Comparative effectiveness and safety of empagliflozin on cardiovascular mortality and morbidity in adults with type 2 diabetes

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Background: Based on a single placebo-controlled randomized clinical trial, empagliflozin is licensed to reduce cardiovascular death in diabetes and comorbid cardiovascular disease.

Methods: We examined the comparative effectiveness of empagliflozin on mortality and cardiovascular morbidity in type 2 diabetes. We conducted random-effects direct frequentist meta-analyses of aggregate data and appraised the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Our search in PubMed, EMBASE, the Cochrane Library, clinicaltrials.gov, and PharmaPendium up to May 2017 identified 11 meta-analyses, multiple publications, and unpublished data from 29 randomized controlled trials (RCTs).

Results: Empagliflozin reduces all-cause mortality [relative risk (RR) of death, 0.69; 95% confidence interval (CI): 0.58–0.82; number needed to treat (NNT) to postpone mortality in one patient, 39; 95% CI: 26–79; 1 RCT of 7,020 patients) in patients with but not without (RR, 0.90; 95% CI: 0.36–2.23; 14 RCTs of 7,707 patients) established cardiovascular disease when compared with placebo. Empagliflozin reduces cardiovascular mortality (RR, 0.62; 95% CI: 0.50–0.78; NNT, 45; 95% CI: 30–90; 1 RCT of 7,020 patients) in patients with but not without (RR, 0.98; 95% CI: 0.29–3.33; 10 RCTs of 5,429 patients) established cardiovascular disease when compared with placebo. There are no differences in cardiovascular morbidity and mortality and all-cause mortality between empagliflozin and metformin (4 RCTs of 1,344 patients), glimepiride (1 RCT of 1,549 patients), linagliptin (2 RCTs of 1,348 patients), or sitagliptin (3 RCTs of 1,483 patients). Two network meta-analyses concluded that sodium-glucose cotransporter 2 (SGLT2) inhibitors, mostly due to empagliflozin, decrease all-cause and cardiovascular mortality but increase the risk of nonfatal stroke, genital infection, and volume depletion.

Conclusions: We conclude that empagliflozin reduces all-cause and cardiovascular mortality in patients with established cardiovascular disease and type 2 diabetes. Sparse direct evidence suggests no difference in mortality between empagliflozin and metformin, glimepiride, linagliptin, or sitagliptin. Long-term comparative safety needs to be established.

Keywords: Quality of evidence; type 2 diabetes; cardiovascular morbidity; all-cause mortality; cardiovascular mortality; empagliflozin; metformin; glimepiride; linagliptin; sitagliptin

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Introduction

One of the main goals in managing type 2 diabetes in adults is prevention of cardiovascular morbidity and mortality (1,2). Only a few of the available diabetes medications have shown benefits in reducing cardiovascular risks; most available drug classes such as thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors have been approved based on their ability to decrease glycosylated hemoglobin A1c (HbA1c) rather than their ability to prevent morbidity and mortality (3,4). Network meta-analyses of SGLT2 inhibitors suggest lower risk of all-cause and cardiovascular mortality from 3 oral SGLT2 inhibitors combined, at the expense of higher risk of nonfatal stroke [pooled relative risk (RR) 1.30; 95% confidence interval (CI): 1–1.68], genital infection (pooled RR 4.75; 95% CI: 4.00–5.63), and volume depletion (pooled RR 1.53; 95% CI: 1.27–1.83) (5,6). However, the reduction in the risk of mortality and morbidity is mostly attributable to one drug, empagliflozin, the only drug approved by the FDA in 2016 to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease (5,6).

Older meta-analyses focused on intermediate outcomes of empagliflozin when compared with placebo; e.g., HbA1c, blood pressure, and body weight (7-15). The most recent high-quality meta-analyses included 13 (6) and 16 (5) randomized controlled trials (RCTs) that reported mortality and morbidity in adults with type 2 diabetes treated with empagliflozin but did not examine the comparative effectiveness of empagliflozin and other specific antidiabetic drugs (5,6). Clinicians have to select specific drugs for individual patients rather than relying on drug class benefits and harms.

To support clinical decisions at point of care with all available evidence, we conducted a rapid review of the published and unpublished data from the recently completed RCTs, meta-analyses of RCTs, and primary observational studies that compared the effects of empagliflozin with those of other antidiabetic drugs on all-cause and cardiovascular mortality and morbidity.

Methods

We used a standard recommended methodology in conducting systematic literature reviews and meta-analyses from the Cochrane Collaboration and the Agency for Healthcare Research and Quality (16,17). We developed a priori protocol for a systematic literature review to answer the clinical question about the efficacy and comparative effectiveness of empagliflozin and other antidiabetic medications against mortality and cardiovascular morbidity in adults with type 2 diabetes.

We defined the target population as adults with type 2 diabetes. Eligible interventions included SGLT2 inhibitor empagliflozin when compared with placebo or other antidiabetic medications. Eligible outcomes included all-cause and underlying cause-specific mortality, myocardial infarction (MI), stroke, incidence or progression of heart failure, and hospitalizations for major cardiovascular events. Intermediate outcomes included diabetes control as HbA1c <7% or as defined in the primary studies. We reviewed the frequency and severity of hypoglycemia as well as any harms from examined treatments.

We conducted a comprehensive search in PubMed, EMBASE, the Cochrane Library, www.clinicaltrials.gov and PharmaPendium (www.pharmapendium.com) up to May 2017 to find systematic reviews, published and unpublished RCTs, and nationally representative controlled observational studies that reported adjusted effect estimates (16,17). All of the authors determined the studies' eligibility. All citations found during the searches are stored in a reference database.

The data was extracted from the Clinical Trials Transformation Initiative (CTTI) (https://www.ctti-clinicaltrials.org/aact-database), checked for quality, and stored in the HPCC platform (High-Performance Computing Cluster, https://hpccsystems.com/).

We performed direct frequentist meta-analyses of aggregate data when definitions of the active and control intervention and patient outcomes were deemed similar for pooling (18). We used random effects models to address inevitable differences in patient characteristics across primary RCTs. For each abstracted hypothesis, we calculated absolute risk difference and RR with 95% CI. We calculated number needed to treat (NNT) and number of attributable events per 1,000 treated with 95% CI based on statistically significant differences in absolute risks of the outcomes. We examined consistency in results across studies with chi-square tests and I^2 statistics and concluded statistically significant heterogeneity if I^2 was >50% (16). Statistically significant heterogeneity did not preclude statistical pooling (18). However, we planned exploring heterogeneity with a priori defined patient characteristics, drug doses, and study quality if this information was available in the studies (18).

We used consensus method guidelines for systematic review and meta-analyses that do not recommend conducting post hoc analyses of statistical power (19-22). Instead, we downgraded our confidence in true treatment effects based on calculated optimal information size as the number of patients required for an adequately powered individual trial (23). Since power is more closely related to number of events than to sample size, we concluded imprecision in treatment effects if fewer than 250 patients experienced the event (23).

We used Statistics/Data Analysis, STATA software (StataCorp LP, College Station, Texas). Statistical significance was evaluated at a 95% confidence level.

We evaluated the quality of systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) (24). For primary RCTs, we used the Cochrane risk of bias tool on a 3-point scale: high bias, low bias, and unclear (25,26). A low risk of bias was assumed when RCTs met all the risk-of-bias criteria, a medium risk of bias if at least 1 of the risk-of-bias criteria was not met, and a high risk of bias if 2 or more risk-of-bias criteria were not met. An unknown risk of bias was assigned for the studies with poorly reported risk-of-bias criteria. We assigned high risk of bias to all observational studies.

The authors assigned the quality of evidence ratings as high, moderate, low, or very low, according to risk of bias in the body of evidence, directness of comparisons, precision and consistency in treatment effects, and the evidence of reporting bias, using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (27).

A high quality of evidence was assigned to well-designed RCTs with consistent findings. The quality of evidence was downgraded to moderate if at least 1 of 4 quality of evidence criteria was not met; for example, moderate quality of evidence was assigned if there was a high risk of bias in the body of evidence or if the results were not consistent or precise. The quality of evidence was downgraded to low if 2 or more criteria were not met. We concluded a high risk of bias in the body of evidence if at least one RCT had high risk of bias. We downgraded the quality of evidence when we suspected high risk of publication bias due to unavailability of the results in clinicaltrials.gov or journal articles.

A low quality of evidence was assigned to nonrandomized studies, but the rating was upgraded if there was a strong or dose-response association (28). Evidence was defined as insufficient when no studies provided valid information about treatment effects. This approach was applied regardless of whether the results were statistically significant.

Results

Our comprehensive search in PubMed, EMBASE, the Cochrane Library, and clinicaltrials.gov up to May 2017 identified 11 meta-analyses, multiple publications as well as unpublished data from 29 RCTs, and one non-randomized study that examined the benefits and harms of empagliflozin in people with type 2 diabetes (5-14,29). We also identified 2 high-quality meta-analyses and multiple publications as well as unpublished data from 9 RCTs that directly compared empagliflozin with other antidiabetic drugs in people with type 2 diabetes (5-7,30-48).

Primary studies enrolled adults with type 2 diabetes and various baseline degrees of cardiovascular risk, permitted administration of metformin and other antidiabetic drugs, and aimed mostly at diabetes control and drug safety. Only one large non-inferiority trial, the EMPA-REG OUTCOME trial, was designed to examine difference in a composite outcome defined as the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke in adults with type 2 diabetes and high cardiovascular risk (49).

Efficacy

Moderate-quality evidence suggests that empagliflozin reduces all-cause mortality (7,11,40,44,46,47,49-61) and increases the rates of diabetes control without increasing the risk of serious adverse effects and hypoglycemia when compared with placebo in adults with type 2 diabetes (*Table 1*) (50,51,70). The increase in rates of glycemic improvement starts at the dose of 10 mg/day (150 attributable events per 1,000 treated, *Figure 1*) and increases to 210 attributable events per 1,000 treated after the larger dose of empagliflozin (25 mg/day, *Figure 1*).

Low-quality evidence suggests that empagliflozin reduces cardiovascular mortality, the risk of hospitalization for any cause (73), and hospitalizations for heart failure (59), as well as the risk of developing heart failure (73), developing or worsening of nephropathy (58), and the risk of treatment discontinuation due to lack of efficacy, at the expense of higher risk of adverse effects (*Table 1*) (7,11,40,44,46,47,49-61,70,75-77). The observed improvement in patient outcomes is attributable to the largest RCT, EMPA-REG OUTCOME, which enrolled patients with established

Table 1 Empagliflozin versus placebo in adults with type 2 diabetes

Outcomes	Risk with intervention per 1,000	Risk with comparator per 1,000, attributable avoided events per 1,000 treated [95% CI]	Relative measure of association (95% CI)	Number of participants (studies); quality of evidence (GRADE)
All-cause death	26	41, 12 [6–19]	RR 0.70 (0.59–0.84), NNTp 83 [53–167]	14,727 (7,11,34,35,38,40,44,46,47) (15 RCTs) (49-69); moderate‡
All-cause death*	57	83, 26 [13–39]	RR 0.69 (0.58–0.82), NNTp 39 [26–79], HR 0.68 (0.57–0.82)	7,020 (1 RCT**) (59); low‡
All-cause death	2	2	RR 0.90 (0.36–2.23)	7,707 (7,11,31,32,34,35,38,40,44) (14 RCTs) (46,47,50-56,60-67,69-71); low
Cardiovascular death	16	28, 13 [6–19]	RR 0.63 (0.51–0.79), NNTp 77 [53–167]	12,449 (31,32,34,38,40,44,46,47,49-52) (11 RCTs) (54-59,61,62,65-71); low‡
Cardiovascular death*	37	59, 22 [11–33]	RR 0.62 (0.50–0.78), NNTp 45 [30–90], HR 0.62 (0.49–0.77)	7,020 (1 RCT**) (59); very low‡
Cardiovascular death	1	1	RR 0.98 (0.29–3.33)	5,429 (10 RCTs) (31,32,34,38,40,44,46,47,50-52,54-56,61,62,65-67,69-71); low
Composite primary outcome*	105	121	RR 0.86 (0.75–0.99), HR 0.86 (0.74–0.99)	7,020 (1 RCT**) (59); low‡
Composite primary outcome plus hospitalization*	128	143	RR 0.90 (0.79–1.01), HR 0.89 (0.78–1.01)	7,020 (1 RCT**) (59); low
Proportion of patients with HbA1c <7%	276	89, 174 [99–249]	RR 2.81 (1.65–4.81), NNT 6 [4–10]	2,468 (5 RCTs) (31,32,50,51,62,63,70,71); moderate‡
Myocardial infarction	20	27	RR 0.84 (0.68–1.04)	15,592 (31,32,34,35,38,40,44,46,47,49-59) (17 RCTs) (61-72); low
Fatal or nonfatal myocardial infarction*	48	54	RR 0.88 (0.71–1.09), HR 0.87 (0.70–1.09)	7,020 (1 RCT**) (59); very low
Silent myocardial infarction*	8	6	RR 1.26 (0.70–2.29), HR 1.28 (0.70–2.33)	7,020 (1 RCT**) (59); very low
Hospitalization for unstable angina*	28	28	RR 1.00 (0.75–1.34), HR 0.99 (0.74–1.34)	7,020 (1 RCT**) (59); very low
Coronary revascularization procedure*	70	80	RR 0.88 (0.74–1.05), HR 0.86 (0.72–1.04)	7,020 (1 RCT**) (59); low
Hospitalization for heart failure*	27	41, 14 [5–23]	RR 0.66 (0.51–0.86), NNTp 72 [43–219], HR 0.65 (0.50–0.85)	7,020 (1 RCT**) (59); very low‡

Table 1 *(continued)*

Table 1 *(continued)*

Outcomes	Risk with intervention per 1,000	Risk with comparator per 1,000, attributable avoided events per 1,000 treated [95% CI]	Relative measure of association (95% CI)	Number of participants (studies); quality of evidence (GRADE)
All-cause hospitalization*	368	396, 28 [4–53]	RR 0.93 (0.87–0.99), NNTp 35 [19–234]	7,020 (1 RCT**) (73); low‡
Investigator-reported heart failure*	44	61, 18 [6–29]	RR 0.71 (0.58–0.87), NNTp 56 [34–156]	7,020 (1 RCT**) (73); very low‡
Stroke	16	15	RR 1.16 (0.90–1.52)	15,184 (31,32,35,38,40,44,49-59) (14 RCTs) (61-72); low
Fatal or nonfatal stroke*	35	30	RR 1.18 (0.90–1.56), HR 1.18 (0.89–1.56)	7,020 (1 RCT**) (59,74); very low
Nonfatal stroke*	32	26	RR 1.24 (0.93–1.67), HR 1.24 (0.92–1.67)	7,020 (1 RCT**) (59,74); very low
Transient ischemic attack*	8	10	RR 0.84 (0.51–1.41), HR 0.85 (0.51–1.42)	7,020 (1 RCT**) (59,74); very low
Incident or worsening nephropathy	127	188, 61 [41–81]	RR 0.68 (0.60–0.76), NNT 16 [12–24], HR 0.61 (0.53–0.70)	6,185 (1 RCT**) (58); low‡
Diabetes-related blindness	1	1	RR 1.00 (0.18–5.43)	7,020 (1 RCT**) (58); very low
Initiation of renal replacement therapy	3	6	RR 0.46 (0.22–0.98)	7,020 (1 RCT**) (58); very low‡
Total, serious adverse events	60	70	RR 0.97 (0.80–1.19)	7,602 (12 RCTs) (7,11,31,32,38,40,44,50,51,53-56,60,62-64,66,67,70-72); moderate
Total, other adverse events	300	381	RR 1.01 (0.9–1.15)	8,775 (7,11,31,32,38,40,44,50,51,53-56) (16 RCTs) (60-67,70-72,75-80); moderate
Treatment discontinuation due to adverse effects	12	17	RR 0.56 (0.20–1.59)	1,522 (3 RCTs) (31,70-72); low
Confirmed hypoglycemic adverse event	278	279	RR 1.00 (0.92–1.08)	7,020 (1 RCT**) (59); low
Hypoglycemic adverse event requiring assistance	13	15	RR 0.87 (0.58–1.31)	7,020 (1 RCT**) (59); very low

Population: adults with uncontrolled type 2 diabetes (7%≤ HbA1c ≤10%) and established cardiovascular disease; settings: outpatient; intervention: empagliflozin, any dose, orally, once daily; comparator: placebo. NNT is calculated as 1/absolute risk difference; attributable events per 1,000 treated as the number of excessive or avoided events per 1,000 treated that are attributed to active treatment; attributable events per 1,000 treated are calculated as absolute rate difference multiplied by 1,000. *, composite outcome of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke death in adults at high risk of cardiovascular disease or with established cardiovascular disorder; **, results from EMPA-REG OUTCOME trial (49,57-59,68), the only RCT designed to examine differences in cardiovascular mortality and morbidity; ‡, favors empagliflozin. HbA1c, hemoglobin A1c; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; NNT, number needed to treat to achieve an outcome in one patient; NNTp, number needed to treat to prevent an outcome in one patient (when the outcome is more probable with control intervention); RCT, randomized controlled trial; RR, relative risk.

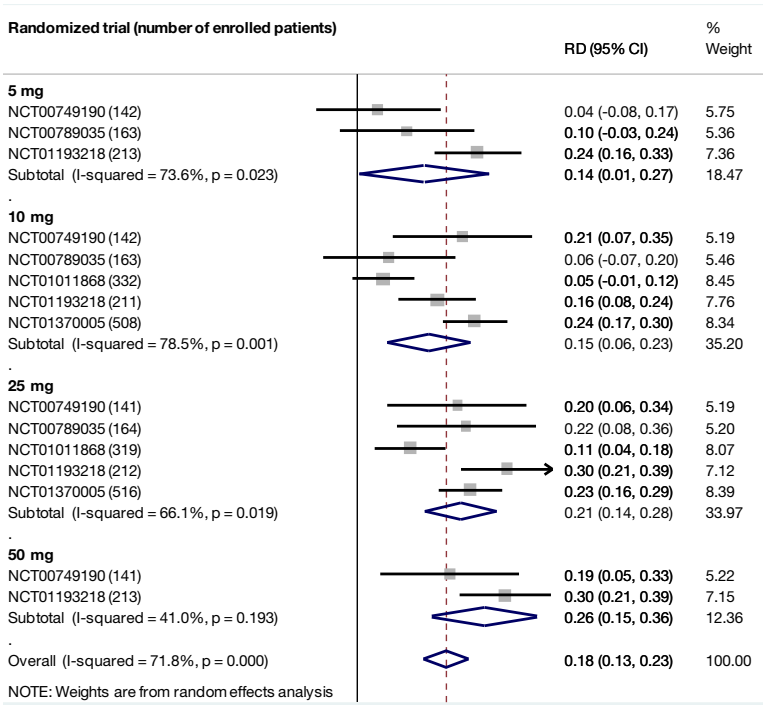

Figure 1 Diabetes control (HbA1c <7%) after different doses of empagliflozin when compared with placebo (random effects meta-analysis of randomized trials of adults with type 2 diabetes). RD, absolute risk difference.

cardiovascular diseases (59). Sensitivity analyses excluding this RCT demonstrate no protective effects from empagliflozin against all-cause and cardiovascular mortality in all other RCTs combined (*Table 1*). There are no differences in the risk of stroke or coronary events between empagliflozin and placebo (*Table 1*) (40,44,49-59,61,70).

Subgroup analysis of the EMPA-REG OUTCOME trial demonstrates that empagliflozin is better than placebo in reducing the risk of major cardiovascular events in older patients and adults with HbA1c 7.0–8.5% (P value for interaction <0.05, *Table S1*). Baseline heart failure does not modify empagliflozin effects on cardiovascular mortality and the risk of major cardiovascular effects (data not shown) (73). Empagliflozin is not better than placebo in adults with BMI ≥30 kg/m^2 (P value for interaction 0.06, *Table S1*).

Safety analyses demonstrate that empagliflozin increases the risk of genital infection, thirst, and polyuria and reduces the risk of acute renal injury and failure, hypertension, and worsening of heart failure (*Table S2*) (7,11,31,40,50,51,53-56,58,59,62-67,77,78,81-83). Empagliflozin's safety profile is similar in patients with normal and impaired baseline renal function (*Table S2*).

Post-marketing surveillance suggests more than 1900 case reports of various adverse effects, including fungal and urinary tract infections, diabetic ketoacidosis, unintentional weight loss, pollakiuria, dizziness, dehydration, nausea, and vomiting reported by patients taking empagliflozin among other drugs for type 2 diabetes (*Table S3*). In addition, the European Medicines Agency recently requested that information on potential risk of toe amputation be included in prescribing information for all SGLT2 inhibitors (84).

Comparative effectiveness

Low-quality evidence suggests that there are no differences in mortality, morbidity, diabetes control, and serious adverse effects between empagliflozin and metformin (*Table 2*) (5,31,33,34,37,39,43,46-48,81). Empagliflozin reduces the risk of total non-serious adverse effects when compared with metformin, with 51 avoided adverse events per 1,000 treated (*Table 2*) (5,31,33,34,37,39,43,46-48,81). Very low-quality evidence from a single RCT suggests that empagliflozin decreases HbA1c, the risk of hypoglycemia, and total non-serious adverse effects when compared with glimepiride, at the expense of higher cumulative risk of total combined serious adverse effects (*Table 3*) (36,42,45). There

Table 2 Empagliflozin versus metformin in adults with type 2 diabetes

Outcomes	Risk with intervention per 1,000	Risk with comparator per 1,000, attributable avoided events per 1,000 treated [95% CI]	Relative measure of association (95% CI)	Number of participants (studies); quality of evidence (GRADE)
All-cause death	1	1	RR 0.35 (0.02–5.36)	1,344 (4 RCTs) (5,31,33,34,37,43,46-48); low
Cardiovascular death	0	0	RR inestimable	1,073 (3 RCT) (5,31,34,37,46-48); low
Myocardial infarction	5	1	RR 1.18 (0.31–4.58)	2,024 (5 RCTs) (5,31,33,34,37,39,43,46-48); low
Stroke	1	3	RR 0.54 (0.09–3.08)	2,024 (5 RCTs) (5,31,33,34,37,39,43,46-48); low
HbA1c <7.0%	331	390	RR 0.85 (0.66–1.10)	539 (2 RCTs) (31,33,43); low
Hypoglycemia	10	15	RR 0.55 (0.13–2.41)	1,290 (3 RCTs) (33,37,43,48,81); low
Total, non-serious adverse effects	214	262, 48 [5–92]	RR 0.80 (0.64–0.99), NNTp 21 [11–200]	1,614 (3 RCTs) (31,33,43,81); low‡
Total, serious adverse events	26	25	RR 0.80 (0.39–1.63)	1,532 (3 RCTs) (31,33,43,81); low

Population: adults with uncontrolled type 2 diabetes (7%≤ HbA1c ≤10%); settings: outpatient; intervention: empagliflozin, any dose, orally, once daily; comparator: metformin (500–1,000 mg twice daily). Attributable events per 1,000 are treated as the number of excessive or avoided events per 1,000 treated that are attributed to active treatment; attributable events per 1,000 treated are calculated as absolute rate difference multiplied by 1,000. ‡, favors empagliflozin. HbA1c, hemoglobin A1c; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNTp, number needed to treat to prevent an outcome in one patient (when the outcome is more probable with control intervention); RCT, randomized controlled trial; RR, relative risk.

are no differences in any specific serious harms between empagliflozin and glimepiride (data not shown).

Low-quality evidence suggests that there are no differences in mortality, morbidity, and serious adverse effects between empagliflozin and linagliptin (*Table 4*) (5,34,35,46,47). Empagliflozin decreases HbA1c and the risk of total non-serious adverse effects (*Table 4*) (5,34,35,46,47). Low-quality evidence suggests that there are no differences in mortality, morbidity, and total adverse effects between empagliflozin and sitagliptin (*Table 5*) (5,32,33,38,40,43,44).

Specific adverse effects differ among examined drugs, according to the labeling information (*Table S4*). These differences should be taken into account when selecting specific drugs for patients with higher baseline risk of specific harms. Combined drug formulations would likely result in a cumulative increase in the risk of specific adverse effects.

Post-marketing surveillance suggests that lactic acidosis (6,754 cases), diarrhea (3,774 cases), and acute renal failure (3,754 cases) are the most common adverse effects reported in patients taking metformin among other drugs for type 2 diabetes (*Table S3*). Hypoglycemia (675 cases), hypoglycemic coma (142 cases), and acute renal failure (126 cases) are the most common adverse effects reported in patients taking glimepiride among other drugs for type 2 diabetes (*Table S3*). Pancreatitis (328 cases), nausea (216 cases), and rash (178 cases) are the most common adverse effects reported in patients taking linagliptin among other drugs for type 2 diabetes (*Table S3*). Pancreatitis (2,459 cases), pancreatic carcinoma (1,604 cases), diarrhea (1,175 cases), nausea (1,175 cases), and hypoglycemia (1,163 cases) are the most common adverse effects reported in patients taking sitagliptin among other drugs for type 2 diabetes (*Table S3*).

Discussion

Our findings that empagliflozin decreases overall and cardiovascular mortality are in concordance with high-quality meta-analyses (5,6). The results are applicable to predominantly white adults with HbA1c 7–10% and established cardiovascular disease. Although the tests for

Table 3 Empagliflozin versus glimepiride in adults with type 2 diabetes

Outcomes	Risk with intervention per 1,000	Risk with comparator per 1,000, attributable avoided events per 1,000 treated [95% CI]	Relative measure of association (95% CI)	Number of participants (studies); quality of evidence (GRADE)
All-cause death	7	6	RR 1.01 (0.29–3.49)	1,549 (1 RCT) (36,42,45); very low
Cardiovascular death	1	3	RR 0.51 (0.05–5.58)	1,549 (1 RCT) (36,42,45); very low
Myocardial infarction	1	9	RR 0.14 (0.02–1.17)	1,549 (1 RCT) (36,42,45); very low
Stroke	9	4	RR 2.37 (0.61–9.12)	1,549 (1 RCT) (36,42,45); very low
Change from baseline in HbA1c	NR	NR	MD −0.11 (−0.19 to −0.03), SMD −0.13 (−0.23 to −0.03)	1,545 (1 RCT) (36,42,45); very low‡
Hypoglycemia events	24	242, 217 [185–250]	RR 0.10 (0.06–0.16), NNTp 5 [4–5]	1,545 (1 RCT) (36,42,45); very low‡
Total, non-serious adverse events	639	724, 85 [39–131]	RR 0.88 (0.82–0.95), NNTp 12 [8–26]	1,545 (1 RCT) (36,42,45); very low‡
Total, serious adverse events	155	114, 41 [7–75]	RR 1.36 (1.06–1.76), NNT 24 [13–135]	1,545 (1 RCT) (36,42,45); very low‡‡
Urinary tract infection	124	126	RR 0.98 (0.75–1.27)	1,545 (1 RCT) (36,42,45); very low

Population: adults with uncontrolled type 2 diabetes (7%≤ HbA1c ≤10%); settings: outpatient; intervention: empagliflozin, any dose, orally, once daily; comparator: glimepiride. ‡, favors empagliflozin; ‡‡, favors glimepiride. HbA1c, hemoglobin A1c; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; NNT, number needed to treat; NNTp, number needed to treat to prevent an outcome in one patient (when the outcome is more probable with control intervention); RCT, randomized controlled trial; RR, relative risk; SMD, standardized mean difference.

Table 4 Empagliflozin versus linagliptin in adults with type 2 diabetes

Outcomes	Risk with intervention per 1,000	Risk with comparator per 1,000, attributable avoided events per 1,000 treated [95% CI]	Relative measure of association (95% CI)	Number of participants (studies); quality of evidence (GRADE)
All-cause death	4	0	RR 1.99 (0.23–17.40)	1,348 (2 RCTs) (5,34,35,46,47); low
Cardiovascular death	0	0	RR inestimable	404 (1 RCT) (5,34,46,47); very low
Myocardial infarction	1	0	RR 1.01 (0.04–24.81)	1,348 (2 RCTs) (5,34,35,46,47); low
Stroke	1	0	RR 1.01 (0.04–24.81)	944 (1 RCT) (5,35); low
Change from baseline in HbA1c after empagliflozin 10 mg	NR	NR	MD −0.16 (−0.35 to 0.03), SMD −0.20 (−0.44 to 0.04)	546 (1 RCT) (34,46,47); very low
Change from baseline in HbA1c for treatment-naive patients after empagliflozin 25 mg	NR	NR	MD −0.28 (−0.47 to −0.09), SMD −0.35 (−0.59 to −0.10)	549 (1 RCT) (34,46,47); very low‡
Total, serious adverse events	47	34	RR 1.45 (0.85–2.46)	1,762 (2 RCTs) (34,35,46,47); low
Total, non-serious adverse events	189	265, 57 [15–99]	RR 0.77 (0.64–0.92), NNTp 18 [10–67]	1,762 (2 RCTs) (34,35,46,47); low‡

Population: adults with uncontrolled type 2 diabetes (7%≤ HbA1c ≤10%); settings: outpatient; intervention: empagliflozin, 10–25 mg orally once/day; comparator: linagliptin. ‡, favors empagliflozin. HbA1c, hemoglobin A1c; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; NNTp, number needed to treat to prevent an outcome in one patient (when the outcome is more probable with control intervention); RCT, randomized controlled trial; RR, relative risk; SMD, standardized mean difference.

Table 5 Empagliflozin versus sitagliptin in adults with type 2 diabetes

Outcomes	Risk with intervention per 1,000	Risk with comparator per 1,000, attributable avoided events per 1,000 treated (95% CI)	Relative measure of association (95% CI)	Number of participants (studies); quality of evidence (GRADE)
All-cause death	0	3	RR 0.17 (0.01–4.07)	1,483 (3 RCTs) (5,32,33,38,40,43,44); low
Cardiovascular death	0	3	RR 0.17 (0.01–4.07)	1,095 (2 RCTs) (5,32,38,40,44); low
Myocardial infarction	2	3	RR 0.37 (0.06–2.36)	1,483 (3 RCTs) (5,32,33,38,40,43,44); low
Stroke	1	11	RR 0.08 (0.01–0.51)	1,483 (3 RCTs) (5,32,33,38,40,43,44); low
Hypoglycemia (adjuvant metformin)	14	54	RR 0.26 (0.05–1.26)	271 (1 RCT) (33,43); low
Total, non-serious adverse effects (adjuvant metformin)	372	464	RR 0.80 (0.58–1.12)	271 (1 RCT) (33,43); very low
Total, serious adverse events (adjuvant metformin)	79	161	RR 0.49 (0.23–1.04)	271 (1 RCT) (33,43); very low
Total, non-serious adverse effects	124	135	RR 0.92 (0.72–1.18)	1,601 (2 RCTs) (32,38,40,44); low
Total, serious adverse events	28	20	RR 1.23 (0.50–3.04)	1,094 (2 RCTs) (32,38,40,44); low

Population: Adults with uncontrolled type 2 diabetes (7%≤ HbA1c ≤10%); settings: outpatient; intervention: empagliflozin, any dose, orally, once daily; comparator: sitagliptin. HbA1c, hemoglobin A1c; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, relative risk.

statistical interaction were not significant, ethnic and gender differences in drug benefits need further investigation. Previously published network meta-analyses also suggest that empagliflozin has a favorable benefits-to-harm profile, because it decreases HbA1c and arterial blood pressure without increased risk of hypoglycemia or weight gain (9,85). The evidence regarding the effects of empagliflozin on quality of life and the long-term safety of empagliflozin is insufficient.

Our review also found low-quality evidence that all-cause and cardiovascular mortality and morbidity are comparable after empagliflozin when compared with metformin, glimepiride, linagliptin, or sitagliptin in adults with type 2 diabetes. We downgraded the quality of evidence due to risk of bias in the body of evidence and small number of events in RCTs. We also concluded reporting bias, because reporting of patient morbidity and specific adverse effects was inconsistent across studies, and the results of several completed studies were not available for the analysis. None of the head-to-head RCTs were powered to detect differences in mortality and morbidity. A single RCT suggested reduction in mortality and cardiovascular morbidity after empagliflozin when compared with placebo in adults with established cardiovascular disorder (58,59,68). This pivotal RCT provided only indirect comparative evidence that empagliflozin may be a drug of choice in people with type 2 diabetes and comorbid cardiovascular disorder (58,59,68).

The direct evidence regarding the comparative effectiveness of empagliflozin and other antidiabetic drugs including other SGLT2 inhibitors is insufficient. A recent single RCT demonstrated that injectable liraglutide reduces the risk of major cardiovascular events [hazard ratio (HR) 0.87; 95% CI: 0.78–0.97] and all-cause mortality (HR 0.85; 95% CI: 0.74–0.97) in adults with type 2 diabetes and high cardiovascular risk when compared with placebo (86). Although the RR reduction is larger with empagliflozin, well-designed direct RCTs are needed to conclude the comparative effectiveness of the 2 drugs. Previously published network meta-analyses of intermediate outcomes also suggest that empagliflozin has a favorable benefits-to-harms profile, because it decreases HbA1c without increased risk of hypoglycemia or weight gain (9,15,85).

Our rapid review has several limitations. We did not contact drug manufacturers or principal investigators regarding unpublished or missing data. We do not know how many unregistered, unpublished studies have been conducted. We found no observational studies that provide adjusted for confounding estimates of the comparative effectiveness and safety of empagliflozin and other antidiabetic drugs.

Evidence-based guidelines recommend SGLT2 inhibitors among other available drug classes for adults with type 2 diabetes who could not control diabetes with behavioral changes and metformin (1,2,4). A British guideline based on comprehensive evidence specifies that empagliflozin in combination with metformin should be recommended only to patients who cannot tolerate sulfonylureas or have a high risk of hypoglycemia or its consequences (3).

Future research should examine the long-term comparative benefits and harms of empagliflozin and other drug choices in patient subpopulations by demographics, comorbidities, and concomitant treatments.

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Footnote

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Supplementary

Table S1 Composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke after empagliflozin versus placebo in subgroups of adults with type 2 diabetes and established cardiovascular disease

Outcomes	Risk with intervention per 1,000	Risk with comparator per 1,000, attributable avoided events per 1,000 treated [95% CI]	Relative measure of association (95% CI)	Number of participants (studies); quality of evidence (GRADE)
Age (years)				
<65	97	93	RR 1.04 (0.84–1.27), HR 1.04 (0.84–1.29)	3,893 (1 RCT) (59); low
≥65	114	155, 41 [15–67]	RR 0.74 (0.61–0.89), NNTp 24 [15–66], HR 0.71 (0.59–0.87)	3,127 (1 RCT) (59); very low‡
Sex				
Male	110	126	RR 0.87 (0.74–1.02), HR 0.87 (0.73–1.02)	5,016 (1 RCT) (59); low
Female	91	107	RR 0.85 (0.64–1.12), HR 0.83 (0.62–1.11)	2,004 (1 RCT) (59); very low
Race				
White	108	122	RR 0.88 (0.75–1.03), HR 0.88 (0.74–1.04)	5,081 (1 RCT) (59); low
Asian	79	114, 35 [3–67]	RR 0.69 (0.50–0.95), NNTp 29 [15–352], HR 0.68 (0.48–0.95)	1,517 (1 RCT) (59); very low‡
Black/African-American	165	117	RR 1.41 (0.80–2.49), HR 1.48 (0.80–2.72)	357 (1 RCT) (59); very low
Hispanic/Latino	83	124, 42 [5–78]	RR 0.66 (0.47–0.93), NNTp 24 [13–197], HR 0.63 (0.44–0.90)	1,265 (1 RCT) (59); very low‡
Not Hispanic/Latino	110	120	RR 0.91 (0.78–1.06), HR 0.91 (0.77–1.07)	5,747 (1 RCT) (59); low
Location				
Europe	117	117	RR 1.00 (0.81–1.24), HR 1.02 (0.81–1.28)	2,885 (1 RCT) (59); very low
North America	122	136	RR 0.90 (0.67–1.19), HR 0.89 (0.65–1.21)	1,394 (1 RCT) (59); very low
Latin America	74	119, 46 [7–84]	RR 0.62 (0.42–0.90), NNTp 22 [12–135], HR 0.58 (0.39–0.86)	1,081 (1 RCT) (59); very low‡
Africa	123	137	RR 0.90 (0.49–1.64), HR 0.86 (0.45–1.65)	313 (1 RCT) (59); very low
Asia	79	111	RR 0.71 (0.51–1.00), HR 0.70 (0.49–1.01)	1,347 (1 RCT) (59); very low
HbA1c				
<8.5%	100	130, 30 [10–49]	RR 0.77 (0.65–0.91), NNTp 34 [20–97], HR 0.76 (0.64–0.90)	4,819 (1 RCT) (59); low‡
≥8.5%	114	101	RR 1.13 (0.87–1.47), HR 1.14 (0.86–1.50)	2,201 (1 RCT) (59); very low
BMI (kg/m^2)				
<30	99	132, 33 [10–57]	RR 0.75 (0.61–0.91), NNTp 30 [18–99], HR 0.74 (0.60–0.91)	3,399 (1 RCT) (59); very low‡
≥30	110	110	RR 1.00 (0.82–1.21), HR 0.98 (0.80–1.21)	3,621 (1 RCT) (59); low
SBP/DBP (mmHg)				
≥140/≥90	120	140	RR 0.86 (0.70–1.05), HR 0.83 (0.66–1.03)	2,714 (1 RCT) (59); very low
<140/<90	95	108	RR 0.88 (0.73–1.06), HR 0.89 (0.73–1.08)	4,306 (1 RCT) (59); low
Estimated glomerular filtration rate (mL/min/1.73m^2)				
≥90	97	90	RR 1.08 (0.77–1.51), HR 1.10 (0.77–1.57)	1,538 (1 RCT) (59); very low
60–90	87	112, 25 [4–46]	RR 0.78 (0.64–0.95), NNTp 40 [22–251], HR 0.76 (0.61–0.94)	3,663 (1 RCT) (59); very low‡
≤60	145	163	RR 0.89 (0.71–1.12), HR 0.88 (0.69–1.13)	1,819 (1 RCT) (59); very low
Urine albumin-to-creatinine ratio (mg/g)				
<30	86	97	RR 0.89 (0.73–1.09), HR 0.89 (0.72–1.10)	4,171 (1 RCT) (59); very low
30–300	118	133	RR 0.89 (0.70–1.13), HR 0.89 (0.69–1.16)	2,013 (1 RCT) (59); very low
>300	169	223	RR 0.76 (0.56–1.02), HR 0.69 (0.49;0.96)	769 (1 RCT) (59); very low
Cardiovascular risk				
Only cerebrovascular disease	102	89	RR 1.15 (0.76–1.74), HR 1.15 (0.74–1.78)	960 (1 RCT) (59); very low
Only coronary artery disease	96	113	RR 0.84 (0.70–1.02), HR 0.83 (0.68–1.02)	4,072 (1 RCT) (59); low
Only peripheral artery disease	61	63	RR 0.97 (0.50–1.88), HR 0.94 (0.47–1.88)	603 (1 RCT) (59); very low
2 or 3 high cardiovascular risk categories	156	193	RR 0.81 (0.63–1.03), HR 0.79 (0.61–1.04)	1,329 (1 RCT) (59); very low
Metformin				
No	119	155, 36 [2–71]	RR 0.77 (0.60–0.97), NNTp 27 [14–459], HR 0.72 (0.56–0.94)	1,827 (1 RCT) (59); very low‡
Yes	99	109	RR 0.91 (0.77–1.08), HR 0.92 (0.77–1.10)	5,193 (1 RCT) (59); low
Sulfonylurea				
No	110	129	RR 0.86 (0.72–1.02), HR 0.85 (0.70–1.02)	4,014 (1 RCT) (59); low
Yes	97	110	RR 0.88 (0.71–1.10), HR 0.87 (0.69–1.11)	3,006 (1 RCT) (59); very low
Insulin				
No	92	117, 24 [3–46]	RR 0.79 (0.65–0.97), NNTp 41 [22–341], HR 0.79 (0.64–0.97)	3,633 (1 RCT) (59); very low‡
Yes	118	125	RR 0.94 (0.78–1.14), HR 0.93 (0.75–1.13)	3,387 (1 RCT) (59); low
Thiazolidinediones				
No	104	121, 17 [1–34]	RR 0.86 (0.74–0.99), NNTp 58 [30–866], HR 0.85 (0.73–0.98)	6,721 (1 RCT) (59); low‡
Yes	116	109	RR 1.07 (0.54–2.10), HR 1.13 (0.55–2.31)	2,99 (1 RCT) (59); very low
DPP-4 inhibitor				
No	102	123, 21 [4–38]	RR 0.83 (0.71–0.96), NNTp 47 [26–231], HR 0.81 (0.70–0.95)	6,224 (1 RCT) (59); low‡
Yes	127	105	RR 1.21 (0.80–1.83), HR 1.27 (0.82–1.98)	796 (1 RCT) (59); very low
Statins/ezetimibe				
No	103	129	RR 0.80 (0.60–1.06), HR 0.79 (0.59–1.07)	1,580 (1 RCT) (59); very low
Yes	105	118	RR 0.89 (0.76–1.04), HR 0.88 (0.74–1.04)	5,440 (1 RCT) (59); low
Antihypertensives				
No	87	98	RR 0.89 (0.44–1.78), HR 0.94 (0.45–1.95)	353 (1 RCT) (59); very low
Yes	105	122	RR 0.86 (0.75–1.00)	6,667 (1 RCT) (59); low
ACE inhibitor/ARB				
No	102	131	RR 0.78 (0.58–1.06), HR 0.77 (0.56–1.07)	1,354 (1 RCT) (59); very low
Yes	105	118	RR 0.89 (0.76–1.04), HR 0.88 (0.75–1.04)	5,666 (1 RCT) (59); low
Calcium channel blockers				
No	102	116	RR 0.88 (0.74–1.04), HR 0.87 (0.73–1.05)	4,703 (1 RCT) (59); low
Yes	111	131	RR 0.85 (0.67–1.06), HR 0.83 (0.65–1.06)	2,317 (1 RCT) (59); very low
Beta blockers				
No	97	108	RR 0.90 (0.71–1.16), HR 0.90 (0.70–1.17)	2,466 (1 RCT) (59); very low
Yes	108	128	RR 0.85 (0.72–1.00), HR 0.83 (0.70–1.00)	4,554 (1 RCT) (59); very low
Diuretics				
No	86	103	RR 0.84 (0.69–1.03), HR 0.83 (0.67–1.02)	3,985 (1 RCT) (59); very low
Yes	128	146	RR 0.88 (0.73–1.06), HR 0.88 (0.71–1.07)	3,035 (1 RCT) (59); very low
Acetylsalicylic acid				
No	109	131	RR 0.83 (0.60–1.14), HR 0.80 (0.57–1.12)	1,217 (1 RCT) (59); very low
Yes	104	119	RR 0.87 (0.75–1.02), HR 0.87 (0.74–1.02)	5,803 (1 RCT) (59); low

Population: adults with uncontrolled type 2 diabetes (7%≤ HbA1c ≤10%) and established cardiovascular disease; settings: outpatient; intervention: empagliflozin, any dose, orally, once daily; comparator: placebo. ‡, favors empagliflozin. HbA1c, hemoglobin A1c; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; NNTp, number needed to treat to prevent an outcome in one patient; RCT, randomized controlled trial; RR, relative risk; SBP, systolic blood pressure.

Table S2 Adverse effects after empagliflozin versus placebo in subgroups of adults with type 2 diabetes

Outcomes	Risk with intervention per 1,000	Risk with comparator per 1,000, attributable avoided events per 1,000 treated [95% CI]	Relative measure of association (95% CI)	Number of participants (studies); quality of evidence (GRADE)
Urinary tract infection	180	181	RR 0.99 (0.89–1.10)	7,020 (1 RCT) (59); low
Male patients	105*	94*	RR 1.12 (0.93–1.33)	5,016 (1 RCT) (59); low
Female patients	364*	406*	RR 0.90 (0.80–1.01)	2,004 (1 RCT) (59); low
Complicated urinary tract infection	17	18	RR 1.00 (0.69–1.44)	7,020 (1 RCT) (59); very low
Genital infection	64	18, 46 [37–55]	RR 3.57 (2.59–4.91), NNT 22 [18–27]	7,020 (1 RCT) (59); low§
Male patients	50*	15*, 35 [26–44]	RR 3.34 (2.21–5.07), NNT 29 [23–39]	5,016 (1 RCT) (59); very low§
Female patients	100*	26*, 74 [54–94]	RR 3.84 (2.34–6.30), NNT 14 [11–19]	2,004 (1 RCT) (59); very low§
Volume depletion	51	49	RR 1.03 (0.83–1.28)	7,020 (1 RCT) (59); very low
Acute renal failure	52	66, 14 [2–26]	RR 0.79 (0.65–0.96), NNTp 72 [39–500]	7,020 (1 RCT) (59); very low‡
Acute kidney injury	10	16, 6 [0–12]	RR 0.61 (0.39–0.93), NNTp 160 [83–2,123]	7,020 (1 RCT) (59); very low‡
Thirst	31	3, 29 [15–43]	RR 7.39 (1.43–38.17), NNT 34 [23–67]	1,150 (2 RCTs) (7,31,50,51,62); low§
Pollakiuria	50	21, 30 [12–48]	RR 2.08 (1.06–4.08), NNT 33 [21–83]	1,533 (5 RCTs) (7,11,50,51,62,77,78,81-83); low§
Diabetic ketoacidosis	1	0	RR 1.99 (0.22–17.80)	7,020 (1 RCT) (59); very low
Thromboembolic event	6	9	RR 0.75 (0.42–1.31)	7,020 (1 RCT) (59); very low
Bone fracture	38	39	RR 0.98 (0.76–1.25)	7,020 (1 RCT) (59); very low
Sudden death	11	16	RR 0.69 (0.46–1.05)	7,020 (1 RCT) (59); very low
Fatal worsening of heart failure	2	8, 6 [2–10]	RR 0.29 (0.14–0.60), NNTp 173 [103–527]	7,020 (1 RCT) (59); very low‡
Fatal acute myocardial infarction	3	5	RR 0.68 (0.31–1.48)	7,020 (1 RCT) (59); very low
Fatal stroke	3	5	RR 0.72 (0.34–1.56)	7,020 (1 RCT) (59); very low
Fatal cardiogenic shock	1	1	RR 0.50 (0.10–2.46)	7,020 (1 RCT) (59); very low
Hypertension	15	31	RR 0.42 (0.22–0.81)	3,393 (6 RCTs) (40,53-56,63-67,77,78); low‡
Acute kidney injury	21	36	RR 0.59 (0.34–1.04)	1,819 (1 RCT) (58); very low
Acute renal failure	112	143	RR 0.78 (0.61–1.01)	1,819 (1 RCT) (58); very low
Bone fracture	47	53	RR 0.89 (0.59–1.36)	1,819 (1 RCT) (58); very low
Complicated urinary tract infection	31	28	RR 1.09 (0.62–1.92)	1,819 (1 RCT) (58); very low
Confirmed hypoglycemic adverse event	323	384, 61 [14–108]	RR 0.84 (0.74–0.96), NNTp 16 [9–69]	1,819 (1 RCT) (58); very low‡
Cystitis	0	0	RR inestimable	1,819 (1 RCT) (58); very low
Cystitis bacterial	0	0	RR inestimable	1,819 (1 RCT) (58); very low
Cystitis glandularis	0	0	RR inestimable	1,819 (1 RCT) (58); very low
Cystitis hemorrhagic	0	0	RR inestimable	1,819 (1 RCT) (58); very low
Diabetic ketoacidosis	2	2	RR 1.00 (0.09–11.02)	1,819 (1 RCT) (58); very low
Escherichia urinary tract infection	0	2	RR 0.17 (0.01–4.10)	1,819 (1 RCT) (58); very low
Genital infection	53	16, 50 [52–20]	RR 3.21 (1.66–6.20), NNT 28 [50–19]	1,819 (1 RCT) (58); very low§
Hyperkalemia	39	69, 19 [7–53]	RR 0.56 (0.37–0.84), NNTp 33 [19–134]	1,819 (1 RCT) (58); very low‡
Hypoglycemic adverse event requiring assistance	19	30	RR 0.64 (0.35–1.18)	1,819 (1 RCT) (58); very low
Kidney infection	1	3	RR 0.25 (0.02–2.76)	1,819 (1 RCT) (58); very low
Nephritis	0	0	RR inestimable	1,819 (1 RCT) (58); very low
Pyelonephritis	3	3	RR 1.00 (0.18–5.45)	1,819 (1 RCT) (58); very low
Pyelonephritis acute	3	2	RR 2.00 (0.22–17.88)	1,819 (1 RCT) (58); very low
Pyelonephritis chronic	4	7	RR 0.63 (0.17–2.32)	1,819 (1 RCT) (58); very low
Thromboembolic event	11	12	RR 0.93 (0.37–2.32)	1,819 (1 RCT) (58); very low
Urinary tract infection	229	217	RR 1.05 (0.88–1.27)	1,819 (1 RCT) (58); low
Urinary tract infection, fungal	2	0	RR 2.51 (0.12–52.12)	1,819 (1 RCT) (58); very low
Urinary tract infection, pseudomonal	0	0	RR inestimable	1,819 (1 RCT) (58); very low
Urosepsis	7	3	RR 2.25 (0.49–10.40), Peto OR 3.13 (1.10–8.95) (68)	1,819 (1 RCT) (58); very low§
Volume depletion	67	81	RR 0.83 (0.59–1.16)	1,819 (1 RCT) (58); very low
Acute kidney injury	5	9	RR 0.63 (0.32–1.24)	5,199 (1 RCT) (58); very low
Acute renal failure	32	39	RR 0.80 (0.60–1.08)	5,199 (1 RCT) (58); very low
Bone fracture	35	34	RR 1.03 (0.76–1.39)	5,199 (1 RCT) (58); very low
Complicated urinary tract infection	13	14	RR 0.93 (0.57–1.52)	5,199 (1 RCT) (58); very low
Confirmed hypoglycemic adverse event	263	242	RR 1.09 (0.98–1.20)	5,199 (1 RCT) (58); low
Cystitis	0	1	RR 0.10 (0.00–2.07)	5,199 (1 RCT) (58); very low
Cystitis, bacterial	0	1	RR 0.17 (0.01–4.07)	5,199 (1 RCT) (58); very low
Cystitis glandularis	0	0	RR 1.49 (0.06–36.59)	5,199 (1 RCT) (58); very low
Cystitis, hemorrhagic	0	1	RR 0.17 (0.01–4.07)	5,199 (1 RCT) (58); very low
Diabetic ketoacidosis	1	0	RR 2.49 (0.12–51.75)	5,199 (1 RCT) (58); very low
Escherichia urinary tract infection	0	0	RR inestimable	5,199 (1 RCT) (58); very low
Genital infection	68	19, 26 [60–39]	RR 3.68 (2.56–5.30), NNT 20 [26–17]	5,199 (1 RCT) (58); very low§
Hyperkalemia	13	21	RR 0.64 (0.41–0.98)	5,199 (1 RCT) (58); very low‡
Hypoglycemic adverse event requiring assistance	12	10	RR 1.10 (0.64–1.92)	5,199 (1 RCT) (58); very low
Kidney infection	1	0	RR 3.48 (0.18–67.33)	5,199 (1 RCT) (58); very low
Nephritis	0	0	RR 1.49 (0.06–36.59)	5,199 (1 RCT) (58); very low
Pyelonephritis	3	1	RR 2.24 (0.48–10.34)	5,199 (1 RCT) (58); very low
Pyelonephritis, acute	1	3	RR 0.40 (0.11–1.48)	5,199 (1 RCT) (58); very low
Pyelonephritis, chronic	1	3	RR 0.41 (0.13–1.36)	5,199 (1 RCT) (58); very low
Thromboembolic event	5	8	RR 0.65 (0.32–1.33)	5,199 (1 RCT) (58); very low
Urinary tract infection	162	169	RR 0.96 (0.85–1.10)	5,199 (1 RCT) (58); low
Urinary tract infection, fungal	0	0	RR 1.49 (0.06–36.59)	5,199 (1 RCT) (58); very low
Urinary tract infection, pseudomonal	0	0	RR 1.49 (0.06–36.59)	5,199 (1 RCT) (58); very low
Volume depletion	45	38	RR 1.19 (0.90–1.58)	5,199 (1 RCT) (58); very low
Large intestine polyp	2	0	Peto OR 7.36 (1.27–42.54)	4,678 (1 RCT) (68); very low§
Bladder cancer	2	0	Peto OR 7.37 (1.28–42.59)	4,675 (1 RCT) (68); very low§
Balanitis candida	51	0	Peto OR 73.44 (9.20–586.20)	417 (1 RCT) (64); very low§

Population: adults with uncontrolled type 2 diabetes (7%≤ HbA1c ≤10%); settings: outpatient; intervention: empagliflozin, any dose, orally, once daily; comparator: placebo. ‡, favors empagliflozin; §, favors placebo; *, risk with intervention and control do not sum due to differences in the number of women and men in the trial. HbA1c, hemoglobin A1c; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat; NNTp, number needed to treat to prevent an outcome in one patient; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

Table S3 Post-marketing reports search results for empagliflozin

Drug	# Reports	Adverse events	Reports by gender	Reports by age
Empagliflozin	1,969	Diabetic ketoacidosis [205], fungal infection [173], weight decreased [156], ketoacidosis [95], blood glucose increased [92], pollakiuria [92], dizziness [91], dehydration [76], nausea [73], vomiting [69], urinary tract infection [65], diarrhea [60], glycosylated hemoglobin increased [51], rash [49], fatigue [43], back pain [42], headache [36], malaise [36], asthenia [35], drug ineffective [34]	Female [928], male [873]	20+ [1,107], <20 [7]
Metformin hydrochloride	34,605	Lactic acidosis [6,754], diarrhea [3,774], renal failure acute [3,754], blood glucose increased [3,005], hypoglycemia [2,166], vomiting [2,140], nausea [1,994], metabolic acidosis [1,631], hypotension [1,191], renal failure [1,169], drug ineffective [1,105], therapeutic agent toxicity [1,012], malaise [1,010], abdominal pain [959], dehydration [925], dyspnea [925], completed suicide [889], asthenia [860], blood creatinine increased [835], dizziness [825]	Female [17,969], male [13,371]	20+ [23,180], <20 [531]
Glimepiride	3,207	Hypoglycemia [675], blood glucose increased [211], hypoglycemic coma [142], renal failure acute [126], loss of consciousness [114], drug interaction [108], nausea [98], malaise [97], hyperglycemia [90], asthenia [89], blood glucose decreased [87], depressed level of consciousness [85], renal failure [83], dizziness [79], drug ineffective [77], dyspnea [75], vomiting [72], pyrexia [69], confusional state [68], medication error [68]	Male [1,534], female [1,355]	20+ [2,367], <20 [41]
Linagliptin	4,627	Pancreatitis [328], blood glucose increased [270], nausea [216], rash [178], hypoglycemia [163], drug ineffective [140], diarrhea [137], dizziness [127], abdominal pain [125], vomiting [110], urticaria [108], pruritus [92], headache [91], abdominal pain upper [84], glycosylated hemoglobin increased [84], renal failure acute [79], pancreatitis acute [78], weight decreased [76], dyspnea [72], pneumonia [71]	Female [2,140], male [2,075]	20+ [2,938], <20 [6]
Sitagliptin phosphate	30,135	Pancreatitis [2,459], blood glucose increased [1,960], pancreatic carcinoma [1,604], drug ineffective [1,487], diarrhea [1,175], nausea [1,175], hypoglycemia [1,163], headache [1,037], death [888], dizziness [860], rash [820], weight decreased [693], inappropriate schedule of drug administration [692], vomiting [670], edema peripheral [621], abdominal pain [620], constipation [620], dyspnea [584], hypertension [584], renal failure acute [575]	Female [13,727], male [12,378]	20+ [16,317], <20 [45]

Data from https://www.pharmapendium.com. Retrieved March 30, 2017.

Table S4 Adverse effects reported in drug labels

Adverse effects	Glimepiride	Metformin	Sitagliptin	Linagliptin	Empagliflozin
Abdominal pain		Yes	Yes		
Agranulocytosis	Yes				
Alopecia	Yes				
Anaphylactic shock	Yes				
Anaphylactic reactions	Yes		Yes	Yes	
Angioedema	Yes		Yes	Yes	
Anorexia		Yes			
Aplastic anemia	Yes				
Arthralgia	Yes		Yes	Yes	Yes
Asthenia	Yes				
Back pain			Yes		
Blurred vision	Yes				
Bronchospasm				Yes	
Bullous rash			Yes	Yes	
Candidiasis					Yes
Chest pain (unspecified)		Yes			
Chills		Yes			
Cholestasis	Yes	Yes			
Constipation			Yes		
Cough				Yes	
Cystitis					Yes
Dehydration					Yes
Diabetic ketoacidosis					Yes
Diarrhea		Yes	Yes	Yes	
Diuresis					Yes
Dizziness	Yes	Yes			
Dysgeusia	Yes	Yes			
Dyspepsia		Yes			
Dyspnea	Yes				
Elevated hepatic enzymes	Yes	Yes	Yes		
Erythema	Yes				
Exfoliative dermatitis			Yes	Yes	
Flatulence		Yes			
Flushing	Yes	Yes			
Headache	Yes	Yes	Yes		
Hemolysis	Yes				
Hemolytic anemia	Yes				
Hepatic failure	Yes				
Hepatitis	Yes	Yes			
Hypercholesterolemia					Yes
Hyperlipidemia					Yes
Hypoglycemia	Yes	Yes	Yes	Yes	Yes
Hyponatremia	Yes				
Hypotension	Yes				Yes
Hypovolemia					Yes
Increased urinary frequency					Yes
Infection		Yes	Yes		Yes
Jaundice	Yes				
Lactic acidosis		Yes			
Leukopenia	Yes				
Maculopapular rash	Yes				
Malaise		Yes			
Megaloblastic anemia		Yes			
Metabolic acidosis		Yes			
Metallic taste		Yes			
Myalgia	Yes	Yes	Yes	Yes	
Nocturia					Yes
Oral ulceration				Yes	
Orthostatic hypotension					Yes
Palpitations		Yes			
Pancreatitis			Yes	Yes	
Pancytopenia	Yes				
Pemphigus			Yes	Yes	
Peripheral edema			Yes		
Pharyngitis			Yes	Yes	
Phimosis					Yes
Photosensitivity	Yes				
Polydipsia					Yes
Polyuria					Yes
Porphyria	Yes				
Pruritus	Yes		Yes	Yes	
Purpura	Yes				
Rash (unspecified)		Yes	Yes	Yes	
Renal failure (unspecified)			Yes		Yes
Secondary failure	Yes				
SIADH	Yes				
Stevens-Johnson syndrome	Yes		Yes		
Stomatitis				Yes	
Syncope					Yes
Thrombocytopenia	Yes				
Urticaria	Yes		Yes	Yes	
Vaginitis					Yes
Vasculitis	Yes		Yes		
Vitamin B12 deficiency		Yes			
Weakness	Yes				
Weight gain	Yes			Yes	
Weight loss		Yes		Yes	
Hyperhidrosis		Yes			
Vomiting		Yes	Yes		
Nausea	Yes	Yes	Yes		Yes
Balanitis					Yes

Report from Elsevier Clinical Pharmacology drug database: http://www.clinicalpharmacology-ip.com/default.aspx. SIADH, syndrome of inappropriate antidiuretic hormone secretion.