Meta-Analysis of Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Cardiovascular Outcomes and All-Cause Mortality among Patients with Type 2 Diabetes Patients

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Running title: SGLT2 inhibitors and cardiovascular outcomes

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Abstract

The benefit or risk of sodium-glucose cotransporter 2 (SGLT2) inhibitors on cardiovascular (CV) outcomes in patients with type 2 diabetes mellitus (T2DM) has not been established. We aimed to assess the comparative CV safety and mortality risk associated with the use of SGLT2 inhibitors. PubMed, EMBASE, CENTRAL and ClinicalTrials.gov were systematically searched up to January 27, 2016 to identify randomized controlled trials (RCTs) with the use of SGLT2 inhibitors of at least 24 weeks' duration. The primary outcomes included all-cause mortality and major adverse cardiovascular events (MACE). A random-effects network meta-analysis was performed to calculate the odds ratio (OR) with 95% confidence interval (CI). We identified 37 eligible trials involving 29,859 patients that compared three SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) to placebo and other active antidiabetic treatments. Of all direct and indirect comparisons, only empagliflozin compared with placebo was significantly associated with lower risk of all-cause mortality (OR, 0.67; 95% CI 0.56 to 0.81) and MACE (OR, 0.81; 95% CI 0.70 to 0.93). However, the significant effect of empagliflozin was largely driven by one large randomized trial (EMPA-REG OUTCOME trial). Neither dapagliflozin nor canagliflozin was significantly associated with any harm. In conclusion, current RCT evidence suggests that three common SGLT2 inhibitors are not associated with increased risk of all-cause mortality and CV outcomes when used to treat T2DM patients. Though empagliflozin may have a protective effect, further confirmative data from rigorous RCTs are needed.

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

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a novel class of glucose-lowering agents for treating type 2 diabetes mellitus (T2DM), which act insulin independent to selectively inhibit renal glucose reabsorption, thereby increasing urinary glucose excretion[1]. SGLT2 inhibitors have the potential to improve cardiovascular (CV) risk profiles (e.g., lower blood pressure and weight loss) [2]. In 2008, the U.S. Food and Drug Administration (FDA) required a careful CV safety assessment for all novel glucose-lowering agents [3]. Recently, one large rigorously conducted clinical trial (EMPA-REG OUTCOME trial) found that patients with T2DM at high risk for CV events achieved a CV benefit from empagliflozin as compared with placebo [4]. However, despite such intriguing results, it remains uncertain whether the CV benefits are attributable specifically to empagliflozin alone or represent a class effect [5]. By contrast to conventional pairwise meta-analysis comparing only two interventions (A *vs.* B), a network meta-analysis is a useful method for comparing multiple interventions (A *vs.* B *vs.* C *vs.* …) , as it analyzed simultaneously both direct comparisons of interventions within randomized controlled trials (RCTs) and indirect comparisons across trials referred to a common comparator (e.g., placebo) [6]. We therefore conducted a network meta-analysis of all available RCTs to comprehensively assess the comparative effects of SGLT2 inhibitors on CV safety and mortality and clarify whether potential effects on CV outcomes are a specific drug effect or a class effect.

Methods

This review was performed according to the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions [7] and was registered with PROSPERO (number, CRD42015026853).

An electronic search was performed in PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) through January 27, 2016 to identify eligible RCTs with a combination of relevant search terms (**Supplementary Table 1**). No limitations of language and year of publication were applied. Additional data from the reference lists of relevant reviews and ClinicalTrials.gov were further searched to ensure identification of published and unpublished trials.

Eligible trials met the following criteria: 1) RCTs with follow-up duration at least 24 weeks; 2) Adults (≥18 years of age) with T2DM; 3) SGLT2 inhibitors with any licensed dose used as monotherapy or in combination with other antidiabetic drugs compared with placebo, another SGLT2 inhibitor, or other active antidiabetic treatments; and 4) At least one of our selected CV outcomes was reported in the published article, or the results were presented on ClinicalTrials.gov. Our primary outcomes included all-cause mortality and major adverse cardiovascular events (MACE), including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The secondary outcomes included heart failure or heart failure requiring hospitalization, unstable angina or unstable angina requiring hospitalization, atrial fibrillation, and transient ischemic attack. The CV events were reported by investigators as an adverse event (or serious adverse event) identified in the database using pre-specified lists from the Medical Dictionary for Regulatory Activities (MedDRA).

Two reviewers independently selected the studies and extracted relevant information about trial characteristics and outcomes. If multiple reports from the same trial were retrieved, only the most complete and/or longest follow-up data were used. If CV events were not reported in the manuscript, data from the “Serious Adverse Events” section on

the ClinicalTrials.gov were extracted. In addition, if specific CV events were not reported on ClinicalTrials.gov, the incidence of the events was assumed to be zero. If two different groups of randomization of non-overlapping patient groups (e.g., A vs B and C vs D) were included in the same report, each group was considered separately. If three arms (e.g., A vs B vs A+B) were evaluated in the RCTs, data from only two arms (A vs B) were included. When placebo was switched to an active comparator in the extended period of trials, only the period with placebo was documented. In addition, two reviewers independently critically assessed all included RCTs according to the modified Cochrane risk of bias tool, which is described in the Cochrane Collaboration's tool for assessing risk of bias [8]. If any data were unclear or missing, the authors of the original RCTs were contacted for further information. Any disagreements were resolved by consensus or by discussion with a third reviewer.

Pairwise and network meta-analyses were conducted to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for the primary and secondary outcomes.
For pairwise meta-analyses, a Peto OR was calculated for the effect sizes from direct comparisons because of very low event rate [9]. An I^2 statistic was used to evaluate the presence of heterogeneity within meta-analyses, with I^2 of 25%, 50%, and 75% indicating a low, moderate, and high level of evidence of statistical heterogeneity, respectively.

For indirect and mixed comparisons, a network meta-analysis with a random-effects model was performed to compare different SGLT2 inhibitors. For zero-event RCT, a 0.5 zero-cell correction was applied before meta-analysis[10]. The network meta-analysis was performed with STATA version 14 using the “mvmeta” command and programmed STATA routines [11,12]. To rank the SGLT2 inhibitors for a specified outcome, we estimated

the relative ranking probability of each treatment using surface under the cumulative ranking curve (SUCRA) and mean ranks. For all-cause mortality and CV outcomes, higher SUCRA score and lower mean rank indicate a safer intervention[13]. In addition, a clustered ranking plot of the network was performed to group the treatments based on the SUCRA probabilities for MACE and any-cause mortality. The heterogeneity variance (tau) was used to estimate the extent of between-study heterogeneity[14].

To check for the presence of inconsistency, a loop inconsistency–specific approach was introduced to evaluate the difference between direct and indirect estimates for a specific comparison [15]. To check the assumption of consistency in the entire network, a design-by-treatment interaction model using the χ^2 test was used [16]. Otherwise, to investigate the robustness of the findings, we assessed the effect of differing trial and participant characteristics on the primary outcomes in sensitivity analyses by restricting to trials with follow-up at least 52 weeks, white patients, SGLT2 inhibitors combination therapy, and trials without pre-specified CV events as primary outcomes. In addition, when primary outcomes with any SGLT2 inhibitor detected a significant difference, a cumulative meta-analysis was conducted to assess the robustness of evidence over time[17]. Finally, a comparison-adjusted funnel plot was used to assess small study effects within a network of interventions [18].

Results

A total of 1,268 citations were retrieved through electronic search, from which 172 potentially eligible reports were identified by reviewing study titles and abstracts. Finally, 37 eligible RCTs involving 28,859 patients were included in this meta-analysis (**Figure 1**). These patients were randomly assigned to a SGLT2 inhibitor (canagliflozin, dapagliflozin,

or empagliflozin) or control groups (placebo or other active anti-diabetic treatments). Sample sizes of individual trials ranged between 180 and 7,020 participants, and the periods of follow-up ranged from 24 to 160 weeks. Of all the trials, only three included patients with pre-existing CV disease (more than 90%) [4,19,20]. One extension trial provided two independent RCT datasets for two different comparisons (empagliflozin versus metformin and empagliflozin versus sitagliptin), which we considered separately [21]. The data of two trials were presented together on ClinicalTrials.gov, so we included the combined data as one trial [22,23]. Detailed information is presented in the **Supplementary Table 2**.

Quality assessment of the 37 RCTs is summarized as follows: 30 RCTs reported adequate random sequence generation, and 26 RCTs reported adequate allocation concealment. Masking conditions were high in two RCTs, which were both "open label" in their extended periods. In addition, only one RCT pre-specified CV events as primary outcomes, and none of the studies had incomplete outcome data (**Supplementary Figure 1**). All of the trials were funded by industry. Moreover, the comparison-adjusted funnel plot showed no small study effects for the primary outcomes of interest (**Supplementary Figure 2**).

Networks of eligible comparisons for the primary outcomes are presented in **Figure 2,** and the results for direct comparisons and network estimates are presented in the appendix (**Supplementary Tables 3-5 and Supplementary Figures 3-8**). The results of our pairwise meta-analysis were consistent with the results of our network meta-analysis. In the network meta-analyses, low statistical heterogeneity was observed in networks (tau≈0). No loop inconsistency was detected in the loop of comparisons between direct

and indirect evidence (all 95%CIs across zero). In addition, no global inconsistency was detected within any network (all P>0.05) (**Supplementary Tables 6-7**).

Among the 37 trials selected, 34 (involving 26,565 patients with 1,016 events) provided adequate data for MACE outcomes. Empagliflozin was significantly associated with a lower risk of MACE than placebo (OR, 0.81; 95% CI, 0.70 to 0.93), but there was no significant difference between dapagliflozin (OR, 0.81; 95%CI, 0.46 to 1.45) or canagliflozin (OR, 1.10; 95%CI, 0.53 to 2.29) and placebo (**Figure 3**). Similar rates of MACE were found among these three SGLT2 inhibitors (**Supplementary Figure 3**). All-cause mortality was reported in all 37 trials (28,859 patients with 537 events). Only empagliflozin was significantly better at reducing all-cause mortality than placebo (OR, 0.67; 95%CI, 0.56 to 0.81), and there were no significant differences between the other two SGLT2 inhibitors and placebo (canagliflozin: OR, 0.85; 95%CI, 0.36 to 2.05; dapagliflozin: OR, 1.12; 95%CI, 0.51 to 2.44) (**Figure 3**). There was no significant difference between these three SGLT2 inhibitors (**Supplementary Figure 4**). A clustered ranking plot based on SUCRA probabilities suggests that empagliflozin appeared to reduce risk of MACE and any-cause mortality more than the other two SGLT2 inhibitors (**Figure 4 and Supplementary Table 8**).

In terms of heart failure or heart failure requiring hospitalization, only empagliflozin was associated with lower incidence than placebo (OR, 0.65; 95%CI, 0.50 to 0.84); the other two SGLT2 inhibitors had no effects on this outcome (dapagliflozin: OR, 0.60; 95%CI, 0.27 to 1.33; canagliflozin: OR, 0.68; 95%CI, 0.22 to 2.06) (**Figure 3**). The risk of heart failure or heart failure requiring hospitalization was similar between these three SGLT2 inhibitors (**Supplementary Figure 5**). SGLT2 inhibitors were generally similar to

placebo for risks of unstable angina or unstable angina requiring hospitalization, atrial fibrillation, and transient ischemic attack (**Figure 3**). There was no significant difference in these events between these SGLT2 inhibitors. (**Supplementary Figure 6-8**).

In the sensitivity analyses restricting to trials with follow-up of at least 52 weeks (22 RCTs), white patients (34 RCTs), and SGLT2 inhibitors in combination with other active antidiabetic drugs (24 RCTs), the results were unchanged. However, the significant results of empagliflozin for MACE and all-cause mortality outcomes in complete analysis were largely driven by the EMPA-REG OUTCOME trial, which used CV outcomes as primary outcomes [4]. MACE (OR, 0.70; 95%CI, 0.41 to1.19) and all-cause mortality (OR, 0.70; 95%CI, 0.29 to1.70) for empagliflozin were not significantly different from those associated with placebo when we restricted to the trials without pre-specified CV outcomes as primary outcomes (excluding EMPA-REG OUTCOME trial). A cumulative meta-analysis by publication year of trials showed that empagliflozin was significantly associated with a reduced risk for primary outcomes since 2015 when the trial was published by Zinman et al in 2015 (**Supplementary Figure 9**) [4]. It also indicated that the significant CV benefit of empagliflozin was largely driven by the EMPA-REG OUTCOME trial.

Discussion

Our network meta-analysis of all eligible RCTs involving 30,250 patients showed that none of the three SGLT2 inhibitors was harmful for CV outcomes or all-cause mortality. For the primary outcomes, only empagliflozin appeared associated with a lower risk of MACE and all-cause mortality compared to placebo, whereas neither dapagliflozin nor canagliflozin was significantly associated with any harm. With respect to secondary

outcomes, only empagliflozin had lower risk of heart failure or heart failure requiring hospitalization than placebo, and all three SGLT2 inhibitors had similar risk of unstable angina or unstable angina requiring hospitalization, atrial fibrillation, and transient ischemic attack. However, the protective effect of MACE and all-cause mortality from empagliflozin was largely driven by the EMPA-REG OUTCOME trial. Our findings regarding the CV benefits of empagliflozin should be interpreted cautiously. Further evidence from trials using primary CV outcomes is needed to confirm these results.

Our findings from pairwise and network meta-analyses showed that SGLT2 inhibitors were not associated with any increased risk of all-cause mortality and CV outcomes, and only empagliflozin showed a CV protective benefit, which was consistent with two meta-analyses [24,25]. The potential effect of glucose-lowering agents on CV events might depend on how their differing modes of action modulate CV risk factors [26]. Unlike other glucose-lowering agents, SGLT2 inhibitors offer an insulin-independent mechanism of action by selectively inhibiting renal glucose reabsorption to increase urinary glucose excretion[1]. Thus, SGLT2 inhibitors possibly improve a variety of CV risk factors [26]. Evidence from meta-analyses and clinical trials has shown that SGLT2 inhibitors could meaningfully reduce blood pressure and weight [27]. Interestingly, data showed that empagliflozin could also reduce arterial stiffness [28], which is a strong independent predictor of CV events and death [29]. In addition, SGLT2 inhibitors could reduce total fat mass and regional adipose tissue distribution, which are both associated with CV complications [30]. However, the precise mechanisms underlying the CV benefits of SGLT2 inhibitors are still unclear.

Of the SGLT2 inhibitors, our meta-analysis provided evidence for a reduction in MACE and all-cause mortality by empagliflozin only. Indeed, the findings from the first main CV outcomes research (EMPA-REG OUTCOME trial) of empagliflozin in patients with high risk of CV disease contributed predominantly to our results, and no significant difference between empagliflozin and placebo remained after excluding this trial, which comprised more than about 84% percent of events (MACE with 853 events and 1,016 events from this trial and all trials, respectively) [4]. The conflicting results might be caused by the fact that more non-serious CV events were recorded in EMPA-REG OUTCOME trial, but only rare serious or fatal CV events were reported in most of the phase II and III RCTs, yielding low sample size/power to detect a statistical difference in these small RCTs, even in the meta-analysis. Therefore it is not surprising that there was no significant difference between the other two SGLT2 inhibitors (dapagliflozin and canagliflozin) and placebos in terms of MACE and all-cause mortality, which was consistent with three pairwise meta-analyses [2,24,27]. Two meta-analyses showed that the combined SGLT-2 inhibitor group (mainly dapagliflozin and canagliflozin) was not significantly associated with an reduced risk for MACE compared with placebo or active treatments[2 27], and one meta-analysis indicated that canagliflozin and dapagliflozin did not significantly affect mortality or CV outcomes[24]. However, one meta-analysis found a lower risk of MACE from dapagliflozin than control [25]. The CV safety of dapagliflozin and canagliflozin needed to be explored further, due to current evidence from small-scale, short-term RCTs without pre-specified CV outcomes as primary outcomes. Therefore, to address the CV safety issue, in addition to the EMPA-REG OUTCOME trial, several large RCTs using CV events as primary outcomes are still ongoing, including CANVAS,

CANVAS-R, DECLARE-TIMI58, and CREDENCE. In future these large outcome studies will not only provide enough statistical power to confirm our findings, but also solve the issue of whether SGLT2 inhibitors offer a specific drug effect or a class effect in terms of CV benefits.

Consistent with the findings of the EMPA-REG OUTCOME trial, empagliflozin was the only SGLT2 inhibitor to reduce the risk of heart failure or heart failure requiring hospitalization, compared with placebo. However, there was a trend toward reduced risk of heart failure with the use of dapagliflozin or canagliflozin. The protective effect of SGLT2 inhibitors (mainly empagliflozin) against heart failure is possibly attributable to improvements in CV risk factors. SGLT2 inhibitors were not associated with increased risk for unstable angina or unstable angina requiring hospitalization, atrial fibrillation, or transient ischemic attack. However, these findings need to be confirmed in future outcome research studies with adequate power.

Compared with two previous meta-analyses[24,25], our comprehensive network meta-analysis has two major strengths. First, network meta-analysis was introduced to simultaneous analysis of both direct and indirect comparisons to provide evidence of comparative effects among SGLT2 inhibitors. Secondly, sensitivity and cumulative meta-analyses were conducted to test the evidence sufficiency and finding robustness.

However, some limitations of our study merit further discussion. First, a major limitation was that few RCTs of SGLT2 inhibitors include CV outcomes as primary outcomes. Thus, one of the domains of risk of bias (pre-specified CV outcomes as adverse event of interest) was judged as high. Secondly, only rare serious or fatal CV events (often zero events) were reported in the phase II or III clinical trials, which

resulted in a low statistical power to calculate the exact incidence of some CV event, which might also partly explain the majority of CV cases from the EMPA-REG OUTCOME trial. Thirdly, the network meta-analysis model was based on the assumption that patient characteristics from selected trials were sufficiently similar (e.g., trials comparing canagliflozin with placebo were similar to trials comparing dapagliflozin with placebo in terms of CV risk factors at baseline). Varied background treatments and patients' characteristics among the RCTs might contribute to clinical heterogeneity, though low statistical heterogeneity and absence of inconsistency of our network model were detected in the network meta-analysis. Fourthly, different types of active comparators were combined into a control group to increase the power, but might contribute to heterogeneity. Finally, due to the fact that no trials of newer SGLT2 inhibitors (such as ipragliflozin, ertugliflozin, remogliflozin, luseogliflozin, tofogliflozin, or sotagliflozin) were included, the CV outcomes for these agents remain uncertain.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Figure Legends:

Figure 1. Flow chart of the identification of eligible trials.

Figure 2. Network of available SGLT2 inhibitor comparisons for MACE (left) and all-cause mortality (right). The size of the nodes corresponds to the number of trials including respective treatments. The directly compared treatments are linked with a line, the thickness of which corresponds to the number of trials that assessed this comparison. CANA = canagliflozin; DAPA = dapagliflozin; EMPA = empagliflozin; PLA = placebo; ACT = active treatments.

Figure 3. Network meta-analysis of SGLT2 inhibitor compared with placebo on primary and secondary outcomes. Common heterogeneity for every outcome in the network meta-analysis was low (tau≈0). Treatments are ranked by SUCRA values. MACE = major adverse cardiovascular events; CANA = canagliflozin; DAPA = dapagliflozin; EMPA = empagliflozin; PLA = placebo; ACT = active treatments.

Figure 4. Clustered ranking plot of the network based on the SUCRA probabilities for MACE and any-cause mortality. Each symbol represents a group of treatments that belong to the same cluster. Treatments lying in the upper right corner are considered to be safer than the other treatments for both outcomes. MACE = major adverse cardiovascular events; CANA = canagliflozin; DAPA = dapagliflozin; EMPA = empagliflozin; PLA = placebo; ACT = active treatments.

Fig.1

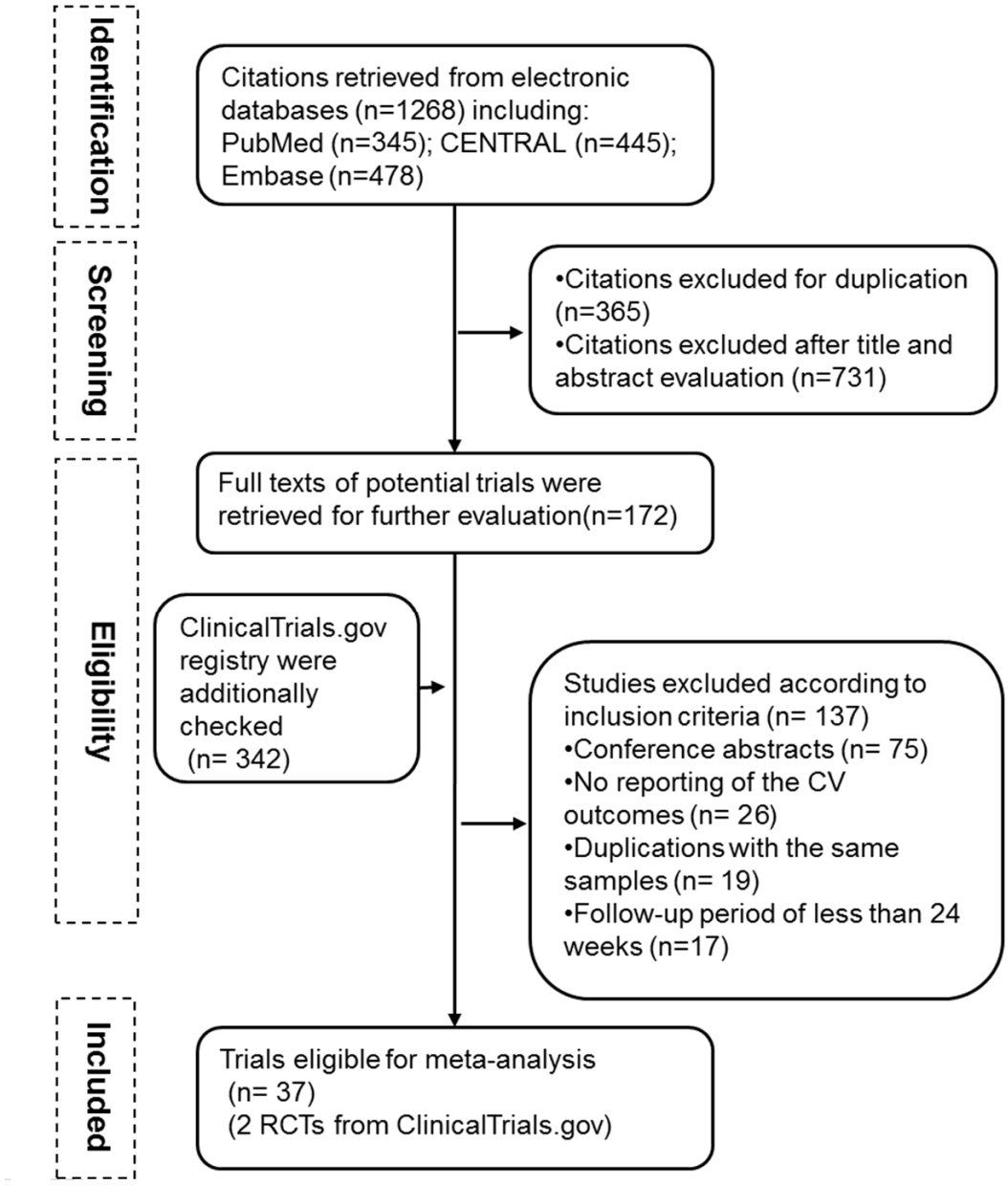
Identification
Screening
Eligibility
Included
Citations retrieved from electronic databases (n=1268) including: PubMed (n=345); CENTRAL (n=445); Embase (n=478)
•Citations excluded for duplication (n=365)
•Citations excluded after title and abstract evaluation (n=731)
Full texts of potential trials were retrieved for further evaluation(n=172)
ClinicalTrials.gov registry were additionally checked (n= 342)
Studies excluded according to inclusion criteria (n= 137)
•Conference abstracts (n= 75)
•No reporting of the CV outcomes (n= 26)
•Duplications with the same samples (n= 19)
•Follow-up period of less than 24 weeks (n=17)
Trials eligible for meta-analysis (n= 37)
(2 RCTs from ClinicalTrials.gov)

Fig.2

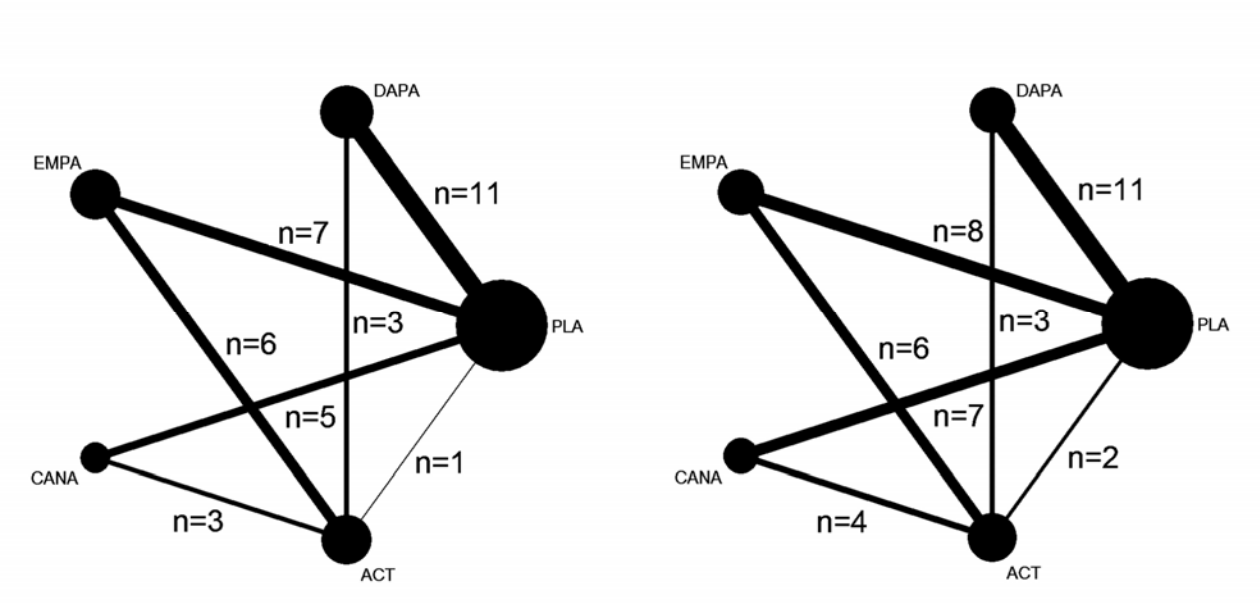
DAPA
EMPA
n=11
n=7
n=3
PLA
n=6
n=5
n=1
CANA
n=3
ACT
DAPA
EMPA
n=11
n=8
n=3
PLA
n=6
n=7
n=2
CANA
n=4
ACT

Fig .3

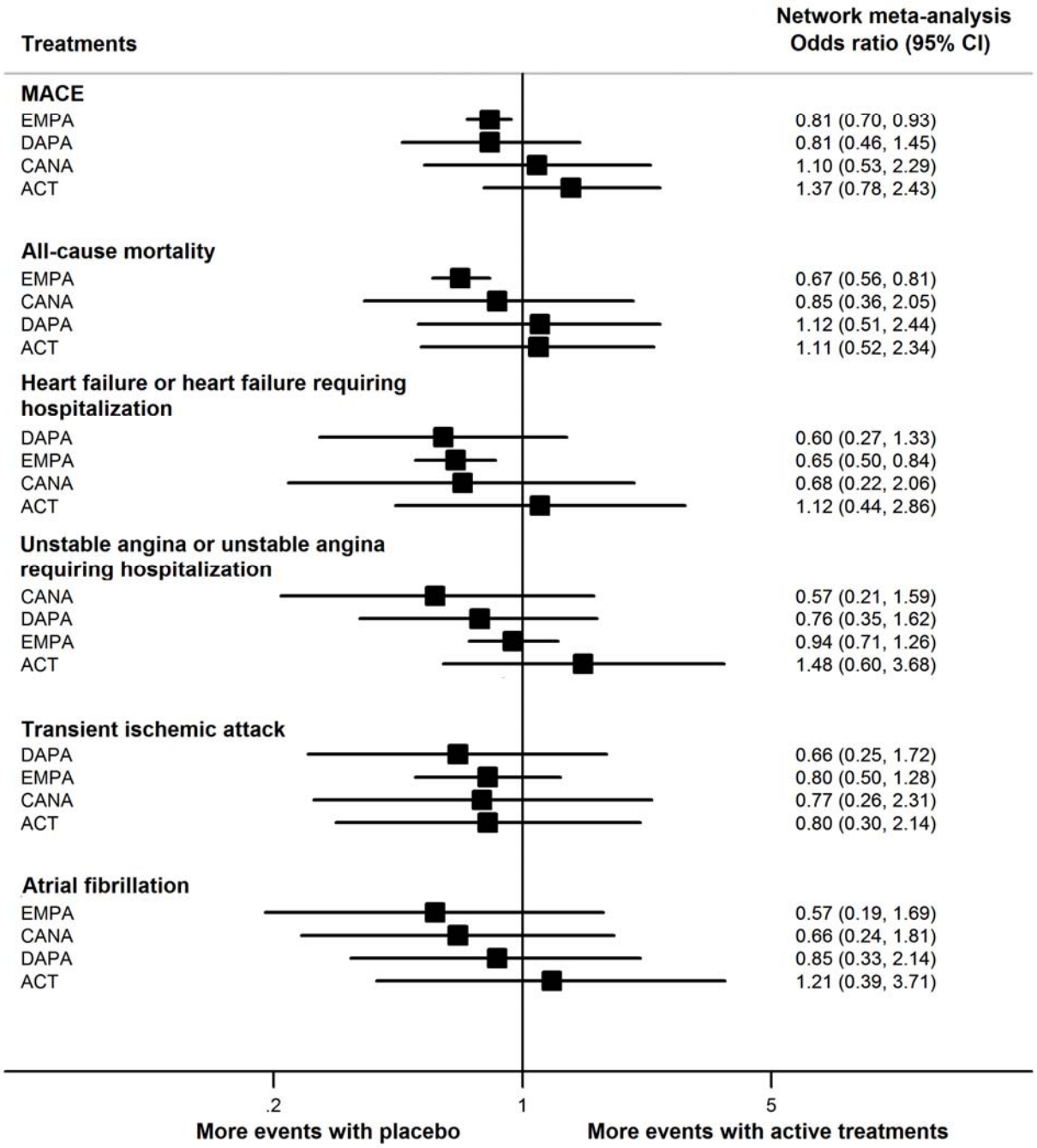
Treatments
Network meta-analysis
Odds ratio (95% CI)
MACE
EMPA
0.81 (0.70, 0.93)
DAPA
0.81 (0.46, 1.45)
CANA
1.10 (0.53, 2.29)
ACT
1.37 (0.78, 2.43)
All-cause mortality
EMPA
0.67 (0.56, 0.81)
CANA
0.85 (0.36, 2.05)
DAPA
1.12 (0.51, 2.44)
ACT
1.11 (0.52, 2.34)
Heart failure or heart failure requiring hospitalization
DAPA
0.60 (0.27, 1.33)
EMPA
0.65 (0.50, 0.84)
CANA
0.68 (0.22, 2.06)
ACT
1.12 (0.44, 2.86)
Unstable angina or unstable angina requiring hospitalization
CANA
0.57 (0.21, 1.59)
DAPA
0.76 (0.35, 1.62)
EMPA
0.94 (0.71, 1.26)
ACT
1.48 (0.60, 3.68)
Transient ischemic attack
DAPA
0.66 (0.25, 1.72)
EMPA
0.80 (0.50, 1.28)
CANA
0.77 (0.26, 2.31)
ACT
0.80 (0.30, 2.14)
Atrial fibrillation
EMPA
0.57 (0.19, 1.69)
CANA
0.66 (0.24, 1.81)
DAPA
0.85 (0.33, 2.14)
ACT
1.21 (0.39, 3.71)
.2
1
5
More events with placebo
More events with active treatments

Fig.4

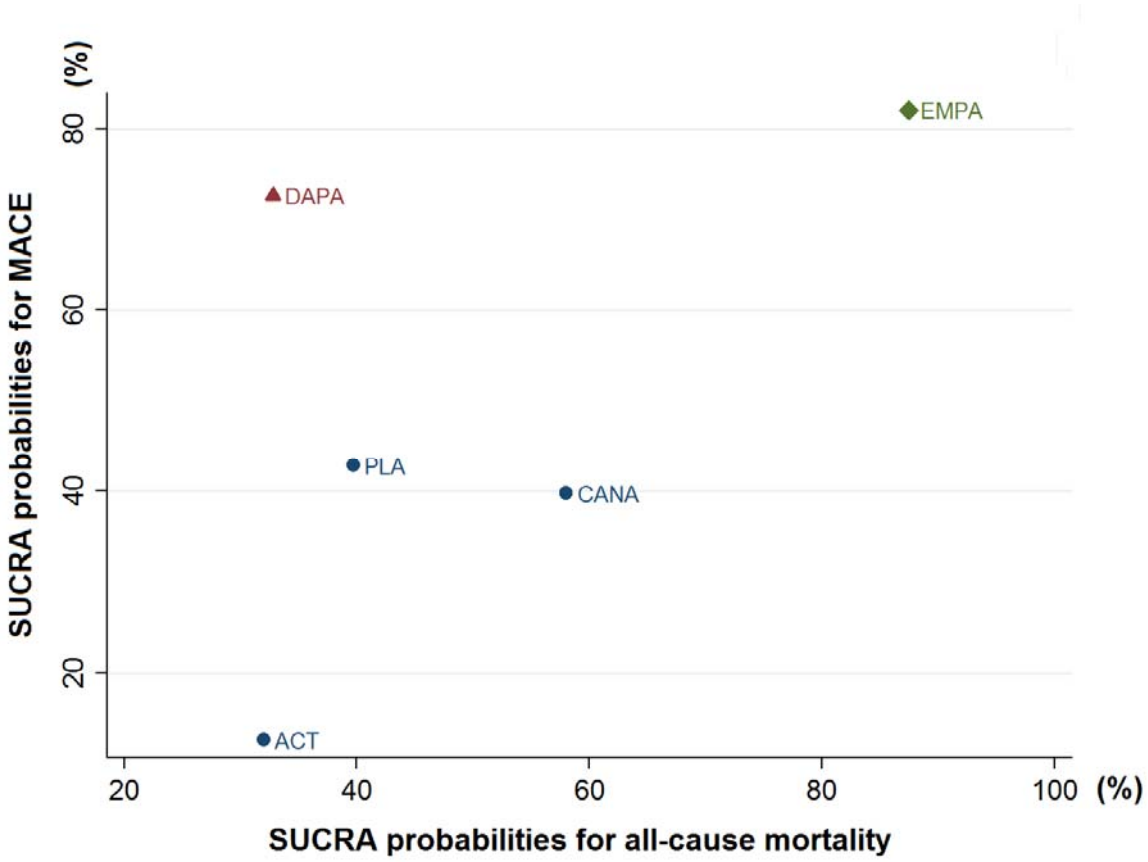
SUCRA probabilities for MACE
(%)
80
60
40
20
EMPA
DAPA
PLA
CANA
ACT
20
40
60
80
100
(%)
SUCRA probabilities for all-cause mortality

Table 1 Sensitivity analyses for the odds ratios with 95% confidence interval and rank order of MACE and all-cause mortality

Treatments	Complete analysis	SUCRA rank	Follow-up periods ≥ 52 weeks	SUCRA rank	White patients	SUCRA rank	Non-pre-specified CV outcomes[a]	SUCRA rank	SGLT2 inhibitors combination therapy	SUCRA rank
MACE										
DAPA	0.81 (0.46, 1.45)	2	0.76 (0.34, 1.72)	2	0.83 (0.47,1.48)	2	0.80 (0.45, 1.43)	2	0.88 (0.48, 1.61)	2
EMPA	0.81 (0.70, 0.93)	1	0.81 (0.70, 0.93)	1	0.81 (0.70,0.94)	1	0.70 (0.41, 1.19)	1	0.81 (0.70, 0.93)	1
CANA	1.10 (0.53, 2.29)	3	1.27 (0.57, 2.82)	3	1.18 (0.56,2.48)	3	1.03 (0.48, 2.22)	3	1.30 (0.60, 2.82)	3
ACT	1.37 (0.78, 2.43)	4	1.45 (0.80, 2.63)	4	1.56 (0.86,2.81)	4	1.24 (0.64, 2.42)	4	1.66 (0.90, 3.04)	4
Heterogeneity (tau)	≈0 Low		≈0 Low		≈0 Low		≈0 Low		≈0 Low	
All-cause mortality										
DAPA	1.12 (0.51, 2.44)	3	1.35 (0.42, 4.31)	3	1.10 (0.50,2.41)	4	1.12 (0.51, 2.46)	3	1.30 (0.56, 2.99)	4
EMPA	0.67 (0.56, 0.81)	1	0.67 (0.56, 0.81)	1	0.67 (0.55,0.81)	1	0.70 (0.29, 1.70)	1	0.67 (0.56, 0.81)	1
CANA	0.85 (0.36, 2.05)	2	1.07 (0.37, 3.14)	2	0.82 (0.34,2.00)	2	0.86 (0.35, 2.12)	2	0.94 (0.36, 2.44)	2
ACT	1.11 (0.52, 2.34)	4	1.07 (0.47, 2.42)	4	1.02 (0.45,2.30)	3	1.13 (0.46, 2.76)	4	0.93 (0.39, 2.18)	3
Heterogeneity (tau)	≈0 Low		≈0 Low		≈0 Low		≈0 Low		≈0 Low	

[a]Excluded the main CV outcome study (EMPA-REG OUTCOME trial).

MACE = major adverse cardiovascular events; SUCRA = surface under the cumulative ranking; SGLT2 = sodium glucose cotransporter 2; CV = cardiovascular; CANA = canagliflozin; DAPA = dapagliflozin; EMPA = empagliflozin; PLA = placebo; ACT = active treatments.