

Adverse Drug Events Associated with sitagliptin Versus canagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus: A Systematic Comparison Through a Meta-Analysis

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ABSTRACT

Introduction: In this meta-analysis, we aimed to systematically compare the adverse drug events associated with sitagliptin (100 mg) versus canagliflozin 100 or 300 mg in patients who were treated for type 2 diabetes mellitus (T2DM).

Methods: Online databases were searched for relevant studies comparing sitagliptin (100 mg) versus canagliflozin. Adverse drug events were considered as the clinical endpoints. The analysis was carried out by RevMan software whereby risk ratios (RR) and 95% confidence intervals (CI) were generated.

Results: Five studies with a total number of 2322 patients were included. When sitagliptin

(100 mg) was compared with canagliflozin (100 mg), the endpoints of any adverse events, adverse events leading to drug discontinuation, serious adverse events, urinary tract infections, hypoglycemia, and adverse events related to hypovolemia were not significantly different: (RR 1.10, 95% CI 1.00–1.21; $P = 0.05$), (RR 1.20, 95% CI 0.67–2.16; $P = 0.54$), (RR 0.90, 95% CI 0.49–1.66; $P = 0.73$), (RR 1.26, 95% CI 0.77–2.08; $P = 0.36$), (RR 1.01, 95% CI 0.30–3.43; $P = 0.99$), and (RR 1.76, 95% CI 0.52–5.94; $P = 0.36$), respectively. However, canagliflozin was associated with increased genital mycotic infection (RR 4.32, 95% CI 2.11–8.83; $P = 0.0001$). When genital mycotic infections associated with sitagliptin versus canagliflozin were compared in male and female patients separately, the risk was still significantly higher with canagliflozin: (RR 7.00, 95% CI 2.44–20.06; $P = 0.003$) and (RR 4.02, 95% CI 2.22–7.27; $P = 0.00001$), respectively. The same results were obtained when sitagliptin (100 mg) was compared to canagliflozin 300 mg. **Conclusions:** Canagliflozin was associated with a significantly higher risk of genital mycotic infections when compared to sitagliptin. However, the other adverse drug events were similarly manifested when sitagliptin 100 mg was compared to either canagliflozin 100 or 300 mg.

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Keywords: Adverse drug events; Canagliflozin; Hypoglycemia; Sitagliptin; Type 2 diabetes mellitus; Urinary tract infection

Abbreviations

AEs	Adverse events
HbA1c	Glycosylated hemoglobin
T2DM	Type 2 diabetes mellitus
UTI	Urinary tract infections

INTRODUCTION

Today, new treatment regimens for type 2 diabetes mellitus (T2DM) are constantly being developed in order to stabilize blood glucose level among the large population of patients suffering from this chronic disease. Even if the previously used oral antihyperglycemic drugs are still as important, newer drugs will in the future replace metformin and sulfonylurea. In this new era of 2018, we are focusing on new add-on oral hypoglycemic drugs which could possibly be adopted by the population of patients with T2DM [1].

Recently, sitagliptin [2] and canagliflozin [3], two new emerging oral antidiabetic drugs which are used as add-on therapy to metformin and sulfonylurea, have been in the headlines.

Canagliflozin, which is a sodium-glucose co-transporter 2 (SGLT2) inhibitor, reduces the blood sugar level by increasing the amount of glucose excreted by the kidneys, and it is normally available in a dosage of 100 or 300 mg. SGLT2 proteins are responsible for 90% of the glucose that is reabsorbed by the kidneys, so, by inhibiting the action of these proteins, canagliflozin causes less glucose to be reabsorbed, and more glucose to be excreted via urine. This mechanism is associated with a low risk of hypoglycemia. New research has shown that this drug improves glycated HbA1c, blood pressure, and body weight [4].

Sitagliptin, which is available in a dosage of 100 mg, is a competitive dipeptidyl peptidase-4 (DPP-4) inhibitor. DPP-4 breaks down the incretins GLP-1 and GIP, which are gastrointestinal hormones released in response to a meal. By preventing the inactivation of these hormones, sitagliptin actually stimulates insulin production and inhibits glucagon release by the pancreas [5]. Sitagliptin also improves

glycated HbA1c without significantly altering the blood pressure and body weight.

Even if these add-on oral hypoglycemic agents are effective [6], the adverse events related to these newer drugs have seldom been systematically analyzed.

In this meta-analysis, we aimed to systematically compare the adverse drug events observed with sitagliptin (100 mg) versus canagliflozin 100 or 300 mg in patients who were treated for T2DM.

METHODS

Searched Databases and Search Strategies

Following the PRISMA guideline [7], MEDLINE and EMBASE, two major databases, as well as the Cochrane library, www.ClinicalTrials.gov, and Google Scholar were searched electronically for relevant English publications comparing sitagliptin (100 mg) versus canagliflozin (100 or 300 mg) in patients who were being treated for T2DM. The following search terms were used:

- Sitagliptin versus canagliflozin and diabetes mellitus
- Dipeptidyl peptidase-4 inhibitor and canagliflozin
- Sitagliptin and sodium-glucose transport (SGLT-2) inhibitors
- Dipeptidyl peptidase-4 inhibitor and sodium-glucose transport (SGLT-2) inhibitors

Criteria for Inclusion

Studies were included if

- They were randomized controlled trials or observational cohorts comparing sitagliptin (100 mg) with canagliflozin (100 mg or 300 mg or both) in patients with T2DM.
- They reported adverse drug events among their clinical outcomes.

Criteria for Exclusion

Studies were excluded if

- They were meta-analysis, review articles, review of the literatures, case-control studies, letters of correspondence.
- They did not compare sitagliptin (100 mg) with canagliflozin.
- They did not report adverse drug events among their clinical outcomes.
- They included patients with type 1 diabetes mellitus.
- They were repeated studies involving the same data.

Outcomes and Follow-up

The following adverse drug events were considered as the clinical endpoints in this analysis:

- Any adverse events
- Adverse events leading to drug discontinuation
- Serious adverse events (potentially fatal and life-threatening)
- Urinary tract infections
- Hypoglycemia
- Genital mycotic infections
- Adverse events related to hypovolemia

The follow-up time period varied between 12 and 52 weeks.

The adverse events and the follow-up periods reported in each study are listed in Table 1.

Data Extraction and Review

Data were independently extracted by two reviewers. Useful data which were extracted included the type of study (randomized controlled trials, retrospective cohorts); the total number of patients who were treated with sitagliptin (100 mg), canagliflozin (100 mg), and canagliflozin (300 mg); the adverse drug events which were reported; the total number of events in each subgroup; the baseline features of the participants; and the background oral hypoglycemic drugs which were used.

Any disagreement which followed during the data extraction process was resolved by consensus.

The methodological quality of the trials was assessed with reference to the criteria proposed by the Cochrane Collaboration [8].

Table 1 Reported adverse drug outcomes

Studies	Outcomes reported	Follow-up period
Lavalle-González [9]	Any AE, AE leading to drug discontinuation, serious AE, UTI, genital mycotic infection in men and women, postural dizziness, orthostatic hypotension	52 weeks
Rodbard [10]	Any AE, AE leading to drug discontinuation, serious AE, UTI, genital mycotic infection in men and women, documented hypoglycemia, severe hypoglycemia	26 weeks
Rosenstock [11]	Any AE, AE leading to drug discontinuation, serious AE, UTI, vulvovaginal mycotic infection, symptomatic hypoglycemia, AE related to hypovolemia, symptomatic genital infection	12 weeks
Scherthaner [12]	Any AE, AE leading to drug discontinuation, serious AE, death, UTI, genital mycotic infection in men and women, postural dizziness, orthostatic hypotension	52 weeks
Shao [13]	Any AE, AE leading to drug discontinuation, genital mycotic infection, UTI, AE related to hypovolemia, hypoglycemia	24 weeks

AE adverse events, *UTI* urinary tract infection

Statistical Analysis

The statistical analysis was carried out by the well-known meta-analysis software Revman 5.3

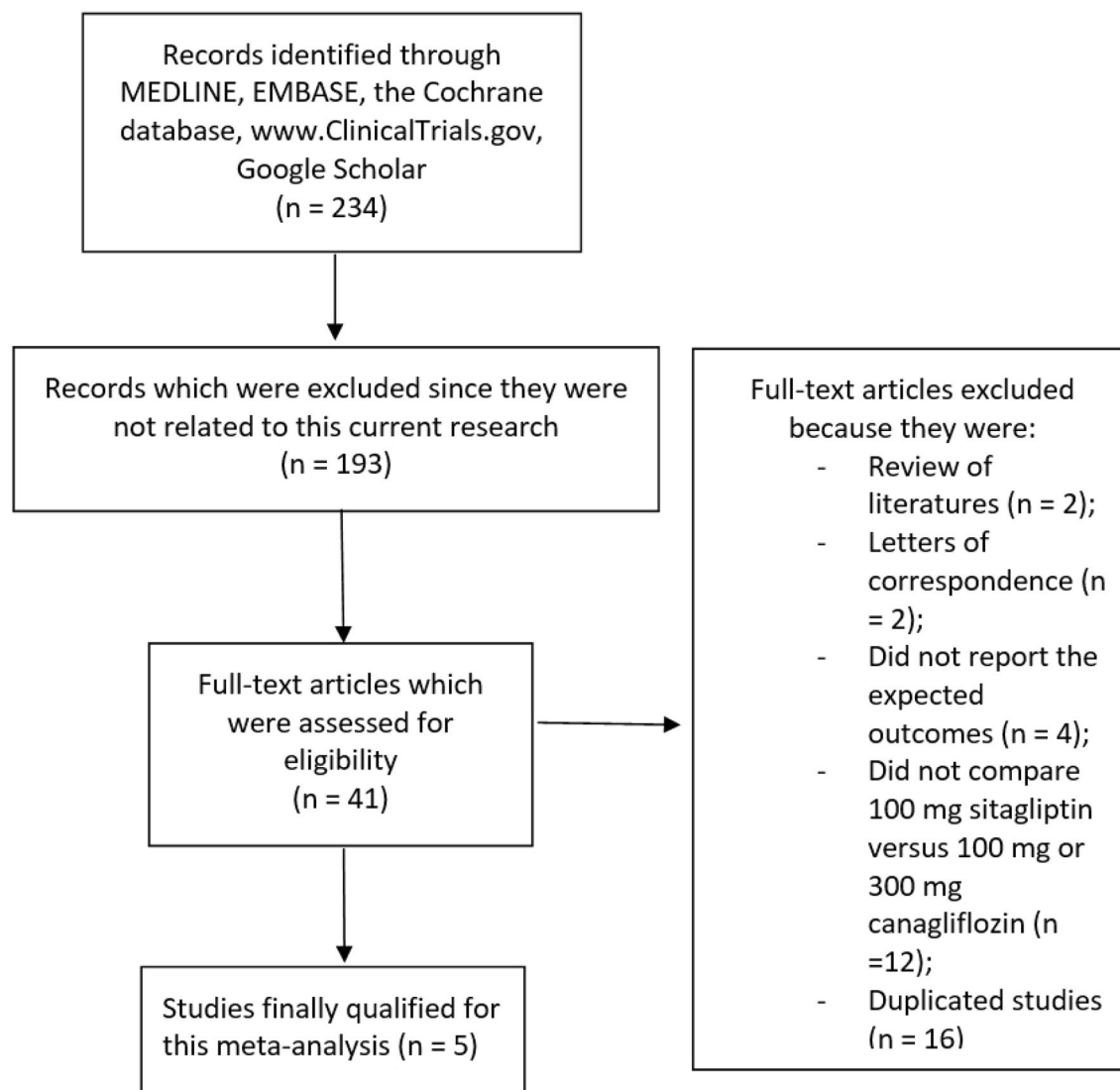


Fig. 1 Flow diagram representing the study selection

(latest version) whereby risk ratios (RR) and 95% confidence intervals (CI) were generated.

Heterogeneity, which is common in meta-analyses, was assessed by two simple statistical methods:

- The Q statistic test whereby a P value greater than 0.05 was considered statistically significant
- The I^2 statistic test whereby a low level of heterogeneity was denoted by a low I^2 value

A fixed-effects statistical model was used if I^2 was less than 50%, whereas a random-effects model was used if I^2 was greater than 50%.

Additionally, sensitivity analysis was also carried out by an exclusion method to confirm a consistent result throughout. Each of the studies was excluded one by one and a new analysis was carried out each time. The result obtained was compared with the original result to observe any significant change.

Since this analysis included a small number of studies, publication bias was only visually

Table 2 General features of the studies

Studies	No. of patients treated with 100 mg CANA (<i>n</i>)	No. of patients treated with 300 mg CANA (<i>n</i>)	No. of patients treated with sitagliptin 100 mg (<i>n</i>)	Types of study	Background drugs
Lavalle-González [9]	368	367	366	RCT	Metformin monotherapy
Rodbard [10]	108	–	108	RCT	Metformin and sitagliptin
Rosenstock [11]	64	64	65	RCT	Metformin
Schernthaner [12]	–	377	378	RCT	Metformin + sulfonylurea
Shao [13]	–	22	35	Retrospective cohort	–
Total no. of patients (<i>n</i>)	540	830	952		

CANA canagliflozin, RCT randomized controlled trials

Table 3 Baseline features of the studies

Studies	Age (years) C1/C3/S	Male (%) C1/C3/S	HbA1c (%) C1/C3/S	Duration of DM (years) C1/C3/S	FPG (mmol/L) C1/C3/S
Lavalle-González [9]	55.5/55.3/55.5	47.3/45.0/47.0	7.9/7.9/7.9	6.7/7.1/6.8	9.3/9.6/9.4
Rodbard [10]	57.4/–/57.5	61.7/–/51.9	8.5/–/8.4	9.8/–/10.1	10.3/–/10.0
Rosenstock [11]	51.7/55.2/51.7	56.0/44.0/58.0	7.83/7.69/7.73	6.1/5.8/5.6	–
Schernthaner [12]	–/56.6/56.7	–/45.1/43.1	–/8.1/8.1	–/9.4/9.7	–/9.4/9.2
Shao [13]	–/45.2/45.5	–/59.1/60.0	–/9.4/9.3	–12.6/9.4	–

HbA1c glycosylated hemoglobin, DM diabetes mellitus, FPG fasting plasma glucose, C1 canagliflozin 100 mg, C3 canagliflozin 300 mg, S sitagliptin

assessed through funnel plots. Other methods would be inappropriate to represent publication bias because of the small number of studies included.

Compliance with Ethics Guidelines

This meta-analysis is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Searched Outcomes

A total of 234 publications were initially obtained by searching the online databases. On the basis of an initial assessment of the titles and abstracts, 193 articles were excluded since they were not related to the current research.

Forty-one (41) full-text articles were assessed for eligibility. Further assessment and review

Table 4 Results of this analysis

Outcomes assessed	RR with 95% CI	<i>P</i> value	<i>I</i> ² (%)
SITA 100 mg versus CANA 100 mg			
Any adverse event	1.10 [1.00–1.21]	0.05	21
AE leading to drug discontinuation	1.20 [0.67–2.16]	0.54	25
Serious AE	0.90 [0.49–1.66]	0.73	0
Urinary tract infection	1.26 [0.77–2.08]	0.36	0
Genital mycotic infection (overall)	4.32 [2.11–8.83]	0.0001	0
Hypoglycemia	1.01 [0.30–3.43]	0.99	36
AE related to hypovolemia	1.76 [0.52–5.94]	0.36	0
SITA 100 mg versus CANA 300 mg			
Any adverse event	1.18 [0.93–1.49]	0.17	85
AE leading to drug discontinuation	1.14 [0.87–1.49]	0.33	38
Serious AE	0.95 [0.61–1.47]	0.82	0
Urinary tract infection	0.80 [0.52–1.23]	0.31	0
Genital mycotic infection (overall)	4.51 [2.67–7.63]	0.00001	0
Hypoglycemia	0.94 [0.32–2.78]	0.91	0
AE related to hypovolemia	1.08 [0.36–3.25]	0.89	6

RR risk ratios, CI confidence intervals, AE adverse events; CANA canagliflozin, SITA sitagliptin

resulted in further elimination of studies because of the following reasons:

- They were a review of the literature (2).
- They were letters of correspondence (2).
- They did not report the expected clinical outcomes (4).
- They did not compare sitagliptin with 100 or 300 mg canagliflozin (12).
- They were repeated studies involving similar data (16).

Finally only five articles [9–13] were confirmed and included in this meta-analysis as shown in Fig. 1.

General Features

Five studies with a total of 2322 patients were included in this analysis of whom 952 participants were treated with sitagliptin, 540 participants were treated with 100 mg canagliflozin,

and 830 participants were treated with 300 mg canagliflozin (Table 2). Four of the studies were randomized controlled trials and one study was a retrospective cohort. In all four trials, metformin was used as the background oral hypoglycemic drug.

Baseline Features of the Participants

The baseline features are listed in Table 3. A mean age ranging from 45.2 to 57.5 years was reported among the participants. Fasting plasma glucose varied from 9.2 to 10.3 mmol/L, whereas glycated HbA1c varied from 7.69% to 9.4%. The duration of disease ranged from 5.6 to 12.6 years. According to Table 3, there was no significant difference in baseline features among the participants who were treated with sitagliptin versus canagliflozin.

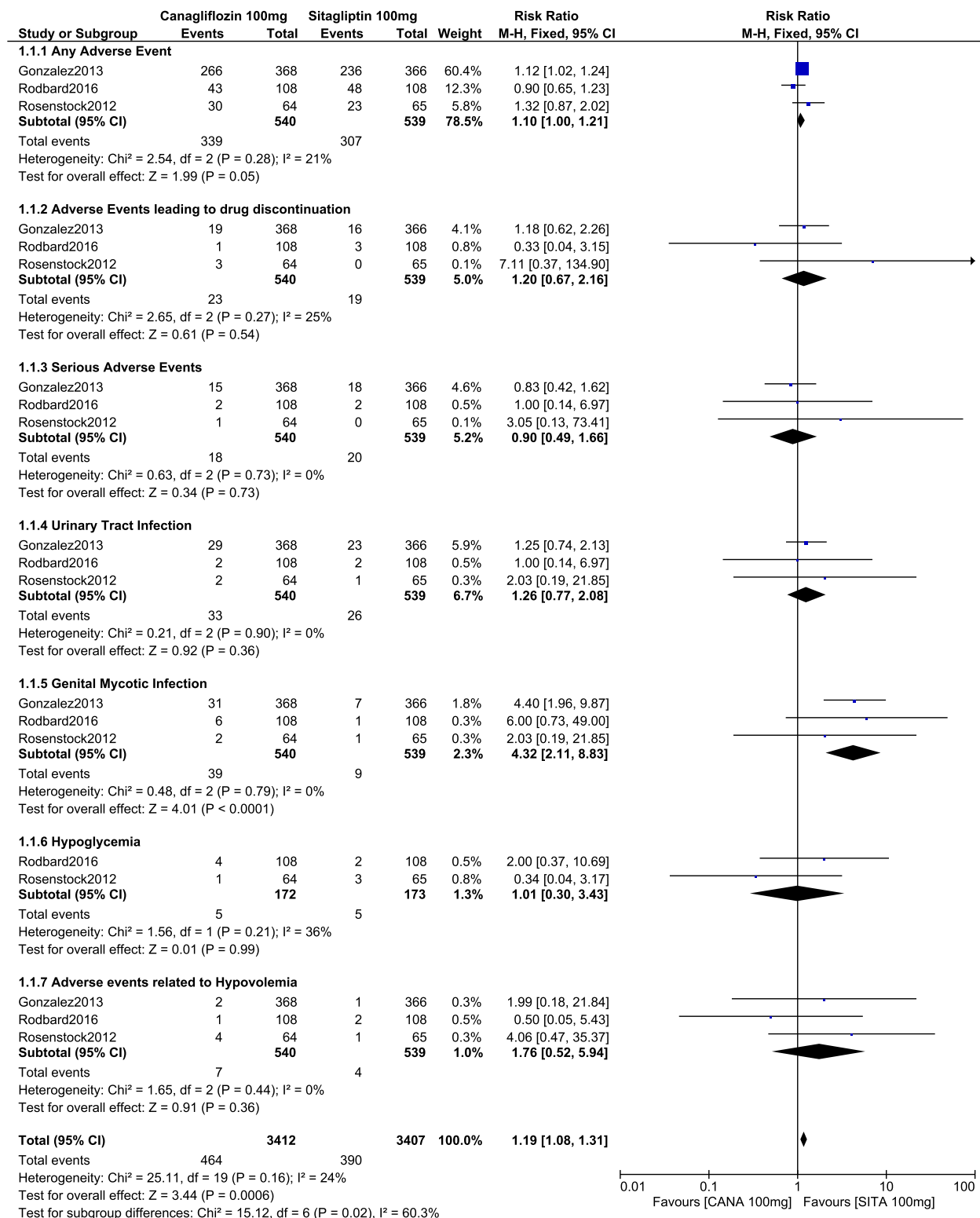


Fig. 2 Adverse drug events observed with sitagliptin (100 mg) versus canagliflozin 100 mg in patients with type 2 diabetes mellitus

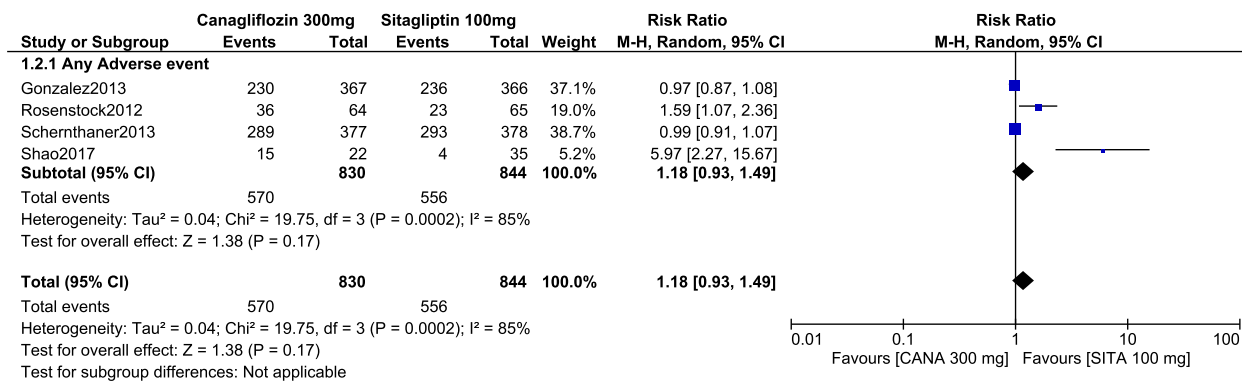


Fig. 3 “Any adverse drug event” observed with sitagliptin (100 mg) versus canagliflozin 300 mg in patients with diabetes mellitus

Sitagliptin (100 mg) Versus 100 mg Canagliflozin

Results of this analysis are listed in Table 4.

When sitagliptin (100 mg) was compared with canagliflozin (100 mg), the endpoints any adverse events, adverse events leading to drug discontinuation, serious adverse events, urinary tract infections, hypoglycemia, and adverse events related to hypovolemia were not significantly different: (RR 1.10, 95% CI 1.00–1.21; $P = 0.05$), (RR 1.20, 95% CI 0.67–2.16; $P = 0.54$), (RR 0.90, 95% CI 0.49–1.66; $P = 0.73$), (RR 1.26, 95% CI 0.77–2.08; $P = 0.36$), (RR 1.01, 95% CI 0.30–3.43; $P = 0.99$), and (RR 1.76, 95% CI 0.52–5.94; $P = 0.36$), respectively, as shown in Fig. 2. However, the risk of genital mycotic infection was significantly higher with canagliflozin (RR 4.32, 95% CI 2.11–8.83; $P = 0.0001$).

Sitagliptin (100 mg) Versus 300 mg Canagliflozin

When sitagliptin (100 mg) was compared with canagliflozin (300 mg), still no significant difference was observed in any adverse event (RR 1.18, 95% CI 0.93–1.49; $P = 0.17$) as shown in Fig. 3. The outcomes adverse events leading to drug discontinuation, serious adverse events, urinary tract infections, hypoglycemia, and adverse events related to hypovolemia were also not significantly different: (RR 1.14, 95% CI 0.87–1.49; $P = 0.33$), (RR 0.95, 95% CI

0.61–1.47; $P = 0.82$), (RR 0.80, 95% CI 0.52–1.23; $P = 0.31$), (RR 0.94, 95% CI 0.32–2.78; $P = 0.91$), and (RR 1.08, 95% CI 0.36–3.25; $P = 0.89$), respectively, as shown in Fig. 4. However, canagliflozin 300 mg was associated with a significantly higher risk of genital mycotic infections (RR 4.51, 95% CI 2.67–7.63; $P = 0.00001$).

Genital Mycotic Infections in Male and Female Patients with Sitagliptin (100 mg) Versus Canagliflozin

When genital mycotic infections observed with sitagliptin versus canagliflozin were compared in male and female patients separately, the risk was still significantly higher with canagliflozin: (RR 7.00, 95% CI 2.44–20.06; $P = 0.003$) and (RR 4.02, 95% CI 2.22–7.27; $P = 0.00001$) as shown in Figs. 5 and 6, respectively.

Consistent results were obtained when sensitivity analyses were carried out, and evidence of low publication bias was observed through the funnel plots (Fig. 7a, b) which were generated.

DISCUSSION

Previous studies have shown that canagliflozin significantly improves HbA1c compared to sitagliptin. Several outcomes representing efficacy were assessed, and canagliflozin 100 mg

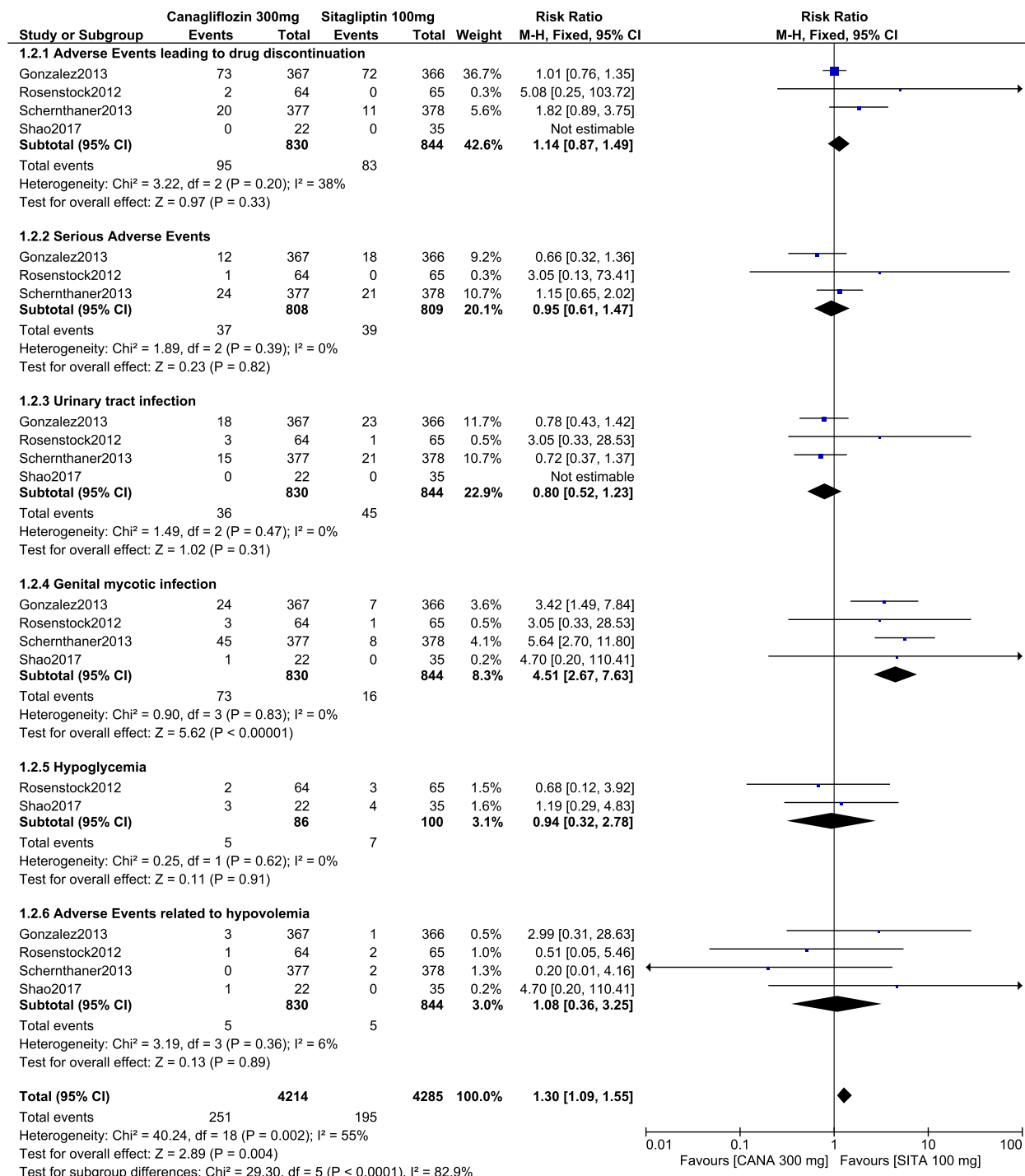


Fig. 4 Other adverse drug events observed with sitagliptin (100 mg) versus canagliflozin 300 mg in patients with diabetes mellitus

was observed to be comparable or superior to sitagliptin 100 mg, and canagliflozin 300 mg was definitely superior to sitagliptin 100 mg

[14]. However, adverse drug events were not often assessed. This analysis was carried out to compare sitagliptin (100 mg) with canagliflozin

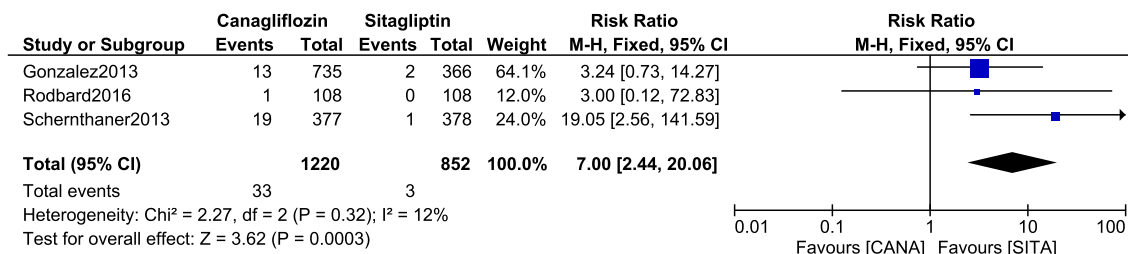


Fig. 5 Genital mycotic infections observed in male patients who were treated with sitagliptin (100 mg) versus canagliflozin

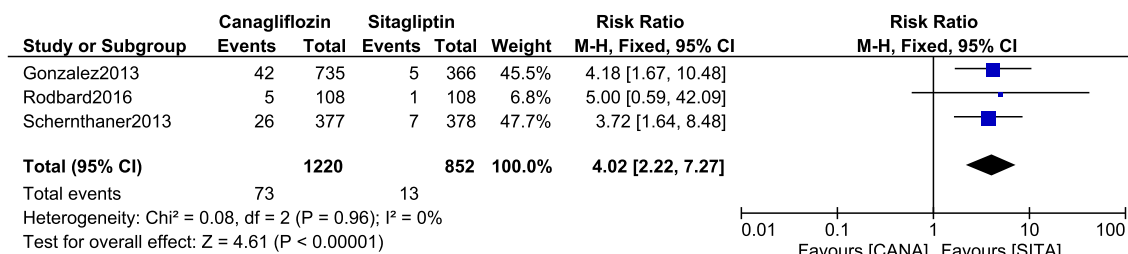


Fig. 6 Genital mycotic infections observed in female patients who were treated with sitagliptin (100 mg) versus canagliflozin

100 or 300 mg in patients who were treated for T2DM.

The current results showed that canagliflozin is associated with significantly higher risk of genital mycotic infections in comparison to sitagliptin. However, the other adverse drug events were not significantly different.

Similar to this analysis, a phase 3 trial in 169 centers in 22 countries also showed comparable adverse drug outcomes between sitagliptin and canagliflozin [9]. Similarly, canagliflozin was associated with a significantly higher risk of genital mycotic infections in both male and female patients, further supporting the results of this analysis.

Another multicenter trial conducted in 47 centers within five countries also supported the current analysis, showing that the risk of genital mycotic infections was significantly higher in patients who were treated with canagliflozin as compared to sitagliptin [10].

Nevertheless, one trial showed that the risk of adverse drug events was higher with 300 mg canagliflozin [11]; however, a recent meta-analysis did not show any significant adverse

drug events with 100 versus 300 mg canagliflozin [12].

In this analysis, we have learnt that both canagliflozin and sitagliptin were tolerable as add-on therapies to metformin or sulfonylurea; however, canagliflozin was associated with a significantly higher risk of genital mycotic infections. Even if several studies have already compared newer oral hypoglycemic drugs and their dosages [12, 15–17], future studies with larger sample sizes and longer follow-up periods should be carried out to confirm the results.

Novelty

This analysis is new because it is the first systematic analysis to compare sitagliptin with canagliflozin; and this is an important issue which should find a place in the treatment strategy for T2DM. The total number of participants was enough to reach a conclusion. In addition, genital mycotic infections were also separately compared in male and female patients separately. Almost all the subgroups reported low heterogeneity, which is another

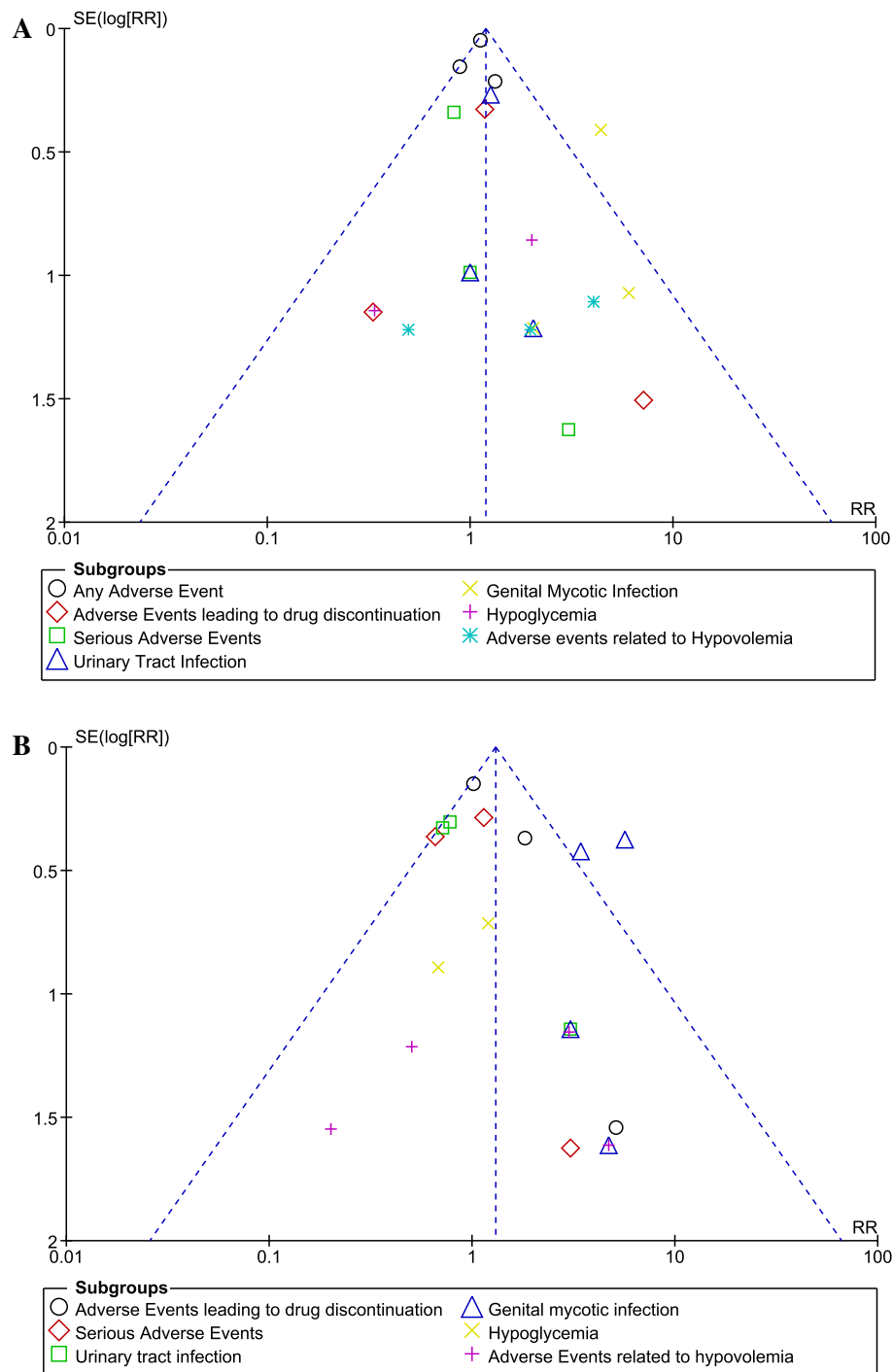


Fig. 7 a, b Funnel plots showing low publication bias

novelty of this analysis. Finally, funnel plots clearly showed evidence of low publication bias among the studies that assessed the clinical adverse drug events.

Limitations

Limitations were as followed: the follow-up periods were not taken into consideration and

this could have affected the results. One retrospective study was also included among all the randomized controlled trials, and this might have affected the results to some extent. However, the impact was reduced since the number of patients from that particular study was very much lower compared to the randomized trials. In addition, the total number of participants was limited; however, only a few trials have been published on this aspect, and nothing could have been done to improve this part. The background oral hypoglycemic drug could also have influenced the results and the same background drug was not reported in all the studies. In addition, it should not be ignored that in this analysis, only sitagliptin and canagliflozin were compared. The results should not be generalized to other DPP-4 and SGLT2 inhibitors. Another limitation could be the funding sources of the original investigations (studies which were included in this analysis) which might have contributed to the risk of bias.

CONCLUSIONS

Canagliflozin was associated with a significantly higher risk of genital mycotic infections when compared to sitagliptin. However, the other adverse drug events were similarly manifested when sitagliptin 100 mg was compared to either canagliflozin 100 or 300 mg.

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Disclosures. Dr. Pravesh Kumar Bundhun and Dr. Feng Huang have nothing to disclose.

Compliance with Ethics Guidelines. This meta-analysis is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. All data generated or analyzed during this study are included in this published article.

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