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

Ayodele Odutayo, DPhil*; Bruno R. da Costa, PhD*; Tiago V. Pereira, PhD; Vinay Garg, MD; Samir Iskander, MSc; Fatimah Roble, BSc; Rahim Lalji MSc; Cesar A. Hincapié PhD; Aquila Akingbade, BSc; Myanca Rodrigues MSc; Arnav Agarwal, MD; Vishy Lawandy BSc; Pakazeh Saadat MSc; Jacob A. Udell MPH; Francesco Cosentino PhD; Peter J. Grant, FMedSci; Subodh Verma, MD, PhD; Peter Jüni MD

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
Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are glucose-lowering agents for the treatment of type 2 diabetes (T2DM). 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. SGLT-2 inhibitors also reduce mortality and cardiovascular outcomes, although existing studies suggest this benefit is limited to adults with established 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.

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 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. 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. The combination of these individual end points in a composite outcome could dilute or entirely miss specific differences between agents. We did not extract results for chronic kidney disease or adverse events (Data S1).

Nonstandard Abbreviations and Acronyms

| Acronym | Definition |
|---------|------------|
| CrI     | credibility interval |
| HHF     | hospitalization for heart failure |
| SGLT-2  | sodium-glucose cotransporter 2 |
| T2DM    | type 2 diabetes |
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 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, \( \tau^2 \), to ensure that differences in characteristics of patients included in currently available trials would be appropriately reflected by \( \tau^2 \), 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. These probabilities take into account both the magnitude of the summary RR and the corresponding uncertainty. 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. This model appropriately accounts for the inherent correlation between treatment effect and control group event rate. 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. 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, 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. 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%. 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 probability for superiority 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 \( \tau^2 \) 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, 8,9,10 3 were conducted for canagliflozin, 9,10,12 2 were conducted for dapagliflozin, 5,10,13 and R 3.2.5 (Auckland, New Zealand).

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 (66–64)   | 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.

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 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 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).

Table 2 presents the results of fixed-effect and random-effects summary estimates of all outcomes with heterogeneity estimates. There was positive 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 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
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%. 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

| Outcome                  | Trials | Events | Participants | All Trials | Rate Ratio | 95% CrI | Superior | RR<0.8 | RR<1 | RR>1 | 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] | 19   | 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       | [0.56; 1.04] | 39.5 | 95.2 | 4.8  | 0.1     |
| Dapagliflozin            | 14     | 868    | 23995        |            | 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     | 285    | 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    | 22237        |            | 0.95       | [0.65; 1.33] | 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       |

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.
was minimal ($\tau^2$, 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).

### 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 | $\tau^2$ (95% CrI) | Evidence grade |
|----------------------------|----------------------|-----------------------------|---------------------|----------------|
| 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 (0.75–1.03)     | 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 (0.71–1.05)     | 0.83 (0.57–1.15)            | 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)     | 0.96 (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.
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.
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 S3 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 mortality.
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. 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. We therefore used Bayesian meta-regression, which appropriately accounts for...
the inherent correlation between treatment effect and control group event rate. 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. 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. 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,3 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. 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.

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.

ARTICLE INFORMATION
Received October 27, 2020; accepted July 7, 2021.

Affiliations
Department of Medicine and Institute of Health Policy, Management and Evaluation, Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael’s Hospital, University of Toronto, Canada (A.O., B.R.d.C., T.V.P., S.I., C.A.H., P.S., P.J.); Department of Health Sciences, University of Leicester, UK (T.V.P.); Faculty of Medicine, Department of Medicine, University of Toronto, Ontario, Canada (V.G., F.R., A.A., B.L., J.A.U.); Department of Chiropractic Medicine, Faculty of Medicine, University of Zurich and Balgrist University Hospital, Zurich, Switzerland (R.L., C.A.H.); Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland (R.L., C.A.H.); Faculty of Medicine, Queen’s University, Kingston, Ontario, Canada (A.A.); Health Research Methodology Graduate Program, Department of Health Research Methods, Evidence & Impact, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada (M.R.); Cardiology Unit, Department of Medicine Soina, Karolinska Institute & Karolinska University Hospital, Stockholm, Sweden (F.C.); Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds/Leeds Teaching Hospitals NHS Trust, LIGHT Laboratories, Leeds, UK (P.J.G.); and Departments of Surgery, and Pharmacology and Toxicology, University of Toronto, Ontario, Canada (S.V.).

Acknowledgments
We would like to acknowledge the Community of Support (COS) program at the University of Toronto, which provided training opportunities for S. Iskander, F. Roble, A. Akingbade, M. Rodrigues, and B. Lavendy. The COS aims to provide opportunities to Black and aboriginal students and to
support their application to medical school. These students are underrepresented in medical education in Canada. We would also like to acknowledge Dr David Cherney for his assistance with interpretation of data and revisions on initial drafts of the manuscript.

Author contributions: Conception and design of the study; Drs Odutayo, da Costa, Pereira, and Jün; acquisition of data: Dr Odutayo, Dr Garg, S. Iskander, F. Robb, R. Lalji, Dr Hincapié, A. Akingbade, A. Agarwal, B. Lawndy, and P. Saadat; statistical analysis: Drs Odutayo, da Costa, Pereira, and Jün; interpretation of data: all authors; drafting the work: Drs Odutayo and Jün; critical revisions for important intellectual content: all authors; full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of data analysis: Drs Odutayo, da Costa, and Jün; final approval of the study and agree to be accountable for all aspects of the work: all authors; Drs Odutayo, da Costa, and Jün had full access to all the data in the study, Drs Odutayo, da Costa, and Jün take responsibility for the integrity of the data and the accuracy of the data analysis.

Sources of Funding

Dr Jün is a Tier 1 Canada Research Chair in Clinical Epidemiology of Chronic Diseases. This research was completed, in part, with funding from the Canada Research Chairs Programme.

Disclosures

Dr Odutayo is a recipient of the Boehringer Ingelheim Cardiovascular Clinical Trials Forum Advanced Fellowship in Cardiovascular Clinical Trials. This fellowship was received after the work in this article was completed. Dr Pereira is funded by the Chevening Scholarship Program (Foreign and Commonwealth Office, United Kingdom). J.A. Uedel has received honoraria for consultancy from Amgen, AstraZeneca, Boehringer-Ingelheim, Janssen, Merck, Novartis, and Sanofi; lecture fees from Boehringer-Ingelheim, Janssen, and Sanofi Pasteur; and research grants to his institutions for clinical trials from AstraZeneca, Boehringer-Ingelheim, Novartis, and Sanofi. Dr Cosentino has been an advisory board member and has received speaker’s fee with AstraZeneca. Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Novo Nordisk, and Pfizer; and chairs the task force responsible for the 2019 European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases. P.J. Grant has received personal fees for advisory boards and lectures from AstraZeneca, Bayer, Eli Lilly, Boehringer Ingelheim, Merck, Amgen, Novo Nordisk, and Janssen; and co-chairs the task force responsible for the 2019 ESC/EASD Guidelines on diabetes, pre-diabetes, and cardiovascular diseases. Dr Verma holds a Tier 1 Canada Research Chair in Cardiovascular Surgery; and reports receiving research grants and/or speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, ECPharmacom Ltd, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, PhaseBio, Sanofi, Sun Pharmaceuticals, and the Toronto Knowledge Translation Working Group. He is the president of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. Dr Jün served as an unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical, and The Medicines Company; and reported receiving research grants to the institution from AstraZeneca, Biotronik, Biosensors International, Eli Lilly, and The Medicines Company; and honoraria to the institution for participation in advisory boards from Amgen, but has not received personal payments by any pharmaceutical company or device manufacturer. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
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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$.mp.
3. slgt2 inhibitor$.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) |               | Dapagliflozin     | Placebo   | 102                    | 409               | 409            | 53.9     | 254 (47)             | 31.5    | 8.1       | 6.1                    |
| Barnett (2014) | EMPA-REG   | Empagliflozin     | Placebo   | 52                     | 741               | 738            | 63.9     | 308 (42)             | 30.7    | 8.0       | .                      |
| Bhatt (2021)  |               | Sotagliflozin     | Placebo   | 10584                  | 10584             | 10584          | 69.0     | 4754 (45)            | 31.8    | 8.3       | .                      |
| Bhatt (2021)  |               | SOLOIST-WHF       | Sotagliflozin | 1222                  | 1222             | 1222          | 69.0     | 412 (34)             | 31.0    | 7.1       | .                      |
| Bode (2015)   |               | Canagliflozin     | Placebo   | 104                    | 714               | 714            | 63.6     | 318 (45)             | 31.6    | 7.7       | 11.7                   |
| Bolinder (2014) |            | Dapagliflozin     | Placebo   | 102                    | 182               | 182            | 60.7     | 80 (44)              | 31.9    | 7.2       | 5.8                    |
| Cannon (2020) |               | Ertugliflozin     | Placebo   | 183                    | 8246              | 8246           | 64.4     | 2477 (30)            | 31.9    | 8.2       | 13.0                   |
| Cefalu (2015) |               | Dapagliflozin     | Placebo   | 52                     | 922               | 922            | 62.9     | 290 (32)             | 32.8    | 8.1       | 12.4                   |
| DagogoJack (2018) |          | VERTIS SITA2     | Ertugliflozin | 52                    | 464               | 462            | 59.1     | 199 (43)             | 30.8    | 8.0       | 9.5                    |
| DeFronzo (2015) |              | Empagliflozin     | Placebo   | 52                     | 405               | 397            | 56.2     | 312 (46)             | 31.0    | 8.0       | .                      |
| Ferrannini (2010) |            | Dapagliflozin     | Placebo   | 24                     | 353               | 353            | 52.6     | 256 (53)             | 32.7    | 7.9       | 0.4                    |
| Forst (2014)  |               | CANTATA-MP       | Canagliflozin | 26                    | 342               | 342            | 57.3     | 126 (37)             | 32.5    | 7.9       | 10.5                   |
| Frias (2016)  |               | DURATION-8       | Dapagliflozin | 28                    | 462               | 461            | 54.0     | 357 (52)             | 33.0    | 9.3       | 7.4                    |
| Grunberger (2018) |           | VERTIS RENAL     | Ertugliflozin | 52                    | 468               | 467            | 67.3     | 236 (51)             | 32.5    | 8.2       | 14.2                   |
| Hadjadj (2016) |               | Empagliflozin     | Placebo   | 24                     | 1021              | 1021           | 52.6     | 580 (44)             | 30.4    | 8.7       | .                      |
| Haering (2015) |               | EMPA-REG EXTEND-   | Empagliflozin | 76                    | 669               | 666            | 57.2     | 327 (49)             | 28.2    | 8.1       | .                      |
| Henry (2012)  |               | Dapagliflozin     | Placebo   | 24                     | 395               | 395            | 51.9     | 333 (56)             | 9.2     | 2.1       | 1.6                    |
| Henry (2012)  |               | Dapagliflozin     | Placebo   | 24                     | 419               | 419            | 51.6     | 330 (52)             | 9.1     | 2.1       | .                      |
| Jabbour (2014) |               | Dapagliflozin     | Placebo   | 48                     | 451               | 451            | 54.9     | 202 (45)             | 7.9     | 5.7       | 5.7                    |
| Ji (2014)     |               | Dapagliflozin     | Placebo   | 24                     | 393               | 393            | 51.3     | 136 (35)             | 25.6    | 8.3       | 1.4                    |
| Kadowaki (2017) |              | Canagliflozin     | Placebo   | 24                     | 138               | 138            | 57.2     | 31 (22)              | 26.0    | 8.0       | 7.4                    |
| Study                          | Treatment 1     | Treatment 2     | Study 2 | Study 3 | Study 4 | Study 5 | Study 6 |
|-------------------------------|----------------|----------------|---------|---------|---------|---------|---------|
| Kaku (2014)                   | Dapagliflozin  | Placebo        | 24      | 261     | 261     | 58.8    | 106 (41) |
| Kawamori (2018)               | Empagliflozin  | Placebo        | 52      | 275     | 275     | 59.9    | 61 (22)  |
| Kohan (2014)                  | Dapagliflozin  | Placebo        | 104     | 252     | 252     | 67.0    | 88 (35)  |
| Kovacs (2015)                 | EMPA-REG      | Placebo        | 76      | 498     | 498     | 54.5    | 257 (52) |
| Lavalle-Gonzalez (2013)       | CANTATA-D     | Placebo        | 26      | 918     | 918     | 55.4    | 679 (53) |
| Leiter (2014)                 | Dapagliflozin  | Placebo        | 52      | 965     | 965     | 53.0    | 318 (33) |
| Lewin (2015)                  | Empagliflozin  | Placebo        | 52      | 408     | 407     | 54.6    | 308 (46) |
| Mathieu (2016)                | Dapagliflozin  | Placebo        | 52      | 320     | 320     | 55.7    | 174 (54) |
| Merker (2015)                 | EMPA-REG      | Placebo        | 76      | 638     | 637     | 55.7    | 276 (43) |
| Neal (2017)                   | CANVAS and    | Placebo        | 10142   | 10142   | 10142   | 63.3    | 3633 (36)|
| Packer (2020)                 | EMPA-REDUCED  | Placebo        | 3730    | 3730    | 3730    | 66.9    | 893 (24) |
| Perkovic (2019)               | CREDENCE      | Placebo        | 4401    | 4401    | 4401    | 63.0    | 1494 (34) |
| Petrie (2020)                 | DAPA-HF       | Placebo        | 96      | 2139    | 2139    | 66.5    | 477 (22) |
| Pratley (2018)                | VERTIS FACTORIAL | Placebo   | 52      | 734     | 734     | 55.2    | 568 (46) |
| Roden (2015)                  | EMPA-REG      | Placebo        | 76      | 676     | 676     | 55.0    | 348 (39) |
| Rosenstock (2012)             | Dapagliflozin  | Placebo        | 48      | 420     | 420     | 53.5    | 212 (50) |
| Rosenstock (2014)             | EMPA-REG      | Placebo        | 52      | 566     | 563     | 56.3    | 307 (55) |
| Rosenstock (2015)             | Dapagliflozin  | Placebo        | 24      | 355     | 355     | 54.0    | 266 (50) |
| Rosenstock (2015)             | EMPA-REG      | Placebo        | 78      | 494     | 494     | 58.8    | 218 (44) |
| Rosenstock (2015)             | EMPA-REG      | Placebo        | 26      | 711     | 711     | 54.9    | 617 (52) |
| Singh (2020)                  | Dapagliflozin  | Placebo        | 52      | 56      | 56      | 67.1    | 19 (34)  |
| Sone (2020)                   | Empagliflozin  | Placebo        | 52      | 269     | 266     | 58.7    | 73 (27)  |
| Study                  | Design       | Treatment            | Comparator   | n  | Event Rate | Event Rate | Incidence | HR (95% CI) |
|------------------------|--------------|----------------------|--------------|----|-----------|-----------|-----------|-------------|
| Stenlof (2013)         | CANTATA-M    | Canagliflozin        | Placebo     | 26 | 584       | 584       | 55.4      | 326 (56)    |
| Strojek (2014)         |              | Dapagliflozin        | Placebo     | 48 | 442       | 442       | 59.8      | 307 (52)    |
| Terra (2017)           | VERTIS MONO  | Ertugliflozin        | Placebo     | 26 | 461       | 461       | 56.4      | 200 (43)    |
| Wheeler (2020)         | DAPA-CKD     | Dapagliflozin        | Placebo     | 2906| 2906      | 2906      | 64.4      | 965 (33)    |
| Wilding (2013)         |              | Canagliflozin        | Placebo     | 52 | 469       | 469       | 56.8      | 230 (49)    |
| Wilding (2014)         |              | Dapagliflozin        | Placebo     | 104| 605       | 605       | 59.3      | 418 (52)    |
| Wiviott (2018)         | DECLARE      | Dapagliflozin        | Placebo     | 17160| 17160     | 17160     | 64.0      | 6422 (37)   |
| Yale (2014)            |              | Canagliflozin        | Placebo     | 52 | 269       | 269       | 68.5      | 106 (39)    |
| Yang (2018)            |              | Dapagliflozin        | Placebo     | 24 | 272       | 272       | 57.5      | 142 (52)    |
| Zinman (2015)          | EMPA-REG OUTCOME | Empagliflozin   | Placebo     | 7020| 7020      | 7020      | 63.1      | 2004 (29)   |
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)          | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Unclear Risk           | Low Risk           | Low Risk   |
| Barnett (2014)         | Low Risk                    | Low Risk               | Low Risk                  | Unclear Risk                  | Low Risk               | Low Risk           | Low Risk   |
| Bhatt (2021)           | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Bhatt (2021)           | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Bode (2015)            | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Bolinder (2014)        | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Cannon (2020)          | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Cefalu (2015)          | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| DagogoJack (2018)      | Low Risk                    | Low Risk               | Low Risk                  | Unclear Risk                  | Low Risk               | Low Risk           | Unclear Risk |
| DeFronzo (2015)        | Low Risk                    | Unclear Risk           | Unclear Risk              | Unclear Risk                  | Low Risk               | Low Risk           | Low Risk   |
| Ferrannini (2010)      | Low Risk                    | Unclear Risk           | Low Risk                  | Low Risk                      | High Risk              | Low Risk           | Unclear Risk |
| Forst (2014)           | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Frias (2016)           | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Unclear Risk |
| Grunberger (2018)      | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Unclear Risk |
| Hadjadji (2016)        | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Haering (2015)         | Low Risk                    | Unclear Risk           | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Henry (2012)           | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Unclear Risk           | Low Risk           | Low Risk   |
| Henry (2012)           | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Jabbour (2014)         | Unclear Risk                | Unclear Risk           | Low Risk                  | Unclear Risk                  | Unclear Risk           | Low Risk           | Unclear Risk |
| Ji (2014)              | Low Risk                    | Unclear Risk           | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Kadowaki (2017)        | Low Risk                    | Unclear Risk           | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Kaku (2014)            | Unclear Risk                | Unclear Risk           | Low Risk                  | Unclear Risk                  | Low Risk               | Unclear Risk       | Low Risk   |
| Kawamori (2018)        | Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Unclear Risk |
| Kohan (2014)           | Unclear Risk                | Unclear Risk           | Low Risk                  | Unclear Risk                  | Low Risk               | Low Risk           | Low Risk   |
| Kovacs (2015)          | Low Risk                    | Unclear Risk           | Unclear Risk              | Unclear Risk                  | Low Risk               | Low Risk           | Low Risk   |
| Lavalle-Gonzalez (2013)| Low Risk                    | Low Risk               | Low Risk                  | Low Risk                      | Low Risk               | Low Risk           | Low Risk   |
| Leiter (2014)          | Low Risk                    | Low Risk               | Unclear Risk              | Unclear Risk                  | Low Risk               | Low Risk           | Low Risk   |
| Lewin (2015)           | Low Risk                    | Unclear Risk           | Low Risk                  | Low Risk                      | Unclear Risk           | Low Risk           | Low Risk   |
| Mathieu (2016)         | Low Risk                    | Unclear Risk           | Low Risk                  | Unclear Risk                  | Low Risk               | Low Risk           | Low Risk   |
| Reference            | Risk Level 1 | Risk Level 2 | Risk Level 3 | Risk Level 4 | Risk Level 5 | Risk Level 6 | Risk Level 7 |
|----------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Merker (2015)        | Unclear Risk | Unclear Risk | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Neal (2017)          | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Packer (2020)        | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Perkovic (2019)      | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Petrie (2020)        | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Pratley (2018)       | Low Risk     | Low Risk     | Low Risk     | Unclear Risk | Low Risk     | Unclear Risk | Unclear Risk |
| Roden (2015)         | Unclear Risk | Unclear Risk | Low Risk     | Low Risk     | Low Risk     | Unclear Risk | Low Risk     |
| Rosenstock (2012)    | Unclear Risk | Unclear Risk | Low Risk     | Unclear Risk | Low Risk     | Low Risk     | Low Risk     |
| Rosenstock (2014)    | Low Risk     | Unclear Risk | Unclear Risk | Unclear Risk | Low Risk     | Low Risk     | Low Risk     |
| Rosenstock (2015)    | Low Risk     | Low Risk     | Low Risk     | Unclear Risk | Low Risk     | Low Risk     | Low Risk     |
| Rosenstock (2015)    | Low Risk     | Unclear Risk | Low Risk     | Unclear Risk | Low Risk     | Low Risk     | Low Risk     |
| Rosenstock (2016)    | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Unclear Risk | Low Risk     |
| Singh (2020)         | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Sone (2020)          | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Unclear Risk | Low Risk     |
| Stenlof (2013)       | Unclear Risk | Unclear Risk | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Strojek (2014)       | Low Risk     | Unclear Risk | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Terra (2017)         | Low Risk     | Unclear Risk | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Wheeler (2020)       | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Wilding (2013)       | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Wilding (2014)       | Low Risk     | Unclear Risk | Low Risk     | Unclear Risk | Low Risk     | Low Risk     | Low Risk     |
| Wiviott (2018)       | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Yale (2014)          | Unclear Risk | Unclear Risk | Unclear Risk | Unclear Risk | Low Risk     | Unclear Risk | Unclear Risk |
| Yang (2018)          | Low Risk     | Unclear Risk | Low Risk     | Low Risk     | Low Risk     | Low Risk     | Low Risk     |
| Zinman (2015)        | Low Risk     | Low Risk     | Low Risk     | Unclear Risk | Low Risk     | Low Risk     | Low Risk     |
| Author                | Study Acronym      | Intervention | Outcomes Reported                                                                 |
|-----------------------|--------------------|--------------|-----------------------------------------------------------------------------------|
| Bailey (2013)         | EMPA-REG RENAL     | Dapagliflozin | Mortality, Acute Myocardial Infarction, Stroke                                    |
| Barnett (2014)        | EMPA-REG RENAL     | Empagliflozin | Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke |
| Bhatt (2021)          | SCORED             | Sotagliflozin | Mortality, Cardiovascular Mortality                                                |
| Bhatt (2021)          | SOLOIST-WHF        | Sotagliflozin | Mortality, Cardiovascular Mortality                                                |
| Bode (2015)           | Canagliflozin      |              | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Stroke     |
| Bolinder (2014)       | EMPA-REG RENAL     | Dapagliflozin | Mortality                                                                         |
| Cannon (2020)         |                    | Dapagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Stroke     |
| Cefalu (2015)         | VERTIS-CV          | Ertugliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Stroke     |
| DagogoJack (2018)     | VERTIS SITa2       | Ertugliflozin | Acute Myocardial Infarction, Stroke                                                |
| DeFronzo (2015)       |                    | Empagliflozin | Mortality, Cardiovascular Mortality                                                |
| Ferrannini (2010)     |                    | Dapagliflozin | Mortality                                                                         |
| Forst (2014)          | CANTATA-MP         | Canagliflozin | Acute Myocardial Infarction, Stroke                                                |
| Frias (2016)          | DURATION-8         | Dapagliflozin | Mortality, Cardiovascular Mortality, Acute Myocardial Infarction, Stroke           |
| Grunberger (2018)     | VERTIS RENAL       | Ertugliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Stroke     |
| Hadjadi (2016)        | EMPA-REG EXTEND- METSU | Empagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Stroke   |
| Haering (2015)        | EMPA-REG EXTEND- METSU | Empagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Stroke   |
| Henry (2012)          |                    | Dapagliflozin | Mortality, Cardiovascular Mortality, Acute Myocardial Infarction, Stroke           |
| Henry (2012)          |                    | Dapagliflozin | Stroke                                                                            |
| Jabbour (2014)        |                    | Dapagliflozin | Mortality                                                                         |
| Ji (2014)             |                    | Dapagliflozin | Acute Myocardial Infarction, Stroke                                                |
| Kadowaki (2017)       | Canagliflozin      |              | Stroke                                                                            |
| Kaku (2014)           | Canagliflozin      |              | Stroke                                                                            |
| Kawamori (2018)       | Empagliflozin      |              | Mortality, Cardiovascular Mortality                                                |
| Kohan (2014)          | Dapagliflozin      |              | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Stroke     |
| Kovacs (2015)         | EMPA-REG EXTEND PICO | Empagliflozin | Mortality, Cardiovascular Mortality, Acute Myocardial Infarction, Stroke          |
| Lavalle-Gonzalez (2013) | CANTATA-D        | Canagliflozin | Mortality, Acute Myocardial Infarction, Stroke                                    |
| Leiter (2014)         | Dapagliflozin      |              | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Stroke     |
| Lewin (2015)          | Empagliflozin      |              | Mortality, Cardiovascular Mortality                                                |
| Mathieu (2016)        | Dapagliflozin      |              | Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke |
| Merker (2015)         | EMPA-REG EXTEND MET | Empagliflozin | Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke            |
| Neal (2017)           | CANVAS and CANVAS-R | Canagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Stroke    |
| Study | Study Design | Treatment | Outcomes |
|-------|--------------|-----------|----------|
| Packer (2020) | EMPA-REDUCED | Empagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure |
| Perkovic (2019) | CREDENCE | Canagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke |
| Petrie (2020) | DAPA-HF | Dapagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure |
| Pratley (2018) | VERTIS FACTORIAL | Ertugliflozin | Acute Myocardial Infarction, Stroke |
| Roden (2015) | EMPA-REG MONO | Empagliflozin | Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke |
| Rosenstock (2012) | EMPA-REG MDI | Empagliflozin | Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke |
| Rosenstock (2014) | EMPA-REG BASAL | Empagliflozin | Acute Myocardial Infarction, Stroke |
| Singh (2020) | REFORM | Dapagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure |
| Sone (2020) | EMPA-REG BASAL | Empagliflozin | Acute Myocardial Infarction, Stroke |
| Stenlof (2013) | CANTATA-M | Canagliflozin | Mortality, Cardiovascular Mortality, Stroke |
| Strojek (2014) | DAPA-HF | Dapagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke |
| Terra (2017) | VERTIS MONO | Ertugliflozin | Stroke |
| Wheeler (2020) | DAPA-CKD | Dapagliflozin | Mortality, Cardiovascular Mortality |
| Wilding (2013) | Canagliflozin | Acute Myocardial Infarction, Stroke |
| Wilding (2014) | Dapagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke |
| Wiviott (2018) | DECLARE | Dapagliflozin | Mortality, Cardiovascular Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke |
| Yale (2014) | Canagliflozin | Mortality, Hospitalization for Heart Failure, Acute Myocardial Infarction, Stroke |
| Yang (2018) | Dapagliflozin | Acute Myocardial Infarction, Stroke |
| Zinman (2015) | 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.

|                                | Tau-2 (95% CrI)       |
|--------------------------------|-----------------------|
| **All Trials**                 |                       |
| 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.

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

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).

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 | Adjusted Rate Ratio | 95% CrI       | Superior RR<0.8 | RR<1 | RR>1 | RR>1.25 |
|--------------------------------|------------|---------------------|---------------|-----------------|------|------|---------|
| **All–Cause Mortality**        |            |                     |               |                 |      |      |         |
| Empagliflozin                  | [0.83]     | 0.83                | [0.64; 1.05]  | 38.57           | 94.3 | 5.7  | 0.11    |
| Canagliflozin                  | [0.86]     | 0.86                | [0.68; 1.09]  | 23.54           | 91.07| 8.93 | 0.25    |
| Dapagliflozin                  | [0.88]     | 0.88                | [0.72; 1.08]  | 15.84           | 91.14| 8.87 | 0.12    |
| Ertugliflozin                  | [0.96]     | 0.96                | [0.72; 1.32]  | 9.91            | 61.7 | 38.3 | 4.57    |
| Sotagliflozin                  | [1.00]     | 1.00                | [0.75; 1.37]  | 5.6             | 48.66| 51.35| 7.47    |
| **Cardiovascular Mortality**   |            |                     |               |                 |      |      |         |
| Empagliflozin                  | [0.83]     | 0.83                | [0.61; 1.15]  | 40.01           | 88.5 | 11.5 | 1.02    |
| Canagliflozin                  | [0.84]     | 0.84                | [0.62; 1.09]  | 35.68           | 91.94| 8.07 | 0.3     |
| Dapagliflozin                  | [0.91]     | 0.91                | [0.71; 1.15]  | 13.53           | 80.98| 19.02| 0.54    |
| Ertugliflozin                  | [0.97]     | 0.97                | [0.67; 1.44]  | 12.99           | 56.12| 43.88| 8.67    |
| Sotagliflozin                  | [0.97]     | 0.97                | [0.68; 1.43]  | 13.79           | 58.25| 41.75| 8.3     |
| **Hospitalization for Heart Failure** |         |                     |               |                 |      |      |         |
| Empagliflozin                  | [0.63]     | 0.63                | [0.47; 0.82]  | 96.21           | 99.93| 0.07 | 0       |
| Canagliflozin                  | [0.63]     | 0.63                | [0.49; 0.82]  | 96.81           | 99.87| 0.14 | 0.01    |
| Dapagliflozin                  | [0.73]     | 0.73                | [0.58; 0.92]  | 79.37           | 99.31| 0.69 | 0.03    |
| Ertugliflozin                  | [0.63]     | 0.63                | [0.43; 0.91]  | 90.9            | 99.3 | 0.69 | 0.05    |
| **Myocardial Infarction**      |            |                     |               |                 |      |      |         |
| Empagliflozin                  | [0.89]     | 0.89                | [0.54; 1.29]  | 31.4            | 72.22| 27.78| 3.77    |
| Canagliflozin                  | [0.87]     | 0.87                | [0.56; 1.20]  | 31.8            | 79.14| 20.86| 1.41    |
| Dapagliflozin                  | [0.88]     | 0.88                | [0.57; 1.19]  | 29.68           | 78.39| 21.6 | 1.13    |
| Ertugliflozin                  | [1.10]     | 1.10                | [0.69; 1.73]  | 8.25            | 33.14| 66.86| 27.18   |
| **Stroke**                     |            |                     |               |                 |      |      |         |
| Empagliflozin                  | [1.19]     | 1.19                | [0.84; 1.53]  | 1.58            | 13.1 | 86.91| 36.84   |
| Canagliflozin                  | [0.95]     | 0.95                | [0.73; 1.22]  | 8.86            | 67.23| 32.77| 1.48    |
| Dapagliflozin                  | [0.88]     | 0.88                | [0.62; 1.14]  | 24.47           | 84.22| 15.78| 0.62    |
| Ertugliflozin                  | [0.94]     | 0.94                | [0.64; 1.26]  | 16.27           | 67.3 | 32.7 | 2.63    |

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 2)            |
| Canagliflozin                    | 3 (1 to 6)            |
| Dapagliflozin                    | 3 (1 to 5)            |
| ErBufliflozin                    | 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)            |
| ErBufliflozin                    | 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)            |
| ErBufliflozin                    | 2 (1 to 4)            |
| Sotagliflozin                    | 5 (5 to 5)            |
| Placebo                          |                       |
|                                 |                       |
| Myocardial Infarction            |                       |
| Empagliflozin                    | 2 (1 to 5)            |
| Canagliflozin                    | 2 (1 to 4)            |
| Dapagliflozin                    | 2 (1 to 5)            |
| ErBufliflozin                    | 5 (1 to 5)            |
| Sotagliflozin                    | 4 (3 to 5)            |
| Placebo                          |                       |
|                                 |                       |
| Stroke                           |                       |
| Empagliflozin                    | 5 (1 to 5)            |
| Canagliflozin                    | 1 (1 to 4)            |
| Dapagliflozin                    | 3 (1 to 5)            |
| ErBufliflozin                    | 3 (1 to 5)            |
| Sotagliflozin                    | 3 (2 to 5)            |

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).

| Outcome                                      | Participants with Established Cardiovascular Disease | Rate Ratio | 95% CrI | Superior | Inferior |
|----------------------------------------------|------------------------------------------------------|------------|--------|----------|----------|
| **All-Cause Mortality**                      |                                                      |            |        | RR<0.8   | RR<1     | RR>1     | RR>1.25 |
| 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**                 |                                                      | 0.78       | [0.67; 0.91] | 61.2 | 99.9 | 0.1 | 0 |
| Empagliflozin                                |                                                      | 0.86       | [0.72; 1.03] | 21.1 | 94.9 | 5.1 | 0 |
| Canagliflozin                                |                                                      | 0.88       | [0.75; 1.03] | 12.8 | 94.4 | 5.6 | 0 |
| Dapagliflozin                                |                                                      | 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**         |                                                      | 0.68       | [0.59; 0.78] | 98.8 | 100 | 0 | 0 |
| Empagliflozin                                |                                                      | 0.64       | [0.52; 0.79] | 98.1 | 100 | 0 | 0 |
| Canagliflozin                                |                                                      | 0.78       | [0.67; 0.91] | 60.7 | 99.9 | 0.1 | 0 |
| Dapagliflozin                                |                                                      | 0.84       | [0.48; 0.86] | 93.1 | 99.9 | 0.1 | 0 |
| **Myocardial Infarction**                    |                                                      | 0.88       | [0.71; 1.09] | 20.8 | 88.2 | 11.8 | 0.1 |
| Empagliflozin                                |                                                      | 0.83       | [0.69; 1.00] | 35.8 | 97.3 | 2.7 | 0 |
| Canagliflozin                                |                                                      | 0.89       | [0.76; 1.05] | 8.7 | 91.7 | 8.3 | 0 |
| Dapagliflozin                                |                                                      | 1.00       | [0.83; 1.22] | 0.8 | 48.6 | 51.4 | 1.2 |
| **Stroke**                                   |                                                      | 1.18       | [0.89; 1.57] | 0.3 | 12.5 | 87.5 | 33.2 |
| Empagliflozin                                |                                                      | 0.86       | [0.68; 1.07] | 28.2 | 91.2 | 8.9 | 0.1 |
| Canagliflozin                                |                                                      | 0.96       | [0.76; 1.21] | 5.8 | 63.5 | 36.5 | 1.2 |
| Dapagliflozin                                |                                                      | 1.00       | [0.77; 1.32] | 5.1 | 49.2 | 50.8 | 6 |

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 | Superior 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          | 21.6          | 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           | 99.9          | 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            |

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 | Ertugliflozin | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|------------|---------------|---------------|---------------|---------------|---------------|---------|
| 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 | Ertugliflozin | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|------------|---------------|---------------|---------------|---------------|---------------|---------|
| 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 | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|------------|---------------|---------------|---------------|---------------|---------------|---------|
| Sotagliflozin | -             | 0.85 (0.62 to 1.16) |               |               |               |         |
| Ertugliflozin | -             | 0.94 (0.69 to 1.29) | 1.11 (0.92 to 1.35) |               |               |         |
| Dapagliflozin | -             | 1.00 (0.71 to 1.39) | 1.18 (0.94 to 1.47) | 1.06 (0.84 to 1.33) |               |         |
| Empagliflozin | -             | 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 | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|----------|---------------|---------------|---------------|---------------|---------------|---------|
|          | -             | -             | -             | -             | -             | -       |
| Sotagliflozin | -             | 1.16(0.92 to 1.46) | Dapagliflozin |               |               |         |
| Ertugliflozin | -             | 1.19(0.89 to 1.56) | 1.02(0.80 to 1.30) | Empagliflozin |             |         |
| Dapagliflozin | -             | 1.18(0.92 to 1.51) | 1.02(0.83 to 1.26) | 1.00(0.77 to 1.29) | Canagliflozin |         |
| Empagliflozin | -             | 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 |
| Canagliflozin | -             |               |               |               |               |         |
| Placebo   | -             |               |               |               |               |         |

### E) Stroke

|          | Sotagliflozin | Ertugliflozin | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|----------|---------------|---------------|---------------|---------------|---------------|---------|
|          | -             | -             | -             | -             | -             | -       |
| Sotagliflozin | -             | 0.99(0.72 to 1.36) | Dapagliflozin |               |               |         |
| Ertugliflozin | -             | 0.86(0.59 to 1.24) | 0.87(0.64 to 1.18) | Empagliflozin |             |         |
| Dapagliflozin | -             | 1.20(0.88 to 1.66) | 1.22(0.94 to 1.57) | 1.40(1.03 to 1.92) | Canagliflozin |         |
| Empagliflozin | -             | 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 |
| Canagliflozin | -             |               |               |               |               |         |
| 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 | Ertugliflozin | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|----------------|---------------|---------------|---------------|---------------|---------------|---------|
| 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        |               |               |               |               |               |         |

### B) Cardiovascular Mortality

|                | Sotagliflozin | Ertugliflozin | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|----------------|---------------|---------------|---------------|---------------|---------------|---------|
| 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 | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|----------------|---------------|---------------|---------------|---------------|---------------|---------|
| Sotagliflozin  | 1.12 (0.82 to 1.52) |               |               |               |               |         |
| Ertugliflozin  | 1.12 (0.80 to 1.58) | 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  |               |               |               |               |               |         |
| Sotagliflozin | Ertugliflozin | Canagliflozin | Placebo |
|-------------|--------------|---------------|---------|
| 1.11 (0.79 to 1.54) | 1.10 (0.77 to 1.61) | 0.99 (0.74 to 1.32) | 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) | Placebo |
|                |                | 0.86 (0.69 to 1.06) |         |

C) Hospitalization for Heart Failure

| Sotagliflozin | Ertugliflozin | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|--------------|--------------|---------------|---------------|---------------|---------|
| -            | 0.85 (0.57 to 1.28) | 1.13 (0.86 to 1.52) | 1.04 (0.75 to 1.39) | Canagliflozin |
| -            | 0.96 (0.65 to 1.45) |               | 1.17 (0.87 to 1.58) |               |
| -            | 0.99 (0.65 to 1.50) |               |               | 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 | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|---------------|---------------|---------------|---------------|---------------|---------|
| -             | -             | -             | -             | -             |         |
| -             | 1.21(0.82 to 2.14) | 1.23(0.79 to 2.14) | 1.24(0.84 to 2.19) | 1.02(0.73 to 1.50) |         |
| -             | 0.82(0.58 to 1.04) | 0.85(0.58 to 1.08) | 0.83(0.57 to 1.13) | 0.83(0.58 to 1.13) |         |
| -             | 1.01(0.64 to 1.53) | 1.03(0.69 to 1.53) | 1.01(0.68 to 1.62) | 1.01(0.68 to 1.62) |         |
| -             | 0.64(0.41 to 1.04) | 0.84(0.53 to 1.28) | 1.39(0.88 to 2.07) | 1.13(0.80 to 1.55) |         |
| -             | 0.58(0.37 to 0.92) | 0.85(0.58 to 1.23) | 0.82(0.63 to 1.06) | 0.82(0.63 to 1.06) |         |

E) Stroke

| Sotagliflozin | Ertugliflozin | Dapagliflozin | Empagliflozin | Canagliflozin | Placebo |
|---------------|---------------|---------------|---------------|---------------|---------|
| -             | -             | -             | -             | -             |         |
| -             | 1.01(0.65 to 1.67) | 0.84(0.51 to 1.39) | 1.17(0.72 to 1.78) | 0.95(0.65 to 1.35) |         |
| -             | 0.65(0.42 to 1.05) | 0.84(0.53 to 1.28) | 1.39(0.88 to 2.07) | 1.13(0.80 to 1.55) |         |
| -             | 0.58(0.36 to 0.92) | 1.16(0.72 to 1.66) | 0.82(0.63 to 1.06) | 0.82(0.63 to 1.06) |         |
| -             | 0.45(0.29 to 0.70) | 1.39(0.88 to 2.07) | 0.82(0.63 to 1.06) | 0.82(0.63 to 1.06) |         |
| -             | 0.33(0.21 to 0.54) | 1.13(0.80 to 1.55) | 0.82(0.63 to 1.06) | 0.82(0.63 to 1.06) |         |

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).