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SYSTEMATIC REVIEW AND META-ANALYSIS

Effects of Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitors on Cardiovascular and Metabolic Outcomes in Patients Without Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized-Controlled Trials

Yao Hao Teo; Yao Neng Teo; Nicholas L. Syn; Cheryl Shumin Kow; Celine Shuen Yin Yoong; Benjamin Y. Q. Tan, MBBS; Tiong-Cheng Yeo, MBBS; Chi-Hang Lee, MD; Weiqin Lin, MBBS; Ching-Hui Sia, MBBS, MRCP

BACKGROUND: Recent studies have increasingly shown that sodium-glucose cotransporter 2 (SGLT2) inhibitors may have beneficial cardiovascular and metabolic effects in patients without diabetes mellitus. Hence, we conducted a systematic review and meta-analysis to determine the effect of SGLT2 inhibitors on cardiovascular and metabolic outcomes in patients without diabetes mellitus.

METHODS AND RESULTS: Four electronic databases (PubMed, Embase, Cochrane, and SCOPUS) were searched on August 30, 2020 for articles published from January 1, 2000 to August 30, 2020, for studies that examined the effect of SGLT2 inhibitors on cardiovascular and metabolic outcomes in patients without diabetes mellitus. A random-effects pairwise meta-analysis model was used to summarize the studies. A total of 8 randomized-controlled trials were included with a combined cohort of 5233 patients. In patients without diabetes mellitus, those with heart failure treated with SGLT2 inhibitors had a 20% relative risk reduction in cardiovascular deaths and heart failure hospitalizations, compared with those who were not treated (risk ratio, 0.78; $P<0.001$). We additionally found that treatment with SGLT2 inhibitors improved multiple metabolic indices. Patients on SGLT2 inhibitors had a reduction in body weight of –1.21 kg ($P<0.001$), body mass index of –0.47 kg/m^2 ($P<0.001$), systolic blood pressure of –1.90 mm Hg ($P=0.04$), and fasting plasma glucose of –0.38 mmol/L ($P=0.05$), compared with those without. There were no between-group differences in NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, waist circumference, diastolic blood pressure, glycated hemoglobin, low-density lipoprotein cholesterol levels, and estimated glomerular filtration rates. Across our combined cohort of 5233 patients, hypoglycemia was reported in 22 patients.

CONCLUSIONS: SGLT2 inhibitors improve cardiovascular outcomes in patients without diabetes mellitus with heart failure. In patients without diabetes mellitus, SGLT2 inhibitors showed positive metabolic outcomes in weight and blood pressure control.

Key Words: nondiabetics ■ sodium/glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitor is a class of antihyperglycemic drugs increasingly used for patients with diabetes mellitus.[1] By blocking glucose reabsorption at the proximal renal tubule, SGLT2 inhibitors increase urinary glucose excretion and hence lower blood glucose in patients with diabetes mellitus.

Correspondence to: Ching-Hui Sia, MBBS, MRCP, Department of Cardiology, National University Heart Centre Singapore, 1E Kent Ridge Road, NUHS Tower Block Level 9, Singapore 119228. E-mail: ching_hui_sia@nuhs.edu.sg

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CLINICAL PERSPECTIVE

What Is New?

- Among patients without diabetes mellitus, those with heart failure treated with sodium-glucose cotransporter 2 inhibitors had a relative risk reduction in cardiovascular deaths and heart failure hospitalizations, compared with those who received placebo.
- Additionally, treatment with sodium-glucose cotransporter 2 inhibitors in patients without diabetes mellitus improved their metabolic parameters including body weight and blood pressure.
- Across a combined cohort of 5233 patients without diabetes mellitus, hypoglycemia was reported in 22 patients.

What Are the Clinical Implications?

- Future research of sodium-glucose cotransporter 2 inhibitors in other subgroups of patients without diabetes mellitus, particularly those without heart failure, is warranted to determine its overall role in the management of patients without diabetes mellitus.

Nonstandard Abbreviations and Acronyms

SGLT2 sodium-glucose cotransporter 2

Beyond and independent of glycemic control, clinical trials have demonstrated an improvement in cardiovascular morbidity and mortality in patients with diabetes mellitus treated with SGLT2 inhibitors compared with placebo.[2–4] Furthermore, treatment with SGLT2 inhibitors in patients with diabetes mellitus was shown to be associated with metabolic benefits such as weight loss,[5,6] blood pressure reduction,[7] and improvement in renal function.[4,8] The efficacy of SGLT2 inhibitors is reflected in the 2019 European Society of Cardiology guideline as a first-line therapy for patients with type 2 diabetes mellitus and established cardiovascular disease.[9]

Despite its initial indication as a diabetic drug with cardiovascular outcome benefits, recent clinical trials have demonstrated similar cardiovascular and metabolic benefits in patients without diabetes mellitus treated with SGLT2 inhibitors. In patients with heart failure (HF), the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure With Reduced Ejection Fraction) study[10] and the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial[11] demonstrated that SGLT2 inhibitors improve cardiovascular outcomes in patients with HF with reduced ejection fraction, regardless of diabetic status. Beyond cardiovascular benefits, recent clinical trials showed that the metabolic benefits of SGLT2 inhibitors extended beyond patients with diabetes mellitus to those without.[12,13] Given the increasing burden of metabolic syndrome and the subsequent morbidity and mortality, there is an urgent need to identify agents that may attenuate the deleterious effects of this condition in patients without diabetes mellitus.[14,15]

To date, there has been no meta-analysis examining whether SGLT2 inhibitor improves cardiovascular or metabolic outcomes in patients without diabetes mellitus. Hence, we conducted a systematic review and meta-analysis to determine the effect of SGLT2 inhibitors on cardiovascular and metabolic outcomes in patients without diabetes mellitus. We hypothesized that in patients without diabetes mellitus, treatment with SGLT2 inhibitors, compared with those without, was associated with improvement in cardiovascular and metabolic outcomes.

METHODS

Ethics approval and consent to participate were not applicable. The data that support the findings of this study are available from the corresponding author upon reasonable request. The meta-analysis was reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses guidelines.[16] Searches of 4 databases (PubMed, Embase, Cochrane, and SCOPUS) were conducted on August 30, 2020 for articles published from January 1, 2000 to August 30, 2020. Literature search was performed using the following terms in combination: (“empagliflozin” OR “canagliflozin” OR “dapagliflozin” OR “Ertugliflozin”) AND ("trial").

Studies evaluating the cardiovascular and metabolic outcomes of SGLT2 inhibitors in patients without diabetes mellitus were included. cardiovascular outcomes included all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, HF hospitalization, and unplanned revascularizations. NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels were also used as a surrogate outcome of HF. Metabolic outcomes included systolic blood pressure, diastolic blood pressure, weight, body mass index, waist circumference, hemoglobin A1c (HbA1c), fasting plasma glucose, low-density lipoprotein cholesterol, and estimated glomerular filtration rate. We included all randomized-controlled trials, according to the population, intervention, comparison, outcome, and study design inclusion and exclusion criteria (Table 1). We excluded all studies that did not report

on cardiovascular or metabolic outcomes in patients without diabetes mellitus.

Four reviewers independently performed the literature search and data extraction, and all disagreements were resolved by mutual consensus. During the title and abstract review stage, an "inclusive" approach was adopted, where only studies that clearly fit the exclusion criteria, such as the study not being a clinical trial, not involving SGLT2 inhibitor use, and/or were focused only on patients with diabetes mellitus, were excluded; the rest of the studies were included. Clinical trials involving SGLT2 inhibitors were selected for full text review to identify if subgroup analysis of patients without diabetes mellitus was performed.

Reviews in SGLT2 inhibitor were identified from the title and abstract review, and separate hand searches of their bibliographies were conducted, with no additional trials identified. Additionally, as the European Society of Cardiology Virtual Congress 2020 took place after the initial database search, hand search was conducted for conference abstracts and press releases from the Virtual Congress 2020, which may not have been included at the time of the initial search. Through this, the EMPEROR-reduced trial[10] was identified, which was jointly published in the *New England Journal of Medicine*. Although the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial was recently presented at the European Society of Cardiology Virtual Congress 2020, subgroup analyses for patients without diabetes mellitus were not available, hence the study was excluded.[17] Hence through hand searches, EMPEROR-reduced trial[10] was additionally included into the study.

Apart from cardiovascular and metabolic outcomes, baseline information of patients without diabetes mellitus were collected for age, sex, body weight, body mass index, systolic blood pressure, diastolic blood pressure, HbA1c, and low-density lipoprotein cholesterol. For the SGLT2 inhibitor regimes, we collected data on the drug name, drug dosage, drug frequency, control group, length of intervention, and mean length of follow-up. Data relating to blinding and withdrawals were extracted to assess risk of bias. Quality control was performed by 2 independent reviewers using the Cochrane Risk of Bias tool,[18] which assesses 7 domains (random sequence generation, allocation concealment, masking of participants and personnel, blinding of outcome assessment; incomplete outcome data, selective outcome reporting, and other sources of bias), as shown in Figure S1. The quality of pooled evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation system,[19] which accounts for statistical heterogeneity, publication bias, risk of bias, indirectness, and statistical imprecision, as shown in Table S1. A Preferred Reporting Items of Systematic Reviews and Meta-Analyses checklist[20] is included in Figure S2.

Table 1. PICOS, Inclusion Criteria, and Exclusion Criteria Applied to Database Search

PICOS	Inclusion Criteria	Exclusion Criteria
Population	• Patients without diabetes mellitus	• Patients with diabetes mellitus • Studies without subgroup analysis of patients without diabetes mellitus
Intervention	• SGLT2 inhibitors, inclusive of empagliflozin, canagliflozin, dapagliflozin, ertugliflozin	
Comparison	• Comparisons of SGLT2 inhibitors with a control group (placebo) on its impact upon cardiovascular outcomes in patients without diabetes mellitus	
Outcome	• All-cause mortality, nonfatal myocardial infarction, non-fatal stroke, heart failure hospitalization, unplanned revascularizations • N-terminal pro-B-type natriuretic peptide • Systolic blood pressure • Diastolic blood pressure • Weight • Body mass index • Waist circumference • Hemoglobin A1c • Fasting plasma glucose • Low-density lipoprotein cholesterol • Estimated glomerular filtration rate	
Study design	• Articles in English or translated to English • Randomized-controlled trials • Conference abstracts, or electronic and print information not controlled by commercial publishing, reporting on randomized-controlled trials • Year of publication: January 1, 2000–August 30, 2020 • Databases: PubMed, Embase, Cochrane, SCOPUS	• Mixed methods research, meta-analyses, systematic reviews, cohort studies, case-control studies, cross-sectional studies, and descriptive papers • Case reports and series, ideas, editorials, and perspectives

PICOS indicates population, intervention, comparison, outcome, and study design; and SGLT2, sodium-glucose cotransporter 2.

Statistical Analysis

The results were quantitatively pooled and analyzed using Review Manager (RevMan) Version 5.4,[21] using general approaches laid out by the Cochrane Handbook.[22] In studies without SDs, *P* values or CIs were converted to SDs.[22] In studies without SDs, *P* values, andCIs, the square-root of weighted mean variance of all other studies was used to estimate the SD.[23] In the Bays 2014[24] study where different dosages of SGLT2 inhibitor are used in subgroups of patients, the mean change of the SGLT2 inhibitor arm is calculated from the weighted mean change of the individual subgroups. For panel data or longitudinal outcomes, preintervention baseline imbalances were corrected using the simple analysis of change scores method.[22] In studies reporting the outcome in different scales, a simple unit conversion was performed. Inverse variance was used in deriving the pooled outcomes. The random-effects model was used to account for between-study variance. Between-study heterogeneity was presented using I2 and τ2 statistics. We considered I2 of <30% to indicate low heterogeneity between studies, 30% to 60% to indicate moderate heterogeneity, and >60% to indicate substantial heterogeneity. Two-sided *P* values of <0.05 were regarded to indicate nominal statistical significance.

RESULTS

The Preferred Reporting Items of Systematic Reviews and Meta-Analyses flowchart is presented in Figure 1. Literature search of the 4 databases (PubMed, Embase, Cochrane, SCOPUS) retrieved 6522 results, and hand search uncovered 1 additional relevant study; 2414 duplicates were removed. Title and abstract screening excluded a further 4055 articles as they did not include patients without diabetes mellitus, did not evaluate

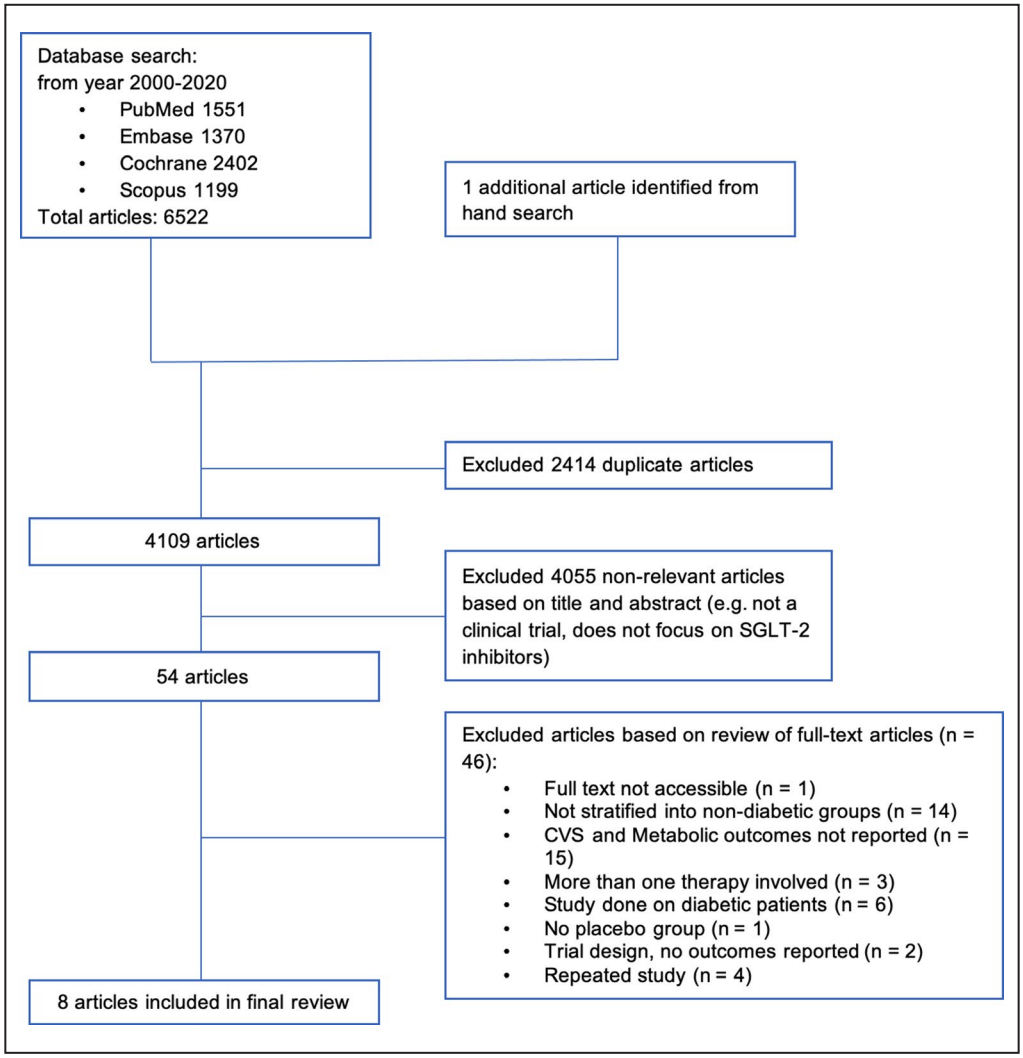

Figure 1. PRISMA flow diagram of study selection.
PRISMA indicates Preferred Reporting Items of Systematic Reviews and Meta-Analyses; and SLGT2, sodium-glucose cotransporter 2.

cardiovascular outcomes or metabolic parameters, or were of an inappropriate study type. Full text screening excluded 46 articles. Eight articles were included for the meta-analysis.[10,12,13,24–28]

Baseline Characteristics

The 8 studies comprised a combined cohort of 5233 patients. In Nassif 2019,[26] Petrie 2020,[27] and Packer 2020,[10] patients without diabetes mellitus had HF. The participant baseline characteristics of the included studies are shown in Table 2.

Across the 8 studies, the SGLT2 inhibitor drug name, dosage, frequency, control group, length of intervention, and length of follow-up were summarized and are included in Table S2. Dapagliflozin, canagliflozin, and empagliflozin were the SGLT2 inhibitors used in 5, 2, and 1 studies respectively. Dapagliflozin and empagliflozin were administered at a dosage of 10 mg throughout the randomized controlled trials. All regimes were given once daily and compared with a control group receiving placebo. The length of follow-up ranged from 12 weeks to 18 months.

Pooled Cardiovascular Outcomes

The pooled cardiovascular outcomes are presented in Figure 2. The 3 studies analyzed focused on patients with HF. Comparing patients receiving SGLT2 inhibitors with patients without, the random effects model demonstrated that the risk ratio for the composite of cardiovascular deaths and HF hospitalization was 0.78 (95% CI, 0.69–0.89; $P<0.001$) (Figure 2A). There was a statistically insignificant change in NT-proBNP.

Pooled Metabolic Outcomes

The pooled metabolic outcomes are presented in Figure 3. In patients without diabetes mellitus, the random effects model demonstrated that patients receiving SGLT2 inhibitors had a mean reduction in body weight of –1.21 kg (95% CI, –1.82 to –0.61; $P<0.001$) (Figure 3A), body mass index of –0.47 kg/m^2 (95% CI, –0.73 to –0.21; $P<0.001$) (Figure 3B), systolic blood pressure of –1.90 mm Hg (95% CI, –3.69 to –0.11; $P=0.04$) (Figure 3D), and fasting plasma glucose of –0.38 mmol/L (95% CI, –0.77 to 0.01; $P=0.05$) (Figure 3G), compared with those without. There were no significant changes in waist circumference, diastolic blood pressure, HbA1c, low-density lipoprotein cholesterol, and estimated glomerular filtration rate. In the combined cohort of 5233 patients, hypoglycemia occurred in 22 patients.

Characteristics of Included Studies

The individual breakdown of the risk of bias and study characteristics are summarized in Table 3. Among the studies included, all studies were randomized-controlled

Table 2. Participant Baseline Characteristics

Study	Sample Size of Patients Without DM	Mean Age, y	Men	Body Weight, kg	Body Mass Index, kg/m^2	Systolic Blood Pressure, mm Hg	Diastolic Blood Pressure, mm Hg	HbA1c/%	LDL-C	Heart Failure
Bays 2014[24]	376	44.8	53	101.3	37	NR	NR	NR	NR	NR
González-Ortiz 2016[25]	32	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hollander 2017[13]	166	45.0	31	103.8	37.6	123.5	NR	5.6	NR	NR
Nassif 2019[26]	97	NR	NR	NR	NR	NR	NR	NR	NR	97
Petrie 2020[27]	2605	66.2	1973	NR	27.2	120.6	NR	5.75	NR	2605
Cherney 2020[12]	53	51	36	83	28	126	76.2	5.6	2.8	NR
Díaz-Cruz 2020[28]	30	NR	NR	77	30.5	120	73.5	5.85	NR	NR
Packer 2020[10]	1874	NR	NR	NR	NR	NR	NR	NR	NR	1874

DM indicates diabetes mellitus; HbA1c, glycated hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; and NR, not reported.

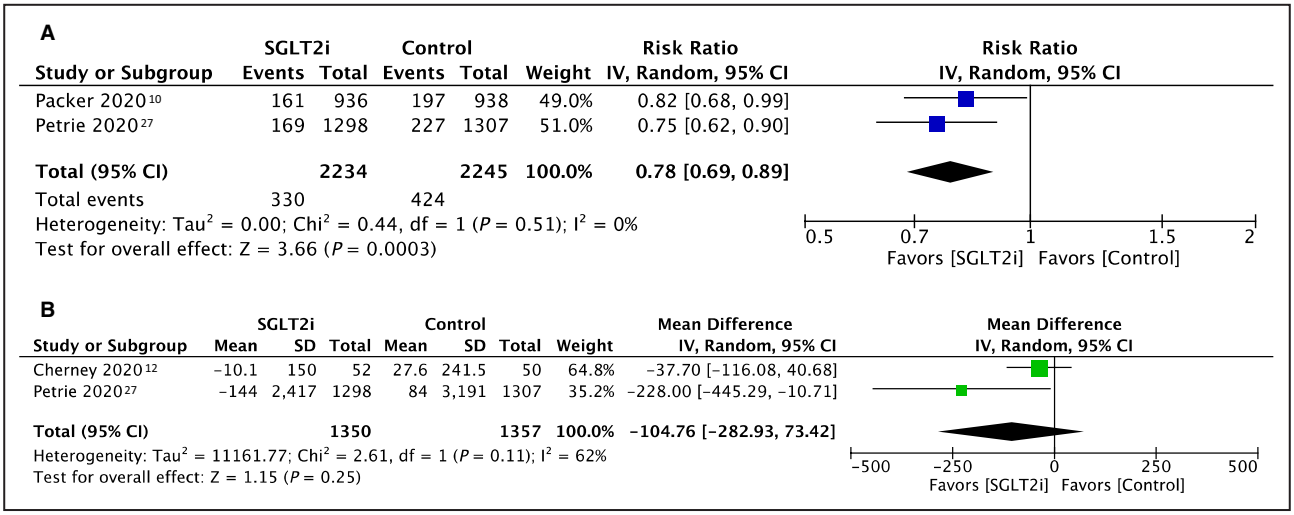

Figure 2. Forest plot of a composite of cardiovascular death and heart failure hospitalization (A) and Forest plot of mean change in NT-proBNP in pg/mL (B).
NT-proBNP indicates N-terminal pro-B-type natriuretic peptide; and SLGT2i, sodium-glucose cotransporter 2 inhibitor.

trials. Among the 8 studies, 3 studies included patients with HF, 3 studies included patients with obesity, 1 study included patients with chronic kidney disease, and 1 study included patients with prediabetes mellitus and prehypertension. All studies were assessed to have a low risk of selection bias (owing to random sequence generation), reporting bias, and other bias. A minority of studies (≤2 trials) were assessed to have an unclear risk of selection bias (owing to allocation concealment) and performance bias. Half of the studies had an unclear risk in detection bias. Two studies[13,24] experienced high dropout rates, contributing to a potential attrition bias; Hollander 2017[13] and Bays 2014[24] reported that 31% and 25% of study participants did not complete the study, respectively.

DISCUSSION

In this pairwise meta-analysis of randomized-controlled trials of patients without diabetes mellitus, we demonstrated that patients with HF treated with SGLT2 inhibitors had a 20% relative risk reduction in cardiovascular deaths and HF hospitalizations, compared with placebo. In addition, we found that treatment with SGLT2 inhibitors was associated with a reduction in body weight, body mass index, systolic blood pressure, and fasting plasma glucose, compared with placebo. There were no differences in serum NT-proBNP level, waist circumference, diastolic blood pressure, serum HbA1c, low-density lipoprotein cholesterol, and estimated glomerular filtration rate.

Patients with HF are at an increased risk of recurrent hospitalizations and mortality.[29] In 2014, in the United States, HF accounted for over 900 000 hospitalizations and totaled an estimated $11 billion in healthcare costs.[30] Hence, to reduce the huge healthcare burden attributed to HF, effective pharmacological therapy is highly sought after. In this meta-analysis, we showed that treatment with SGLT2 inhibitors results in a significant risk reduction in cardiovascular mortality and HF hospitalization in patients without diabetes mellitus. Current guidelines recommends SGLT2 inhibitors for use in the treatment of diabetes mellitus to reduce HF risk.[9] We propose that SGLT2 inhibitors may additionally confer a benefit in the treatment of patients with HF on top of current recommended therapy, even in patients without diabetes mellitus. This might be of consideration to clinical practice while awaiting updates to HF guidelines.

However, there is a lack of studies evaluating cardiovascular outcomes in patients without diabetes mellitus and HF. Furthermore, the effect of SGLT2 inhibitors on the end points of myocardial infarction or stroke have not been explored. In the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial in patients with diabetes mellitus, although statistically insignificant, patients receiving empagliflozin had a lower rate of myocardial infarction and higher rate of stroke.[2] Future studies of SGLT2 inhibitors in patients without diabetes mellitus should additionally focus on capturing these cardiovascular end points to further ascertain the efficacy of SGLT2 inhibitors as patients with HF who require concomitant risk reduction for future MI and stroke.

In patients without diabetes mellitus, we showed that treatment with SGLT2 inhibitors improved metabolic parameters, compared with those who were not treated. Although the absolute changes were modest, this

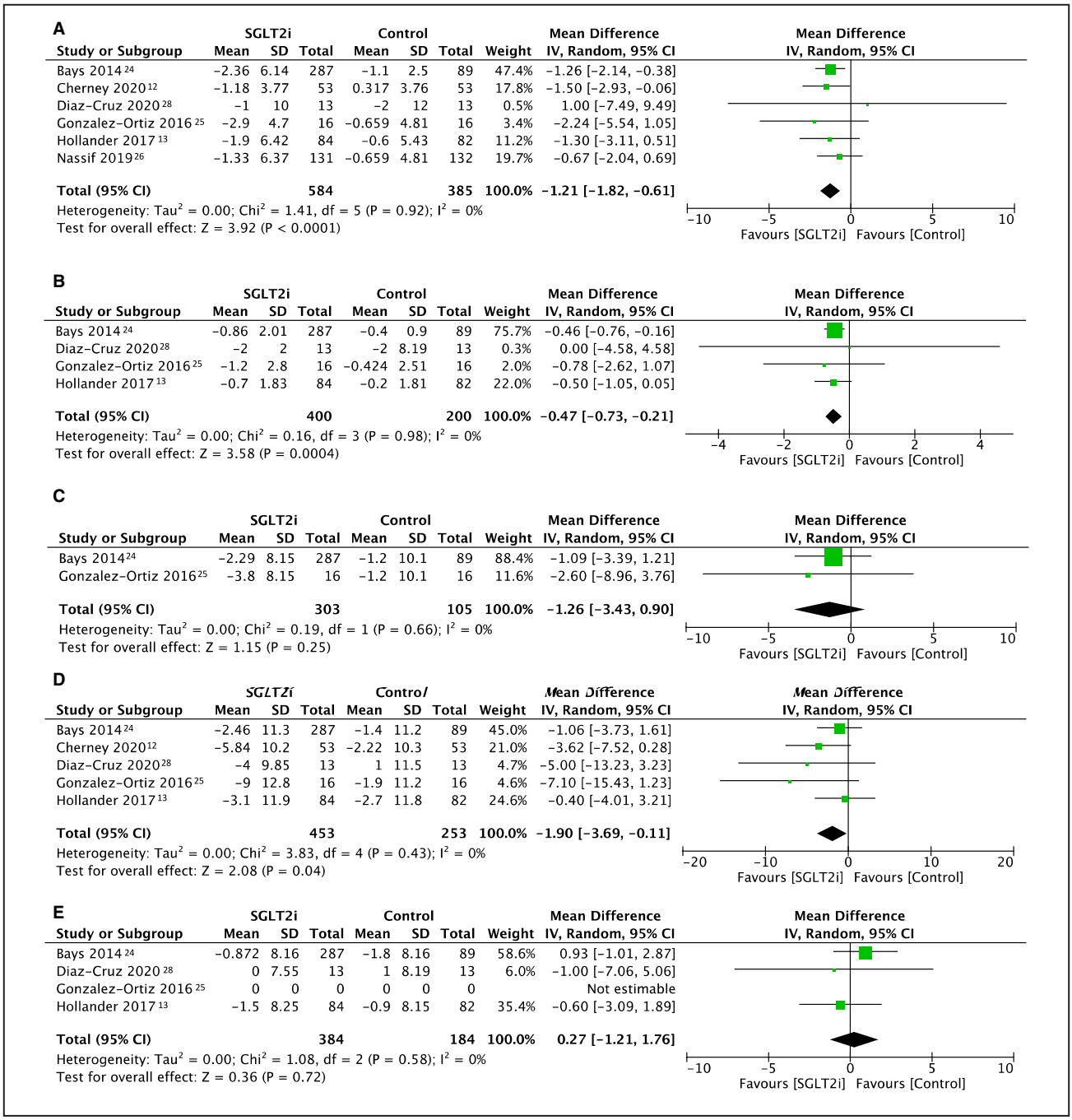

Figure 3. Forest plot of mean change in (A) body weight in kg, (B) BMI in kg/m², (C) waist circumference in cm, (D) systolic blood pressure in mm Hg, (E) diastolic blood pressure in mm Hg, (F) HbA1c in %, (G) fasting plasma glucose in mmol/L, (H) LDL-C in mmol/L, and (I) eGFR in mL/min per 1.73 m².

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; and LDL, low-density lipoprotein.

benefit is seen across body weight and blood pressure parameters and indicates a potential utility of SGLT2 inhibitors in optimizing the cardiovascular risk profile of patients without diabetes mellitus. Although there was a borderline significant reduction in fasting plasma glucose, there was no significant change in HbA1c in patients without diabetes mellitus. Furthermore, across our combined cohort of 5233 patients, hypoglycemia was reported in 22 patients. This suggests a relatively good safety profile of SGLT2 inhibitors in the population without diabetes mellitus. As there are limited studies evaluating the lipid and glucose profile of patients, future research will be needed to fully elucidate the effects of SGLT2 inhibitors in patients without diabetes mellitus.

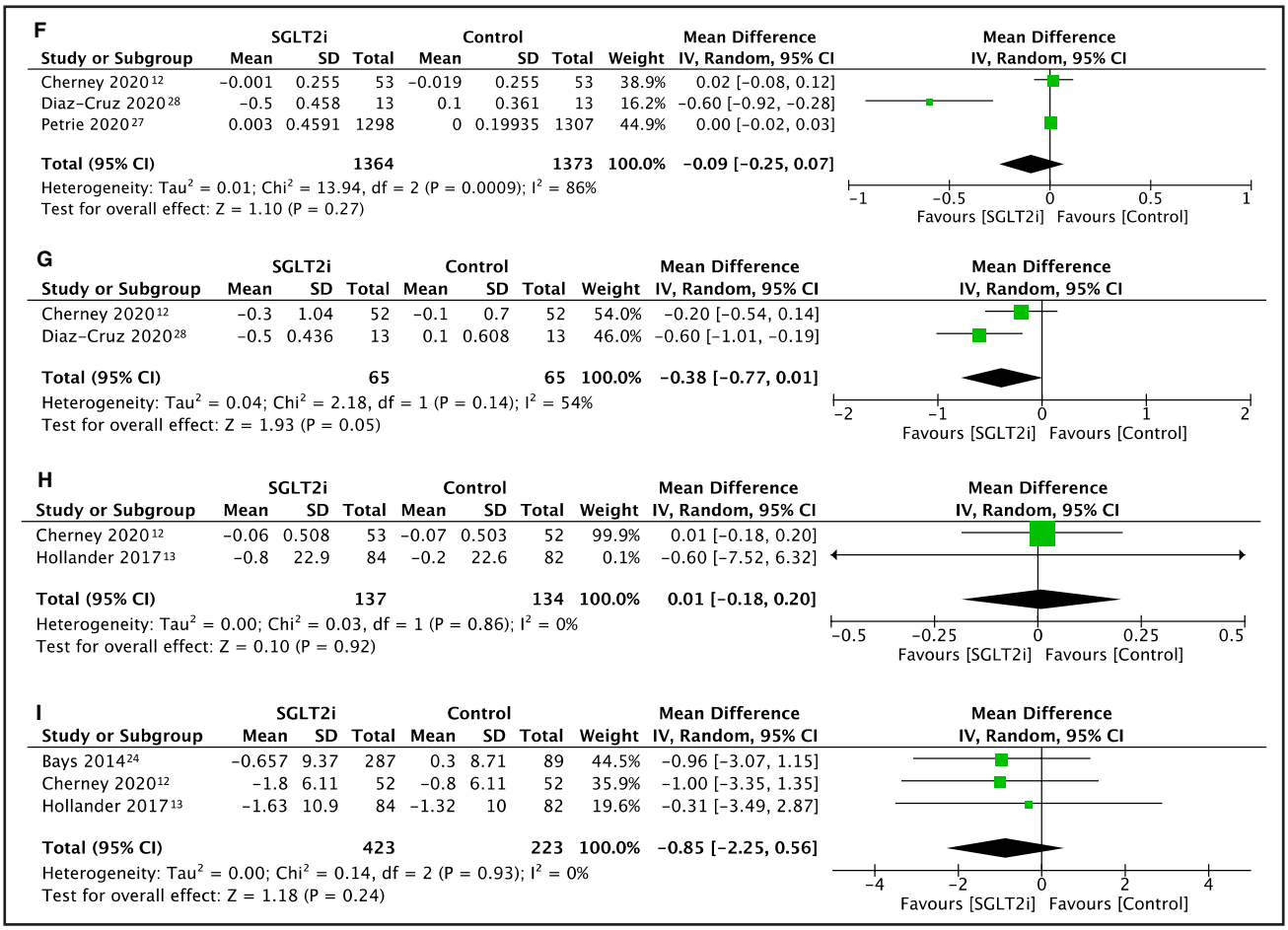

Figure 3. Continued

The pathophysiological mechanisms by which SGLT2 inhibitors lead to improvement in metabolic parameters are proposed to include the natriuretic effects[31] or complementary pathways to those of commonly used antihypertensives,[32] which results in blood pressure lowering and a negative caloric balance from the inhibition of renal glucose reabsorption, hence achieving weight loss.[24] However, the modest improvement in metabolic parameters does not appear to fully account for the significant risk reduction in cardiovascular outcomes in patients without diabetes mellitus. Hence, there is a need to further explore other mechanisms of action of SGLT2 inhibitors on cardiovascular health in patients without diabetes mellitus.

Limitations

Our study should be interpreted in due consideration of the limitations. First, given that many studies did not report baseline characteristics of patients without diabetes mellitus, we do not know if between-study differences may account for differences in study outcomes across patients without diabetes mellitus.

Second, we are unable to comment on the differences in drug efficacy across SGLT2 inhibitors, such as between dapagliflozin and empagliflozin. Further clinical trials or network meta-analysis will be important to derive the efficacy of individual SGLT2 inhibitors.

Third, across the outcomes analyzed, although the quality of evidence assessed using Grading of Recommendations Assessment, Development and Evaluation was high for most outcomes, the quality of evidence for change in NT-proBNP, HbA1c, and fasting plasma glucose was moderate, low, and low, respectively. There was substantial heterogeneity observed for mean change in NT-proBNP (I2=62%) and mean percentage change in HbA1c (I2=86%), and moderate heterogeneity observed for mean change in fasting plasma glucose (I2=54%). The substantial heterogeneity may be attributed to the notable difference in background medical conditions of the 8 included study populations. In the 2 studies analyzed for mean change in NT-proBNP, Cherney

Table 3. Characteristics of Included Studies

Study	Study Population	Location	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias	Mean Length of Follow-Up
Bays 2014[24]	Overweight and obese without diabetes mellitus	Multiple sites in the United States and Puerto Rico	Low risk	Low risk	Low risk	Unclear risk	High risk	Low risk	Low risk	12 wk
González-Ortiz 2016[25]	Overweight and obese without diabetes mellitus	NR	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	3 mo
Hollander 2017[13]	Overweight and obese without diabetes mellitus	18 sites in the United States	Low risk	Unclear risk	Low risk	Low risk	High risk	Low risk	Low risk	26 wk
Nassif 2019[26]	Heart failure with reduced ejection fraction	26 sites in the United States	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	13 wk
Petrie 2020[27]	Heart failure with and without diabetes mellitus	410 centers in 20 countries	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	18 mo (median)
Cherney 2020[12]	Chronic kidney disease without diabetes mellitus	6 hospitals in Canada, Malaysia, and the Netherlands	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	12 wk
Díaz-Cruz 2020[28]	Prediabetes mellitus and prehypertension without pharmacological treatment	NR	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	12 wk
Packer 2020[10]	Heart failure with reduced ejection fraction	520 centers in 20 countries	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	16 mo (median)

NR indicates not reported.

2020[12] studied 102 patients who had chronic kidney disease with proteinuria, whereas Petrie 2020[27] was a comparatively larger trial that studied 2605 patients with HF.

Fourth, there were high dropout rates observed in Hollander 2017[13] and Bays 2014.[24] This may have contributed to a high risk of attrition bias in these trials.

CONCLUSIONS

Among patients without diabetes mellitus, we demonstrated that patients with HF treated with SGLT2 inhibitors had a relative risk reduction in cardiovascular deaths and HF hospitalizations, compared with those who received placebo. Additionally, treatment with SGLT2 inhibitors in patients without diabetes mellitus improved their metabolic parameters including body weight and blood pressure. Future research of SGLT2 inhibitors in other subgroups of patients without diabetes mellitus, particularly those without HF, is warranted to determine its overall role in the management of patients without diabetes mellitus.

ARTICLE INFORMATION

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Affiliations

From the Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (Y.H.T., Y.N.T., N.L.S., C.S.K., C.S.Y., T.Y., C.L., W.L., C.S.); Division of Neurology, University Medicine Cluster, National University Health System, Singapore (B.Y.T.); and Department of Cardiology, National University Heart Centre Singapore, Singapore (T.Y., C.L., W.L., C.S.).

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Disclosures

None.

Supplementary Material

Tables S1–S2
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Outcome Characteristics.

Outcomes	Pooled outcomes (95% CI)	No. of patients (no. of included studies)	Statistical heterogeneity	Quality of evidence (GRADE)
Composite of cardiovascular death and heart failure hospitalization	RR 0.78 (0.69 to 0.89)	4,479 (2 studies)	I^2 = 0% (*P* = 0.51)	⊕⊕⊕⊕
Mean change in NT-proBNP (pg/ml)	WMD -104.76 (-282.93 to 73.42)	2,707 (2 studies)	I^2 = 62% (*P* = 0.11)	⊕⊕⊕⊖[a]
Mean change in body weight (kg)	WMD -1.21 (-1.82 to -0.61)	969 (6 studies)	I^2 = 0% (*P* = 0.92)	⊕⊕⊕⊕
Mean change in BMI (kg/m^2)	WMD -0.47 (-0.73 to -0.21)	600 (4 studies)	I^2 = 0% (*P* = 0.98)	⊕⊕⊕⊕
Mean change in waist circumference (cm)	WMD -1.26 (-3.43 to 0.90)	408 (2 studies)	I^2 = 0% (*P* = 0.66)	⊕⊕⊕⊕
Mean change in systolic blood pressure (mmHg)	WMD -1.90 (-3.69 to -0.11)	706 (5 studies)	I^2 = 0% (*P* = 0.43)	⊕⊕⊕⊕
Mean change in diastolic blood pressure (mmHg)	WMD 0.27 (-1.21 to 1.76)	568 (4 studies)	I^2 = 0% (*P* = 0.58)	⊕⊕⊕⊕
Mean percentage change in HbA1c (%)	WMD -0.09 (-0.25 to 0.07)	2737 (3 studies)	I^2 = 86% (*P* = 0.0009)	⊕⊕⊖⊖[b]
Mean change in fasting plasma glucose (mmol/L)	WMD -0.38 (-0.77 to 0.01)	130 (2 studies)	I^2 = 54% (*P* = 0.14)	⊕⊕⊖⊖[c,d]
Mean change in LDL (mmol/L)	WMD 0.01 (-0.18 to 0.20)	271 (2 studies)	I^2 = 0% (*P* = 0.86)	⊕⊕⊕⊕
Mean change in eGFR (mL/min/1.73 m²)	WMD -0.85 (-2.25 to 0.56)	646 (3 studies)	I^2 = 0% (*P* = 0.93)	⊕⊕⊕⊕

NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; RR, relative risk; WMD, weighted mean difference; ROM, ratio of means.

[a]Downgraded by one level for substantial statistical heterogeneity, but forest plots indicate a consistent direction favouring study-level treatment effect.

[b]Downgraded by two levels for severe statistical heterogeneity.

[c]Downgraded by one level for statistical imprecision.

[d]Downgraded by one level for moderate statistical heterogeneity.

Table S2. Intervention Characteristics.

Study	Article	Drug name	Drug dose	Drug frequency	Control group	Length of intervention	Mean length of follow-up
Bays 2014[24]	Canagliflozin: effects in overweight and obese subjects without diabetes mellitus	Canagliflozin	50mg, 100mg, 300mg	Once daily	Placebo	12 weeks	12 weeks
Gonzalez-Ortiz 2016[25]	Effect of dapagliflozin on visceral adiposity and blood pressure in patients with overweight or obesity without diabetes mellitus	Dapagliflozin	10 mg	Once daily	Placebo	3 months	3 months
Hollander 2017[13]	Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: A randomized clinical trial	Canagliflozin	300 mg	Once daily	Placebo	26 weeks	26 weeks
Nassif 2019[26]	Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial	Dapagliflozin	10 mg	Once daily	Placebo	12 weeks	13 weeks
Petrie 2020[27]	Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients with Heart Failure with and Without Diabetes	Dapagliflozin	10 mg	Once daily	Placebo	18 months (median)	18 months (median)
Cherney 2020[12]	Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised,	Dapagliflozin	10 mg	Once daily	Placebo	6 weeks	12 weeks

	double-blind, crossover trial						
Diaz-Cruz 2020[28]	Effects of dapagliflozin on blood pressure variability in patients with prediabetes and prehypertension without pharmacological treatment: a randomized trial	Dapagliflozin	10 mg	Once daily	Placebo	12 weeks	12 weeks
Packer 2020[10]	Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure (EMPEROR REDUCED)	Empagliflozin	10 mg	Once daily	Placebo	NIL	16 months (median)

Figure S1. Risk of Bias Graph.

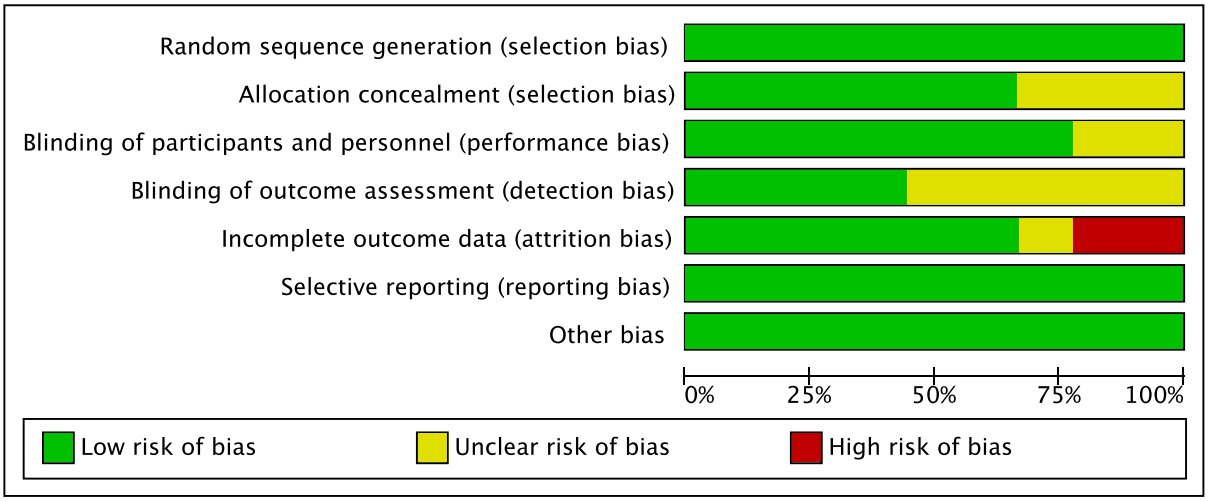

Figure S2. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NIL
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9-10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10-11

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NIL
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14-15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-14
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14-15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NIL
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097