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SHORT COMMUNICATION

Sodium-glucose cotransporter inhibitors may reduce the risk of pneumonia: an updated meta-analysis of cardiovascular outcome trials

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Abstract
The present meta-analysis included 8 cardiovascular outcome trials with 57,185 patients at high cardiometabolic risk. In comparison with placebo, treatment with sodium-glucose cotransporter inhibitors was associated with a significantly lower risk of pneumonia (RR 0.85, 95% CI 0.76–0.95, $p = 0.004$; $I^2 = 0$, $p = 0.48$).

Keywords Cardiovascular · Sodium-glucose cotransporter inhibitor · Canagliflozin · Dapagliflozin · Empagliflozin · Ertugliflozin · Sotagliflozin

Introduction

Sodium-glucose cotransporter inhibitors (SGLTi) have been associated with impressive cardio-nephro-metabolic benefits in patients with and without diabetes [1]. Although they have been linked with increased incidence of lower genital tract infections, a meta-analysis has recently demonstrated a possible protective effect against incident pneumonia [2]. The latter might be of great interest during the current pandemic of coronavirus disease 2019 (COVID-19). In this context, we performed an updated meta-analysis of cardiovascular outcome trials (CVOTs) investigating the association of SGLTi with the risk of incident pneumonia.

Methods

The present meta-analysis was based on PRISMA guidelines. Double-blind placebo controlled randomized trials (RCTs) were included in the present meta-analysis if they: (a) represented CVOTs, (b) compared any SGLTi with placebo and (c) included pneumonia in their reported adverse events. Adverse events reported as 'pneumonia' were the outcome of interest. Relevant trials were identified by searching MEDLINE, EMBASE and CENTRAL databases up to 07 Mar 2021 using the following terms: 'cardiovascular', 'sodium-glucose cotransporter inhibitor', 'canagliflozin', 'dapagliflozin', 'empagliflozin', 'ertugliflozin' and 'sotagliflozin'. Two review authors (FB and GA) independently extracted data using a pre-designed data extraction form that contained publication details, study population, randomization, allocation concealment, details of blinding measures, description of interventions and results. Any differences between them were resolved by consulting the other review authors (HM, EL). Bias risk assessment was based on the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). We estimated treatment effect using risk ratio (RR) and 95% confidence intervals (CI). Analyses were performed with Revman 5.1. RCTs not reporting the outcome of interest have not been included in this analysis. Heterogeneity between trial results was tested using a standard chi-squared test; $p < 0.1$ was considered statistically significant. I^2 statistic was used as a measure of heterogeneity. In case of significant heterogeneity ($I^2 \geq 50\%$), a random-effects model was used.

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Table 1 Characteristics of the trials included in the meta-analysis

	EMPA-REG	CANVAS	DECLARE-TIMI 58	CREDENCE	VERTIS-CV
National clinical trial number	NCT01131676	NCT01032629 NCT01989754	NCT01730534	NCT02065791	NCT01986881
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
Study participants	7020	10,142	17,160	4401	8246
Duration, years	3.1	3.6	4.2	2.62	3.5
Outcome of interest	Primary endpoint: cardiovascular death, myocardial infarction, stroke	Primary endpoint: cardiovascular death, myocardial infarction, stroke	Primary endpoint: cardiovascular death, myocardial infarction, stroke	Secondary endpoint: cardiovascular death, myocardial infarction, or stroke	Primary endpoint: cardiovascular death, myocardial infarction, or stroke
Patients' characteristics					
Age, years	63.2 ± 8.8	63.2 ± 8.3	63.9 ± 6.8	63 ± 9.2	64.4 ± 8.1
Gender (male), %	72.0	64.9	62.6	66.1	69.9
Diabetes duration, years	N/A	13.5 ± 7.7	11 (6–16)	15.8 ± 8.6	13 ± 8.3
Baseline glycated hemoglobin, %	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2	8.3 ± 1.3	8.2 ± 1.1
Baseline body mass index, kg/m^2	30.7 ± 5.2	31.9 ± 5.9	32.1 ± 6.0	31.3 ± 6.2	31.9 ± 5.4
Systolic blood pressure, mmHg	136 ± 17	136 ± 16	135 ± 15	140 ± 15.6	113 ± 14
Diastolic blood pressure, mmHg	77 ± 10	78 ± 10	85 ± 16	78 ± 9	77 ± 8
History of cardiovascular disease, %	99.0	72.2	40.6	50.4	100.0
Heart failure, %	10.5	14.4	10.0	29.4	23.7
Estimated glomerular filtration rate < 60 ml/min/1.73 m^2, %	25.9	20.1	7.4	59.8	21.9
Diabetes, %	100	100	100	100	100

	SOLOIST	DAPA-HF	DAPA-CKD
National clinical trial number	NCT03521934	NCT03036124	NCT03036150
Drug	Sotagliflozin	Dapagliflozin	Dapagliflozin
Comparator	Placebo	Placebo	Placebo
Study participants	1222	4744	4304
Duration, years	0.8	1.5	2.4
Outcome of interest	Primary endpoint: cardiovascular death, hospitalization for heart failure, urgent heart failure visits	Primary endpoint: cardiovascular death, hospitalization for heart failure, urgent heart failure visits	Primary endpoint: a decline of at least 50% in the estimated GFR, onset of end-stage kidney disease
Patients' characteristics			
Age, years	70 (63–76)	66.2 ± 10.9	61.9 ± 12.1
Gender (male), %	66.2	76.6	66.9
Diabetes duration, years	N/A	N/A	N/A
Baseline glycated hemoglobin, %	7.2 (6.4–8.3)	N/A	N/A
Baseline body mass index, kg/m^2	31.1 (26.3–34.5)	28.2 ± 6.0	29.5 ± 6.2
Systolic blood pressure, mmHg	122 (111–135)	122 ± 16	137 ± 17
Diastolic blood pressure, mmHg	73 (66–80)	N/A	78 ± 11
History of cardiovascular disease, %	N/A	N/A	37.4

Table 1 (continued)

	SOLOIST	DAPA-HF	DAPA-CKD
Heart failure, %	100.0	100.0	10.9
Estimated glomerular filtration rate < 60 ml/min/1.73 m^2, %	69.8	40.6	90.0
Diabetes, %	100.0	45.0	67.5

Variables are expressed as mean ± standard deviation or median (interquartile range), unless percentages are shown

EMPA-REG (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients, *CANVAS* Canagliflozin Cardiovascular Assessment Study, *CREDENCE* Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, *DECLARE-TIMI* 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events, *N/A* not applicable, *VERTIS-CV* Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial, *SOLOIST-WHF* Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure, *DAPA-HF* Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure, *DAPA-CKD* A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease, *N/A* not applicable

Results

Our literature search identified eight eligible CVOTs (EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS, CREDENCE, VERTIS-CV, SOLOIST, DAPA-CKD, DAPA-HF; Supplementary Fig. 1) [3–10]. A total of 57,185 subjects (1222–17,160 in each trial) followed-up for 0.8–4.2 years were included. Of those, 93% were diagnosed with type 2 diabetes, 65% with atherosclerotic cardiovascular disease, 23% with heart failure and 32% with chronic kidney disease (Table 1). A total of 1316 cases of pneumonia were recorded during follow-up.

The pooled analysis showed that SGLTi were associated with a significantly reduced risk of pneumonia in comparison with placebo (RR 0.85, 95% CI 0.76–0.95, $p=0.004$; $I^2=0$, $p=0.48$) (Fig. 1). Low bias risk was noted within the included studies (Supplementary Fig. 2).

Discussion

The present meta-analysis shows that treatment with SGLTi is associated with a lower incidence of pneumonia in patients at high cardiometabolic risk compared with placebo.

A recent meta-analysis of 6 CVOTs with 47,728 participants assigned to treatment with either SGLT2i or placebo demonstrated that there was no difference in the risk of upper respiratory tract infection (RR 0.95, 95% CI 0.48–1.88, $I^2=0\%$), lower respiratory tract infection (RR 0.66, 95% CI 0.39–1.13, $I^2=0\%$), viral infection (RR 1.15, 95% CI 0.49–2.71, $I^2=0\%$) and influenza (RR 1.27, 95% CI 0.70–2.32, $I^2=0\%$) [2]. However, the pooled analysis of 5 RCTs ($n=43{,}430$) showed that SGLT2i were associated with decreased risk of pneumonia (RR 0.85, 95% CI 0.75–0.97, $I^2=0\%$) [2]. After incorporating the results of VERTIS-CV, DAPA-CKD and SOLOIST, our meta-analysis is the largest ($n=57{,}185$) and most updated to include all available CVOTs reporting on the risk of pneumonia as an adverse event.

Possible pathophysiological explanations that might account for the observed reduction in the risk of pneumonia include activation of M2 macrophages, inhibition of lipid raft formation, increased production of ketone bodies, prevention of cytosolic pH reduction and induced shift of energy metabolism towards an increased reliance on lipid oxidation [11–13]. The reasons for the differential association of SGLT2i with the risk of pneumonia versus upper or lower respiratory infection are unknown [2]. Considering the inflammatory pathways involved in the pathophysiology of pneumonia, the anti-inflammatory properties of SGLT2i may be more relevant [14]. Furthermore, pneumonia is a more objective endpoint since its diagnosis is established with imaging criteria.

Although almost all included studies were completed before the onset of the current pandemic, SGLTi treatment merits a role in the COVID-19 era [15]. A propensity-score-matched cohort study ($n=24{,}865$) showed no increased risk of COVID-19 amongst patients treated with SGLT2i compared with dipeptidyl-peptidase 4 inhibitors (adjusted hazard ratio: 0.92, 95% CI 0.66–1.29) [16]. Furthermore, background SGLTi treatment in hospitalized diabetic patients with COVID-19 ($n=2666$) has been associated with lower risk of in-hospital mortality (19.4 vs 39.1%, $p=0.003$) as compared with other glucose-lowering drugs [17]. A similar beneficial effect of SGLT2i on the mortality risk in patients with diabetes and COVID-19 (hazard ratio: 0.82, 95% CI 0.74–0.91) has been confirmed by a larger observational cohort ($n=2{,}851{,}465$).[18].

The fact that pneumonia was not the primary outcome of the included studies and was not adjudicated should be acknowledged as a limitation of the present meta-analysis. On the other hand, this is the largest and most updated one to evaluate the association of SGLTi treatment with the risk of pneumonia.

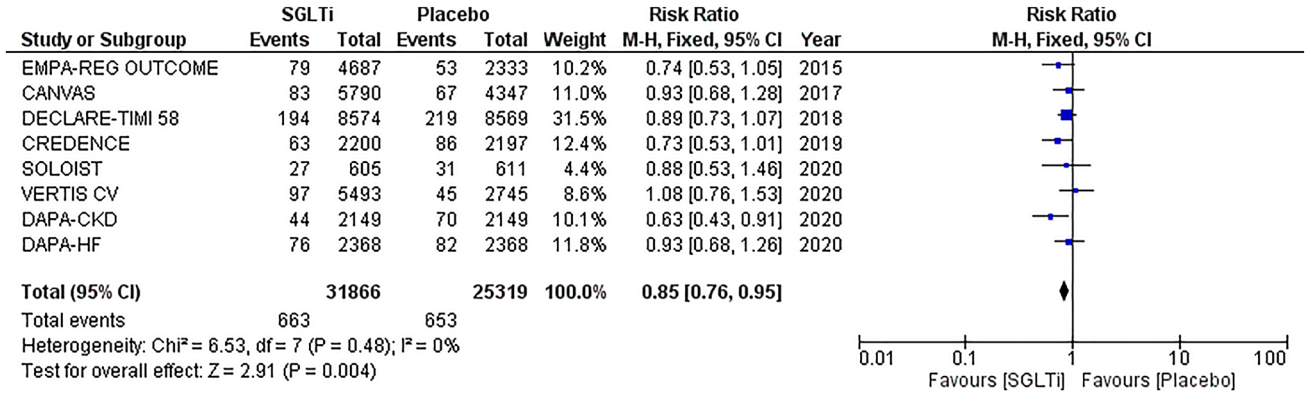

Fig. 1 Forest plot of pneumonia risk. SGLTi sodium-glucose cotransporter inhibitors, CI confidence interval

Conclusions

The present meta-analysis confirms that treatment with SGLTi is associated with a lower risk of pneumonia compared with placebo in patients at high cardiometabolic risk. In this context, ongoing RCTs (DARE-19 and TACTIC-E) will elucidate the efficacy and safety of SGLTi on the progression, complications and mortality associated with COVID-19 [11, 19]. Considering their cardiovascular benefit, SGLTi should not be interrupted during current pandemic. Nevertheless, they should be cautiously used in case of severe disease.[20].

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants The present work is a meta-analysis including already published results from RCTs.[3–10]

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