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

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Abstract

Aims: There is concern about the infection-related safety profile of sodium-glucose co-transporter 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.

Keywords: sodium-glucose co-transporter 2 (SGLT-2) inhibitors – type 2 diabetes mellitus – infections – adverse events – systematic review and meta-analysis

Introduction

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are a novel class of anti-hyperglycemic 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 infection-related 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 meta-analysis 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 triple-blinded RCT; (2) the study population consisted of ≥50 patients aged ≥18 years diagnosed with type 2 diabetes; (3) the study compared the use of any SGLT-2 inhibitor(s) as monotherapy or add-on 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 ≥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 (≥5 criteria satisfied), moderate risk (3-4 criteria satisfied), or high risk (≤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/m^2.

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. Fifty-six 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 infection-related 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 anti-hyperglycemic 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-analyses for genitourinary infections with SGLT-2 inhibitors

Outcome	Comparison	Trials (n)	SGLT-2 inhibitor		Comparator		Random Effects Model Risk Ratio (95% CI)	I^2 (%)* (95% CI)
			Events (n)	Patients (n)	Events (n)	Patients (n)		
Genital Traction Infection	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)
	Canagliflozin (100 mg) vs. Placebo	14	202	2,509	42	2,317	4.11 (2.96-5.73)	0 (0-42)
	Canagliflozin (300 mg) vs. Placebo	11	205	2,269	41	2,085	4.47 (3.20-6.24)	0 (0-52)
	Dapagliflozin (All Doses) vs. Placebo	23	370	5,918	45	3,518	3.45 (2.55-4.66)	0 (0-43)
	Dapagliflozin (5 mg) vs. Placebo	12	68	1,274	21	1,207	2.95 (1.84-4.72)	0 (0-0)
	Dapagliflozin (10 mg) vs. Placebo	20	203	3,271	45	3,281	3.60 (2.53-5.11)	8 (0-43)
	Empagliflozin (All Doses) vs. Placebo	14	569	10,142	74	4,586	3.11 (2.29-4.21)	9 (0-46)
	Empagliflozin (10 mg) vs. Placebo	14	275	4,497	72	4,362	3.33 (2.46-4.49)	5 (0-57)
	Empagliflozin (25 mg) vs. Placebo	16	268	4,694	74	4,586	3.00 (2.08-4.35)	19 (0-55)
	SGLT-2 Inhibitor vs. Active Comparator	22	732	11,208	93	4,758	3.89 (3.14-4.82)	0 (0-46)
	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)
Urinary Tract Infection	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)
	Canagliflozin (300 mg) vs. Placebo	11	156	2,269	129	2,085	1.14 (0.91-1.42)	0 (0-44)
	Dapagliflozin (All Doses) vs. Placebo	23	402	5,918	186	3,518	1.23 (1.03-1.46)	0 (0-25)
	Dapagliflozin (5 mg) vs. Placebo	12	72	1,274	66	1,207	1.07 (0.78-1.48)	0 (0-0)
	Dapagliflozin (10 mg) vs. Placebo	20	233	3,271	173	3,281	1.33 (1.10-1.61)	0 (0-36)
	Empagliflozin (All Doses) vs. Placebo	14	1,365	10,142	673	4,586	0.99 (0.91-1.08)	0 (0-24)
	Empagliflozin (10 mg) vs. Placebo	14	658	4,497	641	4,362	1.01 (0.91-1.11)	0 (0-0)
	Empagliflozin (25 mg) vs. Placebo	16	668	4,694	673	4,586	0.97 (0.88-1.07)	0 (0-41)
	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)
Uro-sepsis	SGLT-2 Inhibitor vs. Placebo	7	17	6,633	5	3,464	1.41 (0.57-3.48)	0 (0-32)
	Canagliflozin vs. Placebo	3	0	977	2	537	0.36 (0.05-2.57)	0 (0-78)
	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
Pyelonephritis	SGLT-2 Inhibitor vs. Placebo	27	45	13,188	31	7,029	0.78 (0.52-1.18)	0 (0-0)
	Canagliflozin vs. Placebo	9	9	3,469	7	1,819	0.70 (0.30-1.66)	0 (0-0)
	Dapagliflozin vs. Placebo	13	5	3,976	3	2,200	0.97 (0.34-2.77)	0 (0-0)
	Empagliflozin vs. Placebo	3	31	5,481	20	2,840	0.79 (0.46-1.35)	0 (0-0)
	SGLT-2 Inhibitor vs. Active Comparator	9	9	5,815	2	2,587	1.22 (0.37-3.96)	0 (0-0)
	Canagliflozin vs. Active Comparator	2	3	1,917	0	719	3.06 (0.17-54.13)	0
	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 I^2 could not be calculated for analyses containing 2 or fewer RCTs.

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

Outcome	Comparison	Trials (n)	SGLT-2 inhibitor		Comparator		Random Effects Model Risk Ratio (95% CI)	I^2 (%)* (95% CI)
			Events (n)	Patients (n)	Events (n)	Patients (n)		
Respiratory Tract Infections								
Nasopharyngitis	SGLT-2 Inhibitor vs. Placebo	42	1,023	11,629	500	5,269	0.93 (0.84-1.03)	0 (0-16)
	Canagliflozin vs. Placebo	2	42	629	12	140	0.83 (0.45-1.52)	0
	Dapagliflozin vs. Placebo	15	388	4,236	179	2,333	1.07 (0.90-1.27)	0 (0-0)
	Empagliflozin vs. Placebo	15	460	5,102	238	2,182	0.90 (0.77-1.04)	0 (0-54)
	SGLT-2 Inhibitor vs. Active Comparator	8	300	3,405	225	1,849	0.89 (0.75-1.05)	0 (0-67)
	Canagliflozin vs. Active Comparator	1	7	321	3	65	0.47 (0.13-1.78)	N/A
	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)
Pharyng-itis	SGLT-2 Inhibitor vs. Placebo	5	23	1,025	9	366	0.83 (0.35-1.96)	0 (0-71)
	Dapagliflozin vs. Placebo	1	7	214	3	68	0.74 (0.20-2.79)	N/A
	Empagliflozin vs. Placebo	1	9	438	1	109	2.24 (0.29-17.49)	N/A
Influenza	SGLT-2 Inhibitor vs. Placebo	9	150	2,633	53	1,123	1.17 (0.82-1.67)	11 (0-53)
	Dapagliflozin vs. Placebo	5	105	1,526	35	618	1.20 (0.82-1.77)	0 (0-78)
	Empagliflozin vs. Placebo	2	39	816	16	413	1.30 (0.51-3.27)	54
	SGLT-2 Inhibitor vs. Active Comparator	6	160	2,637	106	1,561	1.11 (0.87-1.43)	0 (0-63)
	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)
URTI	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
	Dapagliflozin vs. Placebo	10	140	3,018	83	1,475	0.82 (0.56-1.19)	30 (0-67)
	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)
Bronchitis	SGLT-2 Inhibitor vs. Placebo	10	138	3,993	73	1,831	0.94 (0.69-1.27)	5 (0-64)
	Dapagliflozin vs. Placebo	5	68	1,742	43	1,026	0.99 (0.58-1.71)	36 (0-76)
	Empagliflozin vs. Placebo	4	65	2,139	30	749	0.93 (0.60-1.44)	0 (0-73)
	SGLT-2 Inhibitor vs. Active Comparator	2	53	853	44	631	0.97 (0.64-1.50)	14
	Dapagliflozin vs. Active Comparator	1	36	406	32	408	1.13 (0.72-1.78)	N/A

	Empagliflozin vs. Active Comparator	1	17	447	12	223	0.71 (0.34-1.45)	N/A
Gastrointestinal Infections								
Gastro-enteritis	SGLT-2 Inhibitor vs. Placebo	5	19	1,667	20	484	0.38 (0.20-0.72)	0 (0-73)
	Dapagliflozin vs. Placebo	1	4	225	1	54	0.96 (0.11-8.42)	N/A
	Empagliflozin vs. Placebo	2	12	1,251	13	295	0.28 (0.08-0.96)	50
	SGLT-2 Inhibitor vs. Active Comparator	2	43	952	27	536	1.13 (0.70-1.82)	0
	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

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

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

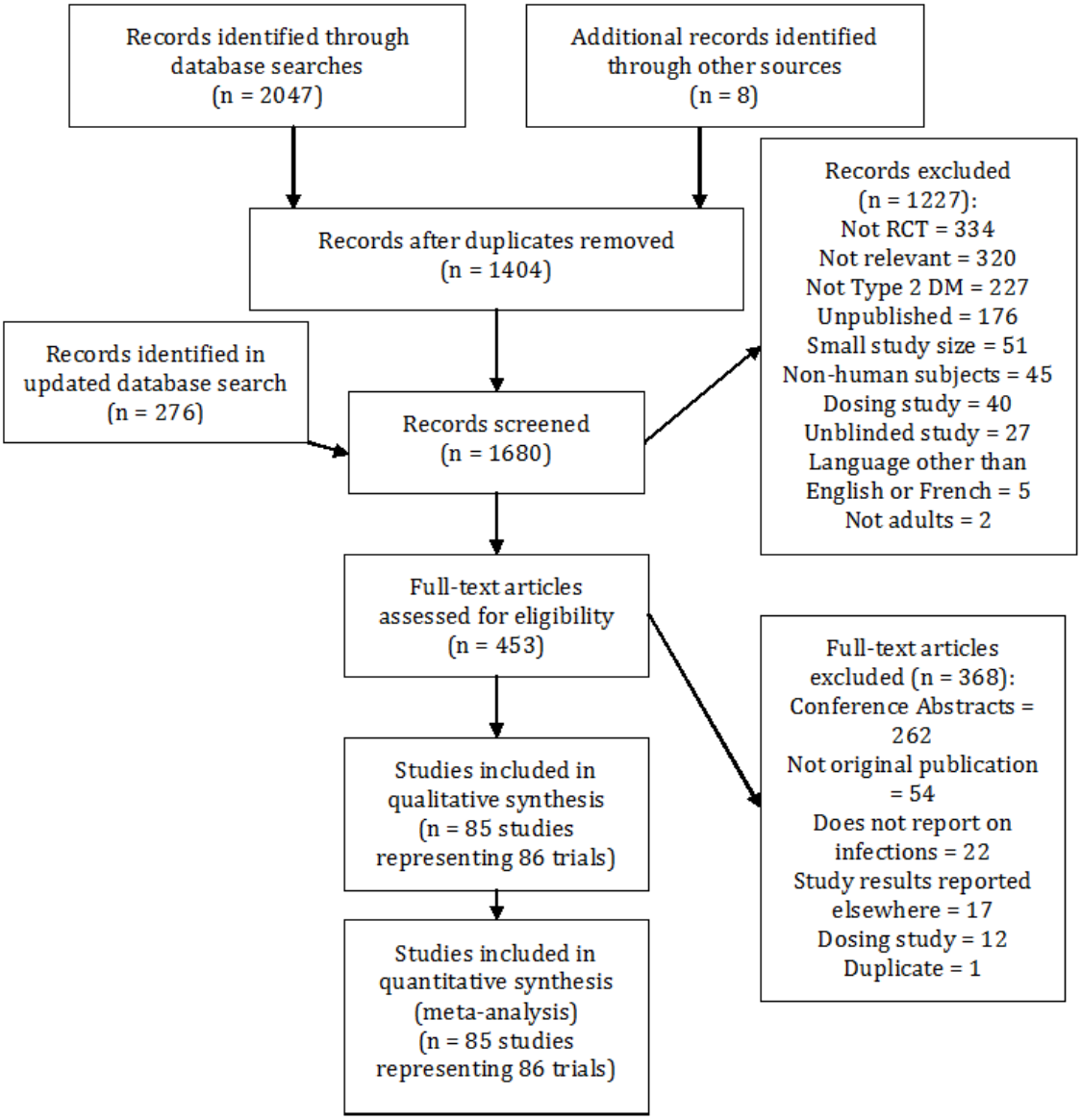

Table S1: PubMed search strategy for RCTs examining the use of SGLT-2 inhibitors

Search Number	Description	Number of publications
1	Sodium-Glucose Transport Proteins [mh] OR Sodium-Glucose Transporter 2 [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]	4422
2	**1** limited to English or French	4216
3[a]	**2** AND (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR randomised[Title/Abstract] OR placebo[Title/Abstract])	270
Date of initial search: April 3, 2015. Date of updated search: February 26, 2017. [a] Modified HIRU therapy search filter for best balance of sensitivity and specificity		

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

Search Number	Description	Number of publications
1	Exp sodium glucose co-transporter 2 inhibitor/ OR exp sodium glucose co-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	6525

	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		

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

Search Number	Description	Number of publications
1	MeSH descriptor: [Sodium-Glucose Transport Proteins] explode all trees OR 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	390
2	**1** limited to clinical trials	304
Date of search: April 3, 2015		

Table S4: ClinicalTrials.gov search strategy for RCTs examining the use of SGLT-2 inhibitors

Search Number	Description	Number of publications
1	Sodium-Glucose Transport Proteins OR Sodium-Glucose Transporter 2 OR sodium glucose transport OR sodium glucose transporter OR sodium glucose co-transport OR sodium glucose co-transporter OR sodium glucose cotransport	97
2	sodium glucose cotransporter OR sglt OR sglt2 OR sglt-2	84
3	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	282
4	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	27
5	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	49
6	WAY-123783 OR WAY123783 OR T-1095 OR T1095 OR ISIS-SGLT2Rx OR ISISSGLT2Rx OR ISIS-388626 OR ISIS388626	6
Date of search: April 3, 2015		

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

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

Rosenstock, 2012 (14)	NCT00642278	12 countries	2008-2009	Poorly-controlled DM2	451	Canagliflozin	Placebo or sitagliptin	14	Janssen
Schernthaner, 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,2014 (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 (27)	NCT02229396	6 countries	2014-2015	DM2 on metformin	695	Dapagliflozin	Exenatide	28	AstraZeneca
Henry Study 1, 2012 (28)	NCT00643851	Multiple countries	2008-2009	DM2 not on treatment	603	Dapagliflozin	Placebo and metformin	24	Bristol-Myers Squibb, AstraZeneca
Henry Study 2, 2012 (28)	NCT00859898	Multiple countries	2009-2010	DM2 not on treatment	641	Dapagliflozin	Placebo and metformin	24	Bristol-Myers Squibb, AstraZeneca
Jabbour, 2014 (29)	NCT00984867	6 countries	2009-2011	Poorly-controlled DM2	451	Dapagliflozin	Placebo	48	Bristol-Myers Squibb, AstraZeneca
Ji, 2014 (30)	NCT01095653	4 countries	2010-2012	DM2 not on treatment	393	Dapagliflozin	Placebo	28	Bristol-Myers Squibb, AstraZeneca
Kaku, 2013 (31)	NCT00972244	Japan	2009-2010	DM2	279	Dapagliflozin	Placebo	16	Bristol-Myers Squibb, AstraZeneca
Kaku, 2014 (32)	N/A	Japan	NR	DM2	261	Dapagliflozin	Placebo	27	Bristol-Myers Squibb, AstraZeneca
Kohan, 2014 (33)	NCT00663260	13 countries	2008-2011	DM2 with CKD	252	Dapagliflozin	Placebo	104	Bristol-Myers Squibb, AstraZeneca
Lambers Heerspink, 2013 (34)	NCT00976495	Canada, Netherlands, USA	2009-2010	DM2 on metformin and/or sulfonylurea	75	Dapagliflozin	Placebo or hydrochlorothiazide	12	Bristol-Myers Squibb, AstraZeneca
Leiter, 2014 (35)	NCT01042977	10 countries	2010-2012	DM2 with CV disease	964	Dapagliflozin	Placebo	52	Bristol-Myers Squibb, AstraZeneca
List, 2009 (36)	NCT00263276	4 countries	2005-2006	DM2 not on treatment	389	Dapagliflozin	Placebo or metformin	16	Bristol-Myers 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
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 hydrochlorothiazide	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	GlaxoSmithKline
Sykes, 2014 (82)	NCT00500331	19 countries	2007-08	DM2 not on treatment	336	Remogliflozin	Placebo or pioglitazone	14	GlaxoSmithKline

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; CKD, chronic kidney disease; NR, not reported.

List of studies included in the systematic review and meta-analysis

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

Study, Year	Registration Number	Overall Risk of Bias at Study Level								Risk of Bias Associated with Infectious AEs		
		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	H	L	H	4/6	M	4	U	Y
Forst, 2014	NCT01106690	L	L	L	H	L	H	4/6	M	4	N	Y
Inagaki, 2013	NCT01022112	L	L	U	H	L	H	3/6	M	3	Y	Y
Inagaki, 2014	NCT01413204	L	L	L	H	L	H	4/6	M	3	Y	Y
Inagaki, 2016	NCT02220920	L	L	U	U	L	H	3/6	M	3	N	Y
Ji, 2015	NCT01381900	L	L	U	L	L	H	4/6	M	4	N	Y
Kadowaki , 2017	NCT02354235	L	L	U	H	L	H	3/6	M	1	Y	Y
Lavalle-Gonzalez, 2013	NCT01106677	L	L	L	H	L	H	4/6	M	4	N	Y
Leiter, 2015	NCT00968812	L	L	L	H	L	H	4/6	M	4	N	Y
Neal, 2015	NCT01032629	L	L	L	L	L	H	5/6	L	4	N	Y
Qiu, 2014	NCT01340664	U	U	L	H	L	H	2/6	H	4	N	Y
Rodbard, 2016	N/A	L	L	U	L	L	H	4/6	M	3	N	Y
Rosenstock, 2016	NCT01809327	L	L	L	L	L	H	5/6	L	3	N	Y
Rosenstock, 2012	NCT00642278	U	U	U	L	L	H	2/6	H	5	U	Y
Schernthaner, 2013	NCT01137812	L	L	L	H	L	H	4/6	M	4	N	Y

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

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

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

† 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 (≥5 criteria satisfied), moderate overall risk (3-4 criteria satisfied), or high overall risk (≤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, 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

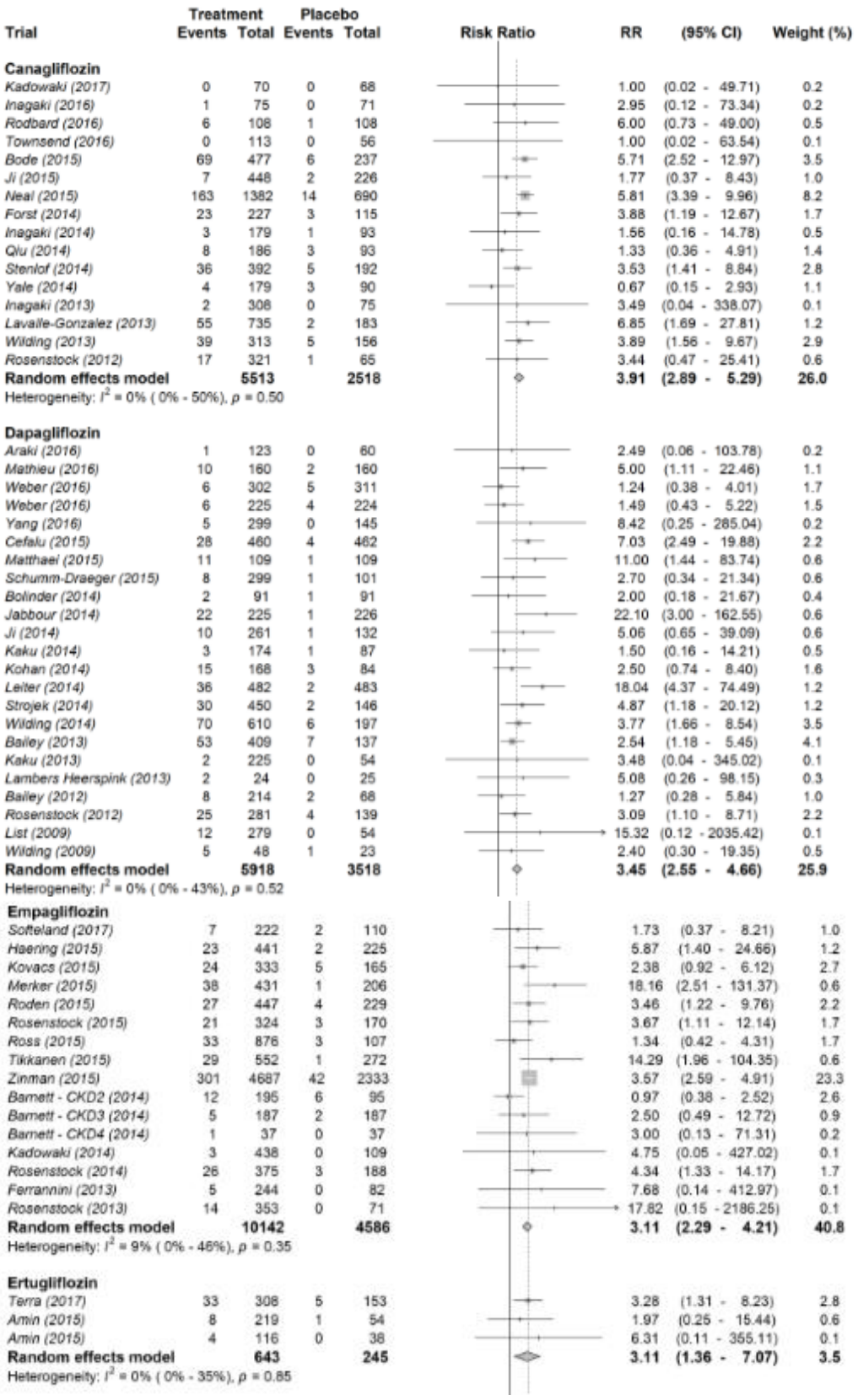


Figure S1 (Continued): Meta-analysis for genital tract infections, SGLT-2 inhibitors versus placebo

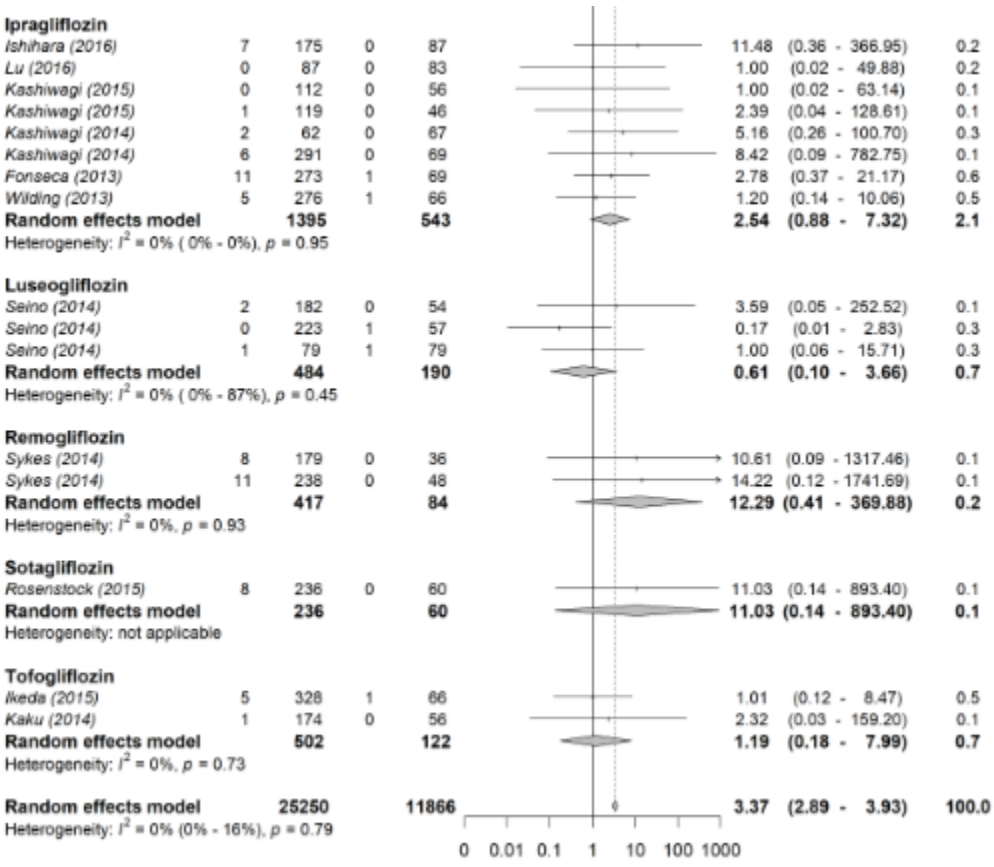


Figure S2: Meta-analysis for genital tract infections, SGLT-2 inhibitors versus active comparators

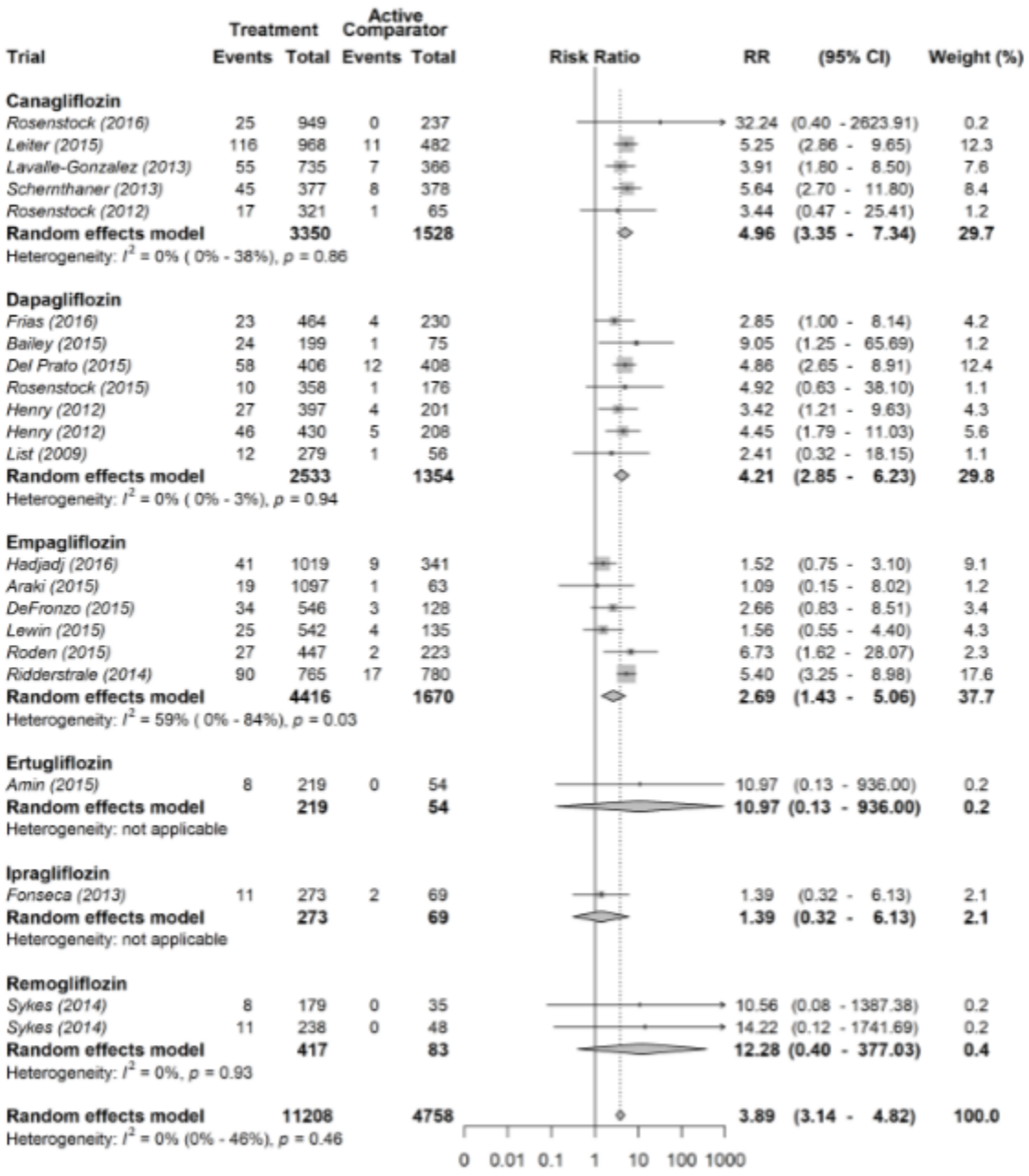


Figure S3: Meta-analysis for urinary tract infections, SGLT-2 inhibitors versus placebo

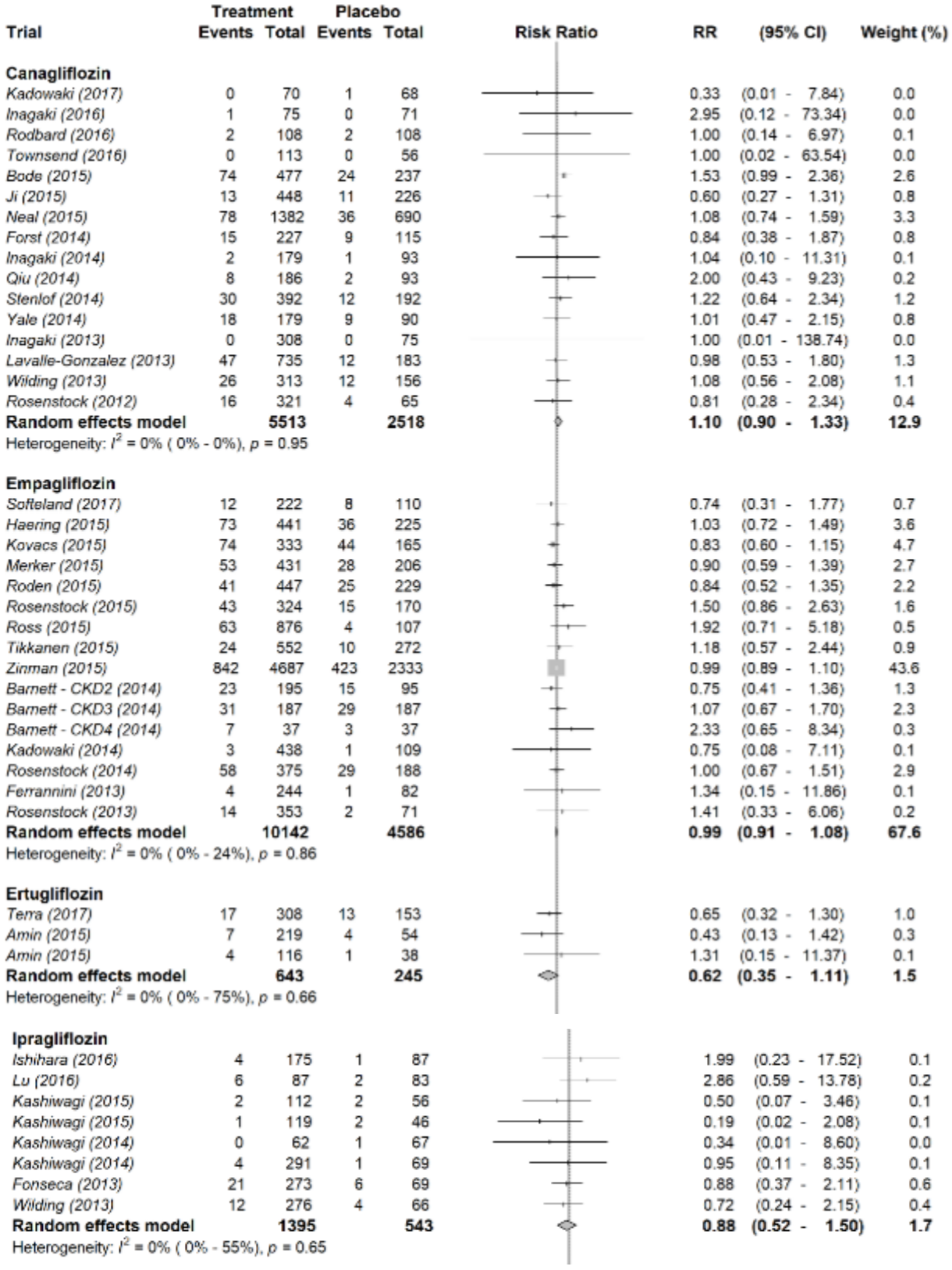


Figure S3 (Continued): Meta-analysis for urinary tract infections, SGLT-2 inhibitors versus placebo

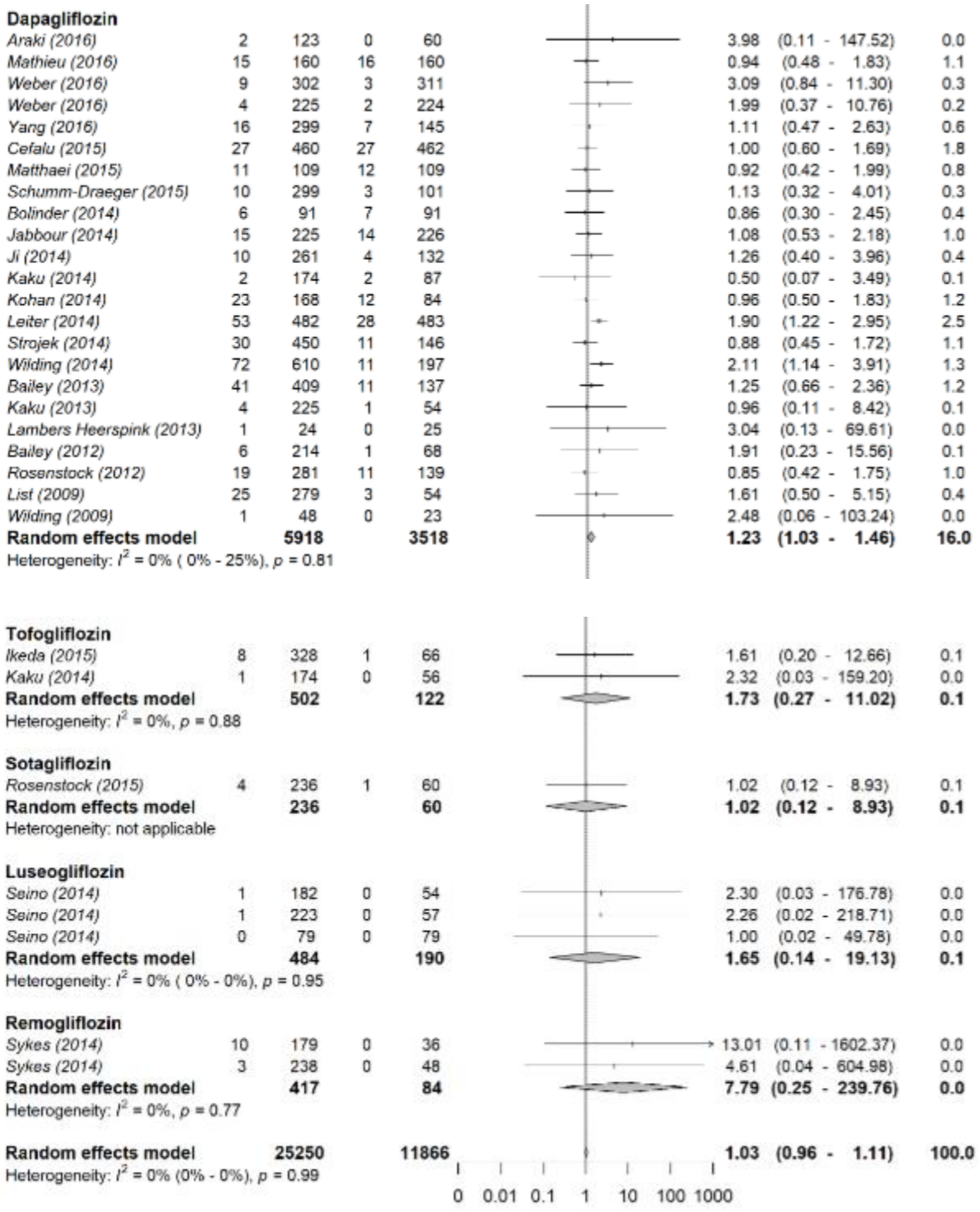


Figure S4: Meta-analysis for urinary tract infections, SGLT-2 inhibitors versus active comparators

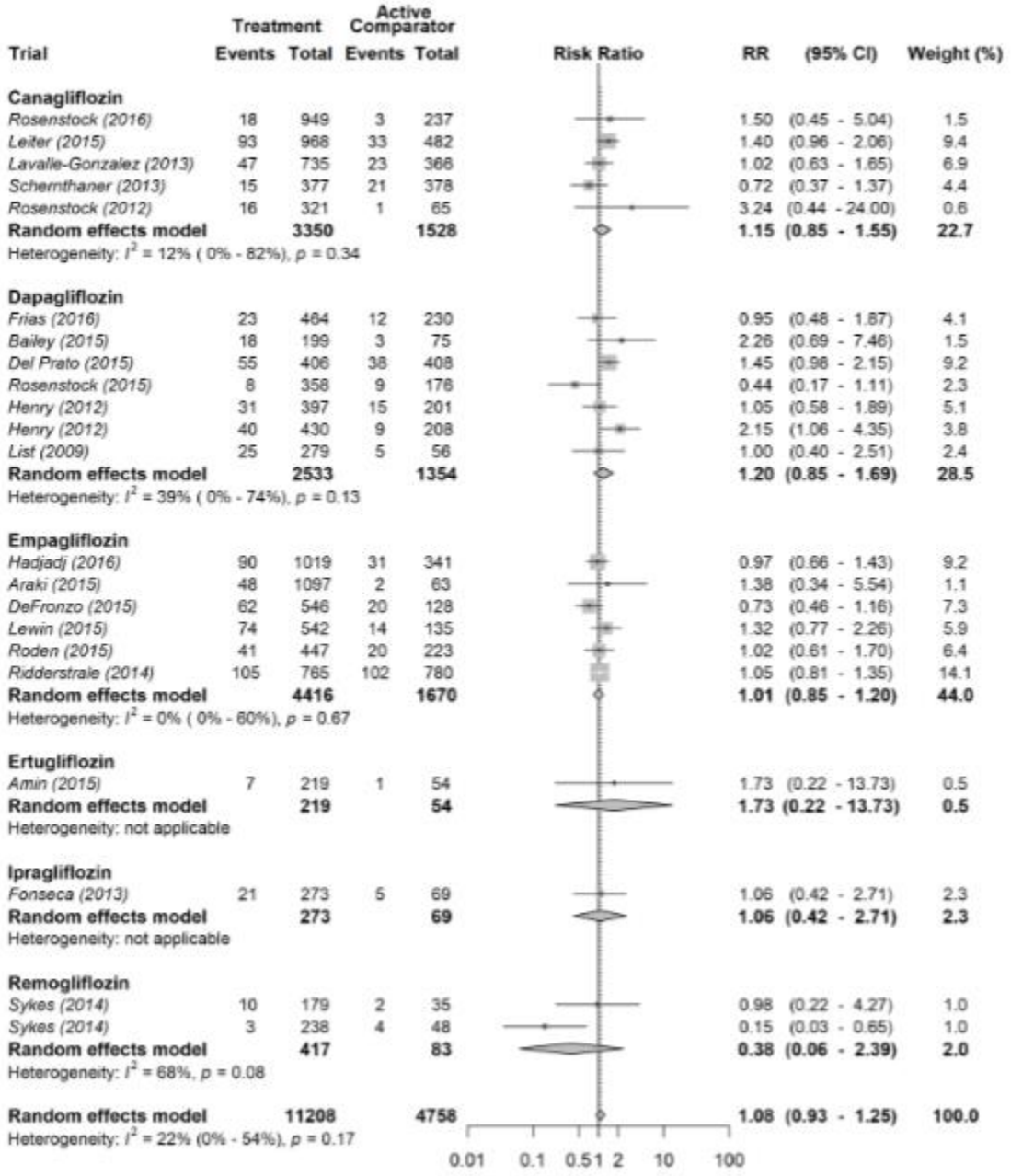


Figure S5: Meta-analysis for urosepsis, SGLT-2 inhibitors versus placebo

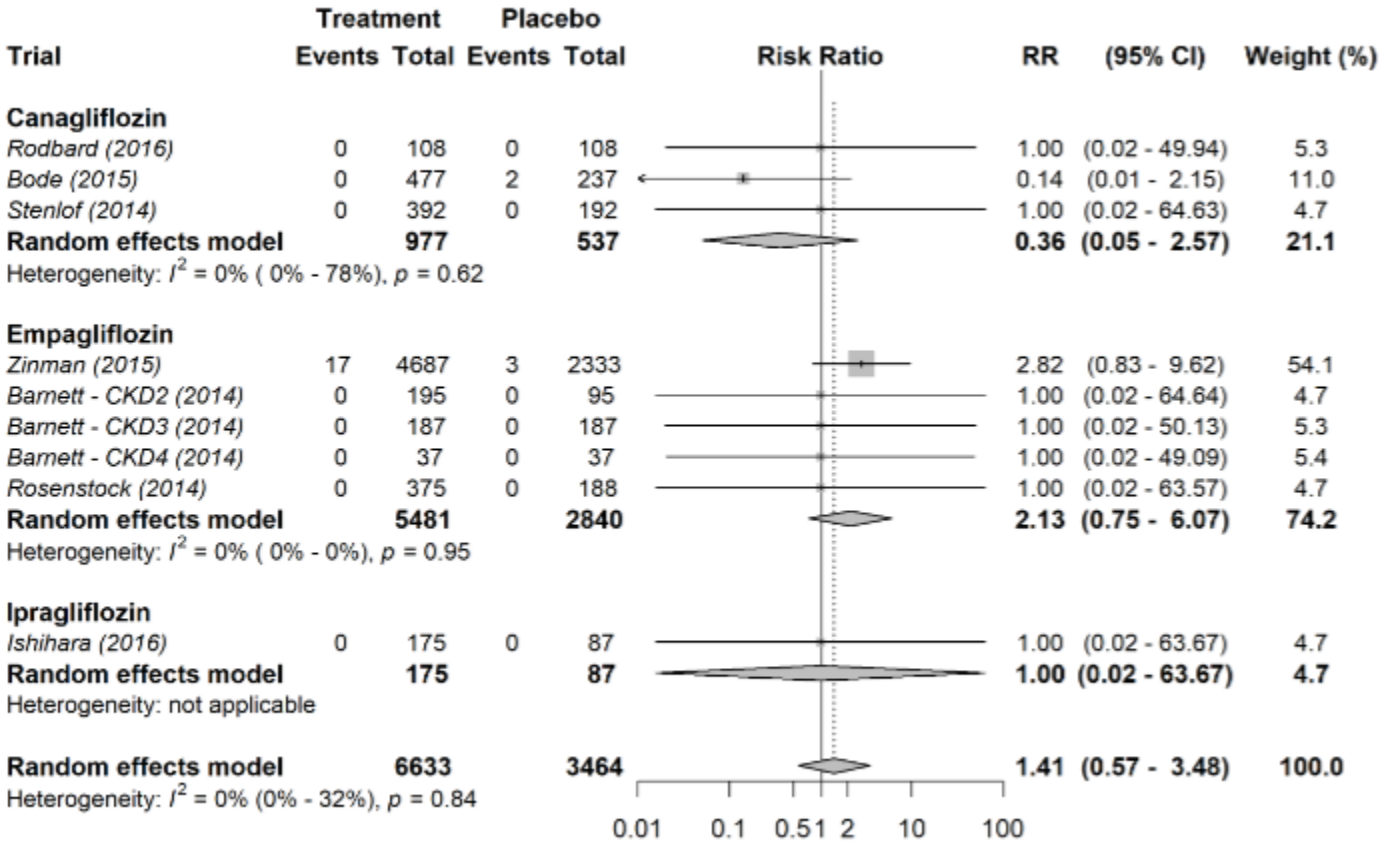


Figure S6: Meta-analysis for urosepsis, SGLT-2 inhibitors versus active comparators

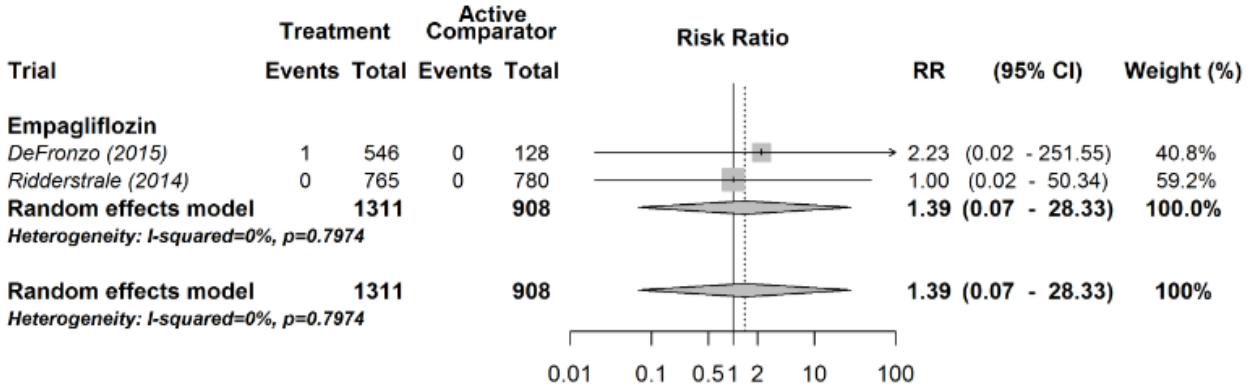


Figure S7: Meta-analysis for pyelonephritis, SGLT-2 inhibitors versus placebo

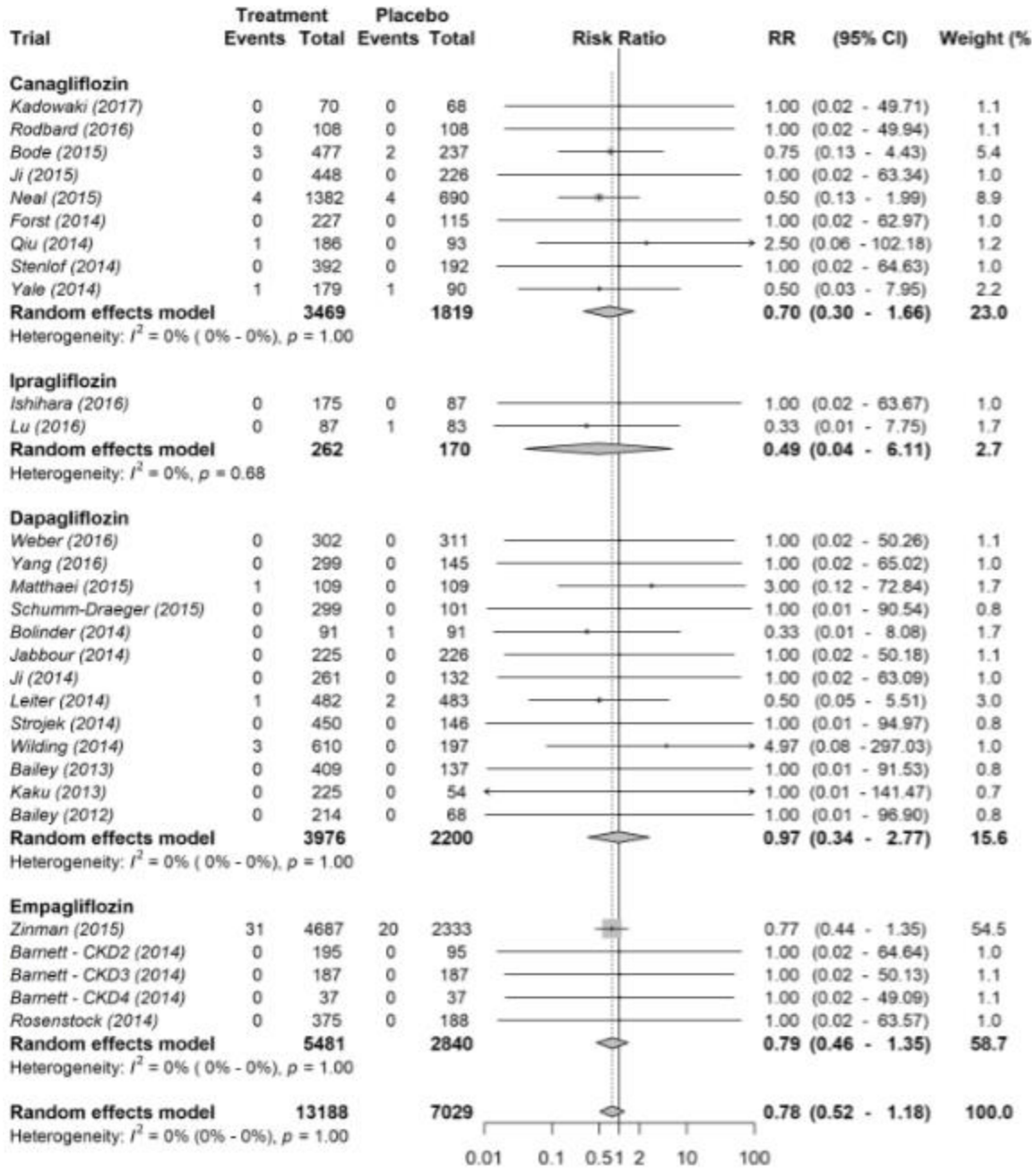


Figure S8: Meta-analysis for pyelonephritis, SGLT-2 inhibitors versus active comparators

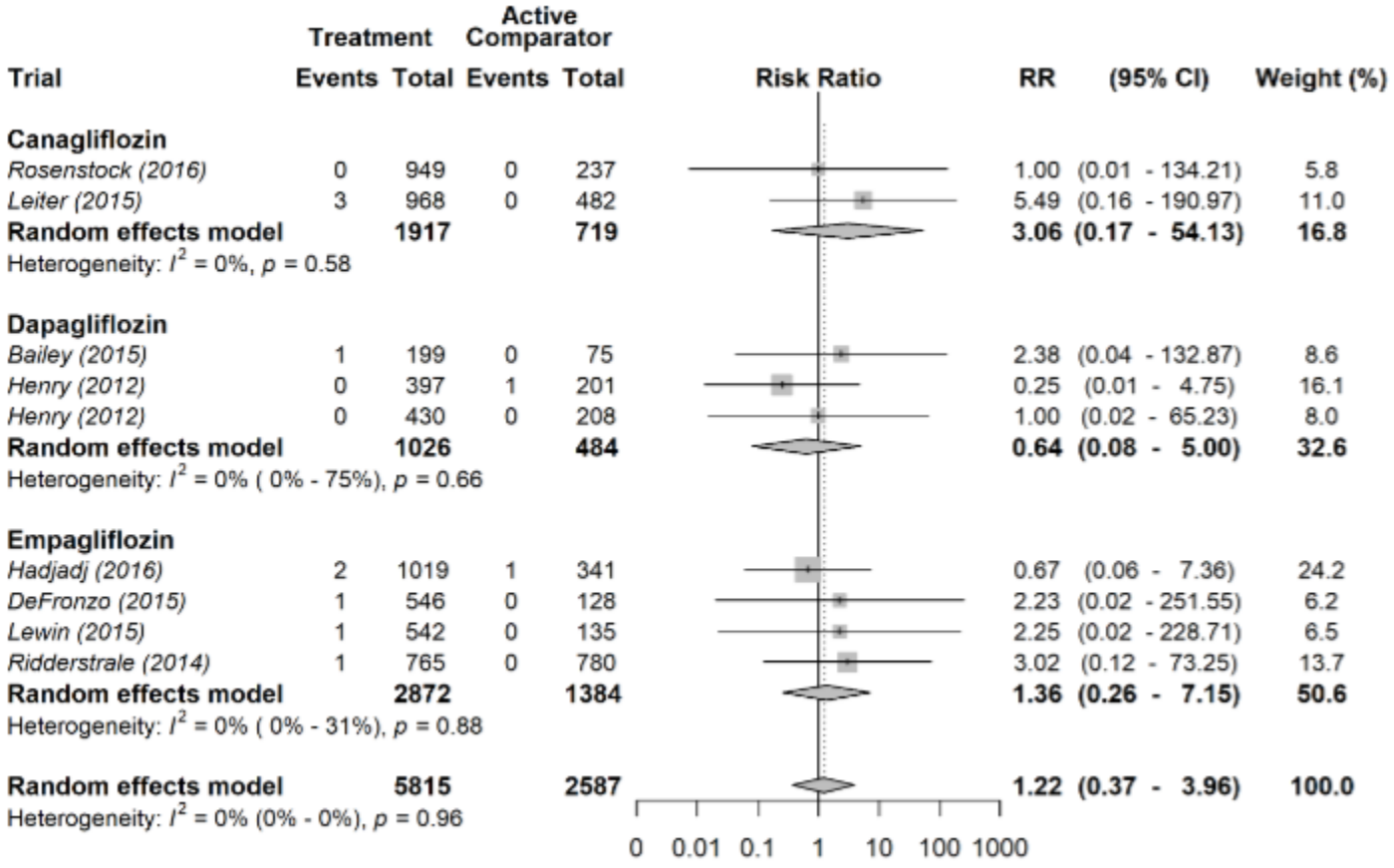
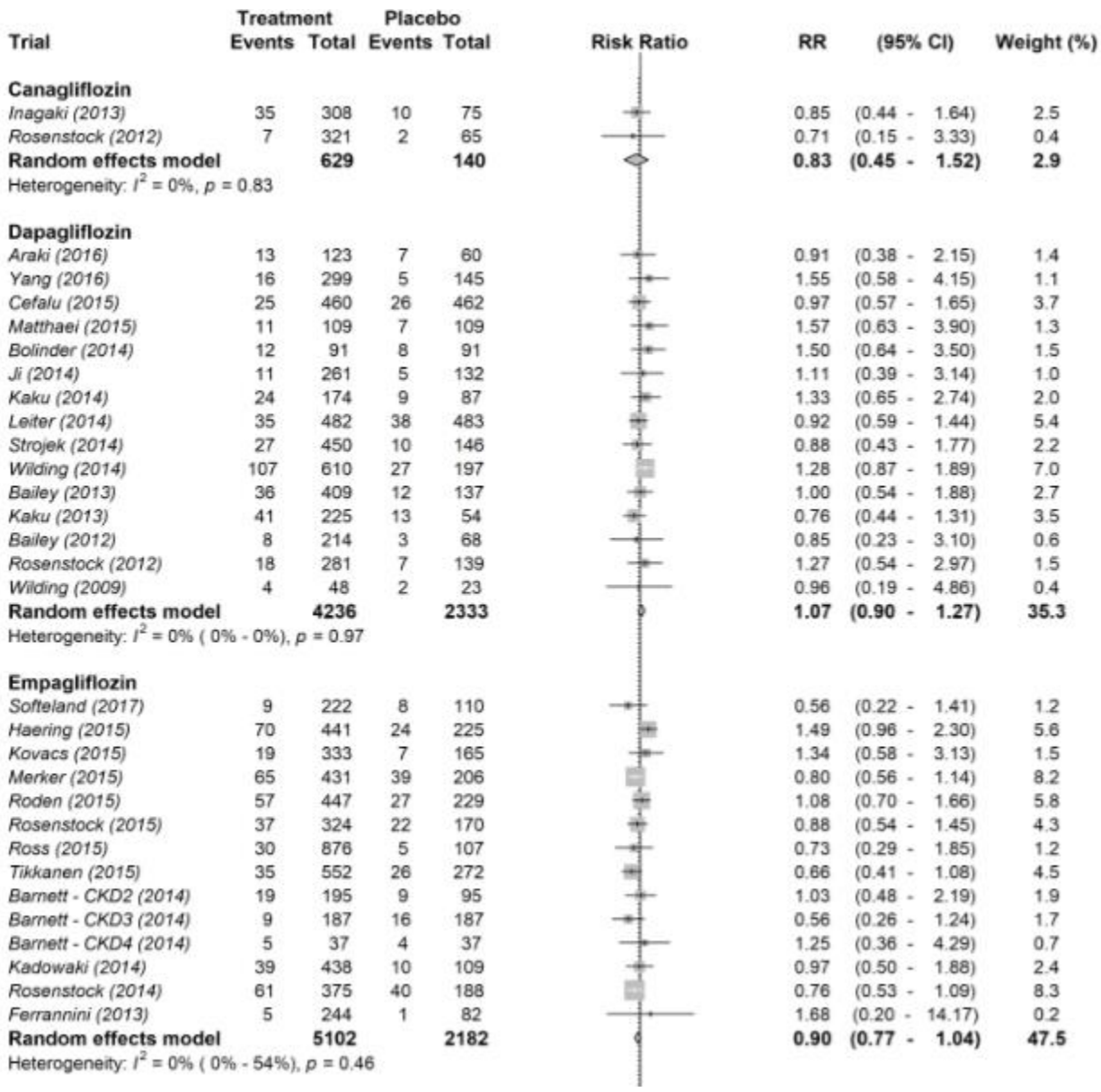


Figure S9: Meta-analysis for nasopharyngitis, SGLT-2 inhibitors versus placebo



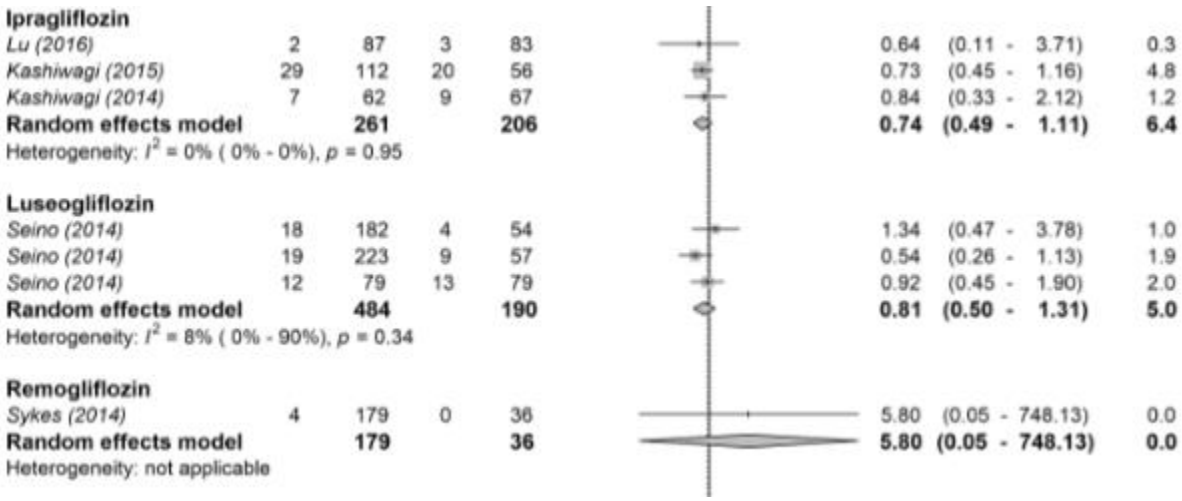

Ipragliflozin
Lu (2016) 2 87 3 83 0.64 (0.11 - 3.71) 0.3
Kashiwagi (2015) 29 112 20 56 0.73 (0.45 - 1.16) 4.8
Kashiwagi (2014) 7 62 9 67 0.84 (0.33 - 2.12) 1.2
Random effects model 261 206 0.74 (0.49 - 1.11) 6.4
Heterogeneity: I^2 = 0% (0% - 0%), p = 0.95
Luseogliflozin
Seino (2014) 18 182 4 54 1.34 (0.47 - 3.78) 1.0
Seino (2014) 19 223 9 57 0.54 (0.26 - 1.13) 1.9
Seino (2014) 12 79 13 79 0.92 (0.45 - 1.90) 2.0
Random effects model 484 190 0.81 (0.50 - 1.31) 5.0
Heterogeneity: I^2 = 8% (0% - 90%), p = 0.34
Remogliflozin
Sykes (2014) 4 179 0 36 5.80 (0.05 - 748.13) 0.0
Random effects model 179 36 5.80 (0.05 - 748.13) 0.0
Heterogeneity: not applicable

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

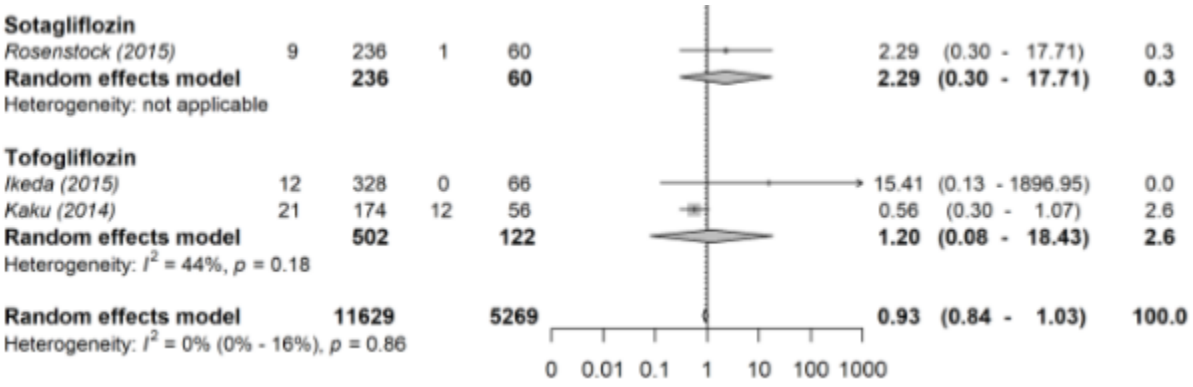


Figure S10: Meta-analysis for nasopharyngitis, SGLT-2 inhibitors versus active comparators

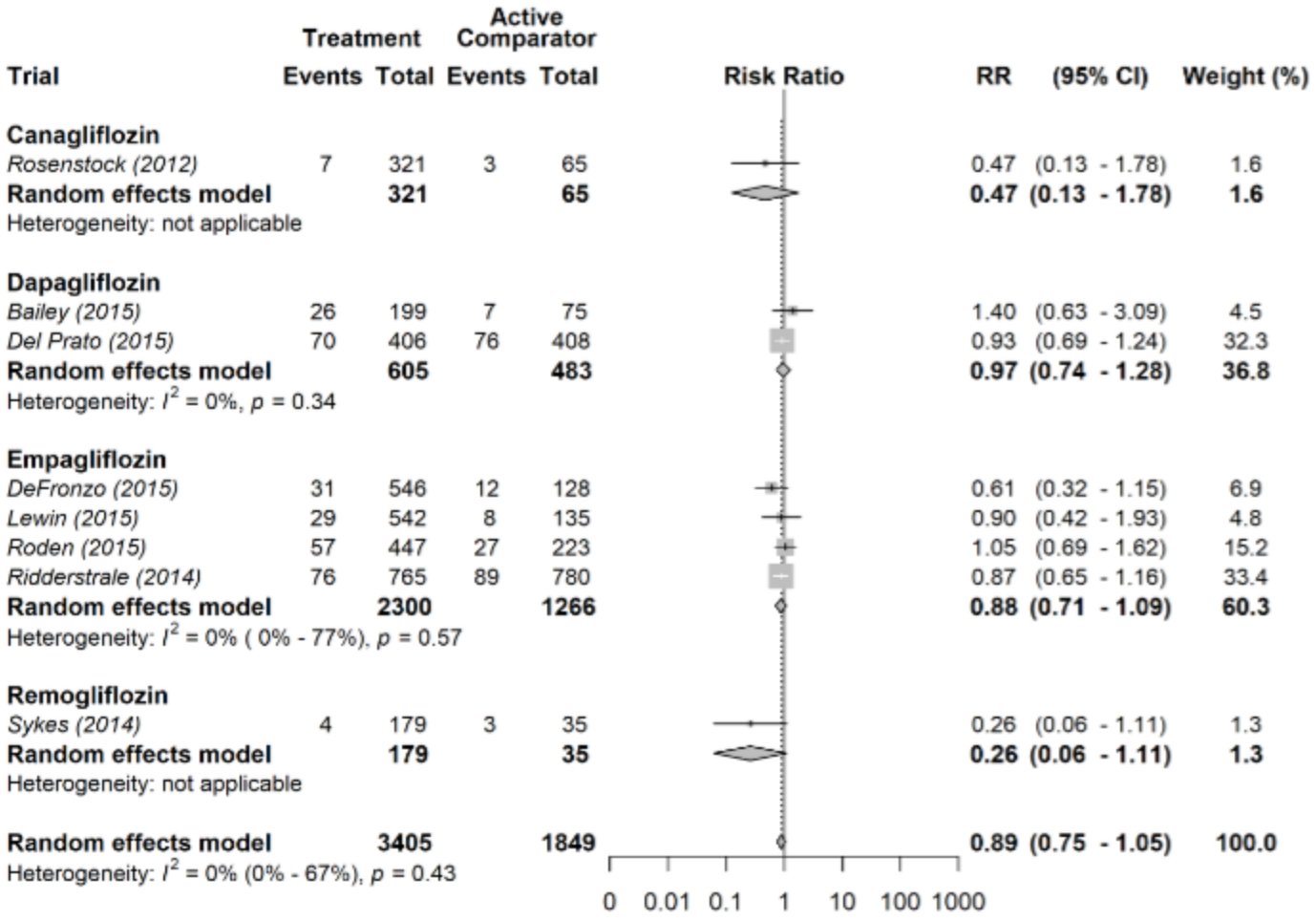


Figure S11: Meta-analysis for pharyngitis, SGLT-2 inhibitors versus placebo

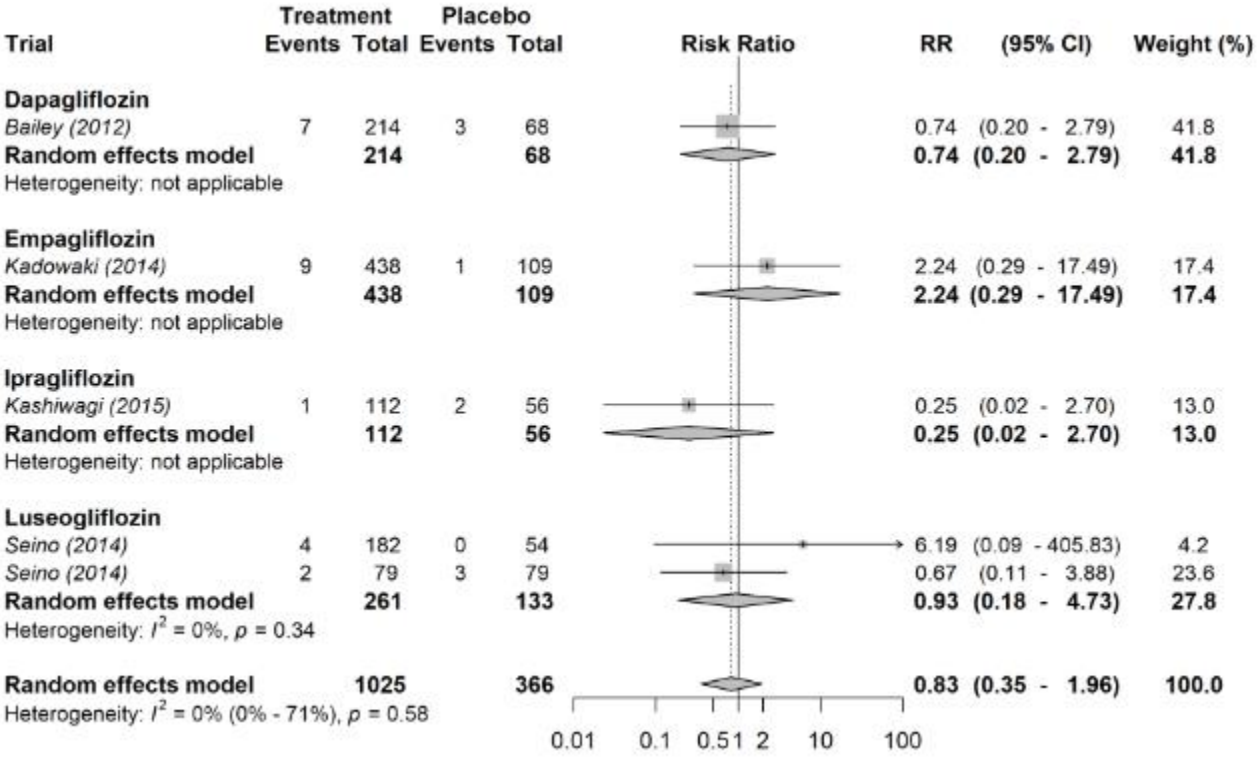


Figure S12: Meta-analysis for upper respiratory tract infection, SGLT-2 inhibitors versus placebo

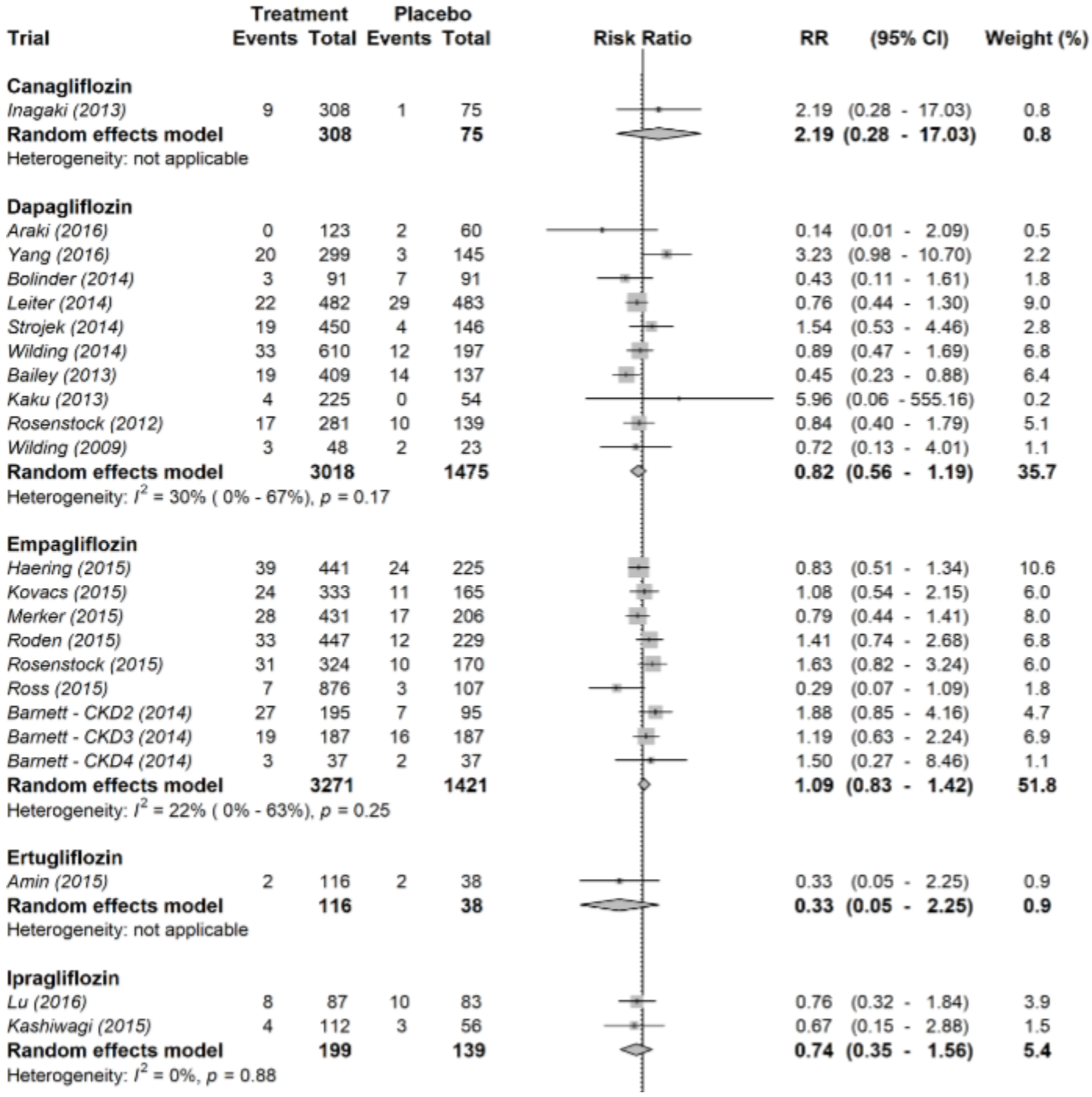


Figure S12 (Continued): Meta-analysis for upper respiratory tract infection, SGLT-2 inhibitors versus placebo

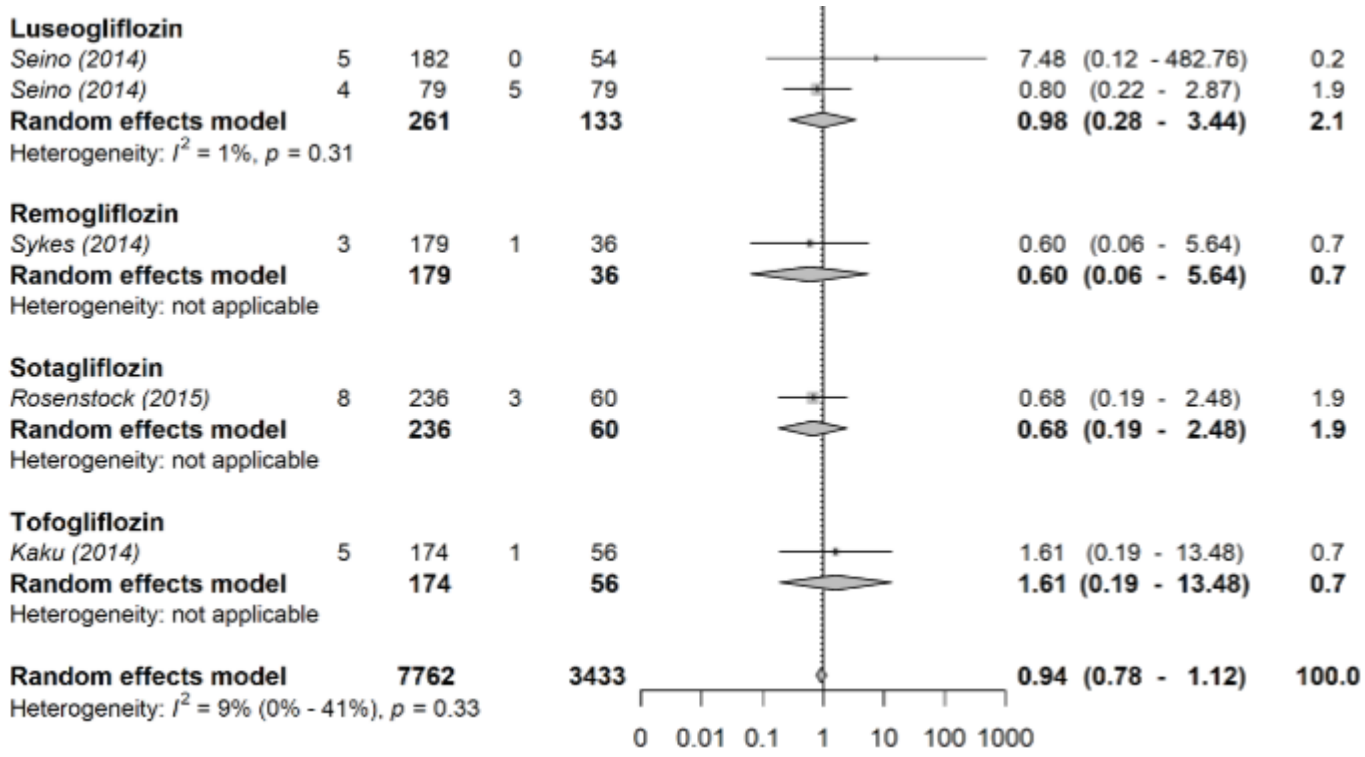


Figure S13: Meta-analysis for upper respiratory tract infection, SGLT-2 inhibitors versus active comparators

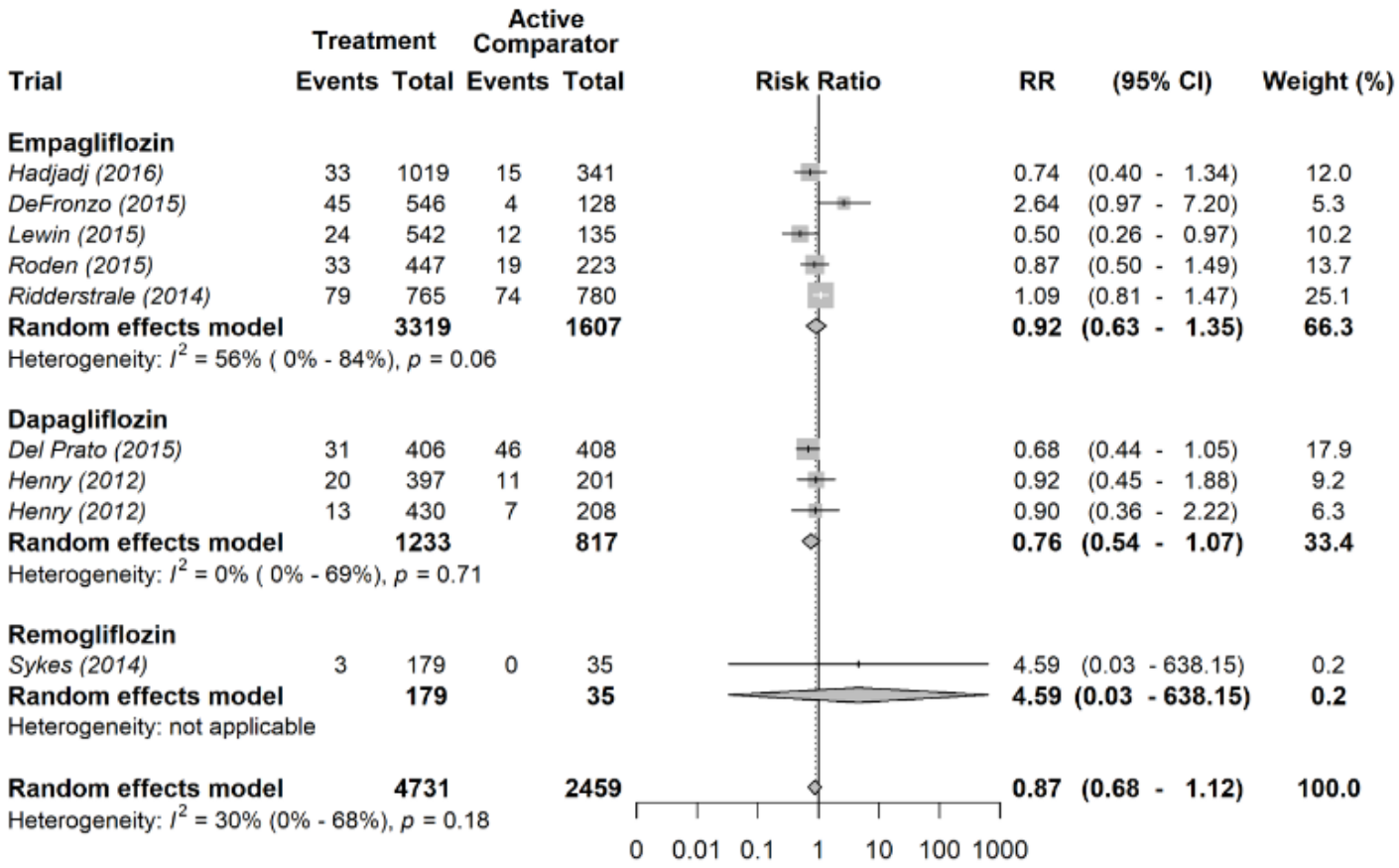


Figure S14: Meta-analysis for influenza, SGLT-2 inhibitors versus placebo

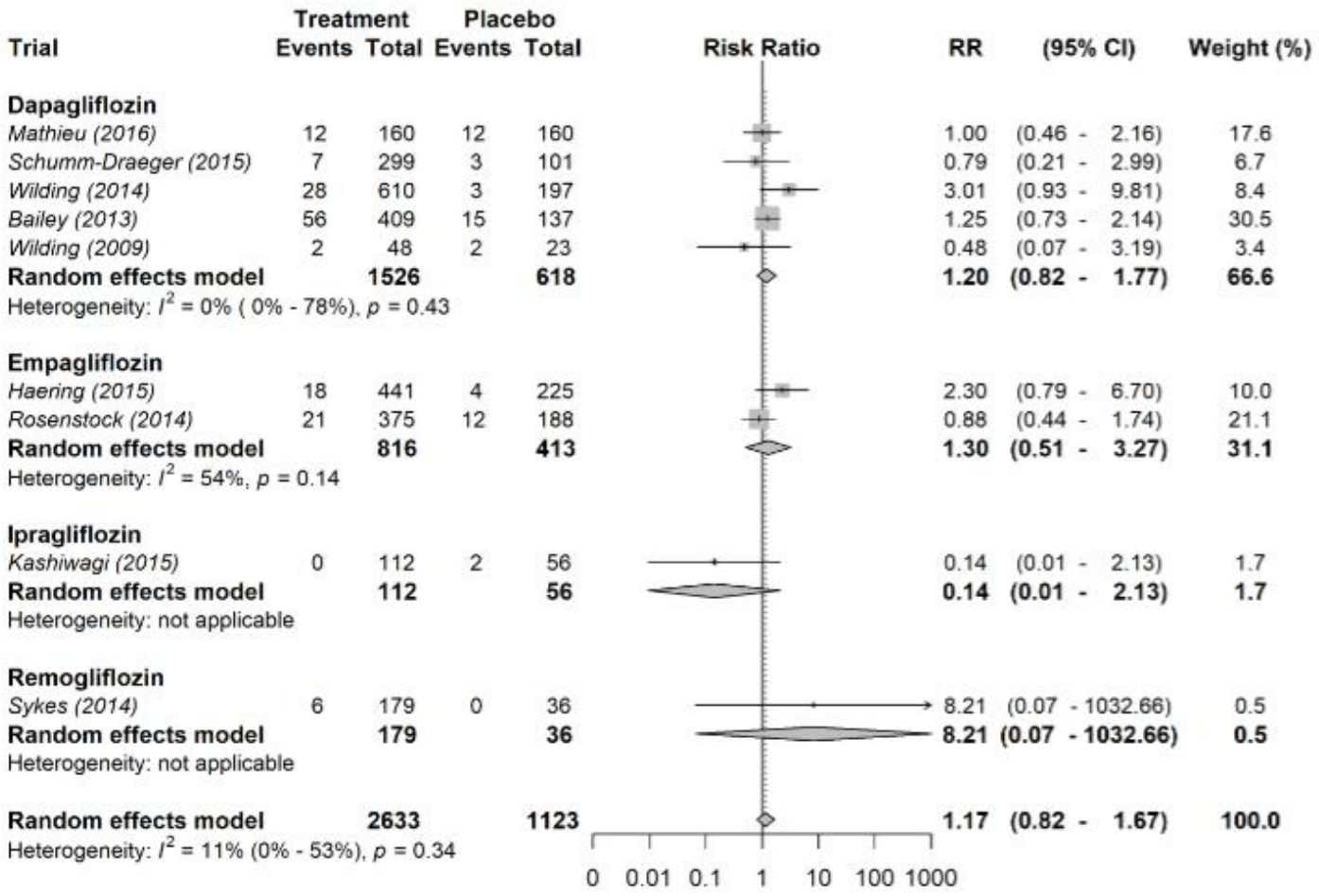


Figure S15: Meta-analysis for influenza, SGLT-2 inhibitors versus active comparators

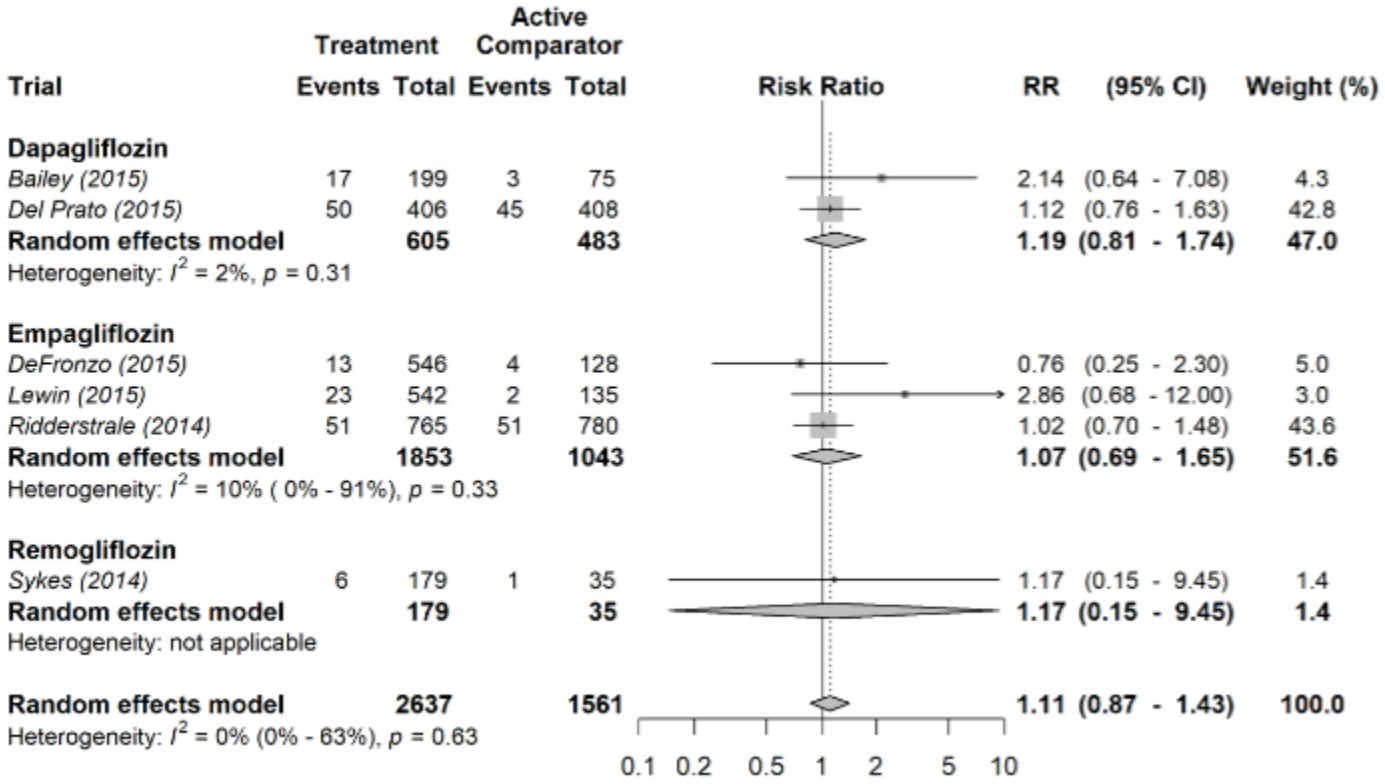


Figure S16: Meta-analysis for bronchitis, SGLT-2 inhibitors versus placebo

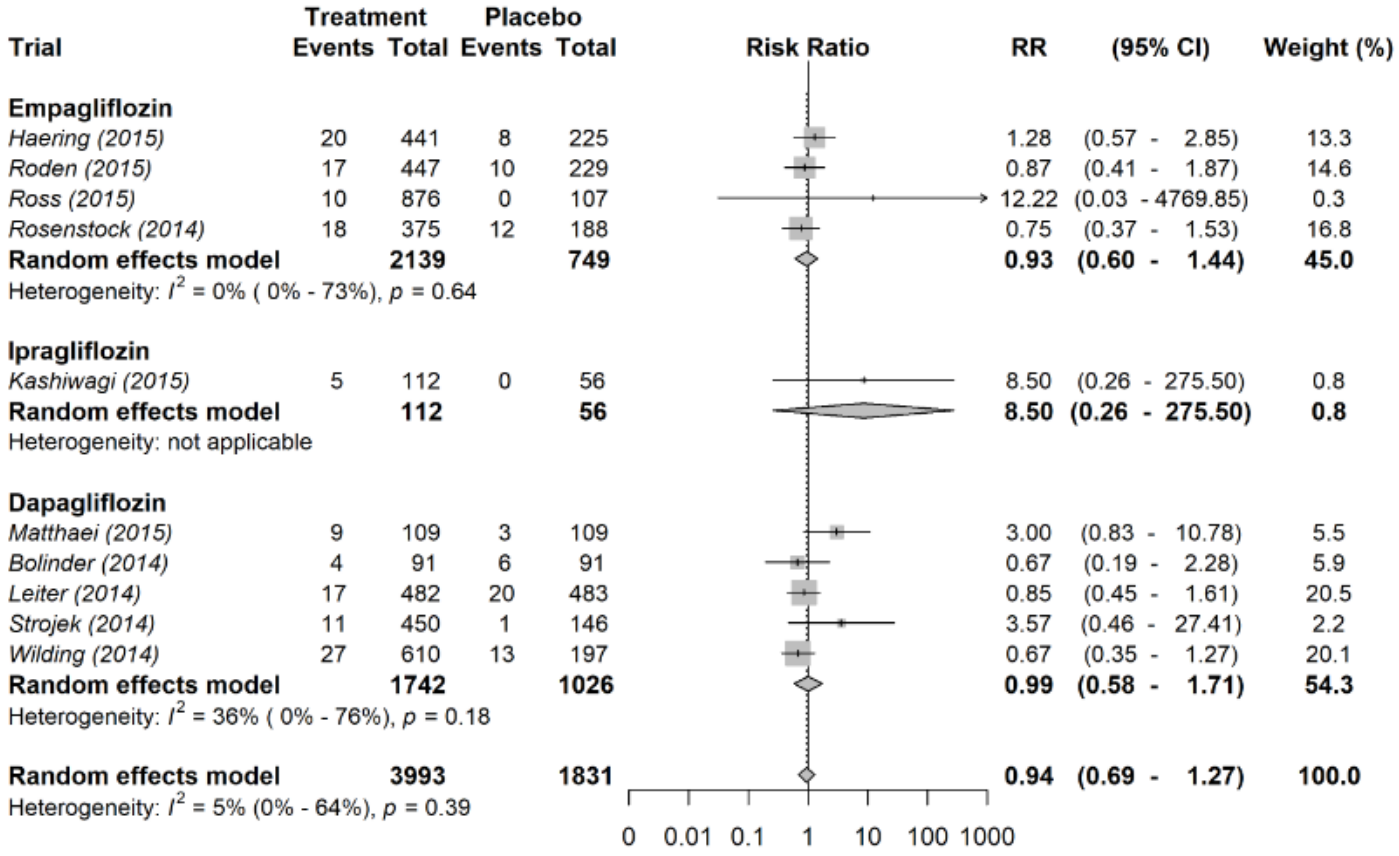


Figure S17: Meta-analysis for bronchitis, SGLT-2 inhibitors versus active comparators

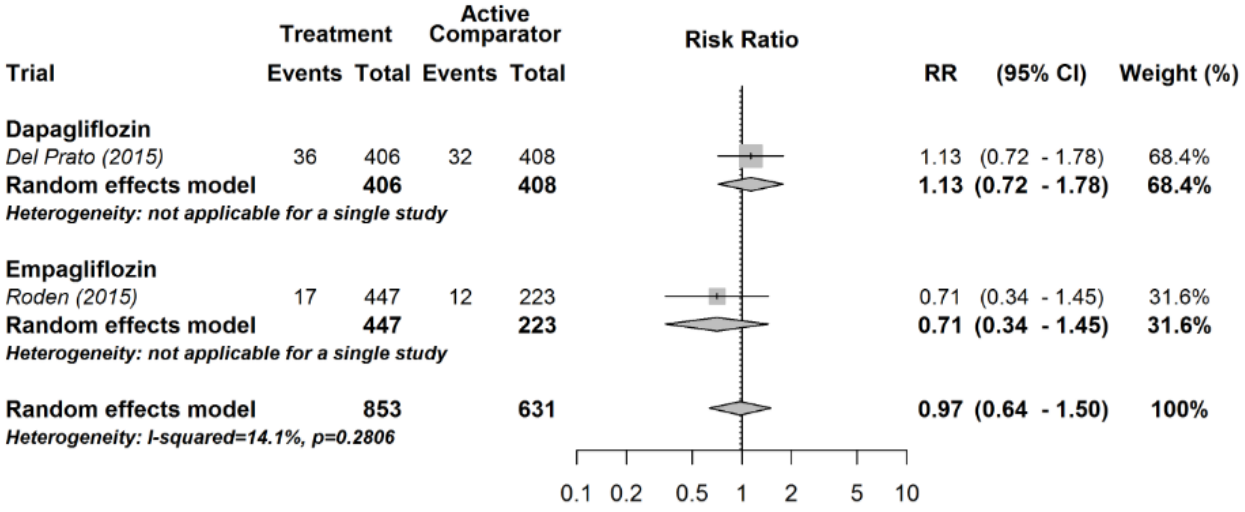


Figure S18: Meta-analysis for gastroenteritis, SGLT-2 inhibitors versus placebo

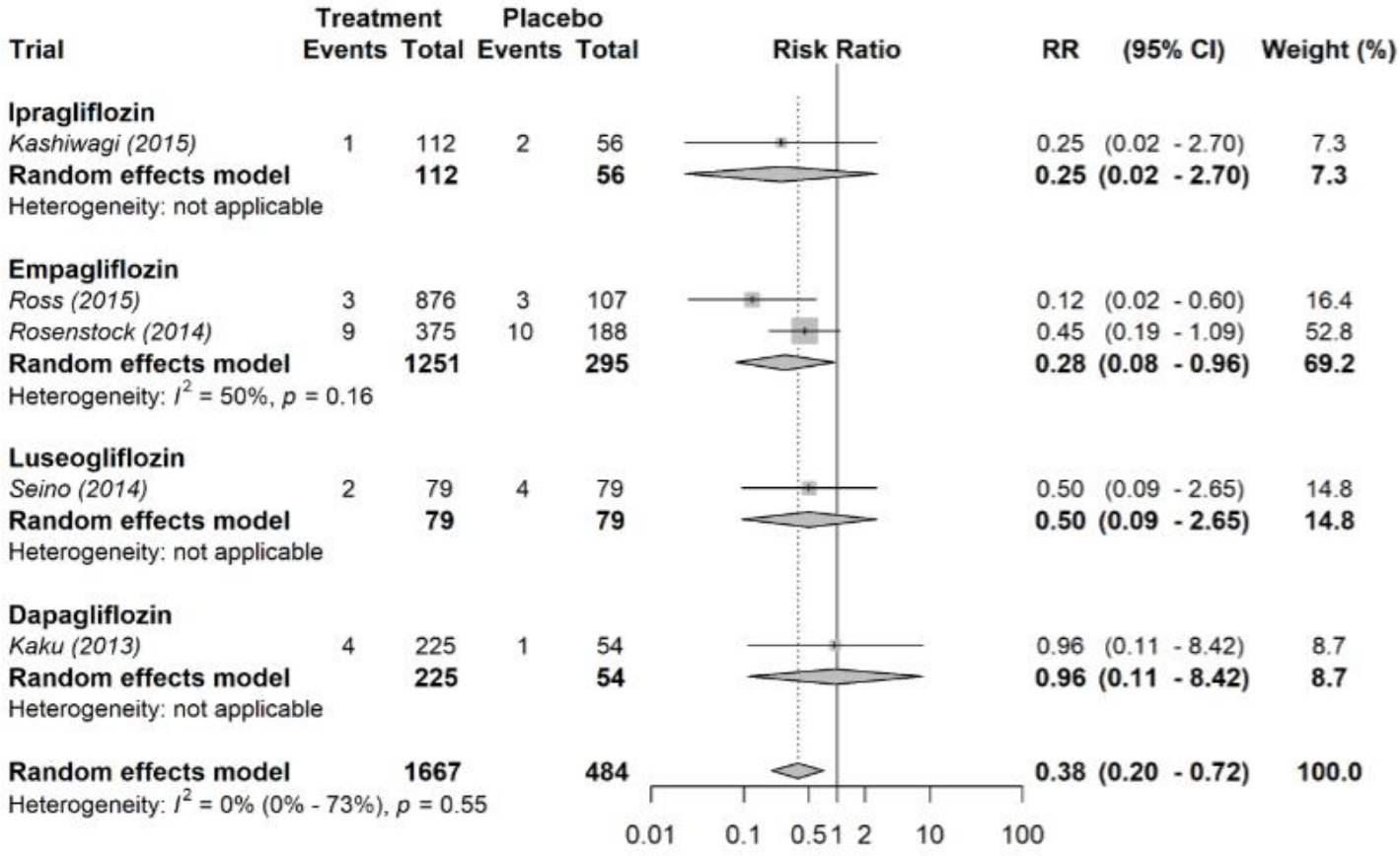


Figure S19: Meta-analysis for gastroenteritis, SGLT-2 inhibitors versus active comparators

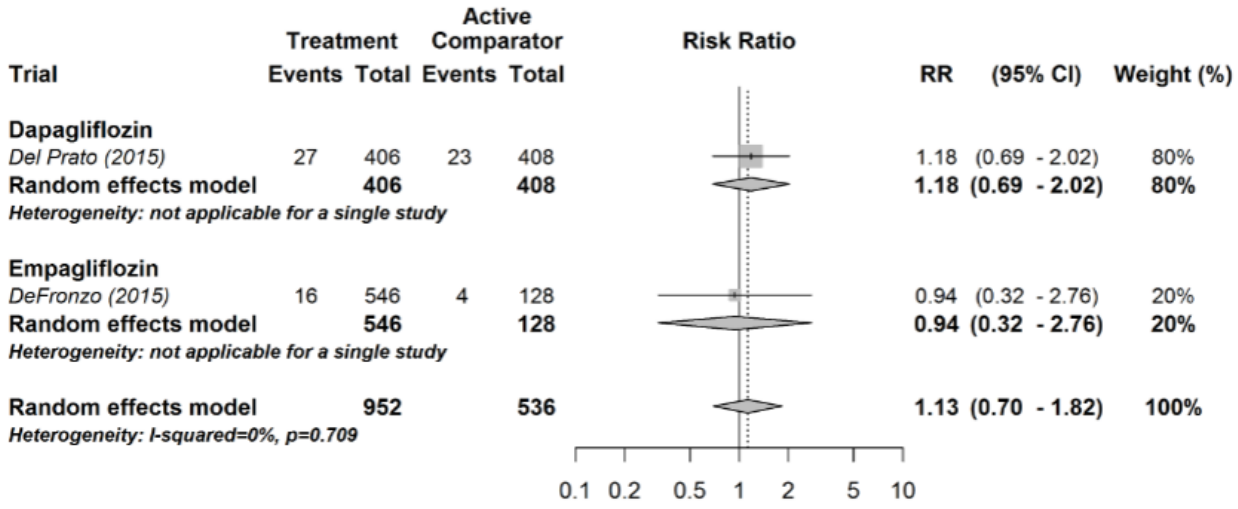


Figure S20: Sensitivity analyses of urinary tract infection stratified by study quality, SGLT-2 inhibitors versus placebo

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

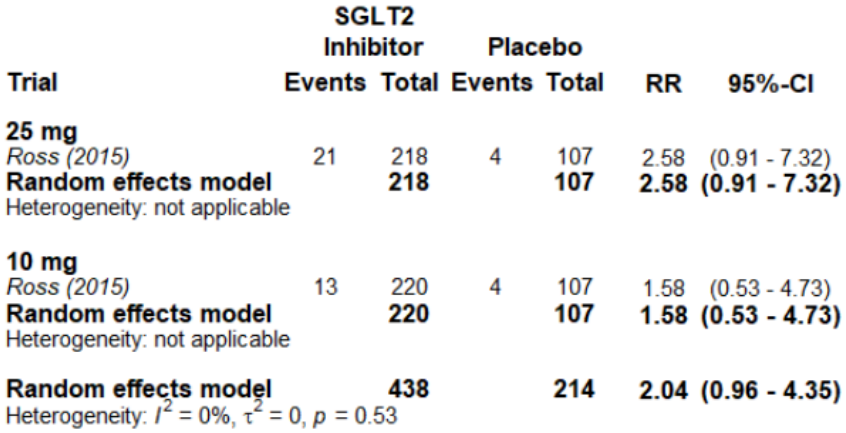
Canagliflozin

Trial	SGLT2 Inhibitor Events	Total	Placebo 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 = 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						
Random effects model		**633**		**626**	**1.06**	**(0.66 - 1.69)**
Heterogeneity: I^2 = 0% (0% - 33%), τ^2 = 0, p = 0.87						

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

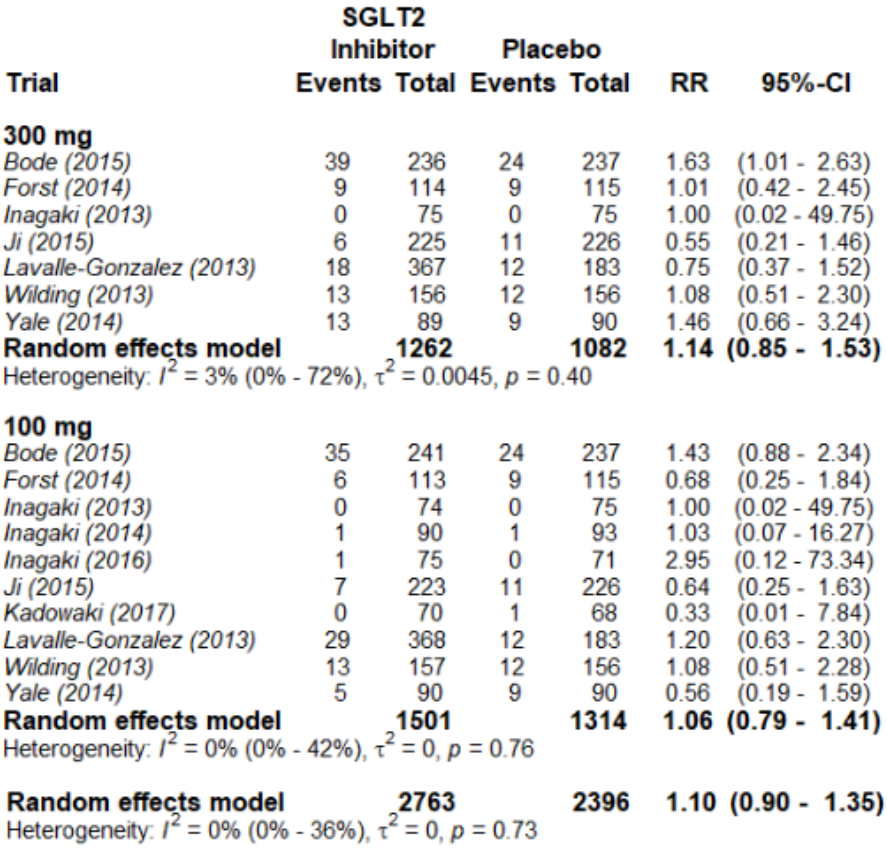
Trial	SGLT2 Inhibitor Events	Total	Placebo Events	Total	RR	95%-CI
10 mg						
Jabbour (2014)	15	225	14	226	1.08	(0.53 - 2.18)
Kaku (2014)	2	88	2	87	0.99	(0.14 - 6.86)
Kohan (2014)	12	85	12	84	0.99	(0.47 - 2.07)
List (2009)	5	47	3	54	1.91	(0.48 - 7.59)
Rosenstock (2012)	7	140	11	139	0.63	(0.25 - 1.58)
Wilding (2009)	0	24	0	23	1.00	(0.02 - 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 - 147.52)
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% - 60%), τ^2 = 0, p = 0.72						
Random effects model		**1100**		**1037**	**1.01**	**(0.73 - 1.38)**
Heterogeneity: I^2 = 0% (0% - 0%), τ^2 = 0, p = 0.95						

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



Trial	SGLT2 Inhibitor Events	Total	Placebo Events	Total	RR	95%-CI
25 mg						
Ross (2015)	21	218	4	107	2.58	(0.91 - 7.32)
Random effects model		**218**		**107**	**2.58**	**(0.91 - 7.32)**
Heterogeneity: not applicable						
10 mg						
Ross (2015)	13	220	4	107	1.58	(0.53 - 4.73)
Random effects model		**220**		**107**	**1.58**	**(0.53 - 4.73)**
Heterogeneity: not applicable						
Random effects model		**438**		**214**	**2.04**	**(0.96 - 4.35)**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.53						

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



Trial	SGLT2 Inhibitor Events	Total	Placebo 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 = 0.0045, 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		**1501**		**1314**	**1.06**	**(0.79 - 1.41)**
Heterogeneity: I^2 = 0% (0% - 42%), τ^2 = 0, p = 0.76						
Random effects model		**2763**		**2396**	**1.10**	**(0.90 - 1.35)**
Heterogeneity: I^2 = 0% (0% - 36%), τ^2 = 0, p = 0.73						

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

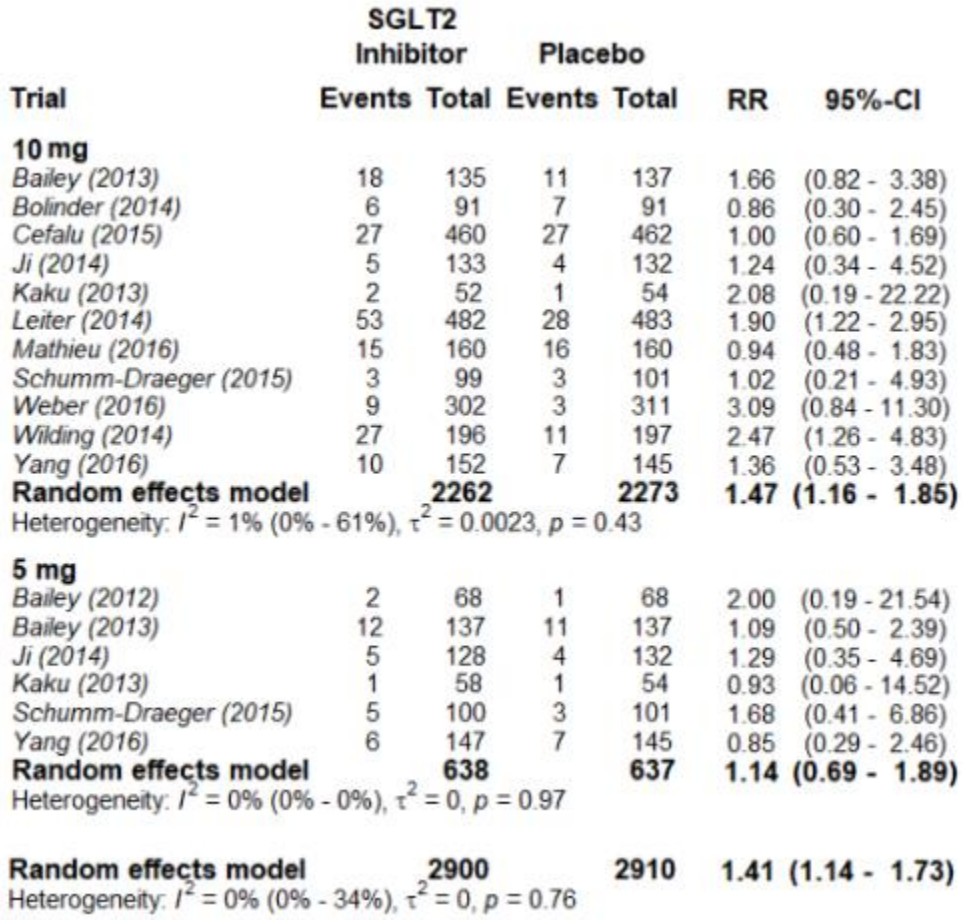


Figure S20f: Risk of UTI in studies of empagliflozin at medium risk of bias

Trial	SGLT2 Inhibitor Events	Total	Placebo 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						
Ferrannini (2013)	1	81	1	82	1.01	(0.06 - 15.91)
Haering (2015)	38	224	36	225	1.06	(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% - 6%), τ^2 = 0, p = 0.94						
Random effects model		**3647**		**3654**	**0.97**	**(0.86 - 1.11)**
Heterogeneity: I^2 = 0% (0% - 0%), τ^2 = 0, p = 0.98						

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

Trial	SGLT2 Inhibitor Events	Total	Placebo Events	Total	RR	95%-CI
300 mg						
Neal (2015)	42	690	36	690	1.17	(0.76 - 1.80)
Random effects model		**690**		**690**	**1.17**	**(0.76 - 1.80)**
Heterogeneity: not applicable						
100 mg						
Neal (2015)	36	692	36	690	1.00	(0.64 - 1.56)
Random effects model		**692**		**690**	**1.00**	**(0.64 - 1.56)**
Heterogeneity: not applicable						
Random effects model		**1382**		**1380**	**1.08**	**(0.79 - 1.48)**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.62						

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

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

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

Trial	SGLT2 Inhibitor Events	Total	Placebo 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, p = 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%, τ^2 = 0, p = 0.77						
Random effects model		**5106**		**5080**	**0.99**	**(0.91 - 1.08)**
Heterogeneity: I^2 = 0% (0% - 66%), τ^2 = 0, p = 0.59						

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

Trial	SGLT2 Inhibitor Events	SGLT2 Inhibitor Total	Placebo Events	Placebo Total	RR	95%-CI
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% - 59%), τ^2 = 0, p = 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		**633**		**626**	**3.23**	**(1.75 - 5.97)**
Heterogeneity: I^2 = 0% (0% - 0%), τ^2 = 0, p = 0.97						

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

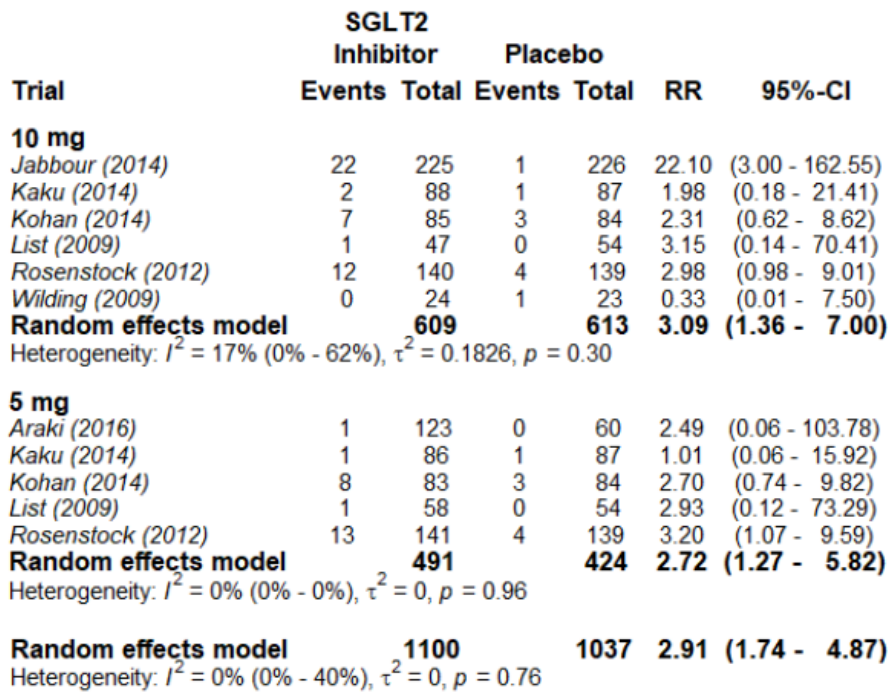


Figure S21c: Risk of genital tract infection in studies of empagliflozin at high risk of bias

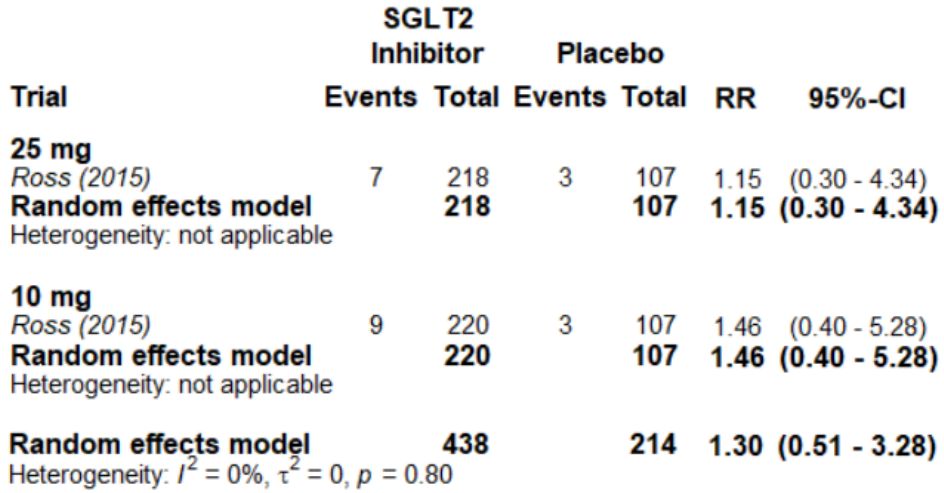


Figure S21d: Risk of genital tract infection in studies of canagliflozin at medium risk of bias

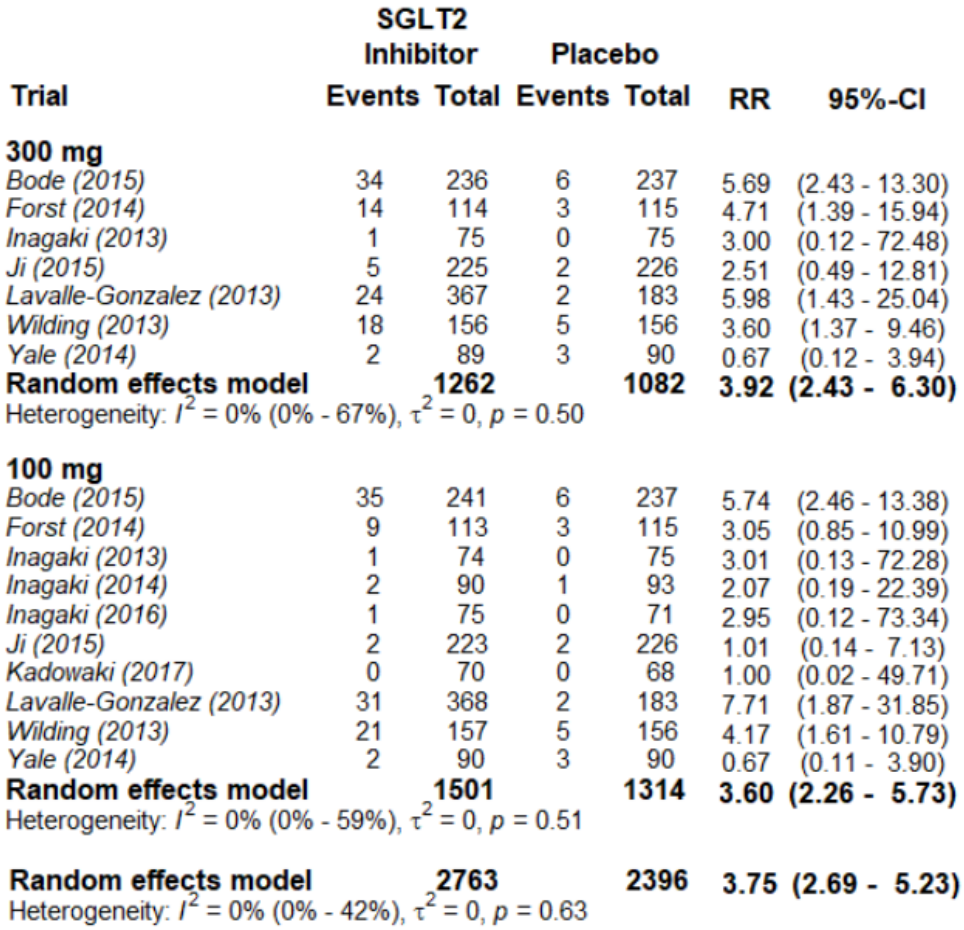


Figure S21e: Risk of genital tract infection in studies of dapagliflozin at medium risk of bias

Trial	SGLT2 Inhibitor Events	Total	Placebo 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% (0% - 56%), τ^2 = 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%), τ^2 = 0, p = 0.58						

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

Trial	SGLT2 Inhibitor Events	Total	Placebo 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% - 60%), τ^2 = 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% - 44%), τ^2 = 0, p = 0.71						
Random effects model		**3647**		**3654**	**3.95**	**(2.83 - 5.50)**
Heterogeneity: I^2 = 0% (0% - 34%), τ^2 = 0, p = 0.71						

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

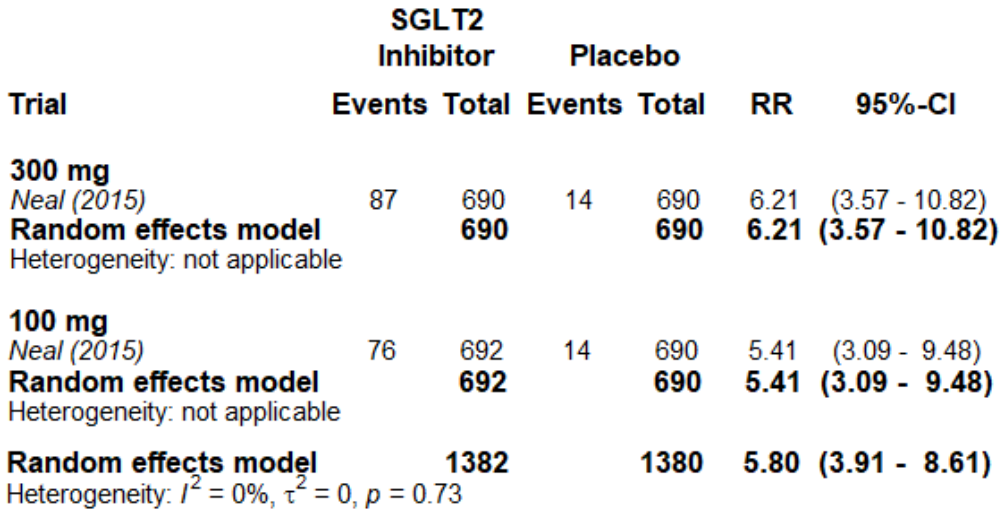


Figure S21h: Risk of genital tract infection in studies of dapagliflozin at low risk of bias

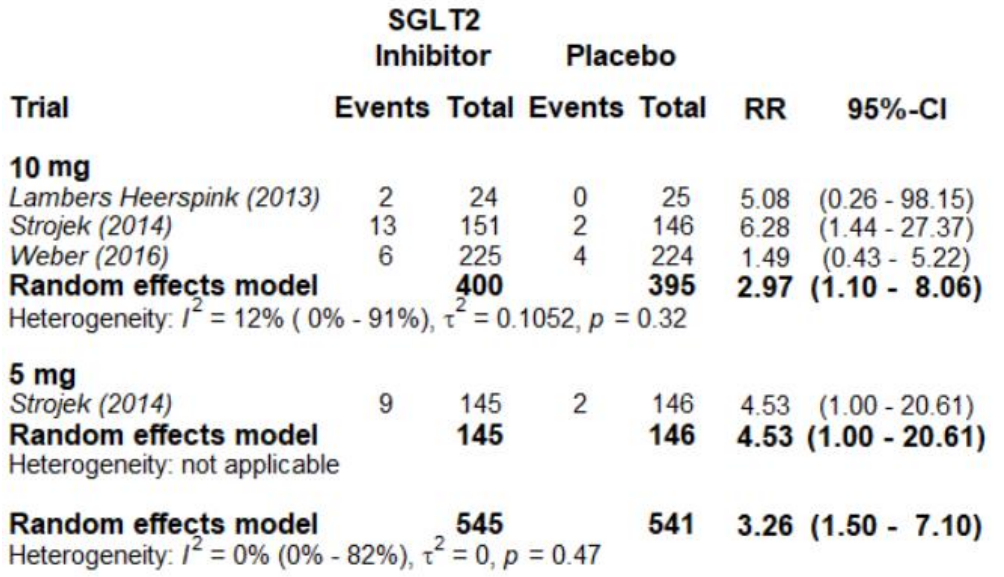


Figure S21i: Risk of genital tract infection in studies of empagliflozin at low risk of bias

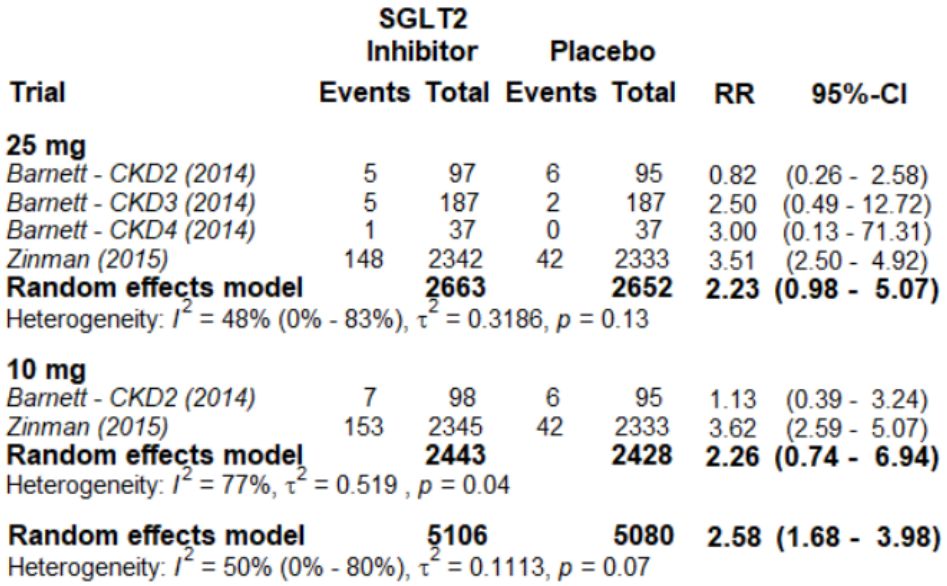


Figure S22: Risk of genital tract infection with exclusion of RCTs with zero events in the treatment and control arms, SGLT-2 inhibitors versus placebo

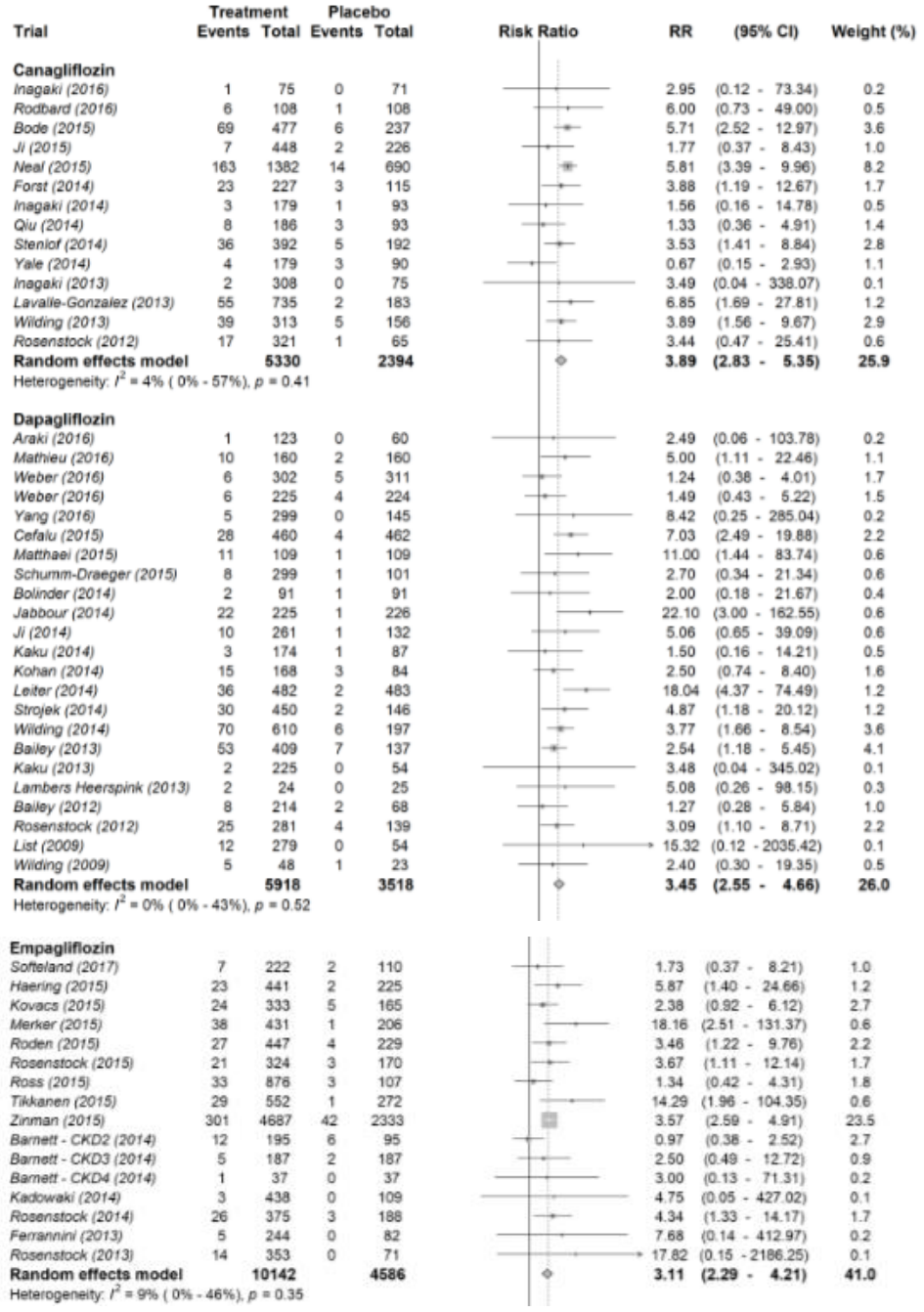


Figure S22 (continued): Risk of genital tract infection with exclusion of RCTs with zero events in the treatment and control arms, SGLT-2 inhibitors versus placebo

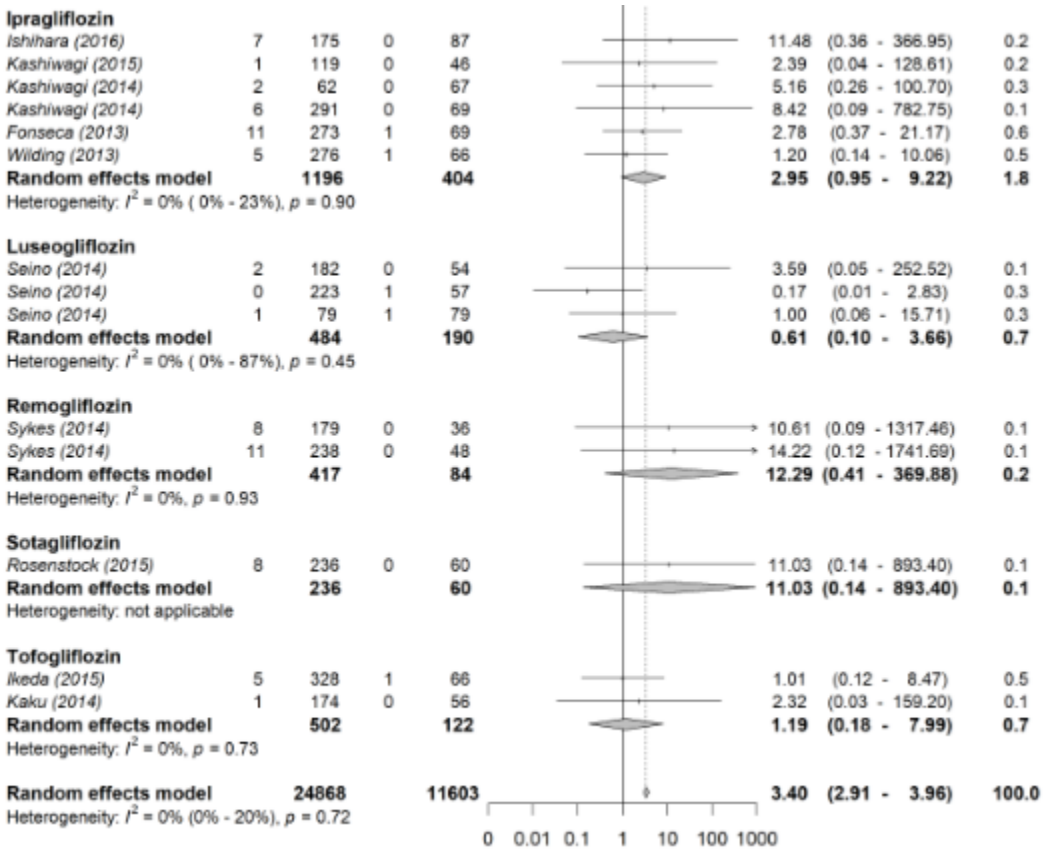


Figure S23: Risk of urinary tract infection with exclusion of RCTs with zero events in the treatment and control arms, SGLT-2 inhibitors versus placebo

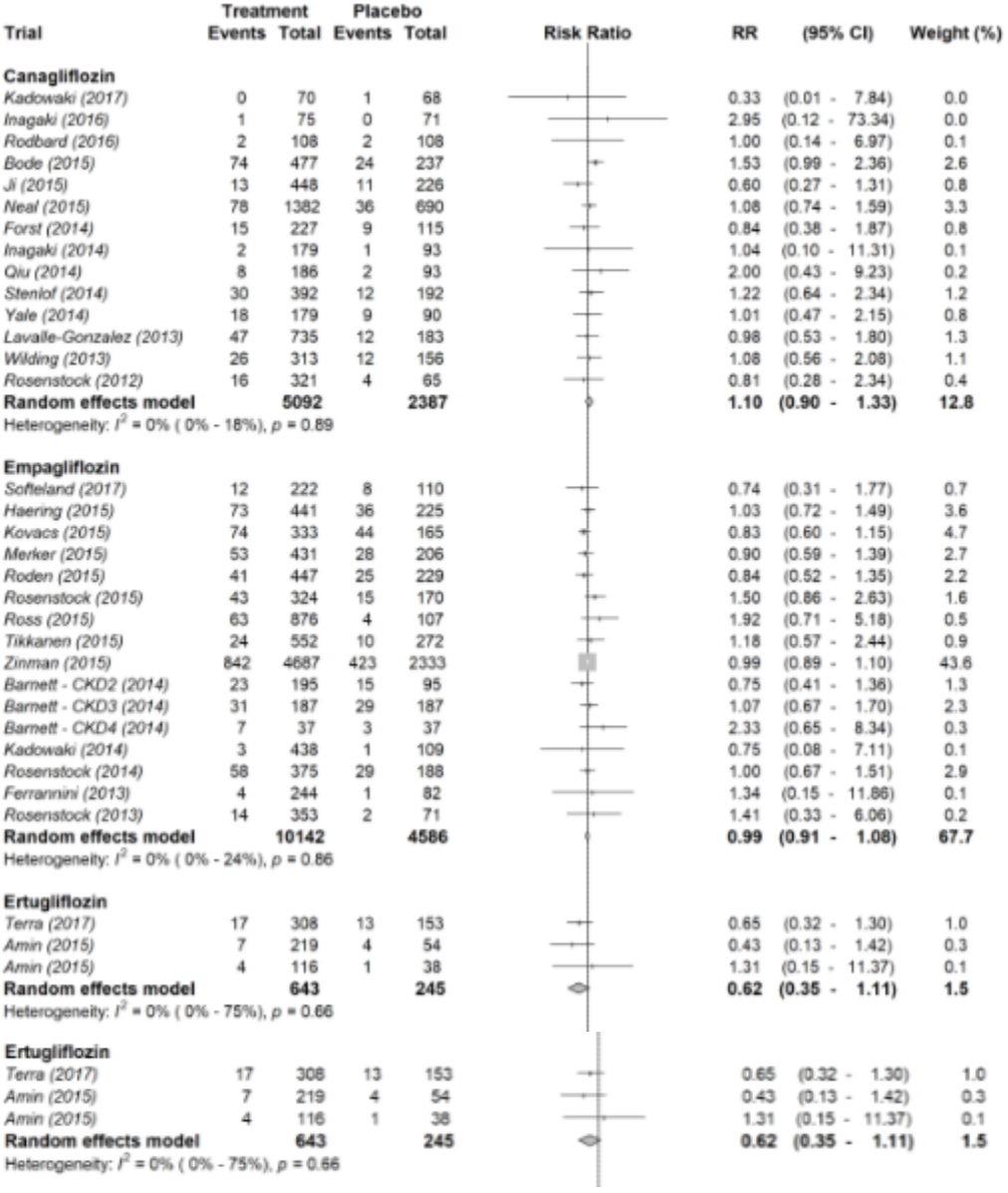


Figure S23 (continued): Risk of urinary tract infection with exclusion of RCTs with zero events in the treatment and control arms, SGLT-2 inhibitors versus placebo

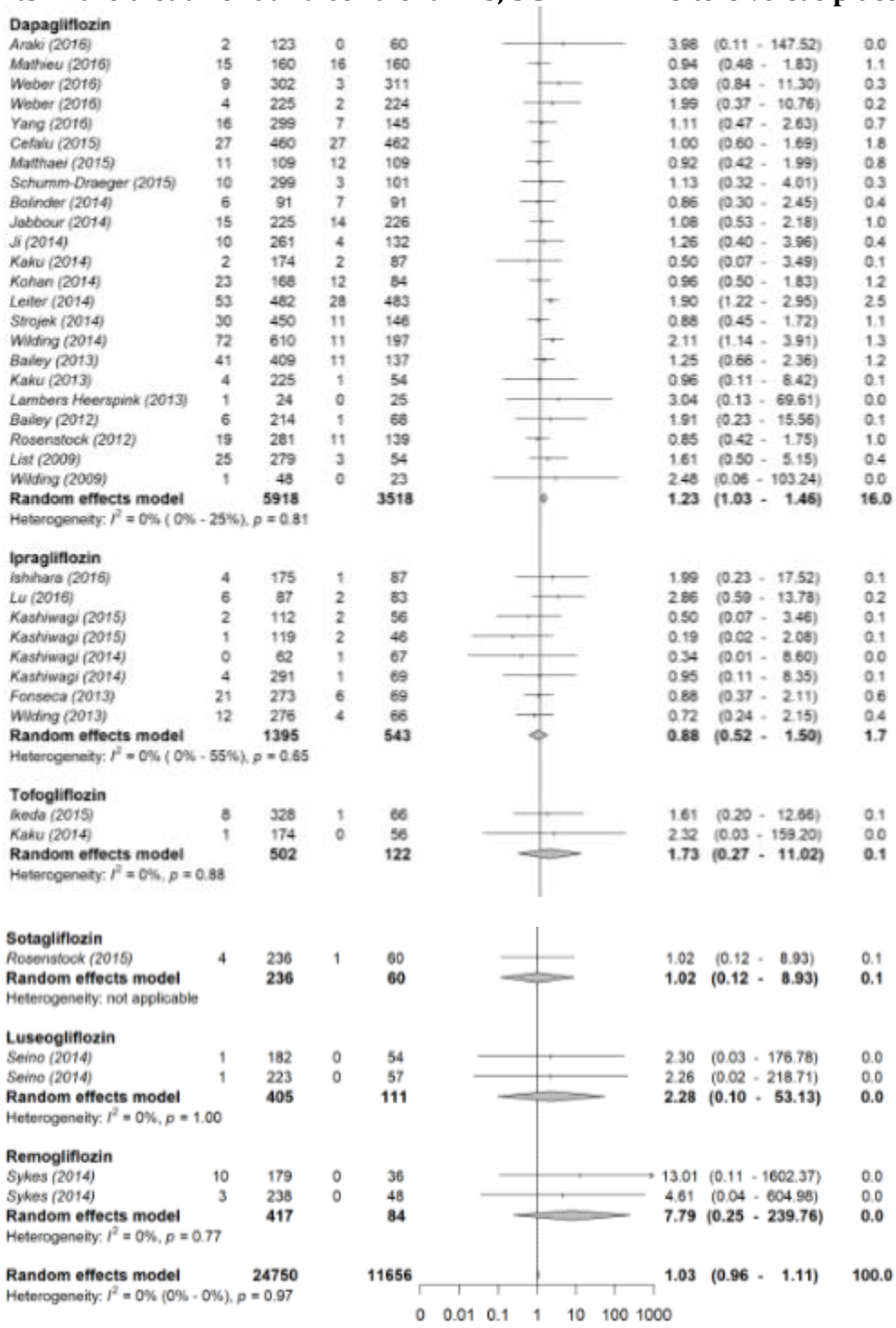


Figure S24: Risk of urinary tract infection stratified by study duration, canagliflozin versus placebo

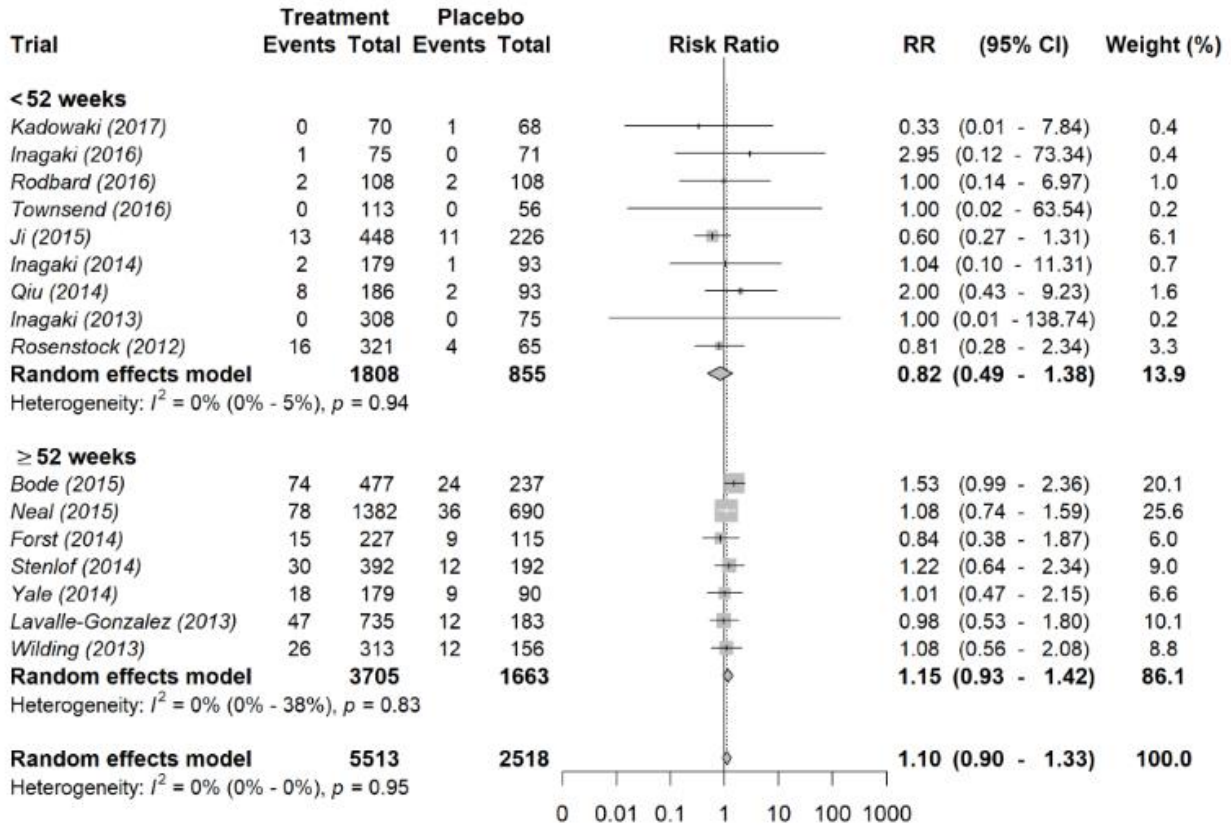


Figure S25: Risk of urinary tract infection stratified by study duration, dapagliflozin versus placebo

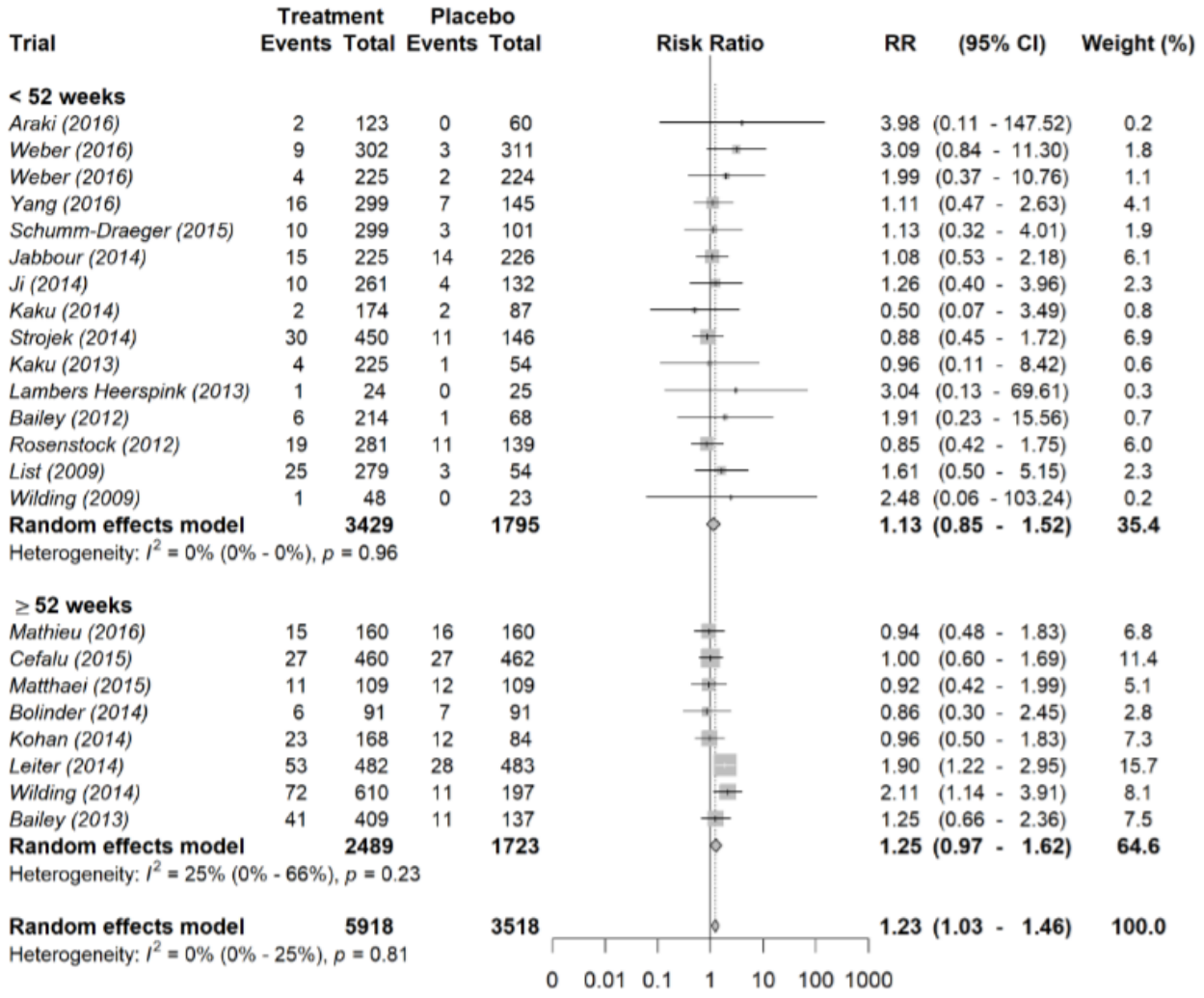


Figure S26: Risk of urinary tract infection stratified by study duration, empagliflozin versus placebo

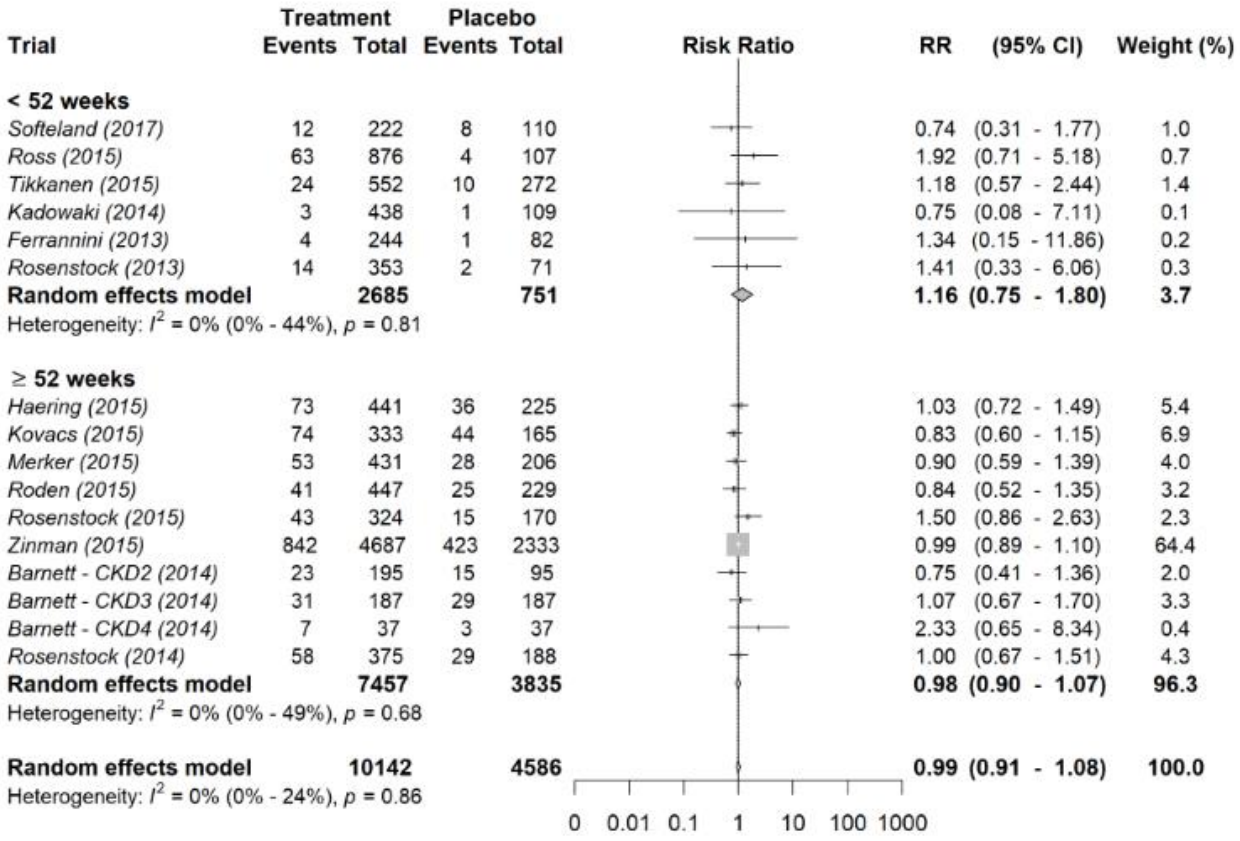


Figure S27: Risk of urinary tract infection with exclusion of RCTs that precluded patients with history of genitourinary infection from study enrolment, SGLT-2 inhibitors versus placebo

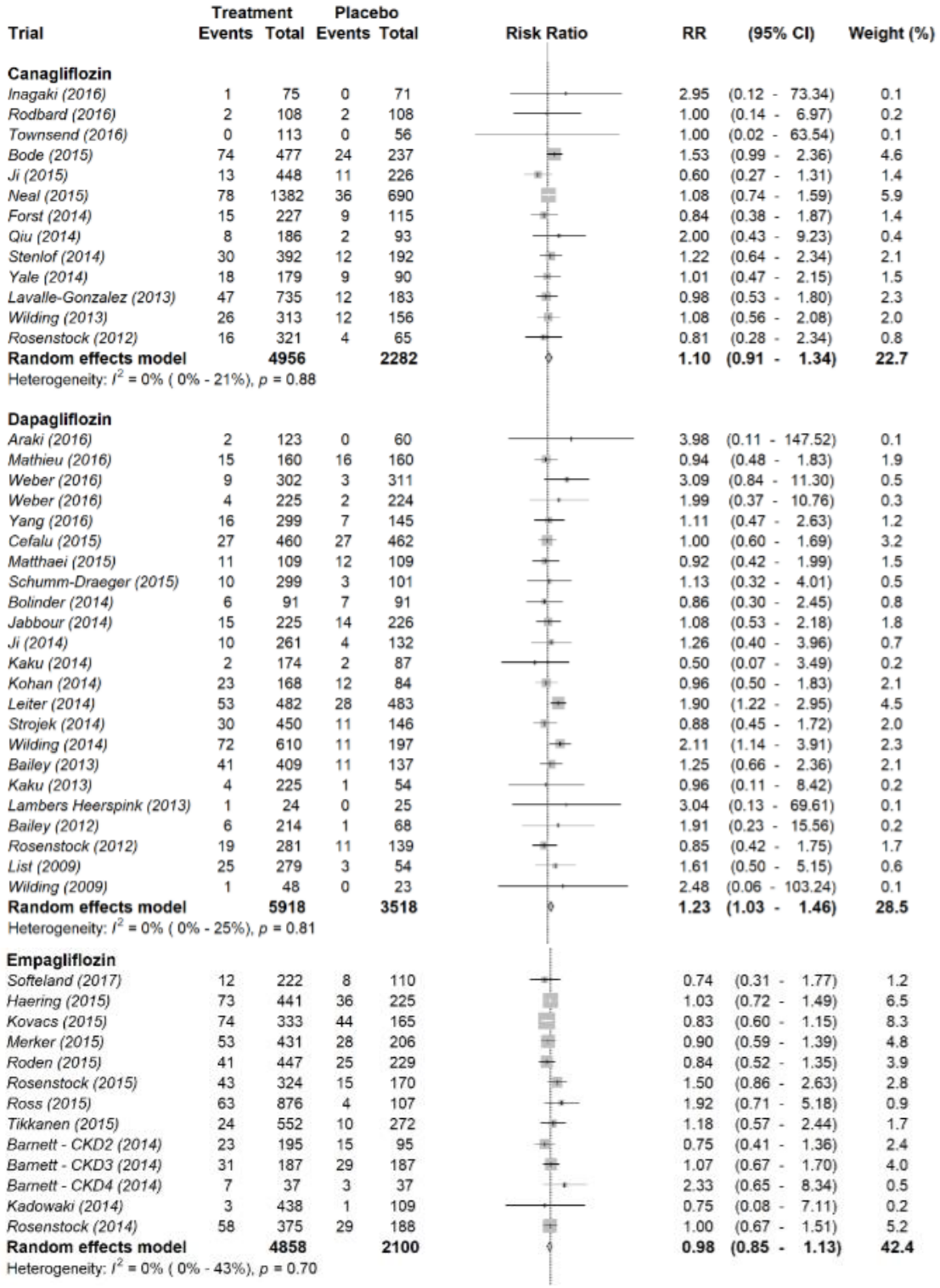


Figure S27 (continued): Risk of urinary tract infection with exclusion of RCTs that precluded patients with history of genitourinary infection from study enrolment, SGLT-2 inhibitors versus placebo

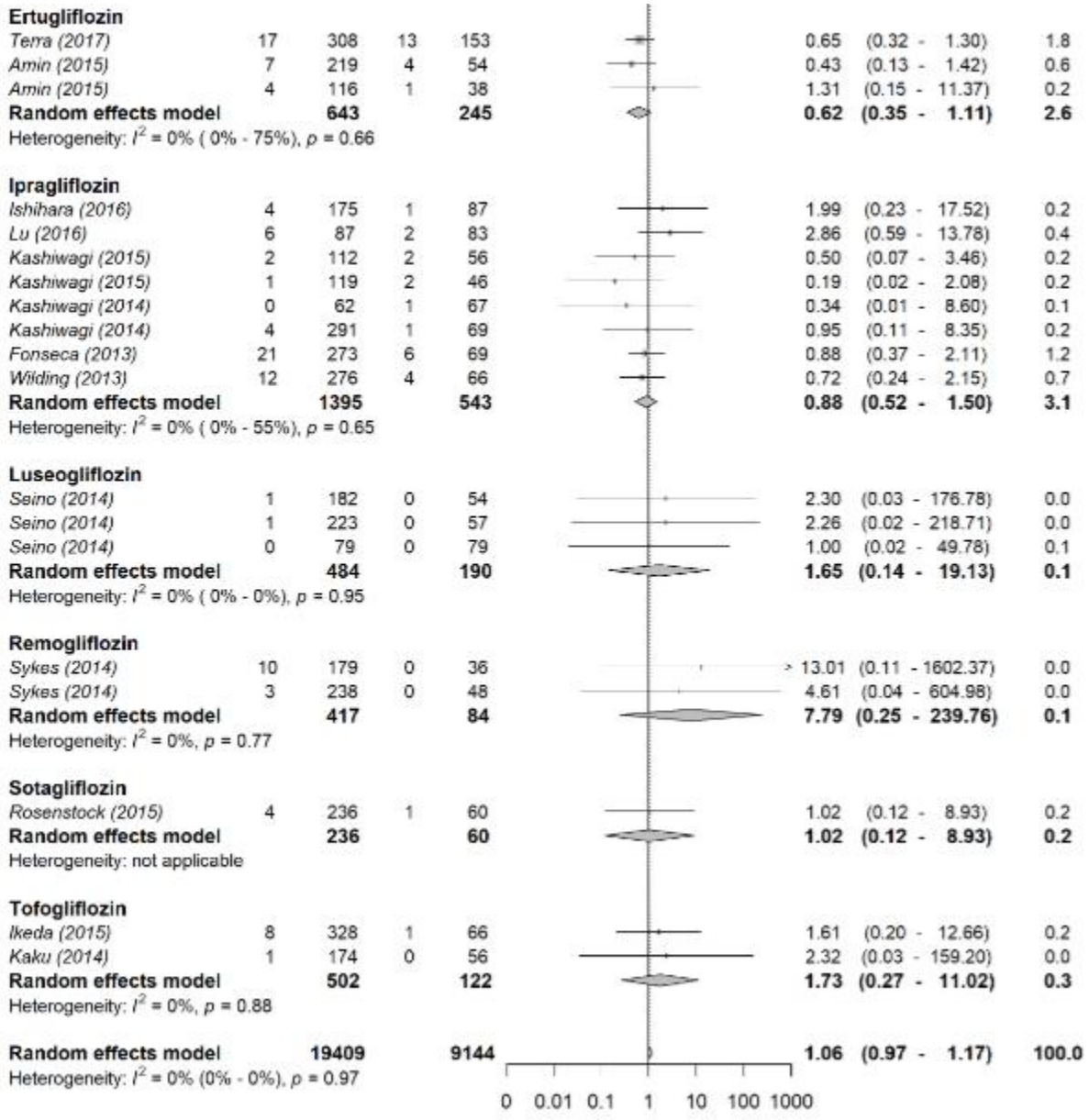


Figure S28: Funnel plot for urinary tract infections, SGLT-2 inhibitors versus placebo

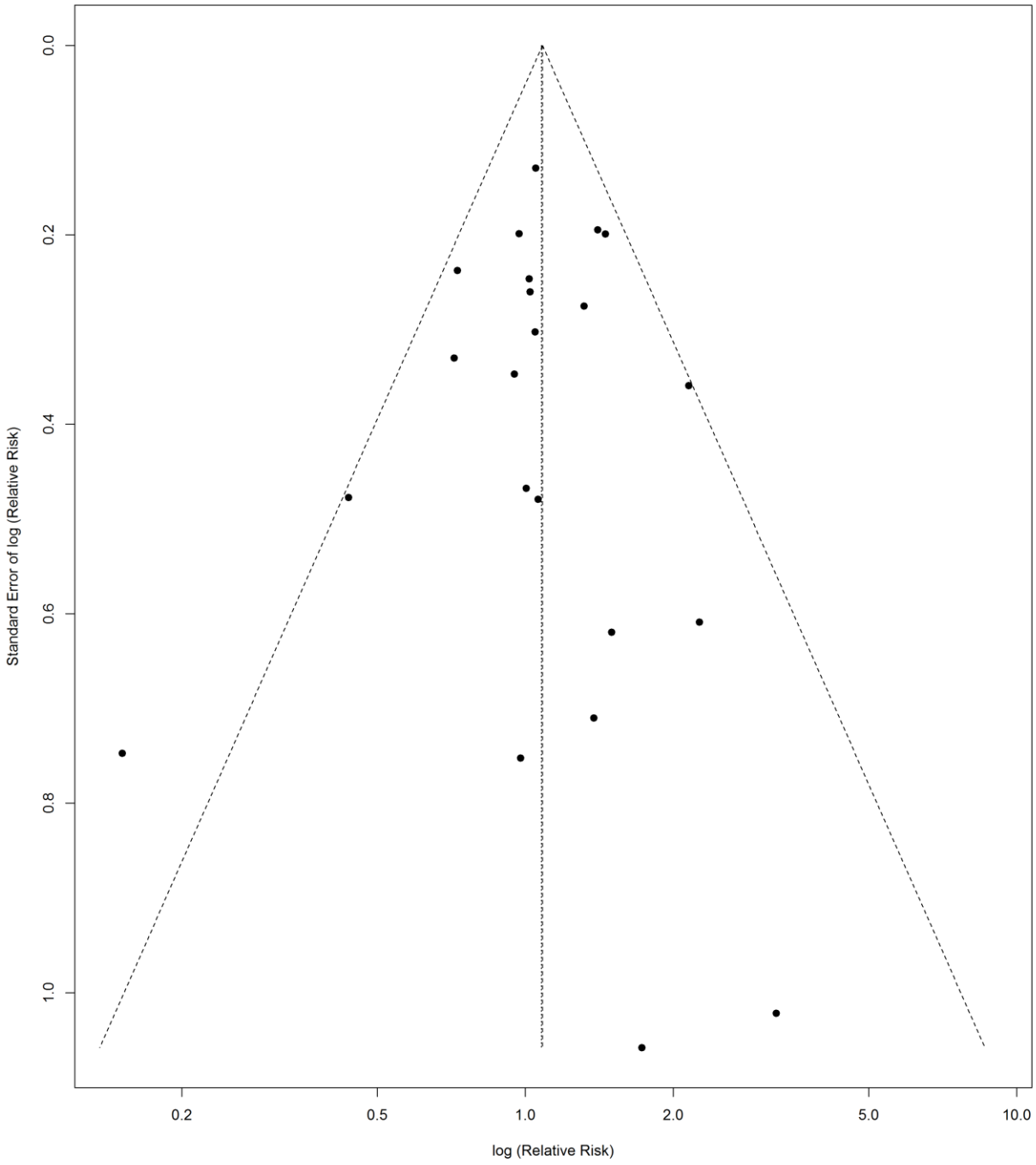


Figure S29: Funnel plot for urinary tract infections, SGLT-2 inhibitors versus active comparators