ISSN 2450–7458
e-ISSN 2450–8187

A.B.M. Kamrul-Hasan[1], Deep Dutta[2], Ershad Mondal[1], Lakshmi Nagendra[3], Mehedi Hasan[4], Md. Shahidullah[5], Kaushik Biswas[6], Saptarshi Bhattacharya[7]

[1]Department of Endocrinology, Mymensingh Medical College, Mymensingh Sadar, Mymensingh 2200, Bangladesh

[2]Department of Endocrinology, CEDAR Superspeciality Healthcare, Dwarka, New Delhi, Delhi 110075, India

[3]Department of Endocrinology, JSS Medical College, JSS Academy of Higher Education and Research, Mysore, Karnataka 570004, India

[4]Department of Internal Medicine, Khwaja Yunus Ali Medical College and Hospital, Enayetpur, Sirajganj 6797, Bangladesh

[5]Non-Communicable Disease Unit, Nutritional Research Division, International Centre for Diarrheal Disease Research (icddr,b), Shaheed Tajuddin Ahmed Ave, Dhaka 1213, Bangladesh

[6]Department of Endocrinology & Metabolism, Medica Superspeciality Hospital, Kolkata 700009, India

[7]Department of Endocrinology, Indraprastha Apollo Hospitals, New Delhi, Delhi 110076, India

Efficacy and Safety of Bexagliflozin, a Selective Sodium-Glucose Cotransporter-2 Inhibitor, in Type 2 Diabetes: A Systematic Review and Meta-Analysis

ABSTRACT

Objective: To summarize the therapeutic effect and safety of bexagliflozin in patients with type 2 diabetes (T2D).

Materials and methods: Randomized controlled trials (RCTs) involving patients with T2D receiving bexagliflozin in the intervention arm and either a placebo or any active comparator in the control arm were searched through electronic databases. The primary outcome was the change from baseline (CFB) in glycated hemoglobin (HbA1c), and secondary outcomes included CFB in body weight, blood pressure, lipids, and adverse events. RevMan web was used to conduct meta-analysis using random-effects models.

Results: From 146 initially screened articles, data from nine RCTs involving 4,330 subjects were analyzed. Bexagliflozin outperformed placebo in terms of HbA1c reductions [standardized mean difference –0.55%, 95% CI (–0.68 to –0.42), $p < 0.00001$, $I^2 = 67\%$]; the degree of HbA1c reduction was similar whether bexagliflozin was used as monotherapy or as an add-on therapy. Higher proportions of subjects achieved HbA1c < 7% with bexagliflozin than in with placebo [odds ratio 2.73, 95% CI (1.80 to 4.14), $p < 0.00001$, $I^2 = 52\%$]. The CFB in HbA1c was identical with bexagliflozin and active comparators. Bexagliflozin had the additional benefits of reducing body weight and blood pressure and increasing HDL-C. Bexagliflozin and placebo had identical adverse event profiles. Compared to the active comparators, bexagliflozin imparted a lower risk of hypoglycemia and a higher risk of genital mycotic infection.

Conclusions: The results of the meta-analysis support the convincing glycemic efficacy and safety profile of bexagliflozin in managing T2D.

PROSPERO registration number: CRD42024498201.

Keywords: bexagliflozin, SGLT2i, type 2 diabetes, HbA1c, hypoglycemia, meta-analysis

Address for correspondence:
Dr. A.B.M. Kamrul-Hasan, Assistant Professor
Department of Endocrinology, Mymensingh Medical College, Mymensingh Sadar, Mymensingh 2200, Bangladesh
E-mail: rangassmc@gmail.com
Clinical Diabetology
DOI: 10.5603/cd.104462
Received: 12.01.2025 Accepted: 29.01.2025
Early publication date: 28.02.2025

Introduction

Sodium-glucose cotransporter (SGLT)-2 inhibitors (SGLT2is) are recommended as part of the glucose-lowering regimen, regardless of glycemic control status and metformin use, for patients with type 2 diabetes (T2D) who have established atherosclerotic cardiovascular disease (ASCVD), indicators of high ASCVD risk, heart failure, or chronic kidney disease (CKD) [1]. The use of SGLT2is is increasing globally, especially among populations at higher risk for ASCVD [2, 3]. As of now, there are five SGLT2is: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and bexagliflozin, all approved by the United States Food and Drug Administration for use in adults with T2D; bexagliflozin is the newest among these, having been approved in January 2023 [4]. Many randomized controlled trials (RCTs) and observational studies have reported the efficacy and safety of bexagliflozin in patients with T2D. However, marked heterogeneities exist in the efficacy and safety outcome data [5–13]. While some meta-analyses have summarized the efficacy and safety of bexagliflozin, they have not included all available RCTs [14–17]. The meta-analyses conducted by Patoulias et al. [14] and McMurray et al. [15] addressed only the cardiovascular safety of bexagliflozin in patients with T2D. Pasqualotto et al. [16] analyzed six RCTs in their meta-analysis; all are placebo-controlled trials [5, 7, 8, 10–12], but they did not include active comparator-controlled RCTs [6, 9, 13]. Dholariya et al. [17] mentioned eight RCTs in the flow diagram for study retrieval and inclusion in the meta-analysis; they ultimately analyzed five of the RCTs in the forest plot for the primary outcome [5, 7, 10–12]. The published meta-analyses did not perform separate analyses of placebo and active comparators to compare with bexagliflozin and they failed to analyze the efficacy of bexagliflozin when used as monotherapy or add-on therapy. Consequently, it became imperative to conduct a new meta-analysis incorporating the findings of the latest RCTs to gain a more comprehensive understanding of the efficacy and safety of bexagliflozin in patients with T2D.

Materials and methods

This meta-analysis complied with the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklists [18]. The systematic review and meta-analysis was registered in PROSPERO, with a registration number CRD42024498201.

A thorough investigation was conducted by searching multiple databases and registers, such as MEDLINE (via PubMed), Scopus, Google Scholar, Cochrane Central Register, International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov. The search covered these sources' inception until April 30, 2024. The search strategy utilized a Boolean approach with the terms (bexagliflozin) AND (type 2 diabetes); the search terms were applied to titles and abstracts only. A thorough and careful search was conducted to find any recently published or unpublished clinical trials in English. This search included examining references within the RCTs included in this study and relevant journals.

The selection of RCTs for this meta-analysis was based on the PICO criteria. The patient population (P) consisted of individuals with T2D; the intervention (I) was the administration of bexagliflozin for managing T2D; the control (C) included individuals receiving either a placebo or another approved oral anti-diabetic drugs (OADs); and the outcomes (O) included glycated hemoglobin (HbA1c). This analysis included RCTs with a minimum 12-week duration with study subjects aged ≥ 18 years and a diagnosis of T2D. The trials had at least two treatment arms/groups, with one receiving bexagliflozin as monotherapy or as part of a standard diabetes treatment regimen and the other receiving a placebo or alternative OAD, alone or in combination. Exclusion criteria excluded animal or healthy human trials, nonrandomized trials, retrospective studies, case reports, letters to editors, articles lacking data with outcomes of interest, and RCTs < 12 weeks in duration.

The primary outcome of this meta-analysis was the change from baseline (CFB) in HbA1c levels. Additional outcomes encompassed the percentage of study subjects achieving HbA1c < 7.0% at the end of the trial and CFB in fasting plasma glucose (FPG), body weight, systolic and diastolic blood pressure (BP), hematocrit (Hct), lipid parameters from baseline to the end of the trial, and adverse events (AEs). The analyses of the outcomes were stratified according to whether the control group received a placebo, which constituted the placebo control group (PCG), or an active comparator (any OAD), which comprised the active control group (ACG).

Data extraction was independently conducted by four review authors using standardized data extraction forms, with details provided elsewhere [19]. The handling of missing data has also been elaborated upon in the same source [19]. Four authors independently performed the risk of bias (RoB) assessment using the RoB tool in the Review Manager (RevMan) computer program, version 7.2.0. [20]. Specific biases have been outlined elsewhere [19].

For analysis, HbA1c levels were presented as percentages (%); the International System of Units (SI units) were used for other variables. The results obtained from studies implemented with varying units were converted

for optimal consistency by applying appropriate conversion factors. The results of the outcomes were expressed as standardized mean differences (SMDs) or mean differences (MDs) for continuous variables and as odds ratios (ORs) or risk ratios (RRs) for dichotomous variables with 95% confidence intervals (CIs). Forest plots were created using the RevMan computer program, version 7.2.0. [20], that portrayed the comparison of SMD (or MD) and OR (or RR) for primary and secondary outcomes, as appropriate, between the bexagliflozin (experimental drug) and control groups (PCG or ACG) in the included studies. Random effects analysis models were chosen for the review to account for the expected heterogeneity arising from differences in population characteristics and research durations. The inverse variance statistical method was applied for all instances. The results included forest plots incorporating data from at least two RCTs. A significance level of $p < 0.05$ was used.

The evaluation of heterogeneity was initially performed by analyzing forest plots. Afterward, a Chi^2 test was conducted with N-1 degrees of freedom and a significance level of 0.05 to ascertain the statistical significance. Additionally, the I^2 test was utilized in the further analysis [21]. The details of interpreting I^2 values have already been elaborated elsewhere [19].

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology assessed the quality of evidence about each meta-analysis outcome [22]. The process of creating the summary of findings (SOF) table and evaluating the quality of evidence as "high," "moderate," "low," or "very low" has been previously described [19]. The assessment of potential publication bias (small-study effect bias) using a funnel plot was not feasible due to the small number (less than ten) of RCTs included in the study [23].

Results

Search results

The study selection process is illustrated in Supplementary Figure 1. Initially, 146 articles were identified; following the screening of titles and abstracts and subsequent full-text reviews, the number of studies considered for this meta-analysis was narrowed to 11. Detailed evaluation led to the inclusion of nine RCTs involving 4,330 subjects with T2D, which met all the inclusion criteria [5–13]. Two studies were excluded because they were conducted on animals (cats) [24, 25].

Study characteristics

In this meta-analysis, which included nine RCTs, subgroup analyses were conducted based on the nature of the control group, either PCG or ACG. Only two RCTs were phase 2 trials; [7, 8] the remaining seven were phase 3 [5, 6, 9–13]. Six RCTs that included a placebo in the control group were analyzed in the PCG [5, 7, 8, 10–12]. Three RCTs that included an OAD in the control group were analyzed in the ACG [6, 9, 13]. Sitagliptin 100 mg once daily [6], glimepiride 2–6 mg once daily,[9] and dapagliflozin 10 mg once daily [13] were used as the active comparator in these three ACG-controlled studies. All studies used bexagliflozin at a dosage of 20 mg once daily in the intervention arm. One study (Halvorsen 2020) had two additional intervention arms of bexagliflozin, 5 mg and 10 mg, once daily; data from the bexagliflozin 20 mg arm was included in the meta-analysis [8]. The details of the included and excluded studies are shown in Table 1 and Supplementary Table 1, respectively.

Risk of bias in the included studies

The bias risk across the nine studies included in the meta-analysis is depicted in Supplementary Figure 2. All nine studies (100%) exhibited a low risk of selection bias, performance bias, detection bias, attrition bias, and reporting bias. The "other bias" category encompassed exploring funding sources, particularly those from pharmaceutical companies, affiliations with pharmaceutical organizations, and potential conflicts of interest. All studies (100%) had a high risk of other biases. The detailed process of bias risk assessment is available as a supplementary file (Suppl. Tab. 2).

Grading of the results

The grades for the certainty of evidence of the key outcomes of this meta-analysis are given in the SoF table (Suppl. Tab. 3).

Effect of bexagliflozin on the glycemic parameters

HbA1c

Bexagliflozin outperformed placebo in terms of HbA1c reductions [SMD –0.55%, 95% CI (–0.68 to –0.42), $p < 0.00001$, $I^2 = 67\%$, moderate certainty of evidence] (Fig. 1A). In subgroup analysis, bexagliflozin was similarly effective ($p = 0.12$, $I^2 = 57.9\%$) when it was used either as add–on therapy to background anti–hyperglycemic agents [SMD –0.47%, 95% CI (–0.54 to –0.39), $p < 0.00001$, $I^2 = 0\%$] or as monotherapy [SMD –0.67%, 95% CI (–0.92 to –0.42), $p < 0.00001$, $I^2 = 69\%$] (Suppl. Fig. 3A). In the placebo-controlled RCTs, greater HbA1c reduction ($p = 0.0002$, $I^2 = 92.6\%$) was achieved with bexagliflozin in phase 2 trials [SMD –0.80%, 95% CI (–0.96 to –0.63), $p < 0.00001$, $I^2 = 0\%$]

Table 1. The Basic Characteristics of the Included Randomized Controlled Trials and Participants

Trial reg. no., Phase of study, Study place, Study ID	Major baseline characteristics of the study subjects	Mode of study drug administration	Study arms	N	Age [y, mean ± SD]	Male/ Female	Diabetes duration [y, mean ± SD]	Baseline HbA1c [%,mean ± SD]	Study duration
NCT02836873, Phase 3, Multi-country, Allegretti 2019 [5]	• CKD stages 3a/3b • Background AHA: treatment naïve or stable treatment regimen for T2DM for preceding 8 weeks	Add-on therapy to existing AHA	Bexagliflozin 20 mg	157	69.3 ± 8.36	92/65	15.54 ± 9.2	8.01 ± 0.79	24 weeks
			Placebo	155	69.9 ± 8.29	104/41	16.28 ± 9.0	7.95 ± 0.81	
NCT03115112, Phase 3, Multi-country, Halvorsen 2019a [6]	• Background AHA: metformin ≥ 1.5 g/day • The dose not changed in the 8 weeks before screening	Add-on therapy to metformin	Bexagliflozin 20 mg	191	59.3 ± 9.7	120/71	8.22 ± 5.7	7.94 ± 0.81	24 weeks
			Sitagliptin 100 mg	193	59.6 ± 9.8	126/67	9.36 ± 5.7	8.03 ± 0.92	
NCT01377844, Phase 2, Multi-country, Halvorsen 2019b [7]	• Background AHA: treatment naïve or one OAD • Stable treatment regimen for diabetes, HTN, and dyslipidemia for preceding 3 months • Those on an OAD, discontinued that at the start of the run-in period	Monotherapy	Bexagliflozin 20 mg	145	56.2 ± 10.9	67/78	7.55 ± 6.6	< 8.5%: 60% ≥ 8.5: 40%	24 weeks* (extended up to 96 weeks)
			Placebo	141	54.9 ± 10.3	49/89	7.38 ± 6.7	< 8.5%: 70.3% ≥ 8.5: 29.7%	
NCT02390050, Phase 2, Multicenter in USA and Japan, Halvorsen 2020 [8]	• Background AHA: treatment naïve or one OAD (discontinued 6–10 weeks before randomization)	Monotherapy	Bexagliflozin 5 mg	72	59.0 ± 10.2	47/25	5.6 ± 5.6	7.77 ± 0.39	12 weeks
			Bexagliflozin 10 mg	72	59.4 ± 9.0	41/31	6.2 ± 5.3	7.73 ± 0.43	
			Bexagliflozin 20 mg	76	59.5 ± 10.8	50/26	6.8 ± 7.0	7.73 ± 0.45	
			Placebo	72	58.8 ± 10.4	42/30	6.3 ± 5.7	7.63 ± 0.44	

NCT02769481, Phase 3, Multi-country, Halvorsen 2023a [9]	• Background AHA: metformin and no more than one other OAD (discontinued 6 weeks before randomization)	Add-on therapy to metformin	Bexagliflozin 20 mg	213	59.5 ± 9.06	118/95	9.35 ± 5.9	8.04 ± 0.77	60 weeks** (extended up to 96 weeks)
			Glimepiride 2, 4, or 6 mg	213	59.7 ± 10.35	130/83	7.97 ± 5.5	7.98 ± 0.70	
NCT03259789, Phase 3, Multicenter in USA and Japan, Halvorsen 2023b [10]	• Background AHA: metformin (≥ 1.5 g/day in USA, ≥ 1.0 g/day in Japan) • The dose not changed in the 8 weeks before screening	Add-on therapy to metformin	Bexagliflozin 20 mg	158	56.0 ± 10.1	100/58	9.31 ± 6.6	8.66 ± 0.87	24 weeks
			Placebo	159	55.6 ± 11.1	94/65	8.88 ± 5.9	8.57 ± 0.79	
NCT02558296, Phase 3, Multi-country [11]	• Stable treatment regimen of AHA for preceding 3 months • Increased risk of CV adverse events	Add-on therapy to existing AHA	Bexagliflozin 20 mg	1133	64.4 ± 7.94	792/341	14.87 ± 8.6	8.32 ± 0.9	24 weeks
			Placebo	567	64.6 ± 8.01	390/177	15.23 ± 9.2	8.33 ± 0.9	
NCT02715258, Phase 3, Multicenter in USA and Canada [12]	• Background AHA: treatment naïve or receiving one OAD (which was discontinued at placebo run-in period) • Doses of antihypertensive and lipid-lowering drugs (if applicable) had not changed for at least 30 days prior to screening	Monotherapy	Bexagliflozin 20 mg	138	55.8 ± 10.21	66/72	9.39 ± 1.9	5.9 ± 5.8	24 weeks
			Placebo	69	54.7 ± 11.02	34/35	9.45 ± 2.1	6.5 ± 5.21	
NCT05159882, Phase 3, Multicenter in China, Xie 2024 [13]	• Background AHA: metformin ≥ 1.5 g/day • The dose not changed in the 8 weeks before screening	Add-on therapy to metformin	Bexagliflozin 20 mg	203	56.2 ± 9.8	124/79	6.6 ± 5.3	8.51 ± 0.85	24 weeks
			Dapagliflozin 10 mg	203	55.9 ± 8.9	103/100	6.4 ± 4.8	8.55 ± 0.80	

*The primary endpoint was assessed at 24 weeks; we analyzed 24-week data for efficacy outcomes and 96-week data for safety outcomes; **The primary endpoint was assessed at 60 weeks; we analyzed 60-week data for efficacy outcomes and 96-week data for safety outcomes; AHA — anti-hyperglycemic agents; CKD — chronic kidney disease; CV — cardiovascular; HbA1c — glycated hemoglobin; OAD — oral anti-diabetic drug; SD — standard deviation; USA — United States of America

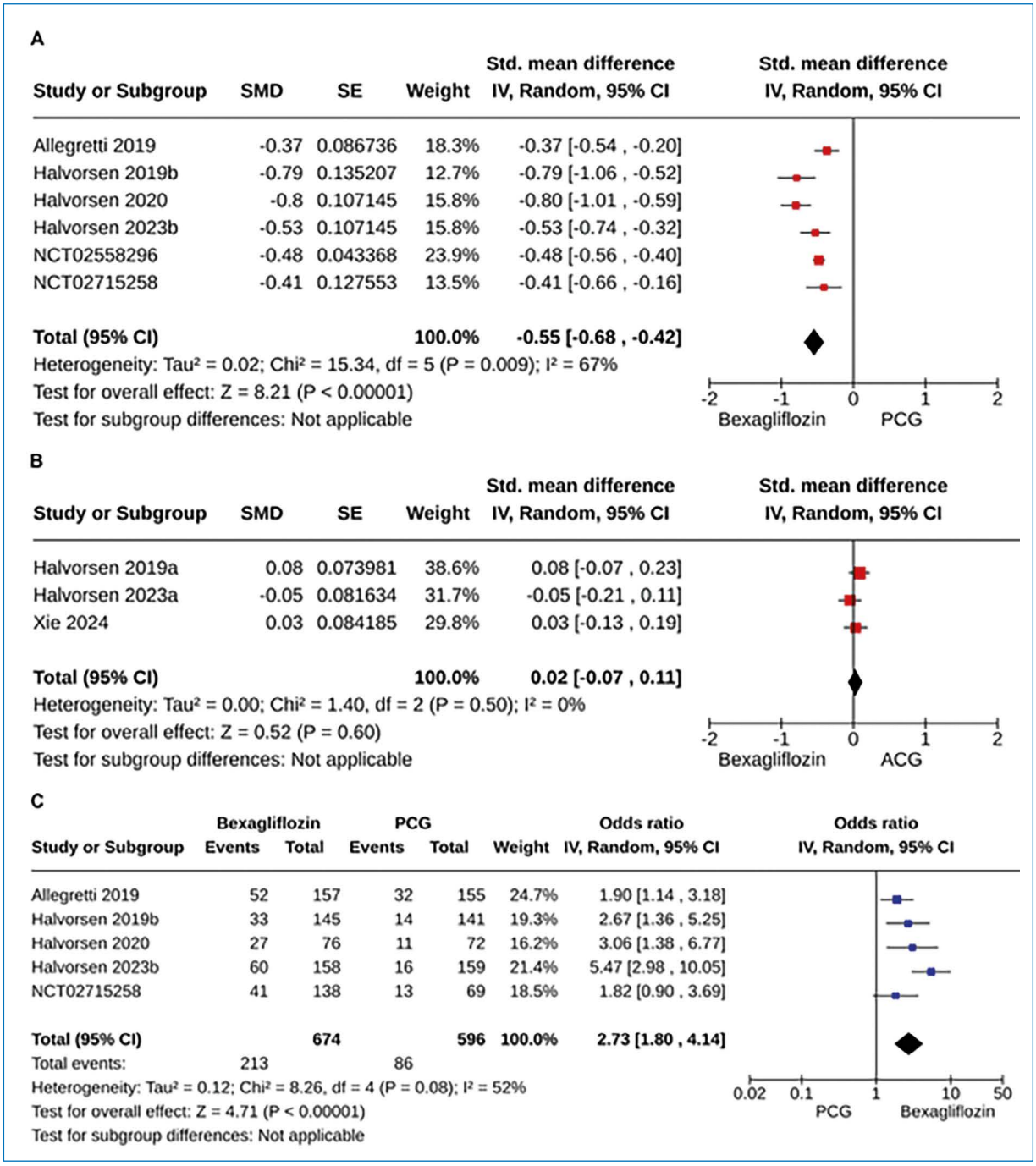

Figure 1. Forest Plot Highlighting (**A**) the change from baseline in HbA1c, bexagliflozin vs. placebo control group (PCG); (**B**) the change from baseline in HbA1c, bexagliflozin vs. active control group (ACG); and (**C**) the proportion of the study subjects who achieved HbA1c < 7.0%, bexagliflozin vs. PCG
CI — confidence interval; HbA1c — glycated hemoglobin; SE — standard error; SMD — standardized mean differences

than in phase 3 trials (SMD –0.46%, 95% CI [–0.53 to –0.39], p < 0.00001, I^2 = 0%) (Suppl. Fig. 3B). The HbA1c reductions in the bexagliflozin group and ACG were comparable [SMD 0.02%, 95% CI (–0.07 to 0.11), p = 0.60, I^2 = 0%] (Fig. 1B).

HbA1c < 7.0%

The proportion of subjects achieving HbA1c < 7% was higher in the bexagliflozin arm than in PCG [OR 2.73, 95% CI (1.80 to 4.14), p < 0.00001, I^2 = 52%, moderate certainty of evidence] (Fig. 1C).

Table 2. The Results of Safety Outcomes in the Meta-Analysis (Bexagliflozin vs. PCG)

Safety variables	No. of RCTs [Ref. no.]	No. of participants with outcome/ /participants analyzed (n)		I^2 (%)	Pooled effect size, RR [95% CI]	P-value
		Bexagliflozin arm	Placebo arm			
Any TEAEs	6 [5, 7, 8, 10–12]	1085/1807	714/1163	0	0.97 [0.91, 1.23]	0.87
Any treatment-related AEs	2 [5, 10]	76/315	54/314	0	1.40 [1.04, 1.88]	0.03
AEs leading to treatment discontinuation	2 [5, 10]	7/315	9/314	0	0.77 [0.28, 2.09]	0.61
AEs leading to study withdrawal	3 [5, 7, 10]	6/460	6/455	29	1.04 [0.22, 4.82]	0.96
Serious AEs	5 [5, 7, 8, 11, 12]	391/1649	230/1004	21	0.86 [0.57, 1.28]	0.45
AEs leading to death	5 [5, 7, 8, 10, 11]	40/1669	26/1094	0	0.77 [0.48, 1.25]	0.30
Hypoglycemia	5 [5, 7, 8, 10, 11]	544/1669	310/1094	0	0.97 [0.87, 1.09]	0.63
GMI	3 [5, 7, 10]	10/460	3/455	0	2.35 [0.63, 8.73]	0.20
UTI	6 [5, 7, 8, 10–12]	174/1807	103/1163	0	1.02 [0.81, 1.29]	0.85
Upper RTI	3 [8, 11, 12]	117/1347	58/708	0	1.03 [0.76, 1.39]	0.86
Nasopharyngitis	4 [5, 8, 10, 11]	119/1524	68/953	0	1.07 [0.80, 1.44]	0.66
Headache	3 [7, 8, 12]	13/359	16/282	0	0.64 [0.31, 1.31]	0.22
Polyuria	4 [5, 8, 10, 12]	36/529	13/455	28	2.18 [0.97, 4.90]	0.06
Pollakiuria	2 [8, 10]	5/234	0/231	0	5.80 [0.70, 47.96]	0.10
Arthralgia	3 [5, 8, 11]	59/1366	35/794	9	0.98 [0.60, 1.62]	0.94
Back pain	2 [8, 11]	66/1209	34/639	0	0.98 [0.66, 1.47]	0.93
Fracture	2 [5, 10]	8/315	6/314	0	1.27 [0.46, 3.49]	0.64
Nausea	4 [5, 8, 11, 12]	67/1504	52/863	0	0.73 [0.51, 1.05]	0.09
Diarrhea	3 [8, 11, 12]	77/1347	38/708	32	0.84 [0.40, 1.77]	0.65

AE — adverse event; CI — confidence interval; GMI — genital mycotic infection; PCG — placebo control group; RCT — randomized controlled trials; RR — risk ratio; RTI — respiratory tract infection; TEAE — treatment-emergent adverse event; UTI — urinary tract infection

FPG

In FPG reduction, bexagliflozin was superior to both PCG [SMD –1.31 mmol/L, 95% CI (–1.61 to –1.02), $p < 0.00001$, $I^2 = 61\%$] (Suppl. Fig. 4A) and ACG [SMD –0.30 mmol/L, 95% CI (–0.50 to –0.09), $p = 0.004$, $I^2 = 0\%$] (Suppl. Fig. 4B).

Effect of bexagliflozin on body weight

Greater reductions in body weight were achieved with bexagliflozin compared to both PCG [SMD –1.93 kg, 95% CI (–2.47 to –1.39), $p < 0.00001$, $I^2 = 72\%$, moderate certainty of evidence] (Suppl. Fig. 5A) and ACG [SMD –2.37 kg, 95% CI (–4.61 to –0.13), $p = 0.04$, $I^2 = 97\%$] (Suppl. Fig. 5B).

Effect of bexagliflozin on blood pressure

Reductions in SBP were higher in the bexagliflozin arm than the PCG arm [SMD –4.49 mmHg, 95% CI (–6.12 to –2.86), $p < 0.00001$, $I^2 = 40\%$, high certainty of evidence] (Suppl. Fig. 6A). Bexagliflozin and ACG achieved comparable reductions in SBP [SMD –2.67 mmHg, 95% CI (–5.76 to 0.42), $p = 0.09$, $I^2 = 71\%$] (Suppl. Fig. 6B). Bexagliflozin also outperformed PCG in lowering DBP [SMD –1.37 mmHg, 95% CI (–2.28 to –0.45), $p = 0.004$, $I^2 = 15\%$, high certainty of evidence] (Suppl. Fig. 6C).

Safety

Comparable CFB in low-density lipoprotein cholesterol (L-DLC) was achieved with bexagliflozin and PCG [MD 0.07 mmol/L, 95% CI (–0.03 to 0.27), $p = 0.18$, $I^2 = 0\%$] (Suppl. Fig. 7A). Increments in high-density lipoprotein cholesterol (H-DLC) were higher with bexagliflozin than PCG [MD 0.09 mmol/L, 95% CI (0.06 to 0.12), $p < 0.00001$, $I^2 = 0\%$, high certainty of evidence] (Suppl. Fig. 7B). A higher increment in Hct from baseline was observed in bexagliflozin than PCG [MD 2.33%, 95% CI (1.06 to 3.60), $p = 0.0003$, $I^2 = 83\%$] (Suppl. Fig. 7C).

Bexagliflozin and PCG were associated with similar risks of any treatment-emergent AEs (TEAEs), treatment-related AEs, AEs leading to treatment discontinuation, AEs leading to study withdrawal, serious AEs, AEs leading to death, hypoglycemia, genital mycotic infection (GMI), urinary tract infection (UTI), upper respiratory tract infection, nasopharyngitis, headache, polyuria, pollakiuria, arthralgia, back pain, fracture, nausea, and diarrhea (Tab. 2). Compared to ACG,

Table 3. The Results of Safety Outcomes in the Meta-Analysis (Bexagliflozin vs. ACG)

Safety variables	No. of RCTs [ref. no.]	No. of participants with outcome/ /participants analyzed (n)		I^2 (%)	Pooled effect size, RR [95% CI]	P-value
		Bexagliflozin arm	Active control arm			
Any TEAEs	3 [6, 9, 13]	389/607	413/609	12	0.96 [0.89, 1.04]	0.32
Any treatment-related AEs	3 [6, 9, 13]	166/607	141/609	41	1.19 [0.92, 1.56]	0.19
AEs leading to treatment discontinuation	2 [6, 13]	8/394	5/396	70	1.60 [0.14, 18.38]	0.71
AEs leading to study withdrawal	3 [6, 9, 13]	10/607	12/609	63	0.84 [0.16, 4.55]	0.84
Serious AEs	2 [9, 13]	34/416	33/416	0	1.03 [0.65, 1.62]	0.91
AEs leading to death	3 [6, 9, 13]	2/607	0/609	0	3.02 [0.31, 28.87]	0.34
Hypoglycemia	3 [6, 9, 13]	49/607	89/609	0	0.55 [0.40, 0.75]	0.0002
GMI	2 [6, 9]	26/404	4/406	0	5.73 [2.13, 15.41]	0.0005
UTI	3 [6, 9, 13]	49/607	35/609	44	1.38 [0.75, 2.52]	0.30
Nasopharyngitis	2 [6, 9]	44/404	54/406	38	0.81 [0.50, 1.31]	0.39
Polyuria	2 [6, 9]	21/404	11/406	0	1.87 [0.91, 3.82]	0.09
Fracture	2 [6, 9]	4/404	3/406	0	1.25 [0.30, 5.17]	0.76
Rash	2 [6, 9]	7/404	7/406	0	1.17 [0.40, 3.45]	0.78

ACG — active control group; AE — adverse event; CI — confidence interval; GMI — genital mycotic infection; RCT — randomized controlled trials; RR — risk ratio; TEAE — treatment-emergent adverse event; UTI — urinary tract infection

bexagliflozin imparted a lower risk of hypoglycemia (RR 0.55 [0.40, 0.75], p = 0.0002, I^2 = 0%) and a higher risk of GMI [RR 5.73 (2.13, 15.41), p = 0.0005, I^2 = 0%]. TEAEs, treatment-related AEs, AEs leading to treatment discontinuation, AEs leading to study withdrawal, serious AEs, AEs leading to death, UTI, nasopharyngitis, polyuria, fracture, and rash were comparable between bexagliflozin and ACG (Tab. 3).

Sensitivity analysis

Leave-one-out sensitivity analyses were performed for all outcomes to detect the changes in the statistical significance levels and significant changes in heterogenicity (at least 2-step change); the results of the analyses for major outcomes are provided as a supplementary file (Suppl. Tab. 4A–4N). There were no changes in the statistical significance levels of efficacy outcomes of bexagliflozin vs. PCG. For the outcome HbA1c < 7.0%, the heterogenicity among the studies was reduced (I^2 = 52% to I^2 = 0%) after removing the study Halvorsen 2023b. The risk of polyuria significantly increased in the bexagliflozin group than in the PCG when Halvorsen 2023b was omitted. There were no changes in the statistical significance levels of other safety outcomes of bexagliflozin vs. PCG. The statistical significance levels of efficacy outcomes of bexagliflozin vs. ACG did not change for HbA1c and SBP. The superiority of bexagliflozin over ACG was lost: for FPG after removing Halvorsen 2019a, for body weight after removing either Halvorsen 2019a or Halvorsen 2023a, and for hypoglycemia and GMI after removing Halvorsen 2023a. Removing Xie 2024 resulted in a significantly increased risk for UTI in bexagliflozin versus ACG.

Discussion

The present meta-analysis incorporated the results of RCTs of bexagliflozin in T2D available to date. It highlights the glycemic efficacy and adverse events of bexagliflozin compared to a placebo and other OADs used as monotherapy or add-on therapy to other glucose-lowering drugs. Bexagliflozin is more effective than placebo and similarly effective to other OADs in reducing HbA1c, with comparable AEs except for a higher GMI risk than ACG.

Bexagliflozin is a potent and highly selective inhibitor with > 2000-fold selectivity for SGLT2 over SGLT1 [26]. This meta-analysis demonstrated 0.55% greater reductions in HbA1c from baseline with bexagliflozin than the placebo. In the meta-analyses of placebo-controlled trials, placebo-subtracted weighted MDs of HbA1c were –0.46% for dapagliflozin, –0.63% for canagliflozin 100 mg, –0.80% for canagliflozin 300 mg, –0.61% for empagliflozin 10 mg, and –0.63% for empagliflozin 25 mg [27, 28]. Yang et al. [29], in their meta-analysis, demonstrated higher HbA1c reductions with other SGLT2is when used as monotherapy than

add-on therapy. The present meta-analysis demonstrated similar HbA1c-lowering efficacy as monotherapy and add-on therapy. Bexagliflozin was as good as other SGLT2 inhibitors in reducing FPG and the percentage of people achieving HbA1c < 7% [27, 28, 30]. Additionally, the comparative HbA1c reductions and higher FPG reductions achieved with bexagliflozin than other OADs, including sitagliptin and glimepiride, further support the glycemic efficacy of bexagliflozin. The greater HbA1c reduction observed with bexagliflozin in the placebo-controlled phase 2 trials compared to phase 3 trials may be attributed to the limited number of phase 2 trials, which had smaller sample sizes and were of shorter duration.

SGLT2 inhibitors reduce body weight from 1 to 5 kg. Weight loss induced by SGLT2is might be directly related to volume depletion and glucose excretion in the kidneys by SGLT2is, resulting in noticeable calorie loss [31]. In this meta-analysis, bexagliflozin was similarly effective in weight reduction to other SGLT2is [27, 28, 30]. BP reduction with SGLT2is occurs due to natriuresis and osmotic diuresis initially and to local renninangiotensin system inhibition later [31]. In this meta-analysis, bexagliflozin showed significant SBP and DBP reductions, comparable to other SGLT2is [27, 28, 30, 31]. SGLT2is are considered to be either lipid-friendly or lipid-neutral drugs [31]. This meta-analysis revealed a small, non-significant increase in LDLC and a significant rise in HDL-C in the bexagliflozin group compared to the PCG. In a meta-analysis by Sánchez-García et al. [32], canagliflozin, dapagliflozin, and empagliflozin were found to significantly increase total cholesterol, LDL-C, non-HDLC, and HDL-C, and decrease triglyceride levels, compared to placebo. In another meta-analysis, Xiong et al. [28] found significantly greater increments in both LDLC and HDL-C with canagliflozin 100 mg and 300 mg compared to placebo. Such an increase in LDL-C may result from natriuresis-induced hemoconcentration and decreased expression of LDL receptors in hepatocytes. The rise in HDL-C and the decrease in triglyceride levels could be related to improving insulin sensitivity and secretion [32]. The increment in Hct with bexagliflozin found in this meta-analysis is supported by similar group effects of SGLT2is, as shown in a previous meta-analysis [33].

The meta-analysis provides quite reassuring safety data for bexagliflozin, as shown by no differences in AEs, including hypoglycemia, diuretic symptoms, GMI, or UTI, between the bexagliflozin and placebo groups. AEs were also comparable between bexagliflozin and ACG, except for higher GMI risk with bexagliflozin. Moreover, hypoglycemia risk was lower with bexagliflozin than with other OADs used as active comparators. The glucose-lowering effects of SGLT2is are dependent on blood glucose levels and they are independent of insulin's actions; thus, they have minimal hypoglycemic potentials [31]. Previous meta-analyses also found identical hypoglycemic risks with other SGLT2 inhibitors compared to placebo [27, 28, 30]. The risk of UTI with bexagliflozin was comparable to PCG and ACG in this meta-analysis. In previous meta-analyses, UTI risk was not increased with canagliflozin, empagliflozin, and ertugliflozin, but dapagliflozin imparted a higher UTI risk than placebo [28, 30, 34]. According to previous reports, SGLT2is are associated with higher risks of GMI [27, 28, 30, 34]. Although GMI risk was higher with bexagliflozin than ACG in this meta-analysis, the risks were similar with bexagliflozin and PCG. Pasqualotto et al. [16], in their meta-analysis, also found identical GMI risks in the bexagliflozin and placebo groups.

The main strength of this meta-analysis is the inclusion of a large population from a fairly large number of studies. The general quality of the included trials was good; all were RCTs and double-blind trials. We have separately analyzed the outcomes comparing bexagliflozin with PCG and ACG. Moreover, sub-analyses of CFB in HbA1c with bexagliflozin monotherapy versus add-on therapy and for phase 2 vs. phase 3 placebo-controlled RCTs were performed; such reports are missing in the previous meta-analyses. Furthermore, the meta-analysis included results of all RCTs available to date. There are also several limitations. One study (NCT02558296) accounted for ~39% of the subjects in the meta-analysis, thus driving most outcomes [11]. Moderate heterogeneity was observed for the primary outcome of HbA1c among the placebo-controlled RCTs, and the certainty of evidence generated for HbA1c was moderate. Moreover, only three RCTs were available for ACG and analyzed in the meta-analysis. Such limited data may be challenging to interpret and may require careful consideration. Another important limitation is that all but one study had follow-up periods of 24 weeks or less; hence, it is difficult to comment on the long-term efficacy and safety of bexagliflozin based on the results of this meta-analysis.

Conclusions

This meta-analysis on the efficacy and safety of bexagliflozin provides reassuring data on good glycemic efficacy, tolerability, and safety over an extended period of clinical use in a diverse group of patients with T2D. Bexagliflozin use was associated with increased GMI risks compared to other OADs but not placebo. Longer-duration trials with multi-ethnic representation might explore the true potential of

the molecule and find its place in the contemporary management of T2D.

Article information

Supplementary material

The Supplementary material for this article can be found online at https://journals.viamedica.pl/clinical_diabetology/article/view/104462.

Data availability statement

Every dataset generated or scrutinized during this research is provided within the confines of this published article.

Author contribution

ABMK and DD conceptualized and designed the study. EM, LN, MH, and MS performed the full-text review and data identification. ABMK, KB, and SB evaluated the quality of the literature. ABMK, DD, and LN collected and analyzed the data and drew the tables and figures. KB and SB adjudicated any disagreements. ABMK and DD wrote the draft, and EM, LN, MH, MS, KB, and SB reviewed and revised the manuscript. ABMK and DD were responsible for the integrity of the work as a whole. Each author made contributions to the article and endorsed the submitted version.

Funding

This publication was prepared without any external source of funding.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

1. American Diabetes Association Professional Practice Committee, American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2024. Diabetes Care. 2024; 47(Suppl 1): S158–S178, doi: 10.2337/dc24-S009, indexed in Pubmed: 38078590.
2. Lin J, Pearson SA, Greenfield JR, et al. Trends in use of sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) in Australia in the era of increased evidence of their cardiovascular benefits (2014-2022). Eur J Clin Pharmacol. 2023; 79(9): 1239–1248, doi: 10.1007/s00228-023-03539-8, indexed in Pubmed: 37449993.
3. Zaghloul N, Awaisu A, Mahfouz A, et al. A 5-year trend in the use of sodium-glucose co-transporter 2 inhibitors and other oral antidiabetic drugs in a Middle Eastern country. Int J Clin Pharm. 2022; 44(6): 1342–1350, doi: 10.1007/s11096-022-01464-x, indexed in Pubmed: 36169802.
4. Hoy SM. Bexagliflozin: First Approval. Drugs. 2023; 83(5): 447–453, doi: 10.1007/s40265-023-01848-x, indexed in Pubmed: 36867399.
5. Allegretti AS, Zhang W, Zhou W, et al. Safety and Effectiveness of Bexagliflozin in Patients With Type 2 Diabetes Mellitus and Stage 3a/3b CKD. Am J Kidney Dis. 2019; 74(3): 328–337, doi: 10.1053/j.ajkd.2019.03.417, indexed in Pubmed: 31101403.
6. Halvorsen YD, Lock JP, Zhou W, et al. A 24-week, randomized, double-blind, active-controlled clinical trial comparing bexagliflozin with sitagliptin as an adjunct to metformin for the treatment of type 2 diabetes in adults. Diabetes Obes Metab. 2019; 21(10): 2248–2256, doi: 10.1111/dom.13801, indexed in Pubmed: 31161692.
7. Halvorsen YDC, Walford GA, Massaro J, et al. A 96-week, multinational, randomized, double-blind, parallel-group, clinical trial evaluating the safety and effectiveness of bexagliflozin as a monotherapy for adults with type 2 diabetes. Diabetes Obes Metab. 2019; 21(11): 2496–2504, doi: 10.1111/dom.13833, indexed in Pubmed: 31297965.
8. Halvorsen YD, Walford G, Thurber T, et al. A 12-week, randomized, double-blind, placebo-controlled, four-arm dose-finding phase 2 study evaluating bexagliflozin as monotherapy for adults with type 2 diabetes. Diabetes Obes Metab. 2020; 22(4): 566–573, doi: 10.1111/dom.13928, indexed in Pubmed: 31749238.
9. Halvorsen YD, Lock JP, Frias JP, et al. A 96-week, double-blind, randomized controlled trial comparing bexagliflozin to glimepiride as an adjunct to metformin for the treatment of type 2 diabetes in adults. Diabetes Obes Metab. 2023; 25(1): 293–301, doi: 10.1111/dom.14875, indexed in Pubmed: 36178197.
10. Halvorsen YD, Conery AL, Lock JP, et al. Bexagliflozin as an adjunct to metformin for the treatment of type 2 diabetes in adults: A 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2023; 25(10): 2954–2962, doi: 10.1111/dom.15192, indexed in Pubmed: 37409573.
11. ClinicalTrials.gov. Bexagliflozin efficacy and safety trial (BEST). ClinicalTrials.gov Identifier: NCT02558296. https://clinicaltrials.gov/ct2/show/study/NCT02558296 (5.01.2025).
12. ClinicalTrials.gov. Safety and efficacy of bexagliflozin as monotherapy in patients with type 2 diabetes. ClinicalTrials.gov Identifier: NCT02715258. https://clinicaltrials.gov/ct2/show/results/NCT02715258 (5.01.2025).
13. Xie L, Han J, Cheng Z, et al. Efficacy and safety of bexagliflozin compared with dapagliflozin as an adjunct to metformin in Chinese patients with type 2 diabetes mellitus: A 24-week, randomized, double-blind, active-controlled, phase 3 trial. J Diabetes. 2024; 16(4): e13526, doi: 10.1111/1753-0407.13526, indexed in Pubmed: 38584148.
14. Patoulias D, Dimosiari A. Meta-analysis Addressing the Cardiovascular Safety of Bexagliflozin in Patients With Type 2 Diabetes Mellitus. Am J Cardiol. 2022; 178: 178–179, doi: 10.1016/j.amjcard.2022.05.005, indexed in Pubmed: 35773042.
15. McMurray JJV, Solomon SD, Lock JP, et al. Meta-analysis of risk of major adverse cardiovascular events in adults with type 2 diabetes treated with bexagliflozin. Diabetes Obes Metab. 2024; 26(3): 971–979, doi: 10.1111/dom.15394, indexed in Pubmed: 38151752.
16. Pasqualotto E, Figueiredo Watanabe JM, Gewehr DM, et al. Efficacy and safety of bexagliflozin in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes Obes Metab. 2023; 25(7): 1794–1802, doi: 10.1111/dom.15051, indexed in Pubmed: 36929659.
17. Dholariya S, Dutta S, Singh R, et al. Bexagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, for improvement of glycemia in type 2 diabetes mellitus: a systematic review and meta-analysis. Expert Opin Pharmacother. 2023; 24(18): 2187–2198, doi: 10.1080/14656566.2023.2269854, indexed in Pubmed: 37817422.

18. Page MJ, McKenzie JE, Bossuyt PM, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. J Clin Epidemiol. 2021; 134(3): 103–112, doi: 10.1016/j.jclinepi.2021.02.003, indexed in Pubmed: 33577987.
19. Kamrul-Hasan ABM, Alam MS, Talukder SK, et al. Efficacy and Safety of Omarigliptin, a Novel Once-Weekly Dipeptidyl Peptidase-4 Inhibitor, in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Endocrinol Metab (Seoul). 2024; 39(1): 109–126, doi: 10.3803/EnM.2023.1839, indexed in Pubmed: 38417828.
20. Review Manager (RevMan) [Computer program]. Version 7.2.0. The Cochrane Collaboration, 2024. Available at revman.cochrane.org. (10.05.2024).
21. Higgins JPT, Altman DG, Gøtzsche PC, et al. Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343: d5928, doi: 10.1136/bmj.d5928, indexed in Pubmed: 22008217.
22. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011; 64(4): 383–394, doi: 10.1016/j.jclinepi.2010.04.026, indexed in Pubmed: 21195583.
23. Debray TPA, Moons KGM, Riley RD. Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: A comparison of new and existing tests. Res Synth Methods. 2018; 9(1): 41–50, doi: 10.1002/jrsm.1266, indexed in Pubmed: 28975717.
24. Benedict SL, Mahony OM, McKee TS, et al. Evaluation of bexagliflozin in cats with poorly regulated diabetes mellitus. Can J Vet Res. 2022; 86(1): 52–58, indexed in Pubmed: 34975223.
25. Hadd MJ, Bienhoff SE, Little SE, et al. Safety and effectiveness of the sodium-glucose cotransporter inhibitor bexagliflozin in cats newly diagnosed with diabetes mellitus. J Vet Intern Med. 2023; 37(3): 915–924, doi: 10.1111/jvim.16730, indexed in Pubmed: 37148170.
26. Zhang W, Welihinda A, Mechanic J, et al. EGT1442, a potent and selective SGLT2 inhibitor, attenuates blood glucose and HbA(1c) levels in db/db mice and prolongs the survival of stroke-prone rats. Pharmacol Res. 2011; 63(4): 284–293, doi: 10.1016/j.phrs.2011.01.001, indexed in Pubmed: 21215314.
27. Xu X, Xu W, Zhuo Q, et al. The efficacy and safety of dapagliflozin combined with oral hypoglycemic agents in patients with type 2 diabetes: a systematic review and meta-analysis. Ann Palliat Med. 2022; 11(3): 1028–1037, doi: 10.21037/apm-22-121, indexed in Pubmed: 35365032.
28. Xiong W, Xiao MY, Zhang M, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2016; 95(48): e5473, doi: 10.1097/MD.0000000000005473, indexed in Pubmed: 27902600.
29. Yang L, Zhang L, He He, et al. Efficacy and Safety of Sodium-Glucose Cotransporter 2 Inhibitors in East Asians with Type 2 Diabetes: A Systematic Review and Meta-Analysis. Diabetes Ther. 2019; 10(5): 1921–1934, doi: 10.1007/s13300-019-0674-7, indexed in Pubmed: 31376072.
30. Zaman M, Memon RS, Amjad A, et al. Effect of ertugliflozin on glycemic levels, blood pressure and body weight of patients with type 2 diabetes mellitus: a systematic review and meta-analysis. J Diabetes Metab Disord. 2020; 19(2): 1873–1878, doi: 10.1007/s40200-020-00623-z, indexed in Pubmed: 33520866.
31. Kalra S. Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors: A Review of Their Basic and Clinical Pharmacology. Diabetes Ther. 2014; 5(2): 355–366, doi: 10.1007/s13300-014-0089-4, indexed in Pubmed: 25424969.
32. Sánchez-García A, Simental-Mendía M, Millán-Alanís JM, et al. Effect of sodium-glucose co-transporter 2 inhibitors on lipid profile: A systematic review and meta-analysis of 48 randomized controlled trials. Pharmacol Res. 2020; 160: 105068, doi: 10.1016/j.phrs.2020.105068, indexed in Pubmed: 32652200.
33. Wang X, Fu R, Liu H, et al. The effects of sodium glucose co-transporter (SGLT) 2 inhibitors on hematocrit levels: a systematic review and meta-analysis of randomized controlled trials. Ann Palliat Med. 2021; 10(6): 6467–6481, doi: 10.21037/apm-21-1022, indexed in Pubmed: 34118855.
34. Li CX, Liu LiY, Zhang CX, et al. Comparative safety of different sodium-glucose transporter 2 inhibitors in patients with type 2 diabetes: a systematic review and network meta-analysis of randomized controlled trials. Front Endocrinol (Lausanne). 2023; 14: 1238399, doi: 10.3389/fendo.2023.1238399, indexed in Pubmed: 37701900.