-16.98 (-22.09 to -11.86)
Test for heterogeneity: τ²=4.54; χ²=9.62, df=9, P=0.38; I²=6%			
Test for overall effect: Z=6.50, P<0.001			
Test for subgroup differences: χ²=6.19; df=2, P=0.05; I²=67.7%			

-100 -75 -50 -25 0 25
Favours sotagliflozin — Favours control

2h-PPG changes from baseline (mg/dL)			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		14.6	-19.80 (-45.06 to 5.46)
Subtotal		14.6	-19.80 (-45.06 to 5.46)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=1.54, P=0.12			
Sotagliflozin 200 mg/day			
Baker 2017 (inTandem4)		14.1	-27.80 (-53.59 to -2.01)
Buse 2018 (inTandem1)		7.4	-17.20 (-55.58 to 21.18)
Danne 2018 (inTandem2)		6.4	-50.30 (-91.85 to -8.75)
Subtotal		27.9	-29.91 (-48.94 to -10.88)
Test for heterogeneity: τ²=0.00; χ²=1.37, df=2, P=0.50; I²=0%			
Test for overall effect: Z=3.08, P=0.002			
Sotagliflozin 400 mg/day			
Baker 2017 (inTandem4)		14.9	-49.80 (-74.71 to -24.89)
Bode 2017		15.9	-56.00 (-79.74 to -32.26)
Buse 2018 (inTandem1)		5.8	-21.70 (-65.75 to 22.35)
Danne 2018 (inTandem2)		8.7	-65.50 (-100.33 to -30.67)
Sands 2015		12.2	-38.00 (-66.34 to -9.66)
Subtotal		57.5	-48.92 (-61.87 to -35.98)
Test for heterogeneity: τ²=0.00; χ²=3.25, df=4, P=0.52; I²=0%			
Test for overall effect: Z=7.41, P<0.001			
Total (95% CI)		100.0	-39.24 (-50.42 to -28.06)
Test for heterogeneity: τ²=57.31; χ²=9.97, df=8, P=0.27; I²=20%			
Test for overall effect: Z=6.88, P<0.001			
Test for subgroup differences: χ²=5.35; df=2, P=0.07; I²=62.6%			

-100 -75 -50 -25 0 25
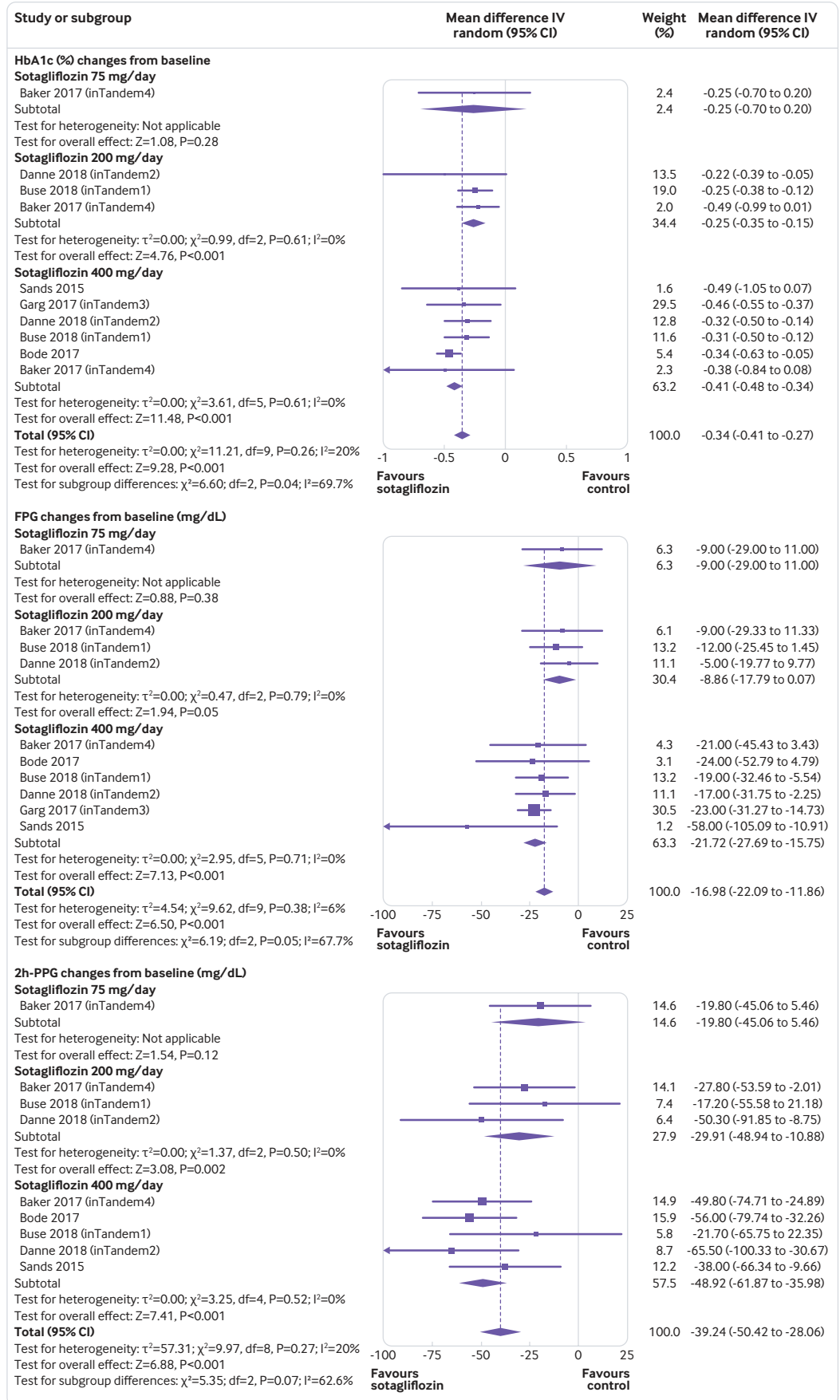Favours sotagliflozin — Favours control

Fig 2 | Forest plot comparing effect of sotagliflozin versus placebo on HbA1c (%), fasting plasma glucose (FPG), and two hour-postprandial plasma glucose (2h-PPG).1 mg/dL=0.0555 mmol/L. IV=inverse variance

the meta-analysis, suggesting a consistent drug effect. Sotagliflozin at 400 mg/day was significantly more effective than 200 mg/day at improving time in range, average daily glucose, and mean amplitude of glucose excursion (supplementary table 4).

Daily total, basal, and bolus insulin dose

Compared with placebo, sotagliflozin reduced daily total (weighted mean difference −8.99%, 95% confidence interval −10.93% to −7.05%, P<0.001, I^2=33%, 10 comparisons, 3238 participants), basal (−8.03%, −10.14% to −5.93%, P<0.001, I^2=0%, 10 comparisons, 3238 participants), and bolus (−9.14%, −12.17% to −6.12%, P<0.001, I^2=67%, 10 comparisons, 3238 participants) insulin dose in patients with type 1 diabetes (supplementary figure 5). Heterogeneity for bolus insulin dose was high, and was accounted for by significant subgroup differences between high dose (400 mg/day) and low dose (200 mg/day) sotagliflozin (supplementary table 4).

Urinary glucose excretion

Pooled data came from two randomised controlled trials.[26] [28] They indicated that daily urinary glucose excretion progressively increased with increasing sotagliflozin dose from 75 mg/day to 200 mg/day, but then urinary glucose excretion reached a plateau at around 60 g/day with either 200 mg/day and 400 mg/day of sotagliflozin (supplementary figure 6; supplementary table 4)

Non-glycaemic outcomes
Body weight

Compared with controls, sotagliflozin induced a significant weight reduction (weighted mean difference −3.54%, 95% confidence interval −3.98% to −3.09%, P<0.001, I^2=18%, 10 comparisons, 3238 participants; fig 3). 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

Compared with placebo, sotagliflozin use was associated with a reduction in systolic blood pressure (weighted mean difference −3.85 mm Hg, 95% confidence interval −4.76 to −2.93, P<0.001, I^2=0%) and in diastolic blood pressure (−1.43 mm Hg, −1.98 to −0.89, P<0.001, I^2=0%, 10 comparisons, 3238 participants; fig 3). These effects were not associated with an increased incidence of ortostatic hypotension (data not shown).

Renal effects: estimated glomerular filtration rate and urinary albumin:creatinine ratio

Compared with placebo, sotagliflozin treatment was associated with a slight reduction in eGFR (weighted mean difference −0.80 mL/min/1.73 m², 95% confidence interval −1.42 to −0.18, P=0.01, I^2=0%, 10 comparisons, 3238 participants; fig 4). The reduction in eGFR occurred only with sotagliflozin at 200 mg/day (fig 4; supplementary table 4). Subgroup analysis showed that the eGFR reduction was observed only in randomised controlled trials lasting 12 weeks or less, but not in trials of longer duration (supplementary table 3). Urinary ACR was evaluated in three phase III randomised controlled trials (2977 participants, with trial duration ranging 24-52 weeks, and mean baseline ACR of participants of 52.6, 31.6, 54.3 mg/g, respectively).[29-31] Pooled analysis of these trials showed that sotagliflozin was associated with a decrease in ACR (weighted mean difference −14.57 mg/g, 95% confidence interval −2.28 to −26.87, P=0.02, I^2=0%, five comparisons; fig 4).

To gain further insight into the effect of time on renal function, we examined the effect of sotagliflozin on eGFR in the two longest trials (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 showed a decline in eGFR, both in absolute terms and as compared with controls. But in the following 28 weeks, the trend was inverted and sotagliflozin induced a significant eGFR increase, both in absolute terms and as compared with controls (supplementary figure 7A-B).

Plasma lipids

No randomised controlled trial reported the effect of active treatment or placebo on low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, or triglyceride.

Safety outcomes
Hypoglycaemia and severe hypoglycaemia

The definitions of hypoglycaemia and severe hypoglycaemia were consistent across all randomised controlled trials and in line with current guideline recommendations (supplementary text). Compared with placebo, sotagliflozin treatment was associated with a lower rate of hypoglycaemia events (weighted mean difference −9.09 events per patient year, 95% confidence interval −13.82 to −4.36, P<0.001, I^2=0%, 10 comparisons, 3238 participants) and with a 31% lower risk of severe hypoglycaemia (relative risk 0.69, 0.49 to 0.98, P=0.04, 10 comparisons, I^2=0%; fig 5).

Diabetic ketoacidosis

Compared with placebo, sotagliflozin was associated with an increased risk of diabetic ketoacidosis (relative risk 3.93, 95% confidence interval 1.94 to 7.96, P<0.001; 10 comparisons, I^2=0%, 3238 participants, trial duration 4-52 weeks; fig 5). Forty six (69%) of all cases of diabetic ketoacidosis occurred at blood glucose levels higher than 250 mg/dL, while the remaining 21 (31%) cases occurred with blood glucose values of 150-250 mg/dL (supplementary table 5). The risk for diabetic ketoacidosis was increased for patients on multiple daily injections (3.22, 1.24 to 9.09, P=0.01; 10 comparisons, I^2=0%, 2072 patients) as well as for patients on continuous subcutaneous infusion (6.40, 2.82 to 15.64, P<0.001; 10 comparisons, I^2=0%, 1166 patients).

Study or subgroup	Mean difference IV random (95% CI)	Weight (%)	Mean difference IV random (95% CI)
Body weight changes from baseline (%)			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		2.3	-1.42 (-4.29 to 1.45)
Subtotal		2.3	-1.42 (-4.29 to 1.45)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=0.97, P=0.33			
Sotagliflozin 200 mg/day			
Baker 2017 (inTandem4)		2.3	-2.75 (-5.63 to 0.13)
Buse 2018 (inTandem1)		13.2	-3.62 (-4.70 to -2.54)
Danne 2018 (inTandem2)		13.4	-2.78 (-3.85 to -1.71)
Subtotal		29.0	-3.17 (-3.90 to -2.43)
Test for heterogeneity: τ²=0.00; χ²=1.25, df=2, P=0.53; I²=0%			
Test for overall effect: Z=8.43, P<0.001			
Sotagliflozin 400 mg/day			
Baker 2017 (inTandem4)		2.3	-2.99 (-5.87 to -0.11)
Bode 2017		4.2	-3.10 (-5.20 to -1.00)
Buse 2018 (inTandem1)		12.5	-4.95 (-6.07 to -3.83)
Danne 2018 (inTandem2)		13.4	-3.51 (-4.58 to -2.44)
Garg 2017 (inTandem3)		34.0	-3.62 (-4.12 to -3.12)
Sands 2015		2.3	-2.98 (-5.85 to -0.11)
Subtotal		68.7	-3.76 (-4.26 to -3.26)
Test for heterogeneity: τ²=0.06; χ²=5.73, df=5, P=0.33; I²=13%			
Test for overall effect: Z=14.65, P<0.001			
Total (95% CI)		100.0	-3.54 (-3.98 to -3.09)
Test for heterogeneity: τ²=0.09; χ²=10.91, df=9, P=0.28; I²=18%			
Test for overall effect: Z=15.52, P<0.001			
Test for subgroup differences: χ²=3.81; df=2, P=0.15; I²=47.6%			

Favours sotagliflozin — Favours control

Study or subgroup	Mean difference IV random (95% CI)	Weight (%)	Mean difference IV random (95% CI)
SysBP changes from baseline (mm Hg)			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		0.8	-8.40 (-18.34 to 1.54)
Subtotal		0.8	-8.40 (-18.34 to 1.54)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=1.66, P=0.10			
Sotagliflozin 200 mg/day			
Baker 2017 (inTandem4)		0.9	-6.80 (-16.68 to 3.08)
Buse 2018 (inTandem1)		11.5	-2.80 (-5.50 to -0.10)
Danne 2018 (inTandem2)		7.4	-2.90 (-6.26 to 0.46)
Subtotal		19.8	-3.01 (-5.07 to -0.95)
Test for heterogeneity: τ²=0.00; χ²=0.59, df=2, P=0.74; I²=0%			
Test for overall effect: Z=2.87, P=0.004			
Sotagliflozin 400 mg/day			
Baker 2017 (inTandem4)		0.8	-14.30 (-24.70 to -3.90)
Bode 2017		2.1	-8.60 (-14.97 to -2.23)
Buse 2018 (inTandem1)		11.1	-4.40 (-7.16 to -1.64)
Danne 2018 (inTandem2)		6.9	-2.80 (-6.30 to 0.70)
Garg 2017 (inTandem3)		57.9	-3.80 (-5.00 to -2.60)
Sands 2015		0.7	-1.70 (-12.62 to 9.22)
Subtotal		79.3	-4.26 (-5.88 to -2.64)
Test for heterogeneity: τ²=0.99; χ²=6.58, df=5, P=0.25; I²=24%			
Test for overall effect: Z=5.15, P<0.001			
Total (95% CI)		100.0	-3.85 (-4.76 to -2.93)
Test for heterogeneity: τ²=0.00; χ²=8.71, df=9, P=0.46; I²=0%			
Test for overall effect: Z=8.23, P<0.001			
Test for subgroup differences: χ²=1.69; df=2, P=0.43; I²=0%			

Favours sotagliflozin — Favours control

Study or subgroup	Mean difference IV random (95% CI)	Weight (%)	Mean difference IV random (95% CI)
DiaBP changes from baseline (mm Hg)			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		1.4	-0.20 (-4.79 to 4.39)
Subtotal		1.4	-0.20 (-4.79 to 4.39)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=0.09, P=0.93			
Sotagliflozin 200 mg/day			
Baker 2017 (inTandem4)		1.4	-1.10 (-5.76 to 3.56)
Buse 2018 (inTandem1)		12.1	-1.50 (-3.06 to 0.06)
Danne 2018 (inTandem2)		11.6	-1.30 (-2.89 to 0.29)
Subtotal		25.1	-1.39 (-2.47 to -0.30)
Test for heterogeneity: τ²=0.00; χ²=0.05, df=2, P=0.98; I²=0%			
Test for overall effect: Z=2.51, P=0.01			
Sotagliflozin 400 mg/day			
Baker 2017 (inTandem4)		1.4	-3.00 (-7.66 to 1.66)
Bode 2017		3.4	-3.30 (-6.24 to -0.36)
Buse 2018 (inTandem1)		12.1	-2.30 (-3.86 to -0.74)
Danne 2018 (inTandem2)		11.7	-0.60 (-2.19 to 0.99)
Garg 2017 (inTandem3)		44.1	-1.30 (-2.12 to -0.48)
Sands 2015		1.0	-1.00 (-6.46 to 4.46)
Subtotal		73.5	-1.47 (-2.10 to -0.84)
Test for heterogeneity: τ²=0.00; χ²=4.34, df=5, P=0.50; I²=0%			
Test for overall effect: Z=4.57, P<0.001			
Total (95% CI)		100.0	-1.43 (-1.98 to -0.89)
Test for heterogeneity: τ²=0.00; χ²=4.68, df=9, P=0.86; I²=0%			
Test for overall effect: Z=5.18, P<0.001			
Test for subgroup differences: χ²=0.30; df=2, P=0.86; I²=0%			

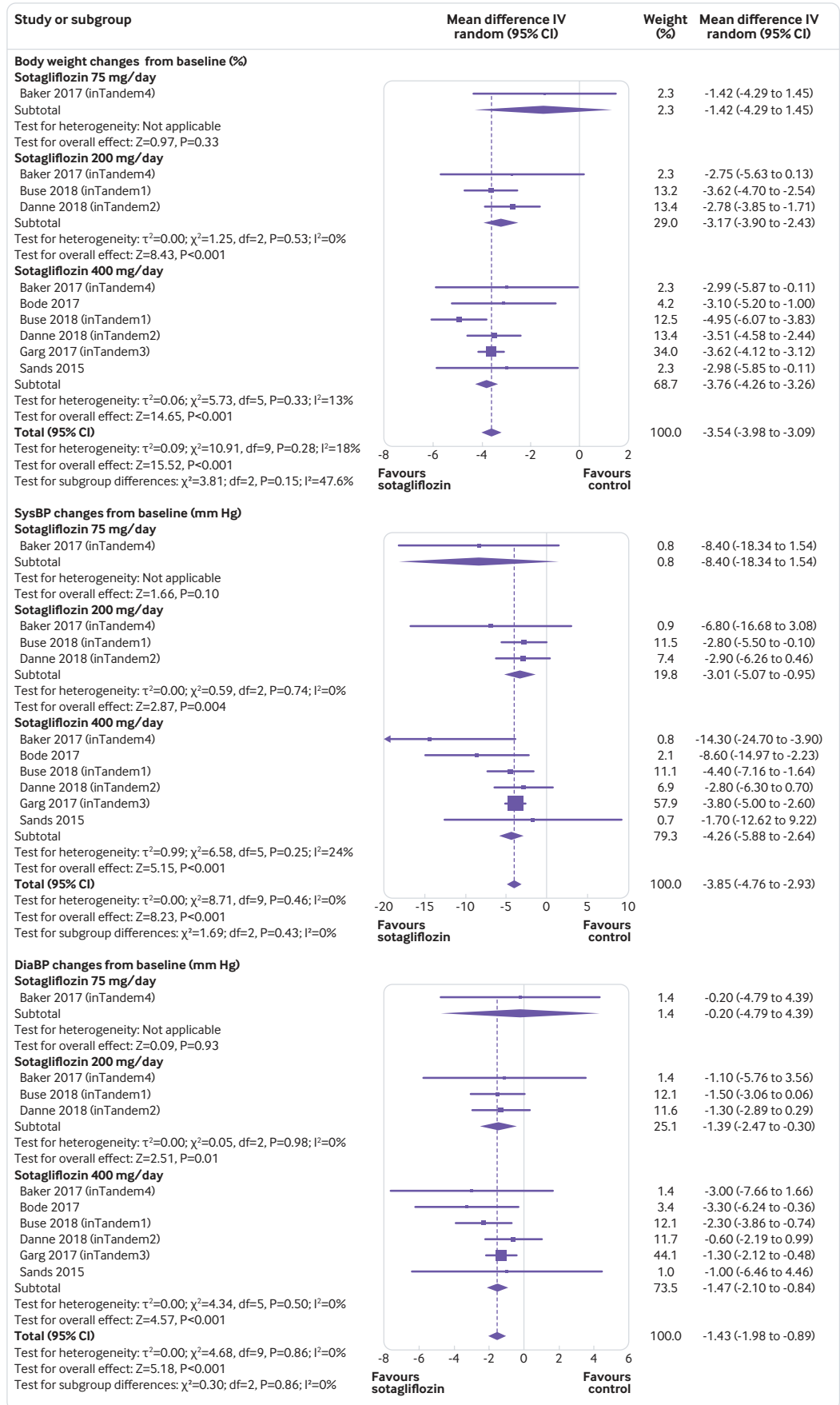Favours sotagliflozin — Favours control

Fig 3 | Forest plot comparing effect of sotagliflozin versus placebo on body weight, systolic blood pressure (sysBP), and diastolic blood pressure (diaBP). IV=inverse invariance
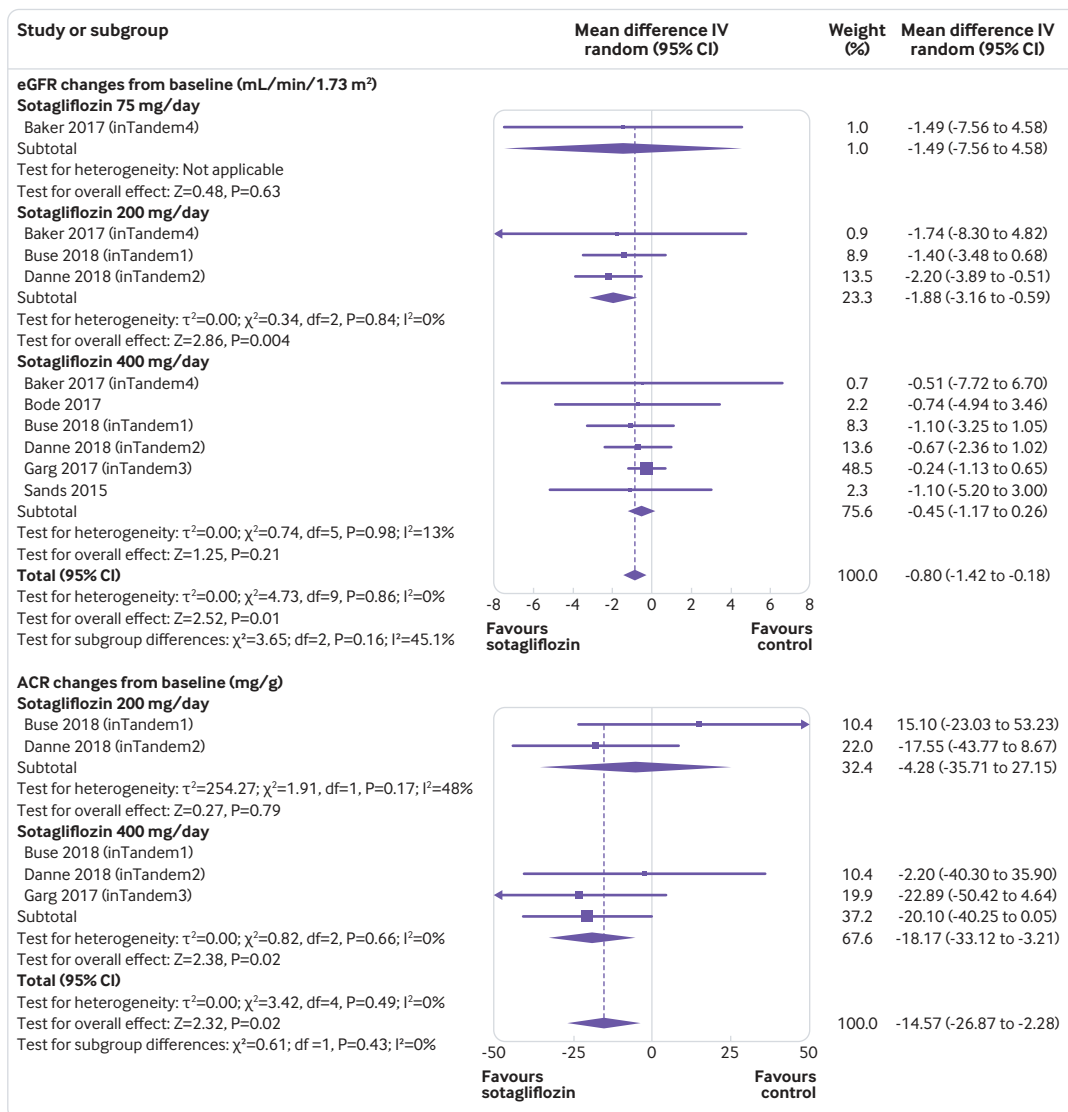
Fig 4 | Forest plot comparing effect of sotagliflozin versus placebo on estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (ACR). IV=inverse invariance

Subgroup analyses showed that the risk of diabetic ketoacidosis varied according to the initial HbA1c of included randomised controlled trials. The risk increased in trials with a mean initial HbA1c lower than 8% (relative risk 6.62, 95% confidence interval 2.04 to 21.48, I²=0%, P=0.002, n=3 trials, 1608 participants), but not in trials with a mean HbA1c of 8% or more (2.21, 0.43 to 11.42, I²=0%, P=0.34, n=3 trials, 1630 participants; supplementary table 3). In a meta-regression model including sotagliflozin dose, trial duration, initial HbA1c, initial fasting plasma glucose, changes in HbA1c and fasting plasma glucose, total bolus and basal insulin doses (baseline, changes, and end-of-treatment doses), fasting and postprandial glycaemia, body weight changes, and volume depletion events, the risk of diabetic ketoacidosis correlated inversely with initial HbA1c (β=−0.331; P=0.009) and with the magnitude of basal insulin dose reduction (β=−0.218; P=0.012; supplementary figure 8).

Urinary tract infections and genital tract infections
Compared with placebo, sotagliflozin did not affect the risk of urinary tract infections (relative risk 0.97, 95% confidence interval 0.71 to 1.33, P=0.84; 10 comparisons, I²=0%, 3238 participants) but was associated with an increased risk of mycotic genital tract infections (3.12, 2.14 to 4.54, P<0.001; 10 comparisons, I²=0%; fig 6). In a meta-regression model, the risk of genital tract infection was not related to sotagliflozin dose, urinary glucose excretion, initial HbA1c, initial fasting plasma glucose, and changes in HbA1c and fasting plasma glucose (all P>0.5).

Gastrointestinal events
Compared with controls, sotagliflozin was associated with an increased risk of diarrhoea (relative risk 1.50, 95% confidence interval 1.08 to 2.10, P=0.02; 10 comparisons, I²=0%, 3238 participants; supplementary figure 9A), but not of other gastrointestinal symptoms (supplementary table 5).

Study or subgroup	Mean difference IV random (95% CI)	Weight (%)	Mean difference IV random (95% CI)
Hypoglycaemia rate (events per patient year)			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		2.2	-8.00 (-39.98 to 23.98)
Subtotal		2.2	-8.00 (-39.98 to 23.98)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=0.49, P=0.62			
Sotagliflozin 200 mg/day			
Baker 2017 (inTandem4)		5.4	-8.00 (-28.33 to 12.33)
Buse 2018 (inTandem1)		10.0	-12.00 (-26.92 to 2.92)
Danne 2018 (inTandem2)		10.1	-17.00 (-31.88 to -2.12)
Subtotal		25.5	-13.13 (-22.48 to -3.77)
Test for heterogeneity: τ²=0.00; χ²=0.53, df=2, P=0.77; I²=0%			
Test for overall effect: Z=2.75, P=0.006			
Sotagliflozin 400 mg/day			
Baker 2017 (inTandem4)		5.4	-3.00 (-23.33 to 17.33)
Bode 2017		7.9	-7.00 (-23.81 to 9.81)
Buse 2018 (inTandem1)		9.7	-6.00 (-21.20 to 9.20)
Danne 2018 (inTandem2)		10.0	-18.00 (-32.93 to -3.07)
Garg 2017 (inTandem3)		38.6	-6.00 (-13.60 to 1.60)
Sands 2015		0.6	-23.00 (-83.08 to 37.08)
Subtotal		72.3	-7.69 (-13.25 to -2.13)
Test for heterogeneity: τ²=0.00; χ²=2.53, df=5, P=0.77; I²=0%			
Test for overall effect: Z=2.71, P=0.007			
Total (95% CI)		100.0	-9.09 (-13.82 to -4.36)
Test for heterogeneity: τ²=0.00; χ²=4.02, df=9, P=0.91; I²=0%			
Test for overall effect: Z=3.77, P<0.001			
Test for subgroup differences: χ²=0.96; df=2, P=0.62; I²=0%			

Scale: -40 -20 0 20 40. Higher with control ← → Higher with sotagliflozin

	Risk ratio (95% CI) M-H random		Risk ratio (95% CI) M-H random
Incident severe hypoglycaemia			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		1.2	0.12 (0.01 to 2.77)
Subtotal		1.2	0.12 (0.01 to 2.77)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=1.32, P=0.19			
Sotagliflozin 200 mg/day			
Baker 2017 (inTandem4)		1.2	1.08 (0.05 to 24.96)
Buse 2018 (inTandem1)		25.0	0.67 (0.33 to 1.33)
Danne 2018 (inTandem2)		13.4	1.07 (0.42 to 2.75)
Subtotal		39.6	0.79 (0.46 to 1.38)
Test for heterogeneity: τ²=0.00; χ²=0.67, df=2, P=0.71; I²=0%			
Test for overall effect: Z=0.82, P=0.41			
Sotagliflozin 400 mg/day			
Baker 2017 (inTandem4)		1.6	0.34 (0.02 to 5.07)
Bode 2017		2.4	0.34 (0.04 to 3.15)
Buse 2018 (inTandem1)		25.0	0.67 (0.33 to 1.34)
Danne 2018 (inTandem2)		10.4	0.42 (0.14 to 1.23)
Garg 2017 (inTandem3)		18.1	0.92 (0.41 to 2.08)
Sands 2015		1.7	1.06 (0.07 to 15.60)
Subtotal		59.2	0.66 (0.42 to 1.03)
Test for heterogeneity: τ²=0.00; χ²=2.02, df=5, P=0.85; I²=0%			
Test for overall effect: Z=1.83, P=0.07			
Total (95% CI)		100.0	0.69 (0.49 to 0.98)
Test for heterogeneity: τ²=0.00; χ²=4.18, df=9, P=0.90; I²=0%			
Test for overall effect: Z=2.07, P=0.04			
Test for subgroup differences: χ²=1.48; df=2, P=0.48; I²=0%			

Scale: 0.01 0.1 1 10 100. Higher with control ← → Higher with sotagliflozin

	Risk ratio (95% CI) M-H random		Risk ratio (95% CI) M-H random
Incident DKA			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		5.1	1.08 (0.05 to 24.96)
Subtotal		5.1	1.08 (0.05 to 24.96)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=0.05, P=0.96			
Sotagliflozin 200 mg/day			
Baker 2017 (inTandem4)		5.1	1.08 (0.05 to 24.96)
Buse 2018 (inTandem1)		11.8	4.59 (0.59 to 35.82)
Danne 2018 (inTandem2)		6.0	6.45 (0.37 to 113.62)
Subtotal		22.9	3.65 (0.83 to 15.94)
Test for heterogeneity: τ²=0.00; χ²=0.80, df=2, P=0.67; I²=0%			
Test for overall effect: Z=1.72, P=0.09			
Sotagliflozin 400 mg/day			
Baker 2017 (inTandem4)		5.1	1.08 (0.05 to 24.96)
Bode 2017		4.9	0.34 (0.01 to 8.14)
Buse 2018 (inTandem1)		6.2	11.81 (0.70 to 198.82)
Danne 2018 (inTandem2)		6.2	9.36 (0.55 to 159.50)
Garg 2017 (inTandem3)		44.0	5.28 (1.82 to 15.30)
Sands 2015		5.7	5.29 (0.27 to 102.49)
Subtotal		72.1	4.41 (1.92 to 10.12)
Test for heterogeneity: τ²=0.00; χ²=4.18, df=5, P=0.52; I²=0%			
Test for overall effect: Z=3.50, P<0.001			
Total (95% CI)		100.0	3.93 (1.94 to 7.96)
Test for heterogeneity: τ²=0.00; χ²=5.75, df=9, P=0.76; I²=0%			
Test for overall effect: Z=3.80, P<0.001			
Test for subgroup differences: χ²=0.73; df=2, P=0.69; I²=0%			

Scale: 0.01 0.1 1 10 100. Higher with control ← → Higher with sotagliflozin

Fig 5 | Forest plot comparing effect of sotagliflozin versus placebo on hypoglycaemia, severe hypoglycaemia, and diabetic ketoacidosis (DKA). IV=inverse invariance; M-H=Mantel-Haenszel

Study or subgroup	Risk ratio (95% CI) M-H random	Weight (%)	Risk ratio (95% CI) M-H random
UTIs			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		1.0	0.12 (0.01 to 2.77)
Subtotal		1.0	0.12 (0.01 to 2.77)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=1.32, P=0.19			
Sotagliflozin 200 mg/day			
Baker 2017 (inTandem4)		1.0	1.08 (0.05 to 24.96)
Buse 2018 (inTandem1)		20.4	1.32 (0.66 to 2.67)
Danne 2018 (inTandem2)		10.6	0.91 (0.34 to 2.40)
Subtotal		32.0	1.16 (0.66 to 2.03)
Test for heterogeneity: τ^2=0.00; χ^2=0.39, df=2, P=0.82; I^2=0%			
Test for overall effect: Z=0.52, P=0.60			
Sotagliflozin 400 mg/day			
Baker 2017 (inTandem4)		1.4	0.34 (0.02 to 5.07)
Bode 2017		2.0	3.07 (0.33 to 28.37)
Buse 2018 (inTandem1)		13.6	0.63 (0.27 to 1.47)
Danne 2018 (inTandem2)		13.9	1.26 (0.54 to 2.94)
Garg 2017 (inTandem3)		35.0	0.93 (0.55 to 1.59)
Sands 2015		1.0	0.35 (0.02 to 8.08)
Subtotal		67.0	0.92 (0.62 to 1.35)
Test for heterogeneity: τ^2=0.00; χ^2=3.33, df=5, P=0.65; I^2=0%			
Test for overall effect: Z=0.45, P=0.65			
Total (95% CI)		100.0	0.97 (0.71 to 1.33)
Test for heterogeneity: τ^2=0.00; χ^2=5.90, df=9, P=0.75; I^2=0%			
Test for overall effect: Z=0.20, P=0.84			
Test for subgroup differences: χ^2=2.19; df=2, P=0.34; I^2=8.5%			

0.005 0.1 1 10 200
Higher with control — Higher with sotagliflozin

Study or subgroup	Risk ratio (95% CI) M-H random	Weight (%)	Risk ratio (95% CI) M-H random
GTIs			
Sotagliflozin 75 mg/day			
Baker 2017 (inTandem4)		1.4	1.08 (0.05 to 24.96)
Subtotal		1.4	1.08 (0.05 to 24.96)
Test for heterogeneity: Not applicable			
Test for overall effect: Z=0.05, P=0.96			
Sotagliflozin 200 mg/day			
Baker 2017 (inTandem4)		1.4	1.08 (0.05 to 24.96)
Buse 2018 (inTandem1)		13.1	3.06 (1.08 to 8.63)
Danne 2018 (inTandem2)		10.1	3.95 (1.21 to 12.89)
Subtotal		24.6	3.20 (1.50 to 6.82)
Test for heterogeneity: τ^2=0.00; χ^2=0.59, df=2, P=0.74; I^2=0%			
Test for overall effect: Z=3.01, P=0.003			
Sotagliflozin 400 mg/day			
Baker 2017 (inTandem4)		1.4	1.08 (0.05 to 24.96)
Bode 2017		1.6	5.11 (0.25 to 103.51)
Buse 2018 (inTandem1)		16.8	3.48 (1.39 to 8.69)
Danne 2018 (inTandem2)		10.3	4.74 (1.47 to 15.27)
Garg 2017 (inTandem3)		42.5	3.02 (1.70 to 5.36)
Sands 2015		1.4	0.35 (0.02 to 8.08)
Subtotal		74.0	3.16 (2.04 to 4.88)
Test for heterogeneity: τ^2=0.00; χ^2=2.97, df=5, P=0.71; I^2=0%			
Test for overall effect: Z=5.17, P<0.001			
Total (95% CI)		100.0	3.12 (2.14 to 4.54)
Test for heterogeneity: τ^2=0.00; χ^2=4.00, df=9, P=0.91; I^2=0%			
Test for overall effect: Z=5.94, P<0.001			
Test for subgroup differences: χ^2=0.44; df=2, P=0.80; I^2=0%			

0.01 0.1 1 10 100
Higher with control — Higher with sotagliflozin

Fig 6 | Forest plot comparing effect of sotagliflozin versus placebo on urinary tract infection (UTI) and genital tract infection (GTI). M-H=Mantel-Haenszel

Other adverse events

Compared with controls, sotagliflozin treatment was associated with an increased risk of acidosis related adverse events (relative risk 3.85, 95% confidence interval 2.33 to 6.36, P<0.001; 10 comparisons, I^2=0%) and volume depletion events (2.19, 1.10 to 4.36, P=0.03; 10 comparisons=10, I^2=0%; supplementary figure 9B; supplementary figure 10A; supplementary table 5). Subgroup analysis revealed that the risk of volume depletion events was increased in the first 12 weeks of treatment, but then subsided (supplementary table 3). Sotagliflozin did not affect the risk of MACE (1.06, 0.40 to 2.82, P=0.91; 10 comparisons, I^2=6%), cancer (0.86, 0.25 to 2.97, P=0.81; nine comparisons,

I^2=0%), or all cause death (0.35, 0.07 to 1.71, P=0.19; nine comparisons, I^2=0%; supplementary table 5; supplementary figure 10B). The effect of sotagliflozin on other adverse events is summarised in supplementary table 5.

Adverse events leading to treatment discontinuation

We then evaluated the proportion of patients experiencing each adverse event who discontinued treatment due to the adverse event. The most common adverse events leading to treatment discontinuation were diabetic ketoacidosis (35.8% of all patients with diabetic ketoacidosis discontinued treatment), diarrhoea (6.9%), genital tract infections (6.3%), severe hypoglycaemia (5.6%), urinary tract

infections (4.4%), and volume depletion events (4.3%).

Dose-response analysis

We analysed dose-response interactions within the three randomised controlled trials that evaluated different sotagliflozin doses. One trial evaluated sotagliflozin 75, 200, and 400 mg/day doses,[28] while two trials assessed the 200 and 400 mg/daydoses[30 31] (supplementary table 1). The 200 mg/day dose had a greater glycosuric effect (urinary glucose excretion) than the 75 mg/day dose (weighted mean difference 16.00 g/day, 95% confidence interval 3.06 to 28.94), but this effect did not increase further with the 400 mg/day dose (13.00 g/day, −1.78 to 27.78; supplementary table 4).

Sotagliflozin 400 mg/day was associated with a greater improvement than the 200 mg/day dose in HbA1c (weighted mean difference −0.22%, 95% confidence interval −0.28% to −0.12%); fasting plasma glucose (−9.82 mg/dL, −17.05 to −2.58); 2h-PPG (−20.51 mg/dL, −33.98 to −7.03); time in range (6.48%, 2.97% to 9.99%); average daily glucose (−11.02 mg/dL, −17.70 to −4.33); daily total (−5.25%, −7.66% to −2.84%), basal (−4.64%, −8.64% to −0.64%), and bolus (−7.85%, −11.96% to −3.75%) insulin dose; body weight (−0.96%, −1.55 to −0.37); systolic blood pressure (−2.51 mm Hg, −3.83 to −1.20); eGFR (1.05 mL/min/1.73 m^2, 0.11 to 22.12); and ACR (−12.29 mg/g, −26.81 to −1.23; supplementary table 4). We did not find any association 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 by alternative pooling methods including Peto's odds ratio, which has a greater power at event rates below 1%,[54] confirmed the results of the main analysis (supplementary table 3).

Grading of evidence

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

Discussion

Our analysis had four main findings. Firstly, in patients with type 1 diabetes, sotagliflozin as add-on treatment to insulin ameliorated glycaemic efficacy outcomes and also showed non-glycaemic benefits, including body weight, blood pressure, and nephropathy marker reduction. Secondly, sotagliflozin treatment was

Table 1 | Sotagliflozin versus placebo: quality of evidence for clinically relevant glycaemic and non-glycaemic effect outcomes in type 1 diabetes. Summary of findings table based on the GRADE approach*

Outcomes and follow-up	Anticipated absolute effects (95% CI)†		Relative effect (95% CI)	No of participants (and RCTs)	Certainty of evidence (GRADE)	Comments
	Risk with placebo	Risk with sotagliflozin				
Sotagliflozin v placebo for type 1 diabetes: glycaemic effect outcomes						
Mean change in HbA1c (%); follow-up 4-52 weeks	Mean change: ranged from −0.99% to 0.04%	Mean change in intervention group: 0.34% (0.41% to 0.27%) lower	—	3238 (6)	High	Large effect. Dose-response gradient across 200-400 mg/day doses
Mean change in fasting plasma glucose (mg/dL); follow-up 4-52 weeks	Mean change: ranged from −11 to 39 mg/dL	Mean change in intervention group: 16.98 mg/dL (22.09 to 11.86) lower	—	3238 (6)	High	Large effect. Dose-response gradient across 200-400 mg/day doses
Mean change in 2 hour-post-prandial plasma glucose (mg/dL); follow-up 4-52 weeks	Mean change: ranged from −18.5 to 0 mg/dL	Mean change in intervention group: 39.24 mg/dL (50.42 to 28.06) lower	—	539 (5)	High	Large effect. Dose-response gradient across 200-400 mg/day doses
Mean change of time in range (%; 70-180 mg/dL); follow-up 4-52 weeks	Mean change: ranged from −1.83% to −0.2%	Mean change in intervention group: 9.73% (6.66% to 12.81%) higher	—	398 (4)	Moderate‡	Large effect. Dose-response gradient across 200-400 mg/day doses
Sotagliflozin v placebo for type 1 diabetes: non-glycaemic effect outcomes						
Mean change in body weight (%); follow-up 4-52 weeks	Mean change: ranged from −0.99% to 0.04%	Mean change in intervention group: 3.54% (3.98% to 3.09%) lower	—	3238 (6)	High	Dose-response gradient across 200-400 mg/day doses
Mean change in systolic blood pressure (mm Hg); follow-up 4-52 weeks	Mean change: ranged from −3.8 to 1.7 mm Hg	Mean change in intervention group: 3.85 mm Hg (4.76 to 2.93) lower	—	3238 (6)	High	Dose-response gradient across 200-400 mg/day doses
Mean change in eGFR (mL/min/1.73 m^2); follow-up 4-52 weeks	Mean change: ranged from −1.09 to 0.34 mL/min/1.73 m^2	Mean change in intervention group: 0.8 mL/min/1.73 m^2 (1.42 to 0.18) lower	—	3238 (6)	High	Dose-response gradient across 200-400 mg/day doses
Mean change in urinary ACR (mg/g); follow-up: range 24 weeks to 52 weeks	Mean change: ranged from 4.1 to 14.9 mg/g	Mean change in intervention group: 14.57 mg/g (26.87 to 2.28) lower	—	2977 (3)	High	Dose-response gradient across 200-400 mg/day doses

1 mg/dL=0.0555 mmol/L.

GRADE=grading of recommendations assessment, development, and evaluation; RCT=randomised controlled trial; eGFR=estimated glomerular filtration rate; ACR=albumin:creatinine ratio.

*GRADE working group grades of evidence: high certainty (very confident that the true effect lies close to that of the estimate of the effect); moderate certainty (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 (confidence in the effect estimate is limited; the true effect could be substantially different from the estimate of the effect); very low certainty (very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect).

†Risk (95% confidence interval) in the intervention group is based on the assumed risk in the comparison group and the relative effect (95% confidence interval) of the intervention.

‡Unclear whether the population undergoing continuous glucose monitoring substudies was representative of the whole trial population in the inTandem1 and inTandem2 trials. For calculation of the optimal information size, α=0.05 and β=0.2 was used.

Table 2 | Sotagliflozin versus placebo: quality of evidence for clinically relevant adverse events in type 1 diabetes. Summary of findings table based on the GRADE approach*

Outcomes and follow-up	Anticipated absolute effects (95% CI)†		Risk ratio (95% CI)	No of participants (and RCTs)	Certainty of evidence (GRADE)	Comments
	Risk with placebo	Risk with sotagliflozin				
Mean change in hypoglycaemia events (events per patient year); follow-up 4-52 weeks	Mean change: ranged from 69 to 179 events per patient year	Mean change in intervention group: 9.09 events per patient year (13.82 to 4.36) lower	—	3238 (6)	High	—
Incidence of severe hypoglycaemia; follow-up 4-52 weeks	43 per 1000	30 per 1000 (21 to 42)	0.69 (0.49 to 0.98)	3238 (6)	High	—
Incidence of diabetic ketoacidosis; follow-up 4-52 weeks	5 per 1000	18 per 1000 (9 to 36)	3.93 (1.94 to 7.96)	3238 (6)	High	Large effect
Incidence of urinary tract infections; follow-up 4-52 weeks	48 per 1000	46 per 1000 (34 to 63)	0.97 (0.71 to 1.33)	3238 (6)	High	—
Incidence of genital tract infections; follow-up 4-52 weeks	23 per 1000	73 per 1000 (50 to 106)	3.12 (2.14 to 4.54)	3238 (6)	High	Large effect
Incidence of diarrhoea; follow-up 4-52 weeks	35 per 1000	52 per 1000 (37 to 73)	1.50 (1.08 to 2.10)	3238 (6)	High	—
Incidence of adverse events leading to treatment discontinuation; follow-up 4-52 weeks	23 per 1000	31 per 1000 (18 to 54)	1.34 (0.78 to 2.30)	3238 (6)	High	—
Incidence of serious adverse events; follow-up 4-52 weeks	69 per 1000	76 per 1.000 (58 to 99)	1.11 (0.85 to 1.44)	3238 (6)	High	—
Incidence of major adverse cardiovascular events; follow-up: 4-52 weeks	5 per 1000	6 per 1000 (2 to 15)	1.06 (0.40 to 2.82)	3238 (6)	Low‡	Few events, OIS not reached
All cause mortality; follow-up 4-52 weeks	2 per 1000	1 per 1000 (0 to 4)	0.34 (0.07 to 1.70)	3238 (6)	Low‡	Few events, OIS not reached

GRADE=grading of recommendations assessment, development, and evaluation; RCT=randomised controlled trial; OIS=optimal information size.
*GRADE working group grades of evidence: high certainty (very confident that the true effect lies close to that of the estimate of the effect); moderate certainty (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 (confidence in the effect estimate is limited; the true effect could be substantially different from the estimate of the effect); very low certainty (very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect).
†Risk (95% confidence interval) in the intervention group is based on the assumed risk in the comparison group and the relative effect (95% confidence interval) of the intervention.
‡Downgraded for imprecision. For calculation of the OIS, α=0.05 and β=0.2 was used.

associated with a significant reduction in the incidence of hypoglycaemia and severe hypoglycaemia. Thirdly, diabetic ketoacidosis was the most serious and frequent adverse event associated with sotagliflozin treatment, which also increased the risk of genital tract infections, diarrhoea, and volume depletion events, but not of urinary tract infections. Finally, the risk of diabetic ketoacidosis varied depending on initial HbA1c levels and basal insulin dose reduction.

Of patients with type 1 diabetes, 30% achieve glycaemic goals, up to 20% have severe hypoglycaemia every year, and 40% are overweight,[3] hence urgently needing adjunctive treatment strategies to complement the glucose lowering effects of insulin and mitigate its unwanted effects. Hypoglycaemia, which results from the total dependence of patients with type 1 diabetes on injected insulin, is of particular concern and can be viewed as the highest unmet need in this population,[9 10] because it is the main factor limiting optimal glucose control. Furthermore, severe hypoglycaemia is a strong predictor of adverse clinical outcomes and death in patients with diabetes.[7-18 60]

None of the drugs recently approved for type 2 diabetes and seeking an indication for type 1 diabetes (including incretin analogues and SGLT2 inhibitors) reduced hypoglycaemic risk, which is either unaffected or increased by these treatments.[22 61 62] Several mechanisms could underlie the hypoglycaemic risk reduction observed with sotagliflozin. The dual intestinal SGLT1 and renal SGLT2 inhibition blunts acute glucose fluctuations and reduces glycaemic variability (supplementary figure 4C-D), thereby limiting the need

for bolus insulin correction doses and the attendant hypoglycaemic risk (supplementary figure 5C).[15 16 63] The reduction in the rate of hypoglycaemic events could have itself contributed to reduce severe hypoglycaemia. The recurrence of hypoglycaemic episodes blunts autonomic and hormonal responses to subsequent hypoglycaemia, impairs hypoglycaemia awareness and glucose counter-regulation, and paves the way to severe hypoglycaemia. This functional impairment in counter-regulatory mechanisms is distinct from autonomic neuropathy, occurs in the short term, and can be rapidly reversed by reducing hypoglycaemia recurrence.[64]

The analysis of pooled results from phase III randomised controlled trials also showed potential renoprotection for sotagliflozin, which reduced microalbuminuria, a marker of early diabetic nephropathy and an independent cardiovascular risk factor (fig 4).[19] The transient eGFR decline observed in the initial 12 weeks of treatment is similar to that observed with other SGLT2 inhibitors[65] and is consistent with renoprotective mechanisms of SGLT2 inhibition, which enhance afferent arteriolar tone, reduce intraglomerular pressure, and relieve glomerular hyperfiltration and barrier damage.[66] However, in patients receiving sotagliflozin, the reduced glomerular perfusion could be aggravated by volume depletion favoured by concomitant osmotic glycosuria (due to renal SGLT2 inhibition) and diarrhoea (induced by intestinal SGLT1 inhibition; supplementary figure 9). Hence, volume depletion should be avoided in the early months of sotagliflozin treatment.

By contrast with SGLT2 inhibitors, sotagliflozin did not increase the risk of urinary tract infections (fig 6). The reduced glycosuric effects of sotagliflozin as compared with SGLT2 inhibitors[62] could have limited the incidence of urinary tract infections, while SGLT1 mediated intestinal glucose malabsorption could have increased diarrhoea, usually mild, thereby self limiting and not inducing treatment discontinuation.

Further supporting the relevance of intestinal SGLT1 inhibition, a dose-response gradient for most glycaemic outcomes was observed with increasing sotagliflozin dose, 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 type 2 diabetes (supplementary table 2).

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

Clinical and policy implications

Sotagliflozin treatment for up to 52 weeks provides consistent glycaemic and non-glycaemic benefits in patients with type 1 diabetes, including the reduction of unwanted effects of insulin treatment (that is, weight gain and hypoglycaemia). These effects make sotagliflozin an attractive adjunctive treatment to insulin in patients with type 1 diabetes, of whom 30% achieve target glycaemic goals, 40% are overweight, and up to 20% per year experience severe hypoglycaemia.[3] The clinical impact of these benefits might be more appreciable in patients at higher risk of severe hypoglycaemia, such as those with recurrent hypoglycaemia and hypoglycaemia unawareness, who represent 17-36% of the general population with type 1 diabetes.[71]

Our analysis could also help minimise the risk of diabetic ketoacidosis in type 1 diabetes 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 diabetic ketoacidosis,[28-31] which often fail to recognise early diabetic ketoacidosis.[72] Future research should define safer protocols for basal insulin dose adjustment. For example, in a recent phase III randomised controlled trial with dapagliflozin that reported no increased risk of diabetic ketoacidosis, participants were instructed to reduce insulin doses by no more than 20% on treatment initiation, to measure ketonaemia whenever glucose readings were consistently elevated, and then subsequently to up-titrate insulin doses back to baseline after positive ketone testing.[73]

Strengths and limitations

Strengths and limitations of our analysis come from the characteristics of included evidence. Strengths include the thorough assessment of efficacy and safety outcomes, and the direct impact of extracted evidence regarding relevant clinical outcomes (such as hypoglycaemia and diabetic ketoacidosis) on decision making in the management of type 1 diabetes. Limitations include the relatively small number and short duration of included trials (not exceeding 52 weeks), which prevented robust assessment of long term hard outcomes such as MACE and overall mortality. Furthermore, although all included randomised controlled trials had good methodological quality, 66% were industry funded, which could make 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]

1. US Center for Disease Control and Prevention. 2019. https://www.cdc.gov/diabetes/library/socialmedia/infographics.html.
2. Turner R, Stratton I, Horton V, et al, UK Prospective Diabetes Study Group. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. *Lancet* 1997;350:1288-93. doi:10.1016/S0140-6736(97)03062-6
3. Miller KM, Foster NC, Beck RW, et al, T1D Exchange Clinic Network. Current state of type 1 diabetes treatment in the US: updated data from the T1D Exchange clinic registry. *Diabetes Care* 2015;38:971-8. doi:10.2337/dc15-0078
4. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med* 2014;371:1972-82. doi:10.1056/NEJMoa1408214
5. Nathan DMDCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care* 2014;37:9-16. doi:10.2337/dc13-2112
6. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: *Standards of medical care in diabetes-2018*. *Diabetes Care* 2018;41(Suppl 1):S73-85. doi:10.2337/dc18-S008
7. Gerstein HC, Miller ME, Byington RP, et al, Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59. doi:10.1056/NEJMoa0802743
8. Zoungas S, Patel A, Chalmers J, et al, ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410-8. doi:10.1056/NEJMoa1003795
9. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384-95. doi:10.2337/dc12-2480
10. Cefalu WT, Tamborlane WV, Skyler JS. Type 1 diabetes at a crossroads!*Diabetes Care* 2015;38:968-70. doi:10.2337/dc15-0615
11. Monnier L, Colette C, Owens D. The glycemic triumvirate and diabetic complications: is the whole greater than the sum of its component parts?*Diabetes Res Clin Pract* 2012;95:303-11. doi:10.1016/j.diabres.2011.10.014
12. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes* 2008;57:1349-54. doi:10.2337/db08-0063
13. Šoupal J, Škrha JJr, Fajmon M, et al. Glycemic variability is higher in type 1 diabetes patients with microvascular complications irrespective of glycemic control. *Diabetes Technol Ther* 2014;16:198-203. doi:10.1089/dia.2013.0205
14. Snell-Bergeon JK, Roman R, Rodbard D, et al. Glycaemic variability is associated with coronary artery calcium in men with type 1 diabetes: the Coronary Artery Calcification in Type 1 Diabetes study. *Diabet Med* 2010;27:1436-42. doi:10.1111/j.1464-5491.2010.03127.x
15. Zinman B, Marso SP, Poulter NR, et al, DEVOTE Study Group. Day-to-day fasting glycaemic variability in DEVOTE: associations with severe hypoglycaemia and cardiovascular outcomes (DEVOTE 2). *Diabetologia* 2018;61:48-57. doi:10.1007/s00125-017-4423-z
16. Pieber TR, Marso SP, McGuire DK, et al, DEVOTE Study Group. DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular outcomes and mortality. *Diabetologia* 2018;61:58-65. doi:10.1007/s00125-017-4422-0
17. Wright LA, Hirsch IB. Metrics beyond hemoglobin A1C in diabetes management: time in range, hypoglycemia, and other parameters. *Diabetes Technol Ther* 2017;19(S2):S16-26. doi:10.1089/dia.2017.0029
18. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017;40:1631-40. doi:10.2337/dc17-1600
19. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669-701. doi:10.2337/dci18-0033
20. American Diabetes Association. 6. Glycemic targets: *Standards of medical care in diabetes-2018*. *Diabetes Care* 2018;41(Suppl 1):S55-64. doi:10.2337/dc18-S006
21. Seidelmann SB, Feofanova E, Yu B, et al. Genetic variants in SGLT1, glucose tolerance, and cardiometabolic risk. *J Am Coll Cardiol* 2018;72:1763-73. doi:10.1016/j.jacc.2018.07.061
22. Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Sodium-glucose co-transporter-2 inhibitors as add-on therapy to insulin for type 1 diabetes mellitus: systematic review and meta-analysis of randomized controlled trials. *Diabetes Obevs Metab* 2018;20:1755-61. doi:10.1111/dom.13260
23. Powell DR, DaCosta CM, Smith M, et al. Effect of LX4211 on glucose homeostasis and body composition in preclinical models. *J Pharmacol Exp Ther* 2014;350:232-42. doi:10.1124/jpet.114.214304
24. Powell DR, Smith M, Greer J, et al. LX4211 increases serum glucagon-like peptide 1 and peptide YY levels by reducing sodium/glucose cotransporter 1 (SGLT1)-mediated absorption of intestinal glucose. *J Pharmacol Exp Ther* 2013;345:250-9. doi:10.1124/jpet.113.203364
25. Meek TH, Dorfman MD, Matsen ME, et al. Evidence that in uncontrolled diabetes, hyperglucagonemia is required for ketosis but not for increased hepatic glucose production or hyperglycemia. *Diabetes* 2015;64:2376-87. doi:10.2337/db14-1562
26. Sands AT, Zambrowicz BP, Rosenstock J, et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. *Diabetes Care* 2015;38:1181-8. doi:10.2337/dc14-2806
27. Bode B, Banks P, Strumph P, Sawhney S. The Sotagliflozin JDRF Study Writing Group. Efficacy and safety of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct to insulin in young adults with poorly controlled type 1 diabetes (JDRF Study). *Diabetologia* 2017;60:S87-8.
28. Baker C, Wason S, Banks P. A 12-week dose-ranging study of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes (inTandem4). *Diabetologia* 2017;60:S409.
29. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med* 2017;377:2337-48. doi:10.1056/NEJMoa1708337
30. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the North American inTandem1 Study. *Diabetes Care* 2018;41:1970-80. doi:10.2337/dc18-0343
31. Danne T, Cariou B, Banks P, et al. HbA$_{1c}$ and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the European inTandem2 Study. *Diabetes Care* 2018;41:1981-90. doi:10.2337/dc18-0342.
32. US Food and Drug Administration. Search results for sotagliflozin. https://search.usa.gov/search?utf8=%E2%9C%93&affiliate=fda&query=sotagliflozin&commit=Search
33. European Medicines Agency. Search results for sotagliflozin. https://www.ema.europa.eu/en/search/search?search_api_views_fulltext=sotagliflozin
34. Pharmaceutical and Medical Devices Agency. Search results for sotagliflozin. https://ss.pmda.go.jp/en_all/search.x?q=sotagliflozin&ie=UTF-8&page=1&x=30&y=11
35. Lexicon Pharmaceuticals. Homepage. 2019. www.lexpharma.com
36. Sanofi. Homepage. 2019. https://www.sanofi.com
37. Esposito K, Giugliano D, Nappo F, Marfella RCampanian Postprandial Hyperglycemia Study Group. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation* 2004;110:214-9. doi:10.1161/01.CIR.0000134501.57864.66
38. Raz I, Ceriello A, Wilson PW, et al. Post hoc subgroup analysis of the HEART2D trial demonstrates lower cardiovascular risk in older patients targeting postprandial versus fasting/premeal glycemia. *Diabetes Care* 2011;34:1511-3. doi:10.2337/dc10-2375
39. US Food and Drug Administration. FDA approves first continuous glucose monitoring system with a fully implantable glucose sensor and compatible mobile app for adults with diabetes. 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm611454.htm
40. Baghurst PA. Calculating the mean amplitude of glycemic excursion from continuous glucose monitoring data: an automated algorithm. *Diabetes Technol Ther* 2011;13:296-302. doi:10.1089/dia.2010.0090
41. Medical dictionary for regulatory activities. Homepage. https://www.meddra.org/. Accessed 21 July 2018.
42. Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions, version 5.2.0. Cochrane Collaboration, updated March 2011. 14 July 2017. https://community.cochrane.org/editorial-and-publishing-policy-resource/cochrane-review-development/cochrane-handbooks/cochrane-handbook-systematic-reviews-interventions
43. Viswanathan M, Patnode CD, Berkman ND, et al. Recommendations for assessing the risk of bias in systematic reviews of health-care interventions. *J Clin Epidemiol* 2018;97:26-34. doi:10.1016/j.jclinepi.2017.12.004
44. Lachin JM. Fallacies of last observation carried forward analyses. *Clin Trials* 2016;13:161-8. doi:10.1177/1740774515602688

45 Lexchin J. Sponsorship bias in clinical research. *Int J Risk Saf Med* 2012;24:233-42.

46 Safer DJ. Design and reporting modifications in industry-sponsored comparative psychopharmacology trials. *J Nerv Ment Dis* 2002;190:583-92. doi:10.1097/00005053-200209000-00002

47 National Research Council. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. *The prevention and treatment of missing data in clinical trials* . National Academies Press, 2010.

48 Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. *JAMA* 2008;299:1813-7. doi:10.1001/jama.299.15.1813

49 Henry DA, Kerridge IH, Hill SR, et al. Medical specialists and pharmaceutical industry-sponsored research: a survey of the Australian experience. *Med J Aust* 2005;182:557-60.

50 Gøtzsche PC, Hróbjartsson A, Johansen HK, Haahr MT, Altman DG, Chan A-W. Constraints on publication rights in industry-initiated clinical trials. *JAMA* 2006;295:1645-6. doi:10.1001/jama.295.14.1645

51 Manager R. (RevMan). Version 5.3. Copenhagen, Denmark: Nordic Cochrane Center, Cochrane Collaboration; 2012. https://community.cochrane.org/help/tools-and-software/revman-5

52 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700. doi:10.1136/bmj.b2700

53 Guyatt GH, Oxman AD, Kunz R, et al, GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *J Clin Epidemiol* 2011;64:1294-302. doi:10.1016/j.jclinepi.2011.03.017

54 Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007;26:53-77. doi:10.1002/sim.2528

55 Fisher DJ, Carpenter JR, Morris TP, Freeman SC, Tierney JF. Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? *BMJ* 2017;356:j573. doi:10.1136/bmj.j573

56 Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383-94. doi:10.1016/j.jclinepi.2010.04.026

57 Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol* 2011;64:1283-93. doi:10.1016/j.jclinepi.2011.01.012

58 European Association for the Study of Diabetes. Efficacy and safety of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct to insulin in young adults with poorly controlled type 1 diabetes (JDRF Study). EASD virtual meeting, oral presentation 186. 2017. https://www.easd.org/virtualmeeting/home.html#!resources/efficacy-and-safety-of-sotagliflozin-a-dual-sglt1-and-sglt2-inhibitor-as-adjunct-to-insulin-in-young-adults-with-poorly-controlled-type-1-diabetes-jdrf-study-15ae18d4-b8f6-439c-87ea-2f19dcad388e

59 European Association for the Study of Diabetes. A 12-week dose-ranging study of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes (inTandem4). EASD virtual meeting, ePoster 186. 2017. https://www.easd.org/virtualmeeting/home.html#!resources/a-12-week-dose-ranging-study-of-sotagliflozin-a-dual-sglt1-and-sglt2-inhibitor-as-adjunct-therapy-to-insulin-in-type-1-diabetes-intandem4-eac92dc0-58bd-48ae-9cba-aa1675a947cf

60 Lee AK, Warren B, Lee CJ, et al. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. *Diabetes Care* 2018;41:104-11. doi:10.2337/dc17-1669

61 NovoNordisk. Novo Nordisk completes second and final phase 3a trial with liraglutide as adjunct therapy to insulin for people with type 1 diabetes (NN9211). Company announcement 51/2015. https://www.novonordisk.com/bin/getPDF.1947182.pdf. Accessed 24 October 2018.

62 Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. *Ann Med* 2012;44:375-93. doi:10.3109/07853890.2011.560181

63 Monnier L, Colette C, Wojtusciszyn A, et al. Toward defining the threshold between low and high glucose variability in diabetes. *Diabetes Care* 2017;40:832-8. doi:10.2337/dc16-1769

64 Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes* 1993;42:1683-9. doi:10.2337/diab.42.11.1683

65 Neuen BL, Ohkuma T, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function. *Circulation* 2018;138:1537-50. doi:10.1161/CIRCULATIONAHA.118.035901

66 Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation* 2016;134:752-72. doi:10.1161/CIRCULATIONAHA.116.021887

67 Janssen Research & Development. Canagliflozin as an adjunctive treatment to diet and exercise alone or co-administered with other antihyperglycemic agents to improve glycemic control in adults with type 2 diabetes mellitus. 11 December 2012. www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf (accessed 13 September 2014).

68 Neumiller JJ. Empagliflozin: a new sodium-glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. *Drugs Context* 2014;3:212262.

69 Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care* 2015;38:1638-42. doi:10.2337/dc15-1380

70 Henry RR, Dandona P, Pettus J, Mudaliar S, Xu J, Hansen L. Dapagliflozin in patients with type 1 diabetes: A post hoc analysis of the effect of insulin dose adjustments on 24-hour continuously monitored mean glucose and fasting β-hydroxybutyrate levels in a phase IIa pilot study. *Diabetes Obes Metab* 2017;19:814-21. doi:10.1111/dom.12882

71 Olsen SE, Asvold BO, Frier BM, Aune SE, Hansen LI, Bjørgaas MR. Hypoglycaemia symptoms and impaired awareness of hypoglycaemia in adults with Type 1 diabetes: the association with diabetes duration. *Diabet Med* 2014;31:1210-7. doi:10.1111/dme.12496

72 Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care* 2015;38:1687-93. doi:10.2337/dc15-0843

73 Dandona P, Mathieu C, Phillip M, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial [correction: *Lancet Diabetes Endocrinol* 2017;5:864-76]. *Lancet Diabetes Endocrinol* 2017;5:864-76.

Web appendix: Supplementary text
Web appendix: Supplementary figures
Web appendix: Supplementary tables