RESEARCH ARTICLE

Clinical relevance between sodium-glucose co-transporter 2 inhibitors and lipid profiles in Asian patients with type 2 diabetes mellitus: a systematic review with a metaanalysis of randomized controlled trials

Junichi Mukai^{*}, Ayano Yoshiyama and Rie Kubota

Abstract

Background: Few systematic reviews have examined the effects of sodium-glucose co-transporter 2 inhibitors (SGLT2is) on lipid profiles in Asian patients with type 2 diabetes mellitus. We conducted a systematic review with a meta-analysis to summarize the available literature and confirm the effects of SGLT2 is on lipid profiles in these patients.

Methods: We searched the electronic databases MEDLINE, CENTRAL, and Ichushi-web for studies from the dates of their earliest publication to July 2018, and there was no language restriction. Trials were included if they were randomized controlled trials (RCTs) (1) comparing the effects of SGLT2 is with a placebo in Asian patients with type 2 diabetes mellitus (18 years or older), and (2) reporting HbA1c and at least one lipid parameter, such as triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), or low-density lipoprotein cholesterol (LDL-C). The weighted mean difference with a 95% confidence interval (CI) was calculated using a random-effects model.

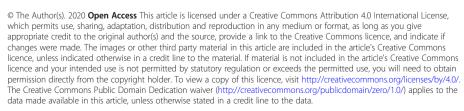
Results: Among the 630 studies retrieved, 17 RCTs that included 4485 patients were ultimately included in our review. Fourteen RCTs were conducted in Japan. The durations of RCTs ranged between 12 and 24 weeks. SGLT2is significantly improved HbA1c [mean difference – 0.80 (95%CI – 0.96 to – 0.64)%, p < 0.00001], TG [mean difference – 16.42 (95%CI – 22.71 to -10.12) mg/dL, p < 0.00001], and HDL-C [mean difference 3.36 (95%Cl 2.73 to 3.98) mg/dL, p < 0.00001], but significantly deteriorated LDL-C [mean difference 3.00 (95%Cl 1.18 to 4.82) mg/dL, p < 0.001]. The LDL-C/HDL-C ratio was not significantly different between SGLT2is and a placebo [mean difference – 0.01 (95%CI – 0.08 to 0.06), p < 0.74].

(Continued on next page)

* Correspondence: mukai11@kitasato-u.ac.jp

BMC

Division of Clinical Pharmacy (Laboratory of Clinical Pharmacy Education) and Research and Education Center for Clinical Pharmacy, School of Pharmacy, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan



Mukai et al. Journal of Pharmaceutical Health Care and Sciences (2020) 6:4 https://doi.org/10.1186/s40780-020-00160-0

Open Access





(Continued from previous page)

Conclusion: The present results suggest that in Asian patients with type 2 diabetes mellitus, TG and HDL-C values were better, while LDL-C values were worse with SGLT2is than with a placebo. However, the negative impact of SGLT2is on lipid profiles was modest. Further RCTs with a longer duration or conducted in other Asian countries are needed to provide further evidence to support the clinical relevance of changes in lipid profiles. The present results will be informative for SGLT2is users with concerns regarding the effects of SGLT2is on lipid profiles.

Keywords: Meta-analysis, Systematic review, Sodium-glucose co-transporter 2 inhibitors, Lipid profiles, Asian descent, Type 2 diabetes mellitus

Background

Sodium-glucose co-transporter 2 inhibitors (SGLT2is) are a new class of oral hypoglycemic agents that exert effects on glycemic control and weight loss [1]. The EMPA-REG OUTCOME study [2], which included patients with type 2 diabetes mellitus at a high risk of cardiovascular events, recently demonstrated that empagliflozin lowered the risk of death from cardiovascular events. The CANVAS program also showed that patients treated with canagliflozin had a lower risk of cardiovascular events [3]. As elevated levels of low-density lipoprotein cholesterol (LDL-C) are a well-established risk factor for cardiovascular disease [4, 5], and SGLT2is may reduce these levels. However, there are two conflicting studies on the effects of SGLT2is. The American Diabetes Association guidelines reported that SGLT2is had a negative impact on LDL-C [6], while an RCT conducted in Japan showed the opposite effects [7]. Racial differences generally exist between Asians and non-Asians. For example, Asians are more likely to have a lower body mass index than those of European descent [8]. They also have a higher percent body fat than Caucasians with the same body mass index [9]. Regarding lipid profiles, a recent study by Zhang and colleagues [10] indicated that the effects of metformin on high-density lipoprotein cholesterol (HDL-C) varied between ethnic groups. Based on these findings, we hypothesized that the effects of SGLT2is on lipid profiles differed between Asian patients and those of European descent.

To the best of our knowledge, few systematic reviews have examined the effects of SGLT2is on lipid profiles in Asian patients with type 2 diabetes mellitus. A systematic review by Cai and colleagues [11] investigated the effects of SGLT2is in these patients; however, the findings obtained need to be interpreted with caution because the term "Asian patients" used in their metaanalysis indicates that there are 50% or more Asian patients in each RCT selected. We herein conducted a systematic review with a meta-analysis to summarize the available literature and evaluate the clinical relevance between SGLT2is and lipid profiles in Asian patients with type 2 diabetes mellitus.

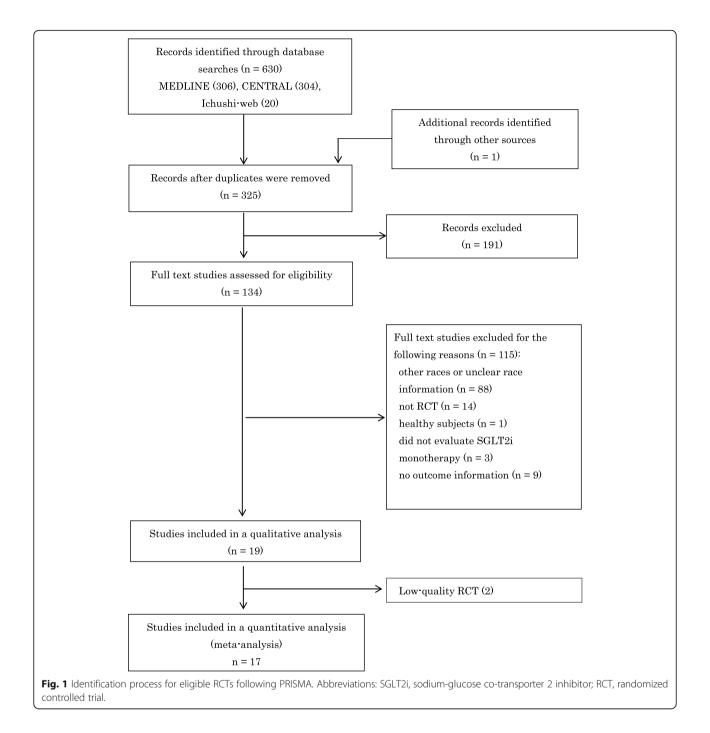
Methods

Searching strategies to identify randomized controlled trials (RCTs)

We searched the electronic databases MEDLINE, The Cochrane Central Register of Controlled Trials (CEN-TRAL), and Japana Centra Revuo Medicina (Ichushi-web) for studies from the dates of their earliest publication to July 2018. We included nine types of SGLT2is: canagliflo-(CANA), dapagliflozin (DAPA), empagliflozin zin (EMPA), ertugliflozin, ipragliflozin (IPRA), luseogliflozin (LUSEO), remogliflozin, sergliflozin, and tofogliflozin (TOFO). We used individual SGLT2i names, alternative names, "sodium-glucose transporter 2", and "SGLT2 inhibitors" as search terms. We restricted our search to "randomized controlled trial" in these electronic databases. A reference search was also implemented from relevant studies in order to identify more RCTs. We did not impose any language restriction. Trials were included if they were RCTs (1) comparing the effects of SGLT2 is with a placebo in Asian patients with type 2 diabetes mellitus (18 years or older), and (2) reporting HbA1c and at least one lipid parameter, such as triglycerides (TG), HDL-C, or LDL-C. We excluded cross-over trials and RCTs involving healthy subjects. The study search was undertaken independently by two authors (AY and JM). Any discrepancies were settled by discussions between the two assessors. We extracted data on the trial country, trial design, comorbidities, co-interventions, daily dose of each SGLT2i, duration of the intervention, and lipid profiles: TG, HDL-C, and LDL-C, at baseline. Lipid profiles were set as the primary endpoint and the LDL-C/HDL-C ratio as the secondary endpoint. In order to convert mmol/L of TG, HDL-C, and LDL-C to mg/dL, we multiplied mmol/L by 88.6, 38.7, and 38.7 respectively. Our systematic review with a metaanalysis did not require Ethics Committee approval.

Quality assessment of each RCT

Study quality was quantified by both the Jadad scale and risk of bias tool. The Jadad scale is used to evaluate the appropriateness of the randomization technique, the method used for double-masking, and descriptions of dropouts or withdrawals [12]. The scale ranges between zero and five. We included studies that scored 4 points



or higher in the analysis. The risk of bias for the studies was assessed based on the Cochrane Handbook [13]. Seven items were examined for the risk of bias: random sequence generation, allocation concealment, the blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, free of selective reporting, and a baseline imbalance for lipid parameters as other sources of bias. Each of the seven items was scored as a "low risk", "unclear risk", or "high risk".

Statistical analysis

We calculated the weighted mean difference with a 95% confidence interval (CI) for each outcome. The heterogeneity of each outcome was evaluated using chisquared and I^2 statistics. A value of 50% or more was defined to represent marked heterogeneity based on the Cochrane handbook [13]. We used a random-effects model (the DerSimonian and Laird method [14]) to assess outcomes more conservatively. In the meta-analysis, multiple SGLT2i groups in a single trial were combined

Author	Country	Comorbid, co-intervention	Doses [mg/day], (n)	Duration (weeks)	HbA1c at baseline (%)	TG at baseline (mg/dL)	HDL-C at baseline (mg/ dL)	LDL-C at baseline (mg/dL)	Jadad Scale
Ji 2014 [<mark>16</mark>]	China, Korea, Taiwan India	Diet and exercise	DAPA: 5 (128), 10 (133), P: (132)	24	DAPA: 8.1, 8.3, P: 8.4	NR	NR	NR	5
Kadowaki 2014 [17]	Japan	Diet and exercise	EMPA: 5 (110), 10 (109), 25 (109), 50 (110), P: (109)	12	EMPA: 7.9, 7.9, 7.9, 8.0, P: 7.9	EMPA:148.8, 128.5, 146.2, 148.8, P: 144.4	EMPA: 55.3, 58.8 57.7, 57.7, P: 57.3	EMPA: 127.3, 125.0, 125.0, 123.8, P: 124.2	4
Kashiwagi 2015A [18]	Japan	Renal impairment, diet/exercise, or using an OHA	IPRA: 50 (118), P: (46)	24	IPRA: 7.5, P: 7.5	IPRA: 137.6, P: 123.4	IPRA: 57.0, P: 56.4	IPRA: 114.3, P: 112.4	5
Lu 2016 [19]	Korea, Taiwan	Diet, exercise, and metformin	IPRA: 50 (87), P: (83)	24	IPRA: 7.7, P: 7.8	NR	NR	NR	5
Kashiwagi 2015B [<mark>20</mark>]	Japan	Diet and metformin	IPRA: (112), P: (56)	24	IPRA: 8.3, P: 8.4	IPRA: 165.4, P: 129.3	IPRA: 53.6, P: 57.4,	IPRA: 108.0, P: 113.6	4
Kashiwagi 2015C [21]	Japan	Sulfonylurea	IPRA: 50 (165), P (75)	24	IPRA: 8.4, P: 8.3	IPRA: 159.6, P: 151.3	IPRA: 57.6, P: 58.4	IPRA: 124.2, P: 120.4	5
Kashiwagi 2015D [22]	Japan	Pioglitazone	IPRA: 50 (97), P: (54)	24	IPRA: 8.2, P: 8.4	IPRA: 142.9, P: 135.2	IPRA: 61.1, P: 61.3	IPRA: 116.7, P: 130.4	5
Kashiwagi 2015E [23]	Japan	Diet and exercise	IPRA: 50 (62), P: (67)	16	IPRA: 8.4, P: 8.3	IPRA: 159.4, P: 148.1	IPRA:56.0, P: 52.1	IPRA: 124.4, P: 127.1	5
Haneda 2016 [24]	Japan	Renal impairment, Diet/exercise or using 1–2 OHAs	LUSEO: 2.5–5.0 (95), P: (50)	24	LUSEO: 7.7, P: 7.7	LUSEO: 147.7, P: 148.1	LUSEO:57.7, P: 52.9	LUSEO: 115.1, P: 119.3	4
Seino 2014A [<mark>25</mark>]	Japan	Diet	LUSEO: 2.5 (79), P: (79)	24	LUSEO: 8.1, P: 8.2	LUSEO: 149.5, P: 141.5	LUSEO: 58. 0, P: 60.2	LUSEO: 131.0, P: 127.8	5
Seino 2014B [<mark>26]</mark>	Japan	Diet	LUSEO: 1.0 (55), 2.5 (56), 5 (54), 10 (58), P: (57)	12	LUSEO: 7.8, 8.1, 7.9, 8.0, P: 7.9	LUSEO: 156.1, 167.6, 136.2, 124.7, P:165.7	LUSEO: 56.7, 53.6, 54.2, 58.7, P: 55.0	LUSEO: 126.1, 128.8, 115.4, 121.4, P: 117.9	5
Seino 2014C [27]	Japan	Diet	LUSEO: 0.5 (60), 2.5 (61), 5 (61), P: (54)	12	LUSEO: 8.2, 8.1, 8.2, P: 7.9	LUSEO: 173.7, 150.2, 160.4, P:170.0	NR	NR	5
Inagaki 2016 [<mark>28</mark>]	Japan	Diet, exercise, and insulin	CANA: 100 (76), P: (70)	16	CANA: 8.9, P: 8.9	CANA: 124.5, P: 144.0	CANA: 61.9, P: 57.6	CANA: 122.4, P: 121.9	5
Ji 2015 [<mark>29</mark>]	China, Malaysia, Vietnam	Metformin alone or metformin plus sulfonylurea	CANA: 100 (223), 300 (227), P (226)	18	CANA: 8.0, 8.0, P: 7.9	CANA: 163.7, 180.8, P: 169.1	CANA: 51.0, 48.8, P: 49.1	CANA: 104.3, 100.8, P: 98.3	4
Inagaki 2014 [<mark>30</mark>]	Japan	Diet and exercise	CANA: 100 (90), 200 (88), P: (93)	24	CANA: 8.0, 8.0, P: 8.0	CANA: 150.9, 148.9, P: 158.1	CANA: 54.9, 55.3, P: 55.8	CANA: 127.3, 120.1, P: 124.8	5
Inagaki 2013 [<mark>3</mark> 1]	Japan	Diet and exercise	CANA: 50 (82), 100 (74), 200 (76), 300 (75), P: (75)	12	CANA: 8.1, 8.1, 8.1, 8.2, P: 8.0	NR	NR	NR	5
Kaku	Japan	Diet and	TOFO: 10 (57), 20	24	TOFO:	NR	NR	NR	5

 Table 1
 Characteristics of 17 randomized, double-blind, controlled trials included in the meta-analysis

Author	Country	Comorbid, co-intervention	Doses [mg/day], (n)	Duration (weeks)		TG at baseline (mg/dL)	HDL-C at baseline (mg/ dL)	LDL-C at baseline (mg/dL)	Jadad Scale
2014 [32]		exercise	(58), 40 (58), P: (56)		8.5, 8.3, 8.4, P: 8.4				

Table 1 Characteristics of 17 randomized, double-blind, controlled trials included in the meta-analysis (Continued)

CANA canagliflozin, DAPA dapagliflozin, EMPA empagliflozin, IPRA ipragliflozin, LUSEO luseogliflozin, TOFO tofogliflozin, OHA oral hypoglycemic agent, P placebo, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TG triglycerides, NR not reported

into a single group [13]. Subgroup analyses were performed by including only Japanese patients and only patients who were treated with SGLT2 is as monotherapy. We used Egger's regression test [15] to assess publication bias more precisely when there were 10 RCTs or more in the meta-analysis [13]. All statistical analyses were performed with SPSS version 23.0 (SPSS Japan Inc., Tokyo, JAPAN) and review manager 5.3 software (Cochrane Collaboration, Oxford, UK). A P value less than 0.05 was considered to be significant.

Results

We identified 630 studies in the database search. One hundred and thirty-four full texts were retrieved after screening titles and abstracts. Seventeen RCTs that include 4485 patients were ultimately included in our review. Figure 1 shows the identification process for eligible RCTs [16–32] following PRISMA [33]. Table 1 shows the characteristics of RCTs included in the meta-analysis. All trials were published in English. Six types of SGLT2is (CANA, DAPA, EMPA, IPRA, LUSEO, and TOFO) were collected.

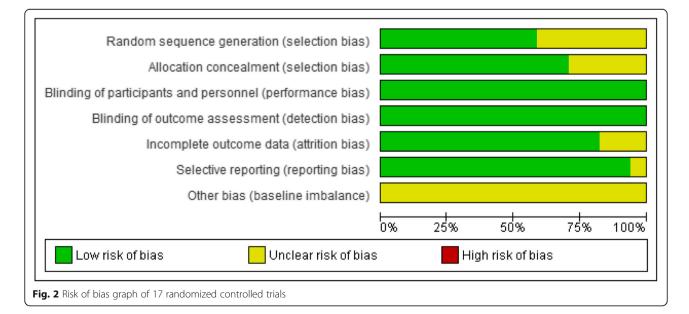
Fourteen studies were conducted in Japan. The durations of RCTs ranged between 12 and 24 weeks.

Quality assessment of each RCT

The Jadad scale of the studies ranged between 4 and 5 points (Table 1). We also assessed the risk of bias of RCTs based on the Cochrane handbook [13]. Most studies were high-quality RCTs. "Low risk" was the highest in the domains of blinding of participants and personnel and blinding of outcome assessments. "Unclear risk" was the highest in the domain of baseline imbalance. "High risk" was not scored in all domains (Fig. 2). Egger's regression test showed no significant results in all primary results.

Relationship between SGLT2is and changes in HbA1

Fifteen trials were included in the meta-analysis. Statistical heterogeneity was observed among trials (I² = 89%). HbA1c values were significantly better with SGLT2is than with a placebo [mean difference – 0.80 (95%CI – 0.96 to – 0.64) %, p < 0.00001], and all types of SGLT2is showed a significant result in the sub-group analysis. The IPRA



Study or Subgroup	S Mean	GLT2is	Total	P Mean	lacebo	Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
1.1.1 DAPA	Mean	30	Total	mean	30	Total	Weight	14, Nandolli, 55% Cl	IV, Nandolli, 55% Cl
Ji2014	-1.0757	0 7067	261	-0.29	0.79	132	7.0%	-0.79 [-0.95, -0.62]	+
Subtotal (95% CI)	-1.07.57	0.7037	261	-0.23	0.73	132	7.0%	-0.79 [-0.95, -0.62]	▲
Heterogeneity: Not ap	nlicable		201			102	110.10	0110[0100,0102]	•
Test for overall effect:		P < 0.000	01)						
1.1.2 CANA									
nagaki2014	-0.7499	0.6586	178	0.29	0.68	93	7.0%	-1.04 [-1.21, -0.87]	-
nagaki2016 Subtotal (95% CI)	-0.97	0.6974	76 254	0.13	0.6693	70 163	6.6% 13.5%	-1.10 [-1.32, -0.88] - 1.06 [-1.20, -0.93]	•
Heterogeneity: Tau² = Test for overall effect:				P = 0.67)	² = 0%				
I.1.3 IPRA									
<ashiwagi2015a< td=""><td>-0.42</td><td>0.51</td><td>118</td><td>-0.17</td><td>0.52</td><td>46</td><td>6.9%</td><td>-0.25 [-0.43, -0.07]</td><td></td></ashiwagi2015a<>	-0.42	0.51	118	-0.17	0.52	46	6.9%	-0.25 [-0.43, -0.07]	
Kashiwagi2015B	-0.87	0.655	112	0.38	0.703	56	6.6%	-1.25 [-1.47, -1.03]	
Kashiwagi2015C	-0.83	0.72	165	0.32	0.96	75	6.4%	-1.15 [-1.39, -0.91]	
<ashiwagi2015d< td=""><td>-0.64</td><td>0.61</td><td>97</td><td>0.22</td><td>0.81</td><td>54</td><td>6.4%</td><td>-0.86 [-1.11, -0.61]</td><td></td></ashiwagi2015d<>	-0.64	0.61	97	0.22	0.81	54	6.4%	-0.86 [-1.11, -0.61]	
<ashiwagi2015e< td=""><td>-0.76</td><td>0.7</td><td>62</td><td>0.54</td><td>1</td><td>67</td><td>6.0%</td><td>-1.30 [-1.60, -1.00]</td><td></td></ashiwagi2015e<>	-0.76	0.7	62	0.54	1	67	6.0%	-1.30 [-1.60, -1.00]	
.u2016 Subtotal (95% CI)	-0.94	0.75	87 641	-0.47	0.81	83 381	6.5% 38.7%	-0.47 [-0.70, -0.24] -0.87 [-1.25, -0.50]	•
Heterogeneity: Tau² = Fest for overall effect:				(P < 0.00	1001); I² =	94%			
1.1.4 LUSEO									
Haneda2016	-0.11	0.5	95	0.09	0.72	50	6.6%	-0.20 [-0.42, 0.02]	
Seino2014A	-0.63	0.75	79	0.13	0.75	79	6.5%	-0.76 [-0.99, -0.53]	
Seino2014B	-0.3927		223	0.22	0.46	57	7.2%	-0.61 [-0.75, -0.48]	-
Seino2014C	-0.5779		182	0.06	0.56	54	6.9%	-0.64 [-0.81, -0.46]	-
Subtotal (95% CI)	-0.5773	0.0140	579	0.00	0.50	240	27.2%	-0.56 [-0.76, -0.36]	•
Heterogeneity: Tau ² = Fest for overall effect:				(P = 0.00	13); I ^z = 79				
1.1.5 EMPA									
Kadowaki2014	-0.52	0.9433	438	0.3	0.94	109	6.8%	-0.82 [-1.02, -0.62]	
Subtotal (95% CI)			438			109	6.8%	-0.82 [-1.02, -0.62]	◆
Heterogeneity: Not ap Fest for overall effect:		P < 0.000	01)						
.1.6 TOFO									
<aku2014< td=""><td>-0.8952</td><td>0.6294</td><td></td><td>-0.028</td><td>0.63</td><td>56</td><td>6.8%</td><td>-0.87 [-1.06, -0.68]</td><td>÷ </td></aku2014<>	-0.8952	0.6294		-0.028	0.63	56	6.8%	-0.87 [-1.06, -0.68]	÷
Subtotal (95% CI)			173			56	6.8%	-0.87 [-1.06, -0.68]	▼
Heterogeneity: Not ap Test for overall effect:		P ≺ 0.000	01)						
fotal (95% CI)			2346			1081	100.0%	-0.80 [-0.96, -0.64]	•
Heterogeneity: Tau² = Test for overall effect: Test for subgroup diff	Z= 9.94 (P ≺ 0.000	01)	,	,,			_	-2 -1 0 1 2 Favors SGLT2is Favors Placebo
3. Relationship be	tween SC	GLT2is an	d char	iges in l	HbA1c. A	bbrev	iations: C		PA, dapagliflozin; EMPA, empagliflozin; IPRA tor; CI, confidence interval; SD,

standard deviation.

group had the highest weight (38.7%), whereas the EMPA and TOFO groups had the lowest weight (6.8% each) (Fig. 3).

Relationship between SGLT2is and changes in TG

Fifteen trials were included in the meta-analysis. Statistical homogeneity was observed among trials (I² = 4%). TG values were significantly better with SGLT2is than with a placebo [mean difference – 16.42 (95%CI – 22.71 to – 10.12) mg/dL, p < 0.00001], and the three types of SGLT2is examined

(IPRA, LUSEO, and EMPA) showed a significant result in the sub-group analysis. The IPRA group had the greatest weight (37.6%), whereas the TOFO group had the lowest weight (1.3%) (Fig. 4).

Relationship between SGLT2is and changes in HDL-C

Fourteen trials were included in the meta-analysis. Statistical homogeneity was observed among trials ($I^2 = 0\%$). HDL-C values were significantly better with SGLT2is than with a placebo [mean difference 3.36 (95%CI 2.73 to 3.98) mg/dL, p < 0.00001], and

Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI 2.1.1 CANA Inagaki2013 -14.6081 54.7395 307 -1.5 55.43 75 18.2% -13.11 [-27.07, 0.85] Inagaki2016 -7.8 64.512 76 -4 64.423 70 8.6% -3.01 [-27.17, 2.86] Subtotal (95% CI) 833 371 30.0% -13.50 [-27.15, 0.16] - Peterogeneity: Tau ²⁺ 38.51; Ch ²⁺ 2.64, df = 2 (P = 0.27); P = 24% Test for overall effect Z = 1.94 (P = 0.05) - - 46.44 69.5% 0.70 [-19.14, 20.54] - Kashiwaqj20156 -11.4 61.72 118 -12.1 47.65 56 7.6% -12.016.30.2, 4.30] - Kashiwaqj20156 -13.8 90.45 165 8.7 90.66 75 6.2% -27.30 [-52.03, -2.57] - Kashiwaqj20156 -12.3 12.44 62 -4.8 64.2 67 3.3% -7.50 [-42.07, 2.07] <
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
J [20] f 5 - 15.7062 215.769 450 21.7 217.98 226 3.2% -37.41 [-72.12, -2.69] Subtotal (95% CI) 833 371 30.0% -13.50 [-27.15, 0.16] Heterogeneity: Tau"= 38.51; Ch"= 2.64, df = 2 (P = 0.27); P = 24% Test for overall effect: Z = 1.94 (P = 0.05) 2.1.2 IPRA Kashiwagi2015A -11.4 61.72 118 -12.1 56.84 46 9.5% 0.70 [-19.14, 20.54] Kashiwagi2015B -30 99.9 112 -12 47.56 56 7.6% -18.00 [-40.30, 4.30] Kashiwagi2015D -23.6 88.4 97 7.6 77.37 54 52% -27.30 [-52.03, -2.57] Kashiwagi2015E -12.3 124.4 62 -4.8 64.2 67 3.3% -7.50 [-42.07, 27.07] Lu2016 -24.6 91.9 87 10.7 79.6 83 5.7% -35.06 [-11, -9.48] Subtotal (95% CI) 641 381 37.6% -18.97 [-30.99, -6.96] Heterogeneity: Tau"= 62.68; Ch"= 6.94, df= 5 (P = 0.23); P = 28% Test for overall effect: Z = 3.09 (P = 0.002) 2.1.3 LUSEO Haneda2016 -12.1 64.65 95 -11.3 57.72 50 8.8% -0.80 [-21.41, 19.81] Seino2014B -2.1.139 115.1813 223 -0.1 114.21 57 3.5% -21.04 [-64.32, 12.24] Seino2014B -2.1.139 115.1813 223 -0.1 114.21 57 7.55 -27.57 [-56.09, 0.95] Subtotal (95% CI) 579 240 24.2% -13.56 [-26.11, -1.01] Heterogeneity: Tau"= 0.00; Ch"= 2.67, df= 3 (P = 0.45); P = 0% Test for overall effect: Z = 2.12 (P = 0.03) 2.1.4 EMPA Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] Heterogeneity: Not applicable
Heterogeneity: Tau ² = 38.51; Chi ² = 2.64, df = 2 (P = 0.27); P = 24% Test for overall effect Z = 1.94 (P = 0.05) 2.1.2 IPRA Kashiwagi2015A -11.4 61.72 118 -12.1 56.84 46 9.5% 0.70 [-19.14, 20.54] Kashiwagi2015B -30 99.9 112 -12 47.56 56 7.6% -18.00 [-40.30, 4.30] Kashiwagi2015D -18.6 90.45 165 8.7 90.66 75 6.2% -27.30 [-52.03, -2.57] Kashiwagi2015D -23.6 88.4 97 7.6 77.37 54 5.2% -31.20 [-58.32, -4.08] Kashiwagi2015E -12.3 124.4 62 -4.8 64.2 67 3.3% -7.50 [-42.07, 27.07] Lu2016 -24.6 91.9 87 10.7 79.6 83 5.7% -35.01 [-41.7, 9.48] Subtotal (95% CI) 641 381 37.6% -18.97 [-30.99, -6.96] Heterogeneity: Tau ² = 62.68; Chi ² = 6.94, df = 5 (P = 0.23); P = 28% Test for overall effect Z = 3.09 (P = 0.002) 2.1.3 LUSEO Haneda2016 -12.1 64.65 95 -11.3 57.72 50 8.8% -0.80 [-21.41, 19.81] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -15.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -15.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -15.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1428667 79 7.1% -15.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1428 57 2.24 Zu Zu Z
Test for overall effect $Z = 1.94$ (P = 0.05) 2.1.2 IPRA Kashiwagi2015A -11.4 61.72 118 -12.1 56.84 46 9.5% 0.70 [-19.14, 20.54] Kashiwagi2015B -30 99.9 112 -12 47.56 56 7.6% -18.00 [-40.30, 4.30] Kashiwagi2015D -23.6 80.4 97 7.6 77.37 54 5.2% -27.30 [-52.03, 2.57] Kashiwagi2015E -12.3 124.4 62 -4.8 64.2 67 3.3% -7.50 [-42.07, 27.07] Lu2016 -24.6 91.9 641 381 37.6% -16.97 [-3.09, 6.96] Heterogeneity. Tau ² = 62.68; Ch ² = 6.94, df = 5 (P = 0.23); P = 28% Test for overall effect $Z = 3.09$ (P = 0.002) 2.1.3 LUSEO Haneda2016 -12.1 64.65 95 -11.3 57.72 50 8.8% -0.80 [-21.41, 19.81] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -18.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -18.80 [-39.96, 6.36] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Subtotal (95% CI) 579 240 24.2% -13.56 [-26.11, -1.01] Heterogeneity. Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); P = 0% Test for overall effect $Z = 2.12$ (P = 0.03) 2.14 EMPA Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] Heterogeneity. Not applicable
Kashiwagi2015A -11.4 61.72 118 -12.1 56.84 46 9.5% 0.70 [+19.14, 20.54] Kashiwagi2015B -30 99.9 112 -12 47.56 56 7.8% -18.00 [+0.30, 4.30] Kashiwagi2015C -18.6 90.45 165 8.7 90.66 75 6.2% -27.30 [-52.03, -2.57] Kashiwagi2015E -12.3 124.4 62 -4.8 64.2 67 3.3% -7.50 [+2.07, 27.07] Lu2016 -24.6 91.9 87 10.7 79.6 83 5.7% -35.30 [61.11, -9.49] Subtotal (95% CI) 641 381 37.6% -18.97 [-30.99, -6.96] Heterogeneity: Tau ² = 62.68; Chi ² = 6.94, df = 5 (P = 0.23); P = 28% -88% -0.80 [-21.41, 19.81] -9.96 Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] -11.4 Seino2014C -18.3665 94.4928 12.2 93.73 54 4.7% -27.57 [-56.09, 0.95] -27.57 [-56.09, 0.95] -27.57 [-56.09, 0.95] -27.57 [-56.09, 0.95] -27.57 [-56.09, 0.95]<
Kashiwagi2015B -30 99.9 112 -12 47.56 56 7.6% -18.00 [-40.30, 4.30] Kashiwagi2015C -18.6 90.45 165 8.7 90.66 75 6.2% -27.30 [-52.03, -2.57] Kashiwagi2015D -23.6 88.4 97 7.6 77.37 54 5.2% -31.20 [-58.32, -4.08] Kashiwagi2015E -12.3 12.4 62.4 64.2 67 -35.30 [-61.11, -9.49] Subtotal (95% CI) 6441 381 37.6% -18.97 [-30.99, -6.96] Heterogeneity: Tau ² = 62.68; Chi ² = 6.94, df = 5 (P = 0.23); P = 28% 78 75.72 50 8.8% -0.80 [-21.41, 19.81] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino2014B -21.139 115.1813 223 -0.1 114.21 57 3.5% -27.57 [-56.09, 0.95] Subtotal (95% CI) 579 240 24.2% -13.56 [-26.11, -1.01] 4.7% Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); i ² = 0% 71% -31.02 [-54.22, -7.83] 4.7% </td
Kashiwagi2015C -18.6 90.45 165 8.7 90.66 75 6.2% -27.30 [52.03, 2.57] Kashiwagi2015D -23.6 88.4 97 7.6 77.37 54 5.2% -31.20 [58.32, 4.08] Kashiwagi2015E -12.3 124.4 62 -4.8 64.2 67 3.3% -7.50 [42.07, 27.07] Lu2016 -24.6 91.9 87 10.7 79.6 83 37.6% -18.97 [-30.99, -6.96] Subtotal (95% CI) 641 381 37.6% -18.97 [-30.99, -6.96] + Heterogeneity: Tau ² = 62.68; Chi ^p = 6.94, df = 5 (P = 0.23); P = 28% - - -18.97 [-30.99, -6.96] + Seino2014A -22.7 74.37 79 -59 74.1438667 79 7.1% -16.80 [-39.96, 6.36] + Seino2014B -21.139 115.1813 223 -0.1 114.21 57 3.5% -21.04 [-54.32, 12.24] + Seino2014C -18.3665 94.4928 182 9.2 93.73 54 4.7% -27.57 [-56.09, 0.95] + + + + + </td
Kashiwagi2015D -23.6 88.4 97 7.6 77.37 54 5.2% -31.20 [-58.32, -4.08] Kashiwagi2015E -12.3 124.4 62 -4.8 64.2 67 3.3% -7.50 [-42.07, 27.07] Lu2016 -24.6 91.9 97 10.7 79.6 83 5.7% -35.30 [-61.11, -9.49] Subtotal (95% CI) 641 381 37.6% -18.97 [-30.99, -6.96] -18.97 [-30.99, -6.96] Heterogeneity: Tau ² = 62.68; Chi ² = 6.94, df = 5 (P = 0.23); i ² = 28% Test for overall effect: Z = 3.09 (P = 0.02) -18.97 [-30.99, -6.96] -18.97 [-30.99, -6.96] 21.3 LUSEO
Kashiwagi2015E -12.3 124.4 62 -4.8 64.2 67 3.3% -7.50 $[42.07, 27.07]$ Lu2016 -24.6 91.9 87 10.7 79.6 83 5.7% -35.30 $[61.11, -9.49]$ Subtotal (95% CI) 641 381 37.6% -18.97 $[-30.99, -6.96]$ Heterogeneity: Tau ² = 62.68; Chi ² = 6.94, df = 5 (P = 0.23); l ² = 28% Test for overall effect: $Z = 3.09$ (P = 0.002) 21.3 80.65 $95 - 11.3$ 57.72 50 8.8% -0.80 [$-21.41, 19.81$] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [$-39.96, 6.36$] Seino2014B -21.139 115.1813 223 -0.1 114.21 57 27.57 [$-56.09, 0.95$] Subtotal (95% CI) 579 240 24.2% -13.56 [$-26.11, -1.01$] 47% Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); l ² = 0% 240 24.2% -31.02 [$-54.22, -7.83$] 438 109 7.1% -31.02 [$-54.22, -7.83$] Butotal (95% CI) 438
Lu2016 -24.6 91.9 87 10.7 79.6 83 5.7% -35.30 [-61.11, -9.49] Subtotal (95% CI) 641 381 37.6% -18.97 [-30.99, -6.96] Heterogeneity: Tau ² = 62.68; Chi ² = 6.94, df = 5 (P = 0.23); l ² = 28% Test for overall effect: Z = 3.09 (P = 0.002) 2.1.3 LUSEO Haneda2016 -12.1 64.65 95 -11.3 57.72 50 8.8% -0.80 [-21.41, 19.81] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino2014B -21.139 115.1813 223 -0.1 114.21 57 3.5% -21.04 [-54.32, 12.24] Seino2014C -18.3665 94.4928 182 9.2 93.73 54 4.7% -27.57 [-56.09, 0.95] Subtotal (95% CI) 579 240 24.2% -13.56 [-26.11, -1.01] Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); l ² = 0% Test for overall effect: Z = 2.12 (P = 0.03) 2.1.4 EMPA Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] Subtotal (95% CI) 438 10.9 7.1% -31.02 [-54.22, -7.83] Heterogeneity: Not applicable
Subtotal (95% CI) 641 381 37.6% -18.97 [-30.99 , -6.96] Heterogeneity: Tau ² = 62.68; Chi ² = 6.94, df = 5 (P = 0.23); I ² = 28% Test for overall effect: Z = 3.09 (P = 0.002) 2.1.3 LUSEO Haneda2016 -12.1 64.65 95 -11.3 57.72 50 8.8% -0.80 [-21.41 , 19.81] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96 , 6.36] Seino2014B -21.139 115.1813 223 -0.1 114.21 57 3.5% -21.04 [-54.32 , 12.24] Seino2014C -18.3665 94.928 182 9.2 93.73 54 4.7% -27.57 [-56.09 , 0.95] Subtotal (95% CI) 579 240 24.2% -13.56 [-26.11 , -1.01] \bullet Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); I ² = 0\% -21.04 [-54.22 , -7.83] \bullet L14 EMPA Kadowaki2014 -19.5122 108.8233 438 109 7.1% -31.02 [-54.22 , -7.83] \bullet Heterogeneity: Not applicable
Heterogeneity: Tau ² = 62.68; Chi ² = 6.94, df = 5 (P = 0.23); I ² = 28% Test for overall effect: Z = 3.09 (P = 0.002) 2.1.3 LUSEO Haneda 2016 -12.1 64.65 95 -11.3 57.72 50 8.8% -0.80 [-21.41, 19.81] Seino 2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino 2014B -21.139 115.1813 223 -0.1 114.21 57 3.5% -21.04 [-54.32, 12.24] Seino 2014C -18.8665 94.4928 182 9.2 93.73 54 4.7% -27.57 [-56.09, 0.95] Subtotal (95% CI) Y 240 24.2% -13.56 [-26.11, -1.01] Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); I ² = 0% Test for overall effect: Z = 2.12 (P = 0.03) 21.4 EMPA Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] Heterogeneity: Not applicable
Test for overall effect: $Z = 3.09 (P = 0.002)$ 21.3 LUSEO Haneda2016 -12.1 64.65 95 -11.3 57.72 50 8.8% -0.80 [-21.41, 19.81] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino2014B -21.139 115.1813 223 -0.1 114.21 57 3.5% -21.04 [-54.32, 12.24] Seino2014C -18.3665 94.4928 182 9.2 93.73 54 4.7% -27.57 [-56.09, 0.95] Subtotal (95% CI) Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); I ² = 0% Test for overall effect: Z = 2.12 (P = 0.03) 21.4 EMPA Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] Subtotal (95% CI) 438 109 7.1% -31.02 [-54.22, -7.83]
Haneda2016 -12.1 64.65 95 -11.3 57.72 50 8.8% -0.80 [-21.41, 19.81] Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino2014B -21.139 115.1813 223 -0.1 114.21 57 3.5% -21.04 [-54.32, 12.24] Seino2014C -18.3665 94.928 182 9.2 93.73 54 4.7% -27.57 [-56.09, 0.95] Subtotal (95% CI) 579 240 24.2% -13.56 [-26.11, -1.01] • Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); P = 0% Test for overall effect: Z = 2.12 (P = 0.03) • 21.4 EMPA Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] • Subtotal (95% CI) 438 109 7.1% -31.02 [-54.22, -7.83] • • Heterogeneity: Not applicable 109 7.1% -31.02 [-54.22, -7.83] • •
Seino2014A -22.7 74.37 79 -5.9 74.1438667 79 7.1% -16.80 [-39.96, 6.36] Seino2014B -21.139 115.1813 223 -0.1 114.21 57 3.5% -21.04 [-54.32, 12.24] Seino2014C -18.3665 94.4928 182 9.2 93.73 54 4.7% -27.57 [-56.09, 0.95] Subtotal (95% CI) 579 240 24.2% -13.56 [-26.11, -1.01] + Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); P = 0% 7 7.1% -31.02 [-54.22, -7.83] + Z1.4 EMPA Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] + Subtotal (95% CI) 438 109 7.1% -31.02 [-54.22, -7.83] +
Seino2014B -21.139 115.1813 223 -0.1 114.21 57 3.5% -21.04 [-54.32, 12.24] Seino2014C -18.3665 94.4928 182 9.2 93.73 54 4.7% -27.57 [-56.09, 0.95] Subtotal (95% CI) 579 240 24.2% -13.56 [-26.11, -1.01] ◆ Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); I ² = 0% 7 7.1% -31.02 [-54.22, -7.83] ◆ Z1.4 EMPA Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] ◆ Subtotal (95% CI) 438 109 7.1% -31.02 [-54.22, -7.83] ◆
Seino2014C -18.3665 94.4928 182 9.2 93.73 54 4.7% -27.57 [-56.09, 0.95] Subtotal (95% CI) 579 240 24.2% -13.56 [-26.11, -1.01] ◆ Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); I ² = 0% 7 7 -5 -6 -13.56 [-26.11, -1.01] ◆ Test for overall effect: Z = 2.12 (P = 0.03) 240 24.2% -31.02 [-54.22, -7.83] ◆ 21.4 EMPA Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] ◆ Subtotal (95% CI) 438 109 7.1% -31.02 [-54.22, -7.83] ◆ Heterogeneity: Not applicable 109 7.1% -31.02 [-54.22, -7.83] ◆
Subtotal (95% CI) 579 240 24.2% -13.56 [-26.11, -1.01] Heterogeneity: Tau ² = 0.00; Chi ² = 2.67, df = 3 (P = 0.45); I ² = 0% Test for overall effect: Z = 2.12 (P = 0.03) 2.1.4 EMPA Kadowaki2014 -19.5122 108.8233 438 11.51 111 109 7.1% -31.02 [-54.22, -7.83] Subtotal (95% CI) 438 109 7.1% -31.02 [-54.22, -7.83] ◆ Heterogeneity: Not applicable - - - - -
Test for overall effect: Z = 2.12 (P = 0.03) 2.1.4 EMPA Kadowaki2014 -19.5122 108.8233 438 111 109 7.1% -31.02 [-54.22, -7.83] Subtotal (95% CI) 438 109 7.1% Heterogeneity: Not applicable
Kadowaki2014 -19.5122 108.8233 438 11.1 109 7.1% -31.02 [-54.22, -7.83] Subtotal (95% CI) 438 109 7.1% -31.02 [-54.22, -7.83] + Heterogeneity: Not applicable
Subtotal (95% CI) 438 109 7.1% -31.02 [-54.22, -7.83] Heterogeneity: Not applicable
2.1.5 TOFO
Kaku2014 -29.752 100.2731 173 -21.5 206.2 56 1.3% -8.25[-64.29, 47.78]
Subtotal (95% Cl) 173 56 1.3% -8.25 [64.29, 47.78]
Heterogeneity. Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)
Total (95% CI) 2664 1157 100.0% -16.42 [-22.71, -10.12]
Heterogeneity: Tau ² = 6.02; Chi ² = 14.56, df = 14 (P = 0.41); l ² = 4% -1 -200 -100 0 100 200 Test for overall effect: Z = 5.11 (P < 0.00001)
Fig. 4 Relationship between SGLT2 is and changes in TG. Abbreviations: CANA, canagliflozin; EMPA, empagliflozin; IPRA, ipragliflozin; LUSEO,
luseogliflozin; TOFO, tofogliflozin; SGLT2i, sodium-glucose co-transporter 2 inhibitor; TG, triglycerides; Cl, confidence interval; SD, standard deviation.

all types of SGLT2is showed a significant result in the sub-group analysis. IPRA group had the greatest weight (40.0%), whereas EMPA group had the lowest weight (6.0%) (Fig. 5).

Relationship between SGLT2is and changes in LDL-C

Fourteen trials were included in the meta-analysis. Statistical homogeneity was observed among trials ($I^2 = 6\%$). LDL-C values were worse with SGLT2is than with a placebo [mean difference 3.00 (95%CI 1.18 to 4.82) mg/dL, p < 0.001], and only the CANA group showed a significant result in the sub-group analysis. The IPRA group had the greatest weight (38.1%), whereas the TOFO group had the lowest weight (7.2%) (Fig. 6).

Relationship between SGLT2is and changes in the LDL-C/ HDL-C ratio

Three trials were included in the meta-analysis. Statistical homogeneity was observed among trials ($I^2 = 1\%$). The LDL-C/HDL-C ratio was not significantly different between SGLT2is and a placebo [mean difference – 0.01 (95%CI – 0.08 to 0.06), p < 0.74], and none of the groups showed a significant result in the subgroup analysis. The CANA group had the greatest weight (81.5%) (Fig. 7).

Additional analyses

The results of the sub-group analysis including only Japanese patients and only patients who were treated with SGLT2is as monotherapy were consistent with the main results (Table 2).

	S	GLT2is			Placebo			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
3.1.1 CANA										
Inagaki2013	4.2795	7.0993	307	0.3	6.93	75	12.5%	3.98 [2.22, 5.74]	-	
Inagaki2016	3.3	8.7178	76	-0.5	8.36660026	70	5.0%	3.80 [1.03, 6.57]		
Ji2015	4.9053	14.9959	450	2.2	15.03	226	6.7%	2.71 [0.31, 5.11]		
Subtotal (95% CI)			833			371	24.2%	3.59 [2.33, 4.85]	♦	
Heterogeneity: Tau ² =	0.00; Chi	² = 0.73, d	f = 2 (P	= 0.69)	; I² = 0%					
Test for overall effect:	Z= 5.57 ((P < 0.000)	01)							
3.1.2 IPRA										
Kashiwagi2015A	4.2	8.8	118	3.4	7.9	46	5.0%	0.80 [-1.98, 3.58]		
Kashiwagi2015B	8.8	8.75	112	4.9	8.85	56	4.8%	3.90 [1.07, 6.73]		
Kashiwagi2015C	2	9.4	165	-0.7	7.18	75	8.2%	2.70 [0.53, 4.87]		
Kashiwagi2015D	3.9	7.63	97	-1.3	8.54	54	5.2%	5.20 [2.46, 7.94]		
Kashiwagi2015E	2.7	6.2	62	-1	6.5	67	8.0%	3.70 [1.51, 5.89]		
Lu2016	2.6	7	87	0.9	7	83	8.7%	1.70 [-0.41, 3.81]		
Subtotal (95% CI)			641			381	40.0%	2.94 [1.75, 4.13]	•	
Heterogeneity: Tau ² =	0.67; Chi	² = 7.17, d	f = 5 (P	= 0.21)	; I² = 30%					
Test for overall effect:				,						
3.1.3 LUSEO										
Haneda2016	4.8	7.46	95	2.1	7.22	50	6.2%	2.70 [0.20, 5.20]		
Seino2014A	2.8	6.8	79	-1.1	6.8	79	8.6%	3.90 [1.78, 6.02]		
Seino2014B	6.0695	7.6257	223	1.9	7.51	57	8.0%	4.17 [1.98, 6.36]	-	
Subtotal (95% CI)			397			186	22.8%	3.67 [2.37, 4.97]	♦	
Heterogeneity: Tau² = Test for overall effect:				= 0.66)	; I² = 0%					
3.1.4 EMPA										
Kadowaki2014 Subtotal (95% CI)	5.6124	12.112	438 438	2.32	12.11	109 109	6.0% 6 .0 %	3.29 [0.75, 5.83] 3.29 [0.75, 5.83]		
Heterogeneity: Not ap	nlicable						01070	0120 [011 0, 0100]	•	
Test for overall effect:		(P = 0.01)								
3.1.5 TOFO										
Kaku2014	3.9035	9.1194	173	-0.2	7.3	56	7.0%	4.10 [1.76, 6.45]		
Subtotal (95% CI)			173			56	7.0%	4.10 [1.76, 6.45]	•	
Heterogeneity: Not ap	plicable									
Test for overall effect:	•	(P = 0.000)	6)							
Total (95% CI)			2482			1103	100.0%	3.36 [2.73, 3.98]	•	
Heterogeneity: Tau² = Test for overall effect: Test for subgroup diff	Z = 10.58	(P < 0.00	001)	•					-20 -10 0 10 20 Favors Placebo Favors SGLT2is	
Fig. 5 Relationship be	etween S	GLT2is ar	nd cha	inges ir	n HDL-C. Abb	oreviati	ions: CAI	NA, canagliflozin; EMf	PA, empagliflozin; IPRA, ipragliflozin; LUSEO,	
iig. 5 Relationship between SGLT2is and changes in HDL-C. Abbreviations: CANA, canagliflozin; EMPA, empagliflozin; IPRA, ipragliflozin; LUSEO, useogliflozin; TOFO, tofogliflozin; SGLT2i, sodium-glucose co-transporter 2 inhibitor; HDL-C, high-density lipoprotein cholesterol; CI, confidence nterval; SD, standard deviation.										

Discussion

We herein conducted a systematic review with a meta-analysis to summarize the available literature and confirm the effects of SGLT2is on lipid profiles in Asian patients with type 2 diabetes mellitus. The present study, which consisted of 17 RCTs including 4485 Asian patients with type 2 diabetes mellitus, suggests that TG and HDL-C values were better, whereas LDL-C values were worse with SGLT2is than with a placebo and also showed that there was no heterogeneity ($I^2 \le 6\%$) in each lipid profile.

Our results for lipid outcomes were consistent with the meta-analysis by Cai and colleagues [11]; a significant, but small change was observed in lipid outcomes, and these outcomes indicated high heterogeneity ($I^2 > 90\%$). This heterogeneity was attributed to their meta-analysis including RCTs with different inclusion criteria [11]. Total heterogeneity ($I^2 \le 6\%$) may also have been attributed to most of the SGLT2i subgroups having low heterogeneity in our analysis. Total heterogeneity was higher when we excluded the subgroup with low heterogeneity to confirm the impact of heterogeneity between SGLT2i groups in our meta-analysis. Incidentally, in our analysis, all SGLT2i groups with different doses in the treatment arm were combined into a single group based on the Cochrane Handbook [13]. In contrast, the study by Cai and colleagues [11] included only the standard dose of SGLT2is in each treatment arm; however, the impact of this methodological difference across meta-analyses currently remains unclear.

An increase of 1 mg/dL in HDL-C from baseline after 3 months may be expected to reduce the risk of major cardiovascular events by 1.1% in the post-hoc analysis of

	s	GLT2is		F	lacebo			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
4.1.1 CANA											
Inagaki2013	5.7586	19.0006	307	-0.9	19.05	75	12.7%	6.66 [1.85, 11.47]			
Inagaki2016	3.7	17.8	76	4.4	27.6	70	5.5%	-0.70 [-8.30, 6.90]	-		
Ji2015		40.4568	450	-0.05	40.59	226	7.4%	9.20 [2.72, 15.68]			
Subtotal (95% CI)			833			371	25.5%	5.51 [0.46, 10.57]	◆		
Heterogeneity: Tau ² =	9.96: Chi ^a	² = 3.99. df	= 2 (P	= 0.14):	I ^z = 50%						
Test for overall effect:											
4.1.2 IPRA											
Kashiwagi2015A	-2.6	21.8	118	-1.8	17.18	46	7.7%	-0.80 [-7.13, 5.53]			
Kashiwagi2015B	6.9	22.32	112	6.6	17.17	56	8.2%	0.30 [-5.81, 6.41]	+		
Kashiwagi2015C	-5	26.69	165	-3.9	21.36	75	7.7%	-1.10 [-7.42, 5.22]			
Kashiwagi2015D	0.8	21.63	97	-3.5	29.64	54	3.9%	4.30 [-4.70, 13.30]	- - -		
Kashiwagi2015E	-1.4	23.9	62	-4.7	16.3	67	6.2%	3.30 [-3.82, 10.42]			
Lu2016	-0.8	29.9	87	-2	27.2	83	4.3%	1.20 [-7.39, 9.79]			
Subtotal (95% CI)			641			381	38.1%	0.78 [-2.08, 3.63]	•		
Heterogeneity: Tau² = Test for overall effect:			= 5 (P	= 0.89);	I² = 0%						
4.1.3 LUSEO											
Haneda2016	2.4	22.38	95	-0.1	21.65	50	5.6%	2.50 [-5.00, 10.00]			
Seino2014A	3.2	21.767	79	-5.2	21.994	79	6.7%	8.40 [1.58, 15.22]			
Seino2014B	3.5601	20.659	223	2.5	20.61	57	8.5%	1.06 [-4.94, 7.06]	+		
Subtotal (95% CI)			397			186	20.8%	3.86 [-0.63, 8.34]	◆		
Heterogeneity: Tau ² = Test for overall effect:			= 2 (P	= 0.26);	I ² = 25%						
4.1.4 EMPA											
Kadowaki2014	-2.1205	31.4182	438	-3.48	28.26	109	8.3%	1.36 [-4.71, 7.43]	+		
Subtotal (95% CI)			438			109	8.3%	1.36 [-4.71, 7.43]	◆		
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 0.44 (I	P = 0.66)									
4.1.5 TOFO											
Kaku2014	-0.1185	22.0981	173	-4.3	21.6	56	7.2%	4.18 [-2.36, 10.73]	+		
Subtotal (95% CI)			173			56	7.2%	4.18 [-2.36, 10.73]	◆		
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 1.25 (I	P = 0.21)									
Total (95% CI)			2482			1103	100.0%	3.00 [1.18, 4.82]	•		
Heterogeneity: Tau ² =	0.77; Chi ^a	² = 13.89, (f=13	(P = 0.3	8); I ² = 69	6		-			
Test for overall effect:									-50 -25 Ó 25 50 Eavars SCLT2is, Eavars Placeba		
			, df = 4	(P = 0.4)	18), I² = 0	%			Favors SGLT2is Favors Placebo		
Test for subgroup differences: Chi ² = 3.50, df = 4 (P = 0.48), I ² = 0% ig. 6 Relationship between SGLT2is and changes in LDL-C. Abbreviations: CANA, canagliflozin; EMPA, empagliflozin; IPRA, ipragliflozin; LUSEO, useogliflozin; TOFO, tofogliflozin; SGLT2i, sodium-glucose co-transporter 2 inhibitor; LDL-C, low-density lipoprotein cholesterol; Cl, confidence											
nterval; SD, standard o	9		Jourul	ii giuci		anspo					

the TNT trial [34]. Similarly, all RCTs included showed consistent increases in HDL-C of 1 mg/dL or more from baseline after approximately 3 months before these RCTs were combined. HDL-C was 3.4 mg/dL higher with SGLT2is than with a placebo in our meta-analysis. This result suggests that SGLT2is exert protective effects against cardiovascular events in Asian populations. The present meta-analysis showed that SGLT2is decreased TG by 16.4 mg/dL and increased LDL-C by 3.0 mg/dL from placebo values. A recent meta-regression analysis with an average median trial duration of 4.8 years showed that the risk ratio of major vascular events was 0.92 per 40 mg/dL reduction in TG [35]. Another metaanalysis with a mean follow-up of 4.3 years [36] reported a 21% reduction in major vascular events per 1 mmol/L (38.7 mg/dL) reduction in LDL-C. Further RCTs with a longer duration are needed to establish whether the modest changes observed in TG and LDL-C in our meta-analysis are of clinical importance because the maximum duration of RCT in our review was too short (at most 24 weeks).

The RCT that included approximately 80% Caucasians also demonstrated that CANA at 300 mg increased TG by 20.2 mg/dL over the placebo value [37], while the results for TG in our meta-analysis showed the opposite effect [mean difference – 16.42 (95%CI – 22.71 to – 10.12) mg/dL]. The EMPA-REG OUTCOME study [2, 38], which included 72% Caucasians, and the RCT by Bode and colleagues [39], comprising 70% or more Caucasians, showed small increases in HDL-C and LDL-C over those with the placebo. The magnitude of effects on HDL-C and LDL-C were equal to the results of the

	S	Mean Difference									
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
5.1.1 CANA											
nagaki2013	-0.0481	0.3525	307	-0.007	0.3525	75	58.7%	-0.04 [-0.13, 0.05]	•		
Ji2015	-0.0102	0.8993	450	-0.09	0.902	226	22.7%	0.08 [-0.06, 0.22]	+		
Subtotal (95% CI)			757			301	81.5%	0.01 [-0.11, 0.12]	•		
Heterogeneity: Tau ² = 0.00; Chi ² = 1.96, df = 1 (P = 0.16); l ² = 49%											
Fest for overall effect:	Z = 0.09 (I	P = 0.92)									
5.1.3 LUSEO											
Haneda2016	-0.133	0.4227	95	-0.103	0.487	50	18.5%	-0.03 [-0.19, 0.13]	+		
ubtotal (95% CI)			95			50	18.5%	-0.03 [-0.19, 0.13]	+		
leterogeneity: Not ap	oplicable										
est for overall effect:	Z = 0.37 (I	P = 0.71)									
otal (95% CI)			852			351	100.0%	-0.01 [-0.08, 0.06]	•		
Heterogeneity: Tau ² = 0.00; Chi ² = 2.02, df = 2 (P = 0.36); I ² = 1%											
est for overall effect:	Z = 0.33 (I	P = 0.74)							Favors SGLT2is Favors Placebo		
est for subgroup dif	ferences: (Chi² = 0.1	3, df = 1	1 (P = 0.1)	72), I ² = 0	1%					
. 7 Relationship be	etween SC	l T2is an	d char	naes in t	he I DI -	C/HDI	-C ratio	Abbreviations: CANA	canagliflozin; LUSEO, luseogliflozin; SGLT2i,		
				5					density lipoprotein cholesterol: Cl. confidenc		

interval; SD, standard deviation.

present study including 100% Asian patients [mean difference 3.36 (95%CI 2.73 to 3.98) mg/dL, mean difference 3.00 (95%CI 1.18 to 4.82) mg/dL, respectively]. Therefore, the effects of SGLT2is on HDL-C and LDL-C do not appear to be dependent on race, although racial differences may explain this smaller increase in TG; however, differences in the types of SGLT2is used, such as CANA and EMPA, or patient backgrounds, which included those treated with antihyperlipidemic therapies or statins, may have affected this result [2, 37–39]. Further studies are needed to verify whether racial differences affect lipid metabolism.

Regardless of the types of SGLT2is, consistent results, such as a decrease in TG and increases in HDL-C and LDL-C, were observed in our meta-analysis. Similarly, weight loss in patients with type 2 diabetes mellitus in UKPDS reduced TG with an increase in HDL-C [40]. Weight loss with SGLT2is may explain, in part, the better TG and HDL-C values observed. Overall, there was no significant change in the LDL-C/HDL-C ratio in our analysis. This result supports the hypothesis that the increase in LDL-C induced by SGLT2is may be counterbalanced by elevated HDL-C [41]. A possible mechanism for the increase observed in LDL-C with SGLT2is is explained using a preclinical model. This increase may be

	Outcome	Trial, n	SGLT2i, n	Placebo, n	Mean difference [95%Cl]	Heterogeneity (%)	Test for the overall effect (p value)
Only Japanese patients	HbA1c (%)	13	1998	866	- 0.83 [- 1.01, - 0.65]	90	< 0.00001
	TG (mg/dL)	13	2127	848	-14.39 [-20.80, -7.98]	0	< 0.0001
	HDL-C (mg/dL)	12	1945	794	3.58 [2.90, 4.25]	0	< 0.00001
	LDL-C (mg/dL)	12	1945	794	2.59 [0.72, 4.46]	0	0.007
	LDL-C/HDL-C ratio	2	402	125	-0.04 [-0.12, 0.04]	0	0.33
Only patients treated with SGLT2i as	HbA1c (%)	8	1596	647	-0.84 [-0.97, -0.70]	77	< 0.00001
monotherapy	TG (mg/dL)	7	1464	497	-17.96 [-27.03, -8.88]	0	0.0001
	HDL-C (mg/dL)	6	1282	443	3.89 [3.01, 4.76]	0	< 0.00001
	LDL-C (mg/dL)	6	1282	443	4.29 [1.81, 6.76]	0	0.0007
	LDL-C/HDL-C ratio	1	307	75	-0.04 [-0.13, 0.05]	NA	0.37

 Table 2 Summary of subgroup analyses

SGLT2i the sodium-glucose co-transporter 2 inhibitor, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TG triglycerides, Cl confidence interval, NA not applicable

due to the delayed clearance of LDL from the circulation along with elevated plasma lipoprotein lipase activity [42].

The present study has some limitations. Although Egger's regression test showed no significant differences in primary outcomes, there may have been a publication bias because we only retrieved published studies. Furthermore, our review was unable to rule out the impact of other antihyperglycemic agents because it included some patients who were treated with an oral hypoglycemic agent or insulin as combination therapy. However, the results of the subgroup analysis that only included patients who were treated with SGLT2is as monotherapy were consistent with the main results (Table 2). Similarly, some lifestyle interventions, such as diet and exercise, which had been performed in most of the RCTs collected, may also have contributed to our lipid outcomes because these interventions are known to affect lipid profiles [43, 44]. The combination of lifestyle intervention(s) and oral hypoglycemic agent therapy is commonly used in clinical practice. In addition, the results obtained are hard to generalize for other Asian populations. The results of the sub-group analysis that included Japanese patients only were consistent with the main results. A possible reason for this is that Japanese patients accounted for 80% of the Asian population in this review. Another limitation is that the numbers of different types of SGLT2is that we pooled were unbalanced. There were also no lipid outcomes including all types of SGLT2is in our meta-analysis. The IRPA group with the highest weight may have affected all lipid profiles.

Conclusion

In summary, the present results suggest that in Asian patients with type 2 diabetes, TG and HDL-C values were better, while LDL-C values were worse with SGLT2is than with a placebo. However, the negative impact of SGLT2is on lipid profiles was modest. Further RCT with a longer duration or conducted in other Asia countries are needed to provide further evidence to support the clinical relevance of changes in lipid profiles. The present results will be informative for SGLT2is users with concerns regarding the effects of SGLT2is on lipid profiles.

Abbreviations

CANA: Canagliflozin; CI: Confidence interval; DAPA: Dapagliflozin; EMPA: Empagliflozin; HDL-C: High-density lipoprotein cholesterol; IPRA: Ipragliflozin; LDL-C: Low-density lipoprotein cholesterol; LUSEO: Luseogliflozin; RCT: Randomized controlled trial; SGLT2i: Sodiumglucose co-transporter 2 inhibitor; TG: Triglycerides; TOFO: Tofogliflozin

Acknowledgments

Not applicable.

Authors' contributions

JM conceived and designed the study. JM and AY performed the systematic review of the literature. JM and AY analyzed and interpreted the data. JM wrote the manuscript. All authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 23 January 2020 Accepted: 3 March 2020 Published online: 14 March 2020

References

- Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2014;16:457–66.
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC. Inzucchi SE; EMPA-REG OUTCOME investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.
- Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR, CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–57.
- Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, Okayama A. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: the Suita study. Atherosclerosis. 2009;203:587–92.
- Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, Tyroler HA. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med. 1990;322:1700–7.
- American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. Diabetes Care. 2019; 42:S90–102.
- Kaku K, Kiyosue A, Inoue S, Ueda N, Tokudome T, Yang J, Langkilde AM. Efficacy and safety of dapagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise. Diabetes Obes Metab. 2014;16:1102–10.
- Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, Zimmet P, Son HY. Epidemic obesity and type 2 diabetes in Asia. Lancet. 2006;368:1681–8.
- WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363:157–63.
- Zhang C, Gao F, Luo H, Zhang CT, Zhang R. Differential response in levels of high-density lipoprotein cholesterol to one-year metformin treatment in prediabetic patients by race/ethnicity. Cardiovasc Diabetol. 2015;14:79.
- Cai X, Gao X, Yang W, Chen Y, Zhang S, Zhou L, Han X, Ji L. No disparity of the efficacy and all-cause mortality between Asian and non-Asian type 2 diabetes patients with sodium-glucose cotransporter 2 inhibitors treatment: a meta-analysis. J Diab Investig. 2018;9:850–61.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.
- Higgins JPT, Green S (eds). Cochrane handbook for systematic reviews of interventions, Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011. http://handbook.cochrane.org/. Accessed 16 July 2019.
- 14. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.
- 15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
- Ji L, Ma J, Li H, Mansfield TA, Tjoen CL, Iqbal N, Ptaszynska A, List JF. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. Clin Ther. 2014;36:84–100 e9.
- 17. Kadowaki T, Haneda M, Inagaki N, Terauchi Y, Taniguchi A, Koiwai K, Rattunde H, Woerle HJ, Broedl UC. Empagliflozin monotherapy in Japanese

patients with type 2 diabetes mellitus: a randomized, 12-week, doubleblind, placebo-controlled, phase II trial. Adv Ther. 2014;31:621–38.

- 18. Kashiwagi A, Takahashi H, Ishikawa H, Yoshida S, Kazuta K, Utsuno A, Ueyama E. A randomized, double-blind, placebo-controlled study on longterm efficacy and safety of ipragliflozin treatment in patients with type 2 diabetes mellitus and renal impairment: results of the long-term ASP1941 safety evaluation in patients with type 2 diabetes with renal impairment (LANTERN) study. Diabetes Obes Metab. 2015;17:152–60.
- Lu CH, Min KW, Chuang LM, Kokubo S, Yoshida S, Cha BS. Efficacy, safety, and tolerability of ipragliflozin in Asian patients with type 2 diabetes mellitus and inadequate glycemic control with metformin: results of a phase 3 randomized, placebo-controlled, double-blind, multicenter trial. J Diab Investig. 2016;7:366–73.
- Kashiwagi A, Kazuta K, Goto K, Yoshida S, Ueyama E, Utsuno A. Ipragliflozin in combination with metformin for the treatment of Japanese patients with type 2 diabetes: ILLUMINATE, a randomized, double-blind, placebocontrolled study. Diabetes Obes Metab. 2015;17:304–8.
- Kashiwagi A, Akiyama N, Shiga T, Kazuta K, Utsuno A, Yoshida S, Ueyama E. Efficacy and safety of Ipragliflozin as an add-on to a sulfonylurea in Japanese patients with inadequately controlled type 2 diabetes: results of the randomized, placebo-controlled, double-blind, phase III EMIT study. Diabetol Int. 2015;6:125–38.
- 22. Kashiwagi A, Shiga T, Akiyama N, Akiyama N, Kazuta K, Utsuno A, Yoshida S, Ueyama E. Efficacy and safety of Ipragliflozin as an addon to pioglitazone in Japanese patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebocontrolled study (the SPOTLIGHT study). Diabetol Int. 2015;6:104–16.
- Kashiwagi A, Kazuta K, Takinami Y, Yoshida S, Utsuno A, Nagase I. Ipragliflozin improves glycemic control in Japanese patients with type 2 diabetes mellitus: the BRIGHTEN study. Diabetol Int. 2015;6:8–18.
- 24. Haneda M, Seino Y, Inagaki N, Kaku K, Sasaki T, Fukatsu A, Kakiuchi H, Sato Y, Sakai S, Samukawa Y. Influence of renal function on the 52-week efficacy and safety of the sodium glucose cotransporter 2 inhibitor luseogliflozin in Japanese patients with type 2 diabetes mellitus. Clin Ther. 2016;38:66–88 e20.
- Seino Y, Sasaki T, Fukatsu A, Ubukata M, Sakai S, Samukawa Y. Efficacy and safety of luseogliflozin as monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, phase 3 study. Curr Med Res Opin. 2014;30:1245–55.
- Seino Y, Sasaki T, Fukatsu A, Ubukata M, Sakai S, Samukawa Y. Dose-finding study of luseogliflozin in Japanese patients with type 2 diabetes mellitus: a 12-week, randomized, double-blind, placebo-controlled, phase II study. Curr Med Res Opin. 2014;30:1231–44.
- Seino Y, Sasaki T, Fukatsu A, Sakai S, Samukawa Y. Efficacy and safety of luseogliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a 12-week, randomized, placebo-controlled, phase II study. Curr Med Res Opin. 2014;30:1219–30.
- Inagaki N, Harashima S, Maruyama N, Kawaguchi Y, Goda M, lijima H. Efficacy and safety of canagliflozin in combination with insulin: a doubleblind, randomized, placebo-controlled study in Japanese patients with type 2 diabetes mellitus. Cardiovasc Diabetol. 2016;15:89.
- Ji L, Han P, Liu Y, Yang G, Dieu Van NK, Vijapurkar U, Qiu R, Meininger G. Canagliflozin in Asian patients with type 2 diabetes on metformin alone or metformin in combination with sulphonylurea. Diabetes Obes Metab. 2015;17:23–31.
- Inagaki N, Kondo K, Yoshinari T, Takahashi N, Susuta Y, Kuki H. Efficacy and safety of canagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, Phase III study. Expert Opin Pharmacother. 2014;15:1501–15.
- Inagaki N, Kondo K, Yoshinari T, Maruyama N, Susuta Y, Kuki H. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab. 2013;15:1136–45.
- 32. Kaku K, Watada H, Iwamoto Y, Utsunomiya K, Terauchi Y, Tobe K, Tanizawa Y, Araki E, Ueda M, Suganami H, Watanabe D. Tofogliflozin 003 Study Group. Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. Cardiovasc Diabetol. 2014;13:65.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264–9.

- Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC. Treating to new targets investigators. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007;357:1301–10.
- Marston NA, Giugliano RP, Im K, Silverman MG, O'Donoghue ML, Wiviott SD, Ference BA, Sabatine MS. Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: a systematic review and meta-regression analysis of randomized controlled trials. Circulation. 2019;140:1308–17.
- Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371:117–25.
- Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, Figueroa K, Wajs E, Usiskin K, Meininger G. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013;15:463–73.
- Zinman B, Inzucchi SE, Lachin JM, Wanner C, Ferrari R, Fitchett D, Bluhmki E, Hantel S, Kempthorne-Rawson J, Newman J, Johansen OE, Woerle HJ, Broedl UC. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME[™]). Cardiovasc Diabetol. 2014;13:102.
- Bode B, Stenlöf K, Harris S, Sullivan D, Fung A, Usiskin K, Meininger G. Longterm efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. Diabetes Obes Metab. 2015;17:294–303.
- Manley SE, Stratton IM, Cull CA, Frighi V, Eeley EA, Matthews DR, Holman RR, Turner RC, Neil HA, United Kingdom Prospective Diabets Study Group. Effects of three months' diet after diagnosis of Type 2 diabetes on plasma lipids and lipoproteins (UKPDS 45). Diabet Med. 2000;17:518–23.
- 41. Halimi S, Vergès B. Adverse effects and safety of SGLT-2 inhibitors. Diabetes Metab. 2014;40:S28–34.
- Basu D, Huggins LA, Scerbo D, Obunike J, Mullick AE, Rothenberg PL, Di Prospero NA, Eckel RH, Goldberg IJ. Mechanism of increased LDL (low-density lipoprotein) and decreased triglycerides with SGLT2 (sodium-glucose Cotransporter 2) inhibition. Arterioscler Thromb Vasc Biol. 2018;38:2207–16.
- Heilbronn LK, Noakes M, Clifton PM. Effect of energy restriction, weight loss, and diet composition on plasma lipids and glucose in patients with type 2 diabetes. Diabetes Care. 1999;22:889–95.
- 44. Kelley GA, Kelley KS. Effects of aerobic exercise on lipids and lipoproteins in adults with type 2 diabetes: a meta-analysis of randomized-controlled trials. Public Health. 2007;121:643–55.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

