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State-of-the-Art Review

Sodium-glucose cotransporter 2 inhibitors and atherosclerosis

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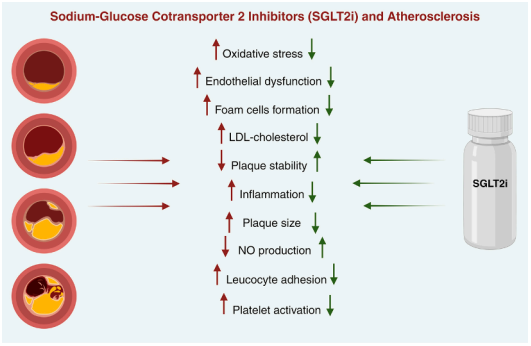
GRAPHICAL ABSTRACT



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ABSTRACT

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have emerged as a promising therapeutic class in cardiovascular disease. This review synthesizes clinical and preclinical evidence on their effects on atherosclerosis, arterial stiffness and related conditions, including dyslipidemia, coronary artery disease, peripheral artery disease, and stroke. The atheroprotective advantages of SGLT2i are attributed to multiple mechanisms, including modulation of inflammatory pathways, improvements in vascular function, and reductions in oxidative stress, in addition to enhanced glycemic control, weight reduction, antihypertensive, and antifibrotic effects. Recent studies highlight their minimal adverse effects and compatibility for combination therapies, further expanding their clinical applications. SGLT2i have redefined the landscape of cardiovascular treatment through their extensive range of benefits, offering significant promise in optimizing outcomes for patients with atherosclerotic cardiovascular disease. By setting new standards of care and maintaining a favorable safety profile, these agents

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continue to advance the paradigm of cardiovascular disease management. While definitive conclusions require further investigation, SGLT2i have become serious contenders in the argument for antiatherosclerotic effects, with accumulating evidence suggesting their positive influence.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains one of the most prevalent causes of morbidity and mortality worldwide [1]. ASCVD may manifest as coronary artery disease (CAD), peripheral artery disease (PAD) or stroke, while arterial stiffness is recognized as a powerful prognostic marker of cardiovascular (CV) risk and mortality [1,2]. Diabetes mellitus has been associated with CV disease through multiple mechanisms, including hyperglycemia and insulin resistance, chronic inflammation, hypertension, dyslipidemia, obesity etc. [3]. Sodium-glucose co-transporter 2 inhibitors (SGLT2i) were originally developed as glucose-lowering agents for type 2 diabetes mellitus (T2DM) but were later shown to have life-saving effects on patients suffering from heart failure (HF) and chronic kidney disease (CKD), irrespective of diabetic status. These cardiometabolic benefits, evidenced in large randomized controlled trials (RCTs), have sparked interest in their potential role in atherosclerosis prevention and treatment [4].

SGLT2i exert their glucose-lowering effect by targeting SGLT2, a protein exclusively situated in the luminal membrane of the proximal tubule's S1 and S2 segments, tasked with the reabsorption of roughly 1 mol of filtered glucose per day. SGLT1, a protein of the same family, is predominantly present in the brush border of the small bowel and less predominantly in the renal cortex, having a minor role in natriuresis [5] (Fig. 1). Beyond their glucose-lowering effects, SGLT2i have shown pleiotropic effects in animal models, such as reducing inflammation, promoting vascular remodeling, delaying vascular aging, and offering systemic cardiometabolic benefits [6].

This review is the first to comprehensively integrate preclinical and clinical evidence on the role of SGLT2i in ASCVD and its manifestations, including CAD, PAD, stroke, and arterial stiffness, while also uniquely examining their drug-drug interactions with anti-atherosclerotic medications and potential adverse effect profiles. By providing a concise and clinically relevant synthesis, this review aims to equip physicians with a clear understanding of the CV benefits and considerations of SGLT2i therapy.

2. Mechanisms linking atherosclerosis to SGLT2i

2.1. Anti-inflammatory and immune-modulatory effects

According to animal studies, SGLT2i exhibit anti-inflammatory properties by suppressing the release of inflammatory cytokines and impeding leukocyte adhesion to endothelial cells and their migration into the vascular intima (Table 1). Empagliflozin, in particular, effectively reduces inflammation by lowering markers such as tumor necrosis factor-alpha (TNF-α), monocyte chemoattractant protein-1, and interleukin-6 (IL-6) [7]. Moreover, empagliflozin, dapagliflozin and ipragliflozin decrease foam cell formation and aggregation by downregulating macrophage proliferation [8,9]. Atherosclerosis progression is further promoted by cytokine activation mediated through the NOD-like receptor protein 3 (NLRP3) inflammasome, and dapagliflozin has been shown to inhibit its activity [10].

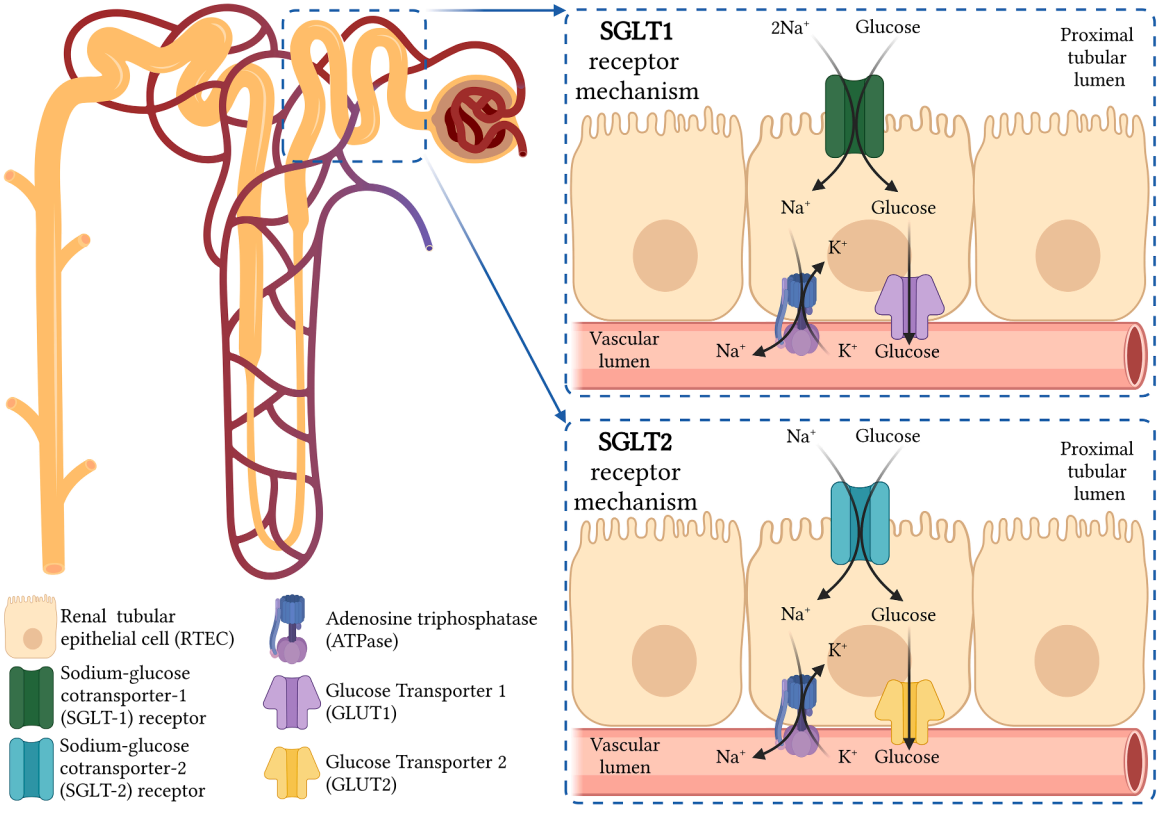

Fig. 1. SGLT1 and SGLT2 receptor mechanisms of glucose reabsorption and natriuresis (created with BioRender.com).

Table 1
Key molecular mechanisms and effects of SGLT2i on atherosclerosis.

Mechanism	Molecular pathway	Biological effects
Anti-inflammatory effects	Decreased action of TNFa, IL-6, MCP-1, and NLPR3 inflammasome	Reduced foam cell formation and aggregation
Immune modulation	Cytokine suppression	Reduced leukocyte adhesion and migration into the vascular intima
Autophagy regulation	Activation of AMPK, GSK3β, SIRT3; inhibition of mTOR	Reduced oxidative stress and balanced autophagy
Cellular senescence downregulation	AMPK activation, PLD-1 suppression	Reduced senescent cell burden
Endothelial function improvement	Increased NO, inhibition of Na-K exchange, downregulation of senescence-associated genes	Vasodilation
Vascular smooth muscle modulation	Inhibition of VSMC proliferation and DNA synthesis	Reduced neointimal proliferation and plaque formation
Atheromatous plaque stabilization	Decreased macrophage accumulation, platelet aggregation and cholesterol crystal deposition	Enhanced plaque stability

Abbreviations: AMPK: AMP-activated protein kinase, GSK3β: glycogen synthase kinase 3 beta, IL-6: interleukin-6, MCP-1: monocyte chemoattractant protein-1, mTOR: mammalian target of rapamycin, NLPR3: NOD-like receptor protein 3, NO: nitric oxide, PLD-1: programmed death ligand-1, SIRT3: sirtuin 3, TNFα: tumor necrosis factor alpha, VSMC: vascular smooth muscle cell.

2.2. Autophagy

Autophagy is a physiological process by which cells degrade and recycle intracellular organelles and molecules to maintain homeostasis. It can be upregulated in response to pathological states and diseases [11]. Recent studies suggest that SGLT2i are able to restore the autophagic balance in affected tissues. Preclinical evidence suggests that empagliflozin and dapagliflozin modulate regulators of autophagy, including the AMP-activated protein kinase (AMPK)–mechanistic target of rapamycin (mTOR) signaling pathway, glycogen synthase kinase 3 beta (GSK3β), and sirtuin 3 axes. AMPK activation acts synergistically with GSK3β to inhibit mTOR and promote autophagy, while SIRT3 enhances mitochondrial autophagy and reduces oxidative stress. Through these mechanisms, they can promote autophagy in dysregulated tissues [12–14]. Nevertheless, hyperactive autophagic degradation may occur promoting atheromatic plaque rupture, in some cases, while SGLT2i may also regulate and prevent this maladaptive response [12,15].

2.3. Cellular senescence

The aging process of cardiomyocytes and cardiac stem cells is accelerated by CV risk factors, including diabetes, largely driven by chronic inflammation, oxidative stress, accumulation of senescent cells, and metabolic disturbances. Cellular senescence contributes to myocardial fibrosis and promotes the development of HF. Preclinical evidence has demonstrated that canagliflozin reduces senescent cell burden and associated markers in CV tissues. Canagliflozin was demonstrated to upregulate AMPK, which in turn reduces programmed cell death ligand 1 and allows for T-cells to attack and eliminate senescent cells. Interestingly, when tested against insulin, canagliflozin exhibited a senolytic effect, whereas insulin promoted pro-senescence pathways [16]. Moreover, in some cases, a hyperactive autophagic flux may occur, with empagliflozin restoring the balance [17].

2.4. Plaque stability and vascular remodeling

Endothelial cells play a critical role in maintaining vascular stability and in preventing thrombogenesis. Endothelial dysfunction, characterized by endothelial cell senescence, elevated microparticle release, decreased nitric oxide (NO) generation, and oxidative stress, is fundamental in atherosclerosis development [18].

SGLT2i attenuate endothelial dysfunction by reversing the heightened expression of senescence genes, reducing oxidative stress and by promoting vasodilation [6]. Vasodilation may occur through increased NO formation and inhibition of the sodium-potassium exchange in the myocardium [19].

Dapagliflozin was shown to reduce the size and burden of atheromatous plaques of the aortic root [9]. In terms of atherosclerotic plaque stability, empirical evidence indicates that dapagliflozin and ipragliflozin attenuate macrophage accumulation, diminish cholesterol crystal deposition, and inhibit platelet aggregation [6].

Empagliflozin has demonstrated efficacy in stabilizing plaques and improving endothelial function, while also modulating mTOR complex 1 signaling [20]. Importantly, it inhibits vascular smooth muscle cell (VSMC) proliferation by reducing DNA synthesis, thereby counteracting neointimal formation and plaque growth. Additionally, empagliflozin and linagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i), exert a synergistic effect in genetically type 1 diabetic (T1DM) mice, leading to reduced neointimal formation following endothelial injury [21].

2.5. Metabolic and systemic cardiovascular effects

Beyond their direct anti-atherosclerotic actions, SGLT2i also improve various CV risk factors by reducing glycemia independently of insulin levels, correcting dyslipidemia by decreasing serum cholesterol, promoting weight loss and uric acid excretion and normalizing blood pressure (Fig. 2) [19].

In addition to these systemic effects, empagliflozin enhances ketone production and alleviates cardiac and perivascular fibrosis [6]. Notably, SGLT2i also increase erythropoiesis and hematocrit levels, possibly through suppression of hepcidin and ferritin [22].

These multi-faceted mechanisms highlight the therapeutic potential of SGLT2i in atherosclerosis and atherosclerotic diseases. Nevertheless, while the beneficial properties of SGLT2i on atherosclerosis have been demonstrated in animal studies (Table 2), validation in clinical trials is crucial. While preclinical studies present compelling evidence for SGLT2i in reducing atherosclerosis, results are not always translated in human trials. Additionally, whether SGLT2i can sustain long-term improvements in plaque stability or prevent acute CV events in diverse populations remains to be determined.

3. Preclinical evidence

3.1. Dyslipidemia

Free fatty acids and TRG (triglyceride-rich lipoproteins) are synthesized through the process of lipogenesis in the liver and adipose tissue, while their breakdown is mediated through lipolysis when fasting. Animal studies have provided evidence that empagliflozin and dapagliflozin may activate lipolysis and attenuate lipogenesis through various mechanisms [14,27,41].

Experimental evidence from various animal models demonstrates consistent findings. In high-fat diet-fed mice, SGLT2i administration led to reductions in hepatic lipogenesis, liver steatosis, and cholesterol accumulation. Oxidative stress and monocyte infiltration were also lowered [27–29]. Empagliflozin treatment similarly reduced serum cholesterol, triglycerides, and liver fat accumulation in diabetic mouse models. Pro-inflammatory cytokines such as IL-6 and TNF-α, were decreased when combined with linagliptin [14,30]. Dapagliflozin was also shown to influence lipid metabolism by promoting the utilization and breakdown of free fatty acids through increased beta-oxidation. Additionally, it may affect lipid absorption through mobilization and diversion of the lipids away from the adipose tissue [42].

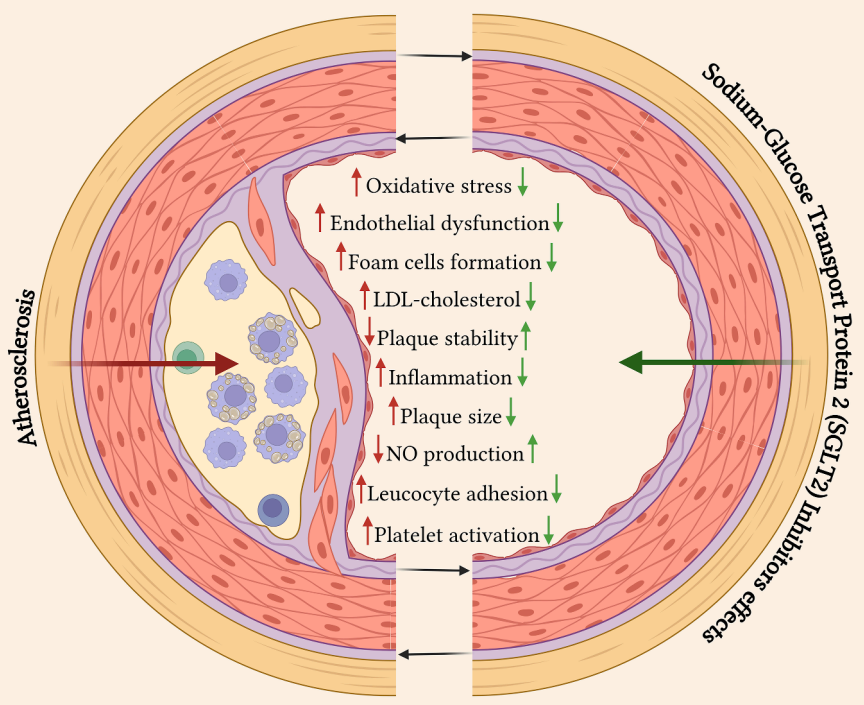

Fig. 2. Sodium-glucose co-transporter-2 inhibitors effects on atherosclerosis (created with BioRender.com).

3.2. *Arterial stiffness*

Existing evidence regarding a possible role of SGLT2i on attenuation of arterial stiffness is quite controversial. Nonetheless, several preclinical studies have shown compelling data on SGLT2i-mediated protection from arterial wall stiffening through different direct mechanisms. These include the upregulation of nitric oxide synthase, the downregulation of pathways involved in the production of reactive oxygen species and proinflammatory cytokines, the increase of circulating vascular progenitor cells, and the attenuation of VSMC proliferation [31,43].

3.3. *Coronary artery disease*

Research on animal studies has provided clear evidence of empagliflozin's effect in downregulating SGLT2 receptors in ischemic territories, thereby reducing the ischemic area [44]. The process of reducing ischemic territory is thought to involve two distinct phases: initially, an acute phase marked by modulation of reactive oxygen species, reduction in ionic exchange, and enhancement of cardiac energy production and utilization via the AMPKα pathway. Subsequently, a delayed phase follows, characterized by anti-inflammatory effects, increased glucose uptake, and heightened production of signal transducer and activator of transcription 3 as a cardioprotective response to ischemia. These two phases have been suggested to serve as the main components of the mechanism of ischemic territory reduction [45]. Further supporting these results, in a study conducted by Zhong et al., sotagliflozin drastically reduced the ischemic area on post-MI murine models and attenuated apoptosis [36].

The beneficial role of empagliflozin in reducing death rates has also been explored in animal models. In a study by Santos-Gallego et al., empagliflozin reduced left ventricular systolic pressure post-MI in non-diabetic pigs, through the modulation of the neurohormonal response, preventing cardiac remodeling and fibrosis [46]. Similarly, canagliflozin was shown to reduce infarct size in non-diabetic rats after 4 weeks of treatment. Dapagliflozin, when administered 15 min before ischemia in Wistar rats, not only reduced infarct size but also decreased the prevalence of arrhythmias and improved systolic function [32,35].

3.4. *Peripheral artery disease*

In a study conducted by Nalugo et al. using murine models, the impact of canagliflozin on diabetic mice was investigated. The research demonstrated that canagliflozin induced lower limb hypoperfusion, impaired angiogenesis, and delayed wound healing. These findings substantiate the previously reported increased risk of amputation observed in patients with T2DM undergoing treatment with canagliflozin [39]. Conversely, in another study of murine diabetic mice experiencing hind-limb ischemia, empagliflozin showed a beneficial effect by decreasing ischemic area and promoting revascularization [38]. Furthermore, a preclinical study conducted by Yang et al. provided evidence that dapagliflozin facilitates angiogenesis and accelerates wound healing [37].

3.5. *Cerebrovascular disease*

Recent preclinical studies suggest that SGLT2i, including canagliflozin, empagliflozin, and dapagliflozin, may improve stroke recovery. Canagliflozin has been shown to reduce infarct size and enhance neurobehavioral outcomes in rodent models following stroke [47]. Empagliflozin appears to aid stroke recovery in T2DM mice by reducing glycemia and oxidative stress, while dapagliflozin supports neurogenesis by increasing immature neurons and synaptic density in the brain. However, it is important to note that these findings are currently limited to preclinical studies [40,48].

4. Clinical evidence

4.1. *Dyslipidemia*

The evidence concerning the impact of canagliflozin, empagliflozin and dapagliflozin on serum cholesterol levels is inconsistent. While some researchers suggest that these medications lower serum cholesterol,

Table 2
Impact of SGLT2 inhibitors on atherosclerosis, dyslipidemia, coronary artery disease, peripheral artery disease and stroke in animal models.

Condition	Author, Year	Type of SGLT2i	Animal model	Control, Dose	Key Findings
Atherosclerosis	[10]	Dapagliflozin	ApoE(-/-) T2DM mice (n = 40), C57BL/6 J non-T2DM mice (n = 6)	STZ; HFD; Dapagliflozin 1 mg/kg or vehicle for 12 weeks.	Improved plaque stability, decreased IL-1β, IL-18, NLRP3 formation, suppressed macrophage infiltration.
	[23]	Dapagliflozin	ApoE (-/-) Irs2(+/-) mice	HFD; Dapagliflozin 3 mg/kg (n = 22) or vehicle (n = 21) for 6 weeks	No effect on atherosclerotic lesion or macrophage infiltration.
	[24]	Empagliflozin	ApoE(-/-) C57BL/6J-ApoEtm1Unc mice	HFD; Empagliflozin 10 mg/kg (n = 10); vehicle (n = 10) for 10 weeks	Slowed atherosclerotic lesion evolution in empagliflozin group.
	[8]	Empagliflozin	ApoE(-/-) C57BL/6 J T2DM mice	STZ; Western diet; Empagliflozin 20 mg/kg or vehicle for 12 weeks	Decreased intra-plaque lipid accumulation, endothelial dysfunction in empagliflozin group.
	[25]	Empagliflozin	ApoE(-/-) mice	Western diet; Empagliflozin 10 mg/kg or water for 12 weeks	Decreased TC, LDL-c, TRG, atherosclerosis.
	[26]	Ipragliflozin	Male C57BL/6 J wild mice	Western diet; Ipragliflozin 10 mg/kg or vehicle for 10 weeks	Decreased macrophage accumulation and fibrosis.
Dyslipidemia	[27]	Dapagliflozin	Male NIH mice	HFD; Dapagliflozin 25 mg/kg for 4 weeks	Decreased lipogenesis and liver steatosis.
	[28]	Dapagliflozin	Male C57BL/6 T2DM mice	Normal diet (n = 6), HFD and low-dose STZ (n = 6); Dapagliflozin 100 mg/kg for 12 weeks	Decreased cholesterol accumulation, oxidative stress.
	[29]	Dapagliflozin, Phlorizin	Ldlr(-/-) C57BL6 T2DM mice	STZ; HFD; Phlorizin 400 mg/kg bid or Dapagliflozin 25 mg/kg or vehicle for 4 weeks	Decreased monocytes, atherosclerotic plaque size in phlorizin and dapaglifozin groups.
	[14]	Empagliflozin	ApoE(-/-) mice	HFD; Empagliflozin 10 mg/kg (n = 8) or vehicle (n = 8) for 5 weeks	Decreased cholesterol, TRG and lipogenesis in empagliflozin group.
	[30]	Empagliflozin	Neonatal male C57BL/6 mice	STZ; HFD; 4 groups (n = 6): Linagliptin 10 mg/kg or empagliflozin 10 mg/kg or linagliptin empagliflozin or vehicle for 4 weeks	Liver TG, IL-6, TNFa reduced in linagliptin, empagliflozin+linagliptin groups.
Arterial stiffness	[31]	Empagliflozin	Aged male C57BL/6 J mice	Empagliflozin 14 mg/kg (n = 29), standard chow (n = 29) for 6 weeks	Decrease in arterial stiffness, endothelial dysfunction in empagliflozin group.
Coronary artery disease	[32]	Dapagliflozin	Wistar I/R rats	4 groups (n = 48): pre-ischemia (Dapagliflozin 1 mg/kg 15 min before ischemia), ischemia (Dapagliflozin 1 mg/kg 15 min into ischemia), reperfusion (Dapagliflozin 1 mg/kg at onset of reperfusion), and control (saline)	Decreased infarct size, arrhythmias, enhanced systolic function in pre-ischemia group.
	[33]	Dapagliflozin	Male C57BL/6 MI mice	4 groups: Sham+Veh, MI+Veh, Sham+Dapagliflozin 10 mg/kg, MI+Dapagliflozin 10 mg/kg	Improved fibrosis post-MI in MI+dapagliflozin group.
	[34]	Dapagliflozin	ApoE(-/-) T2DM mice with RCA stenosis	TS; Normal diet (n = 116); HFD and low-dose STZ (n = 100)	Reduced intra-plaque lipid accumulation, serum TRG.
	[35]	Canagliflozin	Male Zucker diabetic fatty fa/fa rats	HFD; Canagliflozin 100 mg/kg or vehicle for 4 weeks	Reduced infarction size in diabetic and non-diabetic rats in canagliflozin group.
	[36]	Sotagliflozin	Male Sprague-Dawley rats	3 groups: sham, MI+saline, MI+sotagliflozin 10 mg/kg	Reduced hypertrophy, infarct size post-MI in sotagliflozin group in 14 days.
Peripheral artery disease	[37]	Dapagliflozin	Male C57BL/6 HLI mice	Dapagliflozin 1 mg/kg or saline for 2 weeks	Decreased fibrosis, enhanced angiogenesis in dapagliflozin group.
	[38]	Empagliflozin	Male C57BL/6 T2DM HLI mice	HFD; STZ; Empagliflozin 10 mg/kg+DMSO or DMSO every 3 days for 3 weeks	Increased revascularization, decreased ischemic injury in empagliflozin group.
	[39]	Canagliflozin	Wild type mice, db/db mice	Canagliflozin 200 mg/kg or regular chow for 8 weeks	Impaired ischemic tissue recovery, impaired perfusion in diabetic mice.
Stroke	[40]	Empagliflozin	C57BL6J T2DM mice	4 groups (n = 48); Non-T2DM: tMCAO (n = 15), Sham (n = 5) Control: methylcellulose (n = 7), Empagliflozin 10 mg/kg (n = 7) T2DM: tMCAO (n = 30), Sham (n = 10) Control: methylcellulose, (n = 12), Empagliflozin 10 mg/kg (n = 13)	Increased pericyte density, improved stroke recovery in T2DM mice. No effect on non-T2DM mice.

Abbreviations: ApoE(-/-): Apolipoprotein E-knockout, DMSO: Dimethyl sulfoxide, HFD: high-fat diet, HLI: hind limb ischemia, I/R: ischemia-reperfusion, IL-1β: Interleukin 1 beta, IL-18: Interleukin 18, IL-6: Interleukin 6, Irs2: insulin receptor substrate 2, LDL-c: low-density lipoprotein cholesterol, Ldlr: low-density lipoprotein receptor, MI: myocardial infarction, NLRP3: Nod-like receptor protein 3, RCA: right coronary artery, STZ: Streptozotocin, TC: total cholesterol, TG: triglycerides, TNFα: tumor necrosis factor-alpha, tMCAO: transient middle cerebral artery occlusion, TRG: triglycerides, TS: transverse section, T2DM: Type 2 Diabetes Mellitus, Veh: vehicle, WT: wild type.

others argue that the increased lipolysis might actually raise blood cholesterol levels by providing more substrate for cholesterol synthesis (Fig. 3) [49,50]. In a study by Ji et al., dapagliflozin in T2DM patients led to increases in total cholesterol (TC), LDL-c, and HDL-c compared to placebo, while TRG were significantly reduced, particularly in the 5 mg cohort, after 24 weeks [51]. In another study by Taheri et al., HDL-c was increased in the empagliflozin patient group, while changes in TRG, LDL-c and TC were insignificant [52]. Similar results were observed with luseogliflozin in a study by Hajika et al. involving diabetic patients [53]. Furthermore, studies indicate that results may differ according to the dose administered, between Asian and non-Asian cohorts, as well as, between fasting and non-fasting subjects. Interestingly, tests conducted in non-fasting conditions have shown more accurate results, with non-fasting subjects exhibiting reduced cholesterol levels alongside increased fecal cholesterol excretion (Table 3) [41,51,104]. Still, in the 2021 in the Polish lipid guidelines, the experts suggested the double role of glucagon-like peptide-1 (GLP-1) receptor agonists and SGLT2i, not only as very effective anti-diabetic drugs, but also improving (or at least not interfering with) the therapy of atherogenic dyslipidemia [105].

4.2. Arterial stiffness

Based on this evidence, several clinical studies have shown a significant impact of SGLT2i on various measures of arterial stiffness, such

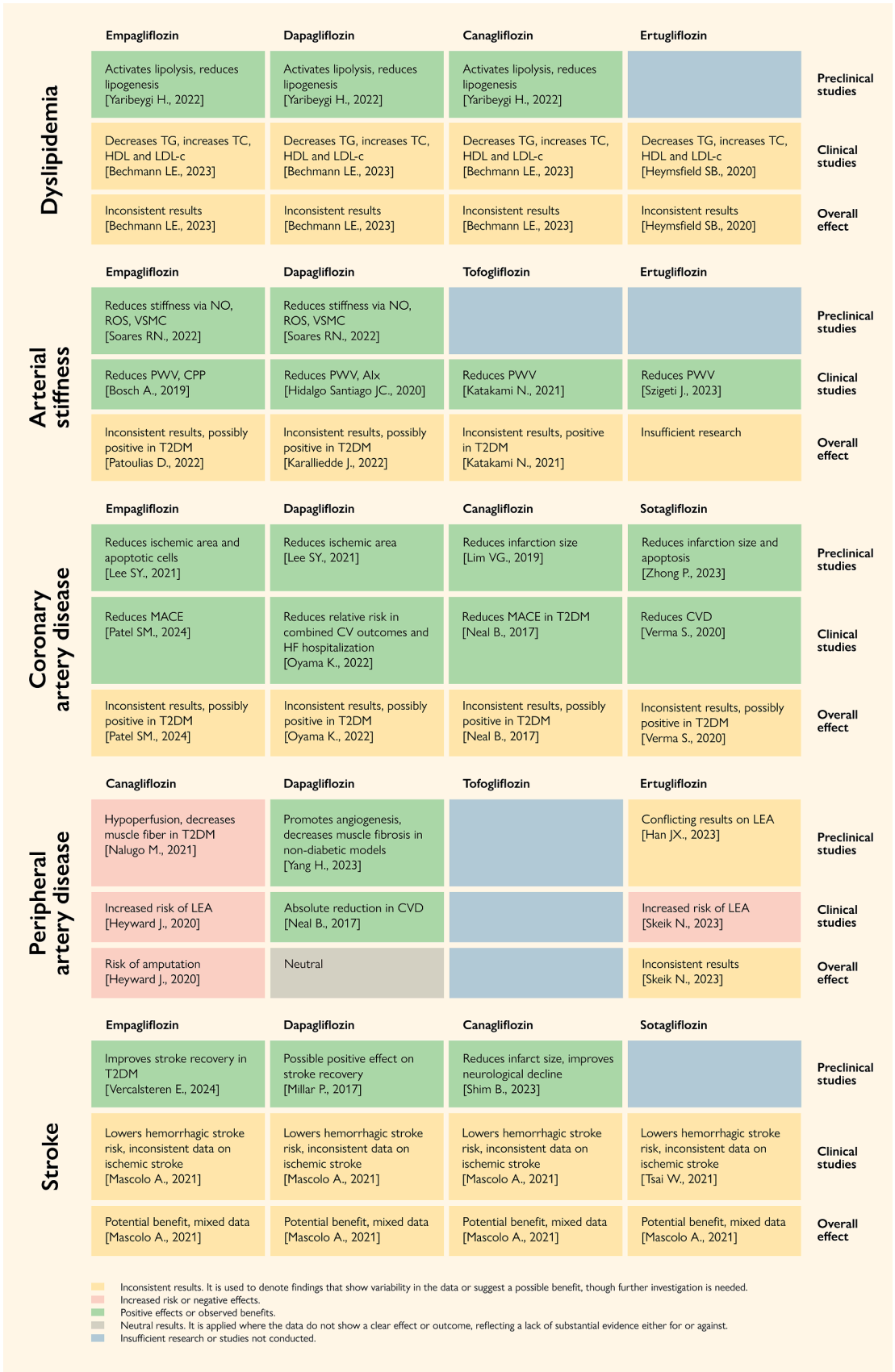

Fig. 3. Comparative analysis of the SGLT2i in dyslipidemia, arterial stiffness, coronary artery disease, peripheral artery disease and stroke.

Table 3
Clinical studies on the effects of SGLT2 inhibitors on dyslipidemia, arterial stiffness, coronary artery disease, peripheral artery disease, and stroke.

Condition	Author, Year	Type of SGLT2i	Therapy Type	Control, Dose	Study Design	Population	Key Findings
Dyslipidemia	[54]	Dapagliflozin	Monotherapy	Dapagliflozin ($n = 31$)	Retrospective Study	$n = 31$, T2DM	Decreases in TC by 17.6 mg/dL, LDL-c by 13.4 mg/dL, TRG by 25.9 mg/dL in 6 months.
	[51]	Dapagliflozin	Monotherapy	Placebo ($n = 132$), Dapagliflozin 5 mg ($n = 128$), Dapagliflozin 10 mg ($n = 133$)	Randomized, blinded, prospective study	$n = 393$, T2DM	Dapagliflozin increased TC, HDL-c, and LDL-c vs placebo; TRG significantly decreased in the 5 mg group in 24 weeks.
	[52]	Empagliflozin	Combination therapy	Placebo, Empagliflozin 10 mg	Randomized clinical trial EMPA-CARD trial	$n = 77$, T2DM, CAD (42 empagliflozin, 35 placebo)	HDL-c increase in empagliflozin group in 26 weeks. Minimal decrease in TC, LDL-c, TRG.
	[53]	Luseogliflozin	Monotherapy	Luseogliflozin 2,5 mg ($n = 25$)	Open-label prospective study	$n = 25$, T2DM	TRG, remnant-like particle cholesterol reduced, HDL-c increased in 24 weeks.
	[55]	Canagliflozin	Monotherapy	Metformin 500 mg ($n = 30$), Canagliflozin 100 mg ($n = 45$)	Open-label, non-randomized, prospective study	$n = 75$, T2DM	HDL-c increase in canagliflozin group in 12 weeks. Negligible decrease in TC and LDL-c.
Arterial stiffness	[56]	Dapagliflozin	Combination therapy	Ramipril 10 mg ($n = 16$), Dapagliflozin 10 mg + Ramipril 10 mg ($n = 17$)	Randomized clinical trial	$n = 33$, T2DM, CKD	No changes in Ao-PWV in 24 weeks.
	[57]	Dapagliflozin	Combination therapy	Dapagliflozin 10 mg ($n = 32$)	Prospective observational study	$n = 32$, T2DM	Marked reduction in VPc-f in 12 months.
	[58]	Dapagliflozin	Combination therapy	Hydrochlorothiazide, 12.5 mg ($n = 10$), Dapagliflozin 10 mg ($n = 16$)	Prospective observational study	$n = 26$, T2DM	Decrease in PWV, increase in flow-mediated dilation in 2 days in dapagliflozin group.
	[59,60]	Empagliflozin	Monotherapy or combination therapy	Placebo ($n = 271$), Empagliflozin 10 mg ($n = 276$), Empagliflozin 25 mg ($n = 276$)	Post-hoc analysis of a randomized, double blind clinical trial EMPA-REG BP trial	$n = 823$, T2DM, HTN	Reductions in SBP, DBP, PP in empagliflozin groups, insignificant reduction in AASI.
	[61]	Empagliflozin	Monotherapy	Placebo, Empagliflozin 25 mg	Randomized, double blind clinical trial	$n = 58$, T2DM	Reduction in arterial stiffness in 4 weeks in empagliflozin group.
	[2]	Empagliflozin/ Dapagliflozin	Combination therapy	Empagliflozin 10 mg ($n = 16$), Dapagliflozin 10 mg ($n = 30$)	Prospective observational study	$n = 46$, T2DM	No modifications in PWV, AIx, PP in 24 weeks.
	[62]	Luseogliflozin	Combination therapy	Luosegliflozin 2,5 mg ($n = 47$)	Prospective observational study	$n = 47$, T2DM	CAVI unmodified in 12 weeks.
	[63,64]	Canagliflozin	Monotherapy	Placebo ($n = 192$), Canagliflozin 100 mg ($n = 195$), Canagliflozin 300 mg ($n = 197$).	Post-hoc analysis of a randomized, double blind clinical trial CANTATA-M trial	$n = 584$, T2DM	Reductions in PP, MAP, double product in 26 weeks in canagliflozin groups.
	[65]	Tofogliflozin	Combination therapy	Conventional treatment ($n = 74$), Tofogliflozin 20 mg ($n = 80$)	Prospective, randomized, open-label study	$n = 154$, T2DM	Significant decrease in baPWV in 104 weeks after adjusting for CV factors.
	[66]	Dapagliflozin/ Empagliflozin/ Ertugliflozin	–	Dapagliflozin ($n = 14$), Empagliflozin ($n = 25$), Ertugliflozin ($n = 1$)	Prospective observational study	$n = 40$, T2DM	Significant decrease in PWV in 3 months and 3,3 years.
Coronary artery disease	[67]	Dapagliflozin	Combination therapy	Placebo ($n = 1998$), Dapagliflozin 10 mg ($n = 2019$)	Randomized, double blind clinical trial DAPA-MI trial	$n = 4017$, MI, LV systolic dysfunction or Q-wave MI	No changes in HF hospitalizations and CV death. Cardiometabolic benefits.
	[68]	Dapagliflozin	Monotherapy or combination therapy	Placebo ($n=$ 8578), Dapagliflozin 10 mg ($n = 8582$)	Randomized, double blind clinical trial DECLARE-TIMI 58 trial	$n = 17,160$, T2DM, ASCVD or with risk factors	Decreased MACE in previous MI. HF hospitalization and CV death rate decreased in dapagliflozin group.
	[69]	Dapagliflozin	Monotherapy or combination therapy	Placebo ($n = 2152$), Dapagliflozin ($n = 2152$)	Randomized, double blind clinical trial DAPA-CKD trial	$n = 4304$, CKD	Composite of renal outcomes or CV death decreased in dapagliflozin group.
	[70,71]	Dapagliflozin	Monotherapy or combination therapy	Placebo ($n = 2371$), Dapagliflozin ($n = 2373$)	Randomized, double blind clinical trial DAPA-HF trial	$n = 4744$, HFrEF	Composite of HF exacerbation or CV death reduced in dapagliflozin group.
	[72]	Dapagliflozin	Combination therapy	Placebo ($n = 3132$), Dapagliflozin ($n = 3131$)	Randomized, double blind clinical	$n = 6263$, HFmrEF, HFpEF	Composite of HF exacerbation or CV death

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Table 3 (*continued*)

Condition	Author, Year	Type of SGLT2i	Therapy Type	Control, Dose	Study Design	Population	Key Findings
					trial DELIVER trial		reduced in dapagliflozin group.
	[73]	Dapagliflozin	Combination therapy	DAPA-free (n = 645), Dapagliflozin 10 mg (n = 141)	Retrospective analysis of a prospective observational study	n = 786, AMI undergoing PCI	Lower MACE incidence, including HF, nonfatal MI, and URR in dapagliflozin group in 23 months.
	[74]	Dapagliflozin	Combination therapy	Vildagliptin 50–100 mg (n = 22), Dapagliflozin 10 mg (n = 21)	Randomized, double blind study	n = 43, T2DM, CAD	BMI, SBP, Hs-TnT, decreased in dapagliflozin group in 6 months.
	[75]	Empagliflozin	Combination therapy	Placebo (n = 3262), Empagliflozin 10 mg (n = 3260)	Randomized, double blind clinical trial EMPACT-MI trial	n = 6522, AMI at risk of HF	Risk of first HF hospitalization, death due to HF reduced in empagliflozin group in 810 days.
	[76]	Empagliflozin	Combination therapy	Placebo (n = 48), Empagliflozin 10 mg (n = 49)	Randomized, double blind clinical trial EMPA-HEART CardioLink-6 trial	n = 97, T2DM, CAD	Decrease in LV mass in empagliflozin group in 6 months. No NT-proBNP modifications.
	[77]	Empagliflozin	Combination therapy	Placebo (n = 50), Empagliflozin 10 mg (n = 46)	Randomized, double blind clinical trial EMBODY trial	n = 96, T2DM, AMI	Insignificant modifications in HRV, HRT.
	[78]	Empagliflozin	Monotherapy or combination therapy	Placebo (n = 3305), Empagliflozin (n = 3304)	Randomized, double blind clinical trial EMPA-KIDNEY trial	n = 6609, CKD	Composite of renal outcomes or CV death reduced in empagliflozin group.
	[79]	Empagliflozin	Combination therapy	Placebo (n = 1867), Empagliflozin (n = 1863)	Randomized, double blind clinical trial EMPEROR-Reduced	n = 3730, HFrEF	Composite of HF admission or CV death reduced in empagliflozin group.
	[80,81]	Empagliflozin	Monotherapy or combination therapy	Placebo (n = 2991), Empagliflozin (n = 2997)	Randomized, double blind clinical trial EMPEROR-Preserved trial	n = 5988, HFpEF	Composite of HF admission or CV death reduced in empagliflozin group.
	[82]	Empagliflozin	Combination therapy	Placebo (n = 265), Empagliflozin (n = 265)	Randomized, double blind clinical trial EMPULSE trial	n = 530, AHF	Reduced death, HF events, improved KCCQ score in empagliflozin group.
	[83]	Empagliflozin	Combination therapy	Empagliflozin 25 mg	Prospective, open-label study	n = 20, T2DM, CAD	Enhanced anti-aggregant effect, reduced platelet reactivity in empagliflozin group in 10 days.
	[84]	Empagliflozin	Combination therapy	Placebo (n = 239), Empagliflozin 10 mg (n = 237)	Randomized, double blind clinical trial EMMY	n = 476, AMI undergoing PCI	Decreased NT-proBNP, improved LVEF in empagliflozin group in 26 weeks.
	[85]	Empagliflozin	Combination therapy	Placebo (n = 38), Empagliflozin 25 mg (n = 37)	Randomized, double blind clinical trial EMPT-ANGINA trial	n = 75, T2DM, RA	Amelioration of angina and functional capacity in empagliflozin group in 8 weeks.
	[86]	Empagliflozin	Combination therapy	Conventional therapy (n = 13), Empagliflozin (n = 15)	Randomized open-label study	n = 28, T2DM, undergoing DES implantation	Neointimal hyperplasia attenuation in empagliflozin group in 12 months.
	[87,88]	Canagliflozin	Combination therapy	Primary prevention: Placebo (n = 1447), Canagliflozin (n = 2039), secondary prevention: placebo (n = 2900), Canagliflozin (n = 3756)	Randomized, double blind clinical trial CANVAS program	n = 10,142, T2DM, CAD or risk factors	Composite of nonfatal MI and CV death, HF hospitalization decreased in canagliflozin groups.
	[89]	Canagliflozin	Combination therapy	Placebo (n = 2199), Canagliflozin (n = 2202)	Randomized, double blind clinical trial CREDENCE trial	n = 4401, T2DM, CKD	Composite of renal outcomes or CV death decreased in canagliflozin group. Lower risk of CV death and AMI.
	[90]	Canagliflozin	Combination therapy	Conventional treatment (n = 63), Canagliflozin (n = 63)	Retrospective open-label study	n = 126, T2DM, AMI undergoing PCI	Decreased NT-proBNP, cTnT, improved LVEF in canagliflozin group in 3 months.
	[91]	Ertugliflozin	Combination therapy	Placebo (n = 2747), Ertugliflozin 5 mg (n = 2752), Ertugliflozin 15 mg (n = 2747)	Randomized, double blind clinical	n = 8246, T2DM, ASCVD	No significant benefit.

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Table 3 (*continued*)

Condition	Author, Year	Type of SGLT2i	Therapy Type	Control, Dose	Study Design	Population	Key Findings
					trial VERTIS CV		
	[92]	Sotagliflozin	Combination therapy	Placebo (n = 5292), Sotagliflozin (n = 5292)	Randomized, double blind clinical trial SCORED trial	n = 10,584, CKD, T2DM	Composite of HF admissions and CV death was reduced in sotagliflozin group.
Peripheral artery disease	[93]	Dapagliflozin	Combination therapy	PAD: Placebo (n = 502), Dapagliflozin 10 mg (n = 521), non-PAD: placebo (n = 8067), Dapagliflozin 10 mg (n = 8053)	Randomized, double blind clinical trial DECLARE-TIMI 58 trial	n = 17,160, T2DM, (PAD=1025)	No modifications in limb events/amputations.
	[94]	Dapagliflozin	Combination therapy	PAD: antidiabetics (n = 26), Dapagliflozin (n = 35), non-PAD: Dapagliflozin (n = 36)	Retrospective study	n = 97, T2DM, (PAD=61)	Statistically insignificant TcPO2 reduction in PAD patients in dapagliflozin group.
	[95]	Dapagliflozin, Canagliflozin, Empagliflozin	Monotherapy	GLP-1RA (n = 5149,826), DPP-4i (n = 5448,225), Other ADD (n = 51,954,353), No ADD (n = 5571,840), SGLT-2i (n = 5169,739)	Retrospective study	n = 3293,983, T2DM	LLA risk lower in SGLT2i vs. DPP-4i and other ADD groups, risk similar with incretins.
	[96]	Canagliflozin	Combination therapy	PAD: Placebo (n = 1452), Canagliflozin (n = 1707), Non-PAD: Placebo (n = 5094), Canagliflozin (n = 6290)	Post-hoc analysis of 2 randomized, double blind clinical trials CANVAS Program and CREDENCE trial	n = 14,543, T2DM (PAD=3159)	MACE reduction in PAD patients in canagliflozin groups in 2,5 years. No adverse limb events.
Stroke	[97]	Empagliflozin	Combination therapy	DDP-4i (n = 39,072), Empagliflozin (n = 39,072)	Retrospective study	n = 440,317, T2DM	Similar stroke risk in both groups in 3 years.
	[98]	Empagliflozin	Combination therapy	Placebo (n = 2333), Empagliflozin 10 mg (n = 2345), Empagliflozin 25 mg (n = 2342)	Randomized, double blind clinical trial EMPA-REG OUTCOME trial	n = 7020, T2DM, high CV risk	Similar outcomes in both groups for stroke and TIA risk in 3,1 years.
	[68]	Dapagliflozin	Monotherapy or combination therapy	Placebo (n = 8578), Dapagliflozin 10 mg (n = 8582)	Randomized, double blind clinical trial DECLARE–TIMI 58 trial	n = 17,160, T2DM	Similar outcomes in both groups for stroke risk in 4,2 years.
	[99]	Dapagliflozin	Monotherapy	DDP-4i (n = 30,681), Dapagliflozin 10 mg (n = 10,227)	Retrospective study	n = 40,908, T2DM	Insignificant risk reduction for stroke in dapagliflozin group.
	[100]	Empagliflozin/ Dapagliflozim	Combination therapy	Empagliflozin (n = 6869), Dapagliflozin (n = 5812)	Retrospective study	n = 12,681, T2DM	Similar outcomes for risk of ischemic stroke in both groups in 1 year.
	[101]	Canagliflozin	Combination therapy	Primary prevention: Placebo (n = 1447), Canagliflozin (n = 2039), secondary prevention: placebo (n = 2900), Canagliflozin (n = 3756)	Randomized, double blind clinical trial CANVAS program	n = 10,142, T2DM (previous stroke/ TIA=1958)	No changes in ischemic stroke risk. Possible protective effect on hemorrhagic stroke.
	[102, 103]	Canagliflozin	Combination therapy	Primary prevention: Placebo (n = 1092), Canagliflozin 100 mg (n = 1089), secondary prevention: placebo (n = 1107), Canagliflozin (n = 1113)	Randomized, double blind clinical trial CREDENCE trial	n = 4401, T2DM, CKD	No changes in ischemic stroke risk. Possible protective effect on hemorrhagic stroke in low eGFR.
	[92]	Sotagliflozin	Combination therapy	Placebo (n = 5292), Sotagliflozin (n = 5292)	Randomized, double blind clinical trial SCORED trial	n = 10,584, CKD, T2DM	Reduction in death due to CV causes or stroke.

Abbreviations: AASI: augmentation index, ADD: anti-diabetic drugs, AHF: acute heart failure, AIx: augmentation index, AMI: acute myocardial infarction, Ao-PWV: aortic pulse wave velocity, ASCVD: atherosclerotic cardiovascular disease, baPWV: brachial-ankle pulse wave velocity, CAD: coronary artery disease, CAVI: cardio-ankle vascular index, CKD: chronic kidney disease, CV: cardiovascular, CVD: cardiovascular disease, DBP: diastolic blood pressure, DPP-4i: dipeptidyl peptidase-4 inhibitors, DES: drug-eluting stent, eGFR: estimated glomerular filtration rate, GLP-1RA: Glucagon-like peptide-1 receptor agonists, HDL-c: high-density lipoprotein cholesterol, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, HRT: heart rate turbulence, HRV: heart rate variability, Hs-TnT: high-sensitivity troponin T, HTN: hypertension, LVEF: left ventricular ejection fraction, LDL-c: low-density lipoprotein cholesterol, LV: left ventricular, MAP: mean arterial pressure, MACE: major adverse cardiovascular events, MI: myocardial infarction, NT-proBNP: N-terminal pro B-type natriuretic peptide, PAD: peripheral artery disease, PCI: percutaneous coronary intervention, PP: pulse pressure, PWV: pulse wave velocity, RA: refractory angina, SBP: systolic blood pressure, SGLT-2i: sodium-glucose cotransporter 2 inhibitors, TC: total cholesterol, TCPO2: transcutaneous oxygen pressure, TRG: triglycerides, T2DM: Type 2 Diabetes Mellitus, URR: unplanned repeat vascularization, VPc-f: vascular pulse contour factor.

as pulse wave velocity (PWV), augmentation index (AIx), and central pulse pressure, independent of their glycosuric and blood pressure-lowering effects, in patients with T2DM [2,66]. Noteworthy, similar results emerged with different SGLT2i and with both short-term and mid-term treatment durations. Thus, for instance, in a prospective observational study including 40 patients with T2DM, PWV values improved significantly at 3 months and 3.3 ± 1.3 years of follow-up (from 10.68 ± 1.35 m/s to 10.05 ± 1.40 m/s and 9.96 ± 1.25 m/s, respectively) after starting SGLT2i (14 patients on dapagliflozin, 25 patients on empagliflozin, 1 patient on ertugliflozin) independently from concomitant reduction of blood pressure [66]. Similarly, in a prospective observational study including 32 patients with T2DM, PWV was significantly reduced at 12 months after initiation of dapaglifozin [from 9.65 (8.75–11.2) m/s to 9.1 (8.4–10.1) m/s], independently from concomitant changes in other clinical variables, including glycated hemoglobin (HbA1c) [Santiago JCH, 2020]. Besides, a prospective observational study including 16 patients with T2DM demonstrated that a 2-day treatment with dapaglifozin significantly reduced PWV (from 10.1 ± 1.6 to 8.9 ± 1.6 m/s) possibly due to concomitant oxidative stress reduction [58]. Consistently, according to a subanalysis of a double-blind placebo-controlled RCT including 58 patients with T2DM, a 6-week treatment with empagliflozin was associated with a significant improvement in central pulse pressure (from 41.9 ± 10.7 mmHg to 39.1 ± 10.2 mmHg) with attenuation of inflammation emerging as one of the main drivers of such an effect [61]. Moreover, a single-center, double-blind, placebo-controlled clinical trial involving 85 patients with T2DM revealed that a 12-week regimen of dapagliflozin resulted in a significant reduction in the 24-hour heart rate-adjusted AIx. The study also observed a significant change in the estimated 24-hour PWV, from 0.02 ± 0.27 to –0.16 ± 0.32, independent of concurrent variations in other clinical parameters, including body mass index and HbA1c [106]. Furthermore, a prespecified sub-analysis of the UTOPIA trial, involving 154 patients with T2DM, revealed that tofogliflozin significantly enhanced mean, right, and left brachial-ankle PWV over a 104-week period, compared to conventional antidiabetic treatments. These findings were consistent even after adjusting conventional CV risk factors [65].

However, some inconsistency has emerged from other studies, leading to hypothesizing that concomitant diseases (mainly presence/absence of T2DM and/or concomitant CV risk factors) may crucially affect possible direct effects of SGLT2i on arterial wall. In a 24-week RCT, the addition of dapagliflozin to ramipril in patients with T2DM, an estimated glomerular filtration rate > 60 mL/min/1.73 m^2, and residual microalbuminuria, did not result in a significant enhancement in mean aortic PWV compared to ramipril monotherapy [56]. Moreover, in a retrospective observational study of 140 patients with obesity and T2DM, treatment with dapagliflozin did not result in notable enhancements in PWV at a 6-month follow-up (Table 3) [107].

In addition, different meta-analyses of clinical studies pooling data of mixed populations have not shown any significant impact of SGLT2i on arterial stiffness. In detail, a meta-analysis including data from 5 RCTs with heterogeneous populations reported that treatment with SGLT2i did not lead to significant changes in PWV measurements [108]. Also, a meta-analysis of 6 RCTs including 452 subjects with and without T2DM showed that treatment with SGLT2i was not associated with a significant reduction in PWV in the overall population but it was significant in T2DM patients [2]. More recently, an updated meta-analysis exploring the effect of SGLT2i on PWV and AIx based on pooled data from 12 studies with different comparators (placebo and active treatments), design (RCTs and crossover studies), and populations (diabetic and non-diabetic) showed no evidence of a favorable effect on arterial stiffness indices mediated by these drugs (Fig. 3) [109].

4.3. Coronary artery disease

SGLT2i have demonstrated CV benefits across multiple clinical trials, though their impact on CAD and cardiac death outcomes associated with atherosclerosis has been varied. Notably, the EMPA-REG OUTCOME trial showed that empagliflozin reduced all-cause and CV death in T2DM patients (by 32 % and 36 % accordingly), while the DECLARE-TIMI 58 trial reported a 16 % relative risk reduction in CV death and MI, limited to patients with prior MI [110,111]. Similarly, the CANVAS trials demonstrated canagliflozin's efficacy in reducing major adverse cardiovascular events (MACE) particularly among diabetic patients with prior CV disease [87].

However, more recent studies focused on acute MI populations provide additional insights. The DAPA-MI trial in MI patients (within 10 days of infarction) without T2DM or HF showed favorable outcomes, with dapagliflozin resulting in a 34 % greater clinical benefit than placebo based on a hierarchical composite of CV outcomes, but without significant reductions in CV-related deaths, underscoring the need for further research in these patient groups [67]. In EMPACT-MI, enrolling patients within 14 days of AMI, HF-related mortality and hospitalizations were reduced in T2DM patients, while the EMMY trial including patients as soon as 72 h after percutaneous coronary intervention, noted 15 % reduction in NT-proBNP and improved cardiac function with empagliflozin [75,84]. Further supporting these findings, the SGLT2-I AMI PROTECT trial reported a 43 % reduction in the composite outcome of CV death, recurrent myocardial infarction (MI), and HF hospitalization associated with SGLT2i use in T2DM patients with acute MI [112].

Beyond acute MI settings, evidence from broader CAD populations also highlights SGLT2i benefits. The EMPA-HEART CardioLink-6 trial found that T2DM patients with CAD experienced significant reductions in left ventricular mass independent of blood pressure effects, though NT-proBNP levels remained unchanged [76]. Conversely, in VERTIS CV, which evaluated T2DM patients with ASCVD, no significant reduction in MACE or CV death was indicated [91].

Expanding beyond CAD-focused trials, multiple SGLT2i trials on HF and CKD have also included substantial ASCVD populations, providing broader insights. In DAPA-HF, which enrolled 56 % of patients with ischemic HF, with or without T2DM, dapagliflozin reduced the risk of CV death by 18 % and the composite outcome of hospitalization for HF or CV death by 25 % [70,71]. Similarly, in EMPEROR-Preserved and EMPEROR-Reduced, which included 35 % and 50 % of patients with CAD or ischemic etiology, empagliflozin reduced the composite outcome of CV death or HF hospitalization by 21 % and 25 %, respectively, independent of diabetic status [79–81]. In the DELIVER trial, enrolling 57 % of patients with ASCVD, the composite outcome of worsening HF and CV death showed a 22 % reduction, though the reduction in CV alone did not reach statistical significance [72]. Finally, in EMPULSE, which included 25 % of patients with prior MI and 29 % with prior coronary revascularization, empagliflozin administered in the setting of acute HF or decompensated chronic HF demonstrated a 36 % greater clinical benefit compared to placebo [82].

Further supporting evidence comes from nephropathy-targeted trials. In CREDENCE, which included T2DM patients, approximately 50 % of participants had established CVD. Canagliflozin reduced the combined risk of end-stage kidney disease (ESKD), doubling of serum creatinine, or death from renal or CV causes by 30 %, and was also associated with a 20 % lower risk of CV death and MI [89]. Similarly, among the 37 % of patients with a history of CV included in DAPA-CKD, dapagliflozin reduced the composite outcome of ESKD, a sustained decline in estimated glomerular filtration rate (eGFR) of at least 50 %, or death from renal or CV causes by 39 %. The secondary composite outcome of hospitalization for HF or CV death was reduced by 29 % [69]. 27 % of included cohorts in EMPA-KIDNEY suffered from CV disease; nevertheless, while the composite outcome of CKD progression or CV death revealed a 28 % reduction, the combination of HF admission or CV death did not show a statistically significant reduction [113]. Finally, in the SCORED trial, a large proportion of the recruited population – approximately 68 % – had ASCVD. Sotagliflozin significantly

reduced the primary composite endpoint, comprising HF admissions and urgent visits, or CV death, by 26 % relative to placebo. The original coprimary endpoints; CV death, MI, or stroke, and CV death or HF hospitalization, were also reduced, by 16 % and 23 %, respectively. Nonetheless, CV death alone did not show a statistically significant reduction (Table 3) [92].

Emerging evidence suggests that SGLT2i may also improve prognosis in CAD patients undergoing myocardial revascularization. Hyperglycemia and insulin resistance in this context are associated with perivascular inflammation and thrombogenesis, partially mediated by upregulated SGLT2 receptor expression. Combining surgical treatment with SGLT2i has shown improved cardiac outcomes. For instance, patients with T2DM and ACS undergoing coronary bypass surgery and treated with empagliflozin demonstrated significant reductions in inflammatory markers (interleukin-1, IL-6, and TNF-α), ACS recurrence, MACE and decreases in the number of future revascularizations, leading to improved prognosis [73,114,115]. Additionally, a study by Hashikata et al. reported a reduction in stent reocclusion due to neointimal hyperplasia in T2DM patients treated with empagliflozin [86].

Meta-analyses of SGLT2i trials have consistently shown reductions in MACE, largely attributed to decreases in CV death. These effects have been observed across different patient populations and appear to be independent of diabetic status. Zelniker et al. reported that MACE reduction was confined to patients with established ASCVD, with no clear benefit observed in non-ASCVD cohorts. The Nuffield Department of Population Health Renal Studies Group highlighted reductions in CKD progression and CV death, but did not observe a significant reduction in non-CV mortality [78,116]. Vaduganathan et al. further corroborated these benefits, emphasizing reductions in CV death and hospitalizations for HF, regardless of ejection fraction [117]. Importantly, while the secondary prevention effect of SGLT2i has been demonstrated in multiple trials through reductions in MACE among T2DM patients with established ASCVD, there is no conclusive evidence supporting a primary prevention benefit in individuals without prior CV events [118].

4.4. Peripheral artery disease

The incidence of PAD is rising in correlation with aging and the increasing prevalence of T2DM, with over 200 million individuals globally suffering from PAD, while a 1 % rise in glycated hemoglobin levels has been linked to a 30 % increase in PAD prevalence among patients with diabetes [119,120]. The recent GBD 2023 analysis suggests that PAD has, nowadays, the worst outcomes in morbidity and mortality within all types of ASCVD diseases, with the worst outcomes in CEE countries. A contributing factor is that this condition is frequently underdiagnosed, particularly within cardiological departments, and is often identified at a very late stage, resulting in many cases necessitating surgical interventions [121].

Considering that T2DM increases the risk of PAD through mechanisms such as vascular inflammation, endothelial dysfunction, vasoconstriction, platelet activation, and thrombotic risk, it is anticipated that SGLT2i will be now used increasingly in patients with both PAD and T2DM [122]. Patients with PAD have a significantly higher risk of adverse CV outcomes, including HF admissions, CV death, and all-cause mortality, compared to those without PAD [123].

Regarding safety, early studies showed a correlation between canagliflozin intake and an increased risk of lower extremity amputation (LEA) [124]. Trials, CANVAS and CANVAS-R investigated 10,142 diabetic patients of different age groups, both male and female, with ASCVD or multiple CV risk factors. The results indicated a higher risk of LEA, particularly at the metatarsal and toe levels, in patients treated with canagliflozin compared to placebo [125]. Risk factors identified in these patients included neuropathy, PAD, and a prior history of amputation, while the proposed underlying mechanism is postulated to be hypoperfusion of the lower limb due to excessive hypovolemia owing to polyuria secondary to glycosuria. However, subsequent studies and regulatory reviews have produced mixed findings, leading to the withdrawal of the FDA's black box warning (Fig. 3) [126,127].

Conversely, the VERTIS-CV trial investigating ertugliflozin did not demonstrate any reduction in MACE or CV death. Additionally, a higher incidence of LEA in the groups treated with ertugliflozin was observed, regardless of the dose (Table 3) [128].

Recent data offer reassurance for empagliflozin and dapagliflozin in PAD populations. In a meta-analysis of the EMPEROR trials, empagliflozin reduced CV risk in both PAD and non-PAD patients, with the absolute risk reduction being more pronounced in those with PAD. While patients with PAD experienced higher rates of adverse events and LEA, empagliflozin was not associated with an increased incidence of these complications [123]. In a meta-analysis by Butt et al. of the DAPA-HF and DELIVER trials, dapagliflozin reduced the composite outcome of CV death or HF exacerbation in both PAD and non-PAD patients, with similar relative benefits. Importantly, adverse events were not increased by dapagliflozin therapy compared to placebo, regardless of PAD status [129].

4.5. Cerebrovascular disease

Several studies have focused on investigating the impact of gliflozins on patients with T2DM to elucidate their effects on stroke and its subtypes. These studies extend beyond assessing SGLT2i solely for their capacity to regulate glucose levels in T2DM, considering their potential cerebrovascular benefits, particularly in stroke prevention. Contrary to previous meta-analyses that suggested a higher risk of stroke with SGLT2i, more recent studies indicate neutral effects on ischemic stroke and potential protective effects against hemorrhagic stroke [130–132].

A meta-analysis by Mascolo et al. compared the impact of SGLT2i on the risk of non-fatal stroke with DPP-4i and non-SGLT2i. Gliflozins were associated with a significant reduction in stroke risk compared to both DPP-4i and non-SGLT2i [133]. Furthermore, SGLT2i were associated with a remarkable 50 % reduction in the risk of hemorrhagic stroke when compared to placebo. As for ischemic stroke, current findings remain inconclusive. Some authors support a neutral effect, while other analyses suggest a reduction in stroke risk among patients with CKD and cohorts with T2DM and atrial fibrillation (AFIB), with Chang et al. reporting a 20 % reduction in stroke risk in the latter. Finally, SGLT2i were also associated with a decreased risk of incident dementia in this patient population [134–136]. Adding to this body of evidence, the SCORED trial demonstrated that sotagliflozin reduced non-fatal stroke events by 34 % in this patient group (Table 3) [137].

CKD represents an independent risk factor for stroke, with its pathophysiology involving multiple mechanisms. These mechanisms include increased blood viscosity and arterial wall stiffness mediated by the activation of the renin-angiotensin-aldosterone system, platelet dysfunction, oxidative stress, immune activation, and a notable prevalence of AFIB among affected individuals. The burden of stroke risk is particularly pronounced in younger individuals and women. For example, those under 40 years with end-stage CKD face a risk over 11 times higher compared to their matched counterparts. While the precise mechanism through which altered kidney function affects how SGLT2i impact the risk of stroke remains unclear, it is hypothesized that the blood pressure-lowering effect of gliflozins may play a significant role [102,136]. Additionally, evidence suggests that gliflozins exhibit antihypertensive effects, which may contribute to a reduction in ischemic stroke risk (Fig. 3) [116,126].

5. Drug-drug interactions between SGLT2i and drugs used for atherosclerosis

Atherosclerosis management usually involves a combination of lipid-lowering medication, antithrombotic prophylaxis, and antihypertensive medication. Recently, colchicine has also been proposed due to its anti-inflammatory properties and attenuating effects on atherosclerosis

progression [119,138]. Since the concomitant use of the aforementioned medications and SGLT2i is common, it is important to investigate any possible interactions or relationships between these drugs.

Regarding statins, while there is some evidence supporting an interaction, the extent and clinical significance of this interaction remain unclear, and more research is required to confirm these findings. One proposed mechanism involves the inhibition of transporter proteins, specifically the breast cancer resistance protein (BCRP), which is involved in statin elimination. Canagliflozin may inhibit BCRP, potentially leading to elevated plasma levels of statins and increased statin myotoxicity. Additionally, a second proposed mechanism suggests that the intrinsic myotoxicity of SGLT2i may augment the already well-known myotoxicity of statins. However, the evidence supporting these mechanisms is very limited, with no real clinical relevance, and further studies are needed to fully understand the potential interactions [139, 140]. Thus, for most of the cases statins might be and, in case of indications e.g., for patients with obesity and/or diabetes, should be concomitantly used with SGLT2i treatment with no safety concerns. As far as aspirin, clopidogrel monotherapies or dual combination administered with SGLT2i are concerned, according to Nusca et al., no significant associations were found [141]. Scheen et al. investigated the relationship between gliflozins and valsartan and ramipril highlighting no significant association between these medications [142]. Although interactions between colchicine and SGLT2i have not yet been observed, it is noteworthy that colchicine has exhibited interactions with various CV drugs. Therefore, physicians should remain vigilant regarding potential interactions when prescribing both colchicine and SGLT2i (Fig. 4) [143].

Gliflozins have been associated with a 10 % risk of urogenital fungal infections in women and a 3 % risk in men, while no association with bacterial infections of the genital tract has been observed [144]. Another rare adverse effect is euglycemic diabetic ketoacidosis (DKA), which was previously thought to occur primarily in patients with T1DM and/or insulinopenia undergoing surgery or experiencing stress or illness. In a study conducted by Sarma et al., the incidence of DKA in hospitalized patients was reported to be 0,2 %, a rate comparable to that observed in patients receiving outpatient treatment with SGLT2i [145]. Hypotension may also occur due to osmotic diuresis, as well as acute kidney failure. Cases of Fournier's gangrene have been noted in association with SGLT2i, particularly canagliflozin, in diabetic patients with risk factors such as recurrent urinary tract infections, genital trauma, reversed colostomy, and colon carcinoma, though its incidence is very rare [146]. Additionally, canagliflozin has been associated with a higher risk of fractures and lower leg amputations, a fact that may be explained by its higher SGLT1i capacity (Figure 6) [147,148].

6. Conclusions

Since their emergence, SGLT2i have showcased their multifaceted beneficial effects and uses, ranging from glycemic control to CV, renal protection and beyond. Preclinical studies provide compelling data on SGLT2i mediating anti-inflammatory, vascular remodeling, plaque stabilizing and metabolic benefits. However, clinical translation of these findings remains variable. In CAD, SGLT2i consistently demonstrate reductions in MACE, particularly among patients with established ASCVD, indicating their benefit on secondary prevention, while there is no evidence for significance in primary prevention. For PAD, evidence is mixed; while some agents such as empagliflozin and dapagliflozin show neutral to beneficial effects, others such as canagliflozin raise safety concerns. Cerebrovascular outcomes are similarly complex, with meta-analyses indicating a neutral effect on ischemic stroke but a potential reduction in hemorrhagic stroke risk. The impact of SGLT2i on arterial stiffness is supported by select clinical trials but not further supported by meta-analyses, suggesting the need for further investigation, particularly in diverse populations and comorbidities. Drug-drug interactions with common anti-atherosclerotic agents appear minimal, with limited evidence suggesting possible interactions with statins via transporter modulation and a low risk of clinically significant effects. Adverse events such as genital infections, diabetic ketoacidosis, and rare complications like Fournier's gangrene and bone fractures remain considerations in clinical practice, particularly in high-risk patient groups. In conclusion, while SGLT2i hold promise for their atheroprotective effects, further validation in large-scale, long-term RCTs is essential to fully elucidate their role in atherosclerotic management.

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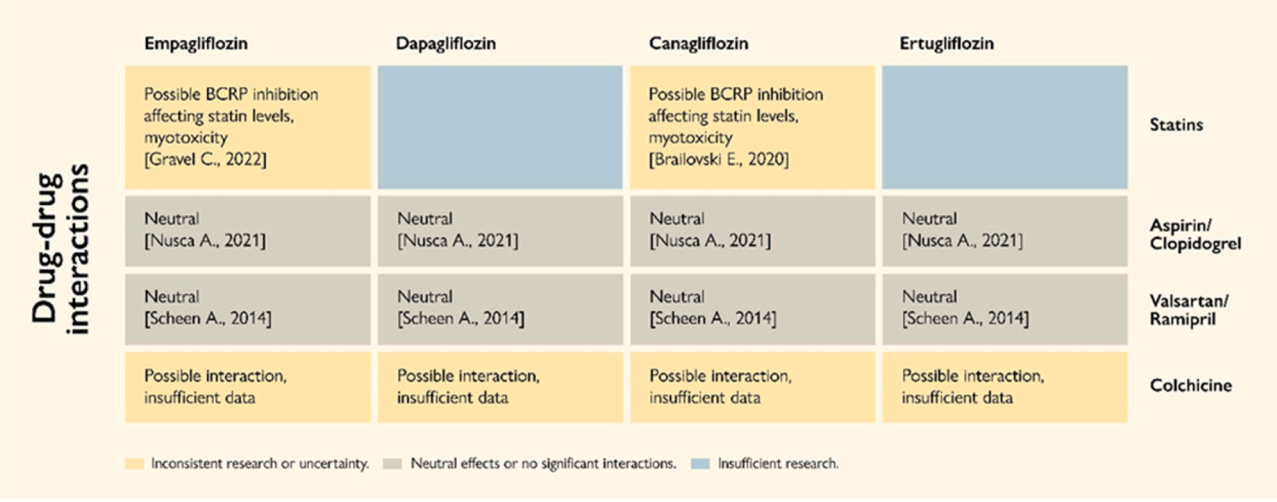

Fig. 4. Drug-drug interactions between SGLT2i and drugs used for atherosclerosis.

CRediT authorship contribution statement

Alexandr Ceasovschih: Methodology, Conceptualization. **Anastasia Balta:** Writing – original draft, Methodology. **Essam Shams Aldeen:** Writing – original draft. **Vanessa Bianconi:** Writing – original draft. **Fotios Barkas:** Writing – review & editing. **Yusuf Ziya Şener:** Writing – review & editing. **Marta Jakubová:** Resources. **Mehmet Birhan Yilmaz:** Validation, Visualization. **Maciej Banach:** Visualization, Validation. **Laurențiu Șorodoc:** Formal analysis, Visualization. **Victoriția Șorodoc:** Project administration.

Declaration of competing interest

Fotios Barkas reports personal research grants from Amgen, Eli Lilly, Novartis and Novo Nordisk; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Novartis, Novo Nordisk, Sanofi, Viatris and Innovis; support for attending meetings and/or travel from Novartis, Novo Nordisk, Sanofi and Viatris, outside the submitted work.

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Alexandr Ceasovschih, Anastasia Balta, Essam Shams Aldeen, Vanessa Bianconi, Yusuf Ziya Şener, Marta Jakubová, Laurențiu Șorodoc and Victoriția Șorodoc declare no competing interests.

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