Efficacy and safety of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: A meta-analysis of randomized controlled trials

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Abstract. Sodium glucose cotransporter-2 (SGLT2) is a sodium-dependent glucose transporter responsible for renal absorption of glucose. Dapagliflozin is an SGLT2 inhibitor used in patients with type 1 diabetes to promote urinary glucose excretion, but to date, randomized controlled trials (RCTs) to evaluate the effect of this drug in this disease have not been systematically evaluated. Therefore, the aim of the present study was to evaluate the efficacy and safety of dapagliflozin, as an adjuvant therapy to insulin, in the treatment of type 1 diabetes mellitus through a systematic review and meta-analysis. The Cochrane Library Database, Medline and Embase databases were used to search articles published between January 1st 2004 and February 5th 2020 with no language restrictions relating to RCTs. After extracting the data, the quality of the RCTs was evaluated and the data were statistically analyzed. A total of 4 RCTs with 1,691 participants were included. Dapagliflozin resulted in decreased glycosylated hemoglobin A1c (0.40-0.45%), body weight (2.52-3.85 kg), mean daily glucose (0.76-0.99 mmol/l) and mean amplitude of glucose excursion (0.54-1.07 mmol/l; all with $P<0.00001$) compared to placebo. Subgroup analysis by dose indicated no significant difference in all efficacy outcome indicators between dapagliflozin at 5 and at 10 mg ($P>0.1$). Compared with placebo, the use of dapagliflozin in patients with type 1 diabetes increased the risk of adverse events and serious adverse events ($P<0.05$), but did not increase the risks of infection, diabetic ketoacidosis (DKA) and discontinuation due to adverse events. Analysis by dose group suggested that no significant difference in all safety outcome indicators between dapagliflozin at 5 and at 10 mg ($P>0.1$). In conclusion, dapagliflozin had a significant effect on type 1 diabetes. However, the use of dapagliflozin significantly increased the incidence of adverse events and serious adverse events compared with placebo. Dapagliflozin-assisted short-term (24 weeks) insulin therapy for type 1 diabetes did not increase the risk of DKA but additional high-quality studies are required to determine its long-term efficacy and safety.

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Introduction

Type 1 diabetes is an autoimmune disease characterized by the gradual destruction of pancreatic B cells, resulting in the loss of endogenous insulin production and consequently hyperglycemia (1). Therefore, the treatment of type 1 diabetes requires lifelong insulin therapy to maintain normal blood glucose levels. The limitations of insulin therapy are an increased risk of hypoglycemia, excessive blood glucose fluctuation and weight gain, which may prevent patients from titrating their daily insulin dose sufficiently to reach the target level of glycosylated hemoglobin A1c (HbA1c) (1,2). Insulin adjuvant drugs may solve these unmet requirements, although most drugs, including pramlintide, enteral insulin therapy and metformin, do not provide sufficient benefits even if they are beneficial (3-9). Sodium glucose cotransporter-2 (SGLT2) is a sodium-dependent glucose transporter and is the major protein responsible for glucose renal absorption. SGLT2 is mainly expressed in the proximal renal tubules of the renal cortex and it is a therapeutic target for blood glucose control (10). SGLT2 inhibitors include dapagliflozin, empagliflozin, and sotagliflozin among other drugs. Previously reviewed meta-analyses have mostly focused on the efficacy and safety of SGLT2 inhibitors as a whole for adjuvant treatment of type 1 diabetes (4). Dapagliflozin, as an SGLT2 inhibitor, acts through an insulin-dependent mechanism to reduce renal glucose reabsorption, thus promoting urinary glucose excretion (11). It has been widely used in patients with type 2 diabetes to improve blood sugar control and minimize hypoglycemia, and it is associated with weight loss and systolic blood pressure drop (12-15). Dapagliflozin has recently reached the third stage of development in patients with type 1 diabetes with successful results and was approved by the European market for specific purposes e.g. in type 1 diabetic adults with body mass index ≥27 kg/m^2) in 2019 (16-21). The

randomized controlled trials (RCTs) to evaluate this drug were so far not systematically evaluated (16-20). In order to obtain conclusions from the evidence available on this new therapeutic approach, a meta-analysis of RCTs was performed to evaluate the efficacy and safety of dapagliflozin in patients with type 1 diabetes.

Materials and methods

Data sources and article search. Studies published between January 2004 and February 5, 2020 in all languages were retrieved using the following databases: Medline, Embase and Cochrane Library. The reference lists in the experimental articles, review articles and reports were manually scanned to identify any other relevant studies. The search terms used were as follows: 'dapagliflozin OR SGLT2 OR sodium-glucose cotransporter 2 inhibitor OR SGLT2 inhibitor OR sodium glucose transporter 2 inhibitors OR SGLT2 inhibitors' and 'diabetes mellitus, type 1 [Mesh] OR diabetes mellitus, type I OR type 1 diabetes OR diabetes mellitus, ketosis-prone OR diabetes, autoimmune OR diabetes mellitus, juvenile-onset OR juvenile-onset diabetes OR diabetes mellitus, insulin-dependent OR IDDM OR diabetes mellitus, insulin-dependent, 1 OR brittle diabetes mellitus OR diabetes mellitus, sudden-onset'.

Study selection. The inclusion criteria were articles in English on RCTs. Trial participants were aged 18 years and above and of any gender or ethnic origin, and the trials compared dapagliflozin with placebo or active comparators used as an additional drug to insulin therapy in type 1 diabetes. Studies that were not on clinical patients, non-RCTs, letters or case reports, as well as articles not reporting outcomes of interest or primary data (editorials, reviews) were excluded.

Outcome measures. The following outcomes were assessed compared with the effects of the placebo: i) Efficacy outcomes: Changes in HbA1c, body weight, mean daily glucose (MDG) and mean amplitude of glucose excursion (MAGE). ii) Safety outcomes: Differences in adverse events, serious adverse events, adverse events leading to discontinuation, infections (urinary tract infections and reproductive tract infections) and diabetic ketoacidosis (DKA). All measures of dispersion were converted to standard deviations.

As an adverse event, any undesirable experience associated with the use of a medical product in a patient (e.g., headache, diarrhea or upper respiratory tract infection) was considered. The event was considered serious when it was life-threatening, or if the outcome was patient death, hospitalization (initial or prolonged), disability or permanent damage (22).

Data extraction and risk of bias assessment. A total of two reviewers (YH, ZJ) performed the data extraction and risk of bias assessment and independently extracted the data in duplicate according to the Cochrane Handbook of Systematic Reviews of Interventions (23) using a pre-designed data collection form. Any discrepancies were resolved through consensus. The quality of the RCTs was assessed using the Cochrane bias risk tool (23).

Data synthesis and analysis. The meta-analysis was performed in accordance with the Cochrane Handbook of Systematic Reviews of Interventions (23) using Revman version 5.3 (https://revman.cochrane.org/#/myReviews), and it was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (24). Weighted mean differences (WMD) and 95% CIs were calculated for continuous outcomes using an inverse variance random-effects model. With regard to dichotomous outcomes, the risk ratio and 95% CI were calculated using the random-effects Mantel-Haenszel approach with the significance threshold set at P=0.05. An *a priori* random-effects model assuming a substantial variability in the treatment effect size across studies was used conservatively.

Heterogeneity analysis. Heterogeneity was evaluated using Cochrane Q and I^2 statistics. If heterogeneity was acceptable (P>0.10, or P≤0.10, but I^2=50%), the fixed effect model was adopted. If heterogeneity did not meet these criteria, the random effect model was adopted. A two-tailed P-value of ≤0.05 was considered to be statistically significant.

Results

Literature retrieval and selection. The literature search in the present study resulted in the retrieval of the records of 2,397 eligible research articles, and of these, 314 were excluded as they were duplicates. After screening the titles and abstracts of the remaining 2,083 studies, a total of 2,056 were excluded according to the inclusion and exclusion criteria, since 27 were duplicates, 1,328 were on type 2 diabetes, 135 were on animal experiments, 535 had no original data and 31 were irrelevant. Finally, a total of 27 full-text articles, including 24 original research articles, were considered. However, 19 of these studies were not using dapagliflozin and thus, they were not included in the present meta-analysis. Therefore, the data of the five studies remaining, which evaluated the effect of dapagliflozin combined with insulin therapy in patients with type 1 diabetes mellitus (n=630), were analyzed (16-20). The studies by Dandona 2017 and Dandona 2018 (16,17) were on the same trial but the follow-up duration was different (24 weeks and 52 weeks, respectively). In Dandona 2018, some patients withdrew, resulting in an inconsistent number of patients compared with Dandona 2017. In order to avoid data duplication, the data from Dandona 2018 were excluded from this meta-analysis. The entire process is summarized in Fig. 1.

Study characteristics. All of the studies included in the present meta-analysis were double-blinded RCTs and were published as full articles between 2016 and 2018. The follow-up duration in the included studies ranged from 1 to 52 weeks. The baseline characteristics were well-balanced in each individual study. Placebo was used as a control in all trials. A summary of the characteristics of the studies included is provided in Table I.

Efficacy outcomes

HbA1c. Dapagliflozin therapy was associated with a significant decrease in HbA1c levels compared with the placebo (WMD: -0.42%, 95% CI: -0.45 to -0.40%, P<0.00001, I^2=93%, 5 comparisons, 1,617 participants; Fig. 2). The effect of 5 and 10 mg dapagliflozin to reduce HbA1c did not exhibit any significant difference.

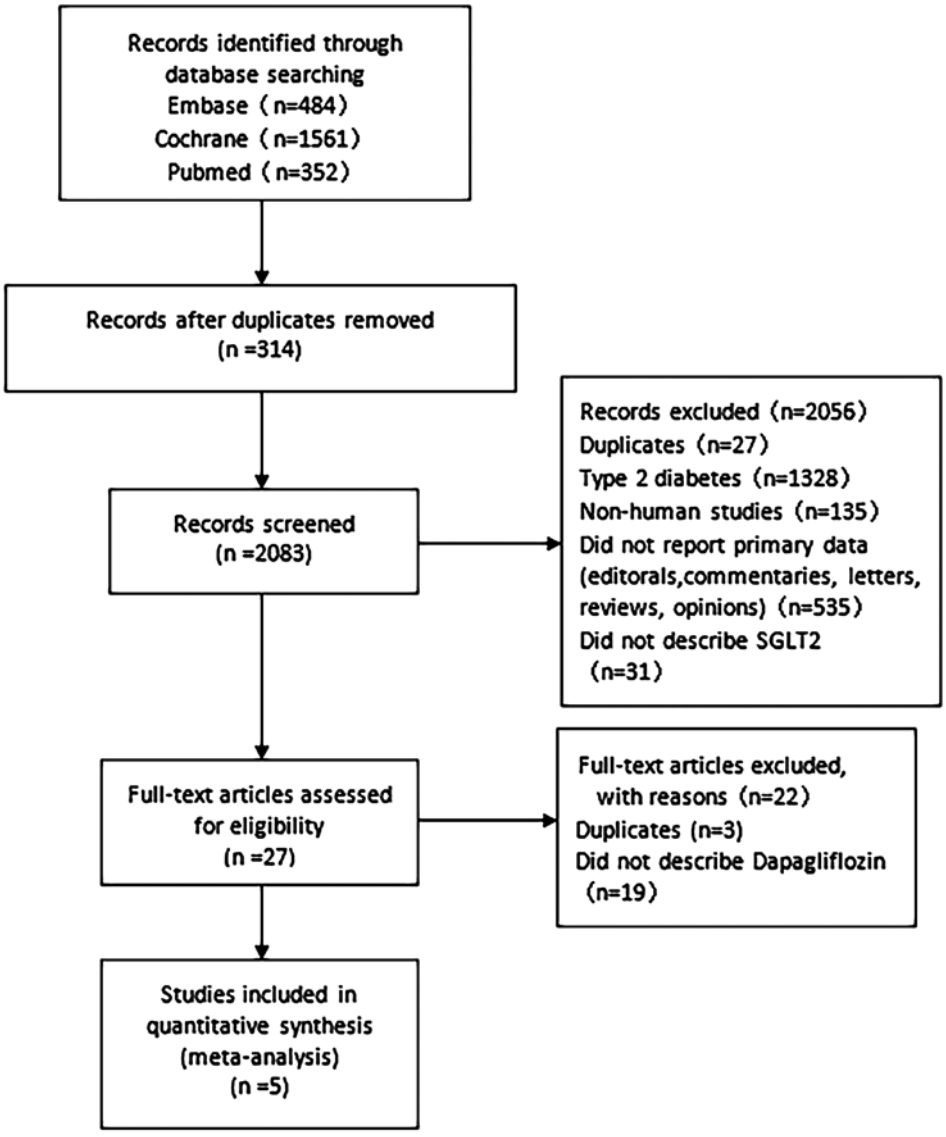

Figure 1. Flow chart of the literature screening.

Body weight. Dapagliflozin significantly reduced the body weight compared with the placebo (WMD: -3.19, 95% CI: -3.85 to -2.52, P<0.00001, I^2=100%, 3 comparisons, 804 participants; Fig. 3). Dapagliflozin at 5 and 10 mg exerted a similar effect on weight loss.

MDG. Dapagliflozin significantly reduced the MDG compared with the placebo (WMD: -0.88, 95% CI: -0.99 to -0.76, P<0.00001, I^2=99%, 7 comparisons, 1,533 participants; Fig. 4). Dapagliflozin at 5 and 10 mg did not exert any differential effect to reduce MDG.

MAGE. Dapagliflozin significantly reduced the average blood glucose fluctuation compared with the placebo (WMD: -0.80, 95% CI: -1.07 to -0.54, P<0.00001, I^2=100%, 6 comparisons, 1,507 participants; Fig. 5). Dapagliflozin at 5 and 10 mg exerted a similar effect to reduce MAGE.

Safety outcomes

Adverse events. The incidence rate of adverse events associated with dapagliflozin treatment was significantly higher than that in the placebo group (risk ratio: 1.11, 95% CI: 1.04-1.17, P=0.001, I^2=0%, 6 comparisons, 1,688 participants; Fig. 6). No significant difference in the incidence of adverse events caused by dapagliflozin between the doses of 5 and 10 mg was observed (P>0.1).

Serious adverse events. The incidence of serious adverse events associated with dapagliflozin treatment was significantly higher than that in the placebo group (risk ratio: 1.61, 95% CI: 1.10-2.34, P=0.01, I^2=0%, 6 comparisons, 1,143 participants; Fig. 7). No significant difference in the incidence of serious adverse events caused by dapagliflozin between the doses of 5 and 10 mg was observed (P>0.1).

Adverse events leading to discontinuation. The proportion of patients who stopped the treatment due to adverse events was evaluated. The incidence of discontinuation due to adverse events in the dapagliflozin treatment group was not significantly different from that in the placebo group (risk ratio: 1.06, 95% CI: 0.69-1.62, P=0.79, I^2=0%, 6 comparisons, 1,688 participants; Fig. 8). No difference in the incidence of

Table I. Characteristics of the studies included.

First author	Year	Country	Periodical	Institution	Follow-up weeks	Intervention	Experimental group (n)	Control group (n)	Clinical Stage	Design	(Refs.)
Dandona	2017	USA	The Lancet Diabetes and Endocrinology	Multi	24	Dapagliflozin	518	260	3	RCT	(16)
Dandona	2018	USA	Diabetes Care	Multi	52	Dapagliflozin	518	260	3	RCT	(17)
Henry	2017	USA	Diabetes, Obesity and Metabolism	Single	2	Dapagliflozin	57	13	2a	RCT	(18)
Kuhadiya	2016	USA	Journal of Clinical Endocrinology and Metabolism	Single	12	Dapagliflozin	20	10	4	RCT	(19)
Mathieu	2018	USA	Diabetes Care	Multi	24	Dapagliflozin	541	272	3	RCT	(20)

RCT, randomized controlled trial.

discontinuation due to adverse events was observed between the 5 and 10 mg dapagliflozin groups (P>0.1).

Infections. The incidence of urinary tract infections and reproductive tract infections was analyzed. The incidence of infection associated with dapagliflozin treatment was not significantly different from that in the placebo group (risk ratio: 1.38, 95% CI: 0.86-2.22, P=0.19, I^2=53%, 7 comparisons, 1,714 participants; Fig. 9). No significant difference was observed in the infection rate between dapagliflozin at 5 and 10 mg (P>0.1).

DKA. The incidence of DKA associated with dapagliflozin treatment was not significantly different from that in the placebo group (risk ratio: 2.41, 95% CI: 0.91-6.38, P=0.08, I^2=13%, 5 comparisons, 1,672 participants; Fig. 10). No significant difference in the incidence of DKA was observed between the dapagliflozin 5 and 10 mg groups (P>0.1).

Quality of the included studies. Risk of a bias assessment using the Cochrane Collaboration's Tool was performed to evaluate the quality of all of the included studies. The overall risk of bias of the five studies was low, other bias are not clear. The results in the quality assessment domain of the included trials are presented in Figs. 11 and 12.

Heterogeneity analysis. Significant heterogeneity (I^2≥50%) was identified among all efficacy outcomes but the heterogeneity among all safety outcomes was low (I^2<50%). Since the number of the included studies was small, it was not possible to perform a large number of subgroup analyses, and thus, only the doses were grouped.

Discussion

The present meta-analysis reported three major results. First of all, dapagliflozin-assisted insulin therapy for type 1 diabetes exerted significant beneficial effects on blood sugar control, blood sugar stability and weight loss. No significant difference in therapeutic efficacy between 5 and 10 mg dapagliflozin was identified. Furthermore, the use of dapagliflozin significantly increased the incidence of adverse events and serious adverse events compared with placebo. Finally, during the treatment of type 1 diabetes with dapagliflozin, the overall risk of infection, DKA and discontinuation caused by adverse events did not increase compared to placebo.

The results of the present study indicated that dapagliflozin-assisted insulin therapy significantly reduced HbA1c, body weight, daily average blood glucose and average blood glucose fluctuation in patients with type 1 diabetes. Further exploration regarding the association between dose and effect revealed no significant difference in effective outcomes between the two subgroups by dose (5 and 10 mg). Due to the complexity of the treatment, hypoglycemia and the possibility of weight gain, achieving and maintaining the target level of HbA1c through insulin optimization strategies remain a major challenge. Although progress has been made in insulin preparation, drug delivery systems and blood glucose monitoring, only one third of the patients are able to reach the blood glucose target, while numerous patients become overweight or obese (25,26). Due to the glucose-dependent and insulin-independent mechanism of dapagliflozin (27), its function is to increase urine glucose excretion without giving rise to a risk of hypoglycemia, thus reducing the degree of fluctuation of the level of glucose in the blood. Therefore, dapagliflozin may not only reduce the daily average blood sugar level and HbA1c, but also reduce blood sugar volatility, thus helping patients with type 1 diabetes to achieve the goal of gaining control of their blood sugar levels. A previous study indicated that weight loss under dapagliflozin was associated with heat loss caused by diabetes (28). Moderate weight loss also has beneficial effects on cardiovascular risk factors (29,30), suggesting that the beneficial effects of dapagliflozin on weight may help reduce cardiovascular risk factors. In addition, based on the

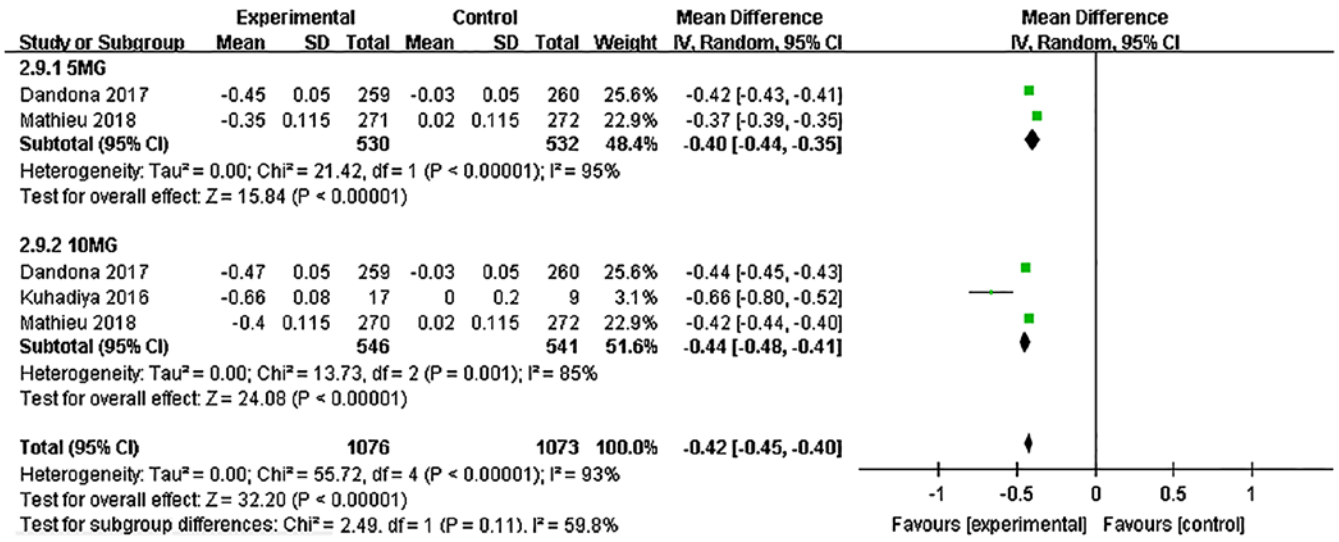

Figure 2. Forest plot of the mean difference in glycosylated hemoglobin A1c. The horizontal lines represent the 95% CI. The solid squares indicate the mean difference and are proportional to the weight used in the meta-analysis. The solid vertical line indicates no effect. The diamond indicates the weighted mean difference; the lateral tips of the diamond indicate the associated 95% CI. SD, standard deviation; IV, inverse variance; df, degrees of freedom.

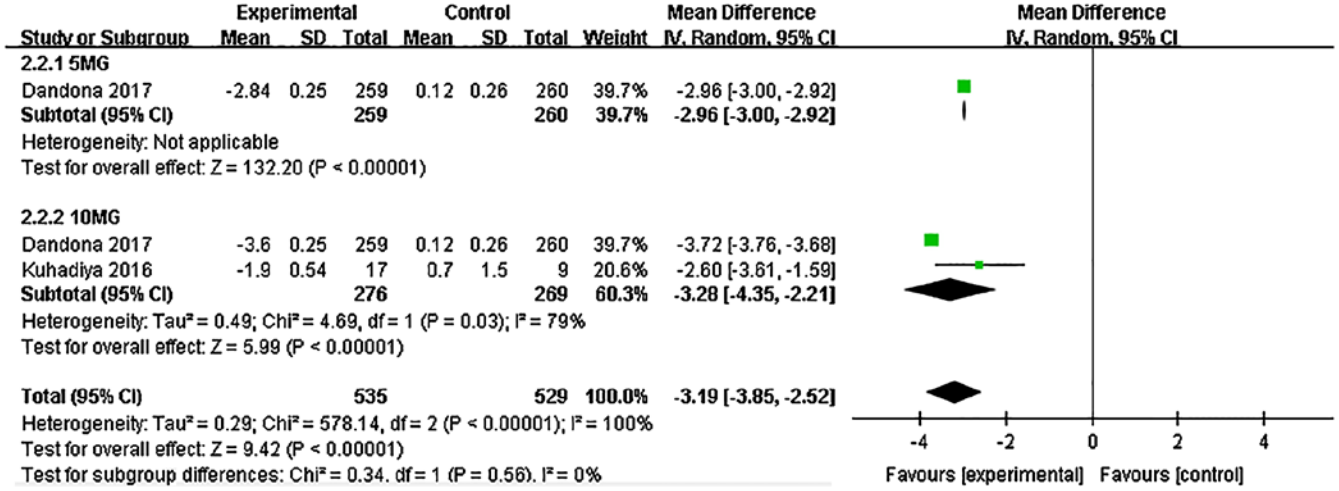

Figure 3. Forest plot of the mean difference in body weight. The horizontal lines represent the 95% CI. The solid squares indicate the mean difference and are proportional to the weight used in the meta-analysis. The solid vertical line indicates no effect. The diamond indicates the weighted mean difference; the lateral tips of the diamond indicate the associated 95% CI. SD, standard deviation; IV, inverse variance; df, degrees of freedom.

positive results from the DEPICT studies (16,17), dapagliflozin 5 mg received market approval in Europe in March 2019 as an additional drug to insulin therapy in patients with type 1 diabetes with a body mass index (BMI) ≥27 kg/m^2 (the BMI restriction reflects safety concerns regarding the DKA risk in those patients with a lower BMI) (31). The present study confirmed that the effect of dapagliflozin at the dose of 5 mg was sufficiently effective. Although the effect of 10 mg was more pronounced, the difference between the two doses was not evident.

A previous study suggested that the use of the lowest dose (dapagliflozin 5 mg) of the SGLT inhibitor was able to reduce the risk of DKA and other adverse events (32). By contrast, the present study indicated that dapagliflozin significantly increased the risk of adverse events and serious adverse events compared with placebo (however, no significant difference between the doses of 5 and 10 mg was observed; P>0.1). This is inconsistent with the association between dose and adverse events indicated by a previous study (32). The heterogeneity of the outcome of adverse reactions was low and this may indicate that the results are credible. Therefore, the correlation between drug dosage and safety requires further exploration and research in the future. With regard to adverse events leading to discontinuation and infections, no significant difference in outcomes was identified and the heterogeneity of the two outcomes was also low. The results actually demonstrated no significant risk of adverse events leading to discontinuation and infections associated with the use of dapagliflozin. Different from previous meta-analyses on SGLT2 (33-35) and clinical studies (16-17), the present meta-analysis on dapagliflozin did not indicate an increase in the risk of DKA and no significant difference was observed between the two different doses. However, a degree of caution should be exercised when interpreting these results as most of the studies included in

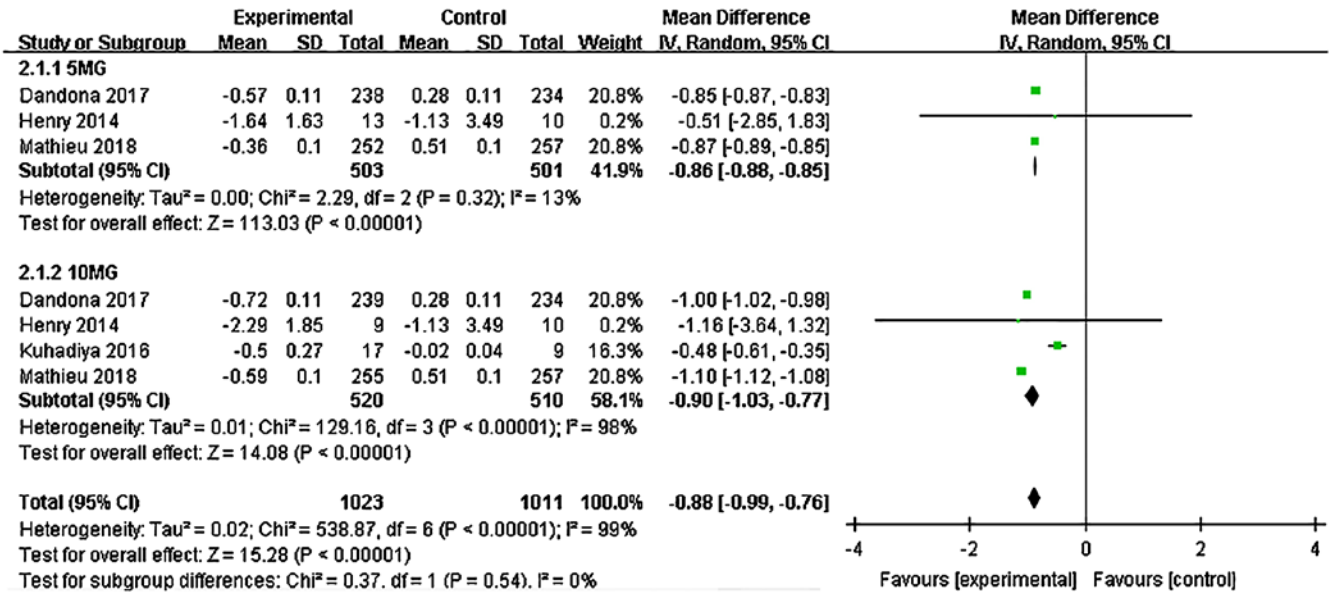

Figure 4. Forest plot of the mean difference in mean daily glucose. The horizontal lines represent the 95% CI. The solid squares indicate the mean difference and are proportional to the weight used in the meta-analysis. The solid vertical line indicates no effect. The diamond indicates the weighted mean difference; the lateral tips of the diamond indicate the associated 95% CI. SD, standard deviation; IV, inverse variance; df, degrees of freedom.

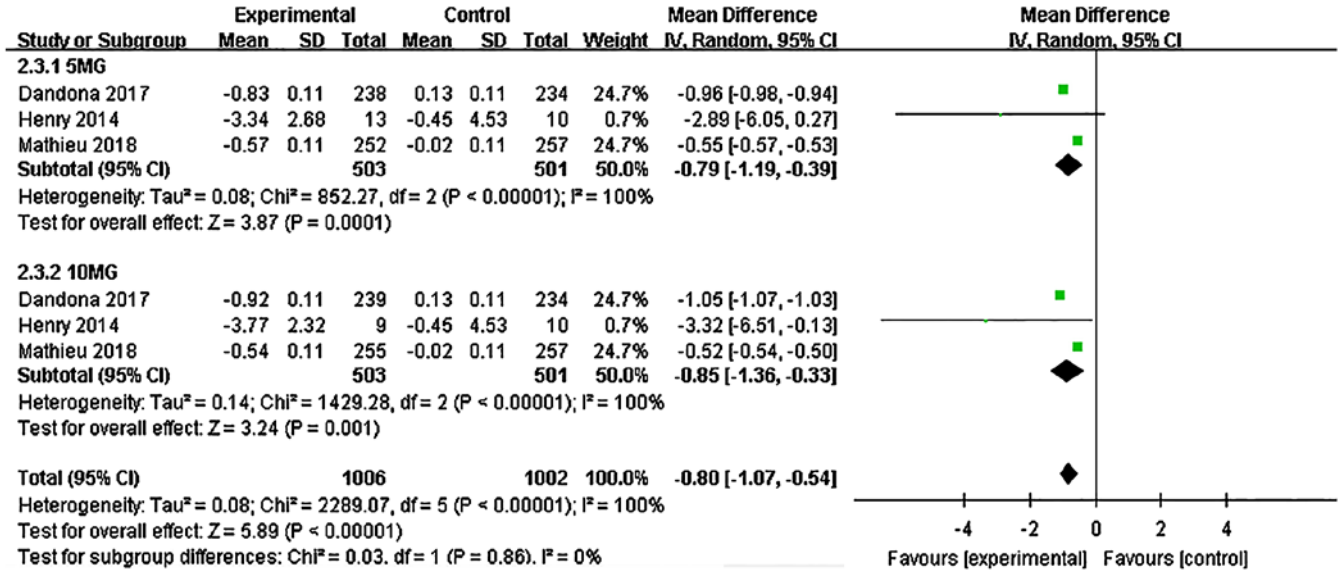

Figure 5. Forest plot of the mean difference in mean amplitude of glucose excursion. The horizontal lines represent the 95% CI. The solid squares indicate the mean difference and are proportional to the weight used in the meta-analysis. The solid vertical line indicates no effect. The diamond indicates the weighted mean difference; the lateral tips of the diamond indicate the associated 95% CI. SD, standard deviation; IV, inverse variance; df, degrees of freedom.

the present analysis had a duration of 24 weeks. It may only be suggested that dapagliflozin-assisted insulin therapy does not increase the risk of DKA in the short term (24 weeks) in patients with type 1 diabetes, while the risk during long-term treatment requires further research. In view of the conclusions made by previous studies (16-20) on the risks of DKA during treatment, it may be assumed that the risk of DKA remains an important issue that cannot be ignored during the treatment with dapagliflozin, and doctors should inform patients of the potential risk of DKA and provide information on how to mitigate the risk. The education of patients and providers should include insulin titration guidance, as mismanagement of this is a major factor responsible for DKA development (36). A reasonable insulin titration strategy, based on SALM-1 testing, is to reduce the insulin dose by no more than 20% after starting to use SGLT-2 inhibitor dapagliflozin, and then titrate back to the initial insulin dose (37). Patients should receive education on the possibility of normal blood glucose DKA and understand the risk factors for DKA, including acute diseases and infections; heavy drinking, strenuous exercise, reduced carbohydrate intake and insufficient insulin dose (e.g. dose omission or pump failure) (37). If the patient's ketone level is abnormal or DKA symptoms occur, the drug should be stopped immediately and medical care should be sought (36).

Previous meta-analyses discussed the efficacy and safety of SGLT2 inhibitors as a whole in adjuvant treatment of type 1

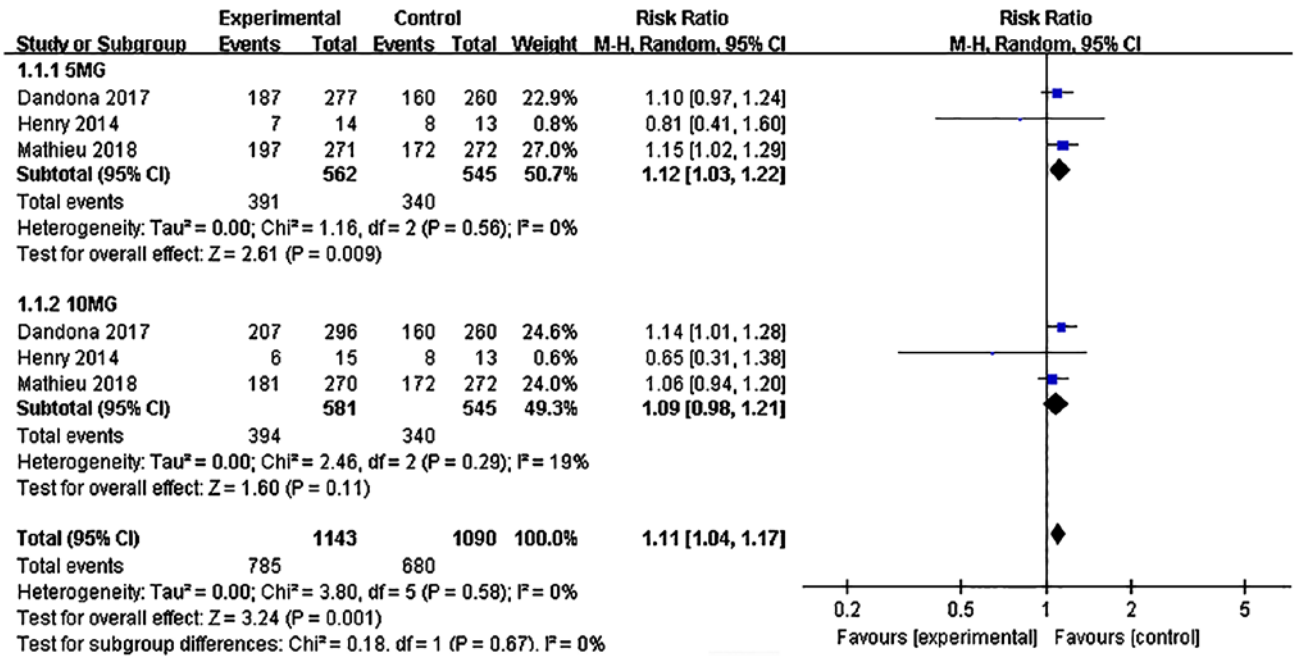

Figure 6. Forest plot of the RR for adverse events. The horizontal lines represent the 95% CI. The solid vertical line indicates no effect. The diamond indicates the weighted mean difference; the lateral tips of the diamond indicate the associated 95% CI. Adverse events included urinary tract infection, reproductive tract infection, hypoglycemia, ketoacidosis, acute kidney injury and fracture. M-H, Mantel-Haenszel; df, degree of freedom; RR, risk ratio.

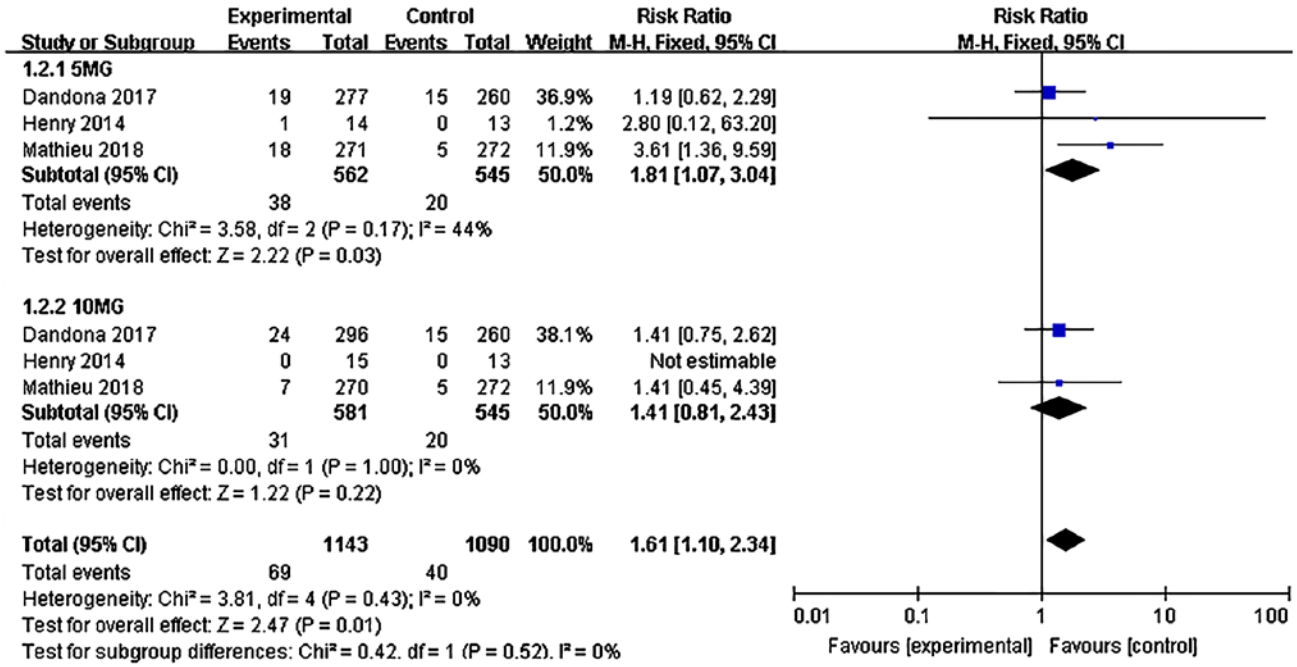

Figure 7. Forest plot of the RR for serious adverse events. The horizontal lines represent the 95% CI. The solid vertical line indicates no effect. The diamond indicates the weighted mean difference; the lateral tips of the diamond indicate the associated 95% CI. The event was considered serious when it was life-threatening, or if the outcome was patient death, hospitalization (initial or prolonged), disability or permanent damage. M-H, Mantel-Haenszel; df, degree of freedom; RR, risk ratio.

diabetes (36,38). Yang *et al* (38) analyzed the role of SGLT2 inhibitors as a whole in three randomized controlled trials, namely, three different drugs (dapagliflozin, empagliflozin, sotagliflozin), among which the study on dapagliflozin was included in the present article (18). El Masri *et al* (34) analyzed the role of SGLT2 inhibitors as a whole in four randomized controlled trials, namely, four different drugs (dapagliflozin, empagliflozin, sotagliflozin and canagliflozin), of which the study on dapagliflozin was included in the present article (19). SGLT2 inhibitors include dapagliflozin, empagliflozin, sotagliflozin, canagliflozin and other drugs, and their efficacy and safety may be different. The present meta-analysis took dapagliflozin as the research object and included four randomized controlled trials to study the same drug. In addition,

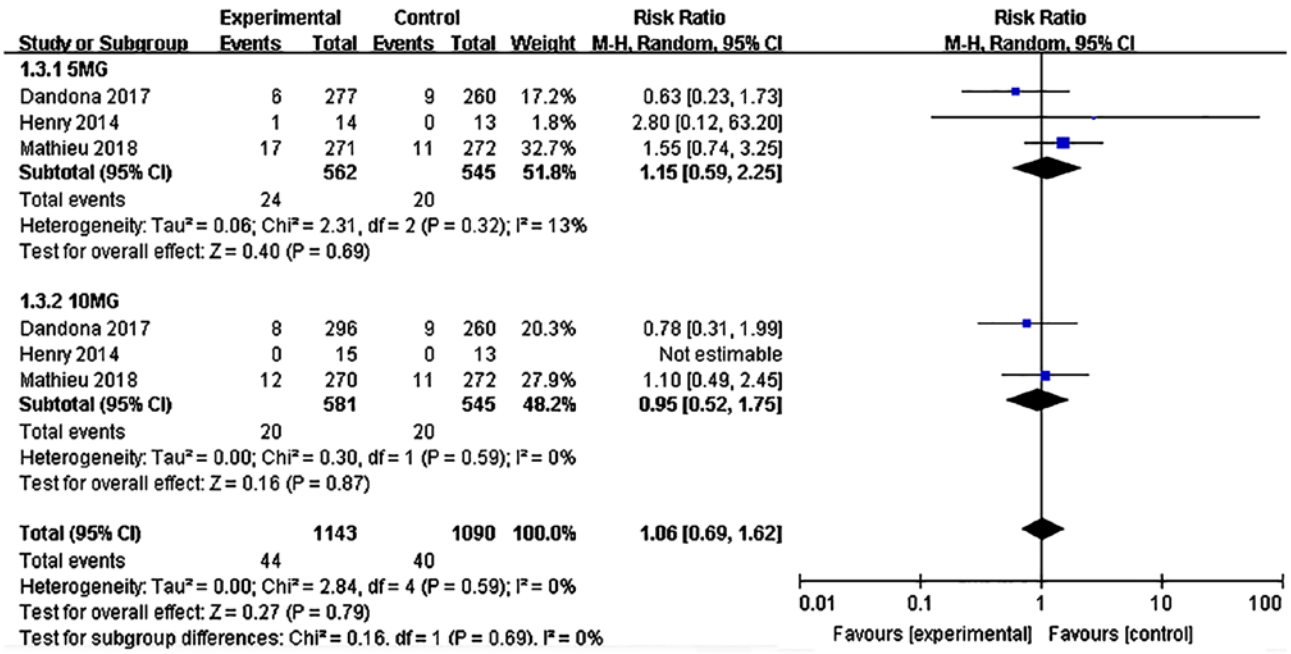

Figure 8. Forest plot of the RR of adverse events leading to discontinuation. The horizontal lines represent the 95% CI. The solid vertical line indicates no effect. The diamond indicates the weighted mean difference; the lateral tips of the diamond indicate the associated 95% CI. M-H, Mantel-Haenszel; df, degree of freedom; RR, risk ratio.

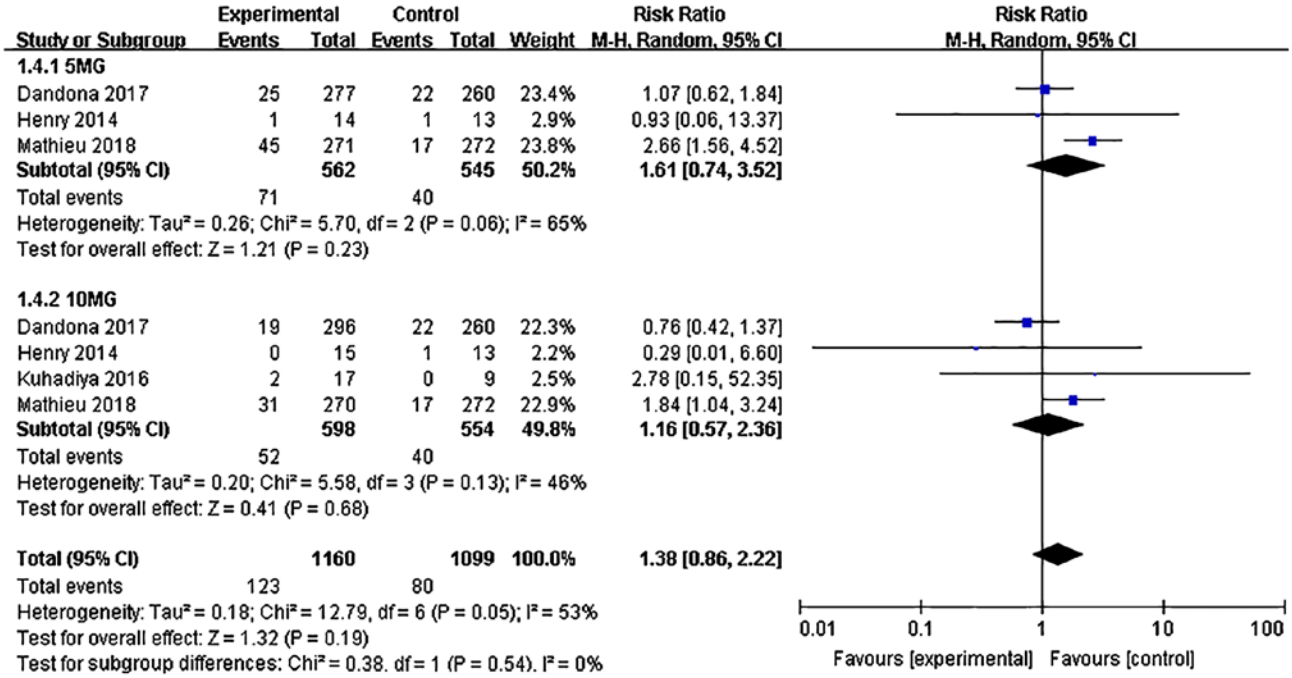

Figure 9. Forest plot of the RR of infections. The horizontal lines represent the 95% CI. The solid vertical line indicates no effect. The diamond indicates the weighted mean difference; the lateral tips of the diamond indicate the associated 95% CI. M-H, Mantel-Haenszel; df, degree of freedom; RR, risk ratio.

subgroup analysis was conducted to analyze the significance of differences in efficacy and safety between 5 mg and 10 mg of dapagliflozin treatment.

Of note, the present study had certain strengths and limitations. The present meta-analysis included four experiments with dapagliflozin as the research object and is, to the best of our knowledge, the first systematic evaluation and meta-analysis of dapagliflozin-assisted insulin therapy in type 1 diabetes. The risk of bias assessment for inclusion in the trial and the grading of the quality of the evidence were included in the present study. All of the five studies were of high quality. The results of the present analysis strongly support the conclusion drawn from a previous relevant review that SGLT-2 inhibitors as adjunctive therapy to insulin provide additional glycemic and non-glycemic benefits for patients with type 1 diabetes (37). However,

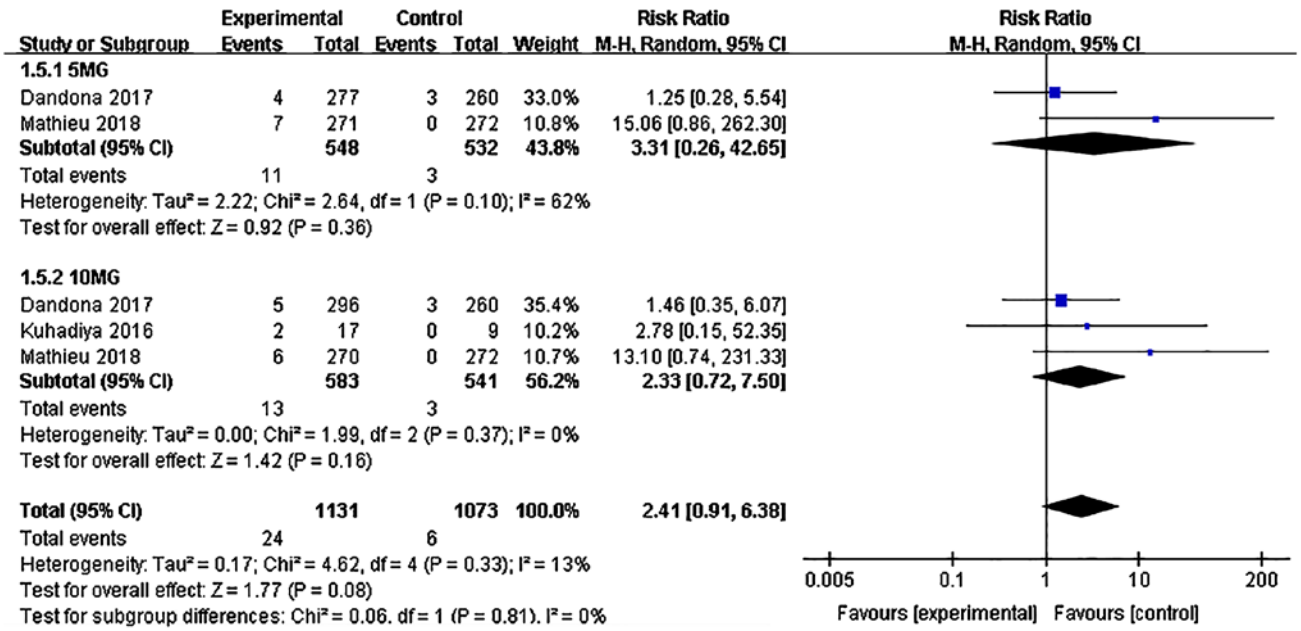

Figure 10. Forest plot of the RR of diabetic ketoacidosis. The horizontal lines represent the 95% CI. The solid vertical line indicates no effect. The diamond indicates the weighted mean difference; the lateral tips of the diamond indicate the associated 95% CI. M-H, Mantel-Haenszel; df, degree of freedom; RR, risk ratio.

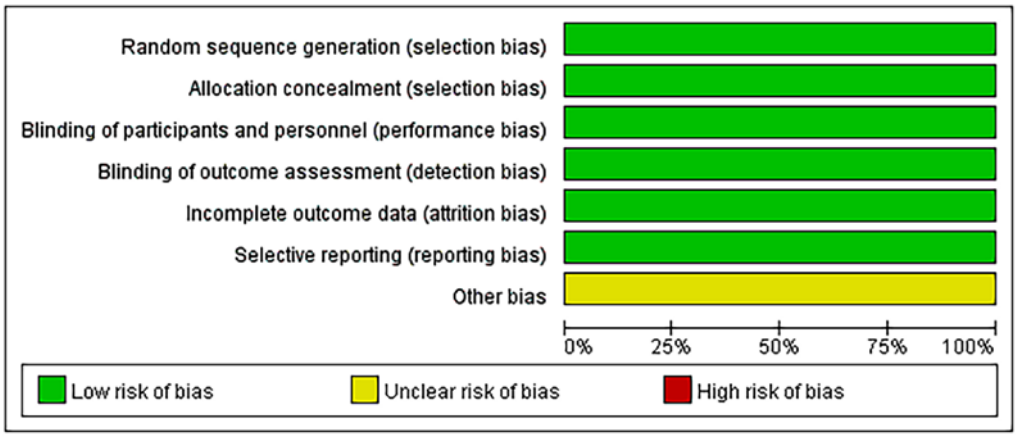

Figure 11. Risk of bias graph.

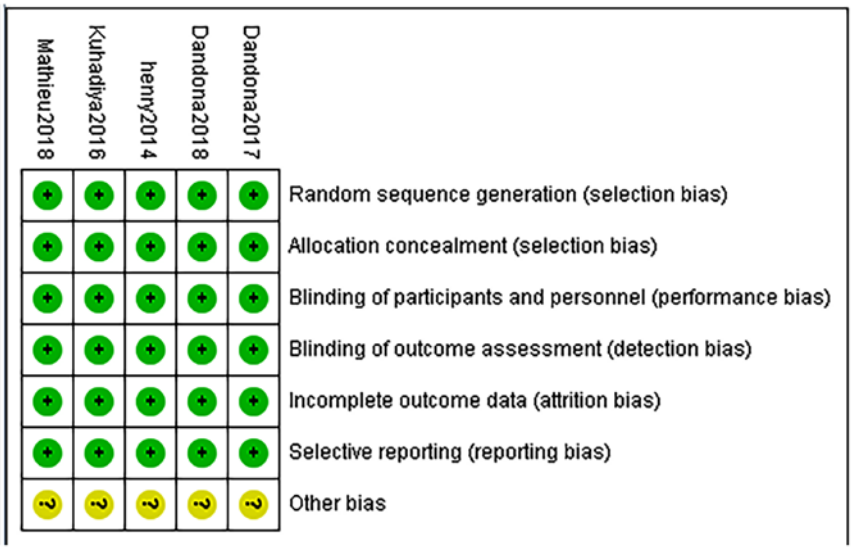

Figure 12. Risk of bias summary.

certain limitations were also present. These include the relatively small number of trials included in the present meta-analysis and the short duration of the treatment (no more than 52 weeks), which did not allow for a robust assessment of long-term results (e.g. pertaining to the risk of DKA). A subgroup and regression analysis was conducted on the follow-up time, which found that the follow-up time had no obvious significance for heterogeneity. Subgroup analysis of the follow-up time in so few test groups may not be meaningful and would not make a positive contribution to the review findings or help to compare and synthesize information about the characteristics of interventions in the study. Confidence in the results comes from the high quality of the included trials. Due to the small number of studies, marked heterogeneity was present for the outcome indicators. The source of heterogeneity in this systematic review was not determined, since more clinical research data is required, and a subgroup analysis by age, drug injection method and region will be considered in further studies. In addition, the high heterogeneity between the results of each group and/or the small number of trials and the contribution of the participants to each subgroup gave rise to uncertainty about the importance of these subgroup differences.

In March 2019, the European Commission approved the adjuvant treatment of type 1 diabetes with dapagliflozin. Similarly, Japan's Ministry of Health, Labor and Welfare approved dapagliflozin as an adjuvant drug for patients with type 1 diabetes using insulin (21). Previous studies pointed out that the use of SGLT2 inhibitors increases the risk of DKA in patients using insulin (39,40). Additional research is required on risk factors of DKA and risk mitigation to determine the characteristics of high-risk patients and prevent such events. However, the present results suggest that dapagliflozin does not increase the risk of DKA in the short term (24 weeks). Although 5 mg dapagliflozin gained marked approval in Europe in March 2019, our study showed that dapagliflozin significantly increased the risk of adverse events and serious adverse events compared with placebo (no significant difference was observed between doses of 5 and 10 mg; $P>0.1$).

In conclusion, the present meta-analysis indicated that dapagliflozin, as an adjuvant drug for insulin therapy in patients with type 1 diabetes, provided a significant benefit. The present results provided a reference for the clinical application and further research on dapagliflozin in the future. Additional prospective RCTs with larger sample sizes and a longer duration are required to further assess the efficacy and safety of dapagliflozin in the treatment of type 1 diabetes.

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Availability of data and materials

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

Authors' contributions

ZJ, YH and YW conceived and designed the study; ZJ and YH performed the database search, study selection and data extraction; ZJ, YH and YW performed the quality assessment of the screened studies; ZJ and YH wrote the manuscript; All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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