Int J Clin Exp Med 2016;9(2):2595-2612
www.ijcem.com /ISSN:1940-5901/IJCEM0017133

Original Article

Safety assessment of canagliflozin for type 2 diabetes mellitus

Guoxin Fan[1*], Ruoshuang Han[2*], Yuxin Zhang[2], Zhiyin Zhang[2], Yifan Liu[2], Dongdong Wang[1], Shisheng He[1], Zhengqi Chen[1]

[1]Department of Orthopedic, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China; [2]Department of Endocrine, Shanghai Tenth People's Hospital, Tongji University School of Medicine, China. [*]Equal contributors.

Received September 30, 2015; Accepted December 19, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Importance: Type 2 diabetesmellitus (T2DM) is chronic, progressive, heavy-burden disease. The efficacy of canagliflozinfor T2DM has been well validated, but its safety profile still remains controversial. Objective: This systematic review and meta-analysis of randomized control trials was performed to assess the safety of canagliflozin, the first approved sodium glucose co-transporter 2 receptor inhibitors (SGLT2), inT2DM patients. Data sources: PubMed, EMBASE, clinicaltrials.gov, and the Cochrane Library. Study selection: Randomized controlled trials (RCTs) of canagliflozin in T2DM patients by February 2015 utilizing the key words "canagliflozin", "JNJ-28431754", "TA-7284" and "invokana" with no language, origin or other limits were screened and selected. Data extraction and synthesis: Review Manager 5.0.24 was used to conduct the meta-analysis. Main outcomes and measures: Genital infection. Results: A total of 14 RCTs were included for meta-analysis. Canagliflozin significantly increase the risk of genital infection [RR=4.80; 95% CI (3.80-6.07); *P*< 0.00001; I^2=0%], vulvovaginal mycotic infection [RR=7.66, 95% CI (3.04, 19.29), P<0.001; I^2=0%], osmotic duresis related AEs [RR=2.95; 95% CI (2.26-3.85); *P*< 0.00001; I^2=0%] and nausea [RR=2.36; 95% CI (1.24-4.50); *P*=0.009; I^2=0%]. Canagliflozin slightly increase the risk of volume depletion related AEs [RR=1.36; 95% CI (0.99-1.88); *P*=0.06; I^2=0%], upper respiratory inflammation [RR=1.29; 95% CI (0.73-2.27); *P*=0.39; I^2=0%] and hypoglycaemia [RR=1.40; 95% CI (0.70-2.79); *P*=0.34; I^2=0%].Canagliflozin did not increase the risk of urinary tract infection [risk ratio (RR)=1.11; 95% CI (0.94-1.29); *P*=0.21; I^2=0%], severe hypoglycaemia [RR=1.01; 95% CI (0.67-1.52); *P* =0.96; I^2=0%], GI related AEs [RR=1.11; 95% CI (0.78-1.59); *P*=0.55; I^2=0%], headache [RR=1.18; 95% CI (0.76-1.82); *P*=0.46; I^2=0%] or dizziness [RR=1.01; 95% CI (0.45-2.28); *P*=0.98; I^2=0%]. Canagliflozin was associated with a lightly lower risk of diarrhoea [RR=0.66; 95% CI (0.36-1.18); *P*=0.16; I^2=0%], death [RR 0.84; 95% CI (0.40-1.76); *P*=0.64; I^2=0%] and nasopharyngitis [RR 0.81; 95% CI (0.58-1.13); *P*=0.21; I^2=0%]. Conclusions and relevance: Canagliflorin is relatively safe for treatment of T2DM patients eitherin monotherapy or add-on treatment, but the increased risk of genital infection, osmotic duresis related AEs and nausea should not be neglected. More long-term clinical trials are required to refine this evidence.

Keywords: Canagliflozin, type 2 diabetes mellitus, sodium-glucose transporter-2 inhibitor, safety

Introduction

Diabetes has become the seventh cause of death in America, and 8.3% Americans were reported to have diabetes [1]. Type 2 diabetesmellitus (T2DM) accounts for 90%diabetes, and the incidence trendwill have a significant increase in the next two decades [2]. Patients with T2DM are resistant to insulin and have a great decrease in glucose-stimulated insulin secretion [3]. These features are associated with the insensitivity of the insulin receptor and the impairment of insulin signaling [4].

Management of T2DM includes diet and exercise, followed by monotherapy with anti-hyperglycemic agents (AHAs) when lifestyle intervention is inadequate [2, 5]. However, many patients didn't achieve expectedgoals with first-line therapy like metformin, thus a combination therapy with a second glycaemia-control agent like sulphonylureas, thiazolidinediones or even insulin is often required [6, 7]. Despite achieving a long-term glucose level control, many of these combination therapy lead to severe insulin resistance anda large amount of complications [8], which make the tolerability and safety

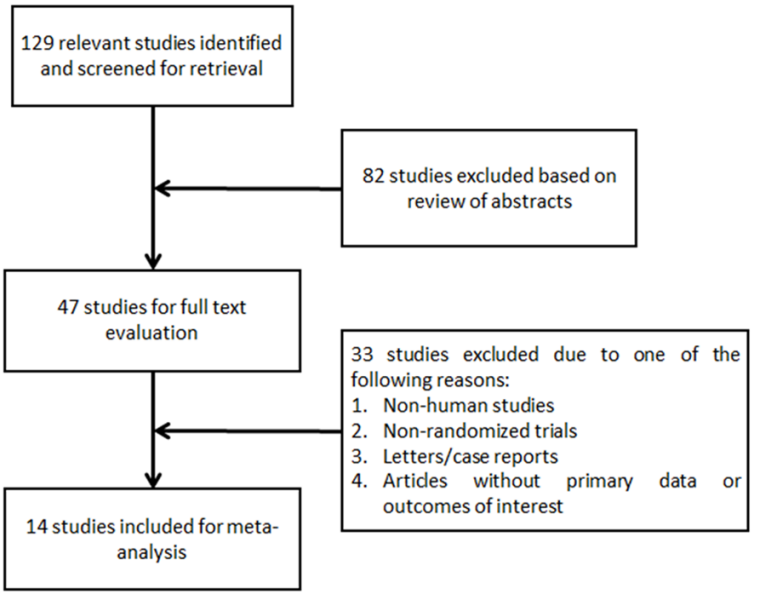


Figure 1. The flow and the results of study selection

of these medications highly concerned. In this regard, a new class of AHAs which can both control the blood glucose level while combined with less complications is strongly expected [9].

Sodium-linked glucose transporter 2 (SGLT2), with an insulin-independent mechanism, is newly developed and may be provedas an attractive alternation [10-12]. SGLT2 is mainly expressed in the early proximal renal tubule, and induces glucose excretion via urine by reducing ingested calories, at the same time achieve good blood glucose control [9]. In April 2013, the U.S. Foodand Drug Administration (FDA) approved canagliflozin as the first SGLT2 class agent for the treatment of T2DM [13]. Canagliflozin is proved to decrease the renal threshold for glucose, thus reduce plasma glucose level and body weight without causing hypoglycemia [1, 10].

Previously, three meta-analysis [14] analyzing the efficacy and safety of the SGLT2 inhibitors (including canagliflozin) for the treatment of T2DM were conducted. However, in Clar and Musso's study [15, 16], only onerandomized controlled trial (RCT) on canagliflozin is included. The efficacy of canagliflozin has been well validated for the treatment of T2DM, but some safety concerns still remain and no pooled analysis of large robust studies with long duration outcomeswas available to clarify this issue [9, 17-19]. The purpose of this meta-analysis is to fully illustrate the clinical safety of canagliflozin as either monotherapy or with other background treatment in T2DM patients.

Methods

Data sources and searches

An exhaustive online search was conducted on mainstream computerized databases of interest, they are: PubMed, MEDLINE, Embase, ClinicalTrials.gov and Cochrane Collaborative database by February 2015. The search terms were "canagliflozin","JNJ-28431754","TA-7284" and "invokana" with no language, origin or other limits. All the retrieved articles were scanned and all additional studies of potential interest were imported into Endnote for further identification and analysis.

Study selection

Inclusion criteria were following the Population Intervention Comparison Outcome (PICO) strategy [20], which were conducted as follows. P: participants were adults of any sex or ethnic origin, who had T2DM and were not adequately-controlled with diet, exercise, or other anti-hyperglycemia drugs like metformin and (or) sulphonylurea and (or) pioglitazone and (or) insulin; I: treatment with canagliflozin; C: comparison with placebo or active comparators such as metformin, glimepiride and sitagliptin; O: rate of the adverse events (AEs) was analyzed to evaluate the safety outcomes. Exclusion criteria were: non-human studies, non-randomized trials, letters/case reports, articles without primary data or outcomes of interest.

Two authors (Yifan Liu and Yuxin Zhang) independently reviewed the titles and abstracts of references extracted from the searches and identified potentially relevant studies. Two reviewers (Ruoshuang Han and Yuxin Zhang) independently analyzed the list of references

Table 1. Characteristics of randomized controlled trials included in the meta-analysis

Author (year) (citation)	Phase n study, NCT	n patients, age (y), BMI (kg/m^2)	Mean initial HbA1c (%)	Duration of T2DM (y)	Canagliflozin dose vs. drug	Background treatment	Treatment duration (weeks)
Rosenstock (2013)	3, NCT00642278	451, 52.9, 31.5	7.8	6	50 mg, 100 mg, 200 mg, 300 mg vs. placebo	Metformin	12 w
Schernthaner (2013)	3, NCT01137812	756, 56.7, 31.6	8.1	9.6	300 mg vs. sitagliptin	Metformin Plus Sulfonylurea	52 w
Lavalle-González (2013)	3, NCT01106677	1284, 55.4, 31.8	7.9	6.9	100 mg, 300 mg vs sitagliptin	Metformin monotherapy	52 w
Forst (2014)	3, NCT01106690	342, 57.4, 32.5	7.9	10.5	100 mg, 300 mg vs placebo/sitagliptin	Metformin and pioglitazone	52 w
Inagaki (2013)	NCT01022112	382, 57.4, 25.7	8.1	-	50 mg, 100 mg, 200 mg, 300 mg vs. placebo	Antidiabetic drugs	12 w
Li (2014)	NCT01381900	676, 56.2, 25.7	8.0	6.7	100 mg, 300 mg vs. placebo	Metformin aloene or Metformin Plus Sulfonylurea	18 w
Wilding (2013)	3, NCT01106625	469, 56.8, 33.1	8.1	9.6	100 mg, 300 mg vs. placebo	Metformin plus sulphonylurea	52 w
Leiter (2014)	3, NCT00968812	1450, 56.2, 31.0	7.8	6.6	100 mg, 300 mg vs. glimepiride	Metformin	104 w
Bays (2014)	2b, NCT00650806	376, 44.8, 37	-	-	50 mg, 100 mg, 300 mg vs. placebo	Nutritional counseling,limitation of calories and routine physical activity	12 w
Bode (2014)	3, NCT01106651	716, 63.6, 31.6	7.7	11.7	100 mg, 300 mg vs. placebo	-	104 w
Nyiryjesy (2012)	2, NCT00642278	215, 52.9, 32.1	7.8	-	50 mg, 100 mg, 200 mg, 300 mg vs. placebo&sitagliptin	Metformin	12 w
Yale (2013)	3	272, 68.5, 33.0	8	16.3	100 mg, 300 mg vs. placebo	AHA therapies at baseline	52 w
Devineni (2012)	1b	29, 48.5, 33.5	8.4	-	100 mg, 300 mg vs. placebo	Insulin and Metformin	4 w
Stenlöf (2014)	3, NCT01081834	587, 55.4, 31.6	8	4.3	Placebo/sitagliptin	Diet and exercise	52 w

Table 2. Quality of evidence for clinically relevant outcomes

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Safety assessment of Canagliflozin (95% CI)
Genital infections	8930 (11 studies)	⊕⊕⊕⊖ MODERATE[1] due to imprecision	OR 5.25 (4.12 to 6.69)	Study population	
				19 per 1000	73 more per 1000 (from 55 more to 96 more)
				Moderate	
				18 per 1000	70 more per 1000 (from 52 more to 91 more)
Osmotic duresis related AEs	8930 (11 studies)	⊕⊕⊕⊕ HIGH	OR 3.05 (2.32 to 4.01)	Study population	
				17 per 1000	32 more per 1000 (from 21 more to 47 more)
				Moderate	
				15 per 1000	29 more per 1000 (from 19 more to 43 more)
Volume depletion related AEs	8968 (12 studies)	⊕⊕⊕⊕ HIGH	OR 1.37 (0.99 to 1.91)	Study population	
				14 per 1000	5 more per 1000 (from 0 fewer to 12 more)
				Moderate	
				15 per 1000	5 more per 1000 (from 0 fewer to 13 more)
Death	7402 (8 studies)	⊕⊕⊕⊕ HIGH	OR 0.84 (0.39 to 1.78)	Study population	
				3 per 1000	1 fewer per 1000 (from 2 fewer to 3 more)
				Moderate	
				4 per 1000	1 fewer per 1000 (from 2 fewer to 3 more)
Severe hypoglycaemia	6836 (9 studies)	⊕⊕⊕⊕ HIGH	OR 1.01 (0.67 to 1.53)	Study population	
				12 per 1000	0 more per 1000 (from 4 fewer to 6 more)
				Moderate	
				6 per 1000	0 more per 1000 (from 2 fewer to 3 more)
Urinary tract infection	8930 (11 studies)	⊕⊕⊕⊖ MODERATE[1] due to imprecision	OR 1.11 (0.94 to 1.32)	Study population	
				63 per 1000	6 more per 1000 (from 4 fewer to 18 more)
				Moderate	
				63 per 1000	6 more per 1000 (from 4 fewer to 19 more)
Headache	1109 (3 studies)	⊕⊕⊕⊖ MODERATE[1] due to imprecision	OR 1.2 (0.74 to 1.94)	Study population	
				61 per 1000	11 more per 1000 (from 15 fewer to 51 more)
				Moderate	
				79 per 1000	14 more per 1000 (from 19 fewer to 64 more)
GI related AES	1642 (4 studies)	⊕⊕⊕⊖ MODERATE[1] due to imprecision	OR 1.13 (0.76 to 1.68)	Study population	
				65 per 1000	8 more per 1000 (from 15 fewer to 40 more)
				Moderate	
				40 per 1000	5 more per 1000 (from 9 fewer to 25 more)
Nasopharyngitis	2014 (3 studies)	⊕⊕⊖⊖ LOW[1,2] due to imprecision, publication bias	OR 0.79 (0.55 to 1.14)	Study population	
				71 per 1000	14 fewer per 1000 (from 31 fewer to 9 more)
				Moderate	
				34 per 1000	7 fewer per 1000 (from 15 fewer to 5 more)
Upper respiratory inflammation	1162 (2 studies)	⊕⊕⊕⊖ MODERATE[1,2] due to imprecision	OR 1.3 (0.72 to 2.37)	Study population	
				34 per 1000	10 more per 1000 (from 9 fewer to 42 more)
				Moderate	
				13 per 1000	4 more per 1000 (from 4 fewer to 17 more)
Nausea	1109 (3 studies)	⊕⊕⊕⊕ HIGH	OR 2.51 (1.26 to 5.03)	Study population	
				18 per 1000	26 more per 1000 (from 5 more to 68 more)
				Moderate	
				23 per 1000	33 more per 1000 (from 6 more to 83 more)
Diarrhoea	1109 (3 studies)	⊕⊕⊕⊖ MODERATE[1] due to imprecision	OR 0.64 (0.35 to 1.19)	Study population	
				46 per 1000	16 fewer per 1000 (from 29 fewer to 8 more)
				Moderate	
				56 per 1000	19 fewer per 1000 (from 36 fewer to 10 more)
Dizziness	592 (2 studies)	⊕⊕⊖⊖ LOW[1,2] due to imprecision, publication bias	OR 1.01 (0.43 to 2.38)	Study population	
				35 per 1000	0 more per 1000 (from 20 fewer to 45 more)
				Moderate	
				23 per 1000	0 more per 1000 (from 13 fewer to 30 more)

Hypoglycaemia	1679 (3 studies)	⊕⊕⊕⊖ MODERATE[1,2,3] due to imprecision	OR 1.41 (0.7 to 2.83)	Study population	
				12 per 1000	5 more per 1000 (from 4 fewer to 21 more)
				Moderate	
				15 per 1000	6 more per 1000 (from 4 fewer to 26 more)

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; OR: Odds ratio; GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. [1]Unconformity. [2]Publication bias. [3]No explanation was provided.

and identified the RCTs of interests. The full-text articles were assessed by two authors (Xiaofei Guan and Yanjie Zhu). Any discrepancies of selection would be resolved by discussion until consensus was reached. If an agreement failed to reach by discussion, a third author (GuoxinFan) was consulted. Data was retrieved from included studies and entered into RevMan 5.0.24 for analysis.

Data extraction and quality assessment

Two reviewers (Ruoshuang Han and Guoxin Fan) independently extracted or check data in duplicate with a predefined protocol following the Cochrane Handbook for Systematic Reviews of Intervention; discrepancies were resolved by discussion. Study characteristics were extracted with Excel; the quality of RCTs was assessed by the Cochrane Risk-of-Bias Tool, attributing 1 point to each item (total score range: 0-8) [21]; the strength of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Data synthesis and analysis

This systematic review with meta-analysis was reported according to PRISMA guidelines [22]. We performed all the analyses using RevMan 5.0.24 (The Nordic Cochrane Centre, Copenhagen, Denmark) from Cochrane Collaboration, 2008). Dichotomous data (AEs) would be presented as relative risk (RR) with 95% confidence interval (CI), while continuous variables asweighed mean differences (MMD) with 95% CI. Treatments were evaluated on an intention-to-treat principle. Statistical heterogeneity was evaluated using I^2 statistic: if no heterogeneity (I^2< 50%) was detected, we would use a fix-effect model; if significant heterogeneity was present (I^2≥ 50%), we would use a random-effect model along with the sensitive analysis to investigate for possible explanations. Two authors (Ruoshuang Han and Yuxin Zhang) independently assessed the risk of bias as described in the Cochrane Handbook for Systematic Reviews of Interventions [23]. If more than 10 studies were included, a funnel plot analysis would be employed to assess the reporting biases [24].

Results

The agreement between two reviewers for study selection was 0.85 and for quality assessment of trials was 0.86.

Search results

The flow and the results of study selection are reported in **Figure 1**. After exclusions, made according to the study protocol, 14 RCTs included for further analysis and discussion.

Study characteristics

The characteristics and results of the included studiesare shown in **Table 1**. All included trials were double-blind RCTs, trial durations rangedfrom 2 to 104 weeks (median 33 weeks). Most trials hadlonger-term extension periods (not completed/reportedin all cases). At the end of selection, 14 RCTs assessing canagliflozin (8015 participants, trial duration ranging 2-104 weeks, daily dose ranging 50-300 mg) were included [2, 5, 6, 25-35]. The mean initial HbA1c across the study population of 11 RCTs ranges from 4.3% to 16.3%, and background anti-diabetic treatments consist of metformin monotherapy in four RCTs [25, 29, 32, 33], metformin plus another agent in five RCTs [6, 28, 30, 31, 36] (including metformin alone or metformin plus sulfonylurea in one RCT), diet and exercise [5, 26] in two RCTs, AHA therapies at baseline [34] in one RCT, unclear anti-diabetic drugs [2] in one RCT and unknown treatment [27] in one RCT.

Figure 2. Cochrane risk of bias of included studies. A: Graph; B: Summary; C: Funnel plot.

Quality of included studies and grading of evidence

Overall quality grading is demonstrated in **Table 2**. Quality of evidence was downgraded due to unconformity and publication bias. Generally speaking, the evidence of 5 outcomes was graded to be high, 7 outcomes were graded to be moderate and 2 outcomes were graded to be low.

Cochrane risk of bias

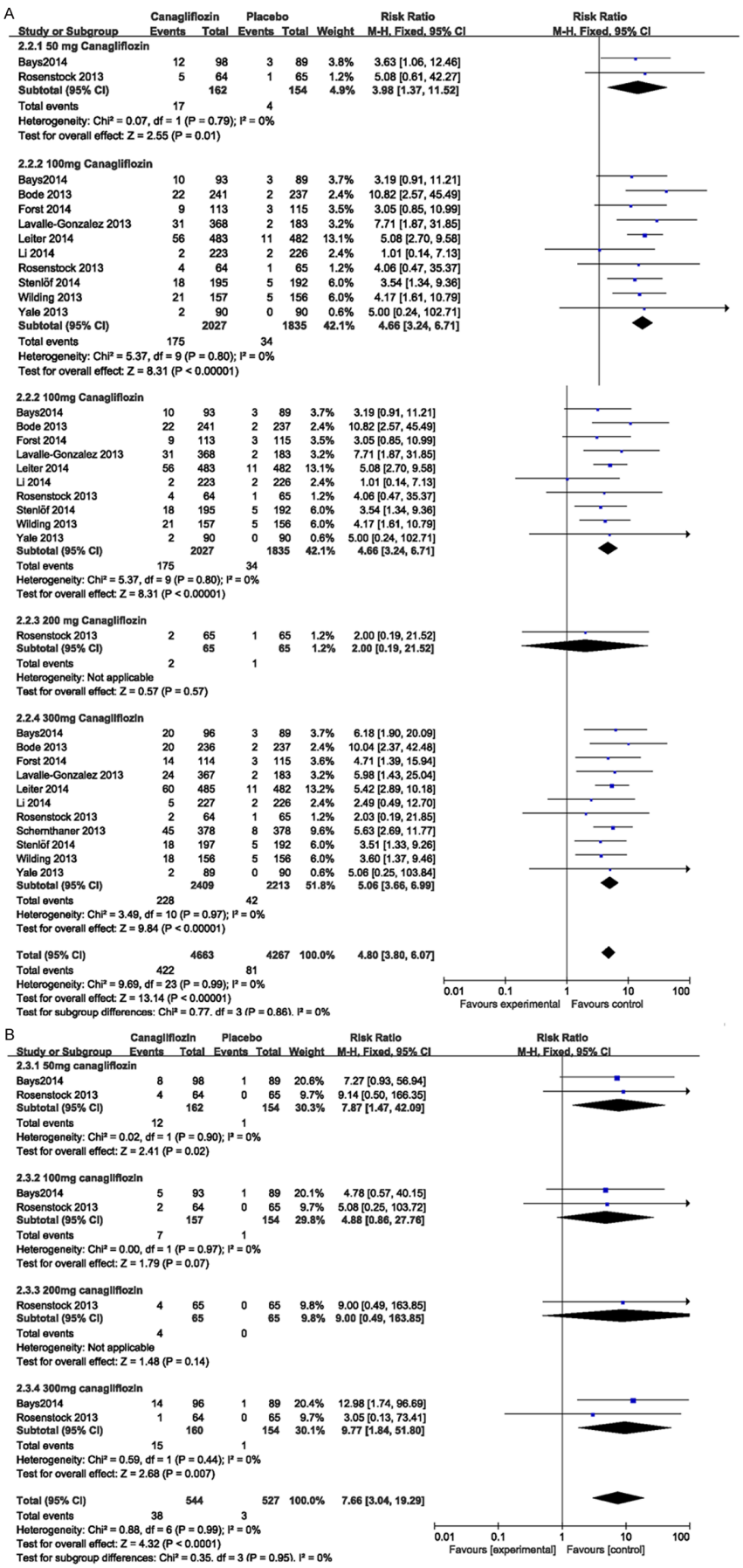
Risk of bias are demonstrated in **Figure 2A**, **2B**. The reporting quality was rated as 'high' in 8 ofthe studies, 'medium' in 5 studies and 'low' in 1 study. The funnel plot did not detect a significant publication bias (**Figure 2C**).

Genital infections and urinary tract infection

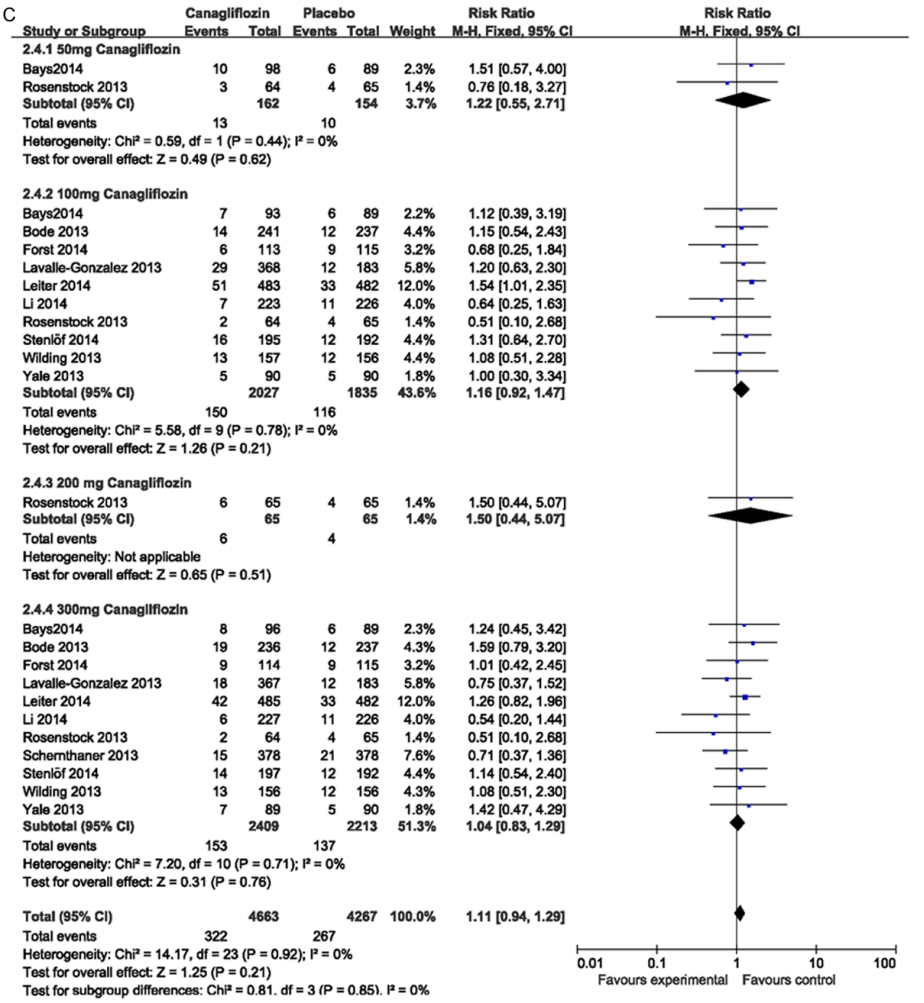
Generally, canagliflozin treatment was associated with an extremely increased risk of genital infections (RR 4.80; 95% CI (3.80-6.07); $P<$ 0.00001; I^2=0%) (**Figure 3A**). In particular, canagliflozin treatment was strongly correlated with a higher risk of vulvovaginal mycotic infection (RR=7.66, 95% CI (3.04, 19.29), P<0.001; I^2=0%) (**Figure 3B**). However, canagliflozin did not increase rate of urinary tract infections (UTIs) (RR 1.11; 95% CI (0.94-1.29); P=0.21; I^2=0%) (**Figure 3C**).

Hypoglycaemia

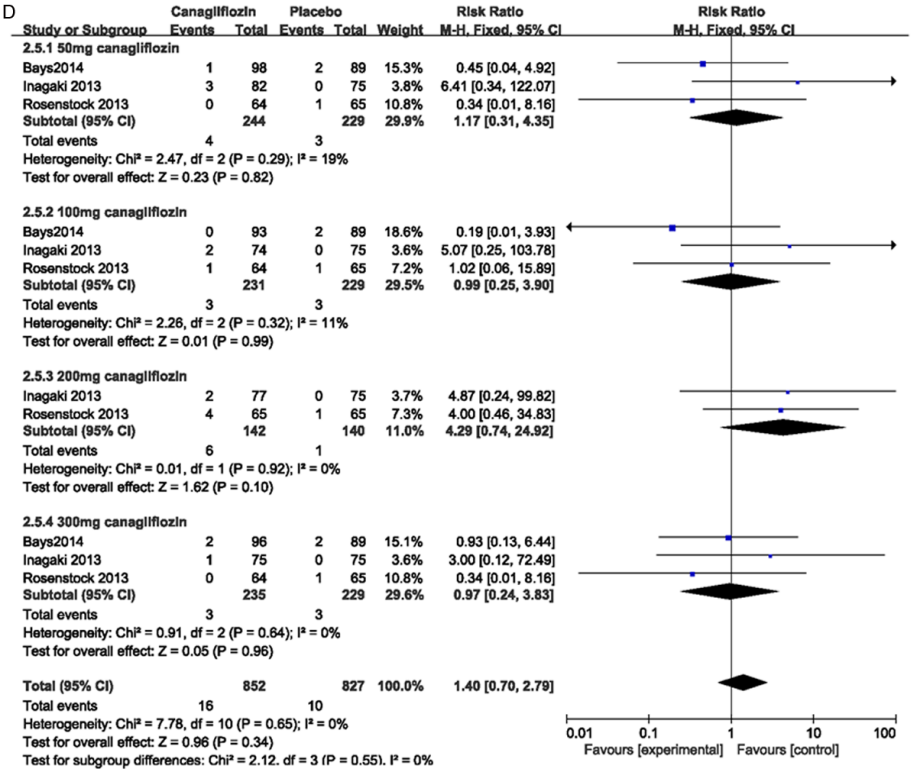
Incidences of hypoglycaemia and severe hypoglycaemia were both low in allclinical trials. Canagliflozin slighty increase the risk of hypoglycaemia (RR 1.40; 95% CI (0.70-2.79); P=0.34; I^2=0%)


A
Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.2.1 50 mg Canagliflozin
Bays2014 12 98 3 89 3.8% 3.63 [1.06, 12.46]
Rosenstock 2013 5 64 1 65 1.2% 5.08 [0.61, 42.27]
Subtotal (95% CI) 162 154 4.9% 3.98 [1.37, 11.52]
Total events 17 4
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.55 (P = 0.01)
2.2.2 100mg Canagliflozin
Bays2014 10 93 3 89 3.7% 3.19 [0.91, 11.21]
Bode 2013 22 241 2 237 2.4% 10.82 [2.57, 45.49]
Forst 2014 9 113 3 115 3.5% 3.05 [0.85, 10.99]
Lavalle-Gonzalez 2013 31 368 2 183 3.2% 7.71 [1.87, 31.85]
Leiter 2014 56 483 11 482 13.1% 5.08 [2.70, 9.58]
Li 2014 2 223 2 226 2.4% 1.01 [0.14, 7.13]
Rosenstock 2013 4 64 1 65 1.2% 4.06 [0.47, 35.37]
Stenlöf 2014 18 195 5 192 6.0% 3.54 [1.34, 9.36]
Wilding 2013 21 157 5 156 6.0% 4.17 [1.61, 10.79]
Yale 2013 2 90 0 90 0.6% 5.00 [0.24, 102.71]
Subtotal (95% CI) 2027 1835 42.1% 4.66 [3.24, 6.71]
Total events 175 34
Heterogeneity: Chi² = 5.37, df = 9 (P = 0.80); I² = 0%
Test for overall effect: Z = 8.31 (P < 0.00001)
2.2.2 100mg Canagliflozin
Bays2014 10 93 3 89 3.7% 3.19 [0.91, 11.21]
Bode 2013 22 241 2 237 2.4% 10.82 [2.57, 45.49]
Forst 2014 9 113 3 115 3.5% 3.05 [0.85, 10.99]
Lavalle-Gonzalez 2013 31 368 2 183 3.2% 7.71 [1.87, 31.85]
Leiter 2014 56 483 11 482 13.1% 5.08 [2.70, 9.58]
Li 2014 2 223 2 226 2.4% 1.01 [0.14, 7.13]
Rosenstock 2013 4 64 1 65 1.2% 4.06 [0.47, 35.37]
Stenlöf 2014 18 195 5 192 6.0% 3.54 [1.34, 9.36]
Wilding 2013 21 157 5 156 6.0% 4.17 [1.61, 10.79]
Yale 2013 2 90 0 90 0.6% 5.00 [0.24, 102.71]
Subtotal (95% CI) 2027 1835 42.1% 4.66 [3.24, 6.71]
Total events 175 34
Heterogeneity: Chi² = 5.37, df = 9 (P = 0.80); I² = 0%
Test for overall effect: Z = 8.31 (P < 0.00001)
2.2.3 200 mg Canagliflozin
Rosenstock 2013 2 65 1 65 1.2% 2.00 [0.19, 21.52]
Subtotal (95% CI) 65 65 1.2% 2.00 [0.19, 21.52]
Total events 2 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)
2.2.4 300mg Canagliflozin
Bays2014 20 96 3 89 3.7% 6.18 [1.90, 20.09]
Bode 2013 20 236 2 237 2.4% 10.04 [2.37, 42.48]
Forst 2014 14 114 3 115 3.6% 4.71 [1.39, 15.94]
Lavalle-Gonzalez 2013 24 367 2 183 3.2% 5.98 [1.43, 25.04]
Leiter 2014 60 485 11 482 13.2% 5.42 [2.89, 10.18]
Li 2014 5 227 2 226 2.4% 2.49 [0.49, 12.70]
Rosenstock 2013 2 64 1 65 1.2% 2.03 [0.19, 21.85]
Schernthaner 2013 45 378 8 378 9.6% 5.63 [2.69, 11.77]
Stenlöf 2014 18 197 5 192 6.0% 3.51 [1.33, 9.26]
Wilding 2013 18 156 5 156 6.0% 3.60 [1.37, 9.46]
Yale 2013 2 89 0 90 0.6% 5.06 [0.25, 103.84]
Subtotal (95% CI) 2409 2213 51.8% 5.06 [3.66, 6.99]
Total events 228 42
Heterogeneity: Chi² = 3.49, df = 10 (P = 0.97); I² = 0%
Test for overall effect: Z = 9.84 (P < 0.00001)
Total (95% CI) 4663 4267 100.0% 4.80 [3.80, 6.07]
Total events 422 81
Heterogeneity: Chi² = 9.69, df = 23 (P = 0.99); I² = 0%
Test for overall effect: Z = 13.14 (P < 0.00001)
Test for subgroup differences: Chi² = 0.77, df = 3 (P = 0.86), I² = 0%
0.01 0.1 1 10 100
Favours experimental Favours control
B
Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.3.1 50mg canagliflozin
Bays2014 8 98 1 89 20.6% 7.27 [0.93, 56.94]
Rosenstock 2013 4 64 0 65 9.7% 9.14 [0.50, 166.35]
Subtotal (95% CI) 162 154 30.3% 7.87 [1.47, 42.09]
Total events 12 1
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.41 (P = 0.02)
2.3.2 100mg canagliflozin
Bays2014 5 93 1 89 20.1% 4.78 [0.57, 40.15]
Rosenstock 2013 2 64 0 65 9.7% 5.08 [0.25, 103.72]
Subtotal (95% CI) 157 154 29.8% 4.88 [0.86, 27.76]
Total events 7 1
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)
2.3.3 200mg canagliflozin
Rosenstock 2013 4 65 0 65 9.8% 9.00 [0.49, 163.85]
Subtotal (95% CI) 65 65 9.8% 9.00 [0.49, 163.85]
Total events 4 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
2.3.4 300mg canagliflozin
Bays2014 14 96 1 89 20.4% 12.98 [1.74, 96.69]
Rosenstock 2013 1 64 0 65 9.7% 3.05 [0.13, 73.41]
Subtotal (95% CI) 160 154 30.1% 9.77 [1.84, 51.80]
Total events 15 1
Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.68 (P = 0.007)
Total (95% CI) 544 527 100.0% 7.66 [3.04, 19.29]
Total events 38 3
Heterogeneity: Chi² = 0.88, df = 6 (P = 0.99); I² = 0%
Test for overall effect: Z = 4.32 (P < 0.0001)
Test for subgroup differences: Chi² = 0.35, df = 3 (P = 0.95), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

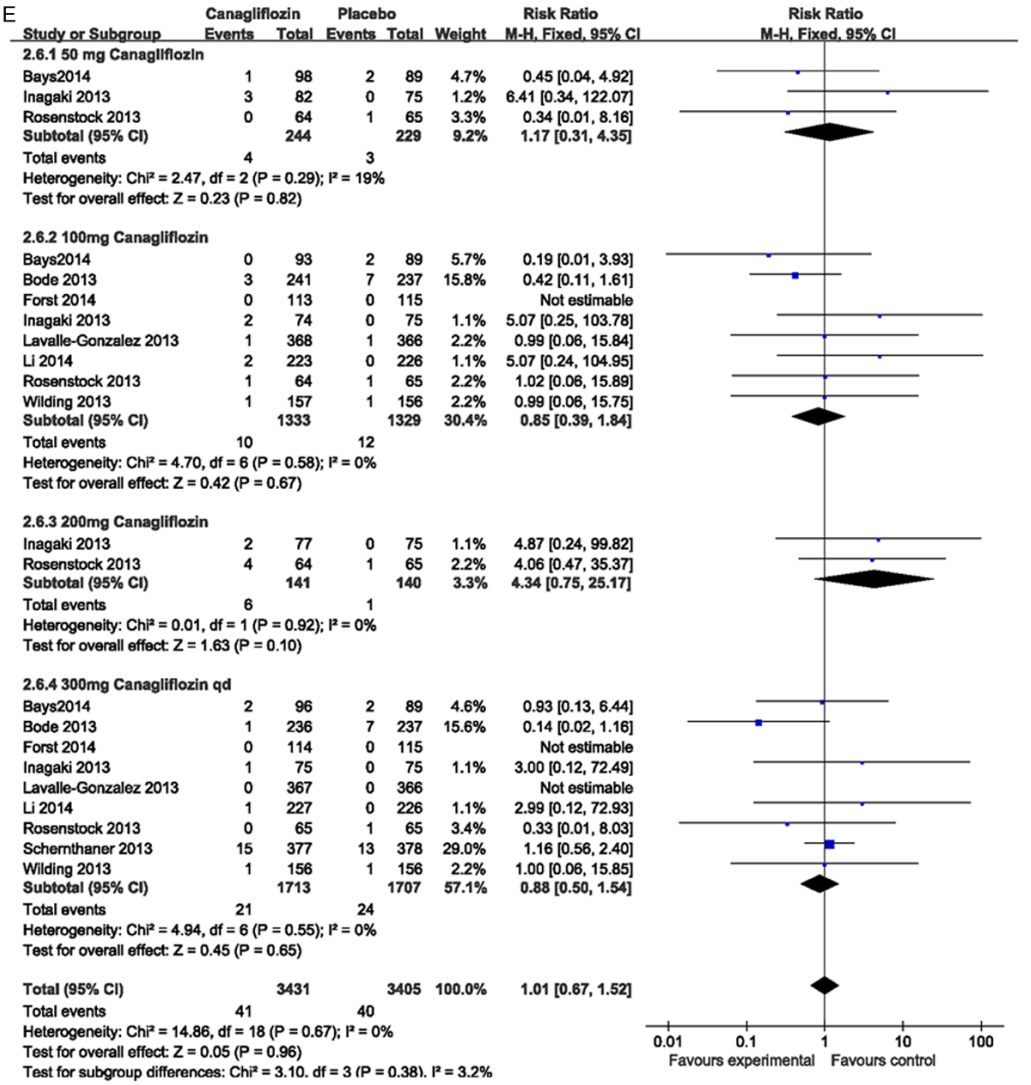
C


Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.4.1 50mg Canagliflozin
Bays2014 10 98 6 89 2.3% 1.51 [0.57, 4.00]
Rosenstock 2013 3 64 4 65 1.4% 0.76 [0.18, 3.27]
Subtotal (95% CI) 162 154 3.7% 1.22 [0.55, 2.71]
Total events 13 10
Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
2.4.2 100mg Canagliflozin
Bays2014 7 93 6 89 2.2% 1.12 [0.39, 3.19]
Bode 2013 14 241 12 237 4.4% 1.15 [0.54, 2.43]
Forst 2014 6 113 9 115 3.2% 0.68 [0.25, 1.84]
Lavalle-Gonzalez 2013 29 368 12 183 5.8% 1.20 [0.63, 2.30]
Leiter 2014 51 483 33 482 12.0% 1.54 [1.01, 2.35]
Li 2014 7 223 11 226 4.0% 0.64 [0.25, 1.63]
Rosenstock 2013 2 64 4 65 1.4% 0.51 [0.10, 2.68]
Stenlöf 2014 16 195 12 192 4.4% 1.31 [0.64, 2.70]
Wilding 2013 13 157 12 156 4.4% 1.08 [0.51, 2.28]
Yale 2013 5 90 5 90 1.8% 1.00 [0.30, 3.34]
Subtotal (95% CI) 2027 1835 43.6% 1.16 [0.92, 1.47]
Total events 150 116
Heterogeneity: Chi² = 5.58, df = 9 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)
2.4.3 200 mg Canagliflozin
Rosenstock 2013 6 65 4 65 1.4% 1.50 [0.44, 5.07]
Subtotal (95% CI) 65 65 1.4% 1.50 [0.44, 5.07]
Total events 6 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
2.4.4 300mg Canagliflozin
Bays2014 8 96 6 89 2.3% 1.24 [0.45, 3.42]
Bode 2013 19 236 12 237 4.3% 1.59 [0.79, 3.20]
Forst 2014 9 114 9 115 3.2% 1.01 [0.42, 2.45]
Lavalle-Gonzalez 2013 18 367 12 183 5.8% 0.75 [0.37, 1.52]
Leiter 2014 42 485 33 482 12.0% 1.26 [0.82, 1.96]
Li 2014 6 227 11 226 4.0% 0.54 [0.20, 1.44]
Rosenstock 2013 2 64 4 65 1.4% 0.51 [0.10, 2.68]
Schernthaner 2013 15 378 21 378 7.6% 0.71 [0.37, 1.36]
Stenlöf 2014 14 197 12 192 4.4% 1.14 [0.54, 2.40]
Wilding 2013 13 156 12 156 4.3% 1.08 [0.51, 2.30]
Yale 2013 7 89 5 90 1.8% 1.42 [0.47, 4.29]
Subtotal (95% CI) 2409 2213 51.3% 1.04 [0.83, 1.29]
Total events 153 137
Heterogeneity: Chi² = 7.20, df = 10 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)
Total (95% CI) 4663 4267 100.0% 1.11 [0.94, 1.29]
Total events 322 267
Heterogeneity: Chi² = 14.17, df = 23 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Chi² = 0.81, df = 3 (P = 0.85), I² = 0%
0.01 0.1 1 10 100
Favours experimental Favours control

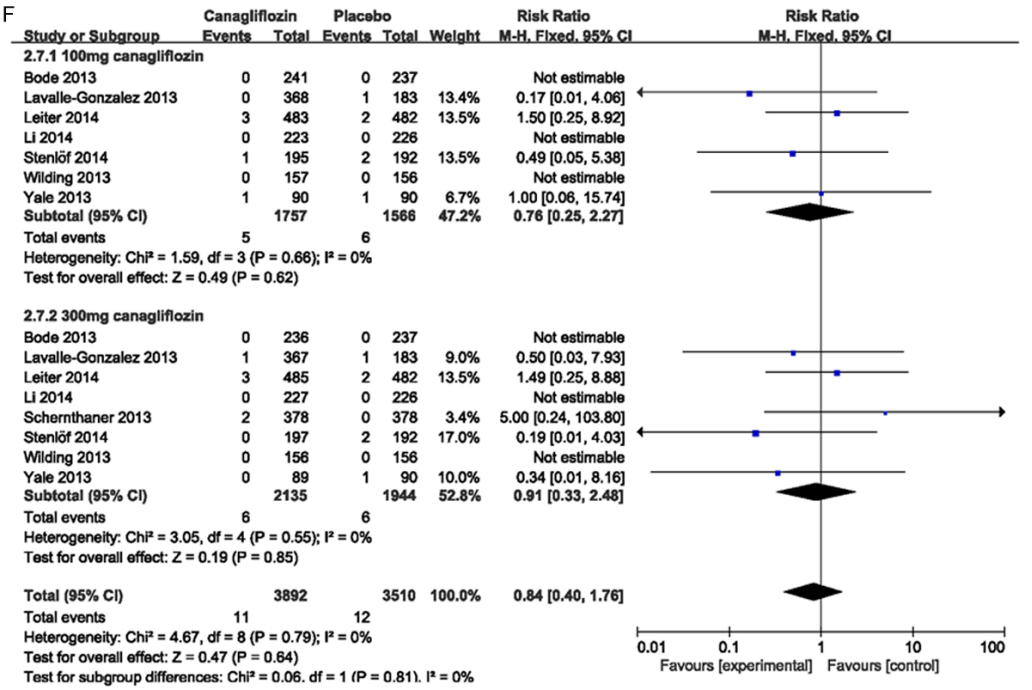
D


Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.5.1 50mg canagliflozin
Bays2014 1 98 2 89 15.3% 0.45 [0.04, 4.92]
Inagaki 2013 3 82 0 75 3.8% 6.41 [0.34, 122.07]
Rosenstock 2013 0 64 1 65 10.8% 0.34 [0.01, 8.16]
Subtotal (95% CI) 244 229 29.9% 1.17 [0.31, 4.35]
Total events 4 3
Heterogeneity: Chi² = 2.47, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 0.23 (P = 0.82)
2.5.2 100mg canagliflozin
Bays2014 0 93 2 89 18.6% 0.19 [0.01, 3.93]
Inagaki 2013 2 74 0 75 3.6% 5.07 [0.25, 103.78]
Rosenstock 2013 1 64 1 65 7.2% 1.02 [0.06, 15.89]
Subtotal (95% CI) 231 229 29.5% 0.99 [0.25, 3.90]
Total events 3 3
Heterogeneity: Chi² = 2.26, df = 2 (P = 0.32); I² = 11%
Test for overall effect: Z = 0.01 (P = 0.99)
2.5.3 200mg canagliflozin
Inagaki 2013 2 77 0 75 3.7% 4.87 [0.24, 99.82]
Rosenstock 2013 4 65 1 65 7.3% 4.00 [0.46, 34.83]
Subtotal (95% CI) 142 140 11.0% 4.29 [0.74, 24.92]
Total events 6 1
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.62 (P = 0.10)
2.5.4 300mg canagliflozin
Bays2014 2 96 2 89 15.1% 0.93 [0.13, 6.44]
Inagaki 2013 1 75 0 75 3.6% 3.00 [0.12, 72.49]
Rosenstock 2013 0 64 1 65 10.8% 0.34 [0.01, 8.16]
Subtotal (95% CI) 235 229 29.6% 0.97 [0.24, 3.83]
Total events 3 3
Heterogeneity: Chi² = 0.91, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)
Total (95% CI) 852 827 100.0% 1.40 [0.70, 2.79]
Total events 16 10
Heterogeneity: Chi² = 7.78, df = 10 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Chi² = 2.12, df = 3 (P = 0.55), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

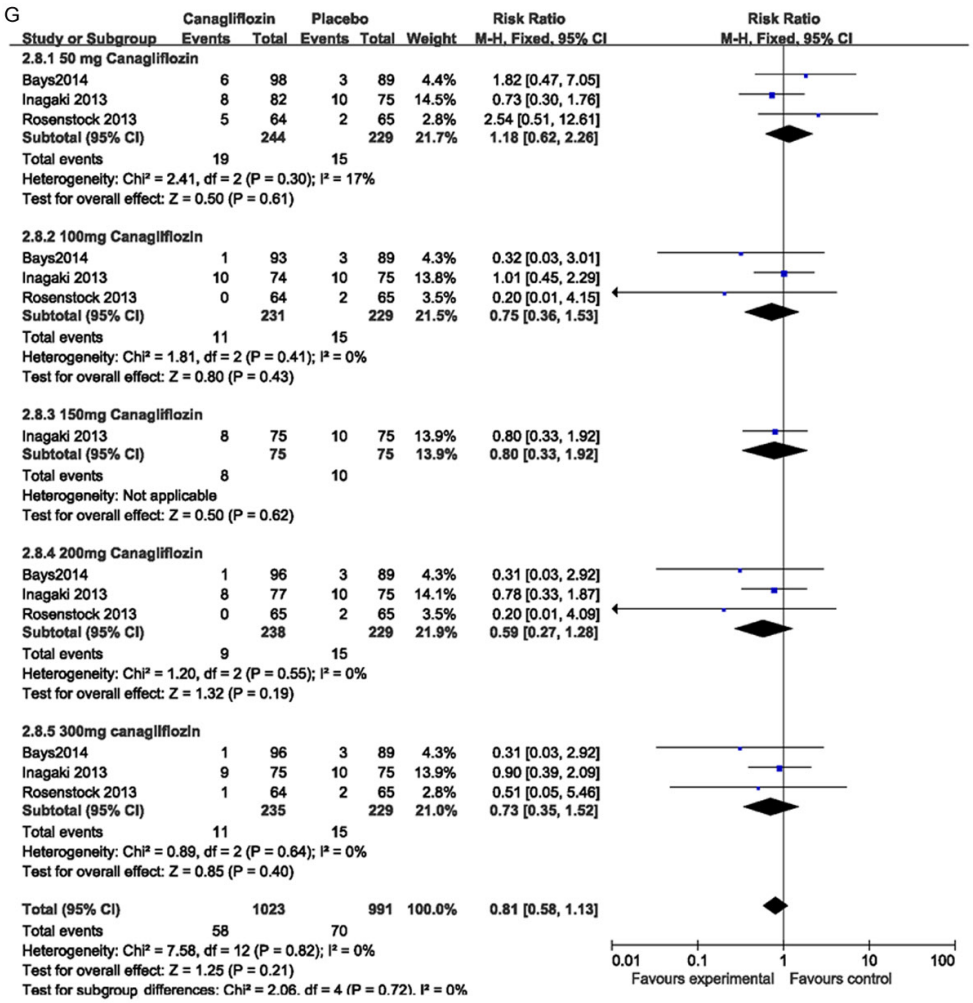
E


Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.6.1 50 mg Canagliflozin
Bays2014 1 98 2 89 4.7% 0.45 [0.04, 4.92]
Inagaki 2013 3 82 0 75 1.2% 6.41 [0.34, 122.07]
Rosenstock 2013 0 64 1 65 3.3% 0.34 [0.01, 8.16]
Subtotal (95% CI) 244 229 9.2% 1.17 [0.31, 4.35]
Total events 4 3
Heterogeneity: Chi² = 2.47, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 0.23 (P = 0.82)
2.6.2 100mg Canagliflozin
Bays2014 0 93 2 89 5.7% 0.19 [0.01, 3.93]
Bode 2013 3 241 7 237 15.8% 0.42 [0.11, 1.61]
Forst 2014 0 113 0 115 Not estimable
Inagaki 2013 2 74 0 75 1.1% 5.07 [0.25, 103.78]
Lavalle-Gonzalez 2013 1 368 1 366 2.2% 0.99 [0.06, 15.84]
Li 2014 2 223 0 226 1.1% 5.07 [0.24, 104.95]
Rosenstock 2013 1 64 1 65 2.2% 1.02 [0.06, 15.89]
Wilding 2013 1 157 1 156 2.2% 0.99 [0.06, 15.75]
Subtotal (95% CI) 1333 1329 30.4% 0.85 [0.39, 1.84]
Total events 10 12
Heterogeneity: Chi² = 4.70, df = 6 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)
2.6.3 200mg Canagliflozin
Inagaki 2013 2 77 0 75 1.1% 4.87 [0.24, 99.82]
Rosenstock 2013 4 64 1 65 2.2% 4.06 [0.47, 35.37]
Subtotal (95% CI) 141 140 3.3% 4.34 [0.75, 25.17]
Total events 6 1
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.63 (P = 0.10)
2.6.4 300mg Canagliflozin qd
Bays2014 2 96 2 89 4.6% 0.93 [0.13, 6.44]
Bode 2013 1 236 7 237 15.6% 0.14 [0.02, 1.16]
Forst 2014 0 114 0 115 Not estimable
Inagaki 2013 1 75 0 75 1.1% 3.00 [0.12, 72.49]
Lavalle-Gonzalez 2013 0 367 0 366 Not estimable
Li 2014 1 227 0 226 1.1% 2.99 [0.12, 72.93]
Rosenstock 2013 0 65 1 65 3.4% 0.33 [0.01, 8.03]
Schernthaner 2013 15 377 13 378 29.0% 1.16 [0.56, 2.40]
Wilding 2013 1 156 1 156 2.2% 1.00 [0.06, 15.85]
Subtotal (95% CI) 1713 1707 57.1% 0.88 [0.50, 1.54]
Total events 21 24
Heterogeneity: Chi² = 4.94, df = 6 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Total (95% CI) 3431 3405 100.0% 1.01 [0.67, 1.52]
Total events 41 40
Heterogeneity: Chi² = 14.86, df = 18 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Chi² = 3.10, df = 3 (P = 0.38), I² = 3.2%
0.01 0.1 1 10 100
Favours experimental Favours control

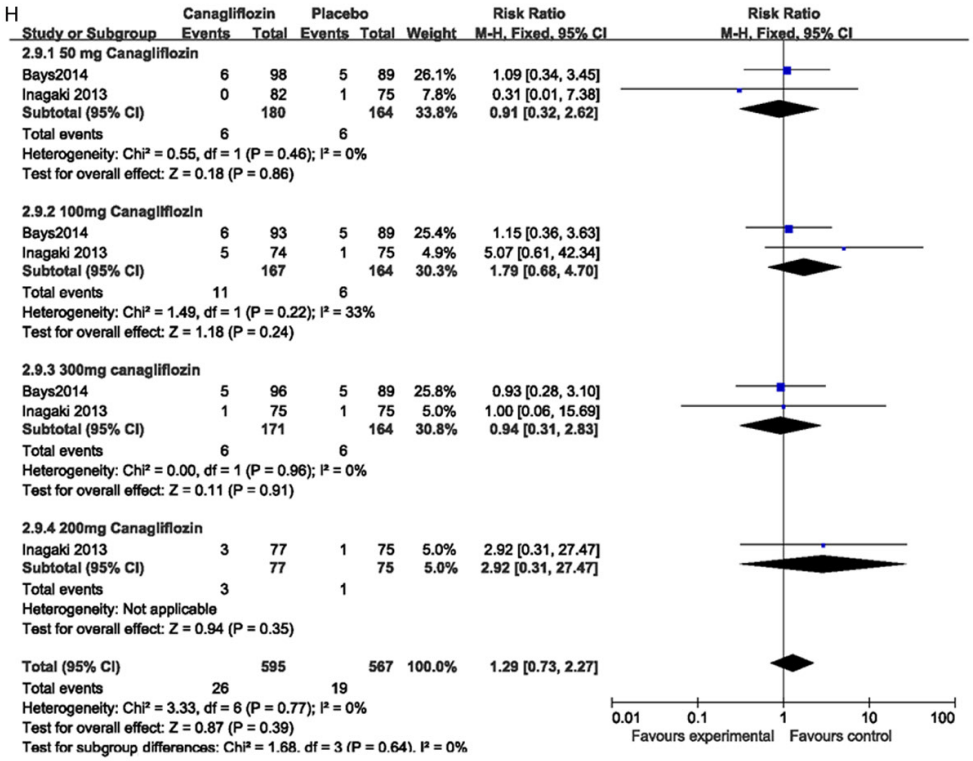
F


Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.7.1 100mg canagliflozin
Bode 2013 0 241 0 237 Not estimable
Lavalle-Gonzalez 2013 0 368 1 183 13.4% 0.17 [0.01, 4.06]
Leiter 2014 3 483 2 482 13.5% 1.50 [0.25, 8.92]
Li 2014 0 223 0 226 Not estimable
Stenlöf 2014 1 195 2 192 13.5% 0.49 [0.05, 5.38]
Wilding 2013 0 157 0 156 Not estimable
Yale 2013 1 90 1 90 6.7% 1.00 [0.06, 15.74]
Subtotal (95% CI) 1757 1566 47.2% 0.76 [0.25, 2.27]
Total events 5 6
Heterogeneity: Chi² = 1.59, df = 3 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
2.7.2 300mg canagliflozin
Bode 2013 0 236 0 237 Not estimable
Lavalle-Gonzalez 2013 1 367 1 183 9.0% 0.50 [0.03, 7.93]
Leiter 2014 3 485 2 482 13.5% 1.49 [0.25, 8.88]
Li 2014 0 227 0 226 Not estimable
Schernthaner 2013 2 378 0 378 3.4% 5.00 [0.24, 103.80]
Stenlöf 2014 0 197 2 192 17.0% 0.19 [0.01, 4.03]
Wilding 2013 0 156 0 156 Not estimable
Yale 2013 0 89 1 90 10.0% 0.34 [0.01, 8.16]
Subtotal (95% CI) 2135 1944 52.8% 0.91 [0.33, 2.48]
Total events 6 6
Heterogeneity: Chi² = 3.05, df = 4 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)
Total (95% CI) 3892 3510 100.0% 0.84 [0.40, 1.76]
Total events 11 12
Heterogeneity: Chi² = 4.67, df = 8 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

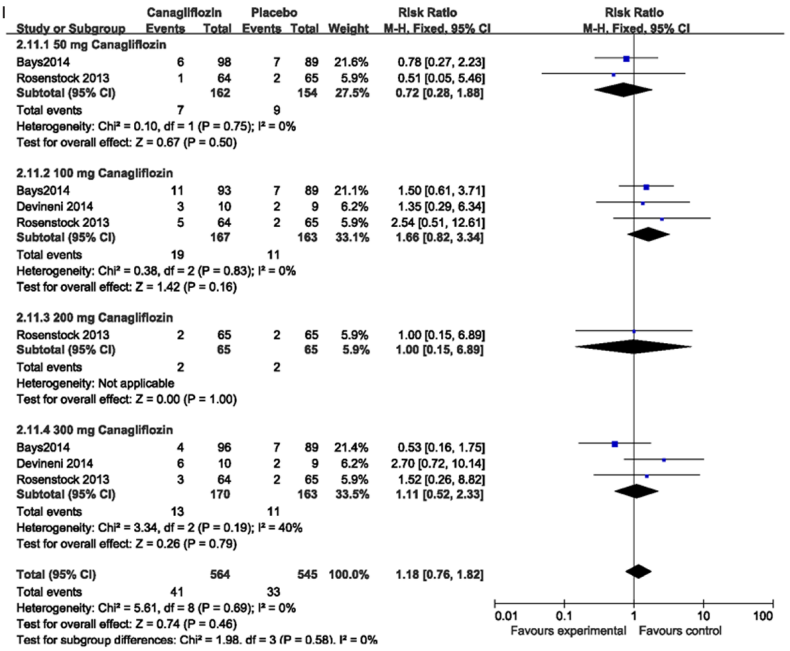
G


Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.8.1 50 mg Canagliflozin
Bays2014 6 98 3 89 4.4% 1.82 [0.47, 7.05]
Inagaki 2013 8 82 10 75 14.5% 0.73 [0.30, 1.76]
Rosenstock 2013 5 64 2 65 2.8% 2.54 [0.51, 12.61]
Subtotal (95% CI) 244 229 21.7% 1.18 [0.62, 2.26]
Total events 19 15
Heterogeneity: Chi² = 2.41, df = 2 (P = 0.30); I² = 17%
Test for overall effect: Z = 0.50 (P = 0.61)
2.8.2 100mg Canagliflozin
Bays2014 1 93 3 89 4.3% 0.32 [0.03, 3.01]
Inagaki 2013 10 74 10 75 13.8% 1.01 [0.45, 2.29]
Rosenstock 2013 0 64 2 65 3.5% 0.20 [0.01, 4.15]
Subtotal (95% CI) 231 229 21.5% 0.75 [0.36, 1.53]
Total events 11 15
Heterogeneity: Chi² = 1.81, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.43)
2.8.3 150mg Canagliflozin
Inagaki 2013 8 75 10 75 13.9% 0.80 [0.33, 1.92]
Subtotal (95% CI) 75 75 13.9% 0.80 [0.33, 1.92]
Total events 8 10
Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)
2.8.4 200mg Canagliflozin
Bays2014 1 96 3 89 4.3% 0.31 [0.03, 2.92]
Inagaki 2013 8 77 10 75 14.1% 0.78 [0.33, 1.87]
Rosenstock 2013 0 65 2 65 3.5% 0.20 [0.01, 4.09]
Subtotal (95% CI) 238 229 21.9% 0.59 [0.27, 1.28]
Total events 9 15
Heterogeneity: Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)
2.8.5 300mg canagliflozin
Bays2014 1 96 3 89 4.3% 0.31 [0.03, 2.92]
Inagaki 2013 9 75 10 75 13.9% 0.90 [0.39, 2.09]
Rosenstock 2013 1 64 2 65 2.8% 0.51 [0.05, 5.46]
Subtotal (95% CI) 235 229 21.0% 0.73 [0.35, 1.52]
Total events 11 15
Heterogeneity: Chi² = 0.89, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)
Total (95% CI) 1023 991 100.0% 0.81 [0.58, 1.13]
Total events 58 70
Heterogeneity: Chi² = 7.58, df = 12 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Chi² = 2.06, df = 4 (P = 0.72), I² = 0%
0.01 0.1 1 10 100
Favours experimental Favours control

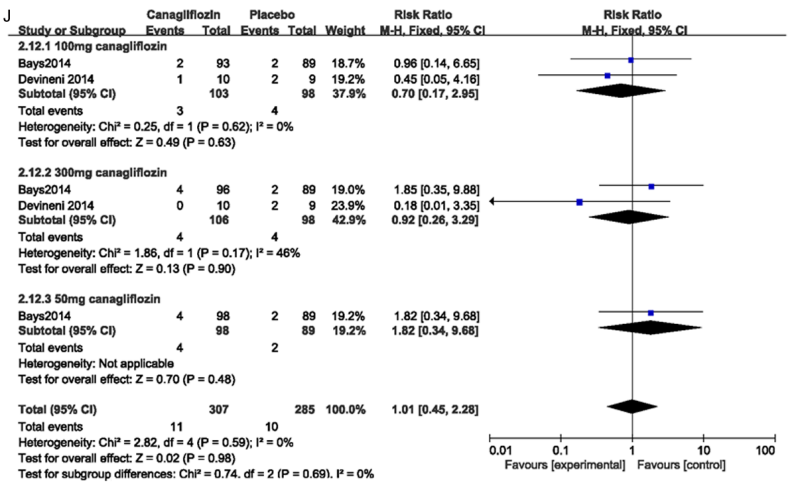
H


Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.9.1 50 mg Canagliflozin
Bays2014 6 98 5 89 26.1% 1.09 [0.34, 3.45]
Inagaki 2013 0 82 1 75 7.8% 0.31 [0.01, 7.38]
Subtotal (95% CI) 180 164 33.8% 0.91 [0.32, 2.62]
Total events 6 6
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)
2.9.2 100mg Canagliflozin
Bays2014 6 93 5 89 25.4% 1.15 [0.36, 3.63]
Inagaki 2013 5 74 1 75 4.9% 5.07 [0.61, 42.34]
Subtotal (95% CI) 167 164 30.3% 1.79 [0.68, 4.70]
Total events 11 6
Heterogeneity: Chi² = 1.49, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 1.18 (P = 0.24)
2.9.3 300mg canagliflozin
Bays2014 5 96 5 89 25.8% 0.93 [0.28, 3.10]
Inagaki 2013 1 75 1 75 5.0% 1.00 [0.06, 15.69]
Subtotal (95% CI) 171 164 30.8% 0.94 [0.31, 2.83]
Total events 6 6
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)
2.9.4 200mg Canagliflozin
Inagaki 2013 3 77 1 75 5.0% 2.92 [0.31, 27.47]
Subtotal (95% CI) 77 75 5.0% 2.92 [0.31, 27.47]
Total events 3 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)
Total (95% CI) 595 567 100.0% 1.29 [0.73, 2.27]
Total events 26 19
Heterogeneity: Chi² = 3.33, df = 6 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.39)
Test for subgroup differences: Chi² = 1.68, df = 3 (P = 0.64), I² = 0%
0.01 0.1 1 10 100
Favours experimental Favours control

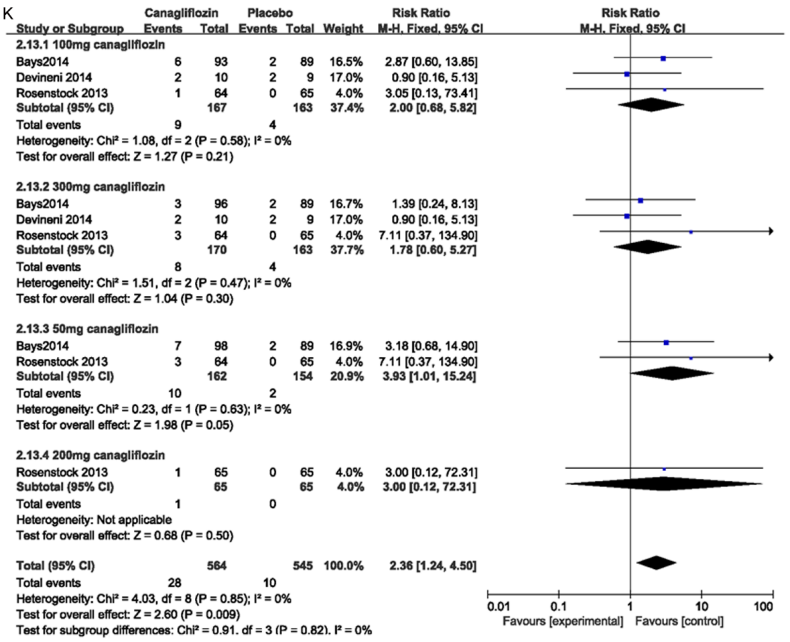
I


Canagliflozin Placebo Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
2.11.1 50 mg Canagliflozin
Bays2014 6 98 7 89 21.6% 0.78 [0.27, 2.23]
Rosenstock 2013 1 64 2 65 5.9% 0.51 [0.05, 5.46]
Subtotal (95% CI) 162 154 27.5% 0.72 [0.28, 1.88]
Total events 7 9
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)
2.11.2 100 mg Canagliflozin
Bays2014 11 93 7 89 21.1% 1.50 [0.61, 3.71]
Devineni 2014 3 10 2 9 6.2% 1.35 [0.29, 6.34]
Rosenstock 2013 5 64 2 65 5.9% 2.54 [0.51, 12.61]
Subtotal (95% CI) 167 163 33.1% 1.66 [0.82, 3.34]
Total events 19 11
Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)
2.11.3 200 mg Canagliflozin
Rosenstock 2013 2 65 2 65 5.9% 1.00 [0.15, 6.89]
Subtotal (95% CI) 65 65 5.9% 1.00 [0.15, 6.89]
Total events 2 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
2.11.4 300 mg Canagliflozin
Bays2014 4 96 7 89 21.4% 0.53 [0.16, 1.75]
Devineni 2014 6 10 2 9 6.2% 2.70 [0.72, 10.14]
Rosenstock 2013 3 64 2 65 5.9% 1.52 [0.26, 8.82]
Subtotal (95% CI) 170 163 33.5% 1.11 [0.52, 2.33]
Total events 13 11
Heterogeneity: Chi² = 3.34, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 0.26 (P = 0.79)
Total (95% CI) 564 545 100.0% 1.18 [0.76, 1.82]
Total events 41 33
Heterogeneity: Chi² = 5.81, df = 8 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Chi² = 1.98, df = 3 (P = 0.58), I² = 0%
0.01 0.1 1 10 100
Favours experimental Favours control

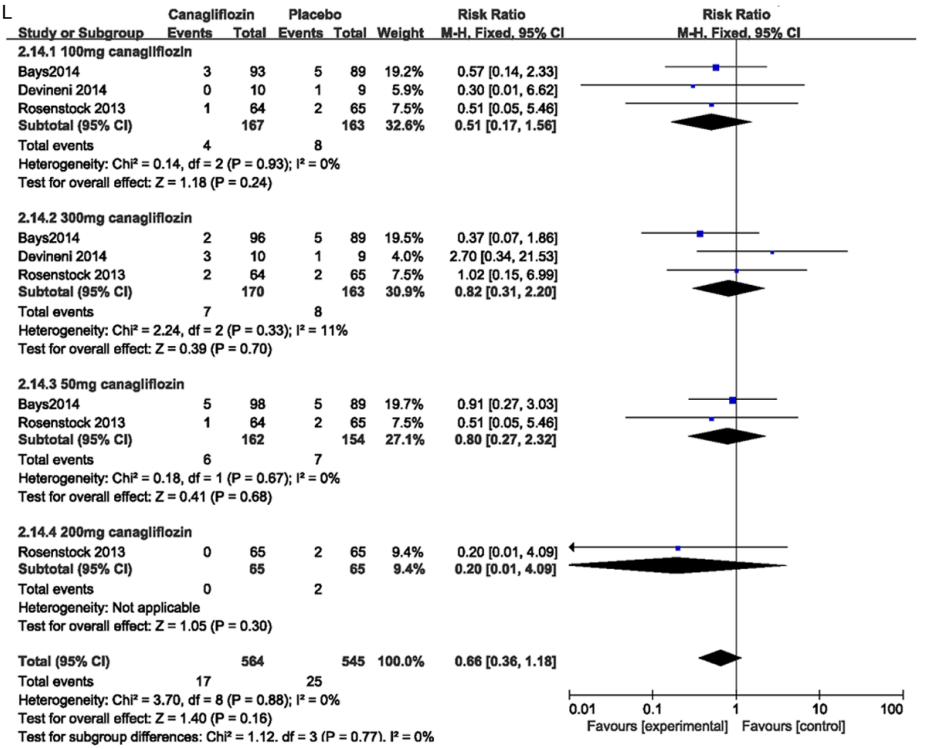
J


Canagliflozin Placebo Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
2.12.1 100mg canagliflozin
Bays2014 2 93 2 89 18.7% 0.96 [0.14, 6.65]
Devineni 2014 1 10 2 9 19.2% 0.45 [0.05, 4.16]
Subtotal (95% CI) 103 98 37.9% 0.70 [0.17, 2.95]
Total events 3 4
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.63)
2.12.2 300mg canagliflozin
Bays2014 4 96 2 89 19.0% 1.85 [0.35, 9.88]
Devineni 2014 0 10 2 9 23.9% 0.18 [0.01, 3.35]
Subtotal (95% CI) 106 98 42.9% 0.92 [0.26, 3.29]
Total events 4 4
Heterogeneity: Chi² = 1.86, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 0.13 (P = 0.90)
2.12.3 50mg canagliflozin
Bays2014 4 98 2 89 19.2% 1.82 [0.34, 9.68]
Subtotal (95% CI) 98 89 19.2% 1.82 [0.34, 9.68]
Total events 4 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Total (95% CI) 307 285 100.0% 1.01 [0.45, 2.28]
Total events 11 10
Heterogeneity: Chi² = 2.82, df = 4 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Chi² = 0.74, df = 2 (P = 0.69), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

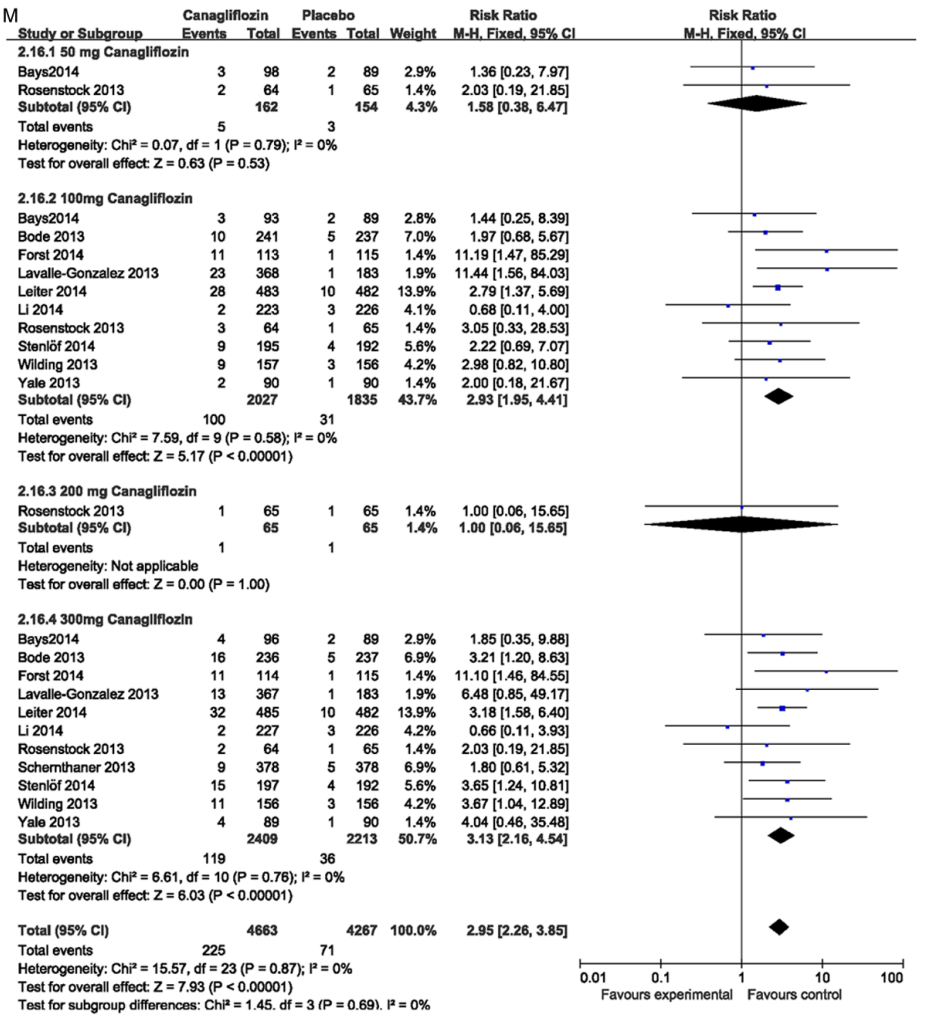
K


Canagliflozin Placebo Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
2.13.1 100mg canagliflozin
Bays2014 6 93 2 89 16.5% 2.87 [0.60, 13.85]
Devineni 2014 2 10 2 9 17.0% 0.90 [0.16, 5.13]
Rosenstock 2013 1 64 0 65 4.0% 3.05 [0.13, 73.41]
Subtotal (95% CI) 167 163 37.4% 2.00 [0.68, 5.82]
Total events 9 4
Heterogeneity: Chi² = 1.08, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.27 (P = 0.21)
2.13.2 300mg canagliflozin
Bays2014 3 96 2 89 16.7% 1.39 [0.24, 8.13]
Devineni 2014 2 10 2 9 17.0% 0.90 [0.16, 5.13]
Rosenstock 2013 3 64 0 65 4.0% 7.11 [0.37, 134.90]
Subtotal (95% CI) 170 163 37.7% 1.78 [0.60, 5.27]
Total events 8 4
Heterogeneity: Chi² = 1.51, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)
2.13.3 50mg canagliflozin
Bays2014 7 98 2 89 16.9% 3.18 [0.68, 14.90]
Rosenstock 2013 3 64 0 65 4.0% 7.11 [0.37, 134.90]
Subtotal (95% CI) 162 154 20.9% 3.93 [1.01, 15.24]
Total events 10 2
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)
2.13.4 200mg canagliflozin
Rosenstock 2013 1 65 0 65 4.0% 3.00 [0.12, 72.31]
Subtotal (95% CI) 65 65 4.0% 3.00 [0.12, 72.31]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Total (95% CI) 564 545 100.0% 2.36 [1.24, 4.50]
Total events 28 10
Heterogeneity: Chi² = 4.03, df = 8 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)
Test for subgroup differences: Chi² = 0.91, df = 3 (P = 0.82), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

L


Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.14.1 100mg canagliflozin
Bays2014 3 93 5 89 19.2% 0.57 [0.14, 2.33]
Devineni 2014 0 10 1 9 5.9% 0.30 [0.01, 6.62]
Rosenstock 2013 1 64 2 65 7.5% 0.51 [0.05, 5.46]
Subtotal (95% CI) 167 163 32.6% 0.51 [0.17, 1.56]
Total events 4 8
Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)
2.14.2 300mg canagliflozin
Bays2014 2 96 5 89 19.5% 0.37 [0.07, 1.86]
Devineni 2014 3 10 1 9 4.0% 2.70 [0.34, 21.53]
Rosenstock 2013 2 64 2 65 7.5% 1.02 [0.15, 6.99]
Subtotal (95% CI) 170 163 30.9% 0.82 [0.31, 2.20]
Total events 7 8
Heterogeneity: Chi² = 2.24, df = 2 (P = 0.33); I² = 11%
Test for overall effect: Z = 0.39 (P = 0.70)
2.14.3 50mg canagliflozin
Bays2014 5 98 5 89 19.7% 0.91 [0.27, 3.03]
Rosenstock 2013 1 64 2 65 7.5% 0.51 [0.05, 5.46]
Subtotal (95% CI) 162 154 27.1% 0.80 [0.27, 2.32]
Total events 6 7
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)
2.14.4 200mg canagliflozin
Rosenstock 2013 0 65 2 65 9.4% 0.20 [0.01, 4.09]
Subtotal (95% CI) 65 65 9.4% 0.20 [0.01, 4.09]
Total events 0 2
Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.30)
Total (95% CI) 564 545 100.0% 0.66 [0.36, 1.18]
Total events 17 25
Heterogeneity: Chi² = 3.70, df = 8 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Chi² = 1.12. df = 3 (P = 0.77). I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

M


Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.16.1 50 mg Canagliflozin
Bays2014 3 98 2 89 2.9% 1.36 [0.23, 7.97]
Rosenstock 2013 2 64 1 65 1.4% 2.03 [0.19, 21.85]
Subtotal (95% CI) 162 154 4.3% 1.58 [0.38, 6.47]
Total events 5 3
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)
2.16.2 100mg Canagliflozin
Bays2014 3 93 2 89 2.8% 1.44 [0.25, 8.39]
Bode 2013 10 241 5 237 7.0% 1.97 [0.68, 5.67]
Forst 2014 11 113 1 115 1.4% 11.19 [1.47, 85.29]
Lavalle-Gonzalez 2013 23 368 1 183 1.9% 11.44 [1.56, 84.03]
Leiter 2014 28 483 10 482 13.9% 2.79 [1.37, 5.69]
Li 2014 2 223 3 226 4.1% 0.68 [0.11, 4.00]
Rosenstock 2013 3 64 1 65 1.4% 3.05 [0.33, 28.53]
Stenlöf 2014 9 195 4 192 5.6% 2.22 [0.69, 7.07]
Wilding 2013 9 157 3 156 4.2% 2.98 [0.82, 10.80]
Yale 2013 2 90 1 90 1.4% 2.00 [0.18, 21.67]
Subtotal (95% CI) 2027 1835 43.7% 2.93 [1.95, 4.41]
Total events 100 31
Heterogeneity: Chi² = 7.59, df = 9 (P = 0.58); I² = 0%
Test for overall effect: Z = 5.17 (P < 0.00001)
2.16.3 200 mg Canagliflozin
Rosenstock 2013 1 65 1 65 1.4% 1.00 [0.06, 15.65]
Subtotal (95% CI) 65 65 1.4% 1.00 [0.06, 15.65]
Total events 1 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
2.16.4 300mg Canagliflozin
Bays2014 4 96 2 89 2.9% 1.85 [0.35, 9.88]
Bode 2013 16 236 5 237 6.9% 3.21 [1.20, 8.63]
Forst 2014 11 114 1 115 1.4% 11.10 [1.46, 84.55]
Lavalle-Gonzalez 2013 13 367 1 183 1.9% 6.48 [0.85, 49.17]
Leiter 2014 32 485 10 482 13.9% 3.18 [1.58, 6.40]
Li 2014 2 227 3 226 4.2% 0.66 [0.11, 3.93]
Rosenstock 2013 2 64 1 65 1.4% 2.03 [0.19, 21.85]
Schernthaner 2013 9 378 5 378 6.9% 1.80 [0.61, 5.32]
Stenlöf 2014 15 197 4 192 5.6% 3.65 [1.24, 10.81]
Wilding 2013 11 156 3 156 4.2% 3.67 [1.04, 12.89]
Yale 2013 4 89 1 90 1.4% 4.04 [0.46, 35.48]
Subtotal (95% CI) 2409 2213 50.7% 3.13 [2.16, 4.54]
Total events 119 36
Heterogeneity: Chi² = 6.61, df = 10 (P = 0.76); I² = 0%
Test for overall effect: Z = 6.03 (P < 0.00001)
Total (95% CI) 4663 4267 100.0% 2.95 [2.26, 3.85]
Total events 225 71
Heterogeneity: Chi² = 15.57, df = 23 (P = 0.87); I² = 0%
Test for overall effect: Z = 7.93 (P < 0.00001)
Test for subgroup differences: Chi² = 1.45. df = 3 (P = 0.69). I² = 0%
0.01 0.1 1 10 100
Favours experimental Favours control

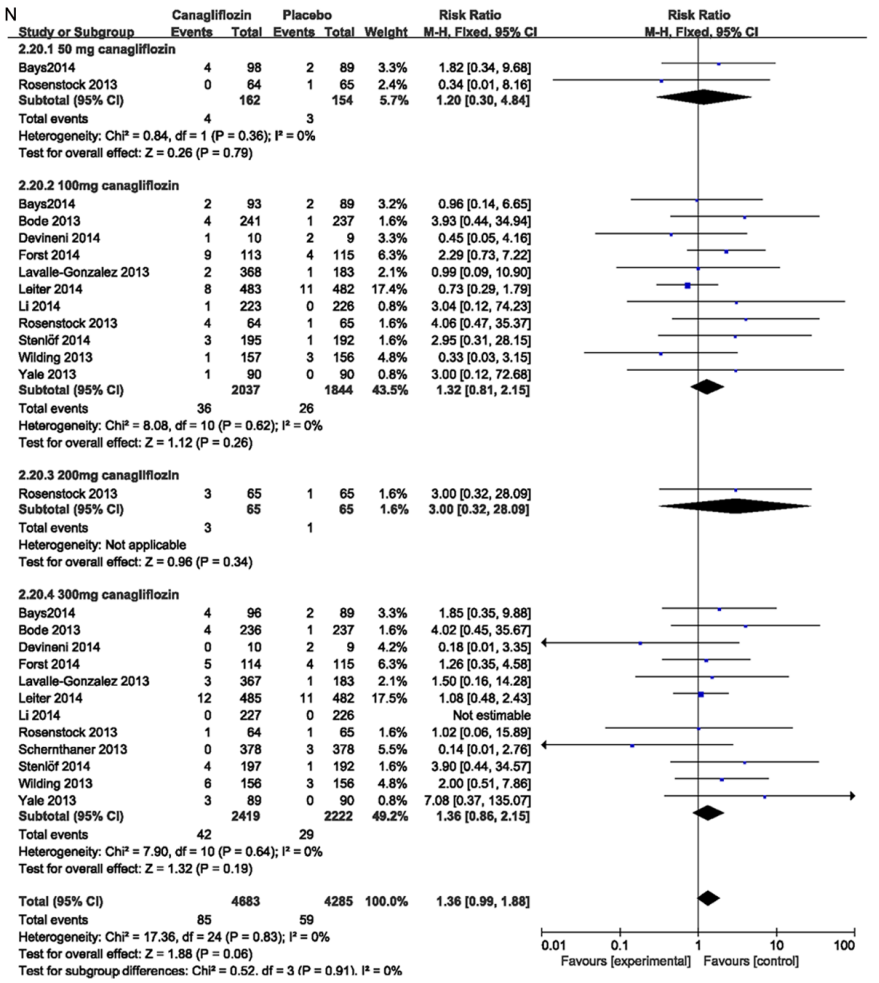

N
Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.20.1 50 mg canagliflozin
Bays2014 4 98 2 89 3.3% 1.82 [0.34, 9.68]
Rosenstock 2013 0 64 1 65 2.4% 0.34 [0.01, 8.16]
Subtotal (95% CI) 162 154 5.7% 1.20 [0.30, 4.84]
Total events 4 3
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)
2.20.2 100mg canagliflozin
Bays2014 2 93 2 89 3.2% 0.96 [0.14, 6.65]
Bode 2013 4 241 1 237 1.6% 3.93 [0.44, 34.94]
Devineni 2014 1 10 2 9 3.3% 0.45 [0.05, 4.16]
Forst 2014 9 113 4 115 6.3% 2.29 [0.73, 7.22]
Lavalle-Gonzalez 2013 2 368 1 183 2.1% 0.99 [0.09, 10.90]
Leiter 2014 8 483 11 482 17.4% 0.73 [0.29, 1.79]
Li 2014 1 223 0 226 0.8% 3.04 [0.12, 74.23]
Rosenstock 2013 4 64 1 65 1.6% 4.06 [0.47, 35.37]
Stenlöf 2014 3 195 1 192 1.6% 2.95 [0.31, 28.15]
Wilding 2013 1 157 3 156 4.8% 0.33 [0.03, 3.15]
Yale 2013 1 90 0 90 0.8% 3.00 [0.12, 72.68]
Subtotal (95% CI) 2037 1844 43.5% 1.32 [0.81, 2.15]
Total events 36 26
Heterogeneity: Chi² = 8.08, df = 10 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)
2.20.3 200mg canagliflozin
Rosenstock 2013 3 65 1 65 1.6% 3.00 [0.32, 28.09]
Subtotal (95% CI) 65 65 1.6% 3.00 [0.32, 28.09]
Total events 3 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)
2.20.4 300mg canagliflozin
Bays2014 4 96 2 89 3.3% 1.85 [0.35, 9.88]
Bode 2013 4 236 1 237 1.6% 4.02 [0.45, 35.67]
Devineni 2014 0 10 2 9 4.2% 0.18 [0.01, 3.35]
Forst 2014 5 114 4 115 6.3% 1.26 [0.35, 4.58]
Lavalle-Gonzalez 2013 3 367 1 183 2.1% 1.50 [0.16, 14.28]
Leiter 2014 12 485 11 482 17.5% 1.08 [0.48, 2.43]
Li 2014 0 227 0 226 Not estimable
Rosenstock 2013 1 64 1 65 1.6% 1.02 [0.06, 15.89]
Scherrthaner 2013 0 378 3 378 5.5% 0.14 [0.01, 2.76]
Stenlöf 2014 4 197 1 192 1.6% 3.90 [0.44, 34.57]
Wilding 2013 6 156 3 156 4.8% 2.00 [0.51, 7.86]
Yale 2013 3 89 0 90 0.8% 7.08 [0.37, 135.07]
Subtotal (95% CI) 2419 2222 49.2% 1.36 [0.86, 2.15]
Total events 42 29
Heterogeneity: Chi² = 7.90, df = 10 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)
Total (95% CI) 4683 4285 100.0% 1.36 [0.99, 1.88]
Total events 85 59
Heterogeneity: Chi² = 17.36, df = 24 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.88 (P = 0.06)
Test for subgroup differences: Chi² = 0.52. df = 3 (P = 0.91). I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
O
Canagliflozin
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.21.1 50 mg Canagliflozin
Bays2014 17 98 9 89 18.3% 1.72 [0.81, 3.65]
Inagaki 2013 3 82 3 75 6.1% 0.91 [0.19, 4.39]
Rosenstock 2013 4 64 2 65 3.9% 2.03 [0.39, 10.70]
Subtotal (95% CI) 244 229 28.3% 1.59 [0.85, 2.96]
Total events 24 14
Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)
2.21.2 100 mg Canagliflozin
Bays2014 12 93 9 89 17.9% 1.28 [0.57, 2.88]
Devineni 2014 2 10 3 9 6.1% 0.60 [0.13, 2.82]
Inagaki 2013 1 74 0 0 Not estimable
Rosenstock 2013 2 64 2 65 3.9% 1.02 [0.15, 6.99]
Subtotal (95% CI) 241 163 27.9% 1.09 [0.56, 2.13]
Total events 17 14
Heterogeneity: Chi² = 0.72, df = 2 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)
2.21.3 200 mg Canagliflozin
Inagaki 2013 1 77 3 75 5.9% 0.32 [0.03, 3.05]
Rosenstock 2013 1 65 2 65 3.9% 0.50 [0.05, 5.38]
Subtotal (95% CI) 142 140 9.8% 0.39 [0.08, 2.00]
Total events 2 5
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)
2.21.4 300 mg Canagliflozin
Bays2014 7 96 9 89 18.2% 0.72 [0.28, 1.85]
Devineni 2014 4 10 3 9 6.1% 1.20 [0.36, 3.97]
Inagaki 2013 1 75 3 75 5.8% 0.33 [0.04, 3.13]
Rosenstock 2013 5 64 2 65 3.9% 2.54 [0.51, 12.61]
Subtotal (95% CI) 245 238 34.0% 0.95 [0.51, 1.77]
Total events 17 17
Heterogeneity: Chi² = 2.76, df = 3 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)
Total (95% CI) 872 770 100.0% 1.11 [0.78, 1.59]
Total events 60 50
Heterogeneity: Chi² = 7.11, df = 11 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Chi² = 3.06. df = 3 (P = 0.38). I² = 2.0%
0.01 0.1 1 10 100
Favours experimental Favours control

Figure 3. Safety profile of canagliflozin compared with active agents or placebo in forest plot. A: Genital infection; B: Vulvovaginal mycotic infection; C: Urinary tract infection; D: Hypoglycaemia; E: Severe hypoglycaemia; F: Dealth; G: Nasopharyngitis; H: Upper respiratory inflammation; I: Headache; J: Dizziness; K: Nausea; L: Diarrhea; M: Osmotic diuresis related AEs; N: Volume depletion related AEs; O: GI related AEs.

(**Figure 3D**), but it did not increase the risk ofsevere hypoglycaemia (RR=1.01; 95% CI (0.67-1.52); P=0.96; I^2=0%) (**Figure 3E**).

Death

A total of 8 RCTs (n=7402) reported 23 deaths. Canagliflozin was associated with a lower death rate (RR 0.84; 95% CI (0.40-1.76); P=0.64; I^2=0%) (**Figure 3F**).

Nasopharyngitis and upper respiratory inflammation

Canagliflozin was revealed to have a relatively lower risk of nasopharyngitis (RR 0.81; 95% CI (0.58-1.13); P=0.21; I^2=0%) (**Figure 3G**). However, canagliflozin was associated with a slightly higher risk of upper respiratory inflammation (RR 1.29; 95% CI (0.73-2.27); P=0.39; I^2=0%) (**Figure 3H**).

Headache and dizziness

Canagliflozin did not increase the risk of headache (RR 1.18; 95% CI (0.76-1.82); P=0.46; I^2=0%) (**Figure 3I**), or the incidence of dizziness (RR 1.01; 95% CI (0.45-2.28); P=0.98; I^2=0%) (**Figure 3J**).

Nausea and diarrhea

A total of 38 patients were identified with nausea among 3 RCTs (n=1109). Canagliflozin was associated with a higher risk of nausea(RR 2.36; 95% CI (1.24-4.50); P=0.009; I^2=0%) (**Figure 3K**). However, canagliflozin was associated with a slightly lower incidence of diarrhea (RR 0.66; 95% CI (0.36-1.18); P=0.16; I^2=0%) (**Figure 3L**).

Other adverse events

Canagliflozinwas revealed to have a strongly higher risk of osmotic diuresis related AEs (RR 2.95; 95% CI (2.26-3.85); P< 0.00001; I^2=0%) (**Figure 3M**), and it slightly increase the risk of volume depletion related AEs(RR 1.36; 95% CI (0.99-1.88); P=0.06; I^2=0%) (**Figure 3N**). However, canagliflozin did not increase the risks of GI related AEs (RR 1.11; 95% CI (0.78-1.59); P=0.55; I^2=0%) (**Figure 3O**). In addition, Bays et al. [26] also reported 9 cases of sinusitis in canagliflozin group, 10 cases of constipation in canagliflozin group and 6 cases in control group. Rosenstock et al. [25] reported 8 cases of pollakiuria in canagliflozin group and 4 in control group.

Discussion

This systematic review provided themost up-to-date summary considering thesafety of canagliflozin as of February 2015.In this meta-analysis, we compared canagliflozinwith placebo or other AHAs from safety aspect. The results demonstrated that canagliflozin significantly increase the risk of genital infections, osmotic duresis related AEs, vulvovaginal mycotic infection and nausea. Canagliflozin was also associated with a slightly increased risk of volume depletion related AEs, upper respiratory inflammation, and hypoglycaemia, but it didn't increase the risk of severe hypoglycemia, UTI, GI related AEs or dizziness.

The meta-analysis showed that canagliflorin act well as an add-on drug to previous conventional AHAs in terms of safety. Previous RCTs demonstrated that a more severe situation of insulin resistance and other complications was made by many AHAsin T2DM patients [8]. For instance, sulphonulureas, glitazonesand insulin lead to weight gain, sulphonylureas and insulin lead to hypoglycaemia and pioglitazone can lead to edema, heart failure and fractures [16]. In our study, canagliflozin showed well tolerance among T2DM patients and most of the AEs mentioned above were hardly significant during the treatment.

The optimum dose of canagliflozin for T2DM treatment remains controversial. In most of included RCTs, 100 and 300 mg canagliflozin were adopted. Previous evidences suggested the preferred dose of canagliflozin was 100 mg per day since AEs appeared to be moderate,andhigher dosage would not lead to improvement in efficiency [15]. From economy aspect, canagliflozin appears to be less competitive compared with sulphonylureas [16].

However, canagliflozin could be the first choice for those T2DM patients who are insufficiently controlled or having problems tolerating conventional drugs like metformin and sulphonylureas.

AEs were evaluated in all RCTs included in this meta-analysis. Overall, canagliflozin was well tolerated in most of the trials. Most of the AEs were mild and transient. Some AEs like genital infection and osmotic duresis were significantly enhanced in canagliflozin groups compared with control. The incidences of some serious AEs like death were slightly lower across placebo andcontrol agents.

UTIs

It is obvious that glucosuria caused by treatment of canagliflozin is likely to induce UTI since glucose is the culture medium of bacteria. Some trails did show the increase risk of UTI, while in our study the incidence of UTI didn't increase with canagliflozin treatment compared with control. UTIs were very common in canagliflozin but usually moderate and responded well to normal therapy. The mechanisms remain controversial. It may be attributed to the increased glycosuria which may predispose to bacteria [15]. Since the results showed that canagliflozin was related to a higher risk of UTIs, T2DM patients treating with canagliflozin should be noted to report clinical signs and symptoms of UTIs to their physicians in time. A monitor for UTIs is appropriate to prevent furtherrenal infections. Future RCTs are expected to evaluate the safety of canagliflozin among patients with renal disfunction

Genetic mycotic infection

Genetic mycotic infectionshowed strong correlations with canagliflozin in our study. Fortunately, the infections are usually not serious and are easy to treat. Nevertheless, both patients and doctors should pay close attention to it.The increased genetic mycotic infection could be related to the increase in urinary glucose excretion by canagliflozin. Infection recurrent frequently and patients with history of genital mycotic infections are more prone to develop this type of infection [37]. Canagliflozin was revealed to increase the incidence of renal-related AEs in subjectswith moderate renal impairment more easily compared with control. In that case, patients with mild tomoderate renal insufficiency should monitor kidney functionand adjust the dosage more carefully.

Osmotic diuresis

Osmotic diuresis is another AE that strongly correlated with canagliflozin treatment. Indeed, the osmotic diuresis we discussed is distinct from classical osmotic diuresis for the loss of sodium, which may attributed to the co-transport with glucose by SGLT2 [9]. Osmotic diuresis along with volume depletion may contribute to the decrease in blood pressure, hypotension, postural dizziness, which may attribute to improvement of T2DM.

Hypoglycemia

Given the mechanism of SGLT2 receptor inhibitors, the risk and severity of hypoglycaemia would be expected to be low. The majority of glucose reabsorption is managed by the early proximal renal tubule in kidney, where SGLT2 is mainly expressed [38, 39]. The threshold for hypoglycemia (RTG) is 72 mg/dL, and the RTG is among 80 to 90 mg/dL with canagliflozin treatment [36], which is not low enough to cause severe hypoglycemia. The background treatment like metformin is presented as the high risk factors to hypoglycemia incidence [40]. Similarly, one previous study carried out by Nauck et al. [41] found that the incident of hypoglycaemia is notably higher in the sulphonyurea group than that in canagliflozin group.The presented meta-analysis also concluded that canaglflozin did not increase the incidence of severe hypoglycemia.Moreover, the ADA guidelines emphasized the necessity to add SGLT2 inhibitor in the treatment of T2DM in order to prevent hypoglycemiawhile reduce the dose of other AHAs (including insulin) at the same time [2].

Other AEs

Other sideeffects include:dizziness, headache, upper respiratory inflammation, nausea, GI related AEs, death, nasopharyngitis and diarrhea. Interestingly, canagliflozinwas associated with a lower risk of diarrhea, death or nasopharyngitis.Several rare AEs that were reported in a single research like increased blood ketone bodies, hypoglycaemia unawareness, gastrointestinal disorders, malaise and pollakiuriawere not included in meta-analysis.

Totally3 systemic reviews [14-16] had assessed the efficacy and safety of the SGLT2 inhibitors (including canagliflorin)in the treatment of T2DM. To compare, our review had several differences and stimulating points. First, only one RCT of canagliflozin was enrolled in Clar [16] and Musso's [15] research, while we included 13 RCTs that solely focus on canagliflozin; Second, they accessed both efficiency and safety while our meta-analysis was dedicated to safety assessment, which would be more specific.In our study, 14 RCTs were included and were divided into 4 subgroups based on the dosage of canagliflozin. 100 mg and 300 mg dosage groups were adopted in most RCTs, whereas the 50 mg and 200 mg groups were only included in 3 RCTs [2, 25, 26], and 1209 patients were enrolled to that arm. Actually, no significant differences were detected between subgroups with different doses. In order to keep the constancy of the meta-analysis, we adopted the overalleffects of each particular AE, regardless of its subgroups. Plus, statics in this meta-analysis showed that the SGLT2 receptor inhibitors might be especially useful in patients with longer duration. The capacity of β cell was diminishedunder long-termtreatment of other agents like sulphonylureas.

There were no strict limitations of the application of canagloflozin. These findings may help physicians make advisable decision for the treatment of T2DM. However, some limitations should be noted in this meta-analysis: 1) The limited number of existing RCTs may increase the risk of overestimating the R^2 in meta-regression. 2) For each AE, we used the whole effects of ranged dose of canagliflozin to keep consistency of the study. However, if significant differences appeared between subgroups, they were discussed separately. 3) Fiveof the included RCTs were sponsored by institutions or corporations, which might introduce some potential bias, due to a concern that industry funding was strongly associated with favorable outcomes. We will update out meta-analysis with further RCTs that have proper registration and less potential biases. 4) There were some additional issues that should be noted in post-marketing surveillance including relationships with cardiovascular events and weight loss, decrease in blood pressure and safety of the appliance in children and pregnancy with T2DM.

Generally, our meta-analysis focused on the overall safety of canagliflozin, disregarded the duration and sample capacity. However, before clinical practicing, evaluation for long-term safety of canagliflozin is needed, which requiresRCTs with adequate power and duration. In conclusion, canagliflorin was a relatively safe T2DM drugs both for monotherapy and add-on treatment assessed from existing researches, but the increased risk of genital infection, osmotic duresis related AEs and nausea should not be neglected.

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Shisheng He and Zhengqi Chen, Department of Orthopedic, Shanghai Tenth People's Hospital, Tongji University School of Medicine, 301 Yanchang Road, Shanghai 200072, China. Tel: +86-18117491620; Fax: +86-21-6630-0588; E-mail: tjhss7418@foxmail.com (SSH); Zhengqichen301@sina.com (ZQC)

References

[1] Riser Taylor S and Harris KB. The clinical efficacy and safety of sodium glucose cotransporter-2 inhibitors in adults with type 2 diabetes mellitus. Pharmacotherapy 2013; 33: 984-999.

[2] Inagaki N, Kondo K, Yoshinari T, Maruyama N, Susuta Y and Kuki H. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab 2013; 15: 1136-45.

[3] Stumvoll M, Goldstein BJ and van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet 2005; 365: 1333-1346.

[4] Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia 2003; 46: 3-19.

[5] Stenlöf K, Cefalu WT, Kim KA, Jodar E, Alba M, Edwards R, Tong C, Canovatchel W and Meininger G. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Curr Med Res Opin 2014; 30: 163-175.

[6] Wilding JP, Charpentier G, Hollander P, Gonzalez-Galvez G, Mathieu C, Vercruysse F, Usiskin K, Law G, Black S, Canovatchel W and Meininger G. Efficacy and safety of canagliflozin in patients with type 2 diabetes melli-

tus inadequately controlled with metformin and sulphonylurea: a randomised trial. Int J Clin Pract 2013; 67: 1267-1282.
[7] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R and Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38: 140-149.
[8] Tahrani AA, Bailey CJ, Del Prato S and Barnett AH. Management of type 2 diabetes: new and future developments in treatment. Lancet 2011; 378: 182-197.
[9] Haas B, Eckstein N, Pfeifer V, Mayer P and Hass MD. Efficacy, safety and regulatory status of SGLT2 inhibitors: focus on canagliflozin. Nutr Diabetes 2014; 4: e143.
[10] Neumiller JJ, White JR Jr and Campbell RK. Sodium-glucose co-transport inhibitors: progress and therapeutic potential in type 2 diabetes mellitus. Drugs 2010; 70: 377-385.
[11] Simonyi G. [New possibility in the oral glucose lowering treatment of type 2 diabetes mellitus: sodium-glucose co-transporter-2 inhibitors]. Orv Hetil 2012; 153: 695-701.
[12] Chao EC and Henry RR. SGLT2 inhibition--a novel strategy for diabetes treatment. Nat Rev Drug Discov 2010; 9: 551-559.
[13] Lamos EM, Younk LM and Davis SN. Canagliflozin, an inhibitor of sodium-glucose co-transporter 2, for the treatment of type 2 diabetes mellitus. Expert Opin Drug Metab Toxicol 2013; 9: 763-775.
[14] Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, Sarigianni M, Matthews DR and Tsapas A. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013; 159: 262-274.
[15] Musso G, Gambino R, Cassader M and Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. Ann Med 2012; 44: 375-393.
[16] Clar C, Gill JA, Court R and Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012; 2.
[17] Boyle LD and Wilding JP. A safety evaluation of canagliflozin : a first-in-class treatment for type 2 diabetes. Expert Opin Drug Saf 2014; 13: 1535-1544.
[18] Mikhail N. Safety of canagliflozin in patients with type 2 diabetes. Curr Drug Saf 2014; 9: 127-132.
[19] Doggrell SA and McIntyre K. Canagliflozin-something new for type 2 diabetes, but is it safe and efficacious? Expert Opin Pharmacother 2014; 15: 437-441.
[20] da Costa Santos CM, de Mattos Pimenta CA and Nobre MR. The PICO strategy for the research question construction and evidence search. Rev Lat Am Enfermagem 2007; 15: 508-511.
[21] J. G. Higgins, S., editors. The Cochrane Collaboration., Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. [updated March 2011]. Available from www.cochrane-handbook.org, (2011).
[22] Knobloch K, Yoon U and Vogt PM. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias. J Craniomaxillofac Surg 2011; 39: 91-92.
[23] In: Higgins JGS, editors. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions version 5.0.2. [updated March 2011]. Available from www.cochrane-handbook. org 2011.
[24] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[25] Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, Capuano G and Canovatchel W. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012; 35: 1232-1238.
[26] Bays HE, Weinstein R, Law G and Canovatchel W. Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. Obesity (Silver Spring) 2014; 22: 1042-1049.
[27] Bode B, Stenlof K, Harris S, Sullivan D, Fung A, Usiskin K and Meininger G. Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. Diabetes Obes Metab 2015; 17: 294-303.
[28] Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W and Meininger G. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. Diabetes Care 2013; 36: 2508-2515.
[29] Lavalle-González FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W and Meininger G. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia 2013; 56: 2582-2592.
[30] Forst T, Guthrie R, Goldenberg R, Yee J, Vijapurkar U, Meininger G and Stein P. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background met-

formin and pioglitazone. Diabetes Obes Metab 2014; 16: 467-477.
[31] Ji L, Han P, Liu Y, Yang G, Dieu Van N, Vijapurkar U, Qiu R and Meininger G. Canagliflozin in Asian patients with type 2 diabetes on metformin alone or metformin in combination with sulphonylurea. Diabetes Obes Metab 2015; 17: 23-31.
[32] Leiter LA, Yoon KH, Arias P, Langslet G, Xie J, Balis DA, Millington D, Vercruysse F, Canovatchel W and Meininger G. Canagliflozin Provides Durable Glycemic Improvements and Body Weight Reduction Over 104 Weeks Versus Glimepiride in Patients With Type 2 Diabetes on Metformin: A Randomized, Double-Blind, Phase 3 Study. Diabetes Care 2015; 38: 355-64.
[33] Nyirjesy P, Zhao Y, Ways K and Usiskin K. Evaluation of vulvovaginal symptoms and Candida colonization in women with type 2 diabetes mellitus treated with canagliflozin, a sodium glucose co-transporter 2 inhibitor. Curr Med Res Opin 2012; 28: 1173-1178.
[34] Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, Figueroa K, Wajs E, Usiskin K and Meininger G. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013; 15: 463-473.
[35] Stein P, Berg JK, Morrow L, Polidori D, Artis E, Rusch S, Vaccaro N and Devineni D. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, reduces post-meal glucose excursion in patients with type 2 diabetes by a non-renal mechanism: results of a randomized trial. Metabolism 2014; 63: 1296-1303.
[36] Devineni D, Morrow L, Hompesch M, Skee D, Vandebosch A, Murphy J, Ways K and Schwartz S. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. Diabetes Obes Metab 2012; 14: 539-545.
[37] Pfister M, Whaley JM, Zhang L and List JF. Inhibition of SGLT2: a novel strategy for treatment of type 2 diabetes mellitus. Clin Pharmacol Ther 2011; 89: 621-625.
[38] Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G and Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes 2005; 54: 3427-3434.
[39] Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabet Med 2010; 27: 136-142.
[40] Nisly SA, Kolanczyk DM and Walton AM. Canagliflozin, a new sodium-glucose cotransporter 2 inhibitor, in the treatment of diabetes. Am J Health Syst Pharm 2013; 70: 311-319.
[41] Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M and Parikh SJ. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 2011; 34: 2015-2022.