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Effects of SGLT2 inhibitors on cardiovascular outcomes and mortality in type 2 diabetes

A meta-analysis

Cai-Yan Zou, MD[a], Xue-Kui Liu, MD[a], Yi-Quan Sang, MD[a], Ben Wang, MD[a], Jun Liang, MD, PhD[a,b,*]

Abstract

Background: Optimal glycemic control is required to restrain the increase of cardiovascular events in patients with type 2 diabetes. The effects of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on cardiovascular events and mortality in those patients are not well established. This meta-analysis was conducted to assess the effects of SGLT2 inhibitors on cardiovascular events and mortality in patients with type 2 diabetes.

Methods: We conducted a systematic literature search of Medline, Embase and Cochrane Library and included randomized controlled trials (RCTs) of 3 different SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) that evaluated the effects on cardiovascular outcomes and mortality in the final meta-analysis. The intervention arm was defined either as SGLT2 inhibitor monotherapy or as SGLT2 inhibitor add-on to other non-SGLT2 inhibitor antidiabetic agents (ADAs).

Results: Forty-two trials with a total of 61,076 patients with type 2 diabetes were included in the meta-analysis. Compared with the control, SGLT2 inhibitor treatment was associated with a reduction in the incidence of major adverse cardiovascular events (MACEs) (OR = 0.86, 95% CI 0.80–0.93, $P < .0001$), myocardial infarction (OR = 0.86, 95% CI 0.79–0.94, $P = .001$), cardiovascular mortality (OR = 0.74, 95% CI 0.67–0.81, $P < .0001$) and all cause mortality (OR = 0.85, 95% CI 0.79–0.92, $P < .0001$). However, the risk of ischemic stroke was not reduced after SGLT2 inhibitor treatment in patients with type 2 diabetes (OR = 0.95, 95% CI 0.85–1.07, $P = .42$).

Conclusion: These data suggest a decreased risk of harm with SGLT2 inhibitor as a class with respect to cardiovascular events and mortality.

Abbreviations: ADA = antidiabetic agent, SGLT2 = Sodium-glucose-cotransporter-2, EAT = epicardial adipose tissue, MACE = major adverse cardiovascular event, PRISMA = Preferred Reporting Items for Systematic Reviews, RCT = randomized controlled trial.

Keywords: cardiovascular outcomes, meta-analysis, mortality, SGLT2 inhibitors, type 2 diabetes

1. Introduction

Type 2 diabetes (T2DM), one of the most severe public health disorders, had a worldwide prevalence of 10% in the general population and affected more than 415 million adults in 2013, and this number has been projected to increase to 592 million by 2035.[1,2] Cardiovascular disease, a serious complication of type 2 diabetes, is primarily associated with excess mortality and morbidity in these patients.[3] More than 70% of type 2 diabetes patients die of cardiovascular causes.[4] The main contributors to the increased risk of cardiovascular disease include chronic hyperglycemia, insulin sensitivity reduction, visceral adiposity, and in particular, the comorbidities of hypertension and increased arterial stiffness.[5]

Existing antidiabetic agents (ADAs) lower blood glucose either by enhancing insulin secretion or by improving insulin sensitivity. Sodium-glucose cotransporter-2 (SGLT2) inhibitors lower blood glucose via an insulin-independent mode of action by reducing glucose renal reabsorption at the S1 segment of the proximal tubules in the kidney.[6,7] Phlorizin, the first SGLT2 inhibitor derived from the bark of apple trees, can cause severe gastrointestinal symptoms due to its property of nonselectively inhibiting SGLT1 and SGLT2.[8] In recent years, SGLT2-specific inhibitors (mainly including canagliflozin, dapagliflozin and empagliflozin) that could avoid gastrointestinal effects have been

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developed.[9] SGLT2 inhibitors have been recommended by clinical guidelines as potential pharmacological approaches for second-line therapy following metformin failure or intolerance.[10] SGLT2 inhibitors were proven to be effective in glycemia and/or HbA1c reduction and were additionally beneficial in terms of weight loss, blood pressure reduction, and intracranial hemodynamics.[11]

Increasing placebo-controlled trials suggested that the risk of cardiovascular outcomes such as major adverse cardiovascular events (MACEs) or at least several of their components were significantly reduced after SGLT2 inhibitor treatment in patients with type 2 diabetes.[12] SGLT2 inhibitors have a protective effect on the myocardium by improving the differentiation of epicardial adipose tissue (EAT) and subsequently reducing the secretion of proinflammatory chemokines.[13,14] This effect would probably be due to their impact on reducing body weight, especially body fat.[14] However, recent work has prompted a novel hypothesis that SGLT2 inhibitors may directly act on cardiac myocytes.[15] Experimental studies demonstrated that SGLT2 inhibitors have positive effects on cardiac function by reducing the overload of intracellular sodium (Na^+), subsequently restoring mitochondrial function and the redox state in the failing heart.[15]

In a recent large multicenter randomized trial (EMPA-REG Outcome Trial), empagliflozin treatment demonstrated a relative risk reduction in MACEs (14%), cardiovascular mortality (38%) and all-cause mortality (32%), which supports the use of empagliflozin in patients with type 2 diabetes and increased cardiovascular risk.[16] The CANVAS Program demonstrated that canagliflozin reduced cardiovascular events compared with placebo.[17] Furthermore, the DECLARE-TIMI 58 trials indicated that dapagliflozin treatment resulted in a lower rate of cardiovascular death in patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease; however, no difference in the MACE rate was seen between the dapagliflozin and placebo groups.[18] Thus far, it remains unconfirmed whether this cardiovascular benefit is extended to the entire class of SGLT2 inhibitors. Here, we assess the effect of SGLT2 inhibitors on cardiovascular events via a comprehensive meta-analysis of data from 42 randomized placebo-controlled trials, including sensitivity and subgroup analyses.

2. Methods

The meta-analysis was performed based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] The authors declare that all supporting data are available within the article and/or its Supplementary materials, http://links.lww.com/MD/D427. This study did not require ethical approval since all analyses were based on previously published studies.

2.1. Data sources and searches

Two investigators (Zou and Liu) performed a systematic search of scientific literature in the databases (from conception through May 12, 2019), including PubMed, Embase, and Cochrane Central Register of Controlled Trials. A combination of the following terms was used: "sodium-glucose cotransporter", "sodium-glucose cotransporter-2 inhibitors", "sglt-2", "sglt2", "canagliflozin", "Invokana", "dapagliflozin", "Farxiga", "empagliflozin", "Jardiance" AND "major adverse cardiovascular events", "mace", "cardiovascular disease", "coronary artery disease", "coronary heart disease", "myocardial infarction", "macrovascular disease", "stroke", "cerebrovascular disease", "cerebral ischemia", "mortality", and "safety". The search terms were used in Text Word and in different combinations as MeSH terms in PubMed, Emtree in Embase and MeSH descriptors in the Cochrane library. There was a limitation regarding language in that we considered only English publications. The search strategy is listed in the Supplemental Digital Content, http://links.lww.com/MD/D427. The citations in the selected trials and meta-analyses were searched manually to find relevant original studies, and study authors were contacted for additional information when necessary. Finally, an electronic search alert was created to cover recent studies.

2.2. Inclusion and exclusion criteria

All relevant data from randomized controlled trials (RCTs) comparing the effects of SGLT2 inhibitors in type 2 diabetes with reported cardiovascular outcomes were eligible for inclusion. The intervention arm was defined either as SGLT2 inhibitor monotherapy or as SGLT2 inhibitor add-on therapy to other non-SGLT2 inhibitor ADAs. The control arm was defined as placebo or non-SGLT2 inhibitor ADAs. The trials were included if they met the following criteria:

(1) all subjects enrolled in individual studies had type 2 diabetes irrespective of sex, age, race, or nationality;
(2) SGLT2 inhibitors, including canagliflozin, dapagliflozin or empagliflozin, were employed in the treatment of patients;
(3) the treatment intervention was SGLT2 inhibitor monotherapy or add-on therapy with any approved agent, and the matching control was defined as type 2 diabetes patients treated with placebo or any other ADAs;
(4) the intervention duration was at least 12 weeks;
(5) the safety outcomes included MACEs (defined as cardiovascular outcomes including no less than one of the following: myocardial infarction, ischemic stroke, or cardiovascular death)[18] or all-cause mortality.

Studies that met the following criteria were excluded:

(1) letters, case reports, editorials, preclinical studies, and trials enrolling patients without diabetes or with type 1 diabetes;
(2) studies describing duplicate data; and
(3) studies lacking key information for further analysis.

2.3. Data extraction and quality assessment

Records retrieved from electronic searches were imported into reference management software EndNote X8 (Thomson Reuters, New York, NY). Two independent investigators (Zou and Liu) evaluated all the references and extracted data, including trial design, population size and demographics, various treatment strategies and cardiovascular outcomes. The decision to include a study was made by consensus, and discrepancies between the two investigators at any stage of the study selection process were arbitrated by a third reviewer (Liang) and resolved by consensus. The full-text versions of all publications that potentially qualified for the meta-analysis were scanned and assessed in detail according to the predefined inclusion and exclusion criteria.

The quality assessment of the trials included was undertaken independently as part of the data extraction process. The Jadad scale for reporting randomized clinical trials was used to assess the

quality of each article.[20] In this scale, articles are evaluated based on randomization (mentioned as randomized gets 1 point and mentioning randomization methods receives another point), blinding (mentioned as double blind gets 1 point and mentioning blinding methods receives another point), and inclusion of participants (mentioning withdrawals and dropouts receives 1 point). Studies with 3 points or more are ranked as high quality.[20]

2.4. Statistical analysis

This meta-analysis was conducted using RevMan statistical software (version 5.3; Nordic Cochrane Center, Copenhagen, Denmark) for dichotomous data with a Mantel-Haenszel fixed-effects model. Pooled odds ratios (ORs) with a 95% confidence interval (95% CI) were estimated to calculate the effect size of categorical data. Subgroup analyses were conducted based on medication for type 2 diabetes patients (SGLT2 inhibitors vs placebo; SGLT2 inhibitor add-on therapy vs placebo; and SGLT2 inhibitor add-on therapy vs ADAs). The heterogeneity across studies was examined using the Chi-squared test and qualified by I^2 statistics, with $I^2 \geq 50\%$ and $P < .10$ indicating significant heterogeneity. The likelihood of publication bias was assessed graphically by generating a funnel plot. All reported P values are two-tailed. Variables with P values $< .05$ were considered statistically significant.

3. Results

3.1. Characteristics of the included studies

The flowchart of the literature search is shown in Figure 1. The initial implementation of the search strategy yielded 1027

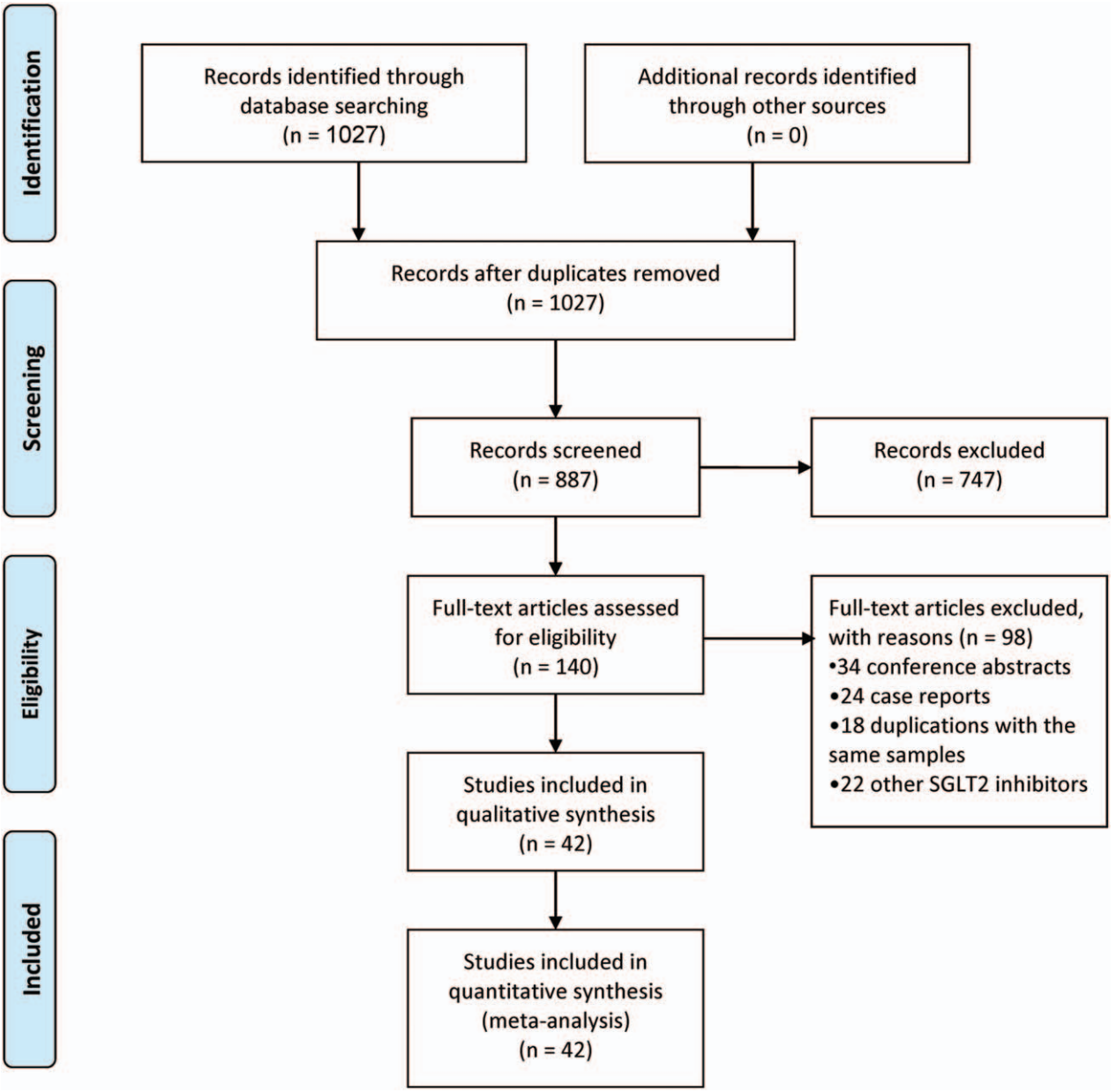


Figure 1. Flowchart of the study selection.

Table 1

Baseline characteristics of included studies.

Author/ year	Participant	Age (yr)	Disease duration (yr)	Intervention	Combination ADA treatment	Control	HbA1c (%)	BMI (kg/m^2)	Follow-up (week)	Jadad score
Bailey 2013[21]	548	53.9	6.1	Dapagliflozin	MET	PBO	8.05	31.5	102	5
Bailey 2015[22]	485	52.2	1.9	Dapagliflozin	None	PBO	7.91	NR	102	5
Barnett 2014[23]	738	62.6	NR	Empagliflozin	MET/SUL/INS	PBO	8.03	31.5	52	3
Bode 2015[24]	714	63.6	11.7	Canagliflozin	None	PBO	7.7	31.6	104	5
Bolinder 2012[25]	182	60.7	5.7	Dapagliflozin	MET	PBO	7.17	31.87	24	3
DeFronzo 2015[26]	812	56.5	NR	Empagliflozin	MET+LINA	LINA	7.96	30.7	52	4
Ferrannini & Berk 2013[27]	388	58.6	NR	Empagliflozin	MET	SITA	7.9	30.25	78	5
Ferrannini & Seman 2013[28]	326	58.0	NR	Empagliflozin	None	PBO	7.9	28.5	12	4
Forst 2014[29]	342	57.4	10.5	Canagliflozin	MET+PIOG	SITA	7.9	32.5	52	5
Fulcher 2015[30]	125	64.8	10.2	Canagliflozin	SUL	PBO	8.4	29.9	18	5
Grandy 2014[31]	182	60.7	5.7	Dapagliflozin	MET	PBO	7.17	31.87	102	3
Häring 2014[32]	706	55.7	NR	Empagliflozin	MET	PBO	7.9	29.2	24	5
Häring 2015[33]	666	57.1	NR	Empagliflozin	MET+SUL	PBO	8.1	28.2	76	4
Inagaki 2013[34]	382	57.4	NR	Canagliflozin	None	PBO	8.09	25.7	12	4
Jabbour 2014[35]	451	54.9	5.67	Dapagliflozin	SITA/SITA+MET	PBO	7.93	NR	24	4
Ji 2015[36]	676	56.3	6.7	Canagliflozin	MET/MET+SUL	PBO	8.0	25.7	18	5
Kadowaki 2014[37]	547	57.5	NR	Empagliflozin	None	PBO	7.95	25.5	12	5
Kaku 2014[38]	261	58.8	4.94	Dapagliflozin	None	PBO	7.48	25.39	24	5
Kohan 2014[39]	252	67.0	16.9	Dapagliflozin	None	PBO	8.35	54.0	104	4
Kovacs 2015[40]	498	54.5	NR	Empagliflozin	PIOG/PIOG+MET	PBO	8.09	29.2	76	5
Lavalle-González 2013[41]	1101	55.4	6.9	Canagliflozin	MET	SITA	7.9	31.8	52	4
Leiter 2014[42]	965	63.8	13.2	Dapagliflozin	OAD/INS/OAD+INS	PBO	8.06	32.8	52	4
Leiter 2015[43]	1450	56.2	6.6	Canagliflozin	MET	GLIM	7.8	31.0	104	5
Nauck 2011[44]	814	58.4	6.3	Dapagliflozin	MET	GLIP	7.72	31.47	52	5
Neal 2017 (CANVAS)[17]	10,142	63.3	13.5	Canagliflozin	None	PBO	8.2	32.0	338	5
Perkovic 2019[45]	4401	63.0	15.8	Canagliflozin	None	PBO	8.3	31.3	42	4
Ridderstråle 2014[46]	1545	55.9	NR	Empagliflozin	MET	GLIM	7.9	31.5	104	5
Roden 2013[47]	676	55.0	NR	Empagliflozin	None	PBO	7.88	28.4	24	3
Rosenstock & Hansen 2015[48]	355	54.0	7.6	Dapagliflozin	MET	SAXA	8.94	31.7	24	5
Rosenstock & Jelaska 2015[49]	494	58.8	NR	Empagliflozin	INS	PBO	8.2	32.2	78	5
Rosenstock 2012[50]	377	52.9	6.0	Canagliflozin	MET	PBO	7.75	31.5	12	5
Rosenstock 2013[51]	424	58.3	NR	Empagliflozin	MET	PBO	8.0	31.4	12	3
Ross 2015[52]	983	58.2	NR	Empagliflozin	MET	PBO	7.77	31.8	16	5
Schernthaner 2013[53]	755	56.7	9.6	Canagliflozin	MET+SUL	SITA	8.1	31.6	52	5
Schumm-Draeger 2015[54]	400	57.7	5.23	Dapagliflozin	MET	PBO	7.8	32.56	16	5
Stenlöf 2014[55]	584	55.4	4.3	Canagliflozin	None	PBO/SITA	8.0	31.6	52	4
Strojek 2014[56]	593	59.8	7.4	Dapagliflozin	SUL	PBO	8.11	29.8	48	5
Tikkanen 2015[57]	818	60.2	NR	Empagliflozin	None	PBO	7.9	32.6	12	3
Wilding 2013[58]	469	56.8	9.6	Canagliflozin	MET+SUL	PBO	8.1	33.1	52	4
Wiviott 2019 (DECLARE-TIMI 58)[18]	17,160	63.9	11.0	Dapagliflozin	None	PBO	8.3	32.1	206	5
Yale 2014[59]	269	68.5	16.3	Canagliflozin	None	PBO	8.0	33.0	52	4
Zinman 2015 (EMPA-REG)[16]	7020	63.1	NR	Empagliflozin	None	PBO	8.1	30.6	162	5

ADA = antidiabetic agent, BMI = body mass index, GLIM = glimepiride, GLIP = glipizide, INS = Insulin, LINA = Linagliptin, MET = metformin, NR = Not reported, NTC = no-treatment-control, OAD = oral hypoglycemic drug, PBO = placebo, PIOG = pioglitazone, SAXA = saxagliptin, SITA = sitagliptin, SUL = sulfonylurea.

potentially relevant citations. According to the predetermined criteria, a total of 42 studies[16–18,21–59] including 61,076 patients with type 2 diabetes published between 2010 and 2019 were included in the meta-analysis. Among these studies, SGLT2 inhibitor monotherapy was used in 15 studies[16–18,22,24,28,34,37–39,45,47,55,57,59], while add-on therapy with SGLT2 inhibitors and other ADAs was used in 27 studies.[21,23,25–27,29–33,35,36,40–44,46,48–54,56,58] The baseline characteristics included age, ranging from 52.20 to 68.50 years; disease duration, from 1.9 to 16.9 years; HbA1c, from 7.17% to 8.94%; body mass index (BMI), from 25.39 to 54.00; and follow-up period, from 12 to 338 weeks. All trials were high quality with more than 3 points according to the Jadad scale. The main characteristics of the selected trials are reported in Table 1.

3.2. Major adverse cardiovascular events

Of the 42 trials fulfilling the inclusion criteria, 37 studies compared the effects of SGLT2 inhibitors and control treatments on cardiovascular outcomes. The results demonstrated that SGLT2 inhibitors significantly reduced the incidence of MACEs compared with control treatment (OR = 0.86, 95% CI 0.80–0.93, $P < .0001$). The subgroup analysis demonstrated that the comparisons of the effects of SGLT2 inhibitor add-on therapy vs placebo and SGLT2 inhibitor add-on therapy vs other ADAs on the risk of MACE also showed significant differences (OR = 0.67, 95% CI 0.47–0.96, $P = .03$; OR = 0.74, 95% CI 0.63–0.88, $P = .0007$, respectively) (Fig. 2A). The sensitivity analysis, by iteratively removing 2 studies[16,18] with larger sample sizes, suggested that the SGLT2 inhibitors also decreased the incidence

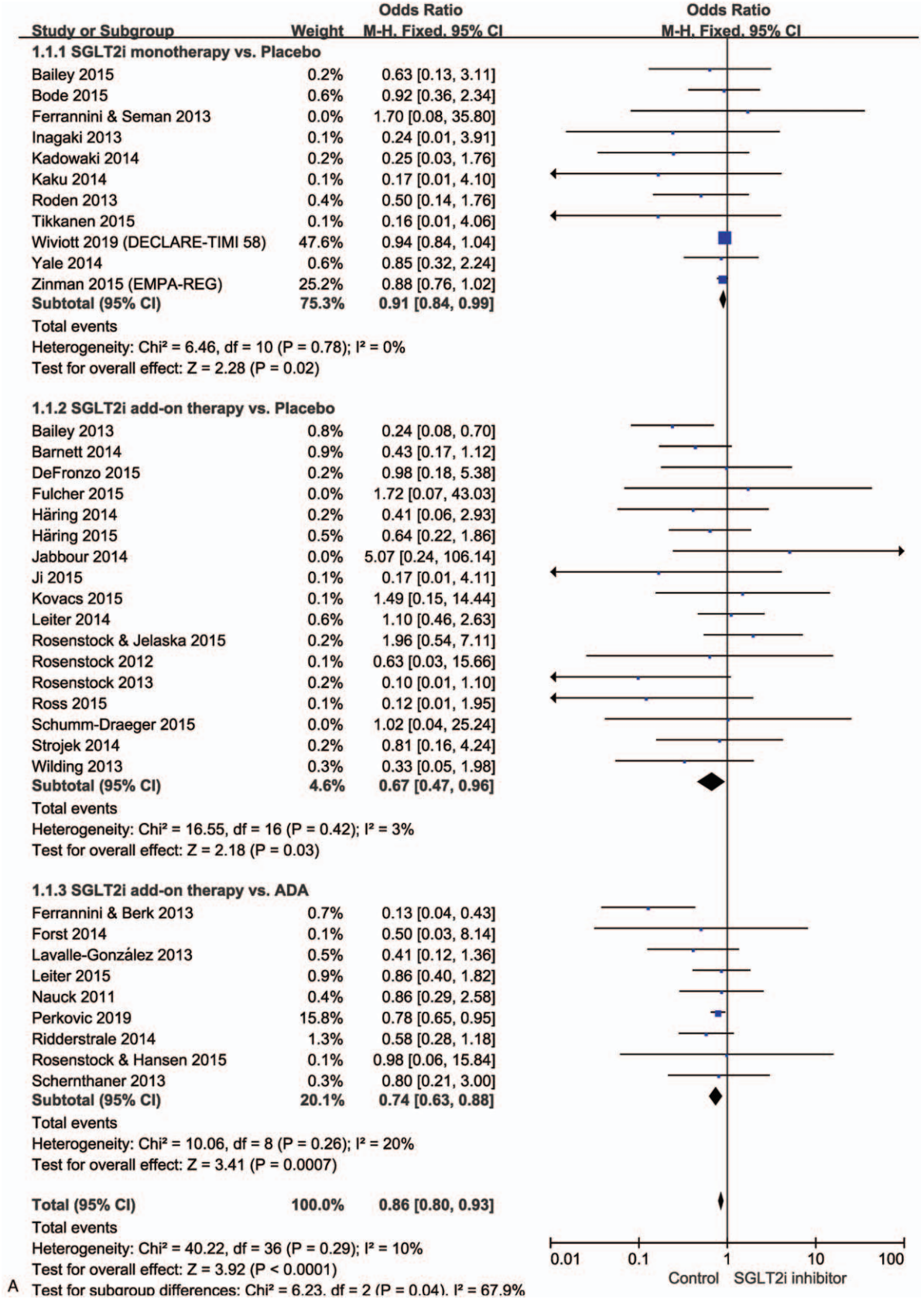
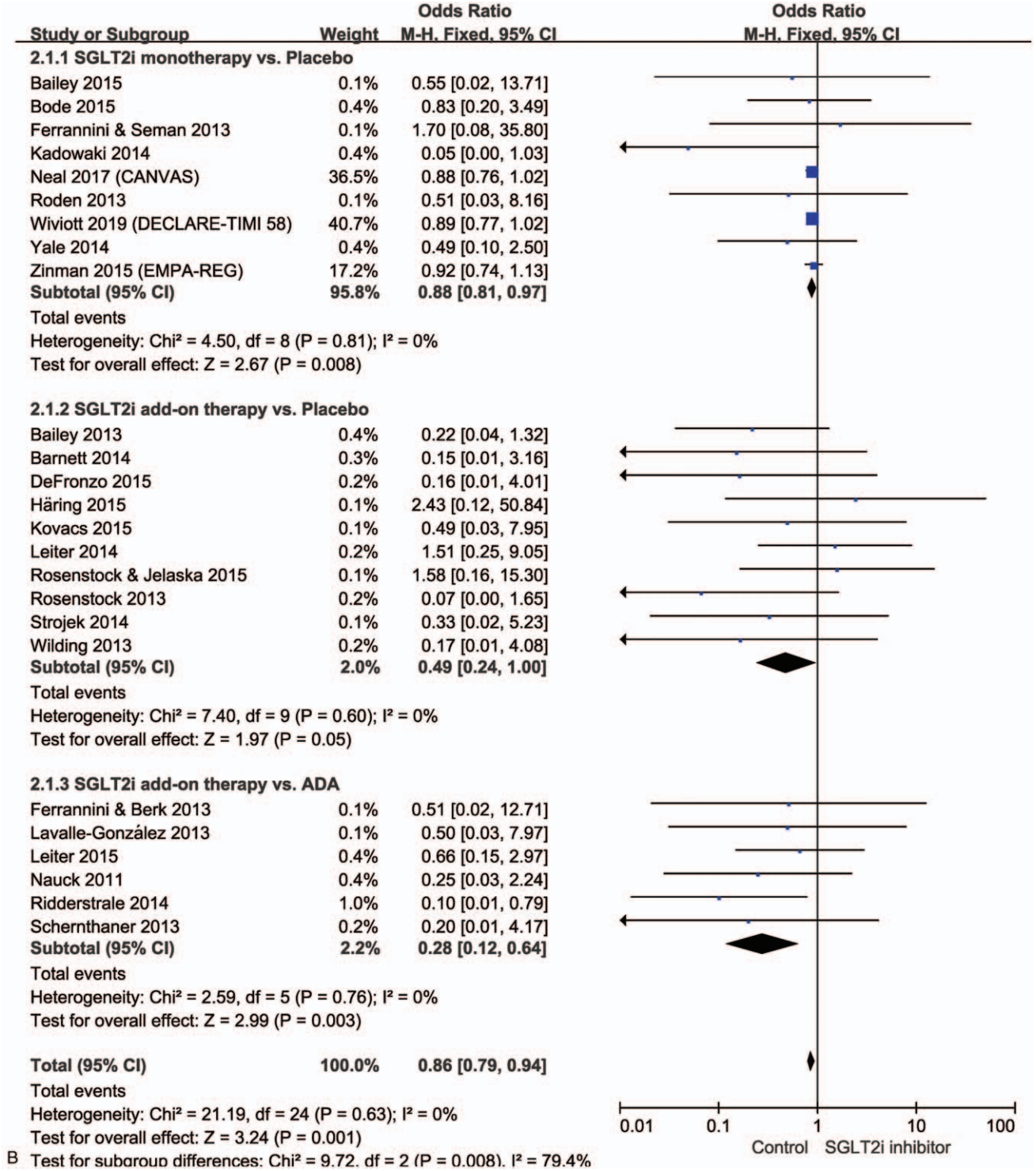


Figure 2. Forest plots for meta-analysis of the effects of SGLT2 inhibitors on cardiovascular outcomes in MACEs (A), myocardial infarction (B), ischemic stroke (C), cardiovascular death (D), and all-cause mortality (E) in patients with type 2 diabetes. Summary effects for all drugs were obtained from a fixed-effects meta-analysis.



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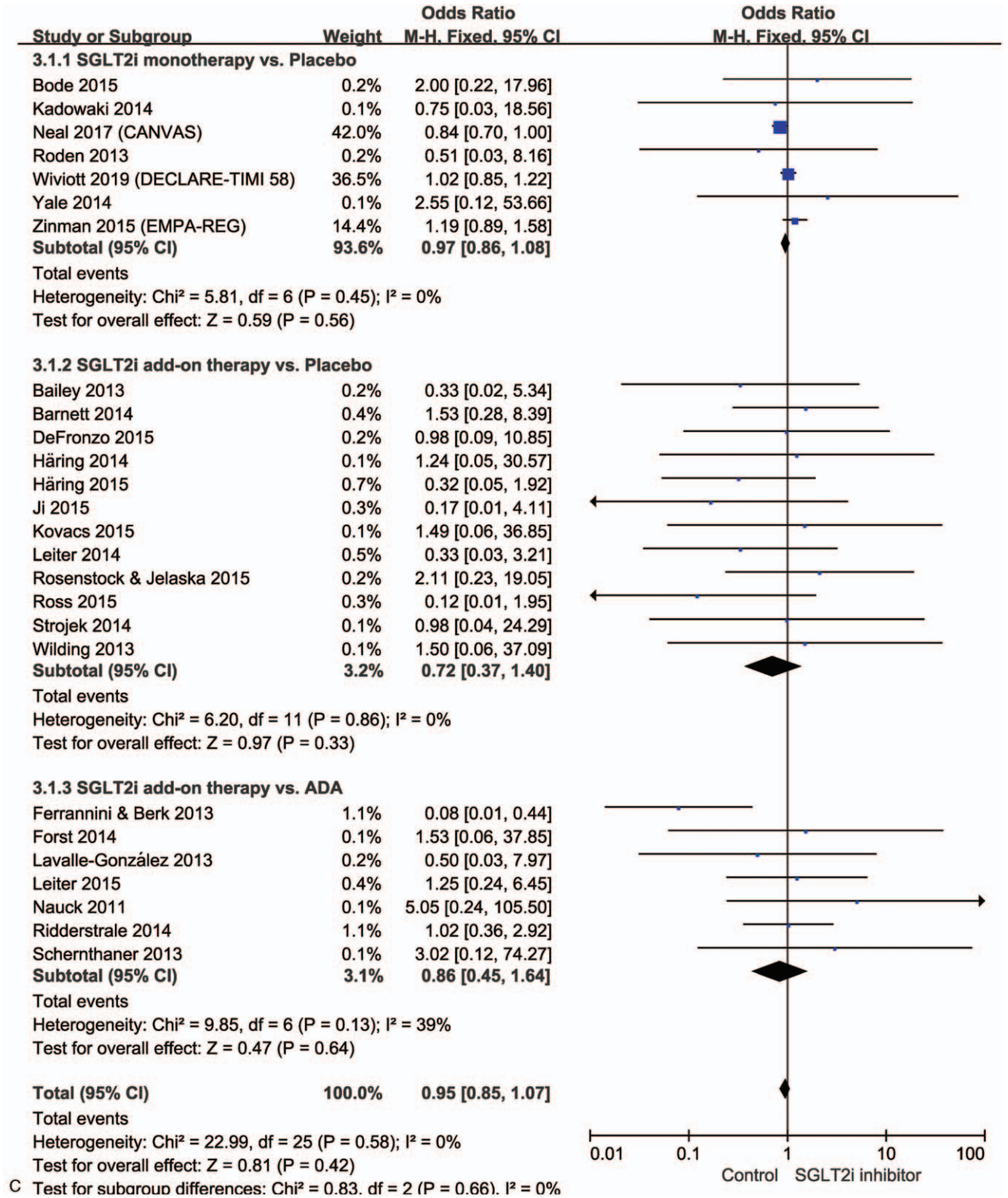
of MACEs compared with the control treatment (OR = 0.72, 95% CI 0.63–0.84, $P < .001$). These results confirm that our findings were not driven by any single study. Heterogeneity testing revealed a very low degree of heterogeneity, with $I^2 = 10\%$ ($P_{hetero} = .29$) (Fig. 2A). Publication bias was evaluated by a funnel plot, which showed no significant evidence of asymmetry (Fig. 3A).

3.3. Myocardial infarction

Twenty-five studies evaluated the effects of SGLT2 inhibitors on the risk of myocardial infarction in patients with type 2 diabetes. The findings indicated that the incidence of myocardial infarction in patients with type 2 diabetes was lower with SGLT2 inhibitor treatment than with controls (OR = 0.86, 95% CI 0.79–0.94, $P = .001$) especially in the comparison between SGLT2 inhibitor



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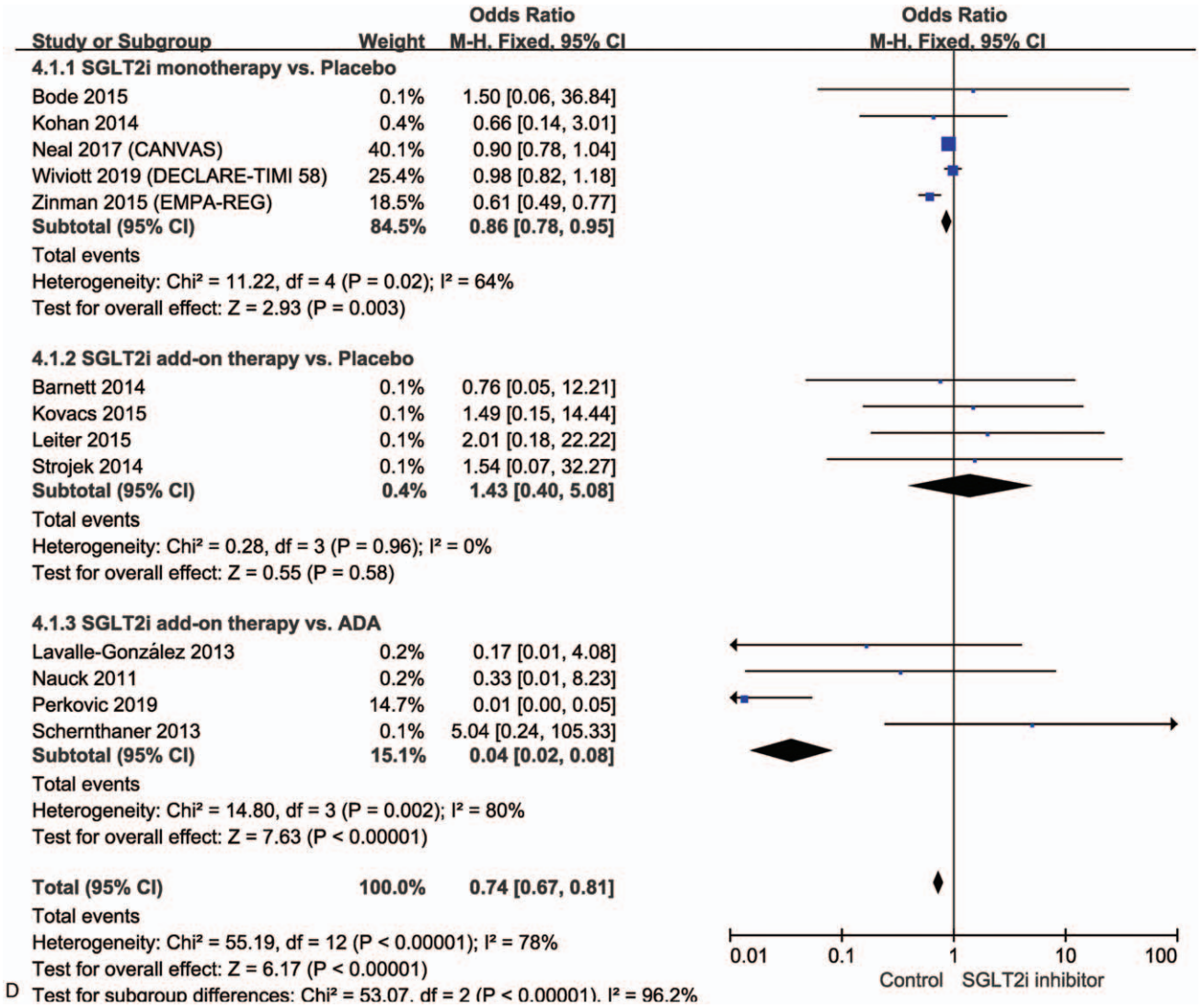
monotherapy vs placebo (OR = 0.88, 95% CI 0.81–0.97, $P = .008$) and SGLT2 inhibitor add-on therapy vs ADA treatment (OR = 0.28, 95% CI 0.12–0.64, $P = .003$). However, no reduction in the risk of myocardial infarction was observed in comparisons between SGLT2 inhibitor add-on therapy vs placebo (OR = 0.49, 95% CI 0.24–1.00, $P = .05$) (Fig. 2B). The sensitivity analysis removing 3 studies[16–18] suggested that SGLT2 inhibitors also decreased the incidence of myocardial



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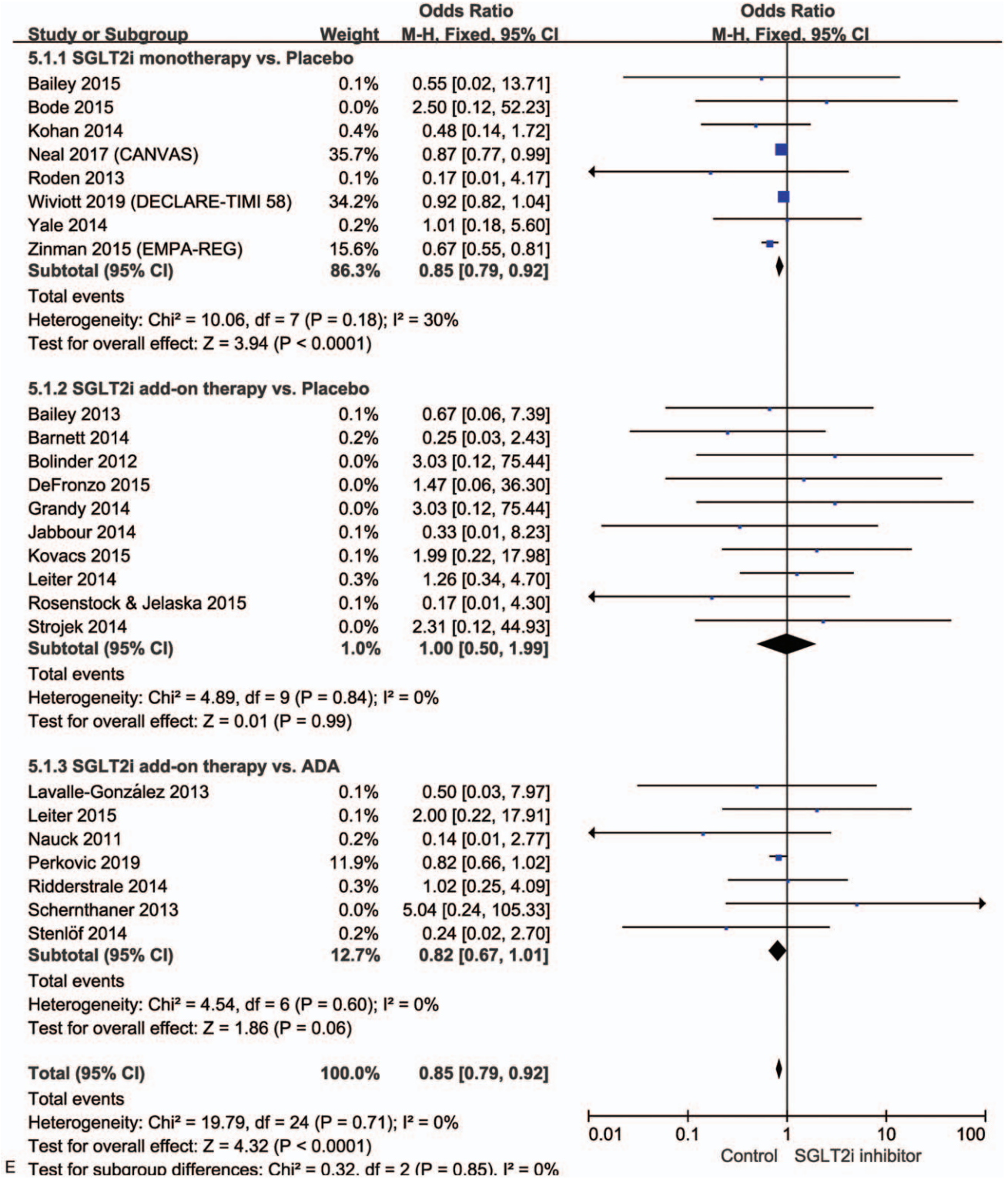
infarction compared with the control treatment (OR = 0.42, 95% CI 0.27–0.65, $P < .001$). There was no heterogeneity among the trials in analyzing the effects of SGLT2 inhibitors on myocardial infarction, with $I^2 = 0\%$ ($P_{hetero} = .63$) (Fig. 2B). The funnel plot showed no significant evidence of asymmetry (Fig. 3B).

3.4. Ischemic stroke

Twenty-six studies were analyzed to assess the effects of SGLT2 inhibitors on the risk of ischemic stroke in patients with type 2 diabetes. SGLT2 inhibitors did not reduce the risk of ischemic stroke compared with control treatment (OR = 0.95, 95% CI 0.85–1.07, $P = .42$). The subgroup analysis also demonstrated that there was no difference in the incidence of ischemic stroke between SGLT2 inhibitor monotherapy vs placebo (OR = 0.97, 95% CI 0.86–1.08, $P = .56$), SGLT2 inhibitor add-on therapy vs placebo (OR = 0.72, 95% CI 0.37–1.40, $P = .33$) or SGLT2 inhibitor add-on therapy vs other ADAs (OR = 0.86, 95% CI 0.45–1.64, $P = .64$) (Fig. 2C). The sensitivity analysis also revealed that the SGLT2 inhibitors had no impact on the incidence of stroke (OR = 0.84, 95% CI 0.55–1.30, $P = .44$). There was no substantial heterogeneity across trials, as all P values were larger than .05 and $I^2 < 50\%$ (Fig. 2C). The funnel plot did not reveal obvious asymmetry (Fig. 3C).

3.5. Cardiovascular death

Thirteen studies were employed to evaluate the effects of SGLT2 inhibitors on the risk of cardiovascular mortality. SGLT2 inhibitors significantly reduced cardiovascular mortality compared with control in patients with type 2 diabetes (OR = 0.74, 95% CI 0.67–0.81, $P < .00001$), especially comparing SGLT2 inhibitor monotherapy vs placebo (OR = 0.86, 95% CI 0.78–0.95, $P = .003$) and SGLT2 inhibitor add-on therapy vs ADA treatment (OR = 0.04, 95% CI 0.02–0.008, $P < .00001$). However, no difference in effects on cardiovascular death was found between SGLT2 inhibitor add-on therapy vs placebo (OR = 1.43, 95% CI 0.40–5.08, $P = .58$) in patients with type 2 diabetes (Fig. 2D). After removing 3 studies[16–18] with larger sample sizes, the sensitivity analysis suggested that SGLT2 inhibitors also



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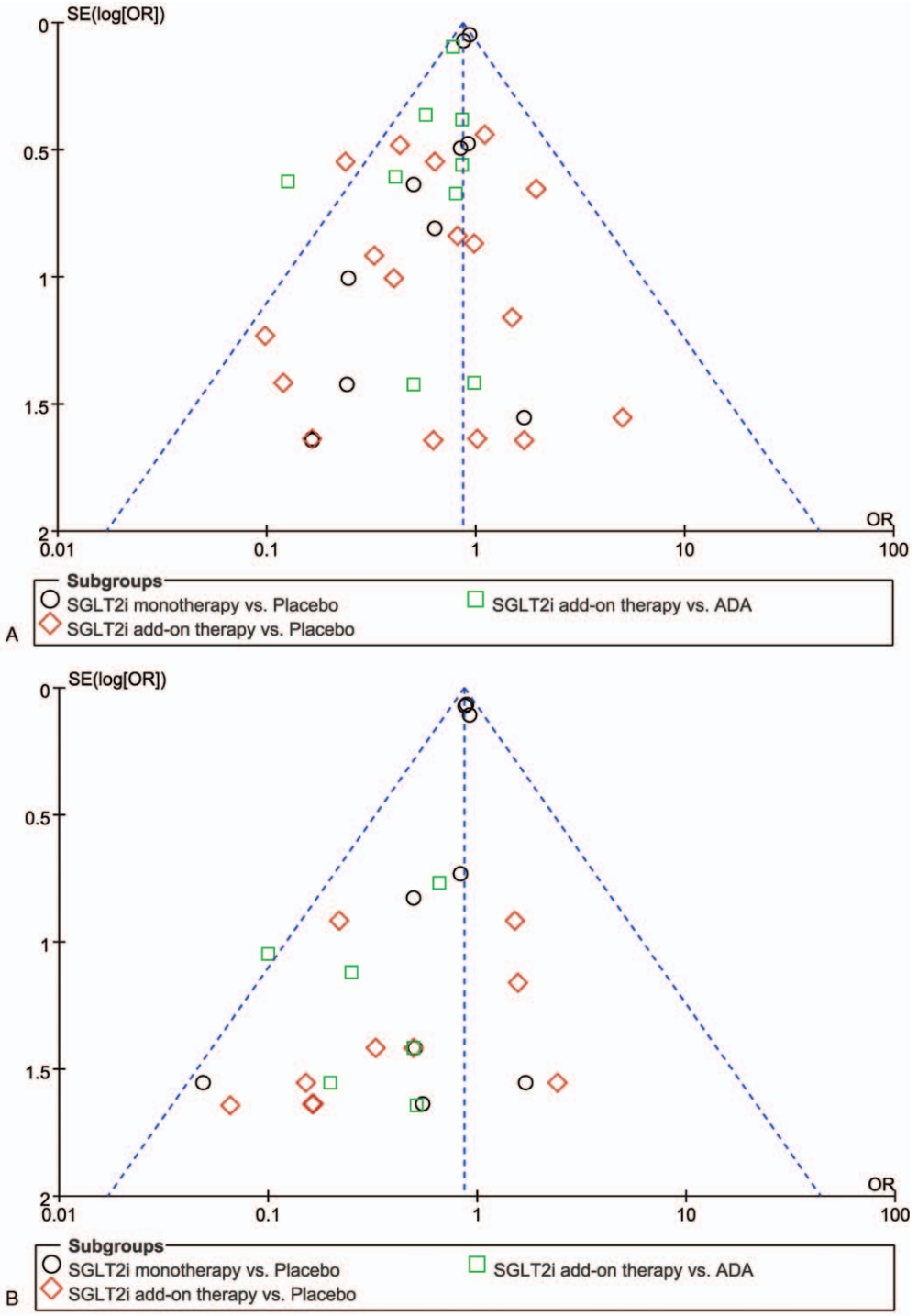

Figure 3. Funnel plot of standard error for SGLT2 inhibitors and control groups to detect publication bias in MACEs (A), myocardial infarction (B), ischemic stroke (C), cardiovascular death (D), and all-cause mortality (E) in patients with type 2 diabetes.

significantly decreased the incidence of cardiovascular death compared with the control treatment (OR = 0.72, 95% CI 0.63–0.84, $P < .001$). For the analysis of the effects of SGLT2 inhibitors on cardiovascular mortality, $I^2 = 78\%$ ($P_{hetero} < .001$), suggesting significant heterogeneity (Fig. 2D). Funnel plot analysis also suggested a relevant publication bias (Fig. 3D).

3.6. All-cause mortality

Twenty-five studies evaluated the effects of SGLT2 inhibitors and control treatments on the risk of all-cause mortality in patients with type 2 diabetes. SGLT2 inhibitors significantly reduced the risk of all-cause mortality compared with control (OR = 0.85, 95% CI 0.79–0.92, $P < 0.0001$), especially in the subgroup

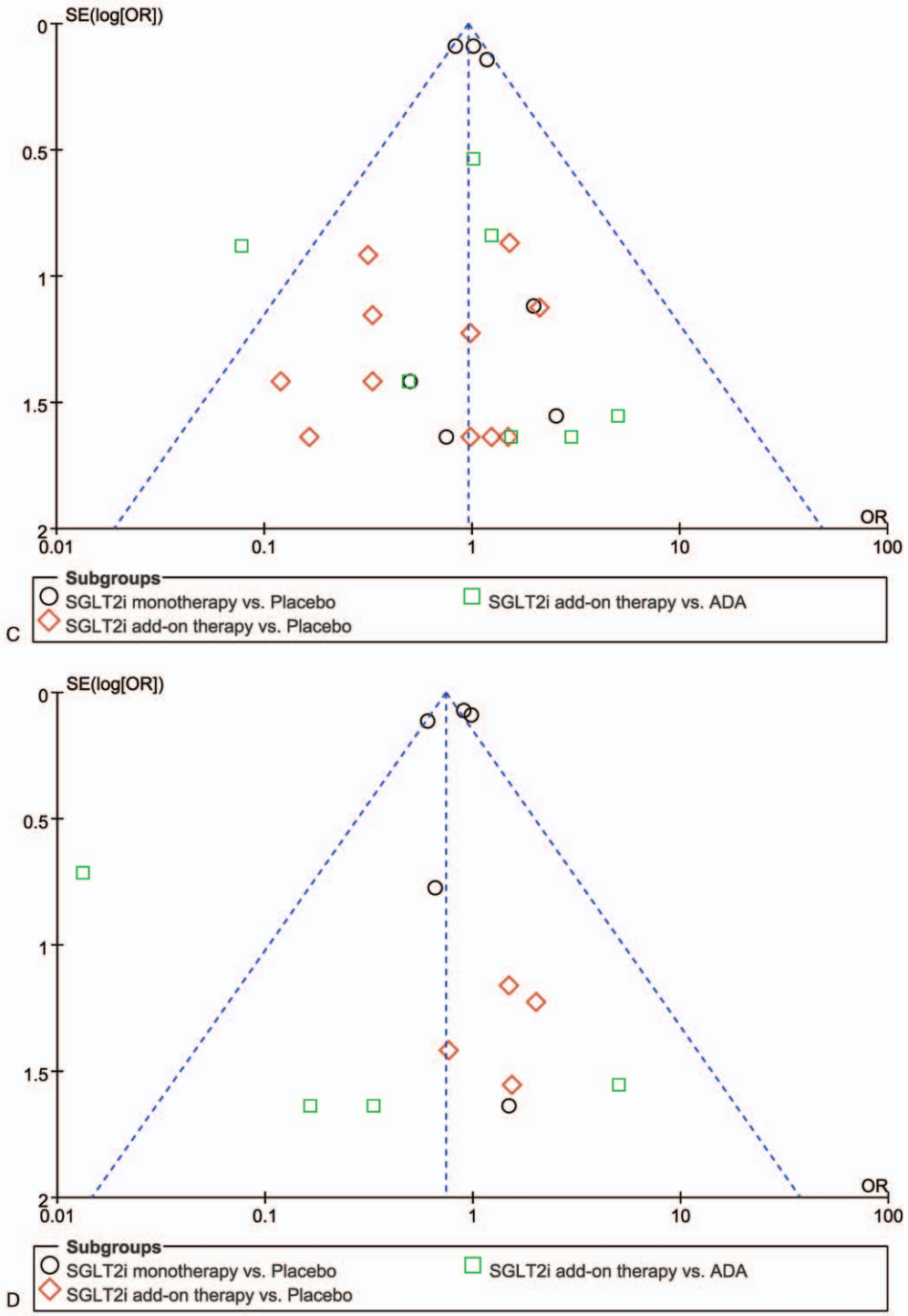

Figure 3. Continued.

analysis of the comparison between SGLT2 inhibitor monotherapy vs placebo (OR = 0.85, 95% CI 0.79–0.92, $P < .001$). There was no difference in comparison between SGLT2 inhibitor add-on therapy vs placebo (OR = 1.00, 95% CI 0.50–1.99, $P = .99$) and SGLT2 inhibitor add-on therapy vs other ADA therapy (OR = 0.82, 95% CI 0.67–1.01, $P = .06$). However, the sensitivity analysis performed by iteratively removing 3 studies[16–18] with larger sample sizes revealed that SGLT2 inhibitors had no impact on the incidence of all-cause mortality compared with the control treatment (OR = 0.82, 95% CI 0.68–1.00, $P = .05$). The induction effects of SGLT2 inhibitors on the incidence of all-cause mortality were mainly contributed by the 3 recent studies.[16–18] Additionally, there was no evidence of substantial heterogeneity between contributing studies ($I^2 = 0\%$; $P_{hetero} = .71$) (Fig. 2E). The funnel plot showed no significant evidence of asymmetry (Fig. 3E).

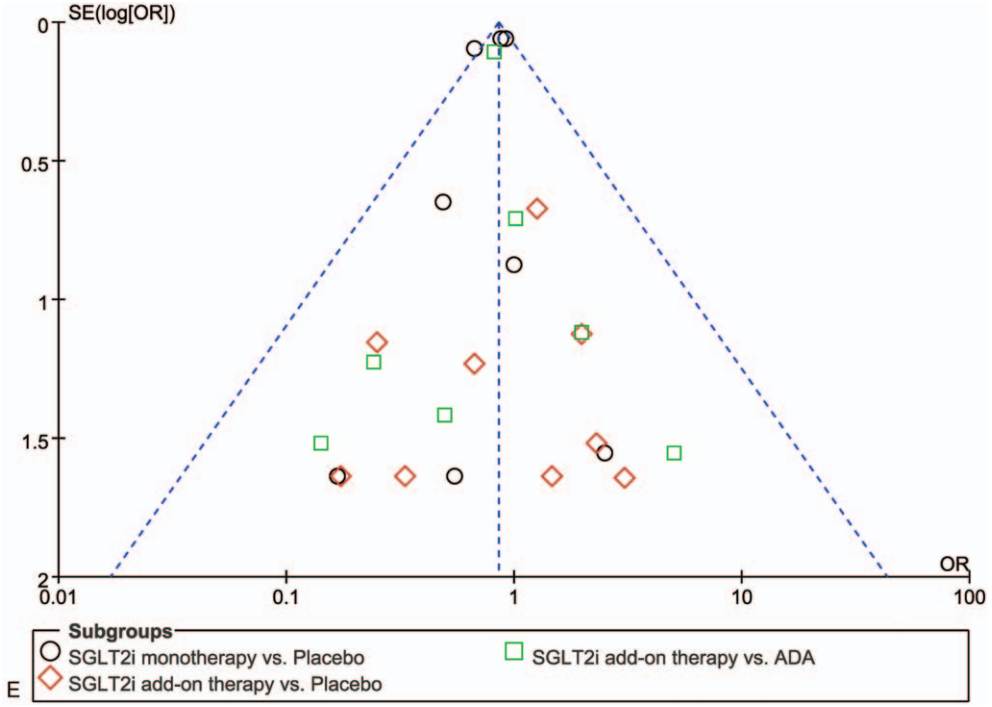

Figure 3. Continued.

4. Discussion

In our meta-analysis of 42 RCTs with 61,076 participants worldwide, we compared SGLT2 inhibitors with placebo or standard ADA treatment in people with type 2 diabetes. In the majority of trials of type 2 diabetes patients in this meta-analysis, SGLT2 inhibitors were associated with decreases in MACEs, myocardial infarction, and cardiovascular death compared with controls. The pooled results also revealed that SGLT2 inhibitor treatment, mainly derived from the SGLT2 inhibitor add-on therapy compared with ADA therapy in the subgroup analysis, reduced the risk of MACEs, myocardial infarction, and cardiovascular mortality. Compared with the placebo, SGLT2 inhibitor add-on therapy was associated only with the incidence reduction in MACEs, and SGLT2 inhibitor monotherapy had no effects on cardiovascular events or all-cause mortality. SGLT2 inhibitor treatment, either as monotherapy or add-on therapy, had no impact on the risk of ischemic stroke, which was consistent with a previous meta-analysis.[60] The main implications of our findings suggest that SGLT2 inhibitor administration, especially SGLT2 inhibitor add-on therapy, is beneficial for type 2 diabetes patients.

In several meta-analyses, favorable effects of SGLT2 inhibitors on reducing fasting blood sugar, HbA1c, body weight, and acute kidney injury were also observed.[61–65] Another meta-analysis assessed the long-term efficacy and safety of SGLT2 inhibitors in the management of type 2 diabetes, and the results showed that SGLT2 inhibitors significantly reduced systolic and diastolic blood pressures after 52 and 104 weeks significantly better than non-SGLT2 inhibitors.[4] However, these previous studies did not evaluate cardiovascular outcomes. Recently, several large trials[16,18,66] and meta-analyses[67,68] were conducted to evaluate the effects of SGLT2 inhibitors on cardiovascular outcomes and mortality in patients with type 2 diabetes. These data suggested the protection of SGLT2 inhibitors against cardiovascular events and death. However, SGLT2 inhibitor monotherapy was used as the intervention in these meta-analyses and clinical trials, and whether SGLT2 inhibitor add-on therapy has similar effects on cardiovascular events was unconfirmed. Interestingly, no clear evidence that individual types of drugs in this class have different effects on cardiovascular outcomes or death was demonstrated. It is plausible that individual agents within this class of drugs, including canagliflozin, dapagliflozin, and empagliflozin, have similar functional effects on cardiovascular events because SGLT2 inhibitors share the same mechanism of action.[60]

Our meta-analysis was conducted on SGLT2 inhibitor trials, including both monotherapy and add-on therapy, and our findings showed possible differences in cardiovascular outcomes, especially MACEs, depending on whether monotherapy or add-on therapy was administered. The overall class of SGLT2 inhibitors is a prominent option in the treatment of type 2 diabetes patients due to its value as add-on therapy to current ADA treatment.[69] A more significant improvement in HbA1c, FPG, body weight, and systolic and diastolic blood pressures was indicated in SGLT2 inhibitor add-on therapy compared with placebo or other ADAs, including metformin or DPP4 inhibitors.[70] In the longer term, SGLT2 inhibitors are more effective than sulfonylurea as an add-on to metformin in reducing HbA1c, weight and blood pressure.[71] Consequently, SGLT2 inhibitor add-on therapy seems to be more cost effective than traditional treatment with generic medications for patients who fail to achieve their glycemic goal on metformin.[72] Although the long-term effects of SGLT2 inhibitors on cardiovascular outcomes are still unclear, our overview analysis suggested that SGLT2 inhibitors as a drug class delivering cardiovascular protection will be supported by accumulating evidence in the future. To our knowledge, this report is the first systematic meta-analysis to include SGLT2 inhibitor add-on therapy compared with non-SGLT2 inhibitors or placebo, thus providing a reliable analysis of the cardiovascular outcomes of this class of medications.

Although we conducted a comprehensive systematic review of RCTs of SGLT2 inhibitors, several limitations need to be considered when interpreting our findings. First, none of the included trials were designed specifically to assess cardiovascular outcomes of SGLT2 inhibitors, even though all trials intended to evaluate the safety of SGLT2 inhibitors in patients with type 2 diabetes. In addition, the included trials had a wide range of clinical characteristics, such as age, disease duration, and follow-up duration, which will inevitably lead to heterogeneity. Second, only 42 studies met the predefined inclusion criteria and were included in the final meta-analysis. The included studies were almost all single-center trials with a relatively small number of patients. In addition, due to the limited number of studies, the latest approved SGLT2 inhibitors, such as ertugliflozin, were not enrolled in this meta-analysis to reduce the heterogeneity that might be derived from excessive interventions. These limitations may impair the power of our study. However, after a comprehensive literature search covering 3 databases was performed and eligible studies were selected by two different investigators according to strict inclusion criteria, most of the included studies had moderate-to-high quality. Therefore, we believe that it is reasonable to draw conclusions from this meta-analysis. Third, several of the endpoints, including cardiovascular and all-cause mortality, occur infrequently, resulting in these individual outcomes being at a higher risk of selective reporting bias than the more common adverse effects.

In summary, our meta-analysis evaluated the effects of SGLT2 inhibitors on cardiovascular outcomes in patients with type 2 diabetes, and the results demonstrated that patients treated with SGLT2 inhibitors, especially as add-on therapy, experienced significant cardioprotective effects and a potential favorable outcome for all-cause mortality. Due to the potential heterogeneity among the included studies, the results of this analysis should be confirmed with new and larger trials in the future.

Author contributions

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