https://doi.org/10.31925/farmacia.2021.5.2 **REVIEW**

A PARADIGM SHIFT FOR THE SGLT2 INHIBITORS – TREATING THE HEART WITH ANTI-HYPERGLYCAEMIC DRUGS

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Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a newer class of anti-hyperglycaemic drugs that act by partially inhibiting glucose reabsorption from the renal filtrate and inducing glycosuria. However, they have several other benefits, independent of the glycaemic control. SGLT2i reduced major cardiovascular events, including new-onset heart failure, in patients with type 2 diabetes mellitus (T2DM), in large randomized clinical trials. These effects have been recently described in patients with HF with reduced ejection fraction, irrespective of their diabetic or glycated haemoglobin status, suggesting that their benefits are driven independently of their glucose lowering properties. This review summarizes the current evidence for their cardioprotective effects, and provides an overview of the possible mechanisms for the cardiovascular benefits. The alleged mechanisms that lead to improve cardiovascular outcome, even though still incompletely understood, include an association between improvement in cardiac pre- and after-load, partially explained by osmotic diuresis and natriuresis, prevention of cardiac remodelling, direct cardiac effects with improved cardiac energetics and ion handling, anti-inflammatory effects, and anti-fibrotic effects. Therefore, in the latest years, both mechanistic insights, as well as major trials data, have repurposed SGLT2i usage from only anti-diabetic to potent HF treatment drugs, and new indications have been attributed to these compounds in HF guidelines.

Rezumat

Inhibitorii cotransportorului 2 sodiu - glucoză (SGLT2i) sunt o clasă relativ recentă de medicamente anti-hiperglicemice care acționează prin inhibarea parțială a reabsorbției glucozei din ultrafiltratul renal și inducerea glicozuriei. Cu toate acestea, ei au și alte beneficii, independente de controlul glicemic. SGLT2i au redus evenimentele cardiovasculare (CV) majore, inclusiv insuficiența cardiacă (IC) „*de novo*", la pacienții cu diabet zaharat de tip 2 (T2DM), în studiile clinice randomizate mari. Aceste efecte au fost descrise recent la pacienții cu IC cu fracție de ejecție redusă, indiferent de prezența sau absența T2DM sau de valorile hemoglobinei glicate, sugerând că beneficiile lor sunt determinate independent de proprietățile de reducere a glicemiei. Acest articol sumarizează dovezile actuale pentru efectele lor cardioprotectoare și oferă o imagine de ansamblu asupra posibilelor mecanisme implicate în inducerea beneficiilor CV. Presupusele mecanisme care conduc la îmbunătățirea prognosticului CV, chiar dacă sunt încă incomplet înțelese, includ o asociere între îmbunătățirea pre- și post-sarcinii ventriculare, explicată parțial prin diureza osmotică și natriureză, prevenirea remodelării cardiace, efecte cardiace directe cu îmbunătățirea energeticii cardiace și cineticii ionilor, efecte anti-inflamatorii și efecte anti-fibrotice. Prin urmare, în ultimii ani, atât cunoștințele fiziopatologice, cât și datele studiilor majore, au redirecționat utilizarea SGLT2i de la medicamente pur antidiabetice la medicamente pentru tratamentul IC, atribuindu-le noi indicații în ghidurile de IC.

Keywords: SGLT2 inhibitors, cardiovascular protection, heart failure

Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2i), developed initially as a class of anti-hyperglycaemic drugs, have both glycaemic and non-glycaemic benefits. Recent advances in the understanding of the non-glycaemic effects of SGLT2i have shown cardiovascular (CV) and renal protection, with potential benefits in heart failure (HF) [23, 25, 40, 51].

The last decade showed a paradigm shift in the use of glucose-lowering drugs in patients with diabetes and CV disease, mainly HF. The initial principle in prescribing these drugs in patients with HF and CV disease was, for many years, safety (using glucose lowering drugs that do not increase CV events). The therapeutically approach of these patients further evolved aiming at efficacy rather than just safety, treating diabetic patients with HF with drugs that

improve CV outcome along with their anti-hyperglycaemic effect. The latest years have revolutionized the use of these drugs with the repurposing to treat HF, even in the absence of diabetes [23, 25].

Briefly, SGLT2 inhibitors act to reduce blood glucose by blocking its reabsorption in the kidneys leading to urinary glucose excretion, reduced blood glucose levels, and reduction of plasma volume and sodium load [31]. These effects are accompanied by other mechanisms that lead to CV and renal protection; thus, several mechanisms have been postulated, such as their favourable effects on blood pressure (BP) reduction, increasing diuresis/natriuresis, improving cardiac energy metabolism, preventing inflammation and decreasing oxidative stress, reducing hyperuricemia, inducing weight loss, inhibiting the sympathetic nervous system, preventing cardiac remodelling, preventing ischemia/reperfusion injury, decreasing epicardial fat mass, increasing erythropoietin (EPO) levels, and improving vascular function [4, 8, 21, 22, 31, 37, 50, 55].

In this review, we provide an overview of the mechanism of action of these medication in type 2 diabetes mellitus (T2DM) and on the CV system. Meanwhile, we analyse the most relevant findings derived from recent randomized clinical trials, supporting the broadening of SGLT2i indication from glucose lowering therapy to cardiovascular protection in diabetic patients, and to HF treatment in diabetic and non-diabetic patients.

SGLT2i and their mechanism of action (Figure 1)

In the normal healthy adult, the kidney can filter and reabsorb approximately 180 g of glucose daily with virtually no glucose excreted in the urine. However, once the maximal limits of reabsorption are reached, the excess glucose starts to get excreted in the urine [25, 51]. The SGLTs are a family of membrane proteins that are associated with the transport of glucose and ions over the brush-border membrane of proximal renal tubules and the intestinal epithelium [3]. These proteins are responsible for the first step of glucose reabsorption through the apical cell membrane *via* a secondary active-transport which is driven by the electro-chemical sodium gradient between the tubular filtrate and the cell. This gradient requires active basolateral Na^+ removal by the Na^+/K^+-ATPase [35]. The second step takes place on the basolateral side where glucose exits the cells, due to its concentration gradient, and re-enters the bloodstream, *via* a facilitative transport (GLUT2), a member of another family of glucose transporter proteins (GLUT) [25].

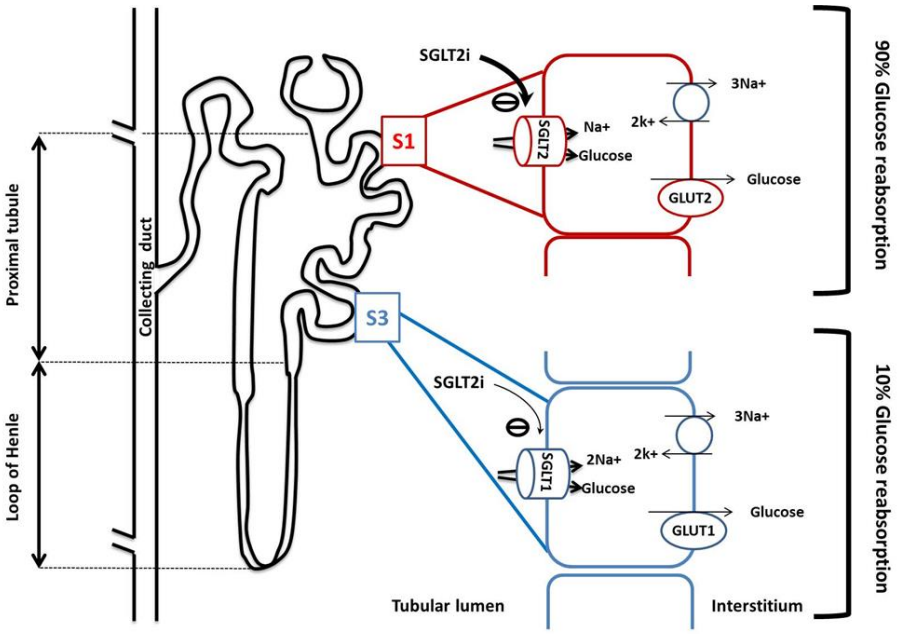

Figure 1.

Sodium glucose co-transporter (SGLT) and glucose handling in the kidney. SGLT2, found in the early part of the proximal tubule (S1), accounts for ~ 90% of whole kidney fractional glucose reabsorption. SGLT2 binds one sodium (Na^+) molecule and one glucose molecule and transports them from the tubular lumen into the tubular cell. GLUT2 (glucose transporter 2) then pumps the glucose molecule into the interstitial fluid. SGLT1 in turn, located in the distal (S3) segment of the proximal tubule, is responsible for the remainder of 10% of whole kidney fractional glucose reabsorption, and transports 2 Na^+ molecule and 1 glucose molecule from the tubular lumen into the tubular cell. GLUT1 then pumps the glucose molecules into the interstitial space. By inhibiting SGLT, the SGLT2 inhibition will result in glycosuria and natriuresis. The Na^+/K^+ pump is responsible for the active transportation of Na^+ from the tubular cell into the interstitial space [3, 24, 34].

Several members of the SGLT family have been identified, however, SGLT1 and SGLT 2 are the main actors in glucose handling in the kidney and the gastro-intestinal tract. SGLT2 is a high-capacity, low-affinity transporter found primarily in the kidney, in the early part of the proximal tubule (S1), and accounts for all glucose reabsorption in this segment and for ~ 90% of whole kidney fractional glucose reabsorption [18, 48]. SGLT1 in turn is a low-capacity, high-affinity transporter which is located primarily in the gastro-intestinal tract but is also found in the S3 segment of the proximal tubule. SGLT1 is responsible for the remainder of 10% of whole kidney fractional glucose reabsorption [51].

Hyperglycaemia increases the amount of glucose filtered in the kidneys along with an increase in the reabsorption capacity by 20% [48]. This is possible mainly by an increased expression of SGLT2 in the proximal tubule. As a consequence, the glycosuric and blood glucose lowering effects of SGLT2 inhibition become more potent in hyperglycaemic states, where SGLT2 is upregulated [6, 19, 42]. In turn, the risk of hypoglycaemia associated with SGLT2 inhibitors is low. This is a result of compensation by SGLT1 in the downstream S3 proximal tubule, which stops glucose excretion when the filtered glucose falls below the transport capacity of SGLT1 [48]. Moreover, SGLT2i leave the metabolic counter-regulation intact, increasing hepatic gluconeogenesis and plasma glucagon levels [28].

Glucose metabolism is a complex process and the SGLT protein family plays many roles. If the SGLT2 is the major acting transporter in the kidney, in the small intestine SGLT1 is a key player in the luminal uptake of dietary glucose. Similar to the kidney re-absorption, after glucose is taken up from the luminal part of the intestinal cell by SGLT1, it then exits through the basolateral membrane into the blood stream *via* GLUT2 [44]. This intestinal SGLT1 glucose uptake also modulates the secretion of incretins, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Moreover, in the distal intestinal segments it has been postulated that glucose is metabolized by the gut microbiome and transformed in short-chain fatty acids (SCFAs) which in turn will induce sustained release of GLP-1 [34, 57]. Therefore, SGLT1 inhibition results in both a direct reduction in glucose uptake and an indirect promotion of sustained release of glucose-lowering incretins [35].

The history of SGLTi starts with phlorizin which gave the drug class name of gliflozins. Phlorizin, a naturally occurring *O*-glucoside molecule, was discovered over 150 years ago and was subsequently found to increase urinary glucose excretion in healthy humans [7]. Despite its glucose lowering effect, phlorizin was not further pursued as an anti-diabetic drug. Firstly, because phlorizin is quickly metabolized in the intestinal tract by *β*-glucosidase upon oral administration. Secondly, it acts as a nonselective SGLT inhibitor; therefore, it also inhibits SGLT1 and leads to gastrointestinal side effects, such as diarrhoea and dehydration [20, 25].

Table I

Main pharmacokinetic parameters of SGLT2 inhibitors with reported CV outcome data. OD – once daily [39, 53]

	CANAGLIFLOZIN	**DAPAGLIFLOZIN**	**EMPAGLIFLOZIN**	**ERTUGLIFLOZIN**
Maximum daily dosage	300 mg OD	10 mg OD	25 mg OD	15 mg OD
Half-life (hours)	11 - 13	12.2 - 12.9	12.4	16.6
Oral bioavailability	65%	78%	60%	100%
Metabolism and elimination	Extensive hepatic glucuronidation	Extensive hepatic glucuronidation	Extensive hepatic glucuronidation	Extensive hepatic glucuronidation
Elimination	Renal excretion as inactive metabolite (< 1% elimination as unchanged drug)	Renal excretion as inactive metabolite (< 2% elimination as unchanged drug)	Renal excretion (28% elimination as unchanged drug)	Renal excretion predominantly as inactive metabolite
SGLT2 selectivity *versus* SGLT1 (SGLT2:SGLT1)	250:1	1200:1	2500:1	2000:1

To overcome these problems, further research led to the identification of the novel C-glucoside-containing selective SGLT2i such as dapagliflozin, canagliflozin, empagliflozin and ertugliflozin. This C-glycosylation makes these molecules resistant to hydrolysis by β-glucosidases, increasing their half-life. Several differences exist between these drugs including their selectivity for the SGLT2 over SGLT1. For instance, it can range from 250:1 for canagliflozin to ~ 2500:1 for empagliflozin [20, 25, 39, 51, 53]. The main pharmacokinetic properties of SGLT2i are summarized in Table I.

SGLT2i and cardioprotection in patients with T2DM – clinical data

Currently, there are four SGLT2i that are approved for T2DM treatment and have been investigated in large cardiovascular outcomes trials in diabetic patients: dapagliflozin, empagliflozin, ertugliflozin and canagliflozin. The summary of these trials characteristics and results are summarized in Table II.

Table II

Comparison of main population characteristics and results between CV outcome SGLT2i trials

	CANAGLIFLOZIN	**DAPAGLIFLOZIN**	**EMPAGLIFLOZIN**	**ERTUGLIFLOZIN**
CVOT in patients with T2DM				
Trial, year of publication	**CANVAS, 2017 [30]**	**DECLARE TIMI 58, 2019 [54]**	**EMPA-REG Outcome, 2015 [59]**	**VERTIS – CV, 2020 [5]**
Number of patients	10,142	17,160	7020	8238
Population	T2DM pts with established ASCVD (72.2%) and pts at risk for ASCVD	T2DM pts with established ASCVD (40.6%) and pts at risk for ASCVD	T2DM pts with established ASCVD	T2DM pts with established ASCVD
	HF 14.4%	HFrEF – 3.9% HFpEF – 7.7%	HF 10.1%	HF 23.9%
Follow up	3.6 years	4.2 years	3.1 years	3.5 years
Dosage	100 or 300 mg OD	10 mg OD	10 or 25 mg OD	5 or 15 mg OD
3P-MACE *vs*. placebo	HR 0.86 95% CI 0.75 - 0.97	HR 0.93 95% CI 0.84 - 1.03	HR 0.86 95% CI 0.74 - 0.99	HR 0.97 95% CI 0.85 - 1.11
CV death	HR 0.87 95% CI 0.72 - 1.06	HR 0.98 95% CI 0.82 - 1.17	HR 0.62 95% CI 0.49 - 0.77	HR 0.92 95% CI 0.77 - 1.11
Non-fatal MI	HR 0.85 95% CI 0.69 - 1.05	HR 0.89 95% CI 0.77 - 1.01	HR 0.87 95% CI 0.7 - 1.09	HR 1.00 95% CI 0.86 - 1.27
Non-fatal stroke	HR 0.90 95% CI 0.71 - 1.15	HR 1.01 95% CI 0.84 - 1.21	HR 1.24 95% CI 0.92 - 1.67	HR 1.00 95% CI 0.76 - 1.32
All-cause death	HR 0.87 95% CI 0.74 - 1.01	HR 0.93 95% CI 0.82 - 1.04	HR 0.68 95% CI 0.57 - 0.82	-
HF Hospitalization	HR 0.67 95% CI 0.52 - 0.87	HR 0.73 95% CI 0.61 - 0.88	HR 0.65 95% CI 0.50 - 0.85	HR 0.70 95% CI 0.54 - 0.90
Composite renal outcome[1]	HR 0.53 95% CI 0.33 - 0.84	HR 0.53 95% CI 0.43 - 0.66	HR 0.61 95% CI 0.53 - 0.70	HR 0.81 95% CI 0.63 - 1.04
Adverse events	Higher risk of GTI, amputation, fracture and volume depletion	Higher risk of GTI, AKI, DKA, hypoglycaemia	Higher risk of UTI, GTI, AKI	Higher risk of UTI, GTI
CVOT in patients WITH OR WITHOUT T2DM				
Trial, year of publication		**DAPA-HF, 2019 [27]**	**EMPEROR -Reduced, 2020 [32]**	
Number of patients		4744	3730	
Population		LVEF < 40% NYHA II-IV Increased NT proBNP GFR ≥ 20 mL/min/1.73 m^2	LVEF < 40% NYHA II-IV Increased NT proBNP GFR ≥ 30 mL/min/1.73 m^2	
- Non-T2DM		58.2%	50.2%	
- Mean age (years)		66.5	66.5	
- Mean LVEF		30.9%	27.2%	
- NT proBNP (median)		1446 pg/mL	1926 pg/mL	
Follow up		18.2 months	16 months	
Dosage		10 mg OD	10 mg OD	
Primary endpoint[2,#]		HR 0.74 95% CI 0.65 - 0.85	HR 0.75 95% CI 0.65 - 0.86	
CV death		HR 0.82 95% CI 0.69 - 0.98	HR 0.92 95% CI 0.75 - 1.12	
All-cause death		HR 0.83 95% CI 0.71 - 0.97	HR 0.92 95% CI 0.77 - 1.10	
HF Hospitalization		HR 0.70 95% CI 0.59 - 0.83	HR 0.69 95% CI 0.59 - 0.81	
Composite renal outcome[3]		HR 0.71 95% CI 0.44 - 1.16	HR 0.5 95% CI 0.32 - 0.77	
Adverse events		No difference vs placebo	Higher risk of GTI	

AKI – acute kidney injury; ASCVD – atherosclerotic cardiovascular (CV) disease; CI – confidence interval; DKA – diabetic ketoacidosis; GTI – genital tract infections; HF – heart failure; HFpEF – HF with preserved ejection fraction; HFrEF – HF with reduced EF; HR – hazard ratio; 3P-MACE – 3 point major adverse cardiac events (death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke); OD – once daily; T2DM – type 2 diabetes mellitus; UTI – urinary tract infections

[1]Composite renal outcome definition:

In CANVAS: 40% reduction in GFR (glomerular filtration rate) sustained for at least 2 measurements, the need for renal replacement therapy or death from renal causes.
In DECLARE TIMI-58: ≥ 40% decrease in estimated GFR to < 60 mL *per* minute *per* 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or CV causes.
In EMPA-REG outcome: need for renal replacement therapy or a profound reduction in the estimated GFR.
In VERTIS CV: death from renal causes, renal replacement therapy, or doubling of the serum creatinine level.
[2]The primary outcome for EMPEROR-Reduced was a composite of CV death or hospitalization for worsening HF; for DAPA-HF was composite of death from CV causes or worsening HF.
[3]The composite kidney outcome for EMPEROR-Reduced was need for renal replacement therapy, a sustained reduction of ≥ 40% in the eGFR or a sustained eGFR < 15 mL *per* min *per* 1.73^2 in patients with a baseline eGFR of ≥ 30 mL *per* min *per* 1.73^2 or a sustained eGFR < 10 mL *per* min *per* 1.73^2 in patients with a baseline eGFR of < 20 mL *per* min *per* 1.73^2; for DAPA-HF was a sustained decline in the eGFR of ≥ 50% for ≥ 28 days, end-stage kidney disease (defined as ≥ 28 days of eGFR < 15 mL *per* min *per* 1.73^2, sustained dialysis, or transplantation), or kidney death and death from any cause.
[#]Cardiovascular outcomes reported for DAPA-HF and EMPEROR reduced were not different between patients with or without T2DM

The first trial published was EMPA-REG OUTCOME (empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) which included a total of 7020 patients with established CV disease and T2DM. They received OD empagliflozin (10 mg or 15 mg) *versus* placebo and were followed for 3.1 years. The trial reached its primary outcome reporting a 14% relative risk (RR) reduction in the 3 point major adverse CV events (3P - MACE), including CV death, nonfatal myocardial infarction (MI) or non-fatal stroke ($p < 0.001$ for non-inferiority and $p = 0.04$ for superiority), for the intervention group. empagliflozin resulted also in a 38% RR reduction of CV death, 35% RR reduction of hospitalization for HF and 32% RR reduction of death from any cause. empagliflozin increased, however, the rates of genital infections [60].
In 2017, results of the CANVAS trial (Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes) were published. The CANVAS trial recruited 10,142 participants with T2DM and high CV risk which were randomly assigned to receive canagliflozin or placebo. They were subsequently followed for a mean of 3.6 years. Canagliflozin resulted in a 14.4% RR in the 3P-MACE (death from CV causes, non-fatal MI, or nonfatal stroke) (p for non-inferiority < 0.001 and p for superiority = 0.02). However, a higher risk of amputation, primarily at the toe and meta-tarsal level, was observed [30]. The CREDENCE trial (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) evaluated the impact of canagliflozin primarily on chronic kidney disease (CKD). It included 4401 patients with T2DM and CKD with albuminuria, randomized to receive canagliflozin 100 mg OD or placebo. Canagliflozin resulted in a RR of 32% for end-stage CKD ($p = 0.002$), 20% for CV death, MI, or stroke ($p = 0.01$), and 39% for hospitalization for HF ($p < 0.001$). In contrast to the CANVAS program, there were no significant differences in rates of amputation or fracture between the intervention and the placebo group [33].
Dapagliflozin was tested for its CV outcomes in T2DM patients in DECLARE TIMI 58 (Dapagliflozin Effect on Cardiovascular Events). The study randomized 17,160 patients, including 10,186 without atherosclerotic CV disease, to either dapagliflozin 10 mg OD or placebo. The follow-up period was 4.2 years. The 3P – MACE (death from CV causes, nonfatal MI, or nonfatal stroke) was not significantly different in the dapagliflozin group *versus* placebo. However, it did result in a 13% RR of CV death or hospitalization for HF ($p = 0.005$), driven mainly by the lower rate of HF hospitalization (RR of 27%). In terms of adverse effects, dapagliflozin induced higher rates of diabetic ketoacidosis (0.3% *vs*. 0.1%, $p = 0.02$) and genital infections (0.9% *vs*. 0.1%, $p < 0.001$) [54].
Cardiovascular outcome for ertugliflozin was published in the VERTIS CV (Cardiovascular Outcomes with ertugliflozin in Type 2 Diabetes) trial in 2020. A total of 8246 patients with T2DM and atherosclerotic CV disease were randomized to ertugliflozin (5 mg or 15 mg OD) or placebo, and were followed for a mean of 3.5 years. There were no differences in the 3P-MACE between the intervention and placebo group (p for non-inferiority < 0.001), and no differences in the secondary endpoint of death from CV causes or HF hospitalization. Moreover, ertugliflozin did not influence the renal endpoint of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level compared to placebo [5].
These trials reported inconsistencies in CV outcomes that are not explained only by differences in the pharmacological properties of the individual drugs. For instance, empagliflozin has the highest SGLT2 selectivity while canagliflozin the lowest. However, both trials investigating these 2 SGLT2i reported superiority in terms of CV outcome. Differences in the CV risk of the studied population might be the explanation for the inconsistencies in CV outcome results. While EMPA-REG OUTCOME and VERTIS CV trials included only patients with established CV disease, DECLARE TIMI 58 and CANVAS trials included patients at risk of CV as well. In fact, DECLARE TIMI 58 trial reported the lowest rate of CV events *per* 1000 patients-years and this might introduce some bias in the statistical analysis, resulting in non-significant differences between the intervention and placebo group [5, 30, 54, 60].
One meta-analysis evaluating 34,322 patients from the DECLARE TIMI 58, CANVAS, and EMPA-REG OUTCOME trials, from which 60.2% had established

atherosclerotic CV disease (ASCVD), showed that SGLT2i have, as the most important and consistent effect, the reduction in RR of HF hospitalisation (31%) and of progression of renal disease (45%), irrespective of the presence or absence of established ASCVD. However, their effect on the 3P-MACE was more modest, with 11% statistically significant reduction in RR which was apparent only in patients with established ASCVD, whereas no effect was observed in patients without ASCVD [59]. Therefore, it appears that the effect of SGLT2i on selected CV outcomes depends on the patient population in which they are used.

SGLT2i mechanisms of cardioprotection (Figure 2)

SGLT2i, as shown above, have been initially developed as glucose lowering drugs. However, extensive data showed that these agents have a favourable metabolic profile and significantly reduce atherosclerotic events, hospitalization for HF, CV and total mortality, and progression of CKD [50]. Moreover, their benefits, especially related to HF and CKD treatment, have been shown to be present in patients without diabetes as well [27, 32].

These positive CV outcomes cannot be solely attributed to the SGLT2i glucose lowering effects as shown in the DAPA-HF and EMPEROR-Reduced trials, where their benefits on HFrEF were independent of the presence or absence of T2DM and the glycaemic status [27, 32]. Although the precise mechanisms are currently incompletely clarified, in recent years various theories have been put forward to explain their CV and renal beneficial effects [31, 50].

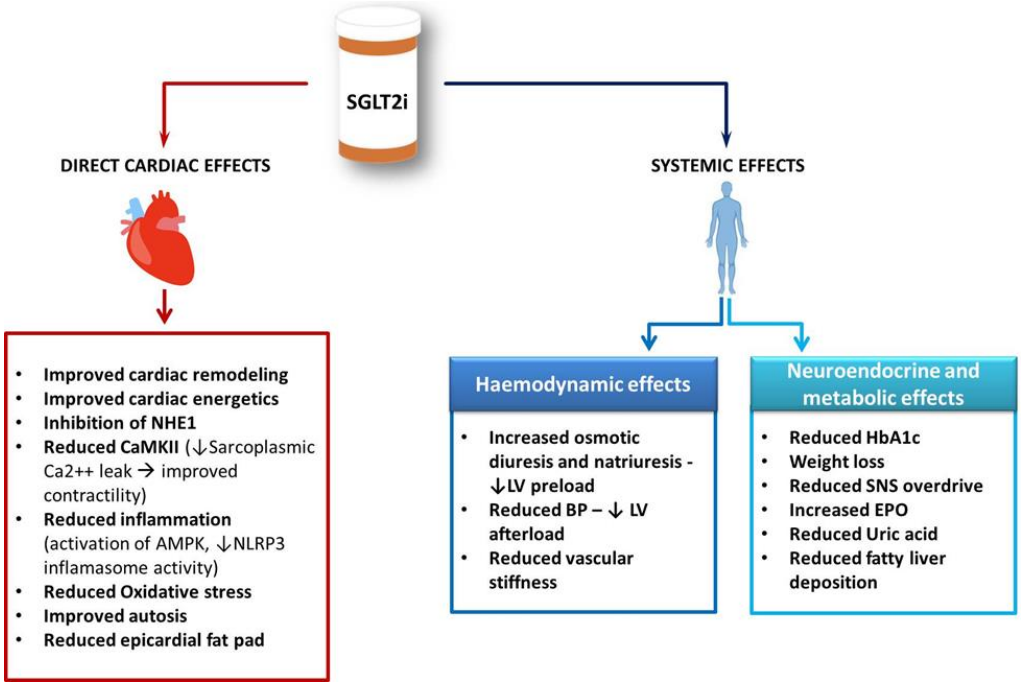

Figure 2.

Proposed mechanisms for sodium-glucose co-transporter 2 inhibitors (SGLT2i) cardioprotection

AMPK – adenosine monophosphate activated protein kinase; CaMKII – Ca^{++}/calmoduline dependent kinase; EPO – erythropoietin; LV – Left ventricle; HbA1c – A1c haemoglobin; NHE1 – Na^{+}/K^{+} exchanger; NLRP3 – Nucleotide-binding domain-like receptor protein 3; SNS – Sympathetic nervous system.

SGLT2i - haemodynamic effects. SGLT2 inhibition in the proximal tubule results in natriuresis and glycosuria which leads to osmotic diuresis. This will in turn improve ventricular loading conditions due to reduction in preload. The diuretic effect of SGLTi is, however, different from that of the conventional diuretics (thiazides and loop diuretics). SGLT2i reduce to a greater extent the interstitial oedema with little or no effect on the intravascular volume, as compared with classical diuretics that will impact mainly on intravascular volume [9].

Another mechanism that improves cardiac dynamics trough reduction of cardiac afterload is SGLT2i induced lowering of arterial blood pressure [15]. Although not fully understood, the antihypertensive effect of SGLT2i is probably driven by several mechanisms which include increased natriuresis and diuresis, improved endothelial function and aortic stiffness, potential vasodilation through voltage-gated K^{+} channels and G protein kinase and loss of body weight [43, 45]. One additional mechanism might be related to the salt sensitiveness of some form of hypertension. Indeed, in a prospective double blind, placebo controlled trial,

SGLT2 inhibition with dapagliflozin resulted in a significant decrease in tissue sodium content of the skin along with reduced body weight and improved BP [14].

The synergistic effect of decreased LV preload and afterload induced by SGLT2i can be one factor leading to favourable cardiac remodelling and, as a consequence, a mechanism for reduced HF adverse events. In the Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects in Patients with Diabetes Mellitus, or Prediabetes, and Heart Failure – SUGAR-DM-HF trial, empagliflozin reduced left ventricular (LV) volumes in patients with HFrEF (HF with reduced ejection fraction) and T2DM or prediabetes [21]. A reduction in LV mass, measured by cardiac magnetic resonance imaging (CMR), was seen with empagliflozin in patients with T2DM and coronary artery disease in the EMPA-HEART CardioLink-6 Randomized Clinical Trial [49]. In the DAPA-LVH trial, dapagliflozin treatment resulted in a significant reduction in LV mass (as assessed by MRI) in patients with LV hypertrophy and T2DM [4].

There have been consisting evidence of an increase in haematocrit with SGLT2i and an analysis from the EMPA-REG OUTCOME trial suggested that the observed increase in haematocrit and haemoglobin levels could explain part of the risk reduction in CV death by empagliflozin [11]. The increased haematocrit levels seen early after the initiation of SGLT2i and maintained during the treatment have been at least partially attributed to haemoconcentration due to diuresis and extravascular fluid depletion. However, treatment with SGLT2i also induce an increase in erythropoietin (EPO) concentration and reticulocyte count, which could be an additional mechanism for the increase in haematocrit and haemoglobin values [26]. Haematocrit elevation leads to increase tissue oxygen supply to the heart with resultant improvement in cardiac function. However, increased EPO levels have also favourable effects on the mitochondrial function of cardiomyocytes, cell proliferation and inflammation, and angiogenesis [31].

SGLT2i - cardiac metabolism and bioenergetics. The healthy heart metabolism relies on substrate flexibility which allows it to switch from one source of energy to another, depending on cardiac workload and metabolite availability. However, the main energy substrate remain fatty acids, followed by glucose and, to a smaller degree, ketones [8]. In disease states of the myocardium there is an altered energy metabolism with carbohydrate metabolism becoming the main source of energy and reducing utilization of fatty acids [22]. SGLT2i have been shown to improve cardiac energetics in HF by increasing circulating ketone levels, secondary to mobilizing adipose tissue fatty acids, which are then used by the liver for ketogenesis. This ketones act as a "supplement" of increasing fuel supply to the failing heart [22]. The beneficial effects of increasing ketone levels by SGLT2i were demonstrated in a non-diabetic ischemia animal model in which the administration of empagliflozin resulted in reduced LV remodelling and improved LV systolic function by turning myocardial fuel metabolism away from the low-yield energy-producing glucose metabolism toward ketogenesis which improves myocardial energy production [36].

SGLT2i - changes in the ion homeostasis of the myocardium. The myocardial Na^+/H^+ exchanger (NHE) 1 isoform acts as a major mechanism for pH regulation during normal physiological processes, but mainly during ischaemia and early reperfusion [16]. Stimulation of NHE1 leads to an increase in cytosolic Na^+ and calcium and, therefore, it has been involved in the physio-pathology of HF by promoting cell damage. Inhibition of NHE1 may lead to cardiac protection and has been recently shown that empagliflozin leads to inhibition of NHE, and determines a reduction of intracellular calcium and Na^+ while increasing the calcium supply to the mitochondria. However, it remains unclear how SGLT2i inhibit NHE1 as SGLT2 have not been found in the heart [2].

Activity of sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) is modulated by SGLT2i. SERCA2a activity controls the contractility and relaxation of the heart through Ca^{2+} handling, affecting cardiac function. This ATPase is down-regulated in failing hearts. In animal models, administration of empagliflozin or dapagliflozin resulted in increased SERCA2a activity, which might contribute to the cardioprotective mechanism of SGLT2i.

Overexpression and activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) has been suggested as another possible cardioprotective mechanism of SGLT2i. CaMKII are known mechanisms in the pathophysiology of HF, leading to contractile dysfunction and arrhythmias by increasing diastolic Ca^{2+} leak from the sarcoplasmic reticulum (SR) and reducing SR Ca^{2+} load [11]. In isolated ventricular cardiomyocytes, empagliflozin reduced CaMKII activity [29].

SGLT2i - effects against inflammation, fibrosis, and apoptosis. Inflammation and fibrosis are key patho-physiological components of HF progression. SGLT2i have been shown in animal models to influence various inflammatory and profibrotic pathways that can lead to cardioprotective effects, such as reduction in the activation of the Nucleotide-Binding Domain-Like Receptor Protein 3 (NLRP3) inflammasome, reduction of macrophage infiltration, increased AMP activated protein kinase (AMPK) signalling pathways and blockage of the transforming growth factor (TGF-β) [29, 46, 47, 56].

Autophagic cell death is a complex process in response to several factors, including cellular stress, ischemic injury or energy deprivation. Reduced activation of autophagy or excessive autophagy may both be harmful. In an animal model, empagliflozin showed a capacity to regulate and optimize the autophagy mechanism [13].

SGLT2i seems to influence the epicardial fat (EPF). Dapagliflozin significantly reduced the epicardial fat, as assessed by echocardiography, independent from body weight reduction [10]. Similar results were obtained with canagliflozine [37]. The epicardial fat pad has been involved in arrhythmogenesis and HF patho-physiology and, therefore, the effect exhibited by SGLT2i adds to their cardioprotective mechanism [31, 55].

SGLT2i and additional metabolic effects. SGLT2i have proven to induce a more favourable metabolic profile by inducing plasma glucose reductions, lower BP and body weight, and changes in the lipid profile [50]. Moreover, their metabolic benefits are reflected also in their hepatoprotective effect in non-alcoholic fatty liver disease (NAFLD) by reducing liver fat deposition in patients with T2DM [38]. Therefore, SGLT2i have the potential to improve cardiometabolic risk in T2DM patients. Meanwhile, SGLT2i have a uricosuric effect reducing plasma uric acid levels by approximately 15% [55]. This mechanism might have an additional beneficial cardioprotective effect, since level of plasma uric acid has been proven to be an independent marker for adverse prognosis in HF [17].

Repurposing SGLT2i

After discovery of SGLT2i CV benefits in patients with T2DM, mainly in HF, a new research direction has developed to answer the question whether these drugs can be repurposed as an HF medication, even in patients without diabetes.

The first trial reporting on the potential benefits of SGLT2i in HFrEF, in both T2DM and nondiabetic patients, was the DAPA-HF, published in 2019 [27]. In this trial, 4744 patients (45% with T2DM), with HFrEF (LV ejection fraction < 40%) and increased NT-proBNP were enrolled and followed for a mean duration of 18.2 months. They were randomized to receive either dapagliflozin 10 mg OD or placebo, in addition to the standard HF therapy. Patients with an estimated GFR < 30 mL/min/1.73 m^2, symptomatic hypotension or systolic BP < 95 mmHg, or T1DM were excluded. The study met its primary outcome, reporting a statistically significant reduction in the composite of worsening HF and CV death by 26% ($p < 0.001$). The primary outcome occurred in 386 (16.3%) patients in the dapagliflozin group and in 502 (21.2%) in the placebo group (hazard ratio 0.74; 95% CI: 0.65 - 0.85). In the dapagliflozin arm, 231 (9.7%) patients were hospitalized for worsening HF compared to 318 (13.4%) in the placebo arm (hazard ratio 0.70; 95% CI: 0.59 - 0.83). Death from CV cause was observed in 227 (9.6%) patients who received dapagliflozin and in 273 (11.5%) who received placebo (hazard ratio 0.82; 95% CI: 0.69 - 0.98). Death from any cause occurred in 276 (11.6%) patients in the dapagliflozin group and in 329 (13.9%) in the placebo group (hazard ratio 0.83; 95% CI: 0.71 - 0.97). An important finding was that the results did not differ between diabetic and non-diabetic patients. Moreover, there were no differences in adverse events between the 2 groups.

In 2020, another trial has reported the effects of empagliflozin in patients with HFrEF with or without diabetes [32]. The EMPEROR-Reduced trial recruited 3730 patients (49% with T2DM), with symptomatic HF ranging from NYHA class II to IV, LV ejection fraction under 40%, and increased NT-proBNP. These patients were randomized to receive empagliflozin 10 mg OD or placebo, in addition to standard HF therapy, and were followed for a period of 16 months. The study met its primary outcome reporting a statistically significant 25% reduction in the composite of CV death or hospitalization for worsening HF. The primary outcome occurred in 361 (19.4%) patients of the empagliflozin group and in 462 (24.7%) in the placebo group (hazard ratio 0.75; 95% CI 0.65 - 0.86). In the empagliflozin arm, 246 (13.2%) patients were hospitalized for HF compared to 342 (18.3%) in the placebo arm (hazard ratio 0.69; 95% CI: 0.59 - 0.81). Death from CV cause was observed in 187 (10.0%) patients who received empagiflozin and in 202 (10.8%) who received placebo (hazard ratio 0.92; 95% CI: 0.75 - 1.12). Death from any cause occurred in 249 (13.4%) patients in the empagliflozin group and in 266 (14.2%) in the placebo group (hazard ratio 0.92; 95% CI: 0.77 - 1.10). Moreover, there was a significant reduction in the secondary endpoints, with 30% for HF hospitalization ($p < 0.001$). As in DAPA-HF with dapagliflozin, empagliflozin effect on outcomes was consistent in patients regardless of the presence or absence of T2DM. Another beneficial effect encountered was the slowing of the annual rate of decline in renal function (assessed as a slope of the estimated GFR analysed on the basis of on-treatment data with a random coefficient model) in the empagliflozin group compared with the placebo group.

Both DAPA-HF and EMPEROR-Reduced trials have reached their primary and secondary endpoints showing their favourable influence on CV outcome in both diabetic and nondiabetic patients. However, even though they were not formally tested for significance, both studies analysed the two components of the primary outcome separately. Thus, in DAPA-HF, the hazard ratio (HR) for CV death was 0.82 (95% CI: 0.69 - 0.98) which is significant, whereas in EMPEROR-Reduced the HR for CV death was 0.92 (95% CI: 0.75 - 1.12), a result that is not nominally significant [27, 32]. This difference on CV death between the two drugs is rather debatable, since in the EMPEROR-Reduced trial, the enrolled patients had a more severe HF, with a lower mean LV ejection fraction, by comparison with DAPA-HF trial, suggesting that these drugs might be less effective on more advanced HF

[12]. A meta-analysis including both these trials showed a significant 31% (hazard ratio 0.69; 95% CI: 0.62 - 0.78; $p < 0.0001$) reduction in first HF hospitalization, a 26% reduction in the combined risk of CV death or first HF hospitalisation (hazard ratio 0.74; 95% CI: 0.68 - 0.82; $p < 0.0001$), a 25% reduction in the combined risk of CV death and HF recurrent hospitalisations (hazard ratio 0.75; 95% CI: 0.68 - 0.84; $p < 0.0001$). The risk of the composite renal end-point was also reduced (hazard ratio 0.62; 95% CI: 0.43 - 0.90; $p = 0.013$). A more modest, but significant 13% reduction in all-cause death (hazard ratio 0.87; 95% CI: 0.77 - 0.98; $p = 0.018$) and a 14% reduction in CV death (hazard ratio 0.86; 95% CI: 0.76 - 0.98; $p = 0.027$) was computed. No heterogeneity of the treatment effects was found in any of these endpoints. Treatment effects were consistent for subgroups, based on age, sex, diabetes, treatment with an angiotensin receptor neprilysine inhibitor (ARNI) and baseline eGFR, but treatment-by-subgroup interactions were found for NYHA functional class, race and region. The hazard ratio for patients with NYHA class III - IV (hazard ratio 0.87; 95% CI: 0.75 - 1.01; $p = 0.064$) was significantly lower from that of patients with NYHA class II (hazard ratio 0.67; 95% CI 0.59 - 0.76; $p < 0.0001$), with a p for interaction of 0.0087 [58]. These findings suggest that the inconsistent results regarding CV mortality in patients treated with either dapagliflozin or empagliflozin can stem from the lower magnitude of effect on this particular outcome along with the possible different effect in various disease states.

These two landmark trials have had a major impact for clinical practice and both ESC and ACC have updated their recommendation on the treatment of patients with HFrEF. Therefore, currently, dapagliflozin and empagliflozin were repurposed and are recommended to reduce the combined risk of HF hospitalization and CV death in symptomatic patients with HFrEF, already receiving guideline-directed optimal therapy, regardless of the presence of T2DM [24, 41]. Several trials investigating the role of SGLT2i in HF with preserved ejection fraction are awaited [1, 52].

Conclusions

Sodium-glucose co-transporter-2 inhibitors have been initially developed only as glucose-lowering drugs, however they have expanded far beyond this purpose after several large clinical trials have shown impressive reduction in major cardiovascular outcomes. Furthermore, dapagliflozin and empagliflozin significantly lowered the risk of HF hospitalization and CV death in patients with HFrEF even in the absence of T2DM, with no serious adverse events. The cardioprotective mechanisms of the SGLT2i, even though still incompletely understood, include an association between improvement in cardiac pre- and after-load, prevention of cardiac remodelling, direct cardiac effects with improved cardiac energetics and ion handling, anti-inflammatory effects, and anti-fibrotic effects. Therefore, both mechanistic insights as well as clinic trial data have shifted SGLT2i classification from only anti-hyperglicaemic drugs to potent HF treatment drugs.

Conflict of interest

The authors declare no conflict of interest.

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