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Systematic review and meta-analysis: SGLT2 inhibitors, blood pressure and cardiovascular outcomes

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ABSTRACT

Objective: Clinical trials suggest that SGLT2 inhibitors reduce the risk of cardiovascular mortality in patients with type 2 diabetes, however the mechanism is unclear. Our objective was to test the hypothesis that blood pressure reduction is one potential mechanism underlying the observed improvements in cardiovascular outcomes with SGLT2 inhibitors.

Methods: We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (inception-June 2019) for randomized controlled trials that reported the effect of SGLT2 inhibitors compared with placebo on cardiovascular outcomes in adults with type 2 diabetes. Two reviewers independently extracted data and assessed study quality. Random effects meta-analyses, stratified meta-analyses and meta-regressions were conducted to evaluate the association between blood pressure reduction in SGLT2 inhibitor treated patients and cardiovascular outcomes.

Results: Of 11,232 articles identified, 40 articles (n = 54,279 participants) were included. The relative risk of cardiovascular mortality was reduced by 18% with the use of SGLT2 inhibitors compared with placebo (RR 0.82; 95%CI 0.74, 0.91, $I^2 = 0.0\%$). Meta-regression analysis revealed no detectable difference in cardiovascular mortality (RR 0.93; 95%CI 0.88, 1.13, p = 0.483), 3-point major adverse cardiovascular events (p = 0.839) or congestive heart failure hospitalizations (p = 0.844) with change in mean systolic blood pressure.

Conclusions: Cardiovascular events are reduced in participants with type 2 diabetes treated with SGLT2 inhibitors compared with placebo. There was no significant relationship between the risk of developing adverse cardiovascular events and blood pressure reduction with SGLT2 inhibitors. There is insufficient evidence to suggest that blood pressure reduction is a significant contributor to the cardiovascular benefits observed.

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1. Introduction

Large randomized controlled trials have demonstrated that sodium-glucose co-transporter-2 (SGLT2) inhibitors are effective in improving cardiovascular outcomes including cardiovascular mortality, stroke, and hospital admissions for congestive heart failure (CHF) in patients with type 2 diabetes and cardiovascular disease [1–4], or those at very high cardiovascular risk [1]. SGLT2 inhibitors also improve renal outcomes including progression to end-stage renal disease and renal-associated mortality in patients with type 2 diabetes [4]. Accordingly, clinical practice guidelines recommend SGLT2 inhibitorsas a second line medication after metformin for management of type 2 diabetes for patients with known cardiovascular disease [5,6].

Benefits of SGLT2 inhibitors have been demonstrated in patients with [7] and without [8] type 2 diabetes, however the mechanism by which cardiovascular and renal outcomes improve is unclear. SGLT2 inhibitors may improve cardiovascular outcomes through multiple, complimentary mechanisms including improvement in glycemic control, altered energy metabolism in the heart, blood pressure reduction, weight loss, and diuresis [9,10]. Blood pressure reduction with SGLT2 inhibitor treatment may be due to the direct effect of these agents on arterial stiffness improvement [11], plasma volume reduction [12], and natriuresis [10], or an indirect effect of weight loss [13]. Elucidating the mechanisms by which SGLT2 inhibitors exert their beneficial effects is important as this knowledge can inform optimal use of these agents.

SGLT2 inhibitors are not currently recommended as an antihypertensive therapy. Given that these agents could plausibly affect positive cardiovascular and renal outcomes via direct antihypertensive properties, the specific role of SGLT2 inhibitors in persons with type 2 diabetes and hypertension needs to be defined. We designed this systematic review and *meta*-analysis to test the hypothesis that the reduction in cardiovascular outcomes in adults with type 2 diabetes is at least in part attributed to the blood pressure decrease associated with SGLT2 inhibitor use. The cardiovascular outcomes of interest included cardiovascular mortality, 3-point major adverse cardiovascular events (MACE; a composite of cardiovascular death, nonfatal stroke and nonfatal myocardial infarction) and CHF hospitalizations.

2. Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. The protocol was registered (PROSPERO CRD42018116683).

2.1. Patient and public involvement

There was no patient or public involvement in the design, conduct, reporting or dissemination of this study.

2.2. Data sources and searches

The search strategy was developed in consultation with two experienced medical research librarians (ZP, DL). A comprehensive search was conducted from inception to 29 June 2019 in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials using Medical Subject Heading terms and keywords related to SGLT2 inhibitors and specific SGLT2 inhibitor drug names (Table A.1). A randomized controlled trials filter was applied to searches in MEDLINE and EMBASE [15]. Reference lists of included articles and relevant reviews were hand searched. Local experts were consulted to identify additional eligible articles.

2.3. Study selection

Titles and abstracts were independently reviewed by two reviewers (JLB, JEB) for possible inclusion using the following criteria: 1) adults ($\geq$18 years) with type 2 diabetes, 2) treatment with any SGLT2 inhibitor alone or in combination with other antidiabetic medications. Full text review was then performed by two independent reviewers (JLB, JEB) using the following inclusion criteria: 1) placebo-controlled randomized trial, 2) adults ($\geq$18 years) with type 2 diabetes, 3) treatment with any SGLT2 inhibitor alone or in combination with other antidiabetic medications, 4) treatment duration $\geq$ 24 weeks, 5) report of cardiovascular outcomes (cardiovascular mortality, 3-point MACE and/or CHF hospitalizations), and 6) report of change in systolic blood pressure with SGLT2 inhibitor use. Articles were excluded for any of the following reasons: 1) no original data, 2) no published full-text article, or 3) non-English language. If data from the same trial were reported across multiple publications, the article with the longest follow-up was selected. Disagreements were resolved through consensus. A kappa statistic was calculated to quantify article selection agreement between reviewers [16].

2.4. Data extraction and quality assessment

JLB and JEB independently extracted all outcome data with subsequent discussion of any discrepancies. Data were collected on trial characteristics, baseline patient characteristics (e.g., age), SGLT2 inhibitor use (e.g., type), change in systolic blood pressure, and cardiovascular outcomes (e.g., cardiovascular death). Trial outcomes were extracted in intention-to-treat categories. The incidence of cardiovascular death was assumed to be zero if no deaths occurred during the trial period or if deaths that occurred were not cardiovascular-related.

Quality assessment was performed by extracting information on key trial validity criteria using the Cochrane Risk of Bias Tool (Modified) for Quality Assessment of Randomized Controlled Trials [17].

2.5. Data synthesis and analysis

As the cardiovascular benefits of SGLT2 inhibitors have been established [1–4,8], the primary goal of this analysis was to examine the association between blood pressure reduction among those treated and not treated with SGLT2 inhibitors and degree of cardiovascular benefit observed. Our analytic plan was structured as follows: 1) Conduct a *meta*-analysis to determine the pooled effect of SGLT2 inhibitors (relative to placebo) on cardiovascular outcomes; 2) Conduct a *meta*-regression analysis to determine if there is a significant linear association between blood pressure reduction and cardiovascular event reduction among those treated with SGLT2 inhibitors; and 3) Conduct stratified *meta*-analyses to determine if trials that progressively achieved lower blood pressure also had greater reported cardiovascular event reduction. Details of these analytic approaches are described herein.

Mantel-Haenszel random effects model *meta*-analyses were conducted to assess the effect of SGLT2 inhibitors compared with placebo on cardiovascular outcomes. Risk ratios (RR) with 95% confidence intervals (95%CI) were used as a common measure of association, and as is common in *meta*-analyses [18,19], HRs were considered interchangeable with RRs. Where appropriate, experimental arms were pooled together to facilitate comparisons between SGLT2 inhibitor treatment groups and placebo. A continuity correction of 1 was used, as required, to calculate pooled estimates when there were zero event cells [20]. Statistical heterogeneity between estimates was assessed using the Cochran's Q test and I^2 statistic. For the I^2 statistic, heterogeneity cut-offs were: low (<25%), moderate (25–50%), and high (>50%) [21]. To interrogate heterogeneity across included trials, stratified analyses were conducted to examine the effect of SGLT2 inhibitors on cardiovascular mortality with 1) continuity correction use, 2) follow-up duration, 3) baseline hemoglobin A1C (A1C), 4) diabetes duration, 5) baseline systolic blood pressure, 6) proportion of males, and 7) SGLT2 inhibitor agent used.

A random effects model *meta*-regression analysis was performed to evaluate the association between degree of blood pressure lowering and cardiovascular mortality, 3-point MACE and CHF hospitalizations. Systolic blood pressure was selected for analysis because baseline and end-of-trial levels were most consistently reported for this measure compared to diastolic blood pressure. We used the weighted least-squares method [22]. The logarithm of relative risk for each cardiovascular outcome was weighted by the inverse variance of each trial and regressed against the difference in change in systolic blood pressure for participants assigned to SGLT2 inhibitors and participants assigned to placebo from baseline to end-of-intervention. Standard errors were calculated. Statistical significance was assessed using the Wald test.

Publication bias was assessed using a funnel plot and Egger's test [23]. Data analyses were conducted using Stata 15.1 (StataCorp, College Station, Texas). A p-value of < 0.05 was used as the level of statistical significance, or 95%CI that did not enclose the null value of 1.

3. Results

3.1. Trial selection

Our search strategy identified 11,232 articles, and 8,235 titles and abstracts were then screened after duplicates were removed. There were 1,867 articles that met criteria for full-text review and forty articles were included [1–4,24–59]. Trial selection process details are presented in a PRISMA flow diagram (Fig. 1) [14]. There was moderate agreement between reviewers at the title and abstract screening stage ($\kappa = 0.659$), and strong agreement for full text screening ($\kappa = 0.850$). The majority of trials were excluded because pre-specified cardiovascular outcomes were not reported (n = 31) or they were secondary publications of trials already included in our review (n = 30).

3.2. Trial characteristics

Characteristics of the 40 included trials (n = 54,279 participants) are presented in Table 1. Notably, four major trials contributed 38,723 (71.3%) of all study participants [1–4]. Nine trials reported the proportion of participants with hypertension [3,4,29,31,38,41,44,54,57], which ranged from 40.9% to 100%. Seven trials reported the proportion taking antihypertensive medications [1,2,29–30,44,46,57]. Six trials specified that antihypertensive regimens should remain stable during the intervention [29,30,33,39,44,52]. Thirty trials reported mean diastolic blood pressure measurements, which ranged from 73.3 to 88.3 mmHg [2–4,46–47,49–50,56,58,26–31,34–36,38–44,52–54].

3.3. Quality assessment

The results of our quality assessment are presented in Table A.2. Overall, the risk of bias was determined to be "low" for 15 trials [2–4,24–25,33,35–36,39,45,49,52,55,58–59], "unclear" for one trial [37], and "high" for 24 trials [1,34,38,50–51,53–54,56,27–32,40–44,46–48]. All included trials received an assessment of "low" risk of bias for the categories of selective outcome reporting and participant and assessor blinding. A minority of trials did not report on sequence generation [32,41–42], or allocation concealment [32,41–42]. Some trials received a rating of "high" risk of bias due to reporting attrition > 10% [1,26–32,34,38,40–44,46–48,50,51,53,54,56,57].

3.4. Cardiovascular outcomes

For trials that reported event rates (n = 39), a total of 551 deaths from cardiovascular causes were reported among the 25,458 participants who were treated with a SGLT2 inhibitor compared to 536 events among 18,719 controls [1,2,4,24–59] (Table 1). Individually, only one trial reported a statistically significant reduction in cardiovascular mortality risk in those treated with a SGLT2 inhibitor compared to placebo [2]. The pooled estimate indicated that treatment with a SGLT2 inhibitor led to an 18% reduction in cardiovascular death (RR 0.82, 95%CI 0.74, 0.91, $I^2 = 0.0\%$; Fig. 2).

The pooled estimates from the four largest trials [1–4], which were designed to assess cardiovascular events, indicated that treatment with a SGLT2 inhibitor relative to placebo led to a 19% reduction in cardiovascular mortality (RR 0.81, 95%CI 0.66, 0.98, $I^2 = 73.7\%$), 12% reduction in 3-point MACE (RR 0.88, 95%CI 0.82, 0.94, $I^2 = 0.0\%$) and 32% reduction in CHF hospitalizations (RR 0.68, 95%CI 0.60, 0.76, $I^2 = 0.0\%$).

Most trials (n = 31) reported zero cardiovascular deaths in the placebo group (n = 5) [26–27,36,54,57], intervention group (n = 2) [41,53], or both (n = 24) [24–25,28,55–56,58,31–34,37–40,45–52] and therefore a continuity correction was required to calculate relative risk. None of these trials were designed to primarily assess cardiovascular mortality. Within these 31 trials, the cardiovascular death event rate was 10/8039 among those randomized to SGLT2 inhibitors and 2/4260 among those randomized to placebo. The pooled point estimate suggested a 31% reduction in cardiovascular mortality for SGLT2 inhibitor use compared with placebo (RR 0.69, 95%CI 0.43, 1.10, $I^2 = 0.0\%$; Fig. 2) [24–28,30–34,36–41,45–59].

Only nine trials reported cardiovascular death in both the placebo and experimental groups (and therefore a continuity correction was not required) [29,35,1–4,42–44]. For these trials, the

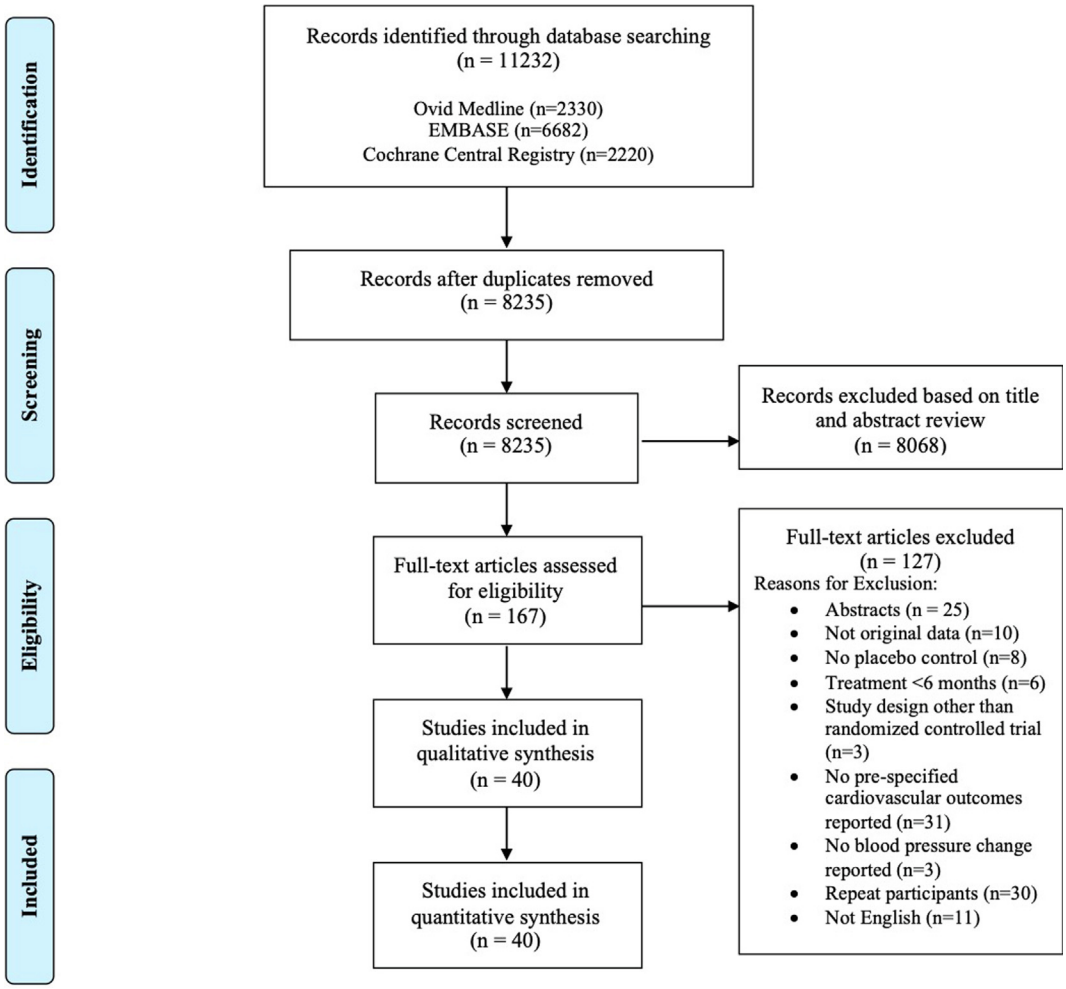

Fig. 1. PRISMA Flow Diagram.

risk of cardiovascular mortality was reduced by 19% for individuals who received SGLT2 inhibitor treatment compared to placebo (RR 0.81, 95%CI 0.68, 0.98, I^2 = 46.7%; Fig. 2).

We conducted stratified analyses based on baseline characteristics, trial characteristics, and treatment effects in order to explore the heterogeneity in cardiovascular mortality (Table A.3). Differences were non-significant when strata were compared for baseline A1C (p = 0.624), baseline systolic blood pressure (p = 0.421), diabetes duration (p = 0.208), biologic sex (p = 0.666), and follow-up duration (p = 0.377). We performed a stratified analysis by drug type when more than two estimates were available. The pooled estimates for relative risk of cardiovascular mortality with a SGLT2 inhibitor compared with placebo were statistically significant for canagliflozin (RR 0.83, 95%CI 0.71, 0.96) and empagliflozin (RR 0.62, 95%CI 0.50, 0.77) but not for dapagliflozin, ertugliflozin or ipragliflozin.

3.5. Blood pressure reduction and cardiovascular outcomes

For every 1 mmHg reduction in systolic blood pressure, there was a statistically non-significant 7% relative risk reduction in cardiovascular mortality (RR 0.93, 95%CI 0.88, 1.3, p = 0.483; Fig. 3). To account for the possibility that the relationship between systolic blood pressure lowering and cardiovascular mortality was non-linear, we re-examined the magnitude of within-group systolic blood pressure reduction from baseline in three distinct strata separately according to trials where patients achieved a mean blood pressure reduction of < 2 mmHg [26,28,38,41–42,45–46,49,51] (RR 0.68; 95%CI 0.15, 2.98, I^2 = 0.0%); 2–4 mmHg [1,2,4,25,27,29,32,35–36,43–44,50,54–58] (RR 0.83; 95%CI 0.75, 0.91, I^2 = 0.0%); and > 4 mmHg [3,24,30–31,33–34,37,39–40,47–48,52–53,59] (RR 0.63; 95%CI 0.33, 1.18, I^2 = 0.0%). Differences between strata were non-significant (p = 0.543).

Further, four trials [1–4] reported on 3-point MACE and CHF hospitalizations. When examined there was no apparent association between blood pressure reduction and 3-point MACE (p = 0.839; Fig. 3) or CHF hospitalizations (p = 0.844; Fig. 3).

3.6. Assessment for publication bias

There was no evidence of publication bias with a visually symmetric funnel plot for the outcome of cardiovascular mortality (Figure A.1). This was formally evaluated with Egger's linear regression test, which showed a statistically non-significant beta-coefficient of bias estimate of −0.15 (95%CI −0.40, 0.11, p = 0.245).

4. Discussion

This systematic review and *meta*-analysis of 40 randomized controlled trials explored the relationship between the magnitude of reduction in systolic blood pressure and cardiovascular outcomes including cardiovascular mortality, 3-point MACE, and CHF hospitalizations using *meta*-regression. There appeared to be

Table 1
Study Characteristics.

Author, Year	Drug	SampleSize	Mean Age (y)	Primary Outcome	Treatment Duration (weeks)	Attrition (%)	Cardiovascular Mortality Events		Mean Baseline SBP (mmHg)		Difference in Change in SBP[¦] (mmHg)
							Placebo	SGLT2	Placebo	SGLT2	
Allegretti, 2019 [24]	Bexagliflozin	312	69.6	A1C	24	5	0/155	0/157	137.6	135.9	−4.00
Bailey, 2012 [25]	Dapagliflozin	282	53.0	A1C	24	7	0/68	0/214	129.3	128	−4.58
Bailey, 2013 [26]	Dapagliflozin	546	53.9	A1C	102	38	0/137	2/409	128	127	−1.73
Bode, 2015 [27]	Canagliflozin	714	63.6	A1C	104	24	0/237	1/477	131.4	131	−6.59
Bolinder, 2014 [28]	Dapagliflozin	182	60.7	Weight[†]	102	23	0/91	0/91	133.3	135	−2.40
Cefalu, 2015 [29]	Dapagliflozin	922	62.4	Composite[§]	52	25	1/459	4/455	133	132	−3.58
Dagogo-Jack, 2018 [30]	Ertugliflozin	462	59.1	A1C	52	13	0/153	0/309	130.2	131	−4.95
Ferdinand, 2019 [31]	Empagliflozin	150	56.8	A1C	24	18	0/72	0/78	148.3	148.9	−7.43
Ferrannini, 2010 [32]	Dapagliflozin	274	52.2	A1C	24	15	0/75	0/199	NR	NR	−2.61
Fioretto, 2018 [33]	Dapagliflozin	321	65.8	A1C	24	3	0/161	0/160	135	135	−3.10
Forst, 2014 [34]	Canagliflozin	342	57.3	A1C	26	23	0/115	0/227	128.2	127	−3.80
Gallo, 2019 [35]	Ertugliflozin	621	56.7	A1C	104	15	2/207	1/411	129.3	130.4	−3.42
Haering, 2015 [36]	Empagliflozin	666	57.1	A1C	72	9	0/225	1/441	128.8	129	−2.15
Ji, 2019 [37]	Ertugliflozin	506	56.4	A1C	26	5	0/167	0/339	NR	NR	−4.70
Ji, 2014 [38]	Dapagliflozin	393	51.3	A1C	24	13	0/132	0/261	123.5	124	−2.56
Kaku, 2014 [39]	Tofogliflozin	230	57.0	A1C	24	8	0/56	0/173	128.3	129	−4.74
Kashiwagi, 2015 [41]	Ipragliflozin	168	56.7	A1C	24	21	1/57	0/112	125.8	126	−3.60
Kashiwagi, 2015 [40]	Ipragliflozin	240	59.7	A1C	24	46	0/75	0/165	129.2	130	−4.20
Kohan, 2014 [42]	Dapagliflozin	252	67.0	A1C	104	45	3/84	4/168	130.7	132	−5.53
Kovacs, 2015 [43]	Empagliflozin	498	54.5	Composite[§]	76	47	1/165	3/433	125.7	126	−2.86
Leiter, 2014 [44]	Dapagliflozin	964	63.6	A1C	52	22	1/482	2/480	134.6	135	−3.00
Mathieu, 2015 [45]	Dapagliflozin	320	55.1	A1C	24	6	0/160	0/160	NR	NR	−3.90
Matthaei, 2015 [46]	Dapagliflozin	216	61.0	A1C	52	13	0/108	0/108	136.4	136	−2.10
Merker, 2015 [47]	Empagliflozin	637	55.7	A1C	76	34	0/207	0/430	128.6	129	−4.05
Neal, 2017 [3]	Canagliflozin	10,142	63.3	3-pt MACE[‡]	188.2	4	12.8*	11.6*	136.9	137	−3.93
Perkovic, 2019 [4]	Canagliflozin	4401	63.0	Composite[#]	31.4	1	140/2059	110/2092	140.2	139.8	−2.38
Rodbard, 2016 [48]	Canagliflozin	213	57.4	A1C	26	17	0/106	0/107	128.7	130	−5.90
Rosenstock, 2015 [49]	Dapagliflozin	355	54.0	A1C	24	8	0/176	0/179	128	129	−2.20
Rosenstock, 2014 [50]	Empagliflozin	563	56.7	A1C	52	16	0/188	0/375	132.6	133	−0.70
Rosenstock, 2012 [51]	Dapagliflozin	420	53.5	A1C	48	19	0/139	0/281	NR	NR	−3.60
Seino, 2014 [52]	Luseogliflozin	158	59.3	A1C	24	6	0/79	0/79	128.9	129	−5.70
Stenlof, 2013 [53]	Canagliflozin	584	55.4	A1C	26	13	1/192	0/392	127.7	128	−4.55
Strojek, 2014 [54]	Dapagliflozin	592	59.8	A1C	48	13	0/145	3/447	133.3	133	−5.06
Terra, 2017 [55]	Ertugliflozin	461	56.4	A1C	26	10	0/153	0/308	NR	NR	−1.71
Wilding, 2013 [56]	Canagliflozin	469	56.8	A1C	52	34	0/156	0/313	130.1	130	−3.40
Wilding, 2014 [57]	Dapagliflozin	807	58.8	A1C	104	36	0/197	3/610	NR	NR	−2.80
Wiviott, 2018 [1]	Dapagliflozin	17,160	63.9	3-pt MACE[‡]	218	31	249/3578	245/8582	134.8	135	−2.70
Yang, 2016 [58]	Dapagliflozin	444	53.7	A1C	24	8	0/145	0/299	126.3	128	−5.09
Yang, 2018 [59]	Dapagliflozin	272	57.5	A1C	24	5	0/133	0/139	131.3	132	−5.00
Zinman, 2015 [2]	Empagliflozin	7020	63.1	3-pt MACE[‡]	133	3	137/2283	172/4687	135.8	136	−3.80

SBP systolic blood pressure; NR not reported; * events per 1000 patient years; † change in total body weight from baseline to end of treatment period; ‡ 3-pt MACE is a composite of cardiovascular mortality, nonfatal stroke and nonfatal myocardial infarction; § co-primary outcome measures were mean change in baseline A1c and proportions of participants achieving a three-outcome measure of combined clinical benefit: simultaneous A1c decrease of 0.5% or greater, total body weight reduction of 3% or greater, and systolic blood pressure reduction of 3 mmHg or greater from baseline; # composite of end-stage kidney disease, serum creatinine doubling from baseline for ≥ 30 days, or death from cardiovascular or renal disease; ¦ the difference in the change in mean systolic blood pressure from baseline to end-of-intervention between the intervention and placebo group

linear relationships between these cardiovascular outcomes and difference in change in systolic blood pressure based on the line of best fit. Our analysis was underpowered to make definitive conclusions, so there is insufficient evidence to suggest that SGLT2 inhibitors reduce cardiovascular mortality through significant blood pressure reduction. We found that the relative risk of cardiovascular mortality is reduced by 18% (RR 0.82, 95%CI 0.74, 0.91) in patients with type 2 diabetes treated with SGLT2 inhibitors compared with placebo.

Our findings are consistent with other published *meta*-analyses and confirm that SGLT2 inhibitors are protective against cardiovascular events [7,60–61]. The observed reductions in cardiovascular events related to SGLT2 inhibitor therapy are primarily based on four large trials [1–4], which were powered to assess for 3-point MACE [1–3] or a composite including death from renal or cardiovascular disease [4]. These trials were substantially larger than the other included reports, and therefore contributed heavily in weight to this *meta*-analysis.

The overall pooled risk estimate for cardiovascular mortality should be interpreted with caution because cardiovascular mortality was a rare occurrence, with most trials reporting zero events. Notably, a continuity correction was applied to 31 trials in order to calculate risk ratio estimates. The low event rates in the included trials may have been due to inclusion of lower-risk patients (e.g., participants with no recent history of cardiovascular events), small sample sizes, and short trial follow-up periods, which were inadequate to detect cardiovascular death.

When our analysis was limited to trials that reported cardiovascular deaths in both groups, the point estimate was consistent with the overall pooled estimate calculated when all trials were included; however, we observed high heterogeneity between trials that reported cardiovascular deaths in both groups. A possible explanation for this heterogeneity could be that individuals at high-risk including those with poor glycemic control, hypertension, and known cardiovascular disease may benefit most from treatment with SLGT2 inhibitors. Indeed, the trends from our strat-

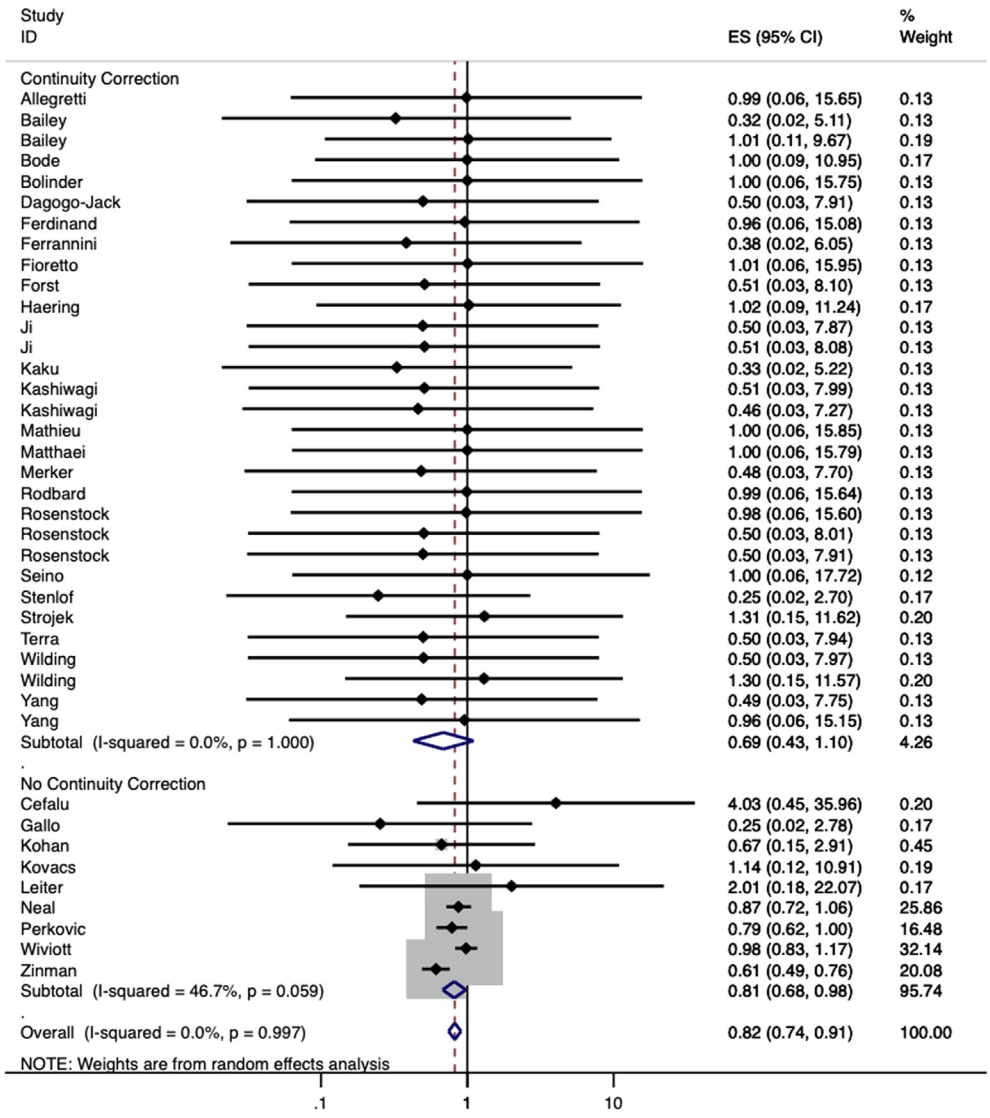

Fig. 2. Meta-Analysis of Risk Ratio for Cardiovascular Mortality Stratified by Requirement of Continuity Correction to Calculate Risk Ratio Secondary to Zero Cells.

ified analyses examining the impact of cardiovascular risk factors suggest that individuals at high-risk due to poor glycemic control and/or hypertension experience more cardiovascular protection with SGLT2 inhibitors than those without these risk factors. To this end, a *meta*-analysis found that SGLT2 inhibitors may have variable effects depending on the baseline characteristics of the population with type 2 diabetes to which they are prescribed [7]. Specifically, reductions in MACE were demonstrated in patients with known cardiovascular disease, while SGLT2 inhibitors had no significant effect compared with placebo in those without known atherosclerotic disease [7]. When taken together, above evidence suggests that individuals with type 2 diabetes at high-risk may benefit most from the use of SGLT2 inhibitors. This is biologically plausible given the combination of vascular, metabolic and natriuretic effects demonstrated by SGLT2 inhibitors.

We were not able to include the DAPA-HF trial [8] in our *meta*-analysis as it was a trial conducted in a heart failure population and while there was a substantial diabetes sub-group, blood pressure reduction within this group was not reported. This trial found that SGLT2 inhibitors are beneficial in individuals with heart failure and a reduced ejection fraction, with or without type 2 diabetes, suggesting that the mechanism for improved cardiovascular outcomes is not primarily related to glycemic control improvements.

Blood pressure reductions with SGLT2 inhibitors have been observed in animal and clinical studies [63]. Theorized mechanisms by which SGLT2 inhibitors affect blood pressure include plasma volume reduction through osmotic diuresis and natriuresis [12,64], arterial stiffness improvement [11] and weight loss [13]. Several complementary mechanisms have been postulated to explain how SGLT2 inhibitors improve cardiovascular outcomes including glycemic control, altered energy metabolism in the heart, blood pressure reduction, weight loss, and diuresis [9,10]. Animal models have shown that vascular dysfunction associated with type 2 diabetes is reduced with SGLT2 inhibitor administration secondary to a reduction in oxidative stress, glucotoxicity, and inflammation [62].

With their diuretic-like effect, SGLT2 inhibitors exhibit a similar response to thiazide and loop diuretics, which reduce blood pressure through natriuresis leading to decreased plasma volume [65]. While no additive blood pressure reduction has been observed when SGLT2 inhibitors were combined with thiazide [65] or loop diuretics [66], additive blood pressure lowering effects have been observed when SGLT2 inhibitors were combined with renin-angiotensin-aldosterone system inhibitors [67], beta blockers, and calcium channel blockers [68]. The additive effects of these pharmacologic agents should be considered in the management of hypertension in the setting of type 2 diabetes.

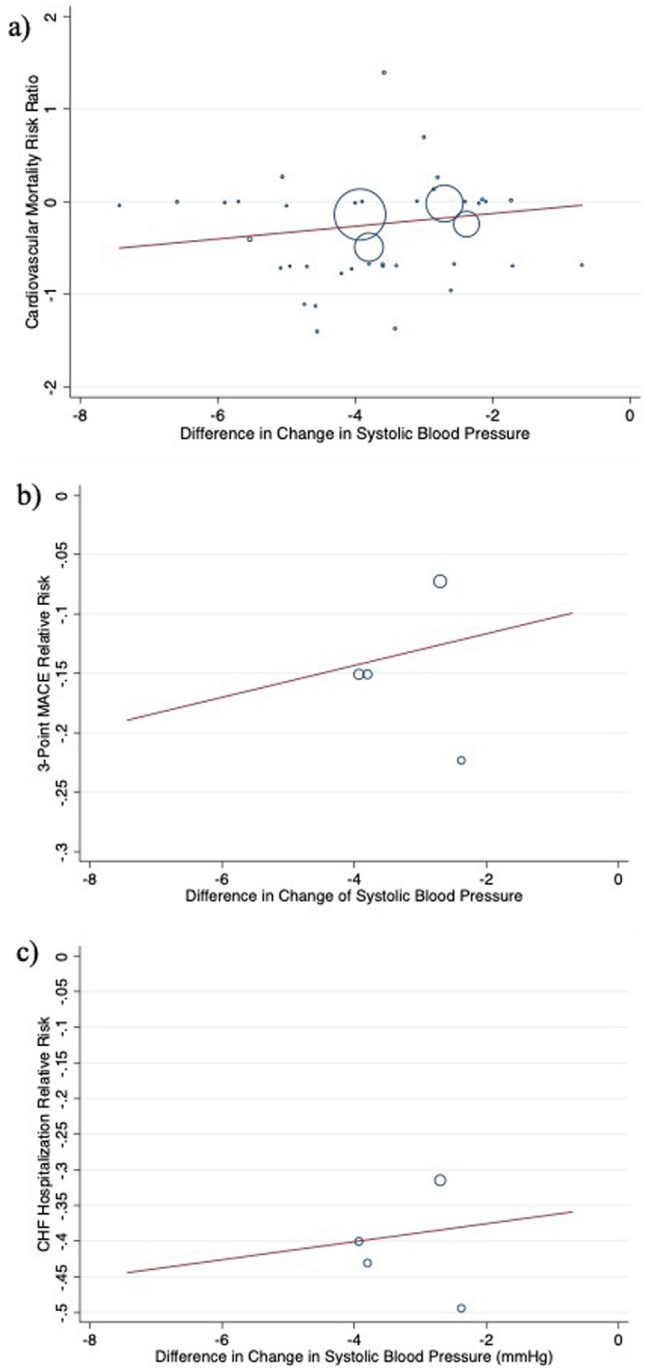

Fig. 3. Meta-regression by mean change in systolic blood pressure for a) cardiovascular mortality risk ratio, b) 3-point MACE risk ratio, and c) CHF hospitalizations risk ratio.

This systematic review and *meta*-analysis has notable strengths. It is the largest *meta*-analysis to date examining the relative risk of cardiovascular disease with SGLT2 inhibitors compared with placebo, including 54,279 participants from 40 clinical trials. We were able to explore the potential relationship between the cardioprotective effects of SGLT2 inhibitors and the magnitude of blood pressure reduction.

Our study has certain limitations. First, the mortality reduction demonstrated by SGLT2 inhibitors is driven largely by a reduction in heart failure deaths. Therefore, natriuresis is likely a major contributing factor in the observed improvements in cardiovascular outcomes. The reported trial data limits our ability to test the mechanism hypothesis and further trial level data including daily body weight, fluid intake and urinary output would help to further explore if natriuresis is the mechanism, or a contributing mechanism, by which cardiovascular outcomes are improved with SGLT2 inhibitor use. Second, the *meta*-regression was underpowered to detect a significant association between blood pressure reduction and cardiovascular outcomes due to a diluted event rate. The results were driven by a few large cardiovascular outcome trials [1–4], however it was necessary to include all trials that reported on cardiovascular mortality to obtain an adequate distribution of blood pressures and conduct a robust *meta*-regression. Third, a HR was used for one included trial [3] instead of a RR. While pooling HRs and RRs together is commonly performed in *meta*-analyses [18,19], the approach may introduce methodological heterogeneity. Finally, a greater distribution of baseline characteristic variables (e.g., A1C, blood pressure) is needed to better understand their relationship with cardiovascular outcomes.

In conclusion, our findings confirm the beneficial effect of SGLT2 inhibitors in reducing cardiovascular events in individuals with type 2 diabetes. Our study lacked the necessary statistical power to definitively answer our research question, thus we do not know with certainty if the cardioprotective effect of SGLT2 inhibitors, though believed to be pleotropic [7], is mediated through blood pressure reduction. Further investigations are needed to explore potential mechanisms so that clinical management can be targeted to those who would receive the most benefit, while minimizing side-effects. While it is unclear if the blood pressure lowering observed with SGLT2 inhibitors contributes to the cardiovascular benefits observed, using SGLT2 inhibitors as an adjunct to recommended antihypertensive agents in adults with diabetes is sensible, particularly in the presence of early renal disease or atherosclerotic cardiovascular disease, to assist in achieving glycemic and blood pressure targets.

Declaration of Competing Interest

There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100725.

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