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Meta-Analysis

Sodium-Glucose Cotransporter 2 Inhibitors and the Risk of Pneumonia and Septic Shock

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Abstract

Context: Individuals with type 2 diabetes mellitus (DM) have an increased risk of pneumonia and septic shock. Traditional glucose-lowering drugs have recently been found to be associated with a higher risk of infections. It remains unclear whether sodium-glucose cotransporter 2 inhibitors (SGLT2is), which have pleiotropic/anti-inflammatory effects, may reduce the risk of pneumonia and septic shock in DM.

Methods: MEDLINE, Embase, and ClinicalTrials.gov were searched from inception up to May 19, 2022, for randomized, placebo-controlled trials of SGLT2i that included patients with DM and reported outcomes of interest (pneumonia and/or septic shock). Study selection, data extraction, and quality assessment (using the Cochrane Risk of Bias Assessment Tool) were conducted by independent authors. A fixed-effects model was used to pool the relative risk (RRs) and 95% CI across trials.

Results: Out of 4568 citations, 26 trials with a total of 59 264 patients (1.9% developed pneumonia and 0.2% developed septic shock) were included. Compared with placebo, SGLT2is significantly reduced the risk of pneumonia (pooled RR 0.87, 95% CI 0.78-0.98) and septic shock (pooled RR 0.65, 95% CI 0.44-0.95). There was no significant heterogeneity of effect size among trials. Subgroup analyses according to the type of SGLT2i used, baseline comorbidities, glycemic control, duration of DM, and trial follow-up showed consistent results without evidence of significant treatment-by-subgroup heterogeneity (all $P_{\text{heterogeneity}} > .10$).

Conclusion: Among DM patients, SGLT2is reduced the risk of pneumonia and septic shock compared with placebo. Our findings should be viewed as hypothesis generating, with concepts requiring validation in future studies.

Key Words: diabetes, pneumonia, respiratory tract infections, septic shock

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HR, hazard ratio; OR, odds ratio; RR, relative risk; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

The increasing prevalence of type 2 diabetes mellitus (DM) poses a significant public health burden worldwide (1). Patients with diabetes have an increased risk of pneumonia: in the United States, the overall incidence rate of pneumonia in 2014 was 1.78-fold higher in patients with diabetes than in individuals without diabetes (34 vs 19 per 1000 person-years) (2). Among patients admitted for pneumonia, those with pre-existing DM or acute hyperglycemia had approximately 80% higher risk of mortality than normoglycaemic individuals (3–6), particularly so in the presence of septic shock (7). Paradoxically, glucose lowering using conventional anti-DM drugs, including metformin (8), dipeptidyl peptidase-4 inhibitor (9), and combination therapy of metformin plus thiazolidinediones (10), did not lower the risk of pneumonia, and might in fact be associated with higher risk of pneumonia (8–10). Moreover, in patients with DM complicated with sepsis and pneumonia, metformin use was associated higher sepsis severity (11). This suggests that glucose lowering per se may not address the excess risk of pneumonia in patients with diabetes.

In recent years, sodium-glucose cotransporter 2 inhibitors (SGLT2is) have emerged as anti-DM drugs with key cardiorenal benefits beyond glucose lowering (12–16). SGLT2is exert pleiotropic and anti-inflammatory effects (17)—both with

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plausible benefits in patients with pneumonia. Findings from individual cardiovascular outcome trials on SGLT2is reporting pneumonia or septic shock as secondary outcomes are inconsistent (12, 18). Compared with placebo, the incidence of pneumonia appeared to be lower with empagliflozin and higher with ertugliflozin in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose (EMPA-REG OUTCOME) (12) and Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS-CV) (19) trials, respectively. Preliminary findings from "off-label" SGLT2i usage in subjects infected with severe or critical severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia suggest benefits in subjects with diabetes (20), and no effects in subjects without diabetes (21). These may be attributed to the more pronounced anti-inflammatory effects in the context of hyperglycemia, where inflammation is more severe (evidenced by the higher levels of interleukin-6, C-reactive protein, and erythrocyte sedimentation rate) than in the normoglycemic state (22–24). We performed a systematic review and meta-analysis of randomized controlled trials to comprehensively evaluate whether SGLT2is reduce the risk of pneumonia and septic shock in patients with DM.

Materials and Methods

This systematic review and meta-analysis were conducted according to the Cochrane Handbook (Version 5.1.0) (25) and the PRISMA statement (26) (Table S1) (27). This study has been registered on PROSPERO (CRD42021249264).

Data Sources and Searches

Ovid MEDLINE, Ovid EMBASE, and ClinicalTrials.gov were searched for eligible studies from inception through May 19, 2022. The search strategy is shown elsewhere (Table S2) (27). Review articles and expert consensus statements were also manually searched for eligible studies.

Study Selection

We included randomized controlled trials that compared SGLT2is with placebo in patients with DM and reported outcomes of interest, pneumonia, and/or septic shock. Trials that randomized patients to combination therapy (eg, SGLT2i plus metformin vs placebo). Sim. ilar to previous meta-analyses (28, 29), only trials that enrolled patients with type 2 diabetes mellitus were included, and trials that enrolled patients with type 1 diabetes were excluded. There were no restrictions on follow-up duration or the language of publication. Titles and abstracts were first screened to assess their potential eligibility, and final eligibility was determined by full-text examination.

Data Extraction and Quality Assessment

The following information was extracted using a prespecified data extraction form: bibliographic information (first author, year of publication), study information (trial name, ClinicalTrials.gov unique identifier, country, sample size, and number of participants in each arm), patient characteristics (age, proportion of male patients, baseline conditions, and comorbidities), treatment information (regimen, dose, duration), and outcome data (number of events for each outcome). If available, we also extracted the definitions of outcome (pneumonia and/or septic shock) used in each trial. As all outcomes of interest were binary, the 2*2 tables for each outcome were extracted, and the outcome data extracted from each study were displayed in the forest plots. When multiple arms of the same drug at different doses were included in a trial, the number of patients, and events were combined, irrespective of the dosage, as recommended in the Cochrane handbook (25) and published previously in other meta-analyses (30–34). When multiple studies of the same trial were found, the most updated publication/record was included.

To assess methodological quality, version 2 of the Cochrane Risk of Bias Assessment Tool was used (35). Bias was assessed from 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (36) was used to assess the certainty of the evidence.

Study selection, data extraction, and quality assessment were conducted by 2 independent authors (H.L.L., and Y.K.T.). Any disagreement was resolved by discussion until consensus was reached, or by consulting a third author (K.H.Y.).

Data Synthesis and Analysis

The placebo arm was defined as the control in all analyses. Estimates derived from intention-to-treat analysis were used (or from per-protocol analysis if intention-to-treat analysis was not available). Relative risks (RRs) and their 95% CI were pooled using a fixed-effects model with inverse-variance weighting. RR < 1 would favor SGLT2is over placebo. The number needed to treat was estimated by the reciprocal of the absolute risk reduction (which was computed by the product of [1 − RR] and the risk of developing the outcome of interest). Subgroup analyses were prespecified according to (1) the SGLT2i agents used (canagliflozin vs dapagliflozin vs empagliflozin vs other SGLT2is [sotagliflozin and ertugliflozin]), (2) baseline conditions (patients with DM only vs patients having concomitant comorbidities, including chronic kidney disease, heart failure, hypertension, and established cardiovascular disease), (3) presence of established atherosclerotic cardiovascular disease (ASCVD) at baseline, (4) mean baseline glycated hemoglobin (HbA1c) above or below median, (5) mean baseline fasting plasma glucose above or below median, (6) mean baseline duration of DM above or below median, (7) mean baseline estimated glomerular filtration rate (eGFR) above or below median, and (8) follow-up duration (<1 vs ≥1 year). We also performed subgroup analysis according to the dose of SGLT2is used. The median values for subgroup analyses 3 to 6 were defined as the median across all trials (31). Additional sensitivity analyses were performed by (1) performing the main analysis with the random-effects model, (2) excluding studies with a high/some concerns overall risk of bias, (3) excluding studies with a high/some concerns risk of bias in "missing outcome data" to account for possible selection bias (due to missing outcomes/individuals) and ascertainment bias (due to lack of prespecification and adjudication on outcomes), (4) by using odds ratio (OR) as the effect measure, (5) excluding studies which used a dual SGLT1/SGLT2 inhibitor (sotagliflozin), and (6) excluding studies not using the commonly used SGLT2is

(canagliflozin/dapagliflozin/empagliflozin). To avoid computational error resulting from studies with 0 events, in accordance to the Cochrane handbook (25), we performed additional sensitivity analyses: (7) excluding studies with 0 events in either arm and pooling results with Peto's method, and (8) excluding studies with zero events in both arms and pooling results with Peto's method. To confirm that the results were not driven by any single study, we performed a leave-one-out analysis, in which each study was iteratively removed and the findings were compared with the overall analysis. Statistical heterogeneity across studies was assessed by the Cochrane's Q test and the I^2 statistic (30). Meta-regression would be used to investigate potential sources of heterogeneity if there was a substantial heterogeneity ($P < .10$ or $I^2 > 50\%$). Funnel plots were used for assessment of publication bias, and Egger's test for asymmetry in funnel plot would only be performed if 10 or more studies were included (25). A trim-and-fill method was employed to adjust for potential bias identified from either visual asymmetry or Egger's test ($P < .10$) (25). The statistical significance level was defined at 0.05 unless otherwise specified. Data analyses were performed using the "*meta*" package in R (version 3.6.3).

Results

Among the 4568 citations identified by literature search, 26 trials with a total of 59 264 patients (34 659 on SGLT2i and 24 605 on placebo) were included (Fig. S1 and Table S3 (27)). The mean age was 63.0 years (range 52.0-68.5) and 36.2% were female (Table 1). Sixteen trials (n = 34 890) enrolled patients with only DM as an inclusion criteria (13, 14, 37–50). For trials which enrolled patients with DM with concomitant comorbidites: 2 trials (n = 15 274) enrolled patients with established cardiovascular disease (12, 19), 5 trials (n = 6131) enrolled patients with established chronic kidney disease (16, 51–54), 1 trial (n = 825) enrolled patients with hypertension (55), 1 trial (n = 922) enrolled patients with hypertension and established cardiovascular disease (18), and 1 trial (n = 1222) enrolled patients with established heart failure (56). Overall, the mean HbA1c was 8.2%, and the mean eGFR was 76.9 mL/min per 1.73 m^2. Twelve trials had a low risk of bias, 9 trials had a high risk of bias, and 7 trials had an unclear risk of bias (Supplementary Appendix Table S4) (27). None of the trials specified a definition for pneumonia or septic shock.

A total of 1126 events of pneumonia were reported out of 24 trials (n = 58 584) within the follow-up (median 1.0 years, range 0.2-4.2 years). There were 589 events of pneumonia among 34 205 patients randomized to SGLT2is and 537 events of pneumonia among 24 379 patients randomized to placebo (1.7% vs 2.2%) with RRs ranging from 0.31 to 3.01 among studies. An SGLT2i was associated with a 13% pooled risk reduction of pneumonia compared with placebo (RR 0.87, 95% CI 0.78-0.98) (Fig. 1). There was no significant intertrial heterogeneity ($P = .99$). No between-subgroup differences were identified in subgroup analysis according to the various SGLT2i agents used and baseline conditions (DM-only trials vs others; presence of ASCVD at baseline vs absence), ($P = .51$, $P = .60$, and $P = .80$, respectively, Table 2). Furthermore, there were no significant difference across trials with high/low mean eGFR (median 81.7 mL/minute per 1.73 m^2, $P = .80$) and short-/long-term follow-up (<1.0 vs ≥1.0 year, $P = .80$, Table 2). When trials were stratified according to mean baseline HbA1c, fasting plasma glucose, and duration of DM, there were no significant differences between subgroups ($P = .68$, $P = .39$, and $P = .62$, respectively). The risk reduction in pneumonia was numerically greater with higher dose of SGLT2i (RR 0.86, 95% CI 0.66-1.13) than with a lower dose of SGLT2i (RR 0.97, 95% CI 0.75-1.26).

A total of 101 events of septic shock were reported out of 10 trials (n = 41 854). There were 44 events of septic shock among 23 198 patients randomized to SGLT2i and 57 events of septic shock among 18 656 patients randomized to placebo (0.2% vs 0.3%), with the RRs ranging from 0.17 to 3.01 across trials. An SGLT2i was associated with a 36% risk reduction in septic shock compared with placebo (RR 0.65, 95% CI 0.44-0.95) (Fig. 2). There was no significant intertrial heterogeneity ($P = .81$). Results were consistent in subgroup analysis according to the SGLT2i agents used, baseline conditions, presence of ASCVD at baseline, eGFR status, baseline HbA1c, baseline fasting plasma glucose, duration of DM, and follow-up duration ($P_{heterogenity} > .10$ for all, Table 3). The risk reduction in septic shock was numerically lower with higher dose of SGLT2i (RR 0.58, 95% CI 0.24-1.41) than with lower dose of SGLT2i (RR 0.47, 95% CI 0.19-1.17), but with very wide CI due to low number of events.

Sensitivity analyses excluding studies with (1) high/unclear overall risk of bias, (2) incomplete outcome data, (3) OR as an effect measure, (4) dual SGLT1/2 inhibitors, and (5) SGLT2i other than canagliflozin/dapagliflozin/empagliflozin yielded similar results (Table S5 (27)). Symmetry was observed in the funnel plots for pneumonia but not for septic shock (Fig. S2 (27)). Egger's test for pneumonia ($P = .1441$) and septic shock ($P = .7545$) did not reveal significant asymmetry. Sensitivity analysis excluding studies with 0 events in either/both arms with Peto's method also yielded similar results (Table S5 (27)). In leave-one-out analysis, the pooled estimate remained stable, despite the association was attenuated (Fig. S3 (27)). The certainty of evidence for both outcomes was high (using GRADE) (Table S6 (27)). All the results were essentially unchanged if the random-effects model (instead of the fixed-effects model) was used (Table S5 (27)).

Discussion

To the best of our knowledge, this meta-analysis is the first to identify a significant risk reduction of pneumonia and septic shock with the use of SGLT2is in patients with DM. Results were consistent irrespective of the type of SGLT2i agent, degree of renal impairment, follow-up duration (short and long term), comorbidities, duration of DM, and extent of glycemic control.

Individuals with DM have an increased risk of pneumonia, which confers high mortality (2, 6). Glucose lowering with traditional therapies has not been proven useful to reduce the risk of pneumonia and septic shock in patients with DM. Conversely, recent population-based studies have found that the use of conventional anti-DM agents, including metformin (8), dipeptidyl peptidase-4 inhibitor (9), and combination therapy of metformin plus thiazolidinediones (10), might be associated with higher risk of pneumonia, despite associated with glucose lowering and risk reduction in cardiovascular disease (29, 57, 58). These observations suggest

Table 1. Baseline characteristics of eligible studies

Trial	ClinicalTrials.gov identifier	Age (years), mean	Male, n (%)	HbA1c (%), mean	Baseline condition	Mean eGFR (mL/min/ 1.73 m^2)	Drug	Dose(s) analyzed	Sample size (SGLT2i/ placebo)	Median follow-up duration (years)
Bode et al, 2013	NCT01106651	63.6	396 (55.5%)	7.7	DM	77.5	Canagliflozin	100 mg, 300 mg (once daily)	477/237	0.5
Bolinder et al, 2014	NCT00855166	60.7	100 (55.6%)	7.2	DM	84.3	Dapagliflozin	10 mg (once daily)	91/91	2.0
CANTATA-M, 2013	NCT01081834	55.4	258 (44.2%)	8.0	DM	87.1	Canagliflozin	100 mg, 300 mg (once daily)	392/192	1.0
CANTATA-MSU, 2013	NCT01106625	56.8	239 (51%)	8.1	DM	90.1	Canagliflozin	100 mg, 300 mg (once daily)	313/156	1.0
CANVAS Program, 2017	NCT01032629; NCT01989754	63.3	6509 (64.2%)	8.2	DM	76.5	Canagliflozin	100 mg, 300 mg (once daily)	5795/4347	2.4
Cefalu et al, 2015	NCT01031680	62.9	624 (68.3%)	8.1	DM + CVD + HTN	NA	Dapagliflozin	10 mg (once daily)	460/462	1.0
CREDENCE, 2019	NCT02065791	63.0	2907 (66.1%)	8.3	DM + CKD	56.2	Canagliflozin	100 mg (once daily)	2202/2199	2.6
DECLARE-TIMI 58, 2019	NCT01730534	63.9	10 738 (62.6%)	8.3	DM	85.3	Dapagliflozin	10 mg (once daily)	8582/8578	4.2
EMPA-REG EXTEND METSU, 2015	NCT01289990	57.1	339 (50.9%)	8.1	DM	87.2	Empagliflozin	10 mg, 25 mg (once daily)	441/225	1.5
EMPA-REG OUTCOME, 2015	NCT01131676	63.1	5016 (71.5%)	8.1	DM + CVD	74	Empagliflozin	10 mg, 25 mg (once daily)	4691/2337	3.1
EMPA-REG RENAL, 2014	NCT01164501	63.9	430 (58.3%)	8.0	DM + CKD	53.2	Empagliflozin	10 mg, 25 mg (once daily)	420/321	1.0
Ferrannini et al, 2010	NCT00528372	52.0	276 (49.5%)	8.3	DM	NA	Dapagliflozin	2.5 mg, 5 mg, 10 mg (once daily)	484/75	0.5
Jabbour et al, 2014	NCT00984867	54.9	245 (54.8%)	7.9	DM	NA	Dapagliflozin	10 mg (once daily)	225/226	0.9
Ji et al, 2015	NCT01381900	56.3	362 (53.6%)	8.0	DM	94	Canagliflozin	100 mg, 300 mg (once daily)	450/226	0.3
Kohan et al, 2014	NCT00663260	67.0	164 (65.1%)	8.3	DM + CKD	44.6	Dapagliflozin	5 mg, 10 mg (once daily)	168/84	2.0
Rosenstock et al, 2012	NCT00683878	53.5	208 (49.5%)	8.4	DM	NA	Dapagliflozin	5 mg, 10 mg (once daily)	281/139	0.9
Rosenstock et al, 2015	NCT01011868	58.8	276 (55.9%)	8.2	DM	84	Empagliflozin	10 mg, 25 mg (once daily)	324/170	1.5
SOLOIST-WHF, 2020	NCT03521934	70.0[a]	810 (66.3%)	7.2	DM + HF	49.7[a]	Sotagliflozin	200 mg (once daily)	608/614	0.8
Strojek et al, 2011	NCT00680745	59.8	285 (48.1%)	8.1	DM	81.7	Dapagliflozin	2.5 mg, 5 mg, 10 mg (once daily)	450/146	0.9
Tikkanen et al, 2015	NCT01370005	60.2	495 (60.1%)	7.9	DM + HTN	84	Empagliflozin	10 mg, 25 mg (once daily)	553/272	0.2
VERTIS Asia, 2019	NCT02630706	56.5	281 (55.5%)	8.1	DM	99.3	Ertugliflozin	5 mg, 15 mg (once daily)	339/167	0.5
VERTIS-CV, 2020	NCT01986881	64.4	5769 (70.0%)	8.3	DM + CVD	76	Ertugliflozin	5 mg, 15 mg (once daily)	5499/2747	3.0
VERTIS-RENAL, 2018	NCT01986855	67.3	231 (49.5%)	8.2	DM + CKD	46.6	Ertugliflozin	5 mg, 15 mg (once daily)	314/154	1.0
VERTIS-SITA2, 2018	NCT02036515	59.1	263 (56.9%)	8.0	DM	87.9	Ertugliflozin	5 mg, 15 mg (once daily)	311/153	1.0
Wilding et al, 2012	NCT00673231	59.3	382 (47.8%)	8.5	DM	78.4	Dapagliflozin	2.5 mg, 5 mg, 10 mg (once daily)	610/197	0.9
Yale et al, 2014	NCT01064414	68.5	163 (60.6%)	8.0	DM + CKD	39.4	Canagliflozin	100 mg, 300 mg (once daily)	179/90	1.0

Abbreviations: CVD, cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus type 2; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; HTN, hypertension; SGLT2i, sodium-glucose cotransporter 2 inhibitor.
[a]Median

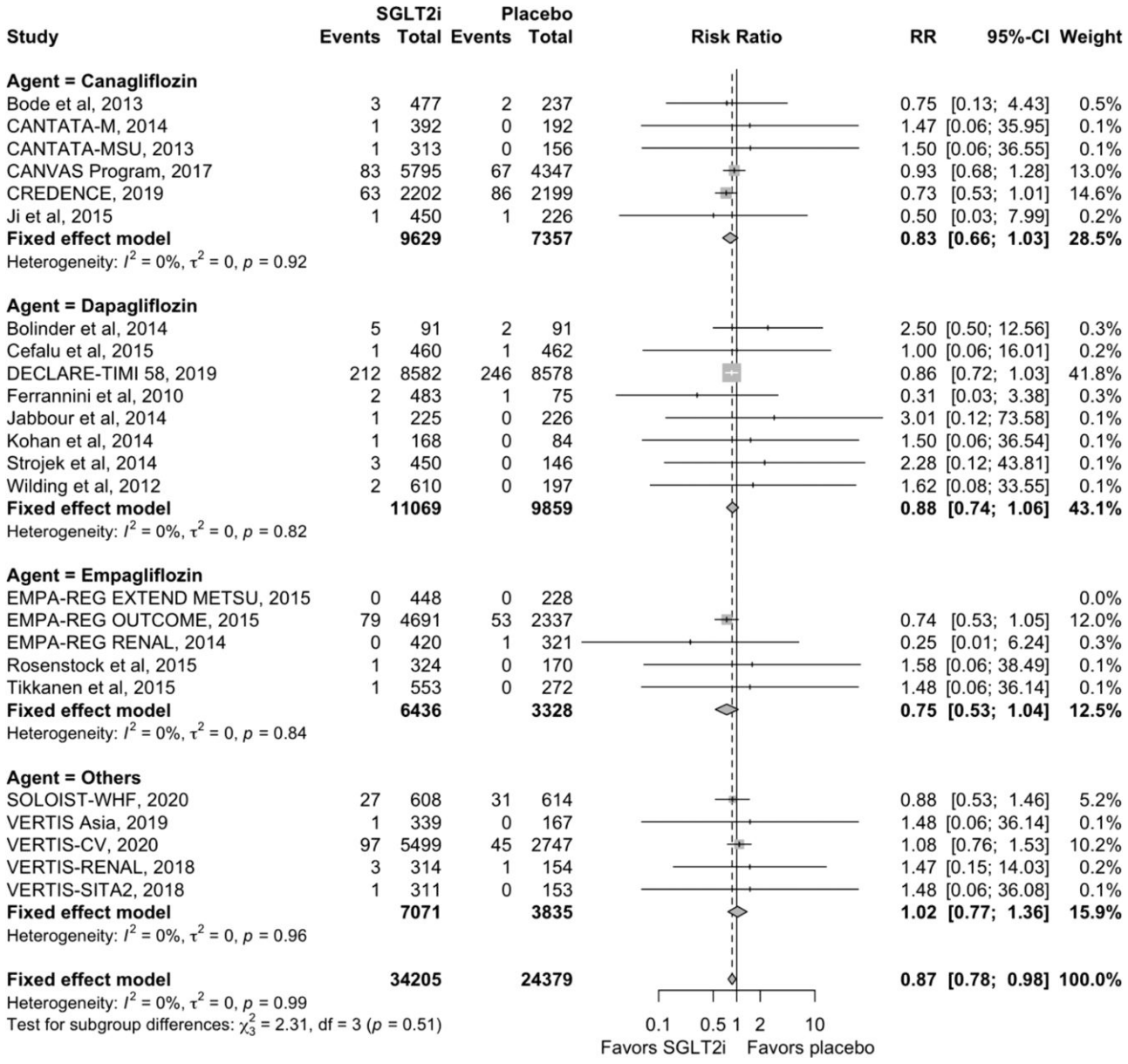

Figure 1. Forest plot of primary analysis for pneumonia.

that glucose lowering per se might not be sufficient in reducing risk of infection. SGLT2i have demonstrated anti-inflammatory properties and cardiorenal benefit beyond glucose lowering, which could collectively play an instrumental role in reducing systemic inflammatory response and infections (17). Suggestive evidence from some, but not all, SGLT2i trials have raised the possibility that these medications may lower the risk of pneumonia. Taken together, the present meta-analysis provides compelling evidence supporting the association of SGLT2i usage with reduced risk of pneumonia and septic shock in patients with DM. Our findings are consistent with the EMPA-REG OUTCOME trial, wherein lower incidence of pneumonia was reported with empagliflozin (12).

The reported incidence of pneumonia in patients with DM is 34 per 1000 person-years (2), much higher than that in documented trials: DECLARE-TIMI 58 (6.4 per 1000 person-year) (14) and EMPA-REG OUTCOME (6.1 per 1000 person-year) (12). This could be attributed to the inclusion of younger and healthier patients, with fewer comorbidities and relatively lower risk of infection, in trials. In computing the absolute effect using a baseline incidence of 34 per 1000 person-years (2) and the relative effect (RR = 0.87), the number needed to treat was estimated at 23 over 10 years. Furthermore, our present meta-analysis showed that SGLT2is conferred a 36% relative risk reduction in septic shock. These estimates may be even larger when comparing SGLT2is with other oral hypoglycemic agents that are associated with increased risk of pneumonia in patients with DM.

Mechanistic understanding of how SGLT2i may reduce the risk of pneumonia and septic shock is incomplete. Possibilities include effective cardiac and renal protection, and anti-inflammatory effects, all of which are directly/indirectly instrumental in reducing the risk of pneumonia (1, 14, 16, 59, 60). Recent studies have shown that SGLT2is reduced inflammatory cytokines levels, including interleukin-6, matrix

Table 2. Results of subgroup analysis for pneumonia

Subgroup		Number of trials	Number of participants	RR (95% CI)	P_{hetero}
Overall		24	58 584	0.87 (0.78-0.98)	
Agent	Canagliflozin	6	16 986	0.83 (0.66-1.03)	.51
	Dapagliflozin	8	20 928	0.88 (0.73-1.06)	
	Empagliflozin	5	9764	0.75 (0.53-1.04)	
	Others[a]	5	10 906	1.02 (0.77-1.36)	
Baseline condition	DM only	16	34 479	0.90 (0.77-1.04)	.60
	Others	9	24 105	0.84 (0.70-1.01)	
Presence of ASCVD at baseline	Yes	3	16 196	0.90 (0.70-1.14)	.80
	No	21	42 388	0.86 (0.76-0.99)	
Mean HbA1c	<median[b]	12	14 032	0.83 (0.64-1.08)	.68
	≥median[b]	12	44 552	0.88 (0.77-1.00)	
Mean FPG	<median[c]	10	12 153	0.80 (0.58-1.09)	.39
	≥median[c]	10	15 402	0.97 (0.72-1.31)	
Mean duration of DM	<median[d]	11	12 823	0.81 (0.59-1.11)	.62
	≥median[d]	11	44 045	0.88 (0.77-1.00)	
Mean eGFR	<median[e]	10	34 021	0.86 (0.73-1.01)	.80
	≥median[e]	11	22 632	0.89 (0.74-1.06)	
Follow-up duration	<1.0 year	9	6355	0.92 (0.57-1.43)	.80
	≥1.0 year	15	52 229	0.87 (0.77-0.98)	

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; P_{hetero}, *P*-value for between-subgroup heterogeneity; RR, risk ratio.
[a]Other SGLT2i, sotagliflozin and ertugliflozin.
[b]Median HbA1c, 8.105%.
[c]Median FPG, 159.75 mg/dL.
[d]Median duration of DM, 8.75 years.
[e]Median eGFR, 81.7 mL/min per 1.73m^2.

metalloproteinase 7, and high-sensitivity C-reactive protein in patients with DM (61–63), and hence may deter the progress of focal infections to septic shock. Similarly, experimental findings from mice with lipopolysaccharide-induced inflammation have shown lower mortality, less renal injury, and lower levels of inflammatory cytokines (including tumor necrosis factor-α, interferon-γ, and I interleukin-1β) when treated with empagliflozin than controls (64). Furthermore, SGLT2i increase hematocrit and hemoglobin, which may improve oxygen delivery to the tissues—an effect that may be particularly important in the setting of sepsis (65, 66). SGLT2is also improve endogenous endothelial repair independent of its glucose-lowering effect (67), which is particularly relevant in sepsis as widespread endothelial dysfunction is the key driver of sepsis-related death (68).

Although the antidiabetic regimen used in the non-SGLT2i arms were not completely defined, most placebo-controlled trials are designed such that the antidiabetic agents (aside from SGLT2is) were balanced between both arms. For instance, in the DECLARE-TIMI 58 trial (14), 81.8% and 82.2% of patients received metformin at baseline in the SGLT2i arm and placebo arm, respectively. Thus, the differences in antidiabetic agents (aside from SGLT2is) can be considered levelled out between both arms in the trials included in the present study. By pooling the effects of SGLT2is across these trials, we were able to evaluate the potential effects of SGLT2is on risk of pneumonia/septic shock. This approach has been adopted in previous meta-analyses to minimize bias (29, 30).

Clinical Implications

In the pharmacological management for patients with type 2 diabetes, current guidelines recommend that metformin should be used as the first-line therapy (69). However, metformin has recently been shown to be associated with a higher risk of pneumonia (8), and the present meta-analysis provides novel evidence supporting the use of SGLT2is in DM to reduce the risk of pneumonia and septic shock; in addition to existing indications such as patients with established ASCVD, kidney disease, or heart failure; as well as those with HbA1c above individualized target or a compelling need to minimize hypoglycemia or weight gain (69). Clinical caution has been advised among patients with severe illness, where precipitation of diabetic ketoacidosis with SGLT2i remains a concern. Yet SGLT2is have a well-established safety profile, having been studied in tens of thousands of patients in clinical trials (including hospitalized patients), and having been prescribed to millions around the world since their approval.

Findings from the current analyses warrant validation in prospective future studies which accounts for race-, region-, and sex-specific differences (70, 71). Utilization of appropriate HbA1c cut-offs for Asians with predisposition towards lean diabetes (wherein diabetes is present despite a low body mass index) (72, 73) is warranted. On the other hand, a study on infection-related hospitalization in the emergency department has shown that approximately 30% to 40% of cases with sepsis were due to respiratory tract infection (particularly pneumonia) (74), but the lack of information on the source of infection precludes any inferences on the independent effects

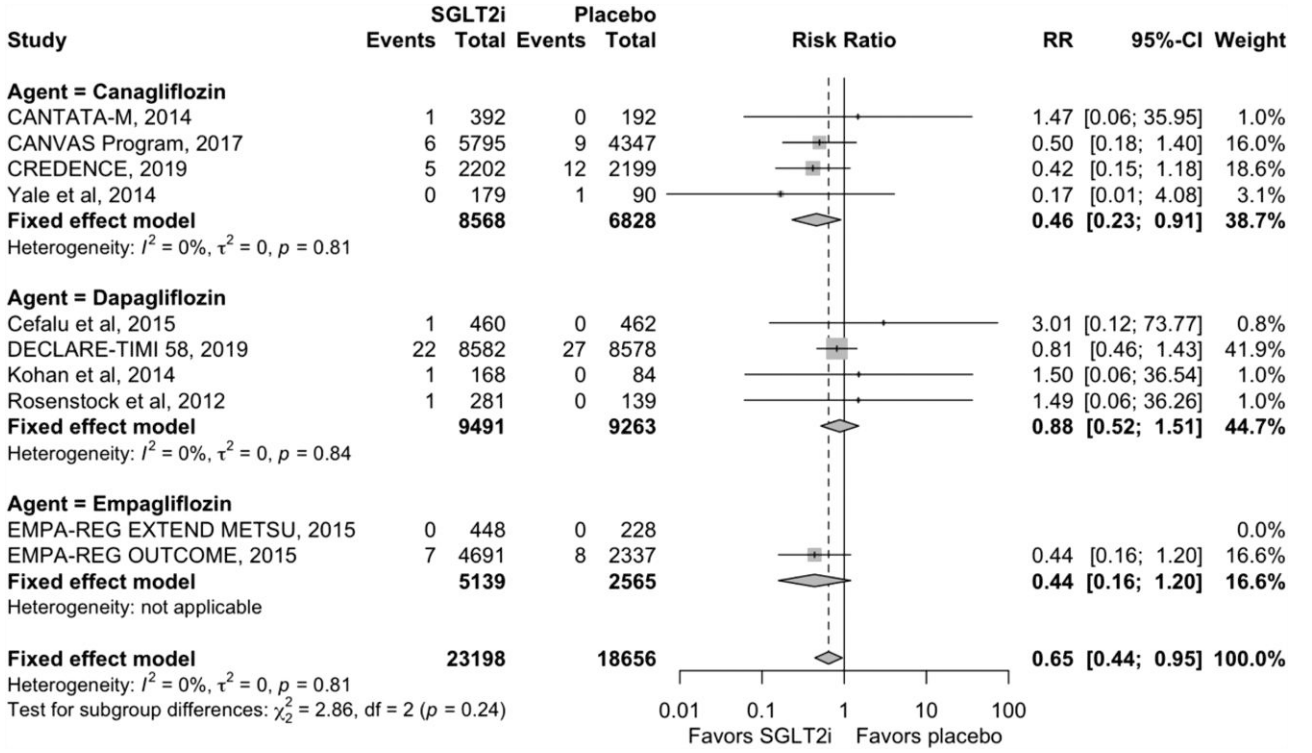

Figure 2. Forest plot of primary analysis for septic shock.

of SGLT2is in reducing these risks, which require evaluation in future studies.

The lower risks of pneumonia and sepsis associated with SGLT2i may be particularly noteworthy in the current COVID-19 pandemic. A retrospective analysis in Singapore has suggested that prior SGLT2i usage in patients infected with SARS-CoV-2 pneumonia was associated with lower risk of mechanical ventilation compared with non-use (20).

Table 3. Results of subgroup analysis for septic shock

Subgroup		Number of trials	Number of participants	RR (95% CI)	P_{hetero}
Overall		10	41 854	0.65 (0.44-0.95)	
Agent	Canagliflozin	4	15 396	0.46 (0.23-0.91)	.24
	Dapagliflozin	4	18 754	0.88 (0.52-1.51)	
	Empagliflozin	2	7704	0.44 (0.16-1.20)	
Baseline condition	DM only	6	36 010	0.69 (0.45-1.05)	.56
	Others	4	5844	0.52 (0.22-1.21)	
Presence of ASCVD at baseline	Yes	2	7950	0.55 (0.22-1.39)	.72
	No	8	33 904	0.67 (0.44-1.01)	
Mean HbA1c	<median[a]	5	9479	0.54 (0.23-1.25)	.65
	≥median[a]	5	32 375	0.67 (0.44-1.04)	
Mean FPG	<median[b]	4	8878	0.60 (0.25-1.46)	.88
	≥median[b]	4	11 415	0.55 (0.23-1.31)	
Mean duration of DM	<median[c]	5	25 868	0.73 (0.46-1.18)	.38
	≥median[c]	5	15 986	0.51 (0.26-0.98)	
Mean eGFR	<median[d]	4	11 950	0.43 (0.22-0.86)	.21
	≥ median[d]	5	28 562	0.74 (0.46-1.20)	
Follow-up duration	<1.0 year	1	420	1.49 (0.06-36.33)	.60
	≥1.0 year	9	41 434	0.64 (0.43-0.94)	

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; P_{hetero}, *P*-value for between-subgroup heterogeneity; RR, risk ratio.
[a]Median HbA1c, 8.165%.
[b]Median FPG, 161.65 mg/dL.
[c]Median duration of DM, 11.45 years.
[d]Median eGFR, 75.25 mL/min per 1.73 m^2.

The dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19) trial has shown dapagliflozin treatment results in a numerically lower rate of organ failure or death (hazard ratio [HR] 0.80, 95% CI 0.58-1.10, $P = .17$) (75). Although the statistically nonsignificant association highlights the need for further studies to confirm the association between SGLT2is and lower risks of critical illness including sepsis (75), our current study provides timely evidence supporting such hypothesis. Furthermore, the HR of 0.80 in DARE-19 was consistent with a recently published nation-wide observational study in England (76), which showed a lower risk of COVID-19-related death with the use of SGLT2is (adjusted HR 0.82, 95% CI 0.74-0.91). Taken together, the above evidence consistently suggests the biological plausibility of SGLT2i in reducing the risk of adverse outcomes, warranting further and larger trials evaluating the benefits of SGLT2i in patients with COVID-19.

Limitations

There are several limitations in this meta-analysis. First, as pneumonia and septic shock were not the prespecified outcomes of the trials included, reporting and ascertainment bias is inevitable and the definitions of these outcomes might vary across trials. We have addressed the lack of centrally adjudicated outcomes by excluding studies with high or unclear overall risk of bias and incomplete outcome data from sensitivity analyses. Nevertheless, future studies with pneumonia/septic shock as prespecified and adjudicated outcomes are required to confirm the findings in the current study. Lack of patient-level data only allowed subgroup analyses at a trial-level. While this study suggests an association between SGLT2is, pneumonia, and septic shock, the nature of this temporal relationship is not explainable with the current data. Due to small sample sizes and low event rates, results and $P_{\text{heterogeneity}}$ should be interpreted with caution. Outcomes on pneumonia- and septic shock–related mortality were not available. Although the associations appeared to be driven by trials of large sample sizes and thus large weights, our leave-one-out analysis revealed consistent results. The risk of reporting bias could not be eliminated as a significant number of trials were excluded for not reporting the outcome of interest. Information on microbiological etiology for pneumonia/septic shock were not available.

Conclusions

The present meta-analysis demonstrated that among patients with DM, SGLT2i consistently reduced the risk of pneumonia and septic shock compared with placebo, and irrespective of the type of SLGT2i used, underlying comorbidities, extent of glycemic control, duration of DM and follow-up. Our hypothesis-generating findings merit confirmation in future studies.

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Author Contributions

H.L.L., C.C., S.V., C.S.P.L., K.H.Y. conceived and designed the study. H.L.L., Y.K.T. acquired the data for analysis. H.L.L., Y.K.T., C.C., N.W.L.H. equally contributed to the analysis and interpretation of data. H.L.L., Y.K.T. drafted the main text, figures and supplementary data. All the other authors equally contributed to revising the manuscript critically for important intellectual content.

Conflict of Interest

C.S.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Abbott, Actelion, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., EchoNous Inc, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd., Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder & non-executive director of Us2.ai. All other authors report no conflict of interest.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

Clinical Trials Information

PROSPERO registration ID: CRD42021249264.

References

1. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case–control study. *Diabetes Care*. 2008;31(8):1541-5.
2. Liu K, Lee GC. Healthcare utilisation and cost expenditures for pneumonia in individuals with diabetes mellitus in the USA. *Epidemiol Infect*. 2019;147:e212.
3. Yang JJ, Yu D, Wen W, Saito E, Rahman S, Shu XO, *et al*. Association of diabetes with all-cause and cause-specific mortality in Asia: a pooled analysis of more than 1 million participants. *JAMA Netw Open*. 2019;2(4):e192696.
4. Lepper PM, Ott S, Nüesch E, von Eynatten M, Schumann C, Pletz MW, *et al*. Serum glucose levels for predicting death in patients admitted to hospital for community acquired pneumonia: prospective cohort study. *BMJ*. 2012;344:e3397.
5. Yende S, van der Poll T, Lee M, Huang DT, Newman AB, Kong L, *et al*. The influence of pre-existing diabetes mellitus on the host immune response and outcome of pneumonia: analysis of two multicentre cohort studies. *Thorax*. 2010;65(10):870-7.
6. Falcone M, Tiseo G, Russo A, Giordo L, Manzini E, Bertazzoni G, *et al*. Hospitalization for pneumonia is associated with decreased 1-year survival in patients with type 2 diabetes: results from a prospective cohort study. *Medicine (Baltimore)*. 2016;95(5):e2531.
7. Garcia-Vidal C, Ardanuy C, Tubau F, Viasus D, Dorca J, Liñares J, *et al*. Pneumococcal pneumonia presenting with septic shock: host- and pathogen-related factors and outcomes. *Thorax*. 2010;65(1):77-81.
8. Yen FS, Wei JC, Yang YC, Hsu CC, Hwu CM. Respiratory outcomes of metformin use in patients with type 2 diabetes and chronic obstructive pulmonary disease. *Sci Rep*. 2020;10(1):10298.
9. Noguchi Y, Esaki H, Murayama A, Sugioka M, Koyama A, Tachi T, *et al*. Association between dipeptidyl peptidase-4 inhibitor and aspiration pneumonia: disproportionality analysis using the

spontaneous reporting system in Japan. *Eur J Clin Pharmacol*. 2020;76(2):299-304.
10. Gorricho J, Garjón J, Alonso A, Celaya MC, Saiz LC, Erviti J, *et al*. Use of oral antidiabetic agents and risk of community-acquired pneumonia: a nested case-control study. *Br J Clin Pharmacol*. 2017;83(9):2034-44.
11. Chen FC, Kung CT, Cheng HH, Cheng CY, Tsai TC, Hsiao SY, *et al*. Metformin affects serum lactate levels in predicting mortality of patients with sepsis and bacteremia. *J Clin Med*. 2019;8(3):318.
12. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-28.
13. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-57.
14. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-57.
15. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al*. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-24.
16. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-306.
17. Lam CSP, Chandramouli C, Ahooja V, Verma S. SGLT-2 inhibitors in heart failure: current management, unmet needs, and therapeutic prospects. *J Am Heart Assoc*. 2019;8(20):e013389.
18. Cefalu WT, Leiter LA, de Bruin TW, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin's effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. *Diabetes Care*. 2015;38(7):1218-27.
19. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, *et al*. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383(15):1425-35.
20. Dalan R, Ang LW, Tan WYT, Fong SW, Tay WC, Chan YH, *et al*. The association of hypertension and diabetes pharmacotherapy with COVID-19 severity and immune signatures: an observational study. *Eur Heart J Cardiovasc Pharmacother*. 2021;7(3):e48-e51.
21. Bossi AC, Forloni F, Colombelli PL. Lack of efficacy of SGLT2-i in severe pneumonia related to novel coronavirus (nCoV) infection: no little help from our friends. *Diabetes Ther*. 2020;11(7):1605-6.
22. Xie L, Xiao Y, Tai S, Yang H, Zhou S, Zhou Z. Emerging roles of sodium glucose cotransporter 2 (SGLT-2) inhibitors in diabetic cardiovascular diseases: focusing on immunity, inflammation and metabolism. *Front Pharmacol*. 2022;13:836849.
23. Debi H, Itu ZT, Amin MT, Hussain F, Hossain MS. Association of serum C-reactive protein (CRP) and D-dimer concentration on the severity of COVID-19 cases with or without diabetes: a systematic review and meta-analysis. *Expert Rev Endocrinol Metab*. 2022;17(1):83-93.
24. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, *et al*. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020;36(7):e3319.
25. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration. 2011.
26. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
27. Li HL, Tse YK, Chandramouli C, Hon NWL, Cheung CL, Lam LY, *et al*. Supplements for the manuscript titled "Sodium-glucose cotransporter 2 inhibitors and the risk of pneumonia and septic shock: A systematic review and meta-analysis" *figshare*. 2022 [updated June 03 2022]. Available from: https://doi.org/10.6084/m9.figshare.19966991.v4
28. Shi FH, Li H, Yue J, Jiang YH, Gu ZC, Ma J, *et al*. Clinical adverse events of high-dose vs low-dose sodium-glucose cotransporter 2 inhibitors in type 2 diabetes: a meta-analysis of 51 randomized clinical trials. *J Clin Endocrinol Metab*. 2020;105(11):dgaa586.
29. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia*. 2017;60(9):1620-9.
30. Li HL, Lip GYH, Feng Q, Fei Y, Tse YK, Wu MZ, *et al*. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and cardiac arrhythmias: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2021;20(1):100.
31. Li HL, Feng Q, Tsoi MF, Fei Y, Cheung BMY. Risk of infections in patients treated with ticagrelor vs. clopidogrel: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother*. 2021;7(3):171-9.
32. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, *et al*. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol*. 2021;6(2):148-58.
33. Neuen BL, Oshima M, Agarwal R, Arnott C, Cherney DZ, Edwards R, *et al*. Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. *Circulation*. 2022;145(19):1460-70.
34. Zou X, Shi Q, Vandvik PO, Guyatt G, Lang CC, Parpia S, *et al*. Sodium-glucose cotransporter-2 inhibitors in patients with heart failure: a systematic review and meta-analysis. *Ann Intern Med*. 2022;175(6):851-861.
35. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
36. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al*. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-6.
37. Bode B, Stenlöf K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract (1995)*. 2013;41(2):72-84.
38. Bolinder J, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, *et al*. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab*. 2014;16(2):159-69.
39. Stenlöf K, Cefalu WT, Kim KA, Jodar E, Alba M, Edwards R, *et al*. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. *Curr Med Res Opin*. 2014;30(2):163-75.
40. Wilding JP, Charpentier G, Hollander P, González-Gálvez G, Mathieu C, Vercruysse F, *et al*. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. *Int J Clin Pract*. 2013;67(12):1267-82.
41. Haering HU, Merker L, Christiansen AV, Roux F, Salsali A, Kim G, *et al*. Empagliflozin as add-on to metformin plus sulphonylurea in patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2015;110(1):82-90.
42. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care*. 2010;33(10):2217-24.
43. Jabbour SA, Hardy E, Sugg J, Parikh S. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2014;37(3):740-50.
44. Ji L, Han P, Liu Y, Yang G, Dieu Van NK, Vijapurkar U, *et al*. Canagliflozin in Asian patients with type 2 diabetes on metformin alone or metformin in combination with sulphonylurea. *Diabetes Obes Metab*. 2015;17(1):23-31.
45. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and

hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. *Diabetes Care*. 2012;35(7):1473-8.
46. Rosenstock J, Jelaska A, Zeller C, Kim G, Broedl UC, Woerle HJ. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2015;17(10):936-48.
47. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2011;13(10):928-38.
48. Ji L, Liu Y, Miao H, Xie Y, Yang M, Wang W, *et al.* Safety and efficacy of ertugliflozin in Asian patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: VERTIS Asia. *Diabetes Obes Metab*. 2019;21(6):1474-82.
49. Dagogo-Jack S, Liu J, Eldor R, Amorin G, Johnson J, Hille D, *et al.* Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: the VERTIS SITA2 placebo-controlled randomized study. *Diabetes Obes Metab*. 2018;20(3):530-40.
50. Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, *et al.* Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med*. 2012;156(6):405-15.
51. Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, *et al.* Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab*. 2013;15(5):463-73.
52. Grunberger G, Camp S, Johnson J, Huyck S, Terra SG, Mancuso JP, *et al.* Ertugliflozin in patients with stage 3 chronic kidney disease and type 2 diabetes mellitus: the VERTIS RENAL randomized study. *Diabetes Ther*. 2018;9(1):49-66.
53. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int*. 2014;85(4):962-71.
54. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, *et al.* Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2014;2(5):369-84.
55. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, *et al.* Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care*. 2015;38(3):420-8.
56. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, *et al.* Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384(2):117-128.
57. Luo S, Schooling CM, Wong ICK, Au Yeung SL. Evaluating the impact of AMPK activation, a target of metformin, on risk of cardiovascular diseases and cancer in the UK Biobank: a Mendelian randomisation study. *Diabetologia*. 2020;63(11):2349-58.
58. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al.* Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008.
59. McDonald HI, Thomas SL, Millett ER, Nitsch D. CKD and the risk of acute, community-acquired infections among older people with diabetes mellitus: a retrospective cohort study using electronic health records. *Am J Kidney Dis*. 2015;66(1):60-8.
60. Klare B, Kubini R, Ewig S. Risk factors for pneumonia in patients with cardiovascular diseases. *Pneumologie*. 2002;56(12):781-8.
61. Iannantuoni F, MdM A, Diaz-Morales N, Falcon R, Bañuls C, Abad-Jimenez Z, *et al.* The SGLT2 inhibitor empagliflozin ameliorates the inflammatory profile in type 2 diabetic patients and promotes an antioxidant response in leukocytes. *J Clin Med*. 2019;8(11):1814.
62. Heerspink HJL, Perco P, Mulder S, Leierer J, Hansen MK, Heinzel A, *et al.* Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. *Diabetologia*. 2019;62(7):1154-66.
63. Soni S, Dyck JRB. The multiple effects of SGLT2 inhibitors suggest potential benefit in COVID-19 patients. *Can J Cardiol*. 2020;36-(10):1691.e3.
64. Maayah ZH, Ferdaoussi M, Takahara S, Soni S, Dyck JRB. Empagliflozin suppresses inflammation and protects against acute septic renal injury. *Inflammopharmacology*. 2020;29(1):269-279.
65. Sano M, Goto S. Possible mechanism of hematocrit elevation by sodium glucose cotransporter 2 inhibitors and associated beneficial renal and cardiovascular effects. *Circulation*. 2019;139(17):1985-7.
66. Aberle J, Menzen M, Schmid SM, Terkamp C, Jaeckel E, Rohwedder K, *et al.* Dapagliflozin effects on haematocrit, red blood cell count and reticulocytes in insulin-treated patients with type 2 diabetes. *Sci Rep*. 2020;10(1):22396.
67. Hess DA, Terenzi DC, Verma S. Heal thyself: SGLT2 inhibition limits regenerative cell exhaustion and heals damaged vessels. *Diabetes*. 2021;70(8):1620-1622.
68. Crouser ED, Matthay MA. Endothelial damage during septic shock: significance and implications for future therapies. *Chest*. 2017;152(1):1-3.
69. American Diabetes Association. Standards of medical care in diabetes-2020 abridged for primary care providers. *Clin Diabetes*. 2020;38(1):10-38.
70. Herman WH. Are there clinical implications of racial differences in HbA1c? Yes, to not consider can do great harm! *Diabetes Care*. 2016;39(8):1458-61.
71. Huang SH, Huang PJ, Li JY, Su YD, Lu CC, Shih CL. Hemoglobin A1c levels associated with age and gender in Taiwanese adults without prior diagnosis with diabetes. *Int J Environ Res Public Health*. 2021;18(7):3390.
72. Chandramouli C, Tay WT, Bamadhaj NS, Tromp J, Teng TK, Yap JJL, *et al.* Association of obesity with heart failure outcomes in 11 Asian regions: a cohort study. *PLoS Med*. 2019;16(9):e1002916.
73. Tromp J, Tay WT, Ouwerkerk W, Teng TK, Yap J, MacDonald MR, *et al.* Multimorbidity in patients with heart failure from 11 Asian regions: a prospective cohort study using the ASIAN-HF registry. *PLoS Med*. 2018;15(3):e1002541.
74. Mayr FB, Yende S, Linde-Zwirble WT, Peck-Palmer OM, Barnato AE, Weissfeld LA, *et al.* Infection rate and acute organ dysfunction risk as explanations for racial differences in severe sepsis. *JAMA*. 2010;303(24):2495-503.
75. Kosiborod MN, Esterline R, Furtado RHM, Oscarsson J, Gasparyan SB, Koch GG, *et al.* Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol*. 2021;9(9):586-594.
76. Khunti K, Knighton P, Zaccardi F, Bakhai C, Barron E, Holman N, *et al.* Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. *Lancet Diabetes Endocrinol*. 2021;9(5):293-303.