Am J Cardiovasc Dis 2024;14(6):295-305
www.AJCD.us /ISSN:2160-200X/AJCD0156634

Review Article

The influence of SGLT-2 inhibitors on lipid profiles in heart failure patients: a systematic review and meta-analysis

Seyed Mohammad Mahdi Meybodi[1,2*], Mohammad Amin Karimi[3*], Kourosh Mousazadeh[4*], Kamyar Khorsand[5*], Samira Masoumi[6], Seyed Abbas Pakmehr[7], Mahsa Asadi Anar[10], Nahid Samadi[8], Mohadeseh Poudineh[9], Mohammad Rahmanian[10], Shirin Yaghoobpoor[10], Arash Rahimi[10], Fariba Arbab Mojeni[11], Seyedeh Zahra Banihashemian[12], Mina Masoodi[13], Komeil Aghazadeh-Habashi[14], Atousa Ghorbani[15], Arezoo Faridzadeh[16,17], Niloofar Deravi[10]

[1]Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran; [2]Young Researchers and Elite Club, Islamic Azad University, Tabriz Branch, Tabriz, Iran; [3]School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [4]Islamic Azad University, Tehran Medical Branch, Tehran, Iran; [5]Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; [6]Islamic Azad University, Pharmaceutical Sciences Branch (IAUPS), Tehran, Iran; [7]School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran; [8]Student Research Committee, Health Research Institute, Babol University of Medical Sciences, Babol, Iran; [9]Student Research Committee, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran; [10]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [11]Student Research Committee, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran; [12]Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran; [13]Faculty of Medicine, Islamic Azad University, Shahrood Branch, Shahrood, Iran; [14]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran; [15]Department of Biology, Faculty of Basic Sciences, Islamic Azad University, East Tehran Branch (Ghiamdasht), Tehran, Iran; [16]Department of Immunology and Allergy, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [17]Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. [*]Equal contributors.

Received March 18, 2024; Accepted August 29, 2024; Epub December 15, 2024; Published December 30, 2024

Abstract: Background and aim: Sodium-glucose cotransporter two inhibitors can reduce cardiovascular events by modulating lipid profiles in patients with heart failure, irrespective of diabetes status. In this study, we aimed to assess the effects of SGLT-2 inhibitors on the lipid profiles of patients with heart failure via a meta-analysis. Methods: The PubMed, Scopus, Web of Science, and Google Scholar databases were searched up to 2023 to retrieve relevant article titles, abstracts, and full texts. STATA software was used to conduct the meta-analysis. Result: The Forest plot of fasting blood sugar levels in patients receiving SGLT-2 inhibitors differed significantly from those the in control group (mean difference = -0.08, 95% CI [-0.13, -0.02], $P < 0.05$). Analysis of lipid profile parameters, including total cholesterol, triglyceride, HDL, and LDL in patients with HF receiving SGLT-2 inhibitors, did not show a notable difference from the control group ($P > 0.005$). However, the mean difference was towards the reduction of LDL, cholesterol, and triglycerides and showed an increase in HDL levels. Egger's test for publication bias revealed some publication bias ($P < 0.05$). Conclusion: Our topic analysis did not reveal any notable alterations in the lipid profile. To arrive at a more definite agreement, further research on subjects with heart failure is necessary because there is currently insufficient evidence.

Keywords: SGLT-2 inhibitors, heart failure, lipid, HDL, LDL, cholesterol, triglyceride lipid profiles, dapagliflozin, empagliflozin, canagliflozin

Introduction

Among the different types of sodium-glucose transporter proteins in humans, we can mention SGLT1 (mainly in the intestine) and SGLT2 (mainly in the kidney cortex), the latter of which plays an important role in glucose reabsorption; SGLT2 inhibitors (SGLT-2i), including dapa-

https://doi.org/10.62347/AAPZ2726

gliflozin, canagliflozin, and empagliflozin, can effectively control blood sugar levels; In this way, by inhibiting the sodium-glucose cotransporter in the proximal area of the nephron, while inhibiting the reabsorption of glucose in the kidneys, they increase its urinary excretion [1-3]. Additionally, these medications have a significant impact on lipid metabolism, influencing cellular processes to reduce lipid accumulation and body fat [1].

The following class of medications has been demonstrated to offer advantageous effects in safeguarding the heart and kidneys under various conditions: type 2 diabetes, chronic kidney disease, and heart failure (HF). The therapeutic advantages of SGLT-2i in individuals with heart failure were first observed in patients with a lower ejection fraction and are currently highly recommended as an essential component of comprehensive disease management [4].

Enhancing the management of diabetic dyslipidemia may potentially lead to a decrease in cardiovascular risk. SGLT-2i have a moderate but positive effect on all components of diabetic dyslipidemia, including triglycerides, high-density lipoprotein cholesterol (HDL-C) and smalldense low-density lipoprotein (sdLDL) particles. As a result, they help reduce the cardiovascular risk associated with this type of dyslipidemia. These actions may have influenced the cardioprotective advantages of this class of medication. Conversely, SGLT-2i have been shown to cause a slight increase in the low-density lipoprotein (LDL-C) concentration. This increase could be linked to an elevated risk of cardiovascular issues as LDL-C is a significant determinant of cardiovascular risk [5].

The prescription of SGLT-2i has expanded beyond treating diabetes to include heart failure, since clinical studies have shown its efficacy in preventing hospitalization for heart failure in individuals with or without diabetes. SGLT-2i exhibit additional effects beyond their initial hypoglycemic response, such as diuretic, antihypertensive, hemopoietic, and inhibitory activities on sympathetic nerve activity [6].

Although several ideas have been proposed to elucidate the processes by which SGLT-2i decrease the occurrence of cardiovascular events, the precise functions of these systems remain uncertain. Multiple clinical studies have repeatedly shown the efficacy of SGLT-2i, with positive results such as reduced blood sugar levels, prevention of heart failure hospitalizations, and maintenance of kidney function. However, contradictory results have been reported regarding the effectiveness of SGLT-2i in preventing heart attacks, strokes, and cardiac deaths related to atherosclerotic cardiovascular disease (ASCVD) [7]. ASCVD is potentially linked to dyslipidemia, and previous studies have suggested that SGLT-2i may elevate the levels of low-density lipoprotein (LDL) cholesterol [8]. Consequently, the impact of SGLT-2i on ASCVD risk may be less pronounced than their effects on heart failure or renal protection in terms of lipid profiles. However, only a limited number of studies have been conducted on the impact of SGLT-2i on lipid profiles in individuals with cardiac disease [9].

In light of this apparent discrepancy, our objective was to perform an initial meta-analysis to assess the effect of SGLT-2i on the lipid profiles of individuals with heart failure.

Method

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Our design protocol was registered within the Open Science Framework (OSF).

Search strategy

Initially, a comprehensive search was performed in PubMed (Medline) Scopus (December 13, 2023) to identify relevant studies.

Specific search terms including (“heart failuire”) OR (Cardiac Failure) OR (Myocardial Failure) AND (“lipid profile”) OR (lipid) OR (“ldl”) OR (“hdl”) OR (“TG”) OR (“triglyceride”) AND (SGLT2) OR (“Sodium-Glucose Transporter 2 Inhibitors”) OR (“SGLT-2 Inhibitors”) OR (Gliflozin) was used. The search strategy was based on the title, abstract, and suitable keywords and tags using advanced search features for each search engine. There were no limitations regarding time or language. Two researchers independently assessed the study titles and abstracts after searching, eliminating duplicates, and retrieving the initial articles. Conflicts were resolved by a third researcher. The next stage

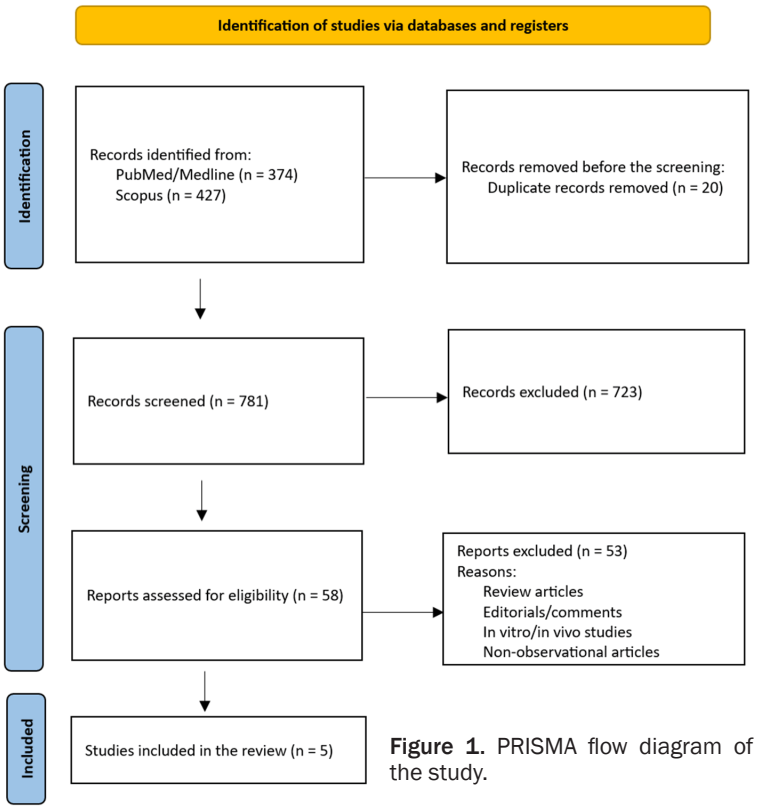

Figure 1. PRISMA flow diagram of the study.

involved checking the entire text of the identified articles for precise inclusion criteria. All studies that satisfied the inclusion criteria were included.

Criteria for inclusion and exclusion

The authors of the current investigation included published articles with lipid profile information from patients with heart failure and matching controls who received SGLT-2i and placebo, respectively. Cohorts, cross-sectional studies, and randomized controlled trials (RCTs) were all included. Reviews, case reports, case series, letters to the editor, abstracts, and posters were excluded from other studies. Articles without open access and papers written in languages other than English were also excluded.

Methodological quality assessment

The quality of the included studies was evaluated using the JBI criteria assessment checklist, which can be accessed at https://jbi.global/critical-appraisal-tools [10]. Disagreements were settled by scientific consensus after two team members independently assessed all texts of every included study. Two independent authors then produced a data extraction form that included the following information: author, year, country, study design, name of the SGLT-2i medication, mean age, participants, and outcome.

Statistical analysis

For data analysis, we used STATA Ver.17 software developed by StataCorp LP, a company based in College Station, Texas, United States. The findings are presented as mean differences and 95% confidence intervals, graphically represented in a forest plot. Heterogeneity among the eligible studies was assessed using the same software. A random-effects model was employed in cases with significant heterogeneity (I^2 > 50%). Additionally, sensitivity analysis was performed by systematically excluding outlier studies and repeating the meta-analysis. This ensured the reliability and consistency of our findings. Egger's funnel plots were used to examine the possibility of publication bias.

Result

Study characteristics

A PRISMA flow diagram summarizing the screening process and exclusions (**Figure 1**). Database searches (PubMed, Scopus, and Google Scholar) yielded 801 potentially relevant documents. Of these 801 documents, 20 were duplicate hits, which were eliminated from further consideration. We reviewed the titles and abstracts of 781 documents to determine their potential relevance, excluding 723 because of the irrelevance of the review. We obtained and reviewed 58 full-text documents and formally excluded 53 (that had no relevant outcomes). Five studies met all the eligibility criteria and were included in the review.

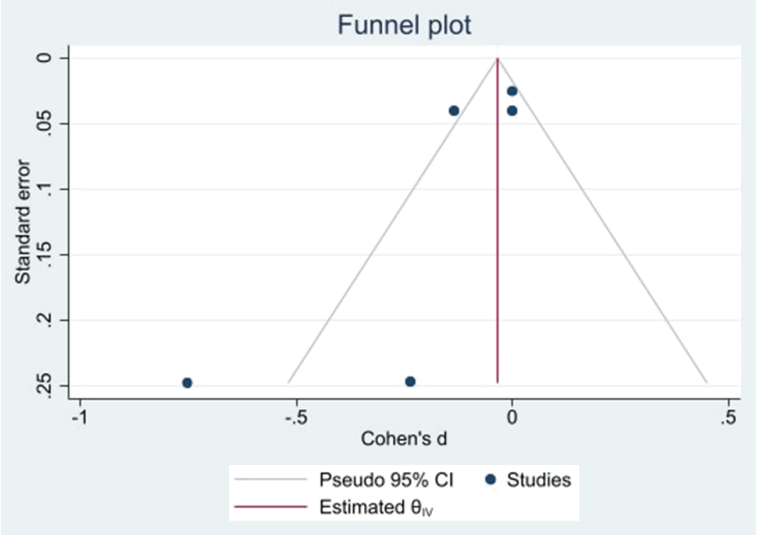

Figure 2. Funnel plot illustrating publication bias of our study (P < 0.05).

Baseline characteristics

Five studies, comprising 6589 patients, were included in this systematic review and meta-analysis. The mean patient age was 61.84± 2.84 years. The study period will be from 2018 to 2022. The studies were conducted in geographically diverse settings in more than five countries. Most participants were recruited from Asia, and the sample sizes ranged from 25 to 4687 patients (**Tables 1**, **2**).

Meta-analysis

The forest plot of fasting blood sugar levels in patients receiving SGLT-2i differed significantly from those in the control group (mean difference = -0.08, 95% CI [-0.13, -0.02], P < 0.05) (**Figure 3**). Analysis of lipid profile parameters, including total cholesterol, triglyceride, HDL, and LDL, in HF patients receiving SGLT-2i did not show a notable difference from the control group (P > 0.005). However, the mean difference was towards a reduction in LDL, cholesterol, and triglyceride levels and an increase in HDL levels (**Figures 4**-**8**). Egger's test for publication bias revealed some degree of publication bias (P < 0.05) (**Figure 2**).

Discussion

Regardless of the ASCVD status at baseline, several seminal trials have offered strong evidence for the cardiovascular and renal advantages of SGLT-2i. Empagliflozin was linked to a lower risk of cardiovascular death (HR, 0.86; 95 percent CI, 0.74 to 0.99; P = 0.04 for superiority) in patients with type 2 diabetes and pre-existing ASCVD in the EMPA-REG outcome trial [11]. In individuals with type 2 diabetes, of whom two-thirds had developed ASCVD, canagliflozin demonstrated a decreased risk for HHF and cardiovascular death (HR, 0.78; 95 percent CI, 0.52-0.87; P = 0.02) and composite renal outcomes (HR, 0.60; 95 percent CI, 0.47 to 0.77; P < 0.001) [12]. In patients with type 2 diabetes who had developed ASCVD (40 percent) or were at high risk for ASCVD (60 percent) in the DECLARE-TIMI 58 trial, dapagliflozin demonstrated a decreased rate of cardiovascular mortality and heart failure (HR, 0.83; 95 percent CI, 0.73-0.95; P = 0.005) compared with placebo [13]. SGLT-2i use was linked, independent of baseline ASCVD status, to a lower risk of severe adverse cardiovascular events, heart failure, and adverse kidney outcomes in a meta-analysis [14]. According to a study by Langlest et al., the health benefit of empagliflozin did not differ between baseline LDL-C categories. The relatively high incidence of heart disease events and low rates of statin use in the subgroups with the highest baseline LDL-C levels are also important [15].

Beyond its glucose-lowering effect, SGLT-2i's benefits can be explained by several mechanisms, including improved cardiac metabolism, decreased myocardial necrosis and fibrosis, improved ventricular loading conditions through natriuresis and osmotic diuresis, and restored tubuloglomerular feedback [11]. Furthermore, preclinical and clinical research has demonstrated that SGLT-2i have pleiotropic effects on endothelial function by reducing oxidative stress and inflammation, as well as plaque size and susceptibility [11, 16]. By reducing hyperglycemia, these agents indirectly mitigate the generation of free radical species that contribute to oxidative stress [17, 18].

These agents have demonstrated the ability to positively modulate parameters such as blood

Table 1. Data from included studies regarding demographic and lipid profile of patients

Author	Year	Country	SGLT2	N Cases	Age (Years)	BMI (kg/m^2)	FBS	TG	Chol	LDL	HDL
Arintaya Phrommintikul	2019	Thailand	Dapagliflozin	25	62.6±8.27	25.63±3	148.56±42.29	163±66.09	144.86±33.23	82.2±30.45	47.1±16.75
Akira Sezai	2019	Japan	Canagliflozin	35	71.4±11.3	24.3±1		107.7±10.2	143.1±5.3	70.4±3.9	59.2±3
Jayoung Lim	2022	South Korea	Dapagliflozin	921	56±4.25		157±15.25		159±13	104±10.25	47±3.5
Jayoung Lim	2022	South Korea	Empagliflozin	921	56±4		158±17.75		161±12.5	106±10.5	46±3.5
Shihchen Kuo	2018	USA	Empagliflozin	4687	63.2±8.8	30.6±4.3		1.91±0.99	4.22±1.04	2.21±0.89	1.14±0.29

Note: numbers are presented as mean ± SD, and Mg/dl. SGLT2: Sodium-glucose co-transporter-2 inhibitors; BMI: Body Mass Index; FBS: Fasting Blood Sugar; TG: triglycerides; Chol: cholesterol; LDL: Low-Density Lipoproteins; HDL: High-Density Lipoproteins.

Table 2. Data from included studies regarding demographic and lipid profile of healthy controls

Author	Year	Country	SGLT2	N healthy controls	Age (Years)	BMI (kg/m^2)	FBS	TG	Chol	LDL	HDL
Arintaya Phrommintikul	2019	Thailand	Dapagliflozin	49	63.22±7.91	25.28±3.06	143.49±35.2	168.07±65.43	153.1±35.73	91.74±37.2	45.88±13.7
Akira Sezai	2019	Japan	Canagliflozin	35	71.4±11.3	25.6±1.1		159.2±19	147.4±6.1	82.4±4.8	52.6±2.5
Jayoung Lim	2022	South Korea	Dapagliflozin	1842	57±4.5		159±20.25		161±15.75	102±13	46±2.5
Jayoung Lim	2022	South Korea	Empagliflozin	1842	57±4.5		159±20.25		161±15.75	102±13	46±3.5
Shihchen Kuo	2018	USA	Empagliflozin	2333	63.2±8.8	30.7±5.2		1.91±0.99	4.22±1.07	2.21±0.91	1.14±0.29

Note: numbers are presented as mean ± SD, and Mg/dl. SGLT2: Sodium-glucose co-transporter-2 inhibitors; BMI: Body Mass Index; FBS: Fasting Blood Sugar; TG: triglycerides; Chol: cholesterol; LDL: Low-Density Lipoproteins; HDL: High-Density Lipoproteins.

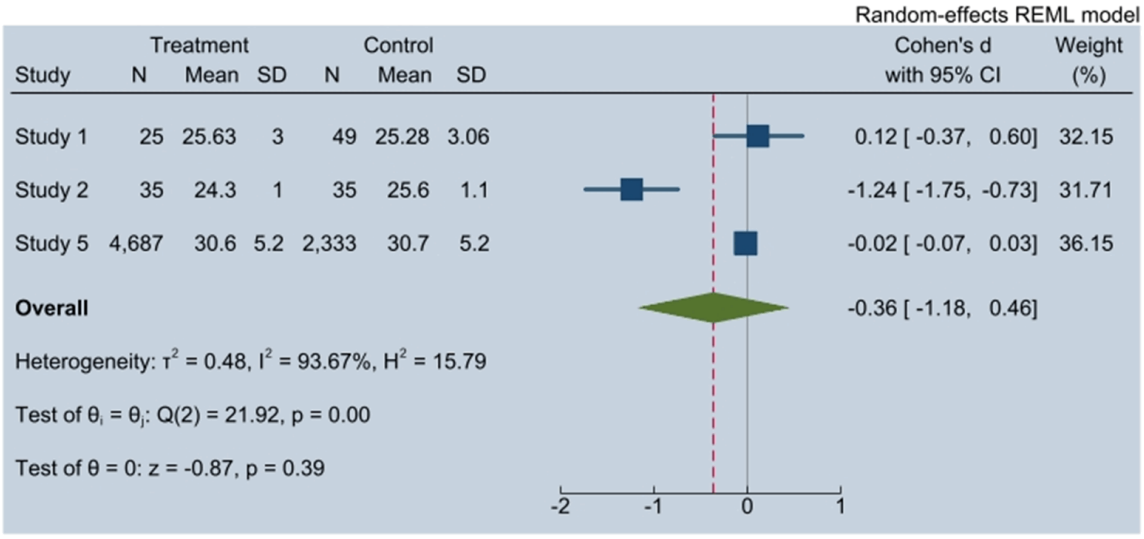

Figure 3. Forest plot depicting BMI mean difference of participants that showed no significant difference (P > 0.05).

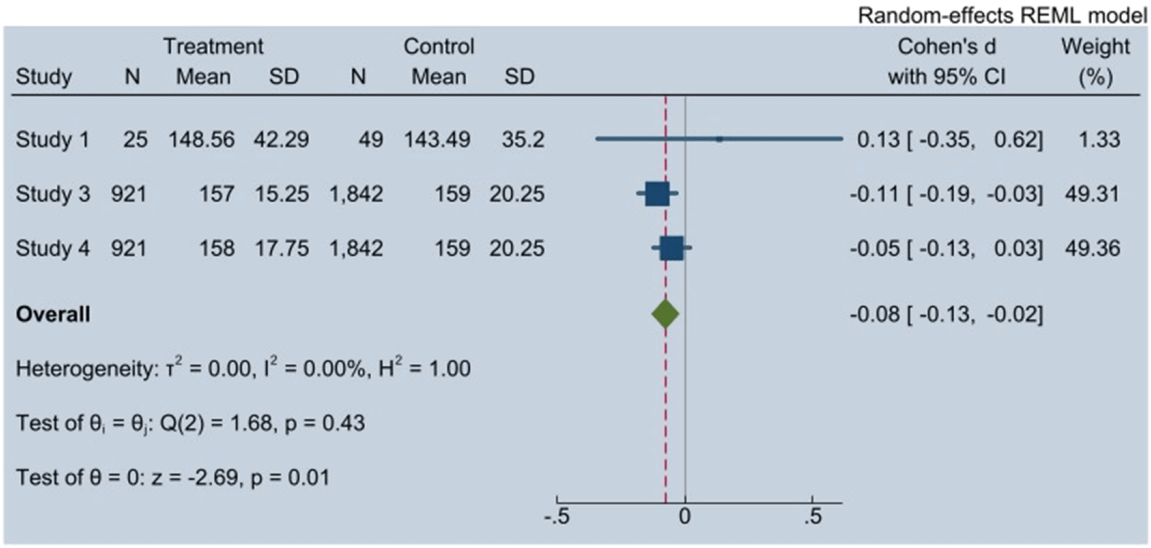

Figure 4. Forest plot depicting FBS mean difference of participants that showed significant statistical difference (P < 0.05).

pressure, weight, visceral adiposity, hyperinsulinemia, arterial stiffness, albuminuria, circulating uric acid levels, and oxidative stress [19]. However, it is important to note that small increases in LDL-C levels have also been observed with this class of medications. While the clinical significance of these LDL increases remains a topic of ongoing investigation, they may theoretically offset some of the cardiovascular benefits conferred by the other favorable metabolic effects of SGLT2 inhibitors [20-22].

Comparisons between dapagliflozin and empagliflozin

In the cohort study done by Modzelewski et al., patients initiated on empagliflozin had a lower risk of experiencing the composite outcome of all-cause mortality or hospitalization compared to those started on dapagliflozin in the year following SGLT-2i therapy. Specifically, 32.2% of empagliflozin-treated patients reached this endpoint versus 34.8% of those receiving dapa-

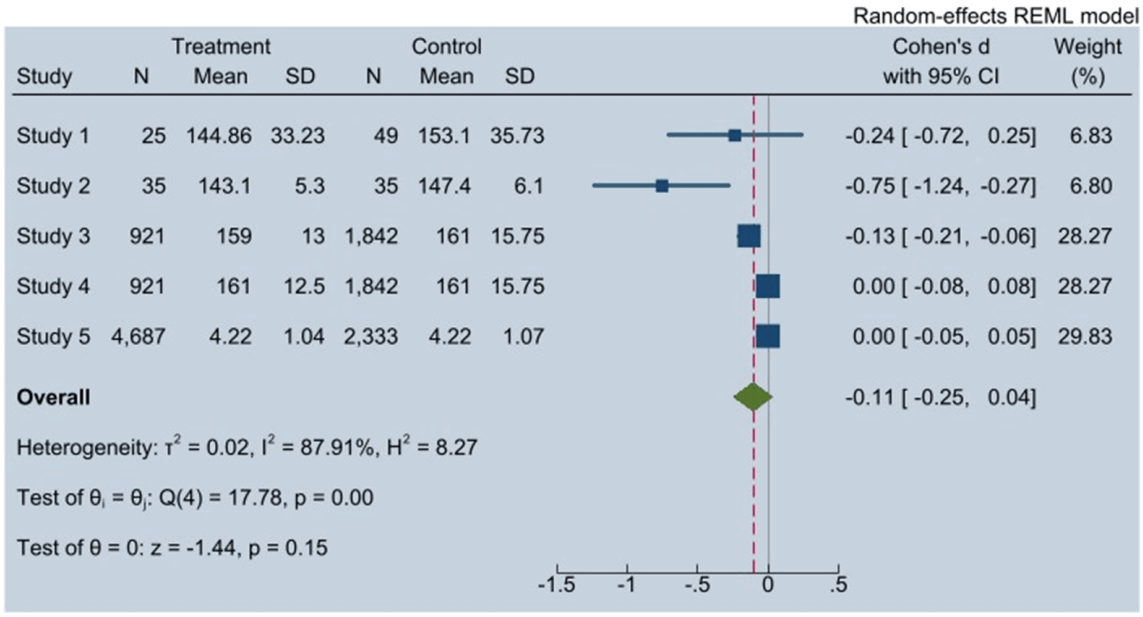

Figure 5. Forest plot depicting the cholesterol mean difference of participants that showed no significant difference (P > 0.05).

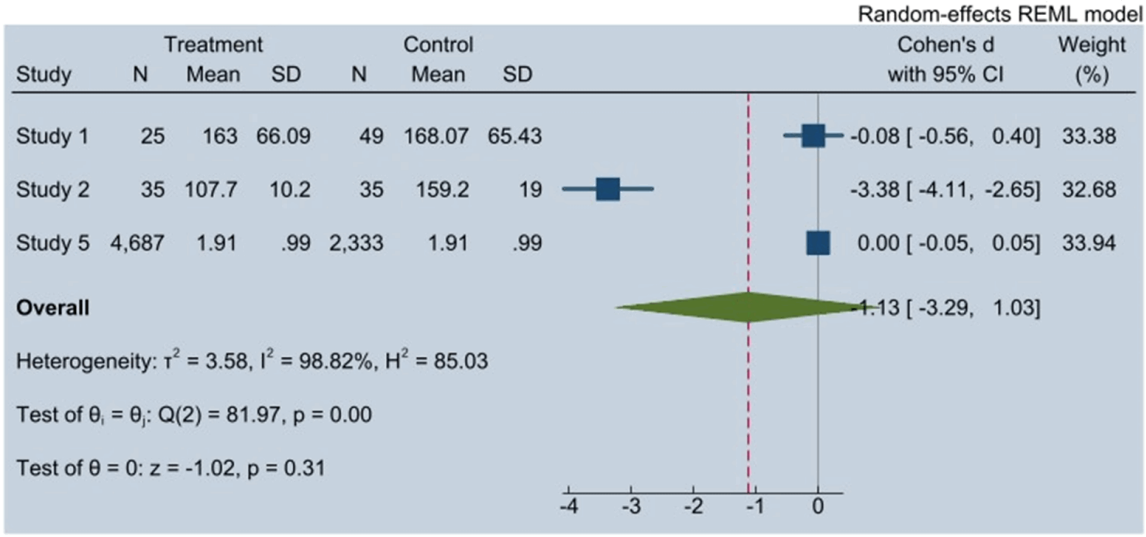

Figure 6. Forest plot depicting triglyceride mean difference of participants that showed no significant difference (P > 0.05).

gliflozin, representing a 10% relative risk reduction (HR 0.90, 95% CI 0.86-0.94) [23].

A class effect has been proposed for this pharmacological entity because of the comparable pharmacological profiles and concordant effects of different SGLT-2i. The reported clinical results of clinical trials have occasionally varied, although this has been explained by variations in the inclusion criteria, baseline characteristics, and outcome definitions. Nevertheless, several studies have indicated that the type of medication may impact SGLT-2i effects. A multi-institutional cohort study by Shao et al. suggested that dapagliflozin may be more effective than empagliflozin in preventing heart failure [24]. In another trial by Shao et al., patients with type 2 diabetes without ASCVD

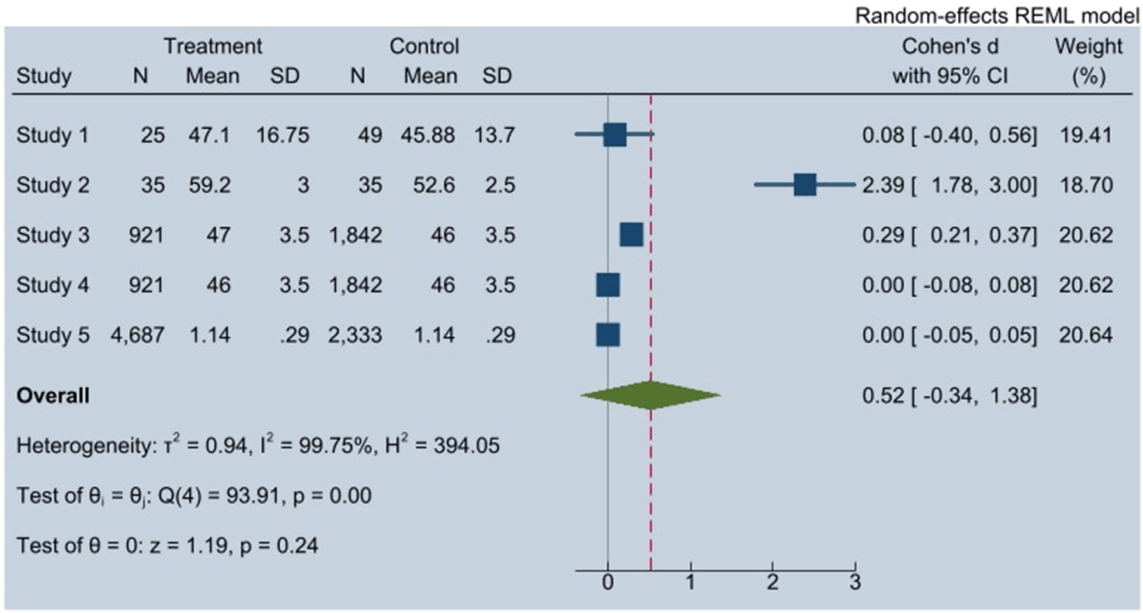

Figure 7. Forest plot depicting HDL mean difference of participants that showed no significant difference (P > 0.05).

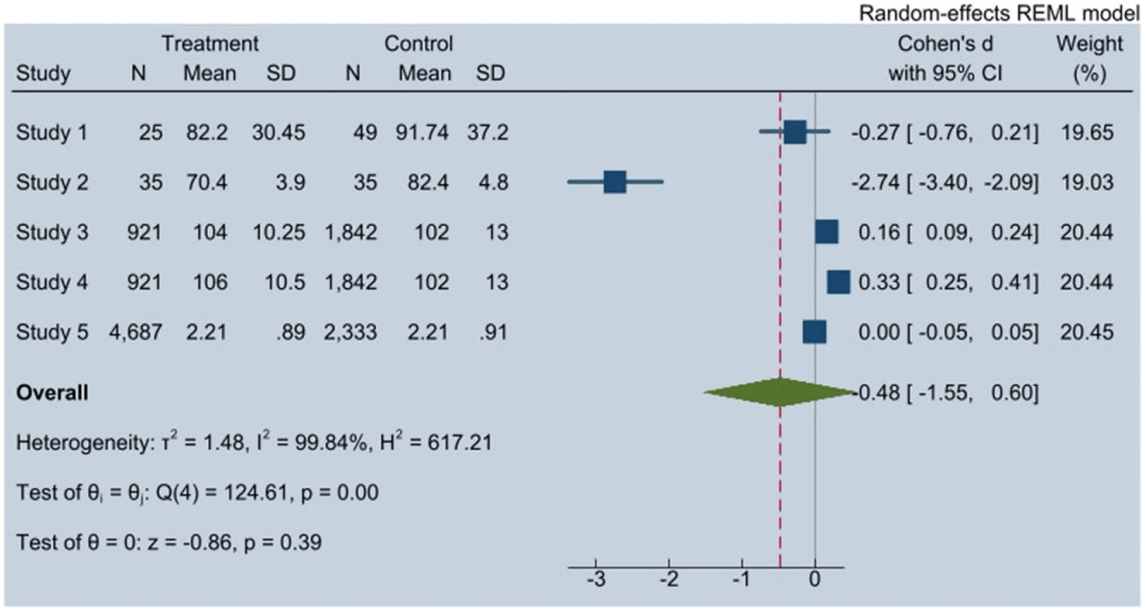

Figure 8. Forest plot depicting LDL mean difference of participants that showed no significant difference (P > 0.05).

showed equal HHF risks to dapagliflozin, although dapagliflozin had a more favorable HHF risk reduction than empagliflozin [25]. The SGLT-2:SGLT-1 receptor selectivity ratio, which is lower for dapagliflozin (1200:1) than for empagliflozin (2500:1), may account for the more potent effects of dapagliflozin than empagliflozin on HF outcomes [26]. More precisely, SGLT-1 overexpression in the myocardium, where SGLT-2 receptors are not expressed, is linked to myocardial ischemia and hypertrophy. According to this study, SGLT-2i, which has a higher impact on SGLT-1 and a lower selectivity for SGLT-2 receptors, may be even more effective in preventing HF [27]. Furthermore, dapagliflozin did not increase the plasma levels of

noradrenaline or aldosterone in comparison with empagliflozin, which may be beneficial for the prevention of heart failure [28].

The trial headed by Lim et al. demonstrated consistently decreased event rates compared to the DPP4i group, with benefits for HF and renal outcomes being similar between the dapagliflozin and empagliflozin groups [12]. These two SGLT-2i treatments had comparable patterns of GFR alterations and were much more beneficial than DPP4i therapy (control group). These results imply that there may be a class effect for SGLT-2i, as using it consistently improves HF and renal outcomes regardless of the subtype. Notably, they did not find a better advantage with dapagliflozin than with empagliflozin in terms of HF and renal outcomes, in contrast to the studies conducted by Shao et al. [24, 25]. Future research is necessary to compare the impact of SGLT-2i class on renal outcomes and heart failure using nationwide real-world data or in a prospective trial, even though the current findings support such an effect.

Effect of canagliflozin on heart

Among individuals with type 2 diabetes, the WATCH-DM and TRS-HFDM risk scores have demonstrated the ability to reliably identify those at high risk of heart failure hospitalization. Patients identified as high-risk using these tools may be the most likely to derive benefit from treatment with canagliflozin [29]. The available evidence indicates that SGLT2 inhibitors may be more effective than GLP-1 receptor agonists or DPP-4 inhibitors in reducing the risk of hospitalization for heart failure in individuals with type 2 diabetes [30].

After starting the medication, both ANP and BNP were reduced by canagliflozin's effects on the heart. However, Canagliflozin reduced cardiac stress, decreased diastolic dysfunction, and lowered LVM. Patients with diabetes typically have higher levels of LVM, and this variation is thought to be a risk factor for cardiovascular conditions, such as heart failure and unexpected death. In earlier study, the effects of oral antidiabetic medications on the LVM were not consistently observed. To examine how LVM changed after taking different medications, such as sulfonylureas (gliclazide and glyburide), an α-glucosidase inhibitor (voglibose), metformin, thiazolidinediones (pioglitazone and rosiglitazone), and a DPP-4 inhibitor (sitagliptin), Ida et al. [11] conducted a meta-analysis of 11 RCTs. They found that only gliclazide reduced LVM. Only two papers have discussed how SGLT-2i treatment affects heart weight. LVM was reduced after three months in 37 patients receiving canagliflozin medication, according to Matsutani et al., and at six months in 58 patients receiving dapagliflozin, according to Soga et al. [12]. The effects of SGLT-2i on heart weight were investigated in a prospective trial. These findings were anticipated [13]. Numerous publications have documented an increase in BNP with SGLT-2i, along with a decrease in pericardial fat volume [14]. According to the current study, canagliflozin may hasten reverse remodeling as soon as treatment starts. In their trial of canagliflozin, Matutani et al. observed a decrease in E/e' after three months, and Soga et al. reported a decrease in their patients on dapagliflozin at six months. Matutani et al. also noted that individuals with improved hemoglobin levels had significantly decreased E/e'. According to an animal study on empagliflozin, improved cardiac insulin levels and passive myofilament stiffness may result in improved diastolic function [16]. Of the patients in our study, thirty-three (94 percent) had HFpEF and only two had HFrEF. Effective treatments for HFpEF are nonexistent, although β-blockers, ACE inhibitors, and mineralocorticoid receptor antagonists have been shown to be effective for HFrEF. Dapagliflozin decreased heart failure hospitalization in patients with or without HFrEF, as well as cardiovascular death and ACM among HFrEF patients, according to the ADECLARE-TIMI 58 study [24]. These findings and those of Sezai et al. imply that canagliflozin may be helpful for HFpEF, although further research is necessary to fully understand this problem [11].

This article summarizes the possible effects of SGLT2 inhibitors on lipid metabolism and provides a better understanding of the intricate molecular mechanisms these medicines offer by drawing on a wealth of pertinent clinical and fundamental research studies and reviews.

This study's limitations include the fact that we only included the most significant clinical trials in our description and that we only looked up English-language papers in the PubMed, Scopus, Web of Science databases which were open access.

Conclusion

SGLT2 inhibitors have multiple effects on lipid metabolism. Less lipid oxidation occurs in visceral fat, serum lipoprotein levels are regulated, the ratio of LDL particles is positively altered, lipid oxidation is decreased, and substrate utilization is shifted to the use of ketone bodies, which are more effective in myocardial metabolism and produce fewer reactive oxygen species during oxidation. They also have an impact on β-oxidation and the movement of lipid molecules within cells. The overall rise in LDL levels might be offset by these advantageous alterations in lipid metabolism. These results might indicate that, despite the fact that type 2 diabetes patients are the main target audience for SGLT2 inhibitors, these uses may not be limited to them in the near future.

Acknowledgements

The authors would like to thank the researchers' whose work was included in this study.

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Niloofar Deravi and Mahsa Asadi Anar, Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Arabi Ave, Daneshjoo Blvd, Velenjak, Tehran 19839-63113, Iran. Tel: +98-9196208617; E-mail: niloofarderavi@sbmu.ac.ir (ND); mahsa.boz@gmail.com (MAA); Dr. Kamyar Khorsand, Ahvaz Jundishapur University of Medical Sciences, Golestan BLV, Ahvaz 61357-15794, Iran. E-mail: khorsandkamyar76@gmail.com

References

[1] Szekeres Z, Toth K and Szabados E. The effects of SGLT2 inhibitors on lipid metabolism. Metabolites 2021; 11: 87.

[2] Bechmann LE, Emanuelsson F, Nordestgaard BG and Benn M. SGLT2-inhibition increases total, LDL, and HDL cholesterol and lowers triglycerides: meta-analyses of 60 randomized trials, overall and by dose, ethnicity, and drug type. Atherosclerosis 2024; 394: 117236.

[3] Talha KM, Anker SD and Butler J. SGLT-2 inhibitors in heart failure: a review of current evidence. Int J Heart Fail 2023; 5: 82-90.

[4] Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, McMurray JJV and Solomon SD. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet 2022; 400: 757-767.

[5] Filippas-Ntekouan S, Tsimihodimos V, Filippatos T, Dimitriou T and Elisaf M. SGLT-2 inhibitors: pharmacokinetics characteristics and effects on lipids. Expert Opin Drug Metab Toxicol 2018; 14: 1113-1121.

[6] Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, Woerle HJ, von Eynatten M and Broedl UC. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol 2014; 13: 28.

[7] Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH and Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019; 393: 31-39.

[8] Basu D, Huggins LA, Scerbo D, Obunike J, Mullick AE, Rothenberg PL, Di Prospero NA, Eckel RH and Goldberg IJ. Mechanism of increased LDL (Low-Density Lipoprotein) and decreased triglycerides with SGLT2 (Sodium-Glucose Cotransporter 2) inhibition. Arterioscler Thromb Vasc Biol 2018; 38: 2207-2216.

[9] Ejiri K, Miyoshi T, Kihara H, Hata Y, Nagano T, Takaishi A, Toda H, Namba S, Nakamura Y, Akagi S, Sakuragi S, Minagawa T, Kawai Y, Nishii N, Fuke S, Yoshikawa M, Nakamura K and Ito H; MUSCAT-HF Study Investigators. Effects of luseogliflozin and voglibose on high-risk lipid profiles and inflammatory markers in diabetes patients with heart failure. Sci Rep 2022; 12: 15449.

[10] Barker TH, Stone JC, Sears K, Klugar M, Tufanaru C, Leonardi-Bee J, Aromataris E and Munn Z. The revised JBI critical appraisal tool for the assessment of risk of bias for randomized controlled trials. JBI Evid Synth 2023; 21: 494-506.

[11] Zinman B, Lachin JM and Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2016; 374: 1094.

[12] Lim J, Hwang IC, Choi HM, Yoon YE and Cho GY. Comparison of cardiovascular and renal outcomes between dapagliflozin and empagliflozin in patients with type 2 diabetes without prior cardiovascular or renal disease. PLoS One 2022; 17: e0269414.

[13] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM and Sabatine MS; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019; 380: 347-357.

[14] McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, Gantz I, Terra SG, Masiukiewicz U and Cannon CP. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021; 6: 148-158.

[15] Langslet G, Zinman B, Wanner C, Hantel S, Espadero RM, Fitchett D and Johansen OE. Cardiovascular outcomes and LDL-cholesterol levels in EMPA-REG OUTCOME®. Diab Vasc Dis Res 2020; 17: 1479164120975256.

[16] Pahud de Mortanges A, Salvador D Jr, Laimer M, Muka T, Wilhelm M and Bano A. The role of SGLT2 inhibitors in atherosclerosis: a narrative mini-review. Front Pharmacol 2021; 12: 751214.

[17] Merhi Z, Thornton K, Bennett-Toomey JN, Hennebold JD and Buyuk E. Advanced glycation end products upregulate insulin receptor substrate-1 (IRS-1) in granulosa cells. Fertil Steril 2017; 108: e29.

[18] Yamagishi S, Maeda S, Matsui T, Ueda S, Fukami K and Okuda S. Role of advanced glycation end products (AGEs) and oxidative stress in vascular complications in diabetes. Biochim Biophys Acta 2012; 1820: 663-671.

[19] Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC and Johansen OE. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. Diab Vasc Dis Res 2015; 12: 90-100.

[20] Hach T, Gerich J, Salsali A, Kim G, Hantel S, Woerle H and Broedl U. Empagliflozin improves glycemic parameters and cardiovascular risk factors in patients with type 2 diabetes (T2DM): pooled data from four pivotal phase III trials. Diabetologie Und Stoffwechsel 2014; 9: P142.

[21] Monami M, Nardini C and Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014; 16: 457-466.

[22] Sinclair A, Bode B, Harris S, Vijapurkar U, Mayer C, Fung A, Shaw W, Usiskin K, Desai M and Meininger G. Efficacy and safety of canagliflozin compared with placebo in older patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. BMC Endocr Disord 2014; 14: 37.

[23] Modzelewski KL, Pipilas A and Bosch NA. Comparative outcomes of empagliflozin to dapagliflozin in patients with heart failure. JAMA Netw Open 2024; 7: e249305.

[24] Shao SC, Chang KC, Hung MJ, Yang NI, Chan YY, Chen HY, Kao Yang YH and Lai EC. Comparative risk evaluation for cardiovascular events associated with dapagliflozin vs. empagliflozin in real-world type 2 diabetes patients: a multi-institutional cohort study. Cardiovasc Diabetol 2019; 18: 120.

[25] Shao SC, Chang KC, Lin SJ, Chang SH, Hung MJ, Chan YY and Lai EC. Differences in outcomes of hospitalizations for heart failure after SGLT2 inhibitor treatment: effect modification by atherosclerotic cardiovascular disease. Cardiovasc Diabetol 2021; 20: 213.

[26] Anker SD and Butler J. Empagliflozin, calcium, and SGLT1/2 receptor affinity: another piece of the puzzle. ESC Heart Fail 2018; 5: 549-551.

[27] Perry RJ and Shulman GI. Sodium-glucose cotransporter-2 inhibitors: understanding the mechanisms for therapeutic promise and persisting risks. J Biol Chem 2020; 295: 14379-14390.

[28] Nakagaito M, Joho S, Ushijima R, Nakamura M and Kinugawa K. Comparison of canagliflozin, dapagliflozin and empagliflozin added to heart failure treatment in decompensated heart failure patients with type 2 diabetes mellitus. Circ Rep 2019; 1: 405-413.

[29] Khan MS, Segar MW, Usman MS, Patel KV, Van Spall HGC, DeVore AD, Vaduganathan M, Lam CSP, Zannad F, Verma S, Butler J, Tang WHW and Pandey A. Effect of canagliflozin on heart failure hospitalization in diabetes according to baseline heart failure risk. JACC Heart Fail 2023; 11: 825-835.

[30] Kramer CK, Ye C, Campbell S and Retnakaran R. Comparison of new glucose-lowering drugs on risk of heart failure in type 2 diabetes: a network meta-analysis. JACC Heart Fail 2018; 6: 823-830.