

# Effect of SGLT inhibitors on weight and lipid metabolism at 24 weeks of treatment in patients with diabetes mellitus

### A systematic review and network meta-analysis

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#### Abstract

**Background:** The goals of improving quality of life and increasing longevity are receiving growing amounts of attention. Body weight and lipid metabolism are closely related to various complications of diabetes. The aim of this study was to rank SGLT inhibitors according to their efficacy with regard to weight and evaluate the effect of SGLT inhibitors on lipid metabolism at 24 weeks of treatment.

**Methods:** The Web of Science, PubMed, Cochrane Library, Embase, and Clinical Trials databases were electronically searched to collect randomized controlled trials involving patients with type 2 diabetes mellitus through June 2020. Two researchers independently screened and evaluated the selected studies and extracted the outcome indexes. ADDIS 1.16.5 and STATA 16 software were used to perform the network meta-analysis and draw the plots.

**Results:** Ultimately, 36 studies were selected and included in this study. We found that all SGLT inhibitors were effective at reducing weight; canagliflozin was the most effective. SGLT inhibitors and placebo were not associated with significantly different serum cholesterol levels. SGLT inhibitors lowered serum triglyceride levels and increased serum high-density and low-density lipoprotein cholesterol levels. SGLT inhibitors also reduced the level of alanine aminotransferase.

**Conclusions:** SGLT inhibitors can bring about weight loss in patients with T2DM and can also improve lipid metabolism. Therefore, patients with hyperlipidemia who have been unsuccessful at losing weight should consider taking SGLT inhibitors. In addition, SGLT inhibitors are hepatoprotective and appear to be safe for patients with mild to moderate liver dysfunction.

#### Trial Registration: CRD42020198516.

**Abbreviations:** CANA = canagliflozin, CI = confidence interval, DAPA = dapagliflozin, DM = diabetes mellitus, EMPA = empagliflozin, ERTU = ertugliflozin, HDL/HDL-C = high-density lipoprotein/high-density lipoprotein cholesterol, HMG-CoA = hydroxy-methyl-glutaryl CoA, LDL/LDL-C = low-density lipoprotein/low-density lipoprotein cholesterol, MD = mean difference, PROSPERO = International Prospective Register of Systematic Reviews, RCTs = randomized controlled trials, SGLT = sodium-dependent glucose transporter, SOTA = sotagliflozin, T2DM = type 2 diabetes mellitus.

Keywords: lipid metabolism, network meta-analysis, sodium-glucose transporter 1, sodium-glucose transporter 2, type 2 diabetes mellitus

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Data sharing not applicable to this article as no datasets were generated or analyzed during the present study.

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#### 1. Introduction

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic disorders characterized by long-term high blood sugar levels.<sup>[1]</sup> Most diabetes patients have type 2 diabetes mellitus (T2DM). As of 2019, an estimated 463 million people had diabetes worldwide.<sup>[2]</sup> The incidence of diabetes grows annually.<sup>[3,4]</sup> In 2019, diabetes caused approximately 4.2 million deaths, and it was the seventh leading cause of death.<sup>[5,6]</sup> Therefore, drugs for treating diabetes have long been the focus of attention of various research teams.

Sodium-dependent glucose transporter (SGLT) inhibitors are a new class of drugs for the treatment of T2DM.<sup>[7]</sup> There are five main SGLT inhibitors, namely, dapagliflozin (DAPA), canagliflozin (CANA), empagliflozin (EMPA), ertugliflozin (ERTU), and sotagliflozin (SOTA).<sup>[8]</sup> Among them, only SOTA is a dual SGLT-1/2 inhibitor. These drugs reduce blood glucose levels by interfering with SGLT, reducing glucose absorption or increasing glucose excretion. In previous studies, we verified the efficacy of SGLT inhibitors for the treatment of T2DM.<sup>[9]</sup> However, with regard to their effects on lipid metabolism in patients with T2DM, a reliable systematic review has not yet been performed.

Obesity, especially central obesity, affects blood lipid metabolism and exacerbates insulin resistance in diabetic patients,<sup>[10]</sup> and abnormal lipid metabolism is an important risk factor for complications of diabetes.<sup>[11]</sup> In central obesity, fat usually accumulates in the liver. Liver fat deposits and high blood sugar have toxic effects on liver cells, and the main site of lipid metabolism and drug metabolism is the liver; therefore, it is necessary to evaluate the hepatic function of patients taking oral SGLT inhibitors. Studying the effect of SGLT inhibitors on lipid metabolism could elucidate their relationship with diabetes complications. The focus of this study was to evaluate the effect of SGLT inhibitors on lipid metabolism in patients with T2DM.

#### 2. Methods

The original plan of this study was to perform a network metaanalysis. After data extraction, it was found that the data for the secondary outcomes were insufficient. Therefore, a common meta-analysis was performed for the levels of triglycerides, cholesterol, HDL-C, LDL-C, and ALT.

#### 2.1. Design and registration

A network meta-analysis was conducted to evaluate the efficacy and safety of SGLT inhibitors in patients with T2DM. This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), with registration number: CRD42020198516 (https://www.crd.york.ac.uk/PROS PERO). No ethics approval was required because this study used data that were already in the public domain.

#### 2.2. Study selection

**2.2.1. Study type.** This network meta-analysis quantitatively analyzed data from randomized controlled trials (RCTs).

**2.2.2.** Study subjects. The subjects of this study were patients with T2DM. There were no restrictions on age, weight, HbA1c level, drug history, etc. However, patients with serious underlying acute or chronic diseases and heart or kidney failure were excluded.

**2.2.3.** Intervention measures. This network meta-analysis only included single-drug studies, and studies involving drug combinations were not included. Five drugs were included in this study, and each drug can be administered in two different doses; therefore, there were 10 interventions. In addition to the placebo group, a total of 11 interventions were included.

**2.2.4. Outcome Indicators.** The primary outcome indicator was weight. Other outcome indicators included changes in levels of ALT, cholesterol, triglycerides, high-density lipoprotein/high-density lipoprotein cholesterol (HDL/HDL-C) and low-density lipoprotein/low-density lipoprotein cholesterol (LDL/LDL-C).

In a preliminary analysis, it was found that weight was strongly affected by the duration of treatment. To reduce the heterogeneity among the studies, limitations were placed on the duration of treatment. Results after treatment for longer than 24 weeks were included because we found that after 24 weeks, weight remained relatively stable. Therefore, we chose 24 weeks ( $\pm 2$  weeks) as the timepoint for data selection.

**2.2.5.** Exclusion criteria. Studies with data that could not be extracted or utilized, studies with animal experiments, and literature reviews were excluded.

#### 2.3. Data sources and searches

We searched for publications through June 2020 in the following databases: Web of Science, PubMed, the Cochrane Library, EMBASE, and Clinical Trials. The search terms included "SGLT," "diabetes," and "mellitus." In Figure 1, we use the PubMed database as an example.

## 2.4. Study screening, data extraction, and assessment of the risk of bias

Data were collected independently by two researchers. The unqualified studies were eliminated, and the qualified studies were selected after reading the title, abstract and full text. Then, the research data were extracted and checked, disagreements were discussed, and a decision was made regarding study inclusion by the authors. The extracted data included the following:

- the basic information about the study, including title, author and year of publication;
- 2. the characteristics of the included study, consisting of the study duration, the sample sizes of the test group and the control group, and the intervention measures
- 3. the outcome indicators and data; and
- 4. the information needed to assess the risk of bias.

The risk of bias in the included studies was assessed using the RCT bias risk assessment tool recommended in the Cochrane Handbook for Systematic Reviews of Interventions (5.1.0).<sup>[12]</sup>

#### 2.5. Statistical analysis

This network meta-analysis was performed using the Bayesian method. STAT MP 16 and ADDIS 1.16.5 software were used to draw the plots and perform the network meta-analysis, and RevMan 5.4 software was used for the common meta-analysis. The continuous variables are expressed as the mean difference (MD) as an effect indicator. Effect estimates and 95% confidence

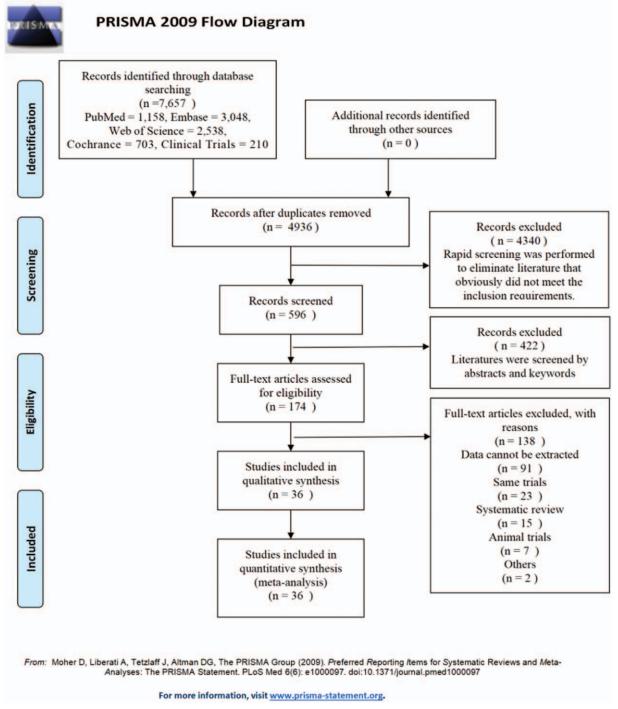


Figure 1. PubMed database retrieval strategy and PRISMA flow diagram.

intervals (CIs) were calculated. A network meta-analysis was performed for weight, and a common meta-analysis was performed for other outcome indexes due to the lack of data. A random effects model was used in the network meta-analysis, and a fixed model was used in the common meta-analysis. The core results of the network meta-analysis included a network evidence plot, network SUCRA plot, pairwise comparison plot and network node-splitting analysis of inconsistency. If an inconsistency was observed, the cause was identified, explained and analyzed, and the inconsistency model was used for analysis. Finally, a funnel plot was drawn if there were more than 15 studies. The significance level was set at  $\alpha = 0.05$ .

#### 3. Results

#### 3.1. Included studies and patients

From the databases, we retrieved a total of 7,657 studies. Ultimately, 36 studies<sup>[13–48]</sup> were selected and included. No gray

literature was included in this study. The specific flow diagram is shown in Figure 1. When the data from the included studies were pooled, the total number of enrolled patients was 17,561. In each study, the characteristics of the patients in the groups were similar.

We originally planned to include five well-known SGLT inhibitors in this study. However, the data in the SOTA-related RCTs did not meet the inclusion criteria. Therefore, there are no SOTA data included in these results.

## 3.2. Characteristics of the included studies and quality assessment

All included studies were RCTs. The basic characteristics and quality assessment of the studies are presented in Table 1.

#### 3.3. Network meta-analysis results

**3.3.1. Weight.** Thirty-six studies reported comparisons of weight. The core results of the network analysis are shown in Figure 2. According to the node-splitting analysis, the consistency model adopted in this study was reliable. The pairwise comparison plot shows the results of the comparisons between all the included interventions. Among the four SGLT-2 inhibitors, the SUCRA plot shows that 300 mg CANA (high dose) and 100 mg CANA (low dose) should be the most effective. Funnel plots were generated. The funnel plots were bilaterally symmetrical, and most studies fell within the 95% confidence interval. These results suggest that this study has no clear publication bias.

#### 3.4. Common meta-analysis results

**3.4.1.** Cholesterol. Three studies reported differences in cholesterol between the SGLT inhibitor group and the placebo group. A fixed-effect model was adopted; as the dose of SGLT inhibitors increased, serum cholesterol also increased (low dose:  $I^2 = 0\%$  [MD = 0.03, 95% CI (-3.18, 3.24), P = .99]; high dose:  $I^2 = 46\%$  [MD = 2.52, 95% CI (-0.19, 5.23), P = .07]) (Fig. 3, upper left).

**3.4.2.** Triglyceride. Five studies reported differences in triglyceride levels between the SGLT inhibitor group and the placebo group. A random effect model was adopted; as the dose of SGLT inhibitors increased, the serum triglyceride level decreased (low dose:  $I^2 = 0\%$  [MD=-9.65, 95% CI (-15.41, -3.88), P = 0.001]; high dose:  $I^2 = 54\%$  [MD=-8.65, 95% CI (-16.65, -0.66), P = .03]) (Fig. 3, upper right).

**3.4.3.** *HDL/HDL-C.* Five studies reported differences in HDL/ HDL-C levels between the SGLT inhibitor group and the placebo group. A fixed effect model was adopted; compared with the placebo, oral SGLT inhibitors were associated with increased serum HDL/HDL-C levels (low dose:  $I^2 = 0\%$  [MD=4.52, 95% CI (2.14,6.90), P = .0002]; high dose:  $I^2 = 0\%$  [MD=4.57, 95% CI (2.51, 6.63), P < 0.0001]) (Fig. 3, lower left).

**3.4.4.** LDL/LDL-C. Five studies reported differences in LDL/ LDL-C levels between the SGLT inhibitor group and the placebo group. A fixed effect model was adopted; as the dose of SGLT inhibitors increased, the serum LDL/LDL-C level also increased (low dose:  $I^2 = 0\%$  [MD=2.54, 95% CI (-1.23,6.31), P = 0.19]; high dose:  $I^2 = 48\%$  [MD=6.54, 95% CI (3.15, 9.93), P = .0002]) (Fig. 3, lower right).

**3.4.5.** ALT. Three studies reported differences in ALT levels between the SGLT inhibitor group and the placebo group. A fixed

effect model was adopted; compared with the placebo, oral SGLT inhibitors were associated with decreased serum ALT levels (low dose:  $I^2 = 0\%$  [MD=-3.08, 95% CI (-5.19, -0.97), *P*=.004]; high dose:  $I^2 = 0\%$  [MD=-3.86, 95% CI (-5.93, -1.78), *P*=.0003]) (Fig. 4).

#### 4. Discussion

Since no studies on dual SGLT-1/2 inhibitors were included in this study, these results only pertain to SGLT-2 inhibitors. RCTs on SOTA were excluded because the duration of the intervention did not meet the inclusion criteria.<sup>[49]</sup>

Based on this network meta-analysis, we believe that SGLT-2 inhibitors effectively induce weight loss in patients with T2DM; CANA is the most effective, and DAPA is the least effective. Second, SGLT-2 inhibitors can reduce triglyceride levels and increase both HDL-C and LDL-C levels. Finally, SGLT2 inhibitors can decrease serum ALT levels and may have a protective effect on the liver.

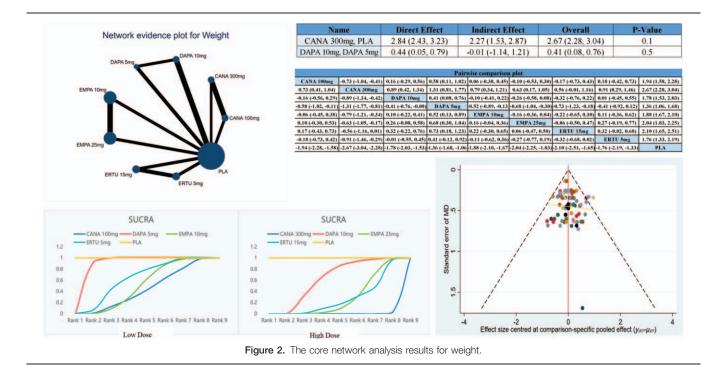
The main function of SGLT is to reabsorb glucose. The sodium–potassium pump consumes ATP and transfers  $Na^+$  to the outside of the cell, causing a decrease in the intracellular  $Na^+$  concentration. The  $Na^+$  in glomerular filtrate (or in intestinal juice) enters the cell along the concentration gradient, and glucose is brought into the cell concurrently by the action of sodium-dependent glucose transporters. This is the mechanism by which SGLT reabsorbs glucose<sup>[50]</sup> (Fig. 5).

Once the mechanism of SGLT is understood, the mechanism by which SGLT inhibitors control blood sugar in patients with T2DM is clear. In the real world, many people with T2DM also have hyperlipidemia; accordingly, T2DM and hyperlipidemia are usually considered sister diseases, and hyperlipidemia is believed to be a secondary disease of T2DM.<sup>[51]</sup> According to a cross-sectional study, approximately 60% of diabetic patients have hypertriglyceridemia.<sup>[52]</sup> The state of hyperlipidemia substantially increases patients' cardiovascular risk.<sup>[53,54]</sup> Compared with other hypoglycemic drugs, the advantage of SGLT-2 inhibitors is that they induce weight loss in patients with T2DM and simultaneously have a beneficial effect on lipid metabolism.<sup>[55]</sup> The results of our study corroborate this conclusion.

SGLT-2 inhibitors probably induce weight loss by reducing the body's total energy intake and promoting osmotic diuresis. However, the effects of SGLT inhibitors on lipid metabolism might be carried out in the following ways. Diabetic dyslipidemia is characterized by elevated serum triglyceride levels, decreased serum high-density lipoprotein cholesterol (HDL-C) levels, and predominant atherosclerotic low-density lipoprotein (LDL) particles.<sup>[56]</sup> There is a dual effect of SGLT-2 inhibitors on lipids: on the one hand, SGLT-2 inhibitors might increase the breakdown of fats, leading to increases in liver levels of cholesterol substrate and hepatic hydroxy-methyl-glutaryl CoA (HMG-CoA). This, in turn, would increase cholesterol synthesis, decrease the activity of LDL receptors and finally lead to an increase in serum LDL-C level. On the other hand, SGLT-2 inhibitors could reduce the systemic toxicity of glucose, thereby reducing triglyceride synthesis in the liver and increasing the breakdown of triglycerides. This, in turn, would reduce the serum triglyceride level and ultimately lead to an increased serum HDL-C level.<sup>[57]</sup>

SGLT inhibitors increase the levels of glucagon-like peptide 1 (GLP-1), one of the brain-gut peptides. GLP-1 can promote the

					Interv	Intervening Measure		s	Sample size				Literature	Literature quality score			
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~	2	2	Diet and	26 weeks	FRTIL 5mg	FRTI 15mg		156			ow risk	l ow risk	l ow risk	l niv risk	Inclear	low risk	nw risk
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			MET and pionlitazone	26 weeks	CANA 100mg	CANA 300mg	PLA	113	114	115	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
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	2015 NCT01289990	9990 Germany	MET and SU	26 weeks	EMPA 10mg	EMPA 25mg	PLA	225	216		Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear
	2014 NCT01159600	9600 Germany	Diet and Exercise	24 weeks	EMPA 10mg	EMPA 25mg	PLA	217	213	207 [	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Hollander, P. 2		9218 US	MET	26 weeks	ERTU 5mg	ERTU 15mg		448	440	_	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Jabbour, Serge A. 2		4867 US	SITA and/or MET	24 weeks	DAPA 10mg	PLA		223	224	_	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
	2019 NCT02630706	0706 China	MET	26 weeks	ERTU 5mg	ERTU 15mg	PLA	170	169	167 L	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
		3218 Japan	Diet and Exercise	26 weeks	EMPA 10mg	EMPA 25mg		267	265	_	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
		-	Teneligliptin	24 weeks	CANA 100mg	PLA		70	68		Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
			MET	24 weeks	EMPA 10mg	EMPA 25mg	PLA	165	168	165 L	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
nzalez, F. J.		_	MET	26 weeks	CANA 100mg	CANA 300mg		368	367	_	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
	_		Diet and Exercise	26 weeks	EMPA 10mg	EMPA 25mg		132	133	_	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
		_	MET and Saxagliptin	24 weeks	DAPA 10mg	PLA		160	160	_	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
			MET and SUL	24 weeks	DAPA 10mg	PLA		108	108		Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
			MET	26 weeks	EMPA 10mg	EMPA 25mg	PLA	217	213	207	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
			MET	26 weeks	ERTU 5mg	ERTU 15mg		250	248		Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
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	_		Glimepiride	24 weeks	DAPA 5mg	DAPA 10mg	PLA	142	151		Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Terra, S. G. 2	2017 NCT01958671	8671. US	Diet and Exercise	26 weeks	ERTU 5mg	ERTU 15mg	PLA	156	152		Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Wilding, J. P. 2	2013 NCT01106625	6625 UK	MET and SUL	26 weeks	CANA 100mg	CANA 300mg	PLA	157	156		Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Wilding, J. P. 2	2012 NCT00673231	3231 US	High doses of insulin	24 weeks	DAPA 5mg	DAPA 10mg	PLA	211	194		Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
	2016 NCT01095666	5666 China	MET	24 weeks	DAPA 5mg	DAPA 10mg	PLA	147	152	145	low risk	low risk	low risk	low risk	low risk	unclear	unclear
Yang, W. 2	2018 NCT02096705	6705 China	Insulin with or without oral	24 weeks	DAPA 10mg	PLA		139	133	_	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
			antihyperglycemic drugs														



glucose-dependent production and release of insulin and inhibit glucagon secretion, gastric emptying, food intake, and nutrient absorption.<sup>[58]</sup> Thus, GLP-1 can reduce blood sugar and control weight, similar to SGLT inhibitors. In a randomized clinical trial by Zambrowicz B, 300 mg of LX4211 (SOTA) was given to

T2DM patients, and the level of GLP-1 substantially increased.  $^{\left[ 59\right] }$ 

This study verifies by serology that SGLT inhibitors can improve the lipid metabolism of patients with T2DM. In an epidemiological investigation, SGLT inhibitors improved ath-

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vacs, C. S.2015	0.4 19	165	-0.4	19	82	16.9%	0.80 [-4.23, 5.83]			•		Kovacs, C. S.2015	-8.6 3		-0.6			-8.00 [-17.10, 1.10			
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st for overall effect.												Heterogeneity, Tau <sup>2</sup> =	0.00; Chi*	= 0.51, df	= 3 (P = 1						
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ovacs, C. S.2015	-0.4 19			19			0.00 [-5.00, 5.00]				1.00	*Forst, T.2014	-1.7 4		15.3 4			-17.00 [-31.11, -2.89			
latthaei, S.2015	3.6 19		-3	19			6.60 [1.53, 11.67]			-		*Kovacs, C. S.2015	2.3 3		-0.6		17.1%	2 90 [-6.13, 11.93			
ibtotal (95% CI)		397			258	58.4%	2.52 [-0.19, 5.23]					*Matthaei, S.2015 *Steniof, K.2013	-6.8 4		2.5 4		9.4%	-9.30 -22.37, 3.77 -17.00 -31.11, -2.89			
eterogeneity: Chi <sup>2</sup> =	3.70 df= 2	(P=0.16	): F=	46%			and the second s					"Steniot, K.2013 Subtotal (95% CI)	-1.7 4	3 109 615	15.3 4			-17.00 [-31.11, -2.89 -8.65 [-16.65, -0.66		-	
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ration overall enect.	1.02 (r	- 0.011										Test for overall effect			n - 4 (r =	0.07), F=					
otal (95% CD		688			406	100.0%	1.48 [-0.59, 3.55]							100							
eterogeneity. Chi#=	5 10 df - 4		1.12-1			- Jone of	and Lanas anol	+		-	+	Total (95% CI)		1206				-8.58 [-12.90, -4.26	1	•	
est for overall effect.			N	1910				-10	-5 0	5	10	Heterogeneity: Tau <sup>2</sup> =				(.30); P=	16%		-	-20 -10 0	10 20
				-	-				Favours SGLT-i	Favours PLA		Test for overall effect								Favours SGLT-I	
est for subaroup diffe	erences: Ch	W= 1.35	df=1	(P=0.)	(5). 1*	= 25.7%						Test for subaroup diff	ferences: C	$hi^2 = 0.04$	df=1 (P	= 0.84), P	= 0%				
						Chole	esterol											Triglycerides			
	SGL			PLA			Mean Difference			fference			SGL		PL			Mean Difference		Mean Diffe	
			Mea		Total		Mean Difference			fference 1, 95% Cl		Study or Subgroup			PL		Weight			Mean Diffe IV, Fixed, 9	
.1.1 low dose	Mean S	D Total		n SD		Weight	Mean Difference IV, Fixed, 95% C	1				5.1.1 low dose	Mean S	D Total	Mean	SD Total	Weight	Mean Difference IV, Fixed, 95% CI			
I.1.1 low dose Bailey, C. J.2010	Mean 5	D Total	0.	4 15	61	Weight 11.5%	Mean Difference IV, Fixed, 95% C 2.90 (-1.69, 7.49	1			-	5.1.1 low dose Bailey, C. J 2010	Mean S	D Total	Mean 3.5	<u>SD Total</u> 25 60		Mean Difference IV, Fixed, 95% CI -0.40 [-8.09, 7.29]			
4.1.1 low dose Bailey, C. J.2010 Forst, T.2014	Mean S	5 126 4 107	0.	4 15 4 14	61 52	Weight 11.5% 11.3%	Mean Difference IV, Fixed, 95% C 2.90 (-1.69, 7.49 4.80 (0.16, 9.44	11 11 11				5.1.1 low dose Bailey, C. J 2010 Forst, T 2014	Mean 5	D Total	Mean 3.5 -0.4	SD Total 25 60 27 52	8.1%	Mean Difference IV, Fixed, 95% CI -0.40 (-8.09, 7.29) 7.50 (-1.34, 16.34)			
I.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015	Mean S 3.3 1 7.2 1 2.3 1	5 126 4 107 9 165	0. 2. -1.	4 15 4 14 5 19	61 52 82	Weight 11.5% 11.3% 9.6%	Mean Difference IV, Fixed, 95% C 2.90 (-1.69, 7.49 4.80 (0.16, 9.44 3.80 (-1.23, 8.83	11 11 11				5.1.1 low dose Bailey, C. J. 2010 Forst, T. 2014 Kovacs, C. S. 2015	Mean 5	D Total 25 126 26 107 30 165	Mean 3.5 -0.4 0	25 60 27 52 28 82	8.1% 11.0%	Mean Difference <u>IV. Fixed, 95% CI</u> -0.40 [-8.09, 7.29] 7.50 [-1.34, 16.34] 2.60 [-4.99, 10.19]			
Study or Subgroup 4.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Koyacs, C. S.2015 Steniof, K.2013 Subded (JOS) CD	Mean S	5 126 4 107 9 165 9 192	0. 2. -1.	4 15 4 14	61 52 82 85	Weight 11.5% 11.3% 9.6% 10.3%	Mean Difference N, Fixed, 95% C 2.90 [-1.69, 7.49 4.80 [0.16, 9.44 3.80 [-1.23, 8.83 6.70 [1.85, 11.55	H H] H] H] H]				5.1.1 low dose Bailey, C. J. 2010 Forst, T. 2014 Kovacs, C. S. 2015 Steniof, K. 2013	Mean 5	D Total 25 126 26 107 30 165 25 192	Mean 3.5 -0.4 0 1	25 60 27 52 28 82 26 85	8.1% 11.0% 14.8%	Mean Difference IV, Fixed, 95% CI -0.40 [-8.09, 7.29] 7.50 [-1.34, 16.34] 2.60 [-4.99, 10.19] 1.90 [-4.66, 8.46]			
4.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015 Steniof, K.2013 Subtotal (95% CI)	Mean S	D Total 5 126 4 107 9 165 9 192 590	0. 2. -1. 4.	4 15 4 14 5 19 5 19	61 52 82	Weight 11.5% 11.3% 9.6% 10.3%	Mean Difference IV, Fixed, 95% C 2.90 (-1.69, 7.49 4.80 (0.16, 9.44 3.80 (-1.23, 8.83	H H] H] H] H]				5.1.1 low dose Bailey, C. J. 2010 Forst, T. 2014 Kovacs, C. S. 2015 Steniof, K. 2013 Subtotal (95% CI)	Mean 5	D Total 25 126 26 107 30 165 25 192 590	Mean 3.5 -0.4 0 1	SD         Total           25         60           27         52           28         82           26         85           279         279	8.1% 11.0% 14.8%	Mean Difference N. Fixed, 95% CI -0.40 [-8.09, 7.29] 7.50 [-1.34, 16.34] 2.60 [-4.99, 10.19]			
I.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Covacs, C. S.2015 Bablotal (95% CI) Heterogeneity, Chi <sup>#</sup>	Mean S 3.3 1 7.2 1 2.3 1 11.2 1 11.2 1	D Total 5 126 4 107 9 165 9 192 590 3 (P = 0.1	0. 2. -1. 4. 2), (*=	4 15 4 14 5 19 5 19	61 52 82 85	Weight 11.5% 11.3% 9.6% 10.3%	Mean Difference N, Fixed, 95% C 2.90 [-1.69, 7.49 4.80 [0.16, 9.44 3.80 [-1.23, 8.83 6.70 [1.85, 11.55	H H] H] H] H]			-	5.1.1 low dose Bailey, C. J. 2010 Forst, T. 2014 Kovacs, C. S. 2015 Steniof, K. 2013	Mean 5 3.1 7.1 2.6 2.9 = 1.81, df =	D Total 25 126 26 107 30 165 25 192 590 3 (P = 0.8	Mean 3.5 -0.4 0 1	SD         Total           25         60           27         52           28         82           26         85           279         279	8.1% 11.0% 14.8%	Mean Difference IV, Fixed, 95% CI -0.40 [-8.09, 7.29] 7.50 [-1.34, 16.34] 2.60 [-4.99, 10.19] 1.90 [-4.66, 8.46]			
I.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Covacs, C. S.2015 Benlof, K.2013 Subtotal (95% Cl) Heterogeneity. Chi <sup>a</sup> : Fest for overall effect	Mean S 3.3 1 7.2 1 2.3 1 11.2 1 11.2 1	D Total 5 126 4 107 9 165 9 192 590 3 (P = 0.1	0. 2. -1. 4. 2), (*=	4 15 4 14 5 19 5 19	61 52 82 85	Weight 11.5% 11.3% 9.6% 10.3%	Mean Difference N, Fixed, 95% C 2.90 [-1.69, 7.49 4.80 [0.16, 9.44 3.80 [-1.23, 8.83 6.70 [1.85, 11.55	H H] H] H] H]				5.1.1 low dose Bailey, C. J. 2010 Forst, T. 2014 Kovacs, C. S. 2015 Stentof, K. 2013 Subtotal (95% Ct) Heterogeneity. Chi <sup>a</sup> , Test for overall effec	Mean 5 3.1 7.1 2.6 2.9 = 1.81, df =	D Total 25 126 26 107 30 165 25 192 590 3 (P = 0.8	Mean 3.5 -0.4 0 1	SD         Total           25         60           27         52           28         82           26         85           279         279	8.1% 11.0% 14.8%	Mean Difference IV, Fixed, 95% CI -0.40 [-8.09, 7.29] 7.50 [-1.34, 16.34] 2.60 [-4.99, 10.19] 1.90 [-4.66, 8.46]			
1.1 low dose ailey, C. J.2010 orst, T.2014 lovacs, C. S.2015 teniot, K.2013 ubtotal (95% CI) leterogeneity. Chi# est for overall effect .1.2 high dose	Mean S 3.3 1 7.2 1 2.3 1 11.2 1 1.35, df = 1.2 3.72 (f	5 126 4 107 9 165 9 192 590 3 (P = 0.1 P = 0.000	0. 2. -1. 4. 2), (* = 2)	n SD 4 15 4 14 5 19 5 19 5 19	61 52 82 85 280	Weight 11.5% 11.3% 9.6% 10.3% 42.8%	Mean Difference <u>N. Fixed, 95%</u> C 2.90 [-1.69, 7.49 4.80 [0.16, 9.44 3.80 [-1.23, 8.83 6.70 [1.85, 11.55 4.52 [2.14, 6.90]	1 1 1 1 1 1 1 1				5.1.1 low dose Bailey, C. J. 2010 Forst, T. 2014 Kovacs, C. S. 2015 Stentot, K. 2013 Subtotal (95% CI) Heterogeneity: Chi <sup>a</sup> , Test for overall effec 5.1.2 high dose	Mean 5 31 7,1 2,6 2,9 = 1.81, df = t Z = 1.32 (	D Total 25 126 26 107 30 165 25 192 590 3 (P = 0.8 P = 0.19)	Mean 3.5 -0.4 0 1 51); I*= 09	SD Total 25 60 27 52 28 82 26 85 279 6	8.1% 11.0% 14.8% 44.7%	Mean Difference N. Fixed, 95% CI -0.40 [-8.09, 7.29] 7.50 [-1.34, 16.34] 2.60 [-4.99, 10.19] 1.90 [-4.66, 8.46] 2.54 [-1.23, 6.31]			
.1.1 low dose lailey, C. J. 2010 orst, T. 2014 lovars, C. S. 2015 teniof, K. 2013 aubtotal (95% CI) leterogeneity, Chi* est for overall effect .1.2 high dose Bailey, C. J. 2010	Mean S 3.3 1 7.2 1 2.3 1 11.2 1 1.35, df= 1.2 3.72 (F 4.4 1	D Total 5 126 4 107 9 165 9 192 590 3 (P = 0.1 > = 0.000 6 121	0. 2. -1. 4. (2),  * = 2) 0.	n SD 4 15 4 14 5 19 5 19 5 19 6 0%	61 52 82 85 280	Weight 11.5% 11.3% 9.6% 10.3% 42.8%	Mean Difference N. Fixed, 95% C 2.90 [-1.69, 7.49 4.80 [0.16, 9.44 3.80 [-1.23, 8.33 4.52 [2.14, 6.90] 4.00 [-0.70, 8.70	1 19 19 19 19 10				5.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015 Steniof, K.2013 Subtotal (95% CI) Heterogeneity, Chi <sup>9</sup> Test for overall effec 5.1.2 high dose "Bailey, C. J.2010	Mean 5 3.1 7.1 2.6 2.9 = 1.81, df = t Z = 1.32 ( 9.5	D         Total           25         126           26         107           30         165           25         192           590         3 (P = 0.8           P = 0.19)         26	Mean 3.5 -0.4 0 1 51); I*= 09 3.5	SD         Total           25         60           27         52           28         82           26         85           279         6           25         61	8.1% 11.0% 14.8% 44.7%	Mean Difference N. Fixed, 95% CI -0.40 [-8.09, 7.29] 750 [-1.34, 16.34] 2.60 [-4.99, 10.19] 1.90 [-6.6, 8.46] 2.54 [-1.23, 6.31] 6.00 [-1.81, 13.81]			
.1.1 low dose halley, C. J. 2010 orst, T. 2014 orvars, C. S. 2015 itentof, K. 2013 habtotal (95% Ct) feterogeneity. Chi*s est for overall effect .1.2 high dose Bailey, C. J. 2010 Forst, T. 2014	Mean S 3.3 1 7.2 1 2.3 1 11.2 1 1.35, df = 1.35, df = 1.2 3.72 (f 4.4 1 8.9 1	D Total 5 126 4 107 9 165 9 192 590 3 (P = 0.1 > = 0.000 6 121 5 109	0. 2. -1. 4. 2), P <sup>a</sup> = 2) 0. 2.	n SD 4 15 4 14 5 19 5 19 5 19 0% 4 15 4 15 4 14	61 52 85 280 62 53	Weight 11.5% 11.3% 9.6% 10.3% 42.8% 11.0% 11.0%	Mean Difference N, Fixed, 95% C 2.90 [-1.69, 7.49 4.80 [0.16, 9.44 3.80 [-1.23, 8.83 6.70 [1.85, 11.55 4.52 [2.14, 6.90 4.00 [-0.70, 8.70 6.50 [1.80, 11.20	1 6 6 6 7 7 7				5.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015 Stertof, K.2013 Subtotal (95% CI) Heterogeneity: ChP Test for overall effec 5.1.2 high dose "Bailey, C. J.2010 "Forst, T.2014	Mean 5 3.1 7.1 2.6 2.9 = 1.81, df= t Z = 1.32 () 9.5 11.3	D         Total           25         126           26         107           30         165           25         192           590         3 (P = 0.8           P = 0.19)         26           26         120           26         120           26         109	Mean 3.5 -0.4 0 1 51); I*= 09 3.5 -0.4	SD         Total           25         60           27         52           28         82           26         85           279         6           25         61           27         53	8.1% 11.0% 14.8% 44.7%	Mean Difference N. Fixed, 95% CI -0.40 [-8.09, 7.29] 7.50 [-1.34, 16.34] 2.50 [-4.99, 16.34] 1.30 [-4.66, 8.46] 2.54 [-1.23, 6.31] 6.00 [-1.81, 13.81] 11.70 [2.94, 20.46]			
1.1.1 low dose Bailey, C. J.2010 Forst, T.2014 (ovacs, C. S.2015 Beniof, K.2013 Sublotal (95% Cf) Heterogeneity. Chi#= Fest for overall effect I.1.2 high dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S. 2015	Mean         S           3.3         1           7.2         1           2.3         1           1.1.2         1           1.35, df =         1           Z = 3.72 (F         1           4.4         1           8.9         1           0         1	D Total 5 126 4 107 9 165 9 192 590 3 (P = 0.1 > = 0.000 6 121 5 109 9 168	0. 2. -1. 4 2), P= 2) 0. 2. -1.	n SD 4 15 4 14 5 19 5 19 6 0% 4 15 4 15 4 14 5 19	61 52 82 85 280 62 53 83	Weight 11.5% 11.3% 9.6% 10.3% 42.8% 11.0% 11.0% 9.7%	Mean Difference M. Food, 95% C 2:00[+69,749 4:00[0.16,944 3:00[+1:23,8:83 6:70[1:85,11:55 4:52[2:14,6:90 4:00[+0:70,8:70 6:50[1:80,11:20] 1:50[-3:50,6:50	1 1 19 19 19 10 10 10 10 10				5.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015 Stentof, K.2013 Subtotal (95% CI) Heterogeneity: Chi <sup>a</sup> Test for overall effec 5.1.2 high dose *Bailey, C. J.2010 *Forst, T.2014 *Kovacs, C. S. 2015	Mean 5 31 7,1 2,6 2,9 = 1.81, df= t Z= 1.32 () 9,5 11.3 -1.5	D         Total           25         126           26         107           30         165           25         192           590         3 (P = 0.8           P = 0.19)         26           26         120           26         120           26         109           30         168	Mean 3.5 -0.4 0 1 51); I*= 09 3.5 -0.4 0	SD         Total           25         60           27         52           28         82           26         85           279         6           25         61           27         53           28         83	8.1% 11.0% 14.8% 44.7% 10.4% 8.3% 11.2%	Mean Difference M. Roed, 95% CI -0.40 [6:0.9, 7:29] 7:50 [-1:34, 16:34] 2:60 [-4:99, 10:19] 1:30 [-4:66, 8:46] 2:54 [-1:23, 6:31] 6:00 [-1:81, 13:81] 11.70 [2:94, 20:46] -1:50 [-50.46, 60]			
1.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015 Steniof, K.2013 Sublotal (95% Ch) Hoterogeneity, Ch <sup>2</sup> Test for overall effect <b>1.1.2 high dose</b> Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015	Mean         S           3.3         1           7.2         1           2.3         1           1.1.2         1           1.1.5         df=           t.Z=3.72 (f           4.4         1           8.9         1           0         1           4.5         1	D Total 5 126 4 107 9 165 9 192 590 3 (P = 0.1 2 = 0.000 6 121 5 109 9 168 5 108	0. 2. -1. 4. 2), P = 2) 0. 2. -1.	n SD 4 15 4 14 5 19 5 19 6 0% 4 15 4 14 5 19 0 15	61 52 82 85 280 62 53 83 108	Weight 11.5% 11.3% 9.6% 10.3% 42.8% 11.0% 9.7% 15.2%	Mean Difference M. Fixed, 95% C 2.90 [-1.69, 7.49 4.80 [10.16, 9.44 3.80 [-1.23, 8.83 6.70 [1.85, 11.55 4.52 [2.14, 6.90] 4.00 [-0.70, 8.70 6.50 [1.80, 11.20 1.50 [-3.50, 6.50	1 1 10 10 10 10 10 10 10 10 10 10 10 10				5.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015 Steniof, K.2013 Subtotal (95% CI) Heterogeneity: Chi <sup>m</sup> Test for overall effec 5.1.2 high dose "Bailey, C. J.2010 "Forst, T.2014 "Kovacs, C. S.2015 "Matthaei, S.2015	Mean 5 3.1 : 7.1 : 2.6 : 2.9 : = 1.81, df = t Z = 1.32 () 9.5 : 11.3 : -1.5 : 5.8 :	D         Total           25         126           26         107           30         165           25         192           590         3 (P = 0.8           P = 0.19)         26           26         120           26         109           26         109           26         109           30         168           29         108	Mean 3.5 -0.4 0 1 51); I*= 09 3.5 -0.4 0 -6.3	SD         Total           25         60           27         52           28         82           26         85           279         56           25         61           27         53           28         83           29         108	8.1% 11.0% 14.8% 44.7% 10.4% 8.3% 11.2% 10.6%	Mean Difference M. Rovd, 95% Cf -0.40 [-8.09, 7.29] 7.50 [-1.34, 16.34] 2.60 [-4.99, 101, 1361] 1.90 [-4.66, 846] 2.54 [-1.23, 6.31] 6.00 [-1.81, 13.81] 11.70 [2.94, 20.46] -1.50 [-6.04, 6.04] 2.10 [4.37, 18.83]			
4.1.1 low dose Bailey, C. J.2010 Forst, T.2017 Steniot, K. 2013 Subtotal (95% Cf) Heterogeneity. Chi*s Test for overail effect 4.1.2 high dose Bailey, C. J.2010 "Forst, T.2014 "Kovacs, C. S.2015 "Matthaei, S.2015 "Matthaei, S.2013	Mean         S           3.3         1           7.2         1           2.3         1           1.1.2         1           1.1.5         df=           t.Z=3.72 (f           4.4         1           8.9         1           0         1           4.5         1	D Total 5 126 4 107 9 165 9 192 590 3 (P = 0.1 2 = 0.000 6 121 5 109 9 168 5 108 9 195	0. 2. -1. 4. 2), P = 2) 0. 2. -1.	n SD 4 15 4 14 5 19 5 19 6 0% 4 15 4 15 4 14 5 19	61 52 85 280 62 53 83 108 85	Weight 11.5% 11.3% 9.6% 10.3% 42.8% 11.0% 11.0% 9.7% 15.2% 10.4%	Mean Difference M. Food, 95% C 2:00[+69,749 4:00[n16,944 3:00[+1:23,8:83 6:70[1:85,11:55 4:52[2:14,6:90 4:00[+0:70,8:70 6:50[180,11:20 1:50[+3:50,6:50 4:50]50,8:50 6:10[1:2,10,4]					5.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015 Stentof, K.2013 Subtotal (95% CII Heterogeneity, Chi <sup>a</sup> Test for overail effec 5.1.2 high dose "Bailey, C. J.2010 "Forst, T.2014 "Kovacs, C. S.2015 "Matthael, S.2015	Mean 5 3.1 : 7.1 : 2.6 : 2.9 : = 1.81, df = t Z = 1.32 () 9.5 : 11.3 : -1.5 : 5.8 :	D         Total           25         126           26         107           30         165           25         192           590         3 (P = 0.8           P = 0.19)         26           26         120           26         109           30         168           29         108           25         195	Mean 3.5 -0.4 0 1 51); I*= 0 3.5 -0.4 0 -6.3 1	SD         Total           25         60           27         52           28         82           26         85           279         53           28         93           29         108           26         85	8.1% 11.0% 14.8% 44.7% 10.4% 8.3% 11.2% 10.6% 14.8%	Mean Difference M. Fixed, 95% CI -0.40 (+0.09, 7.29) 7.50 (+1.34, 16.34) 2.60 (+4.99, 10.19) 1.90 (+4.66, 8.46) 2.54 (-1.23, 6.31) 6.00 (+1.81, 13.811) 1.170 (2.94, 20.46) 1.50 (+0.04, 5.12.65) 6.10 (-0.45, 12.65)			
L.1.10w dose Bailey, C. J.2010 orst, T.2014 covacs, C. S.2015 Stubtotal (95% CD) Heterogeneity, Chi <sup>a</sup> s Fest for overall effect L.1.2 high dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015 Steniof, K.2013 Statotal (95% CD)	Mean         S           3.3         1           7.2         1           2.3         1           1.1.2         1           *1.35, df=         2           2.3         1           *1.35, df=         2           4.4         1           8.9         1           0         1           4.5         1           10.6         1	D         Total           5         126           4         107           9         165           9         192           590         3 (P = 0.000           6         121           5         109           9         168           5         108           9         168           5         701	0. 2 -1. 4 2), P = 2) 0. 2 -1. 4	n SD 4 15 4 14 5 19 5 19 6 0% 4 15 4 14 6 19 0 15 5 19	61 52 85 280 62 53 83 108 85	Weight 11.5% 11.3% 9.6% 10.3% 42.8% 11.0% 11.0% 9.7% 15.2% 10.4%	Mean Difference M. Fixed, 95% C 2.90 [-1.69, 7.49 4.80 [10.16, 9.44 3.80 [-1.23, 8.83 6.70 [1.85, 11.55 4.52 [2.14, 6.90] 4.00 [-0.70, 8.70 6.50 [1.80, 11.20 1.50 [-3.50, 6.50					5.1.1 low dose Bailey, C. J. 2010 Forst, T.2014 Kovacs, C. S.2015 Shentof, K.2013 Subtotal (95% CI) Heterogeneily: Ch <sup>9</sup> Test for overall effec 5.1.2 high dose "Bailey, C. J.2010 "Forst, T.2014 "Kovacs, C. S.2015 "Stentof, K.2013 "Subtotal (95% CI)	Mean 5 31 : 71 26 29 =1.81, df = t Z = 1.32 0 95 11.3 : -1.5 5.8 7.1	D         Total           25         126           26         107           30         165           25         192           590         3 (P = 0.19)           26         120           26         120           26         120           26         120           26         120           26         120           26         120           26         120           26         120           26         120           27         195           700         700	Mean 3.5 -0.4 0 1 51); I*= 0 -0.4 0 -6.3 1	SD         Total           25         60           27         52           28         82           26         85           279         6           25         61           27         53           28         83           29         108           26         85           390         390	8.1% 11.0% 14.8% 44.7% 10.4% 8.3% 11.2% 10.6% 14.8%	Mean Difference M. Fixed, 95% CI -0.40 (+0.09, 7.29) 7.50 (+1.34, 16.34) 2.60 (+4.99, 10.19) 1.90 (+4.66, 8.46) 2.54 (-1.23, 6.31) 6.00 (+1.81, 13.811) 1.170 (2.94, 20.46) 1.50 (+0.04, 5.12.65) 6.10 (-0.45, 12.65)			
1.1 flow dose laaley, C. J.2010 orst, T.2014 lovacs, C. S.2015 tentof, K.2013 ubtotal (95% CD letrogeneity, Ch <sup>2</sup> est for overall effect .1.2 high dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015 Matthaei, S.2015 Matthaei, S.2015 Matthaei, K.2013 ubtotal (95% CD	Mean         S           3.3         1           7.2         1           2.3         1           1.2.3         1           1.1.2         1           1.1.35, df =         2           2.4.4         1           8.9         1           0         1           4.4         1           0.1         1           4.5         1           10.6         1           -2.54, df =         -2.54, df =	D         Total           5         126           4         107           9         165           9         192           590         3 (P = 0.12)           5         109           6         121           5         109           9         168           5         108           9         195           7011         4 (P = 0.6	0. 2. -1. 4 (2),   <sup>4</sup> = 2) 0. 2. -1. 4. (4),   <sup>4</sup> =	n SD 4 15 4 14 5 19 5 19 6 0% 4 15 4 14 6 19 0 15 5 19	61 52 85 280 62 53 83 108 85	Weight 11.5% 11.3% 9.6% 10.3% 42.8% 11.0% 11.0% 9.7% 15.2% 10.4%	Mean Difference M. Food, 95% C 2:00[+69,749 4:00[n16,944 3:00[+1:23,8:83 6:70[1:85,11:55 4:52[2:14,6:90 4:00[+0:70,8:70 6:50[180,11:20 1:50[+3:50,6:50 4:50]50,8:50 6:10[1:2,10,4]					5.1.1 low dose Bailey, C. J.2010 Forst, T.2014 Kovacs, C. S.2015 Stentof, K.2013 Subtotal (95% CII Heterogeneity, Chi <sup>a</sup> Test for overail effec 5.1.2 high dose "Bailey, C. J.2010 "Forst, T.2014 "Kovacs, C. S.2015 "Matthael, S.2015	Mean 5 3.1 : 7.1 : 2.6 : 2.9 : = 1.81, df = t Z = 1.32 () 9.5 : 11.3 : -1.5 : 5.8 : 7.1 : = 7.72, df =	D         Total           25         126           26         126           26         107           30         165           25         192           590         3 (P = 0.8           P = 0.19)         108           26         109           30         168           29         108           25         195           7000         4 (P = 0.1	Mean 3.5 -0.4 0 1 51); I <sup>p</sup> = 0° 3.5 -0.4 0, -6.3 1 10); I <sup>p</sup> = 48	SD         Total           25         60           27         52           28         82           26         85           279         6           25         61           27         53           28         83           29         108           26         85           390         390	8.1% 11.0% 14.8% 44.7% 10.4% 8.3% 11.2% 10.6% 14.8%	Mean Difference M. Fixed, 95% CI -0.40 (+0.09, 7.29) 7.50 (+1.34, 16.34) 2.60 (+4.99, 10.19) 1.90 (+4.66, 8.46) 2.54 (-1.23, 6.31) 6.00 (+1.81, 13.811) 1.170 (2.94, 20.46) 1.50 (+0.04, 5.12.65) 6.10 (-0.45, 12.65)			
4.1.1 low dose Bailey, C. J2010 Forst, T. 2014 Koxosc, C. S. 2015 Sibilotal (95% C) Heterogenetik, Chr <sup>4</sup> - Test for overall effect 4.1.2 high dose Bailey, C. J2010 Forst, T. 2014 "Koxosc, C. S. 2015 Matthael, S. 2015 Matthael, S. 2015 Matthael, S. 2015 Matthael, S. 2015 Matthael, S. 2015 Test for overall effect	Mean         S           3.3         1           7.2         1           2.3         1           1.2.3         1           1.1.2         1           1.1.35, df =         2           2.4.4         1           8.9         1           0         1           4.4         1           0.1         1           4.5         1           10.6         1           -2.54, df =         -2.54, df =	D Total 5 126 4 107 9 165 9 192 590 3 (P = 0.1 P = 0.000 6 121 5 109 9 168 5 108 9 195 701 4 (P = 0.6	0. 2. -1. 4 (2),   <sup>4</sup> = 2) 0. 2. -1. 4. (4),   <sup>4</sup> =	n SD 4 15 4 14 5 19 5 19 6 0% 4 15 4 14 6 19 0 15 5 19	61 52 85 280 62 53 83 108 85 391	Weight 11.5% 11.3% 9.6% 10.3% 42.8% 11.0% 9.7% 11.0% 9.7% 15.2% 10.4% 57.2%	Mean Difference N, Fixed, 95% C 2.30 [-1.60, 7.49 4.80 [0.16, 9.44 3.80 [-1.23, 833 4.70 [1.80, 11.55 4.52 [2.14, 6.90 4.00 [-0.70, 8.70 6.50 [1.80, 11.20 1.50 [-3.50, 6.50 4.50 [1.50, 1.50, 6.50 4.57 [2.51, 6.63]	11 19 19 19 19 19 19 19 19 19 19 19 19				5.1.1 how does Bailey, C. J.2010 Forst, T.2014 Kovars, C. S.2015 Bienlof, K.2013 Subtoal, (295, CI) Heterograndi, Chi <sup>m</sup> Test for overall affec 5.1.2 high dose "Bailey, C. J.2010 "Forst, T.2014 "Kovars, C. S.2015 "Matthesi, S.2015 "Matthesi, S.2013 Subtoal, (295). CI Heterograndi, Chi <sup>m</sup> Test for overall effec	Mean 5 3.1 : 7.1 : 2.6 : 2.9 : = 1.81, df = t Z = 1.32 () 9.5 : 11.3 : -1.5 : 5.8 : 7.1 : = 7.72, df =	D         Total           25         126           26         107           30         165           25         192           590         3 (P = 0.8           26         120           26         120           26         120           26         120           26         129           26         129           27         108           29         108           29         108           29         108           25         195           700         4 (P = 0.1           P = 0.000         100	Mean 3.5 -0.4 0 1 51); I*= 09 -0.4 0 -6.3 1 10); I*= 48 (2)	SD Total 25 60 27 52 28 82 26 85 279 6 25 61 27 53 28 93 28 93 29 108 26 85 390 %	8.1% 11.0% 14.8% 44.7% 10.4% 8.3% 11.2% 10.6% 14.8% 55.3%	Mean Difference M. Fixed, 95% CI -0.40 [-809, 7.29] 7.50 [-1.34, 16.34] 2.60 [-4.99, 10.19] 1.30 [-4.60, 8.46] 2.54 [-1.23, 6.31] 11.70 [2.94, 20.46] 1.50 [-0.4, 6.34] 1.210 [4.37, 19.83] 6.10 [-0.45, 19.83] 6.54 [3.15, 9.93]			
1.110w dose Bailey, C. J2010 Forst, T.2014 Koraca, C. S.2015 Steniot, K.2013 Subtotal (95% CI) Bailey, C. J2010 Forst, T.2014 Kooxec, C. S.2015 Matthael, S.2015 Steniot, K.2013 Subtotal (95% CI)	Mean         S           3.3         1           7.2         1           2.3         1           1.2         1           1.1.2         1           1.1.2         1           1.1.2         1           1.1.2         1           2.3         7.2           4.4         1           8.9         1           0         1           4.5         1           1.0.6         1           2.54.df=         2           2.4.35 (f)         2	D Total 5 126 4 107 9 165 9 192 590 3 (P = 0.1 2 = 0.000 6 121 5 109 9 168 5 108 9 195 701 4 (P = 0.6 2 < 0.000 1291	0. 2. -1. 4. (2),  *= 2) 0. 2. -1. 4. (4),  *=	n SD 4 15 4 14 5 19 5 19 6 0% 4 15 4 15 4 14 5 19 6 0% 6 19 0 15 5 19 6 0%	61 52 85 280 62 53 83 108 85 391	Weight 11.5% 11.3% 9.6% 10.3% 42.8% 11.0% 9.7% 11.0% 9.7% 15.2% 10.4% 57.2%	Mean Difference M. Food, 95% C 2:00[+69,749 4:00[n16,944 3:00[+1:23,8:83 6:70[1:85,11:55 4:52[2:14,6:90 4:00[+0:70,8:70 6:50[180,11:20 1:50[+3:50,6:50 4:50]50,8:50 6:10[1:2,10,4]					5.11 how does Bailey, C. 32010 Forst, 7.2014 (worars, C. S.2015 Blenich (X.2013 Subtotal (95% CI) Heiterogeneity, C.In Fast for overail effec 5.12 high dose "Bailey, C. J.2010 Heiterogeneity, C.II Subtotal (95% CI) Heiterogeneity, C.II Teat for overail effec Total (95% CI)	Mean         5           31         .7           7.1         .2.6           2.9            =1.81, df=            t Z=1.32 ()            9.5            11.3            -1.5            5.8         .7           7.1            = 7.72, df=         t Z= 3.76 ()	D         Total           25         126           26         107           30         165           25         192           55         192           30         167           26         120           26         120           26         120           26         109           30         168           29         108           25         195           700         4 (P = 0.1           P = 0.000         1290	Mean 3.5 -0.4 0 1 51); I*= 0* -0.4 0, -6.3 1 0); I*= 48 (2)	SD         Total           25         60           27         52           28         82           26         85           279         6           25         61           27         53           28         83           29         108           26         85           390         %           669         669	8.1% 11.0% 14.8% 44.7% 10.4% 8.3% 11.2% 10.6% 14.8%	Mean Difference M. Fixed, 95% CI -0.40 (+0.09, 7.29) 7.50 (+1.34, 16.34) 2.60 (+4.99, 10.19) 1.90 (+4.66, 8.46) 2.54 (-1.23, 6.31) 6.00 (+1.81, 13.811) 1.170 (2.94, 20.46) 1.50 (+0.04, 5.12.65) 6.10 (-0.45, 12.65)	+	M. Fixed. 3	ss a
1.1 I low dose anley, C. J 2010 ords, T. 2014 (owars, C. S. 2015 beniof, K. 2013 untotati (95% CD telerogeneity, Chr <sup>a</sup> - est for overall effect 1.1.2 high dose Bailey, C. J 2010 Forst, T. 2014 Kovars, C. S. 2015 Matthael, S. 2015 Steniof, K. 2013 subtotati (95% CD deterogeneity, Chr <sup>a</sup> - fest for overall effect otal (95% CD)	Mean         S           3.3         1           7.2         1           2.3         1           1.1.2         1           \$\$1.35, df=         2           \$\$2.372 (f)         44           \$\$4.9         1           \$\$0.1         4.5           \$\$1.06         1           \$\$2.54, df=         2           \$\$2.54, df=         2           \$\$2.54, df=         3.89, df=	D Total 5 126 4 107 9 165 9 192 590 3 (P = 0.1 2 = 0.000 6 121 5 108 9 195 701 4 (P = 0.6 2 < 0.000 1291 8 (P = 0.3 2 < 0.000 1291 8 (P = 0.3 2 < 0.000 1291 14 (P = 0.6 2 < 0.000 19 10 19 10 10	0. 2. -1. 4. (2),  *= 2) 0. 2. -1. 4. (4),  *= (1) (7),  *=	n SD 4 15 4 14 5 19 5 19 6 0% 4 15 4 15 4 14 5 19 6 0% 6 19 0 15 5 19 6 0%	61 52 85 280 62 53 83 108 85 391	Weight 11.5% 11.3% 9.6% 10.3% 42.8% 11.0% 9.7% 11.0% 9.7% 15.2% 10.4% 57.2%	Mean Difference N, Fixed, 95% C 2.30 [-1.60, 7.49 4.80 [0.16, 9.44 3.80 [-1.23, 833 4.70 [1.80, 11.55 4.52 [2.14, 6.90 4.00 [-0.70, 8.70 6.50 [1.80, 11.20 1.50 [-3.50, 6.50 4.50 [1.50, 1.50, 6.50 4.57 [2.51, 6.63]	11 19 19 19 19 19 19 19 19 19 19 19 19			10	5.1.1 how does Bailey, C. J.2010 Ford, T.2014 Kovars, C. S.2015 Subtoda, (K.2013 Subtoda, (K.2013 Helerogeneit), Chi <sup>m</sup> Test for overall effec 5.1.2 high dose 5.1.2 high dose Tabley, C. J.2010 Ford, T.2014 Wowas, C. S.2015 Matthesi, S.2015 Matt	Mean 5 31 7,1 2,6 2,9 = 1,81, df = t Z = 1,32 () 95 11,3 -1,5 5,8 7,1 = 7,72, df = t Z = 3,78 () = 1,92, df =	D         Total           25         126           26         107           28         107           20         167           25         192           50         3 (P = 0.8           P = 0.19)         26           26         120           26         120           26         109           20         168           25         195           7000         4 (P = 0.1           P = 0.000         1290           2 8 (P = 0         29	Mean 3.5 -0.4 0 1 3.5 -0.4 51); I*= 0 3.5 -0.4 0 -6.3 1 10); I*= 48 (2) 15); I*= 3 10 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -7.5 -6.3 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5 -7.5	SD         Total           25         60           27         52           28         82           26         85           279         6           25         61           27         53           28         83           29         108           26         85           390         %           669         669	8.1% 11.0% 14.8% 44.7% 10.4% 8.3% 11.2% 10.6% 14.8% 55.3%	Mean Difference M. Fixed, 95% CI -0.40 [-809, 7.29] 7.50 [-1.34, 16.34] 2.60 [-4.99, 10.19] 1.30 [-4.60, 8.46] 2.54 [-1.23, 6.31] 11.70 [2.94, 20.46] 1.50 [-0.4, 6.34] 1.210 [4.37, 19.83] 6.10 [-0.45, 19.83] 6.54 [3.15, 9.93]	-20	M. Fixed. 3	Sh G
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Figure 3. Forest plot comparing lipid metabolism between the SGLT inhibitor and placebo groups.

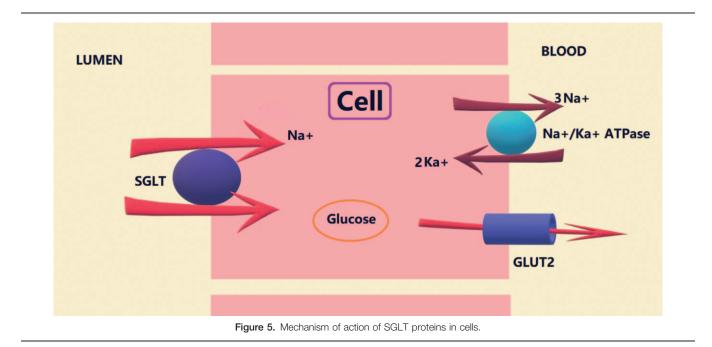
	5	SGLT			PLA			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
1.1.1 low dose									
Bailey, C. J.2010	-5.1	16	122	-3.1	13	60	23.6%	-2.00 [-6.35, 2.35]	
Forst, T.2014	-3.1	26.6	95	1.9	32.4	39	3.4%	-5.00 [-16.49, 6.49]	• • • • • • • • • • • • • • • • • • • •
Stenlof, K.2013	-3.3	8	195	0.04	11	96	73.0%	-3.34 [-5.81, -0.87]	
Subtotal (95% CI)			412			195	100.0%	-3.08 [-5.19, -0.97]	<b>•</b>
Heterogeneity: Chi <sup>2</sup> =	0.39, df	= 2 (P	= 0.82	); I <sup>2</sup> = 09	6				
Test for overall effect:	Z = 2.88	6 (P = 0	0.004)						
1.1.2 high dose									
*Bailey, C. J.2010	-6	11	122	-3.1	13	60	29.5%	-2.90 [-6.72, 0.92]	
*Forst, T.2014	-7	27.9	87	1.9	32.4	39	3.1%	-8.90 [-20.64, 2.84]	+
*Stenlof, K.2013	-4	9	197	0.04	11	96	67.3%	-4.04 [-6.57, -1.51]	
Subtotal (95% CI)			406			195	100.0%	-3.86 [-5.93, -1.78]	•
Heterogeneity: Chi <sup>2</sup> =	0.97, df	= 2 (P	= 0.62	);  2 = 09	6				
Test for overall effect:	Z= 3.63	B (P = 0	0.0003)	)					
									St. 10 10 10 10 10 10 10 10 10 10 10 10 10
									-10 -5 0 5 10
									Favours SGLT Favours PLA
									Favours SOLT Favours FLA

Figure 4. Forest plot comparing the ALT levels between the SGLT inhibitor and placebo groups.

erosclerosis and reduce the risk of cardiovascular and cerebrovascular events.<sup>[60]</sup> The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) study results were presented at the 66th Annual Meeting of the American College of Cardiology. The study included 300,000 patients with T2DM. Compared with other hypoglycemia drugs, SGLT-2 inhibitors reduced all-cause mortality by 51% and heart failure in-hospital mortality by 39%. The mechanism underlying the protective effect of SGLT inhibitors is currently unclear. In addition to improving lipid metabolism, they may also have beneficial effects on myocardial fibers by activating the Stat3 signaling pathway<sup>[61]</sup> or by inhibiting the exchange of Na+/H+ in cardiomyocytes, reducing the concentration of cytoplasmic Na+ and Ca2+, and increasing the concentration of mitochondrial Ca2+, thereby exerting a protective effect on the myocardium.<sup>[62]</sup> It is not clear whether the SGLT-2 protein is expressed in the heart.

The limitations of this network meta-analysis are as follows:

- 1. The laboratory examination data related to lipid metabolism were limited, making it impossible to conduct a network metaanalysis for all the outcome. A common meta-analysis was performed instead.
- 2. The results of laboratory tests for triglycerides and cholesterol are highly dynamic, which could have interfered with the results.
- 3. Different types of SGLT inhibitors might have different effects on the levels of triglyceride, cholesterol and ALT.



#### 5. Conclusions

SGLT inhibitors can induce weight loss in patients with T2DM and improve lipid metabolism. Therefore, diabetic patients with uncontrolled weight should consider taking SGLT inhibitors. In addition, they are safe in patients with mild to moderate liver dysfunction.

#### **Author contributions**

Conceptualization: Mao-bing Chen, Wei-yan Cui, Qi-han Zheng.

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Methodology: Wei-yan Cui, Qi-han Zheng.

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Writing – review & editing: Mao-bing Chen, Hua Wang.

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