

BMJ Open Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis

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ABSTRACT

Objective To estimate the association between the use of sodium glucose co-transporter-2 (SGLT2) inhibitors and postmarket harms as identified by drug regulatory agencies.

Design We conducted a systematic review and meta-analysis of randomised controlled trials (RCT). Six large databases were searched from inception to May 2018. Random effects models were used to estimate pooled relative risks (RRs).

Intervention SGLT2 inhibitors, compared with placebo or active comparators.

Primary outcomes Acute kidney injury (AKI), diabetic ketoacidosis (DKA), urinary tract infections (UTI), bone fractures and lower limb amputations.

Results We screened 2418 citations of which 109 were included. Most studies included one of four SGLT2 inhibitors, dapagliflozin, canagliflozin, empagliflozin and ipragliflozin. When compared with placebo, SGLT2 inhibitors were found to be significantly protective against AKI (RR=0.59; 95% CI 0.39 to 0.89; $I^2=0.0\%$), while no difference was found for DKA (RR 0.66; 95% CI 0.30 to 1.45, $I^2=0.0\%$), UTI (RR 1.02; 95% CI 0.95 to 1.09, $I^2=0.0\%$) or bone fracture (RR 0.87; 95% CI 0.69 to 1.09, $I^2=1.3\%$). Three studies reported on amputation, with one finding a significant increase risk. No increased risk for either outcome was found when compared with active controls. Subgroup analysis did show an increased risk of UTI with dapagliflozin only (RR 1.21; 95% CI 1.02 to 1.43, $I^2=0.0\%$), but no other analysis supported an increased risk of AKI, DKA, UTI or fracture.

Conclusions Current evidence from RCTs does not suggest an increased risk of harm with SGLT2 inhibitors as a class over placebo or active comparators with respect to AKI, DKA, UTI or fracture. However, wide CIs for many comparisons suggest limited precision, and therefore clinically important adverse events cannot be ruled out. Dapagliflozin, appears to independently increase the risk of UTI, although the mechanism for this intraclass variation in risk is unclear.

PROSPERO registration number CRD42016038715.

INTRODUCTION

The sodium glucose co-transporter 2 (SGLT2) inhibitors are novel glucose-lowering therapies

Strengths and limitations of this study

- This study provides a comprehensive systematic review of potential serious adverse events related to use of sodium glucose co-transporter-2 (SGLT2) inhibitors identified by drug regulatory agencies.
- This study considered select outcomes to provide focused attention on the issues concerning regulators; however, this means that additional knowledge of the clinical benefits and harms needs to be considered before applying the results of this study.
- Several of the outcomes (eg, acute kidney injury, diabetic ketoacidosis, limb amputations) we evaluated occur infrequently and, in some cases, were not reported by individual studies.
- Certain outcomes may have been inadequately characterised within study reports. For example, while urinary tract infections were commonly reported among randomised controlled trials included in this meta-analysis, data on complicated versus uncomplicated infections were not.
- Our objective is to summarise the current state of knowledge surrounding key postmarket safety concerns of the SGLT2 inhibitors compared with active and non-active comparators in patients with type 2 diabetes.

available for the management of type 2 diabetes. Clinical guidelines recommend the SGLT2 inhibitors as one of numerous potential pharmacological approaches for second-line therapy following metformin failure or intolerance.^{1 2} Some clinical guidelines recommend the SGLT2 inhibitors, empagliflozin or canagliflozin, or the glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide, as preferred second-line therapies in patients with cardiovascular disease who have failed to achieve glycaemic control while on monotherapy.¹ This paradigm shift in the management of type 2 diabetes is largely supported by evidence from recent landmark

clinical trials.^{3–6} In 2015, the Empagliflozin Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) trial showed that the SGLT2 inhibitor, empagliflozin, significantly reduced the risk for composite end point of cardiovascular death, myocardial infarction or stroke by 14% and all-cause mortality by 32%, in a population with existing cardiovascular disease.⁵ The Canagliflozin Cardiovascular Assessment Study (CANVAS), Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) have also demonstrated similar benefits with canagliflozin, liraglutide and semaglutide respectively.^{3,4}

Considering the relative potential harms and benefits, clinicians and policy makers must continue to integrate new pharmacotherapeutic evidence to optimise health outcomes. Although the EMPA-REG trial showed that the SGLT2 inhibitor, empagliflozin, significantly reduces the risk of cardiovascular morbidity and mortality, regulatory agencies including the Food and Drug Administration (FDA), the European Medicines Associations and Health Canada have issued safety warnings for several adverse events. These include acute kidney injury (AKI), diabetic ketoacidosis (DKA), urinary tract infections (UTI), bone fractures and lower limb amputations, based primarily on case report data.^{7–14}

With respect to AKI, there is conflicting information coming forward from clinical trials and case reports. Despite early indication of a protective effect from SGLT2 inhibitors,¹⁵ the FDA published in a safety communication in June 2016 that 101 cases of AKI were reported among users of canagliflozin and dapagliflozin.¹² In May 2015, the FDA published a safety update indicating an increased risk of UTI and DKA. Among patients taking SGLT2 inhibitors, they identified 19 cases of life-threatening infections that originated as a UTI, and 73 cases of DKA. However, to date clinical trial evidence does not support these potential risks. Previously published meta-analyses of randomised controlled trials (RCT) found no increased risk of UTIs, except within a subgroup of dapagliflozin,^{15–18} and one study found an increased risk with empagliflozin 25 mg users.¹⁸ A previous meta-analysis on the risk of DKA currently showed no increased risk.¹⁹ In January 2016, the FDA issued an expanded warning regarding a potential increased risk for fracture with canagliflozin.⁹ Two published meta-analyses^{20,21} of SGLT2 inhibitors did not find an increased risk, nor did a pooled analysis of eight canagliflozin trials.²² Finally, in May 2017, the FDA supported earlier speculation of increased risk of low limb amputation¹¹ with evidence gathered from re-analysis of the CANVAS and CANVAS renal end points (CANVAS-R) trials, demonstrating a twofold increased risk.²³ No meta-analysis of RCTs currently exists with respect to amputation.

In light of recent guideline changes that promote preferential use of the SGLT2 inhibitors, clinicians and policy

makers need to continue examining the potential risks to their patients. Our objective is to address the current knowledge gap surrounding the postmarket safety of the SGLT2 inhibitors compared with active and non-active comparators in patients with type 2 diabetes. We have conducted a systematic review and meta-analysis of RCTs to estimate the risk of AKI, DKA, UTI, bone fracture and lower limb amputation.

METHODS AND ANALYSIS

Study design

This study has been designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement on systematic reviews and meta-analysis.²⁴ This protocol has been registered (CRD42016038715) with PROSPERO (International Prospective Register of Systematic Reviews).^{25,26}

Patient involvement

Patients were not engaged in the development of this protocol.

Search strategy

A comprehensive search strategy was developed with an experienced health science librarian (MS). The search strategy for published studies was developed in the PubMed database, and comprised keywords and MEDLINE controlled vocabulary or medical subject headings. A methodological search filter was applied to identify RCTs²⁶ and the search was limited to English language publications. This search strategy served as a template for additional search strategies tailored to other databases, including the Cochrane Library, EMBASE and International Pharmaceutical Abstracts. In addition, the reference lists of topical review articles, editorials and included studies were hand-searched to identify other potentially relevant studies. A list of search terms is provided in section 1 of the online supplementary appendix.

The search for unpublished studies and materials included ProQuest Dissertations and Theses Global (ProQuest), and clinical trial registries (ClinicalTrials.gov). Inclusion of unpublished data from the FDA has been shown to substantially impact the effect estimates of meta-analyses of drug trials.²⁷

Eligibility criteria

We included RCTs with a study population consisting of patients 18 years of age and older with a diagnosis of type 2 diabetes. Studies were required to have a formal definition of type 2 diabetes based on established diagnostic criteria during the time of the study. No restriction was applied with respect to history of diabetes medication use. One of the RCT study groups was required to be one of the following SGLT2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, ipragliflozin or any other investigational or approved SGLT2 inhibitor during study period. Eligible comparators included second-generation

sulfonylureas (glyburide, gliclazide, glimepiride, glipizide—first-generation sulfonylureas excluded as they have a limited role in clinical practice), basal insulins (Neutral Protamine Hagedorn (NPH), lente, glargine, detemir, degludec), dipeptidyl peptidase-4 (DPP-4) inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin), GLP-1 receptor agonists (dulaglutide, exenatide, liraglutide), thiazolidinediones (pioglitazone, rosiglitazone), α -glucosidase inhibitors (acarbose) or placebo/no treatment. All premixed or acute care insulin protocols were excluded. Any investigational agents other than SGLT2 inhibitors were excluded.

The outcomes of this study include the serious safety events as highlighted through the federal regulatory drug safety communications.^{7–11} These include AKI, DKA, UTI, bone fractures and lower limb amputations.

Studies were eligible regardless of duration of follow-up, or publication date; however, non-English citations were excluded. Language restriction does not appear to bias estimates of therapeutic interventions.^{28 29}

Study selection and data extraction

We used DistillerSR, a systematic review software,³⁰ for screening and data extraction. Studies went through a two-level screening process. First, titles and abstracts were reviewed using the inclusion and exclusion criteria. Studies that met those criteria, or where a clear decision could not be made, were moved to second-level screening. At level two screening, full-text articles were retrieved and the same criteria applied. Duplicate screening was carried out using the ‘liberal accelerated’ method at both level one and level two, which was first applied by Khangura *et al.*³¹ This method involves having a second reviewer only evaluate studies that were deemed not relevant by the lead reviewer. This reduces the overall number of papers that require duplicate screening without increasing the risk of having appropriate studies inadvertently excluded.

Information extracted included study characteristics (country, definitions of exposure(s) and controls), patient characteristics (sex, age, duration of diabetes) and outcome data (a complete list of extracted variables is available in section 2 of the online supplementary appendix). Where the data conflicted between the published paper and other sources (eg, ClinicalTrials.gov), the data from the published paper were used. Data were only supplemented from other sources when gaps in information existed. In cases where more than one publication reported data on the same study, preference was taken to studies that reported numbers of events (vs only relative risk (RR) or HR) and the most recent were used for data extraction. The exception to this rule was when there was a change to the intervention or comparator groups (eg, drug, dose, etc) for study extensions, then data from the original publication were used. Any disagreements were resolved through discussion and consensus. Where necessary, a third reviewer was consulted. All DistillerSR screening and extraction forms were created a priori and piloted using a small sample of eligible studies.

Risk of bias assessment

Each included study was critically appraised using the Cochrane Collaboration domain-based tool for assessing the risk of bias for RCTs.³² This tool captures six main sources of bias, including: randomisation sequence, allocation concealment, blinding of participant and researcher, blinded outcome assessment, incomplete outcome data and selective reporting. A seventh category captures any other potential sources of bias. Bias was assessed at the study level. Low risk of bias was defined as an assessment on the risk of bias tool that included no more than two categories with ‘unclear risk’. Studies were defined as high risk if they had: three or more categories of ‘unclear risk’; one or more categories of ‘medium risk’

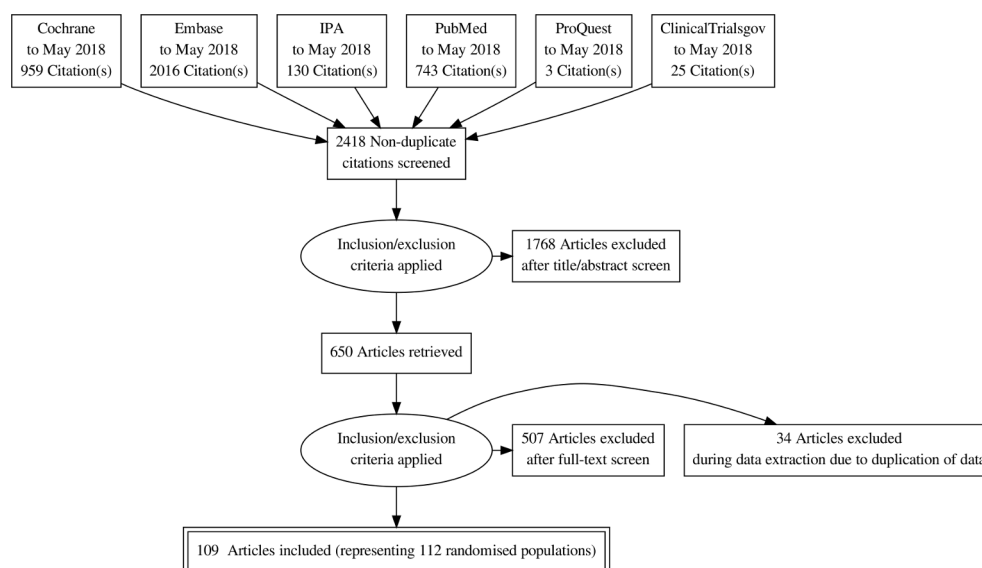


Figure 1 Flow diagram for included studies.

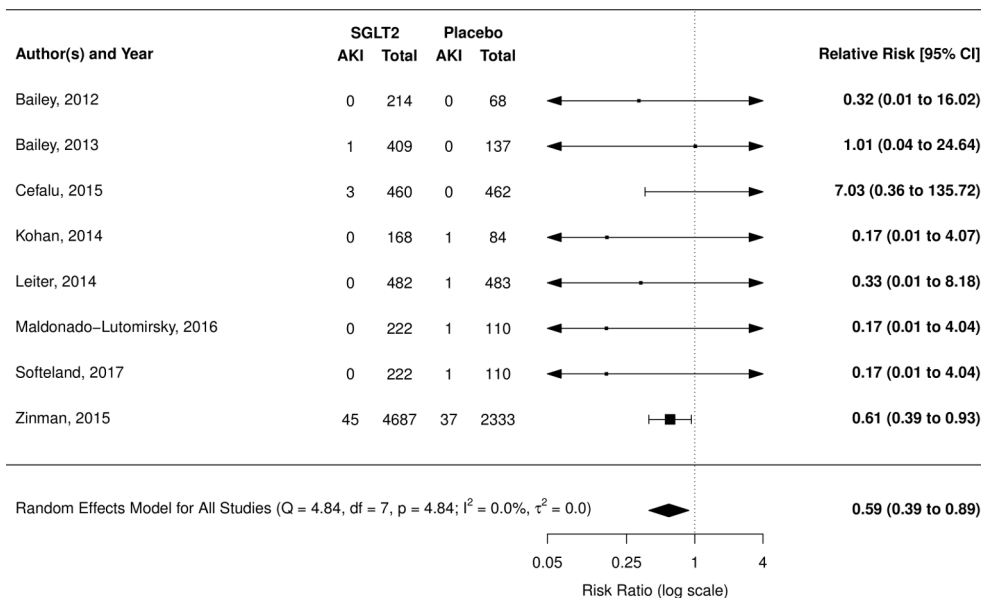


Figure 2 Risk of acute kidney injury (AKI) with sodium glucose co-transporter-2 (SGLT2) inhibitors compared with placebo.

or one or more categories of ‘high risk’. Publication bias was examined using funnel plots.

Data synthesis

We conducted a series of pair-wise random effects meta-analyses to estimate the pooled treatment effect using RRs, using the restricted maximum likelihood method.³³ The primary analysis was split into two comparisons, with the first between SGLT2 inhibitors and placebo, and the second between SGLT2 inhibitors and any active comparator. If there were zero events reported, a default value of 0.5 was added to all groups within that study. Statistical heterogeneity was evaluated using the I² statistic, with significant heterogeneity defined as an I²>50%.³⁴ To explore treatment effect heterogeneity, we conducted

numerous subgroup analyses according to individual SGLT2 inhibitors, risk of bias and concurrent use of other diabetes medications. Concurrent/prior use was defined as any previous use of antidiabetic agents that were used prior to enrolment or added as background therapy after enrolment. If patients could be therapy-naïve or have used other medications to meet enrolment criteria, then they were categorised as concurrent/prior use. Treatment-naïve was defined as patients who have never had an antidiabetic medication in the past, have not been on any other antidiabetic medication in weeks leading up to enrolment or were able to go through a washout prior to enrolment. We also conducted sensitivity analyses to explore the impact of methodological decisions within

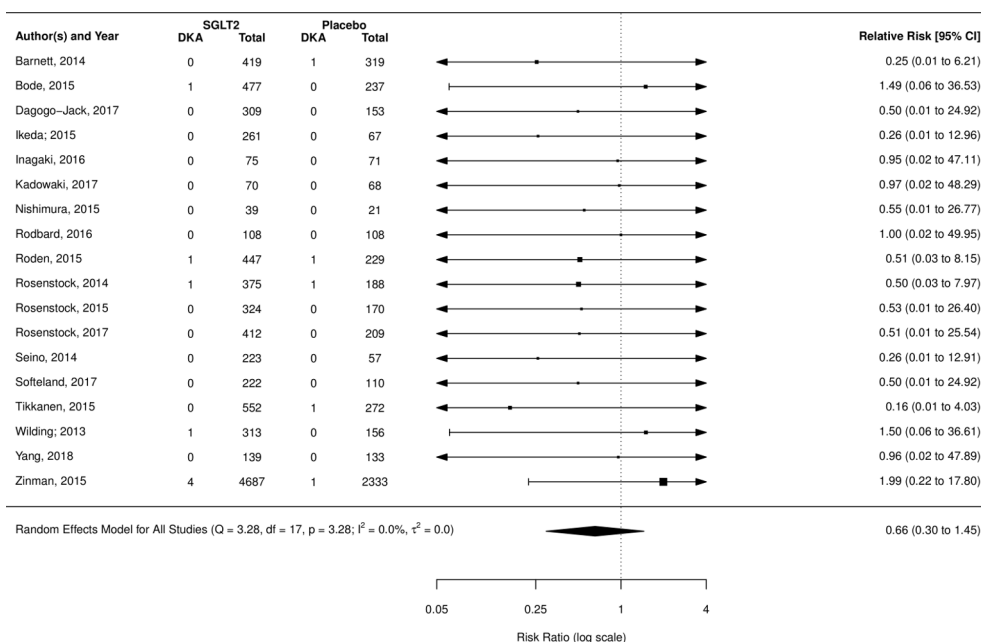


Figure 3 Risk of diabetic ketoacidosis (DKA) from sodium glucose co-transporter-2 (SGLT2) inhibitors compared with placebo.

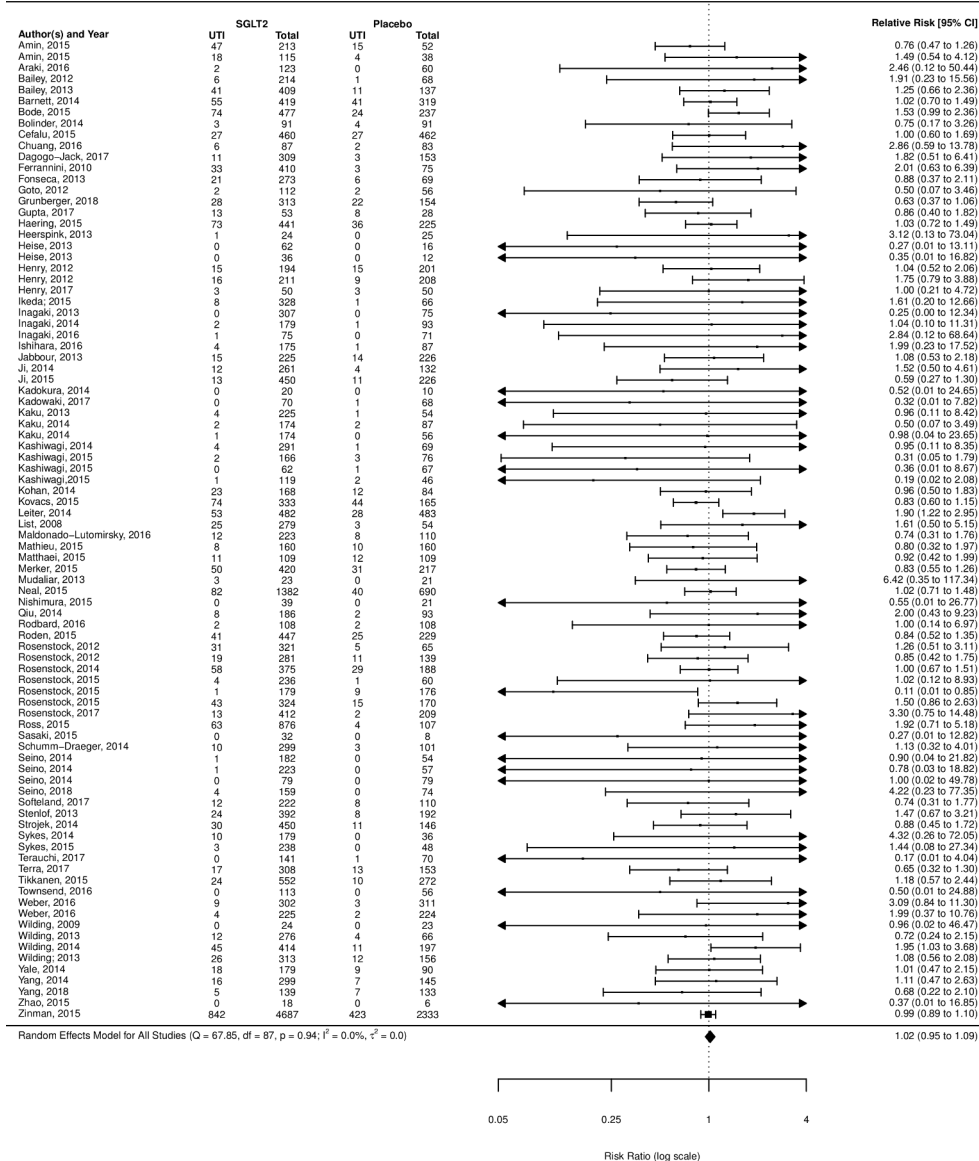


Figure 4 Risk of urinary tract infection (UTI) with sodium glucose co-transporter-2 (SGLT2) inhibitor compared with placebo.

our analysis. First, we pooled studies that had at least one reported event. Second, we repeated our analyses using fixed-effects models. All analyses were conducted using R statistical software (V.3.4.1). Technical online supplementary appendix, statistical code and dataset can be granted by contacting the corresponding author.

RESULTS

Included studies

A total of 2418 unique titles and abstracts were screened. Of these, 650 proceeded to full-text screening. A total of 143 citations met our inclusion criteria; however, 34 were excluded at the data extraction phase due to duplication of data, from the publication of extension studies or post hoc analyses. A final total of 109 publications were included,^{5 23 35–141} representing 112 randomised populations (figure 1). Three publications reported on multiple unique populations. Most studies included one

of the four marketed SGLT2 inhibitors, dapagliflozin (34 studies), canagliflozin (20 studies), empagliflozin (25 studies) and ipragliflozin (11 studies); while 21 studies included one of five non-marketed agents. With respect to comparators, 4 conducted within-class comparisons, 92 compared with placebo, 8 compared with metformin, 10 compared with an incretin agent, 5 compared with a sulfonylurea and 3 compared with pioglitazone. A total of nine studies included more than one unique comparator. One publication, reporting on the combined results of the CANVAS program²³ studies only, provided events as rates per 1000 person-years. Data from this publication were only used for the amputation outcome assessment, data from an earlier publication on a subset of this population was used for other outcomes as actual event numbers were reported.⁸² Section 3 of the online supplementary appendix outlines the characteristics of each of the included studies.

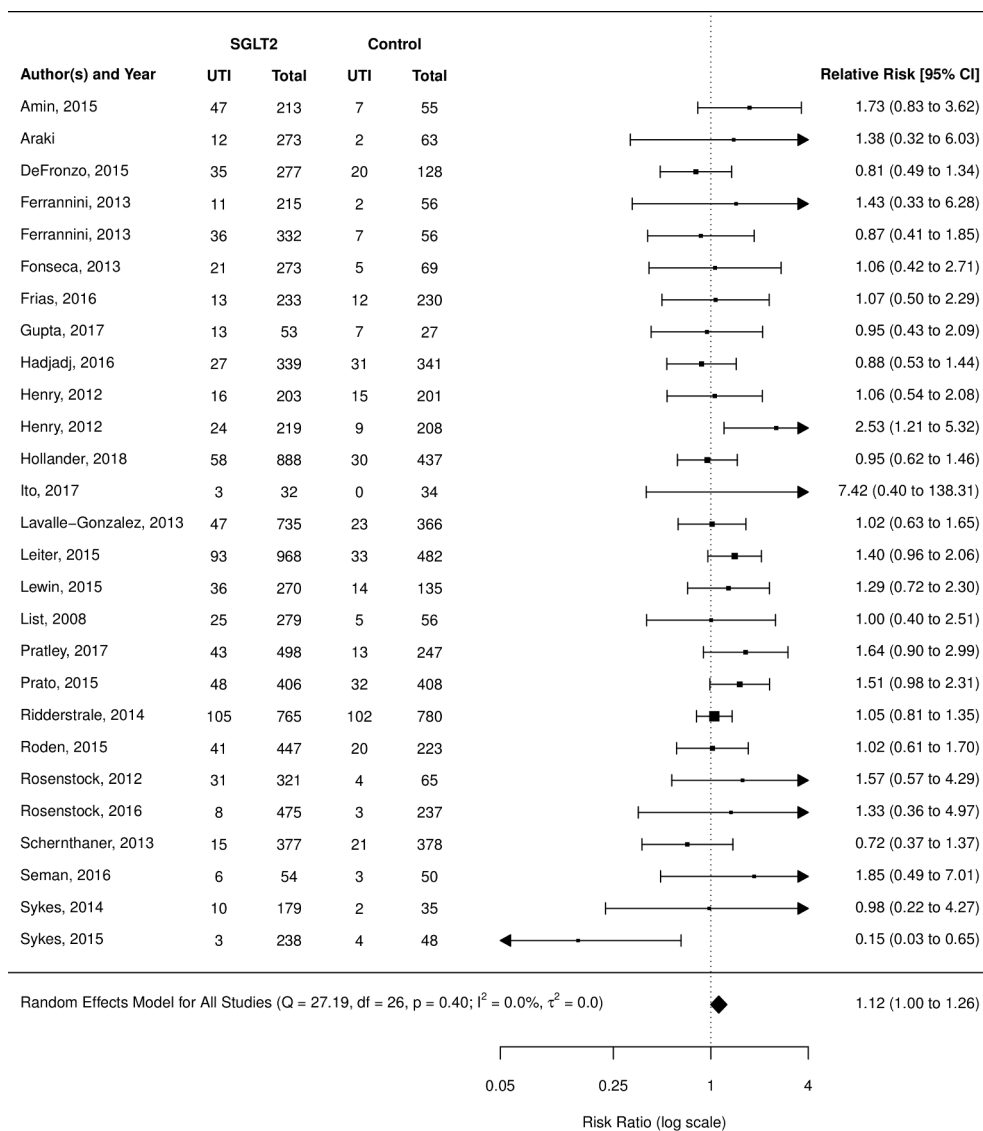


Figure 5 Risk of urinary tract infection (UTI) with sodium glucose co-transporter-2 (SGLT2) inhibitors compared with other active treatments.

Primary analysis

Acute kidney injury

AKI was reported in 11 RCTs (8 placebo comparison and 3 active comparison trials): meta-analysis was only possible with placebo-controlled trials. Overall, SGLT2 inhibitors were found to have a protective effect (RR 0.59; 95% CI 0.39 to 0.89, I²=0.0%); however, this estimate is heavily weighted by one study using empagliflozin, the EMPA-REG trial (figure 2).⁵ Pooled estimate after removing the EMPA-REG trial was non-significant (RR 0.48; 95% CI 0.14 to 1.64; I²=0.0%).

Diabetic ketoacidosis

DKA was reported in 26 RCTs (18 placebo comparison, 8 active comparisons and 1 within class comparison trial). Neither placebo (RR 0.66; 95% CI 0.30 to 1.45, I²=0.0%) (figure 3) nor incretin (RR 0.43; 95% CI 0.069 to 2.75; I²=0.0%; three studies) (forest plot, online supplementary appendix section 4) comparisons showed a significant

difference in risk of DKA. Additional analysis using only placebo-controlled trials that had at least one event also yielded no significant difference (RR 0.73; 95% CI 0.25 to 2.16; I²=0.0%; seven studies) (forest plot, online supplementary appendix section 4).

Urinary tract infections

UTI was the most frequently reported outcome examined (110 of 112 studies reported). When compared with placebo, SGLT2 inhibitors as a class did not demonstrate a significant increased risk (RR 1.02; 95% CI 0.95 to 1.09) (figure 4); however, subgroup analysis of the individual agents did show a significantly increased risk of UTIs in users of dapagliflozin (RR 1.21; 95% CI 1.02 to 1.43), but not empagliflozin, canagliflozin, ipragliflozin or non-marketed SGLT2 inhibitors (grouped) (supplementary appendix). When compared with active treatments, SGLT2 inhibitors grouped together did not demonstrate an

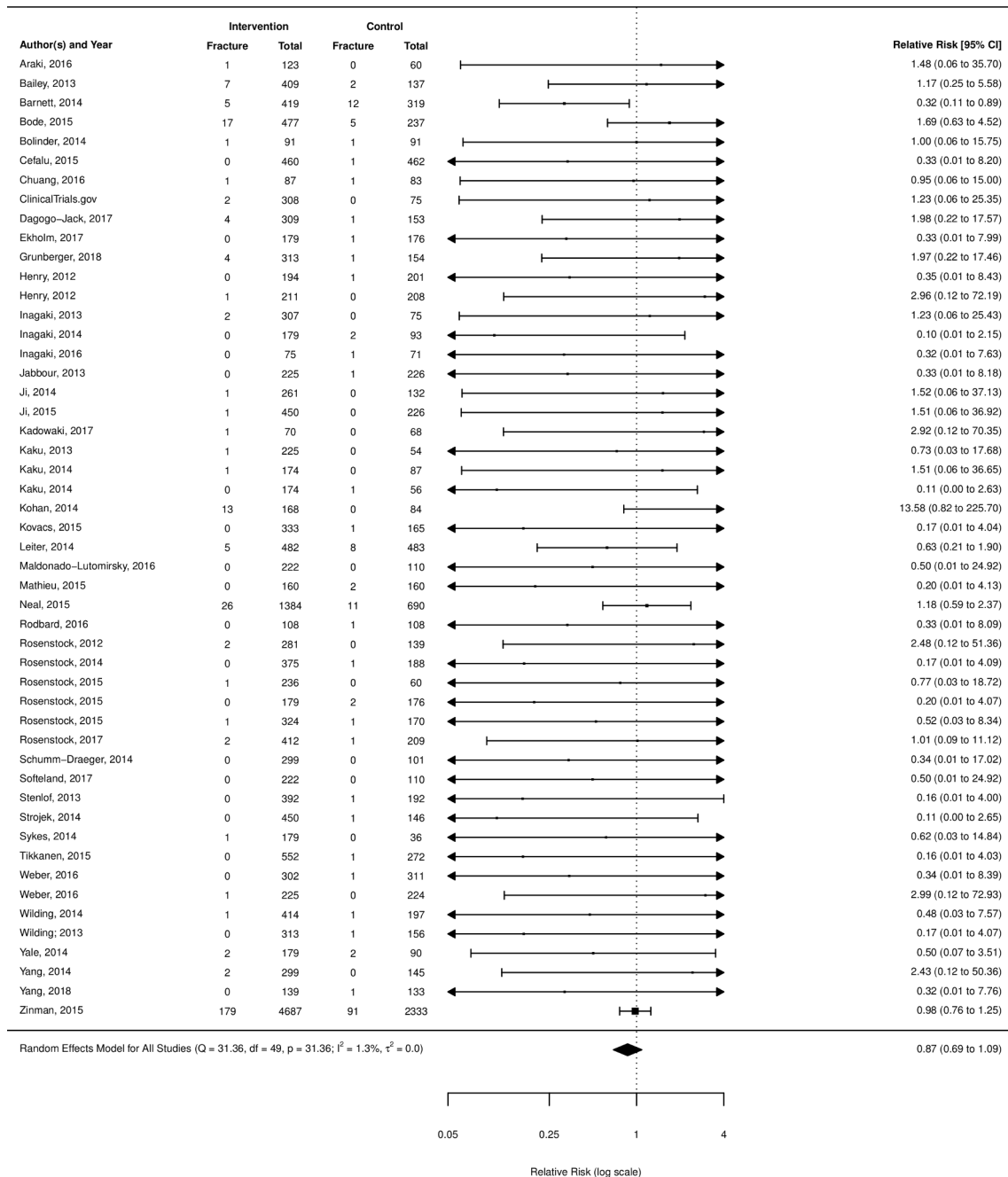


Figure 6 Risk of fracture with sodium glucose co-transporter-2 inhibitors compared with placebo.

increased risk of UTIs over metformin, sulfonylureas, incretins or glitizones (figure 5); however, when broken down by individual SGLT2 inhibitor, dapagliflozin showed an increased risk of UTI over active comparators grouped together (RR 1.42; 95% CI 1.07 to 1.87) (forest plot, online supplementary appendix section 4).

Bone fracture

Bone fracture was reported in 63 RCTs (47 placebo comparisons, 14 active comparison and 2 within class comparisons). SGLT2 inhibitors were not found to have an increased risk of fractures over placebo (RR 0.87; 95% CI 0.69 to 1.09) (figure 6), metformin

(RR 0.69; 95% CI 0.19 to 2.51; I²=0.0%; six studies), sulfonylureas (RR 1.15; 95% CI 0.66 to 2.00; I²=0.0%; three studies) or incretins (RR 1.38; 95% CI 0.31 to 6.17; I²=0.0%; three studies). A subgroup analysis of canagliflozin compared with placebo alone, the agent identified by the FDA as having an increased risk, was also non-significant (RR 1.02; 95% CI 0.63 to 1.65; I²=0.0%; 12 studies) (additional forest plots, online supplementary appendix section 4).

Lower limb amputation

Data were identified on amputation for three studies.^{23 46 107} One case of amputation was found in the ClinicalTrials.gov data for trial number NCT01422876

in a user of empagliflozin 25 mg, no cases were reported for other treatment groups. The second study reported data from the CANVAS program, showed a rate of amputation among users of canagliflozin (100–300 mg) was 6.3 per 1000 patient-years, compared with 3.4 per 1000 patient-years for placebo, this difference was statistically significant ($p < 0.001$). Actual number of events were not reported. The third study reported one case in each of the treatment groups, ertugliflozin (1/888) and glimepiride (1/437).

Subgroup and sensitivity analyses

Several subgroup analyses were conducted to examine the impact of prior and concurrent use of other anti-diabetic agents; the influence of risk of bias as per the quality appraisal and the impact of the definition of UTI used as outlined in table 1. Overall, these additional analyses did not change the findings of the primary analysis. There was a decreased risk of AKI in the treatment-naïve group, and the low risk of bias group, but this was consistent with the main analysis and driven by the same one

Table 1 Subgroup analysis among placebo-controlled trials

Group	Relative risk (95% CI; I ² %)	No. of studies	Total no. of outcomes/patients
Prior use of antidiabetics			
AKI			90/10 651
Prior/concurrent diabetes therapy	0.51 (0.14 to 1.84; 0.72)	6	
Treatment-naïve	0.60 (0.39 to 0.92; 0.00)	2	
DKA			13/14 353
Prior/concurrent diabetes therapy	0.65 (0.25 to 1.71; 0.00)	14	
Treatment-naïve	0.66 (0.16 to 2.71; 0.00)	4	
UTI			3405/39 331
Prior/concurrent diabetes therapy	1.04 (0.93 to 1.16; 8.22)	64	
Treatment-naïve	1.00 (0.91 to 1.10; 0.00)	23	
Fracture			445/29 668
Prior/concurrent diabetes therapy	0.81 (0.57 to 1.14; 2.61)	39	
Treatment-naïve	0.79 (0.46 to 1.36; 6.30)	11	
Risk of bias			
AKI			90/10 651
Low risk of bias	0.58 (0.38 to 0.89; 0.0)	4	
High risk of bias	0.71 (0.12 to 4.37; 25.5)	4	
DKA			13/14 353
Low risk of bias	0.85 (0.28 to 2.61; 0.0)	10	
High risk of bias	0.49 (0.003 to 71.59; 94.8)	8	
UTI			3405/39 331
Low risk of bias	1.00 (0.92 to 1.08; 0.0)	51	
High risk of bias	1.05 (0.11 to 10.43; 99.7)	37	
Fracture			445/29 668
Low risk of bias	0.95 (0.76 to 1.18; 0.0)	22	
High risk of bias	0.58 (0.04 to 8.77; 97.0)	27	
Definition of UTI			
UTI			3405/39 331
Predefined list of terms	0.99 (0.91 to 1.07; 0.0)	19	
Suggestive of UTI	1.13 (0.87 to 1.47; 0.0)	11	
Positive culture	0.91 (0.51 to 1.62; 24.27)	2	
As per investigator	0.82 (0.41 to 1.61; 0.0)	2	
Not defined	1.08 (0.90 to 1.29; 15.47)	54	

AKI, acute kidney injury; DKA, diabetic ketoacidosis; UTI, urinary tract infection.

large study.¹⁴² When the analyses were re-run using a fixed-effects model, the risk estimates remained the same or had slightly smaller CIs. Forest plots for the fixed-effects analysis are mentioned in section 5 of the online supplementary appendix.

Risk of bias

Generally, studies were of good methodological quality; however, numerous studies were deemed high risk of selective reporting after outcome data were retrieved from ClinicalTrials.gov that were not reported in the peer-reviewed publication (28%). Other potential sources of bias came from unclear reporting of methodological processes like randomisation sequence (32%) or blinded outcome assessment (17%), while most sources of bias came from lack of blinding of the researchers and participants (13%) and of the outcome assessors (9%). Risk of bias assessment for individual studies are available in section 6 of the online supplementary appendix. Funnel plots do not suggest the presence of publication bias (see section 7 of the online supplementary appendix).

DISCUSSION

This study provides a comprehensive review of the RCT literature with respect to key safety outcomes identified through postmarketing surveillance systems and communicated to health professionals and the public by drug regulators. We pooled outcome data from over 100 RCTs (including unpublished data only available through ClinicalTrials.gov) to quantify the association between SGLT2 inhibitors and AKI, DKA, UTI and bone fracture. We found that SGLT2 inhibitors as a class do not appear to increase the risk of DKA, UTI and bone fracture, and may have a protective effect with respect to AKI, although this effect was heavily weighted by one large RCT. With respect to UTI, overall findings do not hold in subgroup analysis by individual drug, suggesting that increased risk of UTI is associated only with dapagliflozin.

Despite early indication of a protective effect from SGLT2 inhibitors on kidney function,¹⁵ the FDA published in a safety communication in June 2016 that 101 cases of AKI were reported among users of canagliflozin and dapagliflozin.¹² SGLT2 inhibitors may provide a long-term protective effect on the kidneys via reduced transglomerular pressure, similar to the effects of agents that target the renin-angiotensin-aldosterone (RAAS) axis.¹⁴³ Szalat *et al* proposed three possible mechanisms that may explain the potential for an increased risk of AKI with SGLT2 inhibitors: (1) excessive diuresis leading to volume depletion, a particular concern for those who are haemodynamically unstable and volume-depleted; (2) a greater drop in transglomerular pressure due to the concomitant action of SGLT2 inhibition and RAAS blockade and (3) renal medullary hypoxic injury, likely occurring in patients taking concomitant agents that impair medullary oxygenation (eg, non-steroidal anti-inflammatory drugs, radio-contrast dyes).¹⁴³ Additional potential mechanisms

of renal injury include an increase in the urinary uric acid level leading to both crystal-dependent and crystal-independent tubular injury, and activation of aldose reductase resulting in fructose generation ultimately leading to increased oxidative stress, uric acid, cytokine release and inflammation.¹⁴⁴ This systematic review highlights a lack of reporting of AKI with only 11 of 111 randomised comparisons having published data on this outcome. Although an overall protective effect was found, this finding was driven by one large RCT that compared empagliflozin with placebo. Evidence to support or refute the potential risk of AKI with use of canagliflozin or dapagliflozin was insufficient. Case reports filed with the FDA suggest that this adverse outcome frequently occurs early in therapy (within 1 month of initiation) and therefore this lack or reporting should not be due to the duration of clinical trials. Recent observational data also support clinical trial data on AKI. Nadkarni *et al* reported on the incidence of AKI among two cohorts comparing patients with type 2 diabetes using SGLT2 inhibitors to non-users.¹⁴⁵ After an average follow-up time of 14 months, adjusted HR (aHR) showed SGLT2 inhibitors to be protective in one cohort (aHR 0.4 (95% CI 0.2 to 0.7); $p=0.004$) and favouring SGLT2 inhibitors, although not statistically significant, in the second cohort (aHR 0.6 (95% CI 0.4 to 1.1); $p=0.09$). These findings were not driven by users of empagliflozin, rather 91.2% and 71.4% of SGLT2 inhibitor users in these cohorts were taking either canagliflozin or dapagliflozin, respectively.

Reports of euglycaemic DKA among patients with type 2 diabetes is concerning, as a diagnosis can easily be missed. Although rare, the SGLT2 inhibitors are thought to increase the risk by two potential mechanisms: (1) they increase urinary glucose excretion which leads to a reduction in insulin secretion and stimulates free fatty acid production which are later converted to ketone bodies and (2) they stimulate glucagon secretion which may lead to an overproduction of ketone bodies.¹⁴⁶ An accurate assessment of the potential increased risk of DKA among users of SGLT2 inhibitors was difficult with the data reported within RCTs. Baseline incidence rates of DKA in patients with type 2 diabetes was found to be 1.34 per 1000 person-years in a 20-year retrospective Danish cohort study, with declining incidence each year.¹⁴⁷ Therefore, most RCTs had insufficient sample size to detect any cases. Of the 16 RCTs that reported DKA, only 7 (representing 11004 patients) had one or more cases. Our findings are consistent with published observational literature, which indicates no increased risk, however CIs were wide. A case-control study using Truven MarketScan data (a large US claims database),¹⁴⁸ and a cross-sectional using the FDA Adverse Event Reporting System database¹⁴⁹ examining this issue have recently been published. Both studies used DPP-4 inhibitors as the active comparator given they have no known risk for DKA and are used in a similar fashion as second-line therapy in type 2 diabetes, and both showed significant increased risk with SGLT2 inhibitors (case-control: sevenfold increased risk among 140352 patients; cross-sectional: HR 2.2; 95% CI 1.4 to 3.6, among 416 670). In contrast, the Danish cohort study did

not find an increased risk of DKA in individuals taking SGLT2 inhibitors compared with other diabetes therapies (HR 1.6; 95% CI 0.6 to 3.5), although the upper bound of the 95% CI does not rule out significant harm.¹⁴⁷ No meta-analyses assessing this outcome were found.

Given the mechanism of action of the SGLT2 inhibitors, which work by inhibiting glucose reabsorption in the kidney leading to increase glucose excretion in the urine, an increased risk of UTI is plausible. In May 2015, the FDA reported in a safety update that 19 cases of life-threatening kidney or blood infections that originated as a UTI had been identified in patients taking a SGLT2 inhibitor. However, a meta-analysis published in 2017 included 77 RCTs representing 50 820 patients and found no increased risk of UTIs in SGLT2 inhibitor users (RR 1.05; 95% CI 0.98 to 1.12).¹⁷ The previous meta-analysis limited inclusion to studies of at least 24 weeks and having a full-text publication. Our study findings are consistent and add to the literature via the inclusion of 35 more studies, resulting in a more precise effect estimate. Importantly, subgroup analysis of individual SGLT2 inhibitors suggest variation of UTI risk within class, whereby dapagliflozin may increase UTI risk when compared with both placebo and active controls. A reasonable biologic mechanism for an increased risk of UTIs among dapagliflozin users is unclear; however, some early pathophysiological studies suggest that the dose-response relationship with urinary glucose excretion seems to plateau at the beginning of the normal recommended doses for most SGLT2 inhibitors,^{126 136 150–153} although continues through the normal dosing range for dapagliflozin.¹⁵⁴

In January 2016, the FDA issued an expanded warning regarding a potential increased risk for fracture with canagliflozin.⁹ A disruption in calcium-phosphate homeostasis is one potentially contributing mechanism.²⁰ SGLT2 inhibitors increase serum phosphate levels via increased tubular reabsorption of phosphate. Increased phosphate levels then stimulate parathyroid hormone release which may enhance bone resorption leading to an increased fracture risk in patients using SGLT2 inhibitors.¹⁵⁵ In an RCT conducted by Bode *et al*, additional investigation into the change in bone mineral density in canagliflozin versus placebo users was conducted.¹¹⁹ Their results showed a decreased placebo-corrected bone mineral density in the canagliflozin users at 2 years of 0.9%–1.2% at the hip, 0.3%–0.7% at the lumbar spine, 0.5% at the femoral neck and 0.4% at the distal forearm. Two meta-analyses have been published examining the risk of fracture when comparing SGLT2 inhibitors with placebo.^{20 21} Ruanpeng *et al*²⁰ included 20 RCTs, and Tang *et al* included 38 RCTs. Neither meta-analysis in pooled or subgroup analysis of individual SGLT2 inhibitors demonstrated a significant increased risk of fracture. A pooled analysis of eight canagliflozin RCTs also found no increased risk.²² The results of this current study support the existing literature, demonstrating risk neutrality, with the addition of new RCT literature (a total of 58 RCTs, 45 of which were placebo controlled).

To date, research evidence on the risk of amputations among users of SGLT2 inhibitors is limited to results from the combined CANVAS and CANVAS-R trials. Only two other studies reported amputations, with a combined total of three events. Further data are needed to establish the true risk as well as to identify if this may be a class effect or agent specific.

Limitations

Although we conducted a comprehensive systematic review of RCTs of SGLT2 inhibitors, there are still limitations to be considered when interpreting our findings. First, our review focused on select adverse events and excluded any benefits. Although this narrows the focus and requires the consideration of additional literature to make clinical decisions on appropriate use of SGLT2 inhibitors, it also provides a succinct and in-depth assessment of the unexpected adverse effects that have been reported postmarket. Second, several of the outcomes (eg, AKI, DKA, limb amputations) we evaluated occur infrequently. This also resulted in these individual outcomes to be at a higher risk of selective reporting bias than the more common adverse effects. We did our best to account for this risk by supplementing unreported outcomes with data from ClinicalTrials.gov; however, it is possible the cases of these outcomes were not recorded or reported through either of these sources. Third, certain outcomes may have been inadequately characterised within study reports. For example, while UTIs were commonly reported among RCTs included in this meta-analysis, data on complicated versus uncomplicated infections were not. The FDA highlighted 19 cases of life-threatening infections stemming from UTIs. It is possible that SGLT2 inhibitors play a role in the progression of UTI to more complicated clinical outcomes. Fourth, the limited duration of included RCTs (36% of studies were <24 weeks and 63% <1 year) precludes the estimation of long-term effects of SGLT2 inhibitors. This may be important in case of declining bone integrity. Finally, it was difficult to accurately assess the methodological quality of the included studies given the fact we were examining secondary and rarely reported outcomes. It has been noted that traditional quality appraisal forms are not always well suited to systematic reviews of adverse events. This is due to the fact that sometimes data on adverse effects may be collected after allocation is known, or through self-assessment questionnaires.¹⁵⁶

CONCLUSION

Despite the growing body of evidence on the new SGLT2 inhibitors, there remains minimal evidence demonstrating the comparative safety with respect to the more serious and unexpected outcomes. Current evidence from RCTs does not suggest an increased risk of harm with SGLT2 inhibitors, as a class, over placebo or active comparators with respect to the AKI, DKA, UTI or fracture. There appears to be treatment effect heterogeneity for the risk

of UTI among specific SGLT2 inhibitors. Larger sample sizes and more long-term evidence, including observational studies, is needed to refine our estimates of the risk of AKI, DKA, fracture and amputation among SGLT2 inhibitor users.

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Contributors JRD led the review and was involved at every stage, including protocol development, search strategy design, screening, data extraction, quality appraisal, analysis and manuscript preparation. CG was involved in screening, data extraction, quality appraisal and manuscript revisions and final approval. EC was involved in data cleaning and analysis, manuscript revisions and final approval. CAM was involved in project conception, protocol development and manuscript revisions and final approval. KAB was involved in project conception, protocol development and manuscript revisions and final approval. KJ was involved in project conception, protocol development and manuscript revisions and final approval. MS was involved in search strategy design, literature search and manuscript revisions and final approval. JH was involved in screening, data extraction, quality appraisal and manuscript revisions and final approval. DC was involved in screening, data extraction, quality appraisal and manuscript revisions and final approval. HN was involved in interpretation of study results, manuscript revisions and final approval. JMG supervised this research and was involved in protocol development, consensus on disagreements in data extraction, data analysis, interpretation of results, manuscript revisions and final approval.

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