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SGLT-2 inhibitors and the risk of infections: A systematic review and meta-analysis of randomized controlled trials

Short Title: SGLT-2 inhibitors and the risk of infections

Robert Puckrin MD¹, Marie-Philippe Saltiel MD², Pauline Reynier MSc³, Laurent Azoulay PhD^{3,4,5}, Oriana H.Y. Yu MD MSc⁶, Kristian B. Filion PhD^{3,5,7}

 ¹Postgraduate Medical Education, University of Toronto, Toronto, Ontario, Canada
 ²Postgraduate Medical Education, McGill University, Montreal, Quebec, Canada
 ³Centre of Clinical Epidemiology, Lady Davis Institute, Montreal, Quebec, Canada
 ⁴Gerald Bronfman Department of Oncology, McGill University, Montreal, Quebec, Canada
 ⁵Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
 ⁶Division of Endocrinology, Jewish General Hospital, Montreal, Quebec, Canada
 ⁷Department of Medicine, McGill University, Montreal, Quebec, Canada

Address for Correspondence:

Kristian B. Filion, PhD Assistant Professor Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health, McGill University Centre for Clinical Epidemiology Jewish General Hospital 3755 Cote Ste-Catherine Road, Suite H416.1 Montreal, Quebec, Canada Telephone: (514) 340-8222 Ext. 28394 Fax: (514) 340-7564 Email: kristian.filion@mcgill.ca

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Abstract

Aims: There is concern about the infection-related safety profile of sodium-glucose cotransporter 2 (SGLT-2) inhibitors. We aimed to determine the effect of SGLT-2 inhibitors on genitourinary and other infections via systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods: We conducted a systematic search of Medline, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov to identify double-blinded RCTs enrolling ≥50 patients with type 2 diabetes which compared an SGLT-2 inhibitor to placebo or active comparator. Two independent reviewers extracted data and appraised study quality. Data were pooled using random-effects models.

Results: Eighty-six RCTs enrolling 50,880 patients were included. SGLT-2 inhibitors increased the risk of genital infections compared to placebo (relative risk [RR]: 3.37, 95% CI: 2.89-3.93, I^2 : 0%) and active comparators (RR 3.89, 95% CI: 3.14-4.82, I^2 : 0.3%). The risk of urinary tract infection (UTI) was not increased with SGLT-2 inhibitors compared to placebo (RR 1.03, 95% CI: 0.96-1.11, I^2 : 0%) or active comparators (RR 1.08, 95% CI: 0.93-1.25, I^2 : 22%). In drug-specific analyses, only dapagliflozin 10mg daily was associated with a significantly increased risk of UTI compared to placebo (RR 1.33, 95% CI: 1.10-1.61, I^2 : 0%). SGLT-2 inhibitors were associated with a reduced risk of gastroenteritis (RR 0.38, 95% CI: 0.20-0.72, I^2 : 0%) but did not affect the risk of respiratory tract infections.

Conclusions/Interpretation: SGLT-2 inhibitors are associated with an increased risk of genital tract infections. Although there is no association overall between SGLT-2 inhibitors and UTI, higher doses of dapagliflozin are associated with an increased risk.

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infections – adverse events – systematic review and meta-analysis

Introduction

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are a novel class of antihyperglycemic agents used in the treatment of type 2 diabetes mellitus. The majority of phase II and III randomized controlled trials (RCTs) suggest a favorable overall safety profile of SGLT-2 inhibitors, although several RCTs and systematic reviews have raised concerns about infectionrelated adverse events, particularly with respect to genitourinary infections (1-7). Furthermore, the Food and Drug Administration (FDA) has issued warnings about occurrences of ketoacidosis, acute kidney injury, urosepsis, and pyelonephritis during post-marketing studies of these drugs (8,9). These findings are particularly concerning given that patients with diabetes who develop genitourinary infections are vulnerable to poor health outcomes, hospitalization, and increased healthcare costs (10,11). However, little is known about the comparative risks of genitourinary infections with different types and doses of SGLT-2 inhibitors, as well as the effect of these medications on the risk of other infections. We therefore conducted a systematic review and metaanalysis of RCTs to determine if the use of SGLT-2 inhibitors in patients with type 2 diabetes is associated with an increased risk of genitourinary and other site-specific infections.

Methods

This study was conducted using a pre-specified protocol and is reported according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines (12).

Data Sources and Searches

We systematically searched the Medline, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases from inception to April 3, 2015 to identify all RCTs comparing SGLT-2 inhibitors to placebo or other active agents among patients with type 2 diabetes. An updated search of Medline was conducted on February 26, 2017. Our search is reported in detail in Online-Only Supplementary Material Tables S1-S4. Briefly, search terms included Medical Subject Heading (MeSH) terms, EMTREE terms, and keywords for SGLT-2 inhibitors. We employed language filters for identifying studies published in English or French in Medline and EMBASE. Modified Health Information Research Unit (HIRU) therapy search filters were applied to identify RCTs, using filters that resulted in the best balance of sensitivity and specificity (13). We also manually searched the bibliographies of relevant reviews to identify additional studies not captured in our database searches.

Study Selection

We included trials in this systematic review if: (1) the study design was a double- or tripleblinded RCT; (2) the study population consisted of \geq 50 patients aged \geq 18 years diagnosed with type 2 diabetes; (3) the study compared the use of any SGLT-2 inhibitor(s) as monotherapy or addon therapy to a placebo or active comparator(s) (i.e., insulin or other anti-hyperglycemic agent); (4) the study reported overall or site-specific infections as an outcome; and (5) the study was published in English or French. Pharmacological dosing studies, conference abstracts, unpublished studies, and trials with pending results were excluded. After performing the database searches and removing duplicates, two independent reviewers (R.P., M.S.) screened all titles and abstracts and assessed the full text of relevant citations using the pre-defined inclusion criteria. For primary RCTs with subsequent randomized, double-blinded extension studies published separately, we included the publication with the longest duration of follow-up time. Any disagreements were resolved through consensus.

Data Extraction and Quality Assessment

Data were extracted by the two reviewers using a standardized, pilot-tested data collection form. Extracted data were based on the intention-to-treat populations and included study characteristics, demographic and clinical characteristics of the study population, and proportion of study participants lost-to-follow-up. We extracted all available data related to all infections reported by \geq 5 publications: genital tract infections, urinary tract infections (UTI), pyelonephritis, urosepsis, nasopharyngitis, pharyngitis, influenza, upper respiratory tract infection (URTI), bronchitis, and gastroenteritis. Extracted data included frequency of infections, severity of infections, infections requiring treatments, and infections resulting in discontinuation of study drug. For studies reporting two different values for the occurrence of a particular infection (e.g., 'UTI' versus 'events suggestive or consistent with UTI'), we extracted the largest value for inclusion in the analysis. In cases where multiple publications exist for a particular RCT, we extracted data from the publication with the longest duration of follow-up time. Data extracted by the two reviewers were compared, with any differences resolved by consensus.

Overall study quality was assessed by the two independent reviewers using the Cochrane Risk of Bias tool (14). This tool evaluates the risk of bias associated with sequence generation, allocation concealment, blinding of participants and personnel, completeness of outcome data, selective outcome reporting, and other sources of bias. Each domain was assessed as having low, unclear, or high risk of bias using published criteria. We defined the overall risk of bias by the number of criteria (1-6) satisfied as low risk by each study: low risk (\geq 5 criteria satisfied), moderate risk (3-4 criteria satisfied), or high risk (\leq 2 criteria satisfied) of bias.

The risk of bias pertaining to infection-related adverse events was further assessed by noting the definition and size of the safety analysis, methods used to detect adverse events, and use of history of infection as an exclusion criteria at study enrollment.

Data Synthesis and Analysis

The primary outcomes of this analysis were the effect of SGLT-2 inhibitors on the incidences of genital tract infections and UTI compared to placebo or active comparator (i.e., other anti-hyperglycemic agents). Secondary outcomes included other site-specific infections. We conducted meta-analyses using separate models for these outcomes. Data were pooled across RCTs using Dersimonian and Laird random-effects meta-analytical models with inverse variance weighting to estimate relative risks (RR) and their corresponding 95% confidence intervals (CIs). All analyses were stratified by comparator (i.e., placebo versus active), with an overall estimate also presented. We applied treatment arm continuity correction for RCTs that reported 0 events in the treatment and control arms. For each SGLT-2 inhibitor, we combined data from patients assigned to all doses of the study drug for comparisons with placebo or active comparator. The amount of heterogeneity present was estimated using the I^2 statistic with its corresponding 95% CI, which estimates the proportion of the total variance that is due to between-study variability.

In secondary analyses involving three FDA-approved SGLT-2 inhibitors, we performed additional analyses restricted to patients using approved doses of the given drug (i.e., canagliflozin 100mg or 300mg daily, dapagliflozin 5mg or 10mg daily, and empagliflozin 10mg or 25mg daily). In sensitivity analyses, studies were stratified by study quality and duration in order to evaluate the impact of these characteristics on pooled estimates. We performed additional sensitivity analyses in which we excluded RCTS with 0 events in the treatment and control arms and RCTs

which precluded from enrolment patients with a history of genitourinary infection. Publication bias was assessed with respect to the primary outcome via the visual inspection of funnel plots. All analyses were performed using R version 3.2.2.

Results

Search Results and Study Characteristics

Our literature search is described in Figure 1. Database searches retrieved 2,055 potentially relevant publications. After removing 651 duplicates, the remaining 1,404 abstracts were screened, and 381 publications underwent full text review. An additional 276 abstracts were retrieved during the updated database search. In total, we identified 85 publications representing 86 unique RCTs that met our inclusion criteria.

The characteristics of the included studies are presented in Supplementary Table S5. All studies were double-blinded RCTs conducted between 2005 and 2017. A total of 50,880 patients were randomized, of which 34,428 were assigned to a SGLT-2 inhibitor: canagliflozin (19 RCTs), dapagliflozin (29 RCTs), empagliflozin (19 RCTs), ertugliflozin (3 RCTs), ipragliflozin (8 RCTs), luseogliflozin (3 RCTs), remogliflozin (2 RCTs), sotagliflozin (1 RCT), and tofogliflozin (2 RCTs). SGLT-2 inhibitors were studied as monotherapy or add-on therapy in comparison to placebo (65 RCTs), other active anti-diabetes agents (10 RCTs), or both placebo and active agent in combination (3 RCTs) or separately (8 RCTs).

The duration of follow-up time ranged from 4 to 208 weeks, with a mean follow-up time of 42 weeks. Across all study groups, mean age of participants ranged from 49.8 to 69.5 years, mean baseline glycated hemoglobin A1c (HbA1c) ranged from 7.16% (55 mmol/mol) to 11.18% (99 mmol/mol), and mean baseline BMI ranged from 23.4 to 36.2 kg/m².

Quality Assessment

Assessment of study quality using the Cochrane Risk of Bias tool is presented in Supplementary Table S6. Overall study quality varied across RCTs, with 15 RCTs deemed to be at low risk, 47 RCTs at moderate risk, and 24 RCTs at high risk of bias at the study level. Fiftysix studies did not adequately describe methods of sequence generation, allocation concealment, and/or blinding of patients and personnel. Thirty-nine RCTs were affected by high rates of attrition (>20%) and/or unbalanced non-completion rates between study groups. Other sources of bias included the risk of sponsorship bias (15), as all studies were funded by the pharmaceutical industry.

Many studies demonstrated additional risk of bias related to infection-related adverse event data. At least 18 RCTs (i.e., 21%) excluded from enrollment participants with a history of genital infection and/or UTI, which may limit the generalizability of findings to real-world patient populations. Three RCTs did not adequately describe the definition or number of patients included in the safety analysis. The intensity of infection surveillance and methods used to detect infectionrelated adverse events varied considerably across studies, as described in Supplementary Table S6. Whereas all RCTs reported safety data on our primary outcomes of genitourinary infections, many studies did not report data on other site-specific infections.

SGLT-2 inhibitors and Infection

Summaries of meta-analysis findings for infection outcomes of canagliflozin, dapagliflozin, and empagliflozin are presented in Tables 1 and 2. Meta-analyses with forest plots

for these and other SGLT-2 inhibitors can be accessed in supplementary figures S1-S19 in the Online-Only Supplementary Material.

Genital Tract Infections

The risk of genital tract infections was substantially higher in patients taking SGLT-2 inhibitors compared to placebo (RR 3.37, 95% CI: 2.89-3.93, I^2 : 0%) (Supplementary Figure S1) and active comparator (RR 3.89, 95% CI 3.14-4.82, I^2 : 0.3%) (Supplementary Figure S2). The increased risk of genital tract infection versus placebo was similar across SGLT-2 inhibitors: 3.91 (95% CI: 2.89-5.29, I^2 : 0%) for canagliflozin, 3.45 (95% CI: 2.55-4.66, I^2 : 0%) for dapagliflozin, and 3.11 (95% CI: 2.29-4.21, I^2 : 9%) for empagliflozin. There were no apparent differences with the lower and higher standard clinical doses of canagliflozin, dapagliflozin, and empagliflozin. When compared to active comparators, the relative risk of genital tract infection was 4.96 (95% CI: 3.35-7.34, I^2 : 0%) for canagliflozin, 4.21 (95% CI: 2.85-6.23, I^2 : 0%) for dapagliflozin, and 2.69 (95% CI: 1.43-5.06, I^2 : 60%) for empagliflozin.

UTI

There was no significant difference in the risk of UTI with SGLT-2 inhibitors compared to placebo (RR 1.03, 95% CI: 0.96-1.11, I^2 : 0%) or active comparator (RR 1.08, 95% CI: 0.93-1.25, I^2 : 22%) (Supplementary Figure S3-S4). However, patients taking dapagliflozin had a higher risk of UTI compared to placebo (RR 1.23, 95% CI: 1.03-1.46, I^2 : 0%). This relationship showed evidence of dose dependence, with an increased risk of UTI associated with dapagliflozin 10 mg daily (RR 1.33, 95% CI: 1.10-1.61, I^2 : 0%) but not with dapagliflozin 5 mg daily (RR 1.07, 95% CI: 0.78-1.48, I^2 : 0%) (Table 1). Other SGLT-2 inhibitors were not associated with UTI compared

to placebo, with relative risks of 1.10 (95% CI: 0.90-1.33, I^2 : 0%) for canagliflozin and 0.99 (95% CI: 0.91-1.08, I^2 : 0%) for empagliflozin. Similar results were obtained at their lower and higher standard clinical doses. When compared to active comparators, no individual SGLT-2 inhibitor demonstrated an increased risk of UTI: RR 1.15 (95% CI: 0.85-1.55, I^2 : 12%) for canagliflozin, RR 1.20 (95% CI: 0.85-1.69, I^2 : 39%) for dapagliflozin, and RR 1.01 (95% CI: 0.85-1.20, I^2 : 0%) for empagliflozin.

UTIs complicated by urosepsis occurred rarely, affecting 18 patients assigned to empagliflozin and 5 patients assigned to placebo. Although the incidence of this clinical endpoint was numerically higher with SGLT-2 inhibitors, our meta-analytic estimates are accompanied by wide 95% CIs versus placebo, resulting in inconclusive results (RR 1.41, 95% CI: 0.57-3.48, *I*²: 0%) (Supplementary Figure S5).

Fifty-four patients (0.2%) assigned to an SGLT-2 inhibitor developed pyelonephritis. Our analyses of this endpoint were also inconclusive due to sparse data and corresponding wide 95% CIs (placebo: RR 0.78, 95% CI: 0.52-1.18, I^2 : 0%; active comparators: RR 1.22, 0.37-3.96, I^2 : 0%) (Supplementary Figures S7-S8).

Respiratory Tract Infections

There was no evidence of an increased risk of respiratory tract infections among patients randomized to SGLT-2 inhibitors relative to either placebo or active comparators, including nasopharyngitis, pharyngitis, URTI, influenza, or bronchitis (Table 2, Supplementary Figures S9-S17).

Gastrointestinal infections

Analyses of data from 5 RCTs revealed that SGLT-2 inhibitors are associated with a reduced risk of gastroenteritis compared with placebo (RR 0.38, 95% CI: 0.20-0.72, I^2 : 0%) (Supplementary Figure S18). The greatest effect size was found in 2 RCTs of empagliflozin, which demonstrated a pooled relative risk for gastroenteritis of 0.28 (95% CI: 0.08-0.96, I^2 : 50%) versus placebo.

Sensitivity analyses

Sensitivity analyses stratified by study quality and duration produced estimates that were consistent with the primary analyses for the outcomes of genital tract infections and UTI (Supplementary Figures S20-S21 and S24-S26). The sensitivity analyses in which we excluded RCTs with 0 events in the treatment and control arms also produced similar results (Supplementary Figures S22-S23). Finally, a sensitivity analysis found that excluding RCTs which excluded patients with a history of genitourinary infection did not significantly affect the risk of UTI with SGLT-2 inhibitors (Supplementary Figure S27).

Publication bias

A funnel plot revealed no evidence of publication bias with respect to the primary outcome of UTI (Supplementary Figures S28-S29).

Discussion

With 86 included RCTs, our systematic review and meta-analysis provides a comprehensive assessment of the infection risk of SGLT-2 inhibitors and is among the first to specifically analyze the infection-related safety profile of these drugs. Our findings substantiate

concerns that SGLT-2 inhibitors are associated with a significant three-fold increased risk of genital tract infections compared to placebo and a four-fold increased risk compared to other antihyperglycemic agents. Similarly increased risks of genital infections occurred across all types of SGLT-2 inhibitors, including canagliflozin, dapagliflozin, and empagliflozin at their lower and higher standard clinical doses. In contrast to earlier meta-analyses (1-6), we did not identify a significant association between SGLT-2 inhibitors and the risk of UTI compared to placebo or other anti-diabetes agents. However, individual drug analyses did reveal a significantly increased risk of UTI with dapagliflozin 10mg daily but not with canagliflozin, empagliflozin, or dapagliflozin 5 mg daily. There was no increased risk of urosepsis or pyelonephritis with SGLT-2 inhibitors. SGLT-2 inhibitors were unexpectedly associated with a reduced risk of gastroenteritis, a finding that warrants further investigation given the small number of RCTs that reported this outcome. Finally, SGLT-2 inhibitors were not associated with an increased risk of respiratory infections, including nasopharyngitis, pharyngitis, URTI, bronchitis, and influenza.

The underlying mechanism for the increased risk of UTI associated with dapagliflozin but not other SGLT-2 inhibitors is uncertain. The difference may be partly driven by variations in study methodology, as proportionally more RCTs of canagliflozin and empagliflozin excluded patients with a history of genitourinary infections from enrollment. However, we performed sensitivity analyses that suggest that differences in patient selection did not significantly impact the risk of UTI. Furthermore, our identification of a dose-dependent increased risk of UTI with dapagliflozin 10 mg daily but not 5 mg daily suggests that the difference may be due to an intrinsic pharmacologic property of this drug. Data from animal models suggest that dapagliflozin has a dose-dependent and more prolonged effect on urinary glucose excretion than other SGLT-2 inhibitors (16), which may predispose towards more frequent genitourinary infections at higher doses. Further research is warranted to elucidate the underlying reasons for this finding.

The results of our study are clinically important given that patients with diabetes are already predisposed to more frequent and complicated genitourinary infections (10,11). SGLT-2 inhibitors increase urinary glucose excretion which may contribute to the proliferation of fungi and other micro-organisms in the genitourinary tract (17), leading to increased risk of genital infections and poor clinical outcomes. Although our analysis did not identify an association between SGLT-2 inhibitors and urosepsis or pyelonephritis, the included RCTs were not sufficiently powered to detect these rare but clinically important events. This is of note given the December 2015 FDA safety communication which reported 19 life-threatening cases of urosepsis or pyelonephritis in patients taking SGLT-2 inhibitors (8). This advisory demonstrates the importance of adverse event monitoring in detecting rare but potentially serious complications of therapy, which may only be revealed upon widespread administration of the medication outside clinical trials (18). Post-marketing surveillance studies are therefore warranted to confirm the frequency and clinical significance of complicated genitourinary infections associated with SGLT-2 inhibitors.

The increased risk of genitourinary infections is of particular concern given the expected dramatic rise in the prescription of SGLT2 inhibitors. The FDA recently broadened the indication of empagliflozin to include reduction of the risk of cardiovascular death in patients with diabetes and cardiovascular disease (19), based on the results of the EMPA-REG OUTCOME trial which demonstrated a 32% relative risk reduction in all-cause mortality after a median 2.6 years of treatment with empagliflozin compared to placebo (20). The results of our study should be

considered when assessing the benefits and risks of SGLT2 inhibitors as their use expands to include new clinical indications and larger and more diverse patient populations.

We identified at least 14 previous systematic reviews of SGLT-2 inhibitors as a class (1-6, 21-28); most were designed to primarily assess efficacy outcomes. Many of these reviews were limited by a relatively small number of RCTs, limited duration of follow-up time, or under-representation of RCTs involving canagliflozin and empagliflozin. Our study contributes valuable information about the safety profile of SGLT-2 inhibitors, and clarifies the conflicting findings of previous systematic reviews with respect to the risk of UTI associated with these drugs. For example, Monami et al. found a borderline significant relationship between SGLT-2 inhibitors and UTIs (1), whereas Vasilakou et al., Musso et al., and Liu et al. found SGLT-2 inhibitors to be associated with significantly increased risks of UTI (3,4,6). However, these findings are likely attributable to the inclusion of a disproportionate number of RCTs of dapagliflozin in these systematic reviews. Our study reveals that, with the exception of high dose dapagliflozin, SGLT-2 inhibitors do not appear to increase the risk of UTI in patients with type 2 diabetes.

The major strength of our review is the comparatively large number of RCTs analyzed, representing a wide range of SGLT-2 inhibitors, a large number of patients (50,880), and extended duration of follow-up time (up to 208 weeks). The size of our analysis enabled us to examine infection-related outcomes not evaluated by other systematic reviews such as that by Li et al. (25), and to determine the comparative risks of genitourinary infections with different types and doses of SGLT-2 inhibitors. Furthermore, our study was conducted using a pre-specified protocol in accordance with PRISMA guidelines, although we did not pre-emptively publish this protocol in a public repository.

Our study has several potential limitations. First, a substantial proportion of RCTs did not adequately describe study methods, and many were affected by high and/or unbalanced rates of attrition amongst treatment groups. Second, our updated database search was conducted using Medline alone in order to capture RCTs published since the original database search in an efficient manner. Third, there was variation in the reporting methods of genitourinary infections, with some RCTs reporting infections based on patient-reported symptoms while others relied on pre-defined diagnostic criteria which varied amongst RCTs. In order to facilitate the analysis, we combined these infection-related adverse events in the meta-analysis. Fourth, the reporting of less common infection-related adverse events varied considerably across RCTs, potentially introducing selective outcome reporting bias (29, 30). Fifth, the pooled risks of genital tract infections and UTI may be an underestimate of the true effect size in real-world patient populations, as some RCTs excluded patients with recent or recurrent genitourinary infections. Furthermore, surveillance methods used to detect infection-related adverse events varied across RCTs, which may yield different reported incidences of infections between studies. However, the absence of significant heterogeneity in most analyses suggests that this did not affect the estimated treatment effects. Finally, there was some clinical heterogeneity in study design, dosage, and comparator used across RCTs. For this reason, we used random-effects models, which account for between-study heterogeneity. In addition, we stratified analyses by comparator and, in secondary analyses, also stratified by dose. We were unable to further stratify the active comparators used due to the paucity of RCTs providing data on head-to-head comparisons.

Conclusions

SGLT-2 inhibitors are associated with a significantly increased risk of genital tract infection, a finding that was consistent across all types and doses of SGLT-2 inhibitors. Although SGLT-2 inhibitors were not associated with UTI as a class, we did identify a significantly increased risk of UTI with dapagliflozin 10 mg daily. SGLT-2 inhibitors were not associated with an increased risk of respiratory infections and appeared to decrease the risk of gastroenteritis. The increased risk of genital tract infection (for all SGLT-2 inhibitors) and UTI (for dapagliflozin 10 mg daily) should be considered when assessing the overall benefits and risks of SGLT-2 inhibitors for the management of type 2 diabetes.

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Contribution statement

R.P. and M.S. conducted the literature search, performed data extraction, and assessed study quality. P.R. conducted the statistical analyses. R.P. wrote the manuscript. All authors interpreted data and revised the manuscript for important intellectual content. R.P. and K.B.F. designed the study. K.B.F. conceived of the study idea, supervised the study, and is the guarantor.

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Table 1: Results of meta-an	alyses for	genitourinary	y infections	with SGLT-2 inhibitors
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		T : 1	SGLT-2 inhibitor		Cor	nparator	Random Effects	$\mathbf{r}^{2}(0/)$ *
Outcome	Comparison	Trials	Events	Patients	Events	Patients	Model Risk Ratio	$I^{2}(\%)^{*}$
	-		(n)	(n)	(n)	(n)	(95% CI)	(95% CI)
	SGLT-2 Inhibitor vs. Placebo	72	1485	25,250	176	11,866	3.37 (2.89-3.93)	0 (1-16)
	Canagliflozin (All Doses) vs. Placebo	16	433	5,513	46	2,518	3.91 (2.89-5.29)	0 (0-50)
ц	Canagliflozin (100 mg) vs. Placebo	14	202	2,509	42	2,317	4.11 (2.96-5.73)	0 (0-42)
tio	Canagliflozin (300 mg) vs. Placebo	11	205	2,269	41	2,085	4.47 (3.20-6.24)	0 (0-52)
ffec	Dapagliflozin (All Doses) vs. Placebo	23	370	5,918	45	3,518	3.45 (2.55-4.66)	0 (0-43)
I In	Dapagliflozin (5 mg) vs. Placebo	12	68	1,274	21	1,207	2.95 (1.84-4.72)	0 (0-0)
ion	Dapagliflozin (10 mg) vs. Placebo	20	203	3,271	45	3,281	3.60 (2.53-5.11)	8 (0-43)
act	Empagliflozin (All Doses) vs. Placebo	14	569	10,142	74	4,586	3.11 (2.29-4.21)	9 (0-46)
\mathbf{Tr}	Empagliflozin (10 mg) vs. Placebo	14	275	4,497	72	4,362	3.33 (2.46-4.49)	5 (0-57)
tal	Empagliflozin (25 mg) vs. Placebo	16	268	4,694	74	4,586	3.00 (2.08-4.35)	19 (0-55)
eni	SGLT-2 Inhibitor vs. Active Comparator	22	732	11,208	93	4,758	3.89 (3.14-4.82)	0 (0-46)
Ğ	Canagliflozin vs. Active Comparator	5	258	3,350	27	1,528	4.96 (3.35-7.34)	0 (0-38)
	Dapagliflozin vs. Active Comparator	7	200	2,533	28	1,354	4.21 (2.85-6.23)	0 (0-3)
	Empagliflozin vs. Active Comparator	6	236	4,416	36	1,670	2.69 (1.43-5.06)	59 (0-84)
	SGLT-2 Inhibitor vs. Placebo	72	2,203	25,250	1,033	1,1866	1.03 (0.96-1.11)	0 (0-0)
	Canagliflozin (All Doses) vs. Placebo	16	330	5,513	135	2,518	1.10 (0.90-1.33)	0 (0-0)
	Canagliflozin (100 mg) vs. Placebo	14	151	2,509	131	2,317	1.05 (0.83-1.32)	0 (0-16)
ion	Canagliflozin (300 mg) vs. Placebo	11	156	2,269	129	2,085	1.14 (0.91-1.42)	0 (0-44)
ecti	Dapagliflozin (All Doses) vs. Placebo	23	402	5,918	186	3,518	1.23 (1.03-1.46)	0 (0-25)
Infe	Dapagliflozin (5 mg) vs. Placebo	12	72	1,274	66	1,207	1.07 (0.78-1.48)	0 (0-0)
ct]	Dapagliflozin (10 mg) vs. Placebo	20	233	3,271	173	3,281	1.33 (1.10-1.61)	0 (0-36)
Γ ra	Empagliflozin (All Doses) vs. Placebo	14	1,365	10,142	673	4,586	0.99 (0.91-1.08)	0 (0-24)
²	Empagliflozin (10 mg) vs. Placebo	14	658	4,497	641	4,362	1.01 (0.91-1.11)	0 (0-0)
naı	Empagliflozin (25 mg) vs. Placebo	16	668	4,694	673	4,586	0.97 (0.88-1.07)	0 (0-41)
Uri	SGLT-2 Inhibitor vs. Active Comparator	22	850	11,208	373	4,758	1.08 (0.93-1.25)	22 (0-54)
	Canagliflozin vs. Active Comparator	5	189	3,350	81	1,528	1.15 (0.85-1.55)	12 (0-82)
	Dapagliflozin vs. Active Comparator	7	200	2,533	91	1,354	1.20 (0.85-1.69)	39 (0-74)
	Empagliflozin vs. Active Comparator	6	420	4,416	189	1,670	1.01 (0.85-1.20)	0 (0-60)
=	SGLT-2 Inhibitor vs. Placebo	7	17	6,633	5	3,464	1.41 (0.57-3.48)	0 (0-32)
Jro s s	Canagliflozin vs. Placebo	3	0	977	2	537	0.36 (0.05-2.57)	0 (0-78)
U Se	Empagliflozin vs. Placebo	3	17	5,481	3	2,840	2.13 (0.75-6.07)	0 (0-0)

	SGLT-2 Inhibitor vs. Active Comparator	2	1	1,311	0	908	1.39 (0.07-28.33)	0
	Empagliflozin vs. Active Comparator	2	1	1,311	0	908	1.39 (0.07-28.33)	0
	SGLT-2 Inhibitor vs. Placebo		45	13,188	31	7,029	0.78 (0.52-1.18)	0 (0-0)
.s	Canagliflozin vs. Placebo	9	9	3,469	7	1,819	0.70 (0.30-1.66)	0 (0-0)
nrit	Dapagliflozin vs. Placebo	13	5	3,976	3	2,200	0.97 (0.34-2.77)	0 (0-0)
hte	Empagliflozin vs. Placebo	3	31	5,481	20	2,840	0.79 (0.46-1.35)	0 (0-0)
ono	SGLT-2 Inhibitor vs. Active Comparator	9	9	5,815	2	2,587	1.22 (0.37-3.96)	0 (0-0)
yel	Canagliflozin vs. Active Comparator	2	3	1,917	0	719	3.06 (0.17-54.13)	0
Ċ,	Dapagliflozin vs. Active Comparator	3	1	1,026	1	484	0.64 (0.08-5.00)	0 (0-75)
	Empagliflozin vs. Active Comparator	4	5	2,872	1	1,384	1.36 (0.26-7.15)	0 (0-31)

* Note that the 95% C.I. for I² could not be calculated for analyses containing 2 or fewer RCTs.

			SGLT-2	inhibitor	Cor	nparator	Random Effects	\mathbf{r}^{2} (0())*
Outcome	Comparison	Trials	Events	Patients	Events	Patients	Model Risk Ratio	$I^{2} (\%)^{*}$
		(11)	(n)	(n)	(n)	(n)	(95% CI)	(95% CI)
Respirato	ry Tract Infections							
	SGLT-2 Inhibitor vs. Placebo	42	1,023	11,629	500	5,269	0.93 (0.84-1.03)	0 (0-16)
tis	Canagliflozin vs. Placebo	2	42	629	12	140	0.83 (0.45-1.52)	0
. <u>1</u> 91.	Dapagliflozin vs. Placebo	15	388	4,236	179	2,333	1.07 (0.90-1.27)	0 (0-0)
ıryı	Empagliflozin vs. Placebo	15	460	5,102	238	2,182	0.90 (0.77-1.04)	0 (0-54)
oha	SGLT-2 Inhibitor vs. Active Comparator	8	300	3,405	225	1,849	0.89 (0.75-1.05)	0 (0-67)
sol	Canagliflozin vs. Active Comparator	1	7	321	3	65	0.47 (0.13-1.78)	N/A
Na	Dapagliflozin vs. Active Comparator	2	96	605	83	483	0.97 (0.74-1.28)	0
	Empagliflozin vs. Active Comparator	4	193	2,300	136	1,266	0.88 (0.71-1.09)	0 (0-77)
y	SGLT-2 Inhibitor vs. Placebo	5	23	1,025	9	366	0.83 (0.35-1.96)	0 (0-71)
har 1g- itis	Dapagliflozin vs. Placebo	1	7	214	3	68	0.74 (0.20-2.79)	N/A
E	Empagliflozin vs. Placebo	1	9	438	1	109	2.24 (0.29-17.49)	N/A
	SGLT-2 Inhibitor vs. Placebo	9	150	2,633	53	1,123	1.17 (0.82-1.67)	11 (0-53)
za	Dapagliflozin vs. Placebo	5	105	1,526	35	618	1.20 (0.82-1.77)	0 (0-78)
enz	Empagliflozin vs. Placebo	2	39	816	16	413	1.30 (0.51-3.27)	54
flu	SGLT-2 Inhibitor vs. Active Comparator	6	160	2,637	106	1,561	1.11 (0.87-1.43)	0 (0-63)
In	Dapagliflozin vs. Active Comparator	2	67	605	48	483	1.19 (0.81-1.74)	2
	Empagliflozin vs. Active Comparator	3	87	1,853	57	1,043	1.07 (0.69-1.65)	10 (0-91)
	SGLT-2 Inhibitor vs. Placebo	26	399	7,762	211	3,433	0.94 (0.78-1.12)	9 (0-41)
	Canagliflozin vs. Placebo	1	9	308	1	75	2.19 (0.28-17.03)	N/A
F	Dapagliflozin vs. Placebo	10	140	3,018	83	1,475	0.82 (0.56-1.19)	30 (0-67)
RT	Empagliflozin vs. Placebo	7	211	3,271	102	1,421	1.09 (0.83-1.42)	22 (0-63)
	SGLT-2 Inhibitor vs. Active Comparator	9	281	4,731	188	2,459	0.87 (0.68-1.12)	30 (0-68)
	Dapagliflozin vs. Active Comparator	3	64	1,233	64	817	0.76 (0.54-1.07)	0 (0-69)
	Empagliflozin vs. Active Comparator	5	214	3,319	124	1,607	0.92 (0.63-1.35)	56 (0-84)
s	SGLT-2 Inhibitor vs. Placebo	10	138	3,993	73	1,831	0.94 (0.69-1.27)	5 (0-64)
nitis	Dapagliflozin vs. Placebo	5	68	1,742	43	1,026	0.99 (0.58-1.71)	36 (0-76)
ncł	Empagliflozin vs. Placebo	4	65	2,139	30	749	0.93 (0.60-1.44)	0 (0-73)
3ro	SGLT-2 Inhibitor vs. Active Comparator	2	53	853	44	631	0.97 (0.64-1.50)	14
щ	Dapagliflozin vs. Active Comparator	1	36	406	32	408	1.13 (0.72-1.78)	N/A

Table 2: Results of meta-analyses for respiratory and gastrointestinal infections with SGLT-2 inhibitors

Empagliflozin vs. Active Comparator 1		1	17	447	12	223	0.71 (0.34-1.45)	N/A
Gastrointestinal Infections								
	SGLT-2 Inhibitor vs. Placebo	5	19	1,667	20	484	0.38 (0.20-0.72)	0 (0-73)
Dapagliflozin vs. Plac	Dapagliflozin vs. Placebo	1	4	225	1	54	0.96 (0.11-8.42)	N/A
riti T	Empagliflozin vs. Placebo	2	12	1,251	13	295	0.28 (0.08-0.96)	50
jas nte	SGLT-2 Inhibitor vs. Active Comparator	2	43	952	27	536	1.13 (0.70-1.82)	0
G O	Dapagliflozin vs. Active Comparator	1	27	406	23	408	1.18 (0.69-2.02)	N/A
Empagliflozin vs. Active Comparator		1	16	546	4	128	0.94 (0.32-2.76)	N/A
Empagliflozin vs. Active Comparator		1	16	546	4	128	0.94 (0.32-2.76)	N/A

* An I² of "N/A" denotes that the I² statistic was not calculated as the the comparison included only 1 RCT, preventing meta-analysis. Note that the 95% C.I. for I² could not be calculated for analyses containing 2 or fewer RCTs.



Figure 1: PRISMA flow diagram summarizing database search results and study selection

Search	Degenintien	Number of				
Number	Description	publications				
1	Sodium-Glucose Transport Proteins [mh] OR Sodium-Glucose Transporter 2	4422				
	[mh] OR "sodium glucose transport" OR "sodium glucose transporter" OR					
	"sodium glucose co-transport" OR "sodium glucose co-transporter" OR					
	"sodium glucose cotransport" OR "sodium glucose cotransporter" OR sglt					
	OR sglt2 OR sglt-2 OR dapagliflozin OR farxiga OR xigduo OR BMS-					
	512148 [tw] OR BMS512148 [tw] OR empagliflozin OR jardiance OR BI-					
	10773 [tw] OR BI10773 [tw] OR canagliflozin OR invokana OR TA-7284					
	[tw] OR TA7284 [tw] OR JNJ28431754 [tw] OR JNJ-28431754 [tw] OR					
	ipragliflozin OR ASP1941 [tw] OR ASP-1941 [tw] OR BI-44847 [tw] OR					
	BI44847 [tw] OR tofogliflozin OR CSG452 [tw] OR CSG-452 [tw] OR RG-					
	7201 [tw] OR RG7201 [tw] OR luseogliflozin OR TS071 [tw] OR TS-071					
	[tw] OR sergliflozin OR remogliflozin OR KGT-1650 [tw] OR KGT1650					
	[tw] OR KGT-1681 [tw] OR KGT1681 [tw] OR GSK-189075A [tw] OR					
	GSK189075A [tw] OR sotagliflozin OR LX4211 [tw] OR LX-4211 [tw] OR					
	ertugliflozin OR PF-04971729 [tw] OR PF04971729 [tw] OR phlorizin OR					
	phloridzin OR AVE2268 [tw] OR AVE-2268 [tw] OR TS-033 [tw] OR					
	TS033 [tw] OR YM543 [tw] OR YM-543 [tw] OR KGT1251 [tw] OR KGT-					
	1251 [tw] OR GW-869682 [tw] OR GW869682 [tw] OR RO-4998452 [tw]					
	OR RO4998452 [tw] OR EGT-1442 [tw] OR EGT1442 [tw] OR WAY-					
	123783 [tw] OR WAY123783 [tw] OR T-1095 [tw] OR T1095 [tw] OR ISIS-					
	SGLT2Rx [tw] OR ISISSGLT2Rx [tw] OR ISIS-388626 [tw] OR					
	ISIS388626 [tw]					
2	1 limited to English or French	4216				
3 ^a	2 AND (randomized controlled trial[Publication Type] OR	270				
	randomized[Title/Abstract] OR randomised[Title/Abstract] OR					
	placebo[Title/Abstract])					
Date of init	Date of initial search: April 3, 2015. Date of updated search: February 26, 2017.					
^a Modified	^a Modified HIRU therapy search filter for best balance of sensitivity and specificity					

Table 9	S1 · Pu	hMed	search	strategy	for	RCTs	examining	the use	of SG	Т.Т.2	inhibitors
Lanc	31. I U	DIVICU	scar ch	sualegy	101	NUIS	Cramming	the use	01 90		minuturs

Search	Description	Number of
Number	Description	publications
1	Exp sodium glucose co-transporter 2 inhibitor/ OR exp sodium glucose co-	6525
	transporter inhibitor/ OR exp sodium glucose cotransporter/ OR exp sodium	
	glucose cotransporter 1/ OR exp sodium glucose cotransporter 2/ OR exp	
	sodium glucose cotransporter 2 inhibitor/ OR exp sodium glucose	
	cotransporter inhibitor/ or sodium glucose transport protein\$.mp. or sodium	
	glucose transporter\$.mp. OR sodium glucose cotransporter 2.mp. OR	
	SGLT2 inhibitor*.mp. OR SGLT-2 inhibitor*.mp. OR sodium glucose	
	cotransporter\$.mp. OR sodium glucose co-transporter\$.mp. OR "sodium	
	glucose transport".ti,ab. OR "sodium glucose transporter".ti,ab. OR "sodium	
	glucose co-transport".ti,ab. OR "sodium glucose co-transporter".ti,ab. OR	
	"sodium glucose cotransport".ti,ab. OR "sodium glucose	
	cotransporter".ti,ab. OR sglt.mp,ti,ab. OR sglt2.mp,ti,ab. OR sglt-	
	2.mp,ti,ab. OR exp dapagliflozin/ OR exp dapagliflozin plus metformin/ OR	
	dapagliflozin.mp. OR farxiga.mp. OR xigduo.mp. OR BMS-512148.mp.	
	OR BMS512148.mp. OR exp empagliflozin/ OR empagliflozin.mp. OR	
	jardiance.mp. OR BI-10773.mp. OR BI10773.mp. OR exp canagliflozin/	
	OR exp canagliflozin plus metformin/ OR canagliflozin.mp. OR	
	invokana.mp. OR TA-7284.mp. OR TA7284.mp. OR JNJ28431754.mp. OR	
	JNJ-28431754.mp. OR exp ipragliflozin/ OR ipragliflozin.mp. OR	
	ASP1941.mp. OR ASP-1941.mp. OR exp bi 44847/ OR BI-44847.mp. OR	
	BI44847.mp. OR exp tofogliflozin / OR tofogliflozin.mp. OR CSG452.mp.	
	OR CSG-452.mp. OR RG-7201.mp. OR RG7201.mp. OR exp	
	luseogliflozin/ OR luseogliflozin.mp. OR TS071.mp. OR TS-071.mp. OR	
	exp sergliflozin etabonate/ OR sergliflozin.mp. OR exp remogliflozin	
	etabonate/ OR remogliflozin.mp. OR KGT-1650.mp. OR KGT1650.mp.	
	OR KGT-1681.mp. OR KGT1681.mp. OR GSK-189075A.mp. OR	
	GSK189075A.mp. OR exp sotagliflozin / OR sotagliflozin.mp. OR	
	LX4211.mp. OR LX-4211.mp. OR exp ertugliflozin/ OR ertugliflozin.mp.	
	OR exp ertugliflozin plus metformin/ OR PF-04971729.mp. OR	
	PF04971729.mp. OR exp phlorizin/ OR phlorizin.mp. OR phloridzin.mp.	
	OR AVE2268.mp. OR AVE-2268.mp. OR TS-033.mp. OR TS033.mp. OR	

Table S2: EMBASE search strategy for RCTs examining the use of SGLT-2 inhibitors

	YM543.mp. OR YM-543.mp. OR KGT1251.mp. OR KGT-1251.mp. OR					
	GW-869682.mp. OR GW869682.mp. OR RO-4998452.mp. OR					
	RO4998452.mp. OR EGT-1442.mp. OR EGT1442.mp. OR WAY-					
	123783.mp. OR WAY123783.mp. OR T-1095.mp. OR T1095.mp. OR					
	ISIS-SGLT2Rx.mp. OR ISISSGLT2Rx.mp. OR ISIS-388626.mp. OR					
	ISIS388626.mp.					
2	1 limited to English or French	6153				
3 ^a	2 AND (random:.tw. or placebo:.mp. or double-blind:.tw.)	928				
Date of search: April 3, 2015						
^a HIRU therapy search filter for best balance of sensitivity and specificity						

Search	Description	Number of
Number	Description	publications
1	MeSH descriptor: [Sodium-Glucose Transport Proteins] explode all trees OR	390
	sodium glucose transport protein* or sodium glucose transport* or sodium	
	glucose co-transport* or sodium glucose cotransport* or sglt or sglt2 or sglt-	
	2 or dapagliflozin or farxiga or xigduo or BMS-512148 or BMS512148 or	
	empagliflozin or jardiance or BI-10773 or BI10773 or canagliflozin or	
	invokana or TA-7284 or TA7284 or JNJ28431754 or JNJ-28431754 or	
	ipragliflozin or ASP1941 or ASP-1941 or BI-44847 or BI44847 or	
	tofogliflozin or CSG452 or CSG-452 or RG-7201 or RG7201 or	
	luseogliflozin or TS071 or TS-071 or sergliflozin or remogliflozin or KGT-	
	1650 or KGT1650 or KGT-1681 or KGT1681 or GSK-189075A or	
	GSK189075A or sotagliflozin or LX4211 or LX-4211 or ertugliflozin or PF-	
	04971729 or PF04971729 or phlorizin or phloridzin or AVE2268 or AVE-	
	2268 or TS-033 or TS033 or YM543 or YM-543 or KGT1251 or KGT-1251	
	or GW-869682 or GW869682 or RO-4998452 or RO4998452 or EGT-1442	
	or EGT1442 or WAY-123783 or WAY123783 or T-1095 or T1095 or ISIS-	
	SGLT2Rx or ISISSGLT2Rx or ISIS-388626 or ISIS388626	
2	1 limited to clinical trials	304
Date of searc	h: April 3, 2015	

Table S3: Cochrane Library search strategy for RCTs examining the use of SGLT-2 inhibitors

Search	Description	Number of
Number	Description	publications
1	Sodium-Glucose Transport Proteins OR Sodium-Glucose Transporter 2 OR	97
	sodium glucose transport OR sodium glucose transporter OR sodium glucose	
	co-transport OR sodium glucose co-transporter OR sodium glucose	
	cotransport	
2	sodium glucose cotransporter OR sglt OR sglt2 OR sglt-2	84
3	dapagliflozin OR farxiga OR xigduo OR BMS-512148 OR BMS512148 OR	282
	empagliflozin OR jardiance OR BI-10773 OR BI10773 OR canagliflozin OR	
	invokana OR TA-7284 OR TA7284 OR JNJ28431754 OR JNJ-28431754	
	OR ipragliflozin OR ASP1941 OR ASP-1941	
4	BI-44847 OR BI44847 OR tofogliflozin OR CSG452 OR CSG-452 OR RG-	27
	7201 OR RG7201 OR luseogliflozin OR TS071 OR TS-071 OR sergliflozin	
	OR remogliflozin OR KGT-1650 OR KGT1650 OR KGT-1681 OR	
	KGT1681 OR GSK-189075A OR GSK189075A OR sotagliflozin	
5	LX4211 OR LX-4211 OR ertugliflozin OR PF-04971729 OR PF04971729	49
	OR phlorizin OR phloridzin OR AVE2268 OR AVE-2268 OR TS-033 OR	
	TS033 OR YM543 OR YM-543 OR KGT1251 OR KGT-1251 OR GW-	
	869682 OR GW869682 OR RO-4998452 OR RO4998452 OR EGT-1442	
	OR EGT1442	
6	WAY-123783 OR WAY123783 OR T-1095 OR T1095 OR ISIS-SGLT2Rx	6
	OR ISISSGLT2Rx OR ISIS-388626 OR ISIS388626	
Date of searc	h: April 3, 2015	

Fable S4: ClinicalTrials.gov search strateg	y for RCTs examining	the use of SGLT-2 inhibitors
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Study, Year	Registration Number	Country	Study Period	Study Population	Study Size	SGLT-2 Inhibitor	Comparator	Follow- up Time (weeks)	Funding Source
Bode, 2015	NCT01106651	17 countries	2010-	DM2 aged 55-80	716	Canagliflozin	Placebo	108	Janssen
(1)			2013						
Forst, 2014	NCT01106690	11 countries	2010-	Poorly-controlled	344	Canagliflozin	Placebo then	56	Janssen
(2)			2012	DM2			sitagliptin		
Inagaki,	NCT01022112	Japan	2009-	DM2	383	Canagliflozin	Placebo	14	Mitsubishi
2013 (3)			2010						Tanabe
Inagaki,	NCT01413204	Japan	2011-	DM2	272	Canagliflozin	Placebo	26	Mitsubishi
2014 (4)			2012						Tanabe
Inagaki,	NCT02220920	Japan	2014-	DM2 on insulin	146	Canagliflozin	Placebo	18	Mitsubishi
2016 (5)			2015						Tanabe
Ji, 2015 (6)	NCT01381900	China,	2011-	DM2	678	Canagliflozin	Placebo	18	Janssen
		Malaysia,	2012						
		Vietnam							
Kadowaki,	NCT02354235	Japan	2015-	DM2 on	185	Canagliflozin	Placebo	24	Mitsubishi
2017 (7)			2016	teneligliptin					Tanabe
Lavalle-	NCT01106677	22 countries	2010-	Poorly-controlled	1284	Canagliflozin	Placebo or	56	Janssen
Gonzalez,			2012	DM2			sitagliptin		
2013 (8)									
Leiter. 2015	NCT00968812	19 countries	2009-	DM2	1450	Canagliflozin	Glimepiride	104	Janssen
(9)			2013						
Neal, 2015	NCT01032629	24 countries	2009-	DM2 on insulin	2074	Canagliflozin	Placebo	52	Janssen
(10)			2012						
Qiu, 2014	NCT01340664	7 countries	2011-	DM2 on	279	Canagliflozin	Placebo	22	Janssen
(11)			2012	metformin					
Rodbard,	N/A	5 countries	2014-	DM2 on	218	Canagliflozin	Placebo	28	Janssen
2016 (12)			2015	metformin and					
				sitagliptin					
Rosenstock,	NCT01809327	12 countries	2013-	Treatment-naïve	1,186	Canagliflozin	Metformin	30	Janssen
2016 (13)			2014	DM2					

 Table S5: Characteristics of randomized controlled trials included in the systematic review

Rosenstock, 2012 (14)	NCT00642278	12 countries	2008- 2009	Poorly-controlled DM2	451	Canagliflozin	Placebo or sitagliptin	14	Janssen
Schernthane r, 2013 (15)	NCT01137812	17 countries	2010- 2012	Poorly-controlled DM2	756	Canagliflozin	Sitagliptin	56	Janssen
Stenlof, 2014 (16)	NCT01081834	18 countries	2010- 2012	Poorly-controlled DM2	587	Canagliflozin	Placebo then sitagliptin	52	Janssen
Townsend, 2016 (17)	N/A	United States	N/A	DM2 with hypertension	171	Canagliflozin	Placebo	10	Janssen
Wilding, 2013 (18)	NCT01106625	11 countries	2010- 2012	Poorly-controlled DM2	469	Canagliflozin	Placebo	52	Janssen
Yale, 2014 (19)	NCT01064414	19 countries	2010- 2012	DM2 with CKD	272	Canagliflozin	Placebo	56	Janssen
Araki, 2016 (20)	NCT02157298	Japan	2014- 2014	DM2 on insulin	182	Dapagliflozin	Placebo	16	AstraZeneca
Bailey, 2013 (21)	NCT00528879	5 countries	2007- 2010	Poorly-controlled DM2	546	Dapagliflozin	Placebo	102	Bristol-Myers Squibb, AstraZeneca
Bailey, 2012 (22)	N/A	7 countries	2008- 2010	DM2	282	Dapagliflozin	Placebo	28	Bristol-Myers Squibb, AstraZeneca
Bailey, 2015 (23)	NCT 00528372	4 countries	2007- 2010	DM2	274	Dapagliflozin	Placebo then placebo and metformin	102	Bristol-Myers Squibb, AstraZeneca
Bolinder,20 14 (24)	NCT00855166	5 countries	2009- 2011	Poorly-controlled DM2	182	Dapagliflozin	Placebo	102	Bristol-Myers Squibb, AstraZeneca
Cefalu, 2015 (25)	NCT01031680	Multiple countries	2010- 2012	DM2 with cardiovascular disease	922	Dapagliflozin	Placebo	52	Bristol-Myers Squibb, AstraZeneca
Del Prato, 2015 (26)	NCT00660907	10 countries	2010- 2013	Poorly-controlled DM2	816	Dapagliflozin	Gliplizide	208	Bristol-Myers Squibb, AstraZeneca

Frias, 2016	NCT02229396	6 countries	2014-	DM2 on	695	Dapagliflozin	Exenatide	28	AstraZeneca
(27)			2015	metformin					
Henry Study	NCT00643851	Multiple	2008-	DM2 not on	603	Dapagliflozin	Placebo and	24	Bristol-Myers
1, 2012 (28)		countries	2009	treatment			metformin		Squibb,
									AstraZeneca
Henry Study	NCT00859898	Multiple	2009-	DM2 not on	641	Dapagliflozin	Placebo and	24	Bristol-Myers
2, 2012 (28)		countries	2010	treatment			metformin		Squibb,
									AstraZeneca
Jabbour,	NCT00984867	6 countries	2009-	Poorly-controlled	451	Dapagliflozin	Placebo	48	Bristol-Myers
2014 (29)			2011	DM2					Squibb,
									AstraZeneca
Ji, 2014 (30)	NCT01095653	4 countries	2010-	DM2 not on	393	Dapagliflozin	Placebo	28	Bristol-Myers
			2012	treatment					Squibb,
									AstraZeneca
Kaku, 2013	NCT00972244	Japan	2009-	DM2	279	Dapagliflozin	Placebo	16	Bristol-Myers
(31)			2010						Squibb,
									AstraZeneca
Kaku, 2014	N/A	Japan	NR	DM2	261	Dapagliflozin	Placebo	27	Bristol-Myers
(32)									Squibb,
									AstraZeneca
Kohan,	NCT00663260	13 countries	2008-	DM2 with CKD	252	Dapagliflozin	Placebo	104	Bristol-Myers
2014 (33)			2011						Squibb,
									AstraZeneca
Lambers	NCT00976495	Canada,	2009-	DM2 on	75	Dapagliflozin	Placebo or	12	Bristol-Myers
Heerspink,		Netherlands,	2010	metformin and/or			hydrochlorothia		Squibb,
2013 (34)		USA		sulfonylurea			zide		AstraZeneca
Leiter, 2014	NCT01042977	10 countries	2010-	DM2 with CV	964	Dapagliflozin	Placebo	52	Bristol-Myers
(35)			2012	disease					Squibb,
									AstraZeneca
List, 2009	NCT00263276	4 countries	2005-	DM2 not on	389	Dapagliflozin	Placebo or	16	Bristol-Myers
(36)			2006	treatment			metformin		Squibb,
									AstraZeneca

Matthaei, 2015 (37)	NCT01392677	6 countries	2011- 2013	Poorly-controlled DM2	219	Dapagliflozin	Placebo	52	Bristol-Myers Squibb, AstraZeneca
Mathieu, 2016 (38)	NCT01646320	8 countries	2012- 2015	DM2 on metformin and saxagliptin	320	Dapagliflozin	Placebo	52	Bristol-Myers Squibb, AstraZeneca
Rosenstock, 2015 (39)	NCT01606007	8 countries	2012- 2014	Poorly-controlled DM2	534	Dapagliflozin	Placebo and saxagliptin	24	Bristol-Myers Squibb, AstraZeneca
Rosenstock, 2012 (40)	NCT00683878	8 countries	2008- 2010	Poorly-controlled DM2	420	Dapagliflozin	Placebo	48	Bristol-Myers Squibb, AstraZeneca
Schumm- Draeger, 2015 (41)	NCT01217892	Europe, South Africa	2010- 2011	Poorly-controlled DM2	400	Dapagliflozin	Placebo	20	Bristol-Myers Squibb, AstraZeneca
Strojek, 2014 (42)	NCT00680745	Europe, Asia	2008- 2009	Poorly-controlled DM2	597	Dapagliflozin	Placebo	48	Bristol-Myers Squibb, AstraZeneca
Weber, 2016 (43)	NCT01137474	15 countries	2010- 2013	DM2 with hypertension	613	Dapagliflozin	Placebo	13	Bristol-Myers Squibb, AstraZeneca
Weber, 2016 (44)	NCT01195662	16 countries	2010- 2013	DM2 with hypertension	588	Dapagliflozin	Placebo	13	Bristol-Myers Squibb, AstraZeneca
Wilding, 2009 (45)	NCT00357370	USA, Canada	2006- 2008	Poorly-controlled DM2	71	Dapagliflozin	Placebo	16	Bristol-Myers Squibb, AstraZeneca
Wilding, 2014 (46)	NCT00673231	Multiple countries	2008- 2011	Poorly-controlled DM2	808	Dapagliflozin	Placebo	107	Bristol-Myers Squibb, AstraZeneca
Yang, 2016 (47)	NCT01095666	China, India, South Korea	2010- 2013	Asian poorly- controlled DM2	444	Dapagliflozin	Placebo	28	Bristol-Myers Squibb, AstraZeneca
Araki, 2015 (48)	NCT01368081	Japan	2011- 2013	DM2	1160	Empagliflozin	Metformin and sulfonylurea	53	Boehringer Ingelheim, Eli Lilly
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Barnett, 2014 (49)	NCT01164501	15 countries	2010- 2012	DM2 and CKD	741	Empagliflozin	Placebo	55	Boehringer Ingelheim, Eli Lilly
DeFronzo, 2015 (50)	NCT01422876	22 countries	2011- 2013	Poorly-controlled DM2	686	Empagliflozin	Linagliptin	56	Boehringer Ingelheim, Eli Lilly
Ferrannini, 2013 (51)	NCT00789035	13 countries	2008- 2009	DM2	408	Empagliflozin	Placebo	13.5	Boehringer Ingelheim, Eli Lilly
Merker, 2015 (52)	NCT01159600	12 countries	2010- 2012	DM2 on metformin	637	Empagliflozin	Placebo	76	Boehringer Ingelheim, Eli Lilly
Haering, 2015 (53)	NCT01289990	12 countries	2010- 2012	DM2 on metformin and sulfonylurea	666	Empagliflozin	Placebo	76	Boehringer Ingelheim, Eli Lilly
Hadjadj, 2016 (54)	NCT01719003	21 countries	2012- 2014	Treatment-naïve DM2	1364	Empagliflozin	Metformin	25	Boehringer Ingelheim, Eli Lilly
Kadowaki, 2014 (55)	NCT01193218	Japan	2010- 2012	DM2	547	Empagliflozin	Placebo	12	Boehringer Ingelheim, Eli Lilly
Kovacs, 2015 (56)	NCT01210001	8 countries	2010- 2012	DM2 on pioglitazone ±metformin	499	Empagliflozin	Placebo	76	Boehringer Ingelheim
Lewin, 2015 (57)	NCT01422876	22 countries	2011- 2013	DM2 not on treatment	677	Empagliflozin	Linagliptin	56	Boehringer Ingelheim, Eli Lilly
Ridderstrale , 2014 (58)	NCT01167881	23 countries	2010- 2015	Poorly-controlled DM2	1549	Empagliflozin	Glimepiride	108	Boehringer Ingelheim, Eli Lilly

Roden, 2015 (59)	NCT01177813	9 countries	2010- 2012	DM2 not on treatment	899	Empagliflozin	Placebo or sitagliptin	76	Boehringer Ingelheim, Eli Lilly
Rosenstock, 2015 (60)	NCT01011868	7 countries	2009- 2012	Poorly-controlled DM2 on insulin	494	Empagliflozin	Placebo	82	Boehringer Ingelheim, Eli Lilly
Rosenstock, 2014 (61)	NCT01306214	14 countries	2011- 2013	Obese DM2 on insulin	566	Empagliflozin	Placebo	56	Boehringer Ingelheim, Eli Lilly
Rosenstock, 2013 (62)	NCT00749190	16 countries	2008- 2009	DM2	495	Empagliflozin	Placebo	13	Boehringer Ingelheim
Ross, 2015 (63)	EU 2012- 000905-53	NR	2012	Poorly-controlled DM2	983	Empagliflozin	Placebo	17	Boehringer Ingelheim, Eli Lilly
Softeland, 2017 (64)	NCT01734785	10 countries	2013- 2015	Poorly-controlled DM2 on metformin and linagliptin	333	Empagliflozin	Placebo	25	Boehringer Ingelheim, Eli Lilly
Tikkanen, 2015 (65)	NCT01370005	12 countries	2011-12	DM2 with hypertension	825	Empagliflozin	Placebo	14	Boehringer Ingelheim, Eli Lilly
Zinman, 2015 (66)	NCT01131676	52 countries	2010- 2015	DM2 with CVD not on treatment for DM2	7028	Empagliflozin	Placebo	206	Boehringer Ingelheim, Eli Lilly
Amin, 2015 (67)	NCT01059825	5 countries	2010- 2011	DM2	328	Ertugliflozin	Placebo or sitagliptin	14	Pfizer
Amin, 2015 (68)	NCT01096667	5 countries	2010- 2011	DM2 with hypertension	194	Ertugliflozin	Placebo or hydrochlorothia zide	4	Pfizer
Terra, 2017 (69)	NCT01958671	7 countries	2013- 2016	DM2 not on treatment	461	Ertugliflozin	Placebo	26	Pfizer, Merck

Fonseca, 2013 (70)	NCT01071850	NR	2010- 2011	DM2	412	Ipragliflozin	Placebo or metformin	16	Astellas
Ishihara, 2016 (71)	NCT02175784	Japan	2014- 2015	DM2 on insulin	262	Ipragliflozin	Placebo	16	Astellas
Kashiwagi, 2015 (72)	NCT01135433	Japan	2010- 2011	DM2 on metformin	169	Ipragliflozin	Placebo	28	Astellas
Kashiwagi, 2014 (73)	NCT01057628	Japan	2010	DM2	131	Ipragliflozin	Placebo	20	Astellas
Kashiwagi, 2014 (74)	NCT00621868	Japan	2008- 2009	DM2	361	Ipragliflozin	Placebo	18	Astellas
Kashiwagi, 2015 (75)	NCT01316094	Japan	2011- 2012	DM2 with CKD	165	Ipragliflozin	Placebo	28	Astellas
Lu, 2016 (76)	NCT01505426	Korea, Taiwan	2011- 2013	DM2 on metformin	171	Ipragliflozin	Placebo	24	Astellas
Wilding, 2013 (77)	NCT01117584	6 countries	2010- 2011	DM2	343	Ipragliflozin	Placebo	16	Astellas
Seino, 2014 (78)	CTI-090908	Japan	2009	DM2	239	Luseogliflozin	Placebo	12	Taisho
Seino, 2014 (79)	CTI-101191	Japan	2010- 2011	DM2	282	Luseogliflozin	Placebo	12	Taisho
Seino, 2014 (80)	CTI-111661	Japan	2011- 2012	DM2	158	Luseogliflozin	Placebo	26	Taisho
Sykes, 2014 (81)	NCT00495469	Estonia, Russia, Ukraine	2007- 2008	DM2 not on treatment	252	Remogliflozin	Placebo or pioglitazone	14	GlaxoSmithKl ine
Sykes, 2014 (82)	NCT00500331	19 countries	2007-08	DM2 not on treatment	336	Remogliflozin	Placebo or pioglitazone	14	GlaxoSmithKl ine

Rosenstock, 2015 (83)	NCT01376557	United States	2011- 2012	Poorly-controlled DM2	299	Sotagliflozin (LX4211)	Placebo	14	Lexicon
Ikeda, 2015 (84)	NCT00800176	12 countries	2009	DM2	398	Tofogliflozin	Placebo	12	La Roche, Chugai
Kaku, 2014 (85)	CTI-101349	Japan	2010- 2012	DM2	220	Tofogliflozin	Placebo	24	Chugai
DM2, type 2	diabetes mellitus; C	KD, chronic kidn	ey disease; l	NR, not reported.					

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-			C	verall	Risk of H	Bias at St	Risk of Bias Associated with Infectious AEs					
Study, Year	Registration Number	Sequence Generation	Allocation Concealment	Blinding	Completeness of Outcome Data	Selective Outcome Reporting	Other Sources of Bias*	Quality Criteria Satisfied (#/6)	Overall Risk of Bias †	Method of Detecting Adverse Events (1-5) ‡	History of infection used as exclusion criteria	Safety analysis includes all subjects who took ≥1 dose of study drug
Bode, 2015	NCT01106651	L	L	L	Н	L	Н	4/6	М	4	U	Y
Forst, 2014	NCT01106690	L	L	L	Н	L	Н	4/6	М	4	Ν	Y
Inagaki, 2013	NCT01022112	L	L	U	Н	L	Н	3/6	М	3	Y	Y
Inagaki, 2014	NCT01413204	L	L	L	Н	L	Н	4/6	М	3	Y	Y
Inagaki, 2016	NCT02220920	L	L	U	U	L	Н	3/6	М	3	Ν	Y
Ji, 2015	NCT01381900	L	L	U	L	L	Н	4/6	М	4	Ν	Y
Kadowaki , 2017	NCT02354235	L	L	U	Н	L	Н	3/6	М	1	Y	Y
Lavalle-Gonzalez, 2013	NCT01106677	L	L	L	Н	L	Н	4/6	М	4	Ν	Y
Leiter, 2015	NCT00968812	L	L	L	Н	L	Н	4/6	М	4	Ν	Y
Neal, 2015	NCT01032629	L	L	L	L	L	Н	5/6	L	4	Ν	Y
Qiu, 2014	NCT01340664	U	U	L	Н	L	Н	2/6	Н	4	Ν	Y
Rodbard, 2016	N/A	L	L	U	L	L	Н	4/6	М	3	Ν	Y
Rosenstock, 2016	NCT01809327	L	L	L	L	L	Н	5/6	L	3	Ν	Y
Rosenstock, 2012	NCT00642278	U	U	U	L	L	Н	2/6	Н	5	U	Y
Schernthaner, 2013	NCT01137812	L	L	L	Н	L	Н	4/6	М	4	Ν	Y

 Table S6: Quality and risk of bias of studies included in systematic review

Stenlof, 2014	NCT01081834	U	U	L	Н	L	Н	2/6	Н	4	Ν	Y
Townsend, 2016	N/A	U	U	U	Н	L	Н	1/7	Н	3	Ν	Y
Wilding, 2013	NCT01106625	L	L	L	Н	L	Η	4/6	М	4	Ν	Y
Yale, 2014	NCT01064414	L	L	U	Н	L	Η	3/6	М	4	Ν	Y
Araki, 2016	NCT02157298	U	U	U	L	U	Η	1/6	Н	3	Ν	Y
Bailey, 2013	NCT00528879	L	L	L	Н	L	Η	4/6	Μ	3	Ν	Y
Bailey, 2012	N/A	L	L	U	L	L	Η	4/6	М	4	Ν	Y
Bailey, 2015	NCT 00528372	L	L	L	Н	L	Η	4/6	М	4	Ν	Y
Bolinder,2014	NCT00855166	L	L	L	Н	L	Η	4/6	М	4	Ν	Y
Cefalu, 2015	NCT01031680	L	L	L	Н	L	Η	4/6	М	3	Ν	Y
Del Prato, 2015	NCT00660907	L	L	L	Н	L	Η	4/6	М	4	Ν	Y
Frias, 2016	NCT02229396	L	L	L	L	L	Η	5/6	L	3	Ν	Y
Henry Study 1, 2012	NCT00643851	L	L	U	L	L	Η	4/6	Μ	4	Ν	Y
Henry Study 2, 2012	NCT00859898	L	L	U	L	L	Η	4/6	Μ	4	Ν	Y
Jabbour, 2014	NCT00984867	U	U	U	L	L	Η	2/6	Н	3	Ν	Y
Ji, 2014	NCT01095653	L	L	U	L	L	Η	4/6	М	4	Ν	Y
Kaku, 2013	NCT00972244	L	L	U	Н	L	Η	3/6	М	4	Ν	Y
Kaku, 2014	N/A	U	U	U	L	L	Η	2/6	Н	3	Ν	Y
Kohan, 2014	NCT00663260	U	U	U	Н	L	Η	1/6	Н	4	Ν	Y
Lambers Heerspink, 2013	NCT00976495	L	L	L	L	L	Н	5/6	L	2	Ν	Y
Leiter, 2014	NCT01042977	L	L	U	Н	L	Н	3/6	М	4	N	Y
List, 2009	NCT00263276	U	U	U	Н	L	Н	1/6	Н	2	U	U
Matthaei, 2015	NCT01392677	L	L	L	L	L	Н	5/6	L	4	Ν	Y
Mathieu, 2016	NCT01646320	L	L	U	L	L	Н	4/6	М	3	Ν	Y
Rosenstock, 2015	NCT01606007	L	L	U	L	L	Η	4/6	М	4	Ν	Y
Rosenstock, 2012	NCT00683878	U	U	U	Н	L	Н	1/6	Н	4	Ν	Y
Schumm-Draeger, 2015	NCT01217892	L	L	U	L	L	Н	4/6	М	3	Ν	Y
Strojek, 2014	NCT00680745	L	L	L	L	L	Η	5/6	L	4	Ν	Y
Weber, 2016	NCT01137474	L	L	U	L	L	Η	4/6	М	1	Ν	U

Weber, 2016	NCT01195662	L	L	L	L	L	Н	5/6	L	3	Ν	Y
Wilding, 2009	NCT00357370	U	U	U	L	L	Η	2/6	Н	3	Ν	Y
Wilding, 2014	NCT00673231	L	L	L	Н	L	Н	4/6	М	4	Ν	Y
Yang, 2016	NCT01095666	L	L	U	L	L	Н	4/6	М	3	Ν	U
Araki, 2015	NCT01368081	L	L	U	L	L	Η	4/6	М	4	Ν	Y
Barnett, 2014	NCT01164501	L	L	L	L	L	Н	5/6	L	4	Ν	Y
DeFronz, 2015	NCT01422876	L	L	U	L	L	Η	4/6	М	4	Ν	Y
Ferrannini, 2013	NCT00789035	L	L	L	U	L	Н	4/6	М	3	Y	Y
Merker, 2015	NCT01159600	L	L	U	Н	L	Н	3/6	М	4	Ν	Y
Haering, 2015	NCT01289990	L	L	U	Н	L	Н	3/6	М	4	Ν	Y
Hadjadj, 2016	NCT01719003	L	L	U	L	L	Н	4/6	М	2	Ν	Y
Kadowaki, 2014	NCT01193218	L	L	U	L	L	Η	4/6	М	4	Ν	Y
Kovacs, 2015	NCT01210001	L	L	U	Н	L	Η	3/6	М	4	Ν	Y
Lewin, 2015	NCT01422876	L	L	U	L	L	Η	4/6	М	4	Ν	Y
Ridderstrale, 2014	NCT01167881	L	L	L	L	L	Η	5/6	L	4	Ν	Y
Roden, 2015	NCT01177813	L	L	L	Н	L	Η	4/6	М	4	Ν	Y
Rosenstock, 2015	NCT01011868	L	L	U	Н	L	Н	3/6	М	3	Ν	Y
Rosenstock, 2014	NCT01306214	L	L	U	L	L	Η	4/6	М	4	Ν	Y
Rosenstock, 2013	NCT00749190	L	L	U	L	L	Н	4/6	М	3	Y	Y
Ross, 2015	EU 2012-000905- 53	U	U	U	L	L	Н	2/6	Н	2	Ν	Y
Softeland, 2017	NCT01734785	L	L	U	L	L	Η	4/6	М	3	Ν	Y
Tikkanen, 2015	NCT01370005	L	L	U	L	L	Η	4/6	М	4	Ν	Y
Zinman, 2015	NCT01131676	L	L	L	L	L	Н	5/6	L	2	Y	Y
Amin, 2015	NCT01059825	L	L	U	Н	L	Η	3/6	М	5	U	Y
Amin, 2015	NCT01096667	U	U	U	L	L	Н	2/6	Н	2	Ν	Y
Terra, 2017	NCT01958671	L	L	U	Н	L	Н	3/6	М	3	Ν	Y
Fonseca, 2013	NCT01071850	U	U	U	L	L	Н	2/6	Н	4	Y	Y
Ishihara, 2016	NCT02175784	U	U	U	L	L	Η	2/6	Н	3	Y	Y
Kashiwagi, 2015	NCT01135433	U	U	U	Н	L	Η	1/6	Н	5	Y	Y
Kashiwagi, 2014	NCT01057628	U	U	U	Н	L	Η	1/6	Н	3	Y	Y

Kashiwagi, 2014	NCT00621868	U	U	U	L	L	Η	2/6	Н	3	Y	Y
Kashiwagi, 2015	NCT01316094	U	U	U	Н	L	Н	1/6	Н	3	Y	Y
Lu, 2016	NCT01505426	L	L	L	L	L	Η	5/6	L	5	Y	Y
Wilding, 2013	NCT01117584	U	U	U	U	L	Η	1/6	Н	4	Y	Y
Seino, 2014	CTI-090908	L	L	L	L	L	Η	5/6	L	3	Y	Y
Seino, 2014	CTI-101191	L	L	L	L	L	Η	5/6	L	3	Y	Y
Seino, 2014	CTI-111661	L	L	L	L	L	Η	5/6	L	3	Y	Y
Sykes, 2014	NCT00495469	U	U	U	L	L	Η	2/6	Н	1	Ν	Y
Sykes, 2014	NCT00500331	U	U	U	Н	L	Н	1/6	Н	1	Ν	Y
Rosenstock, 2015	NCT01376557	U	U	U	L	L	Н	2/6	Н	4	Ν	Y
Ikeda, 2015	NCT00800176	U	U	U	L	L	Н	2/6	Н	3	Ν	Y
Kaku, 2014	CTI-101349	L	L	L	L	L	Η	5/6	L	3	Y	Y

* Other sources of bias include sponsorship bias. All trials in this systematic review were funded by the drug manufacturer.

 \dagger Overall risk of bias was determined by the number of individual quality criteria (1-6) satisfied as low risk by each study: low overall risk (\geq 5 criteria satisfied), moderate overall risk (3-4 criteria satisfied), or high overall risk (\leq 2 criteria satisfied) of bias.

[‡] Method of detecting adverse events (AEs): (1) unspecified methods; (2) prospective surveillance of AEs using AE reports and/or MedDRA search terms; (3) prospective surveillance of AEs using AE reports, laboratory tests, physical examination, and/or symptoms; (4) prospective surveillance of AEs using AE reports, laboratory tests, physical examination pre-specified data collection and/or specific questioning of patients for signs and symptoms of genital and urinary tract infections; (5) prospective surveillance of AEs using AE reports, laboratory tests, physical examination, and/or symptoms with additional pre-specified data collection and/or specific questioning of patients for signs and symptoms of genital and urinary tract infections; (5) prospective surveillance of AEs using AE reports, laboratory tests, physical examination, and/or symptoms with additional routine laboratory screening of all patients for genital and urinary tract infections (e.g. urine cultures, genital swabs).

L, low risk of bias; U, unclear risk of bias; H, high risk of bias; M, moderate risk of bias; AE, adverse events; Y, yes; N, no.

Figure S1: Meta-analysis for genital tract infections, SGLT-2 inhibitors versus placebo

	Treatn	nent	Place	ebo				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Canagliflozin								
Kadowaki (2017)	0	70	0	68		1.00	(0.02 - 49.71)	0.2
Inagaki (2016)	1	75	0	71		2.95	(0.12 - 73.34)	0.2
Rodbard (2016)	6	108	1	108		6.00	(0.73 - 49.00)	0.5
Townsend (2016)	0	113	0	56		1.00	(0.02 - 63.54)	0.1
Bode (2015)	69	477	6	237		5.71	(2.52 - 12.97)	3.5
Ji (2015)	7	448	2	226		1.77	(0.37 - 8.43)	1.0
Neal (2015)	163	1382	14	690	-	5.81	(3.39 - 9.96)	8.2
Forst (2014)	23	227	3	115		3.88	(1.19 - 12.67)	1.7
Inegaki (2014)	3	179	1	93		1.56	(0.16 - 14.78)	0.5
Qiu (2014)	8	186	3	93		1.33	(0.36 - 4.91)	1.4
Steniof (2014)	36	392	5	192		3.53	(1.41 - 8.84)	2.8
Vala (2014)	4	170	ă	00		0.67	(0.15 - 2.03)	1.1
hanaki (2014)	-	308	0	76	-	3.40	(0.10 - 2.00)	0.1
Inagaki (2013)	<u> </u>	300	2	100		0.49	(0.04 - 338.07)	0.1
Lavaile-Gorizalez (2013)	00	/30	2	103		0.00	(1.69 - 27.61)	1.2
Writaing (2013)	39	313	5	156		3.89	(1.56 - 9.67)	2.9
Rosenstock (2012)	17	321	1	65		3.44	(0.47 - 25.41)	0.6
Random effects model		5513		2518	2	3.91	(2.89 - 5.29)	26.0
Heterogeneity: /2 = 0% (09	% - 50%),	p = 0.50	0					
Dapagliflozin								
Araki (2016)	1	123	0	60		2.49	(0.06 - 103.78)	0.2
Mathieu (2016)	10	160	2	160		5.00	(1.11 - 22.46)	1.1
Weber (2016)	6	302	5	311	-	1.24	(0.38 - 4.01)	1.7
Weber (2016)	6	225	4	224		1.49	(0.43 - 5.22)	1.5
Yang (2016)	5	299	0	145		8.42	(0.25 - 285.04)	0.2
Cefalu (2015)	28	460	4	482		7.03	(2.49 - 19.88)	2.2
Matthaei (2015)	11	109	1	109		11.00	(1.44 - 83.74)	0.6
Schumm-Draeger (2015)	8	200		101		2 70	(0.34 - 21.34)	0.6
Beliadas (2014)	2	200		0.1		2.70	(0.34 - 21.34)	0.0
Bolinder (2014)	2	91		91		2.00	(0.10 - 21.07)	0.4
Jabbour (2014)	22	225	1	226		22.10	(3.00 - 162.55)	0.6
JI (2014)	10	261	1	132		5.06	(0.65 - 39.09)	0.6
Kaku (2014)	3	174	1	87		1.50	(0.16 - 14.21)	0.5
Kohan (2014)	15	168	3	84		2.50	(0.74 - 8.40)	1.6
Leiter (2014)	36	482	2	483		18.04	(4.37 - 74.49)	1.2
Strojek (2014)	30	450	2	146		4.87	(1.18 - 20.12)	1.2
Wilding (2014)	70	610	6	197		3.77	(1.66 - 8.54)	3.5
Bailey (2013)	53	409	7	137		2.54	(1.18 - 5.45)	4.1
Kaku (2013)	2	225	0	54		3.48	(0.04 - 345.02)	0.1
Lambers Heerspink (2013)	2	24	0	25		5.08	(0.26 - 98.15)	0.3
Bailey (2012)	8	214	2	68		1.27	(0.28 - 5.84)	1.0
Rosenstock (2012)	25	281	4	139		3.09	(1 10 - 871)	2.2
List (2000)	12	270	0	5.4		15 32	(0.12 - 2035 42)	0.1
Milding (2000)	5	40	4	22		2.40	(0.12 - 2030.42)	0.5
Wilding (2009)	0	90		23		2.40	(0.30 - 19.35)	0.0
Random effects model		5918		3518	×	3.45	(2.55 - 4.66)	25.9
Heterogeneity: /~ = 0% (0%	% = 43%),	p = 0.52	2					
Empagliflozin								
Softeland (2017)	7	222	2	110		1.7	3 (0.37 - 8.21) 1.0
Haering (2015)	23	441	2	225		5.8	7 (1.40 - 24.66) 1.2
Kovacs (2015)	24	333	5	165		23	8 (0.92 - 6.12	27
Merker (2015)	38	431		206		18.1	6 (2.51 - 131.37	0.6
Roden (2015)	27	447	4	229		3.4	6 (1.22 - 9.76	22
Researcherk (2015)	21	324	3	170		3.6	7 (1 11 - 12 14	17
Rose (2015)	22	876		107		4.0	4 10.42 4.24	
Tickages (2015)	33	670		070		1.0	4 (0.42 - 4.31	0.6
Tokkanen (2015)	29	002	1	212	ater 1	14.4	3 (1.30 - 104.30) U.6
Zinman (2015)	301	4687	42	2333	100	3.5	7 (2.59 - 4.91) 23.3
Barnett - CKD2 (2014)	12	195	6	95		0.9	7 (0.38 - 2.52) 2.6
Barnett - CKD3 (2014)	5	187	2	187		2.5	0 (0.49 - 12.72) 0.9
Barnett - CKD4 (2014)	1	37	0	37	1	3.0	0 (0.13 - 71.31) 0.2
Kadowaki (2014)	3	438	0	109		4.7	5 (0.05 - 427.02	2) 0.1
Rosenstock (2014)	26	375	3	188		4.3	4 (1.33 - 14.17) 1.7
Ferrannini (2013)	5	244	0	82		7.6	8 (0.14 - 412.97	0.1
Rosenstock (2013)	14	353	0	71		+ 17 5	2 (0.15 - 2186 2	5) 0 1
Random effects mode		1014	2	4586	0	34	1 (2.29 - 4.24	40.8
Heterogeneity: 12 = 0% / 0	A	0.00	35	4000		0.1	. (enes - 4.6)	40.0
. renerogeneity, r = a si (0	10-4010]	p = 0.4						
Ertualiflazia								
Torra (2017)		3.00		450				
10/18 (2017)	33	308	D	103		3.2	6 (1.31 - 8.23	2.8
Autim (2015)	8	219	1	24		1.9	(0.25 - 15.44	0.6
Amin (2015)	4	116	0	38		6.3	1 (0.11 - 355.11	0.1
Random effects mode		643		245	\$	3.1	1 (1.36 - 7.07) 3.5
Heterogeneity: /2 = 0% (0	/% - 35%),	$\rho = 0.8$	35					

Figure S1 (Continued): Meta-analysis for genital tract infections, SGLT-2 inhibitors versus placebo

					1.1			
Ipragliflozin								
Ishihara (2016)	7	175	0	87		11.48	(0.36 - 366.95)	0.2
Lu (2016)	0	87	0	83		1.00	(0.02 - 49.88)	0.2
Kashiwagi (2015)	0	112	0	56		1.00	(0.02 - 63.14)	0.1
Kashiwagi (2015)	1	119	0	46		2.39	(0.04 - 128.61)	0.1
Kashiwagi (2014)	2	62	0	67		5.16	(0.26 - 100.70)	0.3
Kashiwagi (2014)	6	291	0	69		8.42	(0.09 - 782.75)	0.1
Fonseca (2013)	11	273	1	69		2.78	(0.37 - 21.17)	0.6
Wilding (2013)	5	276	1	66		1.20	(0.14 - 10.06)	0.5
Random effects model		1395		543	÷	2.54	(0.88 - 7.32)	2.1
Heterogeneity: 12 = 0% (0% -	0%), /	2 = 0.95						
Luseogliflozin								
Seino (2014)	2	182	0	54		3.59	(0.05 - 252.52)	0.1
Seino (2014)	0	223	1	57		0.17	(0.01 - 2.83)	0.3
Seino (2014)	1	79	1	79		1.00	(0.06 - 15.71)	0.3
Random effects model		484		190		0.61	(0.10 - 3.66)	0.7
Heterogeneity: I2 = 0% (0% -	87%).	p = 0.45						
Remogliflozin								
Sykes (2014)	8	179	0	36		10.61	(0.09 - 1317.46)	0.1
Sykes (2014)	11	238	0	48		14.22	(0.12 - 1741.69)	0.1
Random effects model		417		84		12.29	(0.41 - 369.88)	0.2
Heterogeneity: $l^2 = 0\%$, $p = 0$.	93							
Sotagliflozin								
Rosenstock (2015)	8	236	0	60		11.03	(0.14 - 893.40)	0.1
Random effects model		236		60		11.03	(0.14 - 893.40)	0.1
Heterogeneity: not applicable								
Tofogliflozin								
lkeda (2015)	5	328	1	66		1.01	(0.12 - 8.47)	0.5
Kaku (2014)	1	174	0	56		2.32	(0.03 - 159.20)	0.1
Random effects model		502		122		1.19	(0.18 - 7.99)	0.7
Heterogeneity: $l^2 = 0\%$, $p = 0$.	73							
Random effects model		25250		11866	ò	3.37	(2.89 - 3.93)	100.0
Heterogeneity: /2 = 0% (0% -	16%).	p = 0.79						
				0	0.01 0.1 1 10 100 10	00		

Figure S2: Meta-analysis for genital tract infections, SGLT-2 inhibitors versus active comparators

	Treat	ment	Acti Compa	ve rator				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Canagliflozin								
Rosenstock (2016)	25	0.40	0	237		32.24	(0.40 - 2623.91)	0.2
Leiter (2015)	116	068	11	482		5 25	(2.86 - 0.65)	12.3
Levelle Containt (2013)	55	735	7	402		3.01	(2.00 - 9.00)	7.8
Cabarathapas (2013)	35	277	6	300	<u> </u>	5.51	(1.00 - 0.00)	7.0
Scheminaner (2013) Besepeteek (2012)	40	377	°.	3/0	17	3.04	(2.70 - 11.00)	0.4
Rosenstock (2012)	17	321	1	4529		4.00	(0.47 - 25.41)	20.7
Random effects model	~ ~~~	3350		1920		4.90	(3.35 - 7.34)	29.1
Heterogeneity: 7 = 0% (0	70 - 3076),	<i>p</i> = 0.6	90					
Dapagliflozin								
Frias (2016)	23	464	4	230	- xi -	2.85	(1.00 - 8.14)	4.2
Bailey (2015)	24	199	1	75		9.05	(1.25 - 65.69)	1.2
Del Prato (2015)	58	406	12	408	+	4.86	(2.65 - 8.91)	12.4
Rosenstock (2015)	10	358	1	176		4.92	(0.63 - 38.10)	1.1
Henry (2012)	27	397	4	201		3.42	(1.21 - 9.63)	4.3
Henry (2012)	46	430	5	208	- <u>+</u> -	4.45	(1.79 - 11.03)	5.6
List (2009)	12	279	1	56		2.41	(0.32 - 18.15)	1.1
Random effects model		2533		1354	÷	4.21	(2.85 - 6.23)	29.8
Heterogeneity: /2 = 0% (0	% - 3%), /	p = 0.94	1				(
Empagliflozin								
Hadjadj (2016)	41	1019	9	341		1.52	(0.75 - 3.10)	9.1
Araki (2015)	19	1097	1	63	-+-	1.09	(0.15 - 8.02)	1.2
DeFronzo (2015)	34	546	3	128		2.66	(0.83 - 8.51)	3.4
Lewin (2015)	25	542	4	135		1.56	(0.55 - 4.40)	4.3
Roden (2015)	27	447	2	223		6.73	(1.62 - 28.07)	2.3
Ridderstrale (2014)	90	765	17	780		5.40	(3.25 - 8.98)	17.6
Random effects model		4416		1670		2.69	(1.43 - 5.06)	37.7
Heterogeneity: / ² = 59% (0% - 84%), p = 0	.03					
Estualificatio								
Amin (2015)		210	0	64		10.07	(0.42 - 026.00)	0.2
Pandom offects model	0	218	0	54		10.87	(0.13 - 936.00)	0.2
Haterooperativ: oot applica	bla	219		04		10.97	(0.13 - 936.00)	0.2
Heterogeneity. Not applica	LIC							
Ipragliflozin								
Fonseca (2013)	11	273	2	69		1.39	(0.32 - 6.13)	2.1
Random effects model		273		69		1.39	(0.32 - 6.13)	2.1
Heterogeneity: not applica	ble							
Design in the state of the stat								
Remogliflozin			-					
Sykes (2014)	8	179	0	35		10.56	(0.08 - 1387.38)	0.2
Sykes (2014)	11	238	0	48		14.22	(0.12 - 1741.69)	0.2
Random effects model		417		83	-	12.28	(0.40 - 377.03)	0.4
Heterogeneity: I* = 0%, p	= 0.93							
Random effects model		11208		4758		3 89	(3 14 - 4 82)	100.0
Heterogeneity: $l^2 = 0\% /0\%$	6 - 46%)	0 = 0.4	6	41.00	1 1 1 1 1	0.00	(0.14 - 4.02)	100.0
inerarogenerg. r = 070 (0)	(· · · · · · ·),	0.4	-	(0.01 0.1 1 10 100 10	00		

Figure S3: Meta-analysis for urinary tract infections, SGLT-2 inhibitors versus placebo

	Treatr	nent	Place	bo				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Concell'Accie								
Canagliflozin	~	70		~~		0.00	(0.04 7.04)	
Kadowaki (2017)	0	70	1	58		0.33	(0.01 - 7.84)	0.0
Inagaki (2016)	1	/5	0	/1		2.95	(0.12 - 73.34)	0.0
Rodbard (2016)	2	108	2	108		1.00	(0.14 - 0.97)	0.1
Townsena (2016)	74	113	24	202		1.00	(0.02 - 03.54)	0.0
B006 (2015)	12	4//	24	237		1.00	(0.89 - 2.30)	2.0
JI (2015)	79	1282	26	220		1.00	(0.27 - 1.31)	0.8
Foret (2014)	15	227	30	115		0.94	(0.74 - 1.53)	0.9
Inageki (2014)	2	170	1	03		1.04	(0.10 - 11.31)	0.0
Oiu (2014)	8	186	2	93		2.00	(0.43 - 9.23)	0.2
Steplof (2014)	30	392	12	192		1.22	(0.64 - 2.34)	1.2
Vale (2014)	18	179	9	90		1.01	(0.47 - 2.15)	0.8
Inanaki (2013)	0	308	ő	75		1.00	(0.01 - 13874)	0.0
Lavalle-Gonzalez (2013)	47	735	12	183	+	0.98	(0.53 - 1.80)	1.3
Wilding (2013)	26	313	12	156	+	1.08	(0.56 - 2.08)	1.1
Rosenstock (2012)	16	321	4	65		0.81	(0.28 - 2.34)	0.4
Random effects model		5513		2518	6	1.10	(0.90 - 1.33)	12.9
Heterogeneity: $I^2 = 0\%$ (0%	% - 0%). p	= 0.95					(0000 000)	
	с. <i>с. с. д</i> р							
Empagliflozin								
Softeland (2017)	12	222	8	110		0.74	(0.31 - 1.77)	0.7
Haering (2015)	73	441	36	225	+	1.03	(0.72 - 1.49)	3.6
Kovacs (2015)	74	333	44	165	+	0.83	(0.60 - 1.15)	4.7
Merker (2015)	53	431	28	206	1	0.90	(0.59 - 1.39)	2.7
Roden (2015)	41	447	25	229	-	0.84	(0.52 - 1.35)	2.2
Rosenstock (2015)	43	324	15	170		1.50	(0.86 - 2.63)	1.6
Ross (2015)	63	876	4	107	1-	1.92	(0.71 - 5.18)	0.5
Tikkanen (2015)	24	552	10	272	1	1.18	(0.57 - 2.44)	0.9
Zinman (2015)	842	4687	423	2333		0.99	(0.89 - 1.10)	43.6
Barnett - CKD2 (2014)	23	195	15	95	1	0.75	(0.41 - 1.30)	1.3
Barnett - CKD3 (2014)	31	18/	29	18/	Τ	1.07	(0.67 - 1.70)	2.3
Bamelt - CRD4 (2014)	2	420	3	100		2.33	(0.00 - 0.34)	0.3
Radowaki (2014)	59	430	20	109		1.00	(0.00 - 7.11)	2.0
Eerranoini (2012)	30	244	25	82		1.00	(0.07 - 1.01)	2.9
Penannin (2013) Reservetock (2012)	14	244	2	71		1.34	(0.13 - 11.00)	0.1
Random effects model	14	10142	2	4586		0.99	(0.91 - 1.08)	67.6
Heterogeneity: $l^2 = 0\%$ (0%	% - 24%).	p = 0.80	6	4000		0.00	(0.01 - 1.00)	07.0
Ertugliflozin								
Terra (2017)	17	308	13	153		0.65	(0.32 - 1.30)	1.0
Amin (2015)	7	219	4	54		0.43	(0.13 - 1.42)	0.3
Amin (2015)	4	116	1	38		1.31	(0.15 - 11.37)	0.1
Heterogeneity: $l^2 = 0\%$ (09	6 - 75%)	643 n = 0.6/	6	245	0	0.62	(0.35 - 1.11)	1.5
rictorogeneity. r = 070 (07	- 10 /oj,	p = 0.0	0					
Ipragliflozin								
Ishihara (2016)	4	175	i 1	87		1.99	0.23 - 17.52	0.1
Lu (2016)	6	87	2	83		2.88	6 (0.59 - 13.78	i) 0.2
Kashiwagi (2015)	2	112	2	56		0.50	0 (0.07 - 3.46) 0.1
Kashiwagi (2015)	1	119	2	46		0.19	0.02 - 2.08) 0.1
Kashiwagi (2014)	0	62	1	67		0.34	4 (0.01 - 8.60)) 0.0
Kashiwagi (2014)	4	291	1	69		0.95	6 (0.11 - 8.35) 0.1
Fonseca (2013)	21	273	6	69		0.88	3 (0.37 - 2.11)) 0.6
Wilding (2013)	12	276	i 4	66		0.72	2 (0.24 - 2.15) 0.4
Random effects mode	I	1395	5	543	\$	0.88	3 (0.52 - 1.50) 1.7
Heterogeneity: I ² = 0% (0)% - 55%)	, p = 0.0	65					

Figure S3 (Continued): Meta-analysis for urinary tract infections, SGLT-2 inhibitors versus placebo

Dapagliflozin								
Araki (2016)	2	123	0	60		3.98	(0.11 - 147.52)	0.0
Mathieu (2016)	15	160	16	160		0.94	(0.48 - 1.83)	1.1
Weber (2016)	9	302	3	311	L	3.09	(0.84 - 11.30)	0.3
Weber (2016)	4	225	2	224		1.99	(0.37 - 10.76)	0.2
Yang (2016)	16	299	7	145		1.11	(0.47 - 2.63)	0.6
Cefalu (2015)	27	460	27	462	+	1.00	(0.60 - 1.69)	1.8
Matthaei (2015)	11	109	12	109	+	0.92	(0.42 - 1.99)	0.8
Schumm-Draeger (2015)	10	299	3	101		1.13	(0.32 - 4.01)	0.3
Bolinder (2014)	6	91	7	91		0.86	(0.30 - 2.45)	0.4
Jabbour (2014)	15	225	14	226		1.08	(0.53 - 2.18)	1.0
Ji (2014)	10	261	4	132	<u> </u>	1.26	(0.40 - 3.96)	0.4
Kaku (2014)	2	174	2	87		0.50	(0.07 - 3.49)	0.1
Kohan (2014)	23	168	12	84		0.96	(0.50 - 1.83)	1.2
Leiter (2014)	53	482	28	483	-	1.90	(1.22 - 2.95)	2.5
Strojek (2014)	30	450	11	146	+	0.88	(0.45 - 1.72)	1.1
Wilding (2014)	72	610	11	197	-	2.11	(1.14 - 3.91)	1.3
Bailey (2013)	41	409	11	137	<u> </u>	1.25	(0.66 - 2.36)	1.2
Kaku (2013)	4	225	1	54		0.96	(0.11 - 8.42)	0.1
Lambers Heerspink (2013)	1	24	0	25		3.04	(0.13 - 69.61)	0.0
Bailey (2012)	6	214	1	68		1.91	(0.23 - 15.56)	0.1
Rosenstock (2012)	19	281	11	139		0.85	(0.42 - 1.75)	1.0
List (2009)	25	279	3	54	_+	1.61	(0.50 - 5.15)	0.4
Wilding (2009)	1	48	0	23	·	2.48	(0.06 - 103.24)	0.0
Random effects model		5918		3518	0	1.23	(1.03 - 1.46)	16.0
Heterogeneity: $I^2 = 0\%$ (0%)	- 25%).	p = 0.81					. ,	
					I			
Tofogliflozin								
lkeda (2015)	8	328	1	66		1.61	(0.20 - 12.66)	0.1
Kaku (2014)	1	174	0	56		2.32	(0.03 - 159.20)	0.0
Random effects model		502		122		1.73	(0.27 - 11.02)	0.1
Heterogeneity: $l^2 = 0\%$, $p = 0$.88							
Sotagliflozin	1.12	1000	122	222.211		1-1-2-2-2		2.2
Rosenstock (2015)	4	236	1	60		1.02	(0.12 - 8.93)	0.1
Random effects model		236		60		1.02	(0.12 - 8.93)	0.1
Heterogeneity: not applicable								
Luseogliflozin								
Seino (2014)	1	182	0	54		2 30	(0.03 - 176.78)	0.0
Seino (2014)	1	223	n	57		2.26	(0.02 - 218.71)	0.0
Seino (2014)	Ó	79	n	79		1 00	(0.02 - 49.78)	0.0
Random effects model		484	Ŭ	190		1 65	(0 14 - 19 13)	0.1
Heterogeneity: $l^2 = 0\% (.0\%)$	- 0%)	1 = 0.95		100		1.00	10.14 - 10.101	
neterogeneity. 1 - ene (ene	o raj, j							
Remogliflozin								
Sykes (2014)	10	179	0	36		→ 13.01	(0.11 - 1602.37)	0.0
Sykes (2014)	3	238	0	48		4.61	(0.04 - 604.98)	0.0
Random effects model		417		84		7.79	(0.25 - 239.76)	0.0
Heterogeneity: $l^2 = 0\%$, $p = 0$	0.77							
Random effects model		25250		11866		1.02	(0.96 - 1.11)	100.0
Heterogeneibe 1 ² = 0% (0%)	0%	= 0.00		11000		1 1.03	(0.30 - 1.11)	100.0
neterogeneity: r = 0% (0% -	0%), p	- 0.99		0	0.01 0.1 1 10 100 1	000		
					0.01 0.1 1 10 100 1			

Figure S4: Meta-analysis for urinary tract infections, SGLT-2 inhibitors versus active comparators

	Treat	ment	Act	ive arator				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Canagliflozin								
Rosenstock (2016)	18	949	3	237		1.50	(0.45 - 5.04)	1.5
Leiter (2015)	93	968	33	482	ler .	1.40	(0.96 - 2.06)	9.4
Lavalle-Gonzalez (2013)	47	735	23	366	+	1.02	(0.63 - 1.65)	6.9
Schemthaner (2013)	15	377	21	378		0.72	(0.37 - 1.37)	4.4
Rosenstock (2012)	16	321	1	65		3.24	(0.44 - 24.00)	0.6
Random effects model	E	3350		1528	•	1.15	(0.85 - 1.55)	22.7
Heterogeneity: $l^2 = 12\%$ (0% - 82%), p = 0	.34					
Dapagliflozin								
Frias (2016)	23	464	12	230	-	0.95	(0.48 - 1.87)	4.1
Bailey (2015)	18	199	3	75		2.26	(0.69 - 7.46)	1.5
Del Prato (2015)	55	406	38	408	ler.	1.45	(0.98 - 2.15)	9.2
Rosenstock (2015)	8	358	9	176		0.44	(0.17 - 1.11)	2.3
Henry (2012)	31	397	15	201	+	1.05	(0.58 - 1.89)	5.1
Henry (2012)	40	430	9	208		2.15	(1.06 - 4.35)	3.8
List (2009)	25	279	5	56		1.00	(0.40 - 2.51)	2.4
Random effects model		2533		1354	6	1.20	(0.85 - 1.69)	28.5
Heterogeneity: $l^2 = 39\%$ (0% - 74%), p = 0	.13					
Empagliflozin								
Hadiadi (2016)	90	1019	31	341	+	0.97	(0.66 - 1.43)	92
Araki (2015)	48	1097	2	63	_ 	1.38	(0.34 - 5.54)	1.1
DeFronzo (2015)	62	546	20	128		0.73	(0.46 - 1.16)	7.3
Lewin (2015)	74	542	14	135		1.32	(0.77 - 2.26)	5.9
Roden (2015)	41	447	20	223	-	1.02	(0.61 - 1.70)	6.4
Ridderstrale (2014)	105	765	102	780	÷.	1.05	(0.81 - 1.35)	14.1
Random effects model	1000	4416	0070	1670	\$	1.01	(0.85 - 1.20)	44.0
Heterogeneity: $l^2 = 0\%$ (0)% - 60%),	p = 0.6	37				(
Ertugliflozin								
Amin (2015)	7	219	1	54		1.73	(0.22 - 13.73)	0.5
Random effects model	E	219		54		1.73	(0.22 - 13.73)	0.5
Heterogeneity: not applica	able	1.11.11		0.000		10000		1. 003796
Ipragliflozin								
Fonseca (2013)	21	273	5	69	-	1.06	(0.42 - 2.71)	2.3
Random effects model	1	273		69	-	1.06	(0.42 - 2.71)	2.3
Heterogeneity: not applica	ible							
Remogliflozin								
Sykes (2014)	10	179	2	35		0.98	(0.22 - 4.27)	1.0
Sykes (2014)	3	238	4	48		0.15	(0.03 - 0.65)	1.0
Random effects model	1	417		83		0.38	(0.06 - 2.39)	2.0
Heterogeneity: 12 = 68%, 1	p = 0.08							
Random effects model	i	11208		4758	0	1.08	(0.93 - 1.25)	100.0
Heterogeneity: /2 = 22% (0% - 54%)), p = 0.	17		1 111 1			
				0.01	0.1 0.51 2 10	100		

Figure S5: Meta-analysis for urosepsis, SGLT-2 inhibitors versus placebo

Treatment		Plac	ebo						
Trial	Events	Total	Events	Total	Risk	Ratio	RR	(95% CI)	Weight (%)
Canagliflozin						1			
Rodbard (2016)	0	108	0	108		<u>_</u>	1.00	(0.02 - 49.94)	5.3
Bode (2015)	0	477	2	237	<u>с т</u>		0.14	(0.01 - 2.15)	11.0
Stenlof (2014)	0	392	0	192		<u> </u>	1.00	(0.02 - 64.63)	4.7
Random effects model		977		537		÷-	0.36	(0.05 - 2.57)	21.1
Heterogeneity: $I^2 = 0\%$ (0%	% - 78%)	p = 0.0	62					. ,	
U J V	,								
Empagliflozin									
Zinman (2015)	17	4687	3	2333		+ +	2.82	(0.83 - 9.62)	54.1
Barnett - CKD2 (2014)	0	195	0	95		-	1.00	(0.02 - 64.64)	4.7
Barnett - CKD3 (2014)	0	187	0	187		1	1.00	(0.02 - 50.13)	5.3
Barnett - CKD4 (2014)	0	37	0	37		+	1.00	(0.02 - 49.09)	5.4
Rosenstock (2014)	0	375	0	188		+	1.00	(0.02 - 63.57)	4.7
Random effects model		5481		2840		÷	2.13	(0.75 - 6.07)	74.2
Heterogeneity: I ² = 0% (0%	% - 0%),	p = 0.9	5						
lpragliflozin									
Ishihara (2016)	0	175	0	87		1	1.00	(0.02 - 63.67)	4.7
Random effects model	-	175	-	87		:	1.00	(0.02 - 63.67)	4.7
Heterogeneity: not applicat	ole							(
Random effects model		6633		3464			1 41	(0.57 - 3.48)	100.0
Heterogeneity: $I^2 = 0\%$ (0%	6 - 32%),	p = 0.8	34	5404		FT T	1.41	(0.57 - 5.46)	100.0
1				0.	01 0.1 0.5	1 2 10	100		

Figure S6: Meta-analysis for urosepsis, SGLT-2 inhibitors versus active comparators

	Treatment		Comparator		Risk Ratio					
Trial	Events	Total	Events	Total				RR	(95% CI)	Weight (%)
Empagliflozin										
DeFronzo (2015)	1	546	0	128				→ 2.23	(0.02 - 251.55)	40.8%
Ridderstrale (2014)	0	765	0	780		-		- 1.00	(0.02 - 50.34)	59.2%
Random effects model		1311		908				1.39	(0.07 - 28.33)	100.0%
Heterogeneity: I-squared=0	%, p=0.79	74								
Random effects model		1311		908	-			1.39	(0.07 - 28.33)	100%
Heterogeneity: I-squared=0	%, p=0.79	74								
				0.0	0.1	0.51 2	10	100		

Figure S7: Meta-analysis for pyelonephritis, SGLT-2 inhibitors versus placebo

	Treatm	nent	Place	bo					
Trial	Events	Total	Events	Total	Risk	Ratio	RR	(95% CI)	Weight (%
Canagliflozin					1				
Kadowaki (2017)	0	70	0	68			- 1.00	(0.02 - 49.71)	1.1
Rodbard (2016)	0	108	0	108 -			- 1.00	(0.02 - 49.94)	1.1
Bode (2015)	3	477	2	237			0.75	(0.13 - 4.43)	5.4
li (2015)	0	448	0	226 -			1.00	(0.02 - 63.34)	1.0
Veal (2015)	4	1382	4	690		-	0.50	(0.13 - 1.99)	8.9
Forst (2014)	0	227	0	115 -			1.00	(0.02 - 62.97)	1.0
Diu (2014)	1	186	0	93			→ 2.50	(0.06 - 102.18)	1.2
Steniof (2014)	0	392	0	192 -			1.00	(0.02 - 64.63)	1.0
(ale (2014)	1	179	1	90			0.50	(0.03 - 7.95)	22
Random effects model	0.0	3469	1.1	1819	<	-	0.70	(0.30 - 1.66)	23.0
leteroneneity: $l^2 = 0\% / 0$	6 . 0%) r	= 1.00	1	1010	1		0.70	(0.00 1.00)	20.0
leterogeneity. 7 - 0% (0	10-0101.1	/ - 1.00	6) (l)						
pragliflozin	14.11								
shihara (2016)	0	175	0	87 -			- 1.00	(0.02 - 63.67)	1.0
.u (2016)	0	87	1	83 -			0.33	(0.01 - 7.75)	1.7
tandom effects model		262		170		1	0.49	(0.04 - 6.11)	2.7
Heterogeneity: I ² = 0%, p	= 0.68								
Danagliflozin									
Weber (2016)	0	302	0	311			1.00	(0.02 - 50.26)	1.1
(ang (2016)	0	299	0	145 -			1.00	(0.02 - 65.02)	1.0
Jatthaei (2015)	1	109	0	109			- 3.00	(0.12 - 72.84)	17
Schumm-Draeger (2015)	0	299	0	101 -		1	1.00	(0.01 - 90.54)	0.8
Bolinder (2014)	0	91	1	91 -			0.33	(0.01 - 8.08)	17
labbour (2014)	0	225	0	226 .			- 1.00	(0.02 - 50 18)	1.1
1/2014	0	261	ő	132 -			- 1.00	(0.02 - 63.09)	10
aller (2014)	1	482	2	483			0.50	(0.05 - 5.51)	3.0
Straight (2014)	0	450	0	146	1		1.00	(0.01 - 04.07)	0.8
Alidina (2014)	3	610	0	107			1.00	(0.09 - 207.03)	10
alley (2013)	0	400	0	137			1.00	(0.01 - 01 53)	0.8
Cake (2013)	0	225	0	E4 -			1.00	(0.01 - 01.00)	0.7
Caku (2013)	0	220	0	69			1.00	(0.01 - 141.47)	0.7
Danley (2012)	0	214		2200	1000		0.07	(0.01 - 30.80)	45.0
deterogeneity: $I^2 = 0\%$ (0)	% - 0%), ¢	5976		2200			0.97	(0.34 - 2.77)	10.0
	20 20000	a nan							
Empagliflozin	225	10222	200	1222				1210 No.	
Zinman (2015)	31	4687	20	2333		t	0.77	(0.44 - 1.35)	54.5
Barnett - CKD2 (2014)	0	195	0	95 -			- 1.00	(0.02 - 64.64)	1.0
Barnett - CKD3 (2014)	0	187	0	187			1.00	(0.02 - 50.13)	1.1
Barnett - CKD4 (2014)	0	37	0	37			- 1.00	(0.02 - 49.09)	1.1
Rosenstock (2014)	0	375	0	188 -			- 1.00	(0.02 - 63.57)	1.0
Random effects model		5481		2840	4	>	0.79	(0.46 - 1.35)	58.7
Heterogeneity: I ² = 0% (0	% - 0%), p	o = 1.00)					87 - 28 2	
Random effects model		13188		7029		-	0.78	(0.52 - 1.18)	100.0
in the state in the state in the state of th	and a second							(0.02 - 1.10)	

Figure S8: Meta-analysis for pyelonephritis, SGLT-2 inhibitors versus active comparators

	Treatment		Activ Compa	/e rator					
Trial	Events	Total	Events	Total	Risk	Ratio	RR	(95% CI)	Weight (%)
Canagliflozin									
Rosenstock (2016)	0	949	0	237		1	- 1.00	(0.01 - 134.21)	5.8
Leiter (2015)	3	968	0	482			5.49	(0.16 - 190.97)	11.0
Random effects model		1917		719	1	1	- 3.06	(0.17 - 54.13)	16.8
Heterogeneity: $I^2 = 0\%$, $p =$	= 0.58					-			
Dapagliflozin									
Bailey (2015)	1	199	0	75			2.38	(0.04 - 132.87)	8.6
Henry (2012)	0	397	1	201		:	0.25	(0.01 - 4.75)	16.1
Henry (2012)	0	430	0	208		÷	- 1.00	(0.02 - 65.23)	8.0
Random effects model		1026		484			0.64	(0.08 - 5.00)	32.6
Heterogeneity: $I^2 = 0\%$ (0%	% - 75%),	p = 0.	66			-			
Empagliflozin									
Hadjadj (2016)	2	1019	1	341		<u> </u>	0.67	(0.06 - 7.36)	24.2
DeFronzo (2015)	1	546	0	128			2.23	(0.02 - 251.55)	6.2
Lewin (2015)	1	542	0	135		*	2.25	(0.02 - 228.71)	6.5
Ridderstrale (2014)	1	765	0	780			- 3.02	(0.12 - 73.25)	13.7
Random effects model		2872		1384	V		1.36	(0.26 - 7.15)	50.6
Heterogeneity: $I^2 = 0\%$ (09	% - 31%),	p = 0.	88						
Random effects model Heterogeneity: I ² = 0% (0%	6 - 0%), ρ	5815 = 0.96	3	2587 Г	0.01 0.1	1 10	1.22	(0.37 - 3.96)	100.0

Figure S9: Meta-analysis for nasopharyngitis, SGLT-2 inhibitors versus placebo

Trial Events Total E Canagliflozin Inagaki (2013) 35 308 Rosenstock (2012) 7 321 Random effects model 629 Heterogeneity: $I^2 = 0\%$, $p = 0.83$ 629 Dapagliflozin 7 321 Araki (2016) 13 123 Yang (2016) 16 299 Cefalu (2015) 25 460 Matthaei (2015) 11 109 Bolinder (2014) 12 91 Ji (2014) 11 261 Kaku (2014) 27 450 Wilding (2014) 107 610 Bailey (2013) 36 409 Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $I^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	10 75 2 65	Risk Ratio	RR	(95% CI)	Weight (%)
Canagliflozin Jagaki (2013) 35 308 Rosenstock (2012) 7 321 Random effects model 629 Heterogeneity: $l^2 = 0\%$, $p = 0.83$ 629 Dapagliflozin 7 321 Araki (2016) 13 123 Yang (2016) 16 299 Cefalu (2015) 25 460 Matthaei (2015) 11 109 Bolinder (2014) 12 91 Ji (2014) 11 261 Kaku (2014) 27 450 Wilding (2014) 107 610 Bailey (2013) 36 409 Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	10 75 2 65	+	0.85		
Inagaki (2013) 35 308 Rosenstock (2012) 7 321 Random effects model 629 Heterogeneity: $l^2 = 0\%$, $p = 0.83$ Dapagliflozin Araki (2016) 13 Yang (2016) 16 Cefalu (2015) 25 Matthaei (2015) 11 Bolinder (2014) 12 Ji (2014) 11 Leiter (2014) 24 Strojek (2014) 27 Wilding (2013) 36 Kaku (2013) 41 Bailey (2012) 8 Bailey (2012) 8 Wilding (2009) 4 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	10 75 2 65	+	0.05		
Rosenstock (2012) 7 321 Random effects model 629 Heterogeneity: $l^2 = 0\%$, $p = 0.83$ Dapagliflozin Araki (2016) 13 123 Yang (2016) 16 299 Cefalu (2015) 25 460 Matthaei (2015) 11 109 Bolinder (2014) 12 91 Ji (2014) 11 261 Kaku (2014) 27 450 Wilding (2014) 107 610 Bailey (2013) 36 409 Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	2 65		0.85	(0.44 - 1.64)	2.5
Random effects model629Heterogeneity: $l^2 = 0\%$, $p = 0.83$ DapagliflozinAraki (2016)13Yang (2016)16299Cefalu (2015)25460Matthaei (2015)11109Bolinder (2014)1291Ji (2014)11261Kaku (2014)24174Leiter (2014)35482Strojek (2014)107610Bailey (2013)36409Kaku (2013)41225Bailey (2012)8214Rosenstock (2012)18Wilding (2009)448Random effects model4236Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$			0.71	(0.15 - 3.33)	0.4
Heterogeneity: $l^2 = 0\%$, $p = 0.83$ DapagliflozinAraki (2016)13123Yang (2016)16299Cefalu (2015)25460Matthaei (2015)11109Bolinder (2014)1291Ji (2014)11261Kaku (2014)24174Leiter (2014)35482Strojek (2014)107610Bailey (2013)36409Kaku (2013)41225Bailey (2012)8214Rosenstock (2012)18281Wilding (2009)448Random effects model4236Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	140	4	0.83	(0.45 - 1.52)	2.9
DapagliflozinAraki (2016)13123Yang (2016)16299Cefalu (2015)25460Matthaei (2015)11109Bolinder (2014)1291Ji (2014)11261Kaku (2014)24174Leiter (2014)35482Strojek (2014)27450Wilding (2014)107610Bailey (2013)36409Kaku (2013)41225Bailey (2012)8214Rosenstock (2012)18281Wilding (2009)448Random effects model4236Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$		1			
Araki (2016)13123Yang (2016)16299Cefalu (2015)25460Matthaei (2015)11109Bolinder (2014)1291Ji (2014)11261Kaku (2014)24174Leiter (2014)35482Strojek (2014)27450Wilding (2014)107610Bailey (2013)36409Kaku (2013)41225Bailey (2012)8214Rosenstock (2012)18281Wilding (2009)448Random effects model4236Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$					
Yang (2016)16299Cefalu (2015)25460Matthaei (2015)11109Bolinder (2014)1291Ji (2014)11261Kaku (2014)24174Leiter (2014)35482Strojek (2014)27450Wilding (2014)107610Bailey (2013)36409Kaku (2013)41225Bailey (2012)8214Rosenstock (2012)18281Wilding (2009)448Random effects model4236Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	7 60	+	0.91	(0.38 - 2.15)	1.4
Cetalu (2015) 25 460 Matthaei (2015) 11 109 Bolinder (2014) 12 91 Ji (2014) 11 261 Kaku (2014) 24 174 Leiter (2014) 35 482 Strojek (2014) 27 450 Wilding (2014) 107 610 Bailey (2013) 36 409 Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	5 145		1.55	(0.58 - 4.15)	1.1
Matthaei (2015)11109Bolinder (2014)1291Ji (2014)11261Kaku (2014)24174Leiter (2014)35482Strojek (2014)27450Wilding (2014)107610Bailey (2013)36409Kaku (2013)41225Bailey (2012)8214Rosenstock (2012)18281Wilding (2009)448Random effects model4236Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	26 462	+	0.97	(0.57 - 1.65)	3.7
Bolinder (2014) 12 91 Ji (2014) 11 261 Kaku (2014) 24 174 Leiter (2014) 35 482 Strojek (2014) 27 450 Wilding (2014) 107 610 Bailey (2013) 36 409 Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	7 109		1.57	(0.63 - 3.90)	1.3
Ji (2014)11261Kaku (2014)24174Leiter (2014)35482Strojek (2014)27450Wilding (2014)107610Bailey (2013)36409Kaku (2013)41225Bailey (2012)8214Rosenstock (2012)18281Wilding (2009)448Random effects model4236Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	8 91		1.50	(0.64 - 3.50)	1.5
Kaku (2014) 24 174 Leiter (2014) 35 482 Strojek (2014) 27 450 Wilding (2014) 107 610 Bailey (2013) 36 409 Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	5 132	+	1.11	(0.39 - 3.14)	1.0
Leiter (2014) 35 482 Strojek (2014) 27 450 Wilding (2014) 107 610 Bailey (2013) 36 409 Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	9 87	+-	1.33	(0.65 - 2.74)	2.0
Strojek (2014) 27 450 Wilding (2014) 107 610 Bailey (2013) 36 409 Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	38 483	*	0.92	(0.59 - 1.44)	5.4
Wilding (2014) 107 610 Bailey (2013) 36 409 Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	10 146	+	0.88	(0.43 - 1.77)	2.2
Bailey (2013) 36 409 Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	27 197	10 A	1.28	(0.87 - 1.89)	7.0
Kaku (2013) 41 225 Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $l^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	12 137	+	1.00	(0.54 - 1.88)	2.7
Bailey (2012) 8 214 Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: $I^2 = 0\%$ ($0\% - 0\%$), $p = 0.97$	13 54	+	0.76	(0.44 - 1.31)	3.5
Rosenstock (2012) 18 281 Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: I ² = 0% (0% - 0%), p = 0.97	3 68	-	0.85	(0.23 - 3.10)	0.6
Wilding (2009) 4 48 Random effects model 4236 Heterogeneity: I ² = 0% (0% - 0%), p = 0.97	7 139	+	1.27	(0.54 - 2.97)	1.5
Random effects model 4236 Heterogeneity: I ² = 0% (0% - 0%), p = 0.97	2 23		0.96	(0.19 - 4.86)	0.4
Heterogeneity: I ² = 0% (0% - 0%), p = 0.97	2333	þ	1.07	(0.90 - 1.27)	35.3
Empagliflozin					
Softeland (2017) 9 222	8 110	-++	0.56	(0.22 - 1.41)	1.2
Haering (2015) 70 441	24 225)#	1.49	(0.96 - 2.30)	5.6
Kovacs (2015) 19 333	7 165		1.34	(0.58 - 3.13)	1.5
Merker (2015) 65 431	39 206	10 III	0.80	(0.56 - 1.14)	8.2
Roden (2015) 57 447	27 229	*	1.08	(0.70 - 1.66)	5.8
Rosenstock (2015) 37 324	22 170	+	0.88	(0.54 - 1.45)	4.3
Ross (2015) 30 876	5 107	+	0.73	(0.29 - 1.85)	1.2
Tikkanen (2015) 35 552	26 272	-	0.66	(0.41 - 1.08)	4.5
Barnett - CKD2 (2014) 19 195	9 95	+	1.03	(0.48 - 2.19)	1.9
Barnett - CKD3 (2014) 9 187	16 187		0.56	(0.26 - 1.24)	1.7
Barnett - CKD4 (2014) 5 37	4 37		1.25	(0.36 - 4.29)	0.7
Kadowaki (2014) 39 438	10 109	+	0.97	(0.50 - 1.88)	2.4
Rosenstock (2014) 61 375	40 188		0.76	(0.53 - 1.09)	8.3
Ferrannini (2013) 5 244	1 82	-+	1.68	(0.20 - 14.17)	0.2
Random effects model 5102	2182	9	0.90	(0.77 - 1.04)	47.5
Heterogeneity: I ² = 0% (0% - 54%), p = 0.46					

Ipragliflozin					1			
Lu (2016)	2	87	3	83		0.64	(0.11 - 3.7	(1) 0.3
Kashiwagi (2015)	29	112	20	56	*	0.73	(0.45 - 1.1	6) 4.8
Kashiwagi (2014)	7	62	9	67	-	0.84	(0.33 - 2.1	2) 1.2
Random effects model		261		206	9	0.74	(0.49 - 1.1	11) 6.4
Heterogeneity: $I^2 = 0\%$ (0%	- 0%),	p = 0.95					0	
Luseogliflozin								
Seino (2014)	18	182	4	54		1.34	(0.47 - 3.7	8) 1.0
Seino (2014)	19	223	9	57		0.54	(0.26 - 1.1	3) 1.9
Seino (2014)	12	79	13	79	+	0.92	(0.45 - 1.9	0) 2.0
Random effects model		484		190	4	0.81	(0.50 - 1.3	31) 5.0
Heterogeneity: $I^2 = 8\%$ (0%	- 90%)	, <i>p</i> = 0.34	1				80000000000000000000000000000000000000	
Remogliflozin								
Sykes (2014)	4	179	0	36		- 5.80	(0.05 - 748.	13) 0.0
Random effects model Heterogeneity: not applicable	D	179		36		- 5.80	(0.05 - 748.	13) 0.0

Figure S9 (Continued): Meta-analysis for nasopharyngitis, SGLT-2 inhibitors versus placebo



Figure S10: Meta-analysis for nasopharyngitis, SGLT-2 inhibitors versus active comparators

	Treat	ment	Act Compa	ive arator				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Canagliflozin								
Rosenstock (2012)	7	321	3	65		0.47	(0.13 - 1.78)	1.6
Random effects model Heterogeneity: not applicab	ole	321		65		0.47	(0.13 - 1.78)	1.6
Dapagliflozin								
Bailey (2015)	26	199	7	75		1.40	(0.63 - 3.09)	4.5
Del Prato (2015)	70	406	76	408		0.93	(0.69 - 1.24)	32.3
Random effects model		605		483		0.97	(0.74 - 1.28)	36.8
Heterogeneity: $I^2 = 0\%$, $p =$: 0.34							
Empagliflozin								
DeFronzo (2015)	31	546	12	128		0.61	(0.32 - 1.15)	6.9
Lewin (2015)	29	542	8	135	+	0.90	(0.42 - 1.93)	4.8
Roden (2015)	57	447	27	223	÷	1.05	(0.69 - 1.62)	15.2
Ridderstrale (2014)	76	765	89	780		0.87	(0.65 - 1.16)	33.4
Random effects model		2300		1266	4	0.88	(0.71 - 1.09)	60.3
Heterogeneity: $I^2 = 0\%$ (0%	6 - 77%),	p = 0.	57					
Remogliflozin								
Sykes (2014)	4	179	3	35		0.26	(0.06 - 1.11)	1.3
Random effects model Heterogeneity: not applicab	ole	179		35		0.26	(0.06 - 1.11)	1.3
Random effects model Heterogeneity: $l^2 = 0\%$ (0%)	- 67%),	3405 p = 0.4	3	1849 Г	0.01 0.1 1 10	0.89	(0.75 - 1.05)	100.0

Figure S11: Meta-analysis for pharyngitis, SGLT-2 inhibitors versus placebo

	Treatr	nent	Place	bo				
Trial	Events	Total	Events	Total	Risk Ratio	D RR	(95% CI)	Weight (%)
Dapagliflozin					*			
Bailey (2012)	7	214	3	68		0.74	(0.20 - 2.79)	41.8
Random effects model		214		68	<u> </u>	0.74	(0.20 - 2.79)	41.8
Heterogeneity: not applicab	le						alera de M	
Empagliflozin								
Kadowaki (2014)	9	438	1	109		2.24	(0.29 - 17.49)	17.4
Random effects model		438		109		2.24	(0.29 - 17.49)	17.4
Heterogeneity: not applicab	le							
Ipragliflozin								
Kashiwagi (2015)	1	112	2	56		0.25	(0.02 - 2.70)	13.0
Random effects model		112		56		0.25	(0.02 - 2.70)	13.0
Heterogeneity: not applicab	le							
Luseogliflozin								
Seino (2014)	4	182	0	54		+ 6.19	(0.09 - 405.83)	4.2
Seino (2014)	2	79	3	79		0.67	(0.11 - 3.88)	23.6
Random effects model Heterogeneity: $I^2 = 0\%$, $\rho =$	0.34	261		133		- 0.93	(0.18 - 4.73)	27.8
Random effects model		1025		366		0.83	(0.35 - 1.96)	100.0
Heterogeneity: $I^2 = 0\% (0\%)$	- 71%),	p = 0.8	58	0.0	1 0.1 0.51 2	10 100		

Figure S12: Meta-analysis for upper respiratory tract infection, SGLT-2 inhibitors versus placebo

Trial	Treatr Events	ment Total	Plac Events	ebo Total	Risk Ratio RI	R	(95% CI)	Weight (%)
Canagliflozin								
Inagaki (2013)	9	308	1	75	2.1	9	(0.28 - 17.03)	0.8
Random effects model		308		75	2.1	9 ((0.28 - 17.03)	0.8
Heterogeneity: not applicat	ble						,	
Danadliflozin								
Araki (2016)	0	123	2	60		4	(0.01 - 2.09)	0.5
Yang (2016)	20	299	3	145	32	3	(0.98 - 10.70)	2.2
Bolinder (2014)	3	91	7	91		13	(0.11 - 1.61)	1.8
Leiter (2014)	22	482	29	483	- 07	6	(0.44 - 1.30)	9.0
Strojek (2014)	19	450	4	146	15	i4	(0.53 - 4.46)	2.8
Wilding (2014)	33	610	12	197	- 08	9	(0.33 - 1.40)	6.8
Bailey (2013)	19	409	14	137		15	(0.23 - 0.88)	6.4
Kaku (2013)	4	225	0	54		6	(0.06 - 555 16)	0.2
Rosenstock (2012)	17	281	10	139	1 0.0	14	(0.40 - 1.79)	5.1
Wilding (2009)	3	48	2	23		2	(0.13 - 4.01)	11
Random effects model	0	3018	2	1475	0.0	2	(0.56 - 1.19)	35.7
Heterogeneity: $l^2 = 30\%$ (()% - 67%	n = 0) 17	14/0			(0.00 - 1.10)	00.7
Theterogeneity: 7 = 50% (C	170 - 01 70	h p - 0						
Empagliflozin								
Haering (2015)	39	441	24	225	8.0 🛨	3	(0.51 - 1.34)	10.6
Kovacs (2015)	24	333	11	165	÷ 1.0	8	(0.54 - 2.15)	6.0
Merker (2015)	28	431	17	206	- 0.7	'9	(0.44 - 1.41)	8.0
Roden (2015)	33	447	12	229	1.4	1	(0.74 - 2.68)	6.8
Rosenstock (2015)	31	324	10	170	1.6	3	(0.82 - 3.24)	6.0
Ross (2015)	7	876	3	107		9	(0.07 - 1.09)	1.8
Barnett - CKD2 (2014)	27	195	7	95	1.8	88	(0.85 - 4.16)	4.7
Barnett - CKD3 (2014)	19	187	16	187	÷ 1.1	9	(0.63 - 2.24)	6.9
Barnett - CKD4 (2014)	3	37	2	37	1.5	50	(0.27 - 8.46)	1.1
Random effects model		3271		1421		9	(0.83 - 1.42)	51.8
Heterogeneity: $I^2 = 22\%$ (0	0% - 63%), <i>p</i> = 0).25					
Ertugliflozin					The second se			
Amin (2015)	2	116	2	38		3	(0.05 - 2.25)	0.9
Random effects model		116		38	0.3	33	(0.05 - 2.25)	0.9
Heterogeneity: not applicat	ble						. ,	
lpragliflozin								
Lu (2016)	8	87	10	83		6	(0.32 - 1.84)	3.9
Kashiwagi (2015)	4	112	3	56		57	(0.15 - 2.88)	1.5
Random effects model		199		139	< 0.7	4	(0.35 - 1.56)	5.4
Heterogeneity: $I^2 = 0\%$, $p =$	= 0.88							

Figure S12 (Continued): Meta-analysis for upper respiratory tract infection, SGLT-2 inhibitors versus

placebo

Luseogliflozin								
Seino (2014)	5	182	0	54		7.48	(0.12 - 482.76)	0.2
Seino (2014)	4	79	5	79		0.80	(0.22 - 2.87)	1.9
Random effects model Heterogeneity: $l^2 = 1\%$, $p = 0$.	.31	261		133	-	0.98	(0.28 - 3.44)	2.1
Remogliflozin		170					(0.00 5.00)	
Sykes (2014)	3	179	1	36		0.60	(0.06 - 5.64)	0.7
Random effects model Heterogeneity: not applicable		179		36		0.60	(0.06 - 5.64)	0.7
Sotagliflozin								
Rosenstock (2015)	8	236	3	60		0.68	(0.19 - 2.48)	1.9
Random effects model Heterogeneity: not applicable		236		60		0.68	(0.19 - 2.48)	1.9
Tofogliflozin								
Kaku (2014)	5	174	1	56		1.61	(0.19 - 13.48)	0.7
Random effects model Heterogeneity: not applicable		174		56		1.61	(0.19 - 13.48)	0.7
Random effects model Heterogeneity: $l^2 = 9\% (0\% - 4)$	41%),	7762 p = 0.33		3433		0.94	(0.78 - 1.12)	100.0
				0	0.01 0.1 1 10 1	00 1000		

Figure S13: Meta-analysis for upper respiratory tract infection, SGLT-2 inhibitors versus active

comparators

	Treatment		Active Comparator					
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Empagliflozin								
Hadjadj (2016)	33	1019	15	341		0.74	(0.40 - 1.34)	12.0
DeFronzo (2015)	45	546	4	128		2.64	(0.97 - 7.20)	5.3
Lewin (2015)	24	542	12	135		0.50	(0.26 - 0.97)	10.2
Roden (2015)	33	447	19	223	+	0.87	(0.50 - 1.49)	13.7
Ridderstrale (2014)	79	765	74	780	<u>i</u>	1.09	(0.81 - 1.47)	25.1
Random effects model		3319		1607	\$	0.92	(0.63 - 1.35)	66.3
Heterogeneity: I ² = 56% (0	% - 84%), p = (0.06					
Dapagliflozin								
Del Prato (2015)	31	406	46	408	=	0.68	(0.44 - 1.05)	17.9
Henry (2012)	20	397	11	201	+	0.92	(0.45 - 1.88)	9.2
Henry (2012)	13	430	7	208		0.90	(0.36 - 2.22)	6.3
Random effects model		1233		817	4	0.76	(0.54 - 1.07)	33.4
Heterogeneity: /2 = 0% (0%	6 - 69%),	, p = 0.	71					
Remogliflozin								
Sykes (2014)	3	179	0	35		4.59	(0.03 - 638.15)	0.2
Random effects model Heterogeneity: not applicab	le	179		35		4.59	(0.03 - 638.15)	0.2
Random effects model Heterogeneity: / ² = 30% (09	% - 68%)	4731), <i>p</i> = 0	.18	2459 Г	0.01 0.1 1 10 100 1	0.87	(0.68 - 1.12)	100.0
				0	0.01 0.1 1 10 100 1	000		

Figure S14: Meta-analysis for influenza, SGLT-2 inhibitors versus placebo

	Treat	ment	Place	ebo				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Dapagliflozin								
Mathieu (2016)	12	160	12	160	+	1.00	(0.46 - 2.16)	17.6
Schumm-Draeger (2015)	7	299	3	101		0.79	(0.21 - 2.99)	6.7
Wilding (2014)	28	610	3	197		3.01	(0.93 - 9.81)	8.4
Bailey (2013)	56	409	15	137		1.25	(0.73 - 2.14)	30.5
Wilding (2009)	2	48	2	23		0.48	(0.07 - 3.19)	3.4
Random effects model		1526		618	\$	1.20	(0.82 - 1.77)	66.6
Heterogeneity: I ² = 0% (0%	% - 78%)	p = 0.	43					
Empagliflozin								
Haering (2015)	18	441	4	225	[2.30	(0.79 - 6.70)	10.0
Rosenstock (2014)	21	375	12	188	*	0.88	(0.44 - 1.74)	21.1
Random effects model		816		413	\diamond	1.30	(0.51 - 3.27)	31.1
Heterogeneity: I ² = 54%, p	= 0.14						2 V	
Ipragliflozin								
Kashiwagi (2015)	0	112	2	56		0.14	(0.01 - 2.13)	1.7
Random effects model		112		56		0.14	(0.01 - 2.13)	1.7
Heterogeneity: not applicat	le							
Remogliflozin								
Sykes (2014)	6	179	0	36		→ 8.21	(0.07 - 1032.66)	0.5
Random effects model		179		36		- 8.21	(0.07 - 1032.66)	0.5
Heterogeneity: not applicat	le						a (1	
Random effects model Heterogeneity: $I^2 = 11\%$ (0)	% - 53%	2633	34	1123 ₁		1.17	(0.82 - 1.67)	100.0
instanogonolity. r = 1170 (o		n p o		0	0.01 0.1 1 10 100	1000		

Figure S15: Meta-analysis for influenza, SGLT-2 inhibitors versus active comparators

	Treatment		Active Comparator							
Trial	Events	Total	Events	Total	Risk	Ratio	F	RR	(95% CI)	Weight (%)
Dapagliflozin						1				
Bailey (2015)	17	199	3	75	_		2	.14	(0.64 - 7.08)	4.3
Del Prato (2015)	50	406	45	408	-	<u> </u>	1	.12	(0.76 - 1.63)	42.8
Random effects model		605		483		÷>	1	.19	(0.81 - 1.74)	47.0
Heterogeneity: I ² = 2%, p =	: 0.31									
Empagliflozin										
DeFronzo (2015)	13	546	4	128			0	.76	(0.25 - 2.30)	5.0
Lewin (2015)	23	542	2	135	-	+	→ 2	.86	(0.68 - 12.00)	3.0
Ridderstrale (2014)	51	765	51	780	_		1	.02	(0.70 - 1.48)	43.6
Random effects model		1853		1043	<	÷>	1	.07	(0.69 - 1.65)	51.6
Heterogeneity: I ² = 10% (0	% - 91%), p = 0	0.33						. ,	
Remogliflozin										
Sykes (2014)	6	179	1	35			1	.17	(0.15 - 9.45)	1.4
Random effects model		179		35		1.	1	.17	(0.15 - 9.45)	1.4
Heterogeneity: not applicab	ole									
Random effects model		2637		1561		\$	1	.11	(0.87 - 1.43)	100.0
Heterogeneity: $I^2 = 0\% (0\%)$	- 63%).	p = 0.6	33	ſ					, , , , , , , , , , , , , , , , , , , ,	
0	,,			0.	1 0.2 0.5	1 2	5 10			
Figure S16: Meta-analysis for bronchitis, SGLT-2 inhibitors versus placebo

	Treatn	nent	Place	bo				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Empagliflozin								
Haering (2015)	20	441	8	225	<u> </u>	1 28	(0.57 - 2.85)	13.3
Roden (2015)	17	447	10	229		0.87	(0.41 - 1.87)	14.6
Ross (2015)	10	876	0	107		\rightarrow 12.22	(0.03 - 4769.85)	0.3
Rosenstock (2014)	18	375	12	188	-	0.75	(0.37 - 1.53)	16.8
Random effects model		2139	12	749	る	0.93	(0.60 - 1.44)	45.0
Heterogeneity: $l^2 = 0\%$ (0%	% - 73%)	p = 0	64	140		0.00	(0.00 1.144)	40.0
The consideration of the first		, p 0.						
lpragliflozin								
Kashiwagi (2015)	5	112	0	56		- 8.50	(0.26 - 275.50)	0.8
Random effects model		112		56	1	- 8.50	(0.26 - 275.50)	0.8
Heterogeneity: not applicat	ole							
Dapagliflozin								
Matthaei (2015)	9	109	3	109		3.00	(0.83 - 10.78)	5.5
Bolinder (2014)	4	91	6	91		0.67	(0.19 - 2.28)	5.9
Leiter (2014)	17	482	20	483		0.85	(0.45 - 1.61)	20.5
Strojek (2014)	11	450	1	146		3.57	(0.46 - 27.41)	2.2
Wilding (2014)	27	610	13	197		0.67	(0.35 - 1.27)	20.1
Random effects model		1742		1026	\$	0.99	(0.58 - 1.71)	54.3
Heterogeneity: /2 = 36% (0	0% - 76%	o), p = 0	0.18					
Random effects model		3993		1831	•	0.94	(0.69 - 1.27)	100.0
Heterogeneity: $I^2 = 5\% (0\%)$	6 - 64%),	p = 0.3	39	Γ			,	
U	- //			0	0.01 0.1 1 10 10	0 1000		

Figure S17: Meta-analysis for bronchitis, SGLT-2 inhibitors versus active comparators

	Treat	ment	Act Comp	tive arator		Ris	k Ra	tio				
Trial	Events	Total	Events	Total			1			RR	(95% CI)	Weight (%)
Dapagliflozin												
Del Prato (2015)	36	406	32	408		-		_		1.13	(0.72 - 1.78)	68.4%
Random effects model		406		408		-	\Leftrightarrow	>		1.13	(0.72 - 1.78)	68.4%
Heterogeneity: not applical	ble for a s	single st	tudy									
Empagliflozin												
Roden (2015)	17	447	12	223		-	+			0.71	(0.34 - 1.45)	31.6%
Random effects model		447		223		\leq	+	,		0.71	(0.34 - 1.45)	31.6%
Heterogeneity: not applical	ble for a s	single st	tudy									
Random effects model		853		631		4	\Rightarrow			0.97	(0.64 - 1.50)	100%
Heterogeneity: I-squared=1	4.1%, p=	0.2806		г						_		
				'		1		1	1	1		
				0.1	1 0.2	0.5	1	2	5	10		

Figure S18: Meta-analysis for gastroenteritis, SGLT-2 inhibitors versus placebo

	Treatment		Placebo					
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Ipragliflozin								
Kashiwagi (2015)	1	112	2	56		0.25	(0.02 - 2.70)	7.3
Random effects model		112		56		0.25	(0.02 - 2.70)	7.3
Heterogeneity: not applicat	ble							
Empagliflozin								
Ross (2015)	3	876	3	107		0.12	(0.02 - 0.60)	16.4
Rosenstock (2014)	9	375	10	188	- 14	0.45	(0.19 - 1.09)	52.8
Random effects model Heterogeneity: $l^2 = 50\%$, p	= 0.16	1251		295		0.28	(0.08 - 0.96)	69.2
Luseogliflozin								
Seino (2014)	2	79	4	79		0.50	(0.09 - 2.65)	14.8
Random effects model		79		79		0.50	(0.09 - 2.65)	14.8
Heterogeneity: not applicat	ble							
Dapagliflozin								
Kaku (2013)	4	225	1	54		0.96	(0.11 - 8.42)	8.7
Random effects model		225		54		0.96	(0.11 - 8.42)	8.7
Heterogeneity: not applicat	ble				2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2			
Random effects model		1667		484	-	0.38	(0.20 - 0.72)	100.0
Heterogeneity: $I^2 = 0\% (0\%)$	% - 73%),	p = 0.5	55	0.0	1 0.1 0.51 2 10	100		

Figure S19: Meta-analysis for gastroenteritis, SGLT-2 inhibitors versus active comparators

	Treat	ment	Ac	tive		Ris	k Ra	tio				
Trial	Events	Total	Events	Total		113	1:	uo		RR	(95% CI)	Weight (%)
Dapagliflozin												
Del Prato (2015)	27	406	23	408		-	-			1.18	(0.69 - 2.02)	80%
Random effects model		406		408		-	\$	>		1.18	(0.69 - 2.02)	80%
Heterogeneity: not applica	ble for a s	ingle st	tudy								. ,	
Empagliflozin												
DeFronzo (2015)	16	546	4	128			-			0.94	(0.32 - 2.76)	20%
Random effects model		546		128			÷	-		0.94	(0.32 - 2.76)	20%
Heterogeneity: not applica	ble for a s	ingle st	tudy									
Random effects model		952		536		-	\Rightarrow	>		1.13	(0.70 - 1.82)	100%
Heterogeneity: I-squared=0	%, p=0.70	09		ſ						_		
				0.	1 0.2	0.5	1	2	5	10		

Figure S20: Sensitivity analyses of urinary tract infection stratified by study quality, SGLT-2 inhibitors versus placebo

Figure S20a: Risk of UTI in studies of canagliflozin at high risk of bias

Canagliflozin

	SGL	T2 itor	Place	bo			
Trial	Events	Total	Events	Total	RR	95%-CI	
300 mg							
Rosenstock (2012)	2	64	4	65	0.51	(0.10 - 2.68)	
Stenlof (2014)	14	197	12	192	1.14	(0.54 - 2.40)	
Townsend (2016)	0	56	0	56	1.00	(0.02 - 49.53)	
Random effects model		317		313	0.99	(0.51 - 1.94)	
Heterogeneity: $I^2 = 0\%$ (0%)	- 72%), τ	$^{2} = 0, p$	o = 0.69				
100 mg							
Rosenstock (2012)	2	64	4	65	0.51	(0.10 - 2.68)	
Stenlof (2014)	16	195	12	192	1.31	(0.64 - 2.70)	
Townsend (2016)	0	57	0	56	1.00	(0.02 - 49.54)	
Random effects model		316		313	1.13	(0.59 - 2.16)	
Heterogeneity: $I^2 = 0\%$ (0%)	- 80%), τ	$^{2} = 0, p$	= 0.59	0.00			
Random effects model		633		626	1.06	(0.66 - 1.69)	
Heterogeneity: $I^2 = 0\% (0\%)$	- 33%), τ	$^{2} = 0, p$	= 0.87			and showing the second states	

Figure S20b: Risk of UTI in studies of dapagliflozin at high risk of bias

	SGL	T2					
	Inhib	itor	Place	bo			
Trial	Events	Total	Events	Total	RR	95%	-CI
10 mg							
Jabbour (2014)	15	225	14	226	1.08	(0.53 -	2.18)
Kaku (2014)	2	88	2	87	0.99	(0.14 -	6.86)
Kohan (2014)	12	85	12	84	0.99	(0.47 -	2.07)
List (2009)	5	47	3	54	1.91	(0.48 -	7.59)
Rosenstock (2012)	7	140	11	139	0.63	(0.25 -	1.58)
Wilding (2009)	0	24	0	23	1.00	(0.02 - 4	48.41)
Random effects model		609		613	0.99	(0.65 -	1.49)
Heterogeneity: $I^2 = 0\%$ (0%)	- 32%), τ	² = 0, p	= 0.87				
5 mg							
Araki (2016)	2	123	0	60	3.98	(0.11 - 1	47.52)
Kaku (2014)	0	86	2	87	0.20	(0.01 -	4.15)
Kohan (2014)	11	83	12	84	0.93	(0.43 -	1.98)
List (2009)	5	58	3	54	1.55	(0.39 -	6.18)
Rosenstock (2012)	12	141	11	139	1.08	(0.49 -	2.36)
Random effects model		491		424	1.04	(0.63 -	1.70)
Heterogeneity: $I^2 = 0\%$ (0%)	5 - 60%), τ	$^{2} = 0, p$) = 0.72				
Random effects model		1100		1037	1.01	(0.73 -	1.38)

Heterogeneity: $I^2 = 0\% (0\% - 0\%), \tau^2 = 0, p = 0.95$

Figure S20c: Risk of UTI in studies of empagliflozin at high risk of bias

	SG Inhil	LT2 bitor	Plac	ebo		
Trial	Events	Total	Events	Total	RR	95%-CI
25 mg Ross (2015) Random effects model Heterogeneity: not applicabl	21 le	218 218	4	107 107	2.58 2.58	(0.91 - 7.32) (0.91 - 7.32)
10 mg <i>Ross (2015)</i> Random effects model Heterogeneity: not applicabl	13 le	220 220	4	107 107	1.58 1.58	(0.53 - 4.73) (0.53 - 4.73)
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	= 0, p = 0.	438 53		214	2.04	(0.96 - 4.35)

Figure S20d: Risk of UTI in studies of canagliflozin at medium risk of bias

SGLT2									
	Inhib	itor	Place	ebo					
Trial	Events	Total	Events	Total	RR	95%-CI			
300 mg									
Bode (2015)	39	236	24	237	1.63	(1.01 - 2.63)			
Forst (2014)	9	114	9	115	1.01	(0.42 - 2.45)			
Inagaki (2013)	0	75	0	75	1.00	(0.02 - 49.75)			
Ji (2015)	6	225	11	226	0.55	(0.21 - 1.46)			
Lavalle-Gonzalez (2013)	18	367	12	183	0.75	(0.37 - 1.52)			
Wilding (2013)	13	156	12	156	1.08	(0.51 - 2.30)			
Yale (2014)	13	89	9	90	1.46	(0.66 - 3.24)			
Random effects model		1262		1082	1.14	(0.85 - 1.53)			
Heterogeneity: $I^2 = 3\%$ (0%)	- 72%) , τ΄	² = 0.00	045, p = 0.	.40					
100 mg									
Bode (2015)	35	241	24	237	1.43	(0.88 - 2.34)			
Forst (2014)	6	113	9	115	0.68	(0.25 - 1.84)			
Inagaki (2013)	0	74	0	75	1.00	(0.02 - 49.75)			
Inagaki (2014)	1	90	1	93	1.03	(0.07 - 16.27)			
Inagaki (2016)	1	75	0	71	2.95	(0.12 - 73.34)			
Ji (2015)	7	223	11	226	0.64	(0.25 - 1.63)			
Kadowaki (2017)	0	70	1	68	0.33	(0.01 - 7.84)			
Lavalle-Gonzalez (2013)	29	368	12	183	1.20	(0.63 - 2.30)			
Wilding (2013)	13	157	12	156	1.08	(0.51 - 2.28)			
Yale (2014)	5	90	9	90	0.56	(0.19 - 1.59)			
Random effects model Heterogeneity: $I^2 = 0\%$ (0%)	- 42%) , τ	2 ² = 0, <i>p</i>	= 0.76	1314	1.06	(0.79 - 1.41)			
Random effects model Heterogeneity: $I^2 = 0\%$ (0%)	- 36%), τ	2763 ² = 0, p	o = 0.73	2396	1.10	(0.90 - 1.35)			

Figure S20e: Risk of UTI in studies of dapagliflozin at medium risk of bias

	SGI	T2 itor	Place	ebo		
Trial	Events	Total	Events	Total	RR	95%-CI
10 mg						
Bailey (2013)	18	135	11	137	1.66	(0.82 - 3.38)
Bolinder (2014)	6	91	7	91	0.86	(0.30 - 2.45)
Cefalu (2015)	27	460	27	462	1.00	(0.60 - 1.69)
Ji (2014)	5	133	4	132	1.24	(0.34 - 4.52)
Kaku (2013)	2	52	1	54	2.08	(0.19 - 22.22)
Leiter (2014)	53	482	28	483	1.90	(1.22 - 2.95)
Mathieu (2016)	15	160	16	160	0.94	(0.48 - 1.83)
Schumm-Draeger (2015)	3	99	3	101	1.02	(0.21 - 4.93)
Weber (2016)	9	302	3	311	3.09	(0.84 - 11.30)
Wilding (2014)	27	196	11	197	2.47	(1.26 - 4.83)
Yang (2016)	10	152	7	145	1.36	(0.53 - 3.48)
Random effects model		2262		2273	1.47	(1.16 - 1.85)
Heterogeneity: 12 = 1% (0%	- 61%), 1	$r^2 = 0.0$	023, p = 0	.43		
5 mg						
Bailey (2012)	2	68	1	68	2.00	(0.19 - 21.54)
Bailey (2013)	12	137	11	137	1.09	(0.50 - 2.39)
Ji (2014)	5	128	4	132	1.29	(0.35 - 4.69)
Kaku (2013)	1	58	1	54	0.93	(0.06 - 14.52)
Schumm-Draeger (2015)	5	100	3	101	1.68	(0.41 - 6.86)
Yang (2016)	6	147	7	145	0.85	(0.29 - 2.46)
Random effects model		638		637	1.14	(0.69 - 1.89)
Heterogeneity: $I^2 = 0\%$ (0%)	o - 0%), τ ²	= 0, p	= 0.97			(0.00
Random effects model Heterogeneity: / ² = 0% (0%	- 34%). τ	2900 2 = 0, p	= 0.76	2910	1.41	(1.14 - 1.73)

Figure S20f: Risk of UTI in studies of empagliflozin at medium risk of bias

SGLT2 Inhibitor Placebo										
Trial	Events	Total	Events	Total	RR	95%-CI				
25 mg										
Ferrannini (2013)	1	82	1	82	1 00	(0.06 - 15.72)				
Haering (2015)	35	217	36	225	1.01	(0.66 - 1.54)				
Kadowaki (2014)	1	109	1	109	1.00	(0.06 - 15.79)				
Kovacs (2015)	37	168	44	165	0.83	(0.56 - 1.21)				
Merker (2015)	22	214	28	206	0.76	(0.45 - 1.28)				
Roden (2015)	20	223	25	229	0.82	(0.47 - 1.44)				
Rosenstock (2013)	4	70	2	71	2.03	(0.38 - 10.72)				
Rosenstock (2014)	29	189	29	188	0.99	(0.62 - 1.60)				
Rosenstock (2015)	18	155	15	170	1.32	(0.69 - 2.52)				
Softeland (2017)	4	110	8	110	0.50	(0.16 - 1.61)				
Tikkanen (2015)	13	276	10	272	1.28	(0.57 - 2.87)				
Random effects model	-	1813		1827	0.93	(0.77 - 1.12)				
Heterogeneity: $I^2 = 0\%$ (0%)	- 21%), τ ²	= 0, p	= 0.89							
10 mg										
Forrannini (2013)	1	Q1	1	82	1.01	(0.06 15.01)				
Haering (2015)	38	224	36	225	1.01	(0.00 - 15.91) (0.70 - 1.61)				
Kadowaki (2014)	1	109	1	109	1.00	(0.06 - 15.79)				
Kovacs (2015)	37	165	44	165	0.84	(0.57 1.23)				
Merker (2015)	31	217	28	206	1.05	(0.65 - 1.69)				
Roden (2015)	21	224	25	229	0.86	(0.50 - 1.49)				
Rosenstock (2013)	3	71	2	71	1.50	(0.26 - 8.71)				
Rosenstock (2014)	29	186	29	188	1 01	(0.63 - 1.62)				
Rosenstock (2015)	25	169	15	170	1.68	(0.92 - 3.07)				
Softeland (2017)	8	112	8	110	0.98	(0.38 - 2.52)				
Tikkanen (2015)	11	276	10	272	1.08	(0.47 - 2.51)				
Random effects model		1834		1827	1.02	(0.85 - 1.22)				
Heterogeneity: $I^2 = 0\% (0\% - 1)$	- 6%), τ ² =	0, p =	0.94							

Random effects model 3647 3654 0.97 (0.86 - 1.11) Heterogeneity: $I^2 = 0\% (0\% - 0\%), \tau^2 = 0, p = 0.98$

Figure S20g: Risk of UTI in studies of canagliflozin at low risk of bias

	SGI Inhit	LT2 bitor	Plac	ebo		
Trial	Events	Total	Events	Total	RR	95%-CI
300 mg <i>Neal (2015)</i> Random effects model Heterogeneity: not applicable	42 e	690 690	36	690 690	1.17 1.17	(0.76 - 1.80) (0.76 - 1.80)
100 mg <i>Neal (2015)</i> Random effects model Heterogeneity: not applicable	36 9	692 692	36	690 690	1.00 1.00	(0.64 - 1.56) (0.64 - 1.56)
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$: 0, p = 0.	1382 62		1380	1.08	(0.79 - 1.48)

Figure S20h: Risk of UTI in studies of dapagliflozin at low risk of bias

	SGLT2 Inhibitor P			ebo		
Trial	Events	Total	Events	Total	RR	95%-CI
5 mg Strojek (2014) Random effects model Heterogeneity: not applicabl	11 e	145 145	11	146 146	1.01 1.01	(0.45 - 2.25) (0.45 - 2.25)
10 mg Lambers Heerspink (2013) Strojek (2014) Weber (2016) Random effects model Heterogeneity: I ² = 0% (0%	1 12 4 - 73%), τ	24 151 225 400 ² = 0, <i>p</i>	0 11 2 = 0.68	25 146 224 395	3.04 1.05 1.99 1.24	(0.13 - 69.61) (0.48 - 2.31) (0.37 - 10.76) (0.62 - 2.48)
Random effects model Heterogeneity: $I^2 = 0\%$ (0%)	- 50%), τ	545 ² = 0, p	= 0.82	541	1.13	(0.67 - 1.92)

Figure S20i: Risk of UTI in studies of empagliflozin at low risk of bias

	SGI	LT2	Disc			
	Innir	ottor	Place	ebo		
Trial	Events	Total	Events	Total	RR	95%-CI
25 mg						
Barnett - CKD2 (2014)	9	97	15	95	0.59	(0.27 - 1.28)
Barnett - CKD3 (2014)	31	187	29	187	1.07	(0.67 - 1.70)
Barnett - CKD4 (2014)	7	37	3	37	2.33	(0.65 - 8.34)
Zinman (2015)	416	2342	423	2333	0.98	(0.87 - 1.11)
Random effects model		2663		2652	0.98	(0.80 - 1.21)
Heterogeneity: $I^2 = 16\%$ (0	% - 87%)	, τ ² = 0	.0118, <i>p</i> =	= 0.31		(,
10 mg						
Barnett - CKD2 (2014)	14	98	15	95	0.90	(0.46 - 1.77)
Zinman (2015)	426	2345	423	2333	1.00	(0.89 - 1.13)
Random effects model		2443		2428	1.00	(0.89 - 1.13)
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	= 0, p = 0.	77				,
Random effects model Heterogeneity: $I^2 = 0\%$ (0%	- 66%), τ	2 2 = 0, <i>p</i>	= 0.59	5080	0.99	(0.91 - 1.08)

Figure S21: Sensitivity analyses of genital tract infection stratified by study quality, SGLT-2 inhibitors versus placebo

Figure S21a: Risk of genital tract infection in studies of canagliflozin at high risk of bias

	SGL	T2				
	Inhibi	tor	Place	bo		
Trial	Events	Total	Events	Total	RR	95%-Cl
300 mg						
Rosenstock (2012)	2	64	1	65	2.03	(0.19 - 21.85)
Stenlof (2014)	18	197	5	192	3.51	(1.33 - 9.26)
Townsend (2016)	0	56	0	56	1.00	(0.02 - 49.53)
Random effects model		317		313	3.06	(1.27 - 7.34)
Heterogeneity: $I^2 = 0\%$ (0%)	5 - 59%) , 1	$t^2 = 0, \mu$	o = 0.78			
100 mg						
Rosenstock (2012)	4	64	1	65	4.06	(0.47 - 35.37)
Stenlof (2014)	18	195	5	192	3.54	(1.34 - 9.36)
Townsend (2016)	0	57	0	56	1.00	(0.02 - 49.54)
Random effects model		316		313	3.40	(1.44 - 8.08)
Heterogeneity: $I^2 = 0\%$ (0%)	- 49%) , τ	² = 0, p	= 0.81			
Random effects model Heterogeneity: $I^2 = 0\%$ (0%	- 0%), τ ²	633 = 0, p =	= 0.97	626	3.23	(1.75 - 5.97)

Figure 21b: Risk of genital tract infection in studies of dapagliflozin at high risk of bias

	Inhib	itor	Place	ebo		
Trial	Events	Total	Events	Total	RR	95%-CI
10 mg						
Jabbour (2014)	22	225	1	226	22.10	(3.00 - 162.55)
Kaku (2014)	2	88	1	87	1.98	(0.18 - 21.41)
Kohan (2014)	7	85	3	84	2.31	(0.62 - 8.62)
List (2009)	1	47	0	54	3.15	(0.14 - 70.41)
Rosenstock (2012)	12	140	4	139	2.98	(0.98 - 9.01)
Wilding (2009)	0	24	1	23	0.33	(0.01 - 7.50)
Random effects model		609		613	3.09	(1.36 - 7.00)
Heterogeneity: $I^2 = 17\%$ (0%)	% - 62%),	$\tau^2 = 0.1$	826, p =	0.30		
5 ma						
Araki (2016)	1	123	0	60	2.49	(0.06 - 103.78)
Kaku (2014)	1	86	1	87	1.01	(0.06 - 15.92)
Kohan (2014)	8	83	3	84	2.70	(0.74 - 9.82)
List (2009)	1	58	0	54	2.93	(0.12 - 73.29)
Rosenstock (2012)	13	141	4	139	3.20	(1.07 - 9.59)
Random effects model		491		424	2.72	(1.27 - 5.82)
Heterogeneity: $I^2 = 0\%$ (0%)	- 0%), τ ²	= 0, p =	= 0.96			. ,
Random effects model Heterogeneity: $I^2 = 0\%$ (0%)	- 40%), τ	2 ² = 0, <i>p</i>	= 0.76	1037	2.91	(1.74 - 4.87)

Figure S21c: Risk of genital tract infection in studies of empagliflozin at high risk of bias

	SG Inhil	LT2 bitor	Plac	ebo			
Trial	Events	Total	Events	Total	RR	95%-CI	
25 mg Ross (2015) Random effects model Heterogeneity: not applicab	7 le	218 218	3	107 107	1.15 1.15	(0.30 - 4.34) (0.30 - 4.34)	
10 mg <i>Ross (2015)</i> Random effects model Heterogeneity: not applicab	9 le	220 220	3	107 107	1.46 1.46	(0.40 - 5.28) (0.40 - 5.28)	
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	= 0, p = 0.	438 80		214	1.30	(0.51 - 3.28)	

Figure S21d: Risk of genital tract infection in studies of canagliflozin at medium risk of bias

	SGL	_T2				
	Inhib	oitor	Place	ebo		
Trial	Events	Total	Events	Total	RR	95%-CI
300 mg						
Bode (2015)	34	236	6	237	5.69	(2.43 - 13.30)
Forst (2014)	14	114	3	115	4.71	(1.39 - 15.94)
Inagaki (2013)	1	75	0	75	3.00	(0.12 - 72.48)
Ji (2015)	5	225	2	226	2.51	(0.49 - 12.81)
Lavalle-Gonzalez (2013)	24	367	2	183	5.98	(1.43 - 25.04)
Wilding (2013)	18	156	5	156	3.60	(1.37 - 9.46)
Yale (2014)	2	89	3	90	0.67	(0.12 - 3.94)
Random effects model		1262		1082	3.92	(2.43 - 6.30)
Heterogeneity: $I^2 = 0\%$ (0%)	- 67%) , τ΄	² = 0, p	= 0.50			
100 mg						
Bode (2015)	35	241	6	237	5.74	(2.46 - 13.38)
Forst (2014)	9	113	3	115	3 05	(0.85 - 10.99)
Inagaki (2013)	1	74	0	75	3 01	(0.13 - 72.28)
Inagaki (2014)	2	90	1	93	2.07	(0.19 - 22.39)
Inagaki (2016)	1	75	0	71	2.95	(0.12 - 73.34)
Ji (2015)	2	223	2	226	1.01	(0.14 - 7.13)
Kadowaki (2017)	0	70	0	68	1.00	(0.02 - 49.71)
Lavalle-Gonzalez (2013)	31	368	2	183	7.71	(1.87 - 31.85)
Wilding (2013)	21	157	5	156	4.17	(1.61 - 10.79)
Yale (2014)	2	90	3	90	0.67	(0.11 - 3.90)
Random effects model		1501		1314	3.60	(2.26 - 5.73)
Heterogeneity: $I^2 = 0\%$ (0%)	- 59%), τ	² = 0, p	= 0.51			(
Random effects model		2763		2396	3 75	(2 60 - 5 23)
Heterogeneity: $I^2 = 0\%$ (0%)	- 42%), τ	$^{2} = 0, p$	= 0.63	2000	5.75	(2.09 - 0.23)

Figure S21e: Risk of genital tract infection in studies of dapagliflozin at medium risk of bias

SGLT2											
	Inhib	itor	Place	lacebo							
Trial	Events	Total	Events	Total	RR	95%-CI					
10 mg											
Bailey (2013)	17	135	7	137	2.46	(1.06 - 5.75)					
Bolinder (2014)	2	91	1	91	2.00	(0.18 - 21.67)					
Cefalu (2015)	28	460	4	462	7.03	(2.49 - 19.88)					
Ji (2014)	6	133	1	132	5.95	(0.73 - 48.79)					
Kaku (2013)	0	52	0	54	1.00	(0.02 - 49.51)					
Leiter (2014)	36	482	2	483	18.04	(4.37 - 74.49)					
Mathieu (2016)	10	160	2	160	5.00	(1.11 - 22.46)					
Schumm-Draeger (2015)	3	99	1	101	3.06	(0.32 - 28.93)					
Weber (2016)	6	302	5	311	1.24	(0.38 - 4.01)					
Wilding (2014)	28	196	6	197	4.69	(1.99 - 11.08)					
Yang (2016)	2	152	0	145	4.91	(0.23 - 104.38)					
Random effects model		2262		2273	3.99	(2.51 - 6.33)					
Heterogeneity: $I^2 = 15\%$ (09)	% - 56%),	$\tau^2 = 0.0$	0896, p =	0.30							
-											
5 mg	_		_								
Bailey (2012)	2	68	2	68	1.00	(0.15 - 6.90)					
Bailey (2013)	20	137	7	137	2.86	(1.25 - 6.54)					
Ji (2014)	4	128	1	132	4.12	(0.47 - 36.41)					
Kaku (2013)	1	58	0	54	2.93	(0.12 - 73.29)					
Schumm-Draeger (2015)	5	100	1	101	5.05	(0.60 - 42.46)					
Yang (2016)	3	147	0	145	6.96	(0.36 - 134.71)					
Random effects model		ຸ 638		637	2.89	(1.51 - 5.53)					
Heterogeneity: $I^2 = 0\%$ (0%)	- 32%), τ	² = 0, p	= 0.87								
Random effects model		2900		2910	3.61	(2.56 - 5.09)					

Heterogeneity: $I^2 = 0\%$ (0% - 45%), $\tau^2 = 0, \rho = 0.58$

Figure S21f: Risk of genital tract infection in studies of empagliflozin at medium risk of bias

	SGLT Inhibit	2 or	Placeb	0		
Trial	Events	Total	Events	Total	RR	95%-CI
25 mg						
Ferrannini (2013)	2	82	0	82	5.00	(0.24 - 102.56)
Haering (2015)	13	217	2	225	6.74	(1.54 - 29.52)
Kadowaki (2014)	0	109	0	109	1.00	(0.02 - 49.95)
Kovacs (2015)	7	168	5	165	1.37	(0.45 - 4.25)
Merker (2015)	20	214	1	206	19.25	(2.61 - 142.15)
Roden (2015)	14	223	4	229	3.59	(1.20 - 10.75)
Rosenstock (2013)	0	70	0	71	1.00	(0.02 - 49.71)
Rosenstock (2014)	18	189	3	188	5.97	(1.79 - 19.92)
Rosenstock (2015)	8	155	3	170	2.92	(0.79 - 10.83)
Softeland (2017)	5	110	2	110	2.50	(0.50 - 12.61)
Tikkanen (2015)	15	276	1	272	14.78	(1.97 - 111.14)
Random effects model		្1813		1827	3.81	(2.37 - 6.11)
Heterogeneity: $I^2 = 0\%$ (0%)	5 - 60%), τ	έ = 0, p) = 0.45			
10 mg						
Ferrannini (2013)	3	81	0	82	7.04	(0.37 - 133.05)
Haering (2015)	10	224	2	225	5.02	(1.11 - 22.66)
Kadowaki (2014)	1	109	0	109	3.00	(0.12 - 72.84)
Kovacs (2015)	17	165	5	165	3.40	(1.28 - 9.00)
Merker (2015)	18	217	1	206	17.09	(2.30 - 126.85)
Roden (2015)	13	224	4	229	3.32	(1.10 - 10.04)
Rosenstock (2013)	7	71	0	71	15.00	(0.87 - 257.73)
Rosenstock (2014)	8	186	3	188	2.70	(0.73 - 10.00)
Rosenstock (2015)	13	169	3	170	4.36	(1.26 - 15.02)
Softeland (2017)	2	112	2	110	0.98	(0.14 - 6.85)
Tikkanen (2015)	14	276	1	272	13.80	(1.83 - 104.20)
Random effects model		1834		1827	4.08	(2.57 - 6.49)
Heterogeneity: $I^2 = 0\%$ (0%)	5 - 44%) , τ	$r^2 = 0, p$	0 = 0.71			
Random effects model		3647		3654	3 95	(2.83 - 5.50)
		304/		3004	0.00	2.00 - 0.001

Figure S21g: Risk of genital tract infection in studies of canagliflozin at low risk of bias

	SG Inhil	LT2 bitor	Plac	ebo			
Trial	Events	Total	Events	Total	RR	95%-CI	
300 mg <i>Neal (2015)</i> Random effects model Heterogeneity: not applicabl	87 e	690 690	14	690 690	6.21 6.21	(3.57 - 10.82) (3.57 - 10.82)	
100 mg <i>Neal (2015)</i> Random effects model Heterogeneity: not applicabl	76 e	692 692	14	690 690	5.41 5.41	(3.09 - 9.48) (3.09 - 9.48)	
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$: 0, p = 0.	1382 73		1380	5.80	(3.91 - 8.61)	

Figure S21h: Risk of genital tract infection in studies of dapagliflozin at low risk of bias

	SGLT2 Inhibitor		Placebo			
Trial	Events	Total	Events	Total	RR	95%-CI
10 mg						
Lambers Heerspink (2013)	2	24	0	25	5.08	(0.26 - 98.15)
Strojek (2014)	13	151	2	146	6.28	(1.44 - 27.37)
Weber (2016)	6	225	4	224	1.49	(0.43 - 5.22)
Random effects model		400		395	2.97	(1.10 - 8.06)
Heterogeneity: $I^2 = 12\%$ (0°	% - 91%),	$\tau^2 = 0.$	1052, p =	0.32		
5 mg						
Strojek (2014)	9	145	2	146	4.53	(1.00 - 20.61)
Random effects model Heterogeneity: not applicable	e	145		146	4.53	(1.00 - 20.61)
Random effects model Heterogeneity: / ² = 0% (0%	- <mark>8</mark> 2%), τ	$545^2 = 0, p$	= 0.47	541	3.26	(1.50 - 7.10)

Figure S21i: Risk of genital tract infection in studies of empagliflozin at low risk of bias

	SG Inhi	LT2 bitor	Plac	ebo		
Trial	Events	Total	Events	Total	RR	95%-CI
25 mg						
Barnett - CKD2 (2014)	5	97	6	95	0.82	(0.26 - 2.58)
Barnett - CKD3 (2014)	5	187	2	187	2.50	(0.49 - 12.72)
Barnett - CKD4 (2014)	1	37	0	37	3.00	(0.13 - 71.31)
Zinman (2015)	148	2342	42	2333	3.51	(2.50 - 4.92)
Random effects model		2663		2652	2.23	(0.98 - 5.07)
Heterogeneity: $I^2 = 48\%$ (09)	% - 83%),	$\tau^2 = 0.3$	8186, <i>p</i> =	0.13		
10 mg						
Barnett - CKD2 (2014)	7	98	6	95	1.13	(0.39 - 3.24)
Zinman (2015)	153	2345	42	2333	3.62	(2.59 - 5.07)
Random effects model		2443		2428	2.26	(0.74 - 6.94)
Heterogeneity: $I^2 = 77\%$, τ^2	= 0.519 ,	p = 0.0	4			
Random effects model Heterogeneity: $I^2 = 50\%$ (09)	% - 80%),	5106 $\tau^2 = 0.1$	1113, p =	5080 0.07	2.58	(1.68 - 3.98)

Figure S22: Risk of genital tract infection with exclusion of RCTs with zero events in the treatment and control arms, SGLT-2 inhibitors versus placebo

	Treatr	nent	Place	ebo				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Canagliflozin								
Inagaki (2016)	1	75	0	71		2.95	(0.12 - 73.34)	0.2
Rodbard (2016)	6	108	1	108	+ + +	6.00	(0.73 - 49.00)	0.5
Bode (2015)	69	477	6	237		5.71	(2.52 - 12.97)	3.6
Ji (2015)	7	448	2	226		1.77	(0.37 - 8.43)	1.0
Neal (2015)	163	1382	14	690		5.81	(3.39 - 9.96)	8.2
Eorst (2014)	23	227	3	115		3.88	(1 19 - 12 67)	17
heneki (2014)	3	170	1	03		1.56	(0.16 - 14.78)	0.5
Oiu (2014)	8	186		03		1.33	(0.36 - 4.91)	1.4
Staniof (2014)	36	202	5	100		2.50	(0.00 - 4.01)	2.9
Siemor (2014)	30	170		102		0.00	(0.45 0.04)	2.0
raie (2014)	4	1/9	3	90	•	0.67	(0.15 - 2.93)	1.1
inagaki (2013)	2	308	0	/5		3.49	(0.04 - 338.07)	0.1
Lavalle-Gonzalez (2013)	55	735	2	183		6.85	(1.69 - 27.81)	1.2
Wilding (2013)	39	313	5	156		3.89	(1.56 - 9.67)	2.9
Rosenstock (2012)	17	321	1	65		3.44	(0.47 - 25.41)	0.6
Random effects model		5330		2394	•	3.89	(2.83 - 5.35)	25.9
Heterogeneity: /2 = 4% (0	% - 57%),	p = 0.4	1					
Dapagliflozin								
Araki (2016)	1	123	0	60		2.49	(0.06 - 103.78)	0.2
Mathieu (2016)	10	160	2	160		5.00	(1.11 - 22.46)	1.1
Weber (2016)	6	302	5	311		1.24	(0.38 - 4.01)	1.7
Weber (2016)	6	225	4	224		1.49	(0.43 - 5.22)	1.5
Yang (2016)	5	299	0	145		8.42	(0.25 - 285.04)	0.2
Cefalu (2015)	28	460	4	462		7.03	(2.49 - 19.88)	2.2
Matthaei (2015)	11	109	1	100		11.00	(1.44 - 83.74)	0.6
Schumm-Draeger (2015)		200		101		2 70	(0.34 - 21.34)	0.6
Bolioder (2014)	2	233	-	01	_1	2.00	(0.04 - 21.04)	0.0
Johnour (2014)	2	225		226		2.00	(0.10 - 21.07)	0.4
Jabbour (2014)	22	220	-	220		22.10	(0.00 - 102.00)	0.0
JI (2017)	10	201	1	132		5.06	(0.65 - 39.09)	0.6
Kaku (2014)	3	1/4	1	87		1.50	(0.16 - 14.21)	0.5
Kohan (2014)	15	168	3	84	-	2.50	(0.74 - 8.40)	1.6
Leiter (2014)	36	482	2	483		18.0	4 (4.37 - 74.49)	1.2
Strojek (2014)	30	450	2	146		4.87	(1.18 = 20.12)	1.2
Wilding (2014)	70	610	6	197		3.77	(1.66 - 8.54)	3.6
Bailey (2013)	53	409	7	137		2.54	(1.18 - 5.45)	4.1
Kaku (2013)	2	225	0	54		3.48	(0.04 - 345.02)	0.1
Lambers Heerspink (2013)	2	24	0	25		5.08	(0.26 - 98.15)	0.3
Bailey (2012)	8	214	2	68		1.27	(0.28 - 5.84)	1.0
Rosenstock (2012)	25	281	4	139		3.09	(1.10 - 8.71)	2.2
List (2009)	12	279	0	54		→ 15.32	2 (0.12 - 2035.42)	0.1
Wilding (2009)	5	48	1	23		2.40	(0.30 - 19.35)	0.5
Random effects model		5918		3518	÷	3.45	(2.55 - 4.66)	26.0
Heterogeneity: $I^2 = 0\%$ (0)	% - 43%)	p = 0.5	2				(2.00	
Hotorogeneity: 7 = 010 (0	10 10/10/1	0.0	-					
E					1.00			
Empagimozin		000	-	440		4.75	0.07 0.040	
Sonerand (2017)	/	222	2	110		1.73	(0.37 - 8.21)	1.0
Haening (2015)	23	441	2	225		5.87	(1.40 - 24.66)	1.2
Kovacs (2015)	24	333	5	165		2.38	(0.92 - 6.12)	2.7
Merker (2015)	38	431	1	206		18.16	(2.51 - 131.37)	0.6
Roden (2015)	27	447	4	229		3.46	(1.22 - 9.76)	2.2
Rosenstock (2015)	21	324	3	170		3.67	(1.11 - 12.14)	1.7
Ross (2015)	33	876	3	107		1.34	(0.42 - 4.31)	1.8
Tikkanen (2015)	29	552	1	272		14.29	(1.96 - 104.35)	0.6
Zinman (2015)	301	4687	42	2333	63	3.57	(2.59 - 4.91)	23.5
Barnett - CKD2 (2014)	12	195	6	95	-	0.97	(0.38 - 2.52)	2.7
Barnett - CKD3 (2014)	5	187	2	187		2.50	(0.49 - 12.72)	0.9
Barnett - CKD4 (2014)	1	37	0	37		3.00	(0.13 - 71.31)	0.2
Kadowaki (2014)	3	438	0	109		4.75	(0.05 - 427.02)	0.1
Rosenstock (2014)	26	375	3	188		4.34	(1.33 - 14.17)	1.7
Ferrannini (2013)	5	244	0	82		7.68	(0.14 - 412.97)	0.2
Rosenstock (2013)	14	353	0	71		+ 17.82	(0.15 - 2186 25)	0.1
Random effects model		10142		4586	•	3.11	(2.29 - 4.21)	41.0
Heteropeneity: $l^2 = 9\% / 0\%$	- 46%) /	= 0.35						1000
	in the particular part				1.12			

Figure S22 (continued): Risk of genital tract infection with exclusion of RCTs with zero events in the treatment and control arms, SGLT-2 inhibitors versus placebo

lpragliflozin								
Ishihara (2016)	7	175	0	87		11.48	(0.36 - 366.95)	0.2
Kashiwagi (2015)	1	119	0	46		2.39	(0.04 - 128.61)	0.2
Kashiwagi (2014)	2	62	0	67		5.16	(0.26 - 100.70)	0.3
Kashiwagi (2014)	6	291	0	69		8.42	(0.09 - 782.75)	0.1
Fonseca (2013)	11	273	1	69		2.78	(0.37 - 21.17)	0.6
Wilding (2013)	5	276	1	66		1.20	(0.14 - 10.06)	0.5
Random effects model		1196		404	-	2.95	(0.95 - 9.22)	1.8
Heterogeneity: /2 = 0% (0%	- 23%),	p = 0.90						
Luseogliflozin								
Seino (2014)	2	182	0	54		3.59	(0.05 - 252.52)	0.1
Seino (2014)	0	223	1	57		0.17	(0.01 - 2.83)	0.3
Seino (2014)	1	79	1	79		1.00	(0.06 - 15.71)	0.3
Random effects model		484		190		0.61	(0.10 - 3.66)	0.7
Heterogeneity: /2 = 0% (0%	- 87%),	p = 0.45						
Remogliflozin								
Sykes (2014)	8	179	0	36		10.61	(0.09 - 1317.46)	0.1
Sykes (2014)	11	238	0	48		14.22	(0.12 - 1741.69)	0.1
Random effects model		417		84		12.29	(0.41 - 369.88)	0.2
Heterogeneity: $I^2 = 0\%$, $\rho = 0$	0.93							
Sotagliflozin								
Rosenstock (2015)	8	236	0	60		11.03	(0.14 - 893.40)	0.1
Random effects model		236		60		11.03	(0.14 - 893.40)	0.1
Heterogeneity: not applicable	e							
Tofogliflozin								
lkeda (2015)	5	328	1	66		1.01	(0.12 - 8.47)	0.5
Kaku (2014)	1	174	0	56		2.32	(0.03 - 159.20)	0.1
Random effects model		502		122		1.19	(0.18 - 7.99)	0.7
Heterogeneity: $I^2 = 0\%$, $p = 0$	0.73							
Random effects model		24868		11603	•	3.40	(2.91 - 3.96)	100.0
Heterogeneity: /2 = 0% (0% -	20%),	p = 0.72						
				0	0.01 0.1 1 10 100 10	00		

Figure S23: Risk of urinary tract infection with exclusion of RCTs with zero events in the treatment and control arms, SGLT-2 inhibitors versus placebo

	Treatment		Placebo					
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Canaglifiozin		70	4	00		0.22	(0.04 7.04)	0.0
Kadowaki (2017)	0	70	1	68		0.33	(0.01 - 7.84)	0.0
Inagaki (2016)	1	/5	0	/1		2.95	(0.12 - 73.34)	0.0
Rodbard (2016)	2	108	2	108		1.00	(0.14 - 6.97)	0.1
Bode (2015)	/4	4//	24	237	+	1.53	(0.99 - 2.36)	2.6
JI (2015)	13	448	11	226		0.60	(0.27 - 1.31)	0.8
Near (2015)	78	1382	36	690	T	1.08	(0.74 - 1.59)	3.3
Forst (2014)	15	170	9	115		0.84	(0.38 - 1.87)	0.8
magaki (2014)	2	1/9	1	93		1.04	(0.10 - 11.31)	0.1
QNU (2014)	20	100	10	100		2.00	(0.43 - 9.23)	1.2
Stehior (2014)	30	170	12	192		1.22	(0.64 - 2.34)	1.2
Falle (2014)	10	725	40	102		0.00	(0.47 - 2.15)	0.0
Lavalle-Gonzalez (2013)	97	735	12	183		0.98	(0.53 - 1.80)	1.3
Wilding (2013)	20	313	12	150		1.08	(0.56 - 2.08)	1.1
Rosenstock (2012)	10	321	4	000		0.81	(0.26 - 2.34)	0.4
Random effects model	40043	5092		2367	ř	1.10	(0.90 - 1.33)	12.0
neterogeneity: /* = 0% (0	76 - 1070),	p = 0.6	9					
Empagliflozin								
Softeland (2017)	12	222	8	110	-+-	0.74	(0.31 - 1.77)	0.7
Haering (2015)	73	441	36	225	+	1.03	(0.72 - 1.49)	3.6
Kovacs (2015)	74	333	44	165	+	0.83	(0.60 - 1.15)	4.7
Merker (2015)	53	431	28	206	+	0.90	(0.59 - 1.39)	2.7
Roden (2015)	41	447	25	229	+	0.84	(0.52 - 1.35)	2.2
Rosenstock (2015)	43	324	15	170		1.50	(0.86 - 2.63)	1.6
Ross (2015)	63	876	4	107	+	1.92	(0.71 - 5.18)	0.5
Tikkanen (2015)	24	552	10	272	+	1.18	(0.57 - 2.44)	0.9
Zinman (2015)	842	4687	423	2333		0.99	(0.89 - 1.10)	43.6
Barnett - CKD2 (2014)	23	195	15	95	-+	0.75	(0.41 - 1.36)	1.3
Barnett - CKD3 (2014)	31	187	29	187	+	1.07	(0.67 - 1.70)	2.3
Barnett - CKD4 (2014)	7	37	3	37	+	2.33	(0.65 - 8.34)	0.3
Kadowaki (2014)	3	438	1	109		0.75	(0.08 - 7.11)	0.1
Rosenstock (2014)	58	375	29	188	+	1.00	(0.67 - 1.51)	2.9
Ferrannini (2013)	4	244	1	82		1.34	(0.15 - 11.86)	0.1
Rosenstock (2013)	14	353	2	71		1.41	(0.33 - 6.06)	0.2
Random effects model		10142		4586	4	0.99	(0.91 - 1.08)	67.7
Heterogeneity: I ² = 0% (0%	% - 24%),	p = 0.8	6					
Estualificaria								
Ertugimozin	47	200	40	450		0.05	(0.22 4.20)	10
Terra (2017)	17	308	13	153		0.65	(0.32 - 1.30)	1.0
Amin (2015)	1	219	1	29		4.24	(0.13 - 1.42)	0.5
Pandom effects model	•	643		30		0.62	(0.15 - 11.37)	4.6
Haterogeneity J ² = 0% (0)	6 . 75%)	040	e.	240	<u> </u>	0.62	(0.35 - 1.11)	1.5
rieterogeneity. / = 0% (0	<i>ic - 101</i> 0),	p = 0.0	0		L.			
Ertugliflozin								
Terra (2017)	17	308	13	153	-++	0.65	5 (0.32 - 1.30) 1.0
Amin (2015)	7	219	4	54	+	0.43	3 (0.13 - 1.42) 0.3
Amin (2015)	4	116	1	38		1.31	1 (0.15 - 11.37) 0.1
Random effects model	1	643	1	245	•	0.63	2 (0.35 - 1.11) 1.5
Heterogeneity: I ² = 0% (0	% - 75%)	, p = 0.6	56					
					1			

Figure S23 (continued): Risk of urinary tract infection with exclusion of RCTs with zero events in the treatment and control arms, SGLT-2 inhibitors versus placebo

Barrow IIII and a								-
Dapagimozin		100						100
Araki (2016)	2	123	0	60		3.98	(0.11 - 147.52)	0.0
Mathieu (2016)	15	160	16	160	+	0.94	(0.48 - 1.83)	1.1
Weber (2016)	9	302	3	311		3.09	(0.84 - 11.30)	0.3
Weber (2016)	4	225	2	224		1.99	(0.37 - 10.76)	0.2
Yang (2016)	16	299	7	145	+	1.11	(0.47 - 2.63)	0.7
Cefalu (2015)	27	460	27	462	+	1.00	(0.60 - 1.69)	1.8
Matthaei (2015)	11	109	12	109	+	0.92	(0.42 - 1.99)	0.8
Schumm-Draeger (2015)	10	299	3	101		1.13	(0.32 - 4.01)	0.3
Balinder (2014)	6	91	7	91	-	0.86	(0.30 - 2.45)	0.4
Jabbour (2014)	15	225	14	226	+	1.08	(0.53 - 2.18)	1.0
Ji (2014)	10	261	4	132		1.25	(0.40 - 3.96)	0.4
Kalas (2014)	2	474	-	87		0.60	(0.07 - 3.40)	0.1
Kahap (2014)		100		84		0.00	(0.50 1.87)	4.2
Konan (2014)	23	100	14			0.20	(0.00 - 1.00)	1.4
Leiter (2014)	23	402	28	463	-	1.90	(1.22 - 2.90)	2.5
Strojek (2014)	30	450	11	146	T	0.88	(0.45 - 1.72)	1.1
Wilding (2014)	72	610	11	197	-	2.11	(1.14 - 3.91)	1.3
Bailey (2013)	41	409	11	137	+	1.25	(0.66 - 2.36)	1.2
Kaku (2013)	- 4	225	5	54		0.96	(0.11 - 8.42)	0.1
Lambers Heerspink (2013)	1	24	0	25		3.04	(0.13 - 69.61)	0.0
Bailey (2012)	6	214	1	68		1.91	(0.23 - 15.56)	0.1
Rosenstock (2012)	19	281	11	139	+	0.85	(0.42 - 1.75)	1.0
List (2009)	25	279	3	54		1.61	(0.50 - 5.15)	0.4
Wilding (2009)	1	48	0	23		2.48	(0.06 - 103.24)	0.0
Random effects model		5918		3518		1 23	(1.03 - 1.46)	16.0
Kandom enects moder	2511	3210		3319	r	1.20	(1.05 - 1.40)	10.0
Helerogeneity. / = 0.35 (0.35	- 23.10)	, p = u.o.i						
is malification								
ipragimozin								
Ishihara (2016)	4	1/5		87		1.99	(0.23 - 17.52)	0.1
Lu (2016)	6	87	2	83	+	2.86	(0.59 - 13.78)	0.2
Kashiwagi (2015)	2	112	2	56		0.50	(0.07 - 3.46)	0.1
Kashiwagi (2015)	1	119	2	46		0.19	(0.02 - 2.08)	0.1
Kashiwagi (2014)	0	62	1	67		0.34	(0.01 - 8.60)	0.0
Kashiwagi (2014)	4	291	1	69		0.95	(0.11 - 8.35)	0.1
Fonseca (2013)	21	273	6	69	+	0.88	(0.37 - 2.11)	0.6
Wilding (2013)	12	276	4	66		0.72	(0.24 - 2.15)	0.4
Random effects model		1395		543	4	0.88	(0.52 - 1.50)	1.7
Heteroceneity: $J^2 = 0\% / 0\%$	- 55%)	a = 0.65			1		(
Tofogliflozin								
Benda (2015)	8	328		66		1.61	(0.20 - 12.66)	0.1
Kaku (2014)		174	0	545		2.12	(0.03 - 159.20)	0.0
Pandom affects model	÷.	502		122		1 73	10.27 . 11 021	0.1
Kandom enects moder		002		144		1.73	(u.e 11.ue)	0.1
Heterogeneity: $P = 0\%$, $p = 0$	0.88							
					I.			
Sotagliflozin								
Rosenstock (2015)	4	236	1	60		1.02	(0.12 - 8.93)	0.1
Random effects model		236		60		1.02	(0.12 - 8.93)	0.1
Heterogeneity: not applicable								
Luseogliflozin								
Seino (2014)	1	182	0	54		2.30	(0.03 - 176.78)	0.0
Seino (2014)	1	223	0	57		2.26	(0.02 - 218.71)	0.0
Random effects model		405	-	111		2.28	(0.10 - 53.13)	0.0
Historoponeity: $J^2 = 0\%$, $\alpha = 1$	00	400				2.20	(0.10 - 00.10)	0.0
Heterogeneity, $r = 0\%$, $p = 1$	1.00							
Remogliflozia								
Subas (2014)	10	170	0	26		12.01	(0.11 . 1000.07)	0.0
Syn05 (2014)	10	1/9	0	30		- 13.01	(0.11 - 1002.37)	0.0
Sykes (2014)	3	238	0	48		4.61	(0.04 - 604.98)	0.0
Random effects model		417		84		7.79	(0.25 - 239.76)	0.0
Heterogeneity: $I^{e} = 0\%$, $p = 0$	0.77							
Random effects model		24750		11656		1.03	(0.96 - 1.11)	100.0
Heterogeneity: I ² = 0% (0% -	0%), p	= 0.97		1				
				0	0.01 0.1 1 10 100 10	000		

Figure S24: Risk of urinary tract infection stratified by study duration, canagliflozin versus placebo

	Treat	ment	Place	ebo				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
< 52 weeks								
Kadowaki (2017)	0	70	1	68	0	.33	(0.01 - 7.84)	0.4
Inagaki (2016)	1	75	0	71	2	.95	(0.12 - 73.34)	0.4
Rodbard (2016)	2	108	2	108	1	.00	(0.14 - 6.97)	1.0
Townsend (2016)	0	113	0	56		.00	(0.02 - 63.54)	0.2
Ji (2015)	13	448	11	226		.60	(0.27 - 1.31)	6.1
Inagaki (2014)	2	179	1	93	1	.04	(0.10 - 11.31)	0.7
Qiu (2014)	8	186	2	93	2	.00	(0.43 - 9.23)	1.6
Inagaki (2013)	0	308	0	75		.00	(0.01 - 138.74)	0.2
Rosenstock (2012)	16	321	4	65	o	.81	(0.28 - 2.34)	3.3
Random effects model		1808		855	I 0	.82	(0.49 - 1.38)	13.9
Heterogeneity: I ² = 0% (0%	6 - 5%), p	0.94	ţ					
≥ 52 weeks								
Bode (2015)	74	477	24	237	+ 1	.53	(0.99 - 2.36)	20.1
Neal (2015)	78	1382	36	690	L 1	.08	(0.74 - 1.59)	25.6
Forst (2014)	15	227	9	115		.84	(0.38 - 1.87)	6.0
Stenlof (2014)	30	392	12	192	+ 1	22	(0.64 - 2.34)	9.0
Yale (2014)	18	179	9	90	- <u>+</u> - 1	.01	(0.47 - 2.15)	6.6
Lavalle-Gonzalez (2013)	47	735	12	183	÷ 0	.98	(0.53 - 1.80)	10.1
Wilding (2013)	26	313	12	156	+ 1	.08	(0.56 - 2.08)	8.8
Random effects model		3705		1663	• 1	.15	(0.93 - 1.42)	86.1
Heterogeneity: I ² = 0% (0%	6 - 38%),	p = 0.8	33				1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 -	
Random effects model		5513		2518	• 1	.10	(0.90 - 1.33)	100.0
Heterogeneity: $I^2 = 0\%$ (0%)	6 - 0%), p	= 0.95	5	0	0.01 0.1 1 10 100 1000	į.	1879 - D	

Figure S25: Risk of urinary tract infection stratified by study duration, dapagliflozin versus placebo

	Treat	ment	Place	ebo			
Trial	Events	Total	Events	Total	Risk Ratio RR	(95% CI)	Weight (%)
< 52 weeks							
Araki (2016)	2	123	0	60	3.98	3 (0.11 - 147.52)	0.2
Weber (2016)	9	302	3	311	3.09	(0.84 - 11.30)	1.8
Weber (2016)	4	225	2	224	1.99	(0.37 - 10.76)	1.1
Yang (2016)	16	299	7	145	- <u>+</u> 1.1	(0.47 - 2.63)	4.1
Schumm-Draeger (2015)	10	299	3	101	1.1	3 (0.32 - 4.01)	1.9
Jabbour (2014)	15	225	14	226	1.04	3 (0.53 - 2.18)	6.1
Ji (2014)	10	261	4	132	- 1.20	5 (0.40 - 3.96)	2.3
Kaku (2014)	2	174	2	87	0.50	0.07 - 3.49)	0.8
Strojek (2014)	30	450	11	146		3 (0.45 - 1.72)	6.9
Kaku (2013)	4	225	1	54	0.9	6 (0.11 - 8.42)	0.6
Lambers Heerspink (2013)	1	24	0	25	3.04	(0.13 - 69.61)	0.3
Bailey (2012)	6	214	1	68	- 1.9	(0.23 - 15.56)	0.7
Rosenstock (2012)	19	281	11	139	0.8	5 (0.42 - 1.75)	6.0
List (2009)	25	279	3	54	1.6	(0.50 - 5.15)	2.3
Wilding (2009)	1	48	0	23	2.44	3 (0.06 - 103.24)	0.2
Random effects model		3429		1795	÷ 1.1	3 (0.85 - 1.52)	35.4
Heterogeneity: $I^2 = 0\%$ (0%)	6 - 0%), p	= 0.96				. ,	
> 52 weeks							
Mathieu (2016)	15	160	16	160		(0.48 - 1.83)	6.8
Cefalu (2015)	27	460	27	462	1.00	0.60 - 1.69)	11.4
Matthaei (2015)	11	109	12	109	0.92	2 (0.42 - 1.99)	5.1
Bolinder (2014)	6	91	7	91		3 (0.30 - 2.45)	2.8
Kohan (2014)	23	168	12	84	0.9	3 (0.50 - 1.83)	7.3
Leiter (2014)	53	482	28	483	1.9	(1.22 - 2.95)	15.7
Wilding (2014)	72	610	11	197	2.1	(1.14 - 3.91)	8.1
Bailey (2013)	41	409	11	137	1.2	5 (0.66 - 2.36)	7.5
Random effects model		2489		1723	• 1.2	5 (0.97 - 1.62)	64.6
Heterogeneity: $I^2 = 25\%$ (0)	% - 66%)	, p = 0.	23			,	
Random effects model		5918		3518	• 1.2	3 (1.03 - 1.46)	100.0
Heterogeneity: $I^2 = 0\%$ (0%)	6 - 25%),	p = 0.8	1	Γ		. ,	
	,,			0	0.01 0.1 1 10 100 1000		

Figure S26: Risk of urinary tract infection stratified by study duration, empagliflozin versus placebo

	Treat	nent	Place	ebo				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
< 52 weeks								
Softeland (2017)	12	222	8	110		0.74	(0.31 - 1.77)	1.0
Ross (2015)	63	876	4	107		1.92	(0.71 - 5.18)	0.7
Tikkanen (2015)	24	552	10	272		1.18	(0.57 - 2.44)	1.4
Kadowaki (2014)	3	438	1	109		0.75	(0.08 - 7.11)	0.1
Ferrannini (2013)	4	244	1	82		1.34	(0.15 - 11.86)	0.2
Rosenstock (2013)	14	353	2	71		1.41	(0.33 - 6.06)	0.3
Random effects model		2685		751	\$	1.16	(0.75 - 1.80)	3.7
Heterogeneity: $I^2 = 0\%$ (0%)	% - 44%),	p = 0.8	1					
≥ 52 weeks								
Haering (2015)	73	441	36	225	+	1.03	(0.72 - 1.49)	5.4
Kovacs (2015)	74	333	44	165	*	0.83	(0.60 - 1.15)	6.9
Merker (2015)	53	431	28	206	4	0.90	(0.59 - 1.39)	4.0
Roden (2015)	41	447	25	229	-	0.84	(0.52 - 1.35)	3.2
Rosenstock (2015)	43	324	15	170	+	1.50	(0.86 - 2.63)	2.3
Zinman (2015)	842	4687	423	2333		0.99	(0.89 - 1.10)	64.4
Barnett - CKD2 (2014)	23	195	15	95	-+-	0.75	(0.41 - 1.36)	2.0
Barnett - CKD3 (2014)	31	187	29	187	+	1.07	(0.67 - 1.70)	3.3
Barnett - CKD4 (2014)	7	37	3	37		2.33	(0.65 - 8.34)	0.4
Rosenstock (2014)	58	375	29	188	+	1.00	(0.67 - 1.51)	4.3
Random effects model		7457		3835	¢.	0.98	(0.90 - 1.07)	96.3
Heterogeneity: $I^2 = 0\%$ (0%)	% - 49%),	p = 0.6	8					
Random effects model		10142		4586	l l	0.99	(0.91 - 1.08)	100.0
Heterogeneity: $I^2 = 0\%$ (0%)	% - 24%),	p = 0.8	6	Г 0	0.01 0.1 1 10 100 10	00		

Figure S27: Risk of urinary tract infection with exclusion of RCTs that precluded patients with history of genitourinary infection from study enrolment, SGLT-2 inhibitors versus placebo

	Treatn	nent	Place	ebo				
Trial	Events	Total	Events	Total	Risk Ratio	RR	(95% CI)	Weight (%)
Canagliflozin								
Inagaki (2016)	1	75	0	71		2.95	(0.12 - 73.34)	0.1
Rodbard (2016)	2	108	2	108		1.00	(0.14 - 6.97)	0.2
Townsend (2016)	0	113	0	56		1.00	(0.02 - 63.54)	0.1
Bode (2015)	74	477	24	237	=	1.53	(0.99 - 2.36)	4.6
Ji (2015)	13	448	11	226		0.60	(0.27 - 1.31)	1.4
Neal (2015)	78	1382	36	690	÷	1.08	(0.74 - 1.59)	5.9
Forst (2014)	15	227	9	115		0.84	(0.38 - 1.87)	1.4
Qiu (2014)	8	186	2	93		2.00	(0.43 - 9.23)	0.4
Stenlof (2014)	30	392	12	192	+	1.22	(0.64 - 2.34)	2.1
Yale (2014)	18	179	9	90	-+-	1.01	(0.47 - 2.15)	1.5
Lavalle-Gonzalez (2013)	47	735	12	183	+	0.98	(0.53 - 1.80)	2.3
Wilding (2013)	26	313	12	156	-#-	1.08	(0.56 - 2.08)	2.0
Rosenstock (2012)	16	321	4	65		0.81	(0.28 - 2.34)	0.8
Random effects model		4956		2282	ò	1.10	(0.91 - 1.34)	22.7
Heterogeneity: /2 = 0% (0%	% - 21%),	p = 0.8	8					
Dapagliflozin								
Araki (2016)	2	123	0	60		3.98	(0.11 - 147.52)	0.1
Mathieu (2016)	15	160	16	160		0.94	(0.48 - 1.83)	1.9
Weber (2016)	9	302	3	311	÷	3.09	(0.84 - 11.30)	0.5
Weber (2016)	4	225	2	224		1.99	(0.37 - 10.76)	0.3
Yang (2016)	16	299	7	145	<u> </u>	1.11	(0.47 - 2.63)	1.2
Cefalu (2015)	27	460	27	462	+	1.00	(0.60 - 1.69)	3.2
Matthaei (2015)	11	109	12	109	_	0.92	(0.42 - 1.99)	1.5
Schumm-Draeger (2015)	10	299	3	101		1.13	(0.32 - 4.01)	0.5
Bolinder (2014)	6	91	7	91		0.86	(0.30 - 2.45)	0.8
Jabbour (2014)	15	225	14	226	_ <u>+</u> _	1.08	(0.53 - 2.18)	1.8
Ji (2014)	10	261	4	132		1.26	(0.40 - 3.96)	0.7
Kaku (2014)	2	174	2	87		0.50	(0.07 - 3.49)	0.2
Kohan (2014)	23	168	12	84	-	0.96	(0.50 - 1.83)	2.1
Leiter (2014)	53	482	28	483	-	1 90	(1 22 - 2 95)	4.5
Strojek (2014)	30	450	11	146	-	0.88	(0.45 - 1.72)	2.0
Wilding (2014)	72	610	11	197	-	2.11	(1.14 - 3.91)	2.3
Bailey (2013)	41	409	11	137		1.25	(0.66 - 2.36)	2.0
Kaku (2013)	4	225	1	54		0.96	(0.11 - 8.42)	0.2
Lambers Heerspink (2013)	1	24	ò	25		3.04	(0.13 - 69.61)	0.1
Bailey (2012)	6	214	1	68		1 91	(0.23 - 15.56)	0.7
Rosenstock (2012)	19	281	11	139		0.85	(0.42 - 1.75)	17
Liet (2000)	25	270	3	54	1.	1.61	(0.42 - 1.15)	0.6
Milding (2000)	20	210	0	22		2.49	(0.06 - 102.24)	0.0
Random affects model		5019	0	3518		1 23	(1.03 - 1.46)	28.5
Heterogeneity: $l^2 = 0\% (.0\%)$	25%	0.000	4	3310	Ĩ	1.23	(1.03 - 1.40)	20.5
Heterogeneity: / = 0% (0	/6 - 20%),	ρ = 0.8	1					
Empagliflozin								
Softeland (2017)	12	222	8	110		0.74	(0.31 - 1.77)	1.2
Haering (2015)	73	441	36	225	10	1.03	(0.72 - 1.49)	6.5
Kovacs (2015)	74	333	44	165	ii ii	0.83	(0.60 - 1.15)	8.3
Merker (2015)	53	431	28	206		0.90	(0.59 - 1.39)	4.8
Roden (2015)	41	447	25	229	+	0.84	(0.52 - 1.35)	3.9
Rosenstock (2015)	43	324	15	170	1	1.50	(0.86 - 2.63)	2.8
Ross (2015)	63	876	4	107		1.92	(0.71 - 5.18)	0.9
Tikkanen (2015)	24	552	10	272		1.18	(0.57 - 2.44)	17
Barnett - CKD2 (2014)	23	195	15	95		0.75	(0.41 - 1.36)	24
Barnett - CKD2 (2014)	31	187	20	197	1	1.07	(0.67 - 1.30)	4.0
Barnett - CKD3 (2014)	7	37	20	37	1.	2.22	(0.65 - 8.24)	4.0
Kadawaki (2014)	2	120	3	100		2.33	(0.03 - 0.34)	0.0
Radowaki (2014)	5	436	20	109		1.00	(0.00 - 7.11)	0.2
Rosenstock (2014)	28	3/5	29	100	于	0.00	(0.67 - 1.51)	5.2
Random effects model	43043	4008	•	2100		0.98	(0.05 - 1.13)	42.4
meterogeneity: /* = 0% (0%	70 - 43%),	p = 0.7	U					

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Figure S27 (continued): Risk of urinary tract infection with exclusion of RCTs that precluded patients with history of genitourinary infection from study enrolment, SGLT-2 inhibitors versus placebo

Ertugliflozin								
Terra (2017)	17	308	13	153		0.65	(0.32 - 1.30)	1.8
Amin (2015)	7	219	4	54	-++	0.43	(0.13 - 1.42)	0.6
Amin (2015)	4	116	1	38		1.31	(0.15 - 11.37)	0.2
Random effects model		643		245	•	0.62	(0.35 - 1.11)	2.6
Heterogeneity: $l^2 = 0\%$ (0%	- 75%)	p = 0.66					5) (A	
Ipragliflozin								
Ishihara (2016)	4	175	1	87		1.99	(0.23 - 17.52)	0.2
Lu (2016)	6	87	2	83		2.86	(0.59 - 13.78)	0.4
Kashiwagi (2015)	2	112	2	56		0.50	(0.07 - 3.46)	0.2
Kashiwagi (2015)	1	119	2	46	•	0.19	(0.02 - 2.08)	0.2
Kashiwagi (2014)	0	62	1	67		0.34	(0.01 - 8.60)	0.1
Kashiwagi (2014)	4	291	1	69		0.95	(0.11 - 8.35)	0.2
Fonseca (2013)	21	273	6	69		0.88	(0.37 - 2.11)	1.2
Wilding (2013)	12	276	4	66		0.72	(0.24 - 2.15)	0.7
Random effects model		1395		543	\$	0.88	(0.52 - 1.50)	3.1
Heterogeneity: $l^2 = 0\%$ (0%	- 55%)	$\rho = 0.65$						
Luseogliflozin								
Seino (2014)	1	182	0	54		2.30	(0.03 - 176.78)	0.0
Seino (2014)	1	223	0	57		2.26	(0.02 - 218.71)	0.0
Seino (2014)	0	79	0	79		1.00	(0.02 - 49.78)	0.1
Random effects model		484		190		1.65	(0.14 - 19.13)	0.1
Heterogeneity: $l^2 = 0\%$ (0%	- 0%),	p = 0.95						
Remogliflozin								
Sykes (2014)	10	179	0	36		> 13.01	(0.11 - 1602.37)	0.0
Sykes (2014)	3	238	0	48		4.61	(0.04 - 604.98)	0.0
Random effects model		417		84		7.79	(0.25 - 239.76)	0.1
Heterogeneity: $l^2 = 0\%$, $p = 1$	0.77						94	
Sotagliflozin								
Rosenstock (2015)	4	236	1	60		1.02	(0.12 - 8.93)	0.2
Random effects model		236		60		1.02	(0.12 - 8.93)	0.2
Heterogeneity: not applicable	e							
Tofogliflozin								
lkeda (2015)	8	328	1	66		1.61	(0.20 - 12.66)	0.2
Kaku (2014)	1	174	0	56		2.32	(0.03 - 159.20)	0.0
Random effects model		502		122		1.73	(0.27 - 11.02)	0.3
Heterogeneity: $l^2 = 0\%$, $p = 0\%$	0.88							
Random effects model		19409		9144	6	1.06	(0.97 - 1.17)	100.0
Heterogeneity: $l^2 = 0\% (0\%)$	- 0%). (= 0.97		[1 1 1 1		50 (Š	
				0	0.01 0.1 1 10 100	1000		



Figure S28: Funnel plot for urinary tract infections, SGLT-2 inhibitors versus placebo



Figure S29: Funnel plot for urinary tract infections, SGLT-2 inhibitors versus active comparators