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SGLT Inhibitors and HbA1c Reduction in Diabetes Mellitus: Evidence from 24-Week Systematic Review and Meta-Analysis

Robert J. Evans[1]*, Olivia S. Brown[1], Dina M. Saleh[1]

[1]Department of Clinical Sciences, University of Bristol, Bristol, United Kingdom.

Abstract

To assess the impact of canagliflozin, dapagliflozin, ertugliflozin, empagliflozin, and sotagliflozin on glycated hemoglobin (HbA1c) levels in individuals with type 2 diabetes mellitus. Randomized controlled trials enrolling individuals with type 2 diabetes mellitus were retrieved through comprehensive electronic searches of the Web of Science, EMBASE, Cochrane Library, PubMed, and ClinicalTrials databases up to June 2020. Study selection, quality appraisal, and data extraction were independently performed by two investigators. RevMan version 5.3 was utilized to conduct the meta-analysis and produce visual representations.

A total of 27 studies met the inclusion criteria. The meta-analysis demonstrated that SGLT inhibitors significantly lowered HbA1c levels in individuals with type 2 diabetes mellitus. Substantial heterogeneity was observed, prompting subgroup analyses, which revealed that stratifying participants into distinct groups effectively reduced heterogeneity. Although SGLT inhibitors demonstrated favorable reductions in HbA1c among individuals with type 2 diabetes mellitus, potential differences in treatment response across various populations remain. Future studies are encouraged to explore the comparative efficacy and safety of SGLT inhibitors among distinct demographic and clinical subgroups.

Keywords: Meta-analysis, Type 2 diabetes mellitus, Sodium-glucose transporter 2, Sodium-glucose transporter 1

Corresponding author: Robert J. Evans
E-mail: robert.evans@gmail.com

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Introduction

Diabetes mellitus is a metabolic disorder marked by chronic elevations in blood glucose. Both type 1 and type 2 diabetes mellitus (T2DM) commonly present with symptoms such as polyuria, polydipsia, and increased hunger [1, 2]. T2DM typically develops from insulin resistance, in which body cells fail to respond adequately to insulin; as the condition advances, impaired insulin secretion may also occur. Excess body weight and insufficient physical activity are the primary contributing factors [3]. Without proper management, diabetes can result in numerous severe complications [4]. In 2019, an estimated 463 million individuals—nearly 9% of the global adult population—were living with diabetes [5], and approximately 4.2 million deaths were attributed to the disease, making it the seventh leading cause of mortality worldwide [6].

Glycated hemoglobin formation reflects sustained hyperglycemia, serving as an indicator for diagnosing and monitoring diabetes. Among its subfractions, glycated hemoglobin A1c (HbA1c) is widely used and has recently gained greater research interest due to its ease of detection [7, 8]. HbA1c reflects the average blood glucose concentration over roughly three months, corresponding to the lifespan of red blood cells. Persistent elevation of

HbA1c heightens the risk of vascular and metabolic complications, including coronary artery disease, stroke, heart failure, myocardial infarction, blindness, renal impairment, neuropathy, gangrene, erectile dysfunction, postoperative complications, and gastroparesis such as delayed wound healing [9, 10].

A variety of glucose-lowering medications are available, and sodium-dependent glucose transporter (SGLT) inhibitors have become an area of major interest due to their distinct mechanism of reducing blood glucose by promoting urinary glucose excretion [7, 8]. These agents include dual SGLT-1/2 inhibitors and SGLT-2 inhibitors, with common representatives such as canagliflozin (CANA), dapagliflozin (DAPA), ertugliflozin (ERTU), empagliflozin (EMPA), and sotagliflozin (SOTA) [9, 10]. In clinical practice, SGLT inhibitors are frequently prescribed as second-line therapies for glycemic control [11].

The aim of this study was to assess the impact of these SGLT inhibitors on HbA1c levels and to conduct multiple subgroup analyses to examine their effects across different patient populations, thereby supporting evidence-based drug selection in clinical care.

Materials and Methods

Registration and design

This study employed a meta-analytic approach to examine how SGLT inhibitors influence HbA1c levels in people with T2DM. The research protocol was filed with the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD42020185025 (https://www.crd.york.ac.uk/PROSPERO). Because the analysis relied exclusively on previously published data, no ethical review or approval was required [11].

Study selection

Study type

For the quantitative evaluation, the study relied on information reported in randomized controlled trials (RCTs).

Study subjects

This study focused on individuals diagnosed with T2DM, without imposing limits on age, body weight, baseline HbA1c, or prior medication use. Patients with severe acute or chronic illnesses, including cardiac or renal failure, were excluded.

Intervention measures

The primary interventions evaluated in this study were SGLT inhibitors, of which five major agents are currently available: CANA, DAPA, ERTU, EMPA, and SOTA. Considering variations in their dosages, a total of ten distinct intervention regimens were analyzed. Additionally, placebo control groups were incorporated into the network meta-analysis.

The aim of this study was to evaluate the efficacy of individual SGLT inhibitors; studies assessing combination therapies were not considered. Patients were not excluded based on concurrent medications, and studies were included in the meta-analysis as long as the dosage of any background medications remained unchanged throughout the treatment period.

Outcome indicators

The quantitative analysis focused on HbA1c levels recorded at approximately 24 weeks (with a ±2-week window). Evidence from previous studies indicates that HbA1c generally stabilizes after about 12 weeks of treatment with SGLT inhibitors. For this reason, only studies providing HbA1c measurements around the 24-week mark were included in the meta-analysis.

Exclusion criteria

Studies were excluded if the data were unavailable or unusable, if they were conducted in animals, or if they were review articles.

Searches and data sources

We conducted a comprehensive search for studies published up to June 2020 across Web of Science, PubMed, EMBASE, Cochrane Library, and ClinicalTrials databases. While the search terms were in English, no restrictions were placed on publication language, and non-English studies were translated using Google Translate when necessary. The terms used included "diabetes, " "SGLT", and "mellitus". **Figure 1** illustrates the search strategy implemented in PubMed.

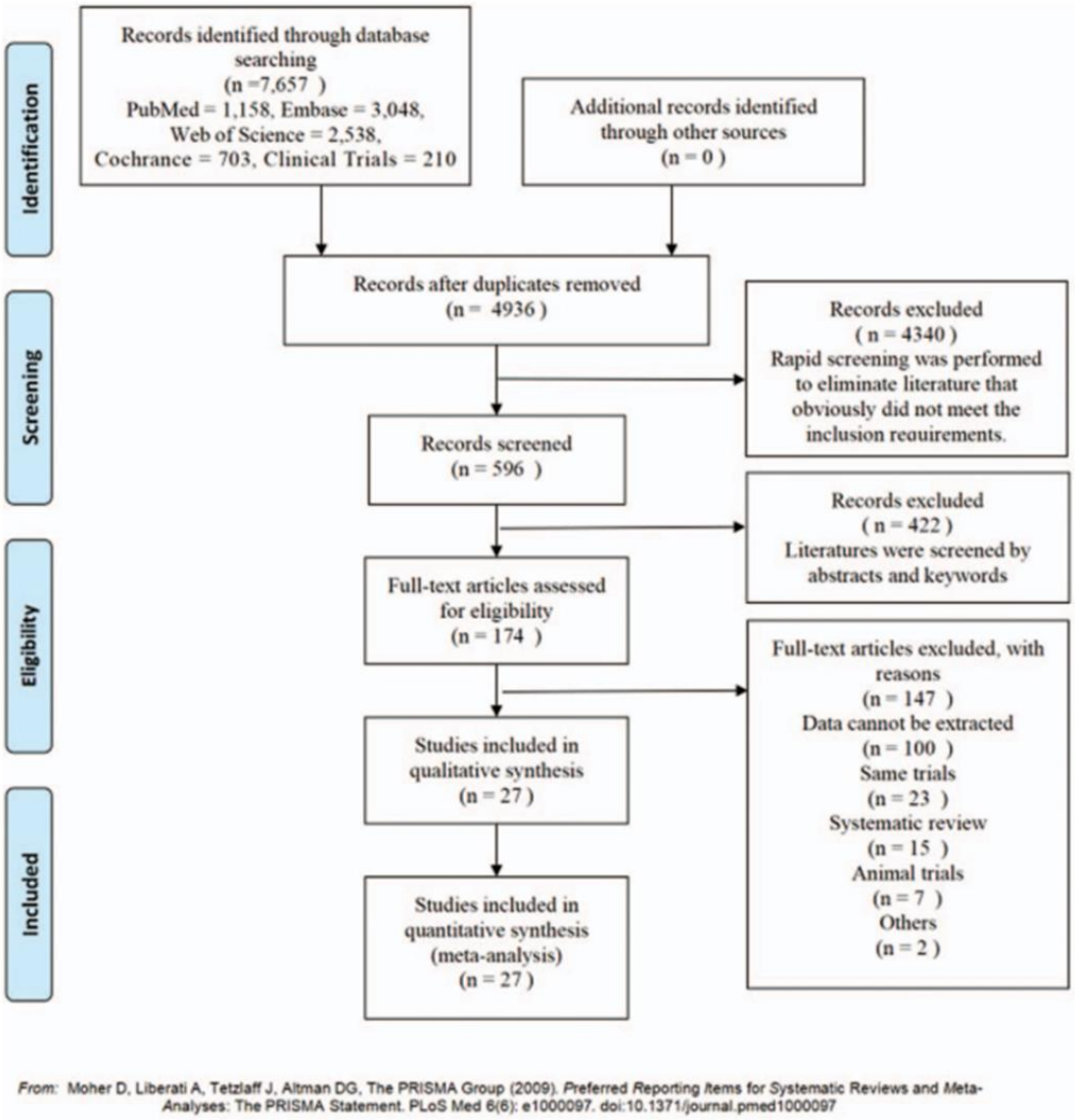


Figure 1. PubMed search strategy and PRISMA flow diagram.

Study screening, risk of bias assessment, and data extraction

Two researchers independently conducted data collection. Studies that did not meet the inclusion criteria were excluded, while eligible studies were identified through review of titles, abstracts, and full texts. Data extraction was then performed and verified, with any discrepancies resolved through discussion or adjudication by the corresponding author. The following information was extracted:

- (1) Basic study information: title, authors, and year of publication;
- (2) Study characteristics: duration, sample sizes for intervention and control groups, and details of interventions;
- (3) Outcome measures and corresponding data;
- (4) Elements required for risk of bias assessment.

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

Statistical analysis

The meta-analysis was performed using RevMan version 5.3. Continuous outcomes were analyzed as mean differences (MD) with corresponding 95% confidence intervals (95% CI). Heterogeneity across studies was assessed using the I^2 statistic. When heterogeneity was low or absent ($I^2 \leq 50\%$), a fixed-effect model was applied. In cases of substantial heterogeneity ($I^2 > 50\%$), potential clinical sources were first explored; after ruling out clear clinical heterogeneity, a random-effects model was employed. Statistical significance was defined at a two-sided α level of 0.05.

Results and Discussion

Studies and included patients

We identified 7,657 records through systematic database searching. After screening and eligibility assessment, 27 studies [13–39] were ultimately included in the review. Grey literature was not considered. The complete selection process is illustrated in **Figure 1**. Data from these studies involved a total of 14,074 participants. In every included study, the baseline characteristics of patients across the comparison groups were well balanced.

Characteristics of the included quality assessment and studies

All studies included in this review were randomized controlled trials (RCTs). The baseline characteristics of the studies and their risk-of-bias assessments are summarized in **Table 1**.

Table 1. Risk-of-bias assessments and basic information of the included studies.

No.	First Author	Year	Trial Registration/ID	Country	Background Therapy	Treatment Duration	Intervention Group 1	Intervention Group 2	Intervention Group 3	Random Sequence Generation	Allocation Concealment	Blinding of Participants & Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Sources of Bias
1	Bailey CJ	2010	NCT00528879	UK	Metformin	24 weeks	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Bailey CJ	2012	–	UK	Diet + exercise	24 weeks	Dapagliflozin 5 mg	Placebo	–	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
3	Bode B	2013	NCT01106651	USA	No restriction	26 weeks	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
4	Bolinder J	2014	NCT00855166	Sweden	Metformin	24 weeks	Dapagliflozin 10 mg	Placebo	–	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
5	Dagogo-Jack S	2018	NCT02036515	USA	Metformin + sitagliptin	24 weeks	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
6	Ferrannini E	2010	NCT00528372	Italy	Diet + exercise	24 weeks	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear

16	15	14	13	12	11	10	9	8	7
Neal B	Matthaei S	Mathieu C	Kovacs CS	Kawamori R	Kadowaki T	Ji L	Jabbour SA	Haering HU	Forst T
2015	2015	2015	2015	2018	2017	2019	2018	2014	2014
NCT01032629	NCT01392677	NCT01646320	NCT01210001	NCT02453555	NCT02354235	NCT02630706	NCT00984867	NCT01159600	NCT01106690
Australia	Germany	Romania	Canada	Japan	Japan	China	USA	Germany	Germany
Insulin ± OADs	Metformin + sulfonylurea	Metformin + saxagliptin	Metformin	Linagliptin	Teneligliptin	Metformin	Sitagliptin ± metformin	Diet + exercise	Metformin + pioglitazone
24 weeks	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks	26 weeks	24 weeks	24 weeks	26 weeks
Canagliflozin 100 mg	Dapagliflozin 10 mg	Dapagliflozin 10 mg	Empagliflozin 10 mg	Dapagliflozin 10 mg	Canagliflozin 100 mg	Ertugliflozin 5 mg	Dapagliflozin 10 mg	Empagliflozin 10 mg	Canagliflozin 100 mg
Canagliflozin 300 mg	Placebo	Placebo	Empagliflozin 25 mg	Placebo	Placebo	Ertugliflozin 15 mg	Placebo	Empagliflozin 25 mg	Canagliflozin 300 mg
Placebo	–	–	Placebo	–	–	Placebo	–	Placebo	Placebo
Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Unclear	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk
Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

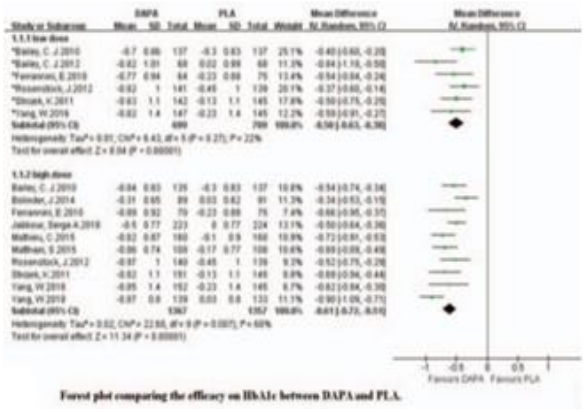
	26	25	24	23	22	21	20	19	18	17
	Yang W	Yang W	Wilding JP	Terra SG	Strojek K	Stenlöf K	Softeland E	Rosenstock J	Rosenstock J	Romera I
	2018	2016	2013	2017	2011	2013	2017	2012	2018	2016
	NCT02096705	NCT01095666	NCT01106625	NCT01958671	NCT00680745	NCT01081834	NCT01734785	NCT00683878	NCT02033889	–
	China	China	UK	USA	Poland	Sweden	Norway	USA	USA	Spain
	Insulin ± oral agents	Metformin	Metformin + sulfonylurea	Diet + exercise	Glimepiride	Diet + exercise	Linagliptin + metformin	Pioglitazone	Metformin	Metformin or sulfonylurea etc.
	24 weeks	24 weeks	24 weeks	26 weeks	24 weeks	26 weeks	24 weeks	24 weeks	26 weeks	24 weeks
	Dapagliflozin 10 mg	Dapagliflozin 5 mg	Canagliflozin 100 mg	Ertugliflozin 5 mg	Dapagliflozin 5 mg	Canagliflozin 100 mg	Empagliflozin 10 mg	Dapagliflozin 5 mg	Ertugliflozin 5 mg	Empagliflozin 10 mg
	Placebo	Dapagliflozin 10 mg	Canagliflozin 300 mg	Ertugliflozin 15 mg	Dapagliflozin 10 mg	Canagliflozin 300 mg	Empagliflozin 25 mg	Dapagliflozin 10 mg	Ertugliflozin 15 mg	Empagliflozin 25 mg
	–	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

27	Roden M	2013	NCT01177813	Germany	Diet + exercise	24 weeks	Empagliflozin 10 mg	Empagliflozin 25 mg	–	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear

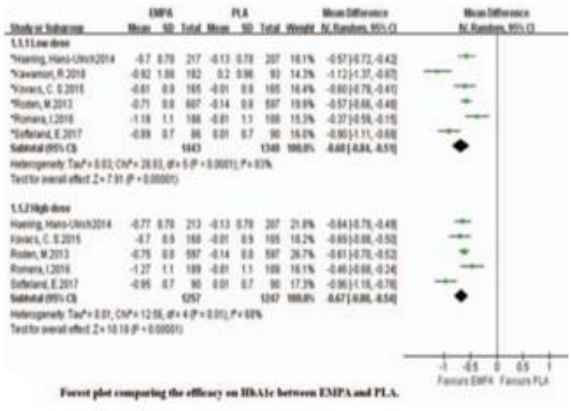
Meta-analysis results

HbA1c

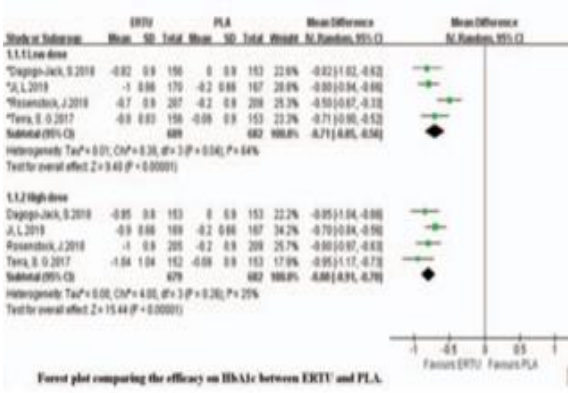
All 27 included studies provided data on changes in HbA1c levels. These comprised 11 trials evaluating dapagliflozin, 6 trials evaluating empagliflozin, 4 trials evaluating ertugliflozin, 6 trials evaluating canagliflozin, and no trials evaluating sotagliflozin **(Figure 2 and Table 2)**.



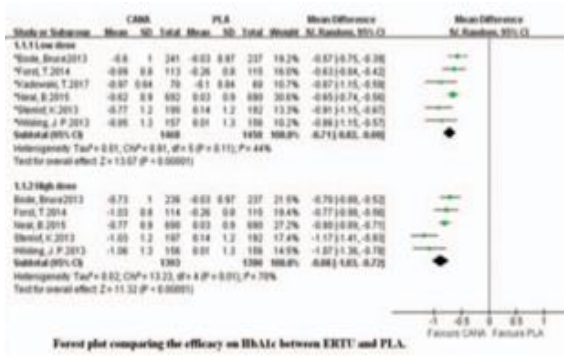
a)



b)



c)



d)

Figure 2. Forest plot showing the effect of sodium-glucose cotransporter (SGLT) inhibitors compared with placebo on glycated hemoglobin A1c (HbA1c) levels.

Table 2. Results from the meta-analysis evaluating SGLT inhibitors versus placebo (PLA).

Comparison	Number of Studies	Mean Difference (%)	95% Confidence Interval	Statistical Model	Heterogeneity (I^2)
Dapagliflozin 5 mg vs Placebo	11	–0.50	–0.63 to –0.38	Random-effects model	22%
Dapagliflozin 10 mg vs Placebo	—	–0.61	–0.72 to –0.51	—	60%
Empagliflozin 10 mg vs Placebo	6	–0.68	–0.84 to –0.51	Random-effects model	83%
Empagliflozin 25 mg vs Placebo	—	–0.67	–0.80 to –0.54	—	68%
Ertugliflozin 5 mg vs Placebo	4	–0.71	–0.85 to –0.56	Random-effects model	64%
Ertugliflozin 15 mg vs Placebo	—	–0.80	–0.91 to –0.70	—	25%

Canagliflozin 100 mg vs Placebo	6	–0.71	–0.82 to –0.60	Random-effects model	44%
Canagliflozin 300 mg vs Placebo	—	–0.88	–1.03 to –0.72	—	70%

Using a random-effects model, all SGLT2 inhibitors demonstrated significantly greater HbA1c reduction compared with placebo:

- 5 mg dose: I^2 = 22%, mean difference (MD) = –0.50% (95% CI: –0.63 to –0.38), P < .00001 10 mg dose: I^2 = 60%, MD = –0.61% (95% CI: –0.72 to –0.51), P < .00001
- 10 mg dose: I^2 = 83%, MD = –0.68% (95% CI: –0.84 to –0.51), P < .0001 25 mg dose: I^2 = 68%, MD = –0.67% (95% CI: –0.80 to –0.54), P < .00001
- **E**5 mg dose: I^2 = 64%, MD = –0.71% (95% CI: –0.85 to –0.56), P < .00001 15 mg dose: I^2 = 25%, MD = –0.80% (95% CI: –0.91 to –0.70), P < .00001
- 100 mg dose: I^2 = 44%, MD = –0.71% (95% CI: –0.82 to –0.60), P < .00001 300 mg dose: I^2 = 70%, MD = –0.88% (95% CI: –1.03 to –0.72), P < .00001

Subgroup analysis

Subgroup analyses were conducted from multiple perspectives to further explore the effects of SGLT2 inhibitors versus placebo **(Table 3)**.

Table 3. Summary of subgroup analysis comparing SGLT2 inhibitors with placebo.

	Drug-naive					Duration of diabetes					Duration of diabetes				
Comparison	Yes		No		*P*	less than 5 years		more than 5 years		*P*	Less duration (half of studies)		More duration (half of studies)		*P*
DAPA 5mg VS PLA	–0.68	[–0.90, –0.45]	–0.46	[–0.56, –0.32]	.07	–0.65	[–0.83, –0.46]	–0.42	[–0.55, –0.29]	.05*	–0.58	[–0.74, –0.42]	–0.43	[–0.57, –0.28]	.16
	41%		0%			0%		0%			23%		0%		
DAPA 10mg VS PLA	–0.66	[–0.95, –0.37]	–0.61	[–0.72, –0.50]	.75	–0.66	[–0.95, –0.37]	–0.61	[–0.72, –0.50]	.75	–0.50	[–0.58, –0.42]	–0.71	[–0.80, –0.62]	**.0007***
	0%		64%			0%		64%			0%		41%		
EMPA 10mg VS PLA	–0.66	[–0.82, –0.49]	–0.75	[–0.99, –0.52]	.52	–	–	–	–	–	–	–	–	–	–
	61%		83%			–		–			–		–		
EMPA 25mg VS PLA	–0.75	[–0.97, –0.53]	–0.63	[–0.71, –0.55]	.30	–	–	–	–	–	–	–	–	–	–
	76%		0%			–		–			–		–		

	Comparison	DAPA 5mg VS PLA	DAPA 10mg VS PLA	CANA 300mg VS PLA	CANA 100mg VS PLA	ERTU 15mg VS PLA	ERTU 5mg VS PLA
BMI	Less than 30	–0.59 [–0.91, –0.27]	–0.79 [–1.06, –0.52]	–1.17 [–1.41, –0.93]	–0.91 [–1.15, –0.67]	–0.95 [–1.17, –0.73]	–0.71 [–0.90, –0.52]
	More than 30	–0.57 [–0.81, –0.32]	–0.58 [–0.73, –0.43]	–0.80 [–0.87, –0.72]	–0.66 [–0.73, –0.59]	–0.77 [–0.86, –0.67]	–0.71 [–0.91, –0.51]
I^2		0% 59%	54% 60%	0% 36%	0% 22%	0% 0%	0% 76%
	P	.91	.18	**.003***	**.05***	.13	.98
BMI	Less (half of studies)	–0.58 [–0.76, –0.41]	–0.63 [–0.76, –0.50]	–1.17 [–1.41, –0.93]	–0.91 [–1.15, –0.67]	–0.95 [–1.17, –0.73]	– –
	More (half of studies)	–0.46 [–0.67, –0.26]	–0.55 [–0.80, –0.31]	–0.80 [–0.87, –0.72]	–0.66 [–0.73, –0.59]	–0.77 [–0.86, –0.67]	– –
I^2		48% 0%	0% 72%	0% 36%	0% 22%	0% 0%	– –
	P	.39	.58	**.003***	**.05***	.13	–
Region	Europe and America	–0.48 [–0.59, –0.37]	–0.57 [–0.66, –0.48]	–1.01 [–1.25, –0.78]	–0.88 [–1.04, –0.73]	–0.81 [–1.05, –0.57]	–0.77 [–0.88, –0.65]
	Others	–0.59 [–0.91, –0.27]	–0.79 [–1.06, –0.52]	–0.78 [–0.86, –0.70]	–0.63 [–0.71, –0.55]	–0.82 [–0.95, –0.69]	–0.66 [–0.97, –0.34]
I^2		0% 34%	54% 41%	55% 0%	0% 0%	72% 0%	0% 82%
	P	.53	.13	.06	**.004***	.93	.51

CANA 300mg VS PLA	CANA 100mg VS PLA	ERTU 15mg VS PLA	ERTU 5mg VS PLA	EMPA 25mg VS PLA	EMPA 10mg VS PLA
–	–0.87	–0.70	–0.80	–0.73	–0.74
–	[–1.15, –0.59]	[–0.84, –0.56]	[–0.94, –0.66]	[–0.87, –0.59]	[–0.94, –0.54]
–	–0.67	–0.86	–0.66	–0.70	–0.79
–	[–0.74, –0.60]	[–0.97, –0.74]	[–0.77, –0.55]	[–1.02, –0.38]	[–1.11, –0.47]
–	0%	0%	0%	56%	80%
–	44%	0%	67%	0%	0%
–	.18	.09	.12	.85	.80
–0.88	–0.77	–0.75	–0.65	–0.74	–0.79
[–1.18, –0.58]	[–1.00, –0.53]	[–0.87, –0.64]	[–0.95, –0.36]	[–0.89, –0.58]	[–1.06, –0.53]
–0.85	–0.66	–0.86	–0.76	–0.69	–0.65
[–1.00, –0.70]	[–0.75, –0.58]	[–0.99, –0.72]	[–0.90, –0.62]	[–0.90, –0.49]	[–0.82, –0.49]
80%	68%	35%	86%	54%	85%
37%	0%	10%	0%	0%	0%
.87	.42	.25	.51	.74	.38
–	–0.67	–0.86	–0.80	–	–0.61
–	[–0.74, –0.60]	[–0.95, –0.74]	[–0.94, –0.66]	–	[–0.68, –0.55]
–	–0.87	–0.7	–0.66	–	–1.12
–	[–1.15, –0.59]	[–0.84, –0.56]	[–0.77, –0.55]	–	[–1.37, –0.87]
–	44%	0%	0%	–	25%
–	0%	0%	67%	–	0%
–	.18	.09	.12	–	**.0001***

- (1) Drug naïvety.
- (2) Duration of diabetes. Two approaches were employed for subgroup stratification: the first divided patients based on a diabetes duration threshold of more than 5 years, while the second divided them into two equal groups according to diabetes duration.
- (3) Body mass index (BMI). Similarly, two stratification methods were used: the first categorized patients by a BMI cutoff of 30 kg/m² or higher, and the second split them into two evenly sized groups based on BMI values.
- (4) Geographical region.

Subgroup analyses revealed reduced heterogeneity in the 10 mg empagliflozin, 15 mg ertugliflozin, 100 mg canagliflozin, and 300 mg canagliflozin treatment arms. Notably, statistically significant differences between subgroups were observed in both the 100 mg and 300 mg canagliflozin groups.

HbA1c primarily reflects the average blood glucose concentration over the preceding 2–3 months and is widely used both for diagnosing diabetes and for assessing

glycemic control in patients with type 2 diabetes mellitus (T2DM) [40, 41]. The present study confirms that sodium-glucose cotransporter (SGLT) inhibitors exert a marked therapeutic benefit in T2DM by significantly lowering HbA1c levels [42, 43]. The included trials were conducted across Europe, America, Asia, and Oceania, and all reported favorable outcomes, indicating that SGLT inhibitors are effective in T2DM patients regardless of geographic region. Nevertheless, considerable heterogeneity was observed for each individual SGLT inhibitor; therefore, a random-effects model was adopted, and subgroup analyses were performed to explore potential sources of this heterogeneity.

The dapagliflozin (DAPA) group comprised 11 studies and exhibited substantial heterogeneity. Subgroup analysis stratified by duration of diabetes markedly reduced heterogeneity and revealed statistically significant differences between subgroups. These findings indicate that the observed heterogeneity in the DAPA group likely stemmed from variations in diabetes duration among the enrolled patients and suggest that T2DM patients with differing disease durations may respond differently to dapagliflozin.

The empagliflozin (EMPA) group included 6 studies and also showed high heterogeneity. Subgroup analysis by geographic region substantially decreased heterogeneity and demonstrated significant inter-subgroup differences. Although most trials mentioned race only in the context of randomization without providing race-specific outcome data, the affiliation country of the first author—particularly the distinction between European/American and non-European/American regions—served as a proxy for racial differences. The subgroup results for the EMPA group suggest that heterogeneity primarily arose from regional (and possibly racial) differences among participants, implying that T2DM patients from different regions may exhibit varying responses to empagliflozin.

The ertugliflozin (ERTU) group consisted of 4 studies with notable heterogeneity. Subgroup analyses based on drug naïvety, diabetes duration, BMI, and region all substantially lowered heterogeneity; however, differences between subgroups did not reach statistical significance. These results suggest that heterogeneity in the ERTU group may be attributable to variations in drug naïvety, diabetes duration, BMI, and geographic region, and that patients differing in these characteristics might respond differently to ertugliflozin.

The canagliflozin (CANA) group included 6 studies and displayed high heterogeneity. Subgroup analyses according to drug naïvety and diabetes duration significantly reduced heterogeneity and showed statistically significant differences between subgroups. The findings indicate that heterogeneity in the CANA group likely originated from differences in drug naïvety and diabetes duration among the included patients, suggesting that T2DM patients varying in these factors may have distinct responses to canagliflozin.

The blood-glucose-lowering mechanism of SGLT inhibitors relies on sodium-glucose cotransporters (SGLT). These transporters are classified into SGLT-1 and SGLT-2 [44, 45]. Their actions are comparable: the Na^+/K^+-ATPase pump on the basolateral membrane hydrolyzes ATP to extrude three sodium ions and import two potassium ions, thereby creating a low intracellular sodium concentration. This gradient drives sodium ions from the tubular lumen into the cell, with glucose being co-transported via SGLT proteins. Glucose ultimately exits the cell into the peritubular capillaries through GLUT2 [46, 47]. **(Figure 3)**.

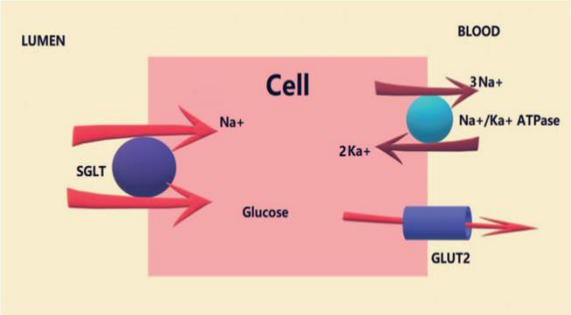


Figure 3. Mechanism of action of sodium-dependent glucose transporters (SGLT) in renal tubular cells. SGLT = sodium-glucose cotransporter.

SGLT-1 is predominantly expressed in the small intestine and kidneys. In the intestine, it facilitates glucose absorption from luminal contents, whereas in the kidney it reabsorbs approximately 10% of filtered glucose from the urine. In contrast, SGLT-2 is almost exclusively located in the proximal renal tubule and accounts for roughly 90% of urinary glucose reabsorption [48, 49]. SGLT inhibitors can target both SGLT-1 and SGLT-2; however, because studies involving sotagliflozin (SOTA) did not meet the inclusion criteria for this analysis, only selective SGLT-2 inhibitors were evaluated [50]. These SGLT-2 inhibitors lower blood glucose primarily by promoting urinary glucose excretion [40, 41].

SGLT inhibitors are widely used in routine clinical practice and are regarded as a suitable monotherapy option, particularly in patients with early-stage type 2 diabetes mellitus (T2DM) [42, 43]. Reducing the overall number of medications improves patients' quality of life [44, 45]. Long-term cardiovascular outcome trials have demonstrated that SGLT-2 inhibitors significantly reduce the risk of the composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [46–49].

The primary objectives of this study were to confirm the glucose-lowering efficacy of SGLT inhibitors in T2DM

and to investigate potential sources of heterogeneity across trials. Four separate meta-analyses were performed, each revealing substantial heterogeneity. These results suggest that the magnitude of HbA1c reduction with SGLT inhibitors may vary across populations, particularly in relation to diabetes duration, body mass index (BMI), and geographic region. The present analysis focused exclusively on HbA1c outcomes; differences in other efficacy endpoints or safety profiles across subpopulations require further dedicated systematic evaluation. Additional high-quality studies are warranted to clarify potential variations in both efficacy and safety of SGLT inhibitors among diverse patient groups.

Limitations of this network meta-analysis:

- Published studies on sotagliflozin (SOTA) did not fulfill the prespecified inclusion criteria; consequently, its efficacy in T2DM could not be assessed.
- Subgroup analyses were unable to fully account for all sources of heterogeneity.

Conclusion

SGLT inhibitors demonstrate clear efficacy in patients with type 2 diabetes mellitus (T2DM); however, their glucose-lowering effect may vary across different patient populations. Further high-quality studies are needed to better characterize potential differences in both the efficacy and safety of SGLT inhibitors among diverse subgroups.

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