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

Short Running Title: Comparative Safety of SGLT2 Inhibitors

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Abstract

Objective: To address the current knowledge gap surrounding the post-market serious safety outcomes of the sodium glucose co-transporter-2 (SGLT2) inhibitors identified by the Food and Drug Administration (FDA), the European Medicines Associations (EMA) and Health Canada.

Design: We conducted a systematic review and meta-analysis of randomized controlled trials (RCT). PubMed, Cochrane Library, EMBASE, International Pharmaceutical Abstracts, ProQuest, and ClinicalTrials.gov were searched from inception to July 2017. Random effects models were used to estimate pooled relative risks.

Intervention: SGLT2 Inhibitors, compared to placebo or active comparators.

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

Results: We screened 1865 citations of which 99 were included in the analysis. Most studies included one of four SGLT2 inhibitors, dapagliflozin, canagliflozin, empagliflozin, and ipragliflozin. When compared to placebo, SGLT2 inhibitors were found to be significantly protective against AKI (RR = 0.59; 95% CI 0.39-0.89; I^2=0.0%), while no difference was found for DKA (RR = 0.65; 95% CI 0.28-1.50; I^2=0.0%), UTI (RR = 1.03; 95% CI 0.96-1.10; I^2=0.0%), or bone fracture (RR = 0.86; 95% CI 0.67-1.09; I^2=2.2%). No increased risk for either outcome was found when compared to active controls, and no studies reported on amputations. Sub-group analysis did show an increased risk of UTI with dapagliflozin only (RR 1.23; 95% CI 1.03-1.46; I^2=4.9%), 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 the AKI, DKA, UTI or fracture. However, wide confidence intervals for many comparisons suggest limited precision, and therefore clinically important adverse events cannot be ruled out. Dapagliflozin, does appear to independently increase the risk of UTI.

Trial Registration: PROSPERO CRD42016038715

Article Summary

- Our objective is to address the current knowledge gap surrounding the post-market safety of the SGLT2 inhibitors compared to active and non-active comparators in patients with type 2 diabetes.

Strengths and Limitations of the Study

- This study provides the most comprehensive systematic review of the serious adverse events related to use of SGLT2 inhibitors identified by major drug regulatory agencies worldwide to date.
- This study only 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 (e.g., AKI, DKA, limb amputations) we evaluated occur infrequently and, in some cases, were not reported at all.
- Certain outcomes may have been inadequately characterized 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.

1.0 Introduction

The sodium glucose co-transporter 2 (SGLT2) inhibitors are a novel drug class available for the management of type 2 diabetes. Clinical guidelines recommend the SGLT2 inhibitors as one of numerous potential pharmacologic approaches for second-line therapy following metformin failure or intolerance.[1, 2] Some clinical guidelines recommend the SGLT2 inhibitor, empagliflozin, 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 glycemic 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.[3–5] In 2015 the EMPA-REG trial showed that the SGLT2 inhibitor, empagliflozin, significantly reduced the risk for composite endpoint of cardiovascular death, myocardial infarction, or stroke by 14% and all-cause mortality by 32%, in a population with existing cardiovascular disease.[3] The LEADER and SUSTAIN-6 trials have also demonstrated similar benefits with liraglutide and semaglutide.[4, 5]

Considering the relative potential harms and benefits, clinicians and policy makers must continue to integrate new pharmacotherapeutic evidence to optimize 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 (EMA) 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. [6–13]

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,[14] the FDA published in a safety communication in June 2016 that 101 cases of AKI were reported among users of canagliflozin and dapagliflozin.[11] To date, no meta-analysis of AKI has been published. In May 2015 the FDA published a safety update indicating an increased risk of DKA and UTI. They identified 73 cases of DKA and 19 cases of life-threatening infections that originated as a UTI, had been identified in patients taking a SGLT2 inhibitor. However, to date clinical trial evidence does not support these potential risks. Four published meta-analyses of randomized control trials (RCT) and found no increased risk of UTIs, except within a sub-group of dapagliflozin,[15–18] and one study found an increased risk with empagliflozin 25mg users.[17] No meta-analysis on the risk of DKA currently exists. In January 2016, the FDA issued an expanded warning regarding a potential increased risk for fracture with canagliflozin.[8] Two published meta-analyses.[18, 19] of SGLT2 inhibitors did not find an increased risk, nor did a pooled analysis of eight canagliflozin trials.[20] Finally, in May 2017, the FDA supported earlier speculation of increased risk of low limb amputation[10] with evidence gathered from re-analysis the CANVAS and CANVAS-R trials, demonstrating a

two-fold increased risk.[21] No meta-analysis of RCTs currently exists with respect to amputation.

In light of recent guideline changes that promote earlier integration of the SGLT2 inhibitors into therapy, 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 post-market safety of the SGLT2 inhibitors compared to 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.

2.0 Methods and Analysis

2.1 Study Design

This study has been designed in accordance with the PRISMA statement on systematic reviews and meta-analysis.[22] This protocol has been registered (CRD42016038715) with PROSPERO (International Prospective Register of Systematic Reviews).[23, 24]

2.2 Patient Involvement

Patients were not engaged in the development of this protocol.

2.3 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 of keywords and MEDLINE controlled vocabulary or “medical subject headings”. A methodological search filter was applied to identify RCTs[25] 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 Appendix.

The search for unpublished studies and materials included ProQuest Dissertations & 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.[26]

2.4 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 a different SGLT2 inhibitor, metformin, second-generation sulfonylureas (glyburide, gliclazide, glimepiride, glipizide –first generation sulfonylureas excluded as they are currently not used in clinical practice), basal insulins (NPH, lente, glargine, detemir, degludec), dipeptidyl peptidase-4 Inhibitors (DPP-4I) (alogliptin, linagliptin, saxagliptin, sitagliptin), GLP-1 agonists (dulaglutide, exenatide, liraglutide), thiazolidinediones (TZDs) (pioglitazone, rosiglitazone), alpha-glucosidase Inhibitors (acarbose) or placebo/no treatment. All premixed or acute care insulin protocols were excluded. Any investigational agents other than SGLT-2 inhibitors were excluded.

The primary outcomes of this study are the serious safety events as highlighted through the federal regulatory drug safety communications.[6–11] 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.[27, 28]

2.5 Study Selection and Data Extraction

We used DistillerSR, a systematic review software,[29] 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. Any studies that meet those criteria, or where a clear decision could not be made, 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.[30] 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 appendix). Where the data conflicted between the published paper and other sources (e.g. 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, 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 (e.g. 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.

2.6 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.[31, 32] This tool captures six main sources of bias, including: randomization 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"; or one or more categories of "high risk". Publication bias was examined using funnel plots.

2.7 Data Synthesis

We conducted a pair-wise random effects meta-analysis to estimate the pooled treatment effect using relative risks. The primary analysis was split into two comparisons, with the first between SGLT2 inhibitors and placebo, and the second SGLT2 inhibitors and any active comparator. Between-study variance was estimated using the restricted maximum likelihood method. If there were zero events reported, a default value of 0.5 was added. Statistical heterogeneity was evaluated using the I2 statistic, with significant heterogeneity defined as an I2 > 75%. 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 anti-diabetic agents that were used prior to enrollment or added as background therapy after enrollment. If patients could be therapy-naïve or have used other medications to meet enrollment criteria, then they were categorized as concurrent/prior use. Treatment-naïve was defined as patients that: have never had an anti-diabetic medication in the past, have not been on any other anti-diabetic medication in weeks leading up to enrolment, or, were able to go through a washout prior to enrolment. We also conduced sensitivity analyses to explore the impact of methodologic decisions within our analysis. First, we pooled studies that had at least one reported event. Second, we repeated our analyses using fixed-effects models. All analysis was conducted using R statistical software (version 3.4.1). Technical appendix, statistical code, and dataset available from the corresponding author.

3.0 Results

3.1 Included Studies

A total of 1865 unique titles and abstracts were screened. Of these, 568 proceeded to full text screening. A total of 129 citations met our inclusion criteria, however 30 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 99 publications were included,[3, 33–124] representing 102 randomized populations (Figure 1). Three publications[45, 52, 119] reported on multiple unique populations. Most studies included one of the four marketed SGLT2 inhibitors, dapagliflozin (31 studies), canagliflozin (20 studies), empagliflozin (25 studies) and ipragliflozin (10 studies); while 16 studies included one of five non-marketed agents. With respect to comparators, 4 conducted within-class comparisons, 85 compared to placebo, 8 compared to metformin, 9 compared to an incretin agent, 4 compared to a sulfonylurea, and 2 compared to pioglitizone. A total of 9 studies included more than one unique comparator. Section 3 of the Online Appendix outlines the characteristics of each of the included studies.

3.2 Primary Analysis

Acute Kidney Injury

Acute kidney injury was reported in 10 RCTs (8 placebo comparison, and 2 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 0.39-0.89, I^2 = 0.0%), however this is estimate is heavily weighted by one study using empagliflozin, the EMPA-REG trial (Figure 2).[125] Pooled estimate after removing the EMPA-REG trial was non-significant (RR 0.48; 95% CI 0.14-1.64; I^2 = 0.0%).

Diabetic Ketoacidosis

Diabetic ketoacidosis was reported in 21 RCTs (16 Placebo comparison, 5 active comparisons, and 1 within class comparison trial). Neither placebo (RR 0.65; 95% CI 0.28-1.50, I^2 = 0.0%) (Figure 3) nor incretin (RR 0.43; 95% CI 0.069-2.75; I^2 = 0.0%; 3 Studies) (Forest plot, online 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 0.25-2.16; I^2 = 0.0%; 7 studies) (Forest plot, online appendix Section 4).

Urinary tract infections

Urinary tract infection was the most frequently reported outcome examined (101 of 102 studies reported). When compared to placebo, SGLT2 inhibitors as a class did not demonstrate a significant increase risk (RR 1.03; 95% CI 0.96-1.10), however subgroup analysis of the individual agents did show a significantly increased risk of UTIs in users of dapagliflozin (RR 1.23; 1.03-1.46), but not empagliflozin, canagliflozin, ipragliflozin or non-marketed SGLT2 inhibitors (grouped) (Figure 4). When compared to active treatments, SGLT2 inhibitors grouped together did not demonstrate an 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 of active comparators grouped together (RR 1.42; 95% CI 1.07-1.87) (Forest plot, online appendix Section 4).

Bone Fracture

Bone fracture was reported in 58 RCTs (45 placebo comparisons, 12 active comparison, and 2 within class comparisons). SGLT2 inhibitors were not found to have an increased risk of fractures over placebo (RR 0.86; 95% CI 0.67-1.09) (Figure 6), metformin (RR 0.69; 95% CI 0.19-2.51; I^2 = 0.0%; 6 studies), sulfonylureas (RR 1.13; 95% CI 0.64-2.01; I^2 = 0.0%; 3 studies) or incretins (RR 1.14; 95% CI 0.20-6.39; I^2 = 0.0%; 3 studies). A sub-group analysis of canagliflozin compared to placebo alone, the agent identified by the FDA as having an increased risk, was also non-significant (RR 1.02; 95% CI 0.63-1.65; I^2 = 0.0%; 12 studies) (Additional forest plots, online appendix Section 4).

Lower Limb Amputation

No studies reported on the outcome of lower limb amputation.

3.2 Sub-group and Sensitivity Analyses

Several sub-group 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 large study.[125] When the analyses were re-run using a fixed-effect models, the risk estimates remained the same or had slightly smaller confidence intervals. Forest plots for the fixed effects analysis are in Section 5 of the online appendix.

3.3 Risk of bias

Generally, studies were of good methodological quality, however numerous studies were deemed high risk of selective reporting after outcome data was 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 randomization sequence (31%) or blinded outcome assessment (15%), while most sources of bias came from lack of blinding of the researchers and participants (11%) and of the outcome assessors (9%). Risk of bias assessment for individual studies are available in Section 6 of the online appendix. Funnel plots do not suggest of the presence of publication bias (see Section 7 of the Online Appendix).

4.0 Discussion

This study provides a comprehensive review of the RCT literature with respect to key safety outcomes identified through post-marketing 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 are risk neutral with respect to DKA, UTI, and bone fracture, and may have a protective effect with respect to AKI, though 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,[14] the FDA published in a safety communication in June 2016 that 101 cases of AKI were reported among users of canagliflozin and dapagliflozin.[11] SGLT2 inhibitors may provide a long-term protective effect on the kidneys via reduced trans-glomerular pressure, similar to the effects of agents that target the renin–angiotensin–aldosterone (RAAS) axis.[126] Szalat et al (2017) proposed in three possible mechanisms that might explain the potential for an increased risk of AKI with SGLT2 inhibitors as identified by the FDA, these are: 1) excessive diuresis leading to volume depletion, a particular concern for those who are hemodynamically unstable and volume-depleted; 2) a greater drop in trans-glomerular 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 (e.g. NSAIDS, radio-contract dyes).[126] This systematic review is the first meta-analysis to address this outcome and highlights a lack of reporting of AKI with only 10 of 102 randomized comparisons having published data on this outcome. Though an overall protective effect was found, this finding was driven by one large RCT that compared empagliflozin to 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 one month of initiation) and therefore this lack or reporting should not be due to the duration of clinical trials. Recent observational data also supports clinical trial data on AKI. Nadkarni et al. (2017) reported on the incidence of AKI among two cohorts comparing patients with type 2 diabetes using SGLT2 inhibitors to non-users.[127] After an average follow-up time of 14 months, adjusted hazard ratios showed SGLT2 inhibitors to be protective in one cohort (aHR 0.4 [95% CI 0.2–0.7]; P= 0.004) and favoring SGLT2 inhibitors, though not statistically significant, in the second cohort (aHR 0.6 [95% CI 0.4–1.1]; 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.

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 1,000 person-years in a 20 year

retrospective Danish cohort study, with declining incidence each year.[128] Therefore, most RCTs had insufficient sample size to detect any cases. Of the 16 RCTs that reported DKA, only 7 (representing 11,004 patients) had one or more cases. Our findings are consistent with published observational literature, which indicates no increased risk, however confidence intervals were wide. A case-control study using Truven MarketScan data (a large US claims database),[129] and a cross-sectional using the FDA Adverse Event Reporting System (FAERS) database[130] 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: 7-fold increased risk among 140,352 patients; cross-sectional: HR 2.2; 95% CI 1.4-3.6, among 416,670). In contrast, the Danish cohort study did not find an increased risk of DKA in individuals taking SGLT2 inhibitors compared to other diabetes therapies (HR 1.6; 95% CI 0.6-3.5), although the upper bound of the 95% confidence interval does not rule out significant harm.[128] 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, which is the largest to date, included 77 RCTs representing 50,820 patients and found no increased risk of UTIs in SGLT2 inhibitor users (RR 1.05; 95% CI 0.98-1.12).[16] 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 25 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 to both placebo and active controls. A reasonable biologic mechanism for an increased risk of UTIs among dapagliflozin users is unclear.

In January 2016, the FDA issued an expanded warning regarding a potential increased risk for fracture with canagliflozin.[8] A disruption in calcium-phosphate homeostasis is one potentially contributing mechanism.[18] In an RCT conducted by Bode et al. (2015), additional investigation into the change in bone mineral density in canagliflozin versus placebo users was conducted.[39] 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. To date, two meta-analyses have been published examining the risk of fracture when comparing SGLT2 inhibitors to placebo[18, 19]. Ruanpeng et al (2017) included 20 RCTs, and Tang et al (2016) 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.[20] 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).

4.1 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. Though 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 post-market. Secondly, several of the outcomes (e.g., AKI, DKA, limb amputations) we evaluated occur infrequently and, in some cases, were not reported at all. Thirdly, certain outcomes may have been inadequately characterized 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 less than 24 weeks and 63% less than one 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 adverse effects may be collected after allocation is known, or through self-assessment questionnaires.[131]

5.0 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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Author Statements:

Jennifer R. Donnan led the review and was involved at every stage, including protocol development, search strategy design, screening, data extraction, quality appraisal, analysis and manuscript preparation.

Catherine Grandy was involved in screening, data extraction, quality appraisal and manuscript revisions and final approval.

Eugene Chibrikov was involved in data cleaning and analysis, manuscript revisions and final approval.

Carlo A. Marra was involved in project conception, protocol development and manuscript revisions and final approval.

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Jenna Hache was involved in screening, data extraction, quality appraisal and manuscript revisions and final approval.

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Hai Nguyen was involved in interpretation of study results, manuscript revisions, and final approval.

John-Michael Gamble 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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Tables

Table 1. Sub-group Analysis

Group	Relative Risk (95% CI, I^2)	# of Studies	Total # of outcomes/patients
Prior use of anti-diabetics			
AKI			
Prior/Concurrent Diabetes Therapy	0.51 (0.14-1.84; 0.72%)	6	90/10,651
Treatment Naïve	0.60 (0.39-0.92; 0.00%)	2	
DKA			
Prior/Concurrent Diabetes Therapy	0.65 (0.23-1.81; 0.00%)	12	13/13,460
Treatment Naïve	0.66 (0.16-2.71; 0.00%)	4	
UTI			
Prior/Concurrent Diabetes Therapy	1.05 (0.95-1.17; 5.36%)	60	3318/37,638
Treatment Naïve	1.00 (0.91-1.10; 0.00%)	23	
Fracture			
Prior/Concurrent Diabetes Therapy	0.80 (0.55-1.15; 4.04%)	35	435/27,953
Treatment Naïve	0.79 (0.46-1.36; 6.30%)	11	
Risk of Bias			
AKI			
Low Risk of Bias	0.58 (0.38-0.89; 0.0%)	4	90/10,651
High Risk of Bias	0.71 (0.12-4.37; 25.5%)	4	
DKA			
Low Risk of Bias	0.89 (0.26-3.01; 0.0%)	8	13/13,460
High Risk of Bias	0.49 (0.003-71.59; 94.8%)	8	
UTI			
Low Risk of Bias	0.99 (0.91-1.08; 0.0%)	47	3318/37,638
High Risk of Bias	1.08 (0.11-10.64; 99.7%)	36	
Fracture			
Low Risk of Bias	0.95 (0.77-1.18; 0.0%)	21	435/27,953
High Risk of Bias	0.56 (0.03-9.50; 97.0%)	25	
Definition of UT			
UTI			
Predefined list of terms	0.99 (0.91-1.07; 0.0%)	19	3318/37,638
Suggestive of UTI	1.13 (0.87-1.47; 0.0%)	11	
Positive culture	0.91 (0.51-1.62; 24.27%)	2	
As per investigator	0.82 (0.41-1.61; 0.0%)	2	
Not defined	1.12 (0.94-1.34; 1.61%)	49	

List of Figures

All figures supplied as separate documents.

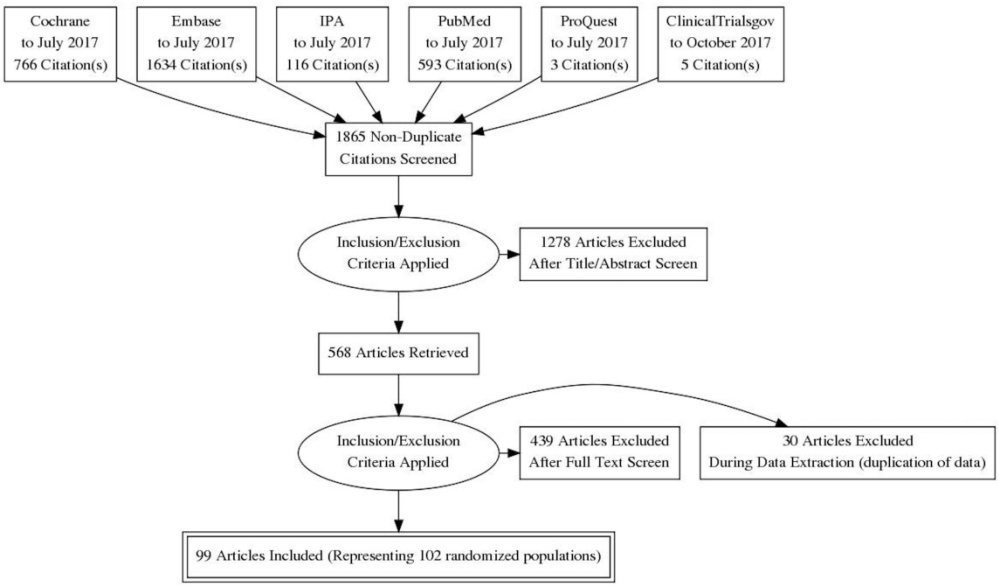

Figure 1. Flow Diagram of Included Studies

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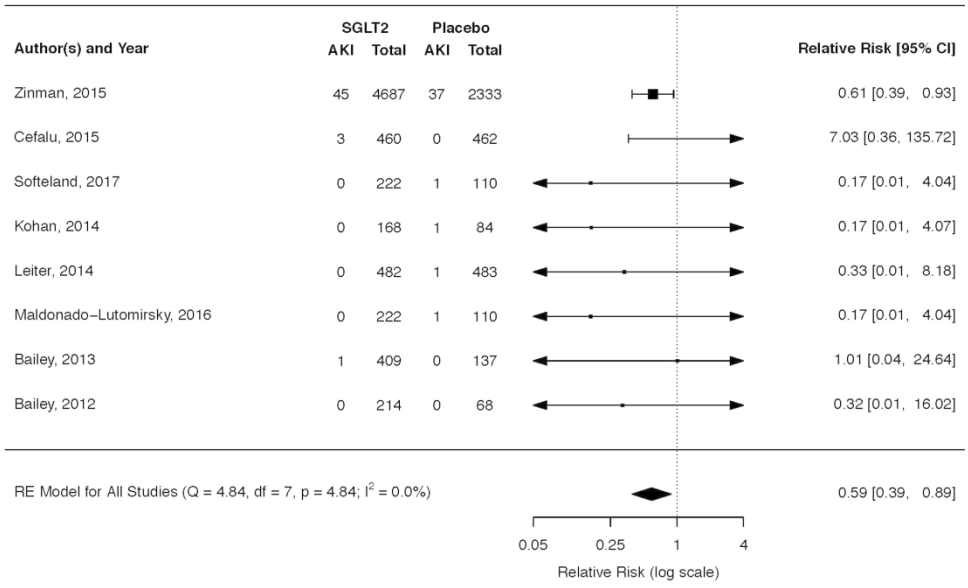

Figure 2. Risk of acute kidney injury with SGLT2 inhibitors compared to placebo

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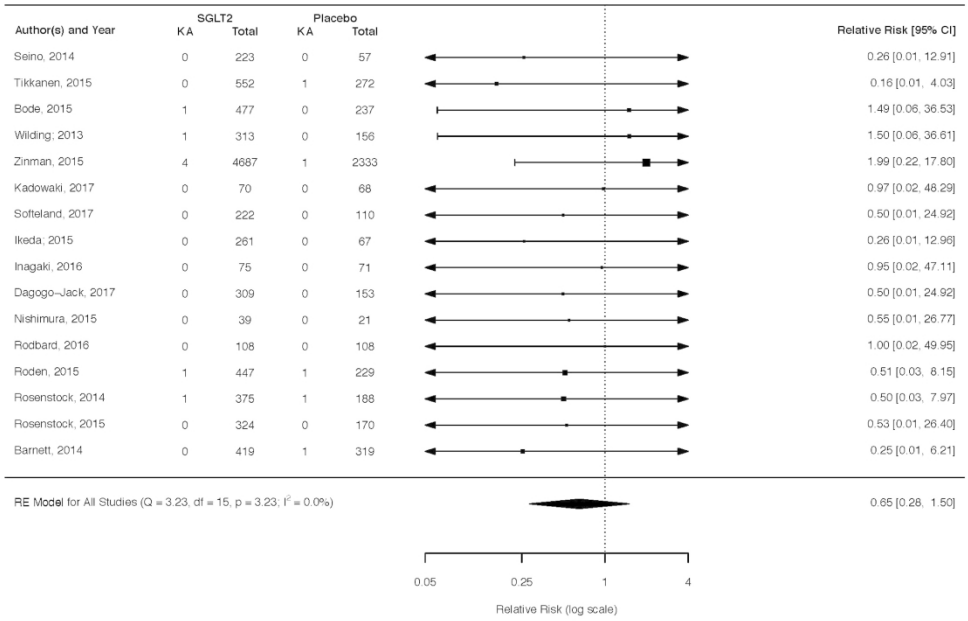

Figure 3. Risk of diabetic ketoacidosis from SGLT2 inhibitors compared to placebo

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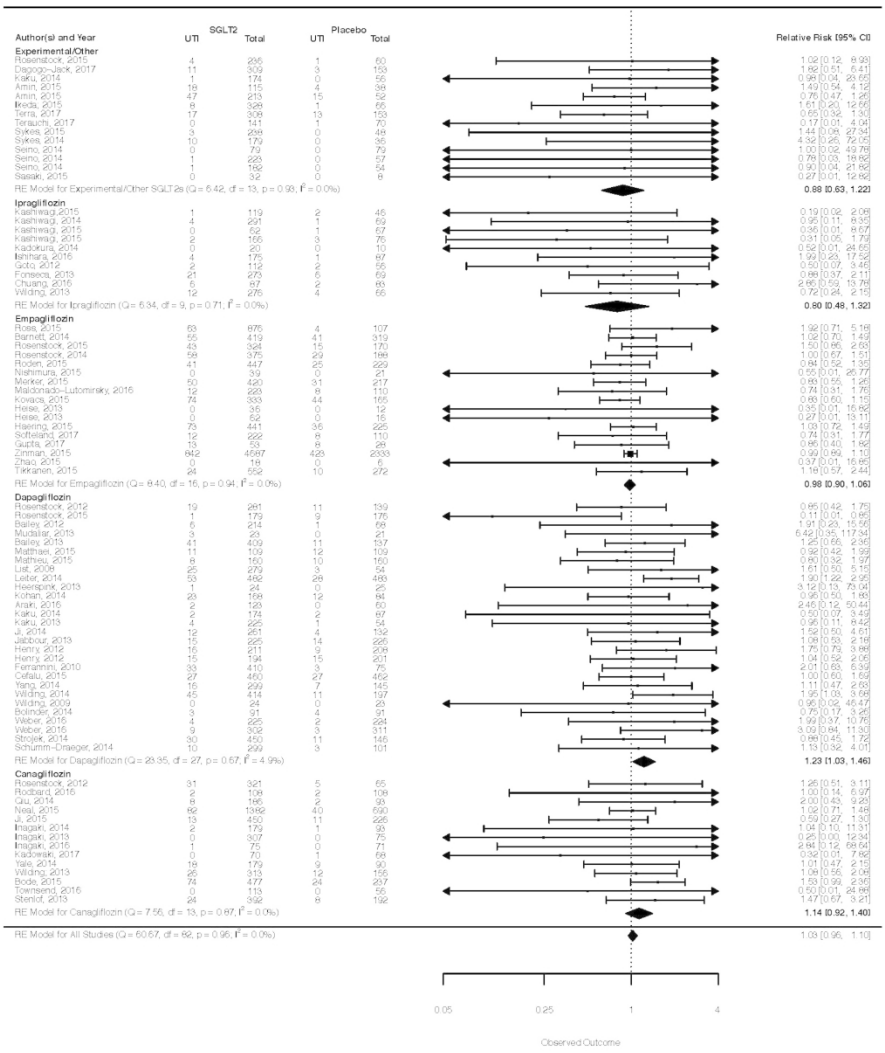


Figure 4. Risk of urinary tract infection with SGLT2 inhibitors compared to placebo

215x279mm (300 x 300 DPI)

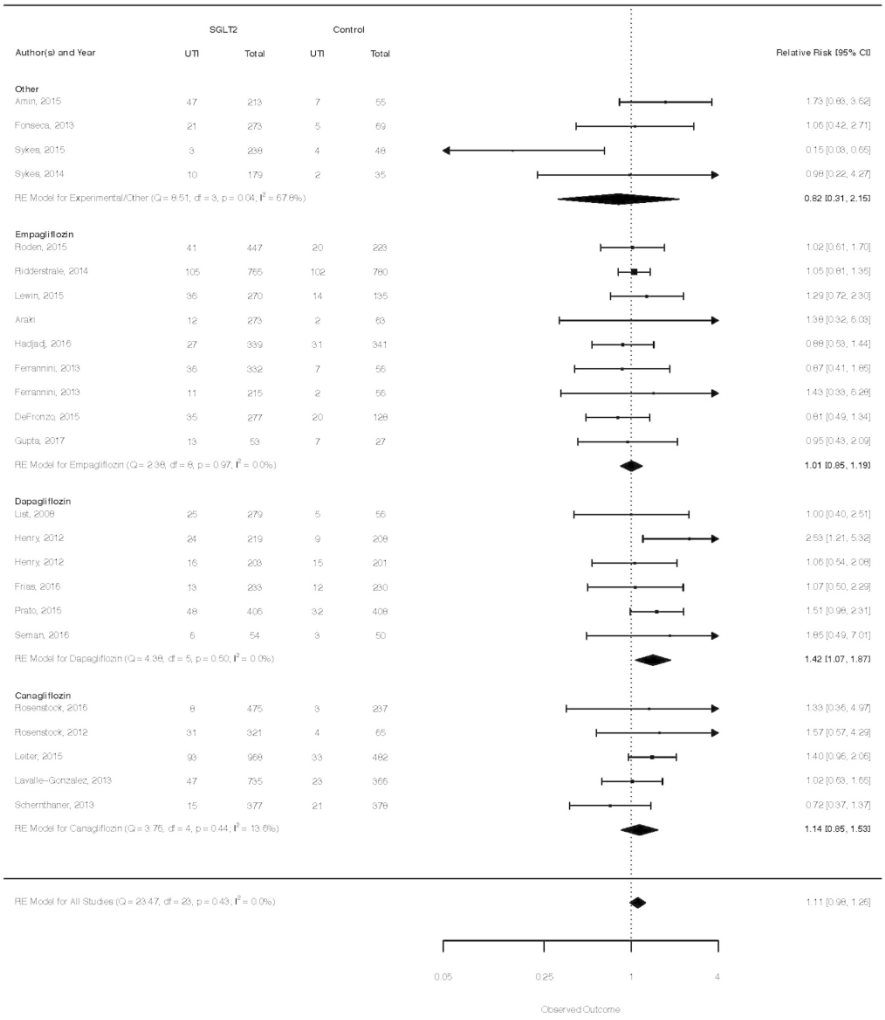


Figure 5. Risk of urinary tract infection with SGLT2 inhibitors compared to active comparators

215x279mm (300 x 300 DPI)

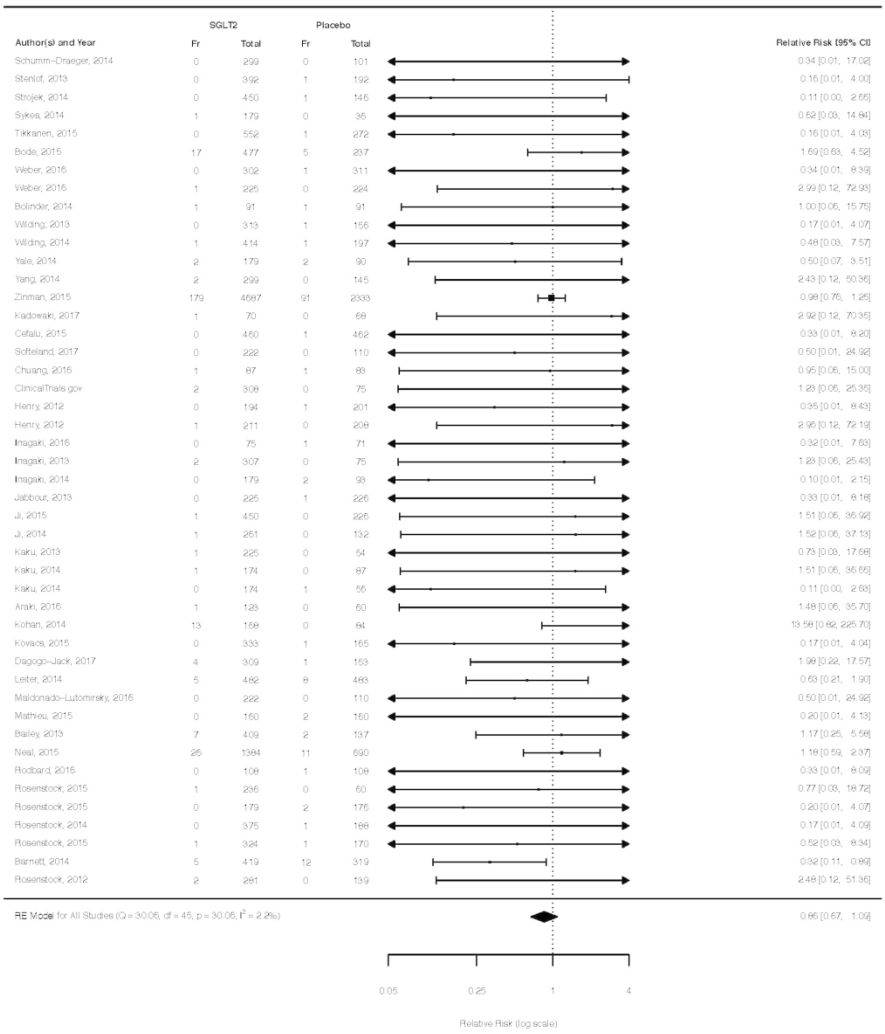


Figure 6. Risk of fracture with SGLT2 inhibitors compared to placebo

215x279mm (300 x 300 DPI)

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

Online Appendix

Section 1: Search Strategies

Table 1A. Pubmed Search Strategy

		Search String	Results
1	Population	"Diabetes Mellitus, Type 2"[Mesh] OR NIDDM[tw] OR t2dm[tw] OR ((“type 2"[tw] OR "type ii"[tw] OR "adult onset"[tw] OR “mature onset”[tw] OR “late onset”[tw] OR “noninsulin-dependent”[tw] OR “non insulin dependent”[tw]) AND diabetes[tw])	156898
2	Intervention: SGLT2s	"Sodium-Glucose Transport Proteins/antagonists and inhibitors"[Mesh] OR "Sodium-Glucose Transporter 2"[Mesh] OR "sodium-glucose co-transporter 2"[tw] OR SGL2[tw] OR SGLT2[tw] OR gliflozin*[tw] OR "Canagliflozin"[Mesh] OR canagliflozin*[tw] OR invokana[tw] OR sulisent[tw] OR "TA 7284"[tw] OR TA7284[tw] OR "JNJ 28431754"[tw] OR JNJ28431754[tw] OR "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol"[Supplementary Concept] OR dapagliflozin*[tw] OR farxiga[tw] OR forxiga[tw] OR “BMS 512148”[tw] OR BMS512148[tw] OR "empagliflozin"[Supplementary Concept] OR empagliflozin*[tw] OR jardiance[tw] OR "BI 10773"[tw] OR BI10773[tw] OR ipragliflozin[Supplementary Concept] OR ipragliflozin*[tw] OR suglat[tw] OR "ASP 1941"[tw] OR ASP1941[tw] OR "1,5-anhydro-1-(5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl)-1-thioglucitol"[Supplementary Concept] OR luseogliflozin*[tw] OR lusefi[tw] OR “TS 071”[tw] OR TS071[tw] OR "remogliflozin etabonate"[Supplementary Concept] OR remogliflozin*[tw] OR "KGT 1681"[tw] OR KGT1681[tw] OR "(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR sotagliflozin*[tw] OR "LX 4221"[tw] OR LX4221[tw] OR "6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [Supplementary Concept] OR tofogliflozin*[tw] OR apleway[tw] OR deberza[tw] OR "CSG 452"[tw] OR CSG452[tw] OR "5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-hydroxymethyl-6,8-dioxabicyclo(3.2.1)octane-2,3,4-triol" [Supplementary Concept] OR ertugliflozin*[tw] OR "PF 04971729"[tw] OR PF04971729[tw]	2323
3	#1 AND #2		1649
4	Study Type Filter: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in	("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[Mesh:NoExp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])	1017106

	MEDLINE: sensitivity- and precision-maximizing version (2008 revision). Available at http://handbook.cochrane.org/chapter_6/box_6_4_b_cochrane_hsss_2008_sensprec_pubmed.htm		
5	#3 AND #4		593

Table 2A: Cochrane Library Search Strategy

#1	([mh "Diabetes Mellitus, Type 2"] or NIDDM or t2dm or (("type 2" or "type ii" or "adult onset" or "mature onset" or "late onset" or "noninsulin-dependent" or "non insulin dependent") and (diabetes)))	23,213
#2	([mh "Sodium-Glucose Transport Proteins"/ai] or [mh "Sodium-Glucose Transporter 2"] or "sodium-glucose co-transporter 2" or SGL2 or SGLT2 or gliflozin* or [mh canigliflozin] or canagliflozin* or invokana or sulisent or "TA 7284" or TA7284 or "JNJ 28431754" or JNJ28431754 or dapagliflozin* or farxiga or forxiga or "BMS 512148" or BMS512148 or empagliflozin* or jardiance or "BI 10773" or BI10773 or ipragliflozin or suglat or "ASP 1941" or ASP1941 or luseogliflozin* or lusefi or "TS 071" or TS071 or remogliflozin* or "KGT 1681" or KGT1681 or sotagliflozin* or "LX 4221" or LX4221 or tofogliflozin* or apleway or deberza or "CSG 452" or CSG452 or ertugliflozin* or "PF 04971729" or PF04971729)	852
#3	#1 AND #2	766

Table 3A: Embase Search Strategy

No.	Query	Results
#5	#3 AND #4	1,634
#4 - EMBASE RCT filter from	random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	1,440,006

Wong 2006, best balance of sensitivity and specificity		
#3	#1 AND #2	3,811
#2	'sodium glucose cotransporter 2'/de OR 'sodium glucose cotransporter 2 inhibitor'/exp OR 'sodium-glucose co-transporter 2':ab,ti OR sgl2:ab,ti OR sglt2:ab,ti OR gliflozin*:ab,ti OR canagliflozin*:ab,ti OR invokana:ab,ti OR sulisent:ab,ti OR 'ta 7284':ab,ti OR ta7284:ab,ti OR 'jnj 28431754':ab,ti OR jnj28431754:ab,ti OR dapagliflozin*:ab,ti OR farxiga:ab,ti OR forxiga:ab,ti OR 'bms 512148':ab,ti OR bms512148:ab,ti OR empagliflozin*:ab,ti OR jardiance:ab,ti OR 'bi 10773':ab,ti OR bi10773:ab,ti OR ipragliflozin*:ab,ti OR suglat:ab,ti OR 'asp 1941':ab,ti OR asp1941:ab,ti OR luseogliflozin*:ab,ti OR lusefi:ab,ti OR 'ts 071':ab,ti OR ts071:ab,ti OR remogliflozin*:ab,ti OR 'kgt 1681':ab,ti OR kgt1681:ab,ti OR sotagliflozin*:ab,ti or 'LX 4221':ab,ti or LX4221:ab,ti or tofogliflozin*:ab,ti or apleway:ab,ti or deberza:ab,ti or 'CSG 452':ab,ti or CSG452:ab,ti or ertugliflozin*:ab,ti or 'PF 04971729':ab,ti or PF04971729:ab,ti	5,218
#1	'non insulin dependent diabetes mellitus'/de OR niddm:ab,ti OR t2dm:ab,ti OR ('type 2':ab,ti OR 'type ii':ab,ti OR 'adult onset':ab,ti OR 'mature onset':ab,ti OR 'late onset':ab,ti OR 'noninsulin dependent':ab,ti OR 'non insulin dependent':ab,ti AND diabetes:ab,ti)	239,937

Table 4A: IPA Search Strategy

S1	TX NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR "late onset" OR "noninsulin dependent" OR "non insulin dependent") AND (diabetes))	Search modes - Boolean/Phrase	5,907
S2	TX "sodium-glucose co-transporter 2" OR sgl2 OR sglt2 OR gliflozin OR canagliflozin OR invokana OR sulisent OR "ta 7284" OR ta7284 OR "jnj 28431754" OR jnj28431754 OR dapagliflozin* OR farxiga OR forxiga OR "bms 512148" OR bms512148 OR empagliflozin* OR jardiance OR "bi 10773" OR bi10773 OR ipragliflozin* OR suglat OR "asp 1941" OR asp1941 OR luseogliflozin* OR lusefi OR "ts 071" OR ts071 OR remogliflozin* OR "kgt 1681" OR kgt1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR tofogliflozin* OR apleway OR deberza OR "CSG452"	Search modes - Boolean/Phrase	282

	OR CSG452 OR ertugliflozin* OR "PF 04971729" OR PF04971729		
S3	S1 AND S2	Search modes - Boolean/Phrase	225
S4	TI randomized OR AB randomized OR TI randomised OR AB randomised OR TI placebo OR AB placebo OR TI randomly OR AB randomly OR TI trial	Search modes - Boolean/Phrase	58,055
S5	S3 AND S4	Search modes - Boolean/Phrase	116

Table 5A: ProQuest Search Strategy

all(NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR "late onset" OR "noninsulin-dependent" OR "non insulin dependent") AND (diabetes))) AND all("sodium-glucose co-transporter 2" OR SGL2 OR SGLT2 OR gliflozin* OR canagliflozin* OR invokana OR sulisent OR "TA 7284" OR TA7284 OR "JNJ 28431754" OR JNJ28431754 OR dapagliflozin* OR farxiga OR forxiga OR "BMS 512148" OR BMS512148 OR empagliflozin* OR jardiance OR "BI 10773" OR BI10773 OR ipragliflozin OR suglat OR "ASP 1941" OR ASP1941 OR luseogliflozin* OR lusefi OR "TS 071" OR TS071 OR remogliflozin* OR "KGT 1681" OR KGT1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR tofogliflozin* OR apleway OR deberza OR "CSG 452" OR CSG452 OR ertugliflozin* OR "PF 04971729" OR PF04971729)	3

Section 2: List of Extracted Variables

Table 6A. List of Extracted Variables

Variable Extraction	Notes
NCT Number, Author and Year	
Country in which the study was conducted	International if applicable
Start and End years	
Observation Period (# of weeks)	
Total number of participants randomized	
Number of Males	
Number of Females	
Background diabetes therapy	
Intervention 1: SGLT2 Agent	This was captured for as many interventions that were used.
Intervention 1: Dose	
Intervention 1: Number of Persons	
Intervention 1: Mean Age	
Intervention 1: Age SD	
Intervention 1: Mean baseline HbA1C	
Intervention 1: A1C SD	
Comparison 1: SGLT2 Agent	This was captured for as many comparison groups that were used.
Comparison 1: Dose	
Comparison 1: Number of Persons	
Comparison 1: Mean Age	
Comparison 1: Age SD	
Comparison 1: Mean baseline HbA1C	
Comparison 1: A1C SD	
Acute Kidney Injury Reported (yes/no)	
Urinary Tract Infection Reported (yes/no)	
Definition of UTI	
Ketoacidosis Reported (yes/no)	
Bone Fracture Reported (yes/no)	
Amputation Reported (yes/no)	
AKI: Outcomes in Intervention 1(n/N)	This was captured for each individual intervention and control group
AKI: Outcomes in Comparison 1 (n/N)	
UTI: Outcomes in Intervention 1(n/N)	
UTI: Outcomes in Comparison 1 (n/N)	
DKA: Outcomes in Intervention 1(n/N)	
DKA: Outcomes in Comparison 1 (n/N)	
BF: Outcomes in Intervention 1(n/N)	

BF: Outcomes in Comparison 1 (n/N)	
Amp: Outcomes in Intervention 1(n/N)	
Amp: Outcomes in Comparison 1 (n/N)	

Section 3: Study Characteristics

Table 7A: Included Study Characteristics

NCT# Author and Year	Country	Study Duration (weeks)	Total Randomized	Background Therapies	Intervention(s)	Comparator(s)	Outcomes Reported
NCT01059825 Amin, 2015	International	12	328	Prior therapy stabilized to metformin	Ertugliflozin 1mg, 5 mg, 10mg , 25mg	Placebo, Sitagliptin 100mg	UTI
NCT01059825 Amin, 2015	International	4	194	Uncontrolled on 2 agents	Ertugliflozin 1mg, 5mg, 25mg	Placebo	UTI
NCT02157298 Araki, 2016	Japan	16	182	Prior insulin therapy DPP4 allowed	Dapagliflozin 5 mg	Placebo	UTI, BF
NCT01368081 Araki	Japan	52	1160	Prior SU	Empagliflozin 10mg, 25mg	Metformin 50-2250mg/day	UTI, BF
NCT00528879 Bailey, 2013	International	102	546	Prior metformin	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI, AKI, BF
None Bailey, 2012	International	24	282	Treatment Naive	Dapagliflozin 1mg, 2.5mg, 5mg	Placebo	UTI, AKI, BF
NCT01164501 Barnett, 2014	International	52	741	Any prior therapies	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF
NCT01106651 Bode, 2015	International	104	716	Prior Naive mono or combo therapy	Canagliflozin 100mg, 300mg	Placebo	UTI, DKA, BF
NCT00855166 Bolinder, 2014	European	102	182	Prior metformin	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01031680 Cefalu, 2015	International	52	922	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, AKI, BF
NCT01505426 Chuang, 2016	Korea and Taiwan	24	171	Prior metformin	Ipragliflozin 50mg	Placebo	UTI, BF
NCT01422876 DeFronzo, 2015	International	52	686	Prior metformin	Empagliflozin 10mg, 25mg	Linagliptin 5mg	UTI
NCT00660907 Prato, 2015	International	208	816	Prior metformin	Dapagliflozin (mixed dose)	Glipizide (mixed doses)	UTI, BF

NCT00881530 Ferrannini, 2013	International	78	271	Treatment Naive	Empagliflozin 10mg, 25mg	Metformin 2000mg max	UTI, BF
NCT00881530 Ferrannini, 2013	International	78	388	Prior metformin	Empagliflozin 10mg, 25mg	Sitagliptin 100mg	UTI, BF
NCT00528372 Ferrannini, 2010	International	24	485	Treatment Naive	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI
NCT01071850 Fonseca, 2013	India, Philippines, Columbia, Mexico, USA	12-	412	Treatment Naive	Ipragliflozin 12.5mg, 50mg, 150mg, 300mg	Placebo, Metormin 1500mg	UTI
NCT02229396 Frias, 2016	International	28	695	Prior metformin	Dapagliflozin 10mg	Exenatide 2mg	UTI, AKI, DKA
NCT01719003 Hadjadj, 2016	International	24	1364	Treatment Naive	Empagliflozin 10mg, 25mg	Metformin 1000mg, 2000mg	UTI, DKA, BF
NCT01289990 Haering, 2015	International	76	666	Prior Metformin and SU	Empagliflozin 10mg, 25mg	Placebo	UTI
None Heise, 2013	Germany	4	78	Not described	Empagliflozin 10mg, 25mg, 100mg	Placebo	UTI
None Heise, 2013	Germany	9 days	48	Prior Naive mono or combo therapy	Empagliflozin 2.5mg, 10mg, 25mg, 100mg	Placebo	UTI
NCT00643851 Henry, 2012	International	24	603	Treatment Naive	Dapagliflozin 5mg	Placebo	UTI, BF
NCT00643851 Henry, 2012	International	24	603	Treatment Naive	Dapagliflozin 5mg	Metformin (mixed doses)	UTI, BF
NCT00859898 Henry, 2012	International	24	641	Treatment Naive	Dapagliflozin 10mg	Placebo	UTI, BF
NCT00859898 Henry, 2012	International	24	641	Treatment Naive	Dapagliflozin 10mg	Metformin (mixed doses)	UTI, BF
NCT00800176 Ikeda; 2015	International	12	398	Naive or metformin	Tofogliflozin 2.5mg, 5mg, 10mg, 20mg, 40mg	Placebo	UTI, DKA
NCT02220920 Inagaki, 2016	Japan	16	146	Prior insulin therapy	Canagliflozin 100mg	Placebo	UTI, DKA, BF
NCT01387737 Inagaki, 2015	Japan	52	1299	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	No comparator	UTI, DKA, BF

NCT01022112 Inagaki, 2013	Japan	12	383	Any prior therapies washed-out	Canagliflozin 50mg, 100mg, 200mg, 300mg	Placebo	UTI, BF
NCT01413204 Inagaki, 2014	Japan	24	272	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	Placebo	UTI, BF
NCT02175784 Ishihara, 2016	Japan	16	262	Prior insulin others allowed	Ipragliflozin 50mg	Placebo	UTI
NCT00984867 Jabbour, 2013	International	48	451	Prior DPP4 maybe metformin no others	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01381900 Ji, 2015	International	18	678	Prior Metformin and maybe SU	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01095653 Ji, 2014	Asia	24	393	Treatment Naive	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
NCT01023945 Kadokura, 2014	Japan	2	30	Treatment Naive or monotherapy	Ipragliflozin 50mg , 100mg	Placebo	UTI
NCT01193218 Kadowaki, 2015	Japan	52	547	Treatment Naive or monotherapy	Empagliflozin 10mg, 25mg	No comparator	UTI, BF
NCT00972244 Kaku, 2013	Japan	12	279	Treatment Naive or 1 or 2 agents at low dose	Dapagliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo	UTI, BF
None Kaku, 2014	Japan	24	261	Treatment Naive or monotherapy	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Kaku, 2014	Japan	24	235	Treatment Naive or washout	Tofogliflozin 10mg, 20mg, 40mg	Placebo	UTI, BF
NCT01242215 Kashiwagi, 2015	Japan	52	245	Prior SU	Ipragliflozin 50mg	Placebo	UTI
NCT01057628 Kashiwagi, 2015	Japan	26	131	Treatment Naive or 1 or 2 agents at low dose	Ipragliflozin 50mg	Placebo	UTI
NCT00621868 Kashiwagi, 2014	Japan	12	361	Treatment Naive or washout	Ipragliflozin 12.5mg, 25mg, 50mg, 100mg	Placebo	UTI
NCT01316094 Kashiwagi,2015	Japan	52	165	Treatment Naive or 1 or 2 agents at low dose	Ipragliflozin 50mg	Placebo	UTI

NCT00663260 Kohan, 2014	International	104	252	Not described	Dapagliflozin 5mg, 10mg	Placebo	UTI, AKI, BF
NCT01210001 Kovacs, 2015	International	76	499	Prior pioglitizone and maybe metformin	Empagliflozin 10mg, 25mg	Placebo	UTI, BF
NCT00976495 Heerspink, 2013	International	12	75	Prior Metformin and maybe SU	Dapagliflozin 10mg	Placebo	UTI
NCT01106677 Lavalle-Gonzalez, 2013	International	52	1284	Prior Metformin and maybe SU but washed-out	Canagliflozin 100mg, 300mg	Sitagliptin 100mg	UTI, DKA, BF
NCT01042977 Leiter, 2014	International	52	964	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, AKI, BF
NCT00968812 Leiter, 2015	International	104	1450	Prior metformin	Canagliflozin 100mg, 300mg	Glimepiride 8mg	UTI, BF
NCT01422876 Lewin, 2015	International	52	677	Treatment Naive	Empagliflozin 10mg, 25mg	Linagliptin 5mg	UTI
NCT00263276 List, 2008	International	12	389	Treatment Naive	Dapagliflozin 2.5mg, 5mg, 10mg, 20mg, 50mg	Placebo, Metformin 1500mg max	UTI
NCT01646320 Mathieu, 2015	International	52	320	Prior metformin and DPP4	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01392677 Matthaei, 2015	International	52	219	Prior Metformin and SU	Dapagliflozin 10mg	Placebo	UTI
None Mudaliar, 2013	International	12	44	Prior Metformin and maybe SU	Dapagliflozin 5mg	Placebo	UTI
NCT01947855 Nishimura, 2015	Japan	4	60	Treatment or monotherapy	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA
NCT01340664 Qiu, 2014	International	18	279	Prior metformin	Canagliflozin 100mg, 300mg	Placebo	UTI
NCT01989754 Rodbard, 2016	International	26	218	Prior metformin and DPP4	Canagliflozin 300mg	Placebo	UTI, DKA, BF
NCT01289990 Roden, 2015	International	76	899	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg	UTI, DKA
NCT00642278 Rosenstock, 2012	International	12	451	Prior metformin	Canagliflozin 50mg, 100mg, 200mg, 300mg, 600mg	Placebo, Sitagliptin 100mg	UTI
NCT01376557	United States	12	299	Prior metformin	Sotagliflozin	placebo	UTI, BF

Rosenstock, 2015					75 mg, 200mg, 400mg		
NCT01809327 Rosenstock, 2016	International	26	1186	Treatment Naive	Canagliflozin 100mg, 300mg	Metformin 500mg	UTI, DKA
NCT01606007 Rosenstock, 2015	International	24	534	Prior metformin	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01306214 Rosenstock, 2014	International	52	563	Prior insulin therapy	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF
NCT01011868 Rosenstock, 2015	International	78	494	Prior insulin maybe metformin and SU	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA
NCT00683878 Rosenstock, 2012	International	48	420	Treatment Naive or stabilized on pioglitizine	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Ross, 2015	International	16	983	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI
None Sasaki, 2015	Japan	7 days	40	Treatment Naive	Luseogliflozin 0.5mg, 1mg, 2.5mg, 5mg	Placebo	UTI
NCT01137812 Schernthaner, 2013	International	52	756	Prior Metformin and SU	Canagliflozin 300mg	Sitagliptin 100mg	UTI, BF
NCT01217892 Schumm-Draeger, 2014	International	16	400	Prior metformin	Dapagliflozin 5mg, 10mg, 20mg	Placebo	UTI, BF
None Seino, 2014	Japan	12	239	Treatment Naive	Luseogliflozin 0.5mg, 2.5mg, 5mg	Placebo	UTI
None Seino, 2014	Japan	12	282	Treatment Naive	Luseogliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo	UTI, DKA
None Seino, 2014	Japan	24	158	Treatment Naive	Luseogliflozin 2.5mg	Placebo	UTI
NCT01081834 Stenlof, 2013	International	26	587	Treatment Naive or washout	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT00680745 Strojek, 2014	International	48	597	Prior SU	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI, BF
NCT00500331 Sykes, 2015	international	12	336	Treatment Naive	Remogliflozin 100mg, 200mg, 500mg, 1000mg, 2000mg	Placebo, Pioglitazone 30mg	UTI
NCT01370005 Tikkanen, 2015	International	12	825	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF

None Townsend, 2016	United States	6	171	Uncontrolled on 1-3 agents	Canagliflozin 100mg, 300mg	Placebo	UTI
None Seman, 2016	Malaysia	12	110	Prior Metformin and SU	Dapagliflozin 10mg	Sulphonylureas (various agents)	UTI
NCT01137474 Weber, 2016	International	12	944	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01195662 Weber, 2016	International	12	449	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01106625 Wilding; 2013	International	52	469	Prior Metformin and SU	Canagliflozin 100mg, 300mg	Placebo	UTI, DKA, BF
NCT01117584 Wilding, 2013	International	12	343	Prior metformin	Ipragliflozin 12.5mg, 50mg, 150mg, 300mg	Placebo	UTI
NCT00357370 Wilding, 2009	International	12	71	Any prior therapies	Dapagliflozin 10mg, 20mg	Placebo	UTI
NCT00673231 Wilding, 2014	international	104	808	Prior insulin others allowed	Dapagliflozin 2.5mg, 5/10mg, 10mg	Placebo	UTI, BF
NCT01064414 Yale, 2014	International	52	269	Treatment Naive or 1 or 2	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01316341 Zhao, 2015	China	9 days	24	Treatment Naive or 1 or 2	Empagliflozin 10mg, 25mg	Placebo	UTI
NCT01131676 Zinman, 2015	International	206	7028	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, DKA, BF
None Goto, 2012		24	168	Prior metformin	Ipragliflozin 50mg	Placebo	UTI
NCT02036515 Dagogo-Jack, 2017	International	26	463	Prior metformin and DPP4	Ertugliflozin 5mg, 15mg	Placebo	UTI, DKA, BF
NCT01734785 Maldonado-Lutomirsky, 2016	International	24	606	Prior metformin and DPP4	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, BF
NCT01289990 Merker, 2015	International	52	637	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI
NCT01032629 Neal, 2015	International	52	2074	Prior insulin therapy	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01167881 Ridderstrale, 2014	International	104	1549	Prior metformin	Empagliflozin 25mg	Glimepiride 1-4mg	UTI, AKI, BF

NCT00495469 Sykes, 2014	UK	12	252	Treatment Naive	Remogliflozin 100mg, 250mg, 500mg, 1000mg	Placebo, Pioglitazone 30mg	UTI, BF
None Tanizawa, 2014	Japan	52	194	Treatment Naive	Tofogliflozin 20mg, 40mg	No comparator	UTI
None Tanizawa, 2014	Japan	52	602	Any prior therapies	Tofogliflozin 20mg, 40mg	No comparator	UTI
NCT01095666 Yang, 2014		24	444	Prior metformin	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Gupta, 2017		76	108	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg	UTI
NCT02354235 Kadowaki, 2017	Japan	24	138	Prior Teneligliptin	Canagliflozin 100mg	Placebo	UTI, DKA, BF
NCT01734785 Softeland, 2017	International	24	333	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, DKA, BF
NCT01958671 Terra, 2017	International	26	461	Treatment Naive	Ertugliflozin 5mg, 15mg	Placebo	UTI
NCT 01022112 Not Published		12	383	Treatment Naive	Canagliflozin 50mg, 100mg, 200mg, 300mg	Placebo	BF
NCT02201004 Terauchi, 2017		16	211	Prior insulin therapy DPP4 allowed	Tofogliflozin 20mg, 40mg	Placebo	UTI

Section 4: Additional Forest Plots

Figure 1A: Risk of Acute Kidney Injury with SGLT2 Inhibitors compare to Incretins

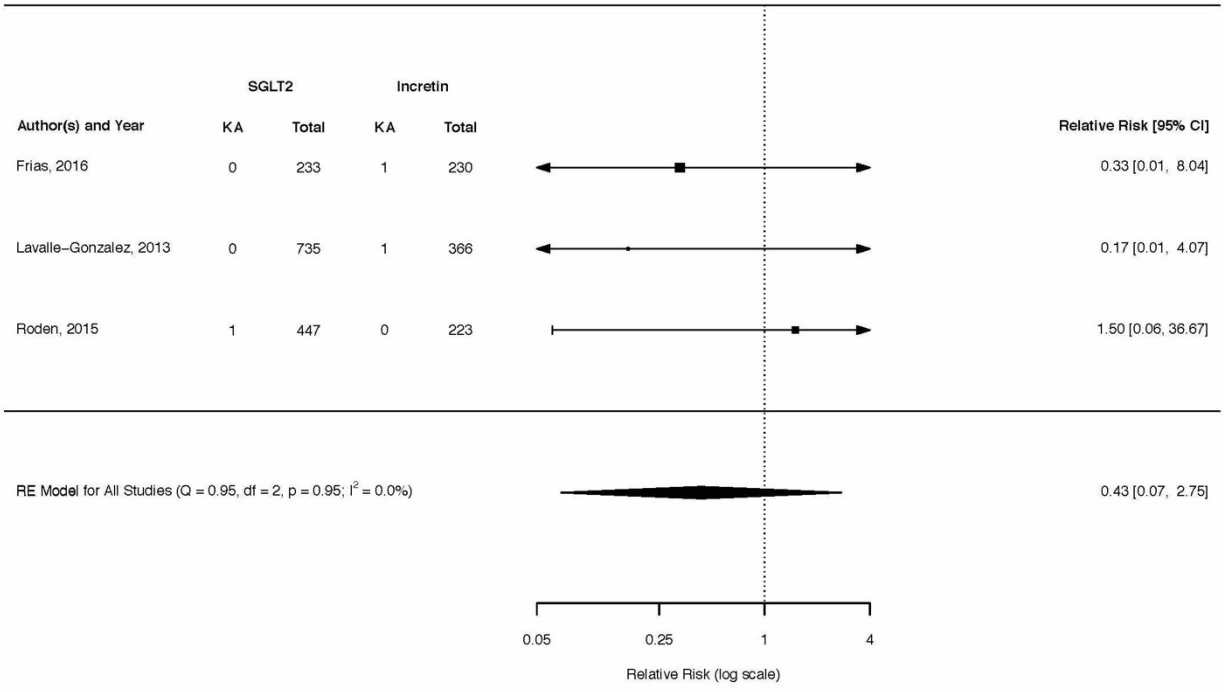


Figure 2A: Risk of Acute Kidney Injury with SGLT2 Inhibitors Compared to Placebo; including studies with at least one outcome.

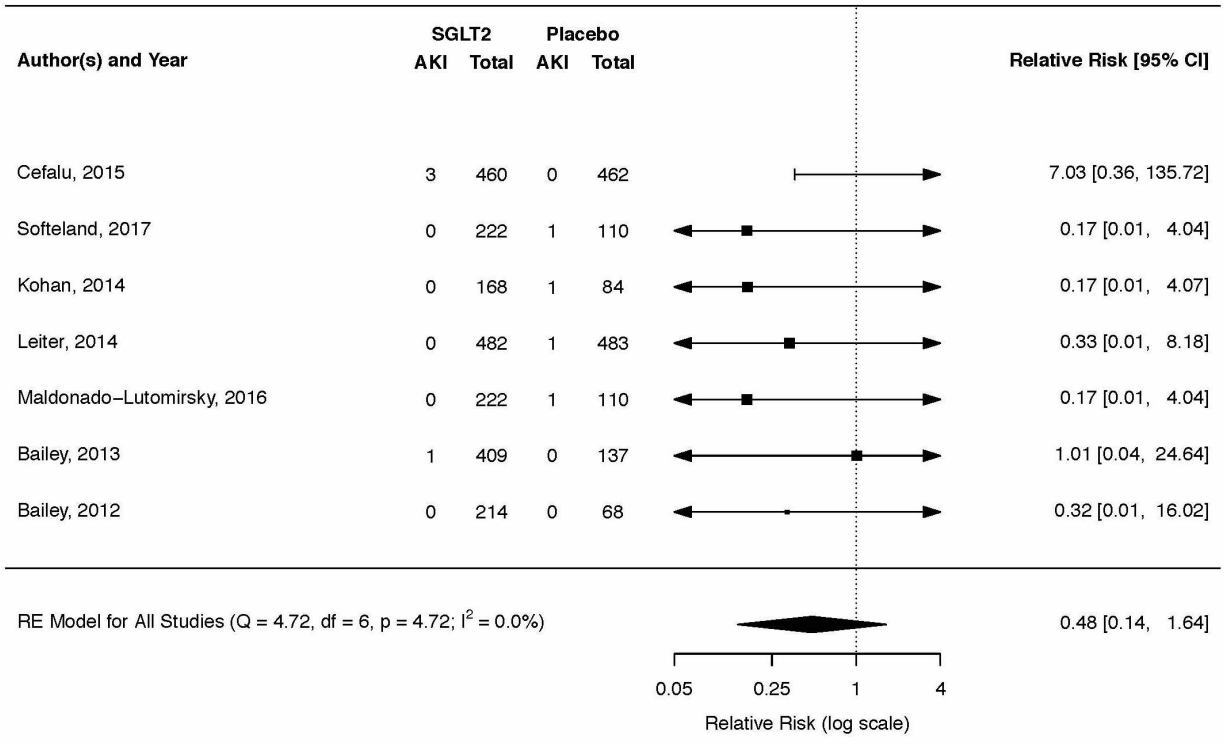


Figure 3A. Risk of Urinary Tract Infections among users of SGLT2 Inhibitors Compared to Active Controls

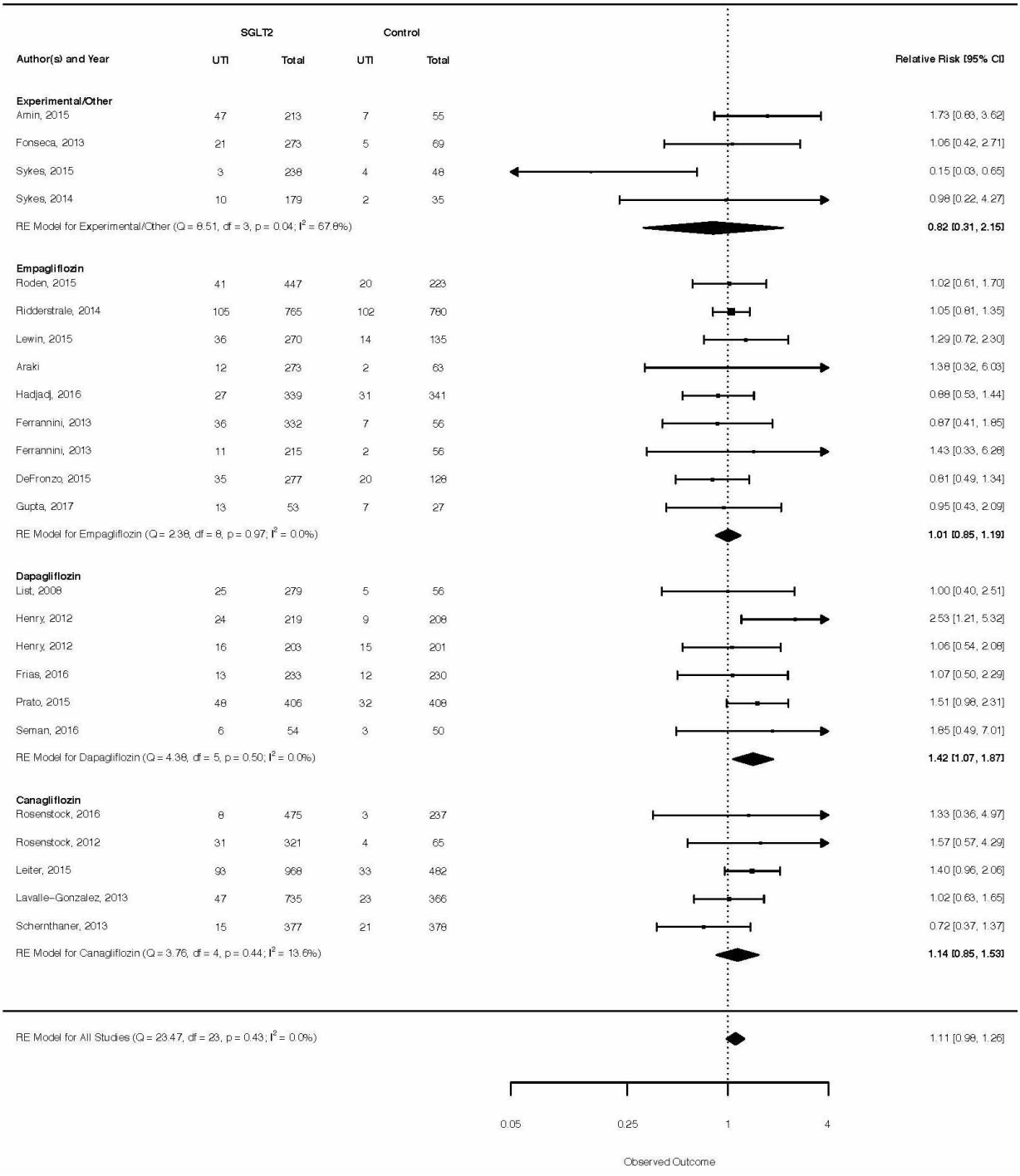


Figure 4A: Risk of Fracture with SGLT2 Inhibitors compared to Metformin

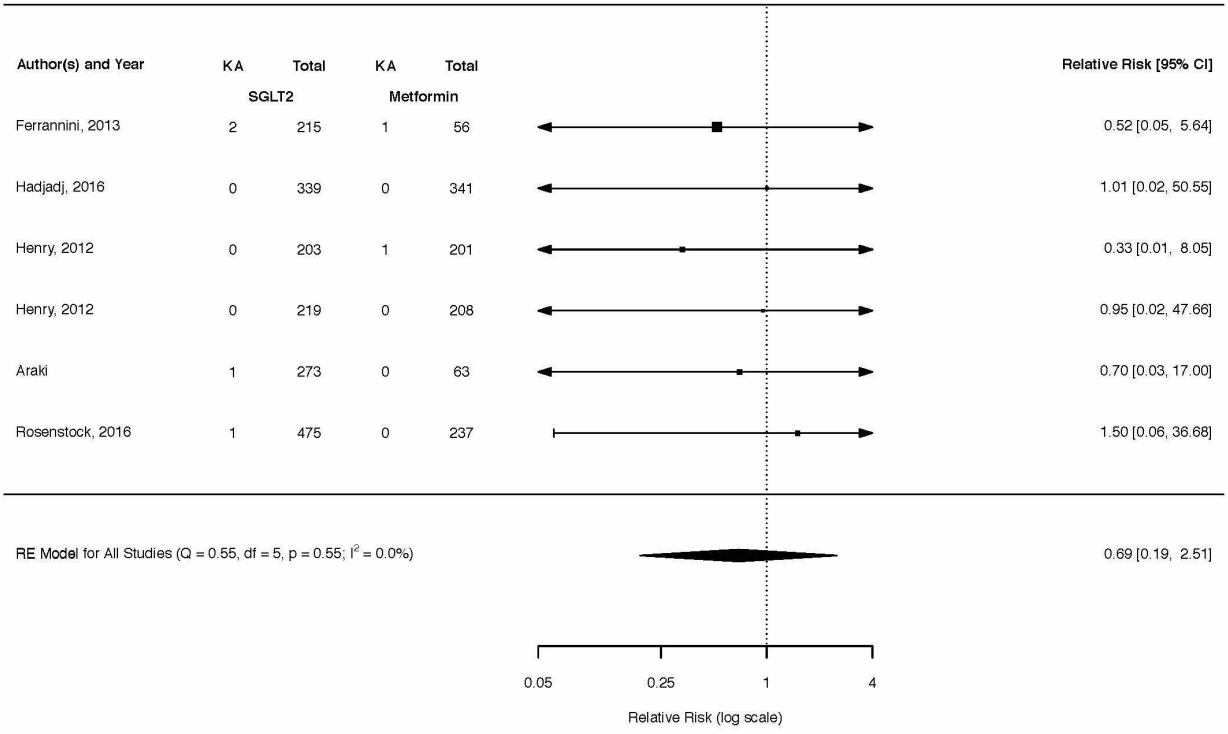


Figure 5A: Risk of Fracture with SGLT2 Inhibitors compared to Sulfonylureas

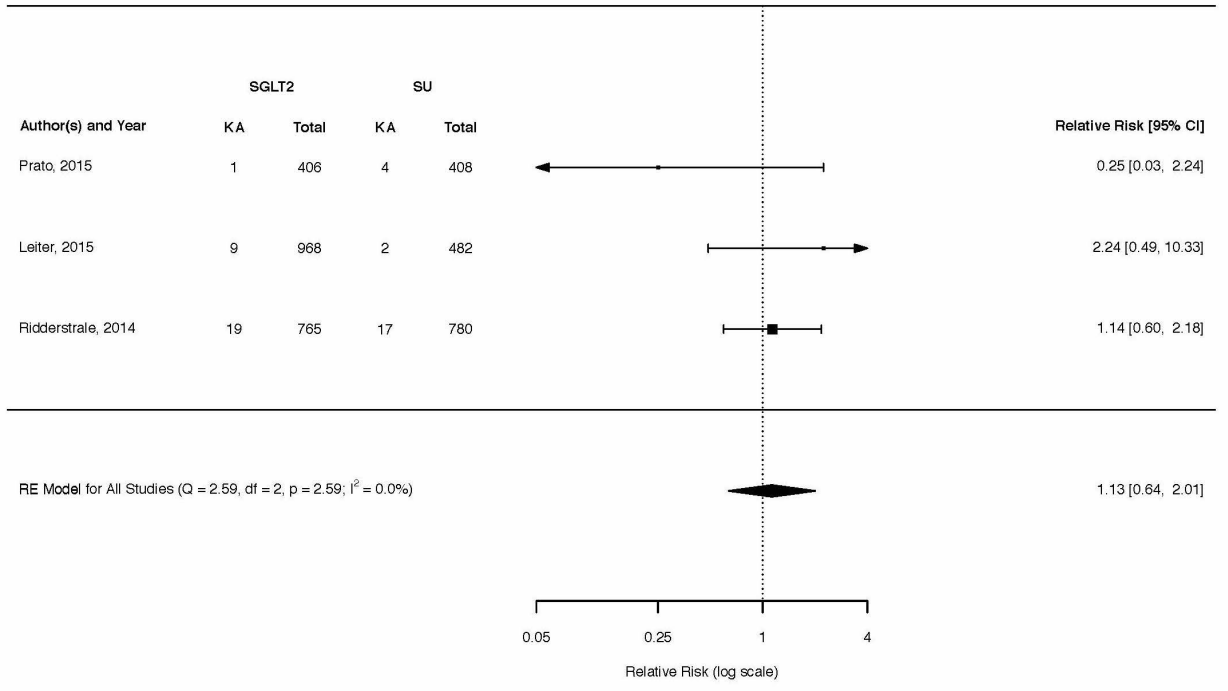


Figure 6A: Risk of Fracture with SGLT2 Inhibitors compared to Incretins

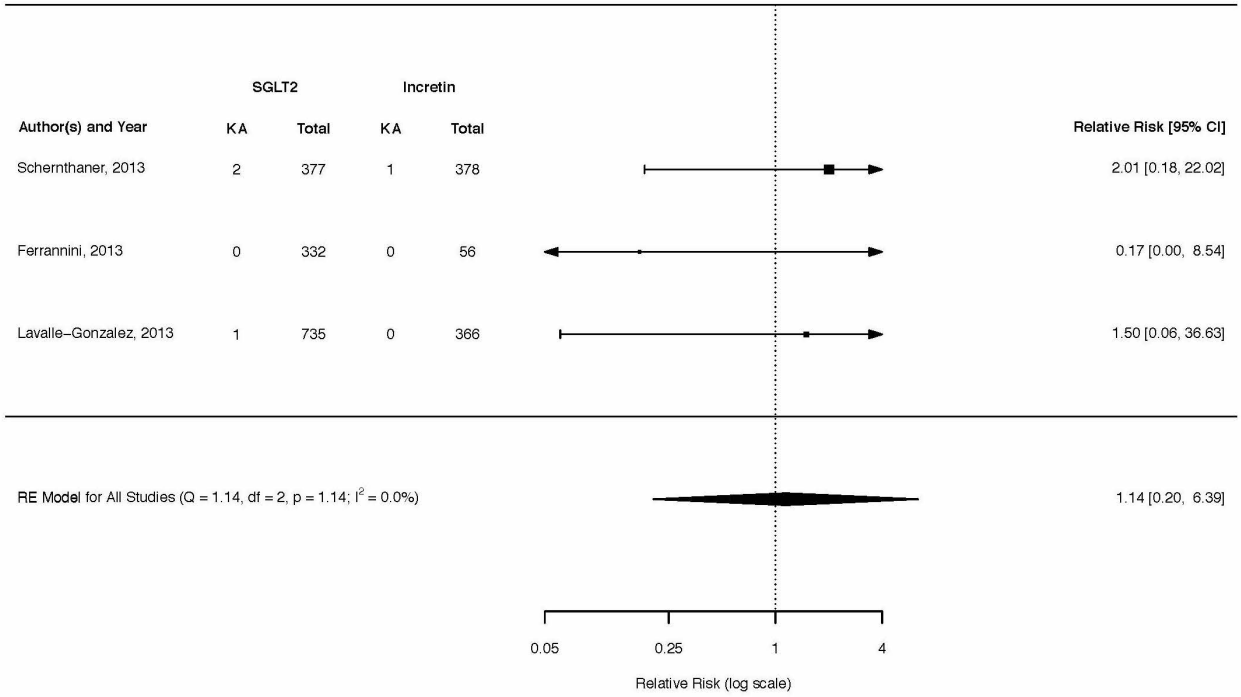
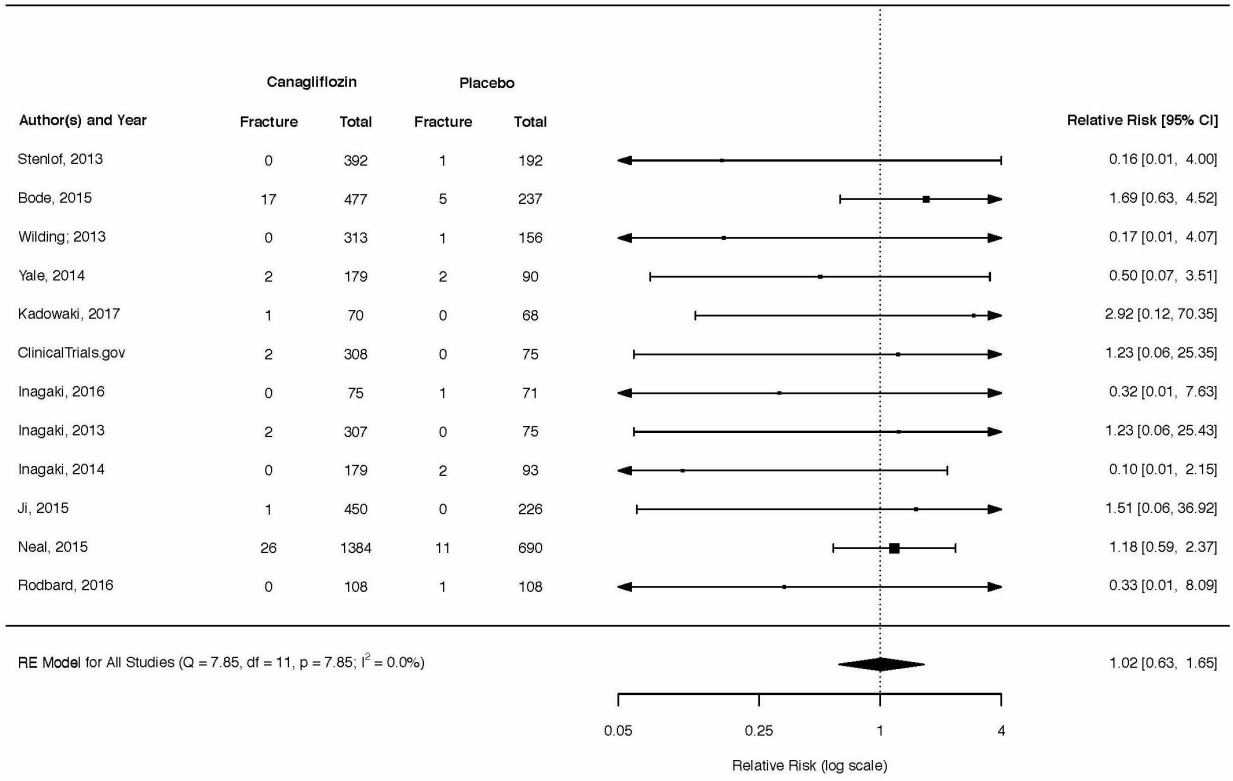


Figure 7A: Risk of Fracture with Canagliflozin compared to Placebo



Section 5: Forest Plots for Fixed Effects Analysis

Figure 8A. Risk of Acute Kidney Injury with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

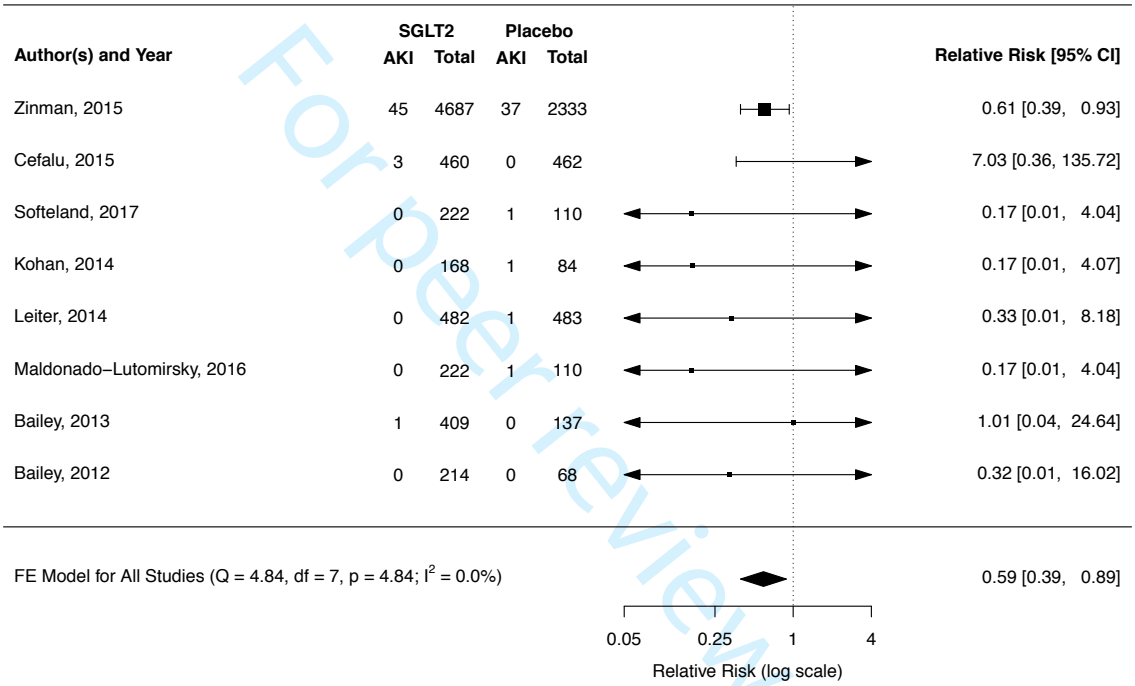


Figure 9A. Risk of Diabetic Ketoacidosis with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

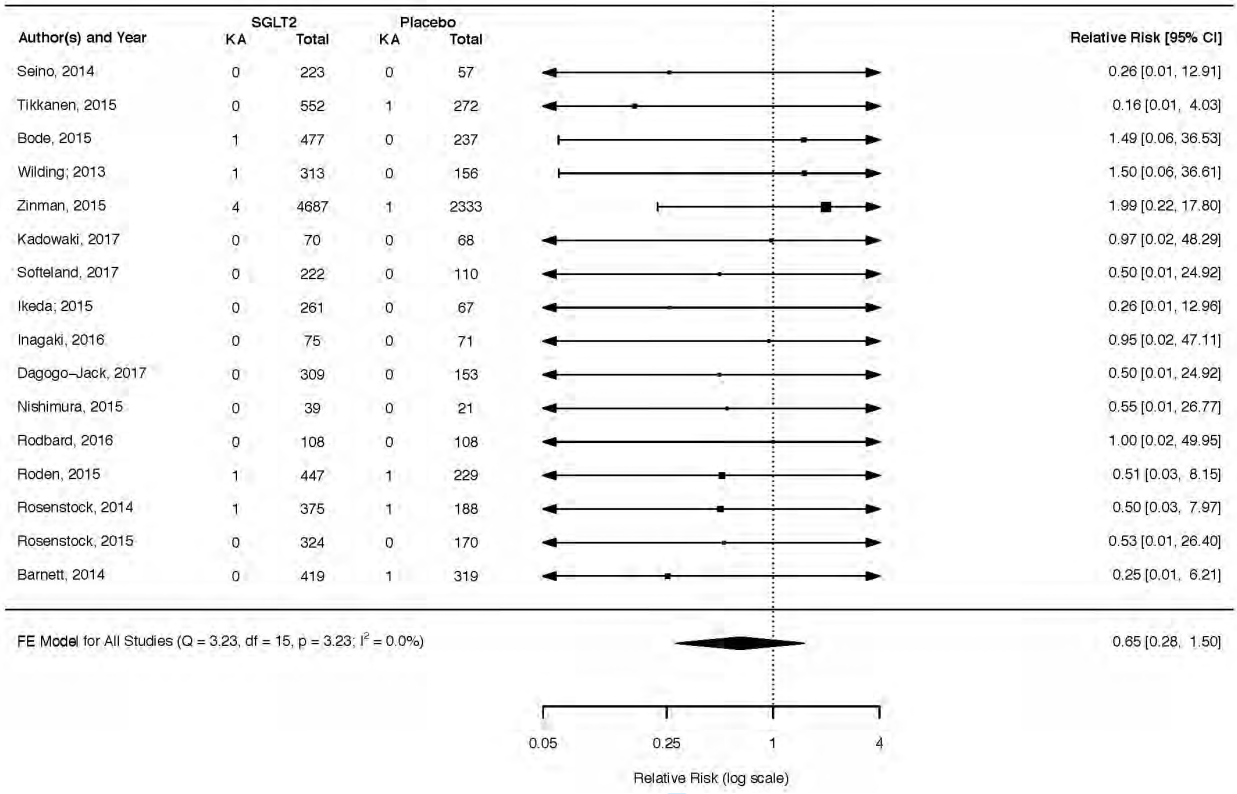


Figure 10A.Risk of Urinary Tract Infection with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

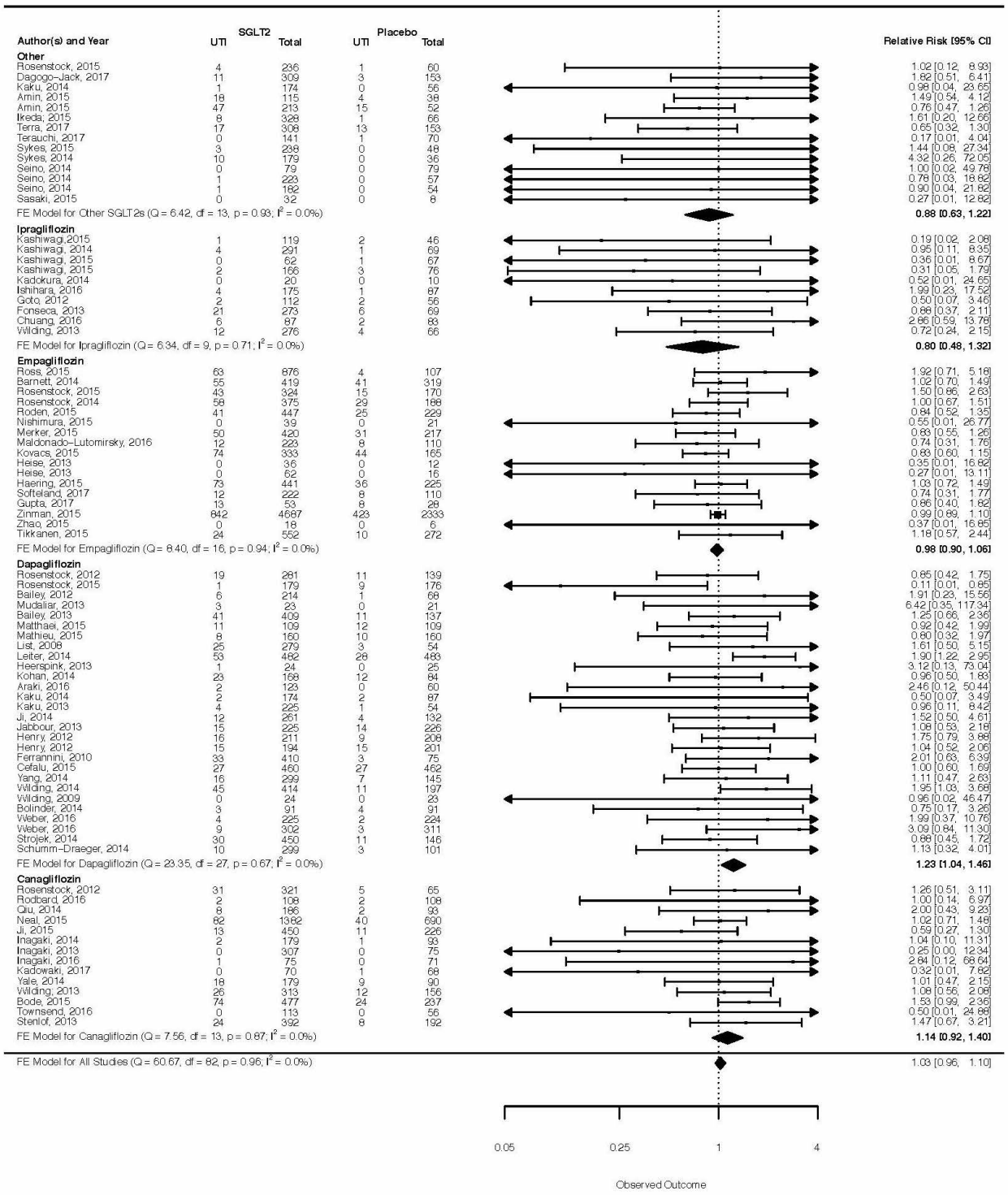
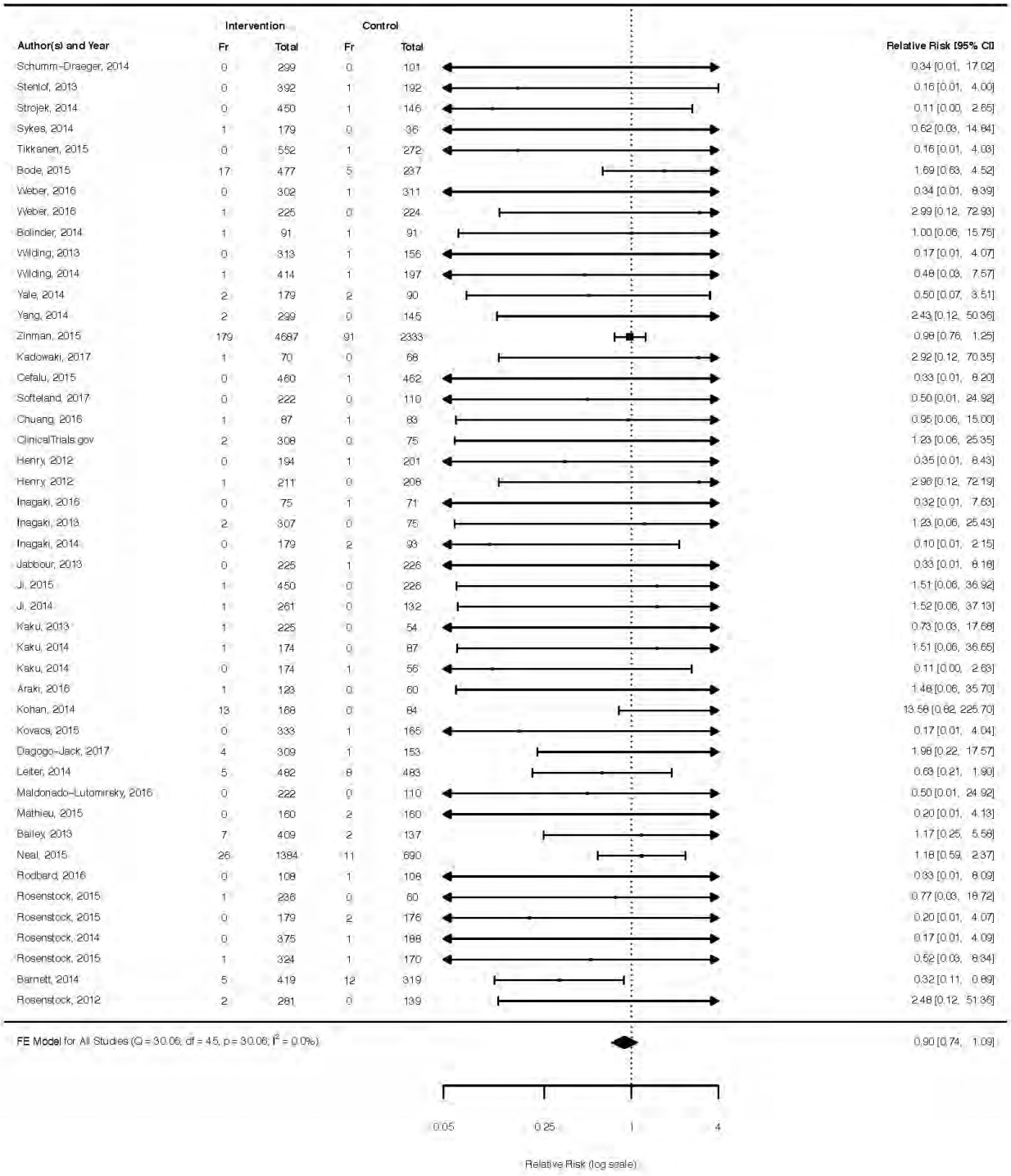


Figure 11A. Risk of Fracture with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model



Section 6: Risk of Bias Assessment

Table 7A. Risk of Bias Assessment for Included Studies

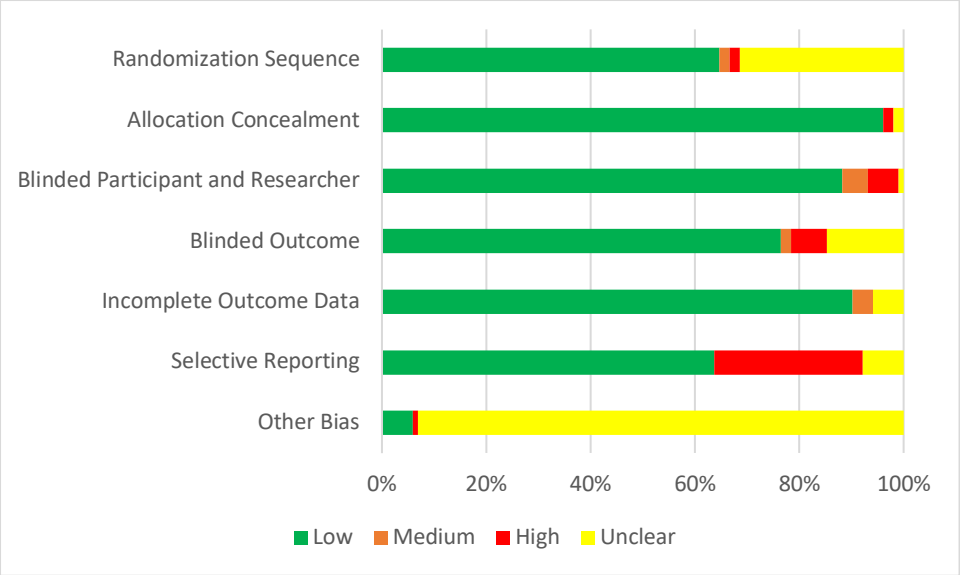
Author and Year	NCT#	Randomization Sequence	Allocation concealment	Double Blinding	Blinded Outcome Assessment	Incomplete Outcome	Selective Reporting	Other	Overall Assessment
Amin, 2015	NCT01059825	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
Amin, 2015	NCT01059825	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear risk	high
Araki, 2016	NCT02157298	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Araki	NCT01368081	Low Risk	Low Risk	Medium Risk	Unclear Risk	Low Risk	High Risk	Unclear risk	high
Bailey, 2013	NCT00528879	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk	Unclear Risk	Unclear risk	high
Bailey, 2012	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
Barnett, 2014	NCT01164501	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Bode, 2015	NCT01106651	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Bolinder, 2014	NCT00855166	Low Risk	Low Risk	Low Risk	Low Risk	low Risk	Low Risk	Unclear risk	low
Cefalu, 2015	NCT01031680	Low Risk	Low Risk	Medium Risk	Low Risk	Low Risk	High Risk	Low Risk	high
Chuang, 2016	NCT01505426	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
DeFronzo, 2015	NCT01422876	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Prato, 2015	NCT00660907	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ferrannini, 2013	NCT00881530	High Risk	High Risk	High Risk	High Risk	Low Risk	High Risk	Unclear risk	high
Ferrannini, 2010	NCT00528372	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear risk	high
Fonseca, 2013	NCT01071850	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Frias, 2016	NCT02229396	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Hadjadj, 2016	NCT01719003	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Haering, 2015	NCT01289990	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Heise, 2013	None	Low Risk	Low Risk	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear risk	high
Heise, 2013	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Henry, 2012	NCT00643851	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high

Henry, 2012	NCT00859898	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ikeda; 2015	NCT00800176	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Inagaki, 2016	NCT02220920	Low Risk	Low Risk	Low Risk	low Risk	Low Risk	Low Risk	Unclear risk	low
Inagaki, 2015	NCT01387737	Unclear Risk	Low Risk	High Risk	High Risk	Medium Risk	Unclear Risk	Unclear risk	high
Inagaki, 2013	NCT01022112	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Inagaki, 2014	NCT01413204	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ishihara, 2016	NCT02175784	Unclear Risk	Low Risk	Medium Risk	Low Risk	Low Risk	Low Risk	Low Risk	high
Jabbour, 2013	NCT00984867	Unclear Risk	Low Risk	Medium Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ji, 2015	NCT01381900	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ji, 2014	NCT01095653	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Kadokura, 2014	NCT01023945	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kadowaki, 2015	NCT01193218	Low Risk	Low Risk	Low Risk	Medium Risk	Low Risk	High Risk	Unclear risk	high
Kaku, 2013	NCT00972244	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	High Risk	Unclear risk	high
Kaku, 2014	none	Unclear Risk	low Risk	Low Risk	Unclear Risk	Medium Risk	Unclear Risk	Unclear risk	high
Kaku, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi, 2015	NCT01242215	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi, 2015	NCT01057628.	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi, 2014	NCT00621868	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi,2015	NCT01316094	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kohan, 2014	NCT00663260	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Kovacs, 2015	NCT01210001	Low Risk	Low Risk	Low Risk	Medium Risk	Low Risk	High Risk	Unclear risk	high
Heerspink, 2013	NCT00976495	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Lavalle-Gonzalez, 2013	NCT01106677	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Leiter, 2014	NCT01042977	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	low
Leiter, 2015	NCT00968812	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Lewin, 2015	NCT01422876	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
List, 2008	NCT00263276	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	high

Mathieu, 2015	NCT01646320	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Matthaei, 2015	NCT01392677	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Mudaliar, 2013	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	high
Nishimura, 2015	NCT01947855	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Qiu, 2014	NCT01340664	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Rodbard, 2016	NCT01989754	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Roden, 2015	NCT01289990	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2012	NCT00642278	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Rosenstock, 2015	NCT01376557	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Rosenstock, 2016	NCT01809327	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2015	NCT01606007	Low Risk	Low Risk	Low Risk	Low risk	Low Risk	Low Risk	Unclear risk	low
Rosenstock, 2014	NCT01306214	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2015	NCT01011868	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2012	NCT00683878	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Ross, 2015	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Sasaki, 2015	None	Low Risk	Low Risk	Medium Risk	High Risk	Unclear Risk	Unclear Risk	High Risk	high
Schernthaner, 2013	NCT01137812	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Schumm-Draeger, 2014	NCT01217892	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Seino, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Seino, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Seino, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Stenlof, 2013	NCT01081834	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear Risk	high
Strojek, 2014	NCT00680745	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Sykes, 2015	NCT00500331	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Tikkanen, 2015	NCT01370005	Medium Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	high
Townsend, 2016	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Seman, 2016	None	Unclear Risk	Low Risk	High Risk	High Risk	Unclear Risk	Unclear Risk	Unclear Risk	high

Weber, 2016	NCT01137474	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk	High Risk	Unclear Risk	high
Weber, 2016	NCT01195662	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Wilding; 2013	NCT01106625	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Wilding, 2013	NCT01117584	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Wilding, 2009	NCT00357370	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Wilding, 2014	NCT00673231	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Yale, 2014	NCT01064414	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Zhao, 2015	NCT01316341	Medium Risk	Low Risk	Low Risk	Low risk	Low Risk	Low Risk	Unclear Risk	high
Zinman, 2015	NCT01131676	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
Goto, 2012	None	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Dagogo-Jack, 2017	NCT02036515	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Maldonado-Lutomirsky, 2016	NCT01734785	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Merker, 2015	NCT01289990	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Neal, 2015	NCT01032629	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Ridderstrale, 2014	NCT01167881	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Sykes, 2014	NCT00495469	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Tanizawa, 2014	None	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Unclear Risk	high
Yang, 2014	NCT01095666	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Gupta, 2017	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Kadowaki, 2017	NCT02354235	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Softeland, 2017	NCT01734785	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Terra, 2017	NCT01958671	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
ClinicalTrials.gov		Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Terauchi, 2017	NCT02201004	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low

Figure 12A. Risk of Acute Kidney Injury with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model



Section 7: Assessment of Publication Bias

Figure 13A. Funnel Plot for Placebo Controlled Trials: Acute Kidney Injury

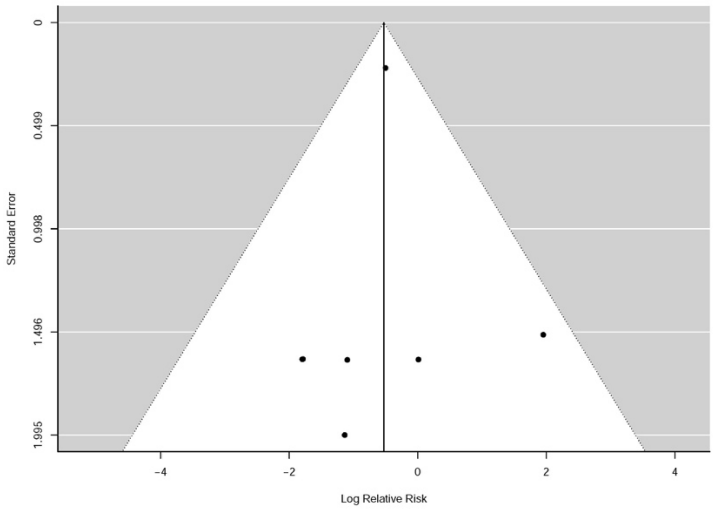


Figure 14A. Funnel Plot for Placebo Controlled Trials: Urinary Tract Infection

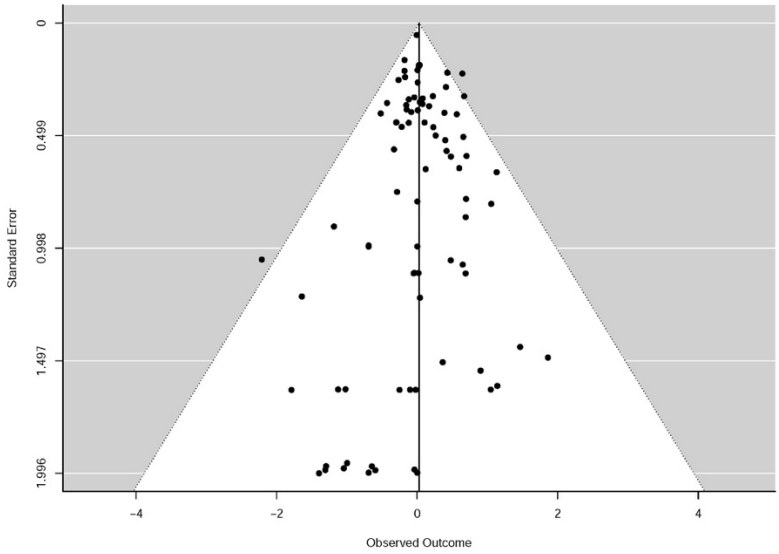


Figure 15A. Funnel Plot for Metformin Controlled Trials: Urinary Tract Infection

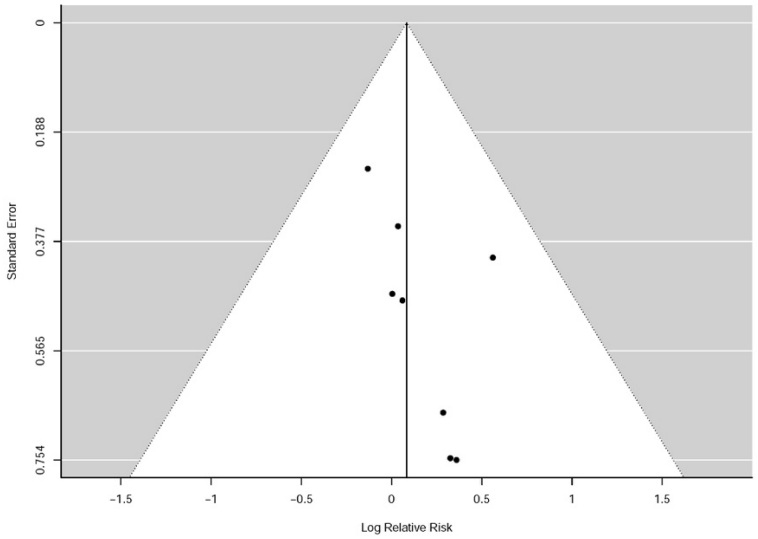


Figure 16A. Funnel Plot for Sulfonylurea Controlled Trials: Urinary Tract Infection

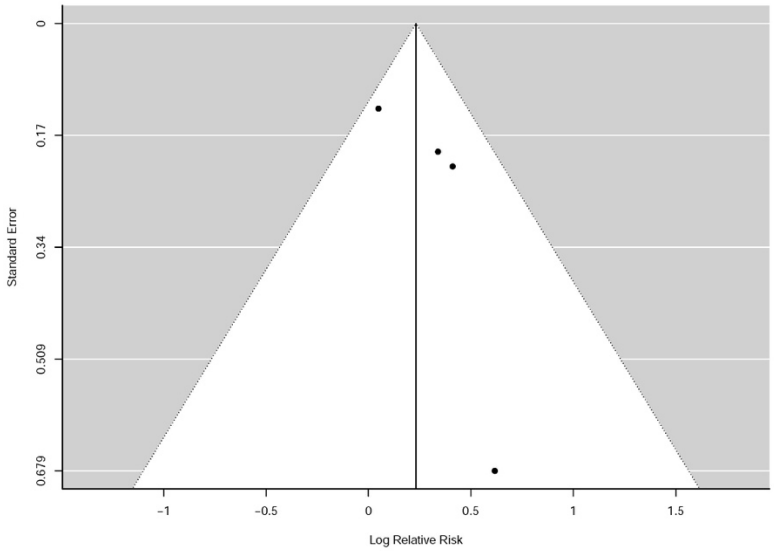


Figure 17A. Funnel Plot for Incretin Controlled Trials: Urinary Tract Infection

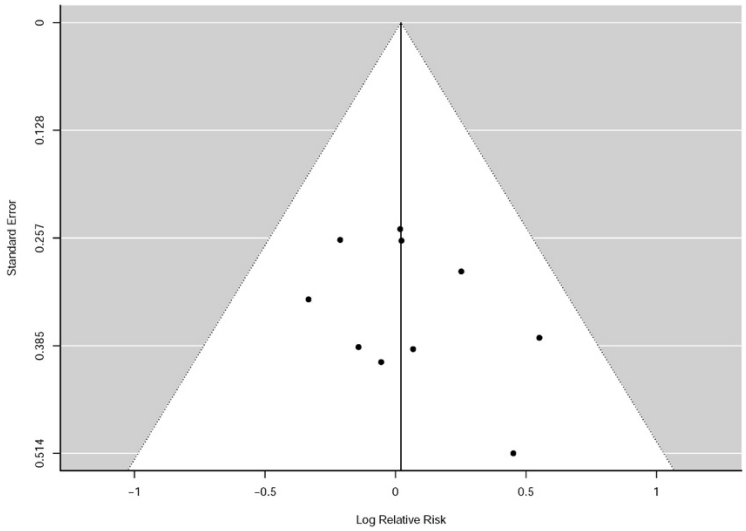
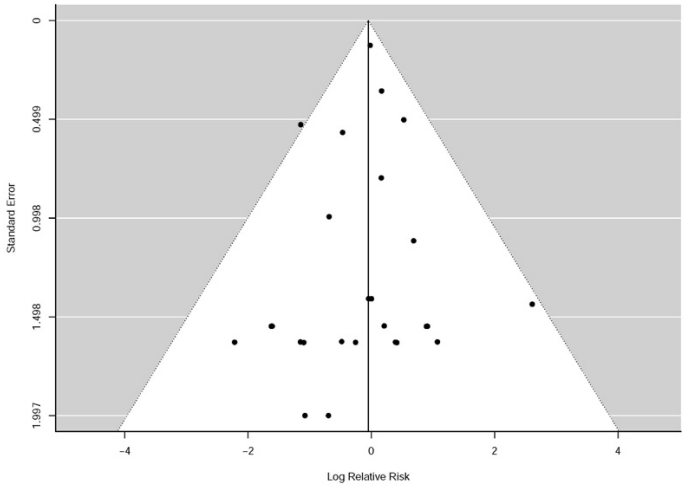


Figure 18A. Funnel Plot for Placebo Controlled Trials: Fracture



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	figures 2-6, appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

BMJ Open

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

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Date Submitted by the Author:	14-Jun-2018
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology, Pharmacology and therapeutics
Keywords:	DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, THERAPEUTICS, Adverse events < THERAPEUTICS

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

Short Running Title: Comparative Safety of SGLT2 Inhibitors

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Key Words: Type 2 Diabetes, SGLT2 Inhibitors, Adverse Events, Systematic Review

Word Count
Abstract: 299 Main Text: 4,479

Abstract

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

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

Intervention: SGLT2 Inhibitors, compared to 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 to placebo, SGLT2 inhibitors were found to be significantly protective against AKI (RR = 0.59; 95% CI 0.39-0.89; I^2=0.0%), while no difference was found for DKA (RR 0.66; 95% CI 0.30- 1.45, I^2 = 0.0%), UTI (RR 1.02; 95% CI 0.95-1.09, I^2 = 0.0%), or bone fracture (RR 0.87; 95% CI 0.69-1.09, 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 to active controls. Sub-group analysis did show an increased risk of UTI with dapagliflozin only (RR 1.21; 95% CI 1.02-1.43, 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 the AKI, DKA, UTI or fracture. However, wide confidence intervals 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.

Trial Registration: PROSPERO CRD42016038715

Article Summary

- Our objective is to summarize the current state of knowledge surrounding key post-market safety concerns of the SGLT2 inhibitors compared to active and non-active comparators in patients with type 2 diabetes.

Strengths and Limitations of the Study

- This study provides a comprehensive systematic review of the serious adverse events related to use of SGLT2 inhibitors identified by major drug regulatory agencies worldwide to date.
- This study only 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 (e.g., AKI, DKA, limb amputations) we evaluated occur infrequently and, in some cases, were not reported at all.
- Certain outcomes may have been inadequately characterized 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.

1.0 Introduction

The sodium glucose co-transporter 2 (SGLT2) inhibitors are a novel drug class available for the management of type 2 diabetes. Clinical guidelines recommend the SGLT2 inhibitors as one of numerous potential pharmacologic approaches for second-line therapy following metformin failure or intolerance.[1, 2] Some clinical guidelines recommend the SGLT2 inhibitor, empagliflozin, 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 glycemic 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.[3–5] In 2015 the EMPA-REG trial showed that the SGLT2 inhibitor, empagliflozin, significantly reduced the risk for composite endpoint of cardiovascular death, myocardial infarction, or stroke by 14% and all-cause mortality by 32%, in a population with existing cardiovascular disease.[5] The LEADER and SUSTAIN-6 trials have also demonstrated similar benefits with liraglutide and semaglutide.[3, 4]

Considering the relative potential harms and benefits, clinicians and policy makers must continue to integrate new pharmacotherapeutic evidence to optimize 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 (EMA) 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.[6–14]

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] To date, no meta-analysis of AKI has been published. 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. Four published meta-analyses of randomized control trials (RCT) and found no increased risk of UTIs, except within a sub-group of dapagliflozin,[15–18] and one study found an increased risk with empagliflozin 25mg users.[18] One meta-analysis on the risk of DKA currently exists, and shows 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 amputation[11] with evidence gathered from re-analysis the CANVAS and CANVAS-R

trials, demonstrating a two-fold increased risk.[23] No meta-analysis of RCTs currently exists with respect to amputation.

In light of recent guideline changes that promote earlier integration of the SGLT2 inhibitors into therapy, 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 post-market safety of the SGLT2 inhibitors compared to 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.

2.0 Methods and Analysis

2.1 Study Design

This study has been designed in accordance with the PRISMA statement on systematic reviews and meta-analysis.[24] This protocol has been registered (CRD42016038715) with PROSPERO (International Prospective Register of Systematic Reviews).[25, 26]

2.2 Patient Involvement

Patients were not engaged in the development of this protocol.

2.3 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 of keywords and MEDLINE controlled vocabulary or Medical Subject Headings (MeSH). A methodological search filter was applied to identify RCTs[27] 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 Appendix.

The search for unpublished studies and materials included ProQuest Dissertations & 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.[28]

2.4 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 are currently not used in clinical practice), basal insulins (NPH, lente, glargine, detemir, degludec), dipeptidyl peptidase-4 Inhibitors (DPP-4I) (alogliptin, linagliptin, saxagliptin, sitagliptin), GLP-1 agonists (dulaglutide, exenatide, liraglutide), thiazolidinediones (TZDs) (pioglitazone, rosiglitazone), alpha-glucosidase Inhibitors (acarbose) or placebo/no treatment. All premixed or acute care insulin protocols were excluded. Any investigational agents other than SGLT-2 inhibitors were excluded.

The outcomes of this study include the serious safety events as highlighted through the federal regulatory drug safety communications.[6–11] 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.[29, 30]

2.5 Study Selection and Data Extraction

We used DistillerSR, a systematic review software,[31] 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. Any studies that meet those criteria, or where a clear decision could not be made, 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.[32] 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 appendix). Where the data conflicted between the published paper and other sources (e.g. 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 (versus only relative risk or hazard ratio) 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 (e.g. 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.

2.6 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.[33, 34] This tool captures six main sources of bias, including: randomization 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"; or one or more categories of "high risk". Publication bias was examined using funnel plots.

2.7 Data Synthesis

We conducted a series of pair-wise random effects meta-analyses to estimate the pooled treatment effect using relative risks, using the restricted maximum likelihood method.[35] The primary analysis was split into two comparisons, with the first between SGLT2 inhibitors and placebo, and the second SGLT2 inhibitors and any active comparator. Between-study variance was estimated using the restricted maximum likelihood method. 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%.[36] 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 anti-diabetic agents that were used prior to enrollment or added as background therapy after enrollment. If patients could be therapy-naïve or have used other medications to meet enrollment criteria, then they were categorized as concurrent/prior use. Treatment-naïve was defined as patients that: have never had an anti-diabetic medication in the past, have not been on any other anti-diabetic medication in weeks leading up to enrolment, or, were able to go through a washout prior to enrolment. We also conduced sensitivity analyses to explore the impact of methodologic decisions within our analysis. First, we pooled studies that had at least one reported event. Second, we repeated our analyses using fixed-effects models. All analysis was conducted using R statistical software (version 3.4.1). Technical appendix, statistical code, and dataset available from the corresponding author.

3.0 Results

3.1 Included Studies

A total of 2418 unique titles and abstracts were screened. Of these, 650 proceeded to full text screening. A total of 144 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, 37–143] representing 112 randomized 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 to placebo, 8 compared to metformin, 10 compared to an incretin agent, 5 compared to a sulfonylurea, and 3 compared to pioglitizone. A total of 9 studies included more than one unique comparator. One publication, reporting on the combined results of the CANVAS program[23] studies only, provided events as rates per 1000 person years. Data from this publication was only used for the amputation outcome assessment, data from an earlier publication on a sub-set of this population was used for other outcomes as actual event numbers were reported.[84] Section 3 of the Online Appendix outlines the characteristics of each of the included studies.

3.2 Primary Analysis

Acute Kidney Injury

Acute kidney injury 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 0.39-0.89, I^2 = 0.0%), however this is 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 0.14-1.64; I^2 = 0.0%).

Diabetic Ketoacidosis

Diabetic ketoacidosis was reported in 26 RCTs (18 Placebo comparison, 8 active comparisons, and 1 within class comparison trial). Neither placebo (RR 0.66; 95% CI 0.30-1.45, I^2 = 0.0%) (Figure 3) nor incretin (RR 0.43; 95% CI 0.069-2.75; I^2 = 0.0%; 3 Studies) (Forest plot, online 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 0.25-2.16; I^2 = 0.0%; 7 studies) (Forest plot, online appendix Section 4).

Urinary tract infections

Urinary tract infection was the most frequently reported outcome examined (110 of 112

studies reported). When compared to placebo, SGLT2 inhibitors as a class did not demonstrate a significant increase risk (RR 1.02; 95% CI 0.95-1.09), however subgroup analysis of the individual agents did show a significantly increased risk of UTIs in users of dapagliflozin (RR 1.21; 1.02-1.43), but not empagliflozin, canagliflozin, ipragliflozin or non-marketed SGLT2 inhibitors (grouped) (Figure 4). When compared to active treatments, SGLT2 inhibitors grouped together did not demonstrate an 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 of active comparators grouped together (RR 1.42; 95% CI 1.07-1.87) (Forest plot, online 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 0.69-1.09) (Figure 6), metformin (RR 0.69; 95% CI 0.19-2.51; I^2 = 0.0%; 6 studies), sulfonylureas (RR 1.15; 95% CI 0.66-2.00; I^2 = 0.0%; 3 studies) or incretins (RR 1.38; 95% CI 0.31-6.17; I^2 = 0.0%; 3 studies). A sub-group analysis of canagliflozin compared to placebo alone, the agent identified by the FDA as having an increased risk, was also non-significant (RR 1.02; 95% CI 0.63-1.65; I^2 = 0.0%; 12 studies) (Additional forest plots, online appendix Section 4).

Lower Limb Amputation

Data was identified on amputation for three studies[23, 48, 109]. One case of amputation was found in the clinicaltrials.gov data for trial number NCT01422876 in a user of empagliflozin 25mg, 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 to 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).

3.2 Sub-group and Sensitivity Analyses

Several sub-group 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 large study.[144] When the analyses were re-run using a fixed-effect models, the risk estimates remained the same or had slightly smaller confidence intervals. Forest plots for the fixed effects analysis are in Section 5 of the online appendix.

3.3 Risk of bias

Generally, studies were of good methodological quality, however numerous studies were deemed high risk of selective reporting after outcome data was 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 randomization 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 appendix. Funnel plots do not suggest of the presence of publication bias (see Section 7 of the Online Appendix).

4.0 Discussion

This study provides a comprehensive review of the RCT literature with respect to key safety outcomes identified through post-marketing 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, though 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 trans-glomerular pressure, similar to the effects of agents that target the renin–angiotensin–aldosterone (RAAS) axis.[145] Szalat et al (2017) 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 hemodynamically unstable and volume-depleted; 2) a greater drop in trans-glomerular 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 (e.g. NSAIDS, radio-contract dyes).[145] 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.[146] This systematic review highlights a lack of reporting of AKI with only 11 of 111 randomized comparisons having published data on this outcome. Though an overall protective effect was found, this finding was driven by one large RCT that compared empagliflozin to 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 one month of initiation) and therefore this lack or reporting should not be due to the duration of clinical trials. Recent observational data also supports clinical trial data on AKI. Nadkarni et al. (2017) reported on the incidence of AKI among two cohorts comparing patients with type 2 diabetes using SGLT2 inhibitors to non-users.[147] After an average follow-up time of 14 months, adjusted hazard ratios showed SGLT2 inhibitors to be protective in one cohort (aHR 0.4 [95% CI 0.2–0.7]; P= 0.004) and favoring SGLT2 inhibitors, though not statistically significant, in the second cohort (aHR 0.6 [95% CI 0.4–1.1]; 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 euglycemic DKA among patients with type 2 diabetes is concerning, as a diagnosis can easily be missed. Though 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.[148] 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 1,000 person-years in a 20 year retrospective Danish cohort study, with declining incidence each year.[149] Therefore, most RCTs had insufficient sample size to detect any cases. Of the 16 RCTs that reported DKA, only 7 (representing 11,004 patients) had one or more cases. Our findings are consistent with published observational literature, which indicates no increased risk, however confidence intervals were wide. A case-control study using Truven MarketScan data (a large US claims database),[150] and a cross-sectional using the FDA Adverse Event Reporting System (FAERS) database[151] 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: 7-fold increased risk among 140,352 patients; cross-sectional: HR 2.2; 95% CI 1.4-3.6, among 416,670). In contrast, the Danish cohort study did not find an increased risk of DKA in individuals taking SGLT2 inhibitors compared to other diabetes therapies (HR 1.6; 95% CI 0.6-3.5), although the upper bound of the 95% confidence interval does not rule out significant harm.[149] 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, which is the largest to date, included 77 RCTs representing 50,820 patients and found no

increased risk of UTIs in SGLT2 inhibitor users (RR 1.05; 95% CI 0.98-1.12).[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 to 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 inhibits[128, 138, 152–155], though continues through the normal dosing range for dapagliflozin[156].

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.[157] In an RCT conducted by Bode et al. (2015), additional investigation into the change in bone mineral density in canagliflozin versus placebo users was conducted.[158] 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. To date, two meta-analyses have been published examining the risk of fracture when comparing SGLT2 inhibitors to placebo[20, 21]. Ruanpeng et al (2017) included 20 RCTs, and Tang et al (2016) 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 one event per trial. Further data is needed to establish the true risk as well as to identify if this may be a class effect or agent specific.

4.1 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. Though 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 post-market. Secondly, several of

the outcomes (e.g., 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. Thirdly, certain outcomes may have been inadequately characterized 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 less than 24 weeks and 63% less than one 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 adverse effects may be collected after allocation is known, or through self-assessment questionnaires.[159]

5.0 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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Jennifer R. Donnan led the review and was involved at every stage, including protocol development, search strategy design, screening, data extraction, quality appraisal, analysis and manuscript preparation.

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John-Michael Gamble 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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Tables

Table 1. Sub-group Analysis among Placebo Controlled Trials

Group	Relative Risk (95% CI, I^2)	# of Studies	Total # of outcomes/patients
Prior use of anti-diabetics			
AKI			
Prior/Concurrent Diabetes Therapy	0.51 (0.14-1.84; 0.72%)	6	90/10,651
Treatment Naïve	0.60 (0.39-0.92; 0.00%)	2	
DKA			
Prior/Concurrent Diabetes Therapy	0.65 (0.25-1.71; 0.00%)	14	13/14,353
Treatment Naïve	0.66 (0.16-2.71; 0.00%)	4	
UTI			
Prior/Concurrent Diabetes Therapy	1.04 (0.93-1.16; 8.22%)	64	3,405/39,331
Treatment Naïve	1.00 (0.91-1.10; 0.00%)	23	
Fracture			
Prior/Concurrent Diabetes Therapy	0.81 (0.57-1.14; 2.61%)	39	445/29,668
Treatment Naïve	0.79 (0.46-1.36; 6.30%)	11	
Risk of Bias			
AKI			
Low Risk of Bias	0.58 (0.38-0.89; 0.0%)	4	90/10,651
High Risk of Bias	0.71 (0.12-4.37; 25.5%)	4	
DKA			
Low Risk of Bias	0.85 (0.28-2.61; 0.0%)	10	13/14,353
High Risk of Bias	0.49 (0.003-71.59; 94.8%)	8	
UTI			
Low Risk of Bias	1.00 (0.92-1.08; 0.0%)	51	3,405/39,331
High Risk of Bias	1.05 (0.11-10.43; 99.7%)	37	
Fracture			
Low Risk of Bias	0.95 (0.76-1.18; 0.0%)	22	445/29,668
High Risk of Bias	0.58 (0.04-8.77; 97.0%)	27	
Definition of UT			
UTI			
Predefined list of terms	0.99 (0.91-1.07; 0.0%)	19	3.405/39,331
Suggestive of UTI	1.13 (0.87-1.47; 0.0%)	11	
Positive culture	0.91 (0.51-1.62; 24.27%)	2	
As per investigator	0.82 (0.41-1.61; 0.0%)	2	
Not defined	1.08 (0.90-1.29; 15.47%)	54	

List of Figures

All figures supplied as separate documents.

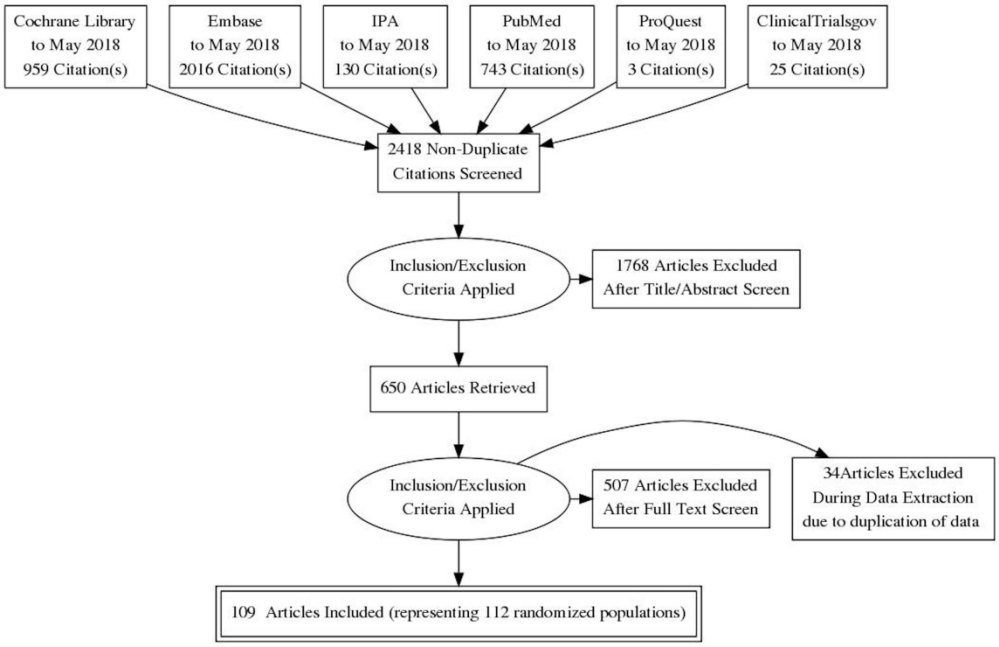

Figure 1 Flow Diagram of Included Studies

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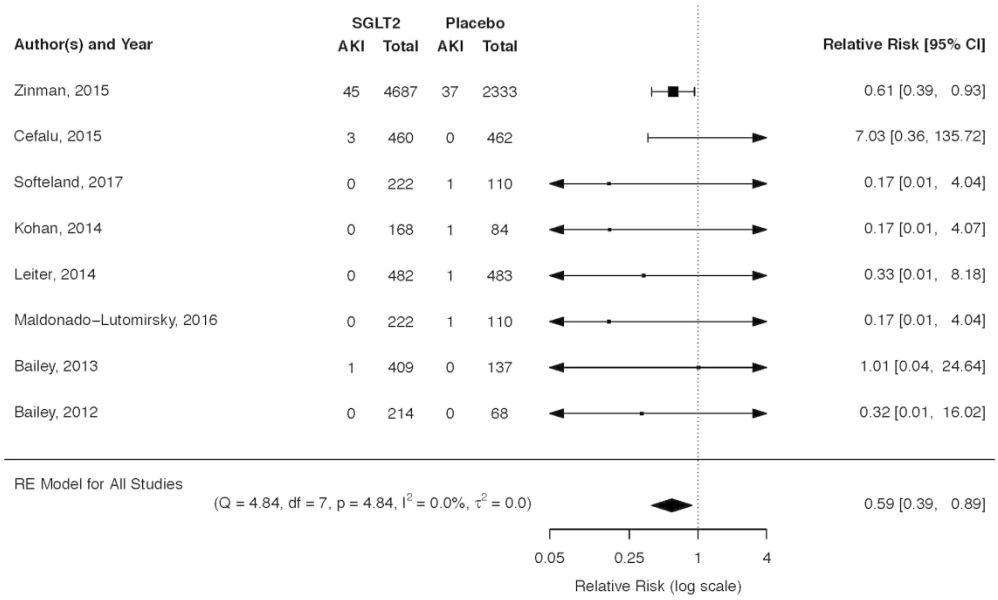

Figure 2. Risk of Acute Kidney Injury with SGLT2 Inhibitors Compared to Placebo

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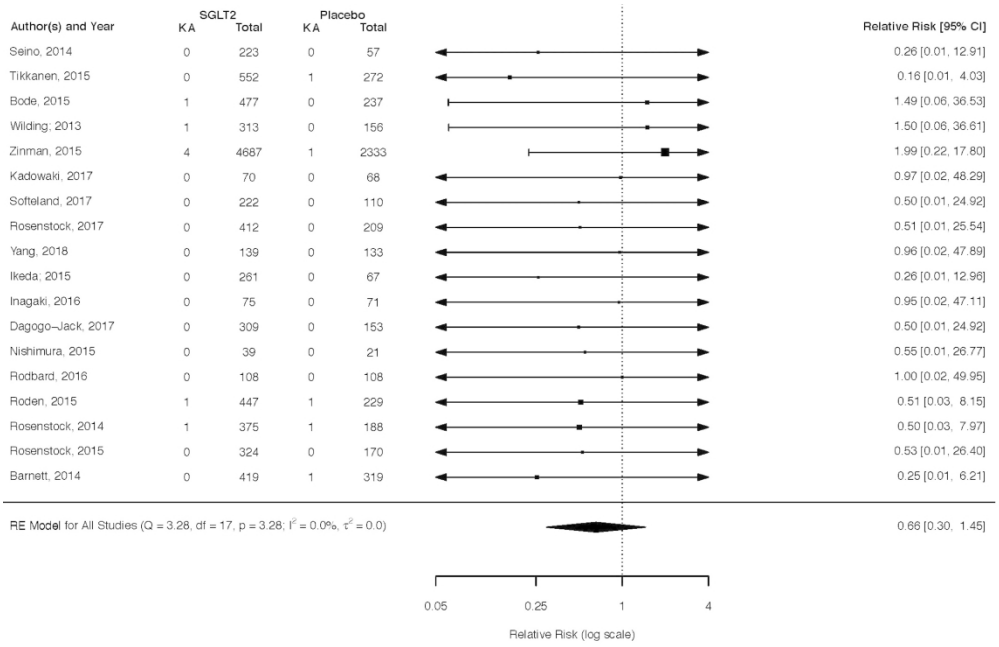

Figure 3. Risk of Diabetic Ketoacidosis from SGLT2 inhibitors compared to placebo

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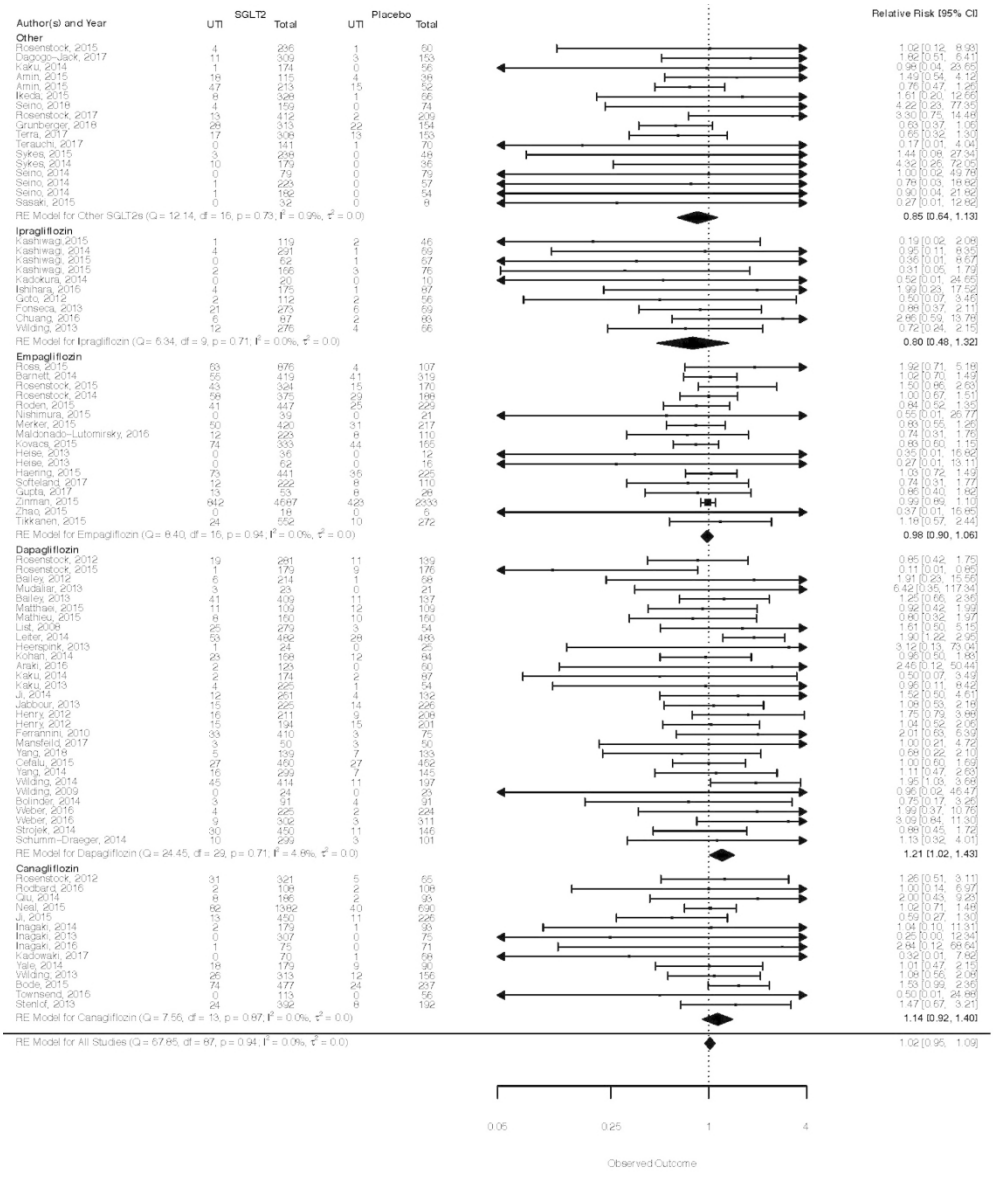

Figure 4. Risk of Urinary Tract Infection with SGLT2 Inhibitors Compared to Placebo

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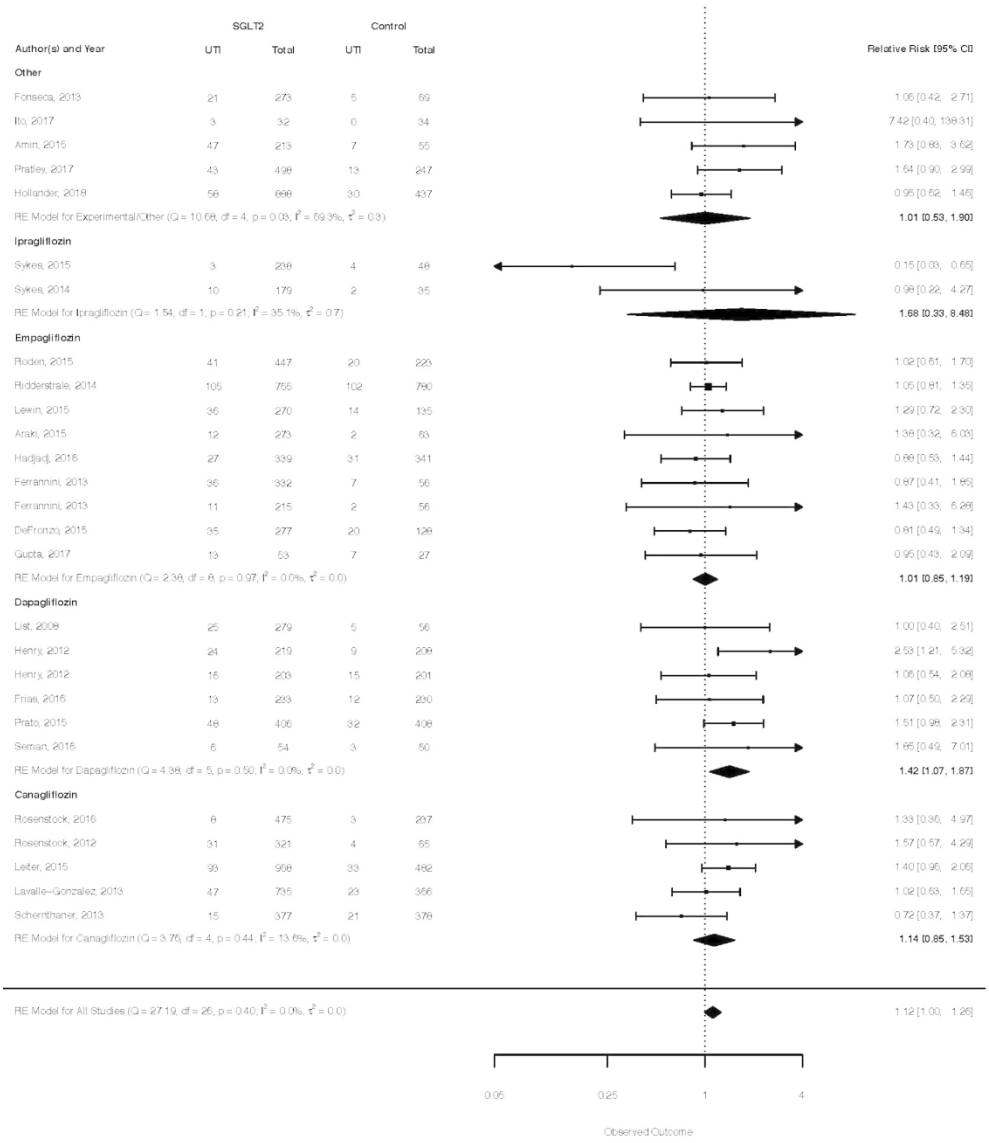


Figure 5. Risk of Urinary Tract Infection with SGLT2 Inhibitors Compared to Active Comparators

208x237mm (300 x 300 DPI)

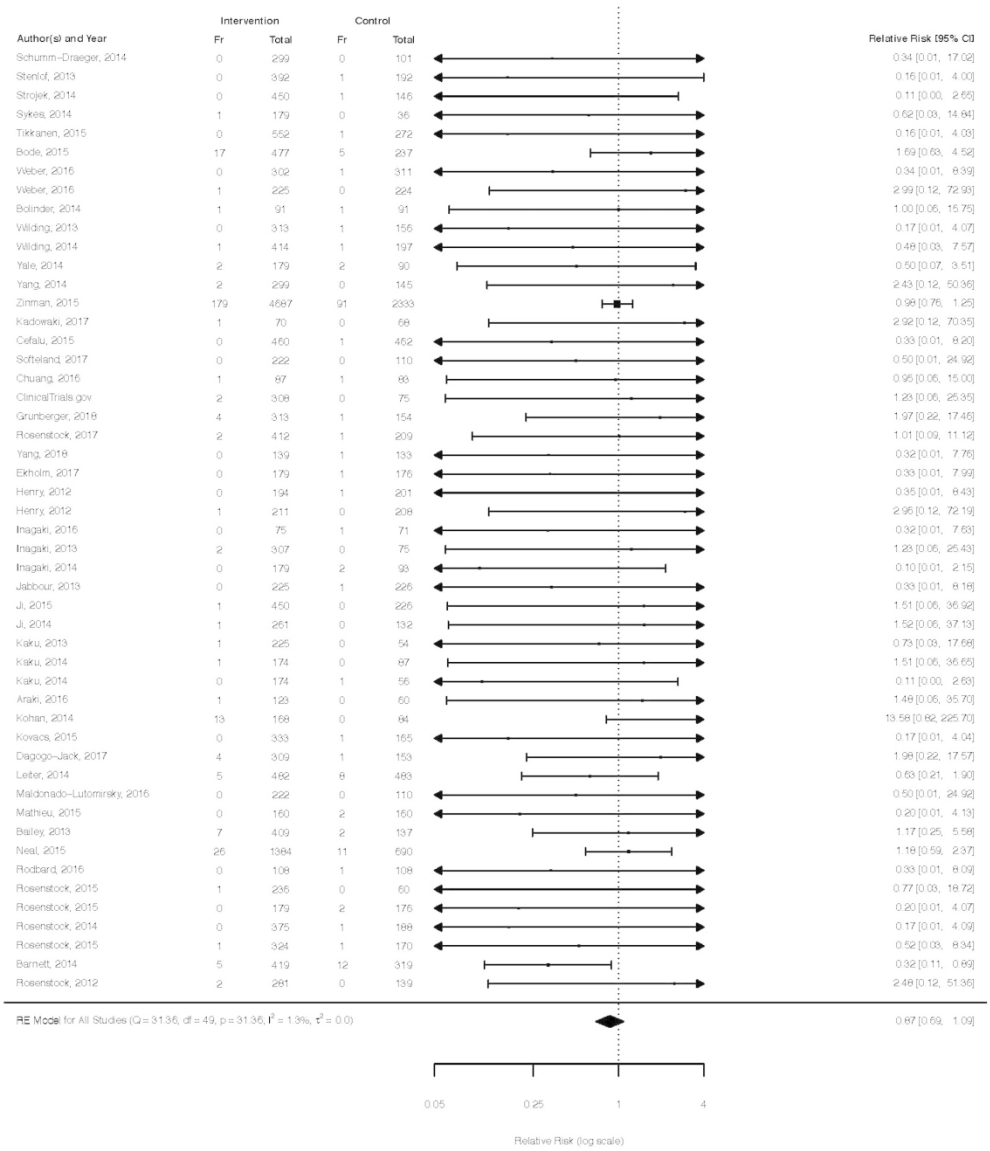


Figure 6. Risk of Fracture with SGLT2 Inhibitors Compared to Placebo

208x240mm (300 x 300 DPI)

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

Online Appendix

Section 1: Search Strategies

Table 1A. Pubmed Search Strategy

		Search String	Results
1	Population	"Diabetes Mellitus, Type 2"[Mesh] OR NIDDM[tw] OR t2dm[tw] OR ((“type 2"[tw] OR "type ii"[tw] OR "adult onset"[tw] OR “mature onset”[tw] OR “late onset”[tw] OR “noninsulin-dependent”[tw] OR “non insulin dependent”[tw]) AND diabetes[tw])	167100
2	Intervention: SGLT2s	"Sodium-Glucose Transport Proteins/antagonists and inhibitors"[Mesh] OR "Sodium-Glucose Transporter 2"[Mesh] OR "sodium-glucose co-transporter 2"[tw] OR SGL2[tw] OR SGLT2[tw] OR gliflozin*[tw] OR "Canagliflozin"[Mesh] OR canagliflozin*[tw] OR invokana[tw] OR sulisent[tw] OR "TA 7284"[tw] OR TA7284[tw] OR "JNJ 28431754"[tw] OR JNJ28431754[tw] OR "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol"[Supplementary Concept] OR dapagliflozin*[tw] OR farxiga[tw] OR forxiga[tw] OR “BMS 512148”[tw] OR BMS512148[tw] OR "empagliflozin"[Supplementary Concept] OR empagliflozin*[tw] OR jardiance[tw] OR "BI 10773"[tw] OR BI10773[tw] OR ipragliflozin[Supplementary Concept] OR ipragliflozin*[tw] OR suglat[tw] OR "ASP 1941"[tw] OR ASP1941[tw] OR "1,5-anhydro-1-(5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl)-1-thioglucitol"[Supplementary Concept] OR luseogliflozin*[tw] OR lusefi[tw] OR “TS 071”[tw] OR TS071[tw] OR "remogliflozin etabonate"[Supplementary Concept] OR remogliflozin*[tw] OR "KGT 1681"[tw] OR KGT1681[tw] OR "(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR sotagliflozin*[tw] OR "LX 4221"[tw] OR LX4221[tw] OR "6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [Supplementary Concept] OR tofogliflozin*[tw] OR apleway[tw] OR deberza[tw] OR "CSG 452"[tw] OR CSG452[tw] OR "5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-hydroxymethyl-6,8-dioxabicyclo(3.2.1)octane-2,3,4-triol" [Supplementary Concept] OR ertugliflozin*[tw] OR "PF 04971729"[tw] OR PF04971729[tw]	2936
3	#1 AND #2		2080
4	Study Type Filter: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-and	("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[Mesh:NoExp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])	1065055

	precision-maximizing version (2008 revision). Available at http://handbook.cochrane.org/chapter_6/box_6_4_b_cochrane_hsss_2008_sensprec_pubmed.htm		
5	#3 AND #4		743

Table 2A: Cochrane Library Search Strategy

#1	([mh "Diabetes Mellitus, Type 2"] or NIDDM or t2dm or (("type 2" or "type ii" or "adult onset" or "mature onset" or "late onset" or "noninsulin-dependent" or "non insulin dependent") and (diabetes)))	25,454
#2	([mh "Sodium-Glucose Transport Proteins"/ai] or [mh "Sodium-Glucose Transporter 2"] or "sodium-glucose co-transporter 2" or SGL2 or SGLT2 or gliflozin* or [mh canigliflozin] or canagliflozin* or invokana or sulisent or "TA 7284" or TA7284 or "JNJ 28431754" or JNJ28431754 or dapagliflozin* or farxiga or forxiga or "BMS 512148" or BMS512148 or empagliflozin* or jardiance or "BI 10773" or BI10773 or ipragliflozin or suglat or "ASP 1941" or ASP1941 or luseogliflozin* or lusefi or "TS 071" or TS071 or remogliflozin* or "KGT 1681" or KGT1681 or sotagliflozin* or "LX 4221" or LX4221 or tofogliflozin* or apleway or deberza or "CSG 452" or CSG452 or ertugliflozin* or "PF 04971729" or PF04971729)	1,082
#3	#1 AND #2	959

Table 3A: Embase Search Strategy

No.	Query	Results
#5	#3 AND #4	2,016
#4 - EMBASE RCT filter from Wong 2006, best balance of sensitivity and specificity	random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	1,533,336
#3	#1 AND #2	4,869
#2	'sodium glucose cotransporter 2'/de OR 'sodium glucose cotransporter 2 inhibitor'/exp OR 'sodium-glucose co-transporter 2':ab,ti OR sgl2:ab,ti OR sglt2:ab,ti OR gliflozin*:ab,ti OR canagliflozin*:ab,ti OR invokana:ab,ti OR sulisent:ab,ti OR 'ta 7284':ab,ti OR ta7284:ab,ti OR 'jnj 28431754':ab,ti OR jnj28431754:ab,ti OR dapagliflozin*:ab,ti OR farxiga:ab,ti OR forxiga:ab,ti OR 'bms 512148':ab,ti OR bms512148:ab,ti OR empagliflozin*:ab,ti OR jardiance:ab,ti OR 'bi 10773':ab,ti OR bi10773:ab,ti OR ipragliflozin*:ab,ti OR suglat:ab,ti OR 'asp 1941':ab,ti OR asp1941:ab,ti OR luseogliflozin*:ab,ti OR lusefi:ab,ti OR 'ts 071':ab,ti OR ts071:ab,ti OR remogliflozin*:ab,ti OR 'kgt 1681':ab,ti OR kgt1681:ab,ti OR sotagliflozin*:ab,ti or 'LX 4221':ab,ti or LX4221:ab,ti or tofogliflozin*:ab,ti or apleway:ab,ti or deberza:ab,ti or 'CSG 452':ab,ti or CSG452:ab,ti or ertugliflozin*:ab,ti or 'PF 04971729':ab,ti or PF04971729:ab,ti	6,675
#1	'non insulin dependent diabetes mellitus'/de OR niddm:ab,ti OR t2dm:ab,ti OR ('type 2':ab,ti OR 'type ii':ab,ti OR 'adult onset':ab,ti OR 'mature onset':ab,ti OR 'late onset':ab,ti OR 'noninsulin dependent':ab,ti OR 'non insulin dependent':ab,ti AND diabetes:ab,ti)	258,521

Table 4A: IPA Search Strategy

#	Query	Limiters/Expanders	Results
S1	TX NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR "late onset" OR "noninsulin dependent" OR "non insulin dependent") AND (diabetes))	Search modes - Boolean/Phrase	6,110
S2	TX "sodium-glucose co-transporter 2" OR sgl2 OR sglt2 OR gliflozin OR canagliflozin OR invokana OR sulisent OR "ta 7284" OR ta7284 OR "jnj 28431754" OR jnj28431754 OR dapagliflozin* OR farxiga OR forxiga OR "bms 512148" OR bms512148 OR empagliflozin* OR jardiance OR "bi 10773" OR bi10773 OR ipragliflozin* OR suglat OR "asp 1941" OR asp1941 OR luseogliflozin* OR lusefi OR "ts 071" OR ts071 OR remogliflozin* OR "kgt 1681" OR kgt1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR tofogliflozin* OR apleway OR deberza OR "CSG452" OR CSG452 OR ertugliflozin* OR "PF 04971729" OR PF04971729	Search modes - Boolean/Phrase	337
S3	S1 AND S2	Search modes - Boolean/Phrase	267
S4	TI randomized OR AB randomized OR TI randomised OR AB randomised OR TI placebo OR AB placebo OR TI randomly OR AB randomly OR TI trial	Search modes - Boolean/Phrase	59,232
S5	S3 AND S4	Search modes - Boolean/Phrase	130

Table 5A: ProQuest Search Strategy

all(NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR "late onset" OR "noninsulin-dependent" OR "non insulin dependent") AND (diabetes))) AND all("sodium-glucose co-transporter 2" OR SGL2 OR SGLT2 OR gliflozin* OR canagliflozin* OR invokana OR sulisent OR "TA 7284" OR TA7284 OR "JNJ 28431754" OR JNJ28431754 OR dapagliflozin* OR farxiga OR forxiga OR "BMS 512148" OR BMS512148 OR empagliflozin* OR jardiance OR "BI 10773" OR BI10773 OR ipragliflozin OR suglat OR "ASP 1941" OR ASP1941 OR luseogliflozin* OR lusefi OR "TS 071" OR TS071 OR remogliflozin* OR "KGT 1681" OR KGT1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR	3

tofogliflozin* OR apleway OR deberza OR "CSG 452" OR CSG452 OR ertugliflozin* OR "PF 04971729" OR PF04971729)	

Section 2: List of Extracted Variables

Table 6A. List of Extracted Variables

Variable Extraction	Notes
NCT Number, Author and Year	
Country in which the study was conducted	International if applicable
Start and End years	
Observation Period (# of weeks)	
Total number of participants randomized	
Number of Males	
Number of Females	
Background diabetes therapy	
Intervention 1: SGLT2 Agent	This was captured for as many interventions that were used.
Intervention 1: Dose	
Intervention 1: Number of Persons	
Intervention 1: Mean Age	
Intervention 1: Age SD	
Intervention 1: Mean baseline HbA1C	
Intervention 1: A1C SD	
Comparison 1: SGLT2 Agent	This was captured for as many comparison groups that were used.
Comparison 1: Dose	
Comparison 1: Number of Persons	
Comparison 1: Mean Age	
Comparison 1: Age SD	
Comparison 1: Mean baseline HbA1C	
Comparison 1: A1C SD	
Acute Kidney Injury Reported (yes/no)	
Urinary Tract Infection Reported (yes/no)	
Definition of UTI	
Ketoacidosis Reported (yes/no)	
Bone Fracture Reported (yes/no)	
Amputation Reported (yes/no)	
AKI: Outcomes in Intervention 1(n/N)	This was captured for each individual intervention and control group
AKI: Outcomes in Comparison 1 (n/N)	
UTI: Outcomes in Intervention 1(n/N)	

UTI: Outcomes in Comparison 1 (n/N)	
DKA: Outcomes in Intervention 1(n/N)	
DKA: Outcomes in Comparison 1 (n/N)	
BF: Outcomes in Intervention 1(n/N)	
BF: Outcomes in Comparison 1 (n/N)	
Amp: Outcomes in Intervention 1(n/N)	
Amp: Outcomes in Comparison 1 (n/N)	

Section 3: Study Characteristics

Table 7A: Included Study Characteristics

NCT# Author and Year	Country	Study Duration (weeks)	Total Randomized	Background Therapies	Intervention(s)	Comparator(s)	Outcomes Reported
NCT01059825 Amin, 2015	International	12	328	Prior therapy stabilized to metformin	Ertugliflozin 1mg, 5 mg, 10mg , 25mg	Placebo, Sitagliptin 100mg	UTI
NCT01059825 Amin, 2015	International	4	194	Uncontrolled on 2 agents	Ertugliflozin 1mg, 5mg, 25mg	Placebo	UTI
NCT02157298 Araki, 2016	Japan	16	182	Prior insulin therapy DPP4 allowed	Dapagliflozin 5 mg	Placebo	UTI, BF
NCT01368081 Araki	Japan	52	1160	Prior SU	Empagliflozin 10mg, 25mg	Metformin 50-2250mg/day	UTI, BF
NCT00528879 Bailey, 2013	International	102	546	Prior metformin	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI, AKI, BF
None Bailey, 2012	International	24	282	Treatment Naive	Dapagliflozin 1mg, 2.5mg, 5mg	Placebo	UTI, AKI, BF
NCT01164501 Barnett, 2014	International	52	741	Any prior therapies	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF
NCT01106651 Bode, 2015	International	104	716	Prior Naive mono or combo therapy	Canagliflozin 100mg, 300mg	Placebo	UTI, DKA, BF
NCT00855166 Bolinder, 2014	European	102	182	Prior metformin	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01031680 Cefalu, 2015	International	52	922	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, AKI, BF
NCT01505426 Lu, 2016	Korea and Taiwan	24	171	Prior metformin	Ipragliflozin 50mg	Placebo	UTI, BF
NCT01422876 DeFronzo, 2015	International	52	686	Prior metformin	Empagliflozin 10mg, 25mg	Linagliptin 5mg	UTI
NCT00660907 Prato, 2015	International	208	816	Prior metformin	Dapagliflozin (mixed dose)	Glipizide (mixed doses)	UTI, BF

NCT00881530 Ferrannini, 2013	International	78	271	Treatment Naive	Empagliflozin 10mg, 25mg	Metformin 2000mg max	UTI, BF
NCT00881530 Ferrannini, 2013	International	78	388	Prior metformin	Empagliflozin 10mg, 25mg	Sitagliptin 100mg	UTI, BF
NCT00528372 Ferrannini, 2010	International	24	485	Treatment Naive	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI
NCT01071850 Fonseca, 2013	India, Philippines, Columbia, Mexico, USA	12-	412	Treatment Naive	Ipragliflozin 12.5mg, 50mg, 150mg, 300mg	Placebo, Metormin 1500mg	UTI
NCT02229396 Frias, 2016	International	28	695	Prior metformin	Dapagliflozin 10mg	Exenatide 2mg	UTI, AKI, DKA
NCT01719003 Hadjadj, 2016	International	24	1364	Treatment Naive	Empagliflozin 10mg, 25mg	Metformin 1000mg, 2000mg	UTI, DKA, BF
NCT01289990 Haering, 2015	International	76	666	Prior Metformin and SU	Empagliflozin 10mg, 25mg	Placebo	UTI
None Heise, 2013	Germany	4	78	Not described	Empagliflozin 10mg, 25mg, 100mg	Placebo	UTI
None Heise, 2013	Germany	9 days	48	Prior Naive mono or combo therapy	Empagliflozin 2.5mg, 10mg, 25mg, 100mg	Placebo	UTI
NCT00643851 Henry, 2012	International	24	603	Treatment Naive	Dapagliflozin 5mg	Placebo	UTI, BF
NCT00643851 Henry, 2012	International	24	603	Treatment Naive	Dapagliflozin 5mg	Metformin (mixed doses)	UTI, BF
NCT00859898 Henry, 2012	International	24	641	Treatment Naive	Dapagliflozin 10mg	Placebo	UTI, BF
NCT00859898 Henry, 2012	International	24	641	Treatment Naive	Dapagliflozin 10mg	Metformin (mixed doses)	UTI, BF
NCT00800176 Ikeda; 2015	International	12	398	Naive or metformin	Tofogliflozin 2.5mg, 5mg, 10mg, 20mg, 40mg	Placebo	UTI, DKA
NCT02220920 Inagaki, 2016	Japan	16	146	Prior insulin therapy	Canagliflozin 100mg	Placebo	UTI, DKA, BF
NCT01387737 Inagaki, 2015	Japan	52	1299	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	No comparator	UTI, DKA, BF

NCT01022112 Inagaki, 2013	Japan	12	383	Any prior therapies washed-out	Canagliflozin 50mg, 100mg, 200mg, 300mg	Placebo	UTI, BF
NCT01413204 Inagaki, 2014	Japan	24	272	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	Placebo	UTI, BF
NCT02175784 Ishihara, 2016	Japan	16	262	Prior insulin others allowed	Ipragliflozin 50mg	Placebo	UTI
NCT00984867 Jabbour, 2013	International	48	451	Prior DPP4 maybe metformin no others	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01381900 Ji, 2015	International	18	678	Prior Metformin and maybe SU	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01095653 Ji, 2014	Asia	24	393	Treatment Naive	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
NCT01023945 Kadokura, 2014	Japan	2	30	Treatment Naive or monotherapy	Ipragliflozin 50mg , 100mg	Placebo	UTI
NCT01193218 Kadowaki, 2015	Japan	52	547	Treatment Naive or monotherapy	Empagliflozin 10mg, 25mg	No comparator	UTI, BF
NCT00972244 Kaku, 2013	Japan	12	279	Treatment Naive or 1 or 2 agents at low dose	Dapagliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo	UTI, BF
None Kaku, 2014	Japan	24	261	Treatment Naive or monotherapy	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Kaku, 2014	Japan	24	235	Treatment Naive or washout	Tofogliflozin 10mg, 20mg, 40mg	Placebo	UTI, BF
NCT01242215 Kashiwagi, 2015	Japan	52	245	Prior SU	Ipragliflozin 50mg	Placebo	UTI
NCT01057628 Kashiwagi, 2015	Japan	26	131	Treatment Naive or 1 or 2 agents at low dose	Ipragliflozin 50mg	Placebo	UTI
NCT00621868 Kashiwagi, 2014	Japan	12	361	Treatment Naive or washout	Ipragliflozin 12.5mg, 25mg, 50mg, 100mg	Placebo	UTI
NCT01316094 Kashiwagi,2015	Japan	52	165	Treatment Naive or 1 or 2 agents at low dose	Ipragliflozin 50mg	Placebo	UTI

NCT00663260 Kohan, 2014	International	104	252	Not described	Dapagliflozin 5mg, 10mg	Placebo	UTI, AKI, BF
NCT01210001 Kovacs, 2015	International	76	499	Prior pioglitizone and maybe metformin	Empagliflozin 10mg, 25mg	Placebo	UTI, BF
NCT00976495 Heerspink, 2013	International	12	75	Prior Metformin and maybe SU	Dapagliflozin 10mg	Placebo	UTI
NCT01106677 Lavalle-Gonzalez, 2013	International	52	1284	Prior Metformin and maybe SU but washed-out	Canagliflozin 100mg, 300mg	Sitagliptin 100mg	UTI, DKA, BF
NCT01042977 Leiter, 2014	International	52	964	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, AKI, BF
NCT00968812 Leiter, 2015	International	104	1450	Prior metformin	Canagliflozin 100mg, 300mg	Glimepiride 8mg	UTI, BF
NCT01422876 Lewin, 2015	International	52	677	Treatment Naive	Empagliflozin 10mg, 25mg	Linagliptin 5mg	UTI
NCT00263276 List, 2008	International	12	389	Treatment Naive	Dapagliflozin 2.5mg, 5mg, 10mg, 20mg, 50mg	Placebo, Metformin 1500mg max	UTI
NCT01646320 Mathieu, 2015	International	52	320	Prior metformin and DPP4	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01392677 Matthaei, 2015	International	52	219	Prior Metformin and SU	Dapagliflozin 10mg	Placebo	UTI
None Mudaliar, 2013	International	12	44	Prior Metformin and maybe SU	Dapagliflozin 5mg	Placebo	UTI
NCT01947855 Nishimura, 2015	Japan	4	60	Treatment or monotherapy	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA
NCT01340664 Qiu, 2014	International	18	279	Prior metformin	Canagliflozin 100mg, 300mg	Placebo	UTI
NCT01989754 Rodbard, 2016	International	26	218	Prior metformin and DPP4	Canagliflozin 300mg	Placebo	UTI, DKA, BF
NCT01289990 Roden, 2015	International	76	899	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg	UTI, DKA
NCT00642278 Rosenstock, 2012	International	12	451	Prior metformin	Canagliflozin 50mg, 100mg, 200mg, 300mg, 600mg	Placebo, Sitagliptin 100mg	UTI
NCT01376557	United States	12	299	Prior metformin	Sotagliflozin	placebo	UTI, BF

Rosenstock, 2015					75 mg, 200mg, 400mg		
NCT01809327 Rosenstock, 2016	International	26	1186	Treatment Naive	Canagliflozin 100mg, 300mg	Metformin 500mg	UTI, DKA
NCT01606007 Rosenstock, 2015	International	24	534	Prior metformin	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01306214 Rosenstock, 2014	International	52	563	Prior insulin therapy	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF
NCT01011868 Rosenstock, 2015	International	78	494	Prior insulin maybe metformin and SU	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA
NCT00683878 Rosenstock, 2012	International	48	420	Treatment Naive or stabilized on pioglitizine	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Ross, 2015	International	16	983	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI
None Sasaki, 2015	Japan	7 days	40	Treatment Naive	Luseogliflozin 0.5mg, 1mg, 2.5mg, 5mg	Placebo	UTI
NCT01137812 Schernthaner, 2013	International	52	756	Prior Metformin and SU	Canagliflozin 300mg	Sitagliptin 100mg	UTI, BF
NCT01217892 Schumm-Draeger, 2014	International	16	400	Prior metformin	Dapagliflozin 5mg, 10mg, 20mg	Placebo	UTI, BF
None Seino, 2014	Japan	12	239	Treatment Naive	Luseogliflozin 0.5mg, 2.5mg, 5mg	Placebo	UTI
None Seino, 2014	Japan	12	282	Treatment Naive	Luseogliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo	UTI, DKA
None Seino, 2014	Japan	24	158	Treatment Naive	Luseogliflozin 2.5mg	Placebo	UTI
NCT01081834 Stenlof, 2013	International	26	587	Treatment Naive or washout	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT00680745 Strojek, 2014	International	48	597	Prior SU	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI, BF
NCT00500331 Sykes, 2015	international	12	336	Treatment Naive	Remogliflozin 100mg, 200mg, 500mg, 1000mg, 2000mg	Placebo, Pioglitazone 30mg	UTI
NCT01370005 Tikkanen, 2015	International	12	825	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF

None Townsend, 2016	United States	6	171	Uncontrolled on 1-3 agents	Canagliflozin 100mg, 300mg	Placebo	UTI
None Seman, 2016	Malaysia	12	110	Prior Metformin and SU	Dapagliflozin 10mg	Sulphonylureas (various agents)	UTI
NCT01137474 Weber, 2016	International	12	944	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01195662 Weber, 2016	International	12	449	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01106625 Wilding; 2013	International	52	469	Prior Metformin and SU	Canagliflozin 100mg, 300mg	Placebo	UTI, DKA, BF
NCT01117584 Wilding, 2013	International	12	343	Prior metformin	Ipragliflozin 12.5mg, 50mg, 150mg, 300mg	Placebo	UTI
NCT00357370 Wilding, 2009	International	12	71	Any prior therapies	Dapagliflozin 10mg, 20mg	Placebo	UTI
NCT00673231 Wilding, 2014	international	104	808	Prior insulin others allowed	Dapagliflozin 2.5mg, 5/10mg, 10mg	Placebo	UTI, BF
NCT01064414 Yale, 2014	International	52	269	Treatment Naive or 1 or 2	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01316341 Zhao, 2015	China	9 days	24	Treatment Naive or 1 or 2	Empagliflozin 10mg, 25mg	Placebo	UTI
NCT01131676 Zinman, 2015	International	206	7028	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, DKA, BF
None Goto, 2012		24	168	Prior metformin	Ipragliflozin 50mg	Placebo	UTI
NCT02036515 Dagogo-Jack, 2017	International	26	463	Prior metformin and DPP4	Ertugliflozin 5mg, 15mg	Placebo	UTI, DKA, BF
NCT01734785 Maldonado-Lutomirsky, 2016	International	24	606	Prior metformin and DPP4	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, BF
NCT01289990 Merker, 2015	International	52	637	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI
NCT01032629 Neal, 2015	International	52	2074	Prior insulin therapy	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01167881 Ridderstrale, 2014	International	104	1549	Prior metformin	Empagliflozin 25mg	Glimepiride 1-4mg	UTI, AKI, BF

NCT00495469 Sykes, 2014	UK	12	252	Treatment Naive	Remogliflozin 100mg, 250mg, 500mg, 1000mg	Placebo, Pioglitazone 30mg	UTI, BF
None Tanizawa, 2014	Japan	52	194	Treatment Naive	Tofogliflozin 20mg, 40mg	No comparator	UTI
None Tanizawa, 2014	Japan	52	602	Any prior therapies	Tofogliflozin 20mg, 40mg	No comparator	UTI
NCT01095666 Yang, 2014		24	444	Prior metformin	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Gupta, 2017		76	108	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg	UTI
NCT02354235 Kadowaki, 2017	Japan	24	138	Prior Teneligliptin	Canagliflozin 100mg	Placebo	UTI, DKA, BF
NCT01734785 Softeland, 2017	International	24	333	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, DKA, BF
NCT01958671 Terra, 2017	International	26	461	Treatment Naive	Ertugliflozin 5mg, 15mg	Placebo	UTI
NCT 01022112 Not Published		12	383	Treatment Naive	Canagliflozin 50mg, 100mg, 200mg, 300mg	Placebo	BF
NCT02201004 Terauchi, 2017		16	211	Prior insulin therapy DPP4 allowed	Tofogliflozin 20mg, 40mg	Placebo	UTI
NCT01986855, Grunberger, 2018	International	52	468	Prior therapies (NOT metformin, pioglitizone)	Ertugliflozin 5mg, 15mg	Placebo	UTI, BF
NCT01999218, Hollander, 2018	International	52	1326	Prior metformin	Ertugliflozin 5mg, 15mg	Glimepiride	AKI, UTI, KA, BF
Ito, 2017	Japan	24	66	Treatment Naive or prior therapy (NOT glitizone or insulin)	Ipragliflozin 50mg	Pioglitazone 15-30mg	UTI, KA
NCT02099110, Pratley, 2017	International	52	1233	Prior metformin	Ertugliflozin 5mg, 15mg	Sitagliptin 100 mg	UTI, KA, BF
NCT02033889, Rosenstock, 2017	International	26	621	Prior metformin	Ertugliflozin 5mg, 15mg	Placebo	UTI, KA, F
Seino, 2018	Japan	16	233	Prior insulin	Luseogliflozin	Placebo	UTI

					2.5mg		
NCT02096705, Yang, 2018	Asia	24	272	Any prior antidiabetic	Dapagliflozin 10mg	Placebo	UTI, KA
NCT02429258, Henry, 2017	Unclear	4	100	Background metformin	Dapagliflozin 10mg	Placebo	UTI
NCT01606007, Ekholm, 2017	Unclear	24	534	Background metformin and saxagliptin	Dapagliflozin 10mg	Placebo	BF
Neal, 2017	International	188	10,142	Any background therapy	Canagliflozin 100-300mg	Placebo	UTI, AKI, DKA, BF, AMP

Section 4: Additional Forest Plots

Figure 1A: Risk of Acute Kidney Injury with SGLT2 Inhibitors compared to Active Comparators

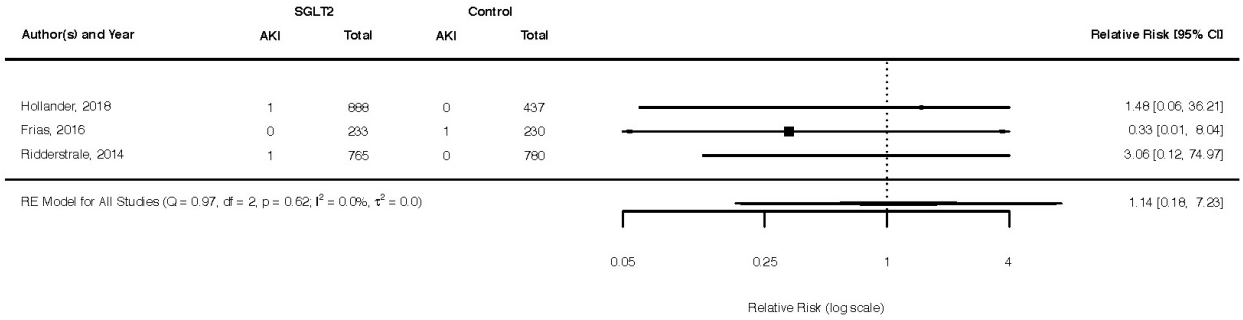


Figure 2A: Risk of Acute Kidney Injury with SGLT2 Inhibitors Compared to Placebo; excluding EMPA-REG.

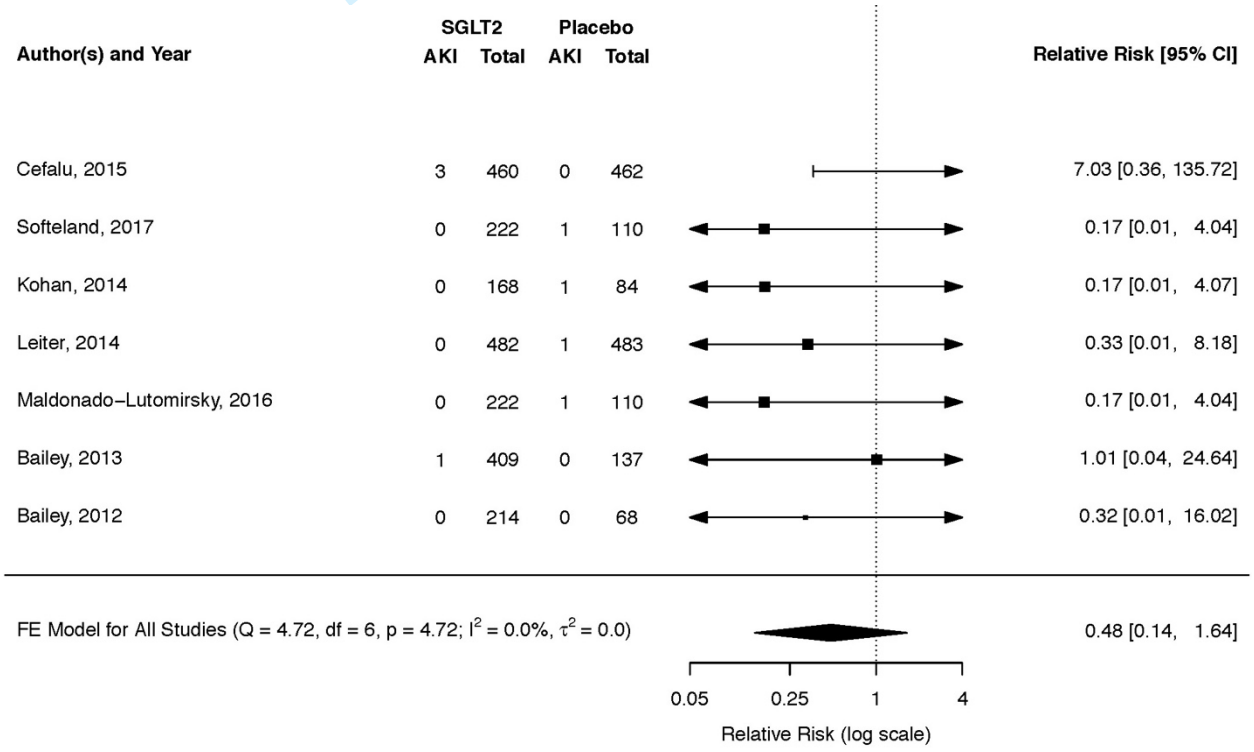


Figure 3A. Risk of Ketoacidosis among users of an SGLT2 Inhibitor compared to an Incretin

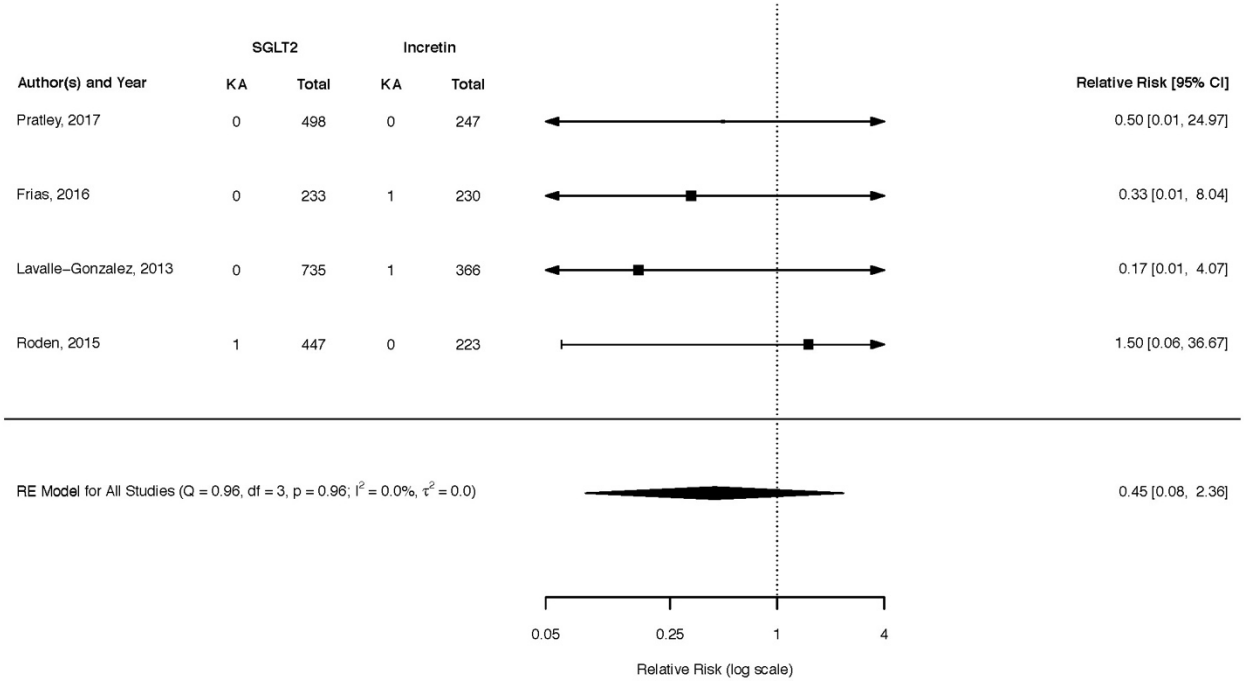


Figure 4A. Risk of Ketoacidosis among users of an SGLT2 Inhibitor Compared to Placebo in Studies with at least one Outcome

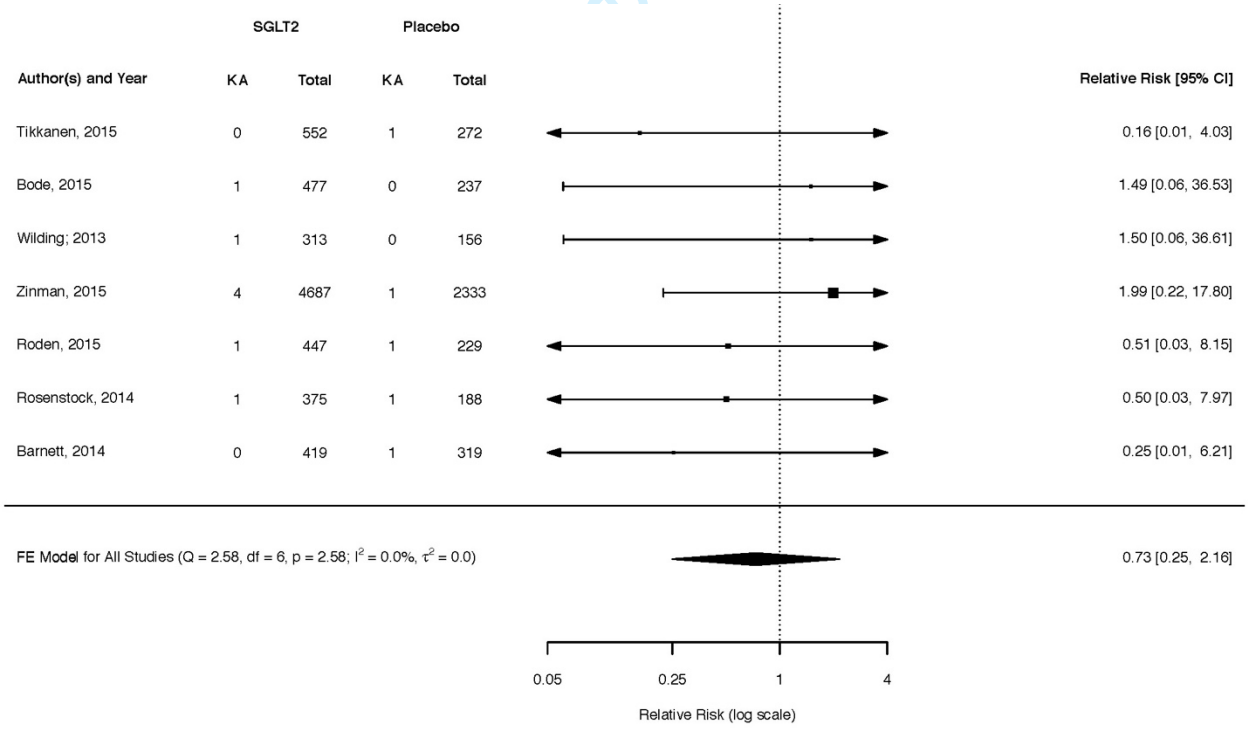


Figure 5A. Risk of Urinary Tract Infections among users of SGLT2 Inhibitors Compared to Active Controls

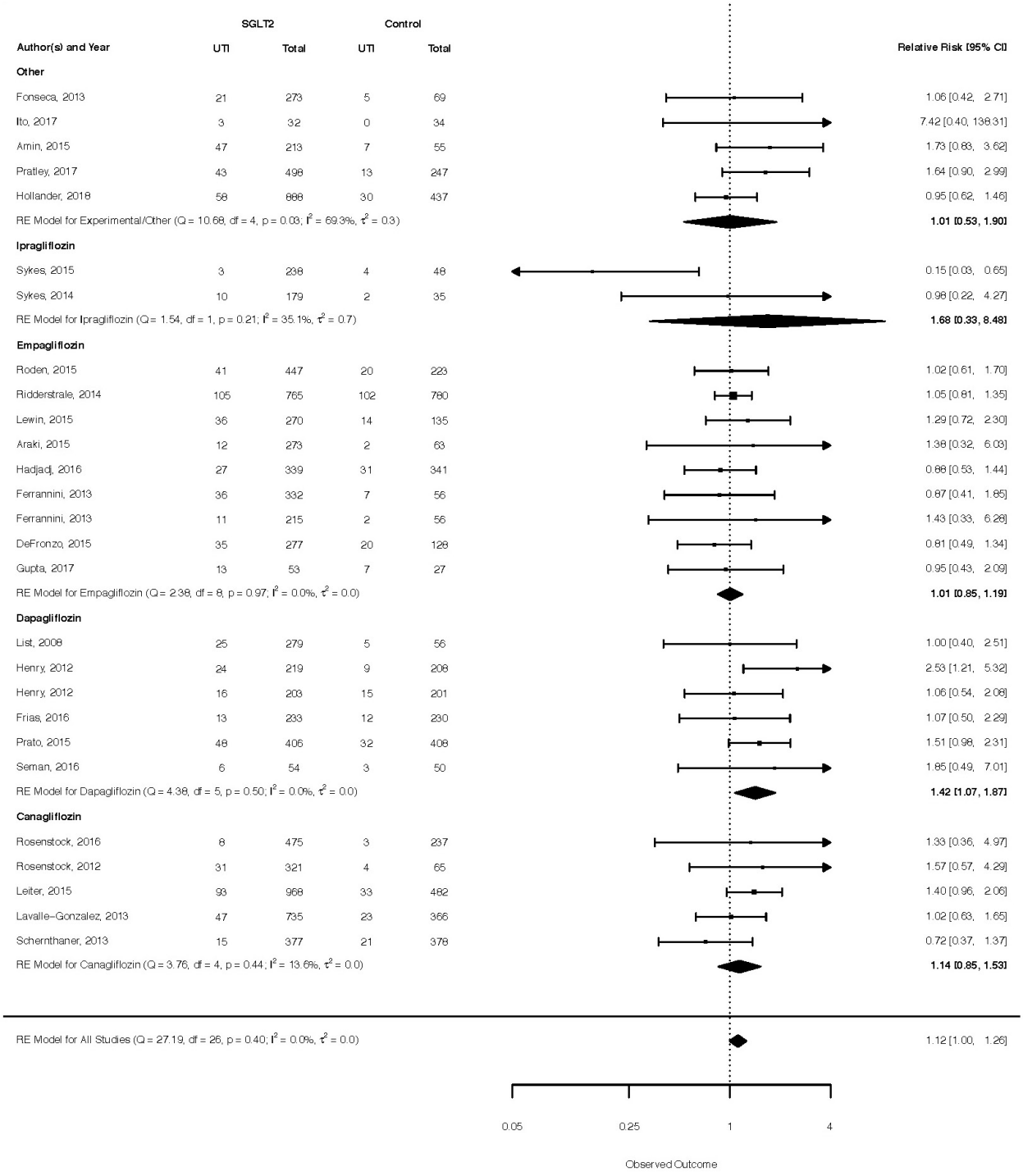


Figure 6A: Risk of Fracture with SGLT2 Inhibitors compared to Metformin

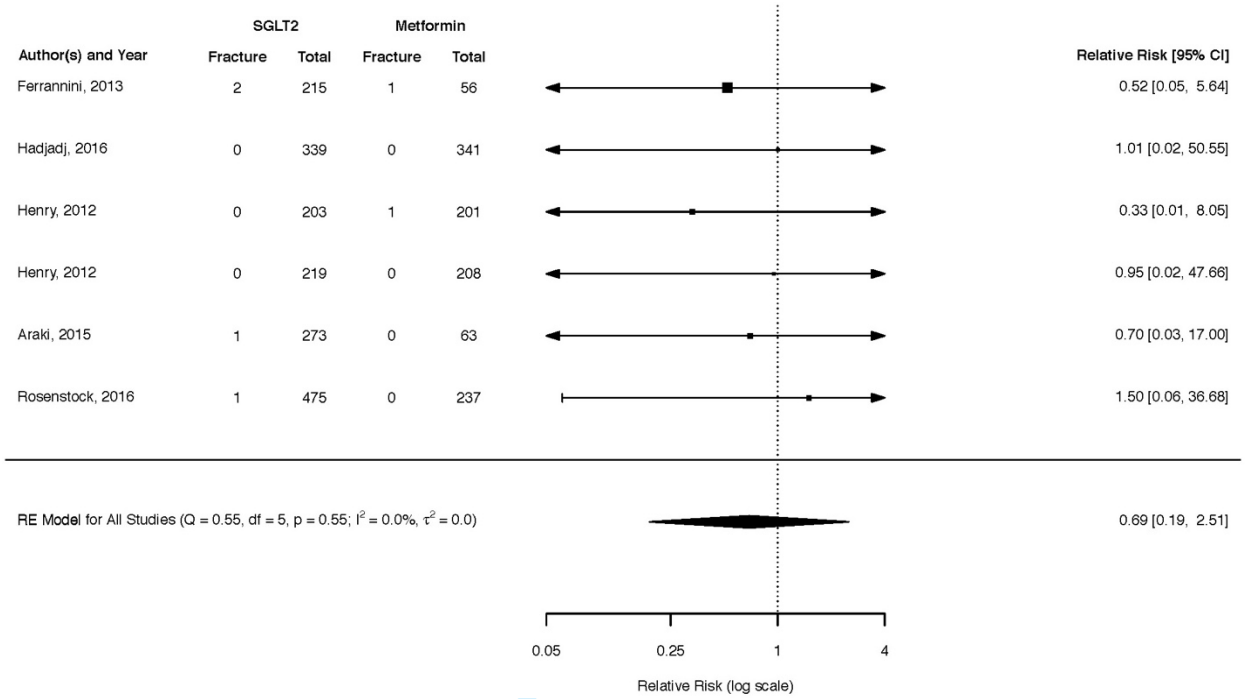


Figure 7A: Risk of Fracture with SGLT2 Inhibitors compared to Sulfonylureas

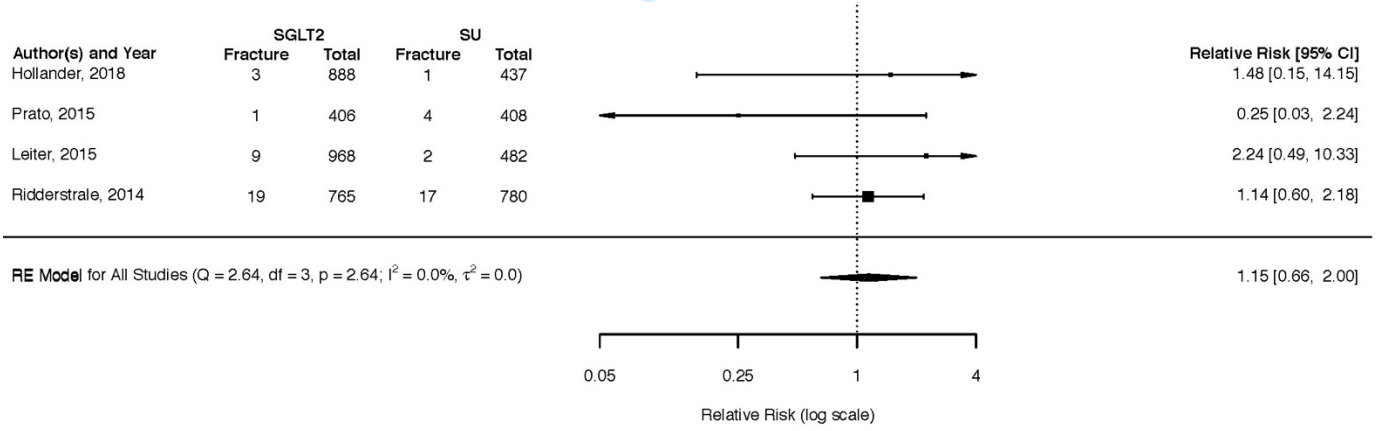


Figure 8A: Risk of Fracture with SGLT2 Inhibitors compared to Incretins

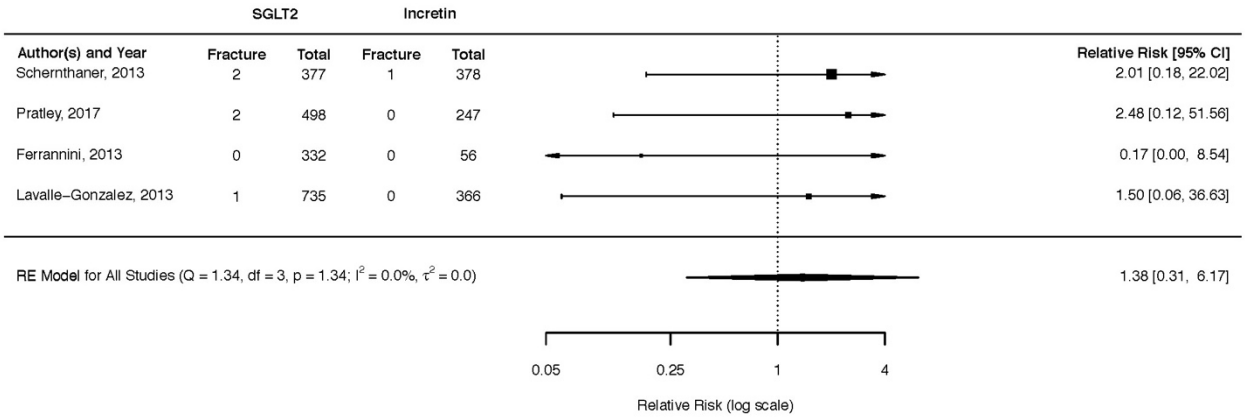
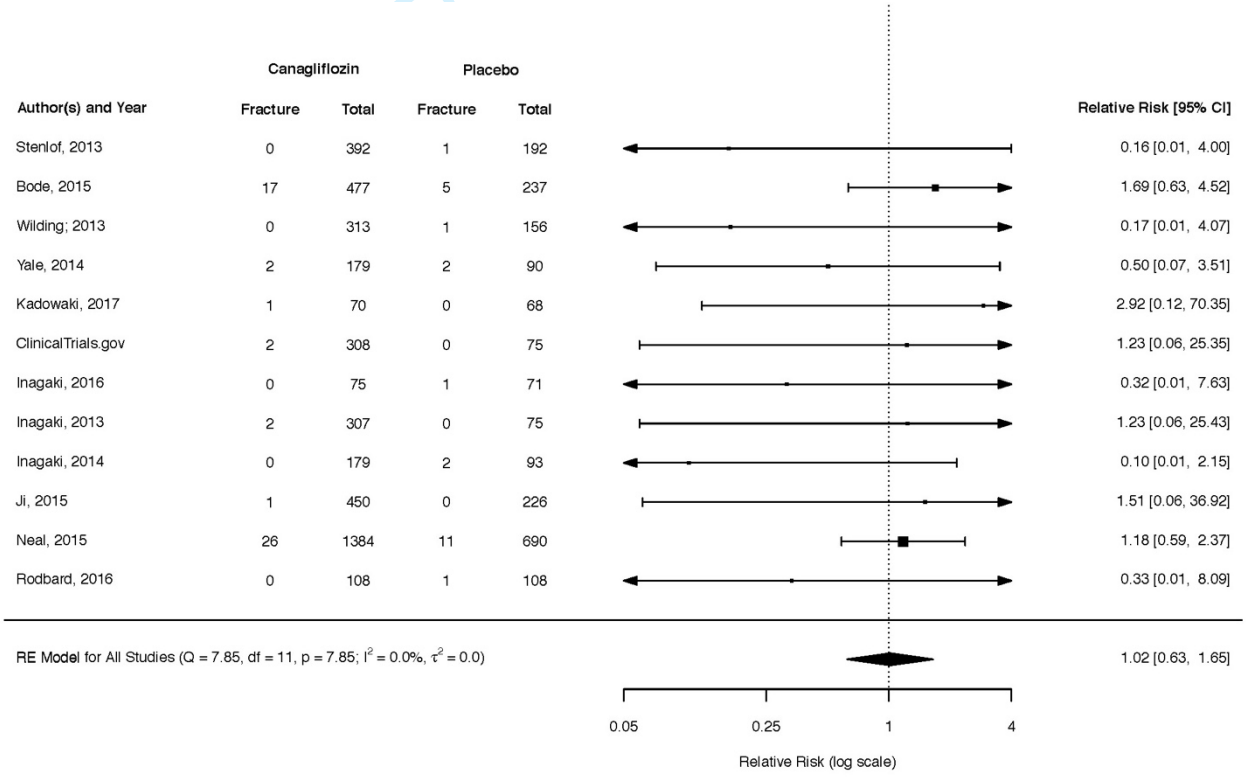


Figure 9A: Risk of Fracture with Canagliflozin compared to Placebo



Section 5: Forest Plots for Fixed Effects Analysis

Figure 10A. Risk of Acute Kidney Injury with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

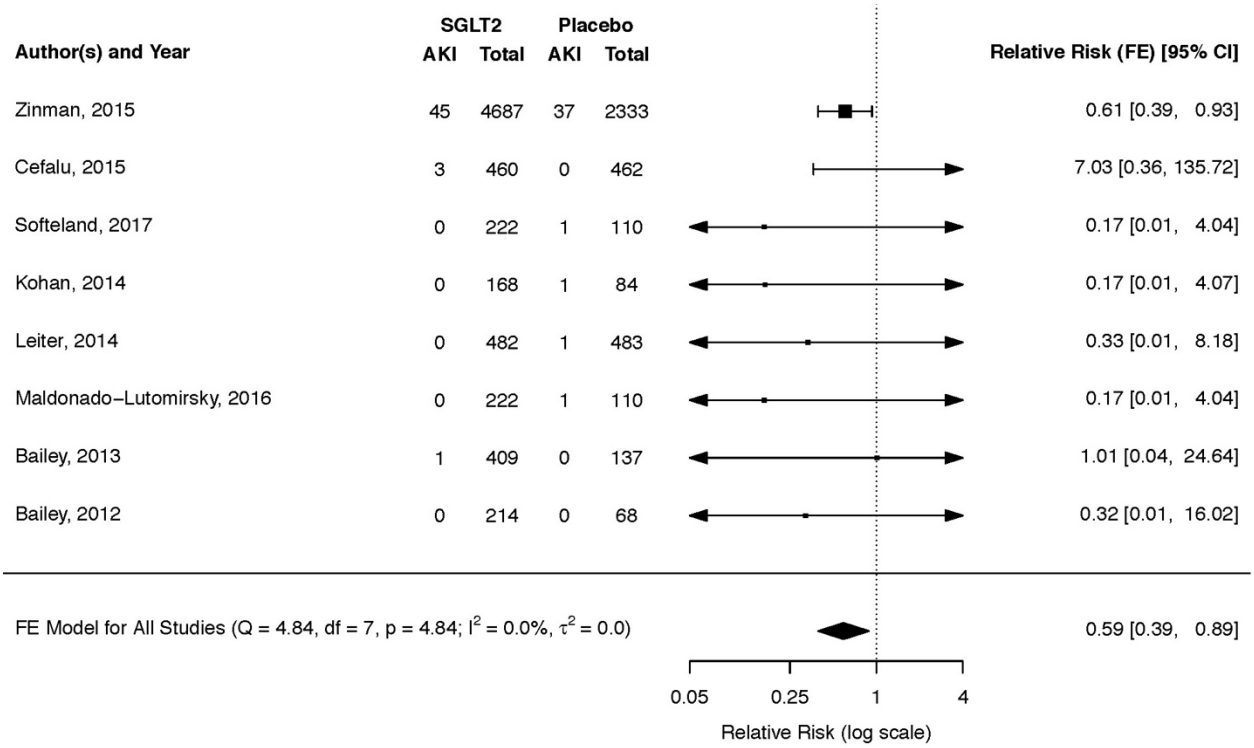


Figure 11A. Risk of Diabetic Ketoacidosis with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

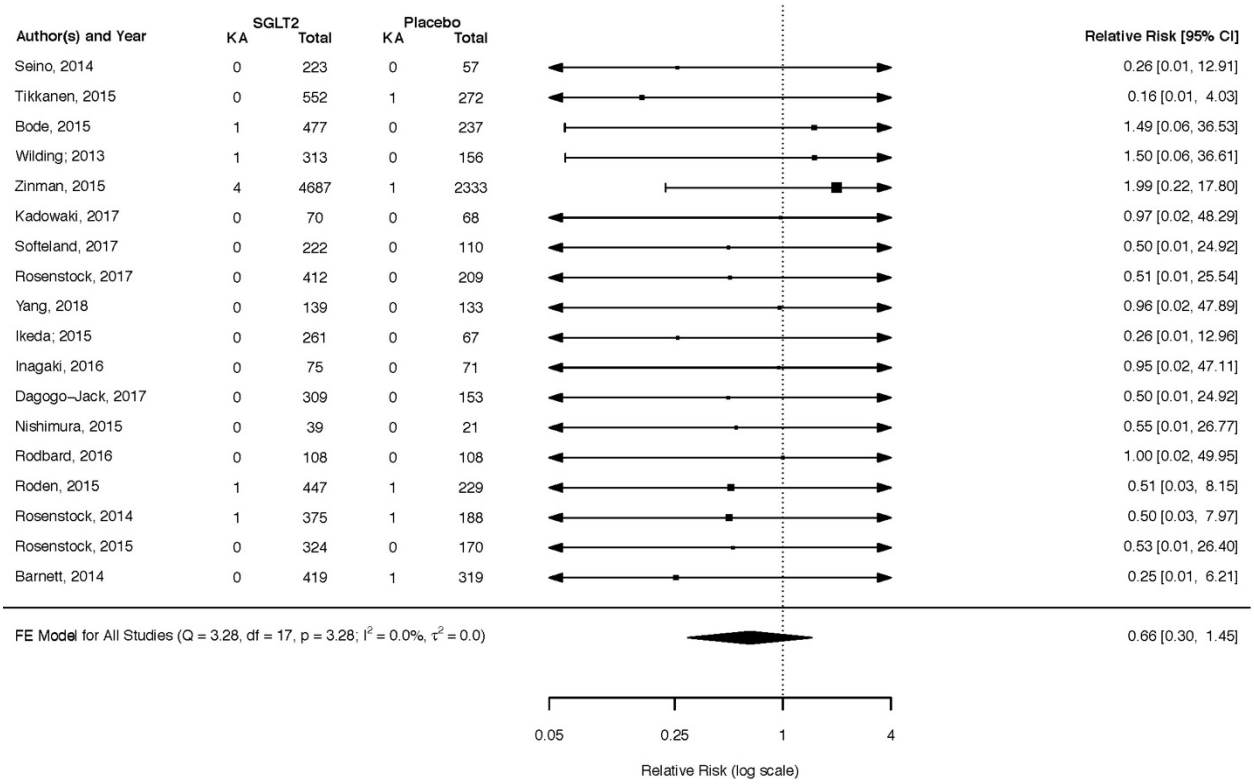


Figure 12A.Risk of Urinary Tract Infection with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

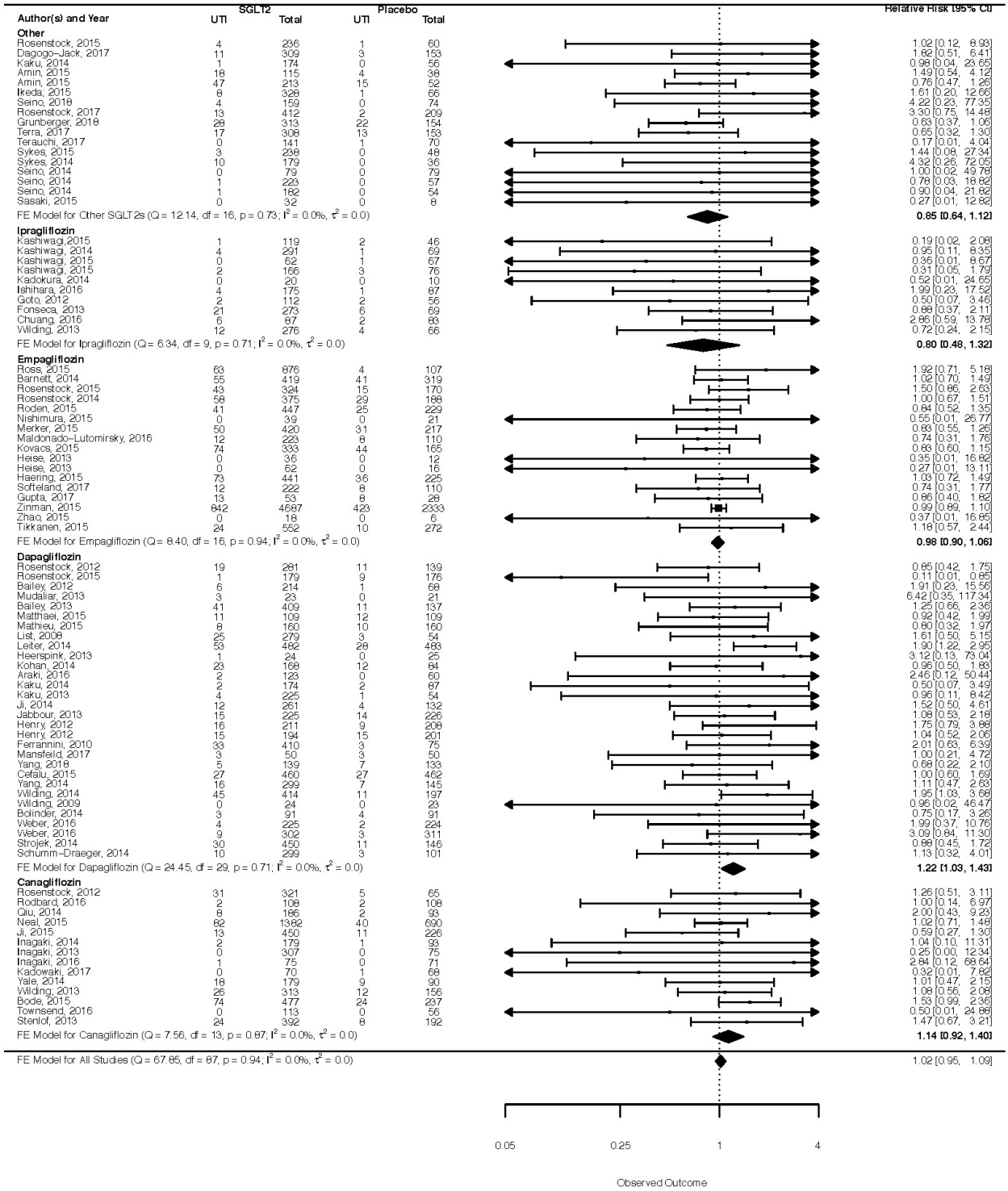
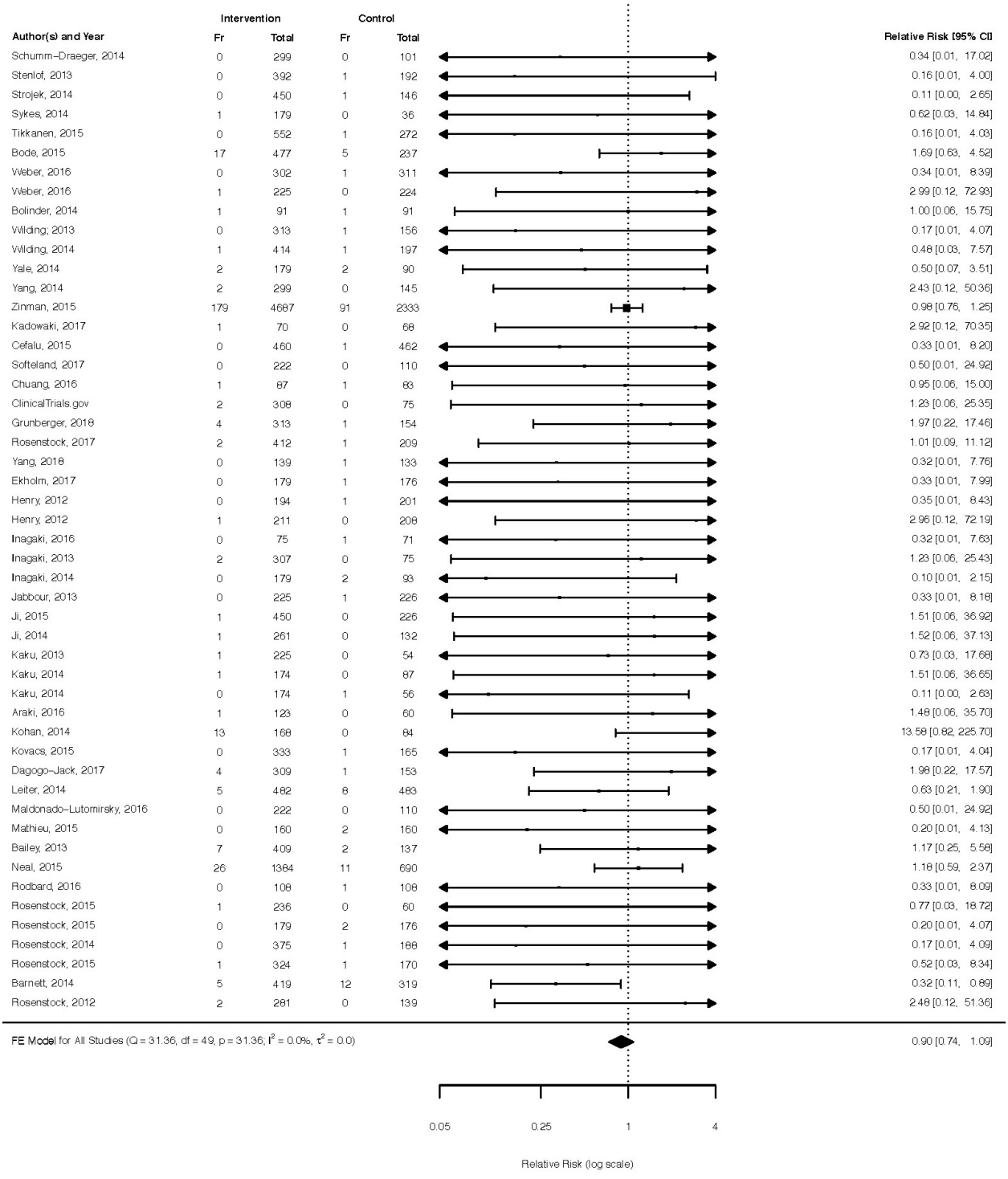


Figure 13A. Risk of Fracture with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model



Section 6: Risk of Bias Assessment

Table 7A. Risk of Bias Assessment for Included Studies

Author and Year	NCT#	Randomization Sequence	Allocation concealment	Double Blinding	Blinded Outcome Assessment	Incomplete Outcome	Selective Reporting	Other	Overall Assessment
Amin, 2015	NCT01059825	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
Amin, 2015	NCT01059825	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear risk	high
Araki, 2016	NCT02157298	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Araki	NCT01368081	Low Risk	Low Risk	Medium Risk	Unclear Risk	Low Risk	High Risk	Unclear risk	high
Bailey, 2013	NCT00528879	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk	Unclear Risk	Unclear risk	high
Bailey, 2012	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
Barnett, 2014	NCT01164501	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Bode, 2015	NCT01106651	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Bolinder, 2014	NCT00855166	Low Risk	Low Risk	Low Risk	Low Risk	low Risk	Low Risk	Unclear risk	low
Cefalu, 2015	NCT01031680	Low Risk	Low Risk	Medium Risk	Low Risk	Low Risk	High Risk	Low Risk	high
Chuang, 2016	NCT01505426	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
DeFronzo, 2015	NCT01422876	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Prato, 2015	NCT00660907	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ferrannini, 2013	NCT00881530	High Risk	High Risk	High Risk	High Risk	Low Risk	High Risk	Unclear risk	high
Ferrannini, 2010	NCT00528372	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear risk	high
Fonseca, 2013	NCT01071850	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Frias, 2016	NCT02229396	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Hadjadj, 2016	NCT01719003	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Haering, 2015	NCT01289990	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Heise, 2013	None	Low Risk	Low Risk	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear risk	high
Heise, 2013	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Henry, 2012	NCT00643851	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high

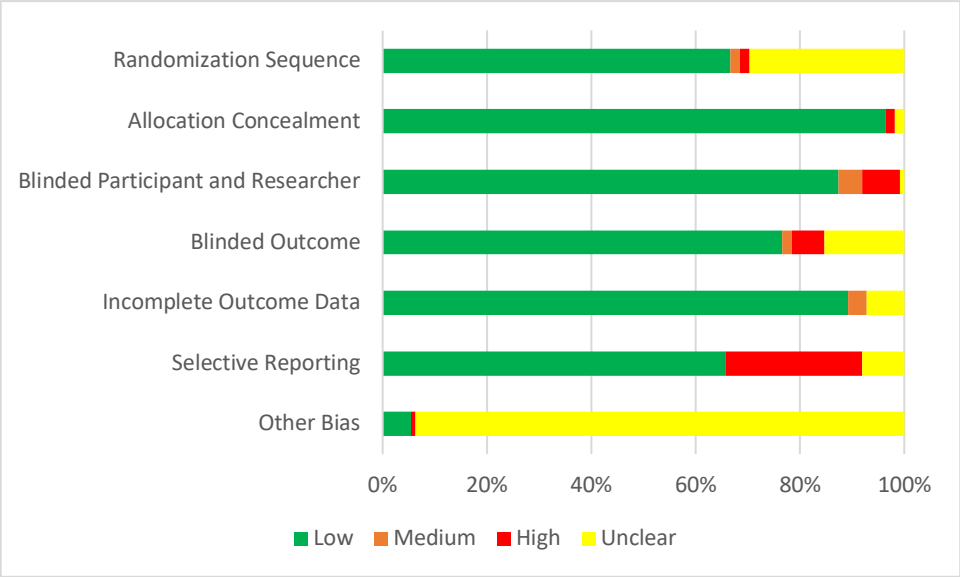
Henry, 2012	NCT00859898	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ikeda; 2015	NCT00800176	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Inagaki, 2016	NCT02220920	Low Risk	Low Risk	Low Risk	low Risk	Low Risk	Low Risk	Unclear risk	low
Inagaki, 2015	NCT01387737	Unclear Risk	Low Risk	High Risk	High Risk	Medium Risk	Unclear Risk	Unclear risk	high
Inagaki, 2013	NCT01022112	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Inagaki, 2014	NCT01413204	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ishihara, 2016	NCT02175784	Unclear Risk	Low Risk	Medium Risk	Low Risk	Low Risk	Low Risk	Low Risk	high
Jabbour, 2013	NCT00984867	Unclear Risk	Low Risk	Medium Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ji, 2015	NCT01381900	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ji, 2014	NCT01095653	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Kadokura, 2014	NCT01023945	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kadowaki, 2015	NCT01193218	Low Risk	Low Risk	Low Risk	Medium Risk	Low Risk	High Risk	Unclear risk	high
Kaku, 2013	NCT00972244	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	High Risk	Unclear risk	high
Kaku, 2014	none	Unclear Risk	low Risk	Low Risk	Unclear Risk	Medium Risk	Unclear Risk	Unclear risk	high
Kaku, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi, 2015	NCT01242215	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi, 2015	NCT01057628.	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi, 2014	NCT00621868	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi,2015	NCT01316094	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kohan, 2014	NCT00663260	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Kovacs, 2015	NCT01210001	Low Risk	Low Risk	Low Risk	Medium Risk	Low Risk	High Risk	Unclear risk	high
Heerspink, 2013	NCT00976495	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Lavalle-Gonzalez, 2013	NCT01106677	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Leiter, 2014	NCT01042977	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	low
Leiter, 2015	NCT00968812	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Lewin, 2015	NCT01422876	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
List, 2008	NCT00263276	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	high

Mathieu, 2015	NCT01646320	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Matthaei, 2015	NCT01392677	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Mudaliar, 2013	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	high
Nishimura, 2015	NCT01947855	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Qiu, 2014	NCT01340664	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Rodbard, 2016	NCT01989754	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Roden, 2015	NCT01289990	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2012	NCT00642278	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Rosenstock, 2015	NCT01376557	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Rosenstock, 2016	NCT01809327	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2015	NCT01606007	Low Risk	Low Risk	Low Risk	Low risk	Low Risk	Low Risk	Unclear risk	low
Rosenstock, 2014	NCT01306214	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2015	NCT01011868	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2012	NCT00683878	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Ross, 2015	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Sasaki, 2015	None	Low Risk	Low Risk	Medium Risk	High Risk	Unclear Risk	Unclear Risk	High Risk	high
Schernthaner, 2013	NCT01137812	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Schumm-Draeger, 2014	NCT01217892	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Seino, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Seino, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Seino, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Stenlof, 2013	NCT01081834	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear Risk	high
Strojek, 2014	NCT00680745	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Sykes, 2015	NCT00500331	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Tikkanen, 2015	NCT01370005	Medium Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	high
Townsend, 2016	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Seman, 2016	None	Unclear Risk	Low Risk	High Risk	High Risk	Unclear Risk	Unclear Risk	Unclear Risk	high

Weber, 2016	NCT01137474	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk	High Risk	Unclear Risk	high
Weber, 2016	NCT01195662	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Wilding; 2013	NCT01106625	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Wilding, 2013	NCT01117584	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Wilding, 2009	NCT00357370	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Wilding, 2014	NCT00673231	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Yale, 2014	NCT01064414	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Zhao, 2015	NCT01316341	Medium Risk	Low Risk	Low Risk	Low risk	Low Risk	Low Risk	Unclear Risk	high
Zinman, 2015	NCT01131676	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
Goto, 2012	None	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Dagogo-Jack, 2017	NCT02036515	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Maldonado-Lutomirsky, 2016	NCT01734785	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Merker, 2015	NCT01289990	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Neal, 2015	NCT01032629	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Ridderstrale, 2014	NCT01167881	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Sykes, 2014	NCT00495469	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Tanizawa, 2014	None	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Unclear Risk	high
Yang, 2014	NCT01095666	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Gupta, 2017	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Kadowaki, 2017	NCT02354235	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Softeland, 2017	NCT01734785	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Terra, 2017	NCT01958671	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
ClinicalTrials.gov		Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Terauchi, 2017	NCT02201004	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Grunberger, 2018	NCT01986855	Low Risk	Low Risk	High Risk	High Risk	High Risk	Low Risk	Unclear Risk	high
Hollander, 2018	NCT01999218	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low
Ito, 2017		Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Unclear risk	High

Pratley, 2017	NCT02099110	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low
Rosenstock, 2017	NCT02033889	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low
Seino, 2018		Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low
Yang, 2018	NCT02096705	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low
Mansfeild, 2017	NCT02429258	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low
Ekholm, 2017	NCT01606007	Unclear Risk	Low Risk	Low Risk	Low Risk	High Risk	High Risk	Unclear Risk	High

Figure 14A. Risk of Bias Assessment



Section 7: Assessment of Publication Bias

Figure 15A. Funnel Plot for Placebo Controlled Trials: Acute Kidney Injury

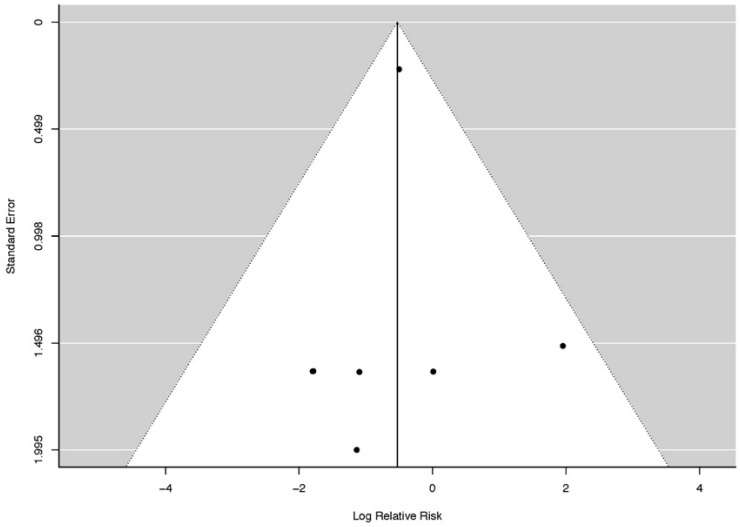


Figure 16A. Funnel Plot for Placebo Controlled Trials: Urinary Tract Infection

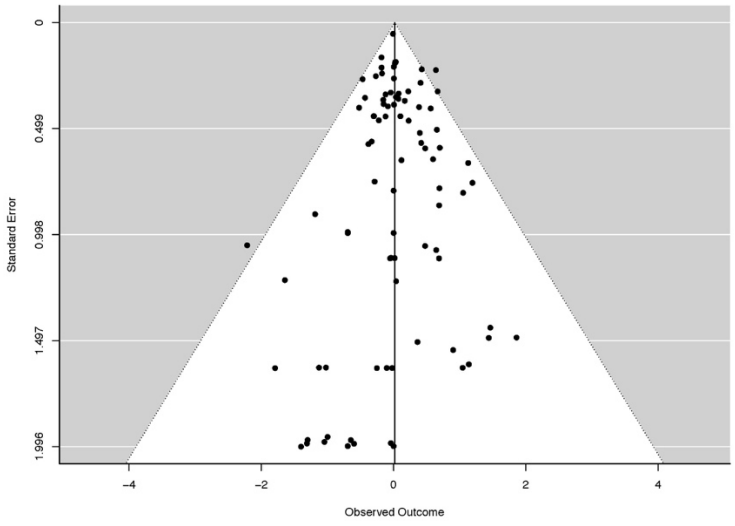


Figure 17A. Funnel Plot for Metformin Controlled Trials: Urinary Tract Infection

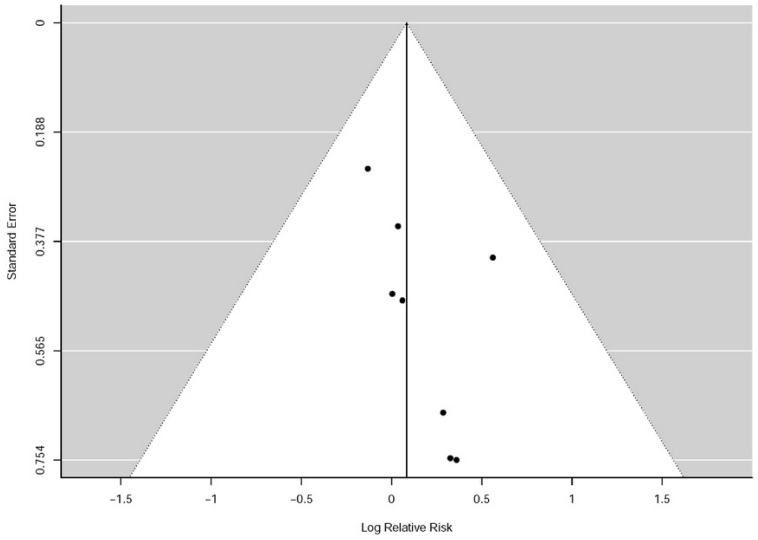


Figure 18A. Funnel Plot for Sulfonylurea Controlled Trials: Urinary Tract Infection

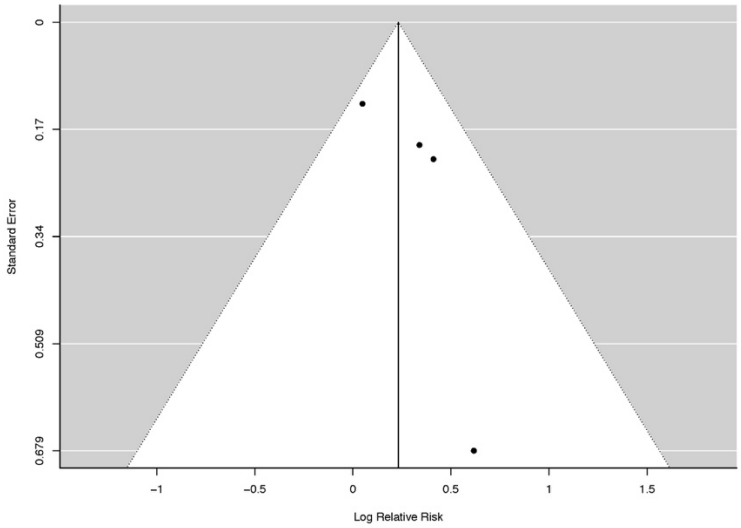


Figure 19A. Funnel Plot for Incretin Controlled Trials: Urinary Tract Infection

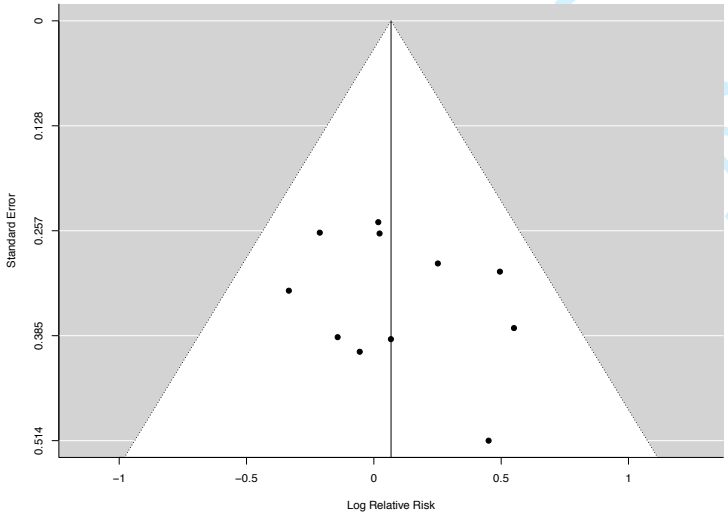
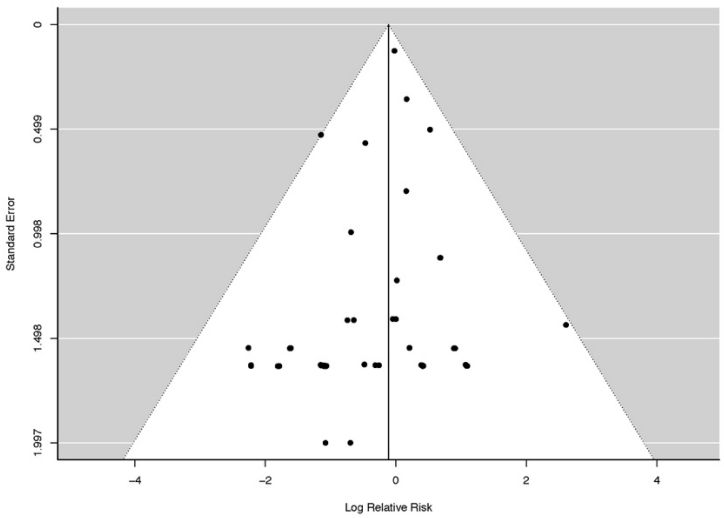


Figure 20A. Funnel Plot for Placebo Controlled Trials: Fracture



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	figures 2-6, appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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