SYSTEMATIC REVIEW AND META-ANALYSIS

Sodium-Glucose Cotransporter 2 Inhibitors, All-Cause Mortality, and Cardiovascular Outcomes in Adults with Type 2 Diabetes: A Bayesian Meta-Analysis and Meta-Regression

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BACKGROUND: This study aimed to assess the effectiveness of sodium-glucose cotransporter 2 inhibitors in reducing the incidence of mortality and cardiovascular outcomes in adults with type 2 diabetes.

METHODS AND RESULTS: We conducted a Bayesian meta-analysis of randomized controlled trials comparing sodium-glucose cotransporter 2 inhibitors with placebo. We used meta-regression to examine the association between treatment effects and control group event rates as measures of cardiovascular baseline risk. Fifty-three randomized controlled trials were included in our synthesis. Empagliflozin, canagliflozin, and dapagliflozin reduced the incidence of all-cause mortality (empagliflozin: rate ratio [RR], 0.79; 95% credibility interval [CrI], 0.63–0.97; canagliflozin: RR, 0.86; 95% CrI, 0.69–1.05; dapagliflozin: RR, 0.86; 95% CrI, 0.72–1.01) and cardiovascular mortality (empagliflozin: RR, 0.78; 95% CrI, 0.61–1.00; canagliflozin: RR, 0.83; 95% CrI, 0.63–1.05; dapagliflozin: RR, 0.88; 95% CrI, 0.71–1.08), with a 90.1% to 98.7% probability for the true RR to be <1.00 for both outcomes. There was little evidence for ertugliflozin and sotagliflozin versus placebo for reducing all-cause and cardiovascular mortality. There was no association between treatment effects for all-cause and cardiovascular mortality and the control group event rates. There was evidence for a reduction in the incidence of heart failure for empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin versus placebo (probability RR <1.00 of ≥99.3%) and weaker, albeit positive, evidence for acute myocardial infarction for the first 3 agents (probability RR <1.00 of 89.0%–95.2%). There was little evidence of any agent except canagliflozin for reducing the incidence of stroke.

CONCLUSIONS: Empagliflozin, canagliflozin, and dapagliflozin reduced the incidence of all-cause and cardiovascular mortality versus placebo. Treatment effects of sodium-glucose cotransporter 2 inhibitors versus placebo do not vary by baseline risk.

Key Words: heart failure ∎ ischemic stroke ∎ meta-analysis ∎ myocardial infarction ∎ type 2 diabetes

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CLINICAL PERSPECTIVE

What Is New?
- Empagliflozin, canagliflozin, and dapagliflozin reduced the incidence of all-cause and cardiovascular mortality versus placebo.
- Treatment effects do not vary by baseline risk.

What Are the Clinical Implications?
- Given the comparable relative treatment effect across baseline risk, sodium-glucose cotransporter 2 inhibitors warrant consideration as the preferred second-line treatment for primary prevention of cardiovascular disease in adults with type 2 diabetes and a baseline risk comparable to participants in the cardiovascular outcome trials.
- Furthermore, given a similar relative treatment effect across baseline risk, adults at the highest absolute risk of all-cause and cardiovascular mortality will derive a greater absolute benefit from sodium-glucose cotransporter 2 inhibitors.

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Nonstandard Abbreviations and Acronyms

CrI	credibility interval
HHF	hospitalization for heart failure
SGLT-2	sodium-glucose cotransporter 2
T2DM	type 2 diabetes

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Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are glucose-lowering agents for the treatment of type 2 diabetes (T2DM).[1–4] When added to guideline-recommended treatment, these agents improve glucose control, reduce body weight, and reduce the incidence of heart failure and progression of renal disease.[2] SGLT-2 inhibitors also reduce mortality and cardiovascular outcomes, although existing studies suggest this benefit is limited to adults with established cardiovascular disease (CVD) and renal disease.[5] Inferences about which patient population will benefit from SGLT-2 inhibitors are challenging because the existing pivotal randomized controlled trials (RCTs) are not directly comparable: cardiovascular outcome trials for empagliflozin and ertugliflozin were restricted to adults with established CVD,[6–8] whereas other outcome trials for canagliflozin,[9,10] dapagliflozin,[11,12] and sotagliflozin[13] have involved a mixture of adults with and without established CVD and renal disease, with the lowest average cardiovascular risk found in patients included in the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) trial for dapagliflozin.

Currently, the effectiveness of SGLT-2 inhibitors for reducing mortality and cardiovascular outcomes across the spectrum of baseline risk remains unclear. We therefore performed a Bayesian meta-analysis integrating all available randomized evidence to determine the effectiveness of different agents versus placebo while incorporating outcome-specific external evidence on between-trial heterogeneity[14] to appropriately reflect the current uncertainty when adequately powered trials are few. We also examined the association between the magnitude of treatment effects and control group event rates for mortality and cardiovascular outcomes as measures of cardiovascular baseline risk.

METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018115077). Institutional review board approval was not required for this study. The data that support the findings of this study are publicly available but can also be made available from the corresponding author on request. We performed a systematic search of MEDLINE and EMBASE from inception to July 2020 (Data S1). We included RCTs of SGLT-2 inhibitors compared with placebo to prevent CVD in adults with T2DM. All studies were required to have at least 24 weeks of randomized treatment and follow-up and at least one event in either control or intervention group.

Data Extraction

Ten reviewers working independently and in duplicate reviewed titles, abstracts, full texts, and trial registries to assess studies for their inclusion and to extract data. The prespecified primary outcome of our analysis was all-cause mortality, and the key secondary outcome was cardiovascular mortality, as these outcomes are considered to be of greatest importance to patients.[15] Additional outcomes of interest were fatal or nonfatal stroke, fatal or nonfatal acute myocardial infarction (AMI), and hospitalization for heart failure (HHF). We did not extract results for major adverse cardiovascular events, defined as the composite of cardiovascular death, myocardial infarction, or stroke, as the importance of individual components of this composite and possibly the direction of treatment effects could vary within and between agents.[16] The combination of these individual end points in a composite outcome could dilute or entirely miss specific differences between agents.[16] We did not extract results for chronic kidney disease or adverse events (Data S1).

Statistical Analysis

We used a Bayesian network meta-analysis, which fully preserves randomized treatment comparisons within trials but allows for increased precision compared with a pairwise Bayesian meta-analysis. Analyses were done using Markov chain Monte Carlo methods with minimally informative but biologically plausible prior distributions for event rates in the control group and treatment effects. We also used outcome-specific informative prior distributions for the variation in treatment effects derived from external evidence[14] as the number of cardiovascular outcome trials adequately powered for the outcomes was limited (Table S1). We used a Poisson model to estimate rate ratios (RRs) as measures of treatment effects based on the arm-specific numbers of patients experiencing an event and accumulated patient-years (Data S1). We assumed a common between-trial variance, τ^2, to ensure that differences in characteristics of patients included in currently available trials would be appropriately reflected by τ^2, with an expected increase in between-trial heterogeneity if these differences in patient characteristics were associated with variation in treatment effects. Summary treatment effect estimates were derived from the median and corresponding 95% credibility intervals (CrIs) from the 2.5th and 97.5th percentile of the posterior distribution. In the presence of minimally informative priors, CrIs can be interpreted similarly to conventional CIs. To better inform clinical decision making, we calculated the posterior probabilities that an intervention would confer risk reductions or increases greater than prespecified thresholds.[17] These probabilities take into account both the magnitude of the summary RR and the corresponding uncertainty.[17] For comparisons to placebo, an RR <0.80 was prespecified as a clinically important threshold in favor of an SGLT-2 inhibitor, an RR <1.00 was prespecified as indicative of any benefit, an RR >1.00 was prespecified for any harm, and an RR >1.25 (the reciprocal of 0.80) was prespecified for a clinically important increase in harm. A posterior probability of 50% for RR <1.00, identical to the toss of a coin, indicates that the summary RR is 1.00. Probabilities are reported to one decimal place.

We used 3 different approaches to examine the association between the magnitude of treatment effects for each individual SGLT-2 inhibitor across the spectrum of baseline risk. First, we used Bayesian meta-regression to assess the association between treatment effects and control group event rates for each individual outcome as a measure of the average cardiovascular risk of patients included in individual trials, while appropriately accounting for potential confounding by type of SGLT-2 inhibitor.[18,19] This model appropriately accounts for the inherent correlation between treatment effect and control group event rate.[18]

We graphically displayed these results using bubble plots and prediction lines with 95% CrIs. Second, we derived treatment effects at the median control group event rate for trials or subgroups of patients without established CVD (primary prevention) and with established CVD (secondary prevention). We then performed sensitivity analyses that were adjusted for potential associations of treatment effects with the control group event rate by deriving marginal treatment effects for each SGLT-2 inhibitor at the median control group event rate of each outcome observed in large SGLT-2 trials (Data S1). Control group event rates were considered a combined proxy measure for the underlying disease severity and any other comorbidities, characteristics that varied among included trials but were not consistently reported. In the setting of heterogeneity for mortality outcomes, variation in relative treatment effects by control group event rate may be contributory.[20] Third, we performed sensitivity analyses that were restricted to trials or subgroups of patients with established CVD.

We used the Grading of Recommendations Assessment, Development, and Evaluation framework to rate the overall quality of the evidence,[21] and used posterior probabilities of superiority (RR <1.00 compared with placebo) to determine whether the evidence in favor of superiority over placebo was convincing. The Grading of Recommendations Assessment, Development, and Evaluation criteria evaluate the quality of studies on a scale of 1 (very low quality) to 4 (high quality) based on the risk of bias, inconsistency/heterogeneity, indirectness, imprecision, and publication bias.[21] We considered the evidence to be convincing if 2 criteria were met: (1) the grade of evidence was high quality and (2) the respective posterior probability for superiority over placebo was >99%.[22,23] If the grade of evidence was high quality and the respective posterior probability for superiority ranged from 95% to 99%, we considered the evidence to be strong. Finally, if the grade of evidence was high quality and the respective posterior probabilities ranged from 75% to 95%, we considered the evidence to be positive. If either the grade of evidence was not high quality or the posterior probabilities were <75%, we considered the evidence to be weak. We initially planned to perform a comparative analysis of SGLT-2 inhibitors. However, given the absence of head-to-head comparisons, all evidence on the comparative effects of the agents would be from indirect evidence and be considered as low-quality evidence. These results would therefore not be clinically informative. Nonetheless, for completeness, we report all indirect comparisons in Data S1.

We estimated between-trial heterogeneity of treatment effects from the median between trial variance τ^2 observed in the posterior distribution, and the goodness of fit of the model to the data, by comparing

the mean residual deviance with the number of contributing data points, calculating the percentage of standardized node-based residuals within 1·96 of the standard normal distribution, and visually inspecting the distribution of residuals on Q-Q plots. Then, we used the deviance information criteria to compare goodness of fit between fixed-effect and random-effects models. We prespecified that we would select the model with the lowest deviance information criterion. The deviance information criterion was lowest for the random-effects model for all-cause mortality and cardiovascular mortality and near identical for AMI and stroke (Table S2). To be parsimonious, we reported the results of the random-effects analysis as the primary analysis. Details about small study effects are in the Supplemental Figures. For all analyses, we used Stata 15 (College Station, TX), OpenBUGS (3.0.7), JAGS (0.5–7), and R 3.2.5 (Auckland, New Zealand).

RESULTS

We included 53 RCTs in our meta-analysis, involving 88 390 adults (216 416 person-years [PYs] of follow-up) with T2DM (Figure S1 through S2). There were 14 RCTs examining empagliflozin (32 081 PYs), 10 for canagliflozin (51 980 PYs), 22 for dapagliflozin (86 741 PYs), 5 for ertugliflozin (30 608 PYs), and 2 for sotagliflozin (15 005 PYs). RCTs for ipragliflozin, luseogliflozin, bexagliflozin, and tofogliflozin were excluded as there were zero events for mortality outcomes in all trials for these agents (Data S1 and Figure S2). Ten cardiovascular or renal outcome trials were included, of which 2 were conducted for empagliflozin,[6,7] 2 were conducted for canagliflozin,[9,10] 3 were conducted for dapagliflozin,[11,12,24] 1 was conducted for ertugliflozin,[8] and 2 were conducted for sotagliflozin,[13,25] and accounted for 62% of participants for empagliflozin (10 750 of 17 388), 78% of participants for canagliflozin (14 543 of 18 688), 71% of participants for dapagliflozin (22 205 of 30 138), 80% of participants for ertugliflozin (8246 of 10 370), and 100% of participants for sotagliflozin (11 806 of 11 806). Five trials included only participants with established CVD,[6–8,24,25] and 3 additional

trials presented results stratified by the presence or absence of CVD.[9,10,12] General characteristics of the included studies, risk-of-bias assessments, and outcomes reported are available in Table 1 and Tables S3 through S5. The number of trials, participants, events, and patient-years underlying individual outcomes are provided in Tables S3 and S6.

All-Cause and Cardiovascular Mortality

Forty RCTs, involving 82 450 adults (5094 events; 212 531 PYs), provided results for all-cause mortality (Table S6). Twenty-seven RCTs, involving 76 391 adults (3281 events; 206 988 PYs), provided results for cardiovascular mortality (Table S6). Figure 1 presents results of random-effects summary estimates of all outcomes based on all participants using placebo as a referent. Table 2 presents the results of fixed-effect and random-effects summary estimates of all outcomes with heterogeneity estimates. There was positive to strong evidence that empagliflozin and canagliflozin reduced the incidence of all-cause mortality (empagliflozin: rate ratio [RR], 0.79; 95% CrI, 0.63–0.97; canagliflozin: RR, 0.86; 95% CrI, 0.69–1.05) and cardiovascular mortality (empagliflozin: RR, 0.78; 95% CrI, 0.61–1.00; canagliflozin: RR, 0.83; 95% CrI, 0.63–1.05). The probability that the true RR of empagliflozin and canagliflozin was <1.00 was 98.7% and 93.6%, respectively, for all-cause mortality and 97.5% and 94.4%, respectively, for cardiovascular mortality. There was positive to strong evidence that dapagliflozin also reduced the incidence of all-cause mortality (RR, 0.86; 95% CrI, 0.72–1.01) and cardiovascular mortality (RR, 0.88; 95% CrI, 0.71–1.08). The probabilities for the true RR <1.00 were 96.5% for all-cause mortality and 90.1% for cardiovascular mortality. There was little evidence that ertugliflozin or sotagliflozin reduced the incidence of all-cause and cardiovascular mortality, with probabilities that the true RR was <1.00 of 68.2% to 68.8% and 63.0% to 78.0%, respectively. Results were similar in fixed-effect meta-analysis (Table 2 and Figure S3). Heterogeneity was minimal (Table 2 and Table S7).

Figure 2 presents the association between treatment effects for all-cause and cardiovascular mortality and the

Table 1. Study Participant Characteristics

Drug type vs placebo	No. of trials	Total No. randomized	Median (IQR)				
			Age, y	Women, %	BMI, kg/m²	HbA1c, %	Diabetes duration, y
Empagliflozin	14	17 388	57 (55–60)	44 (29–46)	30 (28–31)	8.1 (8.0–8.3)	11 (9–14)
Canagliflozin	10	18 688	57 (55–63)	42 (35–52)	32 (31–33)	8.0 (7.9–8.2)	10 (7–14)
Dapagliflozin	22	30 138	58 (54–64)	46 (35–52)	32 (30–33)	8.2 (7.9–8.5)	7 (5–11)
Ertugliflozin	5	10 370	59 (56–64)	44 (43–51)	32 (31–33)	8.2 (8.1–8.2)	10 (7–13)
Sotagliflozin	2	11 806	69 (69–69)	39 (34–45)	31 (31–32)	7.7 (7.1–8.3)	…

BMI indicates body mass index; HbA1c, hemoglobin A1c; and IQR, interquartile range.

Outcome	Trials	Events	Participants	All Trials	Rate Ratio	95% CrI	Superior RR<0.8	Superior RR<1	Inferior RR>1	Inferior RR>1.25
All−Cause Mortality										
Empagliflozin	12	995	15730		0.79	[0.63; 0.97]	54.9	98.7	1.3	0
Canagliflozin	7	1062	17739		0.86	[0.69; 1.05]	24.5	93.6	6.4	0.1
Dapagliflozin	17	1666	28462		0.86	[0.72; 1.01]	20.1	96.5	3.5	0
Ertugliflozin	2	738	8713		0.94	[0.71; 1.26]	11.1	68.2	31.8	2.9
Sotagliflozin	2	633	11806		0.95	[0.73; 1.20]	8.7	68.8	31.2	1.3
Cardiovascular Mortality										
Empagliflozin	7	706	12993		0.78	[0.61; 1.00]	58.3	97.5	2.5	0.1
Canagliflozin	5	706	16552		0.83	[0.63; 1.05]	37.6	94.4	5.6	0.1
Dapagliflozin	11	909	26327		0.88	[0.71; 1.08]	17.7	90.1	9.9	0.1
Ertugliflozin	2	526	8713		0.95	[0.68; 1.34]	13	63	37	5
Sotagliflozin	2	434	11806		0.90	[0.68; 1.20]	19.3	78	22	1.3
Hospitalization for Heart Failure										
Empagliflozin	8	823	14524		0.66	[0.53; 0.79]	97.9	100	0	0
Canagliflozin	4	478	15526		0.64	[0.51; 0.81]	97.2	99.9	0.1	0
Dapagliflozin	10	833	23281		0.74	[0.61; 0.91]	78.5	99.7	0.4	0
Ertugliflozin	2	209	8713		0.63	[0.45; 0.89]	91.3	99.3	0.7	0.1
Myocardial Infarction										
Empagliflozin	10	372	12313		0.83	[0.57; 1.13]	39.3	89	11	0.8
Canagliflozin	7	439	12854		0.83	[0.58; 1.04]	39.5	95.2	4.8	0.1
Dapagliflozin	14	868	23395		0.85	[0.58; 1.08]	33.1	91.9	8.1	0.3
Ertugliflozin	4	493	9909		1.02	[0.73; 1.50]	5.8	44.4	55.6	10.8
Stroke										
Empagliflozin	11	265	12995		1.13	[0.80; 1.55]	2.5	22.8	77.2	25.7
Canagliflozin	10	463	18688		0.82	[0.63; 1.06]	43.6	94.3	5.7	0.4
Dapagliflozin	12	487	22537		0.95	[0.65; 1.23]	13.5	65.2	34.8	1.9
Ertugliflozin	5	239	10370		0.95	[0.65; 1.35]	15.7	61.2	38.8	6

0.5   0.8   1.25   2

Favors SGLT2   Favors Placebo

Figure 1. All-cause mortality, cardiovascular mortality, and cardiovascular events with the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors compared with placebo, according to an analysis of all trials (random-effects network meta-analysis).
Summary estimates are provided and are derived from a random-effects network meta-analysis. Dashed vertical lines correspond to the margins for a large reduction or large increase in the incidence of an outcome. The provided probabilities take into consideration the magnitude of the summary estimate as well as the corresponding uncertainty. Probabilities are rounded to 1 decimal place, unless the probabilities are >99% or <1%, in which case they are rounded to 2 decimal places. Trailing zeroes are not shown. CrI indicates credibility interval; and RR, rate ratio.

control group event rate. Table 3 and Figure S4 present treatment effects adjusted for control group event rates compared with placebo. Table 4 presents the treatment effects at the median control group event rate for a primary prevention and secondary prevention population. There was no association between treatment effects and the control group event rates as measures of the cardiovascular baseline risk (Figure 2 and Table S8). Treatment effects for all-cause and cardiovascular mortality were comparable in the primary and secondary prevention population (Table 4). Results were similar in analyses where treatment effects were adjusted for the median control group event rate and where analyses were limited to trials or subgroups of participants with established CVD (Table 3 and Figure S4).

Hospitalization for Heart Failure

Twenty-four RCTs, involving 62 044 adults (2343 events; 176 451 PYs), provided results for HHF (Table S6). Compared with placebo, empagliflozin reduced the incidence of HHF by 34% (RR, 0.66; 95% CrI, 0.53–0.79; Figure 1). The probability that the true RR was <1.00 was 100.0%. The RR reduction in HHF was 36% for canagliflozin (RR, 0.64; 95% CrI, 0.51–0.81), 26% for dapagliflozin (RR, 0.74; 95% CrI, 0.61–0.91), and 37% for ertugliflozin (RR, 0.63; 95% CrI, 0.45–0.89; Figure 1). The probabilities for RR <1.00 ranged from 99.3% to 99.9% for these agents. The results for HHF as an individual outcome have yet to be reported for sotagliflozin. Results were similar in fixed-effect meta-analysis but less precise (Table 2 and Figure S2). Heterogeneity

Table 2.   All-Cause Mortality, Cardiovascular Mortality, and Cardiovascular Events With the Use of SGLT-2 Inhibitors Compared With Placebo, According to an Analysis of All Trials Using FE and RE Meta-Analysis

Variable	Rate ratio (95% CrI)		Probability of superiority		τ^2 (95% CrI)	Evidence grade
	FE	RE	FE	RE		
All-cause mortality						
Empagliflozin	0.81 (0.71–0.91)	0.79 (0.63–0.97)	99.9	98.7	0.012 (0.001–0.059)	⊕⊕⊕⊕
Canagliflozin	0.86 (0.77–0.98)	0.86 (0.69–1.05)	99.1	93.6		⊕⊕⊕⊕
Dapagliflozin	0.87 (0.79–0.96)	0.86 (0.72–1.01)	99.7	96.5		⊕⊕⊕⊕
Ertugliflozin	0.93 (0.80–1.09)	0.94 (0.71–1.26)	82.2	68.2		⊕⊕⊕*
Sotagliflozin	0.96 (0.83–1.13)	0.95 (0.73–1.20)	67.6	68.8		⊕⊕⊕*
Cardiovascular mortality						
Empagliflozin	0.79 (0.68–0.91)	0.78 (0.61–1.00)	99.9	97.5	0.015 (0.002–0.074)	⊕⊕⊕⊕
Canagliflozin	0.85 (0.73–0.99)	0.83 (0.63–1.05)	98.5	94.4		⊕⊕⊕⊕
Dapagliflozin	0.90 (0.79–1.02)	0.88 (0.71–1.08)	94.7	90.1		⊕⊕⊕⊕
Ertugliflozin	0.95 (0.80–1.14)	0.95 (0.68–1.34)	70.7	63.0		⊕⊕⊕*
Sotagliflozin	0.90 (0.75–1.09)	0.90 (0.68–1.20)	85.1	78.0		
Hospitalization for heart failure						
Empagliflozin	0.67 (0.58–0.77)	0.66 (0.53–0.79)	100.0	100.0	0.006 (0.000–0.056)	⊕⊕⊕⊕
Canagliflozin	0.63 (0.53–0.76)	0.64 (0.51–0.81)	100.0	99.9		⊕⊕⊕⊕
Dapagliflozin	0.74 (0.65–0.85)	0.74 (0.61–0.91)	100.0	99.7		⊕⊕⊕⊕
Ertugliflozin	0.63 (0.48–0.84)	0.63 (0.45–0.89)	99.9	99.3		⊕⊕⊕⊕
Acute myocardial infarction						
Empagliflozin	0.85 (0.7–1.05)	0.83 (0.57–1.13)	93.1	89.0	0.012 (0.001–0.170)	⊕⊕⊕⊕
Canagliflozin	0.86 (0.73–1.00)	0.83 (0.58–1.04)	97.3	95.2		⊕⊕⊕⊕
Dapagliflozin	0.88 (0.76–1.00)	0.85 (0.58–1.08)	97.6	91.9		⊕⊕⊕⊕
Ertugliflozin	1.01 (0.84–1.22)	1.02 (0.73–1.50)	44.9	44.4		⊕⊕⊕*
Stroke						
Empagliflozin	1.14 (0.88–1.47)	1.13 (0.80–1.55)	16.1	22.8	0.010 (0.000–0.110)	⊕⊕⊕*
Canagliflozin	0.81 (0.68–0.97)	0.82 (0.63–1.06)	98.8	94.3		⊕⊕⊕⊕
Dapagliflozin	0.99 (0.83–1.17)	0.95 (0.65–1.23)	56.7	65.2		⊕⊕⊕†
Ertugliflozin	0.98 (0.75–1.27)	0.95 (0.65–1.35)	57.4	61.2		⊕⊕*,†

Posterior probabilities of superiority (rate ratio <1.00) are rounded to 1 decimal place, unless the probabilities are >99% or <1%, in which case they are rounded to 2 decimal places. All studies are graded using a scale of 1 (very low quality), 2 (low quality), 3 (moderate quality) and 4 (high quality). Each ⊕ represents one point on this scale. CrI indicates credibility interval; FE, fixed effect; RE, random effects; and SGLT-2, sodium-glucose cotransporter 2.

*Downgraded because of imprecision.

†Downgraded because of more evidence against the null hypothesis with adjustment for the control group event rate as a measure of baseline risk (the probability that the agents were superior to placebo increased from <60% to ≥90%). This change in probability corresponds to a meaningful change in the Bayes factor.

was minimal (τ^2, 0.006; 95% CrI, 0.000–0.056). There was no association between the treatment effects for HHF and the control group event rate as a measure of baseline risk (Figure 2 and Table S8). Results were unchanged in analyses where treatment effects were adjusted for the median control group event rate and where analyses were limited to trials or subgroups of participants with established CVD (Table 3).

Ischemic Events: AMI and Stroke

Thirty-five RCTs provided results for AMI (63 138 adults; 2351 events; 178 606 PYs), and 38 RCTs provided results for stroke (64 590 adults; 1454 events; 178 449 PYs). Compared with placebo, there was positive to strong evidence that the RR was <1.00 for empagliflozin, canagliflozin, and dapagliflozin, with probabilities ranging from 89% to 95.2%. However, there was little evidence that the RR was <1.00 for ertugliflozin. Furthermore, there was little evidence that empagliflozin reduced the incidence of stroke, and the probability that the true risk reduction was <1.00 was 22.8. For canagliflozin, dapagliflozin, and ertugliflozin, the probability that the RR was <1.00 was 94.3%, 65.2%, and 61.2%, respectively. Results were similar in a fixed-effect meta-analysis (Figure S3). Heterogeneity was minimal for AMI and stroke (τ^2, 0.012 [95% CrI, 0.001–0.170] and 0.010 [95%-CrI, 0.000–0.110], respectively).
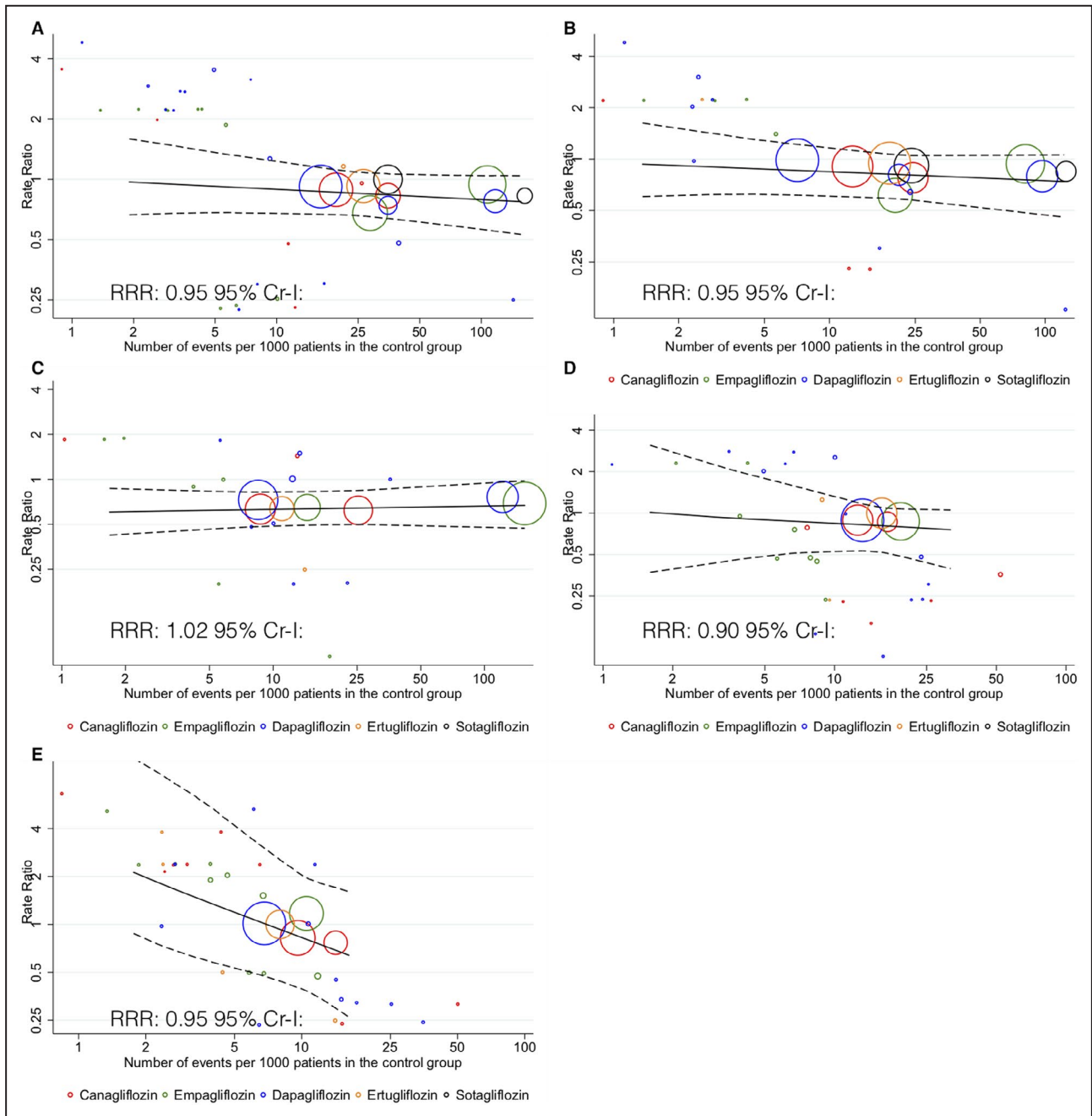
Figure 2. Association between the control group event rate, all-cause mortality (A) and cardiovascular mortality (B), hospitalization for heart failure (C), acute myocardial infarction (D), and stroke (E) with the use of sodium-glucose cotransporter 2 inhibitors compared with placebo.

Dashed lines are the 95% credibility intervals (Cr-Is). The radius of the circle corresponds to the weight of the individual study in the meta-regression analysis. The control group event rate for each outcome examined is taken as a measure of baseline risk. The regression coefficient is the ratio of rate ratios (RRR) per 1-unit increase in the log rate, which corresponds to an increase in all-cause mortality from approximately 10 per 1000 patient-years in patients with multiple risk factors, but without established cardiovascular disease (primary prevention), to approximately 25 per 1000 patient-years in patients with established cardiovascular disease (secondary prevention).

There was no association between the treatment effects for AMI and the control group event rate as a measure of baseline risk (Figure 2 and Table S8). However, there was a strong association between the treatment effect for stroke and the control group event rate (Figure 2 and Table S8). At the control group event rate for the primary prevention population, there was little evidence that canagliflozin, dapagliflozin, and ertugliflozin reduced the incidence of stroke. However, the incidence of stroke was higher with empagliflozin

Table 3. SGLT-2 Inhibitors Compared With Placebo, According to the Primary Analyses of All Trials Compared With Analyses Adjusted for Control Group Event Rates and Restricted to Trials of Participants With Established CVD

Variable	Primary analysis		Adjusted analysis		Restricted analysis	
	Rate ratio (95% CrI)	Probability of superiority	Rate ratio (95% CrI)	Probability of superiority	Rate ratio (95% CrI)	Probability of superiority
All-cause mortality						
Empagliflozin	0.79 (0.63–0.97)	98.7	0.83 (0.64–1.05)	94.3	0.81 (0.62–1.05)	95.5
Canagliflozin	0.86 (0.69–1.05)	93.6	0.86 (0.68–1.09)	91.1	0.87 (0.66–1.14)	87.0
Dapagliflozin	0.86 (0.72–1.01)	96.5	0.88 (0.72–1.08)	91.1	0.89 (0.70–1.17)	83.6
Ertugliflozin	0.94 (0.71–1.26)	68.2	0.96 (0.72–1.32)	61.7	0.93 (0.64–1.33)	68.3
Sotagliflozin	0.95 (0.73–1.20)	68.8	1.00 (0.75–1.37)	48.7	0.84 (0.53–1.33)	78.2
Cardiovascular mortality						
Empagliflozin	0.78 (0.61–1.00)	97.5	0.83 (0.61–1.15)	88.5	0.77 (0.57–1.03)	96.6
Canagliflozin	0.83 (0.63–1.05)	94.4	0.84 (0.62–1.09)	91.9	0.85 (0.62–1.16)	86.7
Dapagliflozin	0.88 (0.71–1.08)	90.1	0.91 (0.71–1.15)	81.0	0.88 (0.66–1.17)	83.9
Ertugliflozin	0.95 (0.68–1.34)	63.0	0.97 (0.67–1.44)	56.1	0.95 (0.64–1.41)	62.1
Sotagliflozin	0.90 (0.68–1.20)	78.0	0.97 (0.68–1.43)	58.3	0.87 (0.52–1.45)	72.1
Hospitalization for heart failure						
Empagliflozin	0.66 (0.53–0.79)	100.0	0.63 (0.47–0.82)	99.9	0.68 (0.55–0.84)	99.8
Canagliflozin	0.64 (0.51–0.81)	99.9	0.63 (0.49–0.82)	99.9	0.64 (0.49–0.83)	99.8
Dapagliflozin	0.74 (0.61–0.91)	99.7	0.73 (0.58–0.92)	99.3	0.79 (0.64–0.97)	98.4
Ertugliflozin	0.63 (0.45–0.89)	99.3	0.63 (0.43–0.91)	99.3	0.64 (0.45–0.92)	99.1
Acute myocardial infarction						
Empagliflozin	0.83 (0.57–1.13)	89.0	0.89 (0.54–1.29)	72.2	0.87 (0.55–1.39)	76.7
Canagliflozin	0.83 (0.58–1.04)	95.2	0.87 (0.56–1.20)	79.1	0.84 (0.61–1.22)	86.9
Dapagliflozin	0.85 (0.58–1.08)	91.9	0.88 (0.57–1.19)	78.4	0.94 (0.68–1.6)	65.5
Ertugliflozin	1.02 (0.73–1.50)	44.4	1.10 (0.69–1.73)	33.1	1 (0.64–1.59)	49.4
Stroke						
Empagliflozin	1.13 (0.80–1.55)	22.8	1.19 (0.84–1.53)	13.1	1.17 (0.75–1.83)	20.6
Canagliflozin	0.82 (0.63–1.06)	94.3	0.95 (0.73–1.22)	67.2	0.86 (0.61–1.22)	83.9
Dapagliflozin	0.95 (0.65–1.23)	65.2	0.88 (0.62–1.14)	84.2	0.95 (0.62–1.37)	62.6
Ertugliflozin	0.95 (0.65–1.35)	61.2	0.94 (0.64–1.26)	67.3	1.00 (0.64–1.56)	49.5

All analyses were performed with a random-effects model. In the restricted analysis, only trials conducted in adults with established CVD or trials providing subgroup results for adults with established CVD were included. Posterior probabilities of superiority (rate ratio <1.00) are rounded to 1 decimal place, unless the probabilities are >99% or <1%, in which case they are rounded to 2 decimal places. CrI indicates credibility interval; CVD, cardiovascular disease; and SGLT-2, sodium-glucose cotransporter 2.

compared with placebo. In contrast, at the control group event rate for the secondary prevention population, canagliflozin and dapagliflozin reduced the incidence of stroke, but there was less evidence for empagliflozin and ertugliflozin.

Additional Analyses

Treatment rankings are provided in Figure S5. Results were unchanged when analyses were restricted to trials or subgroups of patients with established CVD (Table 3 and Figures S6 through S7). There was no evidence of small study effects (Figures S8 through S12). Model fit was adequate for all outcomes and comparisons. The PIE index was 0.68. Results from a sensitivity analysis using minimally informative priors for both baseline event

rate and treatment effect were unchanged from our primary analysis and did not alter conclusions of our network meta-analysis (Table S9). The results for indirect comparisons are summarized in Figures S13 through S14.

DISCUSSION

In this Bayesian meta-analysis of 53 RCTs, 88 390 adults, and 216 416 PYs of accumulated follow-up time, including all published pivotal trials in adults with T2DM, there was positive to strong evidence that empagliflozin, canagliflozin, and dapagliflozin reduced the incidence of all-cause and cardiovascular mortality. As well, there was no association between treatment effects and the control group event rate for all-cause

Table 4.   Treatment Effects Among Adults in a Primary Prevention and a Secondary Prevention Population Based on the Control Group Event Rate

	Primary prevention	Secondary prevention
All-cause mortality	Event rate 19 per 1000 PYs	Event rate 46 per 1000 PYs
Empagliflozin	0.70 (0.59–0.83)	0.79 (0.62–0.97)
Canagliflozin	0.89 (0.79–0.99)	0.82 (0.63–1.04)
Dapagliflozin	0.92 (0.83–1.02)	0.84 (0.68–1.01)
Ertugliflozin	0.97 (0.84–1.12)	0.92 (0.67–1.25)
Sotagliflozin	1.01 (0.75–1.37)	0.96 (0.74–1.25)
Cardiovascular mortality	Event rate 11 per 1000 PYs	Event rate 32 per 1000 PYs
Empagliflozin	0.67 (0.53–0.82)	0.79 (0.57–1.03)
Canagliflozin	0.88 (0.76–1.02)	0.79 (0.60–1.02)
Dapagliflozin	0.96 (0.83–1.10)	0.86 (0.67–1.07)
Ertugliflozin	1.01 (0.84–1.19)	0.92 (0.62–1.34)
Sotagliflozin	0.97 (0.68–1.43)	0.91 (0.67–1.25)
Hospitalization for heart failure	Event rate 11 per 1000 PYs	Event rate 24 per 1000 PYs
Empagliflozin	0.62 (0.48–0.80)	0.64 (0.50–0.80)
Canagliflozin	0.63 (0.53–0.76)	0.64 (0.50–0.84)
Dapagliflozin	0.74 (0.63–0.86)	0.75 (0.60–0.92)
Ertugliflozin	0.63 (0.48–0.84)	0.64 (0.44–0.94)
Acute myocardial infarction	Event rate 7 per 1000 PYs	Event rate 18 per 1000 PYs
Empagliflozin	0.90 (0.58–1.24)	0.82 (0.51–1.12)
Canagliflozin	0.89 (0.64–1.13)	0.80 (0.53–1.04)
Dapagliflozin	0.91 (0.68–1.12)	0.81 (0.51–1.11)
Ertugliflozin	1.06 (0.71–1.41)	1.01 (0.70–1.46)
Stroke	Event rate 8 per 1000 PYs	Event rate 10 per 1000 PYs
Empagliflozin	1.28 (1.05–1.53)	1.02 (0.69–1.32)
Canagliflozin	0.95 (0.79–1.10)	0.81 (0.62–1.02)
Dapagliflozin	0.92 (0.80–1.07)	0.75 (0.51–1.00)
Ertugliflozin	0.98 (0.81–1.18)	0.80 (0.53–1.10)

PY indicates person-year.

and cardiovascular mortality, resulting in comparable treatment effects for primary and secondary prevention populations.

For all agents, we found similarly convincing evidence for a reduction in the incidence of HHF with posterior probabilities ≥99% compared with placebo. In contrast, the direction and magnitude of the effects for reducing the incidence of AMI appeared consistent for empagliflozin, canagliflozin, and dapagliflozin, but the evidence did not meet our threshold to be considered convincing for any agent. Finally, for stroke, effects varied among agents. Analyses demonstrated the strongest evidence for a reduced incidence of stroke was for canagliflozin, whereas there was some evidence, albeit inconclusive, for an increased incidence of stroke with empagliflozin compared with placebo.

Our study has several limitations. First, we conducted an aggregate-level meta-analysis and did not have access to individual patient data. However, we were careful to avoid ecological fallacies in our subgroup analyses by including data that were restricted to trials or subgroups of adults with established CVD.[26] Second, measurement error in the control group event rate can induce a correlation between the observed treatment effect and the control group event rate, even in the absence of any between-trial variation in true treatment effect.[27] We therefore used Bayesian meta-regression, which appropriately accounts for

the inherent correlation between treatment effect and control group event rate.[18] Third, all agents in our study were compared with placebo, which limited any inferences about the comparative efficacy of SGLT-2 inhibitors. Because of our star-shaped network, we were unable to test for inconsistency between direct and indirect estimates. Fourth, ertugliflozin has only been examined in a single large cardiovascular outcomes trial. However, using the Bayesian framework, we incorporated outcome-specific external evidence on between-trial variation in treatment effects. This approach reduces overestimation of the precision of treatment effects as the number of adequately powered trials is limited.[28] Fifth, as expected, CrIs were wider for the random-effects analysis compared with the fixed-effect analysis, resulting in treatment effect estimates for all-cause and cardiovascular mortality that crossed the line of no difference for canagliflozin and dapagliflozin. The difference between fixed-effect and random-effects analysis highlights the need for further RCTs of SGLT-2 inhibitors before definitive conclusions can be made about mortality outcomes. Sixth, we did not examine adverse events, such as ketoacidosis, amputations, and fractures, as this was considered beyond the scope of our study.

Current guidelines recommend the use of SGLT-2 inhibitors in adults with established CVD or at high cardiovascular risk.[29] This recommendation is in part informed by meta-analyses noting that the benefit of SGLT-2 inhibitors for cardiovascular outcomes was limited to this patient subgroup. For instance, in the meta-analysis by Zelniker et al,[5] 3 cardiovascular outcome trials were pooled to derive summary estimates for several outcomes, stratified by established CVD. Of note, in adults without established CVD, SGLT-2 inhibitors did not decrease the incidence of major adverse cardiovascular events.[5] Our study is the most comprehensive analysis to date, including 10 cardiovascular and renal outcome trials. In contrast to prior analyses, we estimated the effects of individual drugs, while carefully examining whether treatment effects were associated with the control group event rates as a combined proxy measure for the underlying percentage of patients with established CVD, their disease severity, and other comorbidities. With this approach, we found positive to strong evidence that empagliflozin, canagliflozin, and dapagliflozin reduced the incidence of all-cause and cardiovascular mortality. In contrast, there was little evidence for ertugliflozin or sotagliflozin for reducing mortality outcomes.

There was no association between treatment effects and the control group event rate for all-cause and cardiovascular mortality, resulting in negligible differences in the predicted treatment effect for a primary and secondary prevention population. The implications of these findings are 2-fold. First, given the comparable relative treatment effect across baseline risk, SGLT-2 inhibitors warrant consideration as the preferred second-line treatment for primary prevention of CVD in adults with T2DM and a baseline risk comparable to participants in the cardiovascular outcome trials. This finding may inform future iterations of guidelines in identifying adults in whom the use of SGLT-2 inhibitors should be preferred. Second, given a similar relative treatment effect across baseline risk, adults at the highest absolute risk of all-cause and cardiovascular mortality will derive a greater absolute benefit from SGLT-2 inhibitors. The potential for a large absolute benefit of SGLT-2 inhibitors in adults with established CVD lends support to the existing European Society of Cardiology guidelines, which recommend SGLT-2 inhibitors as the first-line treatment for the secondary prevention of CVD.[29]

There was an association between treatment effects for stroke and the control group event rate. At the control group event rate for a primary prevention population, empagliflozin was associated with an increased risk of stroke, whereas there was little evidence for an increased risk of stroke associated with the remaining agents. Further research is required to clarify the effect of empagliflozin on the incidence of stroke. Indeed, this finding may be attributable to chance.

In conclusion, there was positive to strong evidence that empagliflozin, canagliflozin, and dapagliflozin reduced the incidence of all-cause and cardiovascular mortality. There is little evidence that treatment effects for all-cause and cardiovascular mortality for any agents vary meaningfully by baseline risk.

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Supplementary Material

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Search Strategy Employed for MEDLINE

This analysis is part of a larger project examining novel glucose lowering treatments for type 2 diabetes. The search strategy below was used to identify a relevant subset of studies of SGLT-2 inhibitors from inception of the database until November 2018. We updated our search strategy to identify studies from November 2018 to April 2019, we excluded search terms 12 to 37 that were not specific to SGLT2-Inhibitors.

1. exp Diabetes Mellitus, Type 2/ or exp DIABETES MELLITUS/ or diabetes.mp.
2. Sodium glucose cotransporter 2 inhibitor$.mp.
3. sglt2 inhibitor$.mp.
4. Canagliflozin.mp.
5. exp CANAGLIFLOZIN/
6. dapagliflozin.mp.
7. empagliflozin.mp.
8. Ertugliflozin.mp.
9. Ipragliflozin.mp.
10. Tofogliflozin.mp.
11. Remogliflozin.mp.
12. glucagon like peptide 1 receptor agonist$.mp.
13. GLP-1 receptor agonist$.mp.
14. exenatide.mp.
15. Liraglutide.mp.
16. exp LIRAGLUTIDE/
17. lixisenatide.mp.
18. albiglutide.mp.
19. dulaglutide.mp.
20. semaglutide.mp.
21. Dipeptidyl-Peptidase 4 Inhibitor$.mp.
22. exp Dipeptidyl-Peptidase IV Inhibitors/
23. DPP4 inhibitor$.mp.
24. Sitagliptin.mp.
25. exp Sitagliptin Phosphate/
26. Vildagliptin.mp.
27. Saxagliptin.mp.
28. Linagliptin.mp.
29. exp LINAGLIPTIN/
30. Gemigliptin.mp.
31. Anagliptin.mp.
32. Teneligliptin.mp.
33. Alogliptin.mp.
34. Trelagliptin.mp.

35. Omarigliptin.mp.
36. Evogliptin.mp.
37. Dutogliptin.mp.
38. exp Clinical Trial/
39. exp Random Allocation/
40. exp Single Blind Method/
41. exp Double Blind Method/
42. (random$ adj5 trial$).tw.
43. (random$ adj5 trial$).tw.
44. (Blind$ adj5 method$).tw.
45. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
46. 38 or 39 or 40 or 41 or 42 or 43 or 44
47. 1 and 45 and 46

Supplemental Methods: Bayesian Meta-Analysis

Data Sources and Study Selection

We also included RCTs of SGLT-2 inhibitors compared to placebo when added to background treatment with existing agents (e.g. metformin) in both groups. Therefore, a study comparing SGLT-2 inhibitors and metformin to metformin alone would warrant inclusion. Finally, we included results from double blind extension studies.

Data Extraction

We did not extract results for major adverse cardiovascular events (MACE) – defined as cardiovascular mortality, non fatal acute myocardial infarction and non-fatal stroke – given the that differences may exist among cardiovascular outcome trials for individual components of MACE. As a composite outcome, MACE can therefore conceal important differences between agents. Furthermore, MACE is only reported in cardiovascular or renal outcome trials and not in other trials in our analysis. Instead, our analysis examines each individual component of MACE separately.

The primary outcome of our analysis was all-cause mortality and cardiovascular events make a large contribution to all-cause mortality. Although SGLT2 inhibitors reduce the incidence of chronic kidney disease progression, renal death are few in these studies and do not make a large contribution to all-cause mortality.

Derivation of Rate Ratios and Exclusion of Trials with Zero Events

We calculated rate ratios based on the incidence rates in the intervention and control group. If incidence rates were unavailable, we used the number of events and the mean follow up time. Finally, if none of the aforementioned details were available, we approximated the mean follow up time by assuming that participants that were lost to follow-up only contributed half of the total follow up time. In our primary analysis, we collapsed treatment arms within trials of the same agent at different doses into a single arm. We excluded a given SGLT-2 inhibitor from our analysis if there were no trials with events in the treatment and control group for a mortality outcome (our primary outcome). As such, only four SGLT-2 inhibitors were included in our analysis: empagliflozin, canagliflozin, dapagliflozin and ertugliflozin.

After restricting our analysis to the aforementioned four SGLT2 inhibitors, we also excluded any trials with zero events in both treatment and control groups. This is because trials with zero cells do not contribute to the estimation of treatment effects and do not allow for accurate estimation of model fit based on the residual deviance.

Specifications Related to the Bayesian Meta-Analysis

Models were run with two chains and 200000 iterations per chain. Results were obtained after a burn-in of 20000 iterations and a thinning of 20 per chain, which resulted in a posterior distribution with a total of 10,000 posterior data points (200000/20). Model convergence was

assessed visually using trace plots and Gelman-Rubin plots. Autocorrelation was assessed using autocorrelation plots.

Small Study Effects and Risk of Bias

Evidence for small study effects was assessed through funnel plots. Asymmetry was assessed visually as well as using Harbord's modification of Egger's Test in Stata. We assessed risk of bias using the Cochrane Risk of Bias tool and each RCT was evaluated to determine whether it was at low risk of bias, high risk of bias or unclear risk of bias.

Definitions Applied for Extraction from Trial Registry

All-Cause Mortality

All deaths, irrespective of cause.

Cardiovascular Mortality

Any of "cardiovascular mortality", "cardiovascular death", and "cardiac death".

Acute Myocardial Infarction

Any fatal and non-fatal acute myocardial infarction including "acute myocardial infarction", "myocardial infarction", and "acute coronary syndrome". If more than one of these phrases was used to report events, the total number of events was taken.

Stroke

Any fatal and non-fatal stroke including "ischemic stroke", "hemorrhagic stroke", "cerebrovascular event", and "cerebral infarction". If more than one of these phrases was used to report events, the total number of events was taken.

Heart Failure

Either heart failure event or heart failure hospitalization. Heart failure hospitalization is preferred but if this is not reported, please extract results for "heart failure events". We will also include "cardiac failure" or "cardiac failure congestive" or "cardiogenic shock", "left ventricular failure", "acute left ventricular failure", and "congestive cardiomyopathy". If more than one of these phrases was used to report events, the total number of events was taken.

Changes to Protocol Compared to Registration on PROSPERO

1. The existing manuscript focuses specifically on mortality and cardiovascular outcomes. Other pre-specified outcomes, including renal outcomes, will be examined separately.
2. We excluded RCTs of ipragliflozin, luseogliflozin, bexagliflozin and tofogliflozin because all studies have zero events in both intervention and control groups.

Table S1. Prior Distributions Employed in the Bayesian Meta-Analysis.

Parameter	Outcome	Distribution	Median	95% Reference Range
Baseline Event Rate	All Outcomes	Log Normal	0.01	0.0005-0.2
Treatment Effect	All Outcomes	Normal	1	0.05-20
Heterogeneity	Mortality	Log Normal	0.019	0.001-0.267
Heterogeneity	Major Morbidity	Log Normal	0.024	0.001-0.741

Table S2. Model Fit of the Fixed and Random Effects in Bayesian Meta-Analysis.

All Trials With at Least 1 Event Overall						
Outcome	Model	Data points	Residual Deviance	Number of residuals (%) within 1.96 SND	DIC	Q-Q Plots
All-cause mortality	Random Effects	80	81	80 (100)	366.6	Adequate
	Fixed Effect	80	87	80 (100)	368.7	Adequate
	Meta-regression	-	-	-	366.7	-
Cardiovascular mortality	Random Effects	54	54	54 (100)	272.0	Adequate
	Fixed Effect	54	60	53 (98)	275.1	Adequate
	Meta-regression	-	-	-	229.1	-
Heart failure	Random Effects	48	44	48 (100)	227.7	Adequate
	Fixed Effect	48	44	48 (100)	225.5	Adequate
	Meta-regression	-	-	-	272.1	-
Acute myocardial infarction	Random Effects	70	79	69 (99)	290.7	Adequate
	Fixed Effect	70	80	69 (99)	289.7	Adequate
	Meta-regression	-	-	-	293.4	-
Stroke	Random Effects	76	70	76 (100)	275.6	Adequate
	Fixed Effect	76	70	76 (100)	274.4	Adequate
	Meta-regression	-	-	-	271.7	-

SND is standard normal distribution; DIC is deviance information criterion

Table S3. General Characteristics of Included Randomized Controlled Trials.

Author	Study Acronym	Intervention	Comparator	Study Duration (weeks)	Number Randomized	Number Analyzed	Mean Age	Number of Women (%)	Mean BMI	Mean Hba1c	Diabetes Duration Years
Bailey (2013)[30]		Dapagliflozin	Placebo	102	409	409	53.9	254 (47)	31.5	8.1	6.1
Barnett (2014)[31]	EMPA-REG RENAL	Empagliflozin	Placebo	52	741	738	63.9	308 (42)	30.7	8.0	.
Bhatt (2021)[13]	SCORED	Sotagliflozin	Placebo		10584	10584	69.0	4754 (45)	31.8	8.3	.
Bhatt (2021)[25]	SOLOIST-WHF	Sotagliflozin	Placebo		1222	1222	69.0	412 (34)	31.0	7.1	.
Bode (2015)[32]		Canagliflozin	Placebo	104	714	714	63.6	318 (45)	31.6	7.7	11.7
Bolinder (2014)[33]		Dapagliflozin	Placebo	102	182	182	60.7	80 (44)	31.9	7.2	5.8
Cannon (2020)[8]	VERTIS-CV	Ertugliflozin	Placebo	183	8246	8246	64.4	2477 (30)	31.9	8.2	13.0
Cefalu (2015)[34]		Dapagliflozin	Placebo	52	922	922	62.9	290 (32)	32.8	8.1	12.4
DagogoJack (2018)[35]	VERTIS SITA2	Ertugliflozin	Placebo	52	464	462	59.1	199 (43)	30.8	8.0	9.5
DeFronzo (2015)[36]		Empagliflozin	Placebo	52	405	397	56.2	312 (46)	31.0	8.0	.
Ferrannini (2010)[37]		Dapagliflozin	Placebo	24	353	353	52.6	256 (53)	32.7	7.9	0.4
Forst (2014)[38]	CANTATA-MP	Canagliflozin	Placebo	26	342	342	57.3	126 (37)	32.5	7.9	10.5
Frias (2016)[39]	DURATION-8	Dapagliflozin	Placebo	28	462	461	54.0	357 (52)	33.0	9.3	7.4
Grunberger (2018)[40]	VERTIS RENAL	Ertugliflozin	Placebo	52	468	467	67.3	236 (51)	32.5	8.2	14.2
Hadjadj (2016)[41]		Empagliflozin	Placebo	24	1021	1021	52.6	580 (44)	30.4	8.7	.
Haering (2015)[42]	EMPA-REG EXTEND-METSU	Empagliflozin	Placebo	76	669	666	57.2	327 (49)	28.2	8.1	.
Henry (2012)[43]		Dapagliflozin	Placebo	24	395	395	51.9	333 (56)	.	9.2	1.6
Henry (2012)[43]		Dapagliflozin	Placebo	24	419	419	51.6	330 (52)	.	9.1	2.1
Jabbour (2014)[44]		Dapagliflozin	Placebo	48	451	451	54.9	202 (45)	.	7.9	5.7
Ji (2014)[45]		Dapagliflozin	Placebo	24	393	393	51.3	136 (35)	25.6	8.3	1.4
Kadowaki (2017)[46]		Canagliflozin	Placebo	24	138	138	57.2	31 (22)	26.0	8.0	7.4

Kaku (2014)[47]		Dapagliflozin	Placebo	24	261	261	58.8	106 (41)	25.3	7.5	4.9
Kawamori (2018)[48]		Empagliflozin	Placebo	52	275	275	59.9	61 (22)	26.2	8.3	8.9
Kohan (2014)[49]		Dapagliflozin	Placebo	104	252	252	67.0	88 (35)	.	8.4	16.9
Kovacs (2015)[50]	EMPA-REG EXTEND PIO	Empagliflozin	Placebo	76	498	498	54.5	257 (52)	29.2	8.1	.
Lavalle-Gonzalez (2013)[51]	CANTATA-D	Canagliflozin	Placebo	26	918	918	55.4	679 (53)	31.8	7.9	6.9
Leiter (2014)[52]		Dapagliflozin	Placebo	52	965	965	63.7	318 (33)	32.8	8.1	13.2
Lewin (2015)[53]		Empagliflozin	Placebo	52	408	407	54.6	308 (46)	31.6	8.0	.
Mathieu (2016)[54]		Dapagliflozin	Placebo	52	320	320	55.1	174 (54)	31.7	8.2	7.6
Merker (2015)[55]	EMPA-REG EXTEND MET	Empagliflozin	Placebo	76	638	637	55.7	276 (43)	29.2	7.9	.
Neal (2017)[10]	CANVAS and CANVAS-R	Canagliflozin	Placebo		10142	10142	63.3	3633 (36)	32.0	8.2	13.5
Packer (2020)[7]	EMPA-REDUCED	Empagliflozin	Placebo		3730	3730	66.9	893 (24)	27.9	.	.
Perkovic (2019)[9]	CREDENCE	Canagliflozin	Placebo		4401	4401	63.0	1494 (34)	31.3	8.3	15.8
Petrie (2020)[24]	DAPA-HF	Dapagliflozin	Placebo	96	2139	2139	66.5	477 (22)	29.3	7.4	.
Pratley (2018)[56]	VERTIS FACTORIAL	Ertugliflozin	Placebo	52	734	734	55.2	568 (46)	31.9	8.6	6.9
Roden (2015)[57]	EMPA-REG MONO	Empagliflozin	Placebo	76	676	676	55.0	348 (39)	28.4	7.9	.
Rosenstock (2012)[58]		Dapagliflozin	Placebo	48	420	420	53.5	212 (50)	.	8.4	5.5
Rosenstock (2014)[59]	EMPA-REG MDI	Empagliflozin	Placebo	52	566	563	56.7	307 (55)	34.8	8.3	.
Rosenstock (2015)[60]		Dapagliflozin	Placebo	24	355	355	54.0	266 (50)	31.7	8.9	7.6
Rosenstock (2015)[61]	EMPA-REG BASAL	Empagliflozin	Placebo	78	494	494	58.8	218 (44)	32.2	8.2	.
Rosenstock (2016)[62]		Canagliflozin	Placebo	26	711	711	54.9	617 (52)	32.5	8.8	3.3
Singh (2020)[63]	REFORM	Dapagliflozin	Placebo	52	56	56	67.1	19 (34)	32.5	7.7	8.8
Sone (2020)[64]		Empagliflozin	Placebo	52	269	266	58.7	73 (27)	26.9	8.8	13.8

Stenlof (2013)[65]	CANTATA-M	Canagliflozin	Placebo	26	584	584	55.4	326 (56)	31.6	8.0	4.3
Strojek (2014)[66]		Dapagliflozin	Placebo	48	442	442	59.8	307 (52)	29.8	8.1	7.4
Terra (2017)[67]	VERTIS MONO	Ertugliflozin	Placebo	26	461	461	56.4	200 (43)	33.0	8.2	5.0
Wheeler (2020)[12]	DAPA-CKD	Dapagliflozin	Placebo		2906	2906	64.4	965 (33)	.	.	.
Wilding (2013)[68]		Canagliflozin	Placebo	52	469	469	56.8	230 (49)	33.1	8.1	9.6
Wilding (2014)[69]		Dapagliflozin	Placebo	104	605	605	59.3	418 (52)	33.1	8.5	13.6
Wiviott (2018)[11]	DECLARE	Dapagliflozin	Placebo		17160	17160	64.0	6422 (37)	32.0	8.3	10.5
Yale (2014)[70]		Canagliflozin	Placebo	52	269	269	68.5	106 (39)	33.0	8.0	16.3
Yang (2018)[71]		Dapagliflozin	Placebo	24	272	272	57.5	142 (52)	26.5	8.5	12.4
Zinman (2015)[6]	EMPA-REG OUTCOME	Empagliflozin	Placebo		7020	7020	63.1	2004 (29)	30.7	8.1	.

Table S4. Risk of Bias in Included Randomized Controlled Trials.

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Bailey (2013)[30]	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk
Barnett (2014)[31]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Bhatt (2021)[13]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Bhatt (2021)[25]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Bode (2015)[32]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Bolinder (2014)[33]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Cannon (2020)[8]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Cefalu (2015)[34]	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
DagogoJack (2018)[35]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear Risk
DeFronzo (2015)[36]	Low Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Ferrannini (2010)[37]	Low Risk	Unclear Risk	Low Risk	Low Risk	High Risk	Low Risk	Unclear Risk
Forst (2014)[38]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Frias (2016)[39]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk
Grunberger (2018)[40]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk
Hadjadj (2016)[41]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Haering (2015)[42]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk
Henry (2012)[43]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Henry (2012)[43]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Jabbour (2014)[44]	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk
Ji (2014)[45]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Kadowaki (2017)[46]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Kaku (2014)[47]	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk
Kawamori (2018)[48]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk
Kohan (2014)[49]	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Kovacs (2015)[50]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Lavalle-Gonzalez (2013)[51]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Leiter (2014)[52]	Low Risk	Low Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Lewin (2015)[53]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk
Mathieu (2016)[54]	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk

Study							
Merker (2015)[55]	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Neal (2017)[10]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Packer (2020)[7]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Perkovic (2019)[9]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Petrie (2020)[24]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Pratley (2018)[56]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk
Roden (2015)[57]	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk
Rosenstock (2012)[58]	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk
Rosenstock (2014)[59]	Low Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Rosenstock (2015)[60]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Rosenstock (2015)[61]	Low Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Rosenstock (2016)[62]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Singh (2020)[63]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Sone (2020)[64]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk
Stenlof (2013)[65]	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Strojek (2014)[66]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Terra (2017)[67]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Wheeler (2020)[12]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Wilding (2013)[68]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Wilding (2014)[69]	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk
Wiviott (2018)[11]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Yale (2014)[70]	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk
Yang (2018)[71]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Zinman (2015)[6]	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk

Table S5. Outcomes Reported by Included Randomized Controlled Trials.

Author	Study Acronym	Intervention	Outcomes Reported
Bailey (2013)[30]		Dapagliflozin	Mortality, Acute Myocardial Infarction, Stroke
Barnett (2014)[31]	EMPA-REG RENAL	Empagliflozin	Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Bhatt (2021)[13]	SCORED	Sotagliflozin	Mortality, Cardiovascular Mortality
Bhatt (2021)[25]	SOLOIST-WHF	Sotagliflozin	Mortality, Cardiovascular Mortality
Bode (2015)[32]		Canagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Bolinder (2014)[33]		Dapagliflozin	Mortality
Cannon (2020)[8]		Dapagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Cefalu (2015)[34]	VERTIS-CV	Ertugliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
DagogoJack (2018)[35]	VERTIS SITA2	Ertugliflozin	Acute Myocardial Infarction, Stroke
DeFronzo (2015)[36]		Empagliflozin	Mortality, Cardiovascular Mortality
Ferrannini (2010)[37]		Dapagliflozin	Mortality
Forst (2014)[38]	CANTATA-MP	Canagliflozin	Acute Myocardial Infarction, Stroke
Frias (2016)[39]	DURATION-8	Dapagliflozin	Mortality, Cardiovascular Mortality, Acute Myocardial Infarction, Stroke
Grunberger (2018)[40]	VERTIS RENAL	Ertugliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Hadjadj (2016)[41]		Empagliflozin	Acute Myocardial Infarction, Stroke
Haering (2015)[42]	EMPA-REG EXTEND-METSU	Empagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Henry (2012)[43]		Dapagliflozin	Mortality, Cardiovascular Mortality, Acute Myocardial Infarction,
Henry (2012)[43]		Dapagliflozin	Stroke
Jabbour (2014)[44]		Dapagliflozin	Mortality
Ji (2014)[45]		Dapagliflozin	Acute Myocardial Infarction, Stroke
Kadowaki (2017)[46]		Canagliflozin	Stroke
Kaku (2014)[47]		Dapagliflozin	Stroke
Kawamori (2018)[48]		Empagliflozin	Mortality, Cardiovascular Mortality, Stroke
Kohan (2014)[49]		Dapagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Kovacs (2015)[50]	EMPA-REG EXTEND PIO	Empagliflozin	Mortality, Cardiovascular Mortality, Acute Myocardial Infarction, Stroke
Lavalle-Gonzalez (2013)[51]	CANTATA-D	Canagliflozin	Mortality, Acute Myocardial Infarction, Stroke
Leiter (2014)[52]		Dapagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Lewin (2015)[53]		Empagliflozin	Mortality, Cardiovascular Mortality, Stroke
Mathieu (2016)[54]		Dapagliflozin	Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction,
Merker (2015)[55]	EMPA-REG EXTEND MET	Empagliflozin	Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Neal (2017)[10]	CANVAS and CANVAS-R	Canagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke

Packer (2020)[7]	EMPA-REDUCED	Empagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure
Perkovic (2019)[9]	CREDENCE	Canagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Petrie (2020)[24]	DAPA-HF	Dapagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure
Pratley (2018)[56]	VERTIS FACTORIAL	Ertugliflozin	Acute Myocardial Infarction, Stroke
Roden (2015)[57]	EMPA-REG MONO	Empagliflozin	Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Rosenstock (2012)[58]		Dapagliflozin	Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction,
Rosenstock (2014)[59]	EMPA-REG MDI	Empagliflozin	Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Rosenstock (2015)[60]		Dapagliflozin	Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Rosenstock (2015)[61]	EMPA-REG BASAL	Empagliflozin	Acute Myocardial Infarction,
Rosenstock (2016)[62]		Canagliflozin	Mortality, Cardiovascular Mortality, Stroke
Singh (2020)[63]	REFORM	Dapagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure
Sone (2020)[64]		Empagliflozin	Mortality, Acute Myocardial Infarction,
Stenlof (2013)[65]	CANTATA-M	Canagliflozin	Mortality, Cardiovascular Mortality, Stroke
Strojek (2014)[66]		Dapagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Terra (2017)[67]	VERTIS MONO	Ertugliflozin	Stroke
Wheeler (2020)[12]	DAPA-CKD	Dapagliflozin	Mortality, Cardiovascular Mortality
Wilding (2013)[68]		Canagliflozin	Acute Myocardial Infarction, Stroke
Wilding (2014)[69]		Dapagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Wiviott (2018)[11]	DECLARE	Dapagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Yale (2014)[70]		Canagliflozin	Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke
Yang (2018)[71]		Dapagliflozin	Acute Myocardial Infarction, Stroke
Zinman (2015)[6]	EMPA-REG OUTCOME	Empagliflozin	Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke

Table S6. Number of Randomized Controlled Trials, Participants and Events for Outcomes of Interest.

Outcome	All SGLT-2 Inhibitors Number of trials (participants [events, person years; event rate])	Empagliflozin Number of trials (participants [events, person years; event rate])	Canagliflozin Number of trials (participants [events, person years; event rate])	Dapagliflozin Number of trials (participants [events, person years; event rate])	Ertugliflozin Number of trials (participants [events, person years; event rate])	Sotagliflozin Number of trials (participants [events, person years; event rate])
All-Cause Mortality	40 (82450 [5094, 212531; 7.8])	12 (15730 [995, 30862]; 4.9)	7 (17739 [1062, 51371; 12.4])	17 (28462 [1666, 86005; 7.6])	2 (8713 [738, 29287; 23.8])	2 (11806 [633, 15005; 99]
Cardiovascular Mortality	27 (76391 [3281, 206988; 12.5])	7 (12993 [706, 27978; 4.3])	5 (16552 [706, 50762; 12.8])	11 (26327 [909, 84118; 7.1])	2 (8713 [526, 29055; 10.8])	2 (11806 [434, 15074; 74.5]
Hospitalization for Heart Failure	24 (62044 [2343, 176451; 11.7])	8 (14524 [823, 28667; 5.7])	4 (15526 [478, 48064; 10.9])	10 (23281 [833, 73449; 12.4])	2 (8713 [209, 26270; 12.5])	-
Acute Myocardial Infarction	35 (63138 [2351, 178606; 9.2])	10 (12313 [372, 25012; 6.2])	7 (12854 [439, 38118; 14.4])	14 (23395 [868, 72739; 10.6])	4 (9909 [493, 31537; 9.2])	-
Stroke	38 (64590 [1454, 178449; 6.4])	11 (12995 [265, 25760; 4.6])	10 (18688 [463, 50255; 5.3])	12 (22537 [487, 71584; 10.9])	5 (10370 [239, 30850; 4.4])	-

Event rates are reported as number of events per 1000 person years after continuity correction to allow for inclusion of studies with zero events in either the control or intervention group.

Table S7. Heterogeneity and 95% Credibility Intervals for the Use of SGLT-2 Inhibitors Compared with Placebo.

All Trials	Tau-2 (95% CrI)
All-Cause Mortality	0.012 (0.001 to 0.059)
Cardiovascular Mortality	0.015 (0.002 to 0.074)
Hospitalization for Heart Failure	0.006 (0.000 to 0.056)
Acute Myocardial Infarction	0.012 (0.001 to 0.170)
Stroke	0.010 (0.000 to 0.110)
Participants with Established Cardiovascular Disease	
All-Cause Mortality	0.017 (0.002 to 0.111)
Cardiovascular Mortality	0.021 (0.002 to 0.126)
Hospitalization for Heart Failure	0.006 (0.000 to 0.064)
Acute Myocardial Infarction	0.017 (0.001 to 0.257)
Stroke	0.013 (0.001 to 0.201)

CrI is credibility interval

Table S8. Regression Coefficients for the Association Between the Control Group Event Rate, All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events.

Outcome	All Trials With at Least 1 Event Overall			
	Fixed treatment effect and fixed slope	**Fixed treatment effect and random slope**	**Random treatment effect and fixed slope***	**Random treatment effect and random slope**
	RRR (95% CI)	**RRR (95% CI)**	**RRR (95% CI)**	**RRR (95% CI)**
All-cause mortality	0.98 (0.90 to 1.07)	0.88 (0.05 to 1.70)	0.95 (0.82 to 1.08)	0.98 (0.78 to 1.21)
Cardiovascular mortality	0.98 (0.90 to 1.07)	0.91 (0.07 to 1.79)	0.95 (0.80 to 1.09)	0.99 (0.80 to 1.24)
Heart Failure	1.02 (0.95 to 1.11)	0.96 (0.03 to 3.35)	1.02 (0.91 to 1.15)	1.03 (0.83 to 1.28)
Acute Myocardial Infarction	0.94 (0.69 to 1.46)	0.96 (0.66 to 1.58)	0.90 (0.61 to 1.45)	0.96 (0.59 to 1.72)
Any stroke	0.59 (0.46 to 0.80)	0.59 (0.44 to 0.85)	0.56 (0.42 to 0.81)	0.57 (0.40 to 0.86)

*Indicates the primary analysis. RRR: ratio of rate ratio; CrI: credible interval. The regression coefficient represents the ratio of rate ratio per 1-unit increase in the log rate of events in the control group, which corresponds to an increase in all-cause mortality from approximately 10 per 1000 patient-years in patients with multiple risk factors, but without established cardiovascular disease (primary prevention) to approximately 25 per 1000 patient-years in patients with established cardiovascular disease (secondary prevention).

Table S9. All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events with the Use of SGLT-2 Inhibitors Compared with Placebo Using Biologically Plausible Versus Minimally Informative Priors.

	All comers		Secondary prevention	
	*Biologically plausible	^Minimally informative	*Biologically plausible	^Minimally informative
All-Cause Mortality				
Empagliflozin	0.79(0.63 to 0.97)	0.81(0.65 to 1.02)	0.81(0.62 to 1.05)	0.80(0.61 to 1.06)
Canagliflozin	0.86(0.69 to 1.05)	0.86(0.69 to 1.08)	0.87(0.66 to 1.14)	0.86(0.65 to 1.13)
Dapagliflozin	0.86(0.72 to 1.01)	0.86(0.73 to 1.04)	0.89(0.70 to 1.17)	0.88(0.69 to 1.16)
Ertugliflozin	0.94(0.71 to 1.26)	0.94(0.70 to 1.28)	0.93(0.64 to 1.33)	0.93(0.64 to 1.36)
Sotagliflozin	0.95(0.73 to 1.20)	0.94(0.72 to 1.20)	0.84(0.53 to 1.33)	0.83(0.51 to 1.33)
Cardiovascular Mortality				
Empagliflozin	0.78(0.61 to 1.00)	0.79(0.62 to 1.04)	0.77(0.57 to 1.03)	0.77(0.56 to 1.03)
Canagliflozin	0.83(0.63 to 1.05)	0.84(0.64 to 1.08)	0.85(0.62 to 1.16)	0.85(0.61 to 1.17)
Dapagliflozin	0.88(0.71 to 1.08)	0.89(0.71 to 1.10)	0.88(0.66 to 1.17)	0.88(0.65 to 1.18)
Ertugliflozin	0.95(0.68 to 1.34)	0.96(0.68 to 1.37)	0.95(0.64 to 1.41)	0.95(0.63 to 1.43)
Sotagliflozin	0.90(0.68 to 1.20)	0.89(0.66 to 1.20)	0.87(0.52 to 1.45)	0.85(0.50 to 1.43)
Hospitalization for Heart Failure				
Empagliflozin	0.66(0.53 to 0.79)	0.66(0.53 to 0.81)	0.68(0.55 to 0.84)	0.68(0.55 to 0.84)
Canagliflozin	0.64(0.51 to 0.81)	0.64(0.51 to 0.81)	0.64(0.49 to 0.83)	0.63(0.48 to 0.82)
Dapagliflozin	0.74(0.61 to 0.91)	0.74(0.61 to 0.91)	0.79(0.64 to 0.97)	0.78(0.63 to 0.97)
Ertugliflozin	0.63(0.45 to 0.89)	0.62(0.44 to 0.88)	0.64(0.45 to 0.92)	0.64(0.45 to 0.93)
Myocardial Infarction				
Empagliflozin	0.85 (0.70 to 1.05)	0.87 (0.70 to 1.08)	0.88 (0.71 to 1.09)	0.87 (0.70 to 1.09)
Canagliflozin	0.86 (0.73 to 1.00)	0.86 (0.73 to 1.00)	0.83 (0.69 to 1.00)	0.83 (0.69 to 1.00)
Dapagliflozin	0.88 (0.76 to 1.00)	0.88 (0.77 to 1.00)	0.89 (0.76 to 1.05)	0.89 (0.76 to 1.05)
Ertugliflozin	1.01 (0.84 to 1.22)	1.01 (0.84 to 1.23)	1.00 (0.83 to 1.22)	1.00 (0.83 to 1.22)
Stroke				
Empagliflozin	1.14 (0.88 to 1.47)	1.19 (0.92 to 1.55)	1.18 (0.89 to 1.57)	1.17 (0.89 to 1.56)
Canagliflozin	0.81 (0.68 to 0.97)	0.82 (0.68 to 0.99)	0.86 (0.68 to 1.07)	0.85 (0.68 to 1.07)
Dapagliflozin	0.99 (0.83 to 1.17)	1.00 (0.83 to 1.19)	0.96 (0.76 to 1.21)	0.96 (0.76 to 1.20)
Ertugliflozin	0.98 (0.75 to 1.27)	0.99 (0.76 to 1.30)	1.00 (0.77 to 1.32)	1.00 (0.76 to 1.32)

*Minimally informative but biological plausible priors: log baseline event rate ~ normal(-4.605170186,2.336113); log treatment effect ~ normal(0,2.336113)

^Minimally informative priors: log baseline event rate ~ normal(0,10000); log treatment effect ~ normal(0,10000)

Figure S1. Flow Diagram for the Identification of Included Studies.

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┌─────────────────────────────────────────┐
│        All Studies Identified, n=11312    │
│                                           │
│  Initial Search (Inception to Nov 2018),  │
│                  n=9665                   │
│              Medline, n=2534              │
│              Embase, n=7122               │
│            Reference review, n=9          │
│                                           │
│  Updated Search (Nov 2018 to August 2020),│
│                  n=1028                   │
│              Medline, n=274               │
│              Embase, n=750                │
│            Reference review, n=4          │
│                                           │
│ Updated Search (August 2020 to June 2021),│
│                  n=619                    │
│              Medline, n=213               │
│              Embase, n=406                │
│            Reference review, n=0          │
└─────────────────────────────────────────┘
                    │
                    ├──────────────►  ┌──────────────────────────────────────┐
                    │                 │ Excluded in Abstract Screen, n=10300   │
                    │                 └──────────────────────────────────────┘
                    ▼
┌─────────────────────────────────────────┐
│         Full Text Review, n=1012          │
└─────────────────────────────────────────┘
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Excluded in Full Text Review, n=959
Duplicate, n=257
No Outcome of Interest, n=153
Incorrect Intervention, n=205
Editorial, n=72
Incorrect Comparator, n=67
Conference Publication, n=53
Secondary Analysis, n=48
Follow-up <24 weeks, n=41
Systematic Review or Meta-analysis, n=14
Incorrect population, n=14
Not randomized, interventional study, n=10
SGLT-2 Inhibitor with zero mortality events, n=15
Observational Study, n=5
Protocol, n=5

Studies Eligible for Inclusion, n=53

Figure S2. Network Plot of Interventions.
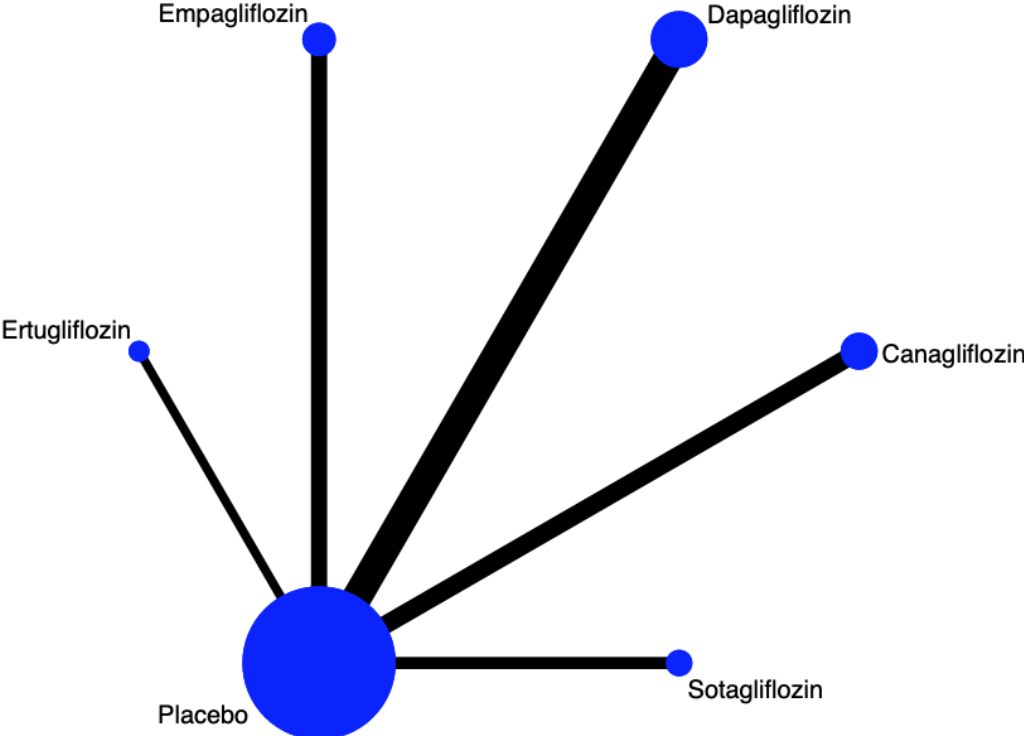
The size of nodes and connecting lines corresponds to the total participants included in trials of the respective intervention.

Figure S3. All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events with the Use of SGLT-2 Inhibitors Compared with Placebo According to an Analysis of All Trials (Fixed Effect Analysis).

Outcome	Trials	Events	Participants	All Trials	Rate Ratio	95% CrI	Superior RR<0.8	Superior RR<1	Inferior RR>1	Inferior RR>1.25
All−Cause Mortality										
Empagliflozin	12	995	15730		0.81	[0.71; 0.91]	44.9	99.9	0.1	0
Canagliflozin	7	1062	17739		0.86	[0.77; 0.98]	10.5	99.1	0.9	0
Dapagliflozin	17	1666	28462		0.87	[0.79; 0.96]	3.4	99.7	0.3	0
Ertugliflozin	2	738	8713		0.93	[0.80; 1.09]	2.2	82.2	17.8	0
Sotagliflozin	2	633	11806		0.96	[0.83; 1.13]	0.9	67.6	32.4	0.1
Cardiovascular Mortality										
Empagliflozin	7	706	12993		0.79	[0.68; 0.91]	58.8	99.9	0.1	0
Canagliflozin	5	706	16552		0.85	[0.73; 0.99]	20.5	98.5	1.5	0
Dapagliflozin	11	909	26327		0.90	[0.79; 1.02]	3.6	94.7	5.3	0
Ertugliflozin	2	526	8713		0.95	[0.80; 1.14]	2.8	70.7	29.3	0.2
Sotagliflozin	2	434	11806		0.90	[0.75; 1.09]	10.2	85.1	14.9	0
Hospitalization for Heart Failure										
Empagliflozin	8	823	14524		0.67	[0.58; 0.77]	99.5	100	0	0
Canagliflozin	4	478	15526		0.63	[0.53; 0.76]	99.5	100	0	0
Dapagliflozin	10	833	23281		0.74	[0.65; 0.85]	85.2	100	0	0
Ertugliflozin	2	209	8713		0.63	[0.48; 0.84]	94.8	99.9	0.1	0
Myocardial Infarction										
Empagliflozin	10	372	12313		0.85	[0.70; 1.05]	26.3	93.1	6.9	0
Canagliflozin	7	439	12854		0.86	[0.73; 1.00]	20	97.3	2.8	0
Dapagliflozin	14	868	23395		0.88	[0.76; 1.00]	9.5	97.6	2.4	0
Ertugliflozin	4	493	9909		1.01	[0.84; 1.22]	0.8	44.9	55.1	1.5
Stroke										
Empagliflozin	11	265	12995		1.14	[0.88; 1.47]	0.3	16.1	83.9	23.9
Canagliflozin	10	463	18688		0.81	[0.68; 0.97]	43.8	98.8	1.3	0
Dapagliflozin	12	487	22537		0.99	[0.83; 1.17]	1.1	56.7	43.3	0.4
Ertugliflozin	5	239	10370		0.98	[0.75; 1.27]	6.9	57.4	42.6	3.3

0.5   0.8   1.25   2

Favours SGLT2   Favours Placebo

RR is rate ratio; CrI is credible interval. Summary estimates are provided and are derived from a fixed effect meta-analysis. Dashed vertical lines correspond to the margins for a large reduction or large increase in the incidence of an outcome. The provided probabilities take into consideration the magnitude of the summary estimate as well as the corresponding uncertainty. Trailing zeroes are not shown.
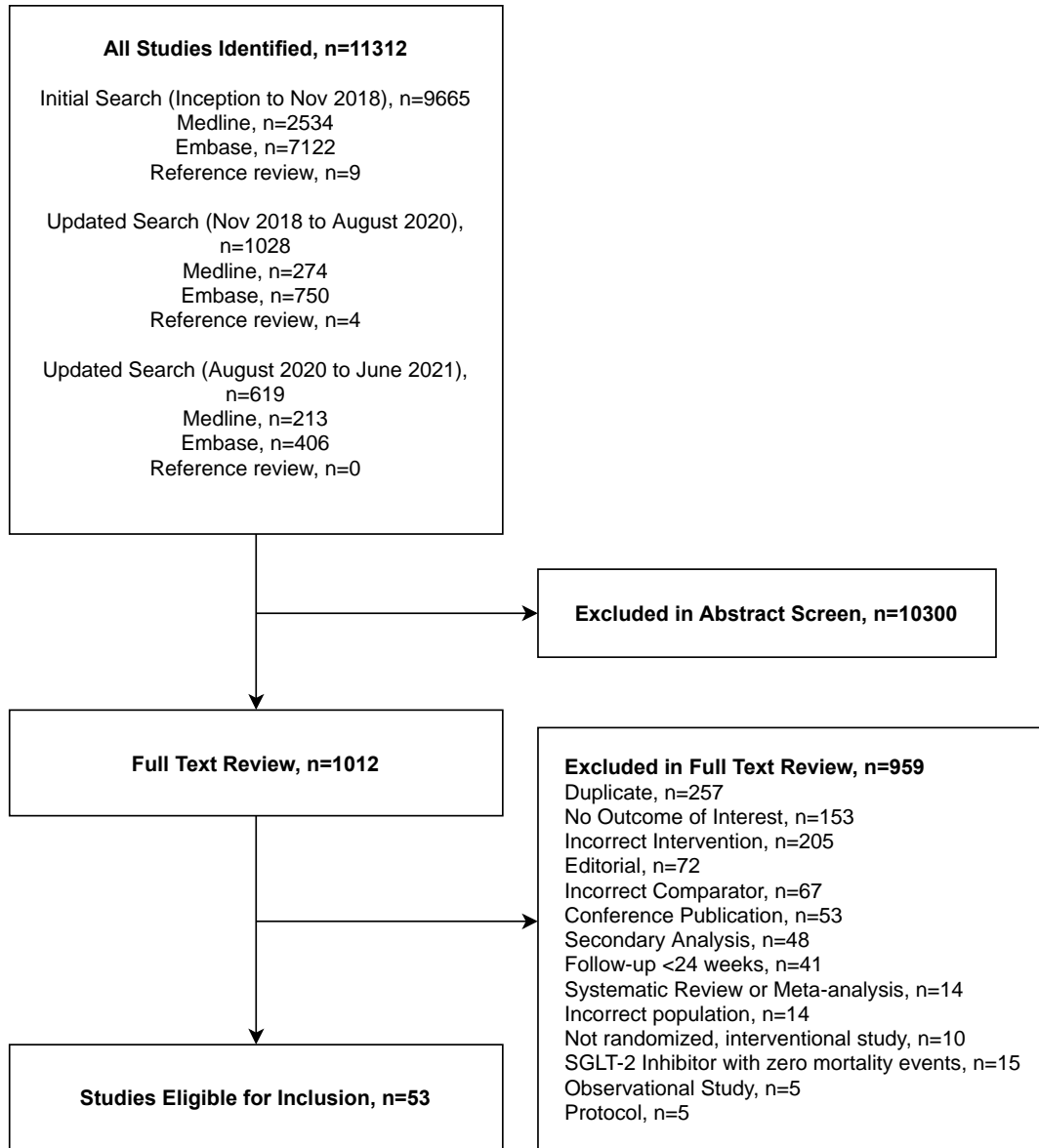
Figure S4. Treatment Effects Adjusted for the Control Group Event Rate for All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events with the Use of SGLT2-2 Inhibitors Compared with Placebo According to an Analysis of All Trials.

Outcome	All Trials	Adusted Rate Ratio	95% CrI	Superior RR<0.8	Superior RR<1	Inferior RR>1	Inferior RR>1.25
All−Cause Mortality							
Empagliflozin		0.83	[0.64; 1.05]	38.57	94.3	5.7	0.11
Canagliflozin		0.86	[0.68; 1.09]	23.54	91.07	8.93	0.25
Dapagliflozin		0.88	[0.72; 1.08]	15.84	91.14	8.87	0.12
Ertugliflozin		0.96	[0.72; 1.32]	9.91	61.7	38.3	4.57
Sotagliflozin		1.00	[0.75; 1.37]	5.6	48.65	51.35	7.47
Cardiovascular Mortality							
Empagliflozin		0.83	[0.61; 1.15]	40.01	88.5	11.5	1.02
Canagliflozin		0.84	[0.62; 1.09]	35.68	91.94	8.07	0.3
Dapagliflozin		0.91	[0.71; 1.15]	13.53	80.98	19.02	0.54
Ertugliflozin		0.97	[0.67; 1.44]	12.99	56.12	43.88	8.67
Sotagliflozin		0.97	[0.68; 1.43]	13.79	58.25	41.75	8.3
Hospitalization for Heart Failure							
Empagliflozin		0.63	[0.47; 0.82]	96.21	99.93	0.07	0
Canagliflozin		0.63	[0.49; 0.82]	96.81	99.87	0.14	0.01
Dapagliflozin		0.73	[0.58; 0.92]	79.37	99.31	0.69	0.03
Ertugliflozin		0.63	[0.43; 0.91]	90.9	99.3	0.69	0.05
Myocardial Infarction							
Empagliflozin		0.89	[0.54; 1.29]	31.4	72.22	27.78	3.77
Canagliflozin		0.87	[0.56; 1.20]	31.8	79.14	20.86	1.41
Dapagliflozin		0.88	[0.57; 1.19]	29.68	78.39	21.6	1.13
Ertugliflozin		1.10	[0.69; 1.73]	8.25	33.14	66.86	27.18
Stroke							
Empagliflozin		1.19	[0.84; 1.53]	1.58	13.1	86.91	36.84
Canagliflozin		0.95	[0.73; 1.22]	8.86	67.23	32.77	1.48
Dapagliflozin		0.88	[0.62; 1.14]	24.47	84.22	15.78	0.62
Ertugliflozin		0.94	[0.64; 1.26]	16.27	67.3	32.7	2.63

Axis: 0.5   0.8   1.25   2

Favours SGLT2   Favours Placebo

RR is rate ratio; CrI is credible interval. Adjusted summary estimates are provided and are derived from a random effects meta-analysis with treatment effects estimated at the median control baseline event rate for each outcome based on the large SGLT-2 trials. Dashed vertical lines correspond to the margins for a large reduction or large increase in the incidence of an outcome. The provided probabilities take into consideration the magnitude of the summary estimate as well as the corresponding uncertainty. Trailing zeroes are not shown.

Figure S5. Treatment Ranking for All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events with the Use of SGLT2-2 Inhibitors Compared with Placebo According to an Analysis of All Trials.

Treatment		Median Rank (95% CrI)
All-Cause Mortality		
Empagliflozin		1 (1 to 5)
Canagliflozin		3 (1 to 6)
Dapagliflozin		3 (1 to 5)
Ertugliflozin		4 (1 to 6)
Sotagliflozin		4 (1 to 6)
Placebo		5 (4 to 6)
Cardiovascular Mortality		
Empagliflozin		2 (1 to 5)
Canagliflozin		2 (1 to 6)
Dapagliflozin		3 (1 to 6)
Ertugliflozin		5 (1 to 6)
Sotagliflozin		4 (1 to 6)
Placebo		5 (4 to 6)
Hospitalization for Heart Failure		
Empagliflozin		2 (1 to 4)
Canagliflozin		2 (1 to 4)
Dapagliflozin		4 (1 to 4)
Ertugliflozin		2 (1 to 4)
Placebo		5 (5 to 5)
Myocardial Infarction		
Empagliflozin		2 (1 to 5)
Canagliflozin		2 (1 to 4)
Dapagliflozin		2 (1 to 5)
Ertugliflozin		5 (1 to 5)
Placebo		4 (3 to 5)
Stroke		
Empagliflozin		5 (1 to 5)
Canagliflozin		1 (1 to 4)
Dapagliflozin		3 (1 to 5)
Ertugliflozin		3 (1 to 5)
Placebo		3 (2 to 5)

Ranking: 1 2 3 4 5 6

CrI is Credibility interval

Figure S6. All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events with the Use of SGLT2-2 Inhibitors Compared with Placebo According to an Analysis of Participants with Established Cardiovascular Disease (Fixed Effect Analysis).

				Superior		Inferior	
Outcome	Participants with Established Cardiovascular Disease	Rate Ratio	95% CrI	RR<0.8	RR<1	RR>1	RR>1.25
All−Cause Mortality							
Empagliflozin		0.81	[0.71; 0.92]	40.7	100	0	0
Canagliflozin		0.88	[0.76; 1.01]	10.4	96.2	3.8	0
Dapagliflozin		0.88	[0.78; 1.00]	6.4	97.5	2.5	0
Ertugliflozin		0.93	[0.80; 1.08]	2.5	82.9	17.2	0
Sotagliflozin		0.84	[0.60; 1.18]	38	84.5	15.5	1
Cardiovascular Mortality							
Empagliflozin		0.78	[0.67; 0.91]	61.2	99.9	0.1	0
Canagliflozin		0.86	[0.72; 1.03]	21.1	94.9	5.1	0
Dapagliflozin		0.88	[0.75; 1.03]	12.8	94.4	5.6	0
Ertugliflozin		0.95	[0.79; 1.14]	2.9	70.6	29.4	0.2
Sotagliflozin		0.87	[0.60; 1.26]	33.9	77.8	22.2	2.9
Hospitalization for Heart Failure							
Empagliflozin		0.68	[0.59; 0.78]	98.8	100	0	0
Canagliflozin		0.64	[0.52; 0.79]	98.1	100	0	0
Dapagliflozin		0.78	[0.67; 0.91]	60.7	99.9	0.1	0
Ertugliflozin		0.64	[0.48; 0.86]	93.1	99.9	0.1	0
Myocardial Infarction							
Empagliflozin		0.88	[0.71; 1.09]	20.8	88.2	11.8	0.1
Canagliflozin		0.83	[0.69; 1.00]	35.8	97.3	2.7	0
Dapagliflozin		0.89	[0.76; 1.05]	8.7	91.7	8.3	0
Ertugliflozin		1.00	[0.83; 1.22]	0.8	48.6	51.4	1.2
Stroke							
Empagliflozin		1.18	[0.89; 1.57]	0.3	12.5	87.5	33.2
Canagliflozin		0.86	[0.68; 1.07]	28.2	91.2	8.9	0.1
Dapagliflozin		0.96	[0.76; 1.21]	5.8	63.5	36.5	1.2
Ertugliflozin		1.00	[0.77; 1.32]	5.1	49.2	50.8	6

0.5   0.8   1.25   2

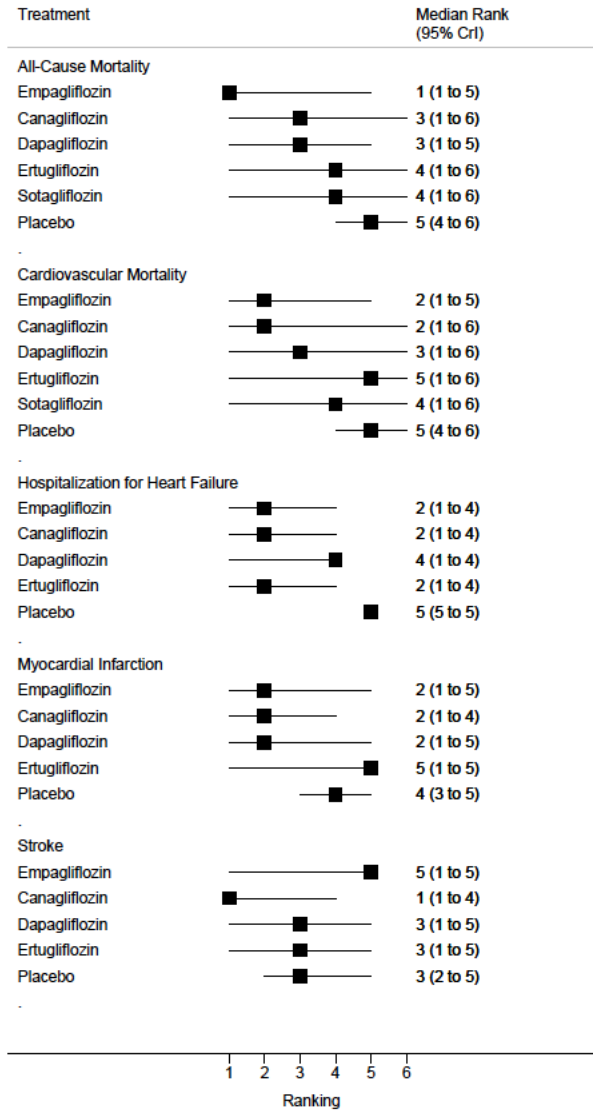Favours SGLT2   Favours Placebo

RR is rate ratio; CrI is credible interval. Summary estimates are provided and are derived from a fixed-effect meta-analysis. Dashed vertical lines correspond to the margins for a large reduction or large increase in the incidence of an outcome. The provided probabilities take into consideration the magnitude of the summary estimate as well as the corresponding uncertainty. Trailing zeroes are not shown.

Figure S7. All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events with the Use of SGLT-2 Inhibitors Compared with Placebo According to an Analysis of Participants with Established Cardiovascular Disease (Random Effects Analysis).
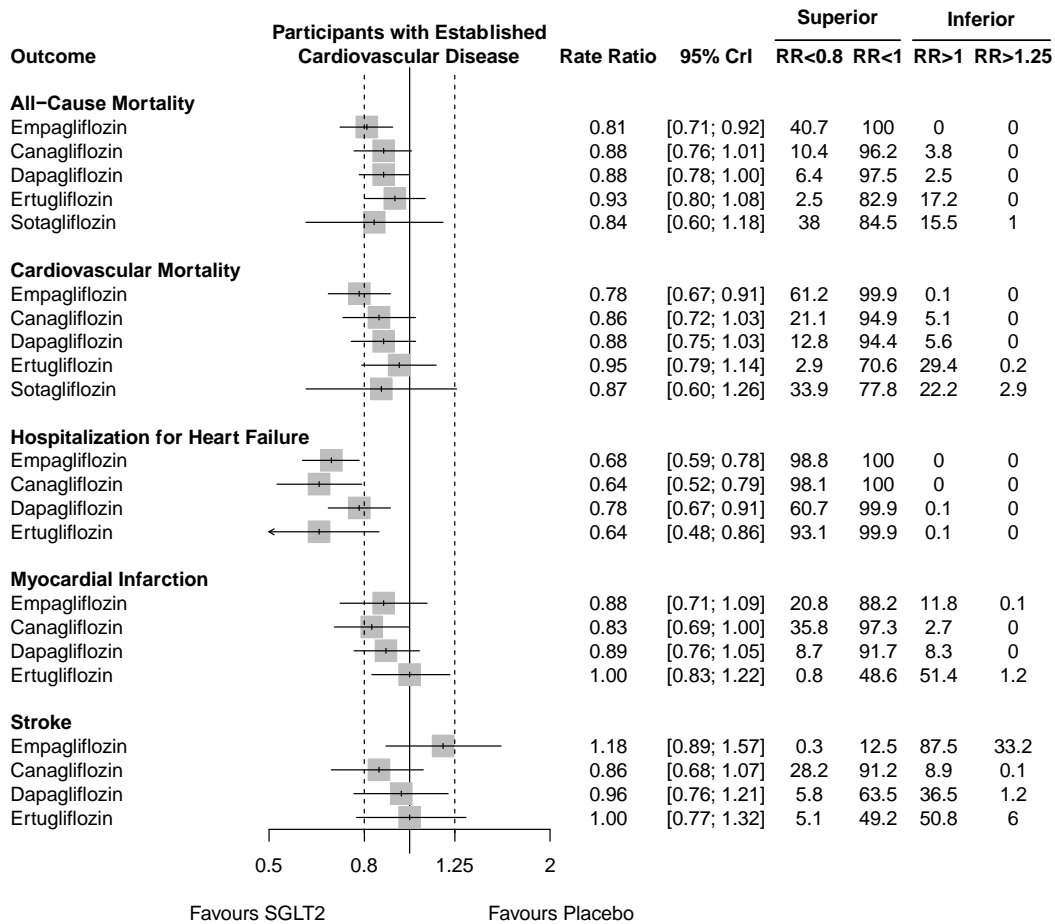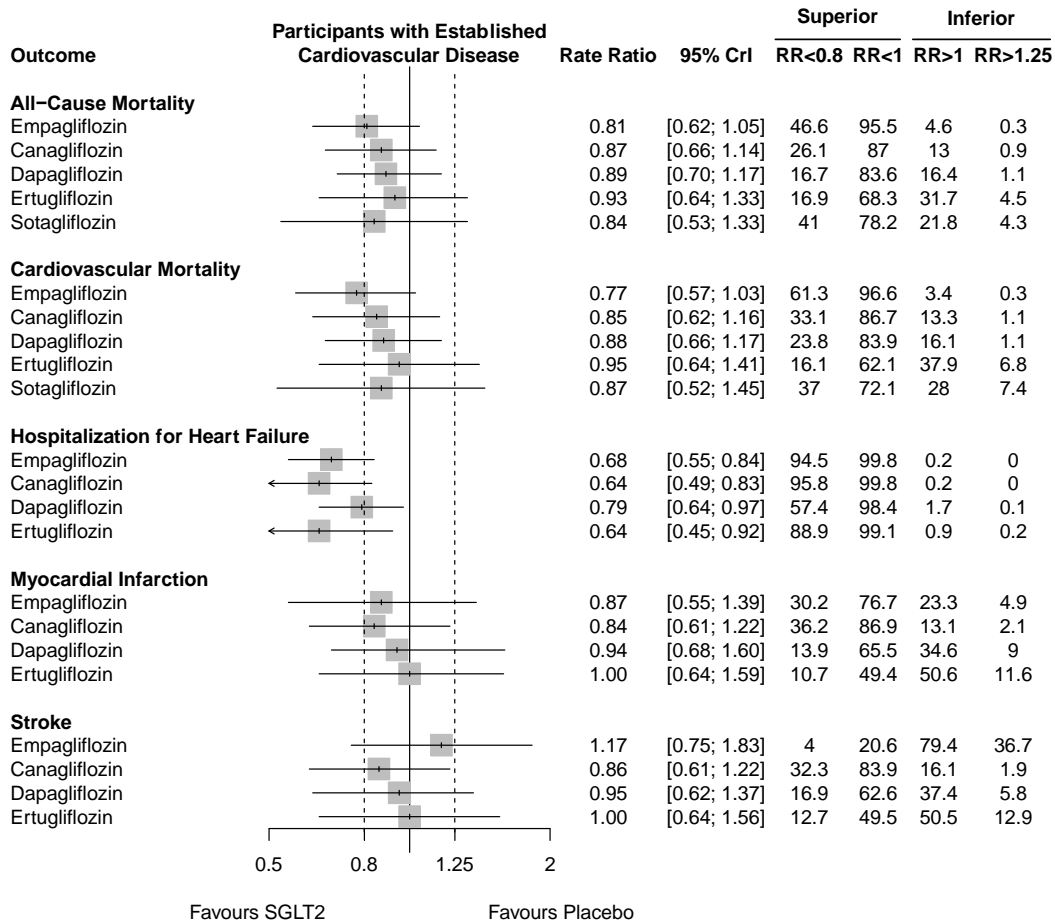
Outcome	Participants with Established Cardiovascular Disease	Rate Ratio	95% CrI	Superior RR<0.8	Superior RR<1	Inferior RR>1	Inferior RR>1.25
All−Cause Mortality							
Empagliflozin		0.81	[0.62; 1.05]	46.6	95.5	4.6	0.3
Canagliflozin		0.87	[0.66; 1.14]	26.1	87	13	0.9
Dapagliflozin		0.89	[0.70; 1.17]	16.7	83.6	16.4	1.1
Ertugliflozin		0.93	[0.64; 1.33]	16.9	68.3	31.7	4.5
Sotagliflozin		0.84	[0.53; 1.33]	41	78.2	21.8	4.3
Cardiovascular Mortality							
Empagliflozin		0.77	[0.57; 1.03]	61.3	96.6	3.4	0.3
Canagliflozin		0.85	[0.62; 1.16]	33.1	86.7	13.3	1.1
Dapagliflozin		0.88	[0.66; 1.17]	23.8	83.9	16.1	1.1
Ertugliflozin		0.95	[0.64; 1.41]	16.1	62.1	37.9	6.8
Sotagliflozin		0.87	[0.52; 1.45]	37	72.1	28	7.4
Hospitalization for Heart Failure							
Empagliflozin		0.68	[0.55; 0.84]	94.5	99.8	0.2	0
Canagliflozin		0.64	[0.49; 0.83]	95.8	99.8	0.2	0
Dapagliflozin		0.79	[0.64; 0.97]	57.4	98.4	1.7	0.1
Ertugliflozin		0.64	[0.45; 0.92]	88.9	99.1	0.9	0.2
Myocardial Infarction							
Empagliflozin		0.87	[0.55; 1.39]	30.2	76.7	23.3	4.9
Canagliflozin		0.84	[0.61; 1.22]	36.2	86.9	13.1	2.1
Dapagliflozin		0.94	[0.68; 1.60]	13.9	65.5	34.6	9
Ertugliflozin		1.00	[0.64; 1.59]	10.7	49.4	50.6	11.6
Stroke							
Empagliflozin		1.17	[0.75; 1.83]	4	20.6	79.4	36.7
Canagliflozin		0.86	[0.61; 1.22]	32.3	83.9	16.1	1.9
Dapagliflozin		0.95	[0.62; 1.37]	16.9	62.6	37.4	5.8
Ertugliflozin		1.00	[0.64; 1.56]	12.7	49.5	50.5	12.9

Axis: 0.5   0.8   1.25   2

Favours SGLT2   Favours Placebo

RR is rate ratio; CrI is credible interval. Summary estimates are provided and are derived from a random effects meta-analysis. Dashed vertical lines correspond to the margins for a large reduction or large increase in the incidence of an outcome. The provided probabilities take into consideration the magnitude of the summary estimate as well as the corresponding uncertainty. The tau2 was 0.019 for All-Cause Mortality, 0.018 for Cardiovascular Mortality, 0.018 for Hospitalization for Heart Failure, 0.025 for Acute Myocardial Infarction and 0.019 for Stroke. Trailing zeroes are not shown.
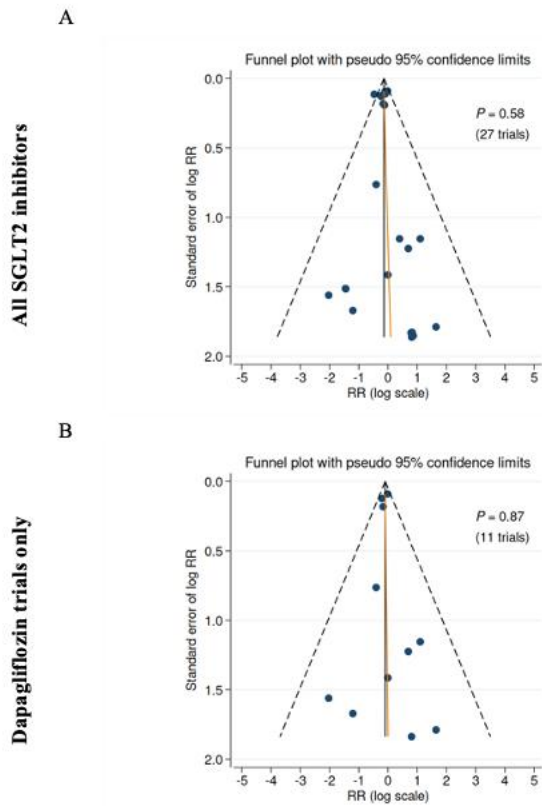
Figure S8. Funnel Plots for the Effect of SGLT2 inhibitors *vs* Placebo/no Intervention on All-Cause Mortality.
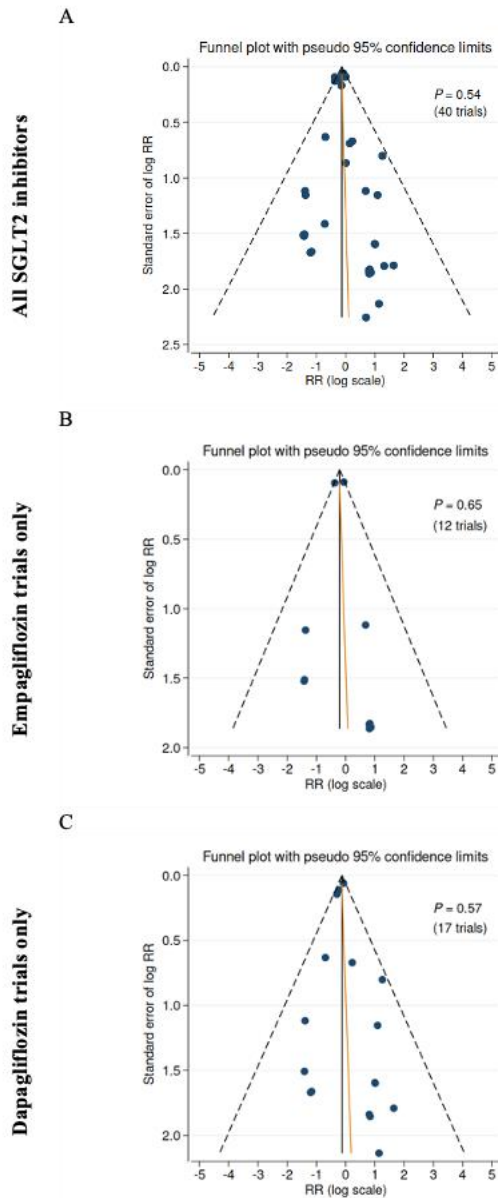
Solid vertical lines represent summary effect estimates on a logarithm scale (incidence rate ratio, RR). Results are based on a fixed-effects model (inverse-variance, frequentist approach). Dashed lines represent 95% confidence limits for the expected distribution of trial estimates in the absence of statistical heterogeneity and small-study bias or publication bias. Yellow lines present the fitted regression line corresponding to Egger's test for funnel plot asymmetry. Analyses for other SGLT2 inhibitors or restricted to adults with established CVD were not possible because the number of trial estimates was smaller than 10.
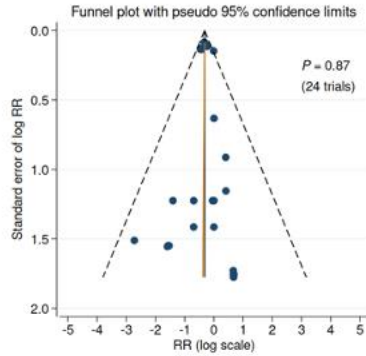
Figure S9. Funnel Plots for the Effect of SGLT2 inhibitors *vs* Placebo/no Intervention on Cardiovascular Mortality.

Solid vertical lines represent summary effect estimates on a logarithm scale (incidence rate ratio, RR). Results are based on a fixed-effects model (inverse-variance, frequentist approach). Dashed lines represent 95% confidence limits for the expected distribution of trial estimates in the absence of statistical heterogeneity and small-study bias or publication bias. Yellow lines present the fitted regression line corresponding to Egger's test for funnel plot asymmetry. Analyses for other SGLT2 inhibitors or restricted to adults with established CVD were not possible because the number of trial estimates was smaller than 10.
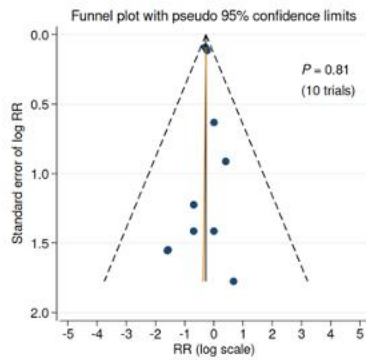
Figure S10. Funnel Plots for the Effect of SGLT2 inhibitors *vs* Placebo/no Intervention on Hospitalization for Heart Failure.
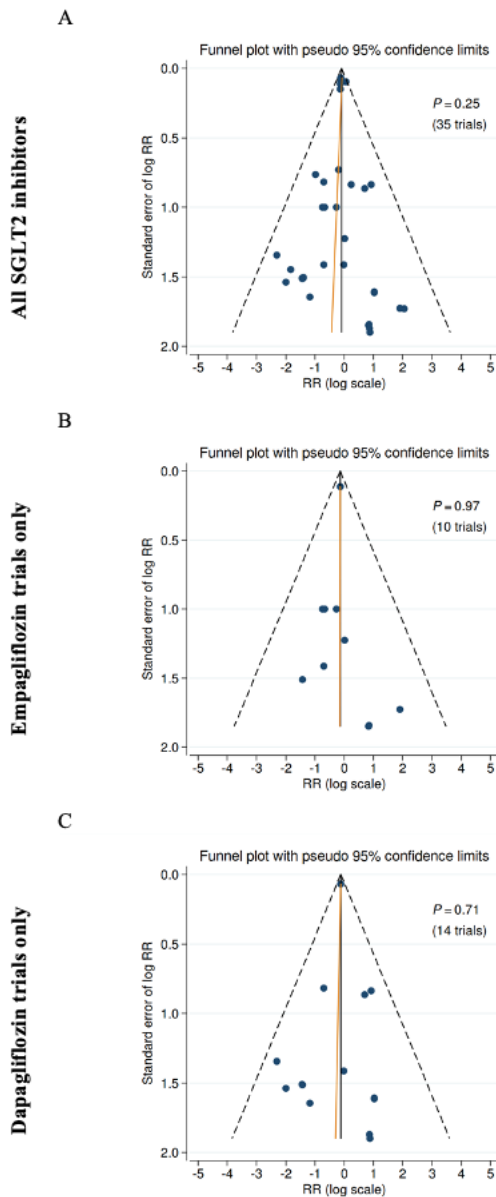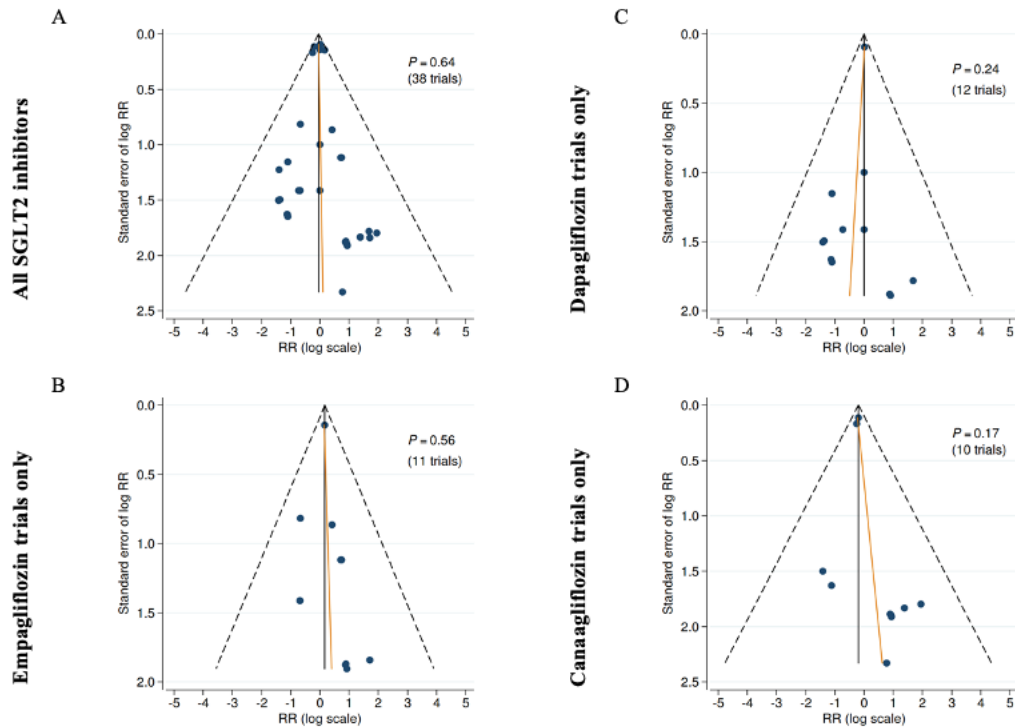

Solid vertical lines represent summary effect estimates on a logarithm scale (incidence rate ratio, RR). Results are based on a fixed-effects model (inverse-variance, frequentist approach). Dashed lines represent 95% confidence limits for the expected distribution of trial estimates in the absence of statistical heterogeneity and small-study bias or publication bias. Yellow lines present the fitted regression line corresponding to Egger's test for funnel plot asymmetry. Analyses for other SGLT2 inhibitors or restricted to adults with established CVD were not possible because the number of trial estimates was smaller than 10.

Figure S11. Funnel Plots for the Effect of SGLT2 inhibitors *vs* Placebo/no Intervention on Acute Myocardial Infarction.

Solid vertical lines represent summary effect estimates on a logarithm scale (incidence rate ratio, RR). Results are based on a fixed-effects model (inverse-variance, frequentist approach). Dashed lines represent 95% confidence limits for the expected distribution of trial estimates in the absence of statistical heterogeneity and small-study bias or publication bias. Yellow lines present the fitted regression line corresponding to Egger's test for funnel plot asymmetry. Analyses for other SGLT2 inhibitors or restricted to adults with established CVD were not possible because the number of trial estimates was smaller than 10.

Figure S12. Funnel Plots for the Effect of SGLT2 inhibitors *vs* Placebo/no Intervention on Stroke.

Solid vertical lines represent summary effect estimates on a logarithm scale (incidence rate ratio, RR). Results are based on a fixed-effects model (inverse-variance, frequentist approach). Dashed lines represent 95% confidence limits for the expected distribution of trial estimates in the absence of statistical heterogeneity and small-study bias or publication bias. Yellow lines present the fitted regression line corresponding to Egger's test for funnel plot asymmetry. Analyses for other SGLT2 inhibitors or restricted to adults with established CVD were not possible because the number of trial estimates was smaller than 10.

Figure S13. League Tables for All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events with the Use of SGLT-2 Inhibitors (Fixed Effect Analysis)

A) All-Cause Mortality

Sotagliflozin					
1.03(0.83 to 1.28)	**Ertugliflozin**				
1.10(0.92 to 1.32)	1.07(0.89 to 1.27)	**Dapagliflozin**			
1.20(0.98 to 1.46)	1.16(0.95 to 1.41)	1.08(0.92 to 1.27)	**Empagliflozin**		
1.12(0.92 to 1.36)	1.08(0.89 to 1.31)	1.01(0.86 to 1.18)	0.93(0.78 to 1.11)	**Canagliflozin**	
0.96(0.83 to 1.13)	0.93(0.80 to 1.09)	0.87(0.79 to 0.96)	0.81(0.71 to 0.91)	0.86(0.77 to 0.98)	**Placebo**

B) Cardiovascular Mortality

Sotagliflozin					
0.95(0.73 to 1.24)	**Ertugliflozin**				
1.00(0.80 to 1.26)	1.06(0.85 to 1.32)	**Dapagliflozin**			
1.15(0.90 to 1.46)	1.21(0.96 to 1.53)	1.14(0.94 to 1.39)	**Empagliflozin**		
1.06(0.84 to 1.35)	1.12(0.89 to 1.41)	1.06(0.87 to 1.28)	0.92(0.75 to 1.14)	**Canagliflozin**	
0.90(0.75 to 1.09)	0.95(0.80 to 1.14)	0.90(0.79 to 1.02)	0.79(0.68 to 0.91)	0.85(0.73 to 0.99)	**Placebo**

C) Hospitalization for Heart Failure

Sotagliflozin					
-	**Ertugliflozin**				
-	0.85(0.62 to 1.16)	**Dapagliflozin**			
-	0.94(0.69 to 1.29)	1.11(0.92 to 1.35)	**Empagliflozin**		
-	1.00(0.71 to 1.39)	1.18(0.94 to 1.47)	1.06(0.84 to 1.33)	**Canagliflozin**	
-	0.63(0.48 to 0.84)	0.74(0.65 to 0.85)	0.67(0.58 to 0.77)	0.63(0.53 to 0.76)	**Placebo**

D) Acute Myocardial Infarction

Sotagliflozin					
-	**Ertugliflozin**				
-	1.16(0.92 to 1.46)	**Dapagliflozin**			
-	1.19(0.89 to 1.56)	1.02(0.80 to 1.30)	**Empagliflozin**		
-	1.18(0.92 to 1.51)	1.02(0.83 to 1.26)	1.00(0.77 to 1.29)	**Canagliflozin**	
-	1.01(0.84 to 1.22)	0.88(0.76 to 1.00)	0.85(0.70 to 1.05)	0.86(0.73 to 1.00)	**Placebo**

E) Stroke

Sotagliflozin					
-	**Ertugliflozin**				
-	0.99(0.72 to 1.36)	**Dapagliflozin**			
-	0.86(0.59 to 1.24)	0.87(0.64 to 1.18)	**Empagliflozin**		
-	1.20(0.88 to 1.66)	1.22(0.94 to 1.57)	1.40(1.03 to 1.92)	**Canagliflozin**	
-	0.98(0.75 to 1.27)	0.99(0.83 to 1.17)	1.14(0.88 to 1.47)	0.81(0.68 to 0.97)	**Placebo**

A is the league table for all-cause mortality; B is cardiovascular mortality; C is heart failure; D is acute myocardial infarction; E is stroke. Rate Ratios and 95% credible interval are for comparison of drug type or control (*vertical*) with reference drug or control (*horizontal*). A rate ratio <1.00 indicates that the outcome is less likely with the intervention (column) than reference (row).

Figure S14. League Tables for All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events with the Use of SGLT-2 Inhibitors (Random Effects Analysis).

A) All-Cause Mortality

Sotagliflozin					
1.00(0.67 to 1.45)	Ertugliflozin				
1.10(0.81 to 1.48)	1.10(0.79 to 1.55)	Dapagliflozin			
1.19(0.86 to 1.67)	1.19(0.85 to 1.73)	1.08(0.83 to 1.44)	Empagliflozin		
1.10(0.80 to 1.54)	1.10(0.78 to 1.59)	1.00(0.76 to 1.33)	0.92(0.68 to 1.24)	Canagliflozin	
0.95(0.73 to 1.20)	0.94(0.71 to 1.26)	0.86(0.72 to 1.01)	0.79(0.63 to 0.97)	0.86(0.69 to 1.05)	Placebo

Sotagliflozin					
	Ertugliflozin				
1.12(0.82 to 1.52)	1.12(0.80 to 1.58)	Dapagliflozin			
1.19(0.86 to 1.67)	1.19(0.84 to 1.75)	1.06(0.81 to 1.43)	Empagliflozin		
1.11(0.79 to 1.54)	1.10(0.77 to 1.61)	0.99(0.74 to 1.32)	0.93(0.68 to 1.25)	Canagliflozin	
0.95(0.73 to 1.21)	0.94(0.71 to 1.28)	0.84(0.71 to 1.01)	0.79(0.63 to 0.98)	0.86(0.69 to 1.06)	Placebo

B) Cardiovascular Mortality

Sotagliflozin					
0.95(0.61 to 1.46)	Ertugliflozin				
1.02(0.73 to 1.47)	1.08(0.73 to 1.62)	Dapagliflozin			
1.15(0.79 to 1.67)	1.22(0.80 to 1.86)	1.13(0.80 to 1.55)	Empagliflozin		
1.09(0.76 to 1.61)	1.15(0.77 to 1.77)	1.06(0.77 to 1.49)	0.94(0.67 to 1.37)	Canagliflozin	
0.90(0.68 to 1.20)	0.95(0.68 to 1.34)	0.88(0.71 to 1.08)	0.78(0.61 to 1.00)	0.83(0.63 to 1.05)	Placebo

Sotagliflozin			
	Ertugliflozin		
1.12(0.82 to 1.52)	1.12(0.80 to 1.58)	Dapagliflozin	
1.19(0.86 to 1.67)	1.19(0.84 to 1.75)	1.06(0.81 to 1.43)	Empagliflozin

1.11(0.79 to 1.54)	1.10(0.77 to 1.61)	0.99(0.74 to 1.32)	0.93(0.68 to 1.25)	**Canagliflozin**	
0.95(0.73 to 1.21)	0.94(0.71 to 1.28)	0.84(0.71 to 1.01)	0.79(0.63 to 0.98)	0.86(0.69 to 1.06)	**Placebo**

C) Hospitalization for Heart Failure

Sotagliflozin					
-	**Ertugliflozin**				
-	0.85(0.57 to 1.28)	**Dapagliflozin**			
-	0.96(0.65 to 1.45)	1.13(0.86 to 1.52)	**Empagliflozin**		
-	0.99(0.65 to 1.50)	1.17(0.87 to 1.58)	1.04(0.75 to 1.39)	**Canagliflozin**	
-	0.63(0.45 to 0.89)	0.74(0.61 to 0.91)	0.66(0.53 to 0.79)	0.64(0.51 to 0.81)	**Placebo**

D) Acute Myocardial Infarction

Sotagliflozin					
-	Ertugliflozin				
-	1.21(0.82 to 2.14)	Dapagliflozin			
-	1.23(0.79 to 2.14)	1.01(0.64 to 1.53)	Empagliflozin		
-	1.24(0.84 to 2.19)	1.03(0.69 to 1.53)	1.01(0.68 to 1.62)	Canagliflozin	
-	1.02(0.73 to 1.50)	0.85(0.58 to 1.08)	0.83(0.57 to 1.13)	0.83(0.58 to 1.04)	Placebo

E) Stroke

Sotagliflozin					
-	Ertugliflozin				
-	1.01(0.65 to 1.67)	Dapagliflozin			
-	0.84(0.51 to 1.39)	0.84(0.53 to 1.28)	Empagliflozin		
-	1.17(0.72 to 1.78)	1.16(0.72 to 1.66)	1.39(0.88 to 2.07)	Canagliflozin	
-	0.95(0.65 to 1.35)	0.95(0.65 to 1.23)	1.13(0.80 to 1.55)	0.82(0.63 to 1.06)	Placebo

A is the league table for all-cause mortality; B is cardiovascular mortality; C is heart failure; D is acute myocardial infarction; E is stroke. Rate Ratios and 95% credible interval are for comparison of drug type or control (*vertical*) with reference drug or control (*horizontal*). A rate ratio <1.00 indicates that the outcome is less likely with the intervention (column) than reference (row).