

Effect of SGLT-2 Inhibitors on Non-alcoholic Fatty Liver Disease among Patients with Type 2 Diabetes Mellitus: Systematic Review with Meta-analysis and Trial Sequential Analysis of Randomized Clinical Trials

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ABSTRACT

Objectives: Non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) is a common problem associated with obesity and type 2 diabetes mellitus (T2DM). There have been anecdotal reports of the efficacy of sodium-glucose cotransporter 2 inhibitors (SGLT2Is) in improving liver function parameters in those with concomitant T2DM and NAFLD/NASH. We sought to systematically evaluate the evidence of SGLT2Is in improving liver function parameters in T2DM patients with NAFLD, considering the risks of random error based on trial sequential analysis (TSA). We also performed a meta-analysis based on a random-effects model. **Methods:** A systematic literature search was performed using the Medline, Cochrane, and Embase databases from inception to 20 October 2018. Primary outcome for meta-analyses was the changes in hepatic enzyme levels (alanine transaminase, aspartate transaminase, and gamma-glutamyl transpeptidase). We also performed a meta-analysis on changes in insulin resistance, glycemic, and lipid parameters using SGLT2Is as a secondary objective. **Results:** Eight eligible randomized controlled studies were eligible for analysis. Meta-analysis showed the efficacy of two SGLT2Is, dapagliflozin, and canagliflozin in reducing these enzymes level. TSA showed that canagliflozin significantly reduced the gamma-glutamyl transpeptidase level by weighted mean difference (-5.474, 95% confidence interval (CI): -6.289--4.659) compared to others comparators, and the evidence is conclusive. Dapagliflozin also had a statistically significant reduction in glycated hemoglobin, which is a parameter of glycemic control and homeostatic model assessment for insulin sensitivity (HOMA-IR), which is a parameter of insulin sensitivity by a weight mean difference, -0.732 (95% CI: -1.087--0.378) and -0.804 (95% CI: -1.336--0.272), respectively. **Conclusions:** This study indicated that canagliflozin effectively improves liver function parameters among patients with diabetes, while dapagliflozin is more effective in improving glycemic indices and insulin sensitivity.

Non-alcoholic fatty liver disease (NAFLD) is a new public health problem and a complication associated with diabetes and metabolic syndrome.¹ The defining feature of NAFLD is excess fat deposition on liver cells (hepatocytes), which may be accompanied by evidence of cell injury with or without the presence of fibrosis and inflammation non-alcoholic steatohepatitis (NASH) or rarely remains as an isolated event (non-alcoholic fatty

liver, NAFL).^{2,3} The importance of recognizing this liver condition lies in the fact that it will overtake hepatitis C infection in the near future as the leading cause of liver failure and the need for transplantation in many developed countries, as well as the absence of FDA-approved therapies for this disease, thereby making the early detection or better still its prevention as an urgent healthcare agenda.⁴⁻⁶

As the pathogenesis of type 2 diabetes mellitus (T2DM) or insulin resistance is closely associated

with the presence of NASH/NAFLD, the use of various antidiabetic drugs such as pioglitazone, metformin, dipeptidyl peptidase-4 inhibitor, and glucagon-like peptidase-1 agonists have been postulated to reduce hepatic inflammation in these liver conditions.⁷⁻¹⁰ Despite many studies, there is a lack of effective treatment for NAFLD/NASH.¹¹ Sodium-glucose cotransporter 2 inhibitors (SGLT2Is) has revolutionized the treatment of T2DM with a unique mechanism of action and efficacy in reducing the glycated hemoglobin (HbA_{1c}) levels. It acts by helping in renal excretion of glucose and, therefore, will cause a reduction of body weight (on average 2.5–3.0 kg) and prevalence of obesity that may improve the liver histology of those with NAFLD/NASH.¹² Drugs in this class includes canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin and tofogliflozin. It can reduce the HbA_{1c} by up to 0.8% and gain a foothold as one of the first-line antidiabetic drugs. Modest blood pressure reduction has also been documented together with a lower risk of hypoglycemia using these drugs.¹³ Furthermore, it is also effective in preventing weight gain.¹⁴

A systematic review published in 2019 summarized its finding based on eight studies^{7,15-21} that showed a significant decrease in alanine transaminase (ALT), and reduction in aspartate transaminase (AST), and gamma-glutamyl transpeptidase (GGT) levels with the use of SGLT2Is.²² Several randomized controlled trials (RCTs) have been recently published that explored its benefits in improving liver functions.^{7,18,23-30} However, there is a lack of systematic review coupled with meta-analysis and trial sequential analysis (TSA) conducted to estimate the effect of SGLT2Is on hepatic enzymes among patients with diabetes. Meta-analysis can provide information on the threshold of statistical significance for weight mean differences. TSA will confirm the result from meta-analysis with a cumulative sample size of all included studies, thus reducing the chance for type 1 error due to systematic error or small sample size effect that could occur in a meta-analysis.

We sought to look at the efficacy of SGLT2Is compared to other antidiabetic drugs in improving the liver function parameters in T2DM patients with NAFLD. As a secondary objective, we will also perform a meta-analysis on changes in insulin

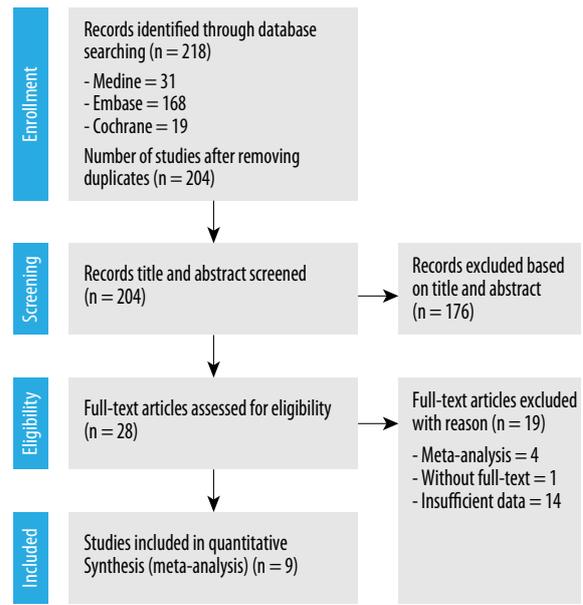


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the literature screening process.

resistance, glycemic and lipid parameters using SGLT2Is in these groups of patients.

METHODS

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).³¹ The protocol was registered in the PROSPERO (Record ID: 126327).

A systematic literature search was performed using three databases, Medline, Cochrane, and Embase, from inception to 20 October 2018. Searches were conducted using Medical Subject Headings terms and corresponding keywords, as shown in Appendix 1.

There were no language or method restrictions, and the eligibility criteria extend to all studies done globally [Figure 1]. Inclusion criteria are RCTs conducted on T2DM patients with NAFLD on treatment with antidiabetic drugs, namely SGLT2Is, along with its effects on NAFLD/NASH. Exclusion criteria will be any other study design such as review articles, prevalence studies, or animal and cells models.

The treatment or intervention group will be patients who are on SGLT2I treatment. The comparator or control group will be placebo/patients who are not on treatment with SGLT2I. Therefore,

the context studied will be patients with T2DM with underlying NAFLD who are randomized to be receiving SGLT2I treatment or other oral antidiabetic drugs.

The primary outcome for these meta-analyses was the changes in hepatic enzymes levels, namely ALT, AST, and GGT. In addition, we also assessed the effect of SGLT2Is on insulin resistance and glycemic and lipid parameters such as triglyceride and cholesterol components.

Articles screening and data extraction was done through a multi-step process. Three independent authors preliminarily screened articles by their titles and abstracts, followed by full-text reading. This was followed by data extraction on the following aspects: primary author, year of publication, study country, sample size of the two groups and levels of liver enzymes level for ALT, AST, and GGT that was available for each of the selected articles. Finally, a standardized data extraction form was created, and the extracted data was inserted into this form. Any disagreement was discussed together with the following authors: ID, FKH, SMC, and SKV.

We used mean \pm standard deviation (SD) to express our outcomes. If the mean difference and SD were not provided, the mean was calculated by subtracting the mean of baseline measurement from the corresponding mean of post-intervention measurement, while the SD was imputed from the endpoint measurement. If the mean difference was provided, but the SD was not, the latter was imputed either from the endpoint measurement or calculated using the confidence intervals (CIs) with the following formula in Excel - "SQRT (sample size)*(upper CI-lower CI)/(T.INV.2T (0.05, \$D\$2-1)*2)".³²

Data for this study was extracted from the RCT studies and meta-analysis (random-effects model) was performed to estimate the pooled risk ratio at 95% CI based on the determination of heterogeneity among these studies by I^2 statistics. In addition, TSA was performed to assess the effect of SGLT2I on NAFLD compared to the control group.³³ The comparative effectiveness of SGLT2I was also studied using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which was not done in previous systematic reviews. This was done to rate the evidence's quality as either high, moderate, low, or very low.

Included trials were independently assessed using the Revised Cochrane Risk of Bias Tool (RoB 2.0). Two authors independently assessed all trials identified for study inclusion after full-text reading (KWL and NKD). Any discrepancies were discussed with the following authors once again (MJS, ID, FKH, SMC, and SKV). Assessment was done across the five domains of bias (bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result).³⁴ GRADE assessments were performed to appraise the quality of the evidence³⁵ which assessed the studies inconsistency, indirectness, imprecision, and publication bias.³⁶⁻³⁷

RESULTS

Through our initial search, we identified 218 eligible manuscripts [Figure 1]. After further de-duplication ($n = 14$), 204 studies were then selected for the next screening step. Through a review of the abstract, title, and keywords, eight studies were finally included, and its characteristics extracted as described in Table 1 and appendices 2a–c. These data were described based on the author's name, antidiabetic drug used, and improvement in liver function as measured by the liver enzyme levels.

Table 1 shows the key characteristics of the included studies, and appendices 2a–c indicates changes in hepatic functions among T2DM patients. In the final analysis, a total sample of 5984 patients with T2DM was included in which patients had used SGLT2Is in the treatment of their T2DM. The overall quality of included studies appeared to be good.

Analysis of the effect of dapagliflozin on ALT reduction using meta-analysis and TSA are provided in Figure 2 and Appendix 3a. The meta-analysis showed that dapagliflozin did not significantly reduce the ALT level by weighted mean difference (-0.151, 95% CI: -0.313–0.012) compared to other comparators. Moreover, the cumulative Z-curve (blue curve) did not cross the conventional boundary (Z -statistic > 1.96) and demonstrated that dapagliflozin did not significantly reduce ALT using the TSA. However, the number of patients included in the TSA did not exceed the required information size (i.e., 602 patients), indicating that the cumulative

Table 1: Characteristics of included studies.

First Author	Year	Area	Treatment group (Intervention)	Comparator group (Control)	Patient characteristics (Inclusion criteria)	Centre	Blind	RCT phase	Trial duration	Hepatic profile collection duration
Eriksson et al, ¹⁸	2018	Sweden	Dapagliflozin 10 mg	Omega-3 4 g	Patients with T2DM (aged 40–75 years)	Multi	Double-blind	2	12 weeks	12 weeks
Eriksson et al, ¹⁸	2018	Sweden	Dapagliflozin 10 mg	Placebo	Patients with T2DM	Multi	Double-blind	2	12 weeks	12 weeks
Guja et al, ²³	2018	USA	Dapagliflozin	Exenatide	Adults with T2DM and inadequate glycemic control	Multi	Double-blind	3	28 weeks	28 weeks
Hayashi et al, ²⁴	2017	Japan	Dapagliflozin 5 mg	Sitagliptin 50 mg	Patients with T2DM taking prescribed oral hypoglycemic agents	Single	Open-label	2	12 weeks	12 weeks
Kurinami et al, ³⁸	2018	Japan	Dapagliflozin 5 mg	Non-SGLT2 (din specify)	Patients with T2DM	Single	Open-label	2	24 weeks	24 weeks
Leiter et al, ²⁷	2016	Germany	Canagliflozin 300 mg	Sitagliptin 100 mg	Patients with T2DM	Multi	Double-blind	3	26 weeks	26 weeks
Leiter et al, ²⁸	2016	Germany	Canagliflozin 100 mg	Placebo	Patients with T2DM	Multi	Double-blind	3	26 weeks	26 weeks
Leiter et al, ²⁸	2016	Germany	Canagliflozin 300 mg	Placebo	Patients with T2DM	Multi	Double-blind	3	26 weeks	26 weeks
Polidori et al, ²⁹	2017	USA	Canagliflozin 100 mg	Placebo	Patients with T2DM	Single	Unknown	3	26 weeks	26 weeks
Polidori et al, ²⁹	2017	USA	Canagliflozin 300 mg	Placebo	Patients with T2DM	Single	Unknown	3	26 weeks	26 weeks
Seko et al, ⁷	2017	Japan	Canagliflozin 100 mg	Placebo	Patients with T2DM with Baseline ALT ≤ 30	Multi	Double-blind	3	12 weeks	12 weeks
Seko et al, ⁷	2017	Japan	Canagliflozin 100 mg	Placebo	Patients with T2DM Baseline ALT > 30	Multi	Double-blind	3	12 weeks	12 weeks
Shimizu et al, ³⁰	2018	Japan	Dapagliflozin 5 mg	Control (did not specify)	Patients with T2DM and NAFLD	Single	Open-label	2	24 weeks	24 weeks

RCT: randomized controlled trial; T2DM: type 2 diabetes mellitus; non-alcoholic fatty liver disease.

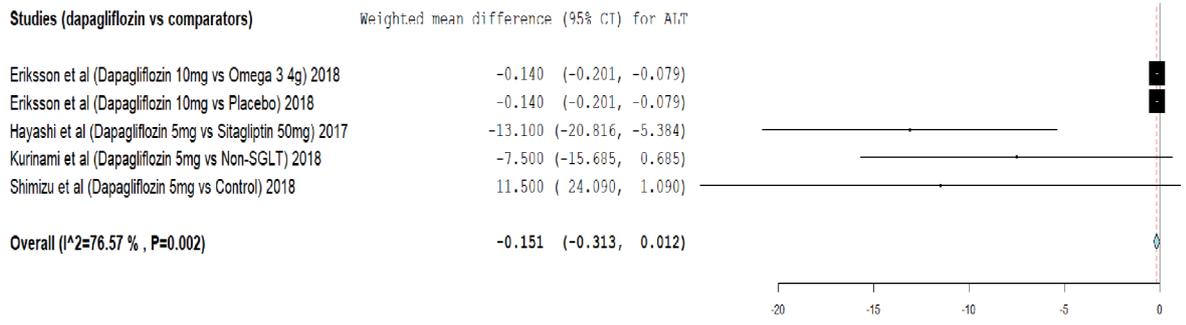


Figure 2: Meta-analysis on the effect of dapagliflozin versus comparators on alanine transaminase (ALT) reduction.

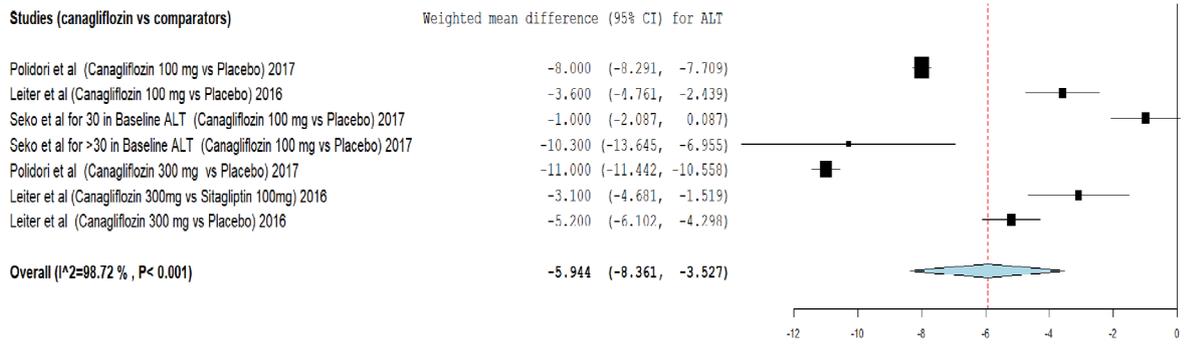


Figure 3: Meta-analysis on the effect of canagliflozin versus comparators on alanine transaminase (ALT) reduction.

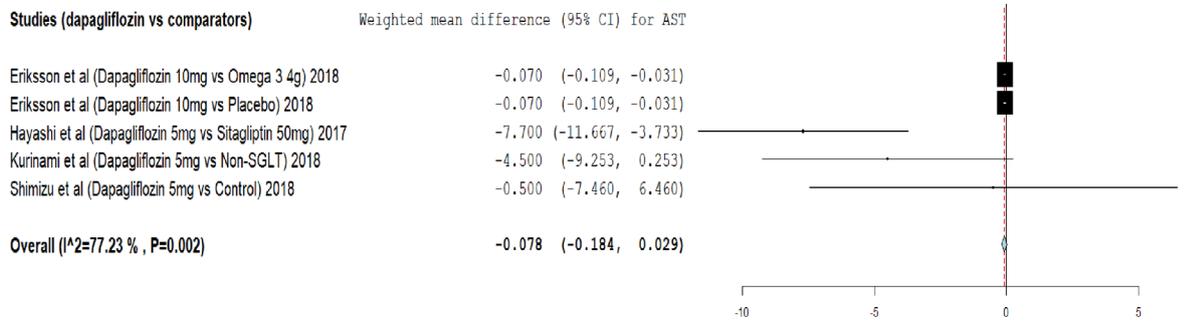


Figure 4: Meta-analysis on the effect of dapagliflozin versus comparators on aspartate transaminase (AST) reduction.

evidence for dapagliflozin not reducing ALT remains inconclusive based on only 266 patients.

Analysis of the effect of canagliflozin on ALT reduction using meta-analysis and TSA are provided in Figure 3 and Appendix 3b. The meta-analysis showed that canagliflozin significantly reduced the ALT level by weighted mean difference (-5.944, 95% CI: -8.361--3.527) compared to other comparators. The cumulative Z-curve (blue curve) crossed the conventional boundary (Z-statistic above 1.96) and demonstrated that canagliflozin significantly reduced ALT using TSA. However,

the number of patients included in the TSA did not exceed the required information size (5364 patients), indicating that the cumulative evidence is still inconclusive.

Analysis of the effect of dapagliflozin on AST reduction using meta-analysis and TSA are provided in Figure 4 and Appendix 3c. The meta-analysis showed that dapagliflozin did not significantly reduce the AST level by weighted mean difference (-0.078, 95% CI: -0.184--0.029) compared to comparators. The cumulative Z-curve (blue curve) did not cross the conventional boundary (Z-statistic

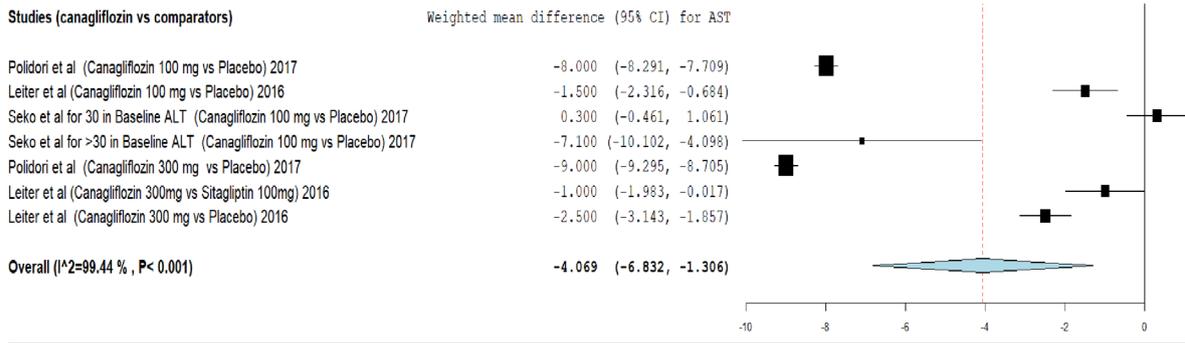


Figure 5: Meta-analysis on the effect of canagliflozin versus comparators on aspartate transaminase (AST) reduction.

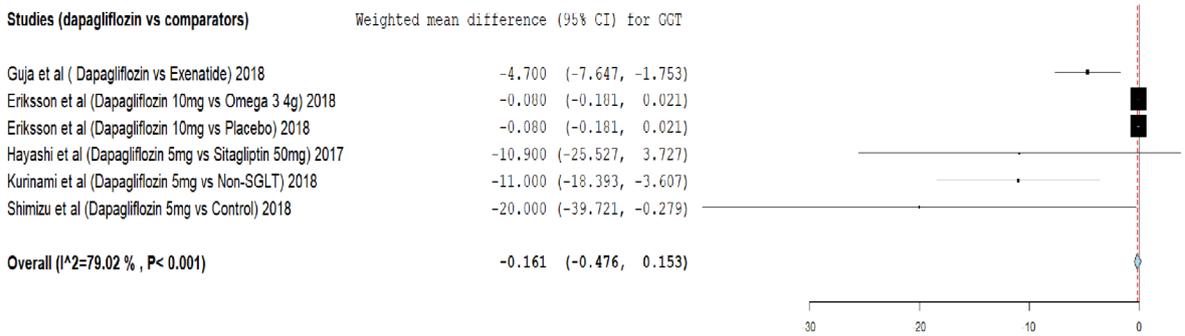


Figure 6: Meta-analysis on the effect of dapagliflozin versus comparators on gamma-glutamyl transpeptidase (GGT) reduction.

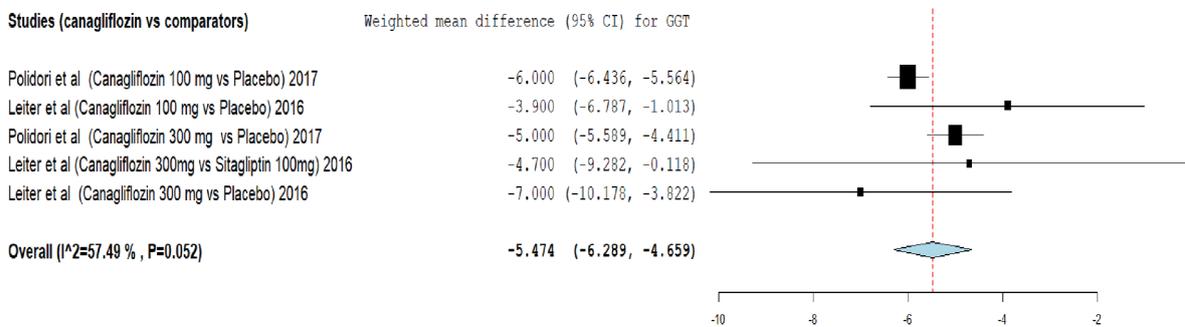


Figure 7: Meta-analysis on the effect of canagliflozin versus comparators on gamma-glutamyl transpeptidase (GGT) reduction.

above 1.96) and demonstrated that dapagliflozin did not significantly reduce AST using TSA. However, the number of patients included in the TSA did not exceed the required information size (3178 patients), indicating that the cumulative evidence remains inconclusive based on the 266 patients.

Analysis of effect of canagliflozin on AST reduction using meta-analysis and TSA are provided in Figure 5 and Appendix 3d. The meta-analysis showed that canagliflozin significantly reduced the AST level by weighted mean difference (-4.069, 95% CI: -6.832--1.306) compared to other comparators.

Moreover, the cumulative Z-curve (blue curve) crossed the conventional boundary (Z-statistic above 1.96) and demonstrated that canagliflozin significantly reduced AST using TSA. However, the number of patients included did not exceed the required information size (7015 patients), indicating that the cumulative evidence remains inconclusive based on 5287 patients.

Analysis of effect of dapagliflozin on GGT reduction using meta-analysis and TSA are provided in Figure 6 and Appendix 3e. The meta-analysis showed that dapagliflozin did not significantly

Table 2: Pooled weighted mean difference and 95% confidence interval of indicators for insulin resistance, glycemia, and lipid parameters between dapagliflozin and comparators.

Parameters	N	Weight mean difference	95% confidence interval	Heterogeneity, I ²	p-value for heterogeneity
Subcutaneous adipose tissue, cm ²	4	-0.340	-0.814–0.133,	86.1	< 0.001
Visceral adipose tissue, cm ²	4	-0.316	-0.704–0.071,	76.4	0.005
HbA _{1c} , %	5	-0.732	-1.087–-0.378	76.5	0.002
HOMA-IR	3	-0.804	-1.336–-0.272,	0.0	0.574
Serum triglyceride, mmol/L	5	0.113	-0.278–0.504,	76.6	0.002
Total cholesterol, mmol/L	4	0.028	-0.223–0.279,	25.1	0.261
Low-density lipoprotein, mmol/L	5	0.118	-0.042–0.277,	0.0	0.873
High-density lipoprotein, mmol/L	5	0.034	-0.076–0.144,	81.2	< 0.001
Adiponectin, µg/L	4	3.311	-3.325–9.947	94.5	< 0.001

HbA_{1c}: glycated hemoglobin; HOMA-IR: homeostatic model assessment for insulin sensitivity.

reduce the GGT level by weighted mean difference (-0.161, 95% CI: -0.476–0.153) compared to comparators. The cumulative Z-curve (blue curve) did not cross the conventional boundary (Z-statistic > 1.96) and demonstrated that dapagliflozin did not significantly reduce GGT using the TSA. However, the number of patients included in our meta-analysis did not exceed the required information size (3923 patients), indicating that the cumulative evidence remains inconclusive based on the 723 patients.

Analysis of effect of canagliflozin on GGT reduction using meta-analysis and TSA are provided in Figure 7 and Appendix 3f. The meta-analysis showed that canagliflozin significantly reduced the GGT level by weighted mean difference (-5.474, 95% CI: -6.289–-4.659) compared to other comparators. The cumulative Z-curve (blue curve) crossed the conventional boundary (Z-statistic > 1.96) and demonstrated that canagliflozin significantly reduced GGT using TSA. In addition, the number of patients included in TSA exceeded the required information size (1627 patients), indicating that the cumulative evidence is conclusive.

Table 2 summarized the results from meta-analysis for subcutaneous adipose tissue, visceral adipose tissue, HbA_{1c}, homeostatic model assessment for insulin sensitivity (HOMA-IR), serum triglyceride, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and adiponectin between dapagliflozin versus comparators. Based on the analysis, dapagliflozin statistical significantly reduced HbA_{1c} and HOMA-IR by weight mean difference = -0.732 (95% CI: -1.087–-0.378)

and -0.804 (95% CI: -1.336–0.272), respectively, compared to comparators. On the other hand, dapagliflozin had no statistically significant changes to subcutaneous adipose tissue, visceral adipose tissue, serum triglyceride, total cholesterol, LDL, HDL, and adiponectin.

Based on the data of included studies, Eriksson et al,¹⁸ reported that 33.3% of participants receiving dapagliflozin monotherapy experienced adverse events compared to placebo (28.6%), omega-3 monotherapy (40%), and dapagliflozin and omega-3 (68.2%).¹⁸ However, the authors did not mention what kind of adverse events were experienced by participants.

Seko et al,⁷ reported that 28.7% of participants in the high ALT and 33.4% of those with low ALT subgroups experienced adverse effects due to canagliflozin. There were no differences in the overall incidence of serious adverse events related to the canagliflozin between the high (1.0%) and low (0.3%) ALT subgroups. In addition, they also observed high and low ALT subgroup had a similar incidence of adverse events associated with symptomatic hypoglycemia, asymptomatic hypoglycemia, female genital infection, and osmotic diuresis, which were < 5%. One concern raised was that ketone bodies were significantly increased in both high and low ALT subgroups compared to placebo.⁷

Guja et al,²³ 2018; Hayashi et al,²⁴ 2017; Kurinami et al,³⁸ 2018; Leiter et al,²⁸ 2016; and Polidori et al,²⁹ 2017 did not report any adverse events from their studies.

Revised Cochrane Risk of Bias Tool assessment findings are given in appendices 4–5. The assessment

indicated that two studies have a low risk of bias for all items,^{7,28} four studies had at least one item with unclear risk of bias,^{23,24,29,30} and three studies showed a high risk of bias.^{18,27,38} The high risk of bias was noted in the randomization process and deviation from the intended intervention in the study by Kurinami et al,³⁸ 2018 as well as bias due to missing outcome data in the study by Eriksson et al,¹⁸ 2018.

GRADE assessment of the overall certainty of the evidence for the association between SGLT and hepatic enzyme levels reduction is presented in Appendix 6. Overall, the grade of evidence is low for the association between dapagliflozin and the reduction in hepatic enzymes levels and the association between canagliflozin and reduction of ALT and AST was also graded as low except for association between canagliflozin and GGT reduction which showed high certainty. These studies had to be downgraded for their inconsistency and imprecision.

DISCUSSION

The present systematic review and meta-analysis of eight randomized controlled trials involved 5984 patients with T2DM. The analysis showed that canagliflozin reduced hepatic enzyme levels but not dapagliflozin. Based on TSA, we observed that the association between canagliflozin and the reduction in GGT is statistically significant, and this conclusive statement is drawn based on the total number of participants reaching the required sample size.

Our results support the use of canagliflozin but not dapagliflozin in the management of NASH/NAFLD as it has been shown to significantly reduced ALT, AST, and GGT as demonstrated in our meta-analysis. This is based on findings from Figures 3–7. This indicates another possible untapped use of canagliflozin in the treatment of NASH/NAFLD. This is in agreement with study by Leiter et al,²⁸ which showed a similar reduction in ALT and AST levels with the use of canagliflozin. The study included four pools of patients: on canagliflozin alone, add-on to metformin, as an add-on to metformin and sulphonylurea, and add-on to metformin plus pioglitazone (i.e., without insulin).²⁸ This indicates the wide range of the benefit of SGLT2Is that extends beyond any other antidiabetic drug that is used. The study also showed the effectiveness of canagliflozin in reducing GGT levels.²⁸

As mentioned earlier, insulin resistance appears to be the main link between T2DM and NAFLD/NASH, with additional contribution from obesity and other metabolic risk factors such as raised triglycerides and reduced HDL-C.³⁹ There is increase transportation of free fatty acids to the liver due to insulin resistance, which diminishes the natural process of lipolysis by the now defuncting insulin.² As a secondary effect, this extra supply of fatty acid will drive the synthesis of triglycerides that is further stimulated by the recurring phenomenon of impaired hepatic fatty acid oxidation secondary to insulin resistance and the excess secretion of very LDL that will further worsen the fatty liver.³

The result in this study differs from the finding in a systematic review by Raj et al.²² The possible explanation for the difference could be due to the fact that the study by Raj et al,²² summarized the finding based on four RCTs^{15–18} and four observational studies^{7,19–21} compared to the nine RCTs in this study. Secondly, their finding was made based on small sample sizes, and the authors did not pool the sample size from each study examining the effect of SGLT, compared to our study that made its conclusion based on a pooled sample size of 5984 patients. Furthermore, Raj et al,²² did not perform any meta-analysis and TSA. Thus, the beneficial effect of SGLT may not be the true effect.

In addition, there may also be a strong molecular basis for the occurrence of NAFLD/NASH. This is based on the theory that carbon monoxide releasing molecule-A1 (CORM-A1) reduces damages to the liver tissue with steatosis via a dual action of improved mitochondrial function and nuclear factor-erythroid 2 related factor 2 activation.⁵ This may indicate that CORM-A1 has a huge potential of being an anti-NASH and anti-NAFLD agent.⁵ However, more researches need to be done on this exciting prospect before it is marketed as a treatment for NAFLD/NASH.

Some literature paradoxically noted that the inflammatory changes in NAFLD/NASH might, in turn, contribute to the development of T2DM that was thought to be mainly autoimmune in origin.^{6,40} Therefore, the relationship between both conditions associated with metabolic syndrome may be a two-way relationship. This opens up the hypothesis that curing NAFLD/NASH may improve hyperglycemia or even revert it totally to normoglycemia, thereby ending the decades of a long

search for a cure for T2DM. Curing T2DM will go a long way in improving the health profile of many people worldwide, and that in turn will churn out more productivity to spur the world's economy.

In addition, when looking at the effect of SGLT2Is on insulin resistance, glycemic, and lipid parameters, it was noted that, dapagliflozin significantly reduced HbA_{1c} which is a parameter of glycemic control and HOMA-IR, which is a parameter of insulin sensitivity by weight mean difference = -0.732 (95% CI: -1.087--0.378) and -0.804 (95% CI: -1.336--0.272), respectively, compared to comparators. This is expected as the primary action of SGLT2Is is in reducing renal tubular glucose reabsorption, which enables a reduction in HbA_{1c} between 0.6–0.8%.⁴¹ SGLT2I can also improve insulin sensitivity via several molecular pathways, including beta function improvement, reduction of oxidative stress and inflammation, as well as disposition of calories and weight loss.⁴² However, there was no significant effect on lipid parameters such as the triglycerides and cholesterol components.

In a study in Japan, treatment of T2DM patients along with biopsy-proven NASH with dapagliflozin resulted in significant reductions in HbA_{1c}, fasting glucose levels, and reduced visceral fat mass as early as four weeks treatment.⁴³ Another Japanese study using serial liver biopsies in five patients receiving 24 weeks of canagliflozin showed remarkable NASH histology improvement.⁴⁴ However, the number of subjects involved was relatively small, and more studies are needed to show a definite significant effect of hepatic fat reduction with SGLT2Is.

Future studies are recommended given the findings of this study to instill confidence in doctors in prescribing SGLT2Is in patients with NASH/NAFLD in view of the potential beneficial added effect in reducing ALT, AST, and GGT. This is to ensure that this drug is safe, effective, and accessible to patients with T2DM and manages to gain a foothold in many clinical practice guidelines on T2DM worldwide to encourage physicians to confidently prescribe it as a management option in patients with NASH/NAFLD.

The potential adverse events with SGLT2Is could be adverse cardiovascular events. Studies reported that dapagliflozin could lead to major adverse cardiovascular events⁴⁵ and canagliflozin could cause genital tract infections and osmotic diuresis-related adverse events.⁴⁶ Overall, there were no new or

unexpected adverse events compared with previous studies with these treatments.

This is the first study of the effect of SGLT2Is on hepatic enzymes performed using meta-analysis with TSA to estimate the effect of SGLT2Is on hepatic enzymes. TSA provides the information on the power of sample size of cumulative meta-analysis and whether it surpasses the conventional and alpha spending boundaries, which indicates whether the evidence of our meta-analysis is statistically significant and conclusive or not. However, the current study has several limitations. Firstly, the majority of TSA indicated that the pooled sample size did not meet the required sample size for drawing the conclusive effect of SGLT2Is. Secondly, there are serious inconsistencies in the pooled weighted mean difference for ALT, AST, and GGT using dapagliflozin, and very serious inconsistencies in pooled weighted mean difference ALT and AST using canagliflozin. Thirdly, there is serious imprecision in pooled weighted mean difference for ALT, AST, and GGT using dapagliflozin. This could be due to low certainty. Fourthly, the majority of studies did not report data on changes in liver attenuation, liver-to-spleen attenuation ratio, liver magnetic resonance imaging proton density fat fraction, and liver fat volume; therefore, we could not assess the effect of SGLT2Is on hepatic fibrosis and hepatic fat content. Notwithstanding these limitations, this study suggests that more, higher quality randomized trials testing the effect of dapagliflozin and canagliflozin on hepatic enzyme levels reduction are needed to address these uncertainties and better understand the differences between SGLT2Is effectiveness. There is also a need for large randomized trials that assess more patients to make a conclusive statement.

TSA also shows that the evidence is still inconclusive for using these SGLT2Is to improve liver function parameters. Therefore, more studies are needed before any recommendations are made regarding using SGLT2Is as a treatment of NAFLD/NASH. However, with the results obtained from this study, promise holds that SGLT2Is may be the answer to the yet non-curative NAFLD/NASH.

CONCLUSION

Canagliflozin but not dapagliflozin is effective in improving ALT, AST, and GGT levels among

patients with diabetes, suggesting they may be useful in managing diabetes with fatty liver.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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APPENDICES ARE GIVEN ON THE FOLLOWING PAGES

Appendix 1: Search strategies.

No	Search term	Search Result on 18/10/18		
		Embase	Cochrane	Medline
1.	exp Sodium-Glucose Transporter 2/ (Sodium adj3 Glucose adj3 Transporter).ti,ab.	1714	156	1356
2.	SGLT\$.tw.	1987	342	1175
3.	exp CANAGLI- FLOZIN/ canagliflozin.ti,ab.	5521	597	3138
4.	dapagliflozin.ti,ab.	1987	330	399
5.	ertugliflozin.ti,ab.	1211	313	620
6.	Ipragliflozin.ti,ab.	1500	473	642
7.	luseogliflozin.ti,ab.	94	52	34
8.	remogliflozin.ti,ab.	228	61	133
9.	sotagliflozin.ti,ab.	140	34	71
10.	sergliflozin.ti,ab.	30	14	17
11.	tofogliflozin.ti,ab.	53	31	24
12.	or/1-13	15	2	15
13.	exp Fatty Liver/ exp Non-alcoholic Fatty Liver Disease/ (fatty adj3 liver).tw.	127	23	64
14.	NAFLD.tw.	7726	1230	4191
15.	steatohepatitis.tw.	62709	638	28202
16.	exp Liver Function Tests/ exp Aspartate Aminotransferases/ exp Alanine Transaminase/ exp Alkaline Phosphatase/ (Liver adj3 enzyme\$.tw.	31681	970	8590
17.	AST.tw.	37331	1518	24079
18.	ALT.tw.	18969	960	9657
19.	ALP.tw.	15178	639	8525
20.	or/15-27	35422	1112	27832
21.	exp Randomized Controlled Trial/ exp Clinical Trial/ controlled clinical trial.pt. randomized controlled trial.pt. Random Allocation/ Double-Blind Method/ Single-Blind Method/ clinical trial.pt. placebo\$.ti,ab. random\$.tw. blind\$.ti,ab. control\$.ti,ab.	78182	966	28544
22.	1333656	93233	1510	29974
23.	0	92433	1220	53066
24.	0	31197	1731	22210
25.	39341	2462	1731	22210
26.	57052	4431	1731	22210
27.	25187	772	1731	22210
28.	323517	11196	1731	22210
29.	516913	139	1731	22210
30.	1333656	174	1731	22210
31.	0	90518	1731	22210
32.	0	458846	1731	22210
33.	75792	20611	1731	22210
34.	119233	128258	1731	22210
35.	30677	18426	1731	22210
36.	0	279302	1731	22210
37.	278636	219959	1731	22210
38.	1336410	705673	1731	22210
39.	374812	253110	1731	22210
40.	4407780	511426	1731	22210
41.	5932670	984258	1731	22210
42.	14 and 28 and 41	168	19	31

Appendix 2a: Changes of ALT among patients with type 2 diabetes mellitus.

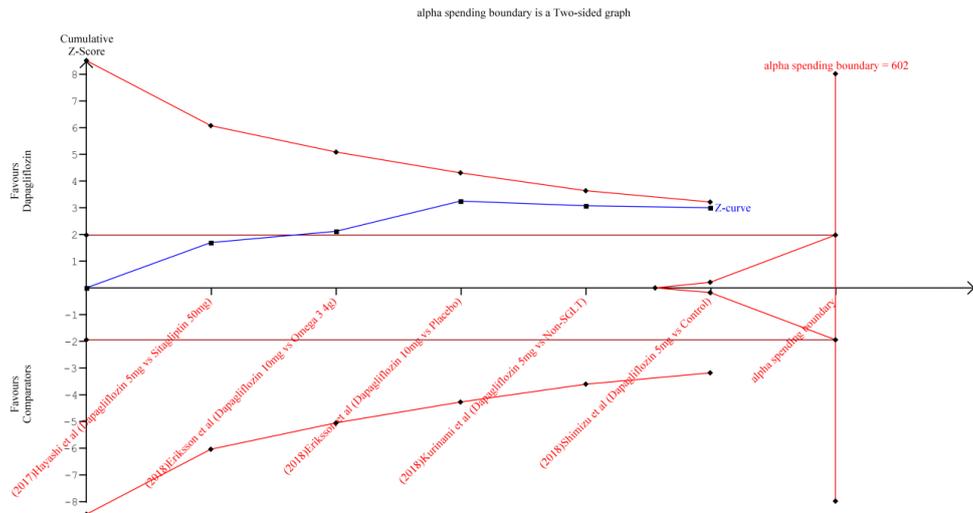
First Author	Year	ALT, IU/L									
		SGLT2Is					Comparator				
		Baseline	Post	n	Mean changes	SD	Baseline	Post	n	Mean changes	SD
Eriksson et al (Dapagliflozin 10 mg vs. omega 3 4 g)	2018	0.67	0.53	20	-0.14	0.14	0.64	0.74	14	0.1	0.28
Eriksson et al (Dapagliflozin 10 mg vs. placebo)	2018	0.67	0.53	20	-0.14	0.14	0.57	0.567	20	-0.003	0.15
Guja et al (Dapagliflozin vs. exenatide)	2018										
Hayashi et al (Dapagliflozin 5 mg vs. sitagliptin 50 mg)	2017	46.6	33.5	40	-13.1	24.9	42.8	44.9	40	-4.9	18.4
Kurinami et al (Dapagliflozin 5 mg vs. non- SGLT)	2018	26.5	19	27	-7.5	21.7	21	20	28	-1	1.28
Leiter et al (Canagliflozin 300 mg vs. sitagliptin 100 mg)	2016	29	25.9	724	-3.1	21.7	28.2	30.3	722	2.1	23.2
Leiter et al (Canagliflozin 100 mg vs. placebo)	2016	27.8	24.2	624	-3.6	14.8	27.6	27.4	809	-0.2	16.9
Leiter et al (Canagliflozin 300 mg vs. placebo)	2016	28.6	23.4	624	-5.2	11.5	27.6	27.4	809	-0.2	16.9
Polidori et al (Canagliflozin 100 mg vs. placebo)	2017	31	23	182	-8	2	31	35	142	4	3
Polidori et al (Canagliflozin 300 mg vs. placebo)	2017	31	20	177	-11	3	31	35	142	4	3
Seko et al al ≤ 30 at baseline ALT (Canagliflozin 100 mg vs. placebo)	2017	20	19	117	-1	6	19.5	19.6	109	0.1	6
Seko et al al > 30 at baseline ALT (Canagliflozin 100 mg vs. placebo)	2017	45.6	35.3	47	-10.3	11.7	48.4	45.2	59	-3.2	17.7
Shimizu et al (Dapagliflozin 5 mg vs. control)	2018	38	26.5	33	-11.5	36.9	33	32	24	-1	29.2

Appendix 2b: Changes of AST among patients with type 2 diabetes mellitus.

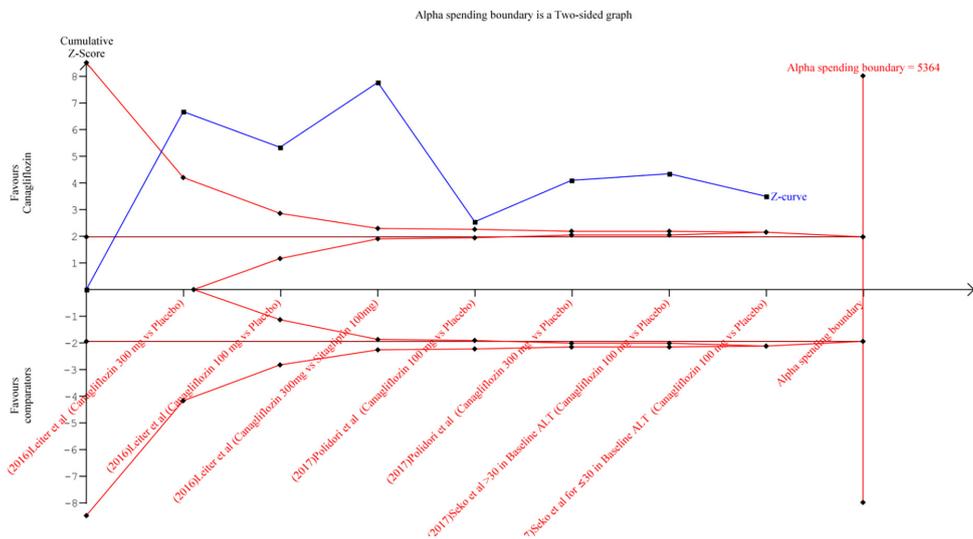
First Author	Year	AST, IU/L									
		SGLT2Is					Comparator				
		Baseline	Post	n	Mean changes	SD	Baseline	Post	n	Mean changes	SD
Eriksson et al (Dapagliflozin 10 mg vs. omega 3 4 g)	2018	0.52	0.45	20	-0.07	0.09	0.51	0.59	14	0.08	0.15
Eriksson et al (Dapagliflozin 10 mg vs. placebo)	2018	0.52	0.45	20	-0.07	0.09	0.49	0.47	20	-0.02	0.12
Guja et al (Dapagliflozin vs. exenatide)	2018										
Hayashi et al (Dapagliflozin 5 mg vs. sitagliptin 50 mg)	2017	34.5	26.8	40	-7.7	12.8	33.2	35.4	40	2.2	14.9
Kurinami et al (Dapagliflozin 5 mg vs. non-SGLT)	2018	25	20.5	27	-4.5	12.6	22	23	28	1	4.5
Leiter et al (Canagliflozin 300 mg vs. sitagliptin 100mg)	2016	23	22	724	-1	13.5	22.8	24.7	722	1.9	15.9
Leiter et al (Canagliflozin 100 mg vs. placebo)	2016	23	21.5	624	-1.5	10.4	22.9	23.3	809	0.4	12.5
Leiter et al (Canagliflozin 300 mg vs. placebo)	2016	23.7	21.2	624	-2.5	8.2	22.9	23.3	809	0.4	12.5
Polidori et al (Canagliflozin 100 mg vs. placebo)	2017	30	22	182	-8	2	30	28	142	-2	2
Polidori et al (Canagliflozin 300 mg vs. placebo)	2017	30	21	177	-9	2	30	28	142	-2	2
Seko et al ≤ 30 at baseline ALT (Canagliflozin 100 mg vs. placebo)	2017	19.8	20.1	117	0.3	4.2	19.8	19.6	109	-0.2	4.3
Seko et al > 30 at baseline ALT (Canagliflozin 100 mg vs. placebo)	2017	36.1	29	47	-7.1	10.5	36.2	33.3	59	-2.9	11.3
Shimizu et al (Dapagliflozin 5 mg vs. control)	2018	28	27.5	33	-0.5	20.4	29.8	27.4	24	-2.4	9.6

Appendix 2c: Changes of GGT among patients with type 2 diabetes mellitus.

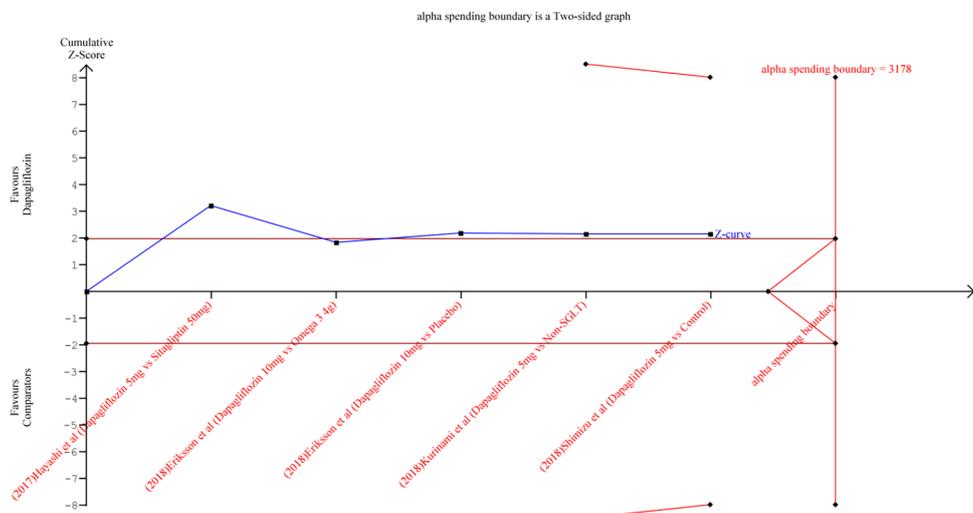
First Author	Year	GGT, IU/L									
		SGLT2Is					Comparator				
		Baseline	Post	n	Mean changes	SD	Baseline	Post	n	Mean changes	SD
Eriksson et al (Dapagliflozin 10 mg vs. omega 3 4g)	2018	0.97	0.89	20	-0.08	0.23	0.9	0.94	14	0.04	0.2
Eriksson et al (Dapagliflozin 10 mg vs. placebo)	2018	0.97	0.89	20	-0.08	0.23	0.54	0.58	20	0.04	0.16
Guja et al (Dapagliflozin vs. exenatide)	2018	37.8	33.1	230	-4.7	22.8	41.3	35.3	227	-6	27.6
Hayashi et al (Dapagliflozin 5 mg vs. sitagliptin 50mg)	2017	53.2	42.3	40	-10.9	47.2	50.9	52.2	40	1.3	22
Kurinami et al (Dapagliflozin 5 mg vs. non- SGLT)	2018	34	23	27	-11	19.6	36	31	28	-5	13.5
Leiter et al (Canagliflozin 300 mg vs. sitagliptin 100mg)	2016	39.5	34.8	724	-4.7	62.9	37.9	37.8	722	-0.1	39.4
Leiter et al (Canagliflozin 100 mg vs. placebo)	2016	37.5	33.6	624	-3.9	36.8	38.8	41.8	809	3	74.3
Leiter et al (Canagliflozin 300 mg vs. placebo)	2016	39.5	32.5	624	-7	40.5	38.8	41.8	809	3	74.3
Polidori et al (Canagliflozin 100 mg vs. placebo)	2017	49	43	182	-6	3	49	61	142	12	7
Polidori et al (Canagliflozin 300 mg vs. placebo)	2017	49	44	177	-5	4	49	61	142	12	7
Shimizu et al (Dapagliflozin 5 mg vs. control)	2018	47	27	33	-20	57.8	37.5	32	24	-5.5	33.3



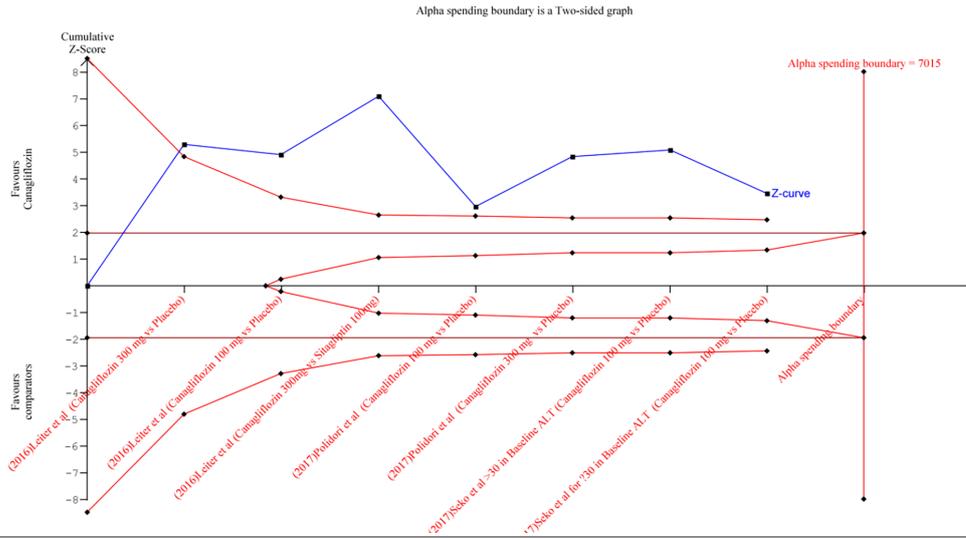
Appendix 3a: Trial sequential analysis on the effect of dapagliflozin vs. comparators on ALT reduction.



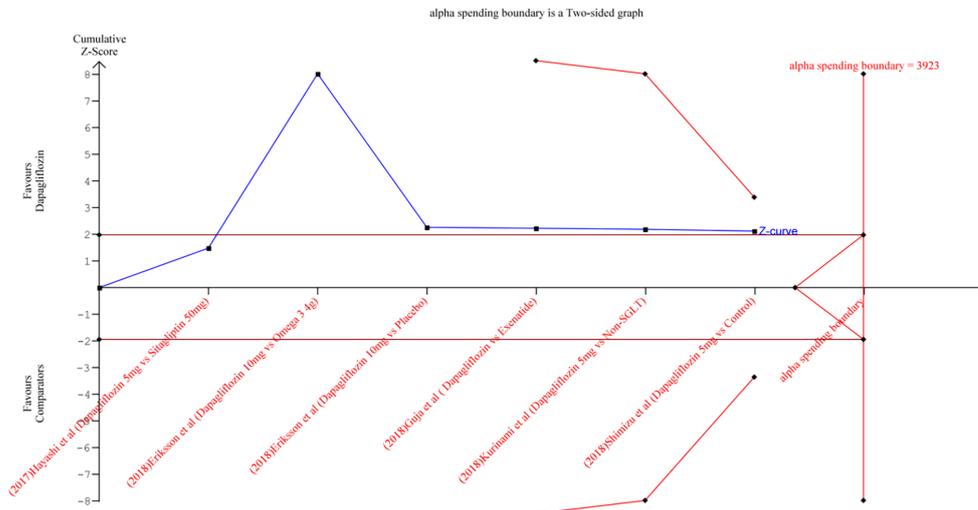
Appendix 3b: Trial sequential analysis on the effect of canagliflozin versus comparators on ALT reduction.



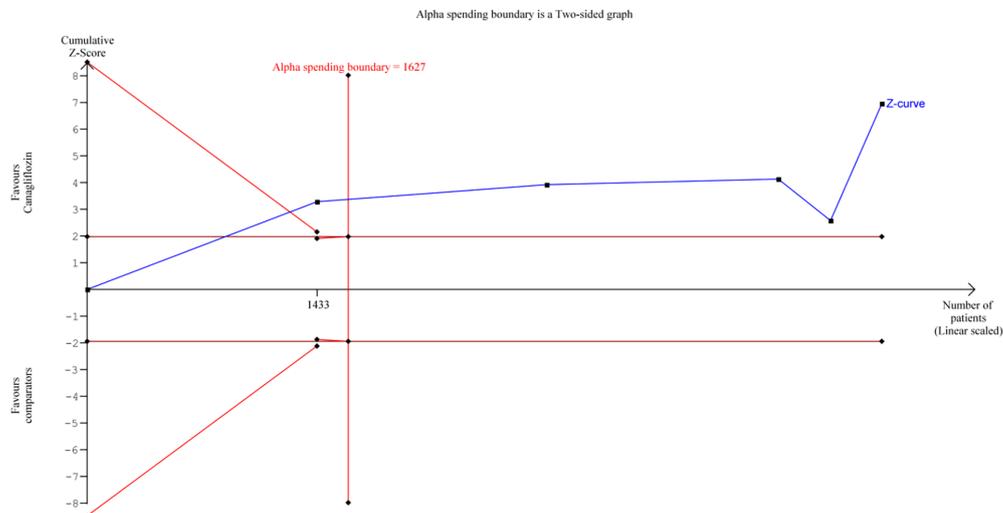
Appendix 3c: Trial sequential analysis on the effect of dapagliflozin versus comparators on AST reduction.



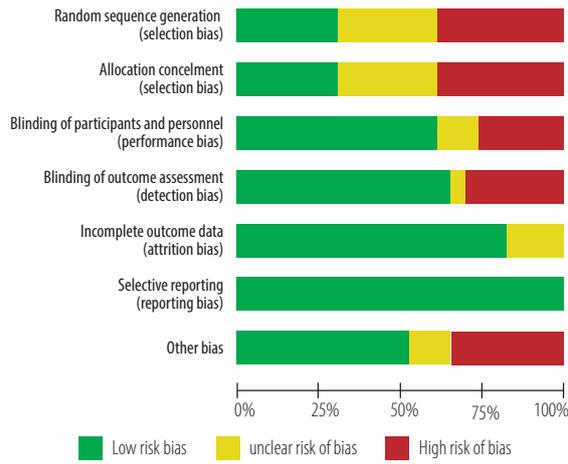
Appendix 3d: Trial sequential analysis on the effect of canagliflozin versus comparators on AST reduction.



Appendix 3e: Trial sequential analysis on the effect of dapagliflozin versus comparators on GGT reduction.



Appendix 3f: Trial sequential analysis on the effect of canagliflozin versus comparators on GGT reduction.



Appendix 4: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Araki et al 2013	?	?	+	+	?	+	?
Araki et al 2016	?	?	+	+	?	+	?
Bandoet al 2017	?	?	?	+	+	+	?
Eriksson al 2018	+	+	+	+	+	+	+
Fushimi al 2015	-	-	?	-	?	+	-
Guja al 2018	?	?	+	+	+	+	+
Hayashi al 2017	?	?	+	+	+	+	+
Ito al 2017	+	+	+	+	+	+	+
Kashiwagi et al 2016	+	+	+	+	+	+	+
Kashiwagi et al 2018	-	-	+	+	+	+	+
Koutsovasilis et al	-	-	-	-	+	+	-
Koutsovasilis et al 2017	-	-	-	-	+	+	-
Koutsovasilis et al 2018	-	-	-	-	+	+	-
Koutsovasilis et al 2018	+	+	+	+	+	+	+
Koutsovasilis et al 2018	-	-	-	-	+	+	-
Leiter et al - PBO 2016	+	+	+	+	+	+	+
Polidori et al - PBO 2017	-	-	-	-	+	+	-
Seko et al 2017	-	-	-	-	+	+	-
Seko et al 2018	+	+	+	+	+	+	+
Shibuya et al 2017	+	+	+	+	+	+	+
Shimizu et al 2018	?	?	+	+	+	+	+
Widing et al 2018	?	?	+	+	+	+	+
Yamamoto et al 2016	-	-	?	?	?	+	-

Appendix 5: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Appendix 6: Grading of Recommendations Assessment, Development and Evaluation quality assessment for the study findings was summarized as follows.

Studies, n	Study design	Risk of bias	Certainty assessment			Patients, n	Effect	Certainty	Importance	
			Inconsistency	Indirectness	Imprecision					Other considerations
6	Randomized trials	not serious	very serious ^a	not serious	DAPAGLIFOZIN VS. COMPARATOR (ALT IMPROVEMENT)	183 257	none	not serious	mean 1.902 SD higher (0.98 higher to 2.823 higher)	⊕○○○ LOW
6	Randomized trials	not serious	not serious	not serious	CANAGLIFOZIN VS. COMPARATOR (ALT IMPROVEMENT)	2424 2859	none	not serious	mean 6.807 higher (2.689 higher to 10.924 higher)	⊕⊕⊕⊕ HIGH
6	Randomized trials	not serious	not serious	not serious	DAPAGLIFOZIN VS COMPARATOR (AST IMPROVEMENT)	183 257	none	not serious	mean 0.737 higher (0.275 higher to 1.199 higher)	⊕⊕⊕⊕ HIGH
6	Randomized trials	not serious	not serious	not serious	CANAGLIFOZIN VS. COMPARATOR (AST IMPROVEMENT)	2424 2859	none	not serious	mean 3.768 higher (2.011 higher to 5.525 higher)	⊕⊕⊕⊕ HIGH
6	Randomized trials	not serious	not serious	not serious	DAPAGLIFOZIN VS. COMPARATOR (GGT IMPROVEMENT)	355 372	none	not serious	mean 4.028 higher (2.763 higher to 5.293 higher)	⊕⊕⊕⊕ HIGH
6	Randomized trials	not serious	not serious	not serious	CANAGLIFOZIN VS. COMPARATOR (GGT IMPROVEMENT)	2424 2859	none	not serious	mean 8.885 higher (1.745 higher to 16.026 higher)	⊕⊕⊕⊕ HIGH