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Current updates of sodium-glucose cotransporter-2 inhibitor effects on atherosclerosis: a systematic review and meta-analysis of randomized controlled trial

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Abstract

Introduction: *Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are an emerging therapy to prevent atherosclerotic cardiovascular disease (ASCVD) progression in diabetic patients. This study aims to demonstrate current evidence of SGLT2i's role in clinical and subclinical atherosclerosis.*

Material and methods: *Systematic randomized controlled trials (RCTs) searching was conducted in Cochrane, PubMed, EMBASE, and MEDLINE. Outcomes extracted from clinical and subclinical atherosclerosis studies.*

Results: *In total, 11 clinical effects and 12 subclinical atherosclerosis studies were included. Meta-analysis was performed on 4 clinical effect studies. Pooled analysis showed SGLT2i significantly decreased MACE (RR 0.92; 95% CI 0.87–0.98; p = 0.03; i2 = 18%), HHF (RR 0.71; 95% CI 0.63–0.80; p < 0.0001; i2 = 0%), and renal outcome (RR 0,73; 95% CI 0.67–0.79; p < 0.0001; i2 = 17%) with no effect on CV death (RR 0,72; 95% CI 0.67–0.78; p < 0.0001; i2 = 32%) and increased amputation rate (RR 1.35; 95% CI 1.05–1.73; p = 0.02; i2 = 43%) compared to placebo. Subgroup analysis from those 4 RCTs showed that SGLT2i benefits are unaffected by age, history of HF, and PAD status. Two RCTs specifically studied the SGLT2i effect on PAD patients with results showing the beneficial effect on MACE and HHF is not significant while showing significant benefit on CV death and renal outcome. The amputation rate was not significantly different in PAD patients. Most studies of subclinical atherosclerosis showed benefits on PWV improvement, conflicting results on FMD, and no benefit on IMT.*

Conclusions: *SGLT2i showed benefits in reducing MACE, HHF, and renal outcome in diabetic patients with ASCVD with adverse events of increased amputation rate. Subclinical atherosclerosis studies showed varied conflicting results.*

Keywords: SGLT2 inhibitor; atherosclerosis; subclinical atherosclerosis; therapy; outcome

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Introduction

Atherosclerosis is a chronic disease characterized by lipid accumulation in the artery segments with smooth muscle cells and fibrous matrix proliferation, gradually forming an atherosclerotic plaque where inflammation generally becomes the pathological basis of the processes [1]. Atherosclerotic cardiovascular diseases (ASCVD) are the leading cause of mortality in type 2 diabetes mellitus (T2DM) patients with 2–4-fold increased risk [2]. Several pathological mechanisms are closely linked between DM and atherosclerosis. Dyslipidaemia, hyperglycaemia, and insulin resistance cause physiological changes that appear as atherosclerotic lesion development [3].

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are novel medications for T2DM patients with mechanisms of action by inhibiting glucose re-absorption in the kidney tubules and hence increasing glucose excretion. In addition to the main mechanism of action, recent evidence recommended SGLT2i use to improve cardiovascular outcomes in patients with T2DM [4]. Multiple pre-clinical and clinical studies revealed the cardiovascular benefits of SGLT2i in improving metabolic-related characteristics and have a potential role in ASCVD protection [5]. Proposed mechanisms of SGLT2i in inhibiting the atheroma development and progression of atherosclerosis are by regulating dyslipidaemia, normalizing endothelial function, lowering oxidative stress and inflammation, preventing the formation of monocyte-macrophage-foam cells, lowering plaque burden and size, changing plaque composition, and enhancing plaque stability [6]. This study aims to demonstrate current updates on SGLT2i's role in clinical and subclinical atherosclerosis.

Material and methods

Protocol and Registration

This systematic review had been registered in PROSPERO (CRD42023459407).

Eligibility Criteria

This study includes randomized controlled trial studies assessing the effect of Sodium-glucose Cotransporter 2 (SGLT-2) inhibitor therapy on the incidence or progression of atherosclerosis in adult patients over 18 years old. Data regarding the drug used, the parameters used to quantify atherosclerosis, and details of outcome from current evidence available were obtained and collected systematically. This study includes trials for diabetic and non-diabetic patients with no limitations of language used and years published. Both symptomatic and subclinical atherosclerosis are included as also all vascular diseases caused by atherosclerosis including peripheral artery disease (PAD), carotid artery stenosis (CAS), abdominal aortic aneurysm (AAA), coronary artery disease (CAD), and renal artery stenosis (RAS) treated with SGLT2 inhibitor. Exclusion criteria in this study were animal studies, molecular studies, review studies, studies assessing the effect of the drug on lipid profile or cardiac fat metabolism, and studies assessing the effect of the drug on general cardiovascular disease not limited to atherosclerosis or heart failure with unspecified causes.

Information sources

Systematic literature searching for peer-reviewed eligible papers was conducted through several databases which include Cochrane, MEDLINE, EMBASE, and EBSCOhost. The search keyword terms are made based on a predetermined PICO.

Search strategy

This systematic review and meta-analysis were conducted based on the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA) 2020 Guideline. Database searching was conducted in several databases including Cochrane, PubMed, EMBASE, and EBSCOhost with no study published time limitation. The PICO used in this study was as follows.

- Patients: diabetic or non-diabetic patients indicated for SGLT-2 therapy;
- Intervention: SGLT-2 inhibitor therapy;
- Comparison: placebo or no therapy;
- Outcome: incidence of PAD, CAS, AAA, RAS, or any Major Adverse Cardiac Event (MACE), and subclinical atherosclerosis based on intima-media thickness (IMT) and pulse wave velocity (PWV).

Search key terms used for literature searching were then constructed based on the study PICO. Limiters from each database were used to limit the search results to only displayed clinical trial studies. No study publication date limitation was applied. This following key term used for each database were as follow (Table 1).

Study selection process

Relevant studies will be imported and managed with the Zotero reference manager created by the authors. Duplicate studies removal will be conducted in this software. Articles will be screened for eligibility in this study based on title, abstract, and inclusion-exclusion criteria. Two independent reviewers (LAN, JEA) will extract data for all included studies. The study selection flow chart was made based on PRISMA 2020 guidelines.

Table 1. Search key terms used for each database

Database	Keyword
Cochrane	#1 MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] explode all trees #2 ("sodium-glucose cotransporter 2 inhibitor'"): ti, ab, kw AND (canagliflozin or 'dapagliflozin or empagliflozin or ertugliflozin or ipragliflozin or luseogliflozin): ti, ab, kw (Word variations have been searched) #3 MeSH descriptor: [Atherosclerosis] explode all trees #4 ("carotid intima-media thickness"): ti, ab, kw OR ("ankle-brachial index" or "coronary artery calcification" or "pulse wave velocity" or "acute coronary syndrome" or "renal artery stenosis" or "peripheral artery disease"): ti, ab, kw (Word variations have been searched) #5 #1 or #2 #6 #3 or #4 #7 #5 and #6
PUBMED	(((((((("sodium glucose cotransporter 2 inhibitor"[All Fields]) OR ("sglt2"[All Fields])) OR ("canagliflozin"[All Fields])) OR ("dapagliflozin"[All Fields])) OR ("empagliflozin"[All Fields])) OR ("ertugliflozin"[All Fields])) OR ("ipragliflozin"[All Fields])) OR ("luseogliflozin"[All Fields])) AND (((((((("atherosclerosis"[All Fields]) OR ("carotid intima media thickness"[All Fields])) OR ("ankle brachial index"[All Fields])) OR ("coronary artery calcification"[All Fields])) OR ("pulse wave velocity"[All Fields])) OR ("acute coronary syndrome"[All Fields])) OR ("renal artery stenosis"[All Fields])) OR ("peripheral artery disease"[All Fields]))
EMBASE	('sodium-glucose cotransporter 2 inhibitor' OR 'sglt2' OR 'canagliflozin' OR 'dapagliflozin' OR 'empagliflozin' OR 'ertugliflozin' OR 'ipragliflozin' OR 'luseogliflozin') AND ('atherosclerosis' OR 'carotid intima-media thickness' OR 'ankle-brachial index' OR 'coronary artery calcification' OR 'pulse wave velocity' OR 'acute coronary syndrome' OR 'renal artery stenosis' OR 'peripheral artery disease')
EBSCOHost	("sodium-glucose cotransporter 2 inhibitor" OR sglt2 OR canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin OR ipragliflozin OR luseogliflozin) AND (atherosclerosis OR "carotid intima-media thickness" OR "ankle-brachial index" OR "coronary artery calcification" OR "pulse wave velocity" OR "acute coronary syndrome" OR "renal artery stenosis" OR "peripheral artery disease") **Limiters** — Publication Type: Adaptive Clinical Trial, Clinical Trial, Controlled Clinical Trial, Randomized Controlled Trial

Outcomes

The authors independently completed the data extraction from all included studies. Discrepancy when comparing both data extraction results was resolved through discussion of all authors. The following data were extracted: (1) first author, (2) year of publication, (3) study design, (4) sample size, (5) subjects characteristics, (6) SGLT-2 inhibitor used and dose, (7) duration of the trial, and (8) placebo or control drug used. The primary outcome in this study was divided into two categories: studies assessing the clinical effect of SGLT2 inhibitor treatment in diabetic patients with confirmed atherosclerotic cardiovascular disease (ASCVD) and studies assessing the effect of SGLT2 inhibitor treatment for subclinical atherosclerosis progression. In terms of clinical effect studies, the following variables were extracted: (1) MACE, (2) hospitalization for heart failure (HHF), (3) cardiovascular (CV) death, (4) composite renal outcome, and (5) amputation rate. For subclinical atherosclerosis studies, the following variables were extracted: (1) flow-mediated dilatation (FMD), (2) pulse wave velocity (PWV), and (3) Intima media thickness (IMT).

Study risk of bias assessment

Assessment of study risk of bias was conducted using the revised Cochrane risk of bias tool (RoB 2.0) which includes bias from five specific domains; (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions which divided into effect of assignment to intervention and effect of adhering to intervention; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each domain will be assigned three levels of bias risk: low risk, some concern, and high risk. Two reviewers (LAN, JEA) independently assessed each study included, and justifications for each assessment were recorded. The discrepancy will be resolved through authors' discussion based on justifications for each risk of bias domain to reach a consensus with a third party involved as an arbiter if necessary. Overall RoB level in any study was determined by the most occurring RoB judgment level (low; some concern; high) in those five domains or by weighing each occurrence of "some concern" and "high risk". The overall RoB level will then be discussed and approved by all authors.

Synthesis methods

Final data extraction of all included studies will be categorized and presented as summary Tables. For quantitative analysis measuring the rate of an event in the treatment and control group, the number of each sample with or without an event in each group was documented. Quantitative analysis was conducted using Cochrane Review Manager (Revman) version 5.4.1. Meta-analysis for the primary outcome was conducted by calculating relative risk using an inverse variance technique using a fixed-effect model for variables with low heterogeneity or a random-effect model for variables with high heterogeneity. To analyse heterogeneity, the findings were given a total value, 95% confidence interval, and I^2. Low, moderate, and high heterogeneity are indicated by I^2 values of 25%, 50%, and 75%, respectively, with I^2 values of more than 50% considered to have considerable heterogeneity. A forest plot was used to help interpret the results. No quantitative analysis for numerical variables expressed in mean difference (MD) was conducted due to the high heterogeneity of variables reported by subclinical atherosclerosis studies included and therefore will only be presented as an outcome table.

Results

Studies selection

The search strategy identified 321 articles and 220 titles and abstracts were then screened after duplicates were removed. 26 articles met the criteria for full-text review and 23 were included [7–29]. Trial selection process details are presented in a PRISMA 2020 flow diagram (Fig. 1).

Studies characteristics

The detailed study characteristics which include first author, year of publication, SGLT2i used, study population, follow-up duration, and outcome measured were presented in Table 2. On the studies category assessing the clinical effect of SGLT2 inhibitor, 4 studies evaluate the effect of dapagliflozin [7–10], 2 studies evaluate ertugliflozin [11, 12], 4 studies evaluate empagliflozin [13–16], and 1 study evaluates canagliflozin [17]. On the studies category assessing subclinical effect of SGLT2 inhibitor, 3 studies evaluate the effect of tofogliflozin [18–20], 4 studies evaluate dapagliflozin [21, 25, 26, 29], 1 study evaluate ipragliflozin [22], 3 studies evaluate empagliflozin [23, 24, 27], and 1 study evaluate canagliflozin [28].

For published studies assessing the effect of SGLT2i in the prognosis of clinical type II diabetes with ASCVD, the published studies measuring the effect of dapagliflozin derived their data from the same trial named DECRALE-TIMI 58 which compared 10 mg/ /day regiment of Dapagliflozin with placebo. This trial includes patients with diabetes type II with an additional ASCVD and/or multiple risk factors [7–10]. Published studies regarding the effect of Ertugliflozin used the same data derived from the VERTIS trial. This trial only includes patients with ASCVD and is divided into three groups in a 1:1:1 ratio. Two regiments of Ertugliflozin were used in this trial; 5 mg and 15 mg per day [11, 12]. The four Empagliflozin studies derived their data from the EMPA-REG trial which includes type II diabetes patients with ASCVD. Two regimens were used in this trial; 10 mg and 25 mg per day [13–16]. Only one study measured the effect of Canagliflozin in ASCVD patients. This study by Neal et al. includes all type II diabetic patients with evidence of ASCVD who were treated with a placebo or two regimens of Canagliflozin; 100 mg and 300 mg per day. The prognosis measured in these studies were Major adverse cardiovascular events (MACE), hospitalization for heart failure (HHF), renal worsening, cardiovascular death (CV death), and some also measured the amputation rate.

The published studies regarding the effect of SGLT2i in the progression of subclinical atherosclerosis are rather diverse. Intima media thickness (IMT) change was studied in three publications in which the two published studies derived from the same trial, the UTOPIA trial by Katakami et al. [18, 20]. The UTOPIA trial includes a total of 340 patients with type II diabetes without CVD which were treated by Tofogliflozin 20 mg per day. Conventional treatment instead of a placebo was used as a control. The other study measuring intima-media thickness change is a study by Tanaka et al. [22]. This study includes 482 type II diabetes with established ASCVD who were treated with Ipragliflozin 50–100 mg/ /day. Conventional therapy was also used as a control.

Brachial artery Flow-mediated dilatation (FMD) which measures endothelial function by assessing its response to releasing nitric oxide after vasodilatation was studied in four publications [21, 25, 26, 29]. The studies that measure this parameter were also highly diverse in terms of what was used as a treatment and control. Shigiyama et al. [21] specifically include type II diabetic patients that take 750 mg of metformin daily. The treatment group in this study was Dapagliflozin 5 mg per day in addition to the baseline 750 mg of metformin. Metformin 1500 mg per day was used as a control group. Lunder et al. [25] is the only study that includes type I diabetes mellitus. Empagliflozin 25 mg per day was used as a treatment and compared to groups that take metformin 2000 mg, a combination of Empagliflozin and metformin 750 mg, or a placebo. Solini et al. [26] specifically include type II diabetic

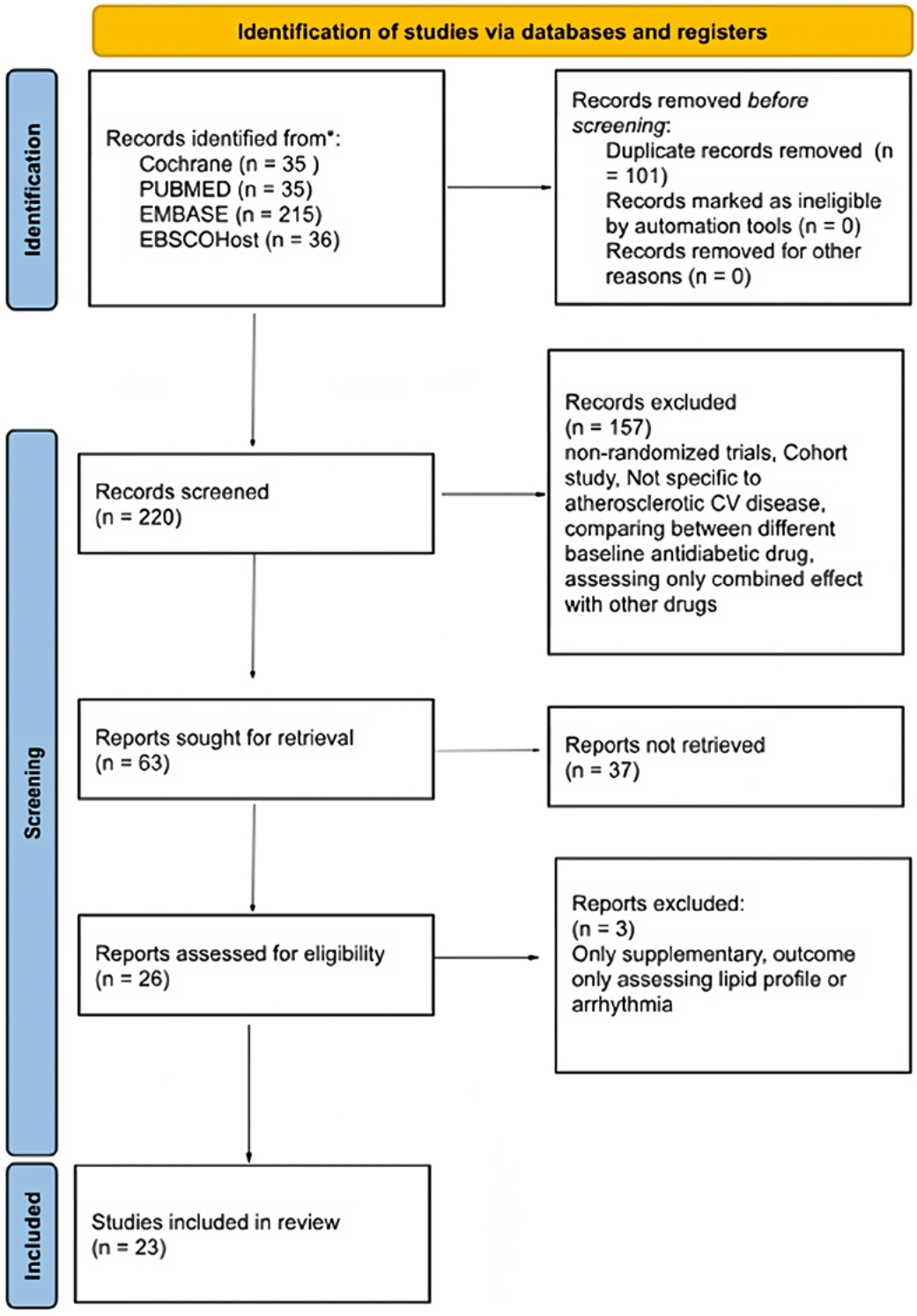

Figure 1. PRISMA 2020 flowchart for study selection

patients with hypertension. Dapagliflozin 10 mg/day was used as a treatment group and hydrochlorothiazide 12.5 mg/day was used as a control. Sposito et al. [29] applied strict criteria of IMT as an inclusion criterion for their study. This study includes type II diabetic patients with a carotid IMT above the 75th percentile and currently taking 1500 mg or metformin. Dapagliflozin 10 mg per day was used as a treatment while Glibenclamide 5 mg per day was used as a control.

Table 2. Study characteristics

Trial name	Study ID [year]	Total population	Population characteristics	SGLT2i treatment group	SGLT2i Dose	Comparison	Follow-up duration	Outcomes measured
DECLARE--TIMI 58	Wiviott (2019) [7]	17,160 patients	Patients with type 2 diabetes and established ASCVD (40.6%) and multiple risk factors (59.4%) divided into a 1:1 ratio	Dapagliflozin	10 mg/day	Placebo	Median 4.2 years (IQR 3.9–4.4)	MACE, HHF, CV death, renal outcome, amputation rate
	Bonaca (2020) [8]	1,025 patients	DECLARE-TIMI 58 patients with established PAD	Dapagliflozin	10 mg/day	Placebo	Median 4.2 years (IQR 3.9–4.4)	MACE, CV death/HHF, renal outcome, amputation rate
	Cahn (2020) [9]	17,160 patients	DECLARE-TIMI 58 patients divided into three age categories; < 65 y.o (n = 9253) ≥ 65 –< 75 y.o (n = 6811) ≥ 75 y.o (n = 1096)	Dapagliflozin	10 mg/day	Placebo	Median 4.2 years (IQR 3.9–4.4)	MACE, HHF, CV death, renal outcome, amputation rate
	Cahn (2021) [10]	10,186 patients	DECLARE-TIMI 58 patients with multiple risk factors	Dapagliflozin	10 mg/day	Placebo	Median 4.2 years (IQR 3.9–4.4)	HHF, renal outcome
VERTIS	Cannon (2020) [11]	8,246 patients	Patients with type 2 diabetes and established ASCVD divided into a 1:1:1 ratio	Ertugliflozin	5 mg/day 15 mg/day	Placebo	Mean 3.5 years	MACE, HHF, CV death, renal outcome, amputation rate
	Cosentino (2020) [12]	8,246 patients	VERTIS patients are divided based on EF and history of HF at baseline	Ertugliflozin	5 mg/day 15 mg/day	Placebo	Mean 3.5 years	HHF, CV death

Table 2. Study characteristics — continued

Trial name	Study ID [year]	Total population	Population characteristics	SGLT2i treatment group	SGLT2i Dose	Comparison	Follow-up duration	Outcomes measured
EMPA REG	Zinman (2015) [13]	7,020 patients	Patients with type 2 diabetes and established ASCVD divided into a 1:1:1 ratio	Empagliflozin	10 mg/day 25 mg/day	Placebo	Median 3.1 years	MACE, HHF, CV death, renal outcome, amputation rate
	Verma (2018) [14]	1,461 patients	EMPA REG patients with established PAD	Empagliflozin	10 mg/day 25 mg/day	Placebo	Median 3.1 years	MACE, HHF, CV death, renal outcome, amputation rate
	Fitchett (2019) [15]	7,020 patients	EMPA REG patients are divided based on prior stroke at baseline and CV risk according to 10-point TIMI risk score (low, intermediate, high)	Empagliflozin	10 mg/day 25 mg/day	Placebo	Median 3.1 years	HHF, CV death
	Ferreira (2020) [16]	7,020 patients	EMPA REG patients are divided based on with or without Metabolic syndrome (Mets) at baseline	Empagliflozin	10 mg/day 25 mg/day	Placebo	Median 3.1 years	MACE, HHF, CV death, renal outcome
CANVAS	Neal (2017) [17]	10,142 patients	Patients with type 2 diabetes and established ASCVD divided into a 1:1:1 ratio	Canagliflozin	100 mg/day 300 mg/day	Placebo	Median 2.42 years	MACE, HHF, CV death, renal outcome
UTOPIA	Katakami (2020) [18]	340 patients	Patients with type 2 diabetes without apparent CVD	Tofogliflozin	20 mg/day	Conventional treatment	104 weeks	Carotid IMT
	Katakami (2021) [19]	340 patients	Patients with type 2 diabetes without apparent CVD	Tofogliflozin	20 mg/day	Conventional treatment	104 weeks	Brachial artery PWV
	Katakami (2022) [20]	340 patients	Patients with type 2 diabetes without apparent CVD	Tofogliflozin	20 mg/day	Conventional treatment	104 weeks	Carotid IMT, Carotid GSM
DEFENCE	Shigiyama (2017) [21]	80 patients	Patients with type 2 diabetes treated with 750 mg metformin	Dapagliflozin	5 mg/day + metformin 750 mg/day	Metformin 1500 mg/day	16 weeks	Brachial FMD
PROTECT	Tanaka (2023) [22]	482 patients	Patients with type 2 diabetes and established ASCVD within 3 months prior were divided into a 1:1 ratio	Ipragliflozin	50–100 mg/day	Conventional therapy	2.0 years	Carotid IMT

Table 2. Study characteristics — continued

Trial name	Study ID [year]	Total population	Population characteristics	SGLT2i treatment group	SGLT2i Dose	Comparison	Follow-up duration	Outcomes measured
Other	Ikonomidis (2020) [23]	180 patients	Patients with type 2 diabetes with high or very high cardiovascular risk are divided into a 1:1:1:1 ratio	Empagliflozin	25 mg/day	• GLP1-RA (liraglutide) • Insulin • GLP1-RA +SGLT2i	1.0 years	Carotid-femoral PWV
	Lunder (2018) [24]	40 patients	Patients with type 1 diabetes	Empagliflozin	25 mg/day	• Metformin 2000 mg • Empa + Met • Placebo	12 weeks	Carotid-femoral PWV, brachial FMD
	Solini (2019) [25]	40 patients	Patients with type 2 diabetes with hypertension	Dapagliflozin	10 mg/day	Hydrochlorothiazide (HCT) 12.5 mg	4 weeks	Carotid-femoral PWV, brachial FMD
	Karalliedde (2022) [26]	33 patients	Patients with type 2 diabetes and residual albuminuria (albumin creatinine ratio (ACR) > 3 mg/mmol) despite RAS inhibition for the past 12 months	Dapagliflozin + Ramipril	10 mg/day	Ramipril 10 mg/day	24 weeks	Aortic PWV
	Kolwelter (2021) [27]	75 patients	Patients with HF reduced ejection fraction NYHA II-III with or without diabetes divided into a 2:1 ratio	Empagliflozin	10 mg/day	Placebo	12 weeks	Aortic PWV
	Ramirez (2018) [28]	30 patients	Patients with type 2 diabetes and hypertension taking amlodipine 10 mg and metformin 750–2000 mg daily	Canagliflozin	300 mg	Perindopril 10 mg	24 weeks	carotid-femoral PWV
	Sposito (2021) [29]	98 patients	Patients with type 2 diabetes and carotid IMT above the 75th percentile currently taking metformin 1500 mg/ /day divided into a 1:1 ratio	Dapagliflozin	10 mg/day	Glibenclamide 5 mg/day	12 weeks	Brachial FMD

Arterial pulse wave velocity (PWV) that measures arterial stiffness was also reviewed in this literature. This study included a total of one study measuring PWV in the brachial artery [19], four studies measuring carotid and femoral arteries [23–25, 28], and two studies measuring aortic PWV [26, 27]. Katakami et al. [19] measured brachial artery PWV using the same patients and treatment protocol as the one used in the UTOPIA trial. Ikonomidis et al. [23] measure the change in carotid-femoral PWV in 180 type II diabetic patients with high or very high cardiovascular risk divided into four groups; Group one taking Empagliflozin 25 mg per day, group two taking metformin 2000 mg, group three taking combination of empagliflozin and metformin, and group four taking placebo. Lunder et al. [24] and Solini et al. [25] protocol was previously described. The same treatment protocol was also used during evaluating the treatment effect on the change in carotid-femoral PWV. Karalliedde et al. [26] study measures the effect of SGLT2i on the change of aortic PWV. This study applied a strict inclusion criterion for kidney function. They only included type II diabetic patients with residual albuminuria defined as an albumin-creatinine ratio above 3 mg/mmol despite RAS inhibition therapy for 12 months. Dapagliflozin combined with ramipril was used as a treatment and single ramipril therapy was used as a control. Kowelter et al. [27] also measure the effect on the aortic PWV. In this study, a strict inclusion criterion was applied which only patients with reduced HF and NYHA class II–III with or without type II diabetes. Empagliflozin 10 mg per day was used as a treatment and placebo was used as a control. Lastly, Ramirez et al. [28] measured the effect of SGLT2i therapy on the changes in carotid-femoral PWV. This study included a type II diabetic patient with hypertension who takes daily 10 mg of amlodipine and 750–2000 mg of metformin. Canagliflozin 300 mg was used as a treatment with Perindopril 10 mg as a control.

Risk of bias assessment

Risk of bias assessment for a randomized controlled trial was conducted using Cochrane's RoB 2.0 (Fig. 2). For clinical atherosclerosis trials, all studies had an overall low risk of bias with only some studies having some concern in only one aspect of bias. However, some studies in subclinical atherosclerosis trials had some bias concerns with one study having a high risk of overall bias.

Clinical atherosclerosis studies

Meta-analysis was performed on four clinical effect studies [7, 11, 13, 17]. Pooled analysis was able to be conducted for 3-points MACE, HHF, CV death, and composite renal outcome. For 3-P MACE, a total of 24557 patients in the SGLT2i group and 18003 patients in the placebo group across four trials were included for the analysis. Pooled analysis showed that SGLT2i significantly decreased 3P-MACE with low heterogeneity among studies (RR 0.92; 95% CI 0.87–0.98; $p = 0.03$; $i^2 = 18\%$) (Fig. 3A). For HHF, a total of 24563 patients in the SGLT2i group and 18005 patients in the placebo group were included. Pooled analysis showed that patients in the SGLT2i group had reduced risk of HHF compared to the placebo group with no heterogeneity among studies (RR 0.71; 95% CI 0.63–0.80; $p < 0.0001$; $i^2 = 0\%$) (Fig. 3B). For renal outcome, studies included in the analysis combined the event of doubling serum creatinine, renal failure, the need for renal replacement therapy, and death from renal causes. The analysis includes a total of 24000 SGLT2i patients and 17733 placebo patients. Pooled analysis showed that SGLT2i therapy significantly reduced the risk for renal outcome with moderate heterogeneity (RR 0,72; 95% CI 0.67–0.78; $p < 0.0001$; $i^2 = 32\%$) (Fig. 3D). For cardiovascular mortality, the pooled analysis includes a total of 24563 SGLT2i patients and 18005 placebo patients. The analysis showed that SGLT2i does not significantly reduce the risk of CV death compared to placebo (RR 0.85; 95% CI 0.71–1.03); $p = 0.10$; $i^2 = 74\%$) (Fig. 3C). The analysis showed high heterogeneity with three included studies [7, 11, 17] showed insignificant reduction in the risk of CV death and one study showed significant risk reduction [13]. The study that shows insignificant risk reduction used Dapagliflozin [7], Ertugliflozin [11], and canagliflozin [17] as a treatment while the study that shows significant risk reduction used empagliflozin [13].

For safety evaluation, pooled analysis was able to be conducted for amputation rate. The analysis included a total of 16496 patients in the SGLT2i group and 9927 patients in the placebo group from across four trials [7, 11, 13, 17]. Pooled analysis showed that SGLT2i significantly increased the amputation rate compared to placebo (RR 1.35; 95% CI 1.05–1.73; $p = 0.02$; $i^2 = 43\%$) (Fig. 4). Moderate heterogeneity between studies was observed. In this analysis, three studies showed an insignificant increase in risk for amputation rate while one study showed a significantly higher risk of amputation rate in the SGLT2i group. The study that shows significantly higher risk used Canagliflozin [17] as a treatment while the other three SGLT2i drugs (dapagliflozin [7], ertugliflozin [11], and empagliflozin [13]) didn't show a significant increase in amputation rate risk.

Subgroup analysis of clinical atherosclerosis studies

Derived from the common trials, several studies published their subgroup analysis (Table 3) [8–10, 12, 14–16]. Overall, subgroup analysis resulted in no

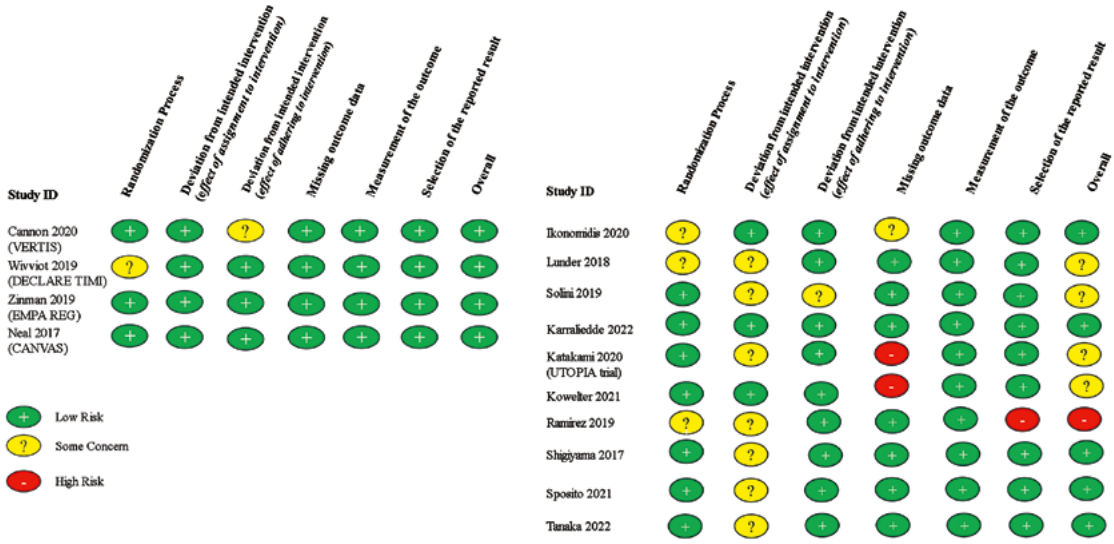

Figure 2. Risk of bias assessment using Cochrane's RoB 2.0 checklist

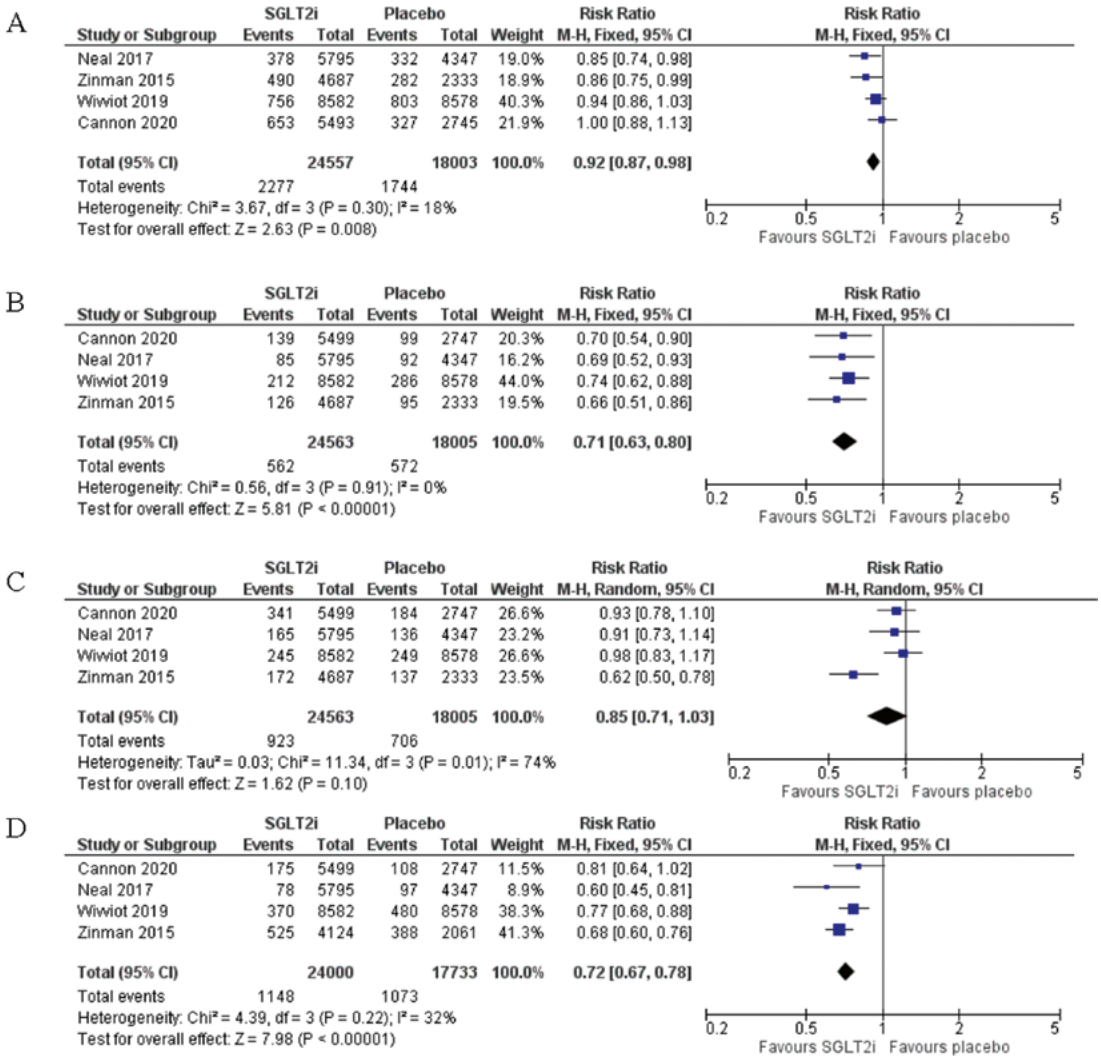

Figure 3. The effect of SGLT2i treatment in clinical cardiac-related outcome and renal outcome in diabetic patients with confirmed atherosclerotic disease. **A.** MACE, **B.** Hospitalization due to heart failure, **C.** Cardiovascular death, **D.** Renal outcome

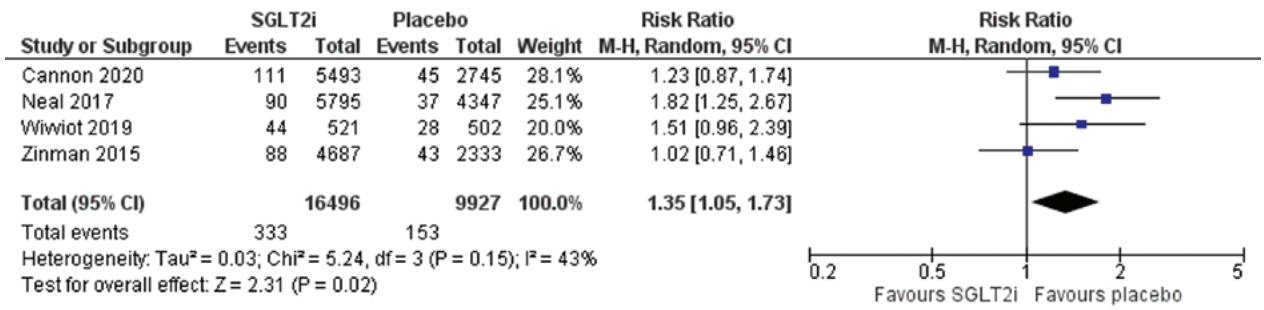

Figure 4. The effect of SGLT2i treatment on amputation rate

significant difference in the clinical improvement effect of SGLT2i in patients across different ages, different baseline ejection fractions, with a history of stroke, with/without metabolic syndrome, and with/without PAD (Table 3).

Subclinical atherosclerosis studies

The effects of SGLT2i treatment on endothelial function shown by flow-mediated dilatation (FMD) are presented in Table 4. Four studies related to SGLT2i effects on FMD with two studies [24, 29] showing significant improvement and two studies [21, 25] showing non-significant results.

The effects of SGLT2i treatment in arterial stiffness shown by pulse-wave velocity (PWV) were presented in Table 5. Seven studies related to SGLT2i effects on PWV with five studies [19, 23, 24, 27, 28] showing significant improvement and two studies [25, 26] showing non-significant results.

The effects of SGLT2i treatment in intima-media thickness (IMT) are presented in Table 6. Three studies [18, 19, 22] related to SGLT2i effects on carotid IMT showed non-significant results.

Discussion

The SGLT2 protein (SLC5A2), one member of the sodium-glucose cotransporter family, carries glucose from the renal tubular lumen to the tubular epithelial cells [4]. SGLT2 is a high-capacity and low-affinity glucose transporter that is mostly expressed in the S1 and S2 segments of the proximal renal tubule [30, 31]. The expression of SGLT2 is increased, and the urine glucose excretion threshold is also higher in hyperglycaemic patients compared to healthy humans [4]. Increasing glucose excretion in urine is the main mechanism by which SGLT2i delivers its hypoglycaemic effects, which are independent of pancreatic beta-cell activity and insulin sensitivity. However, in diabetic patients, the mechanism of SGLT2i's inhibitory action on atherosclerosis, the cause of cardiovascular events, is not fully understood [4, 30]. Some proposed mechanisms of SGLT2 inhibitors related to atherosclerosis by preserving basal and adaptive autophagy by activation of AMPK/mTOR pathway, preventing oxidative stress via suppression of NADPH oxidase expression, preventing inflammation by reducing pro-inflammatory cytokines (IL-1β, IL-18, IL-6, TNFα) and adhesion molecules (MCP-1, ICAM-1 and VCAM-1), and preserving endothelial function by restoring nitric oxide bioavailability [5].

The following meta-analysis highlights the effect of SGLT2 inhibitor therapy on clinical outcomes in diabetic patients with confirmed atherosclerotic cardiovascular disease (ASCVD). A total of four big randomized clinical trials were included for quantitative analysis with additional publications undergoing subgroup analysis from each trial that aims to see the difference of SGLT2i therapy on various characteristics of patients. Relative risk was measured based on the number of clinical outcome events in both SGLT2i and placebo groups using an inverse variance technique with either a fixed--effect model or a random-effect model depending on its heterogeneity. The first variable analyzed was the Three-point Major Cardiovascular Adverse Event (MACE) which consists of either death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction.

Meta-analysis was performed on four clinical effect studies. Pooled analysis showed SGLT2i significantly decreased 3P-MACE and renal outcome, with no effect on CV death, and increased amputation rate compared to placebo. Subgroup analysis on the clinical effects of SGLT2i resulted in no significant difference in the clinical improvement effect of SGLT2i in patients with different ages, different baseline ejection fractions, with a history of stroke, with/without metabolic syndrome, and with/without PAD. This result means that SGLT2i has wide application in various patient conditions such as older ages, reduced ejection fraction, history of stroke, metabolic syndrome, and PAD.

Also, a systematic analysis of the subclinical atherosclerosis effects of SGLT2i was conducted to under-

Table 3. Subgroup analysis of Trials assessing the effect of SGLT2i treatment for diabetic patients with ASCVD

Trial name	Study ID [year]	Total population	Subgroup analysis	SGLT2i treatment group	Comparison	Follow-up duration	Outcomes
DECLARE-TIMI 58	Bonaca (2020) [8]	1,025 patients	Patients with established PAD	Dapagliflozin	Placebo	Median 4.2 years (IQR 3.9–4.4)	No significant difference in MACE incidence in either group Higher incidence of amputation rate in PAD patient No significant difference in the clinical improvement effect of SGLT2i in patients with or without PAD
	Cahn (2020) [9]	17,160 patients	Patients are divided into three age categories; • < 65 y.o • ≥ 65 –< 75 y.o 75 y.o • ≥ 75 y.o				Incidence of MACE increases with age No significant difference in the clinical improvement effect of SGLT2i in all three age groups
	Cahn (2021) [10]	10,186 patients	Patients are divided based on • HbA1c (< 8.0% vs ≥ 8%) • History of smoking • Number of additional risk factors (one vs two vs three)				No significant difference in SGLT2i effect on hospitalization Due to heart failure across all patient grouping
VERTIS	Cosentino (2020) [12]	8,246 patients	Patients are divided based on their initial ejection fraction (EF) • ≤ 45% • > 45% • Unknown	Ertugliflozin	Placebo	Mean 3.5 years	No significant difference in SGLT2i effect on hospitalization due to heart failure across all Patients with different baseline EF

Table 3. Subgroup analysis of Trials assessing the effect of SGLT2i treatment for diabetic patients with ASCVD — continued

Trial name	Study ID [year]	Total population	Subgroup analysis	SGLT2i treatment group	Comparison	Follow-up duration	Outcomes
EMPA REG	Verma (2018) [14]	1,461 patients	Patients with established PAD	Empagliflozin	Placebo	Median 3.1 years	No significant difference in the clinical improvement effect of SGLT2i in patients with or without PAD No significant amputation risk effect of SGLT2i in patients with or without PAD
	Fitchett (2019) [15]	7,020 patients	EMPA REG patients are divided based on prior stroke at baseline and CV risk according to 10-point TIMI risk score (low, intermediate, high)				No significant difference in SGLT2i effect on CV death and HHF in patients with or without prior stroke No significant difference in SGLT2i effect on CV death and HHF across all CV risk groups
	Ferreira (2020) [16]	7,020 patients	EMPA REG patients are divided based on with or without Metabolic syndrome (Mets) at baseline				Patients with Mets had a higher incidence of CV death, HHF, and worsening nephropathy compared to patients without Mets No significant difference in SGLT2i effect on CV death and HHF in patients with or without Mets

Table 4. The effect of SGLT2i treatment on changes in FMD

Study ID [year]	Group	Follow up duration	Baseline FMD (%)	Post-follow--up FMD (%)	FMD from baseline	Times increased	p-value within times	p-value between groups
Shigiyama (2017) [21there is little or no information on the therapeutic effects of SGLT2 inhibitors on the progression of atherosclerosis. This dapagliflozin effectiveness on vascular endothelial function and glycemic control (DEFENCE]	5 mg Dapa + 750 mg Met	16 weeks	4.80 ± 1.86	5.66 ± 2.12	0.85 ± 2.71	–	0.06*	
	Met 1500 mg		5.37 ± 2.95	5.18 ± 2.09	−0.19 ± 2.51	-	0.65	
Lunder (2018) [24]	Empa	12 weeks	–	–	–	2,2-fold	< 0.01*	ns
	Met		–	–	–	1,8-fold	< 0.05*	ns
	Empa + Met		–	–	–	2,6-fold	< 0.001*	ns
Solini (2019) [25and induces epigenetic modifications. Subjects and Methods: Forty hypertensive patients with type 2 diabetes were randomly assigned to 4-week treatment with dapagliflozin 10 mg or hydrochlorothiazide (HCT]	Dapa	4 weeks	4.18 ± 0.63	4.18 ± 0.54	–	–	0.869	
	HCT		4.52 ± 0.61	4.56 ± 0.63	–	–		
Sposito (2021) [29open-label, single-center, randomized clinical trial, 98 patients with T2DM and carotid intima-media thickness above the 75th percentile were randomized 1:1 to 12 weeks of therapy with dapagliflozin or glibenclamide in addition to metformin in glucose--lowering equivalent regimens. The coprimary endpoints were 1-min flow-mediated dilation (FMD]	Dapa	12 weeks	–	–	3.3 ± 8.2	–		0.0001*
	Gliben-clamide		–	–	−1.2 ± 7.5	–	–	

Table 5. The effect of SGLT2i treatment on changes in PWV

Study ID [year]	Artery measured	Follow up duration	Group	Baseline PWV [m/s]	Post-follow-up PWV [m/s]	PWV from baseline [% or SE]	p-value within time	p-value within groups
Katakami (2021) [19]	Brachial artery	104 weeks	Tofo	–	–	−52.5 ± 30.1	–	0.005*
			Conventional	–	–	52.2 ± 29.1	–	
Ikonomidis (2020) [23]	Carotid-femoral	52 weeks	Empa	12 ± 2.8	10.9 ± 2.1	–10.1%	< 0.05*	–
			GLP-1RA	11.6 ± 2.8	10.5 ± 1.9	–8.6%	< 0.05*	–
			Empa + GLP-1RA	12.3 ± 2.6	10.8 ± 2	–13%	< 0.05*	–
			Insulin	11.5 ± 2.7	11.1 ± 2.3	–3.6	ns	–
Lunder (2018) [24]	Carotid-femoral	12 weeks	Empa	–	–	–15.8%		< 0.01*
			Met	–	–	–		ref
			Empa+Met	–	–	–14.3%		< 0.01*
Solini (2019) [25]	Carotid-femoral	4 weeks	Dapa	10.35 ± 1.64	10.18 ± 1.47	–	0.202	0.387
			HCT	11.15 ± 2.61	10.63 ± 2.65	–		
Karalliedde (2022) [26]	Aorta	24 weeks	Dapa + Rami	9.06 ± 1.91	9.13 ± 2.03	–	0.90	–
			Rami	9.88 ± 2.12	10.00 ± 1.84	–	0.81	–
Kolwelter (2021) [27]	Aorta	12 weeks	Empa	9.6 ± 1.6	9.3 ± 1.6	–0.2 ± 0.9	0.121	0.021*
			Placebo	9.0 ± 1.6	9.3 ± 1.8	0.3 ± 0.7	0.06	
Ramirez (2018) [28]	Carotid-femoral	24 weeks	Cana	12 ± 0.3	8.5 ± 0.2	-	0.05*	-
			Perin	11.6 ± 0.2	8.0 ± 0.3	–	0.025*	–

stand the mechanism of how they affect clinical atherosclerosis. Non-invasive atherosclerosis tests have been demonstrated to be useful in evaluating cardiovascular risk, with PWV reflecting arterial stiffness, carotid IMT reflecting structural changes in the artery wall, and FMD reflecting endothelial function [32]. A systematic review was done based on those three parameters. We've found seven studies related to SGLT2i effects on PWV with five studies [19, 23, 24, 27, 28] showing significant improvement and two studies [25, 26] showing non-significant results. Three studies [18, 19, 22] related to SGLT2i effects on carotid IMT showed non-significant results. Four studies related to SGLT2i effects on FMD with two studies [24, 29] showing significant improvement and two studies [21, 25] showing non-significant results. Based on those findings, it was concluded that the possible mechanism of SGLT2i improved clinical atherosclerosis by improving arterial stiffness.

Most cardiovascular risk factors and aging increase arterial stiffness as a result of multiple atherosclerotic risk factors increasing cardiac afterload and myocardial oxygen demand, as well as impairment of myocardial blood flow [33]. Increased MACE like unstable angina, myocardial infarction, coronary revascularization, heart failure, stroke, and mortality are related to elevated arterial stiffness [34]. Reduced elastin/collagen ratio, elastin cross-linking synthesis, calcification, vascular smooth muscle cell stiffness, endothelial dysfunction, and reactive oxygen species-induced inflammation all contribute to arterial wall stiffening [35]. A balance between oxidant and antioxidant pathways is achieved as a result of reduced oxidative stress and inflammation, which is one of the clear cardiovascular benefits associated with SGLT2i use [36]. Thereby, it was hypothesized that the mechanism of SGLT2i improves clinical atherosclerosis by its benefit in reducing oxidative stress which improves the arterial stiffness.

According to Katakami, et al. [18] findings, SGLT2i may have greater effects on small vessels than on large vessels. This may explain why SGLTi didn't improve carotid IMT or FMD since both parameters were associated with large vessel dysfunction. A study by Tochiya, et al. [37] also supports this finding which showed that SGLT2i diastolic function improvement (measured by E/e' ratio) does not correlate with the improvement in FMD-based vascular endothelial function in large

Table 6. The effect of SGLT2i treatment in changes of carotid IMT

Study ID [year]	Artery measured	Follow up duration	Groups	Baseline IMT [mm]	Post-follow-up IMT [mm]	IMT from baseline	p-value within time	p-value within group
Katakami (2020 & 2022) [18, 20]	Common CCA	104 weeks	Tofo	0.87 ± 0.16	0.74 ± 0.14	−0.132 ± 0.007	< 0.001*	0.34
			Conventional	0.87 ± 0.16	0.73 ± 0.14	−0.140 ± 0.006	< 0.001*	
	Right CCA		Tofo	1.05 ± 0.29	0.91 ± 0.30	–0.163 ± 0.013	< 0.001*	0.10
			Conventional	1.06 ± 0.25	0.88 ± 0.21	−0.190 ± 0.012	< 0.001*	
	Left CCA		Tofo	1.13 ± 0.37	0.96 ± 0.38	−0.170 ± 0.020	< 0.001*	0.43
			Conventional	1.12 ± 0.37	0.93 ± 0.31	−0.190 ± 0.020	< 0.001*	
Tanaka (2022) [22prospective, randomized, open-label, and blinded-endpoint investigator-initiated clinical trial, adults with type 2 diabetes and haemoglobin A1C (HbA1c]	CCA	104 weeks	Ipra	0.82 (95% CI 0.79–0.84)	0.81 (95% CI 0.79–0.84)	0.0013 (95% CI −0.0155–0.0182)	–	0.989
			Conventional	0.84 (95% CI 0.82–0.87)	0.84 (95% CI 0.81–0.86)	0.0015 (95% CI −0.0155–0.0184)	–	
	ICA	104 weeks	Ipra	0.79 (95% CI 0.74–0.83)	0.83 (95% CI 0.78–0.88)	0.0167 (95% CI −0.0259–0.0592)	–	0.356
			Conventional	0.85 (95% CI 0.80–0.90)	0.80 (95% CI 0.75–0.85)	−0.0058 (95% CI −0.0500–0.0383)	-	

vessels and may be related to coronary microcirculation improvement.

The role of SGLT2i in increasing renal outcomes may be related to its antioxidant properties. Many factors contribute to the chronic inflammatory state in CKD, including the increased production of proinflammatory cytokines and oxidative stress important markers of inflammation in CKD are C-reactive protein, interleukin-6, interleukin-1, tumour necrosis factor-α, adipokines, adhesion molecules, and the CD40 ligand [38]. CREDENCE and DAPA-CKD, large-scale RCTs that evaluated SGLT2i effects on primary kidney endpoint showed 30–39% reduction of doubling of creatinine, end-stage kidney disease, and mortality from renal or cardiovascular aetiology regardless of diabetes status [39].

The mechanism of how SGLT2i increases the amputation rate in these trials is unknown. The present result showed that the mechanism could not be explained by the decrease in perfusion due to a decrease in arterial diameter or compliance. It was hypothesized that the increased risk of amputation is caused by the increased rate of arterial embolism. SGLT2i has been found to increase blood viscosity due to its diuretic effect with high blood viscosity increasing platelet-to-surface time and therefore promoting more platelet activation and aggregation [40, 41]. Vascular occlusive disease was known to increase the risk of amputation in diabetic patients [42]. Aside from that, the only significant result was a study by Neal, et al. [17] with Canagliflozin which gives notable weight to the meta-analysis. The use of canagliflozin should be evaluated in patients with concomitant diabetes mellitus and PAD which carries a 4x higher risk of amputation [43].

Study limitation

This meta-analysis had several limitations. The first and most notable limitation is the wide variety of

different drugs used as a treatment and control group which raises the heterogeneity in some analyses and limits interpretation, especially for IMT, FMD, and PWV. These subclinical atherosclerosis studies also had several risks of bias which further limits the interpretation.

Conclusion

SGLT2i showed benefits in reducing MACE, HHF, and renal outcomes in diabetic patients with ASCVD with adverse events of increased amputation rate. Subclinical atherosclerosis studies showed varied conflicting results. Most studies of subclinical atherosclerosis showed benefits on PWV improvement, conflicting results on FMD, and no benefit on IMT.

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