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

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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 metaanalyses 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.

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 domainbased 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 12 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 antidiabetic 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

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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% Cl 0.28-1.50, $I^2 = 0.0\%$) (Figure 3) nor incretin (RR 0.43; 95% Cl 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% Cl 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

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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 metaanalyses 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 guality of the included studies given the fact we were examining secondary and rarely reported outcomes. It has been noted that traditional guality 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.

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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

Prior use of anti-diabetics	(95% CI, I ²)	# of Studies	Total # of outcomes/patients
KI			
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	
JKA			
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	
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	
racture			
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		1	
Low Risk of Blas	0.58 (0.38-0.89; 0.0%)	4	90/10,651
High Risk of Blas	0.71 (0.12-4.37; 25.5%)	4	
			10/10 100
LOW RISK OF Blas	0.89(0.26-3.01; 0.0%)	8	13/13,460
	0.49 (0.003-71.59; 94.8%)	8	
JII Lew Diek of Dies	0.00 (0.01 1.00; 0.0%)	47	2240/27 620
LOW RISK OF Blas		47	3318/37,038
	1.08 (0.11-10.64, 99.7%)	30	
Low Pick of Pice	0.05(0.77119;0.09/)	21	125/27 052
High Disk of Bigs	0.55(0.77-1.10, 0.076)	25	435/27,955
)efinition of LIT	0.50 (0.05-9.50, 97.070)	25	
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 for Included Studies

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

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

Figure 4. Risk of urinary tract infections with SGLT2 inhibitor compared to placebo

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

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

ns win. LT2 inhibitors compare.





411x240mm (300 x 300 DPI)

Author(s) and Year	SG AKI	LT2 Total	Pla AKI	cebo Total					Relative Risk [95% Cl
Zinman, 2015	45	4687	37	2333		F	∎-1		0.61 [0.39, 0.93
Cefalu, 2015	3	460	0	462		F			7.03 [0.36, 135.72
Softeland, 2017	0	222	1	110	-	-		-	0.17 [0.01, 4.04
Kohan, 2014	0	168	1	84	-				0.17 [0.01, 4.07
Leiter, 2014	0	482	1	483	-			-	0.33 [0.01, 8.18
Maldonado-Lutomirsky, 2016	0	222	1	110	-	•		-	0.17 [0.01, 4.04
Bailey, 2013	1	409	0	137	-				1.01 [0.04, 24.64
Bailey, 2012	0	214	0	68	◄				0.32 [0.01, 16.02
BE Model for All Studies ($\Omega = 4.84$ df	- 7 n - 4 84 [.]	1 ² - 0.0	%)				-		0.50.10.30 0.80
	– 7, p – 4.04,	1 = 0.0	/0)						0.03 [0.03, 0.03
					0.05	0.25	1	4	
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Figure 2. Risk of acute kidney injury with SGLT2 inhibitors compared to placebo

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Author(s) and Year	SG KA	LT2 Total	Pla KA	cebo Total					Relative Risk [95% CI]
Seino, 2014	0	223	0	57	-				0.26 [0.01, 12.91]
Tikkanen, 2015	0	552	1	272	-				0.16 [0.01, 4.03]
Bode, 2015	1	477	0	237					1.49 [0.06, 36.53]
Wilding; 2013	1	313	0	156					1.50 [0.06, 36.61]
Zinman, 2015	4	4687	1	2333		H			1.99 [0.22, 17.80]
Kadowaki, 2017	0	70	0	68	-				0.97 [0.02, 48.29]
Softeland, 2017	0	222	0	110	-				0.50 [0.01, 24.92]
Ikeda; 2015	0	261	0	67	-				0.26 [0.01, 12.96]
Inagaki, 2016	0	75	0	71	-				0.95 [0.02, 47.11]
Dagogo-Jack, 2017	0	309	0	153	-				0.50 [0.01, 24.92]
Nishimura, 2015	0	39	0	21	-				0.55 [0.01, 26.77]
Rodbard, 2016	0	108	0	108	-				1.00 [0.02, 49.95]
Roden, 2015	1	447	1	229	-				0.51 [0.03, 8.15]
Rosenstock, 2014	1	375	1	188	-				0.50 [0.03, 7.97]
Rosenstock, 2015	0	324	0	170	-				0.53 [0.01, 26.40]
Barnett, 2014	0	419	1	319	-			→	0.25 [0.01, 6.21]
RE Model for All Studies (C	2 = 3.23, df =	15, p = 3.23	; l ² = 0.0%)			-		0.65 [0.28, 1.50]
					0.05	0.25	1	4	
						Relative Risk (log scale)		

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

279x215mm (300 x 300 DPI)

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	so	iLT2	Co	ntrol
luthor(s) and Year	UΠ	Total	υTI	Total
har				
min, 2015	47	213	7	65
onseca, 2013	21	273	5	69
kes, 2015	з	298	4	48
kes, 2014	10	179	2	35
Model for Experimental/Other	(Q = 8.51, df = 3,	p = 0.04; I ² = 67	.8%)	
pagliflozin den 2015	41	447	20	223
iderstrale. 2014	105	765	102	780
vin 2015	36	270	14	135
ki	12	273	2	63
djadj. 2016	27	339	31	341
rannini, 2013	36	332	7	56
rannini, 2013	11	215	2	55
Fronzo, 2015	35	277	20	128
pta, 2017	13	53	7	27
Model for Empagliflozin (Q= 2	238, df = 8, p = 0.	97, $\mathbf{I}^2 = 0.0\%$)		
paglitlozin t, 2008	25	279	5	56
ry 2012	24	219	9	208
ry, 2012	16	203	15	201
2016	13	233	12	230
, 2015	48	406	32	408
n, 2016	6	54	3	50
fodel for Dapagliflozin ($Q = 4$.	38, df = 5, p = 0.9	50; I ² = 0.0%)		
agliflozin				
anstock, 2016	8	475	3	237
senstock, 2012	31	321	4	65
er, 2015	93	968	33	482
are-Gonzalez, 2013	47	735	23	366
erntnaner, 2013	15	377	21	378
Viodel for Canagliflozin (Q = 3.	.76, df = 4, p = 0.4	44, I° = 13.6%)		
E Model for All Studies (Q = 23.4	17, df = 23, p = 0-	43; I ² = 0.0%)		

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

215x279mm (300 x 300 DPI)

	SG	LT2	Pla	cebo
Author(s) and Year	Fr	Tot al	Fr	Total
Schumm-Draeger, 2014	0	299	0	101
Steniof, 2013	0	392	1	192
Strojek, 2014	0	450	1	146
Sykes, 2014	1	179		36
Tikkanen, 2015		552	1	272
Bode, 2015	17	477	5	237
Weber, 2016	0	302	1	311
Weber, 2016	1	225		224
Bolinder, 2014	1	91	1	91
Wilding; 2013		3.13	1	156
Wilding, 2014	1	414	1	197
Yale, 2014	2	179	2	90
Yang, 2014	2	299		145
Zinman, 2015	179	4687	91	2333
Kadowaki, 2017	1	70		68
Cefalu, 2015		460	1	462
Softeland, 2017		222		110
Chuano, 2016	1	87	1	83
ClinicalTrials gov	2	308		75
Henry 2012		194	1	201
Henry 2012	1	911		208
Inacaki 2016		75	1	71
Inscriti 2013	9	9.07		76
Inagaki 2014	0	170		02
Johner 2013		0.05	2	00
5 2015		450		005
5,0014		450		220
ul, 2019 Keley, 0010	1	261	0	132
Naku, 2013	1	252	0	54
каки, 2014	1	174		87
Kaku, 2014		174	1	56
Araki, 2016	1	123	0	60
Kohan, 2014	13	168		84
Kovacs, 2015	0	333	1	165
Dagogo-Jack, 2017	4	3.09	1	153
Leiter, 2014	5	482	8	483
Maldonado-Lutomirsky, 2016	0	222	0	110
Mathieu, 2015	0	160	2	160
Bailey 2013	7	409	5	13.7
Neal, 2015	26	1384	11	690
Rodbard, 2016		108	1	100
Rosenstock, 2015	1	236		60
Rosenstock, 2015	0	179	2	176
Rosenstock, 2014	0	375	1	188
Rosenstock, 2015	1	324	1	170
	5	419	12	319
Barnett 2014	~	-1.1.4	16	0.0
Barnett, 2014 Rosenstock, 2012	2	281		19.0



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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	Interventio n: 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 inpagliflozin [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 etabonate " [Supplementary Concept] OR remogliflozin etabonate " [Supplementary Concept] OR remogliflozin etabonate" [Supplementary Concept] OR remogliflozin [tw] OR KGT 1681 [tw] OR "LX 4221" [tw] OR LX 4221 [tw] OR "KGT 1681" [tw] OR sotagliflozin* [tw] OR "LX 4221" [tw] OR LX 4221 [tw] OR "6-((4- ethylphenyl)-3',4',5',6'-tetrahydro-6'- (hydroxymethyl)-siro(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 CSG 452 [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 sotagliflozin* [tw] OR BE 04971729" [tw] OR BE04971729" [tw]	2323
3	#1 AND #2		1649
4	Study Type Filter: Cochrane Highly Sensitive Search Strategy for identifying randomize	("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
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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	random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	1,440,006
RCT filter from		

Wong best sensi speci	g 2006, balance of tivity and ficity			
#3		#1 AND #2		3,811
#2		'sodium glucose cotransporter 2'/de OR 'sodiu cotransporter 2 inhibitor'/exp OR 'sodium-glu 2':ab,ti OR sgl2:ab,ti OR sglt2:ab,ti OR gliflozin canagliflozin*:ab,ti OR invokana:ab,ti OR sulis 7284':ab,ti OR ta7284:ab,ti OR 'jnj 28431754': jnj28431754:ab,ti OR dapagliflozin*:ab,ti OR f forxiga:ab,ti OR 'bms 512148':ab,ti OR bms512 empagliflozin*:ab,ti OR jardiance:ab,ti OR 'bi bi10773:ab,ti OR ipragliflozin*:ab,ti OR suglat OR asp1941:ab,ti OR luseogliflozin*:ab,ti OR lu 071':ab,ti OR ts071:ab,ti OR remogliflozin*:ab kgt1681:ab,ti OR sotagliflozin*:ab,ti or 'LX 422 or tofogliflozin*:ab,ti or apleway:ab,ti or debe 452':ab,ti or CSG452:ab,ti or ertugliflozin*:ab, or PF04971729:ab,ti	um glucose cose co-transporter *:ab,ti OR ent:ab,ti OR 'ta ab,ti OR arxiga:ab,ti OR 2148:ab,ti OR 10773':ab,ti OR :ab,ti OR 'asp 1941':ab,ti usefi:ab,ti OR 'ts ,ti OR 'kgt 1681':ab,ti OR 21':ab,ti or LX4221:ab,ti erza:ab,ti or 'CSG ti or 'PF 04971729':ab,ti	5,218
#1		'non insulin dependent diabetes mellitus'/de (t2dm:ab,ti OR ('type 2':ab,ti OR 'type ii':ab,ti O 'mature onset':ab,ti OR 'late onset':ab,ti OR 'n dependent':ab.ti OR 'non insulin dependent':a	OR niddm:ab,ti OR OR 'adult onset':ab,ti OR Ioninsulin Ib.ti AND diabetes:ab.ti)	239,937
Table 4	4A: IPA Searc	Ch Strategy	Search modes -	5,907
	onset" OR "noninsulir AND (diabe	"mature onset" OR "late onset" OR n dependent" OR "non insulin dependent") etes))	Boolean/Phrase	

Table 4A: IPA Search Strategy

	dependent':ab,ti OR 'non insulin dependent'	ab,ti AND diabetes:ab,ti)	
Table 4	A: 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

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	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" OR3"late onset" OR "noninsulin-dependent" OR "non insulin dependent") AND (diabetes)))AND all("sodium-glucose co-transporter 2" OR SGL2 OR SGLT2 OR gliflozin* OR3canagliflozin* OR invokana OR sulisent OR "TA 7284" OR TA7284 OR "JNJ 28431754" ORJNJ28431754 OR dapagliflozin* OR farxiga OR forxiga OR "BMS 512148" OR BMS5121480OR 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 OR7remogliflozin* OR "KGT 1681" OR KGT1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR11tofogliflozin* OR apleway OR deberza OR "CSG 452" OR CSG452 OR ertugliflozin* OR "PF04971729" 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
Intervention 1: Dose	used.
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
Comparison 1: Dose	were used.
Comparison 1: Number of Persons	
Comparison 1: Mean Age	
Comparison 1: Age SD	4
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
AKI: Outcomes in Comparison 1 (n/N)	control group
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 i	n Intervention 1(n/N)	
Amp: Outcomes i	n Comparison 1 (n/N)	
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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

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NCT00881530	International	78	271	Treatment Naive	Empagliflozin	Metformin 2000mg	UTI, BI
Ferrannini, 2013					10mg, 25mg	max	
NCT00881530 Ferrannini, 2013	International	78	388	Prior metformin	Empagliflozin 10mg, 25mg	Sitagliptin 100mg	UTI, B
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, A
NCT01719003 Hadjadj, 2016	International	24	1364	Treatment Naive	Empagliflozin 10mg, 25mg	Metformin 1000mg, 2000mg	UTI, D
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, B
NCT00643851 Henry, 2012	International	24	603	Treatment Naive	Dapagliflozin 5mg	Metformin (mixed doses)	UTI, B
NCT00859898 Henry, 2012	International	24	641	Treatment Naive	Dapagliflozin 10mg	Placebo	UTI, B
NCT00859898 Henry, 2012	International	24	641	Treatment Naive	Dapagliflozin 10mg	Metformin (mixed doses)	UTI, B
NCT00800176 Ikeda; 2015	International	12	398	Naive or metformin	Tofogliflozin 2.5mg, 5mg, 10mg, 20mg, 40mg	Placebo	UTI, D
NCT02220920 Inagaki, 2016	Japan	16	146	Prior insulin therapy	Canagliflozin 100mg	Placebo	UTI, D
NCT01387737 Inagaki, 2015	Japan	52	1299	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	No comparator	UTI, D

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

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NCT00663260 Kohan. 2014	International	104	252	Not described	Dapagliflozin 5mg. 10mg	Placebo	UTI, A
NCT01210001 Kovacs, 2015	International	76	499	Prior pioglitizone and maybe metformin	Empagliflozin 10mg, 25mg	Placebo	UTI, E
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, D
NCT01042977 Leiter, 2014	International	52	964	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, A
NCT00968812 Leiter, 2015	International	104	1450	Prior metformin	Canagliflozin 100mg, 300mg	Glimepiride 8mg	UTI, E
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, E
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, E
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, E
NCT01289990 Roden, 2015	International	76	899	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg	UTI, E
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, E

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

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

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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.

	so	LT2	Pla	cebo				
Author(s) and Year	AKI	Total	AKI	Total				Relative Risk [95% CI]
Cefalu, 2015	3	460	0	462		H		7.03 [0.36, 135.72]
Softeland, 2017	0	222	1	110	-	-		0.17 [0.01, 4.04]
Kohan, 2014	0	168	1	84	-			0.17 [0.01, 4.07]
Leiter, 2014	0	482	1	483	-	∎	►	0.33 [0.01, 8.18]
Maldonado-Lutomirsky, 2016	0	222	1	110	-	-		0.17 [0.01, 4.04]
Bailey, 2013	1	409	0	137	◄		* *	1.01 [0.04, 24.64]
Bailey, 2012	0	214	0	68	-			0.32 [0.01, 16.02]
RE Model for All Studies (Q = 4.72, df = 6, p	= 4.72;	l ² = 0.0	%)					0.48 [0.14, 1.64]
					[1	- 1	
					0.05	0.25	1 4	
					R	elative Risk (lo	g scale)	

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

SG	LT2	Co	ntrol
UΠ	Total	UΠ	Total
47	213	7	55
21	273	5	69
3	238	4	48
10	179	2	35
8.51, df = 3,	$p = 0.04; I^2 = 67$.8%)	
41	447	20	223
105	765	102	780
36	270	14	135
12	273	2	63
27	339	31	341
36	332	7	56
11	215	2	56
35	277	20	128
13	53	7	27
df = 8 n = 0.9		,	21
25	270	E	56
21	2/3	5	300
16	219	9	200
10	203	15	201
13	233	12	230
48	406	32	408
6	54	3	50
ar = 5, p = 0.5	i∪; l* = 0.0%)		
8	475	3	237
31	321	4	65
93	968	33	482
47	735	23	366
15	377	21	378
df = 4, p = 0.4	4; I ² = 13.6%)		
f = 23, p = 0.4	l3; l ² = 0.0%)		
	SG UT 47 21 3 10 8.51, df = 3, 1 41 105 36 12 27 36 11 35 13 41 13 36 12 27 36 11 35 13 41 13 36 12 27 36 11 35 13 41 13 41 13 48 16 17 27 36 11 35 13 48 16 17 17 27 36 11 35 13 48 16 13 48 16 13 48 16 17 17 27 36 11 36 12 27 36 11 34 13 48 16 17 27 36 17 27 36 17 27 36 17 27 36 17 27 36 17 27 36 17 27 36 17 27 36 17 27 36 17 27 36 17 27 36 13 48 6 16 17 27 36 17 27 24 16 13 48 6 5 17 27 24 16 13 48 6 5 17 27 24 16 13 48 6 5 17 27 24 16 13 48 6 5 17 27 17 48 15 13 48 6 17 17 17 17 17 17 17 17 17 17 17 17 17	SGLT2 UT Total 47 213 21 273 3 236 10 179 851, df = 3, p = 0.04, l ² = 67 41 447 105 765 36 270 12 273 27 339 36 332 11 215 35 277 13 53 df = 6, p = 0.97, l ² = 0.0%) 25 279 24 219 16 203 13 233 48 406 6 54 df = 5, p = 0.50; l ² = 0.0%) 8 47 735 15 377 df = 4, p = 0.43; l ² = 13.6%)	SGLT2 Co UT Total UT 47 213 7 21 273 5 3 298 4 10 179 2 851. df = 3, p = 0.04, l ² = 6789 102 41 447 20 105 765 102 36 270 14 12 273 2 36 322 7 36 322 7 36 322 7 37 20 3 36 322 7 37 53 7 38 277 20 39 53 7 41 215 2 36 322 7 31 233 7 13 233 12 48 406 32 6 54 3 31 321 4



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



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

	Canagli	iflozin	Plac	ebo
Author(s) and Year	Fracture	Total	Fracture	Total
Stenlof, 2013	0	392	1	192
Bode, 2015	17	477	5	237
Wilding; 2013	0	313	1	156
Yale, 2014	2	179	2	90
Kadowaki, 2017	1	70	0	68
ClinicalTrials.gov	2	308	0	75
Inagaki, 2016	0	75	1	71
Inagaki, 2013	2	307	0	75
Inagaki, 2014	0	179	2	93
Ji, 2015	1	450	0	226
Neal, 2015	26	1384	11	690
Rodbard, 2016	0	108	1	108
RF Model for All Studies (Q	= 7 85 df = 11 p =	= 7 85 [·] 1 ² = 0	0%)	
	· · · · · · · · · · · · · · · · · · ·	,.	,	

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Section 5: Forest Plots for Fixed Effects Analysis

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



	SC	GLT2	Pla	cebo					
Author(s) and Year	KA	Total	KA	Total					Relative Risk [95% Cl
Seino, 2014	0	223	0	57	-	•			0.26 [0.01, 12.91]
Tikkanen, 2015	0	552	1	272	-	•			0.16 [0.01, 4.03]
Bode, 2015	1	477	0	237		-			1.49 [0.06, 36.53]
Wilding; 2013	1	313	Ó	156					1.50 [0.06, 36.61]
Zinman, 2015	4	4687	1	2333		N.			1.99 [0.22, 17.80]
Kadowaki, 2017	0	70	0	68	-				0.97 [0.02, 48.29]
Softeland, 2017	0	222	0	110	-			•	0.50 [0.01, 24.92]
lkeda; 2015	0	261	0	67	-				0.26 [0.01, 12.96]
Inagaki, 2016	0	75	0	71	-			-	0.95 [0.02, 47.11]
Dagogo–Jack, 2017	0	309	0	153	-				0.50 [0.01, 24.92]
Nishimura, 2015	0	39	0	21			•	-	0.55 [0.01, 26,77]
Rodbard, 2016	0	108	0	108	-			-	1.00 [0.02, 49.95]
Roden, 2015	1	447	1	229	-		•	-	0.51 [0.03, 8.15]
Rosenstock, 2014	1	375	1	188			-	-	0.50 [0.03, 7.97]
Rosenstock, 2015	0	324	0	170	-			-	0.53 [0.01, 26.40]
Barnett, 2014	0	419	1	319					0.25 [0.01, 6.21]
FE Model for All Studies (i	Q = 3.23, df =	= 15, p = 3.23	; I ² = 0.0%)	0.05	0.25			0.65 [0.28, 1.50]
					0.05	0.25	Contraction of	4	



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



	Interv	rention	Co	Introl		
Author(s) and Year	Fr	Total	Fr	Total		Relative Risk 195%
Schumm-Draeger, 2014	0	299	n	101	· · · · · · · · · · · · · · · · ·	0.34 (0.01, 17,
tentof 2013	0	303	1	100		0.1610.01 4
aulai 0014	0	0.92		195		0.11(0.01, 4.
strojek, 2014	U	450	1	146		n'u trad's
sykes, 2014	1	179	Ū.	36	←	0.62 [0.03, 14.
ikkanen, 2015	Q	552	1	272	· · · · · · · · · · · · · · · · · · ·	0.16 [0.01, 4,
ode, 2015	17	477	5	237	· · · · · · · · · · · · · · · · · · ·	1,69 [0.63, 4
Veber, 2016	0	302	1	311		0.34 [0.01, 8
Veber, 2016	1	225	a	224		2 99 10 12, 72
olinder 2014		01	4	01		1 00 10 06 15
Ultran 0010		91	-	91		0.17(0.00, 13.
nang, zuna	0	313	-1	155		0.17 [0.01, 4.
/ilding, 2014	1	414	1	197	• • • •	0.48 [0.03, 7
ale, 2014	2	179	2	90		0.50 [0.07, 3.
ang, 2014	2	299	0	145	► •	2.43 [0,12, 50
nman, 2015	179	4687	.91	2333	⊢ i −	0.98 [0.76, 1,
adowaki, 2017	1	70	0	68		2 92 10.12.70
stalu 2015	n	460		160		03310.01 8
elaid, 2013	0	400		402		0.00 [0.0], 0
uneralnu, zur/	0	222	Q	110		0.50(0,01, 24.
nuang 2016	1	87	1	63		0.95 [0.06, 15.
inicalTrials gov	2	308	0	75	- F	1.23 [0.06, 25
enry, 2012	0	194	1	201	<	0.35 (0.01, 8
enry 2012	1	211	0	208		2 96 10.12.72
adaki 2016	n	75	â	71		0321001 7
ogoki 9019	8	1.0	-	/1		SOEDON T
ayanı, 2010	5	307	U	75		1.33 (D)06, 35
agaki, 2014	0	179	2	93	·	0.10[0.01, 2
ibbour, 2013	0	225	1	226	← → →	0.33 [0.01, 0
2015	1	450	0	226	⊢	1.51[0.06, .36.
2014	1	261	o	132		1.52[0.06, 37
aku 2013	1	225	n	54		0.73 (0.03, 17)
sku) 0044		171	0	07		1 61 10 06 96
aku, 2014	1	174	ų	87		1.01[0,00, 30.
aku, 2014	0	174	-1	56	• · · · · · · · · · · · · · · · · · · ·	0.11 [0.00, 2
raki, 2016	1	123	0	60	++	1.48,[0.06, 35
ohan, 2014	13	168	0	84	<u>⊢ i </u>	13.58 (0.82, 225,
ovacs, 2015	0	333	1	165	· · · · · · · · · · · · · · · · · · ·	0.17 [0.01, 4.
adodo-Jack 2017	á	309	3	153		1 98 10 22 17
agugo data, go n	÷.	100	0	100		0.001.001.1
51.61, 2014	0	402	0	465		0.00 [0.21, 1.
aldonado-Lutomirsky, 2016	0	222	Ô	110		0.50 [0.01, 24.
athieu, 2015	0	160	2	160	← →	0.20[0.01, 4
alley, 2013	7	409	2	13.7	· · · · · · · · · · · · · · · · · · ·	1.17 [0.25, 5,
eal, 2015	26	1384	11	690	H	1.18[0.59, 2
odbard 2016	n	108	1	108		0 33 10 01 8
centork 2015		000	0	60		0.77/0.03 18
000100051 2010	1	200	ų.	DU.		
osenstock, 2015	0	179	2	176		0.20[0.01, 4
osenstock, 2014	0	375	1	188	• • • • · · · · · · · · · · · · · · · ·	0.17[0.01, 4
osenstock, 2015	1	3/24	1 -	170	د	0.52 [0.03, 8
arnett, 2014	5	419	12	319	⊢−−−−− −−	0.32[0.11, 0.
osenstock, 2012	2	281	0	139		2.48 (0.12. 51.
			-			
E Model for All Studies (Q = 30.06;	df = 45, p = 30	1.06; l ² = 0.0%)			•	0,90 [0,74, 1
					105 0.25 1 4	

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

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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

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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

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Wabar 2016	NCT01127474	Low Pick	Low Pick	Low Pick	Low Pick	Modium Pick	High Dick	Lincloar Pick	high
Weber, 2010									hish
weber, 2016	NC101195662	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	High Risk	Unclear Risk	nigh
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

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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



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



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



PRISMA 2009 Checklist

3 4 5	Section/topic	#	Checklist item	Reported on page #
6 7	TITLE	-		
8	Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
9 10	ABSTRACT			
11 12 13	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
14 15	INTRODUCTION			
16	Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
17 18 19	Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
20	METHODS			
21 22 23	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
24 25	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
26 27 28	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
29 30	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
31 32	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
34 35	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
36 37	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
38 39 40	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
41	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
42 43 44	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
45 46 47			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Page 1 of 2	<u></u>



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

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Keywords:	DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, THERAPEUTICS, Adverse events < THERAPEUTICS

SCHOLARONE[™] Manuscripts

Comparative	e 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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Word Count Abstract: 299	Main Text: 4,479
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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 postmarket 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 lifethreatening 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 subgroup 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 domainbased 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 12 > 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% Cl 0.30-1.45, $I^2 = 0.0\%$) (Figure 3) nor incretin (RR 0.43; 95% Cl 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% Cl 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

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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 Page 11 of 72

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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: 7fold 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 canadiflozin.[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 selfassessment 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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Conflicts of Interest: None

Data Sharing Statement: All data used in this systematic review and meta-analysis are available through previously published articles and/or through clinical trials.gov. Section 2 of the supplementary appendix includes a complete list of data extraction variables that were collected. Access to the data can be granted by contacting the corresponding author.

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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.

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Kris Aubrey-Bassler was involved in project conception, protocol development and manuscript revisions and final approval.

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Michelle Swab was involved in search strategy design, literature search, and manuscript revisions and final approval.

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

Daniel Curnew was involved in screening, data extraction, quality appraisal and manuscript revisions and final approval.

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 among Placebo Controlled Trials

Group	Relative Risk (95% CL I ²)	# of Studies	Total # of
Prior use of anti-diabetics		oluules	outcomes/patient
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 for Included Studies

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

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

Figure 4. Risk of urinary tract infections with SGLT2 inhibitor compared to placebo

Figure 4. Risk of urinary tract infection with SGLT2 inhibitors compared to other active treatments

Figure 5. Risk of fracture with SGLT2 inhibitors compared to placebo

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25 Citation(s)

34Articles Excluded

During Data Extraction

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Author(s) and Year	AKI	Total	AKI	Total		Relative Risk [95% CI]
Zinman, 2015	45	4687	37	2333	⊢ ∎-i	0.61 [0.39, 0.93]
Cefalu, 2015	3	460	0	462	⊢►	7.03 [0.36, 135.72]
Softeland, 2017	0	222	1	110	←····	0.17 [0.01, 4.04]
Kohan, 2014	0	168	1	84	<>	0.17 [0.01, 4.07]
Leiter, 2014	0	482	1	483	← · · · · · · · · · · · · · · · · · · ·	0.33 [0.01, 8.18]
Maldonado-Lutomirsky, 2016	0	222	1	110	← · · · · · · ·	0.17 [0.01, 4.04]
Bailey, 2013	1	409	0	137	← →	1.01 [0.04, 24.64]
Bailey, 2012	0	214	0	68	← · · · · · · · · · · · · · · · · · · ·	0.32 [0.01, 16.02]
RE Model for All Studies (Q = 4.84, df = 7	, p = 4	.84, I ² =	0.0%,	$\tau^2 = 0.0$		0.59 [0.39, 0.89]
					0.05 0.25 1 4	
					Relative Risk (log scale)	



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			D 1-						
Author(s) and Year	KA	Total	KA	Cebo Total					Relative Risk [95% Cl
Seino, 2014	0	223	0	57	-				0.26 [0.01, 12.91
Tikkanen, 2015	0	552	1	272	-	•			0.16 [0.01, 4.03
Bode, 2015	1	477	0	237	H			→	1.49 [0.06, 36.53
Wilding; 2013	1	313	0	156					1.50 [0.06, 36.61
Zinman, 2015	4	4687	1	2333		H		∎>	1.99 [0.22, 17.80
Kadowaki, 2017	0	70	0	68	•				0.97 [0.02, 48.29
Softeland, 2017	0	222	0	110	•				0.50 [0.01, 24.92
Rosenstock, 2017	0	412	0	209	•				0.51 [0.01, 25.54
Yang, 2018	0	139	0	133	-				0.96 [0.02, 47.89
Ikeda; 2015	0	261	0	67	•				0.26 [0.01, 12.96
Inagaki, 2016	0	75	0	71	•			►	0.95 [0.02, 47.11
Dagogo-Jack, 2017	0	309	0	153	•				0.50 [0.01, 24.92
Nishimura, 2015	0	39	0	21	•		•		0.55 [0.01, 26.77
Rodbard, 2016	0	108	0	108	•				1.00 [0.02, 49.95
Roden, 2015	1	447	1	229	•		-		0.51 [0.03, 8.15
Rosenstock, 2014	1	375	1	188	•			►	0.50 [0.03, 7.97
Rosenstock, 2015	0	324	0	170	•			►	0.53 [0.01, 26.40
Barnett, 2014	0	419	1	319	•				0.25 [0.01, 6.21
RE Model for All Studies (Q = 3.28, df =	= 17, p = 3.28	; I ² = 0.0%	$\tau^2 = 0.0$					0.66 [0.30, 1.45
					·	1	i		
					0.05	0.25	1	4	
						Relative Risk	(log scale)		



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

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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[supplementary Concept] OR ipragliflozin*[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 "LX 4221"[tw] OR LX4221[tw] OR "6-((4-ethylphenyl)henyl)-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)henyl)-1 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	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

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Table	24. Cook man a Likeway Cooncele Street	
Table 2	ZA: Cochrane Library Search Strategy	
#1	([mh "Diabetes Mellitus, Type 2"] or NIDDM or t2dm or (("type 2" or "type i	i" 25,454
	or "adult onset" or "mature onset" or "late onset" or "noninsulin-dependen	.t"
	or "non insulin dependent") and (diabetes)))	
#2	([mh "Sodium-Glucoso Transport Protoins"/ail or [mh "Sodium Glucoso	1 002
#2	Transmenter 2"] or "andium chuses on transmeter 2" or SCL2 or SCLT2 or	1,002
	Transporter 2] or "sodium-glucose co-transporter 2" or SGL2 or SGL12 or	

Table 2A: Cochrane Library Search Strategy

#3	PF04971729) #1 AND #2	959
	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	
	glifiozin* or [mn caniglifiozin] or canaglifiozin* or invokana or sullsent 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	
#2	([mh "Sodium-Glucose Transport Proteins"/ai] or [mh "Sodium-Glucose Transporter 2"] or "sodium-glucose co-transporter 2" or SGL2 or SGLT2 or sliftering on factor of the series of the	1,082
	or "adult onset" or "mature onset" or "late onset" or "noninsulin-dependent" or "non insulin dependent") and (diabetes)))	
#1	([mh "Diabetes Mellitus, Type 2"] or NIDDM or t2dm or (("type 2" or "type ii"	25,454

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
		L	

Table 5A: ProQuest Search Strategy

all(NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR3"late onset" OR "noninsulin-dependent" OR "non insulin dependent") AND (diabetes)))3AND all("sodium-glucose co-transporter 2" OR SGL2 OR SGL72 OR gliflozin* OR6canagliflozin* OR invokana OR sulisent OR "TA 7284" OR TA7284 OR "JNJ 28431754" OR3JNJ28431754 OR dapagliflozin* OR farxiga OR forxiga OR "BMS 512148" OR BMS5121486OR empagliflozin* OR jardiance OR "BI 10773" OR BI10773 OR ipragliflozin OR suglat OR7"ASP 1941" OR ASP1941 OR luseogliflozin* OR lusefi OR "TS 071" OR TS071 OR7remogliflozin* 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)

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					
Intervention 1: Dose	used.					
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					
Comparison 1: Dose	were used.					
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					
AKI: Outcomes in Comparison 1 (n/N)	control group					
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)

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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	Japan	12	383	Any prior	Canagliflozin	Placebo	UTI, B
Inagaki, 2013				therapies washed-out	50mg, 100mg, 200mg, 300mg		
NCT01413204 Inagaki, 2014	01413204Japan24272Any priorCanagliflozinaki, 2014therapies100mg, 200mgwashed-outwashed-out		Canagliflozin 100mg, 200mg	Placebo	UTI, B		
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, B
NCT01381900 Ji, 2015	International	18	678	Prior Metformin and maybe SU	Canagliflozin 100mg, 300mg	Placebo	UTI, B
NCT01095653 Ji, 2014	Asia	24	393	Treatment Naive	Dapagliflozin 5mg, 10mg	Placebo	UTI, B
NCT01023945 Kadokura, 2014	Japan	2	30	Treatment Naive or monotherapy	lpragliflozin 50mg , 100mg	Placebo	UTI
NCT01193218 Kadowaki, 2015	Japan	52	547	Treatment Naive or monotherapy	Empagliflozin 10mg, 25mg	No comparator	UTI, B
NCT00972244 Kaku, 2013	Japan	12	279	Treatment Naive or 1 or 2 agents at low dose	Dapagliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo	UTI, B
None Kaku, 2014	Japan	24	261	Treatment Naive or monotherapy	Dapagliflozin 5mg, 10mg	Placebo	UTI, B
None Kaku, 2014	Japan	24	235	Treatment Naive or washout	Tofogliflozin 10mg, 20mg, 40mg	Placebo	UTI, B
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	lpragliflozin 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	1210001 International 76 499 cs, 2015		Prior pioglitizone and maybe metformin	Prior pioglitizoneEmpagliflozinand maybe10mg, 25mgmetformin		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, B
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, B
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, B

None	United States	6	171	Uncontrolled on	Canagliflozin	Placebo	UTI
Townsend, 2016				1-3 agents	100mg, 300mg		
None	Malaysia	12	110	Prior Metformin	Dapagliflozin	Sulphonylureas	UTI
Seman, 2016				and SU	10mg	(various agents)	
NCT01137474	International	12	944	Any prior	Dapagliflozin	Placebo	UTI, BF
Weber, 2016				therapies 10mg			
NCT01195662	International	12	449	Any prior	Dapagliflozin	Placebo	UTI, BF
Weber, 2016				therapies	10mg		
NCT01106625	International	52	469	Prior Metformin	Canagliflozin	Placebo	UTI, DKA, BF
Wilding; 2013				and SU	100mg, 300mg		
NCT01117584	International	12	343	Prior metformin	Ipragliflozin	Placebo	UTI
Wilding, 2013					12.5mg, 50mg, 150mg,		
					300mg		
NCT00357370	International	12	71	Any prior	Dapagliflozin	Placebo	UTI
Wilding, 2009				therapies 10mg, 20mg			
NCT00673231	international	104	808	Prior insulin	Dapagliflozin	Placebo	UTI, BF
Wilding, 2014		others allowed 2.5mg, 5/10mg, 10mg					
NCT01064414	International	52	269	Treatment Naive	Canagliflozin	Placebo	UTI, BF
Yale, 2014			-	or 1 or 2	100mg, 300mg		
NCT01316341	China	9 days	24	Treatment Naive	Empagliflozin	Placebo	UTI
Zhao, 2015	· · ·			or 1 or 2	10mg, 25mg		
NCT01131676	International	206	7028	Treatment Naive	Empagliflozin	Placebo	UTI, AKI, DKA
Zinman, 2015					10mg, 25mg		BF
None		24	168	Prior metformin	Ipragliflozin	Placebo	UTI
Goto, 2012			4.60		50mg		
NC102036515	International	26	463	Prior metformin	Ertugliflozin	Placebo	UTI, DKA, BF
Dagogo-Jack, 2017			696	and DPP4	Smg, 15mg		
NCT01734785	International	24	606	Prior metformin	Empagliflozin	Placebo	UTI, AKI, BF
Maldonado-				and DPP4	10mg, 25mg		
Lutomirsky, 2016			607		E 1:0 :		
NC101289990	International	52	637	Prior metformin	Empaglifiozin	Placebo	UII
NCT01022620	International	F.2	2074	Drier inculin	LUINE, ZOINE	Dlacaba	
NC101032629	international	52	2074	thorapy:		Placebo	UTI, BF
NCT01167884	International	104	1540	Drior motoresi-	LUUMg, SUUMg	Climonizido 1 Are-	
NCIUII0/881	international	104	1549	Prior mettormin	Empagiifiozin	Gimepiride 1-4mg	U II, АКІ, ВЕ
kidderstrale, 2014					25mg		

NCT00495469	UK	12	252	Treatment Naive	Remogliflozin	Placebo, Pioglitazone	UTI, BF
Sykes, 2014					100mg, 250mg, 500mg, 1000mg	30mg	
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, DK
NCT01734785 Softeland, 2017	International	24	333	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI, AK 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, UT BF
lto, 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
NCT02033889, Rosenstock, 2017	International	26	621	Prior metformin	Ertugliflozin 5mg, 15mg	Placebo	UTI, KA
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

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Section 4: Additional Forest Plots

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

	SGLT2		SGLT2		Control						
Author(s) and Year	AKI	Total	AKI	Total					Relative Risk [95% Cl]		
Hollander, 2018	1	888	0	437			<u> </u>		1.48 [0.06, 36.21]		
Frias, 2016	0	233	1	230	-			- _	0.33 [0.01, 8.04]		
Ridderstrale, 2014	1	765	0	780		-			3.06 [0.12, 74.97]		
BE Model for All Studies (Q = 0.9	97 df= 2 p= 0.62 [.]	$l^2 = 0.0\% \tau^2 = 0$	າດາ						1 14 [0 18 7 23]		
						Т	i				
					0.05	0.25	1	4			

Relative Risk (log scale)

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

	SG	LT2	Plac	cebo			
Author(s) and Year	AKI	Total	AKI	Total			Relative Risk [95% CI]
Cefalu, 2015	3	460	0	462	H	►	7.03 [0.36, 135.72]
Softeland, 2017	0	222	1	110	< ∎		0.17 [0.01, 4.04]
Kohan, 2014	0	168	1	84	← I	►	0.17 [0.01, 4.07]
Leiter, 2014	0	482	1	483	← -	►	0.33 [0.01, 8.18]
Maldonado-Lutomirsky, 2016	0	222	1	110	< ∎		0.17 [0.01, 4.04]
Bailey, 2013	1	409	0	137	•		1.01 [0.04, 24.64]
Bailey, 2012	0	214	0	68	∢ ·	•	0.32 [0.01, 16.02]
FE Model for All Studies (Q = 4.72, df = 6, p $=$	= 4.72;	l ² = 0.0 ⁴	%, τ ² =	0.0)			0.48 [0.14, 1.64]
					Г <u> </u>	i1	
					0.05 0.25	1 4	
					Relative Risk (log	scale)	

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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

	SG	iLT2	Pla	cebo	
Author(s) and Year	KA	Total	KA	Total	Relative Risk [95% Cl]
Tikkanen, 2015	0	552	1	272	0.16 [0.01, 4.03]
Bode, 2015	1	477	0	237	► 1.49 [0.06, 36.53]
Wilding; 2013	1	313	0	156	► 1.50 [0.06, 36.61]
Zinman, 2015	4	4687	1	2333	■ 1.99 [0.22, 17.80]
Roden, 2015	1	447	1	229	• 0.51 [0.03, 8.15]
Rosenstock, 2014	1	375	1	188	0.50 [0.03, 7.97]
Barnett, 2014	0	419	1	319	• 0.25 [0.01, 6.21]
FE Model for All Studies (C	a = 2.58, df =	6, p = 2.58;	l ² = 0.0%, 1	$t^2 = 0.0$)	0.73 [0.25, 2.16]
					0.05 0.25 1 4
					Relative Risk (log scale)

Autorial on Yac Un Total Un Total Un Total Total <t< th=""><th></th><th>so</th><th>LT2</th><th>Co</th><th>ntrol</th><th></th><th></th><th></th><th></th></t<>		so	LT2	Co	ntrol				
Oth Process	Author(s) and Year	UΠ	Total	UΠ	Total				Relative Risk [
Foresco, 2019 21 27 5 69 10 10 Ib, 207 3 32 0 34 7 7 Pather, 2017 43 488 13 247 10 Ib (2017) 43 488 10 247 10 Ib (2017) 43 488 10 247 10 Ib (2017) 43 488 10 247 10 Ib (2017) 15 5 22 75 10 10 Ib (2017) 15 5 72 20 10 10 Ib (2017) 15 5 77 20 10 10 Ib (2017) 15 5 77 20 10 10 Ib (2017)	Other								
No. 2017 3 3.2 0 3.4 7.4 <td< td=""><td>Fonseca, 2013</td><td>21</td><td>273</td><td>5</td><td>69</td><td></td><td>—</td><td></td><td>1.06 [0.42</td></td<>	Fonseca, 2013	21	273	5	69		—		1.06 [0.42
Anne 2015 47 23 7 55 1 1 Panley 2017 49 496 19 207 1 Multiancy 2018 96 690 600 497 1 Inclusions 2016 10 179 2 85 1 1 Synes 2014 10 179 2 85 1 0 0 RE Most for fungition (0= 154, d=1, p=0.21, f= 35 %, c ² = 0.7 F 5 1 0 0 0 0 0 Redok 2015 3 208 12 76 0 1 0	ito, 2017	3	32	0	34		—		7.42 [0.40,
Padiay, 2017 43 49 13 247 1 Matimate, 2019 50 660 30 477 0 Find Construct ExperimentaturCetter (2 = 1006, 4" = 0.00; 1" + 60.96; 4" = 0.00; 1" + 60.96; 4" = 0.00; 1" + 60.96; 4" = 0.00; 1" + 60.96; 4" = 0.00; 1" + 60.96; 4" = 0.00; 1" + 60.96; 4" + 0.00; 1" + 60.96; 4" + 0.00; 1" + 60.96; 4" + 0.00; 1" + 60.96; 4" + 0.00; 1" + 60.96; 4" + 0.00; 1" + 60.96; 4" + 0.00; 1" + 60.96; 4" + 10.00; 4" + 0.00; 1" + 60.96; 4" + 0.00; 1" + 60.96; 4" + 10.00; 4	Amin, 2015	47	213	7	55			· · · · · · · · · · · · · · · · · · ·	1.73 [0.83
Hellandsr, 2018 93 98 90 437 1 1 0 RE Model for Experimental/Chler (G= 10.00, d= 4, p= 0.01, f= 60.90, k= 0.01) 7 2 35 0	Pratley, 2017	43	498	13	247			ı <u>.</u>	1.64 [0.90
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Hollander, 2018	58	888	30	437		H	i	0.95 [0.62
production Syrker, 2015 3 2/8 4 49 0 Syrker, 2014 10 179 2 35 0 El Modal for fragelitheari (0=154, del 4, p=021, f= 256, sc, f= 0.1) 1 1 1 Enzogilitheari 00 223 1 1 1 Rodar, 2015 41 447 20 223 1 1 Rodar, 2015 12 270 14 135 1	RE Model for Experimental/Other	(Q = 10.68, df = 4	l, p = 0.03; l ² = 6	59.3%, τ ² = 0.3)					1.01 0.5
$\begin{aligned} & \text{Sykes} 2015 & 3 & 288 & 4 & 49 \\ & \text{Sykes} 2014 & 10 & 179 & 2 & 35 \\ & Re Model for largelifican (Ga I, St, d = 1, p = 0.21, l^2 = 35 St, e^2 = 0.7) \\ & \text{Re Model for largelifican (Ga I, St, d = 1, p = 0.21, l^2 = 35 St, e^2 = 0.7) \\ & \text{Rodel for largelifican (Ga I, St, d = 1, p = 0.21, l^2 = 35 St, e^2 = 0.7) \\ & \text{Rodel for largelifican (Ga I, St, d = 1, p = 0.21, l^2 = 35 St, e^2 = 0.7) \\ & \text{Rodel for largelifican (Ga I, St, d = 1, p = 0.21, l^2 = 35 St, e^2 = 0.7) \\ & \text{Rodel for largelifican (Ga I, St, d = 1, p = 0.21, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.21, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.21, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.21, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.21, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.21, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{Rodel for Empediation (Ga I, St, d = 1, p = 0.51, l^2 = 0.7) \\ & \text{$	pragliflozin								
Sylea, 2014 10 173 2 35 RE Model for Iprogrittom (Ca 1 54, d' = 1, p = 0.21; f' = 35 1%, $\frac{2}{7} = 0.7$) incadianta Roden, 2015 41 41 447 20 Roden, 2015 41 447 20 Roden, 2015 346 47 41 75 5102 780 incadianta, 2014 105 76 102 780 incadianta, 2014 105 76 102 780 incadianta, 2014 105 76 102 780 incadianta, 2015 12 273 2 60 incadianta, 2015 12 273 2 60 incadianta, 2015 12 273 2 60 incadianta, 2015 12 273 2 66 incadianta, 2015 35 277 20 128 incadianta, 2015 35 277 20 128 incadianta, 2015 35 277 20 128 incadianta, 2017 13 63 7 27 Roden 2017 14 Roden 2018 12 203 10 incadianta, 2016 13 223 12 200 incla 2016 13 223 12 200 incla 2016 6 64 3 2 409 Roden tor Daagofficin (Ca = 248, d' = 0 50), $\frac{1}{7} = 0.01$, $\frac{2}{7} = 0.01$, $\frac{2}{7$	Sykes, 2015	3	238	4	48	← ────			0.15 [0.03
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Sykes, 2014	10	179	2	35				0.98 [0.22
Emposition Roden 2015 41 447 20 223 Riddentrale, 2014 105 705 102 700 11 Lewin, 2015 36 270 14 135 11 Lewin, 2015 12 278 2 66 11 Helidat, 2016 27 39 31 441 11 11 125 2 56 100 Ferramini, 2015 35 277 20 128 56 11 11 215 2 56 11 11 215 2 56 11 11 215 2 56 11 11 215 2 56 11 11 11 215 2 56 11 11 11 215 2 56 11 11 11 215 2 56 11 11 215 2 56 11 11 11 215 21 11 11 11 215 21 11 11 11 215 21 11	RE Model for Ipragliflozin (Q= 1.5	54, df = 1, p = 0.2	1; I ² = 35.1%, τ ²	= 0.7)	996848 ⁴				1.68 0.3
Area At1 47 20 223 1 Ridserdaria, 2014 105 765 102 780 11 Lewin, 2015 36 270 14 135 11 Aradi, 2015 12 273 2 63 11 Farmini, 2015 36 322 7 56 11 Farmini, 2013 11 215 2 56 11 DeFrance, 2015 35 277 20 128 00 Gupta, 2017 13 53 7 27 10 Broadifican (G= 238, dT = p = 0.07, e ² = 0.06, e ² = 0.0 12 10 11 Pagedifican 13 53 7 27 10 Infa, 2006 25 270 5 56 11 Hany, 2012 24 210 9 203 12 200 Infa, 2016 13 233 12 200 11 12 Pradu, 2015 48 406 32 408 10 10 Semand, 2016	Empagliflozin								
Riddentranka, 2014 106 755 102 780 11 Lawin, 2015 36 270 14 135 1 Hadjad, 2016 27 393 31 341 1 Ferrannin, 2015 36 332 7 56 10 DeFrannin, 2015 35 277 20 128 1 Perrannin, 2015 35 277 20 128 1 DeFranz, 2015 35 277 20 128 1 Jult, 2007 13 53 7 27 10 Gauda, 2017 13 53 7 27 10 DeFranz, 2015 35 279 5 56 1 Henry, 2012 24 219 9 203 1 Henry, 2012 16 203 15 201 1 File Model for Depagifiltozin (Cl= 4.38, d= 5, p = 0.50, f ² = 0.0%, c ² = 0.0% 1 1 Resenstock, 2016 8 46 32 409 1 Juarde-Gorazilke, 2013 13 21 <td>Roden, 2015</td> <td>41</td> <td>447</td> <td>20</td> <td>223</td> <td></td> <td>L.</td> <td></td> <td>1.02 [0.6]</td>	Roden, 2015	41	447	20	223		L.		1.02 [0.6]
Lewin, 2015 36 270 14 135 Araki, 2015 12 273 2 65 11 Hadjad, 2016 27 339 31 341 1 1 Ferramini, 2013 36 332 7 56 0 0 Ferramini, 2013 11 215 2 56 0 0 Qipta, 2017 13 53 7 27 0 0 RE Model for Empagificant (0= 2.98, df = 4, p= 0.97, ff = 0.09, cf = 0.0) 7 7 0 0 Pagaillizan 11 215 20 56 1 1 Hany, 2012 24 219 9 208 1 1 Piata, 2015 48 406 32 406 1 1 Seman, 2016 6 54 3 50 1 1 Seman, 2016 8 475 3 237 1 1 Re Model for Dispogifican (0= 4.98, df = 5, p = 0.50, f ² = 0.09, c ² = 0.09 1 1 1 1 Seman, 2016	Ridderstrale, 2014	105	765	102	780				1.05 [0.8]
Acti, 2015 12 273 2 60 1 2 5 0 1 1 1 1 1 2 5 0 1 1 1 1 2 5 5 0 0 0 0 1 1 1 2 5 5 5 0	_ewin. 2015	36	270	14	135				1 29 10 72
International and the length of the leng	Araki, 2015	12	273	2	63				1.3810.32
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Hadiadi 2016	27	339	31	341		· _		0.88 (0.53
Indianting boto 0.0 0.02 0.0 0.02 0.0 0.02 0.0 0.00 Ferranning 2013 11 215 2 56 1.0 0.0 Guipta 2017 13 53 7 27 0.0 0.0 Dapspilitozin 1 1.0 53 7 27 1.0 Henry 2012 24 219 9 208 20 1.0 Henry 2012 16 2.03 1.5 201 1.0 Prias 2016 13 2.03 1.2 200 1.0 Prias 2016 6 5.4 3 5.0 1.0 Prias 2016 6 5.4 3 5.0 1.0 Prias 2016 6 5.4 3 5.0 1.0 Resenstock, 2016 8 4.06 3.2 4.08 1.0 Resenstock, 2016 9 9.068 3.3 4.62 1.0 Lavalle-Gonzalez, 2013 4.7 7.5 2.3 3.66 1.0 Remodel for AII (Studies (C) = 27.19, d* 1, e =	Ferrannini 2013	26	222	7	56				0.87 [0.4
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Dependingen List, 2008 25 279 5 56 11 Henry, 2012 24 219 9 208 12 Henry, 2012 16 203 15 201 11 Frias, 2016 13 233 12 230 11 Prato, 2015 48 406 32 406 11 Seman, 2016 6 54 3 50 11 Resonance, 2016 8 475 3 237 11 Canagliflazin Resenstock, 2012 31 321 4 65 11 Lavaile-Gonzalez, 2013 47 735 23 366 11 Lavaile-Gonzalez, 2013 47 735 23 366 11 RE Model for Canagliflozin (Q= 3.76, df = 4, p = 0.44, l ² = 13.696, r ² = 0.01 1 1 1 RE Model for All Studies (Q = 27.19, df = 26, p = 0.40, l ² = 0.016, r ² = 0.01 1 1 1	ne moder or empagnioziri (G = 2	200, ui = 0, p = 0.	57,1 = 0.0%, t	= 0.0)				—	1.01 10.8
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Henry, 2012 24 219 9 2.08 1 Henry, 2012 16 203 15 201 1 Frias, 2016 13 233 12 230 1 Prato, 2015 48 406 32 408 1 Seman, 2016 6 54 3 50 1 Canagifilozin (Q = 4.38, df = 5, p = 0.50, f ² = 0.0%, t ² = 0.0) Canagifilozin 1 1 Canagifilozin 8 475 3 237 1 Resenstock, 2016 8 475 3 237 1 Canagifilozin 9 968 33 482 1 Laviale-Gonzalez, 2013 47 735 23 366 1 RE Model for Canagifilozin (Q = 3.76, df = 4, p = 0.44; l ² = 13.6%, t ² = 0.0) 1 1 1 RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; l ² = 0.0%, t ² = 0.0) 1 1	Jan, 2000	20	2/9	5					0.50 [0.40
Heating 2012 16 203 19 201 11 Frias, 2016 13 233 12 230 11 Prato, 2015 48 406 32 408 11 Seman, 2016 6 54 3 50 11 Re Model for Dapagiffozin (Q=4.38, df = 5, p = 0.50, l ² = 0.0%, c ² = 0.0) 11 11 11 Canagiffozin 9 475 3 237 11 Resenstock, 2016 8 475 3 237 11 Resenstock, 2012 31 321 4 65 11 Leviter, 2015 93 968 33 482 11 Lavalle-Gonzalez, 2013 47 735 28 366 11 Re Model for Canagifflozin (Q=3.76, df = 4, p = 0.44, l ² = 13.6%, c ² = 0.0) 13 378 13 RE Model for All Studies (Q=27.19, df = 26, p = 0.40, l ² = 0.0%, c ² = 0.0) 1 1	Henry, 2012	24	519	9	208				2.50[1.2
Fridag 2016 13 233 12 230 11 Prato, 2015 48 406 32 408 11 Seman, 2016 6 54 3 50 11 Re Model for Dapagiliflozin (Q = 4.38, df = 5, p = 0.50; l ² = 0.0%, $t2 = 0.0$) 11 11 Canagiliflozin 8 475 3 237 11 Resenstock, 2016 8 475 3 237 11 Identer, 2015 93 968 33 462 11 Lavalle-Gonzalez, 2013 47 735 23 366 13 RE Model for Canagiliflozin (Q = 3.76, df = 4, p = 0.44; l ² = 13.6%, t ² = 0.0) 378 13 14 RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; l ² = 0.0%, t ² = 0.0) 1 1		16	203	15	201				1.06 [0.54
Prato, 2015 46 406 32 406 32 406 32 406 1 Seman, 2016 6 54 3 50 1	-nas, 2016	13	233	12	230		-		1.07 [0.50
Seman, 2016 6 54 3 50 1 RE Model for Dapagliflozin (Q = 4.38, df = 5, p = 0.50; $l^2 = 0.0\%$, $t^2 = 0.0$) 1 Canagliflozin 1 1 1 Resenstock, 2016 8 475 3 237 1 Resenstock, 2012 31 321 4 65 1 Leiter, 2015 93 968 33 482 1 Lavalle-Gonzalez, 2013 47 735 23 366 1 Schernthaner, 2013 15 377 21 378 0. RE Model for Canagliflozin (Q = 3.76, df = 4, p = 0.40; $l^2 = 13.6\%$, $t^2 = 0.0$) 1 1 RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; $l^2 = 0.0\%$, $t^2 = 0.0$) 1	Prato, 2015	48	406	32	408				1.51 [U.98
RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; $f^2 = 0.09$, $r^2 = 0.0) Image: Index for All Studies (Q = 27.19, df = 26, p = 0.40; f^2 = 0.09, r^2 = 0.0) $	Seman, 2016	6	54	3	50		—	-	1.85 [0.48
canagininozin Rosenstock, 2016 8 475 3 237 13 Rosenstock, 2012 31 321 4 65 13 Leiter, 2015 93 968 33 482 14 Lavalle-Gonzalez, 2013 47 735 23 366 11 Schernthaner, 2013 15 377 21 376 00 RE Model for Canagifilozin (Q = 3.76, df = 4, p = 0.44; l ² = 13.6%, c ² = 0.0) 1 1 1 RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; l ² = 0.0%, c ² = 0.0) 1 1 1	niz iviodel for Dapagliflozin (Q = 4		ou, I = U.U‰, t"	= 0.0)				•	1.42 [1.0
Hidden for All Studies (Q = 27.19, df = 26, p = 0.40; $l^2 = 0.096$, $r^2 = 0.0$) 475 3 237 11 Hosenstook, 2012 31 321 4 65 11 Leiter, 2015 93 968 33 482 11 Lavalle-Gonzalez, 2013 47 735 23 366 11 Schernthaner, 2013 15 377 21 376 01 RE Model for Canaglificzin (Q = 3.76, df = 4, p = 0.44; l ² = 13.6%, r ² = 0.0) 1 1 1	Lanagiitiozin								
Hosenstock, 2U12 31 321 4 65 1. Leiter, 2015 93 968 33 482 1. Lavalle-Gonzalez, 2013 47 735 23 366 1. Schernthaner, 2013 15 377 21 378 1. RE Model for Canaglificzin (Q = 3.76, df = 4, p = 0.44; l ² = 13.6%, $r^2 = 0.0$) 1 1. RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; l ² = 0.0%, $r^2 = 0.0$) 1.	Hosenstock, 2016	8	475	3	237		-		1.33 [0.36
Leiter, 2015 93 968 33 462 1 Lavalle-Gonzalez, 2013 47 735 23 366 1 Schernthaner, 2013 15 377 21 378 0 RE Model for Canaglificzin (Q = 3.76, df = 4, p = 0.44; l ² = 13.6%, $r^2 = 0.0$) 1 1 1 RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; l ² = 0.0%, $r^2 = 0.0$) 1 1	Hosenstock, 2012	31	321	4	65		H		1.57 [0.57
Lavalle-Gonzalez, 2013 47 735 23 366 11 Schemthaner, 2013 15 377 21 378 0. RE Model for Canagiliflozin (Q = 3.76, df = 4, p = 0.44; l ² = 13.6%, $r^2 = 0.0$) 1 1 1 RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; l ² = 0.0%, $r^2 = 0.0$) 1 1 1	_eiter, 2015	93	968	33	482			l <u>⊢</u> ∎—1	1.40 [0.96
Schernthaner, 2013 15 377 21 378 0. RE Model for Canagliflozin (Q = 3.76, df = 4, p = 0.44; l^2 = 13.6%, τ^2 = 0.0) 1 1 RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; l^2 = 0.0%, τ^2 = 0.0) 1	_avalle-Gonzalez, 2013	47	735	23	366		F		1.02 [0.63
RE Model for Canaglifiozin (Q = 3.76, df = 4, p = 0.44; l ² = 13.6%, $\tau^2 = 0.0$) RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; l ² = 0.0%, $\tau^2 = 0.0$) 1.	Schernthaner, 2013	15	377	21	378		H		0.72 [0.37
RE Model for All Studies (Q = 27.19, df = 26, p = 0.40; $t^2 = 0.0\%$, $t^2 = 0.0$) 1.	RE Model for Canagliflozin (Q = 3	. 76, df = 4, p = 0.	44; I ² = 13.6%, τ	² = 0.0)				-	1.14 IO.8
	RE Model for All Studies (Q = 27.	19, df = 26, p = 0.	40; Ι ² = 0.0%, τ ²	= 0.0)				•	1.12 11 00
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Figure 6A: Risk of Fracture with SGLT2 Inhibitors compared to Metformin

	SGL	T2	Metfo	rmin					
Author(s) and Year	Fracture	Total	Fracture	Total					Relative Risk [95% CI]
Ferrannini, 2013	2	215	1	56	•				0.52 [0.05, 5.64]
Hadjadj, 2016	0	339	0	341	•				1.01 [0.02, 50.55]
Henry, 2012	0	203	1	201	<				0.33 [0.01, 8.05]
Henry, 2012	0	219	0	208	-				0.95 [0.02, 47.66]
Araki, 2015	1	273	0	63	◀		•		0.70 [0.03, 17.00]
Rosenstock, 2016	1	475	0	237	—		•	►	1.50 [0.06, 36.68]
RE Model for All Studies (Q	e = 0.55, df = 5	ō, p = 0.55	; $l^2 = 0.0\%$, τ^2	= 0.0)					0.69 [0.19, 2.51]
					0.05	0.25	1		
					0.00	Relative Risk (lo	g scale)	-	

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



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

	SGL	.T2	Incre	etin					
Author(s) and Year Schernthaner, 2013	Fracture 2	Total 377	Fracture 1	Total 378		·			Relative Risk [95% Cl] 2.01 [0.18, 22.02]
Pratley, 2017	2	498	0	247		F			2.48 [0.12, 51.56]
Ferrannini, 2013	0	332	0	56					0.17 [0.00, 8.54]
Lavalle-Gonzalez, 2013	1	735	0	366	·			• •	1.50 [0.06, 36.63]
RE Model for All Studies (C	Q = 1.34, df = 3	3, p = 1.34	; $I^2 = 0.0\%$, τ^2	² = 0.0)					. 1.38 [0.31, 6.17]
					0.05	0.25	1	4	
						Relative Risk	(log scale)		

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

	Canagli	flozin	Place	ebo
Author(s) and Year	Fracture	Total	Fracture	Total
enlof, 2013	0	392	1	192
ode, 2015	17	477	5	237
filding; 2013	0	313	1	156
le, 2014	2	179	2	90
dowaki, 2017	1	70	0	68
inicalTrials.gov	2	308	0	75
agaki, 2016	0	75	1	71
agaki, 2013	2	307	0	75
gaki, 2014	0	179	2	93
2015	1	450	0	226
al, 2015	26	1384	11	690
odbard, 2016	0	108	1	108
Model for All Studies (Q	= 7.85, df = 11, p =	= 7.85; l ² = 0	$0.0\%, \tau^2 = 0.0$)	

Relative Risk (log scale)

Section 5: Forest Plots for Fixed Effects Analysis

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

Author(s) and Year	SG AKI	iLT2 Total	Pla AKI	cebo Total		Relative Risk (FE) [95% CI]
Zinman, 2015	45	4687	37	2333	⊢-⊞- 4	0.61 [0.39, 0.93]
Cefalu, 2015	3	460	0	462	⊢	7.03 [0.36, 135.72]
Softeland, 2017	0	222	1	110	<>	0.17 [0.01, 4.04]
Kohan, 2014	0	168	1	84	← · · · · · · · · · ·	0.17 [0.01, 4.07]
Leiter, 2014	0	482	1	483	<>	0.33 [0.01, 8.18]
Maldonado-Lutomirsky, 2016	0	222	1	110	<>	0.17 [0.01, 4.04]
Bailey, 2013	1	409	0	137	← →	1.01 [0.04, 24.64]
Bailey, 2012	0	214	0	68	<→	0.32 [0.01, 16.02]

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Figure 11A. Risk of Diabetic Ketoaciaosis with SGLI2 inhibitors compared to Piacebo - Fixed Effect in

,	Author(s) and Year	SGLT KA	2 Total	Place KA	bo Total		Relative Risk [95% CI]
S	Seino, 2014	0	223	0	57	← →	0.26 [0.01, 12.91]
I	Tikkanen, 2015	0	552	1	272	← →	0.16 [0.01, 4.03]
E	Bode, 2015	1	477	0	237	⊢ - →	1.49 [0.06, 36.53]
١	Wilding; 2013	1	313	0	156	⊢−−−− ►	1.50 [0.06, 36.61]
Z	Zinman, 2015	4	4687	1	2333	⊢∎_►	1.99 [0.22, 17.80]
٢	Kadowaki, 2017	0	70	0	68	←───	0.97 [0.02, 48.29]
5	Softeland, 2017	0	222	0	110	← →	0.50 [0.01, 24.92]
F	Rosenstock, 2017	0	412	0	209	← · · · · · · · · · · · · · · · · · · ·	0.51 [0.01, 25.54]
١	Yang, 2018	0	139	0	133	←───	0.96 [0.02, 47.89]
I	lkeda; 2015	0	261	0	67	←−−− ►	0.26 [0.01, 12.96]
l	Inagaki, 2016	0	75	0	71	←───→	0.95 [0.02, 47.11]
[Dagogo–Jack, 2017	0	309	0	153	← →	0.50 [0.01, 24.92]
٢	Nishimura, 2015	0	39	0	21	←−−−− ►	0.55 [0.01, 26.77]
F	Rodbard, 2016	0	108	0	108	←	1.00 [0.02, 49.95]
F	Roden, 2015	1	447	1	229	←−−− ►	0.51 [0.03, 8.15]
F	Rosenstock, 2014	1	375	1	188	<→	0.50 [0.03, 7.97]
F	Rosenstock, 2015	0	324	0	170	<→	0.53 [0.01, 26.40]
E	Barnett, 2014	0	419	1	319	<→	0.25 [0.01, 6.21]
F	FE Model for All Studies (Q = 3	.28, df = 17	′, p = 3.28; l ²	= 0.0%, t ²	² = 0.0)		0.66 [0.30, 1.45]

FE Model for All Studies (Q = 3.28, df = 17, p = 3.28; l² = 0.0%, τ² = 0.0)

Г т т 0.05 0.25 Relative Risk (log scale)

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	SG	iLT2	Plac	cebo		Relative Risk 195% ClJ
Author(s) and Year Other	UΠ	Total	UΠ	Total		
losenstock, 2015	4	236	1	60 159		1.02 [0.12, 8.93]
(aku, 2014	1	174	0	56	→ → → → → → → → → → → → → → → → → → →	0.98 [0.04, 23.65]
min, 2015 min, 2015	18	115	4	38		1.49 [0.54, 4.12]
eda; 2015	47	328	10	66		1.61 [0.20, 12.66]
eino, 2018 osenstock, 2017	4	159	0	74		4.22 [0.23, 77.35]
runberger, 2018	28	313	22	154	· • • • • • •	0.63 [0.37, 1.06]
rra, 2017 rauchi: 2017	17	308	13	153 70		0.65 [0.32, 1.30]
/kes, 2015	3	238	Ó	48		1.44 [0.08, 27.34]
/kes, 2014 eino, 2014	10	179	0	36		4.32 0.26, 72.05
ano, 2014	Ĩ	223	ŏ	57		0.78 0.03, 18.82
ano, 2014 asaki, 2015	1	182	0	54		0.9010.04, 21.82
E Model for Other SGLT2s (Q = 1)	2.14, df = 16, p =	: 0.73; l ² = 0.0%,	$\tau^2 = 0.0$)	Ū	-	0.85 [0.64, 1.12]
ragliflozin						
ashiwagi,2015 ashiwagi,2014	1	119	2	46		0.19[0.02, 2.08]
ashiwagi, 2015	4	62	ł	67		0.36 [0.01] 8.67]
ashiwaği, 2015 adokura, 2014	2	166	3	76		0.31 [0.05, 1.79]
hihara, 2016	4	175	1	87		1.99 [0.23, 17.52]
oto, 2012 Inseca 2013	2	112	26	56 60		0.50 [0.07, 3.46]
uang, 2016	6	87	ž	83		2.86 [0.59, 13.78]
iaing, 2013 Madal for Iaradiflazia (O 2014	12 1 df = 0 = 0.71	276 1 ² - 0.00 - 2	4	66		0.72 [0.24, 2.15]
wouer or ipragitiozin (Q= 6.34	r, ur = 9, p = 0.71	, ι = 0.0%, τ =	0.0)			0.80 [0.48, 1.32]
ipagiiliozin ss. 2015	63	876	4	107	<u>⊢ :</u>	1.9210.71. 518
rnett, 2014 senstock, 2015	55	419	41	319	i , i −	1.02 0.70 1.49
senstock, 2014	43 58	3⊿4 375	29	188		1.00 [0.67, 1.51]
jen, 2015 himura, 2015	41	447	25	229		0.84 [0.52] 1.35]
rker, 2015	50	420	31	217		0.83 [0.55, 1.26]
Idonado-Lutomirsky, 2016 vacs. 2015	12	223	8	110 165		0.74 [0.31, 1.76]
se, 2013	0	36	0	12	┥ ───────────────	0.35[0.01, 16.82]
se, 2013 erina, 2015	0 73	62 441	0 36	16 225		0.27 [0.01, 13.11] 1.03 [0.72, 1.49]
teland 2017	12	222	8	110		0.74 0.31 1.77
Jia, ∠017 man, 2015	13 842	53 4687	8 423	28 2333		0.86 [0.40, 1.82] 0.99 [0.89, 1.10]
iq. 2015	0	18	0	6	← → →	0.37 [0.01, 16.85]
variert, 2010 Model for Empedificatio (O - 9 -	24 40 df = 16 p = 0	552 - 2004 - 1 ² - 0.004	10 2 – 0 m	2/2		1.10[U.57, 244]
nadiflozin	.o, ai = 10, p = 0		= 0.0)		T	0.00 10.00, 1.001
senstock, 2012	19	281	11	139	· · · · · · · · · · · · · · · · · · ·	0.85 [0.42, 1.75]
senstock, 2015 lev. 2012	1	179 214	9	176		0.11 [0.01, 0.85] 1.91 (0.23, 15.56)
daliar, 2013	3	23	ó	21		6.42 [0.35, 117.34]
iley, 2013 itthaei, 2015	41	409	11	137		1.25 [0.66, 2.36]
hieu, 2015	8	160	10	160		0.80 [0.32, 1.97]
, 2008 .er. 2014	25 53	279 482	3 28	54 489		1.61 [0.50, 5.15] 1.90 [1.22, 2.95]
erspink, 2013	1	24	0	25	⊢	3.12[0.13, 73.04]
ian, ∠014 iki, 2016	23	108	12	84 60		2.46 [0.12, 50.44]
(u, 2014 ku 2013	2	174	2	87		0.50[0.07, 3.49]
2014	4 12	261	4	54 132		1.52 [0.50, 4.61]
ibour, 2013 nrv. 2012	15	225	14	226		1.08 [0.53, 2.18] 1.75 (0.70, 2.99)
nry 2012	15	194	9 15	201		1.04 [0.52, 2.06]
rannini, 2010 Insfeild: 2017	33	410	3	75		2.01 [0.63, 6.39] 1.00 [0.21 / 72]
19, 2018	5	139	7	133		0.68 [0.22, 2.10]
alu, 2015 1a. 2014	27	460	27	462 145		1.00 [0.60, 1.69] 1.11 [0.47, 2.63]
ding, 2014	45	414	11	197	· · · · · · · · · · · · · · · · · · ·	1.95 1.03, 3.68
ang, 2009 inder, 2014	0	24 91	0	23 91		0.96 [0.02, 46.47] 0.75 [0.17, 3.26]
ber, 2016	4	225	2	224	· · · · · · · · · · · · · · · · · · ·	1.99 [0.37, 10.76]
ojek, 2014	9 30	302 450	3 11	311 146		0.88 [0.45, 1.72]
iumm-Draeger, 2014	10	299	3	101	<u>⊢ · · · · · · · · · · · · · · · · · · ·</u>	1.13 [0.32, 4.01]
Model for Dapagliflozin (Q = 24.	.45, df = 29, p = 1	0.71; l ^e = 0.0%, 1	(* = 0.0)		•	1.22 [1.03, 1.43]
nagliflozin senstock 2012	01	301	F	F F		1 26 (0.51 9.11)
dbard 2016	2	108	2	108		1.00[0.14, 6.97]
i, 2014 al. 2015	8	186 13.89	2	93 600		2.00 [0.43, 9.23] 1 02 in 71 - 1 49
2015	13	450	11	226		0.59 [0.27] 1.30]
gaki, 2014 daki, 2013	2	179 307	1	93 75		1.04 [0.10, 11.31] 0.25 in nn - 12.341
gaki, 2016	1	75	ŏ	71		2.84 [0.12] 68.64]
дожакі, 2017 ie. 2014	0 18	70 179	1	68 90		0.32 [0.01, 7.82] 1.01 [0.47] 2 15]
iding; 2013	26	313	12	156	· · · · · · · · · · · · · · · · · · ·	1.08 0.56 2.08
ue, 2015 vinsend, 2016	74 0	477	24 0	237 56	▲	1.53 [U.99, 2.36] 0.50 [0.01, 24 88]
mlof, 2013	24	392	ĕ	192		1.47 [0.67, 3.21]
Model for Canagliflozin ($Q = 7.5$	56, df = 13, p = 0.	.87; $\mathbf{I}^2 = 0.0\%$, τ^2	= 0.0)		•	1.14 [0.92, 1.40]
Model for All Studies (O = 67 8	5. df = 87 n = ∩ 9	$94: ^2 = 0.0\% \pi^2:$	= 0.0)		`	1.0210.95 1.00
	o, al - o , p - o.o		- 0.07		The second se	1.02 [0.00, 1.00]
					0.05 0.25 1 4	
					0.00 0.20 1 4	
					Observed Outcome	

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

BMJ Open

Althorized and Year Pr Total Pr Total Pr Shrum-Derge 2014 0 302 1 102 Image 2014 1 146 Strum-Derge 2015 0 420 1 146 Image 2014 1 170 0 36 Strum-Derge 2015 0 522 1 212 Image 2014 1 101 Image 2014 Viding 2015 0 522 1 311 Image 2014 Image 2014 Image 2014 Viding 2015 0 322 1 311 Image 2014 Image 2014 Image 2014 Viding 2014 1 91 1 91 Image 2014 Image 2014 Image 2014 Viding 2015 0 430 1 92 Image 2014 Image 2014 Viding 2015 1 2019 Image 2014 Image 2014 Image 2014 Viding 2015 1 2019 Image 2014 Image 2014 Image 2014 Viding 2015 1 91 Image 2014 Image 2014 Image 2014 Viding 2016 1 1 1 1 Image 2014 Image 2014 Viding 2015 1 1 1 1 1<	Autor is and Very Fr Total Fr Total Better (J215) 0 200 10 10 Better (J215) 0 320 1 120 Synek, 2014 1 170 0 86 Synek, 2014 1 170 0 86 Dola, 2015 17 477 5 227 Newer, 2016 0 502 1 211 Verser, 2016 0 502 1 211 Verser, 2016 0 323 1 10 Verser, 2016 0 323 1 10 Verser, 2016 0 323 1 10 Verser, 2016 1 226 0 128 Verser, 2016 1 228 0 142 Verser, 2015 1 24 10 10 Verser, 2015 1 270 1 10 Verser, 2016 1 28		Interv	ention	C	ontrol	
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Henry 2012 1 211 0 206 Inagaki, 2016 0 75 1 71 Inagaki, 2013 2 307 0 75 Inagaki, 2014 0 179 2 93 Jabbour, 2013 0 225 1 226 J, 2014 1 261 0 132 Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 87 Kaku, 2014 1 174 1 56 Kowas, 2015 0 333 1 165 Dagoogo-Jack, 2017 4 309 1 153 Maldonado-Lutomirsky, 2016 0 222 110 4 Maldonado-Lutomirsky, 2016 0 286 183 4 Rosenstock, 2015 1 286 108 4 <td< td=""><td>Henry 2012 1 211 0 200 Inagaki, 2013 2 30 75 1 71 Inagaki, 2013 2 307 0 75 1 71 Inagaki, 2014 0 179 2 93 93 J. 2015 1 450 0 226 1 94 J. 2015 1 450 0 226 1 94 Kaku, 2013 1 225 0 54 94 94 Kaku, 2014 1 174 0 87 97 94 Kaku, 2014 1 174 0 87 97 94 97 Arak, 2016 1 123 0 60 94 97 94 94 94 Dagogo-Jack, 2017 4 309 1 153 94 94 94 94 94 94 94 94 94 Balley, 2015 0 160 2 160 94 94 94 94 94 94 <t< td=""><td>Henry, 2012</td><td>0</td><td>194</td><td>1</td><td>201</td><td></td></t<></td></td<>	Henry 2012 1 211 0 200 Inagaki, 2013 2 30 75 1 71 Inagaki, 2013 2 307 0 75 1 71 Inagaki, 2014 0 179 2 93 93 J. 2015 1 450 0 226 1 94 J. 2015 1 450 0 226 1 94 Kaku, 2013 1 225 0 54 94 94 Kaku, 2014 1 174 0 87 97 94 Kaku, 2014 1 174 0 87 97 94 97 Arak, 2016 1 123 0 60 94 97 94 94 94 Dagogo-Jack, 2017 4 309 1 153 94 94 94 94 94 94 94 94 94 Balley, 2015 0 160 2 160 94 94 94 94 94 94 <t< td=""><td>Henry, 2012</td><td>0</td><td>194</td><td>1</td><td>201</td><td></td></t<>	Henry, 2012	0	194	1	201	
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Inagaki, 2013 2 307 0 75 Inagaki, 2014 0 179 2 93 Jabbour, 2013 0 225 1 226 Ji, 2015 1 450 0 226 Ji, 2014 1 261 0 132 Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 07 Kaku, 2014 0 174 1 56 Araki, 2016 1 128 0 60 Kaku, 2014 13 166 0 84 Kovacs, 2015 0 333 1 165 Dagoon-Jack, 2017 4 309 1 153 Lefer, 2014 5 482 8 483 Matcheu, 2015 0 108 1 109 Roderstock, 2017 4 309 1 160 Bailey, 2013 7 409 2 137 Neal, 2015 1 108	Inagaki, 2013 2 307 0 75 Inagaki, 2014 0 179 2 93 Jabbour, 2013 0 225 1 226 J, 2015 1 450 0 226 J, 2014 1 261 0 132 Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 67 Kaku, 2014 0 174 1 56 Kaku, 2014 1 123 0 60 Kohan, 2014 13 166 0 84 Kovacs, 2015 0 333 1 153 Lefer, 2014 5 482 8 483 Madbonabo-Lutomirsky, 2016 2222 0 110 Mathieu, 2015 0 108 1 108 Rosenstock, 2015 1 226 160 4 Rosenstock, 2015 1 226 10 4 Rosenstock, 2015 1 324 1 170 Rose	Inagaki, 2016	0	75	1	71	
Inageki, 2014 0 179 2 93 Jabbaur, 2013 0 225 1 226 J, 2015 1 450 0 226 J, 2014 1 261 0 132 Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 67 Kaku, 2014 0 174 1 56 Kaku, 2014 1 128 0 60 Kohan, 2014 15 168 1 165 Dagogo-Jack, 2017 4 309 1 153 1 165 Leter, 2014 5 482 8 483 1 1 Madchadc-Lutomirsky, 2016 0 160 2 160 1 1 1 Rosens	Inagki, 2014 0 179 2 93 Jabbour, 2013 0 226 1 226 J., 2015 1 450 0 226 J., 2014 1 261 0 132 Kaku, 2014 1 174 0 87 Kaku, 2014 1 174 1 56 Araki, 2016 1 123 0 60 Kohn, 2014 1 188 0 84 Kovacs, 2015 0 333 1 153 Letter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 110 Mathew, 2015 0 160 2 160 Balley, 2013 7 409 2 137 Neel, 2015 1 286 60 60 Rosenatock, 2015 1 286 60 60 Rosenatock, 2015 1 286 60 60 Rosenatock, 2015 1 324 1 170 Bar	Inagaki, 2013	2	307	0	75	
Jabbour, 2013 0 225 1 226 J., 2015 1 450 0 226 J., 2014 1 226 1 226 Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 67 Kaku, 2014 1 174 1 56 Kaku, 2014 0 174 1 56 Araki, 2016 1 123 0 60 Kohan, 2014 13 166 64 166 153 Dagogo-Jack, 2017 4 309 1 153 165 Leiter, 2014 5 462 8 483 165 Matheu, 2015 0 160 2 160 160 Baieg, 2013 7 409 2 137 17 Neal, 2015 1 1266 0 60 106 Rosenstock, 2015 1 1266 0 60 160 Rosenstock, 2015 1 326 0 60 179	Jabbour, 2013 0 225 1 226 J., 2015 1 450 0 226 J., 2014 1 261 0 132 Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 67 Kaku, 2014 0 174 1 56 Kaku, 2014 0 174 1 56 Araki, 2016 1 123 0 60 Kohan, 2014 13 168 0 84 Kohan, 2014 5 482 8 483 Leiter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Malderado 2015 0 160 2 160 2 160 Bailey, 2013 7 409 2 137 409 400 400 Rosenstock, 2015 0 179 2 176 400 400 400 Rosenstock, 2015 1 324 1 <	Inagaki, 2014	0	179	2	93	
J. 2015 1 450 0 2226 J. 2014 1 261 0 132 Kaku 2013 1 225 0 54 Kaku 2014 1 174 0 67 Kaku 2014 0 174 1 56 Araki 2016 1 128 0 60 Kohan 2014 13 168 0 84 Kovacs 2015 0 333 1 165 Dagogo-Jack, 2017 4 309 1 153 Leiter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1384 11 690 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 1 324 1 170 Bairnet, 2014 5 419 12 319 Bairnet, 2014 5 419 12 319	J. 2015 1 246 0 226 J. 2014 1 261 0 132 Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 67 Kaku, 2014 0 174 1 56 Kohan, 2014 13 168 0 84 Kokan, 2015 0 333 1 165 Dagogo-Jack, 2017 4 309 1 153 Leiter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 180 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1384 11 690 Rosenstock, 2015 1 226 10 10 Rosenstock, 2015 1 324 1 170 Rosenstock, 2015 2 201 1 319 Rosenstock, 2012 2 281 0 139 FE Model for All Studies (Q= 31.36, d [±] = 4, p = 31.36, l ² = 0.06, t ² = 0.0)	Jabbour, 2013	0	225	1	226	
J. 2014 1 281 0 132 Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 67 Kaku, 2014 0 174 1 56 Araki, 2016 1 123 0 60 Kohan, 2014 13 168 0 84 Kovacs, 2015 0 333 1 165 Dagogo-Jack, 2017 4 309 1 153 Leiter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Maldonado-Lutomirsky, 2016 0 160 2 160 Bailey, 2013 7 409 2 137 1 Neal, 2015 1 236 0 60 Rosenstock, 2015 1 179 2 176 Rosenstock, 2015 1 324 1 170 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 </td <td>J. 2014 1 261 0 132 Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 67 Kaku, 2014 0 174 1 56 Araki, 2016 1 123 0 60 Kohan, 2014 13 166 0 84 Kovacs, 2015 0 333 1 165 Dagogo-Jack, 2017 4 309 1 153 Letter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Balley, 2013 7 409 2 137 Neal, 2015 26 1384 106 60 Rosenstock, 2015 1 286 0 60 Rosenstock, 2015 1 324 1 170 Banett, 2014 5 419 12 319 FE Model for All Studies (Q= 31.36, d[±]= 4.9, p= 31.36, l[±]= 0.06, s[±]= 0.0) 319</td> <td>Ji, 2015</td> <td>1</td> <td>450</td> <td>0</td> <td>226</td> <td></td>	J. 2014 1 261 0 132 Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 67 Kaku, 2014 0 174 1 56 Araki, 2016 1 123 0 60 Kohan, 2014 13 166 0 84 Kovacs, 2015 0 333 1 165 Dagogo-Jack, 2017 4 309 1 153 Letter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Balley, 2013 7 409 2 137 Neal, 2015 26 1384 106 60 Rosenstock, 2015 1 286 0 60 Rosenstock, 2015 1 324 1 170 Banett, 2014 5 419 12 319 FE Model for All Studies (Q= 31.36, d [±] = 4.9, p= 31.36, l [±] = 0.06, s [±] = 0.0) 319	Ji, 2015	1	450	0	226	
Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 67 Kaku, 2014 0 174 1 56 Araki, 2016 1 123 0 60 Kohan, 2014 13 166 0 84 1 Kovacs, 2015 0 333 1 165 1 Dagogo-Jack, 2017 4 309 1 153 1 Leiter, 2014 5 482 8 483 1 Maldonado-Lutomirsky, 2016 0 226 110 1 1 Mathieu, 2015 0 160 2 160 1 1 Bailey, 2013 7 409 2 137 1 1 690 Rosenstock, 2015 1 236 0 60 1 1 690 Rosenstock, 2015 1 236 0 60 1 1 60 Rosenstock, 2015 1 324 1 1 70 1 1 1 1	Kaku, 2013 1 225 0 54 Kaku, 2014 1 174 0 67 Kaku, 2014 0 174 1 56 Kaku, 2014 0 174 1 56 Kaku, 2014 1 123 0 60 Kohan, 2014 13 168 0 94 Kovacs, 2015 0 333 1 165 Dagogo-Jack, 2017 4 309 1 153 Leiter, 2014 5 462 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 1 236 0 60 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 4 FE Model for All Studes (Q=31.36, df= 49, p=31.36, l ² = 0.09is, e ² = 0.0)	Ji, 2014	1	261	0	132	
Karu, 2014 1 1/4 0 87 Kaku, 2014 0 174 1 56 Araki, 2016 1 123 0 60 Kohan, 2014 13 168 0 84 1 Kovacs, 2015 0 333 1 165 1 Dagogo-Jack, 2017 4 309 1 153 1 Leiter, 2014 5 482 8 483 1 1 Maldonado-Lutomirsky, 2016 0 222 0 110 1 1 Mathieu, 2015 0 160 2 160 1 1 1 Bailey, 2013 7 409 2 137 1 1 60 Rosenstock, 2015 1 236 0 60 1 108 1 108 Rosenstock, 2015 1 1324 1 107 1 1 160 Barnett, 2014 5 419 12 319 1 1 1 1 Barnett, 2014 5 </td <td>Kaku, 2014 1 1/4 0 8/ Kaku, 2014 0 174 1 56 Kaku, 2016 1 123 0 60 Kohan, 2014 13 168 0 84 Kovacs, 2015 0 333 1 165 Dagogo-Jack, 2017 4 309 1 153 Leiter, 2014 5 462 6 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1984 108 108 Rosenstock, 2015 1 236 0 80 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 419 FE Model for All Studes (Q= 31.36, df = 49, p = 31.36; l² = 0.095, l² = 0.0) 5 139 419</td> <td>Kaku, 2013</td> <td>1</td> <td>225</td> <td>0</td> <td>54</td> <td></td>	Kaku, 2014 1 1/4 0 8/ Kaku, 2014 0 174 1 56 Kaku, 2016 1 123 0 60 Kohan, 2014 13 168 0 84 Kovacs, 2015 0 333 1 165 Dagogo-Jack, 2017 4 309 1 153 Leiter, 2014 5 462 6 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1984 108 108 Rosenstock, 2015 1 236 0 80 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 419 FE Model for All Studes (Q= 31.36, df = 49, p = 31.36; l ² = 0.095, l ² = 0.0) 5 139 419	Kaku, 2013	1	225	0	54	
Araki, 2014 0 1/4 1 55 4 1 1 123 0 60	Nation 2014 0 174 1 36 Araki, 2016 1 123 0 60 Kohan, 2014 13 166 0 84 Kovas, 2015 0 333 1 165 Dagogo-Jack, 2017 4 309 1 153 Lefter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neat, 2015 26 1384 11 690 Rosenstock, 2015 1 286 60 60 Rosenstock, 2015 1 286 60 60 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 400 FE Model for All Studies (Q= 31.36, df = 49, p = 31.36; l ² = 0.0%, e ² = 0.0) 139 400	Kaku, 2014	1	174	U	87	
Analy, 2010 1 123 0 00 00 1 123 0 00 1 153 1 166 0 84 1 <td>Anal, 2010 1 123 0 60 60 Kohan, 2014 13 168 0 84 1 Kovacs, 2015 0 333 1 165 1 Dagogo-Jack, 2017 4 309 1 153 1 Leiter, 2014 5 462 8 483 1 Maldonado-Lutomirsky, 2016 0 222 0 110 1 Mathieu, 2015 0 160 2 160 1 1 Bailey, 2013 7 409 2 137 1 1 690 Rodbard, 2016 0 108 1 108 1 108 1 108 Rosenstock, 2015 1 236 0 60 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 1 1 1</td> <td>Kaku, 2014</td> <td>U</td> <td>174</td> <td>1</td> <td>56</td> <td></td>	Anal, 2010 1 123 0 60 60 Kohan, 2014 13 168 0 84 1 Kovacs, 2015 0 333 1 165 1 Dagogo-Jack, 2017 4 309 1 153 1 Leiter, 2014 5 462 8 483 1 Maldonado-Lutomirsky, 2016 0 222 0 110 1 Mathieu, 2015 0 160 2 160 1 1 Bailey, 2013 7 409 2 137 1 1 690 Rodbard, 2016 0 108 1 108 1 108 1 108 Rosenstock, 2015 1 236 0 60 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 108 1 1 1 1	Kaku, 2014	U	174	1	56	
Kovacs, 2015 0 333 1 165 4 Dagogo-Jack, 2017 4 309 1 153 165 Leiter, 2014 5 482 8 483 1 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1364 11 690 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 1 324 1 170 Barrett, 2014 5 419 12 319 Barrett, 2014 5 419 12 319 Hosenstock, 2012 2 261 0 139	Kovacs, 2014 1/3 1/6 0 64 Kovacs, 2015 0 333 1 165 Dagogo-Jack, 2017 4 309 1 153 Leiter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1384 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 236 60 60 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 FE Model for All Studies (Q= 31.36, df = 49, p = 31.36; l ² = 0.0%, e ² = 0.0) 139 140	Koban 2014	10	160	0	00	13
Dagogo-Jack, 2017 4 309 1 153 Leiter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1364 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2015 1 324 1 160 Barnett, 2014 5 419 12 319 Hosenstock, 2012 2 281 0 139	Dagogo-Jack, 2017 4 309 1 153 Lefter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1384 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 236 60 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 FE Model for All Studies (Q= 31.36, df = 49, p = 31.36; l ² = 0.0%, e ² = 0.0) 139 4	Kovacs 2015	0	333	1	165	10
Leiter, 2014 5 462 8 463 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1364 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2015 1 324 1 170 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319	Leiter, 2014 5 482 8 483 Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1384 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 226 0 60 Rosenstock, 2015 0 179 2 176 Barnett, 2014 0 375 1 188 Bosenstock, 2015 1 324 1 170 FE Model for All Studies (Q= 31.36, df = 49, p = 31.36; l ² = 0.0%, e ² = 0.0) 139 4	Dagogo-lack 2017	4	3.00	1	153	
Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1384 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 4 Rosenstock, 2012 2 281 0 139 4	Maldonado-Lutomirsky, 2016 0 222 0 110 Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1384 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 226 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 281 0 139	Leiter, 2014	5	482	8	483	
Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1384 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 261 0 139	Mathieu, 2015 0 160 2 160 Bailey, 2013 7 409 2 137 Neal, 2015 26 1384 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 226 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 FE Model for All Studies (Q=31.36, df = 49, p = 31.36; l ² = 0.0%, e ² = 0.0) Fe = 0.0% e ² = 0.0)	Maldonado-Lutomirsky, 2016	0	222	0	110	(
Bailey, 2013 7 409 2 137 Neal, 2015 26 1364 11 690 Image: Constraint of the second	Bailey, 2013 7 409 2 137 Neal, 2015 26 1384 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2015 0 375 1 168 Rosenstock, 2015 1 324 1 170 Rosenstock, 2015 1 324 1 170 Rosenstock, 2012 2 281 0 139	Mathieu, 2015	0	160	2	160	
Neal, 2015 26 1384 11 690 Image: Constraint of the state of the stat	Neal, 2015 26 1384 11 690 Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2014 0 375 1 188 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 FE Model for All Studies (Q=31.36, df = 49, p = 31.36, l ² = 0.0%, e ² = 0.0) 139 Image: Construct on the studies (Q=31.36, df = 49, p = 31.36, l ² = 0.0%, e ² = 0.0)	Bailey, 2013	7	409	2	137	
Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2014 0 375 1 188 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 12 Rosenstock, 2012 2 281 0 139 139	Rodbard, 2016 0 108 1 108 Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2014 0 375 1 168 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 281 0 139	Neal, 2015	26	1384	11	690	
Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2014 0 375 1 188 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 281 0 139	Rosenstock, 2015 1 236 0 60 Rosenstock, 2015 0 179 2 176 Rosenstock, 2014 0 375 1 168 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 281 0 139	Rodbard, 2016	0	108	1	108	
Rosenstock, 2015 0 179 2 176 Rosenstock, 2014 0 375 1 188 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 12 Rosenstock, 2012 2 281 0 139 139	Rosenstock, 2015 0 179 2 176 Rosenstock, 2014 0 375 1 198 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 281 0 139 FE Model for All Studies (Q=31.36, df = 49, p = 31.36; l ² = 0.0%, t ² = 0.0) Image: Construct of the studies	Rosenstock, 2015	1	236	0	60	(
Rosenstock, 2014 0 375 1 188 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 281 0 139	Rosenstock, 2014 0 375 1 198 Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 281 0 139 FE Model for All Studies (Q=31.36, df = 49, p=31.36; l ² = 0.0%, t ² = 0.0) Image: Construct of the studies of th	Rosenstock, 2015	0	179	2	176	
Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 281 0 139	Rosenstock, 2015 1 324 1 170 Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 281 0 139 FE Model for All Studies (Q=31.36, df = 49, p=31.36, l ² = 0.0%, t ² = 0.0) €	Rosenstock, 2014	0	375	1	188	
Barnett. 2014 5 4 19 12 3 19 Image: mail of the second	Barnett, 2014 5 419 12 319 Rosenstock, 2012 2 281 0 139 FE Model for All Studies (Q=31.36, df = 49, p=31.36; l ² = 0.0%, t ² = 0.0)	Rosenstock, 2015	1	324	1	170	
Rosenstock, 2012 2 281 0 139	Rosenstock, 2012 2 281 0 139 FE Model for All Studies (Q = 31.36, df = 49, p = 31.36; l ² = 0.0%, t ² = 0.0) Image: Comparison of the studies of	Barnett, 2014	5	419	12	319	
	FE Model for All Studies (Q = 31.36, df = 49, p = 31.36; l ² = 0.0%, t ² = 0.0)	Rosenstock, 2012	2	281	0	139	3
FE Model for All Studies (Q = 31.36, df = 49, p = 31.36; l ² = 0.0%, τ ² = 0.0)		FE Model for All Studies (Q = 31.36,	df = 49, p = 31	.36; I ² = 0.0%,	$\tau^2 = 0.0)$		

Relative Risk (log scale)

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
lkeda; 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
li, 2015	NCT01381900	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
i, 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

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



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

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









PRISMA 2009 Checklist

3 4 5	Section/topic	#	Checklist item	Reported on page #
6 7	TITLE	-		
8	Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
9 10	ABSTRACT	-		
11 12 13	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
14 15	INTRODUCTION			
16	Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
17 18 19	Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
20	METHODS			
21 22 23	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
24 25	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
26 27 28	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
29 30	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
31 32 33	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
34 35	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
36 37	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
38 39 40	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
41	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
42 43 44	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
45 46 47			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Page 1 of 2	



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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