Effects of sodium–glucose cotransporter 2 inhibitors in addition to insulin therapy on cardiovascular risk factors in type 2 diabetes patients: A meta-analysis of randomized controlled trials

Bingshu Wu¹⁽¹⁾, Hongzhi Zheng¹, Jianqiu Gu², Yan Guo¹, Yixuan Liu¹, Yingfang Wang¹, Feng Chen¹, Aolin Yang¹, Jiabei Wang¹, Hailong Wang³, Ying Liu⁴, Difei Wang¹*

Departments of ¹Geriatric Endocrinology, ²Endocrinology, and ³Epidemiology and Evidence-based Medicine, The First Affiliated Hospital of China Medical University, and ⁴Department of Biochemistry and Molecular Biology, China Medical University, Shenyang, Liaoning, China

Keywords

Cardiovascular risk factors, Metaanalysis, Sodium–glucose cotransporter 2 inhibitor

*Correspondence

Difei Wang Tel.: +86-24-8328-3761 Fax: +86-24-8328-3761 E-mail address: wdf8lm@163.com

J Diabetes Investig 2019; 10: 446-457

doi: 10.1111/jdi.12876

ABSTRACT

Aims/Introduction: In the present meta-analysis, we aimed to determine the effects of sodium–glucose cotransporter 2 inhibitor (SGLT-2i) in addition to insulin therapy on cardiovascular risk factors in type 2 diabetes patients.

Materials and Methods: Randomized controlled trials were identified by searching the PubMed, Embase and Cochrane Library databases published before September 2017. The intervention group received SGLT-2i as add-on treatment to insulin therapy, and the control group received placebos in addition to insulin. We assessed pooled data, including weighted mean differences and 95% confidence intervals (Cls) using a random-effects model.

Results: A total of 10 randomized controlled trials (n = 5,159) were eligible. The weighted mean differences for systolic blood pressure and diastolic blood pressure were -3.17 mmHg (95% CI -4.53, -1.80, $l^2 = 0\%$) and -1.60 mmHg (95% CI -2.52, -0.69, $l^2 = 0\%$) in the intervention groups. Glycosylated hemoglobin, fasting plasma glucose, postprandial glucose and daily insulin were also lower in the intervention groups, with relative weighted mean differences of -0.49% (95% CI -0.71, -0.28%, $l^2 = 92\%$), -1.10 mmol/L (95% CI -1.69, -0.51 mmol/L, $l^2 = 84\%$), -3.63 mmol/L (95% CI -4.36, -2.89, $l^2 = 0\%$) and -5.42 IU/day (95% CI -8.12, -2.72, $l^2 = 93\%$). The transformations of uric acid and bodyweight were $-26.16 \text{ }\mu\text{mol/L}$ (95% CI -42.14, -10.17, $l^2 = 80\%$) and -2.13 kg (95% CI -2.66, -1.60, $l^2 = 83\%$). The relative risk of hypoglycemia was 1.09 (95% CI 1.02, 1.17, P < 0.01). The relative risks of urinary tract and genital infection were 1.29 (95% CI 1.03, 1.62, P = 0.03) and 5.25 (95% CI 3.55, 7.74, P < 0.01).

Conclusions: The results showed that in the intervention group, greater reductions were achieved for blood pressure, glucose control, uric acid and bodyweight. This treatment regimen might therefore provide beneficial effects on the occurrence and development of cardiovascular events.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that seriously influences the health, quality of life and life expectancy of affected patients. One of the most common macrovascular

Received 29 January 2018; revised 9 May 2018; accepted 11 June 2018

© 2018 The Authors. Journal of Diabetes Investigation published by Asian Association for the Study of Diabetes (AASD) and John Wiley & Sons Australia, Ltd This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes. complications of diabetes is coronary atherosclerotic heart disease. The rate of myocardial infarction and heart failure in diabetes patients is far higher than the rate in patients without diabetes¹. Therefore, when choosing therapies for diabetes patients, we must evaluate whether the treatment will lower the risk of cardiovascular disease associated with selected antidiabetic agents, and whether it can improve prognoses in diabetesassociated cardiovascular disease.

For islets function failure along with the progression of type 2 diabetes, most patients will require insulin therapy, especially in the late stage. However, the long-term use of insulin has side-effects of obesity and sodium retention, which not only increase the difficulty of glycemic control, but also increase the risk of metabolic syndrome (hypertension, hyperlipidemia and hyperuricemia), which increases the occurrence of cardiovascular events. How to reduce these side-effects of insulin therapy is a realistic question.

Sodium-glucose cotransporter 2 inhibitors (SGLT-2is) are a novel class of antihyperglycemic drugs that are independent of insulin release or action. These drugs reduce plasma glucose levels by reducing glucose renal reabsorption and increasing urinary glucose excretion^{2,3}. In addition, SGLT-2is might potentially reduce the risk of cardiovascular events in diabetes patients with high risk factors⁴⁻⁶. It has also been shown that in patients with type 2 diabetes, treatment with SGLT-2is resulted in 39% fewer hospitalizations for heart failure and 51% fewer deaths from any cause than were observed for other type 2 diabetes medicines. When hospitalization for heart failure and death from any cause were combined, the reduction was 46%⁷. Meanwhile, the reduction of cardiovascular risk factors, such as bodyweight, systolic blood pressure (SBP) and diastolic blood pressure (DBP), and uric acid level, were also reported in these studies⁸⁻¹⁰, probably intermediates the cardiovascular protective effects of SGLT-2is.

Therefore, we sought to determine whether SGLT-2is as add-on treatment to insulin therapy could improve cardiovascular risk factors and reduce the side-effects of insulin, and thus benefit cardiovascular outcomes in type 2 diabetes patients.

Recently, some high-quality and randomized controlled studies of the efficacy and safety of SGLT-2is in addition to insulin therapy have emerged. However, there has been no meta-analysis or systematic review on this. Therefore, we carried out the present meta-analysis to evaluate the effects of SGLT-2is in addition to insulin on cardiovascular risk factors in type 2 diabetes patients.

METHODS

The present meta-analysis was carried out in accordance with the recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement¹¹.

Data sources and search strategy

PubMed, Embase and Cochrane Library databases were searched to identify relevant studies published before September

2017. Trials that were published between 2009 and 2017 were manually searched. We first carried out a search using the following MeSH terms: 'canagliflozin,' 'dapagliflozin,' 'ertugliflozin,' 'luseogliflozin,' 'sotagliflozin,' 'ipragliflozin,' 'empagliflozin,' 'tofogliflozin' and 'insulin.' Then, we searched for these MeSH terms and their corresponding entry terms (using every MeSH term) as combinations of terms in the [Title/Abstract] using 'OR.' Finally, we searched the search results for published randomized controlled trials or unpublished trials using 'AND.' The methods used for the literature search are described in detail in the Data S1. All the studies included in this meta-analysis were approved by institutional review boards or independent ethics committees, or in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines for each center. All patients provided written informed consent.

Study selection

We searched for randomized controlled trials carried out to evaluate the efficacy and safety of SGLT-2is administered in combination with insulin in patients with type 2 diabetes. The selection criteria were as follows: the randomized controlled trial had at least an 8-week follow-up period, and it reported cardiovascular outcomes (e.g., blood pressure, glucose control, serum lipid parameters, uric acid levels and changes in serum electrolyte levels) and safety outcomes (e.g., hyperglycemic events, severe hypoglycemic events, urinary tract infections and genital infections).

Data extraction

Studies that were not based on a treatment combining insulin or SGLT-2is, studies with a follow-up period of <8 weeks or studies that included individuals with type 1 diabetes were excluded. When multiple reports described the same randomized controlled trial, the most recent or most complete study was included. Whether other oral medicines were added to the treatment regimen was not an elimination criterion. Single-arm and open-control trials were excluded.

Quality assessment

Two independent reviewers (Bingshu Wu and Difei Wang) evaluated the studies according to the inclusion and exclusion criteria, and assessed the risk of bias according to the Cochrane risk of bias tool¹². The following domains were considered: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Disagreements were resolved in discussions.

Statistical analysis

The effect of administering SGLT-2is in combination with insulin was assessed according to the six following outcomes: blood pressure, glucose control, bodyweight, serum lipid levels, uric acid levels and changes in serum electrolyte levels. All six outcomes were assessed as continuous variables. We calculated pooled outcomes for weighted mean differences (WMDs) and 95% confidence intervals (CIs) using a random-effects model. Heterogeneity was assessed using the I^2 statistic. Values >50% were viewed as indicative of moderate-to-high heterogeneity¹³. We also carried out subgroup analyses and sensitivity analyses to test the heterogeneity and stability of our findings. We used Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata/SE 12.0 (StataCorp, College Station, TX, USA) for all statistical analyses.

RESULTS

Study characteristics and quality assessment results

The search strategy identified 2,890 citations that were published before September 2017 in the PubMed, Embase and Cochrane Library databases. After duplicate studies were eliminated using Endnote reference manager, 676 articles remained. The 676 resulting titles and abstracts were reviewed, and 21 articles were determined to be potentially eligible for inclusion. The full-text of each of these was then retrieved and evaluated. Of these 21 studies, 11 were excluded for the reasons described in Data S1 (flow chart). The 10 remaining trials were published between 2009 and 2017 (Table 1). The trial durations were 12– 104 weeks in length. All participants were adult patients with type 2 diabetes.

For all of the included studies, a risk of bias assessment was carried out using The Cochrane Collaboration risk of bias tool (Figure 2 in Data S1).

Meta-analysis results

The effects of the included treatments on cardiovascular risk factors were determined according to the following characteristics: blood pressure, lipid levels, glycemic efficacy (i.e., changes in the insulin dose or glycosylated hemoglobin [HbA1c], fasting plasma glucose [FPG] or 2-h postprandial glucose [PPG] levels), bodyweight, uric acid and serum electrolyte levels (i.e., sodium, potassium and magnesium).

Blood pressure and lipid levels

Treatment with a single SGLT-2i in addition to insulin \pm other antidiabetic drugs resulted in better blood pressure control than was observed in the placebo groups. The corresponding WMDs were -3.17 mmHg (95% CI -4.53, -1.80, $I^2 = 0\%$) and -1.60 mmHg (95% CI -2.52, -0.69, $I^2 = 0\%$; Figures 1 and 2). After incomplete data were excluded, the results for lipid levels, including total cholesterol, triglyceride, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels, were slightly different or showed no statistical significance in the intervention groups (Data S2).

Glycemic control

When incomplete data was excluded, the SGLT-2i group, to a certain extent, showed lower levels of HbA1c, FPG, PPG and daily insulin than were observed in the control group. The corresponding WMDs were -0.49% (95% CI -0.71, -0.28%,

 $I^2 = 92\%$), -1.10 mmol/L (95% CI -1.69, -0.51, $I^2 = 84\%$), -3.63 mmol/L (95% CI -4.36, -2.89, $I^2 = 0\%$) and -5.42 IU/day (95% CI -8.12, -2.72, $I^2 = 93\%$; Figures 3-6).

Bodyweight

After incomplete data were excluded, bodyweight was significantly lower in the SGLT-2i group than in the control group (Figure 7). The WMD was -2.13 kg (95% CI -2.66, -1.60, $I^2 = 83\%$).

Uric acid

Patients in the experimental groups had substantially lower uric acid levels (-26.16 μ mol/L, 95% CI -42.14, -10.17, $I^2 = 80\%$) than were observed in the placebo-controlled groups (Figure 8).

Serum electrolyte

After incomplete data were excluded, the results showed that serum electrolyte levels, including sodium, potassium and magnesium levels, were slightly altered in the experimental groups (Data S2).

Subgroup analysis

First, considering the impact of the variation of the follow-up period, we analyzed the above indicators in the short-term (<24 weeks) and long-term (>52 weeks) subgroups, separately. The WMD of DBP was greater in the long-term subgroup (-1.96 mmHg, 95% CI -3.32, -0.61, $I^2 = 0\%$) than that in the short-term subgroup (-1.31 mmHg, 95% CI -2.57, -0.04, $I^2 = 2\%$; Figure 9). The WMDs of daily insulin were similar between the subgroups: -5.63 IU/day (95% CI -9.46, -1.81, $I^2 = 96\%$) in the short-term subgroup and -5.23 IU/day (95%) CI -8.70, -1.77, $I^2 = 63\%$) in the long-term subgroup (Figure 10). The WMD of bodyweight was greater in the long-term subgroup (-2.77 kg, 95% CI -3.19, -2.35, $I^2 = 0\%$) than that in the short-term subgroup (-1.59 kg, 95% CI -2.26, -0.93, $I^2 = 85\%$; Figure 11). The difference of SBP, HbA1c and FPG were non-significant or could not be analyzed for enough participants in the subgroups.

Second, to investigate the specific effects of different SGLT-2is, we compared the above indicators for each kind of them as possible (Data S2). Tofogliflozin showed a greater reduction of SBP (-3.37 mmHg, 95% CI -6.64, -0.10, $I^2 = 0\%$) compared with canagliflozin (-3.18 mmHg, 95% CI -2.26, -0.93) and ipragliflozin (-2.90 mmHg, 95% CI -6.41, 0.05). Tofogliflozin also showed a greater reduction of DBP (-2.63 mmHg, 95% CI $-4.86, -0.39, I^2 = 0\%$) than empagliflozin (-1.96 mmHg, 95%) CI -3.32, -0.61, $I^2 = 0\%$). Ipragliflozin showed a greater reduction of HbA1c (-1.34%, 95% CI -1.62, -1.06%) compared with canagliflozin (-0.84%, 95% CI -1.12, -0.56%, $I^2 = 85\%$) and tofogliflozin (-0.83%, 95% CI -1.19, -0.47%, $I^2 = 56\%$). Ipragliflozin also showed a greater reduction of FPG (-2.81 mmol/L, 95% CI -1.12, -0.56) compared with empagliflozin (-0.59 mmol/L, 95% CI -1.12, -0.56, $I^2 = 44\%$), canagliflozin (-1.73 mmol/L, 95% CI -2.95, -0.55) and tofogliflozin

Table 1 Stud	ly characteristics							
Name	Duration of diabetes (years)	Age (years)	BMI (kg/m ²)	HbA1c (%)	Trial duration (weeks)	Interventor	Dose of SGLT-2i	Placebo group
JPW 2009 ¹⁴	12.28/6.27	56.70/8.90	35.51/4.27	8.43/0.83	12	Dapaglifiozin + insulin + OAD	10 mg	Insulin + OAD
JPW 2014 ¹⁵	13.59/7.27	59.31/8.21	33.12/5.32	8.53/0.82	104	Dapagliflozin + insulin ± OAD	2.5 mg 5/10 mg	Insulin ± OAD
JR 2015 ¹⁶	>4.72	58.8/9.90	32.2/5.90	8.2/0.80	78	Empagliflozin + insulin ± OAD	10 mg	Insulin ± OAD
JR 2014 ¹⁷	>8.78	56.7/9.50	34.8/4.10	8.34/0.73	52	Empagliflozin + insulin ± metformin	10 mg	Insulin ± metformin
NI 2016 ¹⁸	13.82/8.51	57.97/10.27	26.45/4.63	8.87/0.82	16	Canagliflozin + insulin	22 mg 100 mg	Insulin
BN 2015 ¹⁹	16.23/7.50	62.67/11.94	33.13/6.40	8.3/0.90	52	Canagliflozin + insulin	100 mg	Insulin
HI 2016 ²⁰	13.17/8.08	58.87/10.50	25.89/3.64	8.653/0.80	16	Ipragliflozin + insulin ± DPP-4	suu mg 50 mg	Insulin ± DPP-4
EA 2016 ²¹	6.77/5.87	58/9.82	26.64/4.51	8.34/0.85	16	Dapagliflozin + insulin ± OAD	5 mg	Insulin ± OAD
KS 2016 ²²	14.91/6.33	57.24/11.73	28.71/5.72	8.67/0.97	24	Tofogliflozin + insulin ± OAD	20 mg	Insulin ± OAD
YT 2017 ²³	14.15/8.81	58.20/10.59	26.16/3.67	8.49/0.72	16	Tofogliflozin + glargine ± OAD Tofogliflozin + insulin ± OAD	20 mg 20 mg	Insulin ± OAD Insulin ± OAD
The data are s ¹ 2016 ²¹ . BMI, bc	hown as the mean∕st vdy mass index; DPP~	andard deviation. 4, dipeptidyl pept	Data were extract idase-4; HbA1c, gly	ted until 16 wee ycosylated hemc	ks (a double-blind - globin; OAD, oral a	treatment) instead of 36 weeks (an open-l intidiabetic drug; SGLT-2i, sodium–glucose	abel extension cotransporter	treatment) from EA 2.

-

Figure 1 | Forest plot of randomized controlled trials: effect on systolic blood pressure. CI, confidence interval; SD, standard deviation.

	Ex	periment	tal	Co	ntrol			Mean difference Mean difference				e	
Study or Subgroup	Mean	SD	Total	Mear	s SD	Total	Weight	IV,Random,95% C		IV,Rai	ndom,95% (Cl	
H. I 2016 50 mg	-0.3	9.9	167	0.3	9.2	87	13.9%	-0.60 [-3.05, 1.85]			-		
J.P.W 2009 10 mg	1.3	10.788	22	-4.1	10.102	14	1.7%	5.40 [-1.55, 12.35]					
J.P.W 2009 20 mg	-5.8	8.4427	22	-4.1	10.102	14	2.1%	-1.70 [-8.06, 4.66]				5	
J.R 2015 10 mg	-2.6	8.259	169	-0.3	7.823	170	28.3%	-2.30 [-4.01, -0.59]					
J.R 2014 10 mg	-1.9	14.018	186	-0.5	6.4343	188	16.9%	-1.40 [-3.61, 0.81]					
K.S 201 6 glargine 20 mg	-3.3	11.14	19	0.5	11.08	15	1.5%	-3.80 [-11.32, 3.72]		_			
K.S 2016 insulin 20 mg	-5.6	13.48	19	0.5	11.08	15	1.2%	-6.10 [-14.36, 2.16]					
N.I2016 100 mg	-1.55	6.1896	76	-0.31	6.1913	70	20.5%	-1.24 [-3.25, 0.77]			-		
Y.T 2017	-1.8	9.4	135	0.4	7.7	66	13.9%	-2.20 [-4.64, 0.24]			-		
Total (95% Cl)			815			639	100.0%	-1.60 [-2.52, -0.69]			•		
Heterogeneity: $\tau^2 = 0.00$, χ^2	= 7.04, 0	df = 8 (P =	= 0.53);	$l^2 = 0\%$)			-	-				
Test for overall $Z = 3.45$ ($P =$	0.0006))							-20	-10	0	10	20
									Favo	rs [experime	ntal] Favors	s [control]	

Figure 2 | Forest plot of randomized controlled trials: effect on diastolic blood pressure. CI, confidence interval; SD, standard deviation.

	Expe	Experimental			erimental Control						Mean difference	Mean difference
Study or Sub group	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl			
BN 2015 300 mg	-0.69	0.9663	664	0.03	0.9227	639	6.8%	-072 [-0.82, -0.62]	•			
BN 2015 100 mg	-0.55	0.9405	664	0.03	0.9227	639	6.8%	-0.58 [-0.68, -0.48]	•			
Eiichi 2016 5 mg	-0.6	1.4092	118	0.04	0.64549	55	6.1%	-0.64 [-0.95, -0.33]				
H. I 2016 50 mg	-1.07	1.6017	168	0.27	0.65	87	6.2%	-1.34 [-1.62, -1.06]	+			
J.P.W 2009 10 mg	-0.7	1.0067	23	0.09	0.622	19	5.1%	-0.79 [-1.29, -0.29]				
J.P.W 2009 20 mg	-0.78	1.0067	23	0.09	0.622	19	5.1%	-0.87 [-1.37, -0.37]				
J.P.W 2014	-0.21	1.5775	132	-0.43	0.783	107	6.1%	0.22 [-0.09, 0.53]				
J.P.W 2014 05/10 mg	-0.39	1.6034	128	-0.43	0.783	107	6.1%	0.04 [-0.27, 0.35]	+			
J.P.W 2014 10 mg	-0.35	1.6004	139	-0.43	0.783	107	6.1%	0.08 [-0.22, 0.38]	+			
J.R 2015 10 mg	-0.5	1.8572	127	0	0.9899	98	5.7%	-0.50 [-0.88, -0.12]				
J.R 2014 10 mg	-0.38	1.678	119	-0.81	0.869	118	5.9%	0.43 [0 09, 0 77]	-			
J.R 2014 25 mg	-0.46	1.6355	118	-0.81	0.869	118	6.0%	0.35 [0.02, 0.68]	-			
J.R 2015 25 mg	-0.6	1.7766	110	0	0.9899	98	5.7%	-0.60 [-0.99, -0.21]				
K.S 2016 glargine 20 mg	-0.8	1.1	19	-0.3	0.56	15	4.7%	-0.50 [-1.07, 0.07]				
K.S 2016 insulin 20 mg	-1	0.93	19	-0.3	0.56	15	5.1%	-0.70 [-1.21, -0.19]				
N. I 2016 100 mg	-1.1	1.406	76	0.13	0.6693	70	5.9%	-1.23 [-1.58, -0.88]				
Y.T 2017	-072	0.71	135	0.35	0.74	66	6.5%	-1.07 [-1.28, -0.86]	-			
Total (95% Cl)			2782			2377	100.0%	-0.49 [-0.71, -0.28]	•			
Heterogeneity: $\tau^2 = 0.18$;	$\chi^2 = 194$.03, df = ⁻	16 (P <	0.00001); <i>I</i> ² = 92%	6						
Test for overall effect: $Z =$	4.44 (P <	< 0.00001)						-4 -2 0 2 4			
			· /						Favors [experimental] Favors [control]			

Figure 3 | Forest plot of randomized controlled trials: effect on glycosylated hemoglobin. Cl, confidence interval; SD, standard deviation.

	Expe	erimental		C	ontrol			Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV,Random, 95% Cl	IV,Random, 95% Cl
Eiichi 2016 5 mg	-1.261	3.9146	118	0.66	0.05	55	7.3%	-1.92 [-2.63, -1.21]	
H. I 2016 50 mg	-2.23	3.9168	123	0.58	2.19	61	6.9%	-2.81 [-3.69, -1.93]	
J.P.W 2009 10 mg	-0.856	3.3215	23	0.989	2.055	22	5.1%	-1.84 [-3.45, -0.24]	
J.P.W 2009 20 mg	-1.522	3.3059	23	0.989	2.055	22	5.1%	-2.51 [-4.11, -0.91]	
J.P.W 2014	-0.14	4.5153	124	-1	2.23046	101	6.9%	0.86 [-0 05, 1.77]	
J.P.W 2014 05/10 mg	-0.89	4.4969	126	-1	2.23046	101	6.9%	0.11 [-0.79, 1.01]	
J.P.W 2014 10 mg	-0.31	4.5657	133	-1	2.23046	101	6.9%	0.69 [-0 20, 1.58]	+
J.R 2015 10 mg	-0.7	3.5714	104	0.2	1.9183	92	7.1%	-0.90 [-1.69, -0.11]	
J.R 2014 10 mg	-0.69	4.1601	117	-0.63	2.0018	111	7.0%	-0.06 [-0 90, 0.78]	-
J.R 2014 25 mg	-0.79	4.1306	118	-0.63	2.0018	111	7.0%	-0.16 [-0.99, 0.67]	
J.R 2015 25 mg	-1	3.4604	92	0.2	1.9183	92	7.1%	-1.20 [-2.01, -0.39]	
K.S 2016 glargine 20 mg	-1.84	1.54	19	-0.61	1	15	7.0%	-1.23 [-2.09, -0.37]	
K.S 2016 insulin 20 mg	-3.41	2.43	19	-0.61	1	15	6.1%	-2.80 [-4.00, -1.60]	
N. I 2016 100 mg	-1.811	4.6366	75	-0.078	2.324	70	6.2%	-1.73 [-2.92, -0.55]	
Y.T 2017	-1.51	2.13	135	0.29	2.33	66	7.4%	-1.80 [-2.47, -1.13]	
Total (95% Cl)			1349			1035	100.0%	-1.10 [-1.69, -0.51]	•
Heterogeneity: $\tau^2 = 1.11$	$\chi^2 = 87.$	79, df = 1	4 (P <	0.00001); $l^2 = 84$	%			
Test for overall effect: Z =	 = 3.67 (P =	= 0.0002)							-4 -2 0 2 4
									Favors [experimental] Favors [control]

Figure 4 | Forest plot of randomized controlled trials: effect on fasting glucose plasma. CI, confidence interval; SD, standard deviation.

	Exp	erimental			Control			Mean difference	Mean difference	
Study or Sub group	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
Eiichi 2016 5 mg	-2.576	6.449	118	0.486	3.3312	55	25.4%	-3.06 [-4.52, -1.60]		
J.P.W 2009 10 mg	-1.905	3.256	19	1.83	3.2304	15	11.2%	-3.74 [-5.93, -1.54]		
J.P.W 2009 20 mg	-2.328	3.68197	18	1.83	3.2304	15	9.7%	-4.16 [-6.52, -1.80]		
Y.T 2017	-3.6	3.06	134	0.18	3.57	66	53.6%	-3.78 [-4.79, -2.77]	•	
Total (95% Cl)			289			151	100.0%	-3.63 [-4.36, -2.89]	•	
Heterogeneity: $\tau^2 = 0$	0.00; $\chi^2 = 0$	0.87, df = 1	3 (P = 0)	.83); / ² =	= 0%			-		
Test for overall effect	: <i>Z</i> = 9.67	(P < 0.000	01)						Favors [experimental] Favors [control]	

Figure 5 | Forest plot of randomized controlled trials: effect on 2-h postprandial glucose. Cl, confidence interval; SD, standard deviation.

	Exp	erimental		С	ontrol			Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random 95% Cl	IV, Random 95% Cl
Eiichi 2016 5 mg	-0.74	2.57796	118	-0.02	2.44139	55	10.2%	-0.72 [-1.52, 0.08]	*
J.P.W 2009 10 mg	-1.4	12.433	24	1.7	12.4048	22	5.9%	-3.10 [-10.28, 4.08]	
J.P.W 2009 20 mg	-0.8	12.5514	24	1.7	12.4048	22	5.9%	-2.50 [-9.72, 4.72]	
J.P.W 2014	4.1	25.0141	130	1.83	23.9342	104	6.6%	2.27 [-4.03, 8.57]	
J.P.W 2014 05/10 mg	1.6	24.8209	128	1.83	23.9342	104	6.6%	-0.23 [-6.53, 6.07]	
J.P.W 2014 10 mg	-0.8	25.9583	140	1.83	23.9342	104	6.6%	-2.63 [-8.93, 3.67]	
J.R 2015 10 mg	-1.2	16.086	115	5.5	16.159	102	8.2%	-6.70 [-11.00, -2.40]	
J.R 2014 10 mg	-0.63	22.812	119	10.2	23.592	115	6.9%	-10.83 [-16.78, -4.88]	
J.R 2014 25 mg	-1.1	22.715	118	10.2	23.592	115	6.9%	–11.30 [–17.25, –5.35]	
J.R 2015 25 mg	-0.5	15.677	96	5.5	16.159	102	8.0%	-6.00 [-10.43, -1.57]	_ -
K.S 2016 glargine 20 mg	-12.7	5.19	19	5.1	3.54	15	9.2%	-17.80 [-20.74, -14.86]	
K.S 2016 insulin 20 mg	-2.6	6.25	19	5.1	3.54	15	8.9%	-7.70 [-11.03, -4.37]	
Y.T 2017	-1.3	4.8	128	-0.2	0.8	64	10.2%	-1.10 [-1.95, -0.25]	•
Total (95% Cl)			1178			939	100.0%	-5.42 [-8.12, -2.72]	
Heterogeneity: $\tau^2 = 18.42$; $\chi^2 = 16$	54.03, df =	= 12 (P	< 0.000	001); <i>l</i> ² = 9	93%		-	-20 -10 0 10 20
Test for overall effect: $Z =$	3.94 (P	< 0.0001)							Favors [experimental] Favors [control]
					~				

Figure 6 | Forest plot of randomized controlled trials: effect on daily insulin. Cl, confidence interval; SD, standard deviation.

	Exp	erimental			Control			Mean difference		Me	an differe	ence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weiht	IV,Random,95% Cl		IV,R	andom,95	5% CI	
Eiichi 2016 5 mg	-0.55	1.71809	118	0.66	1.64594	55	8.3%	-1.21 [-1.74, -0.68]			-		
H. I 2016 50 mg	-1.09	1.27	168	-0.05	1.42	87	8.8%	-1.04 [-1.39, -0.69]			+		
J.P.W 2009 10 mg	-4.5	2.3125	23	-1.9	2.25543	22	5.8%	-2.60 [-3.93, -1.27]			-		
J.P.W 2009 20 mg	-4.3	2.3125	23	-1.9	2.25543	22	5.8%	-2.40 [-3.73, -1.07]			-		
J.P.W 2014	-0.99	4.2205	132	1.83	4.11652	107	6.7%	-2.82 [-3.88, -1.76]			-		
J.P.W 2014 05/10 mg	-1.03	4.15606	128	1.83	4.11652	107	6.7%	-2.86 [-3.92, -1.80]			-		
J.P.W 2014 10 mg	-1.5	4.33171	141	1.83	4.11652	107	6.7%	-3.33 [-4.39, -2.27]					
J.R 2015 10 mg	-2.2	5.3151	113	0.7	5	100	5.6%	-2.90 [-4.29, -1.51]			-		
J.R 2014 10 mg	-1.95	3.9271	119	0.44	3.8606	115	6.9%	-2.39 [-3.39, -1.39]			-		
J.R 2014 25 mg	-2.04	3.9106	118	0.44	3.8606	115	6.9%	-2.48 [-3.48, -1.48]			-		
J.R 2015 25 mg	-2	4.899	96	0.7	5	100	5.6%	-2.70 [-4.09, -1.31]			-		
K.S 2016 glargine 20 mg	-3.4	3.07	19	0.6	1.51	15	5.0%	-4.00 [-5.58, -2.42]					
K.S 2016 insulin 20 mg	2.9	3.31	19	0.6	1.51	15	4.8%	2.30 [0.63, 3.97]			-	-	
N. I 2016 100 mg	-2.13	2.1651	75	0.24	2.1753	70	7.8%	-2.37 [-3.08, -1.66]			-		
Y.T 2017	-1.34	1.62	135	0.03	1.36	64	8.6%	-1.37 [-1.80, -0.94]			+		
Total (95% Cl)			1427			1101	100.0%	-2.13[-2.66, -1.60]		•			
Heterogeneity: $\tau^2 = 0.80$;	$\chi^2 = 82.0$	08, df = 14	(<i>P</i> < 0	.00001)	; $l^2 = 83\%$				+	<u> </u>		<u> </u>	+
Test for overall effect: $Z =$	7.87 (P -	< 0.00001))						-10	-5	0	5	10
									Favo	ors [experim	ental] Fav	ors [control]	



	Exper	iment	al	C	ontrol			Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV,Random,95% Cl	IV,Random,95% Cl
J.R 2015 10 mg	-5	69	129	1	68	121	19.7%	-6.00 [-22.99, 10.99]	
J.R 2014 10 mg	-23	95	186	12	81	188	19.2%	-35.00 [-52.90, -17.10]	+
J.R 2014 25 mg	-42	92	189	12	81	188	19.4%	-54.00 [-71.50, -36.50]	-
J.R 2015 25 mg	-23	68	120	1	68	121	19.6%	-24.00 [-41.17, -6.83]	-
Y.T 2017	-10	41	135	3.89	40.6	66	21.1%	-13.89 [-25.88, -1.90]	-
Total (95% Cl) Heterogeneity: $\tau^2 = 2$ Test for overall effect:	62.96; χ ² = <i>Z</i> = 3.21 (= 19.79 P = 0.0	759 9, df = 4 001)	4 (<i>P</i> = 0.	0005);	684 /² = 809	100.0% %	-26.16 [-42.14, -10.17]	-200 -100 0 100 200 Favors [experimental] Favors [control]

Figure 8 | Forest plot of randomized controlled trials: uric acid. CI, confidence interval; SD, standard deviation.

	Exp	erimenta	I	C	Control			Mean difference	Mean difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl				
1.8.1 <= 24 weeks													
H. I 2016 50 mg	-0.3	9.9	167	0.3	9.2	87	13.9%	–0.60 [–3.05, 1.85]					
J.P.W 2009 10 mg	1.3	10.788	22	-4.1	10.102	14	1.7%	5.40 [-1.55, 12.35]					
J.P.W 2009 20 mg	-5.8	8.4427	22	-4.1	10.102	14	2.1%	–1 .70 [–8.06, 4.66]					
K.S 2016 glargine 20 mg	-3.3	11.14	19	0.5	11.08	15	1.5%	-3.80 [-11.32, 3.72]					
K.S 2016 insulin 20 mg	-5.6	13.48	19	0.5	11.08	15	1.2%	-6.10 [-14.36, 2.16]					
N. I 2016 100 mg	-1.55	6.1896	76	-0.31	6.1913	70	20.5%	-1.24 [-3 .25, 0.77]					
Y.T 2017	-1.8	9.4	135	0.4	/./	66	13.9%	-2.20 [-4.64, 0.24]					
Subtotal (95% CI)		10 - 10	460			281	54.8%	-1.31 [-2.5/, -0.04]	•				
Heterogeneity: $\tau^2 = 0.08$; χ	$f^2 = 6.15$	df = 6 (P	' = 0.41); $l^2 = 2$	%								
lest for overall effect: $Z = $.	2.03 (P =	: 0.04)											
1 9 2 5 - 52 wooks													
LB 2015 10 mg	26	0 250	160	0.2	7072	170	20 20%	2 20 [4 01 0 50]	+				
LR 2014 10 mg	-2.0	0.239	109	-0.5	6 / 3 / 3	1/0	20.3%	-2.30 [-4.01, -0.39]					
Subtotal (95% CI)	-1.9	14.010	355	-0.5	0.4545	358	45.2%	-1.40 [-3.01, 0.01]	•				
Hataragapaity: $t^2 = 0.00$: y	2 - 0.40	df = 1 (G	- 052	$2 \cdot l^2 = 0$	04	550	13.270	1.50[5.52, 0.01]	•				
Test for overall effect: $Z = 0.00$, χ	2 84 (P =	: 0 005)	- 0.52	5), 1 = 0	170								
	2.010	0.005)											
Total (95% CI)			815			639	100.0%	-1.60 [-2.52, -0.69]	•				
Heterogeneity: $T^2 = 0.00$: x	$^{2} = 7.04$	df = 8 (P	$= 0.5^{-3}$	(3): $l^2 = 0$	1%								
Test for overall effect: $Z = 1$	3.45 (P =	0.0006)		-,,					-20 -10 0 10 20				
Test for subgroup differen	ices: \dot{x}^2 =	= 0.48, df	= 1 (P =	= 0.49);	$l^2 = 0\%$				Favors [experimental] Favors [control]				
5 1	~	.,		- //									

Figure 9 | Subgroup analysis of diastolic blood pressure based on duration. Cl, confidence interval; SD, standard deviation.

	Expe	erimental		Co	ontrol			Mean difference	e Mean d	ifference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95%	CI IV, Rando	m, 95% Cl
1.10.1 <= 24 weeks										
Eiichi 2016 5 mg	-0.74	2.57796	118	-0.02	2.44139	55	10.2%	-0.72 [-1.52, 0.0	8]	•
J.P.W 2009 10 mg	-1.4	12.433	24	1.7	12.4048	22	5.9%	-3.10 [-10.28, 4.0	8]	
J.P.W 2009 20 mg	-0.8	12.5514	24	1.7	12.4048	22	5.9%	-2.50 [-9.72, 4.7	2]	
K.S 2016 glargine 20 mg	-12.7	5.19	19	5.1	3.54	15	9.2%	-17.80 [-20.74, -14.8	6] —	
K.S 2016 insulin 20 mg	-2.6	6.25	19	5.1	3.54	15	8.9%	-7.70 [-11.03, -4.3	7] —	
Y.T 2017	-1.3	4.8	128	-0.2	10.8	64	10.2%	-1.10 [-1.95, -0.2	5]	1
Subtotal (95% CI)	2		332			193	50.3%	-5.63 [-9.46, -1.8	1] 🔶	
Heterogeneity: $\tau^2 = 18.6/;$	$\chi^2 = 13$	5.41, df =	5 (P <)	0.00001); $l^2 = 96\%$	ó				
Test for overall effect: $Z = 2$	2.89 (P =	: 0.004)								
1100 c 50 weeks										
$1.10.2 \le 52$ weeks	4.1	25 01 41	120	1 0 2	220242	104	6 6 0/		- 17	
J.P.W 2014	4.1	23.0141	150	1.00	23.9342	104	0.0%	2.27 [-4.05, 6.5	7]	
J.P.W 2014 05/10 mg	1.0	24.0209	120	1.05	22.9342	104	6.60%	-0.23 [-0.33, 0.0	7]	
IR 2015 10 mg	-0.8	16.086	140	1.03	16 150	104	0.0% 8.2%	-2.05 [-0.95, 5.0	/] 	
IR 2014 10 mg	-0.63	22.812	119	10.2	23 592	115	6.2%	-0.70 [-11.00, -2.4	8]	
IR 2014 25 mg	_1 1	22.012	118	10.2	23.592	115	6.9%	_11 30 [_17 25 _5 3	5]	
IR 2015 25 mg	-0.5	15677	96	55	16 159	102	8.0%	-6.00 [-10.43 -1.5	7]	
Subtotal (95% CI)	0.5	151077	846	0.0	101100	746	49.7%	-5.23 [-8.70, -1.7	7] 🔶	
Heterogeneity: $\tau^2 = 13.63$:	$\gamma^2 = 16$.42. $df = 6$	(P = 0)	.00001):	$l^2 = 63\%$					
Test for overall effect: $Z = 2$	2.96 (P =	: 0.003)	v	,						
		,								
Total 95% CI)			1178			939 1	00.0%	-5.42 [-8.12, -2.72]	•	
Heterogeneity: $\tau^2 = 18.42$;	$\chi^2 = 16$	4.03, df =	12 (P <	0.0000)1); <i>l</i> ² = 93	%				+ + +
Test for overall effect: $Z = 3$	3.94 (<i>P</i> =	0.0001)							-20 -10	0 10 20
Test for subgroup differen	ce: $\chi^2 =$	0.02. df =	1 (<i>P</i> =	0.88). <i>l</i> ²	= 0%				Favors [experimental]	Favors [control]

Figure 10 | Subgroup analysis of daily insulin based on duration. Cl, confidence interval; SD, standard deviation.

	Ex	perimenta	al		Control			Mean difference		Mean diffe	erence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl		IV, Random	n, 95% CI	
1.22.1 <=24 weeks Eiichi 2016 5 mg H. 1 2016 50 mg J.P.W 2009 10 mg J.P.W 2009 20 mg K.S 2016 glargine 20 mg K.S 2016 insulin 20 mg N. 1 2016 100 mg Y.T 2017 Subtotal (95% Cl) Heterogeneity: $\tau^2 = 0.66$; Test for overall effect: Z =	-0.55 -1.09 -4.5 -3.4 2.9 -2.13 -1.34 $\chi^{2} = 46$ 4.72 (P	1.71809 1.27 2.3125 2.3125 3.07 3.31 2.1651 1.62 .06, df = 7 < 0.00001	118 168 23 23 19 19 75 135 580 7 (P < 0)	0.66 -0.05 -1.9 -1.9 0.6 0.6 0.24 0.03	1.64594 1.42 2.25543 2.25543 1.51 1.51 2.1753 1.36 ; l ² = 85%	55 87 22 15 15 70 64 350	8.3% 8.8% 5.8% 5.0% 4.8% 7.8% 8.6% 54.9%	-1.21 [-1.74, -0.68] -1.04 [-1.39, -0.69] -2.60 [-3.93, -1.27] -2.40 [-3.73, -1.07] -4.00 [-5.58, -2.42] 2.30 [0.63, 3.97] -2.37 [-3.08, -1.66] -1.37 [-1.80, -0.94] -1.59 [-2.26, -0.93]	-	++ + + + + + + + + + + + + + + + + + +		
1.22.2 >=52 weeks J.P.W 2014 J.P.W 2014 05/10 mg J.P.W 2014 10 mg J.R 2015 10 mg J.R 2014 10 mg J.R 2014 25 mg J.R 2015 25 mg Subtotal (95% Cl) Heterogeneity: $\tau^2 = 0.00$; Test for overall effect: Z =	-0.99 -1.03 -1.5 -2.2 -1.95 -2.04 -2 $\chi^{2} = 2.0$ $\chi^{2} = 2.0$	4.2205 4.15606 4.33171 5.3151 3.9271 3.9106 4.899 04, df = 6 (p < 0.0000	, 132 128 141 113 119 118 96 847 P = 0.9	1.83 1.83 1.83 0.7 0.44 0.44 0.7	4.11652 4.11652 4.11652 5 3.8606 3.8606 5 0%	107 107 100 115 115 100 751	6.7% 6.7% 6.7% 5.6% 6.9% 5.6% 45.1%	-2.82 [-3.88, -1.76] -2.86 [-3.92, -1.80] -3.33 [-4.39, -2.27] -2.90 [-4.29, -1.51] -2.39 [-3.39, -1.39] -2.48 [-3.48, -1.48] -2.70 [-4.09, -1.31] -2.77 [-3.19, -2.35]		++ ++ ++ ++ ++ ++ ++ ++		
Total (95% Cl) Heterogeneity: τ^2 = 0.80; Test for overall effect: Z = Test for subgroup differe	χ ² = 82 7.87 (P nces: τ ²	2.08, df = 1 < 0.00001 = 8.63. df	1427 7 (P <) = 1 (P	0.0000	1); $l^2 = 839$ 3). $l^2 = 88.4$	1101 % 4%	100.0%	-2.13 [-2.66, -1.60]	–10 – Favors [exp	-5 0 perimental]	5 Favors [control]	
Figure 11 Subgroup an	alysis o	f body w	reight	based	on durat	ion. Cl	, confide	ence interval; SD, st	andard deviat	ion.		

(-1.84 mmol/L, 95% CI -2.59, -1.09, $I^2 = 54\%$). Tofogliflozin showed a greater reduction of PBG (-3.78 mmol/L, 95% CI - 4.79, -2.77) than dapagliflozin (-3.06 mmol/L, 95% CI -4.52, -1.60, $I^2 = 0\%$). Ipragliflozin showed a lower reduction of bodyweight (-1.04 kg, 95% CI -1.39, -0.69) than dapagliflozin (-2.48 kg, 95% CI -3.31, -1.66, $I^2 = 75\%$), empagliflozin (-2.56 kg, 95% CI -3.13, -1.99, $I^2 = 0\%$) and canagliflozin (-2.37 kg, 95% CI -3.08, -1.66). The relative risk (RR) of hypoglycemia with canagliflozin and ipragliflozin were 1.23 (95% CI 1.13, 1.35) and 1.95 (95% CI 1.12, 3.39) compared with their control. The RR of genital infection with dapagliflozin, empagliflozin and canagliflozin were 3.94 (95% CI 1.84, 8.45), 4.01 (95% CI 1.73, 9.29) and 6.12 (95% CI 3.57, 10.48), respectively.

Third, we also took subgroup analysis based on the population of participants. In Asian-dominated studies, compared with non-Asian-dominated studies, SGLT-2i showed a greater reduction of HbA1c (-0.96%, 95% CI -1.22, -0.70%, $I^2 = 71\%$ vs -0.26%, 95% CI -0.51, 0%, $I^2 = 92\%$), daily insulin (-6.53 IU/day, 95% CI -11, -2.05, $I^2 = 98\%$ vs -4.82 IU/day, 95% CI -7.69, -1.95, $I^2 = 54\%$) and a lower reduction of bodyweight (-1.36 kg, 95% CI -2.10, -0.62, $I^2 = 88\%$ vs -2.72 kg, 95% CI -3.11, -2.34, $I^2 = 0\%$), SBP (-3.12 mmHg, 95% CI -4.90, -1.35, $I^2 = 0\%$ vs - 3.23 mmHg, 95% CI -5.37, -1.09, $I^2 = 0\%$), PPG (-3.55 mmol/L, 95% CI -4.38, -2.72, $I^2 = 0\%$ vs -3.93 mmol/L, 95% CI -5.54, -2.32, $I^2 = 0\%$) and uric acid (-13.89 µmol/L, 95% CI -25.88, -1.90 vs -29.66 µmol/L, 95% CI -49.51, -9.82, $I^2 = 81\%$).

Sensitivity analysis

Because significant heterogeneity was identified among these pooled studies, with $I^2 > 50\%$ including HbA1c, FPG, daily insulin, bodyweight and uric acid outcomes, sensitivity analyses were carried out. The results showed that there was no change when the model was switched from a random-effects to a fixed-effects model by Review Manager. The influence of the total effect size is slight when it eliminates any single study (by Stata/SE 12.0 in Data S3).

Publication bias

Finally, to assess publication bias of the results (including at least 10 studies) in the present meta-analysis, we constructed funnel plots using Review Manager. The symmetry of the HbA1c funnel plot shows that there was a low risk of publication bias (Data S4).

Safety

The relative odds ratios of adverse events between the intervention and placebo groups are shown in detail in Data S5. The incidence of hypoglycemic events in the SGLT-2i group increased, and the RR was 1.09 (95% CI 1.02, 1.17, P < 0.01). However, there was no significant difference in severe hypoglycemic events between the two groups (RR 1.24, 95% CI 0.84, 1.84, P = 0.29). Genital infection and urinary tract infection were more common (RR 5.25, 95% CI 3.55, 7.74, P < 0.01; RR 1.29, 95% CI

1.03, 1.62, P = 0.03) in the intervention group than in the placebo group.

DISCUSSION

Patients with diabetes, those who are overweight or obese and those with hypertension or dyslipidemia are more vulnerable to cardiovascular disease^{25,26}. The risk of cardiovascular disease is two- to fourfold higher in diabetes patients than in patients without diabetes²⁴. It is therefore vital to study the effects of antidiabetic therapies on diabetes mellitus patients with regard to their protective effects against cardiovascular events. In the present study, we carried out a meta-analysis to evaluate the effects of SGLT-2is administered in addition to insulin therapy on cardiovascular risk factors in patients with type 2 diabetes mellitus. The reduction of cardiovascular risk factors, such as bodyweight, SBP and DBP, and uric acid level, was probably an intermediate outcome mediated by the cardiovascular protective effects of SGLT-2is, as reported in previous studies^{8–10}.

First, the present results show that SGLT-2is, as add-on to insulin with or without other oral antidiabetic drugs, reduced blood pressure in type 2 diabetes patients. SBP was 3.17 mmHg lower and DBP was 1.60 mmHg lower in the intervention group than in the controls. The activity of SGLT-2is involves a mechanism that reduces the amount of glucose absorbed by inhibiting the function SGLT-2 in renal proximal tubules. As glucose reabsorption is reduced in the kidney, the resorption of sodium from the plasma is simultaneously reduced. It is therefore possible that this mechanism might also affect natriuresis and act as a diuretic²⁷⁻²⁹. This might be the reason that SGLT-2i exerts a hypotensive effect. Further subgroup analysis showed the long-term (≥52 weeks) use of SGLT-2i could obviously lower SBP more than that of shortterm use (≤24 weeks). This means SGLT-2i had played a continuous role of lowering blood pressure. The longer it was used, the more effective it was. Among the different kinds of SGLT-2is, tofogliflozin performed better in lowering blood pressure, which might make it a better choice for those patients with hypertension who require SGLT-2is. This finding is extremely important, because it presents us with a therapy that provides benefits in addition to glucose control in diabetes patients with hypertension, cardiovascular disease or heart failure. These benefits include not only the effective control of glucose levels and blood pressure, but also a reduction in cardiac stress, which improves long-term prognoses.

Hence, SGLT-2i in addition to insulin (with or without other drugs) has shown definite effectiveness when used to control glucose levels in type 2 diabetes patients. It appears to maintain HbA1c levels for an extended period time (e.g., 104 weeks). In addition, the average dose of insulin was approximately 5.42 IU/d lower in the SGLT-2i group, which also reflects a hypoglycemic effect. After subgroup analysis, the SGLT-2i group showed an obviously enhanced glycemic control in short-term studies, whereas that in long-term studies was nonsignificant or slight, which might be because of self-adjustment of inulin doses or other oral antidiabetic drugs in the control group. Ipragliflozin showed a stronger hypoglycemic effect, including HbAlc and FPG, in the present results, which should be considered in clinical prescription.

The Asian-dominated population seemed to be more sensitive to the hypoglycemic effect of SGLT-2i, which might be related to the relative higher blood concentration under the same prescribed dose, because the bodyweight of Asians is lower on average than that of Americans or Europeans. Bodyweight was also lower in patients who used a combination therapy that included SGLT-2i. These patients weighed 2.13 kg less in the SGLT-2i group. The reduction of bodyweight was more significant in the long-term subgroup, which was 1.5-fold of that in the short-term subgroup. Most SGLT-2is had similar effects on the reduction of bodyweight, except for ipragliflozin, which had a slight effect. SGLT-2is brought about more bodyweight reduction in the Asian-dominated population, probably because the baseline bodyweight of the non-Asian-dominated population was higher.

Weight gain is the most common side-effect of insulin therapy, and this is therefore a subject of concern in patients on a long-term insulin regimen. Additionally, weight gain can aggravate insulin resistance³⁰, causing glucose levels to increase, and the required doses of insulin and hypoglycemic agents to correspondingly increase. Elevated blood glucose levels can also increase blood pressure, blood lipids levels, uric acid levels and other cardiovascular risk factors. Hence, weight gain not only makes it difficult to decrease glucose levels, but also increases the risk of cardiovascular disease. Increased insulin doses brought about weight gain, and followed metabolic disorders would adversely reduce the efficiency of insulin itself and required an increase of the insulin doses, which becomes a vicious cycle. The reduction of insulin doses means the break of this vicious cycle, and then fewer side-effects. In the present study, we showed that adding SGLT-2is reduced the amount of insulin a patient used and had a significant effect on weight reduction. These results are intensely gratifying, because they show that this treatment increases the ease of controlling blood glucose levels and clearly reduces obesity, which is a major risk factor for cardiovascular disease.

Previous studies have shown that serum uric acid can injure vascular endothelial cells³¹. Furthermore, increased uric acid levels have been associated with an increased risk of coronary heart disease events, heart failure and atrial fibrillation³². The results of the present study show that in the group treated with SGLT-2is, uric acid levels were reduced more than was observed in the control group by 26.16 μ mol/L (Figure 8). These data suggest that SGLT-2is also improve other cardiovascular disease risk factors, including hyperuricemia.

We also studied the risk factors for cardiovascular disease that are associated with lipid levels. We found that treatment with SGLT-2is and insulin with or without other drugs did not significantly transform serum lipid levels (including total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels), with a mild increase of 0.03 mmol/L both in respect to high-density lipoprotein cholesterol and low-density lipoprotein cholesterol compared with the placebo group. The results of the statistical analysis showed that adding SGLT-2is did not significantly alter serum electrolyte levels (i.e., serum sodium, potassium and magnesium levels).

The present analysis of adverse events showed that the incidence rate of genital infection and urinary tract infection were significantly higher in the SGLT-2i-treated group than in the control group. It is vital to drink enough water, especially for older adults, to prevent the incidence of infection events. The present results also showed that the incidence rate of hypoglycemia was higher when SGLT-2i was added. However, there was no significant difference in the number of severe hypoglycemic events between the two groups. These data show that this combination therapy is appropriate to reduce the dose of insulin or other drugs that would otherwise be required to prevent the occurrence of hypoglycemia.

A limitation of the present meta-analysis was that most studies used the last observation carried forward method to evaluate results at the follow-up end-point. The duration of trials ranged from 12 to 104 weeks. The combinations of other hypoglycemic drugs varied across each study, which might have moderated the effect of SGLT-2i on blood pressure or other indicators. Hence, although the class of drugs was identical, the specific drugs and doses were not the same, and this might have affected our analysis of heterogeneity. There were fewer extracted data, which could influence the analysis results, especially in a forest plot of PPG, uric acid and serum electrolytes. These results should therefore be confirmed by larger and longer-term clinical follow-up trials.

In summary, in patients with type 2 diabetes, administering SGLT-2is combined with insulin with or without other hypoglycemic agents improved blood pressure, plasma glucose levels, bodyweight, uric acid levels and other risk factors associated with cardiovascular disease, and thereby reduced the occurrence and development of cardiovascular events.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (31570819), the Science and Technology Projects of Liaoning Province (2015225024), and the Local Development Foundation of Science and Technology guided by the Central Commission (2016007024).

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

 Alvarez CA, Lingvay I, Vuylsteke V, *et al.* Cardiovascular risk in diabetes mellitus: complication of the disease or of antihyperglycemic medications. *Clin Pharmacol Ther* 2015; 98: 145–161.

- 2. Madaan T, Akhtar M, Najmi AK, *et al.* Sodium glucose Co-Transporter 2 (SGLT2) inhibitors: current status and future perspective. *Eur J Pharm Sci* 2016; 93: 244–252.
- 3. Wright EM, Loo DD, Hirayama BA, et al. Biology of human sodium glucose transporters. *Physiol Rev* 2011; 91: 733–794.
- 4. Wu JH, Foote C, Blomster J, *et al.* Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2016; 4: 411–419.
- 5. Basile JN. The potential of sodium glucose cotransporter 2 (SGLT2) inhibitors to reduce cardiovascular risk in patients with type 2 diabetes (T2DM). *J Diabetes Complications* 2013; 27: 280–286.
- 6. Ji L, Guo L, Guo X, *et al.* Expert guidance on clinical practice of sodium glucose co-transporter 2 inhibitor in China. *Chin J Diabetes* 2016; 24: 10.
- Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation* 2017; 136: 249–259.
- 8. Zinman B, Wanner C, Lachin JM, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in Type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
- Ji L, Ma J, Li H, *et al.* Dapagliflozin as monotherapy in drugnaive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. *Clin Ther* 2014; 36: 84–100.
- Bode B, Stenlof K, Harris S, *et al.* Long-term 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.
- 11. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264–269.
- 12. Higgins J, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
- 13. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
- Wilding JP, Norwood P, Tjoen, C, et al. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. *Diabetes Care* 2009; 32: 1656–1662.
- Wilding JP, Woo V, Rohwedder K, et al. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. *Diabetes Obes Metab* 2014; 16: 124–136.
- 16. Rosenstock J, Jelaska A, Zeller C, *et al.* Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controled on basal insulin: a 78-week

randomized, double-blind, placebo-controled trial. *Diabetes Obes Metab* 2015; 17: 936–948.

- Rosenstock J, Jelaska A, Frappin G, *et al.* Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controled Type 2 diabetes. *Diabetes Care* 2014; 37: 1815–1823.
- 18. Inagaki N, Harashima S, Maruyama N, *et al.* Efficacy and safety of ipragliflozin as add-on therapy to insulinin Japanese patients with type2 diabetes mellitus (IOLITE): a multi-centre, randomized, placebo-controled, double-blind study. *Cardiovasc Diabetol* 2016; 15: 89.
- 19. Neal B, Perkovic V, de Zeeuw D, *et al.* Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with Type 2 diabetes. *Diabetes Care* 2015; 38: 403–411.
- 20. Ishihara H, Yamaguchi S, Nakao I, *et al*. Efficacy and safety of ipragliflozin as add-on therapy to insulin in Japanese patients with type 2 diabetes mellitus (IOLITE): a multi-centre, randomized, placebo-controlled, double-blind study. *Diabetes Obes Metab* 2016; 18: 1207–1226.
- Araki E, Onishi Y, Asano M, et al. Efficacy and safety of dapagliflozin over 1 year as add-on to insulin therapy in Japanese patients with type 2 diabetes: the DAISY (Dapagliflozin Added to patients under InSulin therapY) Trial. *Diabetes Obes Metab* 2017; 19: 562–570.
- 22. Suzuki K, Mitsuma Y, Sato T, *et al.* Comparison of combined tofogliflozin and glargine, tofogliflozin added to insulin, and insulin dose-increase therapy in uncontrolled Type 2 diabetes. *J Clin Med Res* 2016; 8: 805–814.
- 23. Terauchi Y, Tamura M, Senda M, *et al.* Efficacy and safety of tofogliflozin in Japanese patients with type 2 diabetes mellitus with inadequate glycaemic control on insulin therapy (J-STEP/INS): results of a 16-week randomized, double-blind, placebo-controlled multicentre trial Diabetes. *Obes Metab* 2017; 19: 1397–1407.
- 24. Xu Y, Wang L, He J, *et al.* Prevalence and control of diabetes in Chinese Adults. *JAMA* 2013; 310: 948–958.
- 25. Ding L, Xu Y, Wang L, *et al.* The cardiometabolic risk profile of Chinese adults with diabetes: a nationwide cross-sectional survey. *J Diabetes Complications* 2016; 10: 1056–8727.
- Snell-Bergeon JK, Wadwa RP. Hypoglycemia, diabetes, and cardiovascular disease. *Diabetes Technol Ther* 2012; 14(Suppl 1): S51–S58.
- 27. Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. *Trends Pharmacol Sci* 2011; 32: 63–71.
- 28. James W. Reed. Impact of sodium–glucose co-transporter 2 inhibitors on blood pressure. *Vasc Health Risk Manag* 2016; 12: 393–405.
- 29. Heerspink HJ, Perkins BA, Fitchett DH, *et al.* Sodium Glucose Cotransporter 2 inhibitors in the treatment of

diabetes: cardiovascular and kidney effects, potential mechanisms and clinical applications. *Circulation* 2016; 134: 752–772.

- 30. Younk LM, Lamos EM, Davis SN, *et al.* The cardiovascular effects of insulin. *Expert Opin Drug Saf* 2014; 13: 955–966.
- 31. Kanbay M, Segal M, Afsar B, *et al.* The role of uric acid in the pathogenesis of human cardiovascular disease. *Heart* 2013; 99: 759–766.
- 32. Wu AH, Gladden JD, Ahmedc M, *et al.* Relation of serum uric acid to cardiovascular disease. *Int J Cardiol* 2016; 213: 4–7.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1| File S1 Research strategy through two methods from PubMed (before September 2017). Figure S1 Flow chart showing the study selection process. Figure S2 Cochrane risk of bias. Graph and summary.

Data S2 Figure S1 Forest plot of randomized controlled trials: effect on lipids of triglyceride. Figure S2 Forest plot of randomized controlled trials: effect on lipids of total cholesterol. Figure S3 Forest plot of randomized controlled trials: effect on lipids of low-density lipoprotein cholesterol. Figure S4 Forest plot of randomized controlled trials: effect on lipids of low-density lipoprotein cholesterol. Figure S5 Forest plot of randomized controlled trials: effect on serum electrolyte of sodium. Figure S6 Forest plot of randomized controlled trials: effect on serum electrolyte of randomized controlled trials: effect on serum electrolyte of randomized controlled trials: effect on serum electrolyte of magnesium. Table S1 Different sodium–glucose cotransporter 2 inhibitors and whether or not Asian-dominated studies compared.

Data S3| Figure S1 Influence analysis of glycosylated hemoglobin. Figure S2 Influence analysis of fasting plasma glucose. Figure S3 Influence analysis of daily insulin. Figure S5 Influence analysis of bodyweight. Figure S5 Influence analysis of uric acid (µmol/L).

Data S4| Figure S1 Funnel plot of glycosylated hemoglobin.

Data S5| Summary of adverse events.