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Adverse Drug Events Related to Canagliflozin: A Meta-Analysis of Randomized, Placebo-Controlled Trials

Shawaqfeh MS*, Bhinder MT, Halum AS, Harrington C, Muflih S and Do T

Nova Southeastern University, Palm Beach Gardens, Florida, United States

Abstract

Canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, was recently approved in United States for the treatment of type 2 diabetes mellitus in combination with diet and exercise. Two strengths were approved, 100 mg and 300 mg. The US label warns of a dose-dependent increase in volume depletion-related adverse reactions on the 300 mg dose. The purpose of this meta-analysis was to assess the dose response of canaglifozin on safety and tolerability outcomes.

A search was performed through MEDLINE, EMBASE, and Cochrane Library for clinical trials comparing canagliflozin with placebo or active controls. Keywords include canagliflozin, and meta-analysis. Reference lists of relevant articles were also used as sources. Two reviewers extracted data and evaluated pertinent studies. Study characteristics, safety outcomes of interest, and risk of bias were collected, verified and further analyzed. Canagliflozin was studied as monotherapy in 2 trials (n=270) and as an add-on therapy in 10 studies (n=2525). Ten of the studies were included in the analysis of selected safety outcomes. Length of intervention ranged from 12 to 52 weeks. All studies were randomized, comparative to either placebo or active controls. Canagliflozin treatment, , increased the risk of vulvovaginal mycotic infection (RR 4.11; CI 3.01-5.60; P<0.01), pollakiuria (RR 2.89, CI 1.84-4.53), polyuria (RR 3.87; CI 1.66-9.05), hypoglycemia (RR 1.22; CI 1.10-1.35) and hypovolemia (RR 2.04; CI 1.13-3.68). There were no significant dose responses among observed safety outcomes with the exception of genital infections (RR 4.12; CI 2.47-6.87). Additionally, the canagliflozin treatment group experienced a 24% reduction in serious adverse events when compared to controls (RR 0.76; 0.62-0.93; P<0.01).

This meta-analysis did not show a dose response effect of canaglifozin on treatment emergent adverse events in type 2 diabetics.

Keywords: Canagliflozin; Meta-analysis; Diabetes; Adverse events

Introduction

Diabetes Mellitus is fast becoming one of the most prevalent chronic diseases in the United States, with 14.3% of the population over 20 years of age suffering from this malady [1]. Patients are educated about the importance of having a multi-pronged approach in management of their disease, where one combines diet and exercise regimens with medications. Due to the constant advancement in medical research and innovation, new treatment regimens are constantly being invented to keep pace with the demand for better antidiabetic medications. As with any drug therapy regimen, there has to be a balance between its effectiveness and tolerability, and this is no different for new antidiabetic medications such as canagliflozin; a sodium-glucose co-transporter 2 (SGLT2) inhibitor. The drug, was the first of its kind (SGLT2s) to be approved for treatment of Type 2 Diabetes Mellitus in the United States [2,3]. These questions were answered in several clinical studies variably; this analysis will compile all these reports together in one report that will strengthen the evidence of adverse events reporting.

The drug is to be used as an adjunct with diet, exercise, and other antidiabetic drug classes. There are 100 mg and 300 mg strengths dosage approved, with the former being the starting dosage, incremented to the latter in patients who have normal renal function. Drug label warns of a dose-dependent increase in volume depletion-related adverse reactions on the 300 mg dose [4] the purpose of this meta-analysis is to assess the occurrence of drug-related adverse events associated with the use of canagliflozin at varying doses. The meta-analysis will have all randomized controlled trials that reported adverse events in a systematic way combined in one report that will verify the significance of dose related adverse events. This type of information will help the clinicians to decide safely about the appropriateness of their selection of canagliflozin.

Method

A systematic review was performed from September 2013–July 2015 using the EMBASE and MEDLINE databases, identifying Cochrane reviews, controlled clinical trials, randomized control trials, meta-analyses and systematic reviews, using search terms canagliflozin, placebo, adverse events, and humans. The studies were limited to those published in the English language, and conducted on humans. The Trial Registry website ClinicalTrials.gov was also searched for studies relating to canagliflozin.

The pertinent data describing adverse events was extracted from the safety results sections of the articles, including relevant text and tables. This data was then subsequently entered into Review Manager Software, Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, and Copenhagen, Denmark) for analysis [5]. The

***Corresponding author:** Shawaqfeh MS, Nova Southeastern University, Palm Beach Gardens, Florida, United States, Tel: 56-805-2243; E-mail: mshawaqfeh@nova.edu

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aforementioned software has been made available by the Cochrane Collaboration to facilitate meta-analyses.

The data was combined for meta-analysis employing the Mantel-Haenszel method, random effects model at 95% confidence for the RR. Study characteristics and safety outcomes of interest were collected, verified and further analyzed, focusing on the frequencies of dose dependent adverse events for both the canagliflozin group and the placebo populations.

Results

Description of the included studies

In the initial stages of the study, there were 678 citations which were subjected to elemental review (Figure 1). Of those studies, randomized, placebo-controlled trials which described data on dose-related adverse events in adult patients taking canagliflozin were sent for further analysis while the others, which did not contain relevant information on adverse reactions, or did not have a placebo control were not included. Following this elemental review, there were 49 articles which were used for adverse event data extraction. Of those articles, 19 were included in the final analysis [6-24]. All of the studies were randomized, placebo controlled trials and one was the US label for brand name canagliflozin (Invokana; Janssen Pharmaceuticals, Inc., Titusville, NJ) [4].

All studies were conducted in adults, from varying centers in over 22 different countries around the world. The studies varied in length from 4 weeks up to 104 weeks. The trials included a total of 8932 patients, with population sizes ranging from 10-1452 patients in each trial. Canagliflozin doses ranged from 10 mg-800 mg/day.

Any adverse event

The overall rate of adverse events (Tables 1 and 2) in both the canagliflozin group and the placebo group were similar with the exception of a few adverse events. Furthermore, there was no dose-

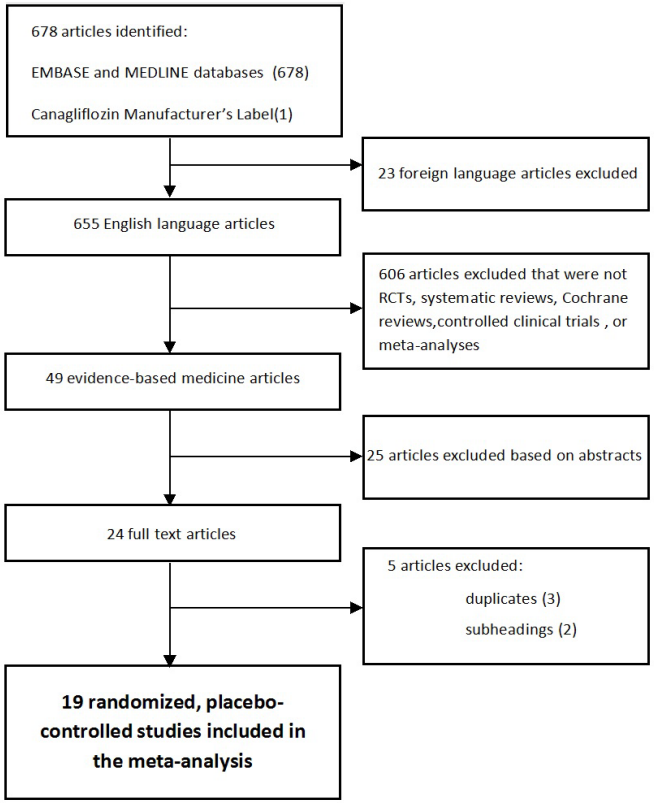

Figure 1: Schematic of search strategy. RCT=Randomized Control Trial.

Table 1: Treatment-emergent adverse events of canagliflozin 100 mg vs. control.

Adverse Event	No. of Studies	No. of Patients		Adverse Event Rate (%)		Risk Ratio
		Drug	Control	Drug	Control	M-H, Random, 95%
Any Adverse Event	16	2521	2512	65	64	1.02 [0.98, 1.06]
Serious Adverse Event	15	2737	2725	6.2	7.2	0.86 [0.71, 1.04]
AEs Leading to Discontinuation	14	2496	2488	4	3.9	1.01 [0.74, 1.39]
Postural Dizziness	8	1495	1480	0.87	0.675	1.20 [0.54, 2.68]
Hypovolamia	7	1505	1497	1.32	0.46	2.52 [1.10, 5.78]
Polyuria	5	1377	1367	0.726	0.14	3.22 [0.86, 12.02]
Pollakiuria	7	1505	1497	3.5	0.868	3.30 [1.48, 7.37]
Hypoglycaemia	11	1446	1435	15.97	11.2	1.40 [1.18, 1.66]
Vulvovaginal Mycotic Infection	9	781	741	12.03	2.56	4.24 [2.65, 6.78]
Genital Mycotic Infections	13	1678	1709	7.15	1.87	3.57 [2.40, 5.32]
Nasopharyngitis	4	295	294	3.72	6.12	0.69 [0.31, 1.52]
Nausea	4	231	228	4.32	2.19	1.68 [0.61, 4.66]
Headache	4	231	228	10.3	5.26	1.82 [0.94, 3.54]
Diarrhea	4	231	228	2.16	4.38	0.51 [0.19, 1.41]
Urinary Tract Infection	13	2422	2413	6.85	5.71	1.20 [0.96, 1.49]
Urinary Tract AEs	2	128	130	9.375	6.92	1.35 [0.59, 3.10]
Postural Hypotension	6	1441	1432	0.55	0.13	2.94 [0.81, 10.75]
Osmotic Diuresis-Related AEs	5	827	823	5.68	2.67	1.98 [1.02, 3.84]
Volume-Related AEs	5	824	827	3.03	1.45	2.09 [1.03, 4.23]

I^2 Index (%) =<50%

Table 2: Treatment-emergent adverse events of canagliflozin 300 mg vs. control.

Adverse Event	No. of Studies	No. of Patients		Adverse Event Rate (%)		Risk Ratio
		Drug	Control	Drug	Control	M-H, Random, 95%
Any Adverse Event	18	2836	2835	67	65	1.02 [0.99, 1.06]
Serious Adverse Event	15	3019	3010	6.29	7.17	0.89 [0.74, 1.07]
AEs Leading to Discontinuation	14	2783	2773	5.19	3.85	1.32 [1.03, 1.69]
Postural Dizziness	8	1857	1843	0.8	0.67	1.31 [0.58, 2.98]
Hypovolemia	8	1879	1875	0.9	0.54	1.63 [0.70, 3.79]
Polyuria	6	1751	1745	1.08	0.11	4.41 [1.45, 13.40]
Pollakiuria	8	1879	1875	2.92	0.96	2.64 [1.52, 4.61]
Hypoglycaemia	10	1721	1713	22.3	17.5	1.32 [1.08, 1.62]
Vulvovaginal Mycotic Infection	10	966	907	11.4	2.86	3.69 [2.45, 5.57]
Genital Mycotic Infections	13	1780	1830	8.53	1.47	4.88 [3.27, 7.28]
Nasopharyngitis	5	317	312	4.73	6.41	0.78 [0.41, 1.51]
Nausea	5	244	238	5.32	2.94	1.50 [0.62, 3.61]
Headache	4	234	228	6.83	5.26	1.37 [0.57, 3.30]
Diarrhea	5	252	246	5.15	4.47	1.13 [0.48, 2.66]
Urinary Tract Infection	13	2708	2698	6.61	5.85	1.14 [0.92, 1.40]
Urinary Tract AEs	2	128	130	9.37	6.92	1.35 [0.59, 3.10]
Postural Hypotension	7	1815	1810	0.49	0.16	1.99 [0.70, 5.62]
Osmotic Diuresis-Related AEs	5	829	823	6.87	2.67	2.42 [1.31, 4.48]
Volume-Related AEs	4	733	734	3.41	1.49	2.20 [1.08, 4.50]

I^2 Index (%) =<50%

dependent response associated with the development of any particular adverse event, generally being equally present in both cohorts. Additionally, the rate of inconsistency or heterogeneity, measured by I^2 was low, with many of the analyses presenting with no inconsistencies at all. The overall rate of any adverse event in the 100 mg Canagliflozin group was 65% and the 100 mg placebo group was 64%, with a risk ratio of 1.02 [0.98, 1.06]. In the 300 mg canagliflozin group, the rate of any adverse event was once again comparable to the placebo at 67% for the canagliflozin group and 65% for the placebo group. The risk ratio was 1.02 [0.99, 1.06].

Vulvovaginal mycotic infections/genital mycotic infections

The adverse events with the highest risk were the vulvovaginal mycotic infections and the genital mycotic infections, which showed a significant difference between the canagliflozin group and the placebo group. The adverse event rate of vulvovaginal mycotic infections (Figure 2) in the 100 mg canagliflozin group was 12% versus 2.56% in the placebo group, with a risk ratio of 4.24 [2.65, 6.78]. In the 300 mg canagliflozin group, the rate of vulvovaginal mycotic infections was 11.4% and the placebo group had 2.86%, with a RR of 3.69 [2.45, 5.57]. In the 100 mg canagliflozin group, the rate of genital mycotic infections was 7% versus 1.8% in the placebo group, RR 3.57 [2.40, 5.32]. In the 300 mg canagliflozin cohort, the rate of genital mycotic infection was 8.53% versus 1.47% in the placebo group with a RR of 4.88 [3.27, 7.28].

Osmotic diuresis-related adverse events

The adverse event rate of osmotic-diuresis related adverse events in the 100 mg group was 5.68% and 2.67% for the drug and placebo respectively, RR 1.98 [1.02, 3.84]. In the 300mg canagliflozin group, the rate of osmotic-diuresis related adverse events was 6.87% and the placebo group had 2.67%, with a RR of 2.42 [1.31, 4.48].

Volume-related adverse events

In the 100mg canagliflozin group, the rate of volume-related adverse events was 3.03% versus 1.45% in the placebo group, RR 2.09 [1.03, 4.23] (Figure 3). In the 300mg canagliflozin cohort, the rate of volume-related adverse events was 3.41% versus 1.49% in the placebo group with a RR of 2.20 [1.08, 4.50].

Hypoglycaemia

The adverse event rate of hypoglycaemia (Figure 4) in the 100 mg canagliflozin group was 15.97% versus 11.2% in the placebo group, with a risk ratio of 1.40 [1.18, 1.66]. In the 300 mg canagliflozin group, the rate of hypoglycaemia was 22.3% and the placebo group had 17.5%, with a RR of 1.32 [1.08, 1.62].

Other adverse events

Urinary tract adverse events had an adverse event rate of 9.375% in the canagliflozin group and 6.92% in the placebo group, RR 1.35 [0.59, 3.10]. The adverse event rate of pollakiuria in the 100 mg cohort was 3.5% for canagliflozin and 0.868% for the placebo, RR 3.30 [1.48, 7.37].

Discussion

There were 16 different types of adverse events associated with the use of canagliflozin. Overall, use of canagliflozin did not increase the incidence of any adverse event or serious adverse events. At the higher dose (300 mg), there was an increased risk of discontinuation of the drug due to adverse events RR 1.32 [1.03, 1.69]. Both the 100 mg and 300 mg dose of canagliflozin increased the risk of genital mycotic/vulvovaginal mycotic infections. To a lesser degree was the incidence of urinary tract adverse events. As is common knowledge, patients suffering from Type 2 Diabetes Mellitus are more prone to both urinary tract infections and genital mycotic infections due to a number of different rationale, such as decreased humoral immunity, increased urination, and possible urinary retention/ incontinence due to diabetic neuropathies.

However, when looking at canagliflozin and all SGLT2's role in the development of genital mycotic infections, one must look at its mechanism which facilitates glycosuria, likely a causative factor. It is

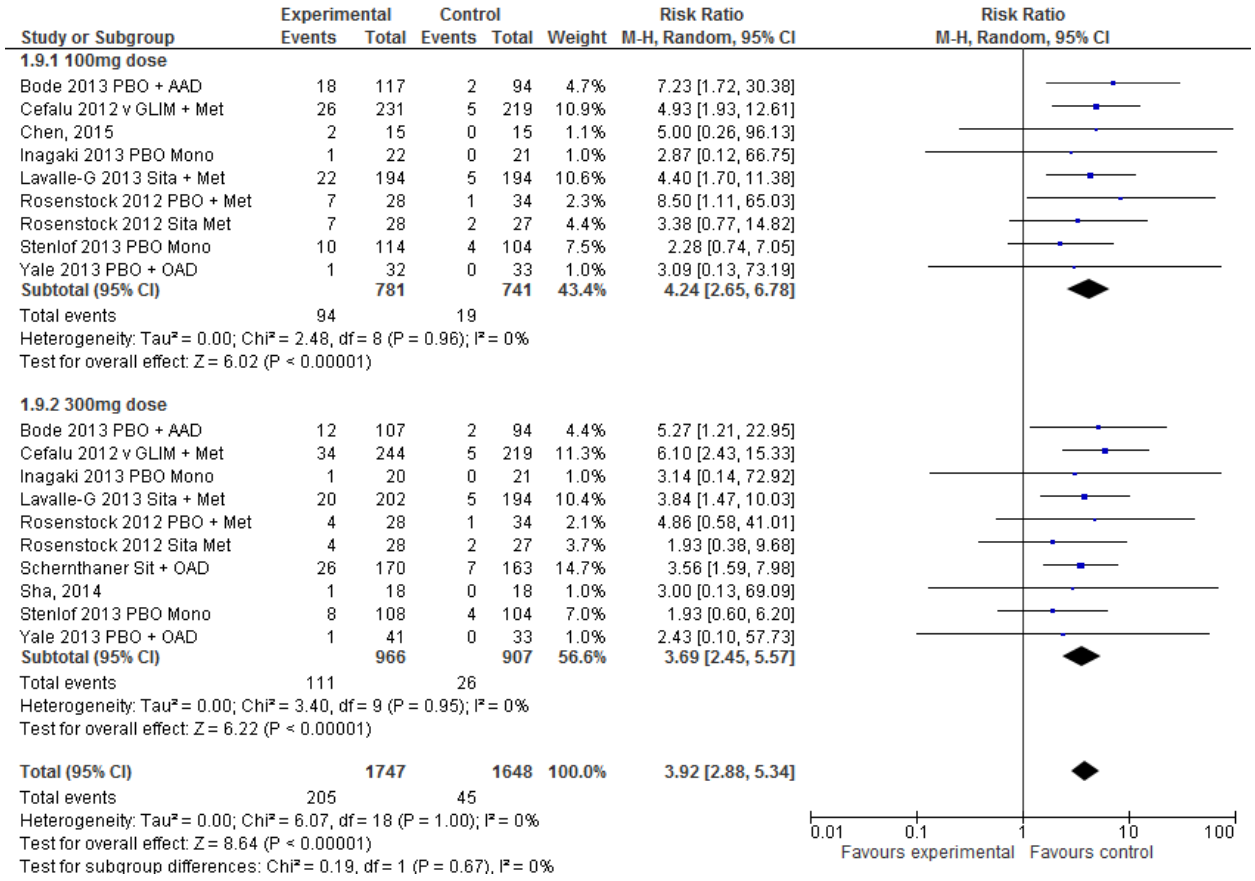

Figure 2: Forest plot of comparison of treatment-emergent vulvovaginal mycotic infection with canagliflozin 100 mg and 300 mg.

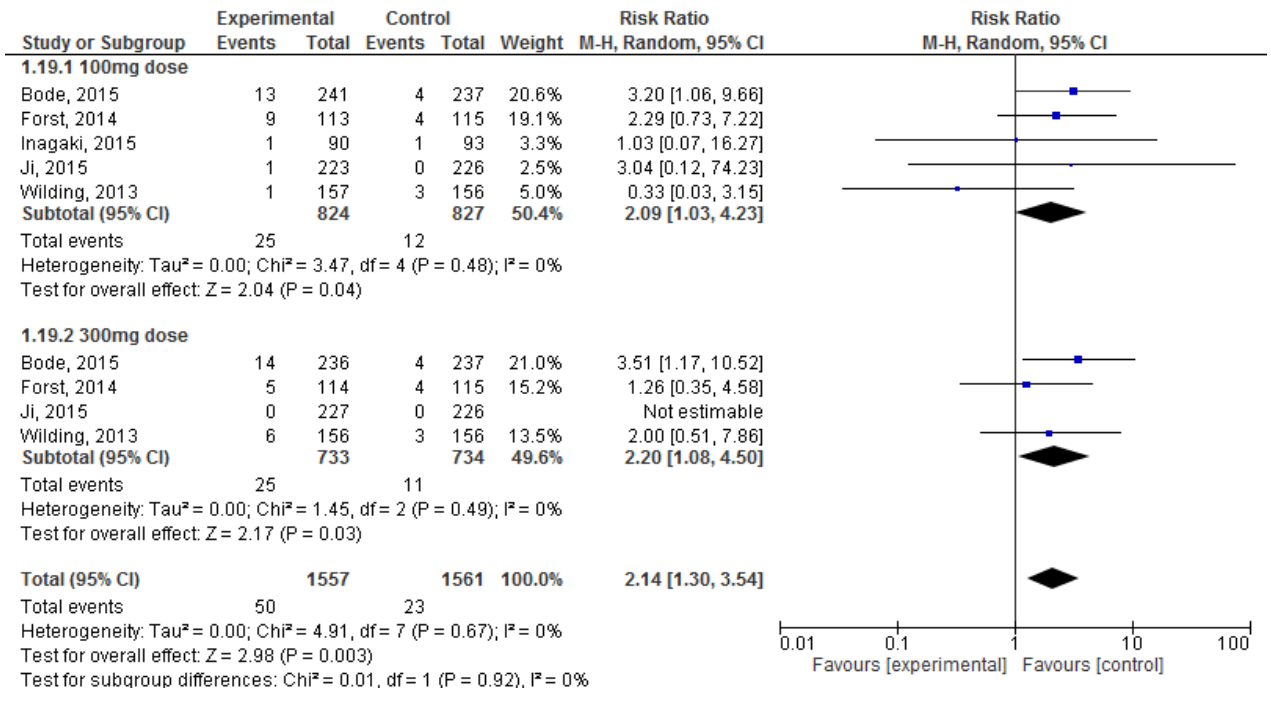

Figure 3: Forest plot of comparison of treatment-emergent volume-related adverse events with canagliflozin 100 mg and 300 mg.

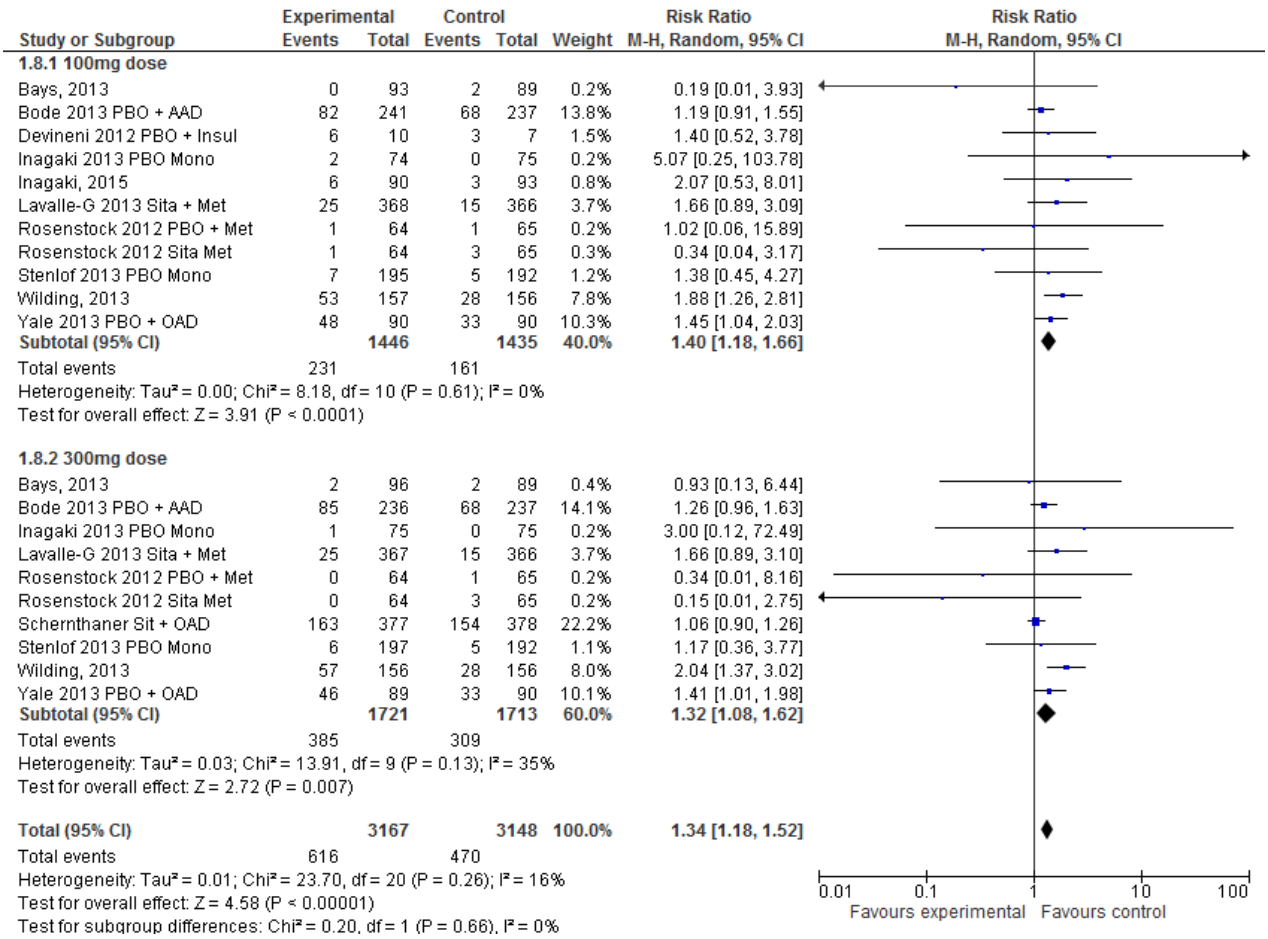

Figure 4: Forest plot of comparison of treatment-emergent hypoglycaemia with canagliflozin 100 mg and 300 mg.

purported that glycosuria maintains a welcoming environment for the major hyphal cell wall protein 1 of the fungi to attach to the uro-epithelium, grow and multiply. The philosophy behind this is that as the major hyphal wall protein 1 (hwp1) plays an integral role in mating, normal hyphal development, cell-to-cell adhesive functions necessary for biofilm integrity, attachment to host, and virulence, it must be involved in the overall mechanism advanced to describe the phenomenon in question [25]. Furthermore, its properties promote the effective interaction between both fungal and host molecules, which leads to effective colonization, especially when humoral immunity is decreased [25] .

It is possible that, due to the widely acknowledged association of increased urinary tract infections and genital mycotic infections associated with diabetes, that there is increased surveillance leading to increased diagnosis of infections [26]. However, as SGLT2s are associated with an increase in osmotic-diuresis related adverse events such as polyuria and pollakiuria, there could be an increased tendency to report infections in those patients [26].

As with any antidiabetic agent, there is always the possibility of patients experiencing hypoglycaemic attacks. As a result of this, patients should exercise caution whenever taking any hypoglycemic agent, being cognizant of the associated clinical manifestations related to the adverse event, in order to prevent development of serious complications. The FDA approval promotes canagliflozin as an adjunct with other antidiabetics. This might add up some concern about the added risks and safety issues in elderly.

It has been reported by the FDA that canagliflozin is associated with an increased risk for bone fractures, thus causing the mentioned organisation to strengthen its warning for the drug [20]. This information is based on new confirmatory information from nine clinical trials [20]. The logic behind the development of these fractures stems from the fact that SGLT2 inhibitors increase serum concentrations of phosphate through increased tubular resorption, which has the potential to adversely affect bone. These inhibitors also increase the concentration of parathyroid hormone, which enhances bone resorption, thus increasing the risk of pathologic fractures [20]. In the included studies of this meta-analysis, there was no reported data relating to the association of canagliflozin with bone fractures. This could be due to the fact that the number of cases is not significant, and, therefore, the results were not included in the studies.

Canagliflozin showed in various studies almost an increasing number of adverse events that was not clearly stating whether these events are dose related or not. But this analysis compiled all reported data from all strictly randomized controlled studies to verify the strength of evidence that the adverse events are dose related or not.

Limitations

The results in this study are limited to the data that is currently

available. A limitation of this study could stem from limited sample sizes and treatment durations in some of the included studies, which could affect conclusions pertaining to the safety and efficacy of canagliflozin. Furthermore, the patient populations reflect the strength of the study. In order to represent a true diabetic population, patients from a broad age group and varying ethnicities, especially black or African-American and Hispanic populations where diabetes is highly prevalent coupled with overweight and obese patients should have been included in the studies to ensure that the data found can be generalized to the diabetic population as a whole. Also, these trials did not report data for subgroups of high risk patients with low renal function, advanced age, or those taking loop diuretics.

Conclusion

Canagliflozin has been associated with an increased incidence of genital mycotic infections and vulvovaginal mycotic infections, and to a lesser degree urinary tract infections. While the exact mechanism is not known, it is believed that there could be an interaction between the glycosuria effect of the SGLT2 and the hwp1 which is allowing fungus to grow and flourish in those regions. No dose dependent adverse events were noted, as they were equally prevalent in both dosing cohorts. The risk of hypoglycaemia is increased, as is the case with most of the antidiabetic agents. The risk of volume depletion is significant, and high-risk patients such as the elderly, those with chronic renal failure, or those taking diuretics should be monitored closely if prescribed canagliflozin.

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