Systematic Review and Meta-Analysis

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Effect of sodium-dependent glucose transporter inhibitors on glycated hemoglobin A1c after 24 weeks in patients with diabetes mellitus

A systematic review and meta-analysis

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Abstract

Background: To evaluate dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, and sotagliflozin according to their effect on the glycated hemoglobin A1c (HbA1c) level in patients with type 2 diabetes mellitus.

Methods: The Web of Science, PubMed, Cochrane Library, EMBASE, and Clinical Trials databases were electronically searched to collect randomized controlled trials of patients with type 2 diabetes mellitus through June 2020. Two researchers independently screened and evaluated the obtained studies and extracted the outcome indexes. RevMan 5.3 software was used to perform the meta-analysis and to create plots.

Results: Finally, 27 studies were selected and included in this study. The meta-analysis results showed that sodium-dependent glucose transporter (SGLT) inhibitors significantly reduced the HbA1c level in patients with type 2 diabetes mellitus. However, these results were highly heterogeneous, so we conducted a subgroup analysis. The results of the subgroup analysis suggested that by dividing populations into different subgroups, the heterogeneity of each group could be reduced.

Conclusions: SGLT inhibitors had a good effect on the HbA1c level in patients with type 2 diabetes mellitus, but there might be differences in the efficacy of SGLT inhibitors in different populations. It is hoped that more studies will be conducted to evaluate the efficacy and safety of SGLT inhibitors in different populations.

Registration Number: CRD42020185025.

Abbreviations: CANA = canagliflozin, CI = confidence interval, DAPA = dapagliflozin, EMPA = empagliflozin, ERTU = ertugliflozin, HbA1c = glycated hemoglobin A1c, MD = mean difference, PROSPERO = International Prospective Register of Systematic Reviews, RCTs = randomized controlled trials, SGLT = sodium-dependent glucose transporter, SOTA = sotagliflozin, T2DM = type 2 diabetes mellitus.

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

1. Introduction

Diabetes mellitus, commonly known as diabetes, is a group of metabolic disorders characterized by prolonged hyperglycemia. Symptoms of diabetes, including type 1 diabetes mellitus and type 2 diabetes mellitus (T2DM), usually include frequent urination, thirst, and increased appetite.[1,2] T2DM begins with insulin resistance, a condition in which cells cannot respond normally to insulin. As the disease progresses, insulin deficiency may also occur. The most common cause is a combination of overweight and insufficient exercise.[3] Without being well controlled, these conditions can lead to serious complications.[4] In 2019, there were approximately 463 million people with diabetes worldwide, close to 9% of adults.[5] In that year, 4.2 million people died of diabetes, the seventh leading cause of death in the world.[6]

The formation of glycated hemoglobin suggests the presence of excessive sugar in the bloodstream, indicating the possibility of diabetes. There are different subfractions of glycated hemoglobin A1c (HbA1c), which are easy to detect and have recently received more attention from researchers.[7,8] HbA1c is measured primarily to determine the 3-month average blood sugar level. Three months is the lifespan of a red blood cell. A persistently elevated level of HbA1c increases the risk of vascular

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complications, such as coronary disease, heart attack, stroke, heart failure, kidney failure, blindness, erectile dysfunction, neuropathy, gangrene, gastroparesis, and short-term complications of surgery such as poor wound healing.[9,10]

There are many types of hypoglycaemic drugs, among which sodium-dependent glucose transporter (SGLT) inhibitors are the focus of current research because they have a unique hypoglycemic mechanism and can remove glucose from the blood.[7,8] SGLT inhibitors are mainly divided into SGLT-2 inhibitors and dual SGLT-1/2 inhibitors. Specific drugs include dapagliflozin (DAPA), canagliflozin (CANA), empagliflozin (EMPA), ertugliflozin (ERTU), and sotagliflozin (SOTA).[9,10] SGLT inhibitors are commonly used as second-line hypoglycemic agents in clinical practice.[11]

The purpose of this study was to evaluate the effects of these SGLT inhibitors on HbA1c and to perform a variety of subgroup analyses to evaluate their effects in different populations, thereby providing a basis for the clinical selection of drugs.

2. Methods

2.1. Design and registration

A meta-analysis was conducted to evaluate the effect of SGLT inhibitors on the HbA1c level in patients with T2DM. This protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42020185025 (https://www.crd.york.ac.uk/PROSPERO). No ethics approval was required because this study used data that were already in the public domain.[11]

2.2. Study selection

2.2.1. Study type. The quantitative analysis of this study included data from randomized controlled trials (RCTs).

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

2.2.3. Intervention measures. First, the targets of this study were SGLT inhibitors; currently, there are 5 major SGLT inhibitors, DAPA, CANA, EMPA, ERTU, and SOTA. Due to their different doses, there were 10 different interventions. Second, the placebo control groups were also included in this network meta-analysis.

The purpose of this study was to compare the efficacy of individual medications, and studies on the efficacy and safety of medication combinations were not included in this study.

This study did not exclude patients based on background medications. If the dose of background medications did not change during the course of treatment, the study was still included in this meta-analysis.

2.2.4. Outcome indicators. The final outcome index included in the quantitative analysis was the HbA1c level at week 24 (±2 weeks).

Through a previous review of the literature, we found that after approximately 12 weeks of oral treatment with SGLT inhibitors, the HbA1c level of patients reached a low point and could be maintained at that level thereafter. Therefore, we included all studies with HbA1c data for week 24.

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

2.3. Data sources and searches

We searched publications through June 2020 using the following databases: Web of Science, PubMed, Cochrane Library, EMBASE, and Clinical Trials. We searched in English as a retrieval strategy. However, we did not limit the retrieved results by language. With the help of translation software (Google Translate), we could read literature in other languages. The search terms included "SGLT," "diabetes," and "mellitus." Figure 1 shows an example of the search in the PubMed database.

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

Data were collected independently by 2 researchers. The unqualified studies were eliminated, and the qualified studies were screened out after reading the title, abstract, and full text. Then, the research data were extracted and checked, and disagreements were resolved by discussion or a decision made by the author. The extracted data included the following:

(1) basic information of the study, including title, author, and year of publication;
(2) characteristics of the included study, consisting of study duration, sample size of test group and control group, and intervention measures;
(3) outcome indicators and data included;
(4) collection of risk assessment elements of bias.

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

2.5. Statistical analysis

RevMan 5.3 software was used for the meta-analysis. The continuous variables are expressed as the mean difference (MD) as effect indicators, and the estimated value and 95% confidence interval (CI) were included as effect analysis statistics. A heterogeneity test was conducted with the results of each study. A fixed-effects model was used for analysis if there was no statistical heterogeneity in the results ($I^2 \leq 50\%$). The sources of heterogeneity were analyzed if $I^2 > 50\%$. After excluding the influence of obvious clinical heterogeneity, a random-effects model was used for analysis. The significance level was set at $\alpha = 0.05$.

3. Results

3.1. Included studies and patients

Through database searches, we retrieved a total of 7657 studies. Finally, 27 studies[13–39] were selected and included. No grey literature was included in this study. The specific flow diagram is shown in Figure 1. Through data collation for the included studies, a total of 14,074 patients were enrolled. In each study, the characteristics of patients in the groups were similar.

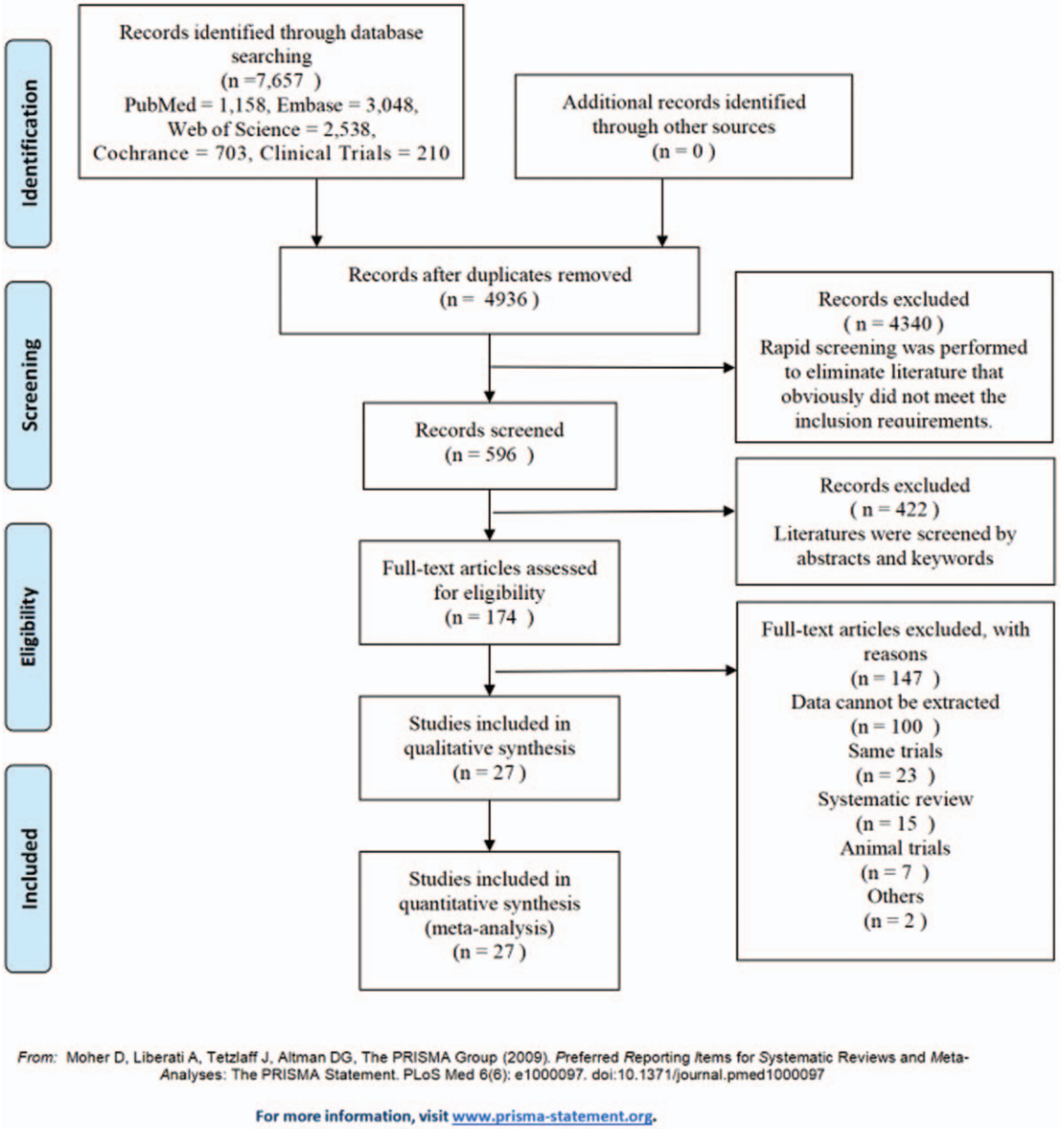

Figure 1. PubMed database retrieval strategy and PRISMA flow diagram.

3.2. Characteristics of the included studies and quality assessment

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

3.3. Meta-analysis results

3.3.1. HbA1c. Twenty-seven studies reported comparisons of the HbA1c level, including 11 articles on DAPA, 6 articles on EMPA, 4 articles on ERTU, 6 articles on CANA, and 0 articles on SOTA (Fig. 2, Table 2).

A random-effects model was adopted, and the HbA1c level in the DAPA group was lower than that in the placebo group: 5 mg DAPA group: $I^2 = 22\%$ [MD = –0.50, 95% CI (–0.63, –0.38), $P < .00001$]; 10 mg DAPA group: $I^2 = 60\%$ [MD = –0.61, 95% CI (–0.72, –0.51), $P < .00001$].

A random-effects model was adopted, and the HbA1c level in the EMPA group was lower than that in the placebo group: 10 mg EMPA group: $I^2 = 83\%$ [MD = –0.68, 95% CI (–0.84, –0.51), $P < .0001$]; 25 mg EMPA group: $I^2 = 68\%$ [MD = –0.67, 95% CI (–0.80, –0.54), $P < .00001$].

A random-effects model was adopted, and the HbA1c level in the ERTU group was lower than that in the placebo group: 5 mg ERTU group: $I^2 = 64\%$ [MD = –0.71, 95% CI (–0.85, –0.56), $P < .00001$]; 15 mg ERTU group: $I^2 = 25\%$ [MD = –0.80, 95% CI (–0.91, –0.70), $P < .00001$].

A random-effects model was adopted, and the HbA1c level in the CANA group was lower than that in the placebo group: 100 mg CANA group: $I^2 = 44\%$ [MD = –0.71, 95% CI (–0.82, –0.56), $P < .00001$]; 300 mg CANA group: $I^2 = 70\%$ [MD = –0.88, 95% CI (–1.03, –0.72), $P < .00001$].

Table 1

Basic information and bias risk assessments of the studies.

										Literature quality score						
No.	First author	Year	Trials No.	Country	Background	Duration of treatment	Group-1	Group-2	Group-3	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
1	Bailey, C. J.	2010	NCT00528879	UK	MET	24 wk	DAPA 5 mg	DAPA 10 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	low risk
2	Bailey, C. J.	2012	–	UK	Diet and Exercise	24 wk	DAPA 5mg	PLA		low risk	low risk	low risk	low risk	low risk	low risk	unclear
3	Bode, Bruce	2013	NCT01106651	US	Unlimited	26 wk	CANA 100 mg	CANA 300 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	unclear
4	Bolinder, J.	2014	NCT00855166	Sweden	MET	24 wk	DAPA 10 mg	PLA		low risk	low risk	low risk	low risk	low risk	low risk	unclear
5	Dagogo-Jack, S.	2018	NCT02036515	US	MET and SITA	24 wk	ERTU 5 mg	ERTU 15 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	unclear
6	Ferrannini, E.	2010	NCT00528372	Italy	Diet and Exercise	24 wk	DAPA 5 mg	DAPA 10 mg	PLA	low risk	low risk	low risk	low risk	unclear	low risk	unclear
7	Forst, T.	2014	NCT01106690	Germany	MET and pioglitazone	26 wk,	CANA 100 mg	CANA 300 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	unclear
8	Haering, Hans-Ulrich	2014	NCT01159600	Germany	Diet and Exercise	24 wk	EMPA 10mg	EMPA 25 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	unclear
9	Jabbour, Serge A.	2018	NCT00984867	US	SITA and/or MET	24 wk	DAPA 10 mg	PLA		low risk	low risk	low risk	low risk	unclear	low risk	unclear
10	Ji, L.	2019	NCT02630706	China	MET	26 wk	ERTU 5 mg	ERTU 15 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	unclear
11	Kadowaki, T.	2017	NCT02354235	Japan	Teneligliptin	24 wk	CANA 100 mg	PLA		low risk	low risk	low risk	low risk	low risk	low risk	unclear
12	Kawamori, R.	2018	NCT02453555	Japan	linagliptin	24 wk	DAPA 10 mg	PLA		low risk	low risk	low risk	low risk	unclear	low risk	unclear
13	Kovacs, C. S.	2015	NCT01210001	Canada	MET	24 wk	EMPA 10 mg	EMPA 25 mg	PLA	low risk	low risk	low risk	low risk	unclear	low risk	unclear
14	Mathieu, C.	2015	NCT01646320	Romania	MET and Saxagliptin	24 wk	DAPA 10 mg	PLA		low risk	low risk	low risk	low risk	unclear	low risk	unclear
15	Matthaei, S.	2015	NCT01392677	Germany	MET and SUL	24 wk	DAPA 10 mg	PLA		low risk	low risk	low risk	low risk	unclear	low risk	unclear
16	Neal, B.	2015	NCT01032629	Australia	Insulin	24 wk	CANA 100 mg	CANA 300 mg	PLA	low risk	low risk	low risk	low risk	unclear	low risk	unclear
17	Romera, I.	2016	–	Spain	MET or SUL and so on.	24 wk	EMPA 10 mg	EMPA 25 mg	PLA	low risk	low risk	low risk	low risk	unclear	low risk	unclear
18	Rosenstock, J.	2018	NCT02033889	US	MET	26 wk	ERTU 5 mg	ERTU 15 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	unclear
19	Rosenstock, J.	2012	NCT00683878	US	Pioglitazone	24 wk	DAPA 5 mg	DAPA 10 mg	PLA	low risk	low risk	low risk	low risk	unclear	low risk	unclear
20	Softeland, E.	2017	NCT01734785	Norway	Linagliptin and MET	24 wk	EMPA 10 mg	EMPA 25 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	unclear
21	Stenlof, K.	2013	NCT01081834	Sweden	Diet and Exercise	26 wk	CANA 100 mg	CANA 300 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	unclear
22	Strojek, K.	2011	NCT00680745	Poland	Glimepiride	24 wk	DAPA 5 mg	DAPA 10 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	unclear
23	Terra, S. G.	2017	NCT01958671.	US	Diet and Exercise	26 wk	ERTU 5 mg	ERTU 15 mg	PLA	low risk	low risk	low risk	low risk	unclear	low risk	unclear
24	Wilding, J. P.	2013	NCT01106625	UK	MET and SUL	24 wk	CANA 100 mg	CANA 300 mg	PLA	low risk	low risk	low risk	low risk	low risk	low risk	unclear
25	Yang, W.	2016	NCT01095666	China	MET	24 wk	DAPA 5 mg	DAPA 10 mg	PLA	low risk	low risk	low risk	low risk	low risk	unclear	unclear
26	Yang, W.	2018	NCT02096705	China	Insulin with or without oral antihyperglycemic drugs	24 wk	DAPA 10 mg	PLA		low risk	low risk	low risk	low risk	low risk	unclear	unclear
27	Roden, M.	2013	NCT01177813	Germany	Diet and Exercise	24 wk	EMPA 10 mg	EMPA 25 mg		low risk	low risk	low risk	low risk	low risk	low risk	unclear

CANA = canagliflozin, DAPA = dapagliflozin, EMPA = empagliflozin.

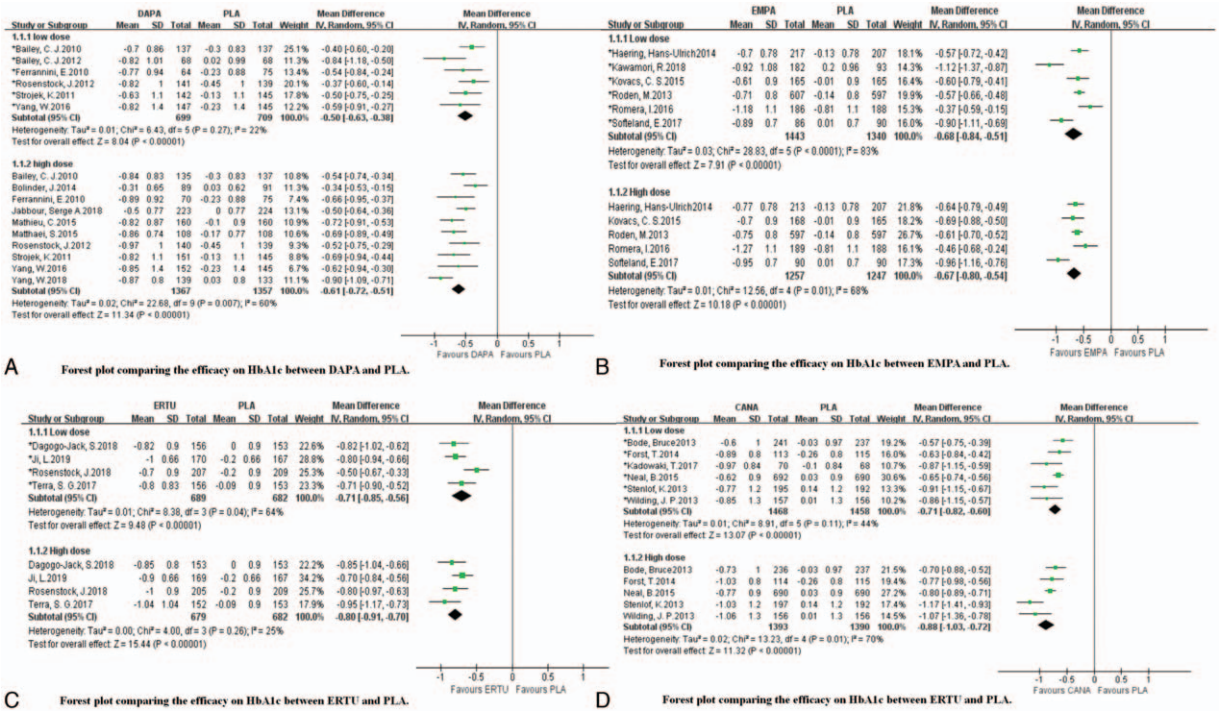

Figure 2. Forest plot comparing the SGLT inhibitors versus the placebo on HbA1c. HbA1c = glycated hemoglobin A1c, SGLT = sodium-dependent glucose transporter.

3.4. Subgroup analysis

We tried to perform subgroup analysis from the following aspects (Table 3):

(1) Drug naivety.
(2) Duration of diabetes. We used 2 methods to establish subgroup analysis. The first method was based on whether the disease history was more than 5 years. The second method was based on even division into 2 groups according to the disease duration.
(3) BMI. We used two methods to establish subgroup analysis. The first method was based on whether BMI was larger than 30. The second method was based on even division into 2 groups according to the BMI.
(4) Region.

Reduced heterogeneity was found through subgroup analysis of the 10 mg EMPA, 15 mg ERTU, 100 mg CANA, and 300 mg CANA groups. Among them, the 100 mg CANA group and the 300 mg CANA group showed significant differences between the subgroups.

4. Discussion

HbA1c is mainly used to evaluate the average blood glucose level over the last 3 months, which could be used in the diagnosis of diabetes and the evaluation of blood glucose control in patients with T2DM.[40,41] This study demonstrate that SGLT inhibitors have a significant therapeutic effect on T2DM by significantly reducing the HbA1c level.[42,43] The studies included in this analysis were performed in Europe, America, Asia, and Oceania. The results of each study were all positive; that is, SGLT inhibitors were effective for patients with T2DM, independent of region. However, there was significant heterogeneity for each SGLT inhibitor, so we chose a random-effects model and performed a subgroup analysis to analyze the possible sources of heterogeneity.

Table 2

The meta-analysis results of SGLT inhibitors versus PLA.

Comparision	Size	Total		I^2	Model
DAPA 5 mg VS PLA	11	−0.5	[−0.63, −0.38]	22%	Random effect model
DAPA 10 mg VS PLA		−0.61	[−0.72, −0.51]	60%	
EMPA 10 mg VS PLA	6	−0.68	[−0.84, −0.51]	83%	Random effect model
EMPA 25 mg VS PLA		−0.67	[−0.80, −0.54]	68%	
ERTU 5 mg VS PLA	4	−0.71	[−0.85, −0.56]	64%	Random effect model
ERTU 15 mg VS PLA		−0.80	[−0.91, −0.70]	25%	
CANA 100 mg VS PLA	6	−0.71	[−0.82, −0.60]	44%	Random effect model
CANA 300 mg VS PLA		−0.88	[−1.03, −0.72]	70%	

CANA = canagliflozin, DAPA = dapagliflozin, EMPA = empagliflozin, ERTU = ertugliflozin, SGLT sodium-dependent glucose transporter.

Table 3

The subgroup analysis results of SGLT inhibitors versus PLA.

Comparison	Drug-naive						BMI						Duration of diabetes						Region					
	Yes		No		I^2	P	Less than 30		More than 30		I^2	P	Less than 5 years		more than 5 years		I^2	P	Less duration (half of studies)		More duration (half of studies)		I^2	P
DAPA 5 mg VS PLA	−0.68	[−0.90, −0.45]	−0.46	[−0.56, −0.32]	41%	.07	−0.59	[−0.27, −0.91]	−0.57	[−0.27, −0.87]	59%	.91	−0.58	[−0.46, −0.83]	−0.42	[−0.29, −0.55]	0%	.05*	−0.58	[−0.42, −0.74]	−0.43	[−0.28, −0.57]	23%	.16
DAPA 10 mg VS PLA	−0.66	[−0.95, −0.37]	−0.61	[−0.72, −0.50]	0%	.75	−0.79	[−0.52, −1.06]	−0.58	[−0.43, −0.73]	54%	.18	−0.63	[−0.50, −0.76]	−0.61	[−0.50, −0.72]	0%	.75	−0.50	[−0.58, −0.42]	−0.71	[−0.62, −0.80]	0%	41%	.0007*
EMPA 10 mg VS PLA	−0.66	[−0.82, −0.49]	−0.75	[−0.99, −0.52]	61%	.52	−0.74	[−0.47, −1.01]	−0.79	[−0.47, −1.11]	80%	.80	−0.79	[−0.53, −1.06]	−0.65	[−0.49, −0.82]	85%	.38	−0.61	[−0.48, −0.68]	−1.12	[−0.87, −1.37]	25%	0%	.0001*
EMPA 25 mg VS PLA	−0.75	[−0.97, −0.53]	−0.63	[−0.71, −0.55]	76%	.30	−0.70	[−0.38, −1.02]	−0.74	[−0.38, −1.02]	56%	.85	−0.74	[−0.58, −0.89]	−0.69	[−0.49, −0.90]	54%	.74	–	–	–	–	–	–
ERTU 5 mg VS PLA	−0.71	[−0.90, −0.52]	−0.71	[−0.91, −0.51]	0%	.98	−0.66	[−0.55, −0.77]	−0.66	[−0.55, −0.78]	67%	.12	−0.65	[−0.50, −0.80]	−0.76	[−0.62, −0.90]	86%	.51	−0.80	[−0.66, −0.94]	−0.66	[−0.55, −0.77]	0%	67%	.12
ERTU 15 mg VS PLA	−0.95	[−1.17, −0.73]	−0.77	[−0.86, −0.67]	0%	.13	−0.95	[−0.73, −1.17]	−0.77	[−0.67, −0.86]	0%	.13	−0.75	[−0.64, −0.87]	−0.86	[−0.72, −0.99]	35%	.25	−0.86	[−0.74, −0.95]	−0.7	[−0.56, −0.84]	0%	0%	.09
CANA 100 mg VS PLA	−0.91	[−1.15, −0.67]	−0.66	[−0.73, −0.59]	0%	.05*	−0.91	[−0.67, −1.15]	−0.66	[−0.59, −0.73]	0%	.05*	−0.77	[−0.53, −1.00]	−0.66	[−0.58, −0.75]	68%	.42	−0.67	[−0.60, −0.74]	−0.87	[−0.59, −1.15]	44%	0%	.18
CANA 300 mg VS PLA	−1.17	[−1.41, −0.93]	−0.80	[−0.87, −0.72]	0%	.003*	−1.17	[−0.93, −1.41]	−0.80	[−0.72, −0.87]	0%	.003*	−0.88	[−0.58, −1.18]	−0.85	[−0.70, −1.00]	80%	.87	–	–	–	–	–	–

CANA = canagliflozin, DAPA = dapagliflozin, EMPA = empagliflozin, ERTU = ertugliflozin, SGLT sodium-dependent glucose transporter.

*The difference between subgroups is statistically significan

A total of 11 studies were included in the DAPA group, with high heterogeneity among the studies. Subgroup analysis according to the duration of diabetes could reduce the heterogeneity, with a significant difference among the subgroups. The results of the subgroup analysis of the DAPA group suggested that the heterogeneity in the DAPA group might be derived from the duration of diabetes in the included patients. This finding also suggests that patients with T2DM for different durations might react differently to DAPA.

A total of 6 studies were included in the EMPA group, with high heterogeneity among the studies. Subgroup analysis according to region could reduce the heterogeneity, with a significant difference among the subgroups. In the included studies, racial factors were usually mentioned only during the assessment of randomization, without a separate presentation of data for different race groups in the results. However, the country where the first author was located, especially according to European/American and non-European/American countries, could indirectly reflect racial differences. The results of the subgroup analysis of the EMPA group suggested that the heterogeneity in the EMPA group might be derived from the different regions of the included patients. This finding also suggests that T2DM patients from different regions might react differently to EMPA.

A total of 4 studies were included in the ERTU group, with high heterogeneity among the studies. Subgroup analysis according to drug naivety, the duration of diabetes, BMI, and region could reduce the heterogeneity significantly, but the differences among the subgroups were not statistically significant. The results of the subgroup analysis of the ERTU group suggested that the heterogeneity in the ERTU group might be derived from differences in the drug naivety, duration of diabetes, BMI, and region of the included patients. This finding also suggests that T2DM patients with differences in these factors might react differently to EMPA.

A total of 6 studies were included in the CANA group, with high heterogeneity among the studies. Subgroup analysis according to drug naivety and the duration of diabetes could significantly reduce the heterogeneity, with significant differences among the subgroups. The results of the subgroup analysis of the CANA group suggested that the heterogeneity in the CANA group might be derived from the drug naivety and duration of diabetes of the included patients. This finding also suggests that T2DM patients with differences in drug naivety and the duration of diabetes might react differently to EMPA.

The mechanism by which SGLT inhibitors control blood sugar is through SGLT. SGLT is divided into SGLT-1 and SGLT-2.[44,45] Their mechanisms of action are similar. When the sodium-potassium ion ATPase pump on the basolateral membrane consumes ATP, it transports 3 sodium ions to the outside and 2 potassium ions to the inside of the cell. The concentration of sodium ions in the cell decreases, and the sodium ions in the lumen tend to flow into the cell due to the difference in ion concentrations. The function of the SGLT protein is to allow glucose and sodium ions to flow into the cell together. Finally, glucose is transported to the capillaries through GLUT2[46,47] (Fig. 3).

SGLT-1 is mainly distributed in the small intestine and kidney. In the small intestine, it can absorb glucose in the intestinal juice, and in the kidney, it is responsible for reabsorbing 10% of the glucose in the urine. SGLT-2 is mainly distributed in the kidney and is responsible for reabsorbing 90% of the glucose in the urine.[48,49] SGLT inhibitors could act on SGLT-1 and SGLT-2. SOTA-related studies were not included in this study, so the drugs included in this study are all SGLT-2 inhibitors.[50] SGLT-2

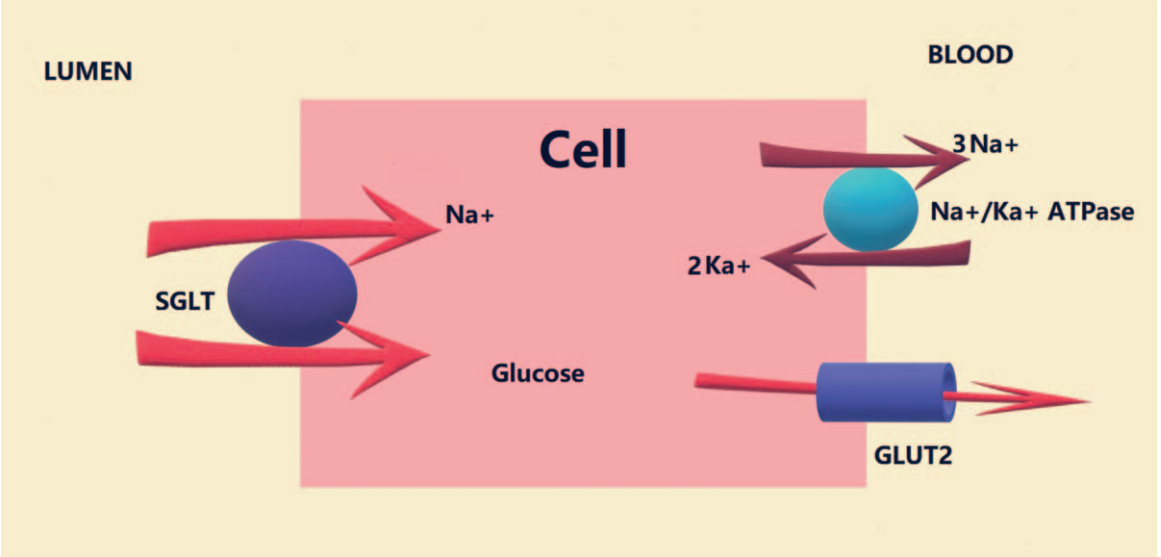

Figure 3. Mechanism of action of the SGLT protein in cells. SGLT = sodium-dependent glucose transporter.

inhibitors achieve the goal of blood sugar control by increasing the excretion of glucose from urine.[40,41]

The use of SGLT inhibitors is common in clinical practice, and it is considered feasible to administer SGLT inhibitors alone in patients in the early stage.[42,43] Reducing the number of pharmacological interventions in patients with T2DM improves their quality of life.[44,45] Long-term follow-up studies showed that the administration of SGLT2 inhibitors was associated with a reduction in the primary composite outcome composed of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.[46–49]

The purpose of this study was not only to verify the efficacy of SGLT inhibitors in T2DM but also to analyze the possible causes of heterogeneity. A total of 4 meta-analyses were conducted in this study, and the results of each showed significant heterogeneity. These findings indicate that the efficacy of SGLT inhibitors in different populations might be different, especially according to differences in the duration of diabetes, BMI, and region. This study only analyzed the effects of SGLT inhibitors on the HbA1c level in different populations, and whether there are differences in other effects or the safety of SGLT inhibitors in different populations remains to be determined by relevant systematic research. It is hoped that more studies will be conducted to evaluate differences in the efficacy and safety of SGLT inhibitors in different populations.

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

(1) The literature on SOTA retrieved in this study did not meet the inclusion criteria; thus, the efficacy of SOTA in T2DM was not analyzed.
(2) Subgroup analysis could not explain all the sources of heterogeneity.

5. Conclusions

SGLT inhibitors have a good effect on patients with T2DM, but there may be differences in the efficacy of SGLT inhibitors in different populations. It is hoped that more studies will be conducted to evaluate the efficacy and safety of SGLT inhibitors in different populations.

Author contributions

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