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RESEARCH ARTICLE

Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

Heidi Storgaard[1]*, Lise L. Gluud[2], Cathy Bennett[3], Magnus F. Grøndahl[1], Mikkel B. Christensen[1,4], Filip K. Knop[1,5,6], Tina Vilsbøll[1,5]

1 Centre for Diabetes Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, **2** Gastrounit, Copenhagen University, Hvidovre Hospital, Hvidovre, Denmark, **3** Centre for Technology Enabled Health Research, Coventry University, Coventry, United Kingdom, **4** Department of Clinical Pharmacology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark, **5** Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, **6** The Novo Nordisk Foundation Centre for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

* Hstorgaard@dadlnet.dk

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Abstract

Objective

Sodium-glucose co-transporter 2 inhibitors (SGLT2-i) are a novel drug class for the treatment of diabetes. We aimed at describing the maximal benefits and risks associated with SGLT2-i for patients with type 2 diabetes.

Design

Systematic review and meta-analysis.

Data Sources and Study Selection

We included double-blinded, randomised controlled trials (RCTs) evaluating SGLT2-i administered in the highest approved therapeutic doses (canagliflozin 300 mg/day, dapagliflozin 10 mg/day, and empagliflozin 25 mg/day) for ≥12 weeks. Comparison groups could receive placebo or oral antidiabetic drugs (OAD) including metformin, sulphonylureas (SU), or dipeptidyl peptidase 4 inhibitors (DPP-4-i). Trials were identified through electronic databases and extensive manual searches. Primary outcomes were glycated haemoglobin A1c (HbA1c) levels, serious adverse events, death, severe hypoglycaemia, ketoacidosis and CVD. Secondary outcomes were fasting plasma glucose, body weight, blood pressure, heart rate, lipids, liver function tests, creatinine and adverse events including infections. The quality of the evidence was assessed using GRADE.

Results

Meta-analysis of 34 RCTs with 9,154 patients showed that SGLT2-i reduced HbA1c compared with placebo (mean difference -0.69%, 95% confidence interval -0.75 to -0.62%). We

AstraZeneca and Boehringer Ingelheim Pharmaceuticals. FKK has received lecture fees from, participated in Advisory Boards of and/or consulted for AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Gilead Sciences, Merck Sharp & Dohme, Novartis, Novo Nordisk, Ono Pharmaceuticals, Sanofi and Zealand Pharma. TV has received lecture fees from, participated in Advisory Boards of and/or consulted for Amgen, AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk and Sanofi. CB is the proprietor of Systematic Research Ltd, a company providing research services, and is an employee of that company, and thus she received consultancy fees for participation in the project. LLG, MG, MC and CB declare no relationships with any organisations that might have an interest in the submitted work within the last three years, or no other relationships or activities that could have influenced the submitted work. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

downgraded the evidence to '*low quality*' due to variability and evidence of publication bias (P = 0.015). Canagliflozin was associated with the largest reduction in HbA1c (-0.85%, -0.99% to -0.71%). There were no differences between SGLT2-i and placebo for serious adverse events. SGLT2-i increased the risk of urinary and genital tract infections and increased serum creatinine, and exerted beneficial effects on bodyweight, blood pressure, lipids and alanine aminotransferase (*moderate to low quality evidence*). Analysis of 12 RCTs found a beneficial effect of SGLT2-i on HbA1c compared with OAD (-0.20%, -0.28 to -0.13%; *moderate quality evidence*).

Conclusion

This review includes a large number of patients with type 2 diabetes and found that SGLT2-i reduces HbA1c with a notable increased risk in non-serious adverse events. The analyses may overestimate the intervention benefit due bias.

Introduction

Patients with type 2 diabetes are characterized by hyperglycaemia with elevated levels of glycated haemoglobin A1c (HbA1c) [1] which may lead to microvascular and macrovascular disease [2, 3]. Between 2012 and 2014, three sodium-glucose co-transporter 2 inhibitors (SGLT2-i), canagliflozin, dapagliflozin and empagliflozin, were approved by the US Food and Drug Administration (FDA) [4–6] and the European Medicines Agency (EMA) [7–10] for the treatment of patients with type 2 diabetes. SGLT2-i inhibit glucose reabsorption in the proximal tubules of the kidneys, increasing urinary glucose excretion and reducing the amount of circulating glucose [11]. SGLT2-i have been assessed as monotherapy or combined with other antidiabetic agents including metformin, sulphonylureas (SU), dipeptidyl peptidase 4 inhibitors (DPP-4-i), thiazolidinediones (pioglitazone) or insulin [12–19].

In 2015 the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend SGLT2-i as second-line agents in the management of type 2 diabetes [20]. A recent randomised controlled trial (RCT) evaluated the effect of empagliflozin on cardiovascular disease (CVD)-associated events in 7,020 patients with type 2 diabetes and a high risk of CVD events [21]. The study found that empagliflozin reduced the relative risk of the CVD events including death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke by 14% (absolute risk reduction of 1.6%) compared to placebo. Whether the effect is specific for empagliflozin or represents a class effect for SGLT2-i will be assessed in on-going RCTs assessing the effect of canagliflozin [22]. and dapagliflozin [23] on CVD in patients with type 2 diabetes. However, the efficacy and safety of SGLT2-i in patients with a low to moderate cardiovascular risk or in a real world setting, where patients often have multiple co-morbidities and are treated with several drugs, have not been established.

In contrast to previous meta-analyses evaluating the effects of SGLT2-i in type 2 diabetes, we only included trials, which used the recommended maximum daily doses of the SGLT2-i [24–36] as we expect these dosages to be the most widely used in the clinic [4–10]. Lower or higher doses of SGLT2-i might overestimate or underestimate the efficacy or the risk of adverse events. The present approach provides the evidenced-based clinician with a clear and balanced summary of the existing evidence.

In addition, three studies found that intensive glucose lowering treatments may harm some patients [37–39] and recently, the safety of SGLT2i was put into question by the regulatory agencies [4–6, 8, 9].

We conducted the present systematic review with meta-analyses of RCTs evaluating the safety and efficacy of the SGLT2-i canagliflozin, dapagliflozin, and empagliflozin administered in highest clinically relevant doses for at least 12 weeks compared to placebo or OAD.

Methods

We conducted our review based on a published protocol (PROSPERO CRD42014008960; S2 File) [40] and adhered to the PRISMA standards [41] for the conduct and reporting of this systematic review and meta-analysis (PRISMA checklist; S3 File).

Search methods

Electronic searches were performed in the Cochrane Library, MEDLINE, EMBASE, the Science Citation Index and the WHO Trial Search Database, using the following search string: "((Sodium glucose (All Fields) AND co-transporter (All Fields)) OR (2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol (Supplementary Concept) OR 2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol (All Fields) OR dapagliflozin (All Fields)) OR (canagliflozin (Supplementary Concept) OR canagliflozin (All Fields)) OR (empagliflozin (Supplementary Concept) OR empagliflozin (All Fields))". Additional manual searches were performed in reference lists of relevant papers. We obtained additional data on e.g. heart rate, ALT and lipids from the study investigators, the manufacturers and the YODA-project (details listed in S1 File) [42–45]. The last search update was October 2015.

Trial eligibility and selection

We included English-language, full paper, double-blind RCTs conducted in adult patients (at least 18 years of age) with type 2 diabetes. The interventions assessed were the recommended daily target doses of the SGLT2-i canagliflozin 300 mg; dapagliflozin 10 mg; empagliflozin 25 mg [4–6, 8]. Controls could receive placebo or OAD including metformin, SU or DPP-4-i. We only included RCTs with a treatment duration of at least 12 weeks. Co-interventions ('add-on' therapies) with other antidiabetic agents were allowed if administered to both the intervention and control groups. We excluded studies, which involved participants with impaired kidney function and SGLT-2i only approved in Japan (ipragliglozin, luseogliflozin, tofogliflozin) or in clinical development (ertugliflozin, remogliflozin, sotagliflozin).

Trial selection was carried out by two review authors (HS and CB) who independently reviewed the search results and selected trials for inclusion, with involvement of a third review author (CB or TV) if necessary to resolve disagreements. Multiple publications, which reported results from the same RCT, were grouped into 'studies' (S1 File).

Outcome variables and measures

Our primary outcomes were HbA1c (change from baseline) and serious adverse events defined as the number of participants experiencing cancer (all cancers, bladder cancer, breast cancer), death, severe hypoglycaemia, ketoacidosis and CVD. The secondary outcomes were fasting plasma glucose (FPG) (mmol/L), change in body weight (kg), systolic and diastolic blood pressure (SBP and DBP (mmHg)), heart rate (beats per minute (bpm)), plasma lipid profile (low-density lipoprotein (LDL) cholesterol (mmol/L) (which is known to increase the risk of CVD),

high-density lipoprotein (HDL) cholesterol (mmol/L) and triglyceride (mmol/L)), alanine amino transferase (U/L), adverse events leading to discontinuation and drug-related adverse events. We also evaluated non-serious adverse events defined as the number of participants experiencing urinary tract infections (UTI), genital tract infections (GTI); 'non-severe' hypoglycaemia, and serum creatinine.

Data extraction and management

Trial characteristics (methods, participants, interventions, study outcomes, potential risks of bias, and funding source) were recorded. Three authors (HS, MFG and MBC) independently identified outcomes from each included study and extracted outcome data into extraction forms (Excel spreadsheets). Consensus was reached through discussion. For trials presenting data from more than one treatment period (e.g. 26 and 52 weeks), data from the longest treatment period were used. For studies with multiple treatment arms for example SGLT2-i, other OAD and placebo. We conducted separate evaluations and analyses of a) SGLT2-i versus placebo and b) SGLT2-i versus other OAD.

Assessment of risk of bias and quality

The bias risk assessment followed the Cochrane Collaboration's risk of bias assessment tool.[46] In each domain, studies were given a rating of low, unclear or high risk. We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to describe the quality of the evidence and the strength of recommendation, 'high' to 'very low'[47, 48].

Statistical analyses

We undertook meta-analyses in RevMan [49] using random-effects models, unless stated otherwise. We chose the random-effects model due to an expected heterogeneity. We conducted the analyses with the assumption that if the estimates were similar, then any small-study effects had little effect on the intervention effect estimate. If the random-effects estimates were more beneficial, we planned to re-evaluate whether it was reasonable to conclude that the intervention was more effective in the smaller studies. However, in all of our analyses, the conclusions of the fixed-effect and random-effects meta-analyses were consistent. Based on the expected clinical heterogeneity, we expected that our analyses would display statistical between-trial heterogeneity ($I^2 > 0\%$). For random-effects models, precision will decrease with increasing heterogeneity and confidence intervals will widen correspondingly. We therefore (*a priori*) planned to report the random-effects model under the assumption that they would provide the most conservative (and a more correct) estimate of the intervention effect. We present results as mean differences (MD) or relative risks (RR) with 95% confidence intervals (CI). For effect sizes of MD, values greater than 0.70 were treated as large; values between 0.40 and 0.70 as moderate; and values less than 0.40 but greater than 0.10 as small.[46] We conducted subgroup analyses on the basis of SGLT2-i type (canagliflozin, dapagliflozin, empagliflozin), and on the basis of the type of OAD (metformin, SU, or DPP-4-i). Differences between subgroups were reported using tests for subgroup differences expressed as P values. I^2 values were used as a measure of heterogeneity and are reported if they exceeded 30%. For meta-analyses with at least 10 RCTs, publication bias and other small study effects were assessed in regression analyses and funnel plots. For continuous variables, linear regression of the intervention effect estimates on their standard errors, weighting by 1/(variance of the intervention effect estimate), was used (Egger test). For dichotomous outcomes Z/sqrt(V) was regressed against sqrt(V) (Harbord test), where Z is the efficient score and V is Fisher's information (the variance of Z under the null hypothesis).

Results

Description of studies

We identified 1,087 potentially eligible records through our searches and included 42 RCTs described in 59 published reports (Fig 1). The total number of participants was 24,500 (S1 File). Thirty-four RCTs compared SGLT2-i versus placebo and 12 compared SGLT2-i versus OAD. Four RCTs were multi-arm, comparing SGLT2-i versus placebo and AD [17, 50–52].

Thirty-four RCTs compared SGLT2-i versus placebo. Seven RCTs evaluated canagliflozin 300 mg,[17, 50, 53–59] 17 evaluated dapagliflozin 10 mg,[12, 18, 19, 51, 60–79] and 10 evaluated empagliflozin 25 mg[13–16, 52, 80–88] (Table 1). Twelve RCTs compared SGLT2-i versus OAD (Table 1). Of these 12 trials, four compared canagliflozin versus glimepiride [89, 90] or sitagliptin[17, 50, 91] and four compared dapagliflozin versus metformin [51, 92], glipizide [93–95] or saxagliptin [96]. The remaining four studies compared empagliflozin versus linagliptin [97, 98], glimepiride [99, 100] or sitagliptin [52]. The maximum doses of metformin were 2000 mg [92] or 1500 mg [51]. The doses of the other OADs was 1 to 8 mg for glimepiride, 20 mg for glipizide, 100 mg for sitagliptin, 5 mg for saxagliptin and 5 mg for linagliptin.

Thirty-one RCTs were multicentre and multinational carried out in USA, Europe and Asia and three RCTs were conducted Japan [68, 69, 83]. The duration of the RCTs ranged from 12 weeks [17, 51, 56, 68, 70, 79–81, 83, 85] to 102 [53, 54, 57, 60–64, 72, 90, 99, 100], or 104 weeks [53, 54], with the longest duration being 208 weeks [93–95].

Excluded studies

We excluded 17 RCTs (S1 File) for the following reasons: the dose used in the RCTs did not meet our criteria, open label extension with optional cross-over of placebo, included patients with kidney disease, was not double blind or assessed the combination of SGLT2-i and OAD or insulin. We did not include any abstracts or RCTs published in other languages than English.

Risk of bias

All RCTs had a low risk of bias in the assessment of randomisation (allocation sequence generation and concealment) and were double blind. One RCT was classified as unclear risk of attrition bias [74]. The published trial report stated that "Approximately 93% of the patients in each treatment arm completed the 24-week double-blind treatment period". The description of the statistical analyses explained that patients were excluded from the analyses if they did not receive the intervention or did not have follow up assessments. We classified three RCTs as unclear or high risk of reporting bias. One RCT did not provide a clear description of secondary/exploratory outcome measures [51]. The second RCT [70] listed the glomerular filtration rate as the only primary outcome in the registered trial protocol, but in the trial publication, primary outcomes included renal function, blood pressure, and circulating plasma volume. The third RCT did not provide information about adverse events [55]. All RCTs were industry-funded and were classified as unclear risk of bias in the domain 'other biases'. Accordingly, none of the trials had a low risk of bias in all domains.

Change in HbA1c

Random-effects meta-analysis of 34 RCTs with 9,154 patients showed that SGLT2-i were associated with a beneficial effect on HbA1c compared with placebo (MD -0.69%, CI -0.75 to -0.62%, Fig 2). Between study heterogeneity was detected (I^2 = 75%) and we found evidence of small study effects in regression analysis (P = 0.015) and visual inspection of a funnel plot. In

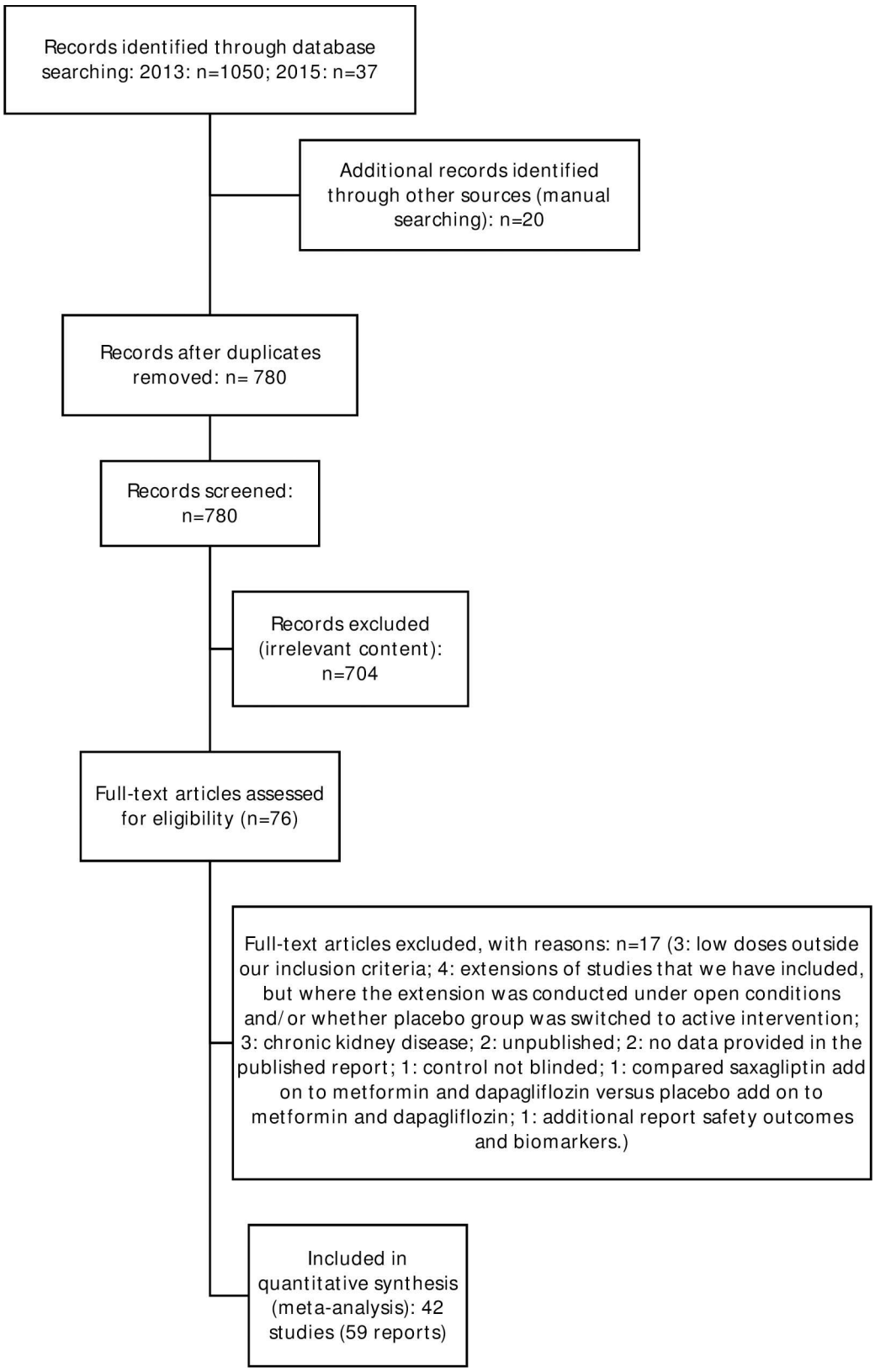

Fig 1. Flowchart for identification and selection of included trials. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

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Table 1. Characteristics of included randomised controlled trials comparing SGLT2-i versus placebo or other oral antidiabetic drugs (OAD).

Study ID	Intervention	Control	Co-intervention	Number of patients	Duration (weeks)	Age SGLT2-i	Age control	BMI SGLT2-i	BMI control	HbA1c SGLT2-i	HbA1c control
Placebo controlled RCTs											
Bode 2013[53, 54]	Canagliflozin 300 mg	Placebo	Pre-existing treatment	714	104*	63.4	63.2	31.5	31.8	7.7	7.8
Forst 2014[55]	Canagliflozin 300 mg	Placebo	Metformin, pioglitazone	344	26	57	58.3	32.8	32.5	7.9	8.0
Gonzalez 2013 [50]	Canagliflozin 300 mg	Placebo	Metformin	1,284	26	55.3	55.3	31.4	31.1	7.9	8.0
Inagaki 2013 [56]	Canagliflozin 300 mg	Placebo	None	383	12	57.1	57.7	25.9	26.4	8.2	8.0
Rosenstock 2012[17]	Canagliflozin 300 mg	Placebo	Metformin	451	12	52.3	53.3	31.6	30.6	7.7	7.8
Stenløf 2013 [57, 58]	Canagliflozin 300 mg	Placebo	none	587	26	55.3	55.7	31.7	31.8	8	8
Wilding 2013 [59]	Canagliflozin 300 mg	Placebo	Metformin, SU	469	78*	56.1	56.8	33.2	32.7	8.1	8.1
Bailey 2010 [60–62]	Dapagliflozin 10 mg	Placebo	Metformin	546	102*	52.7	53.7	31.2	31.8	7.9	8.1
Bolinder 2012 [63, 64, 72]	Dapagliflozin 10 mg	Placebo	Metformin	466	102*	60.6	60.8	32.1	31.7	7.2	7.2
Cefalu 2015 [65]	Dapagliflozin 10 mg	Placebo	Insulin, metformin	922	52*	62.8	63	32.6	32.9	8.2	8.1
Ferrannini 2010[12]	Dapagliflozin 10 mg	Placebo	None	485	24	50.6	52.7	33.6	32.3	8.0	7.8
Jabbour 2014 [66]	Dapagliflozin 10 mg	Placebo	Metformin, sitagliptin	451	24	54.8	55	-	-	7.9	8.0
Ji 2014[67]	Dapagliflozin 10 mg	Placebo	None	393	24	51.2	49.9	-	-	8.3	8.4
Kaku 2013[68]	Dapagliflozin 10 mg	Placebo	None	279	12	56.5	58.4	-	-	8.2	8.1
Kaku 2014[69]	Dapagliflozin 10 mg	Placebo	Not stated	261	24	57.5	60.4	26.1	25.2	7.5	7.5
Lambers Heerspink 2013[70]	Dapagliflozin 10 mg	Placebo	Metformin, SU	75	12	53.7	58	-	-	7.7	7.5
Leiter 2014[71]	Dapagliflozin 10 mg	Placebo	Pre-existing, treatment	964	52*	63.9	63.6	33	32.7	8.0	8.1
List 2009[51]	Dapagliflozin 10 mg	Placebo	None	389	12	54	53	31	32	8.0	7.9
Mathieu 2015 [73]	Dapagliflozin 10 mg	Placebo	Saxagliptin + metformin	320	24	55.2	55	31.2	4.7	8.2	8.2
Matthaei 2015 [74, 75]	Dapagliflozin 10 mg	Placebo	Metformin, SU	218	52*	61.1	60.9	31.9	32	8.1	8.2
Rosenstock 2012[76]	Dapagliflozin 10 mg	Placebo	Pioglitazone	420	48**	53.8	53.5	-	-	8.4	8.3
Strojek 2011 [77, 78]	Dapagliflozin 10 mg	Placebo	Glimepiride	597	48*	58.9	60.3	-	-	8.1	8.2
Wilding 2009 [79]	Dapagliflozin 10 mg	Placebo	Metformin, insulin, pioglitazone, rosiglitazone	71	12	55.7	58.4	35.5	34.8	8.4	8.4

(*Continued*)

Table 1. (*Continued*)

Study ID	Intervention	Control	Co-intervention	Number of patients	Duration (weeks)	Age SGLT2-i	Age control	BMI SGLT2-i	BMI control	HbA1c SGLT2-i	HbA1c control
Wilding 2012 [18, 19]	Dapagliflozin 10 mg	Placebo	Insulin	108	48*	59.3	58.8	33.4	33.1	8.6	8.5
Ferrannini 2013[80, 81]	Empagliflozin 25 mg	Placebo	None	408	12	57	58	28.3	28.8	7.8	7.8
Häring 2013 [13, 14]	Empagliflozin 25 mg	Placebo	Metformin, SU	669	76*	57.4	56.9	28.3	27.9	8.1	8.2
Haring 2014 [82, 84]	Empagliflozin 25 mg	Placebo	Metformin	638	76*	55.6	55.5	29.7	28.7	7.9	7.9
Kadowaki 2014 [83]	Empagliflozin 25 mg	Placebo	None	547	12	57.3	58.7	25.1	25.6	7.9	7.9
Kovacs 2014 [15, 16]	Empagliflozin 25 mg	Placebo	Metformin, pioglitazone	499	76*	54.2	54.6	29.1	29.3	8.1	8.2
Roden 2013 [52]	Empagliflozin 25 mg	Placebo	None	899	24	53.8	54.9	28.2	28.7	7.9	7.9
Rosenstock 2013[85]	Empagliflozin 25 mg	Placebo	Metformin	495	12	59	60	31.5	31.3	8.1	8.0
Rosenstock 2014[86]	Empagliflozin 25 mg	Placebo	Insulin +/- metformin	563	52	58	55.3	35	34.7	8.3	8.3
Rosenstock 2015[87]	Empagliflozin 25 mg	Placebo	Insulin +/- metformin and SU	494	78	59.9	58.1	32.7	31.8	8.1	8.3
Ross 2015[88]	Empagliflozin 25 mg	Placebo	Metformin	983	16	58.1	57.9	32.1	32	7.7	7.7
RCTs with OAD control											
Cefalu 2013 [89, 90]	Canagliflozin 300 mg	Glimepiride 8 mg	Metformin	1,452	104*	55.8	56.3	31.2	30.9	7.8	7.8
Gonzalez 2013 [50]	Canagliflozin 300 mg	Sitagliptin 100 mg	Metformin	1,284	26	55.3	55.5	31.4	32	7.9	7.9
Rosenstock 2012[17]	Canagliflozin 300 mg	Sitagliptin 100mg	Metformin	451	12	52.3	51.7	31.6	31.6	7.7	7.6
Schernthaner 2013[91]	Canagliflozin 300 mg	Sitagliptin 100 mg	Metformin, SU	755	52*	56.6	56.7	31.5	31.7	8.1	8.1
Henry 2012[92]	Dapagliflozin 10 mg	Metformin 1500 mg	None	641	24	51.1	52.7	-	-	9.1	9.1
List 2009[51]	Dapagliflozin 10 mg	Metformin 2000 mg	None	389	12	54	54	31	32	8.0	7.9
Nauck 2011 [93–95]	Dapagliflozin 10 mg	Glipizide 20 mg	Metformin	814	208	58	59	31.7	31.2	7.7	7.7
Rosenstock 2015[96]	Dapagliflozin 10 mg	Saxagliptin5 mg	Metformin	534	24	54	55	31.5	31.8	8.9	9.0
DeFronzo 2015[97]	Empagliflozin 25 mg	Linagliptin 5 mg	Metformin	899	52*	55.5	56.2	31.8	30.6	8.0	8.0
Lewin 2015[98]	Empagliflozin 25 mg	Linagliptin5 mg	None	686	52*	56	53.8	31.2	31.9	8.0	8.1
Ridderstråle 2014[99, 100]	Empagliflozin 25 mg	Glimepiride1 to 4 mg	Metformin	1,549	104*	56.2	55.7	30	30.3	7.9	7.9
Roden 2013 [52]	Empagliflozin 25 mg	Sitagliptin 100 mg	None	677	24	53.8	55.1	28.2	28.2	7.9	7.9

BMI, body mass index (kg/m^2); HbA1c, glycated haemoglobin A1c (%); SU, suphonylureas; RCTs, randomised controlled trials.

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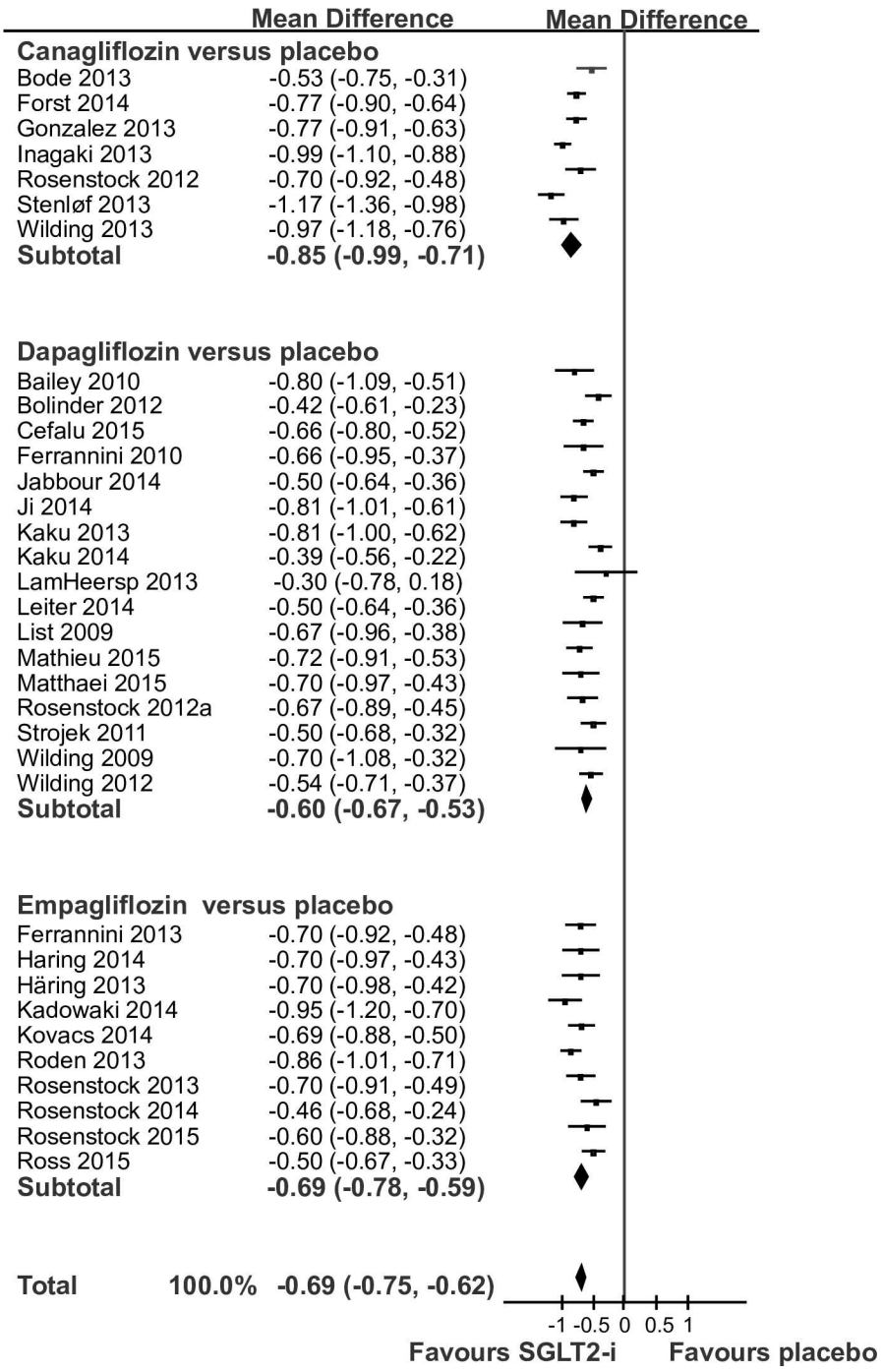

Fig 2. Change in glycated haemoglobin: forest plot of randomized controlled trials comparing sodium-glucose co-transporter 2 inhibitors (SGLT2-i) versus placebo. The plot shows subgroups of trials assessing the different SGLT2-i.

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addition, subgroup analysis showed a clear difference between subgroups (test for subgroup differences P = 0.008). The largest effect size was seen for canagliflozin (-0.85%, -0.99 to -0.71%; Fig 2).

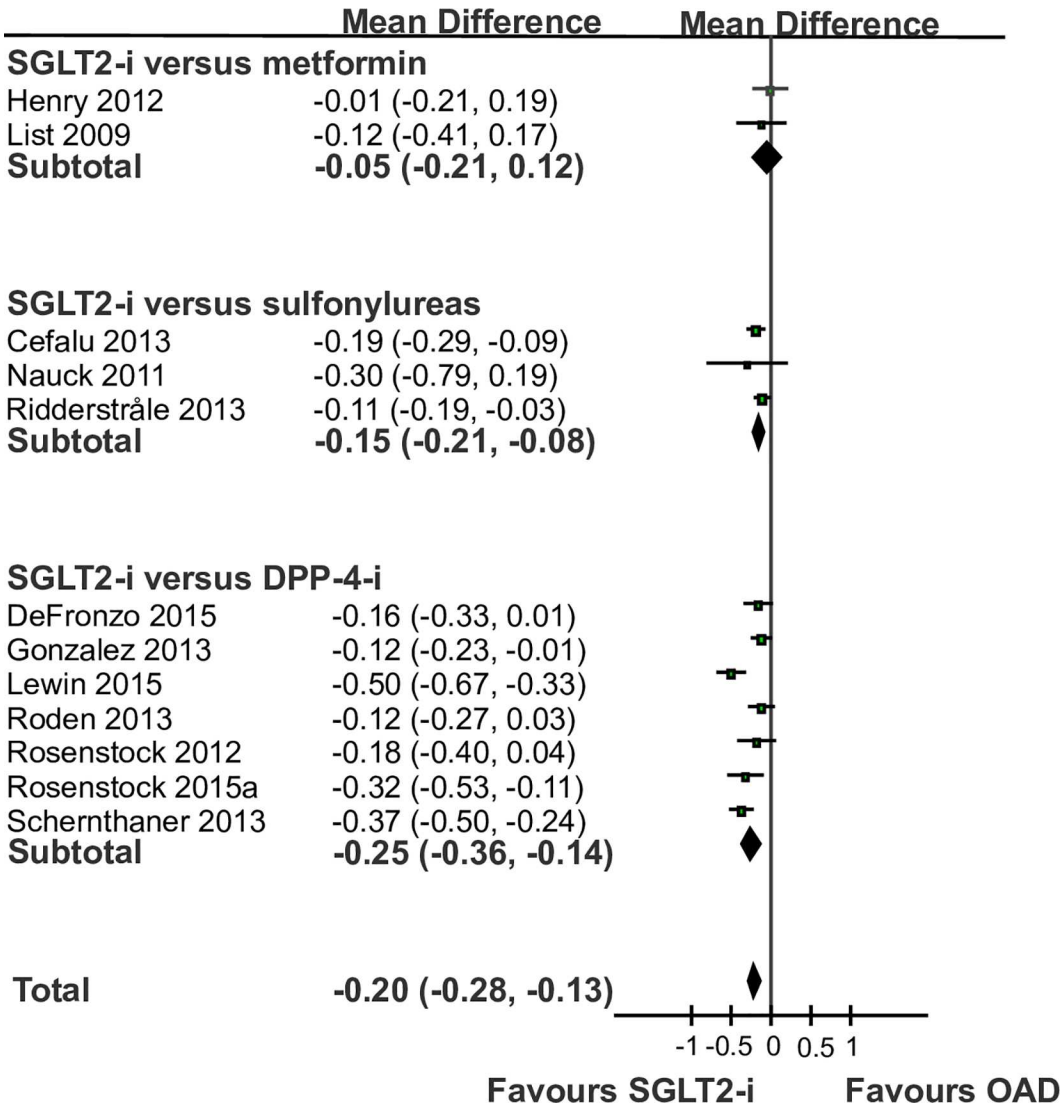

Fig 3. Change in glycated haemoglobin: forest plot of randomized controlled trials comparing sodium-glucose so-transporter 2 inhibitors (SGLT2-i) versus oral antidiabetic drugs (OAD). The plot shows subgroups of trials assessing the different OAD.

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Analyses of 12 RCTs showed that SGLT2-i were associated with a larger reduction in HbA1c than OAD (-0.20%, -0.28–0.13%; Fig 3). There was between study heterogeneity, evidence of small study effects (P = 0.0385), and no difference between subgroups of trials stratified by the OAD (P = 0.11). We found no difference in HbA1c-reduction between SGLT2-i and metformin (-0.05%, 0.21 to 0.12%, Fig 3), but a larger HbA1c reducing effect of SGLT2-i compared with SU (-0.15%, -0.21 to -0.08%) and DPP-4-i (-0.25%, -0.36 to -0.14%).

Serious adverse events

Only a few serious adverse events were recorded and no differences were seen between SGLT2-i versus placebo (RR 0.99, CI 0.87 to 1.12, 34 RCTs, 10,703 patients) or OAD (1.02, 0.78 to 1.34, 12 RCTs, 6,759 patients). Five patients randomized to SGLT2-i and six patients randomized to placebo reported severe hypoglycaemia (0.75, 0.23 to 2.43, n = 5,077 patients).

In trials comparing SGLT2i versus SU, no patients versus three patients experienced a severe hypoglycaemic event (0.13, 0.02 to 0.73, n = 814). No cases of ketoacidosis were reported. In total, 32 of 3,201 patients allocated to SGLT2-i and 29 of 3,223 allocated to placebo developed cancers (1.04, 0.6 to 1.83; 19 RCTs). Only one case of bladder cancer was reported, in the placebo arm of a dapagliflozin study [71]. Six of 2,767 patients were diagnosed with breast cancer in the SGLT2-i arms compared with two of 2,789 patients in the placebo arms (1.73, 0.56 to 5.36; 18 RCTs). When analysing RCTs comparing SGLT2-i with other OAD, seven patients allocated to canagliflozin and three allocated to sitagliptin were diagnosed with other types of cancer than bladder or breast cancer (2.41, 0.69 to 8.37; 2 RCTs). One patient allocated to canagliflozin developed breast cancer [50] and none developed bladder cancer.

CVD events were recorded in 56 of 5,438 patients randomized to SGLT2-i versus 45 of 5,263 randomized to placebo (1.24, 0.86 to 1.81) or OAD (0.78, 0.27 to 2.32).

Secondary outcomes

FPG. As shown in Table 2, analysis of 33 RCTs with 8,914 patients found that FPG levels were 0.9 mmol/L lower in the SGLT2-i arm compared with the placebo arm (-1.0 to -0.8 mmol/L). There was no small study effect (P = 0.122) and a difference between subgroups (P = 0.04). The largest effect size was seen for canagliflozin (Table 2).

We found no difference between SGLT2-i and metformin [51, 92] or SU [57, 90, 93–95, 99, 100] but a beneficial effect compared with DPP-4-i (-1.0, 1.3 to 0.7 mmol/L, Table 3) [17, 50, 52, 91, 96–98]. The between trial heterogeneity was moderate to high in all analyses.

Bodyweight loss. SGLT2-i were associated with a loss of body weight compared with placebo (-2.1 kg, -2.3 to -2.0 kg). The effect was different in subgroups stratified by the type of SGLT2-i (P < 0.01) with the largest weight reduction associated with canagliflozin (Table 2). SGLT2-i also reduced the body weight compared to OAD (Table 3).

Blood pressure and heart rate. SGLT2-i reduced the systolic blood pressure compared with placebo (-3.9 mmHg, -4.6 to -3.3 mmHg), there were subgroup differences (P = 0.03), with the largest effect seen for canagliflozin (Table 2). SGLT2-i also reduced the systolic blood pressure compared with OAD (Table 3). A similar effect was seen in analyses of the diastolic blood pressure (Tables 2 and 3). The heart rate did not differ between patients allocated to SGLT2-i versus placebo (-0.6 bpm, -1.3 to 0.0 bpm) (Table 3). However, there was a difference between subgroups when compared with placebo (P = 0.04) and empagliflozin induced a modest increase in heart rate (Table 2). The heart rate in the SGLT2-i group was lower than in the DPP-4-i group (-1.50 bpm, 2.7 to 0.4 bpm).

Lipids. SGLT2-i was associated with increased HDL cholesterol compared with placebo (0.05 mmol/L, 0.04 to 0.07 mmol/L). A similar result was achieved for LDL cholesterol (0.09 mmol/L, 0.04 to 0.14 mmol/L), whereas triglyceride decreased (-0.09 mmol/L, -0.16 to -0.02 mmol/L). Subgroup analysis showed a difference between subgroups, with the largest effects seen for canagliflozin on HDL cholesterol, LDL cholesterol and triglycerides (Table 2). SGLT2-i increased HDL and LDL cholesterol, but did not reduce triglycerides compared to OAD (SU and DPP-4-i) (Table 3).

Liver function blood tests. Analyses of 18 RCTs with 3,719 patients found evidence that SGLT2-i reduced alanine aminotransferase levels compared with placebo (-2.8 U/L, CI -4.0 to -1.7 U/L) or OAD (Table 3).

Serum creatinine. STLG2-i were associated with a 0.60 μmol/L increase in creatinine compared with placebo (0.1 to 1.1 μmol/L) (Table 2). The largest increase was seen for canagliflozin. Analysis of SGLT2-i versus other OAD showed no difference between SGLT2-i and metformin or DPP-4-i (Table 3).

Table 2. Number of included patients, mean difference and heterogeneity in meta-analyses of double blind, randomised controlled trials comparing SGLT2-i versus placebo.

SGLT2-i	Total n	Mean difference(confidence interval)	I^2(Q)%	Subgroup differences
Fasting plasma glucose (mg/dL)	8,914	-28.1 (-31.1; -25.1)	79.1	P = 0.04
Body weight (kg)	9,612	-2.1 (-2.3; -2.0)	44.5	P < 0.01
Systolic blood pressure (mmHg)	9,336	-3.9 (-4.6; -3.3)	33.6	P = 0.03
Diastolic blood pressure (mmHg)	7,402	-2.0 (-2.4; -1.6)	6.3	P = 0.82
Heart rate (bpm)	4,587	-0.6 (-1.3; 0.0)	48.4	P = 0.04
HDL cholesterol (mmol/L)	4,698	0.05 (0.04; 0.07)	31.0	P = 0.03
Triglycerides (mmol/L)	4,704	-0.09 (-0.16; 0.02)	29.8	P < 0.01
LDL cholesterol (mmol/L)	5,431	0.09 (0.04; 0.14)	55.5	P < 0.01
Alanine aminotransferase (U/L)	3,719	-2.8 (-4.0; -1.7)	44.3	P = 0.59
Creatinine (μmol/L)	5,445	0.6 (0.1; 1.1)	11.3	P = 0.05
Canagliflozin	**Total n**	**MD (CI)**	**I^2(Q)%**	
Fasting plasma glucose (mg/dL)	2,115	-34.0 (-40.4; -27.6)	77	
Body weight (kg)	2,117	-2.6 (-2.9; -2.3)	21	
Systolic blood pressure (mmHg)	2,208	-5.4 (-6.8; -4.0)	42	
Diastolic blood pressure (mmHg)	2,208	-2.1 (-2.8; -1.5)	0	
Heart rate (bpm)	1,336	-1.0 (-1.1; -0.9)	0	
HDL cholesterol (mmol/L)	2,088	0.07 (0.06; 0.09)	0	
Triglyceride (mmol/L)	2,094	-0.21 (-0.30; -0.12)	0	
LDL cholesterol (mmol/L)	2,086	0.19 (0.11; 0.26)	31	
Alanine aminotransferase (U/L)	1,229	-3.5 (-5.8; -1.2)	67	
Creatinine (μmol/L)	1,238	1.8 (0.7; 2.9)	13	
Dapagliflozin	**Total n**	**MD (CI)**	**I^2(Q)%**	
Fasting plasma glucose (mg/dL)	3,844	-24.6 (-28.7; -20.4)	74	
Body weight (kg)	4,432	-2.0 (-2.2; -1.8)	24	
Systolic blood pressure (mmHg)	3,943	-3.5(-4.3; -2.7)	1	
Diastolic blood pressure (mmHg)	2,009	-2.1 (-2.9; -1.3)	8	
Heart rate (bpm)	2,148	-0.7 (-2.1; 0.7)	63	
HDL cholesterol (mmol/L)	175	0.09 (-0.03; 0.21)	NA	
Triglyceride (mmol/L)	175	0.00 (-0.12; 0.12)	NA	
LDL cholesterol (mmol/L)	175	-0.15 (-0.32; 0.02)	NA	
Alanine aminotransferase (U/L)	1,817	-2.1 (-3.8; -0.5)	30	
Creatinine (μmol/L)	2,335	0.3 (-0.4; 1.0)	0	
Empagliflozin	**Total n**	**MD (CI)**	**I^2(Q)%**	
Fasting plasma glucose (mg/dL)	2,955	-29.5 (-33.1; -25.9)	60	
Body weight (kg)	3,063	-2.0 (-2.2; -1.7)	9	
Systolic blood pressure (mmHg)	3,185	-3.2 (-4.2; -2.3)	11	
Diastolic blood pressure (mmHg)	3,185	-1.9 (-2.5; -1.2)	31	
Heart rate (bpm)	1,103	0.5 (-0.7; 1.6)	0	
HDL cholesterol (mmol/L)	2,417	0.04 (0.02; 0.06)	27	
Triglyceride (mmol/L)	2,435	0.00 (-0.09; 0.08)	0	
LDL cholesterol (mmol/L)	3,173	0.06 (0.01; 0.10)	0	
Alanine aminotransferase (U/L)	673	-3.4 (-6.1; -0.6)	46	
Creatinine (μmol/L)	1,872	0.3 (-0.6; 1.1)	15	

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SU, sulphonylureas; DPP-4-i, dipeptidyl peptidase 4 inhibitors; The difference between SGLT2-i was assessed using a test for subgroup differences (reported using P-values)

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Table 3. Number of included patients, mean difference and heterogeneity in meta-analyses of double blind, randomised controlled trials comparing SGLT2-i versus oral antidiabetic drugs.

SGLT2-i versus metformin	Total n	MD (CI)	I^2(Q)%
Fasting plasma glucose (mmol/L)	526	-0.3 (-0.5; 0.0)	54.7
Body weight (kg)	530	-1.3 (-1.8; -0.7)	0.0
Systolic blood pressure (mmHg)	467	-3.8 (-6.8; -0.9)	28.5
Diastolic blood pressure (mmHg)	467	-1.9 (-3.3; -0.6)	0.0
Heart rate (bpm)	467	-0.7 (-2.2; 0.8)	0.0
Alanine aminotransferase (U/L)	457	-3.6 (-6.4; -0.7)	0.0
Creatinine (μmol/L)	456	0.3 (-1.5; 2.1)	0.0
SGLT2-i versus SU	**Total n**	**MD (CI)**	**I^2(Q)%**
Fasting plasma glucose (mmol/L)	2,664	-0.2 (-0.5; 0.1)	93.3
Body weight (kg)	2,811	-4.4 (-4.7; -4.1)	0.0
Systolic blood pressure (mmHg)	2,804	-5.0 (-6.0; -4.0)	18.3
Diastolic blood pressure (mmHg)	2,505	-2.5 (-3.1, -2.0)	0.0
HDL cholesterol (mmol/L)	2,478	0.10 (0.08; 0.12)	0.0
Triglyceride (mmol/L)	2,478	-0.06 (-0.15; 0.02)	0.0
LDL cholesterol (mmol/L)	2,477	0.16 (0.11; 0.21)	0.0
Creatinine (μmol/L)	1,500	-2.0 (-3.1; -0.9)	n/a
SGLT2-i versus DPP-4-i	**Total n**	**MD (CI)**	**I^2(Q)%**
Fasting plasma glucose (mmol/L)	2,813	-0.6 (-0.7; -0.4)	76.6
Body weight (kg)	2,877	-2.5 (-2.6; -2.3)	0.0
Systolic blood pressure (mmHg)	2,884	-3.8 (-4.8; -2.7)	31.5
Diastolic blood pressure (mmHg)	2,884	-1.8 (-2.4; -1.2)	15.1
Heart rate (bpm)	1,995	-1.5 (-2.6; -0.4)	53.8
HDL cholesterol (mmol/L)	2,039	0.08 (0.06; 0.10)	0.0
Triglyceride (mmol/L)	2,047	-0.06 (-0.20; 0.09)	81.4
LDL cholesterol (mmol/L)	2,483	0.13 (0.07; 0.19)	0.0
Alanine aminotransferase (U/L)	1,571	-3.6 (-6.6; -0.6)	80.4
Creatinine (μmol/L)	2,150	-0.2 (-0.9; 0.6)	0.0

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SU, sulphonylureas; DPP-4-i, dipeptidyl peptidase 4 inhibitors.

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Non-serious adverse events. Compared with placebo, SGLT2-i were associated with an increased risk of UTI (1.14, 1.0 to 1.3) and GTI (4.34, 3.35 to 5.63). SGLT2-i were also associated with an increased risk of UTI compared with metformin (2.01, 1.01, 3.98), but not SU (1.05, 0.84 to 1.31) or DPP-4-i (0.89, 0.67 to 1.19). SGLT2-i were associated with an increased risk of GTI compared with metformin (4.48, 1.76 to 11.42), SU (5.41, 3.64 to 8.03) and DPP-4-i (3.69, 2.42 to 5.63; $P < 0.00001$).

An analysis of 33 RCTs with 10,440 patients found fewer episodes of non-severe hypoglycaemia in the placebo group compared to the SGLT2-i group (1.11, 1.03 to 1.2). Subgroup analysis showed a difference between subgroups ($P = 0.04$). The largest risk of hypoglycaemia was seen for canagliflozin (1.53, 1.15 to 2.03). Dapagliflozin (1.07, 0.95 to 1.19) and empagliflozin (1.03, 0.9 to 1.19) did not increase the risk of non-severe hypoglycaemia. SGLT2-i were associated with a decreased risk of non-severe hypoglycaemia compared with SU (0.16, 0.11, 0.22), but not compared with metformin (0.5, 0.18 to 1.43) or DPP-4-i (1.00, 0.49 to 2.02). In the SGLT2-i group, more participants experienced drug-related adverse effects (1.45, 1.27 to 1.66) and discontinued treatment (1.28, 1.08 to 1.51) compared with placebo.

Quality of the evidence

We gave evidence from RCT data a high quality rating, but downgraded it if there was unexplained clinically important heterogeneity, the study methodology had a risk of bias, the evidence was indirect, there was important uncertainty around the estimate of effect, or there was evidence for reporting bias. Therefore, it was possible for RCT data to have a very low quality of evidence if several of these concerns were present. Where we downgraded the evidence, it was mainly because there was risk of bias, small study effects, or considerable heterogeneity. Some outcomes had relatively few events (e.g. mortality) and wide CIs (imprecision). The results of many meta-analyses had moderate to high levels of statistical heterogeneity (inconsistency). The heterogeneity between the trials resulted from differences between the three SGLT2-i and in the outcome measures reported, the duration of follow up and the trials inclusion criteria. In the assessment of the primary outcomes, we downgraded the quality of the evidence for glycated haemoglobin in the analyses comparing SGLT2-I by two levels to low quality, due to heterogeneity and evidence of publication bias or other small study effects. We also downgraded the outcome serious adverse events and analyses comparing SGLT2-i versus OAD to moderate quality evidence due to uncertainty (wide confidence intervals) and heterogeneity, respectively.

Discussion

The highest approved doses of canagliflozin, dapagliflozin and empagliflozin compared with placebo, were effective in reducing HbA1c in patients with type 2 diabetes. In spite of the large number of RCTs with a low risk of bias in several domains, we downgraded the evidence to low quality. Based on our assessment of publication bias and other smalls study effects, we found evidence of bias and therefore a risk that the analyses overestimate the intervention benefit. In the included RCTs, SGLT2-i had no discernible beneficial or harmful effects on serious adverse events including mortality, cancer, ketoacidosis, severe hypoglycaemia, bladder cancer, breast cancer or other cancer types. SGLT2-i also had no effect on CVD events, but SGLT2-i were associated a beneficial effect on CVD-associated risk factors including body weight, blood pressure and lipids (although elevations in LDL lipids may be a concern). As expected, SGLT2-i increased the risk of non-serious adverse events, including serum creatinine levels, UTI and GTI. Additional meta-analyses showed similar effects, when comparing SGLT2-i versus other OAD, but the analyses with active comparators included a smaller number of trials and patients. We also identified important potential limitations, which mainly included a high degree of inconsistency. The inconsistency is likely to reflect clinical heterogeneity in terms of the interventions, populations and follow-up times. Furthermore, selective reporting of outcomes (e.g. CVD, cancer etc.) may also bias the estimates. Therefore, it is possible that the true effect differs somewhat from the estimated effects.

We found statistically clear differences between SGLT2-i in subgroup analyses. The largest effect was seen for canagliflozin in the analyses of HbA1c and CVD-related risk factors. However, none of the trials compared the individual SGLT2-is and the results, therefore, remain exploratory. Thus, the lack of head-to-head comparisons between the SGLT2-i means that we cannot exclude the possibility that the difference between SGLT2-i reflect patient inclusion criteria rather than a true difference between intervention effects.

Patients with type 2 diabetes have a high risk of adverse CVD outcomes [101]. The effects of SGLT2-i on cardiovascular mortality and morbidity in patients with type 2 diabetes are unknown. In one study [21], empagliflozin was associated with a lower rate of cardiovascular events compared with placebo. Despite a sample size of more than 24,500 patients in this review, few RCTs reported CVD as an outcome. In our analyses of CVD events, we found no

differences between SGLT2-i and placebo or OAD. We only found beneficial effect on outcomes that may be associated with a lower risk of CVD.

We found a beneficial effect of SGLT2-i on alanine aminotransferase, which is associated with non-alcoholic fatty liver disease in the early phase. Increasing evidence suggests that non-alcoholic fatty liver disease may increase the risk of CVD [102–104]. SGLT2-i decreased alanine aminotransferase both in comparison to placebo and OAD. While such improvements may be attributed solely to weight loss, rather than drug-specific effects [105] additional evidence is needed to determine the potential clinical implications of the findings.

We included creatinine, which may reflect dehydration due to the glycosuria. On SGLT2-i, approximately 500 ml of water after treatment is initiated [106]. The loss generally decreases during long term treatment. Increased serum creatinine may although reflect a worsening of kidney function which is predictive of CVD [107–109]. The largest increase in creatinine levels was found in RCTs evaluating canagliflozin. Whether this translates to an increased risk of CVD events in patients taking SGLT2-i over the long-term is unclear.

Recently, ketoacidosis has been reported as an adverse effect of SGLT2-i [110]. The RCTs in this review did not routinely report ketoacidosis as an outcome. Theoretically, there is a potential for developing ketoacidosis as a result of the insulin-independent glucose excretion combined with increased glucagon levels [111]. However, a recent large RCT [21] has found a low incidence of ketoacidosis ($\leq 0.1\%$) and that the risk was similar in patients treated with empagliflozin and placebo.

SGLT2-i are widely studied and several reviews and meta-analyses have recently been published [34–36]. Compared to these studies our systematic review with meta-analysis has distinct differences in the dosages and outcomes that we address. Zaccardi et al. performed a network meta-analysis that focused on efficacy and safety of SGLT2-i [34]. In contrast to our meta-analysis, they included trials with several different doses of canagliflozin, dapagliflozin and empagliflozin and they reported fewer secondary outcomes than us (we also include e.g. ALT, Creatinine and heart rate). In another meta-analysis, Wu et al. examined the effects of SGLT2-i on cardiovascular events, death and major safety outcomes in adults with type 2 diabetes [35]. No beneficial effects of SGLT2-i were reported. We analysed both efficacy and safety data. In the network meta-analysis by Shyangdan et al., the primary aim was to compare the efficacy of SGLT2-i [36]. The investigators only included trials on SGLT2-i in monotherapy or as add on to metformin in patients with type 2 diabetes. Only a total of 10 trials were included and no data on adverse events were provided.

Future RCTs would ideally be long-lasting and large-scale comparing SGLT2-i with placebo or existing therapies. Such RCTs should additionally include reporting of serious adverse events such as CVD risk, ketoacidosis and severe hypoglycaemia, and monitoring of renal safety, with adequate follow-up (over one year), to establish the long-term consequences of SGLT2-i therapy.

Conclusion

Based on our review we found evidence that clinically relevant doses i.e. the recommended daily target doses of SGLT2-i that are included in this review, during more than 12 weeks reduce HbA1c levels in patients with type 2 diabetes compared with placebo and other existing oral therapies. We planned to include high-quality RCTs with clinically relevant doses and sufficient follow up to generate an estimate based on the best available evidence. However, our analyses showed evidence of bias and heterogeneity. Likewise, the incidence of serious adverse events including mortality, CVD and cancer was not increased as a result of SGLT2-i, but reporting was inconsistent. Several CVD risk factors such as obesity, blood pressure and HDL

cholesterol may be improved by SGLT2-i therapy, whereas the incidences of UTI and GTI are increased in the SGLT2-i groups. Additional evidence may therefore be needed to determine the benefit and safely of SGLT2-i. The RCTs included in our review were largely carried out in research hospital settings. Given the high prevalence of type 2 diabetes in the general population, RCTs conducted outside the hospital settings seem warranted.

Supporting Information

S1 Fig. Risk of bias across all studies. Low risk of bias: '+' in green circle; unclear risk of bias '?' in yellow circle; no studies were at high risk of bias in any domain.
(TIF)

S2 Fig. Risk of bias summary graph.
(TIF)

S1 File. Data sources. Multiple publications which reported the same RCT were grouped into 'studies'.
(PDF)

S2 File. Study protocol PROSPERO CRD42014008960.
(PDF)

S3 File. PRISMA checklist.
(PDF)

S1 Table. Characteristics of included studies and risk of bias assessments.
(PDF)

S2 Table. Primary outcome effect sizes, all comparisons.
(PDF)

S3 Table. Characteristics of excluded studies.
(PDF)

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Author Contributions

Conceptualization: HS LLG TV.

Data curation: HS.

Formal analysis: CB HS LLG.

Investigation: HS MFG MBC.

Methodology: HS LLG TV.

Project administration: HS.

Resources: HS TV FKK.

Software: HS LLG CB.

Supervision: LLG.

Validation: HS LLG CB.

Visualization: HS CB.

Writing – original draft: CB.

Writing – review & editing: CB HS LLG TV FKK MBC MFG.

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