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Osto, Elena ; Bonacina, Fabrizia ; Pirillo, Angela ; Norata, Giuseppe Danilo

Abstract: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are effective, well-tolerated, and safe glucose-lowering compounds for patients with type 2 diabetes mellitus (T2DM). SGLT2i benefit encompasses protection from heart and kidney failure, independently of the presence of diabetes. In addition, SGLT2i consistently reduce the risk of hospitalization for heart failure and, although with some heterogeneity between specific members of the class, favourably affect the risk of cardiovascular outcomes. The molecular mechanisms underlying the cardiovascular favourable effect are not fully clarified. Studies testing the efficacy of SGLT2i in human cohorts and experimental models of atherosclerotic cardiovascular disease (ASCVD) have reported significant differences in circulating levels and composition of lipoprotein classes. In randomized clinical trials, small but significant increases in low-density lipoprotein cholesterol (LDL-C) levels have been observed, with a still undefined clinical significance; on the other hand, favourable (although modest) effects on high-density lipoprotein cholesterol (HDL-C) and triglycerides have been reported. At the molecular level, glycosuria may promote a starving-like state that ultimately leads to a metabolic improvement through the mobilization of fatty acids from the adipose tissue and their oxidation for the production of ketone bodies. This, however, may also fuel hepatic cholesterol synthesis, thus inhibiting atherogenic lipoprotein uptake from the liver. Long-term studies collecting detailed information on lipid-lowering therapies at baseline and during the trials with SGLT2i, as well as regularly monitoring lipid profiles are warranted to disentangle the potential implications of SGLT2i in modulating lipoprotein-mediated atherosclerotic cardiovascular risk.

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Neutral effect of SGLT2 inhibitors on lipoprotein metabolism: From clinical evidence to molecular mechanisms

Elena Osto [a,b,1], Fabrizia Bonacina [c,2], Angela Pirillo [d,3], Giuseppe Danilo Norata [c,4,*]

[a] Institute for Clinical Chemistry, University Hospital Zurich and University of Zürich, Zurich, Switzerland
[b] Department of Cardiology, Heart Center, University Hospital Zurich and University of Zürich, Zurich, Switzerland
[c] Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy
[d] Center for the Study of Atherosclerosis, E. Bassini Hospital, Cinisello Balsamo, Milan, Italy

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ABSTRACT

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are effective, well-tolerated, and safe glucose-lowering compounds for patients with type 2 diabetes mellitus (T2DM). SGLT2i benefit encompasses protection from heart and kidney failure, independently of the presence of diabetes. In addition, SGLT2i consistently reduce the risk of hospitalization for heart failure and, although with some heterogeneity between specific members of the class, favourably affect the risk of cardiovascular outcomes. The molecular mechanisms underlying the cardiovascular favourable effect are not fully clarified. Studies testing the efficacy of SGLT2i in human cohorts and experimental models of atherosclerotic cardiovascular disease (ASCVD) have reported significant differences in circulating levels and composition of lipoprotein classes. In randomized clinical trials, small but significant increases in low-density lipoprotein cholesterol (LDL-C) levels have been observed, with a still undefined clinical significance; on the other hand, favourable (although modest) effects on high-density lipoprotein cholesterol (HDL-C) and triglycerides have been reported. At the molecular level, glycosuria may promote a starving-like state that ultimately leads to a metabolic improvement through the mobilization of fatty acids from the adipose tissue and their oxidation for the production of ketone bodies. This, however, may also fuel hepatic cholesterol synthesis, thus inhibiting atherogenic lipoprotein uptake from the liver. Long-term studies collecting detailed information on lipid-lowering therapies at baseline and during the trials with SGLT2i, as well as regularly monitoring lipid profiles are warranted to disentangle the potential implications of SGLT2i in modulating lipoprotein-mediated atherosclerotic cardiovascular risk.

1. Introduction

Sodium-glucose cotransporter 2 (SGLT2) is a member of the sodium-glucose cotransporter family located in the early proximal tubule and is responsible for the reabsorption of 80–90% of the glucose filtered by the kidney glomerulus [1,2]. In humans and rodents, renal SGLT2 is mainly expressed in the cortex and specifically in the luminal membrane of the segments S1 and S2 of the proximal tubules [3,4]. Based on its function, the possibility of inhibiting SGLT2 has been investigated as an intriguing opportunity to lower glucose by reducing its reabsorption in proximal tubules and by promoting urinary glucose excretion independently of insulin.

Phlorizin (phloretin-2-B-glucoside) is a natural compound extracted from the root bark of apple trees; initially known for its anti-malarial activity [5], later it was shown to lower plasma glucose levels by inhibiting intestinal and kidney SGLT2 and promoting the excretion of 60–80 g of glucose per day through the urine [6,7]. SGLT2 inhibitors were first developed in Japan in 1996 as analogues of phlorizin (i.e. 4′-dehydroxyphlorizin). In 2000, companion compounds were synthesized with good gastrointestinal absorbance allowing oral

* Correspondence to: Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milan, Italy; Center for the Study of Atherosclerosis, E. Bassini Hospital, Cinisello Balsamo, Milan, Italy.
E-mail address: danilo.norata@unimi.it (G.D. Norata).
[1] https://orcid.org/0000–0001-8196–5696
[2] https://orcid.org/0000–0002-2611–1177
[3] https://orcid.org/0000–0002-2948–6257
[4] https://orcid.org/0000–0002-6081–1257

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administration and devoid of any renal damaging side effects, thus overcoming the poor gastrointestinal absorbance and renal noxious effects of phlorizin [7]. These compounds exerted selective, reversible, and potent inhibition of SGLT2 leading to hypoglycaemic and glycosuric effects in diabetic rodent models [7]. According to these preclinical findings, renal SGLT2 emerged as a very promising therapeutic target for a novel anti-diabetic approach.

Extensive clinical trials have proven the efficacy, tolerability, and safety of different SGLT2 inhibitors (SGLT2i) in lowering plasma glucose and glycated haemoglobin, along with moderate reductions in body weight (on average 1.5–2Kg, placebo-adjusted) which is mainly associated with a decrease in subcutaneous and visceral adipose tissue and lower blood pressure without inducing sympathetic-driven changes in heart rate [8]. Empagliflozin, canagliflozin, and dapagliflozin have been the first SGLT2i approved for the treatment of type 2 diabetes mellitus (T2DM) either as monotherapies or add-on therapy, usually as an adjunct to metformin.

More recently, randomized clinical trials (RCTs) have reported lower rates of major adverse cardiovascular events (MACE) in T2DM patients at high risk of cardiovascular disease (CVD) following the treatment with an SGLT2 inhibitor [9–11]. However, whether the amelioration in the composite cardiovascular outcomes is due to an overall beneficial metabolic effect or it is related to any additional modulatory effect on lipids remains to be elucidated.

This review discusses the available clinical evidence and the potential molecular mechanisms explaining the observed neutral effect of SGLT2i on plasma lipid profile despite the beneficial effect on ASCVD.

1.1. Efficacy of SGLT2i on cardiovascular outcomes in patients with T2DM/metabolic disorders

The relevant impact of SGLT2i on glucose metabolism soon drove the clinical development of these drugs toward the assessment of their cardiovascular efficacy/safety beyond glycaemic control.

The EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) was the first randomized cardiovascular outcome trial conducted in 7020 patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD), in which empagliflozin or placebo was added to standard care [9]. Over a median follow-up of 3.1 years, empagliflozin reduced the occurrence of the primary composite outcome (defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) by 14%. The observed difference in patients treated with empagliflozin was driven by a 38% reduction in death from cardiovascular causes, while no significant between-group differences in the risk of myocardial infarction or stroke were observed [9]. Moreover, empagliflozin reduced the risk of all-cause death by 32% and hospitalization for heart failure (HF) by 35% [9]. Empagliflozin also reduced incident or worsening nephropathy by 39% and incident albuminuria regardless of kidney function status and presence of overt albuminuria. Indeed, trial results were consistent regardless of the age of patients, the presence or absence of HF, and the HF risk at baseline; the risk for HF hospitalization was observed already by the first month of empagliflozin treatment and persisted for the duration of the trial [12]. All these effects were independent of glucose control and were afterwards confirmed in other clinical trials [13–15].

The effect of another SGLT2i, canagliflozin, on cardiovascular outcomes was assessed in the CANVAS program, which enrolled 10,142 patients with T2DM and high cardiovascular risk who were followed for a mean of 3.6 years [10]. Canagliflozin treatment reduced the risk of the primary outcome (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) by 14% and the risk of HF hospitalization by 33% [10]. However, no significant effects were reported on all-cause mortality or when cardiovascular mortality, myocardial infarction, or stroke were considered separately [10].

The DECLARE-TIMI 58 trial enrolled 17160 patients with T2DM who had or were at risk for ASCVD to assess the effect of the SGLT2i dapagliflozin on cardiovascular outcomes [11]. Over a median period of 4.2 years, dapagliflozin was not inferior to placebo with respect to MACE but did not reduce the rate of MACE, although a 27% reduction in the risk of HF hospitalization has been observed, regardless of the ejection fraction (EF) or history of ASCVD or HF [16].

Afterwards, the VERTIS CV trial assessed the cardiovascular effects of another SGLT2i, ertugliflozin, in 8246 patients with T2DM and established ASCVD [17]. After a mean follow-up of 3.5 years, ertugliflozin showed non-inferiority to placebo with respect to MACE. The incidence of death from cardiovascular causes or hospitalization for HF and renal outcomes were not different compared to placebo [17]. Secondary pre-specified analyses showed, however, that ertugliflozin reduced the total number of HF hospitalizations by 30% and the risk of total HF hospitalizations or cardiovascular death by 17% [18].

Overall, a meta-analysis of 6 trials with all 4 different SGLT2i licensed so far (i.e. empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin) highlighted a medication class effect consistent and robust for HF and kidney protection [13]. Likewise, modest and heterogeneous effects of individual drugs on cardiovascular death and atherosclerotic MACE have been evidenced [13].

The reduced risk of HF events in patients treated with an SGLT2i independently of their HF history led to hypothesize favourable cardiovascular effects of SGLT2i beyond glucose control. To test this hypothesis, subsequent randomized controlled trials have assessed the efficacy and safety of dapagliflozin or empagliflozin in patients with HF with reduced ejection fraction (HFrEF, EF $<$40%) with or without T2DM [19,20]. Patients taking SGLT2i had a lower risk of worsening HF, death from cardiovascular causes, or hospitalization for HF than those in the placebo group, regardless of the presence or absence of diabetes [19,20]. Two further large-scale clinical trials have extended these findings also to patients with HF with mildly reduced or preserved ejection fraction, further confirming the cardiovascular benefits of SGLT2i treatment regardless of the presence of T2DM [21,22]. Thus, a class of drugs initially developed as anti-diabetic agents has extended its indication showing protective effects in HF. Furthermore, successful kidney outcome trials support the use of dapagliflozin and empagliflozin for kidney protection regardless of the presence of T2DM [23–25].

1.2. Neutral/adverse effects of SGLT2i on lipid profile and lipoprotein subclasses

The effect of SGLT2i on the reduction of the incidence of cardiovascular events appears to be mainly related to improvements in heart or kidney function in patients with HF or chronic kidney disease (CKD). Indeed, SGLT2i treatment is not always accompanied by a robust reduction in overall CVD mortality, as the occurrence of myocardial infarction or stroke is commonly similar in patients treated with SGLT2i or placebo. An intriguing hypothesis to explain this finding might be related to the limited ability of SGLT2i to influence other cardiovascular risk factors.

A major issue arising from preclinical studies on SGLT2i, indeed, was a potentially unfavourable effect of these drugs on plasma lipid and lipoprotein profile; in particular, LDL-C levels were increased by a small but significant 25%, likely due to reduced LDL catabolism [26]. These findings may be worrisome because of the robust clinical and genetic evidence showing a direct cause-effect relationship between LDL-C levels and the risk of cardiovascular events in patients with and without T2DM.

Two clinical trials with empagliflozin reported small increases in both LDL-C and HDL-C levels (Table 1) [9,27]. A post-hoc analysis of the EMPA-REG OUTCOME trial addressed whether baseline LDL-C levels impacted cardiovascular outcomes in patients treated with empagliflozin (Table 1) [28]. The study found that the beneficial effect of empagliflozin on cardiovascular outcomes was consistent across all categories of LDL-C levels at baseline [28].

Table 1
Lipid profile after SGLT2i therapy in clinical studies.

Clinical studies	Study groups	LDL-C mg/dL [mmol/l]	HDL-C mg/dL [mmol/l]	TG mg/dL [mmol/l]
Haring 2014 [27]	Placebo	95.1 [2.46]	47.2 [1.22]	173.9 [1.96]
	Baseline	95.1 [2.46]	47.2 [1.22]	183.7 [2.07]
	Week 24	92.8 [2.40]	49.5 [1.28]	173.1 [1.95]
	Empagliflozin 10 mg	98.6 [2.55]	52.6 [1.36]	173.1 [1.95]
		4.6 [0.12]	*3.1 [0.08]*	*-9.8 [− 0.11]*
	Baseline	*0.043*	*< 0.001*	*n.s.*
	Week 24	95.9 [2.48]	49.5 [1.28]	163.3 [1.84]
	Difference vs *placebo*	101.7 [2.63]	51.8 [1.34]	159.8 [1.80]
		4.6 [0.12]	*2.3 [0.06]*	*-12.4 [− 0.14]*
	P value	*0.043*	*0.001*	*ns*
	Empagliflozin 25 mg			
	Baseline			
	Week 24			
	Difference vs *placebo*			
	P value			
Bouter 2020 [29]	Before rosuvastatin	100.5 [2.60]	50.3 [1.30]	79.9 [0.90]
		58.0 [1.50]	46.4 [1.20]	71.0[0.80]
		p < 0.01	p = 0.02	p = 0.02
	With rosuvastatin	54.1[1.40]	46.4 [1.20]	79.9 [0.90]
	With dapagliflozin	ns	p = 0.03	ns
Inagaki 2015 [30]	Canagliflozin 100 mg	120.0 [3.10]	53.7 [1.39]	143.6 [1.62]
		118.9 [3.07]	58.0 [1.50]	131.9 [1.49]
	Baseline	*-1.2 [0.03]*	*4.3 [0.11]*	*-11.7 [− 0.13]*
	Week 52	*ns*	*< 0.001*	*0.007*
	Change from baseline	122.1 [3.16]	53.8 [1.39]	152.4 [1.72]
		124.1 [3.21]	58.4 [1.51]	130.7 [1.47]
	P value	*2.1 [0.05]*	*4.7 [0.12]*	*-21.7 [− 0.24]*
	Canagliflozin 200 mg	*0.022*	*< 0.001*	*< 0.001*
	Baseline			
	Week 52			
	Change from baseline			
	P value			
Neal 2017 [10]	Placebo	89 [2.30]	45.5 [1.18]	/
	Baseline	89 [2.30]	47.5 [1.23]	
	Week 52	88 [2.28]	45.5 [1.18]	
	Canagliflozin	93 [2.40]	45.5 [1.18]	
	Baseline	*5.0 [0.13]*	*2.0 [0.05]*	
	Week 52			
	Difference vs *placebo*			

It should be noted, however, that, in the EMPA-REG OUTCOME (but also in other trials), stratified randomization according to baseline LDL-C levels was not included in the trial design. Furthermore, statin use at baseline differed substantially among subgroups of LDL-C, as it was the introduction of lipid-lowering therapy. Therefore, a possible confounding effect of statin use on cardiovascular outcomes cannot be excluded. Of note, adding dapagliflozin 10 mg to rosuvastatin-treated diabetic patients with a well-controlled lipid profile (LDL-C after rosuvastatin: 58 mg/dL, 1.5 mmol/L) did not affect plasma total cholesterol, LDL-C, apoB, or TG levels, and only modestly increased plasma HDL-C (Table 1) [29]. These findings raise a question about the possible underestimated importance of the background lipid-lowering therapy and LDL-C levels at baseline in the interpretation of the effects of SGLT2i treatment on LDL-C. In this small study, for instance, rosuvastatin 10 mg was a standardized treatment for all participants and, at the time of the addition of dapagliflozin, LDL-C levels were optimally controlled [29]. This observation suggests that an SGLT2i-induced increase in LDL-C might not be an issue in a population with optimal lipid-lowering therapy. In the real-world clinical scenario, as reported in large clinical trials, lipid-lowering treatments are not optimally implemented, and less potent statins are commonly used as the first-line approach, coupled with low adherence to therapy. This observation highlights the need for large trials to assess whether the overall lipidemic response to SGLT2 inhibition can be influenced by baseline LDL-C levels as well as the background lipid-lowering therapy. Of note, a study with canagliflozin showed that, although there were no changes in LDL-C levels in the whole study population (Table 1), the subgroup with baseline LDL-C levels < 120 mg/dL (<3.1 mmol/L) showed an increase of LDL-C whereas the subgroup with baseline LDL-C levels > 120 mg/dL (>3.1 mmol/L) had a reduction [30]. Slight increases in LDL-C and HDL-C levels were observed also in the CANVAS program (Table 1) [10].

Different meta-analyses have evaluated the effects of SGLT2i treatment on lipid profile. A meta-analysis of studies in patients with T2DM treated with placebo or canagliflozin 100 mg or 300 mg confirmed the lipid-rising effects of this drug, with canagliflozin 300 mg producing the maximal increases in LDL-C (+6.19 mg/dL, +0.16 mmol/l) and HDL-C (+2.32, +0.06 mmol/L) (Table 2) [31]. Unfortunately, the possible influence of background lipid-lowering medications has not been evaluated. Similar modest raising effects on LDL-C and HDL-C levels were reported in a post hoc analysis of 10 phase 3, 24-week-long placebo-controlled trials of dapagliflozin 10 mg [32] as well as in a post hoc analysis of 3 phase 3 studies of ertugliflozin 5 mg or 10 mg [33] in patients with T2DM (Table 2). A meta-analysis of 34 RCTs with 9154 patients revealed that SGLT2i treatment was associated with an increase

Table 2
Levels of lipids following SGLT2i therapy: data from meta-analyses and post hoc analyses.

Meta-analysis [Ref]	drug	LDL-C Mean difference vs placebo mg/dL [mmol/L]	HDL-C Mean difference vs placebo mg/dL [mmol/L]	TG Mean difference vs placebo mg/dL [mmol/L]
Geng 2022 [31]	Canagliflozin 100	3.87 [0.10]	1.93 [0.05]	/
	Canagliflozin 300	6.19 [0.16]	2.32 [0.06]	
Storgaard 2016 [34]	All	3.48 [0.09]	1.93 [0.05]	-7.99 [− 0.09]
	Canagliflozin	7.35 [0.19]	2.71 [0.07]	-18.64 [− 0.21]
	Dapagliflozin	-5.80 [− 0.15]	3.48 [0.09]	0.00 [0.00]
	Empagliflozin	2.32 [0.06]	1.55 [0.04]	0.00 [0.00]
Sanchez-Garcia 2020 [35]	Canagliflozin	5.03 [0.13]	2.71 [0.07]	-10.65 [− 0.12]
	Dapagliflozin	2.32 [0.06]	2.32 [0.06]	-11.54 [− 0.13]
	Empagliflozin	3.09 [0.08]	1.93 [0.05]	-3.55 [− 0.04]
	Ipragliflozin	3.87 [0.10]	3.88 [0.10]	-17.75 [− 0.20]
	Ertugliflozin	4.25 [0.11]	2.32 [0.06]	-4.44 [− 0.05]
Mukai 2020 [36]	All	3.00 [0.08]	3.36 [0.09]	-16.42 [0.18]5
	Canagliflozin	5.51 [0.14]	3.59 [0.09]	-13.50 [0.15]
	Ipragliflozin	0.78 [0.02]	2.94 [0.08]	-18.97 [0.21]
	Luseogliflozin	3.86 [0.10]	3.67 [0.09]	-13.56 [0.15]
	Empagliflozin	1.36 [0.04]	3.29 [0.08]	-31.02 [0.35]
	Tofogliflozin	4.18 [0.11]	4.10 [0.11]	-8.25 [0.09]
Post hoc analysis [Ref]				
Bays 2017 [32]	Dapagliflozin	4.4 [0.11]	3.8 [0.10]	-2.1 [0.02]
	*Group A	3.4 [0.09]	1.8 [0.05]	-14 [− 0.16]
	*Group B			
Heymsfield 2020 [33]	Ertugliflozin 5 mg	2.0 [0.05]	1.6 [0.04]	-15.7 [− 0.18]
	Ertugliflozin 15 mg	4.3 [0.11]	2.5 [0.06]	-9.9 [− 0.11]

* Group A: patients with elevated triglyceride and reduced HDL-C levels; Group B: reference group

in LDL-C and HDL-C and a decrease in TG levels; when analysed by drug type, the largest effects were seen for canagliflozin (Table 2) [34]. A larger meta-analysis of data from 24,782 patients with T2DM recruited from 48 RCTs confirmed that SGLT2i significantly increase total cholesterol, LDL-C, HDL-C, and non-HDL-C while decreasing TG levels, although this last effect was observed with some drugs (canagliflozin, dapagliflozin, and ipragliflozin) but not others (Table 2) [35]. When analysed in detail, empagliflozin produced the highest increase in total cholesterol (4.25 mg/dL, 0.11 mmol/L), while canagliflozin showed the largest effect in increasing LDL-C (5.03 mg/dL, 0.13 mmol/L) [35]. Similar results were observed in another meta-analysis of 17 RCTs including 4485 Asian diabetic patients (Table 2) [36].

Specific studies aimed at investigating the impact of SGLT2i on lipoprotein subclasses showed for instance that dapagliflozin administered to T2DM patients during a 12-week study was not associated with an increase in LDL-C levels, but rather with a remodelling of LDL particles, resulting in lower levels of the highly atherogenic small dense LDL and higher levels of the less atherogenic large buoyant LDL, an effect that was not observed in patients treated with the dipeptidyl peptidase-4 inhibitor sitagliptin [37]. Moreover, dapagliflozin increased large, cholesterol-rich HDL2-C without affecting the small, cholesterol-poor HDL3-C [37]. Overall, the results of this small study suggest favourable lipoprotein remodelling. However, another small randomized clinical trial in T2DM patients, which tested whether a 12-week treatment with dapagliflozin 10 mg might positively affect HDL particle distribution and function, could not observe any change in HDL-C levels, HDL particle size, or activity of enzymes mediating HDL anti-oxidative properties [38].

Overall, it appears that, despite being statistically significant, changes in lipid parameters produced by SGLT2i are modest and their clinical impact is currently uncertain. Inconsistencies in these studies may be due to small sample sizes, retrospective design, and combination therapies used by diabetic patients. Moreover, although it is expected that a large part of diabetic patients is also on lipid-lowering therapy (mostly on statins), the potential confounding effect of SGLT2i on plasma lipid levels during statin treatment was not addressed. On the same line, it will be important to exclude that the benefits provided by SGTL2i might affect statin compliance in patients thus resulting in the changes reported in plasma lipid profile. Those findings call for specific retrospective analysis or new clinical trials to profile the impact of statin users on plasma lipid changes observed in SGLT2i-treated diabetic patients.

Although to date there is still no mechanistic explanation for the effect of SGLT-2 inhibitor-induced increment in plasma LDL-C concentrations, several studies have investigated this ambiguity by addressing the direct effects of SGLT2 inhibition or indirect effects on liver and systemic metabolism.

Many studies of SGLT2 inhibition have been performed in animals (mice and rats), but none of these models was able to explain the changes in lipid levels observed in humans, likely due to the differences in lipid profiles between rodents and humans. To overcome this diversity, transgenic mice overexpressing CETP and apoB100 (which confer a lipoprotein profile similar to humans) were fed a high-fat diet and then treated with streptozotocin to induce diabetes; the treatment with an SGLT2i (either canagliflozin or an antisense nucleotide [ASO]) resulted in an LDL-C increase associated with delayed clearance of LDL particles from the circulation, together with increased plasma LPL activity (but not expression) and lower circulating TG levels [39]. Of note, mice treated with the SGLT2 ASO had more pronounced lipid changes than mice treated with canagliflozin, which might be related to differences in the duration of the pharmacodynamic effects of SGLT2 ASO versus canagliflozin [39]. Following the treatment with the SGLT2 ASO, the gene expression of ANGPTL4 (an inactivator of LPL) was markedly reduced in metabolic tissues (heart, skeletal muscle, and brown adipose tissue) [39]. Furthermore, delayed clearance of LDL particles from the circulation was observed, associated with a modest reduction of hepatic low-density lipoprotein receptor (LDLR) protein expression [39]. While the results of this work suggest an effect mediated by ANGPTL4 inhibition, the difference observed between genetic versus protein pharmacological inhibition may reflect alternative pathways and/or sites of action of SGLT2i.

When the effect of empagliflozin was assessed in diet-induced insulin-resistant dyslipidemic hamsters, plasma LDL-C levels increased by 25%, concomitant with higher free fatty acids and total ketone body plasma levels; of note, these changes were observed only in the fasting condition [26]. Under this condition, empagliflozin reduced glycogen hepatic levels by 84% and hepatic LDLR by 20%, while the activity of HMGCoA reductase and the levels of total cholesterol and fatty acids in the liver were significantly increased [26]. Lower intestinal cholesterol absorption was also observed, likely due to the stimulation of hepatic cholesterol synthesis by empagliflozin. Again, these alterations were observed only in fasting conditions, but not in the fed state [26].

Studies in patients with T2DM have tried to explore more in detail the possible mechanisms underlying the effect of SGLT2 inhibition on lipid profile, and more specifically on LDL-C levels. No changes in PCSK9 levels have been observed after a 4-week treatment with empagliflozin [40], thus limiting the possibility of an impact of SGLT2i on this pathway. Nevertheless, the LDL-C increase following empagliflozin treatment was paralleled by increases in LDL phospholipids, LDL apoB, and free fatty acids, without changes in LDL particle size [41]. These findings were in contrast with those from other studies, showing that ipragliflozin reduced small dense LDL-C levels (and also LDL-C) [42] and that dapagliflozin also reduced small dense LDL while increasing large buoyant LDL particles (without changes in LDL-C from baseline) [37]. In the latter, an analysis was conducted stratifying patients according to changes in LDL-C; in the subgroup presenting with increased LDL-C (+14%), small dense LDL-C significantly decreased by 20.2%, while the concentration of large buoyant LDL-C increased by 52.7%; in the subgroup presenting decreased LDL-C (−13.6%), both small dense and large buoyant LDL-C were reduced (−19.4% and −9.9%, respectively) [37]. These results suggest that dapagliflozin markedly decreased the levels of highly atherogenic small dense LDL-C and increased levels of the less atherogenic large buoyant LDL-C, particularly in the subgroup of patients whose LDL-C levels increased following dapagliflozin treatment, thus supporting an overall positive effect of the drug on LDL particle profile.

Alterations in the levels of markers of cholesterol synthesis and absorption have been reported under dyslipidemic conditions, including T2DM, reflecting alterations of cholesterol metabolism; such changes have been observed also in healthy subjects with low HDL-C levels, who exhibited lower levels of intestinal absorption marker campesterol compared with subjects with high HDL-C levels [43]. When empagliflozin was tested to evaluate a possible impact on cholesterol synthesis and absorption, higher levels of serum campesterol were observed in diabetic patients with a concomitant significant increase in HDL-C levels (but not LDL-C) [44]. Such changes in plasma campesterol levels were correlated positively with changes in HDL-C [44], suggesting that serum levels of HDL-C might also depend on the intestinal absorption of cholesterol, beyond improved insulin sensitivity. However, the authors did not observe changes in the levels of sitosterol, another absorption marker, after empagliflozin treatment [44]. Of note, empagliflozin reduced lathosterol (a cholesterol synthesis marker) in the subgroup of diabetic patients not taking statins, but not in those under statin treatment (who had lower baseline levels of lathosterol) [44]. However, the direct effect of SGLT2 inhibition on cholesterol synthesis has been questioned as T2DM patients in this group were already under other concomitant treatments [45]; while this evidence further provides a complex scenario on the effect of SGLT2i on plasma LDL-C, on the other hand, it suggests the need of additional studies to disentangle whether the inhibition of SGLT2 may exert a direct effect on cholesterol synthesis.

1.3. Haemoconcentration as a potential mediator of LDL-C increase following SGLT2i treatment

The inhibition of SGLT2 triggers haemodynamic changes that may account, at least in part, for the observed effects on LDL-C levels. Therapy with empagliflozin has been associated with an increased urinary volume and subsequent volume contraction which may result in haemoconcentration, with an increase in haematocrit and serum or plasma albumin levels [46]. If the transient increase in fluid loss is not balanced by an increase in fluid intake or redistribution of fluid between body compartments over time, this may contribute to a persistent increase in haematocrit. The EMPA-REG OUTCOME trial reported persistently higher haematocrit values among empagliflozin-treated patients than in the placebo group [9] and a similar observation derives from an analysis of the DECLARE-TIMI 58 [47]. To assess whether haemoconcentration may contribute to changes in lipids observed in patients treated with SGLT2i, a pooled analysis of four phase 3 trials of empagliflozin was performed, showing modest increases in haematocrit and serum albumin at week 24, a slight increase in the serum levels of LDL-C, HDL-C, and apoA-I, and a reduction in TG [48]. ApoB levels were not significantly increased, which may be the result of two opposite processes, namely haemoconcentration on the one hand and the reduction in TG levels on the other hand [48]. The increases in haematocrit were significantly associated with the increases in all lipid fractions and the increases in serum albumin were significantly associated with the increase in all lipid fractions, except for TG [48]. More in detail, concomitant increases in haematocrit and serum albumin explained ~20%– 60% of the significant LDL-C total percentage increase in empagliflozin-treated patients [48]. However, this finding could not be replicated in another study in which LDL-C levels were significantly increased by 9% after 3 months of treatment with empagliflozin, but no changes were observed at day 1 and day 3 of treatment when haemoconcentration is already occurring [41]. Further studies are required to assess whether haemoconcentration causally contributes to the changes in lipid profile commonly seen after SGLT2 inhibition and to address whether this is a broad-class effect or a molecule-specific effect.

1.4. Systemic metabolic reprogramming following SGLT2i treatment

Could the treatment with SGLT2i switch the balance between energetic substrates and thus influence lipid metabolism? A recent review deeply investigated the possible mechanisms underlying the modulatory effects of SGLT2i on lipid metabolism, highlighting a potential impact on lipid biogenesis, peroxidation, and transport, cholesterol biosynthesis, and fatty acid ß-oxidation [49], thus suggesting that an overall metabolic reprogramming following SGLT2i treatment may contribute to such effects. The inhibition of glucose reabsorption achieved with SGLT2i reduces fasting and postprandial plasma glucose concentrations and leads to a consistent loss of about 200 kcal/day, thus mimicking a fasting-like condition throughout the day [50–53]. This is the consequence of SGLT2i being a class of drugs which i) does not require the action of insulin to lower glycaemia and ii) induces the elimination of glucose and, thus, a net loss of calories. These aspects contribute to lower circulating levels of insulin and increase the glucagon/insulin ratio [50–53]. Along this notion, part of the cardiorenal protective effects of SGLT2i could be the consequence of differential activation of nutrient-sensing pathways induced by the drug treatment. SGLT2i seem to promote a shift in the preference of energetic substrates from carbohydrates toward other substrates [54], and, more specifically, toward lipid utilization for energy production [26].

Normally, during fasting or under starving-like conditions, energy production from lipid oxidation is preferred over glycolysis. This process is favoured by increased lipolysis in the adipose tissue, which augments non-esterified fatty acid (NEFAs) levels in the circulation (thus contributing also to reducing adiposity and improving cardiometabolic health). NEFAs can then be used by the liver to generate ketone bodies, which may serve as an alternative and efficient energy substrate, and may be preferred in some tissues, such as the heart (Fig. 1) [6].

In diet-induced obese rats treated with SGLT2i, lipolysis is accelerated and circulating levels of ketone bodies increased, particularly in fasting conditions [55–57]. Accordingly, in humans, SGLT2i treatment increases plasma levels of 3-hydroxybutyric acid [58], a ketone that is freely taken up by the heart and oxidized more efficiently as compared to fatty acids to generate ATP. Thus, SGLT2i, similarly to caloric restriction, reduce fasting glucose and circulating levels of insulin and promote the increase of the glucagon/insulin ratio along with the production of ketone bodies [52,53,59]. However, while caloric restriction reduces lipid levels, SGLT2i seem to selectively not impact plasma LDL-C and triglyceride levels. At the biochemical level, the increase in ketone bodies observed following SGLT2 inhibition with dapagliflozin could be the consequence of increased oxidation in the liver of adipose tissue-derived FAs; the increased hepatic FA content may fuel the pool of acetyl-CoA, an important precursor for both ketone bodies production and hepatic cholesterol synthesis [60]. As the hepatic levels of cholesterol regulate LDLR expression, the treatment with empagliflozin might therefore reduce both LDLR expression and the hepatic uptake of LDL-C, which in turn increase LDL-C plasma levels (Fig. 2) [26].

Therefore, further studies will need to elucidate the intriguing hypothesis that the neutral/increasing effect of SGLT2i treatment on plasma lipoprotein levels may result from a profound systemic reprogramming of energy metabolism. Of note, a bidirectional relationship between systemic glucose and cholesterol metabolism has been already observed. Indeed, the inhibition of cholesterol synthesis by statins may increase the risk of developing T2DM [61–65]. The pro-diabetic effect has been molecularly correlated with the increased availability of cholesterol in pancreatic beta cells due to higher LDLR expression impairing beta-cell degranulation [66]. This response is commonly observed with different strategies increasing LDLR expression on the beta-cell surface [67,68].

In line with the hypothesis of a dichotomy of glucose vs lipid substrate preference in modulating systemic metabolism, an integrative multi-omic approach combining gene expression, genotype, metabolomics, and clinical data identified a glucose- and lipid-determining regulatory network that inversely regulates lipid and glucose traits [69].

2. Conclusions

Clinical data clearly show a cardiometabolic benefit of SGLT2i

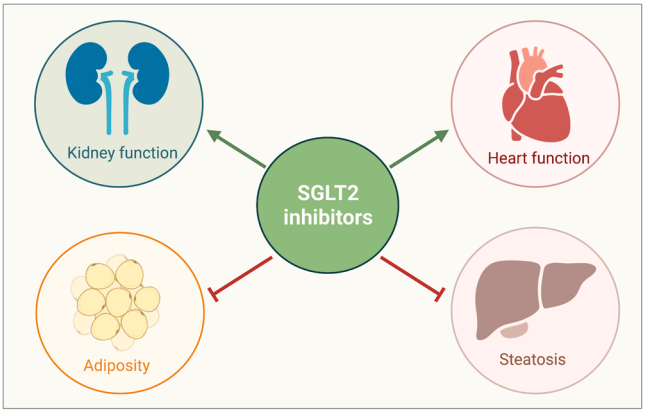

Fig. 1. Multiple protective effects of SGLT2i in diabetic patients. SGLT2i, by inhibiting glucose reabsorption in the kidney, promote several cardiovascular protective effects. The reduction in glycaemia might mimic a starving-like state that would increase fatty acid lipolysis in the adipose tissue thus reducing adiposity. In turn, this would result in improved systemic metabolic health with reduced lipid accumulation in the liver and increased heart function in subjects with a reduced or preserved heart ejection fraction.

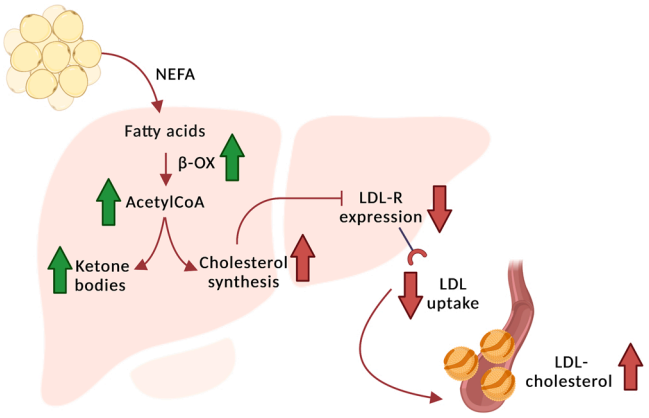

Fig. 2. Potential molecular mechanisms driving dyslipidemia following SGLT2i treatment. Adipose tissue-derived non-esterified fatty acids (NEFA) are oxidized by the liver to produce acetyl-CoA that in turn is used either for the synthesis of ketone bodies or cholesterol biosynthesis. While ketone bodies can be used by the heart for energetic purposes, increased hepatic cholesterol levels down-regulate the expression of the low-density lipoprotein receptor (LDLR), thus decreasing the removal of atherogenic low-density lipoprotein (LDL). Reduced liver LDL catabolism may result in increased plasma levels of LDL-C.

beyond renal inhibition of glucose reabsorption, suggesting that this class of drugs may work also through additional pleiotropic mechanisms. Indeed, the beneficial effect of SGLT2 inhibition extends beyond glycaemic control and not only includes protection from heart failure, but also the improvement in blood pressure, body weight, uric acid concentrations, liver steatosis, oxidative stress, and inflammation [70, 71]. These observations would suggest extending the indication of SGLT2i also to subjects with metabolic syndrome thanks to the possibility of concomitantly controlling multiple metabolic alterations.

Despite these beneficial effects on cardiovascular morbidity and mortality, SGLT2 inhibitors exhibit controversial effects on LDL-C levels. A deeper analysis of the effect on LDL subclasses seems to suggest that SGLT2i might favour the reduction of small dense LDL and the increase of large buoyant LDL, an effect that, however, has been shown with dapagliflozin but has not been confirmed in other studies. Thus, whether changes in lipoprotein levels are compensated by an ameliorated lipoprotein composition warrants further investigation.

At the molecular level, it is plausible that the potential "starving-like" mimicking effects induced by SGLT2i rewire systemic metabolism. Promotion of peripheral lipolysis mobilizes more fatty acids, which reach the liver and, via hepatic beta-oxidation, might be converted into ketone bodies, ready to be used as an efficient substrate to produce energy in tissues such as the heart. However, this process might also promote the activation of the mevalonate pathway and cholesterol biosynthesis, which might explain, at least in part, the slight increase in LDL-C levels in patients treated with SGLT2i observed in some studies. Whether and how this effect might impact the action of these drugs in cardiometabolic disorders is still an open question.

Future long-term studies are needed to answer this question and will imply regular monitoring of patient lipid profile and collecting detailed information on lipid-lowering therapies at baseline and during the trials. This will allow for deepening the knowledge of the real effects of SGLT2i on lipids if any, and possibly ascertaining the potential implications in modulating atherosclerotic cardiovascular risk. Whether the dual SGLT2i and cholesterol synthesis inhibition will converge to further improve cardiovascular outcomes deserves a detailed investigation.

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All authors have participated in Conceptualization, Writing – original draft, and Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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