Original Article

A Systematic Review and Meta-Analysis of Randomized Controlled Trials Comparing the Safety of Dapagliflozin in Type 1 Diabetes Patients

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Abstract

Background and Purpose: The dapagliflozin's safety profile in insulin-treated adult type-1 diabetes mellites (T1DM) patients remains poorly explored. Therefore, this systematic review and meta-analysis compared the risk of all-cause side effects, study discontinuation of participants due to side effects, urinary tract infection (UTI), diabetic ketoacidosis, and hypoglycemia between dapagliflozin 10 mg and dapagliflozin 5 mg, dapagliflozin 10 mg and placebo, and dapagliflozin 5 mg and placebo.

Materials and Methods: Parallel-arm randomized controlled trials juxtaposing the above outcomes between the afore-mentioned interventions were eligible for inclusion in this study and were searched in PubMed, Embase, and Scopus. Utilizing the Cochrane tool, the risk of bias was assessed in the recruited trials. Finally, by random-effect meta-analysis, each outcome was compared among the above interventions, and the risk ratio was estimated.

Results: Four trials of varying length (1-52 weeks) sourcing data from almost 1760 participants from about 32 nations were reviewed. Overall, the trials had a low or unclear risk of bias, and only one was at a high risk of bias. Compared to the placebo, the risk of side effects was higher in those treated with dapagliflozin 5 mg (RR=1.10; 95% CI=1.02-1.18; p=0.014; I^2=0%). UTI risk was less with the 10mg dapagliflozin than its lower dose (RR=0.50; 95% CI=0.32-0.79; p-value=0.003; I^2=0%). All the remaining comparisons were statistically not significantly different between the juxtaposed intervention pairs.

Conclusion: In contrast to placebo, dapagliflozin 5mg increased the risk of overall adversities in insulin-treated type-1 diabetes, and dapagliflozin 10 mg had a reduced risk of UTI than its 5mg preparation.

Key words: Dapagliflozin; Diabetes Mellitus, Type 1; Side Effect, Drug; Drug Toxicity; Sodium-Glucose Transporter 2 Inhibitors

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1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that destroys insulin-producing pancreatic beta cells leading to hyperglycemia necessitating lifelong insulin treatment (1,2). But, due to multiple daily injection requirements, side effects on prolonged use, and frequent need to monitor the blood glucose levels, insulin therapy does not suit every T1DM patient (3). Besides, all T1DM patients do not achieve the desired glycemic control with insulin therapy alone (4). Henceforth, to decrease these insulin associated intricacies in T1DM management, it's essential to research for adjunct therapeutics that can decrease their sole dependence by reducing the required dosage and frequency of administration to achieve the optimum glycemic control. In this regard, sodium-glucose co-transporter-2 (SGLT2) inhibitors have drawn significant attention to the medical community after its successful use in type 2 diabetes patients and have been tested in several clinical trials on T1DM patients contemporarily (5-7).

SGLT2 inhibitors, such as dapagliflozin, empagliflozin, and canagliflozin, are phlorizin based compounds (2,3) that eliminate blood glucose through the kidneys by inhibiting the SGLT2 transport protein, responsible for 90% of renal glucose reabsorption (8,9). Compared to other phlorizin compounds, dapagliflozin is highly selective to SGLT2 protein and more stable due to its prolonged half-life in the body (3,5,10,11). Furthermore, early data from phase three clinical trials suggest that dapagliflozin treatment decreases the mean glucose and glycemic variability in poorly controlled T1DM patients (12). These features make dapagliflozin a fundamental SGLT2 inhibitor to investigate for its use as an insulin-adjunct therapy in T1DM patients. However, because of safety concerns, the drug is not recommended in the treatment of T1DM patients by the US Food and Drug Administration (13). Hence, it is essential to research how different dosages of dapagliflozin determine the risk of side effects in these patients. Unlike for empagliflozin (14,15), systematic review and meta-analysis efforts to distinguish treatment effects of different dosages of dapagliflozin are relatively sparse in the existing literature.

Therefore, this study compared the risk of all-cause side effects (i.e. the aggregated adverse effects due to any cause) between dapagliflozin 10 mg and dapagliflozin 5 mg, dapagliflozin 10 mg and placebo, as well as dapagliflozin 5 mg and placebo. As an auxiliary aim, it attempted to distinguish the risk of study discontinuation of participants due to side effects, urinary tract infection (UTI), diabetic ketoacidosis, and hypoglycemia between each of these intervention pairs. We studied these particular dosages because contemporary clinical trials on T1DM patients have primarily tested dapagliflozin in these dosages (16,17).

2. Methods

2.1. Inclusion Criteria

Study Design: Randomized parallel-arm (of any number) trials of any duration.

Participant Characteristics: Adult (18 years or older) T1DM patients on insulin treatment.

Interventions Tested: The trials should have tested any two or all of the following interventions- dapagliflozin 10 mg, dapagliflozin 5 mg, and placebo. These

interventions should have been prescribed daily during the intervention period.

Outcome: In each of these treatment arms, the number of participants who took at least one dose of the test drug and experienced one or more adverse event of any type was the outcome of interest. The reported side effects, along with their definitions and the insulin dosing, were accepted as per the trialists. When several clinical trials testing the effect of dapagliflozin on T1DM patients were conducted on the same study population or had an identical identification number, we recruited that reporting the highest number of side effects. When the latter was identical between the trials, we incorporated that with a longer follow-up. The secondary outcomes listed above did not comprise the inclusion criteria.

2.2. Exclusion Criteria

Trials with study designs other than those mentioned above, like single-arm trials, cross over trials, or observational studies. When trial participants were diagnosed with diabetes other than type 1 like gestational diabetes, type-2 diabetes, or maturity-onset diabetes of young. If participants received any blood glucose-lowering agent other than insulin and dapagliflozin.

For this systematic review, a pre-published protocol is unavailable.

2.3. Search Strategy

Eligible trials were searched in electronic databases (PubMed, Embase, and Scopus) irrespective of the date or language. The last date of the search was 12-Aug-2019. The titles and abstracts were searched using the succeeding terms: 'type-1' OR 'type 1' OR 'type1' AND 'diabetes' AND 'dapagliflozin' AND 'trial.' Following MeSH descriptors were also used-'Diabetes mellitus, type 1' and 'Sodium-glucose transporter 2 inhibitors.' When available, filters were used to narrow down the search to clinical trials. Additionally, the bibliography of the reviewed papers was scrutinized for eligible trials. This review's trial recruitment process adhered to the PRISMA 2009 flow diagram (18). When the title and abstract of a publication appeared to meet the afore-mentioned eligibility criteria or if a decision about inclusion or exclusion of a study was not possible by reading the excerpts alone, a full-text reading ensued.

2.4. Study Selection and Risk of Bias Assessment

The following details were collected from each trial: trial design, participant characteristics, compared interventions, and outcome. The trialists were not contacted for data. Utilizing the Cochrane Collaboration's tool for assessing the risk of bias in randomized clinical trials, the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and miscellaneous bias was assessed (19).

The authors independently performed the data extraction, and risk of bias assessment and subsequently collated their findings. Any disagreement among the authors was resolved by discussion, and a third-party opinion was not required.

2.5. Statistical Analysis

Using a random-effect model meta-analysis (DerSimonian and Laird method), each outcome was compared between the following interventions – dapagliflozin 10 mg versus dapagliflozin 5mg, dapagliflozin 10 mg versus placebo, and dapagliflozin 5 mg versus placebo, and the summary effects were determined in risk ratios (RR). While comparing the outcome between two intervention arms, a trial was excluded

from meta-analysis if the event did not occur in both. When an event was absent in either of the compared intervention arms, 0.5 was added to each cell of the 2x2 table for meta-analysis. The statistical significance of RR was determined at $p<0.05$ (and 95% confidence interval (CI)). To estimate the heterogeneity, the *p*-value of the Chi^2 statistics (statistically significant at $p<0.1$) and the I^2 statistics (categorized as unimportant, moderate, substantial, and considerable at values 0-40%, 30-60%, 50-90%, and 75-100%, respectively) were used (19). The publication bias was assessed visually using the funnel plots for the primary outcome only.

2.6. Sensitivity Analysis

The robustness of the meta-analysis findings of the primary outcome was judged by the following types of sensitivity analyses. We repeated the meta-analysis first by using a fixed-effect model, then by dropping a trial with every iteration, and finally, by determining effect estimates in risk difference (RD).

The Stata Statistical Software Version 16 was used for the statistical analysis (StataCorp, College Station, Texas, USA).

3. Results

The database search produced 123 search results. After excluding duplicates, 83 papers' titles and abstracts were read. Nine papers required a full-text reading. Finally, we recruited four trials meeting the afore-depicted eligibility criteria in this review (Figure-1) (17,20–22).

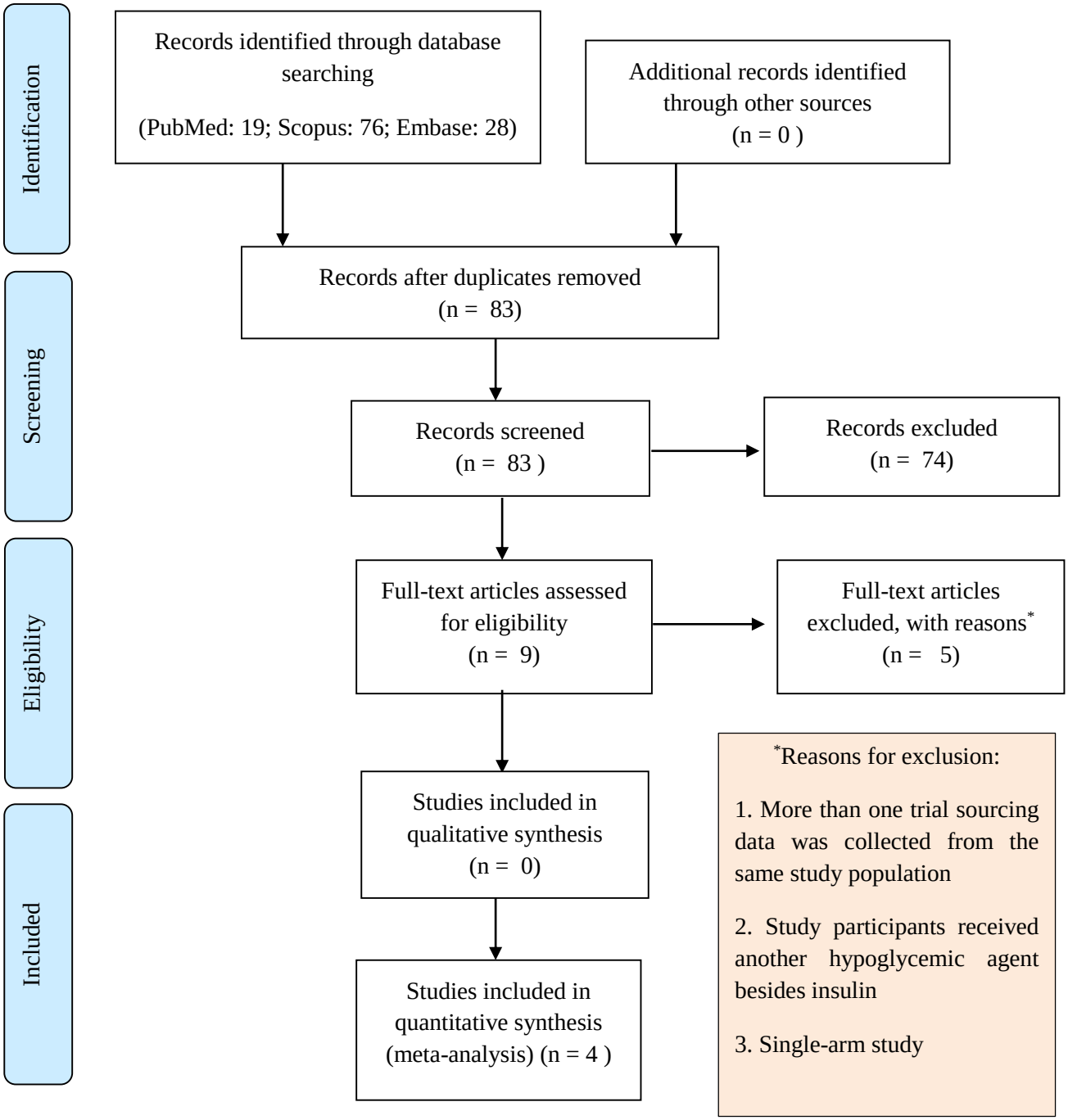

Figure 1. Prisma flow diagram **(23).**

These trials sourced about 1,760 participants (randomized into different treatment arms) from approximately 32 countries (17,20–22). The participants' average age was between 35 to 43 years (17,20–22). These trials' duration ranged between 1-52 weeks (17,20–22). Salient characteristics of the trials are depicted in Table 1.

Table 1. Salient features of reviewed papers

Study	Trial	Participants	Interventions compared	Outcomes
Dandona, 2018(24)	Randomized, parallel-arm, multicenter, double-blinded, placebo-controlled trial. Duration: 52 weeks Consent: obtained. Funding information: provided Trial ID: NCT02268214	Diagnosis: T1DM Randomized (n)=833 Sex(24): male=373/778, females= 405/778 Mean age(24): ~42.43 years (n=778) Sourced from(24): 17 nations	Three groups: 1. Dapagliflozin 5mg (n=277) 2. Dapagliflozin 10mg (n=296) 3. Placebo (n=260)	Overall adverse effects seen in: 1. Dapagliflozin 5mg: n=215 2. Dapagliflozin 10mg: n=236 3. Placebo: n=189
Mathieu, 2018(17)	Randomized, parallel-arm, multi-centric, double blinded, placebo-controlled trial. Duration: 24 weeks Consent: obtained. Funding information: provided Trial ID: NCT02460978	Diagnosis: T1DM Randomized (n) = 815 Sex: male=358, females=455 Mean age: 42.7 years Sourced from 13 countries	Three groups: 1. Dapagliflozin 5mg (n=271) 2. Dapagliflozin 10mg (n=270) 3. Placebo (n=272)	Overall adverse effects seen in: 1. Dapagliflozin 5mg: n=197 2. Dapagliflozin 10mg: n=181 3. Placebo: n=172
Henry, 2015(25)	Randomized, parallel-group, double-blinded, placebo-controlled trial. Duration: 2 weeks. Consent: obtained. Funding information: provided Trial ID: NCT01498185	Diagnosis: T1DM Randomized (n) = 70 Sex (n): male=40, females=30 Mean age: ~35.3 years years Sourced from United States	Four groups: Dapagliflozin 1 mg (n=13) Dapagliflozin 2.5 mg (n=15) Dapagliflozin 5 mg (n=14) Dapagliflozin 10 mg (n=15) Placebo (n=13)	Overall adverse effects seen in: 1. Dapagliflozin 5mg: n=7 2. Dapagliflozin 10mg: n=6 3. Placebo: n= 8
Watada, 2019(20)	Randomized, parallel-group, single-blinded, single-centered, placebo-controlled trial. Duration: seven days (participants followed up until day 14). Consent: obtained. Funding information: provided Trial ID: NCT02582840	Diagnosis: T1DM Randomized (n) = 42 Sex (baseline): male= 18, females=34 Mean age: ~38.9 years years Sourced from Japan.	Three groups: Dapagliflozin 5 mg (n=14) Dapagliflozin 10 mg (n=14) Placebo (n=14)	Overall adverse effects seen in: 1. Dapagliflozin 5mg: n=2 2. Dapagliflozin 10mg: n=5 3. Placebo: n=1

Overall the studies had an unclear risk of selection bias (17,20–22), detection bias (17,20–22), and performance bias (17,21,22). The trial by Watada et al. (2019) (20) suffered from a high risk of performance bias as the investigators were not blinded (Table-2). The bias risks of all trials were also low for attrition bias, reporting bias, and other biases (17,20–22).

Table 2. Risk of bias assessment (19)

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias) All outcomes	Blinding of outcome assessment (detection bias) All outcomes	Incomplete outcome data (attrition bias) All outcomes	Selective reporting (reporting bias)	Other bias
Dandona, 2018(24)	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
	Comments: Precise methods unclear.						
Mathieu, 2018(17)	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Henry, 2015(25)	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
	Comments: Precise methods unclear.						
Watada, 2019(20)	Unclear	Unclear	High Comments: Investigator was not blind	Unclear Comments: not clear if hypoglycemia assessors were blinded	Low risk	Low risk	Low risk
	Comments: precise mechanism not clear						

Dapagliflozin 5 mg increased the risk of overall side effects compared to placebo (random-effect model: RR=1.10; 95% CI=1.02-1.18; p=0.014; I^2=0%; p-value of Chi^2=0.586) (Figure 2). The predictive interval (95% CI=0.93-1.29) suggested that in a future trial dapagliflozin 5mg might have a decreased risk of all-cause side effects compared to the placebo. This risk of side effects did not vary between 10 mg dapagliflozin versus 5 mg dapagliflozin (random-effect model: RR= 0.98; 95% CI=0.89-1.08; p=0.705; I^2=26.6; p-value of Chi^2=0.252) and 10 mg dapagliflozin versus placebo (random-effect model: RR=1.07; 95% CI=0.96-1.20; p=0.205; I^2=27.8; p-value of Chi^2=0.245) (Figure 3-4). These findings remained identical on using fixed-effect model (Figure 2-4). The heterogeneity was unimportant for all meta-analytic comparisons, and the visual assessment of funnel plots (not shown) was not suggestive of any publication bias.

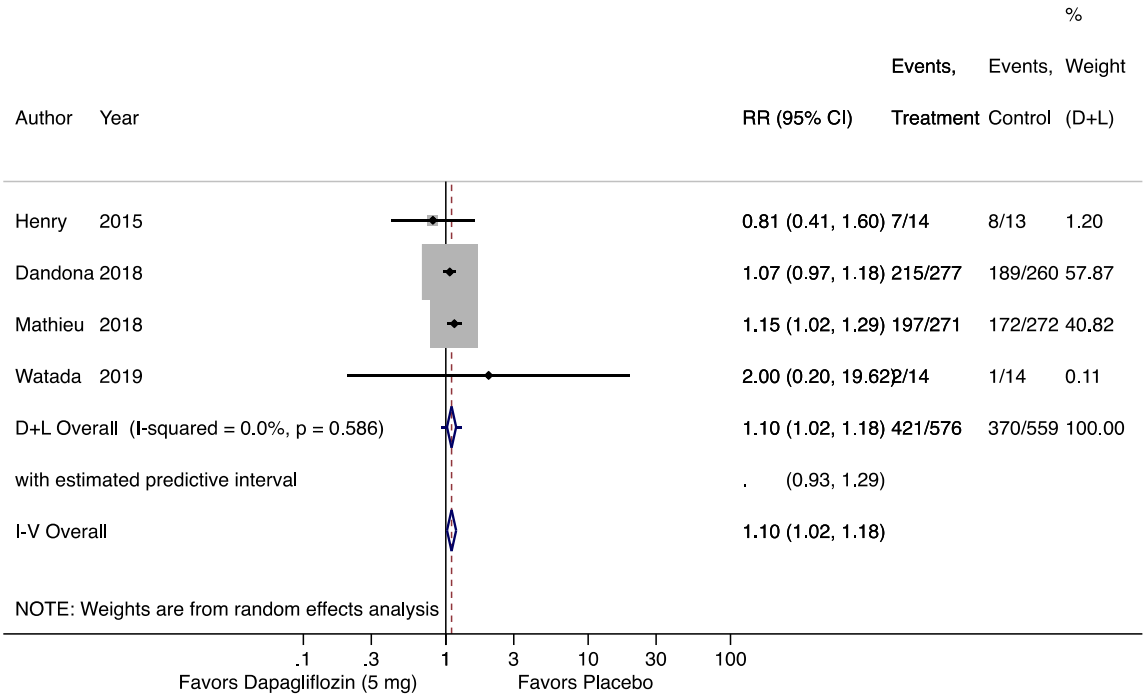

Figure 2. Forest plot comparing the risk of all-cause adverse reactions between Dapagliflozin 5 mg and placebo

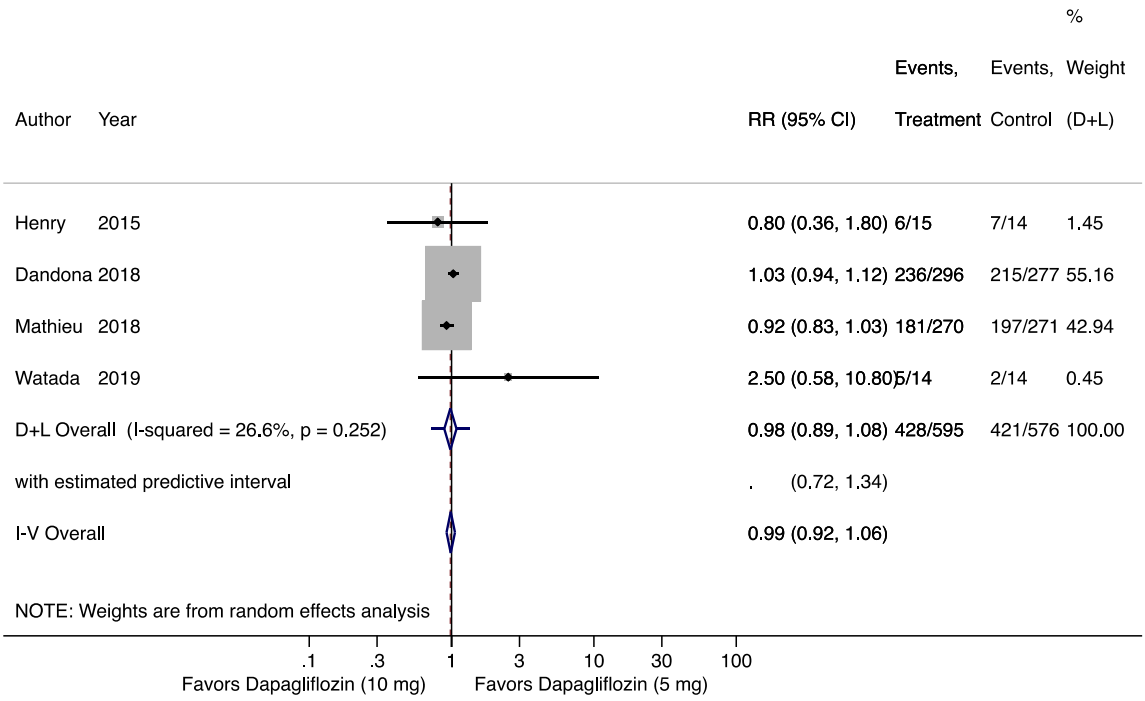

Figure 3. Forest plot comparing the risk of all-cause adverse reactions between Dapagliflozin 10 mg and Dapagliflozin 5 mg

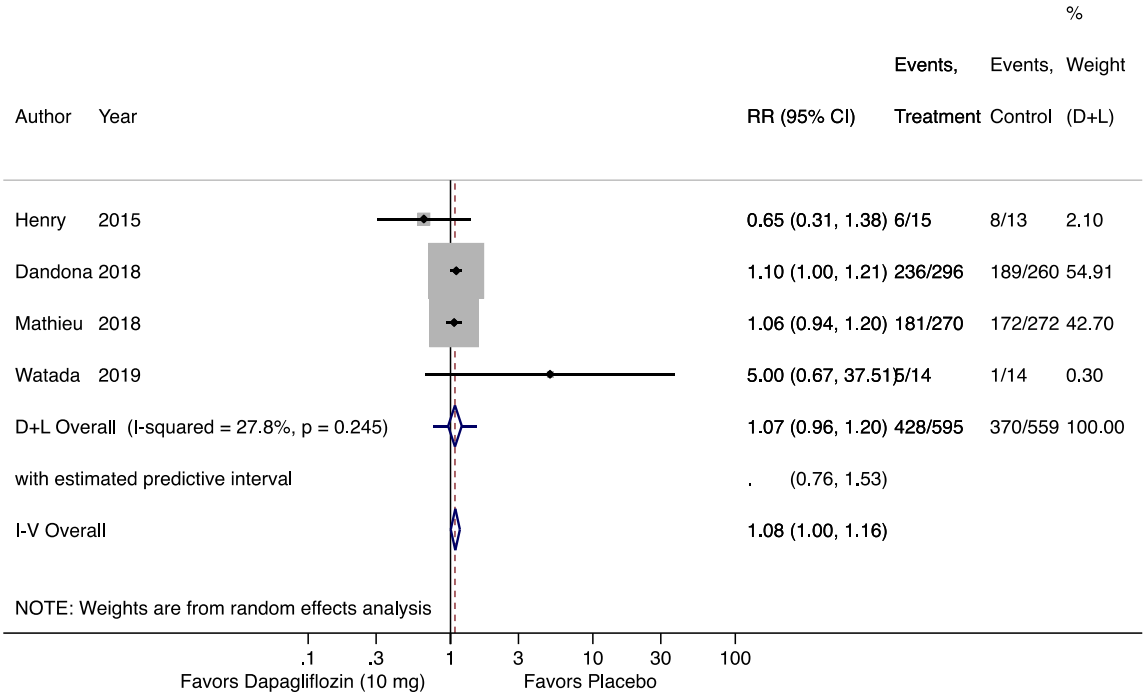

Figure 4. Forest plot comparing the risk of all-cause adverse reactions between Dapagliflozin 10 mg and placebo

Sensitivity analysis for the primary outcomes were closely similar to the preliminary analysis depicting the robustness of the findings (Table 3). On removal of one trial (17) from the meta-analysis, it was revealed that although the effect estimate suggested an increased risk of side effects with 5mg dapagliflozin, statistically it wasn't significantly different from the placebo (RR=1.06; 95%CI=0.97-1.17; p=0.215; I^2=0%; p-value of Chi^2=0.636). Between dapagliflozin 5mg and placebo the RD (RD=0.07; 95%CI=0.02, 0.12; p-value=0.011) for this outcome suggested that the number needed to treat was 14.

Regarding the secondary outcomes, dapagliflozin 10 mg decreased the risk of UTI compared to dapagliflozin 5 mg (random-effect model: RR=0.50; 95% CI=0.32-0.79; p-value=0.003; I^2=0%; p-value of Chi^2=0.717). The remaining comparisons for these outcomes were statistically not significantly different (Table 4).

Table 3. Sensitivity analysis of the primary outcome

Sensitivity analysis (meta-analysis find by excluding one study at a time)						
Intervention compared	Study excluded from meta-analysis	Risk ratio (95% CI) Random-effect model	Risk ratio (95% CI) Fixed-effect model	*p*-value	Heterogeneity I^2 statistics (%)	Heterogeneity *p*-value of Chi^2
Dapagliflozin 10 mg versus placebo	Dandona 2018(24)	1.02 (0.58-1.79)	1.05 (0.93-1.19)	0.946	48.4%	0.144
	Mathieu 2018(17)	1.04 (0.59-1.85)	1.09 (0.99-1.20)	0.884	50.2%	0.134
	Henry 2015(22)	1.09 (0.99-1.19)	1.09 (1.01-1.17)	0.075	16.5%	0.302
	Watada 2019(20)	1.08 (1.00-1.16)	1.08 (1.00-1.16)	0.049	0.0%	0.381
Dapagliflozin 5 mg versus placebo	Dandona 2018(24)	1.14 (1.02-1.28)	1.14 (1.02-1.28)	0.025*	0.0%	0.545
	Mathieu 2018(17)	1.06 (0.97-1.17)	1.06 (0.97-1.17)	0.215	0.0%	0.636
	Henry 2015(22)	1.10 (1.02-1.19)	1.10 (1.02-1.19)	0.011*	0.0%	0.557
	Watada 2019(20)	2.00 (1.02-1.18)	2.00 (1.02-1.18)	0.015*	0.0%	0.434
Dapagliflozin 10 mg versus dapagliflozin 5 mg	Dandona 2018(24)	0.93 (0.83-1.03)	0.93 (0.83-1.03)	0.163	0.0%	0.387
	Mathieu 2018(17)	1.03 (0.94-1.12)	1.03 (0.94-1.12)	0.531	0.0%	0.410
	Henry 2015(22)	0.98 (0.88-1.11)	0.99 (0.92-1.06)	0.785	47.7%	0.148
	Watada 2019(20)	0.98 (0.90-1.07)	0.99 (0.92-1.05)	0.640	21.0%	0.282

Sensitivity analysis (meta-analysis estimating risk differences)					
Intervention compared	Ratio difference (95% CI) Random-effect model	Ratio difference (95% CI) Fixed-effect model	*p*-value	Heterogeneity I^2 statistics (%)	Heterogeneity *p*-value of Chi^2
Dapagliflozin 10 mg versus placebo	0.06 (-0.02, 0.14)	0.06 (0.01, 0.11)	0.160	39.9%	0.172
Dapagliflozin 5 mg versus placebo	0.07 (0.02, 0.12)	0.07 (0.02, 0.12)	0.011*	0%	0.653
Dapagliflozin 10 mg versus dapagliflozin 5 mg	-0.01 (-0.08, 0.07)	-0.01 (-0.06, 0.04)	0.858	32.7%	0.216

***p*-value <0.05**

Table 4. Meta-analysis of secondary outcomes

Outcome	Intervention compared	Trial included in the meta-analysis	RR (95% CI)		*p*-value	Heterogeneity	
			Random-effect model	Fixed-effect model		I^2 statistics (%)	*p*-value of Chi^2
Study discontinuation due to side effects	Dapagliflozin 10 mg versus placebo	Dandona, 2018(24); Mathieu, 2018(17)	1.18 (0.66-2.10)	1.18 (0.66-2.10)	0.579	0%	0.808
	Dapagliflozin 5 mg versus placebo	Dandona, 2018(24);	1.40 (0.80-2.43)	1.40 (0.80-2.43)	0.236	0%	0.792
	Dapagliflozin 10 mg versus dapagliflozin 5 mg	Mathieu, 2018(17); Henry, 2015(25)	0.84 (0.50-1.42)	0.84 (0.50-1.42)	0.524	0%	0.586
Urinary tract infection	Dapagliflozin 10 mg versus placebo	Dandona, 2018(24)	0.71 (0.43-1.17)	0.71 (0.43-1.17)	0.176	0%	0.776
	Dapagliflozin 5 mg versus placebo	Mathieu, 2018(17) Henry, 2015(25)	1.42 (0.93-2.15)	1.42 (0.93-2.15)	0.102	0%	0.626
	Dapagliflozin 10 mg versus dapagliflozin 5 mg	Dandona, 2018(24) Mathieu, 2018(17)	0.50 (0.32-0.79)	0.50 (0.32-0.79)	0.003*	0%	0.717
Diabetic ketoacidosis	Dapagliflozin 10 mg versus placebo	Dandona, 2018(24);	3.02 (0.53-17.38)	2.24 (0.83-6.05)	0.215	39.6%	0.198
	Dapagliflozin 5 mg versus placebo	Mathieu, 2018(17)	3.50 (0.63 - 19.62)	2.61 (0.98-6.95)	0.153	38.9%	0.201
	Dapagliflozin 10 mg versus dapagliflozin 5 mg		0.85 (0.44-1.66)	0.85 (0.44-1.66)	0.642	0%	0.987
Hypoglycemia	Dapagliflozin 10 mg versus placebo	Dandona, 2018(24);	1.10 (0.32-3.80)	1.10 (0.32-3.80)	0.877	0%	0.659
	Dapagliflozin 10 mg versus dapagliflozin 5 mg	Mathieu, 2018(17); Henry, 2015(25)	0.78 (0.14-4.29)	0.89 (0.26-3.00)	0.774	35.6%	0.212
	Dapagliflozin 5 mg versus placebo	Dandona, 2018(24); Mathieu, 2018(17)	1.85 (0.37-9.29)	1.71 (0.48-6.11)	0.454	34.1%	0.218

***p-value <0.05**

4. Discussion

In summary, four trials based on nearly 1760 participants with an average age between 35 to 43 years were reviewed (17,20–22). Overall, these trials'(17,20–22) risk of bias was low or unclear. Only in one trial, the risk of bias was high (20). The risk of cause-irrespective adverse events was also higher in participants treated with dapagliflozin 5mg than the placebo group, and the number needed to treat was 14. Besides, the risk of UTI was less with 10 mg dapagliflozin compared to its 5 mg dosage.

The compared evidence regarding adverse effects between dapagliflozin 5 mg versus placebo was graded using the GRADE approach (26). The evidence was downgraded by one level (due to the high risk of bias in one of the trials)(20) to moderate-quality evidence. For UTI, since only two trials were available for meta-analysis, we did not evaluate its evidence quality.

Here, we compared our findings with that of another systematic review and meta-analysis which had a comparison between SGLT2 inhibitors irrespective of their dosages with placebo in insulin-treated T1DM patients (7). That review did not find any statistically significant difference in the risk of the following outcomes- study discontinuation due to side effects, UTI, and hypoglycemia; however, the risk of hypoglycemia was higher with SGLT2 inhibitor recipients (7). In this paper, the findings were equivalent when each of the two dosages of dapagliflozin was juxtaposed to placebo each, except for hypoglycemia.

Next, we stated the strengths of this review. Best known to us, this was one of the preliminary papers to study the safety profile of dapagliflozin dose wise, by systematic review and meta-analysis in insulin-treated T1DM patients. Besides, this review is likely to be more comprehensive as its database search was not restricted to any date or language. Moreover, as this review included randomized controlled trials only, the highest level of epidemiologic evidence, the generated evidence was likely to be rigorous. Finally, taking together, the lack of heterogeneity (upon meta-analysis) and the geographic diversity among the participants of the reviewed trials (based on more than 30 nations) (17,20–22), suggested that the findings of the present paper were likely to be externally valid.

Regarding the implication of this review, it will perhaps help physicians treating T1DM patients to understand the safety profile of dapagliflozin better.

Nonetheless, this study suffered from certain weaknesses. At the review level, its scope of exploring diverse epidemiological study designs was limited, as the review did not incorporated studies other than randomized controlled trials, like crossover studies, single-arm interventional studies, and good-quality observational studies. Then, the study level limitation was the high and unclear risk of bias components in the trials, as discussed above. Finally, the number of trials available for comparing the interventions were relatively few.

Despite these weaknesses, this was perhaps the best evidence available in this milieu contemporarily, and it was likely to be rigorous despite the paucity of trials as it was based on a relatively large trial population ensuring better retainment of the statistical power.

To conclude, in insulin-treated adult T1DM patients, treatment with daily 5mg dapagliflozin was found to increases the risk of all-cause adverse effects, and

treatment with its 10 mg dose decreased the risk of UTI compared to its 5mg dose.

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Conflicts of Interest

None

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Authors' contribution

SS[1] conceptualized and designed this study, performed database search, study selection, data abstraction, risk of bias assessment, analysis, and first and final draft of this manuscript. SS[2] contributed to the study selection, data abstraction, risk of bias assessment, and hard editing of the first draft.

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