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REVIEW ARTICLE

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The effect of sodium-glucose co-transporter-2 inhibitors on markers of subclinical atherosclerosis

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ABSTRACT

Background: Despite the widespread use of classical cholesterol-lowering drugs to mitigate the adverse impacts of dyslipidaemia on atherosclerosis, many patients still face a substantial residual risk of developing atherosclerotic cardiovascular disease (CVD). This risk is partially attributed to non-traditional pathophysiological pathways. Latest evidence suggests that sodium glucose co-transporter-2 (SGLT2) inhibitors are beneficial for patients suffering from type 2 diabetes mellitus (T2DM) or established CVD by reducing morbidity and mortality. However, the underlying mechanisms of this benefit have not been clearly elucidated. It has been hypothesized that one possible mechanism could be the attenuation of subclinical atherosclerosis (SA) progression.

Aim: The objective of this narrative review is to examine the present evidence concerning the impact of SGLT2 inhibitors on markers of SA.

Results: The current evidence on the efficacy of SGLT2 on SA, endothelial function and arterial stiffness remains controversial. Findings from observational and randomized studies are quite heterogeneous; however, they converge that the antiatherosclerotic activity of SGLT2 inhibitors is not strong enough to be widely used for prevention of atherosclerosis progression in patients with or without T2DM.

Conclusions: Further research is needed to investigate the underlying mechanisms and the possible beneficial impact of SGLT2i on primary and secondary CVD prevention through attenuation of premature atherosclerosis progression.

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Introduction

Atherosclerosis is a complex and multifactorial inflammatory process that commences in childhood but often remains asymptomatic for a long period of time before presenting clinically later in life [1,2]. Accumulating evidence suggests that atherosclerosis should be considered as an immune system-mediated process of the vascular system [3]. Besides, many experimental studies have shown that atherosclerotic plaques are composed of different immune cells like lymphocytes and macrophages [4].

Although classical cholesterol-lowering drugs have been widely used to lessen the negative effects of dyslipidaemia on atherosclerosis, many patients still experience a significant residual risk for developing atherosclerotic cardiovascular disease (CVD), driven by non-traditional pathophysiological pathways of atherogenesis, such as Lp(a), autoimmunity and glucometabolic mediators [5]. Thus, there is a substantial and unmet need to optimize the anti-atherosclerotic therapeutic strategies in order to mitigate the atherosclerotic risk and minimize the occurrence of major adverse cardiovascular events (MACEs).

Latest evidence from landmark trials suggests that sodium glucose co-transporter-2 (SGLT2) inhibitors are beneficial for patients suffering from type 2 diabetes mellitus (T2DM) or established CVD – mainly heart

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failure (HF) – by reducing CVD-related morbidity and mortality [6,7]. Notwithstanding the significant amount of evidence in the field, the precise underlying mechanisms that underpin these advantageous outcomes are still not fully understood. Thus, the actual impact of SGLT-2 inhibitors on subclinical atherosclerosis (SA) markers remains controversial. Besides, the existing evidence is scarce regarding their effects on primary and secondary CVD prevention through attenuation of premature atherosclerosis progression in patients with or without underlying T2DM.

The detection of the exact burden of SA in the general population is practically infeasible [1]. Currently, many non-invasive techniques have been proposed and incorporated into clinical practice, which can effectively contribute to the early detection of SA before its clinical manifestation [1, 8]. These advancements in technology have enabled the clinicians to assess the cardiovascular (CV) risk in a more practical and accurate manner. Unlike the traditional approach that solely relies on CVD risk factors, the new methods also take into account the vascular damage and resulting dysfunction, which is an earlier manifestation of atherosclerosis in asymptomatic adults [9]. In addition, arterial stiffness mainly assessed by pulse wave velocity (PWV) and augmentation index (AIx) has been described as target-organ damage [10,11]. Accumulating evidence suggests that arterial stiffness is strongly related with the incidence, and with the extent of atherosclerotic disease and thus, it should be considered as an independent risk factor of CVD-related outcomes [8, 10–12]. The early diagnosis of premature atherosclerotic disease is of paramount significance, as it paves the way for timely interventions through primary prevention strategies [1].

The aim of this narrative review is to provide a comprehensive analysis of the current evidence on the effects of SGLT2 inhibitors on markers of SA. The focus is primarily on clinical data from observational and randomized studies that assess the impact of SGLT2 inhibitors on intima-media thickness (IMT), epicardial adipose tissue (EAT) and indices of endothelial function and arterial stiffness.

SGLT2 inhibitors, mechanism of action and current indications for use

SGLT-2 inhibitors are a relatively new class of oral antidiabetic drugs that act by inhibiting renal sodium and glucose reabsorption by lowering the renal threshold for glucose absorption in the proximal tubule, thereby causing glycosuria and natriuresis [13]. SGLT-2 inhibitors reduce plasma glucose concentration in patients with hyperglycaemia, but they have a trivial impact on plasma glucose concentrations in normoglycaemic individuals [14]. Except for their glucose-lowering effects, they have been associated with weight loss, blood pressure reduction, and a lower risk of hypoglycaemia compared to commonly prescribed antidiabetic drugs, like insulin and sulfonylureas [7, 14,15]. In clinical practice, SGLT-2 inhibitors are used for the treatment of T2D as a second-line agent after inadequate glycaemic control using metformin, or a first-line agent for high-risk individuals with CVD, HF or chronic kidney disease (CKD) [16–19]. In addition, they have recently received an indication for administration to patients with HF across the spectrum of left ventricular ejection fraction according to the recent guidelines of the American Heart Association [20]. This indication was based on accumulative evidence regarding their beneficial effects on reducing HF hospitalizations and CVD mortality [21], establishing the new fundamental role of SGLT2 inhibitors in the treatment of HF. In addition to the established CV benefits, SGLT-2 inhibitors have a renoprotective profile irrespectively of the severity or the aetiology of kidney disease, as well as of the diabetes status [22]. However, their impact on indices of SA remains controversial.

Potential underlying mechanisms of SGLT2 inhibitors related to atherosclerosis

It is well known that inflammation plays a significant role in atherogenesis and progression of atherosclerosis [3], and particularly in patients with T2DM inflammation in combination with oxidative stress, is considered as main underlying mechanisms involved in the pathogenesis of atherosclerosis [23]. Indeed, many studies have demonstrated that recruitment, activation and differentiation of monocytes, polarization of macrophages, as well as activation of inflammasome and secretion of proinflammatory cytokines are strongly associated not only with the development but also with the vulnerability of the atherosclerotic plaques [3, 24,25]. Accumulating evidence from animal and human studies suggest that treatment with SGLT2 inhibitors reduces inflammatory cell infiltration in atherosclerotic plaques [26–28], decreases circulating inflammatory cytokines, such as CRP, TNF-α, IL-6 and TGF-β [23, 26,27], and modulates the activity of NLRP-3 inflammasome leading to decreased release of IL-1β from macrophages [29].

An early vascular change that is strongly related to atherogenesis and progression of SA is the endothelial dysfunction [30]. It is well established that augmented endothelial reactivity as well as proliferation of

vascular smooth muscle cells (VSMC) can provoke significant vascular damages and poor relaxation of the arteries [31], particularly in patients with T2DM, due to insulin resistance, increased body weight (BW) and impaired blood glucose levels [32]. The underlying pathophysiologic mechanisms that probably are involved include the elevated reactive oxygen species (ROS), the impaired synthesis of nitric oxide (NO) and imbalanced release of chemokines [33,34]. Evidence from animal and human studies suggest that administration of SGLT2 inhibitors potentially act beneficially on vascular endothelial reactivity [35–37], and attenuate VSMC proliferation leading to reduction of oxidative stress and stability of atherosclerotic plaques [38,39].

In addition, as microRNAs (miRNAs) regulate majority of physiological and pathological processes in human, they can also modulate inflammatory and thrombotic pathways involved in atherogenesis. Several miRNAs have been demonstrated as diagnostic and prognostic tools for evaluating the likelihood of plaque destabilization and rupture and, consequently, the elevated risk of clinical atherosclerosis [40]. In particular, decreased levels of miR-143, and increased of miR-34a are associated with endothelial dysfunction and have been associated with elevated risk of progression of atherosclerosis and plaque rupture [41]. In addition, there is accumulative evidence that new anti-diabetic medications, including SGLT2 inhibitors, can modulate miRNAs expression levels and can exert beneficial effects on endothelial cells, VSMC, macrophages and platelets through reducing oxidative stress and inflammation [42]. Recently, it was shown that empagliflozin downregulates miR-34a-5p in NAFLD-associated fibrosis [43] and reduces miR-92 and mi-21 levels in HFpEF patients [44]. Hence, more dedicated investigation is imperative to determine that miRNAs hold potential utility as biomarkers or treatment targets in the context of subclinical and clinical atherosclerosis in routine clinical practice.

Evidence from animal models and clinical studies is controversial regarding the impact of SGLT2 inhibitors on lipid metabolism (LDL, HDL and triglycerides) [26,27, 45], findings that have been confirmed by several meta-analyses [46,47]. Therefore, it is considered less possible that change in lipid metabolism is the main pathophysiologic pathway by which SGLT2 inhibitors exhibit their beneficial CV effects [32, 48]. Finally, glycaemia and improved glycaemic control have been described as a putative underlying mechanism for attenuation of SA driven by newer antidiabetic drug classes [49]. Despite that SGLT2 inhibitors can moderately decrease blood glucose levels through glycosuria [50], many other antidiabetic drugs, including sulfonylureas, thiazolidinediones and insulin, have repeatedly failed to show CV benefit [51], indicating that a glucose-independent mechanism probably plays a more important role [32, 48].

SGLT2 inhibitors and intima-media thickness

One of the most widespread techniques used for the assessment of SA is the IMT of carotids and femoral arteries by ultrasound imaging [1]. Until now, several clinical studies have investigated the impact of SGLT2 inhibitors on the progression of SA in patients with T2DM (Table 1). In their multicentre randomized control trial (RCT), Tanaka et al. found out that ipragliflozin had a neutral effect on IMT of common carotid artery (CCA-IMT) after 2 years of follow-up. Patients in the ipragliflozin arm experienced a mean change in CCA-IMT of 0.0013 mm (95% CI: −0.0155 to 0.0182), while patients in the group of non-SGLT2 inhibitors standard antidiabetic care had a mean change in CCA-IMT of 0.0015 mm (95% CI: −0.0155 to 0.0184), with the estimated difference between the two groups being −0.0001 mm (95% CI: −0.0191 to 0.0189; p = .989) [52]. Similar were the findings of a multicentre, single-arm, observational cohort (FUSION) study from Japan, which showed that treatment with ipragliflozin had a non-significant effect on SA (CCA-IMT = 0.76 ± 0.16 mm at baseline vs. 0.75 ± 0.15 mm after 1 year, p = .40 in right CCA; and CCA-IMT = 0.75 ± 0.18 mm at baseline vs. 0.76 ± 0.17 mm after 1 year, p = .41 in left CCA) [56]

On the other hand, findings from UTOPIA trial revealed that after 2 years of follow-up, both patients receiving tofogliflozin (intervention arm) and non-SGLT2 inhibitors treatment (control group) experienced a significant reduction not only in mean CCA-IMT (mean change = −0.132 mm; SE 0.007 and −0.140 mm; SE 0.006, respectively), but also in maximum left and right CCA-IMT measurements compared to baseline, without important differences in the progression of SA being observed between the two groups (mean change of CCA-IMT = 0.008 mm; 95% CI: [–0.009 to 0.025], p = .34) [54]. However, in a post hoc analysis, tofogliflozin as well as non-SGLT2i hypoglycaemic treatment had a neutral effect on tissue characteristics of the carotid arterial wall as measured by mean, right and left grey-scale median (GSM-CCA) values, and these findings were robust even after adjustments for possible confounding factors like traditional CVD-related risk factors and baseline treatment [53].

Table 1. Summary of observational studies and RCTs assessing the effects of SGLT-2 inhibitors on indices of subclinical atherosclerosis.

Study ID	Country	Type of study	Population (main characteristics)	SGLT2 inhibitor	Follow-up	Main outcomes
SGLT2 inhibitors and IMT						
Tanaka et al. [52]	Japan (39 clinical sites)	Multicentre RCT (PROTECT study)	482 adults with T2D and HbA1c = 6.0–10.0%	Ipragliflozin (50 mg once daily) vs. non-SGLT2i standard of care (control group), 1:1 randomization	24 months	Ipragliflozin had a neutral effect on CCA-IMT status, with the estimated group difference in the ipragliflozin vs. the control group being −0.0001 mm (95% CI: [−0.0191 to 0.0189]; $p = .989$).
Katakami et al. [53]	Japan (22 outpatient clinics)	Multicentre RCT (UTOPIA trial), post hoc analysis	340 adults with T2D and HbA1c = 6.0–9.0% without history of established CVD	Tofogliflozin (20 mg once daily) vs. non-SGLT2i standard of care (control group), 1:1 randomization	2 years	Tofogliflozin had a neutral effect on mean, left and right GSM-CCA values, with the estimated group difference in the tofogliflozin vs. the control group in the change of the mean GSM-CCA being −1.24 (95% CI: [−3.87 to 1.38]; $p = .35$).
Katakami et al. [54]	Japan (22 outpatient clinics)	Multicentre RCT (UTOPIA trial)	340 adults with T2D and HbA1c = 6.0–9.0% without history of established CVD	Tofogliflozin (20 mg once daily) vs. non-SGLT2i standard of care (control group), 1:1 randomization	2 years	Both patients receiving tofogliflozin and non-SGLT2i antidiabetic treatment (control group) experienced a significant reduction in mean CCA-IMT (mean change = −0.132 mm; SE 0.007 and −0.140 mm; SE 0.006, respectively) and in maximum left and right CCA-IMT measures, without important differences in the progression of subclinical atherosclerosis being observed between the two groups (mean change of CCA-IMT: 0.008 mm; 95% CI: [−0.009 to 0.025], $p = .34$).
Ardahanli [55]	Turkey	Single-centre, single-arm, observational prospective cohort study	37 adults with T2D without history of established CVD	Empagliflozin (10 mg or 25 mg once daily), no control group	6 months	Treatment with empagliflozin was associated with a significant reduction in CCA-IMT (7.6 ± 1.7 mm at baseline vs. 6.7 ± 1.3 mm after 6 months, $p < .001$) and in EAT (9.0 ± 2.2 mm at baseline vs. 7.7 ± 1.4 mm after 6 months, $p = .001$).
Nomiyama et al. [56]	Japan	Multicentre, single-arm, observational prospective cohort study (FUSION trial)	134 adults with T2D and HbA1c >6.5%	Ipragliflozin (50 mg once daily, no control group)	1 year	Treatment with ipragliflozin had a neutral effect on CCA-IMT measurements (0.76 ± 0.16 mm at baseline vs. 0.75 ± 0.15 mm after 52 weeks, $p = .40$ in right CCA and 0.75 ± 0.18 mm at baseline vs. 0.76 ± 0.17 mm after 52 weeks, $p = .41$ in left CCA), but it was associated with a reduction in PWV (1632.8 ± 368.5 cm/s at baseline vs. 1572.6 ± 325.4 cm/s after 52 weeks, $p < .05$).
Irace et al. [57]	Italy	Single-centre observational prospective cohort study	35 adults with T2D and HbA1c = 7.0–9.5%	Empagliflozin (10 mg once daily) vs. incretin-based antidiabetic treatment (liraglutide or sitagliptin)	3 months	Treatment with empagliflozin was associated with a significant reduction in CCA-IMT measurements after 1 and 3 months (0.793 ± 0.15 mm and 0.766 ± 0.127 mm; $p < .0001$ respectively compared to baseline measurements: 0.831 ± 0.156 mm), while treatment with liraglutide was associated with a significant reduction in CCA-IMT only after 3 months (baseline 0.879 ± 0.12 mm; 3-months 0.802 ± 0.114 mm; $p < .001$). Patients receiving sitagliptin had no significant changes in CCA-IMT.

BP: blood pressure; BW: body weight; CCA: common carotid artery; CI: confidence interval; CVD: cardiovascular disease; DBP: diastolic blood pressure; DEFENCE: dapagliflozin effectiveness on vascular endothelial function and glycaemic control; EAT: epicardial adipose tissue; eGFR: estimated glomerular filtration rate; GSM: grey-scale median; HbA1c: haemoglobin A1c; IMT: intima-media thickness; MD: mean difference; RCT: randomized control trial; RF: risk factor; SBP: systolic blood pressure; SGLT2i: sodium-glucose cotransporter 2 inhibitors; T2D: type 2 diabetes; UTOPIA: using tofogliflozin for possible better intervention against atherosclerosis for type 2 diabetes patients trial.

According to another single-centre observational cohort study from Turkey on patients with T2D who were treated with empagliflozin, a significant reduction in CCA-IMT was reported (mean change from baseline at 6 months: −1.29 mm, 95% CI: [−1.91 to −0.69], $p < .001$)) [55]. Similar were the findings reported by Irace et al. [57], who concluded that treatment with empagliflozin was associated with a significant reduction in indices of SA after 1 and 3 months (CCA-IMT = 0.793 ± 0.15 mm and 0.766 ± 0.127 mm; $p < .0001$ respectively compared to baseline measurements: CCA-IMT = 0.831 ± 0.156 mm). However, their non-randomized, single-arm design with small sample sizes limit the reliability and generalizability of the results, and so they should be interpreted with caution.

SGLT2i and endothelial dysfunction

Endothelial dysfunction is an early vascular change that is strongly related to atherogenesis and progression of SA. Limited research has been conducted regarding the potential influence of SGLT2i on endothelial function (Table 2), mainly through assessment of flow-mediated vasodilation (FMD) measurements in the brachial artery. According to the DEFENCE study, a multicentre parallel-group RCT from Japan, it was shown that treatment with dapagliflozin as add-on therapy to metformin was not associated with significant changes in FMD compared to control group (ΔFMD% [FMD at week 16 − FMD at baseline] = 0.85 ± 2.71 and −0.19 ± 2.51, $p = .09$, respectively) [58]. Nevertheless, subgroup analysis revealed that dapagliflozin was associated with significant improvement of FMD among individuals with HbA1c >7.0% ($p = .041$) [58]. A sub-analysis of the multicentre PROTECT study reached similar results, as it was shown that treatment with ipragliflozin had a neutral effect on change of FMD measurements at 24 months compared to baseline (5.2 ± 2.6% vs. 5.2 ± 2.6%, $p = .98$) [59]. In addition, findings from another double-blind, placebo-controlled RCT involving patients suffering from T2DM and established CVD demonstrated that treatment with dapagliflozin for 12 weeks as an add-on therapy to metformin and insulin was not associated with significant improvements either in FMD or nitroglycerin-mediated dilation (NMD) values [61]. Moreover, the EMBLEM trial, a multicentre, placebo-controlled RCT, which was conducted in Japan, demonstrated that treatment with empagliflozin for 6 months was not associated with significant changes in values of reactive hyperaemia peripheral arterial tonometry index (RHI) compared to control arm in 117 patients with T2DM and established CVD [63].

On the other hand, according to a single-centre, parallel-group RCT from Brazil among individuals with T2DM and early atherosclerosis, treatment with dapagliflozin was associated with a significant increase in rest FMD ([+3.3 (8.2)%], compared to treatment with glibenclamide [−1.2 (7.5)%], $p = .0001$), indicating that SGLT2i could probably have a beneficial impact on CVD prevention among patients suffering from T2D and SA [60]. Sposito et al. reached similar findings, as they reported that treatment with empagliflozin was associated with significant improvements in FMD values at 1 and 2 min ($p < .05$), according to the single-centre, randomized EXCEED-BHS3 Trial [62]. These beneficial effects of SGLT2i on endothelial function were confirmed by two recent meta-analyses [64,65]. The first one pooled data from 12 RCTs and more than 18,000 patients with T2D and showed that dapagliflozin significantly improved FMD (MD = 1.22, 95% CI: [0.38–2.06]; $p = .005$) compared to control group [65]. The other meta-analysis synthesized data from nine RCTs and two observational studies pooling data from 868 patients and it demonstrated that antidiabetic treatment with SGLT2 inhibitors was associated with significant improvements in FMD levels compared to non-SGLT2i arms (standardized MD = 0.18, 95% CI: [0.02–0.34]; $p = .03$) [64].

SGLT2 inhibitors and arterial stiffness

It is well established that arterial stiffness plays a pivotal and independent role in the development of CVD and in clinical practice, PWV is widely used to quantify the level of arterial stiffness [66]. Until now, several clinical studies have investigated the impact of SGLT2 inhibitors on arterial stiffness in patients with T2DM; however, their findings are contradictory (Table 3).

According to findings of a prespecified sub-analysis of UTOPIA trial, treatment with tofogliflozin was associated with significant improvements in mean, right and left brachial-ankle PWV compared to control group (−104.7 cm/s, 95% CI: [−177.0 to − 32.4]; $p = .005$, −109.3 cm/s, 95% CI: [−184.3 to −34.3]; $p = .005$ and −98.3 cm/s, 95% CI: [−172.6 to −24.1]; $p = .01$, respectively), even after adjusting for classical CVD RFs [67]. In another double-blind, placebo-controlled RCT conducted in Germany, Bosch et al. concluded that treatment with empagliflozin was associated with significant improvements in arterial stiffness indices like central SBP (113.6 ± 12.1 vs. 118.6 ± 12.9 mmHg, $p < .001$), and central pulse pressure (39.1 ± 10.2 vs.

Table 2. Summary of observational studies and RCTs assessing the effects of SGLT-2 inhibitors on indices of endothelial function.

Study ID	Country	Type of study	Population (main characteristics)	SGLT2 inhibitor	Follow-up	Main outcomes
Shigiyama et al. [58]	Japan (15 outpatient clinics)	Multicentre RCT (DEFENCE study)	80 adults with early T2D and HbA1c = 6.0–8.0% treated with 750 mg metformin, but without history of established CVD	Dapagliflozin (5 mg once daily) vs. 750 mg metformin (control group) as an add-on therapy to 750 mg metformin	16 weeks	Treatment with dapagliflozin was not associated with significant changes in FMD compared to control group (ΔFMD% [FMD at week 16 – FMD at baseline] = 0.85 ± 2.71 and −0.19 ± 2.51, p = .09, respectively). Subgroup analysis revealed that dapagliflozin was associated with significant improvement of FMD among individuals with HbA1c >7.0% (p = .041).
Kishimoto et al. [59]	Japan (39 clinical sites)	Multicentre RCT (PROTECT study) sub-analysis	482 adults with T2D and HbA1c = 6.0–10.0%, FMD values were obtained only by 32 individuals in the non-SGLT2i group and 26 individuals in the SGLT2i arm	Ipragliflozin (50 mg once daily) vs. non-SGLT2i standard of care (control group), 1:1 randomization	24 months	Treatment with ipragliflozin as well as non-SGLT2i standard of care (control group) had a neutral effect on change of FMD measurements at 24 months compared to baseline (5.2 ± 2.6% vs. 5.2 ± 2.6%, p = .98 in the SGLT2i group; 5.0 ± 3.2% vs. 5.4 ± 2.9%, p = .34 in the non-SGLT2i group).
Sposito et al. [60]	Brazil	Single-centre RCT (ADDENDA-BHS2 study)	98 adults with T2D, HbA1c = 7.0–9.0% and CCA-IMT > the 75th percentile (subclinical atherosclerosis) treated with metformin	Dapagliflozin (10 mg once daily) vs. glibenclamide (5 mg once daily), randomization 1:1	12 weeks	Treatment with dapagliflozin was associated with a significant increase in rest FMD ([+3.3 (8.2)%], compared to treatment with glibenclamide [–1.2 (7.5)%], p = .0001). In addition, patients in the non-SGLT2i arm compared to SGLT2i group experienced higher resistive indices at 1 min [0.90 (0.11) vs. 0.93 (0.07); p = .03] and 5 min [0.93 (0.07) vs. 0.95 (0.05); p = .02].
Zainordin et al. [61]	Malaysia	Multicentre RCT (EDIFIED trial)	81 adults with T2D, HbA1c = 7.0–10.5% and established CVD treated with metformin and insulin	Dapagliflozin (10 mg once daily) vs. placebo (control group), randomization 1:1	12 weeks	Treatment with dapagliflozin had a neutral effect on ΔFMD, while patients in the control group experienced a non-significant reduction in ΔFMD. No statistically significant differences were observed between the two arms. However, compared to placebo dapagliflozin demonstrated a more beneficial impact on NMD values (19.64 ± 9.71% vs. 15.11 ± 8.44%; p = .038).
Sposito et al. [62]	Brazil	Single-centre RCT (EXCEED-BHS3 Trial)	110 adults with T2D, HbA1c = 7.0–9.0%	Empagliflozin (25 mg once daily) plus evolocumab vs. empagliflozin (control group), randomization 1:1	16 weeks	Subgroup analysis in the SGLT2i arm showed that treatment with empagliflozin was associated with significant improvements in FMD values at 1 and 2 minutes (p < .05).
Tanaka et al. [63]	Japan (16 centres)	Multicentre RCT (EMBLEM Trial)	117 adults with T2D and established CVD	Empagliflozin (10 mg once daily) vs. placebo (control group), randomization 1:1	24 weeks	Treatment with empagliflozin was not associated with significant changes in absolute values of RHI compared to control arm (–0.006 (SD 0.478) in the SGLT2i group and −0.025 (0.454) in the non-SGLT2i group. Also, the adjusted MD in RHI between the two groups was −0.02 (95% CI: −0.199 to 0.158, p = .821)

ADDENDA-BHS2: assessment of dapagliflozin effect on diabetic endothelial dysfunction of brachial artery-Brazilian heart study 2; BP: blood pressure; BW: body weight; CI: confidence interval; CVD: cardiovascular disease; DBP: diastolic blood pressure; DEFENCE: dapagliflozin effectiveness on vascular endothelial function and glycaemic control; EDIFIED: effects of dapagliflozin on endothelial dysfunction in type 2 diabetes with established ischemic heart disease; eGFR: estimated glomerular filtration rate; EXCEED-BHS3 Trial: EXpanded Combination of Evolocumab plus Empagliflozin on Diabetes Trial; FMD: flow-mediated dilation; HbA1c: haemoglobin A1c; MD: mean difference; NMD: nitroglycerin-mediated dilation; RCT: randomized control trial; RF: risk factor; RHI: reactive hyperaemia index; SBP: systolic blood pressure; SGLT2i: sodium-glucose cotransporter 2 inhibitors; T2D: type 2 diabetes.

Table 3. Summary of observational studies and RCTs assessing the effects of SGLT-2 inhibitors on indices of arterial stiffness.

Study ID	Country	Type of study	Population (main characteristics)	SGLT2 inhibitor	Follow-up	Main outcomes
Patoulias et al. [66]	Greece	Single-centre, single-arm, observational prospective cohort study	46 adults with T2D receiving stable medication for T2D and hypertension	Empagliflozin (16 patients) or dapagliflozin (30 patients)	10 months	Treatment with either empagliflozin or dapagliflozin was not associated with significant improvements neither in PWV (p = .65), nor in other markers of arterial stiffness, like AIx (p = .99).
Katakami et al. [67]	Japan (22 out-patient clinics)	Multicentre RCT (UTOPIA trial) sub-analysis	340 adults with T2D and HbA1c = 6.0–9.0% without history of established CVD, evaluation of brachial-ankle PWV was obtained in 154 patients (80 in the tofogliflozin group and 74 in the non-SGLT2i group)	Tofogliflozin (20 mg once daily) vs. non-SGLT2i standard of care (control group), 1:1 randomization	104 weeks	Treatment with tofogliflozin was associated with significant improvements in mean, right and left brachial-ankle PWV compared to control group (–104.7 cm/s, 95% CI: [–177.0 to –32.4]; p = .005, –109.3 cm/s, 95% CI: [–184.3 to –34.3]; p = .005 and –98.3 cm/s, 95% CI: [–172.6 to –24.1]; p = .01, respectively), even after adjusting for classical CVD RFs.
Kourtidou et al. [68]	Greece	Cross-sectional study	40 adults with T2D (15 patients in the SGLT2i arm 25 patients in the non-SGLT2i group)	n/a	–	Compared to patients receiving other antidiabetic agents, treatment with SGLT2i was associated with lower Aix (21.9 ± 11.3 vs. 29.7 ± 12%; p < .05), decreased AIx@75 (21.3 ± 10.9 vs. 32.6 ± 11.3%, p < .005), but it was not associated with significant changes in other indices of arterial stiffness (PWV) and subclinical atherosclerosis (CCA-IMT).
Karalliedde et al. [69]	United Kingdom	Single-centre RCT	33 adults with T2D and eGFR >60 mL/min and residual microalbuminuria after maximum tolerated RAS inhibition	Dapagliflozin (10mg once daily) vs. placebo as an add-on therapy to ramipril (10 mg once daily), randomization 1:1	24 weeks	Treatment with dapagliflozin was not associated with significant improvements in mean aortic PWV compared to control group (9.06 ± 1.91 m/s at baseline, 9.13 ± 2.03 m/s after 24 weeks, mean change = –0.5 m/s, 95% CI: [–1 to 2]; p = .84 in the SGLT2i group vs. 9.88 ± 2.12 m/s at baseline, 10.0 ± 1.84 m/s after 24 weeks, mean change = 0.12 m/s, 95% CI: [–0.89 to 1.13]; p = .81 in the control group).
Bosch et al. [70]	Germany	Single-centre, double-blind, cross-over RCT, post hoc analysis	58 adults with T2D, and HbA1c = 6.5–10.0% and eGFR >60 mL/min	Empagliflozin (25 mg once daily) vs. placebo	6 weeks	Treatment with SGLT2i was associated with significant improvements in arterial stiffness indices like central SBP (113.6 ± 12.1 vs. 118.6 ± 12.9 mmHg, p < .001), and central pulse pressure (39.1 ± 10.2 vs. 41.9 ± 10.7 mmHg, p = .027) compared to control group.
Papado-poulou et al. [71]	Greece	Single-centre, double-blind RCT	85 adults with T2D treated with one or combination therapy of non-SGLT2i antidiabetic agents	Dapagliflozin (10 mg once daily) vs. placebo, randomization 1:1	12 weeks	Treatment with dapagliflozin was associated with significant reductions in 24 h HR-adjusted AIx and with a significant difference in change of estimated 24-h PWV (–0.16 ± 0.32 vs. 0.02 ± 0.27; p = .007) comparing to placebo group.
Hong et al. [72]	Korea	Single-centre, retrospective observational study	140 adults with T2D and obesity without history of established CVD	Dapagliflozin (10 mg once daily) vs. metformin (control group)	6 months	Treatment with dapagliflozin for 6 months was not associated with significant improvements either in aorta or in extremities PWV values. However, subgroup analysis demonstrated that treatment with dapagliflozin was associated with significant reduction in aortic PWV (6.76 ± 1.51 m/s vs. 7.33 ± 1.48 m/s at baseline, p < .01) only among participants who lost BW.
Hidalgo Santiago et al. [73]	Spain	Single-centre, Prospective Observational Study	32 adults with T2D	Dapagliflozin (10 mg once daily)	12 months	Treatment with dapagliflozin led to significant reduction in carotid-femoral PWV (–9.1 m/s, 95% CI [8.4 to 10.1] vs. –9.65 m/s, 95% CI [8.75 to 11.2]; p = .02).
Solini et al. [74]	Italy	Pilot study	26 adults with T2D without history of established CVD	Dapagliflozin (10 mg QD) vs. hydrochlorothiazide (12.5 mg QD) (control group)	2 days	Compared to control group, treatment with SGLT2i significantly increased FMD (2.8 ± 2.2 vs. 4.0 ± 2.1%, p < .05), and significantly decreased aortic PWV (10.1 ± 1.6 to 8.9 ± 1.6 m/s, p < .05) even after adjustments for BP.
Striepe et al. [75]	Germany	Single-centre, double-blind, crossover RCT	76 adults with T2D	Empagliflozin (25 mg once daily) vs. placebo (control group)	6 weeks	Treatment with empagliflozin was associated with significant reductions in ambulatory 24-hour central SBP (p = .059), central DBP (p = .001) and significant difference in PWV (–0.08 ± 0.35 m/s, p = .016) compared to control group.
Bechlioulis et al. [76]	Greece	Single-centre, single-blind, crossover RCT	62 adults with T2D with HbA1c >7%, without a known history of HF	Empagliflozin (25 mg once daily) vs. liraglutide (titrated gradually to 1.8 mg once daily) randomization 1:1, after 3 months SGLT2i was added to the GLP-1 arm and vice versa.	9 months	The differences between the SGLT2i and GLP1-RA groups in ΔPWV (p = .812 and p = .436, respectively) and ΔAIx (p = .740 and p = .870) were not statistically significant neither at 3 nor at 9 months. The differences between the SGLT2i and GLP1-RA groups in ΔPWV and ΔAIx were not statistically significant for the total population of the study comparing baseline measurements with those after 9 months.

AIx: augmentation index; BP: blood pressure; BW: body weight; CI: confidence interval; CVD: cardiovascular disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FMD: flow-mediated dilation; HbA1c: haemoglobin A1c; HR: heart rate; MD: mean difference; PWV: pulse wave velocity; RAS: renin angiotensin system; RCT: randomized control trial; RF: risk factor; RHI: reactive hyperaemia index; SBP: systolic blood pressure; SGLT2i: sodium-glucose cotransporter 2 inhibitors; T2D: type 2 diabetes.

41.9 ± 10.7 mmHg, p = .027) compared to control group, indicating that empagliflozin possibly affects beneficially the vessels partially through anti-inflammatory pathways [70]. In addition, a single-centre double-blind RCT conducted in Greece demonstrated that treatment with dapagliflozin was associated with significant reductions in 24 h HR-adjusted AIx and with a significant difference in change of estimated 24-h PWV (–0.16 ± 0.32 vs. 0.02 ± 0.27; p = .007) compared to placebo group [71]. Similar were the findings of a prospective observational study from Spain involving 32 adults with T2DM administered dapagliflozin for 1 year. Treatment with dapagliflozin improved arterial stiffness, as it led to significant reduction in carotid-femoral PWV (–9.1 m/s, 95% CI: [8.4–10.1] vs. –9.65 m/s, 95% CI: [8.75–11.2]; p = .02) [73]. Besides, one of the earlier pilot studies conducted in the field, Solini et al., demonstrated that compared to control group, treatment with SGLT2 inhibitors only for two days significantly improved both endothelial function and arterial stiffness by increasing FMD (2.8 ± 2.2 vs. 4.0 ± 2.1%, p < .05), and reducing PWV (10.1 ± 1.6 to 8.9 ± 1.6 m/s, p < .05), even after adjusting for confounding factors like BP [74].

On the other hand, a small single-centre RCT from United Kingdom demonstrated that treatment with dapagliflozin as an add-on therapy to ramipril in T2DM patients with eGFR >60 mL/min and residual microalbuminuria was not associated with significant improvements in mean aortic PWV compared to control group (9.06 ± 1.91 m/s at baseline, 9.13 ± 2.03 m/s after 24 weeks, mean change = –0.5 m/s, 95% CI: [–1 to 2]; p = .84 in the SGLT2i group vs. 9.88 ± 2.12 m/s at baseline, 10.0 ± 1.84 m/s after 24 weeks, mean change = 0.12 m/s, 95% CI: [–0.89 to 1.13]; p = .81 in the control group) [69]. According to a single-centre retrospective observational study from Korea, treatment with dapagliflozin for 6 months was not associated with significant improvements either in aorta or in extremities PWV values [72]. However, subgroup analysis demonstrated that treatment with dapagliflozin was associated with significant reduction in aortic PWV (6.76 ± 1.51 m/s vs. 7.33 ± 1.48 m/s at baseline, p < .01) only among participants who lost BW [72], indicating that BW loss is probably one of the main underlying mechanisms related to CVD protection of SGLT2 inhibitors administration.

A recent meta-analysis conducted by Patoulias et al. synthesizing data from 6 studies and 452 subjects showed that antidiabetic treatment with SGLT2i compared to non-SGLT2i group was associated with a non-significant reduction in PWV (MD = –0.14 m/s, 95% CI [–0.31 to 0.03], I^2 = 63%, p = .11) [77]. Notably, subgroup analysis including only T2DM patients (excluding HFrEF patients) demonstrated that treatment with SGLT2 inhibitors was associated with a significant reduction in PWV (MD = –0.17 m/s, 95% CI: [–0.31 to –0.04], I^2 = 0%, p = .01) [77]. Also, in their meta-analysis, pooling data from five studies, Wei et al. reached similar findings, as it was shown that treatment with SGLT2 inhibitors did not lead to significant changes in PWV measurements compared to controls (standardized MD: 0.11, 95% CI: [–0.15 to 0.37]; p = .4) [64].

SGLT2 inhibitors and epicardial adipose tissue

It has been previously described that EAT has atherogenic properties [78], as it has been associated with the progression of the SA and clinical manifestations of CVD mainly the coronary artery disease [79,80]. Only a few studies have investigated the possible impact of SGLT2 inhibitors on EAT (Table 4). According to a single-centre RCT conducted in Japan, treatment with dapagliflozin for 6 months was associated with significant reduction in EAT volume measured by CT and this improvement was greater in the SGLT2i arm compared to the control group (mean change from baseline in EAT volume = –16.4 ± 8.3 vs. 4.7 ± 8.8 cm^3, p = .01) [83]. In addition, a small observational study among 15 adults with T2D demonstrated that canagliflozin was associated with significant reductions in EAT thickness assessed by echocardiography at 3 months, as well as at 6 months compared to baseline [84].

Similar were the findings from two small single-centre, single-arm, pilot studies conducted in Japan [85,86]. The first one showed that 12-week treatment with luseogliflozin was associated with significant decrease of EAT volume measured by MRI compared to baseline (117 [96–136] cm^3 to 111 [88–134] cm^3, p = .048) and this reduction was strongly correlated with the attenuation of systematic inflammation evaluated by CRP (r = 0.493, p = .019) [85]. The second pilot study also demonstrated that treatment with ipragliflozin for 12 weeks was associated with significant decrease of EAT volume measured by MRI compared to baseline (from 102 [79–126] cm^3 to 89 [66–109] cm^3, p = .008) [86]. Notably, according to single-centre RCT from USA, SGLT2 inhibitors show a beneficial profile also in non-diabetic patients with HFrEF [81]. Indeed, treatment with empagliflozin significantly reduced EAT volume evaluated by MRI (–5.14 mL, 95% CI: [–8.36 to –1.92]) compared to control group (–0.75 mL, 95% CI: [–3.57 to 2.06]; p < .05) [81]. The beneficial effect of SGLT2 inhibitors on EAT volume was confirmed by a recent meta-analysis pooling data

Table 4. Summary of observational studies and RCTs assessing the effects of SGLT-2 inhibitors on EAT thickness.

Study ID	Country	Type of study	Population (main characteristics)	SGLT2 inhibitor	Follow-up	Main outcomes
Requena-Ibáñez et al. [81]	USA	Single-centre RCT (EMPA-TROPISM) sub-analysis	62 adults with HFrEF, without history of T2D	Empagliflozin (10 mg once daily) vs. placebo, randomization 1:1	6 months	Treatment with empagliflozin significantly reduced EAT volume evaluated by MRI (−5.14 mL, 95% CI: [−8.36 to −1.92]) compared to control group (−0.75 mL, 95% CI: [−3.57 to 2.06]; $p < .05$), and PWV (−0.58 cm/s, 95% CI: [−0.92 to −0.25] in the SGLT2i arm vs. 0.60 cm/s, 95% CI: [0.14–1.06] in the control group; $p < .01$).
Hiruma et al. [82]	Japan	Single-centre RCT (ASSET study)	44 adults with T2D and HbA1c = 6.0–10.0%	Empagliflozin (10 mg once daily) vs. sitagliptin (50 mg once daily), randomization 1:1	12 weeks	Treatment with empagliflozin was not associated with significant reductions in pericardial, epicardial and paracardial fat content compared to control group.
Sato et al. [83]	Japan	Single-centre RCT	40 adults with T2D and established CAD	Dapagliflozin (10 mg once daily) vs. non-SGLT2i antidiabetic treatment, randomization 1:1	6 months	Treatment with dapagliflozin was associated with significant reduction in EAT volume measured by CT and this improvement was greater in the SGLT2i arm compared to control group (mean change from baseline in EAT volume = −16.4 ± 8.3 vs. 4.7 ± 8.8 cm^3, $p = .01$).
Yagi et al. [84]	Japan	Single-centre observational prospective cohort study	15 adults with T2D	Canagliflozin (100 mg once daily)	6 months	Treatment with canagliflozin was associated with significant reductions in EAT thickness assessed by echocardiography at 3 months (8.1 ± 2.3 mm, $p < .01$), as well as at 6 months (7.3 ± 2.0 mm, $p < .001$) compared to baseline (9.3 ± 2.5 mm).
Bouchi et al. [85]	Japan	Single-centre, single-arm, pilot study	19 adults with T2D, HbA1c = 6.5–9.0% and BMI >25 kg/m^2	Luseogliflozin (2.5 mg once daily, titrated up to 5 mg)	12 weeks	Treatment with luseogliflozin for 12 weeks was associated with significant decrease of EAT volume measured by MRI compared to baseline (from 117 [96–136] cm^3 to 111 [88–134] cm^3, $p = .048$). The decrease of EAT volume was correlated with the attenuation of systematic inflammation evaluated by CRP ($r = 0.493$, $p = .019$).
Fukuda et al. [86]	Japan	Single-centre, single-arm, pilot study	19 adults with T2D, HbA1c = 6.5–9.0% and BMI < 25 kg/m^2	Ipragliflozin (50 mg once daily)	12 weeks	Treatment with ipragliflozin for 12 weeks was associated with significant decrease of EAT volume measured by MRI compared to baseline (from 102 [79–126] cm^3 to 89 [66–109] cm^3, $p = .008$).

BMI: body mass index; BW: body weight; CI: confidence interval; CAD: coronary artery disease; CT: computed tomography; EAT: epicardial adipose tissue; HbA1c: haemoglobin A1c; HFrEF: heart failure with reduced ejection fraction; MD: mean difference; MRI: magnetic resonance imaging; RCT: randomized control trial; SGLT2i: sodium-glucose cotransporter 2 inhibitors; T2D: type 2 diabetes.

from 8 studies and 221 patients, which demonstrated that SGLT2 inhibitors significantly reduced EAT thickness (standardized MD = −0.552, 95% CI: [−0.79 to −0.32]; $I^2 = 67.6\%$, $p < .001$) [87].

Conclusions

Despite the advantages of SGLT2 inhibitors for CV health are well known, there have been ongoing debate regarding the impact of these agents on markers of SA, endothelial function and arterial stiffness. Although the results of observational and randomized trials are extremely diverse, they all converge to the fact that SGLT2 inhibitors' antiatherosclerotic effect is not sufficiently potent to halt the development of atherosclerosis in individuals with or without T2DM. The underlying processes and potential positive effects of SGLT2i on primary and secondary CVD prevention by reducing early atherosclerosis development should be further investigated in the future.

Author contributions

Panagiotis Stachteas: conception and design, analysis and interpretation of the data, drafting and revising of the paper; Paschalis Karakasis: drafting and revising of the paper; Dimitrios Patoulias: conception and design, drafting and revising of the paper; Francesco Clemenza: critical revision of the paper; Nikolaos Fragakis: revising of the paper critically for intellectual content; Manfredi Rizzo: conception and design, revising of the paper critically for intellectual content. All authors have read and approved the final version of the manuscript to be published. All authors agree to be accountable for all aspects of the work.

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Data availability statement

This is a review article analysing secondary data, so data sharing is not applicable.

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