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Effect of Sodium-Glucose Cotransport-2 Inhibitors on Blood Pressure in People With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of 43 Randomized Control Trials With 22 528 Patients

Mohsen Mazidi, PhD; Peyman Rezaie, MSc; Hong-Kai Gao, MD, PhD; Andre Pascal Kengne, MD, PhD

***Background*—**The sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of oral hypoglycemic agents. We undertake a systematic review and meta-analysis of prospective studies to determine the effect of SGLT2 on blood pressure (BP) among individuals with type 2 diabetes mellitus.

***Methods and Results*—**PubMed-Medline, Web of Science, Cochrane Database, and Google Scholar databases were searched to identify trial registries evaluating the impact of SGLT2 on BP. Random-effects models meta-analysis was used for quantitative data synthesis. The meta-analysis indicated a significant reduction in systolic BP following treatment with SGLT2 (weighted mean difference −2.46 mm Hg [95% CI −2.86 to −2.06]). The weighted mean differences for the effect on diastolic BP was −1.46 mm Hg (95% CI −1.82 to −1.09). In these subjects the weighted mean difference effects on serum triglycerides and total cholesterol were −2.08 mg/dL (95% CI −2.51 to −1.64) and 0.77 mg/dL (95% CI 0.33-1.21), respectively. The weighted mean differences for the effect of SGLT2 on body weight was −1.88 kg (95% CI −2.11 to −1.66) across all studies. These findings were robust in sensitivity analyses.

***Conclusions*—**Treatment with SGLT2 glucose cotransporter inhibitors therefore has beneficial off-target effects on BP in patients with type 2 diabetes mellitus and may also be of value in improving other cardiometabolic parameters including lipid profile and body weight in addition to their expected effects on glycemic control. However, our findings should be interpreted with consideration for the moderate statistical heterogeneity across the included studies. **(*J Am Heart Assoc*. 2017;6:e004007. DOI: 10.1161/JAHA.116.004007.)**

Key Words: blood pressure • diabetes mellitus • meta-analysis • Sodium-glucose cotransport-2 inhibitors

Cardiovascular disease is the major cause of morbidity and mortality for individuals with diabetes mellitus and is the largest contributor to the direct and indirect costs of diabetes mellitus.[1] Hypertension is an important cardiovascular risk factor in diabetics, affecting more than half of the patients with type 2 diabetes mellitus (T2D). Several studies have demonstrated the beneficial effects of controlling cardiovascular risk factors in people with diabetes to reduce cardiovascular events.[2,3] However, observational studies have demonstrated that there is often poor control of other cardiovascular risk factors in patients with diabetes[4,5]; hence, a more proactive approach to cardiovascular risk factor management is required in this population. This may necessitate multiple drugs being prescribed, and polypharmacy may have a negative impact on observance. One approach to addressing this is the use of a combination pill, or "polypill."[6] Another approach would be to use compounds that have beneficial pleiotropic properties.

The sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of oral hypoglycemic agents that act primarily by

From the Key State Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China (M.M.); Institute of Genetics and Developmental Biology, International College, University of Chinese Academy of Science, Beijing, China (M.M.); Biochemistry and Nutrition Research Center, School of Medicine, Mashhad University of Medical Science, Mashhad, Iran (P.R.); Department of General Surgery, The General Hospital of Chinese People's Armed Police Forces, Beijing, China (H.-K.G.); Non-Communicable Disease Research Unit, South African Medical Research Council and University of Cape Town, South Africa (A.P.K.).

Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/6/6/e004007/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Hong-Kai Gao, MD, PhD, Department of General Surgery, The General Hospital of Chinese People's Armed Police Forces, Beijing, China. E-mail: moshen@genetics.ac.cn

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increasing the elimination of glucose in the urine. Two agents of this class, dapagliflozin and canagliflozin, are currently approved for marketing in the United States and Europe. In addition to glucose lowering, SGLT2 inhibitors have been reported to be associated with weight loss and to act as osmotic diuretics, resulting in lowering of blood pressure (BP).[7] Therefore, SGLT2 inhibitors could be used to simultaneously improve diabetic control while also lowering BP. However, the putative effects of SGLT2 inhibitors on BP are still contested. Moreover, the individual studies to date have been limited by sample size, research design, and subject traits (sex, ethnicity, age, etc) and have therefore been underpowered to achieve a reliable conclusion. Meta-analysis has the benefit of overcoming these limitations by increasing the sample size. We therefore conducted a systematic review and meta-analysis to determine the effect of SGLT2 inhibitors on BP levels in people with T2D based on available randomized controlled trials (RCTs).

Materials and Methods

Literature Search Strategy

The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8,9] The study protocol was registered with the International Prospective Register of Systematic Reviews, PROSPERO (registration no. CRD42016038789). The primary exposure of interest was the effect of treatment with SGLT2 inhibitors, compared either with placebo or active drugs, on BP.

We searched multiple databases including PUBMED-MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science, SCOPUS, and Google Scholar. To achieve maximum sensitivity of the search strategy and identify all randomized control trials, we combined sodium-glucose cotransport-2, SGLT2 inhibitor, canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, remogliflozin, sergliflozin, tofogliflozin, ASP1941, AVE2268, BI-10773, BMS512148, KGT-1681, TA-7284, TS-033, YM543, hypertension, high BP, systolic hypertension, diastolic hypertension, and hypertension as either keywords or MeSH terms (Tables S1 and S2). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was applied. This search strategy was further supplemented with hand searching of reference lists of included articles and through tracking the citations of eligible references in Google Scholar.

To further minimize the effect of publication bias, a snowball method, characterized by manual checking of references from retrieved articles, was applied in order to ensure complete collection. Furthermore, completed but yet unpublished studies with the drugs specified above were searched in the www.clinicaltrials.gov register. Results of unpublished trials were retrieved, if available, on www.clinicaltrials.gov or www.clinicalstudyresults.org as well as Food and Drug Administration and European Medicines Agency (www.ema.europa.eu) reviews of approved drugs. All these sources were also used to complete information on results of published trials when not reported in publications (including the primary trial publications, and subsequent reviews and/or pooled analyses reporting data on individual trials). To maximize the sensitivity we searched until April 2016. Two researchers (M.M., P.R.) independently searched the database with these search terms to ensure that none of the relevant studies was missed.

Selection Criteria

We included all RCTs that evaluated the use of an SGLT2 inhibitor on the parameters of interest in patients with T2D (comparing SGLT2 inhibitors with placebo or active drugs [oral hypoglycemic agents and/or insulin] different from other SGLT2 inhibitors). Eligible studies had to meet the following criteria: (1) controlled trials with either parallel or crossover design; (2) presentation of sufficient information on primary outcome at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were these: (1) nonclinical studies; (2) observational studies with case-control, cross-sectional, or cohort design; and (3) studies that did not provide data on the levels of the outcomes of interest at baseline and/or at the end of trial. Narrative reviews, comments, opinion pieces, methodological publications, editorials, letters, or any other publications lacking primary data and/or explicit method descriptions, were also excluded. No newspaper and magazine articles (from the hand search of references) were included.

Data Extraction and Critical Appraisal

Initially, duplicate studies were removed, followed by screening of the titles and abstracts by 2 reviewers. To avoid bias, these reviewers were blinded to names, qualifications, or the institutional affiliations of the study authors during data extraction and in making decisions on inclusion or exclusion (the agreement between the researchers was excellent [κ index 0.86; $P<0.001$]). Studies were then either (1) excluded, (2) included, or (3) marked as "pending" if the reviewer was unsure about their eligibility for inclusion. Contradictory judgments or pending studies were temporarily included and moved to the next phase of review of full texts. Once full texts had been retrieved, 2 reviewers independently applied inclusion and exclusion criteria, based on quick assessments of the full texts. Disagreements were resolved at a meeting between reviewers prior to the selected articles being retrieved. Based on PRISMA guidelines, a flow chart was produced to facilitate transparency of the process (Figure 1).

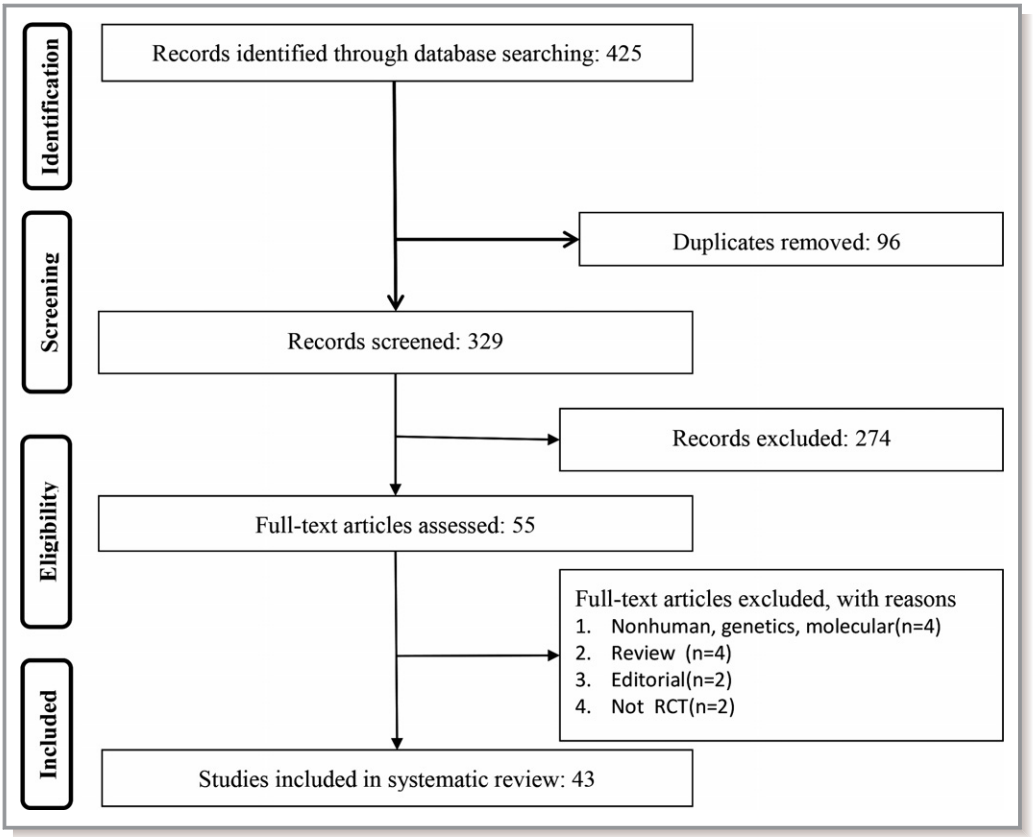

Figure 1. PRISMA flow chart for study selection.

To avoid duplication, for multiple publications that appeared to originate from an overlapping data set that comprised accumulating numbers of patients or increased lengths of follow-up, only the most recent complete reports were included for quantitative assessment at each time interval.

Quality Assessment

A systematic assessment of bias in the included RCTs was performed using the Cochrane criteria.[10,11] The items used for the assessment of each study were the following: adequacy of random sequence generation, allocation concealment, blinding of participants, personnel and outcomes assessment, handling of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias.[10,12] According to the recommendations of the Cochrane Handbook, a judgment of "yes" indicated a low risk of bias, whereas "no" indicated a high risk of bias.[10] Labeling an item as "unclear" indicated an unclear or unknown risk of bias.[10] Disagreements were resolved by discussion and consensus in consultation with a third author (A.P.K.) to resolve persistent inconsistencies.

Data Extraction and Management

The full text of studies meeting inclusion criteria were retrieved and screened to determine eligibility by 2 reviewers (M.M., P.R.). Following assessment of methodological quality, 2 reviewers extracted data onto a purpose-designed data extraction form and independently summarized what they considered to be the most important results from each study. These summaries were compared, and differences were resolved by discussion and consultation with a third reviewer (A.P.K.). Any further calculations on study data considered were conducted by the first reviewer and checked by the second reviewer. Data were sorted by first author, year of publication, country of the study, design, age range of the participants, total sample size, SGLT2 inhibitor, comparator, number of patients, dosage, and follow-up duration (Table 1).[13-55]

Data Synthesis

Based on the recommendations of the Cochrane Handbook, the mean change from baseline in the levels of outcome variables of interest and standard deviations (SD) for both intervention and control groups were used to calculate the effect size.[56] In brief, the net changes in measurements (change scores) were calculated as (measure at end of follow-up)−(measure at baseline). For RCTs, change scores were calculated as ([measure at end of follow-up in the treatment

Table 1. General Characteristics of the Studies Included

First Author, Year of Pub	Country	Age Range, y	Total Sample Size	Male (%)	Sodium-Glucose Cotransporter 2 Inhibitor	Comparator	Background Treatment	Follow-Up Duration (weeks)
Rosenstock, 2012[13]	USA	≥18	451	52%	Canagliflozin	Placebo	Metformin	12
Rosenstock, 2012[14]	USA	≥18	420	208 (49.5)	Dapagliflozin	Placebo+pioglitazone	Pioglitazone	48
Henry, 2012[15]	USA	18 to 77	814	376 (46.1)	Dapagliflozin	Placebo+metformin	Metformin	24
Kashiwagi, 2015[16]	Japan	20 to 74	164	128 (78)	Ipragliflozin	Placebo		
Bailey, 2010[17]	UK	18 to 77	546	292 (53.4)	Dapagliflozin	Placebo		24
Bailey, 2015[18]	UK	18 to 77	278	141 (50.7)	Dapagliflozin	Placebo		24
Bailey, 2013[19]	UK	18 to 77	168		Dapagliflozin	Placebo+metformin	Metformin	102
Devineni, 2012[20]	USA	18 to 65	27	15 (55.5)	Canagliflozin	Placebo		4
Ferrannini, 2013[21]	Italy	18 to 79	326	172 (52.7)	Empagliflozin	Placebo		12
Ferrannini, 2010[22]	Italy	18 to 77	274	132 (48.1)	Dapagliflozin	Placebo		24
Lavalle-González, 2013[23]	Mexico	18 to 80	918	433 (47.1)	Canagliflozin	Placebo+sitagliptin		26
Schernthaner, 2013[24]	Austria	≥18	755	422 (55.9)	Canagliflozin	Sitagliptin		52
Lambers Heerspink, 2013[25]	Netherlands	18 to 70	49	34 (69.3)	Dapagliflozin	Placebo		12
Yamout, 2014[26]	USA	18 to 80	1036	634 (61.1)	Canagliflozin	Placebo		26
Häring, 2013[27]	Germany	≥18	533	339 (63.6)	Empagliflozin	Placebo		24
Tikkanen, 2015[28]	Finland	≥1	823	495 (60.1)	Empagliflozin	Placebo		12
Bolinder, 2014[29]	Sweden	30 to 75	109		Dapagliflozin	Placebo+metformin	Metformin	102
Wilding, 2013[30]	UK	18 to 80	460	239 (51.0)	Canagliflozin	Placebo		52
Wilding, 2014[31]	UK	18 to 80	800	382 (47.7)	Dapagliflozin	Placebo+insulin	Insulin	104
Rosenstock, 2013[32]	USA	18 to 80	424	212 (50)	Empagliflozin	Placebo		12
Yale, 2013[33]	Canada	≥25	269	163 (60.6)	Canagliflozin	Placebo		26
List, 2009[34]	Canada	18 to 79	297	169 (56.9)	Dapagliflozin	Placebo		12
Bolinder, 2011[35]	Sweden	30 to 75	182	100 (54.9)	Dapagliflozin	Placebo+metformin	Metformin	24
Wilding, 2012[36]	UK	18 to 80	800	382 (47.7)	Dapagliflozin	Placebo+insulin	Insulin	48
Kaku, 2014[37]	Japan	≥20	261	155 (59.3)	Dapagliflozin	Placebo		24
Kaku, 2013[38]	Japan	18 to 79	279		Dapagliflozin	Placebo		12
Stenlof, 2013[39]	Sweden	18 to 80	584	258 (44.2)	Canagliflozin	Placebo		26
Strojek, 2011[40]	Poland	≥18	592	285 (48.1)	Dapagliflozin	Placebo+glimepiride	Glimepiride	24
Leiter, 2015[41]	Canada	18 to 80	1450		Canagliflozin	Glimepiride		104
Leiter, 2014[42]	Canada	18 to 80	962	644 (66.9)	Dapagliflozin	Placebo		52
Ji, 2014[43]	China	≥18	376		Dapagliflozin	Placebo		24
Weber, 2016[44]	USA	…	449	247 (55)	Dapagliflozin	Placebo		12
Nauck, 2011[45]	Germany	≥18	814	449 (55.1)	Dapagliflozin	Placebo+metformin	Metformin	52
Inagaki, 2013[46]	Japan	20 to 80	382	260 (68.1)	Canagliflozin	Placebo		12
Neal, 2015[47]	Australia	≥30	2072	1366 (65.9)	Canagliflozin	Placebo		52
Inagaki, 2014[48]	Japan	≥20	271	191 (70.5)	Canagliflozin	Placebo		24
Schumm-Draeger, 2015[49]	Germany	18 to 77	399		Dapagliflozin	Placebo+metformin	Metformin	16
Sha, 2014[50]	USA	25 to 70	36	31 (86.1)	Canagliflozin	Placebo		12
Del Prato, 2015[51]	Italy		299		Dapagliflozin	Glipizide+metformin	Metformin	208
Matthaei, 2015[52]	Germany	≥18	216	90 (41.6)	Dapagliflozin	Placebo		24

Continued

Table 1. Continued

First Author, Year of Pub	Country	Age Range, y	Total Sample Size	Male (%)	Sodium-Glucose Cotransporter 2 Inhibitor	Comparator	Background Treatment	Follow-Up Duration (weeks)
Forst, 2014[53]	Germany	18 to 80	342	216 (63.2)	Canagliflozin	Placebo+sitagliptin	…	52
Sykes, 2015[54]	UK	18 to 70	276	165 (59.7)	Remogliflozin etabonate	Placebo		12
Skyes, 2015[55]	UK	18 to 70	205	99 (48.2)	Remogliflozin etabonate (once daily) Remogliflozin etabonate (twice daily)	Placebo		12

group]−[measure at baseline in the treatment group])−([measure at end of follow-up in the control group]−[measure at baseline in the control group]). Where only standard error of the mean was reported, the SD was estimated as SD=(standard error of the mean)×(square root of n), where n is the number of subjects.[57] If the outcome measures were reported as median and range (or 95% CI), mean and SD values were estimated using the method described by Hozo et al.[58] When the outcome variable was available only in the graphic form, the software GetData Graph Digitizer 2.24 was used to digitize and extract the data.[59] Blood lipid and glucose levels were collated in millimoles per liter; a multiplication factor of 0.0259, 0.0113, or 0.0555 was used to convert cholesterol (total cholesterol, high-density lipoprotein, or low-density lipoprotein), triglycerides, and glucose levels, respectively, from milligrams per deciliter to millimoles per liter as appropriate.[57]

A random-effects model (using the DerSimonian-Laird method) and the generic inverse variance method were used to derive pooled estimates across studies.[60] Heterogeneity was quantitatively assessed using the I^2 index,[60] which measures the extent of true heterogeneity.[61] It can be interpreted as the percentage of the total variability in a set of effect sizes due to true heterogeneity, that is, to between-studies variability.[61] Low, moderate, and high I^2 values are 25%, 50%, and 75%, respectively.[60] When heterogeneity is substantial, a prediction interval rather than a confidence interval can help to provide a better sense of the uncertainty around the effect estimate.[61]

Effect sizes were expressed as weighed mean difference (WMD) and CI. In order to evaluate the influence of each study on the overall effect size, a sensitivity analysis was conducted using the leave-1-out method (ie, removing 1 study each time and repeating the analysis).[62–64]

Publication Bias

Potential publication bias was explored using visual inspection of the Begg funnel plot asymmetry, the Begg rank correlation, and Egger weighted regression tests. The Duval and Tweedie trim-and-fill" and fail-safe N methods were used to adjust the analysis for the effects of publication bias.[65] Meta-analysis

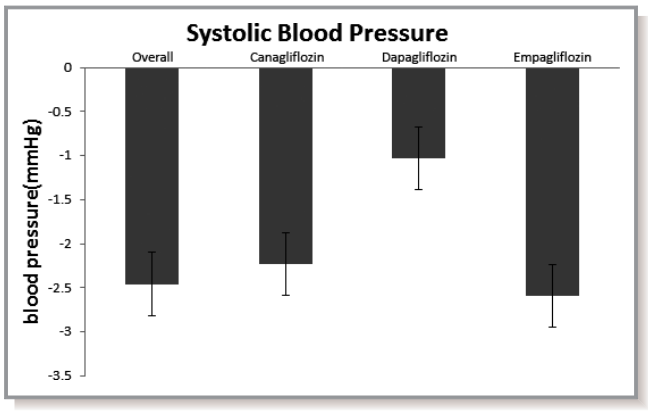

Figure 2. Plot to display weighted mean differences (bars) and 95% CIs (whiskers) for the impact of SGLT2 therapy on systolic blood pressure. SGLT 2, sodium-glucose cotransporter 2.

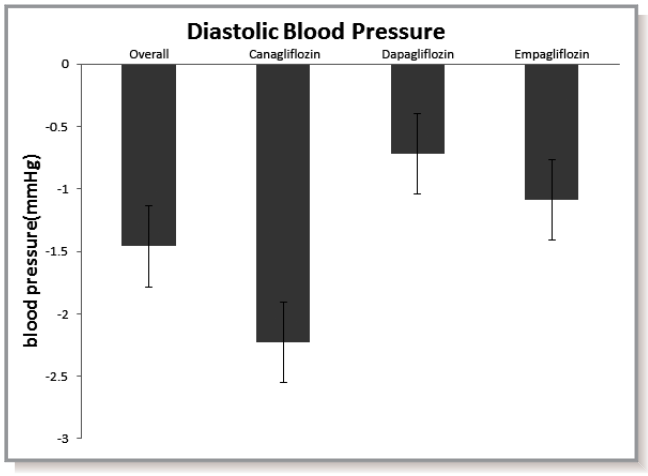

Figure 3. Plot to display weighted mean differences (bars) and 95% CIs (whiskers) for the impact of SGLT2 inhibitor therapy on diastolic blood pressure. SGLT 2, sodium-glucose cotransporter 2.

Table 2. Summary of the Effect of SGLT2 Inhibitors on the Lipid Profile, Glycemia, and Liver and Kidney Function Variables

Variables	Result of the Leave-1-Out Sensitivity Analyses
Triglyceride	
Across all studies	−2.08 mg/dL (95% CI −2.51 to −1.64)
Canagliflozin	−1.02 mg/dL (95% CI −1.08 to −0.96)
Dapagliflozin	−0.68 mg/dL (95% CI −0.76 to −0.60)
Empagliflozin	−0.32 mg/dL (95% CI −0.44 to −0.20)
Remogliflozin	−2.82 mg/dL (95% CI −3.03 to −2.62)
Total cholesterol	
Across all studies	0.77 mg/dL (95% CI 0.33-1.21)
Canagliflozin	1.61 mg/dL (95% CI 1.53-1.68)
Dapagliflozin	0.41 mg/dL (95% CI 0.32-0.50)
Empagliflozin	0.56 mg/dL (95% CI 0.43-0.70)
Remogliflozin	0.26 mg/dL (95% CI 0.11-0.40)
HDL-cholesterol	
Across all studies	3.89 mg/dL (95% CI 3.23-4.56)
Canagliflozin	2.14 mg/dL (95% CI 2.08-2.20)
Dapagliflozin	0.57 mg/dL (95% CI 0.46-0.67)
Empagliflozin	2.96 mg/dL (95% CI 2.78-3.14)
Remogliflozin	3.27 mg/dL (95% CI 3.04-3.50)
Fasting blood glucose	
Across all studies	−2.40 mg/dL (95% CI −2.68 to −2.11)
Canagliflozin	−0.92 mg/dL (95% CI −0.98 to −0.87)
Dapagliflozin	−0.75 mg/dL (95% CI −0.79 to 0.70)
Empagliflozin	−1.35 mg/dL (95% CI −1.45 to −1.24)
Remogliflozin	−0.88 mg/dL (95% CI −1.11 to −0.66)
HbA1c	
Across all studies	−2.48% (95% CI −2.73 to −2.24)
Canagliflozin	−0.81% (95% CI −0.85 to −0.77)
Dapagliflozin	−0.81% (95% CI −0.85 to 0.78)
Empagliflozin	−1.61% (95% CI −1.70 to −1.52)
Remogliflozin	−4.47% (95% CI −4.75 to −4.19)
Body weight	
Across all studies	−1.88 kg (95% CI −2.11 to −1.66)
Canagliflozin	−1.70 kg (95% CI −1.75 to −1.65)
Dapagliflozin	−1.05 kg (95% CI −1.09 to 1.01)
Empagliflozin	−1.46 kg (95% CI −1.56 to −1.37)
Eemogliflozin	−1.19 kg (95% CI −1.34 to −1.04)
Waist circumference	
Across all studies	−2.89 cm (95% CI −4.32 to −1.46)
Canagliflozin	−3.68 cm (95% CI −3.89 to −3.47)
Dapagliflozin	0.17 cm (95% CI 0.04-0.30)
Empagliflozin	−3.08 cm (95% CI −3.26 to −2.91)
Alanine transamidase	
Across all studies	−0.21 IU/L (95% CI −0.33 to −0.10)
Canagliflozin	−0.23 IU/L (95% CI −0.30 to 0.16)
Aspartate transamidase	
Across all studies	0.55 IU/L (95% CI −0.63 to 1.74)
Canagliflozin	−0.10 IU/L (95% CI −0.20 to −0.01)
Creatinine	
Across all studies	0.16 Imol/L (95% CI −0.11 to 0.43)
Canagliflozin	0.08 Imol/L (95% CI 0.02-0.15)
Dapagliflozin	0.41 Imol/L (95% CI 0.35-0.47)
Estimated glomerular filtration rate	
Across all studies	−0.98 mL/[min·1.73 m^2] (95% CI −1.69 to −0.27)
Canagliflozin	−0.51 mL/[min·1.73 m^2] (95% CI −0.56 to −0.46)
Dapagliflozin	−0.89 mL/[min·1.73 m^2] (95% CI −0.99 to −0.78)
Empagliflozin	0.004 mL/[min·1.73 m^2] (95% CI −0.14 to 0.15)
Urea	
Across all studies	0.99 mmol/L (95% CI 0.35-1.64)
Canagliflozin	0.01 mmol/L (95% CI −0.08 to 0.06)
Dapagliflozin	−0.92 mmol/L (95% CI 0.84-1.00)

was conducted using Comprehensive Meta-Analysis (CMA) V3 software (Biostat, Englewood, NJ).[66]

Results

Summary of Searches and Study Selection Process

A total of 425 unique citations were identified through searches, of which 329 records remained after removal of duplicates. After screening via titles and abstracts, 55 articles remained for further evaluation; of these, several were excluded for the following reasons: nonhuman, or genetic and molecular studies (n=4), review articles (n=4), editorial articles (n=2), and nonrandomized clinical trials (n=2) (Figure 1). Therefore, 43 studies were finally included in the meta-analysis.

Risk of Bias Assessment

There was unclear risk of bias in some items, including allocation concealment, blinding of participants and personnel, blinding of outcome assessment, random sequence

generation, incomplete outcome data, and other biases. Four studies had moderate risk of bias,[13,17,26,36] whereas other studies evaluated had a low risk of bias based on selective outcome reporting. Details of the quality of bias assessment are shown in Table S3.

Characteristics of the Included Studies

The characteristics of the included studies are summarized in Table 1. These studies were published between 2008 and 2015 from 14 countries including the United States of America (8 studies), United Kingdom (8 studies), Japan (5 studies), Germany (5 studies), Canada (4 studies), Italy (3 studies), Sweden (3 studies), and 1 study from each of Mexico, Austria, Netherlands, Finland, Poland, China, and Australia. The number of participants included in studies ranged from 27[20] to 2072.[47] All of these studies were randomized clinical trials with durations of 4 weeks (1 trial), 12 weeks (12 trials), 24 weeks (11 trials), 26 weeks (4 trials), 48 weeks (2 trials), 52 weeks (7 trials), 102 weeks (2 trials), 104 weeks (2 trials), and 208 weeks (1 trial). The SGLT2 inhibitors studied were dapagliflozin (22 trials), canagliflozin (14 trials), empagliflozin (4 trials), remogliflozin (2 trials), and pragliflozin (1 trial). SGLT2 inhibitors were compared with placebo (42 trials), metformin (7 trials), sitagliptin (3 trials), pioglitazone (1 trial), glimepiride (2 trials), and glipizide (1 trial). The participants in 8 trials received metformin as the only background antidiabetic therapy, and in other studies, participants were on background treatments with pioglitazone (2 trials), insulin (2 trials), and glimepiride (1 trial). The major demographic and clinical features were expressed as mean±SD, and the age of the participants ranged from 1 to 80 years.

The average follow-up time by SGLT2 ranged from 4 to 104 weeks (median 26 weeks) in studies using canagliflozin, 12 to 52 weeks (median 12 weeks) in studies using empaglifozin, 12 to 208 weeks (median 24 weeks) in studies using dapagliflozin, 12 weeks in the 2 studies using remogliflozin, and 24 weeks in the single study using pragliflozin.

Pooled Estimate of the Effect of SGLT2 Therapy on Systolic and Diastolic Blood Pressure

The pooled estimate (WMD) of the effect of SGLT2 on systolic BP (SBP) levels was −2.46 mm Hg (95% CI −2.86 to −2.06, I^2 62.1%) across all studies; −2.23 mm Hg (95% CI −2.28 to −2.18, I^2 48.1%) across studies using canagliflozin; −1.03 mm Hg (95% CI −1.09 to −0.97, I^2 47.2%) across studies using dapagliflozin; and −2.59 mm Hg (95% CI −2.70 to −2.49, I^2 45.23%) across studies using empagliflozin (Figure 2).

The pooled estimate (WMD) of the effect of SGLT2 on diastolic BP (DBP) levels was −1.46 mm Hg (95% CI −1.82 to −1.09, I^2 56.3%) across all studies; −2.23 mm Hg (95% CI −2.30 to −2.16, I^2 42.3) across studies using canagliflozin; −0.72 mm Hg (95% CI −0.78 to −0.66, I^2 32.1%) across studies using dapagliflozin; −1.09 mm Hg (95% CI −1.18 to −1.01, I^2 30.0%) across studies using empagliflozin (Figure 3). In meta-regression analyses, length of follow-up did not influence the effects of SGLT2 on either SBP (β=0.0042, *P*=0.375) or DBP (β=0.0006, *P*=0.926).

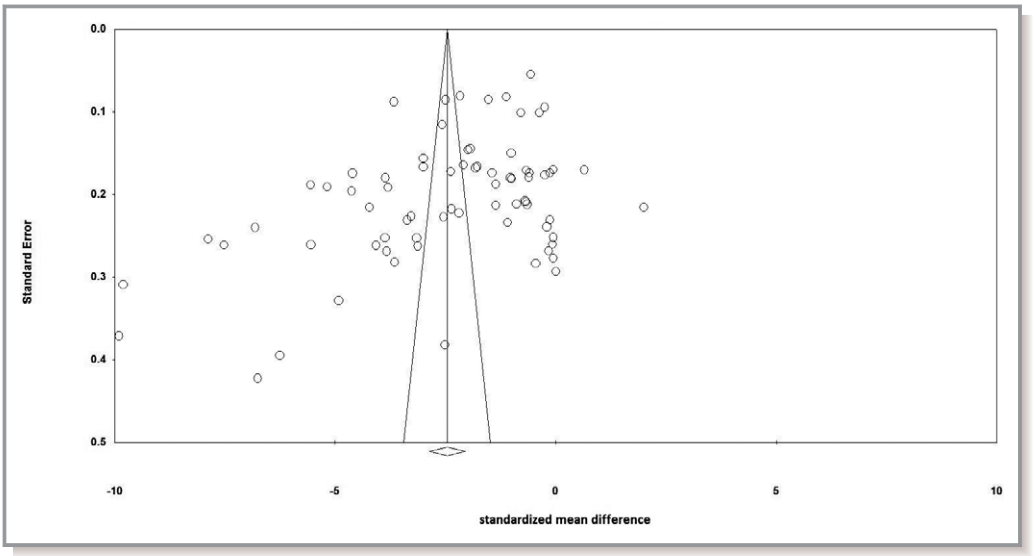

Figure 4. Funnel plots for publication bias in the studies selected for the analysis of the effects of SGLT2 inhibitors on systolic blood pressure. Open circles represent observed published studies; open diamond represents the observed effect size. SGLT 2, sodium-glucose cotransporter 2.

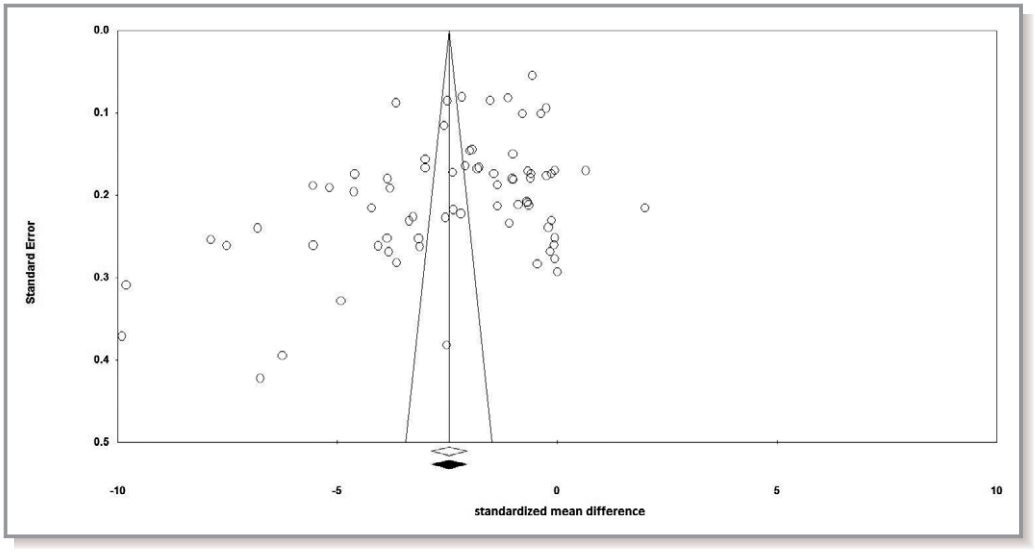

Figure 5. Trim-and-fill method (systolic blood pressure) to impute potentially missing studies. No potentially missing study was imputed in funnel plot. Open circles represent observed published studies; open diamond represents the observed effect size; closed diamond represents imputed effect size.

A summary of the effects of SGLT2 on the lipid profile, glycemia, and liver and kidney function variables is shown in Table 2.

Sensitivity Analysis

In leave-1-out sensitivity analyses, the pooled effect estimates remained similar across all studies and their subgroups, which confirmed that the significant difference between the studied groups is the overall effect of all included studies.

Publication Bias

Visual inspection of funnel plot symmetry suggested no potential publication bias for the comparison of SBP levels between SGLT2 inhibitor–treated groups and placebo groups (Figure 4). However, the presence of publication bias was suggested by Egger linear regression (intercept=−9.01, standard error=2.71; 95% CI=−14.43, −3.59; t=3.31, *df*=71.00, 2-tailed *P*<0.001) and Begg rank correlation test (Kendall τ with continuity correction=−0.22, z=2.84, 2-tailed *P*<0.001). After adjustment of effect size for

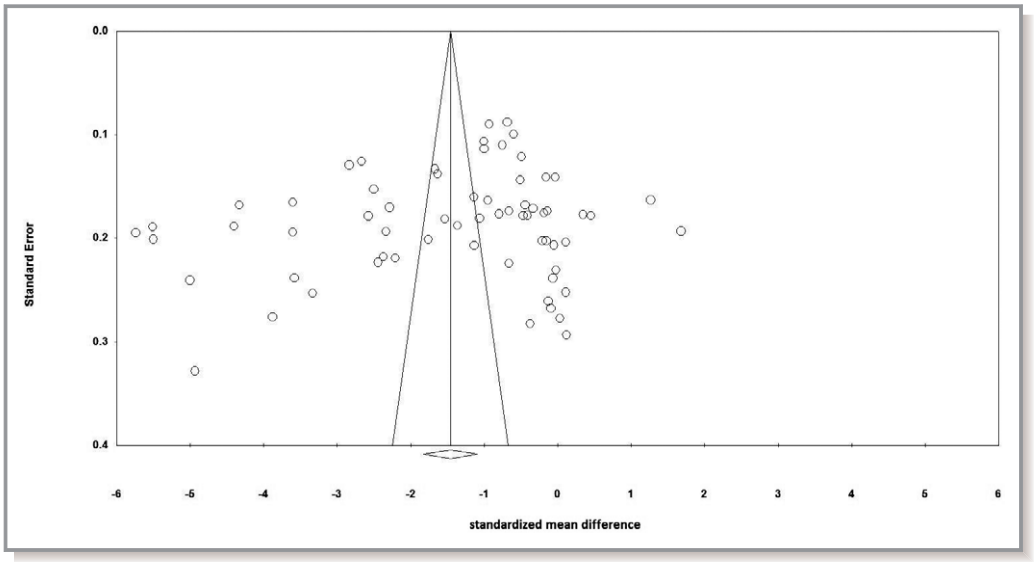

Figure 6. Funnel plots for publication bias in the studies selected for the analysis of the effects of SGLT2 inhibitors on diastolic blood pressure. Open circles represent observed published studies; open diamond represents the observed effect size. SGLT 2, sodium-glucose cotransporter 2.

potential publication bias using the trim-and-fill correction, no potentially missing studies were imputed in funnel plot (WMD −2.46 mm Hg, 95% CI −2.86 to −2.06) (Figure 5). The fail-safe N test showed that 2294 studies would be needed to bring the WMD down to a nonsignificant value (P>0.05).

Visual inspection of funnel plot symmetry suggested no potential publication bias for the comparison of DBP levels between SGLT2 inhibitor–treated groups and placebo groups (Figure 6); this was in line with Egger linear regression (intercept=−5.69, standard error=3.74; 95% CI=−13.1, 1.7; t=1.52, df=63.00, 2-tailed P=0.133) and Begg rank correlation test (Kendall τ with continuity correction=−0.12, z=1.52, 2-tailed P=0.126). After adjustment of the effect size for potential publication bias using the trim-and-fill correction, 1 potentially missing study was imputed in funnel plot (WMD −1.50 mm Hg, 95% CI −1.87, −1.13; Figure 7). The fail-safe N test showed that 377 studies would be needed to bring the WMD down to a nonsignificant value (P>0.05).

Discussion

The SGLT2 is a high-capacity and low-affinity protein that is abundantly expressed in the most proximal part of the renal tubule and has an important role in the reabsorption of glucose. This systematic review and meta-analysis suggests that SGLT2 significantly reduces SBP and DBP, although findings have to be interpreted in the context of some moderate level of heterogeneity.

Dapagliflozin was the first SGLT2 inhibitor to be approved for the treatment of patients with T2D, initially in Europe and subsequently in United States and Japan.[67,68] Several studies have reported beneficial effects of dapagliflozin on SBP and DBP, especially in patients with T2D.[22,36] It has been reported that treatment either as monotherapy or add-on therapy with another SGLT2 inhibitor such as canagliflozin, empagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin is associated with a small but significant reduction in SBP and DBP.[67] Our findings of the effects of SGLT2 inhibitors on BP are similar to a recent systematic review by Baker et al[69] and a recent meta-analysis of efficacy and safety of SGLT2 inhibitors.[70]

In addition to their effects on glucose excretion, SGLT inhibitors also inhibit sodium reabsorption in the proximal convoluted tubule.[67] The BP reductions observed with the SGLT2 inhibitors may result from their chronic natriuretic and osmotic diuretic effects. It has been reported that SGLT2 inhibitors increase urinary output by between 107 and 470 mL/d.[69] Therefore, the increased urinary sodium excretion may reduce plasma volume, resulting in reduced BP, particularly with increasing age.[20] Moreover, Imprialos et al have also reported a potential direct natriuretic effect of SGLT2 inhibitors.[67]

Other possible mechanisms accounting for the BP-lowering effects of SGLT2 inhibitors include nephron remodeling, reduction in arterial stiffness, and the effects on weight loss.[71] SGLT2 inhibitors, in addition to being effective in the treatment of T2D, appear to have benefits beyond glucose lowering, including effects on weight loss and raising high-density lipoprotein cholesterol levels.[70,72] Therefore, SGLT2

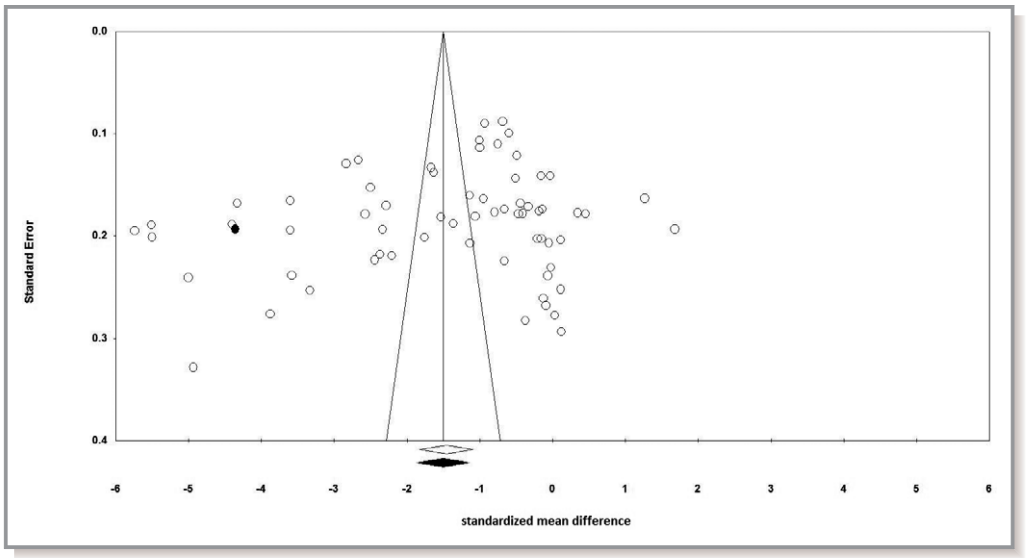

Figure 7. Trim-and-fill method (diastolic blood pressure) to impute potentially missing studies. One potentially missing study was imputed in funnel plot. Open circles represent observed published studies; open diamond represents observed effect size; closed diamond represents imputed effect size; closed circle represent imputed study.

inhibitors may play a significant role in reducing cardiovascular risk factors in people with T2D.

Canagliflozin and dapagliflozin inhibit SGLT2 activity in the proximal tubule, blocking the reabsorption of glucose back into the bloodstream. Furthermore, canagliflozin also blocks intestinal SGLT1, thereby reducing glucose absorption, although by a small magnitude.[39] The SGLT2 inhibitors are reported to have different effects on BP. Clar et al reported that dapagliflozin treatment was associated with a reduction in SBP ranging from −1.3 to −7.2 mm Hg in the patients treated with doses of 10 mg.[73] Rosenstock et al reported a reduction in SBP in response to canagliflozin treatment ranging from −0.9 mm Hg with 50 mg once daily to −4.9 mm Hg with 300 mg once daily (compared to −1.3 mm Hg with placebo and −0.8 mm Hg with sitagliptin).[13]

In the different studies we reviewed, patients received the SGLT2 inhibitors against different treatment backgrounds. For example, canagliflozin and dapagliflozin are available with metformin in a combination preparation; empagliflozin is available in a combination preparation with linagliptin (a DPP-4 inhibitor). The SGLT2 inhibitors (gliflozins) may often be taken with sulfonylureas, pioglitazone, and insulin.

Two large RCTs are currently in progress to assess the cardiovascular safety of the SGLT2 inhibitors. The Canagliflozin Cardiovascular Assessment Study (CANVAS)[74] enrolled patients with T2D at high cardiovascular risk to assess the possible effect of canagliflozin on the incidence of clinical events, and The Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58) is a 6-year trial assessing whether dapagliflozin reduces the risk of the composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke in patients with T2D.[69] The findings of these 2 large RCTs may elucidate the clinical efficacy of SGLT2 inhibitors and provide a definitive answer on their effects on metabolic parameters, especially cardiovascular-related metabolic factors.

We acknowledge several limitations in our review and meta-analysis. First, the majority of the included studies had relatively small sample sizes, potentially leading to unstable estimates of treatment effects, because smaller trials might be methodologically less robust and are prone to report larger effect sizes.[75,76] Therefore, the present meta-analysis may have been underpowered to detect a true effect. Second, the background therapies of participants were not uniform, including the use of metformin monotherapy and metformin in combination with pioglitazone, which might be associated with the heterogeneity of our results. Third, the follow-up periods were short, and investigation of SGLT2 long-term efficacy and safety is still necessary. Last, there was some moderate heterogeneity across studies included in meta-analysis overall and by specific SGLT2 inhibitor that was not explained by differences in the length of follow-up across studies. However, the pooled estimates showed the same direction of effects across different SGLT2 inhibitors, supporting the clinical plausibility of the effects observed across studies. Possible reasons for the heterogeneity include differences in background treatments and particularly BP-lowering therapies across studies, which we could not, unfortunately, account for. However, because differences in such therapies would tend to occur randomly, they are unlike to account for the overall effects observed across studies.

Conclusion

SGLT2 glucose cotransporter inhibitors have a beneficial off-target effect on BP in T2D patients. They also appear to have effects on other cardiometabolic parameters including lipid profile and body weight. In conclusion, these inhibitors have numerous potentially beneficial clinical effects when used as monotherapy or add-on therapy with other drugs, especially in patients with T2D and cardiovascular disease. However, our findings should be interpreted with consideration for the moderate statistical heterogeneity across included studies.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Search terms used for systematically reviewing the articles indexed on the Sodium glucose co-transport-2 inhibitors in type 2 diabetes in PUBMED/MEDLINA and Scopus		
No	**Concept**	**Search terms**
1#	**SGLT2**	Sodium Glucose co-transport-2 inhibitor' or 'SGLT-2 inhibitor' or 'Canagliflozin' or 'Dapagliflozin' or 'Empagliflozin' or 'Ipragliflozin' or 'Remogliflozin' or 'Sergliflozin' or 'Tofogliflozin' or 'ASP1941' or 'AVE2268' or 'BI-10773' or 'BMS512148' or 'KGT-1681' or 'TA-7284' or 'TS-033' or 'YM543'
2#	**hypertension**	Hypertension [tw] OR high blood pressure [tw] OR systolic hypertension [tw] OR diastolic hypertension [tw] OR Hypertension [MeSH terms]
3	**Combination**	1 AND 2

Table S2. Search terms used for systematically reviewing the articles indexed on the Sodium glucose co-transport-2 inhibitors in type 2 diabetes in EMBASE		
No	**Concept**	**Search terms**
# 1	**SGLT2**	Sodium Glucose co-transport-2 inhibitor' or 'SGLT-2 inhibitor' or 'Canagliflozin' or 'Dapagliflozin' or 'Empagliflozin' or 'Ipragliflozin' or 'Remogliflozin' or 'Sergliflozin' or 'Tofogliflozin' or 'ASP1941' or 'AVE2268' or 'BI-10773' or 'BMS512148' or 'KGT-1681' or 'TA-7284' or 'TS-033' or 'YM543'
# 2	**Hypertension**	Hypertension OR high blood pressure OR systolic hypertension OR diastolic hypertension
# 3	**Combination**	1 AND 2

Table S3. Quality of bias assessment of the included studies according to the Cochrane guidelines.

first author, year of pub	Random sequence generation	Allocation concealment	Selective reporting	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Other bias
JULIO ROSENSTOCK 2012 [1]	H	L	L	H	L	H	L
JULIO ROSENSTOCK 2012[2]	L	L	L	L	L	L	L
R. R. Henry 2012[3]	L	H	L	L	L	L	L
A. Kashiwagi 2014[4]	L	L	H	L	L	L	H
C. J. Bailey 2010[5]	H	L	L	L	L	H	H
Clifford J Bailey 2014[6]	L	L	L	L	L	L	L
Clifford J Bailey 2013[7]	L	L	L	L	L	H	L
D. Devineni 2012[8]	L	H	L	L	U	L	L
E. Ferrannini 2013[9]	L	L	L	L	L	L	L
ELE FERRANNINI 2010[10]	L	L	H	L	L	L	L
F. J. Lavalle-González 2013[11]	H	L	L	L	H	L	L
GUNTRAM SCHERNTHANER 2013[12]	L	L	L	L	L	L	L

H. J. Lambers Heerspink 2013[13]	L	H	L	L	L	L	L
Hala Yamout 2014[14]	H	L	H	L	L	L	U
HANS-ULRICH HÄRING, 2013[15]	L	L	L	L	L	H	H
Ilkka Tikkanen, 2014[16]	L	L	L	L	L	L	L
J. Bolinder, 2014[17]	L	L	L	L	L	H	L
J. P. H. Wilding, 2013[18]	L	L	L	L	L	L	L
J. P. H. Wilding, 2014[19]	U	L	L	L	L	L	L
J. Rosenstock, 2013[20]	L	L	H	L	L	L	L
J.-F. Yale, 2013[21]	H	L	L	H	L	L	L
JAMES F. LIST, 2008[22]	L	L	L	L	L	L	L
Jan Bolinder, 2012[23]	H	L	L	L	L	L	L
John P.H. Wilding, 2012[24]	U	L	H	L	L	L	H
K. Kaku, 2013[25]	L	L	L	L	L	L	L
K. Kaku, 2014[26]	L	U	L	L	L	L	L
K. Stenlof, 2012[27]	L	L	L	L	L	L	L
K. Strojek, 2011[28]	L	L	L	L	L	L	L
Lawrence A. Leiter, 2014[29]	L	L	L	U	L	L	L
Lawrence A. Leiter, 2014[30]	L	L	L	L	L	L	L

Linong Ji, 2014[31]	L	L	L	L	L	L	L
Michael A Weber, 2015[32]	H	L	L	L	L	L	L
MICHAEL A. NAUCK, 2011[33]	L	L	L	L	L	L	L
N. Inagaki, 2013[34]	L	L	L	L	L	L	L
Bruce Neal, 2014[35]	L	L	L	L	L	L	U
Nobuya Inagaki, 2014[36]	L	L	L	L	L	U	L
P.-M. Schumm-Draeger, 2014[37]	L	L	L	L	L	L	L
S. Sha, 2014[38]	L	L	L	L	L	L	L
Stefano Del Prato 2015[39]	L	U	L	L	L	L	L
Stephan Matthaei, 2015[40]	U	L	L	L	L	L	L
T. Forst, 2014[41]	L	L		L	L	L	L
Sykes A.P ,2015[42]	L	L	L	L	L	L	L
Skyes A.P, 2015[43]	L	L	L	L	U	L	L

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

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