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REVIEW

Sodium-glucose co-transporter-2 inhibitors: peculiar "hybrid" diuretics that protect from target organ damage and cardiovascular events

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Heart failure;
Cardiovascular disease;
Renal protection

Abstract *Aims:* Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been proven to lead to relevant cardiovascular benefits, regardless of glycemic control function. SGLT2i have on the one hand led to reduction in cardiovascular events such as heart failure and on the other hand to renal protection. Blood pressure reduction and kidney function play a central role in these outcomes. This focused review describes the main mechanisms and clinical aspects of SGLT2i.
Data synthesis: These drugs act on the proximal renal tubule and behave as diuretics with a "hybrid" mechanism, as they can favour both natriuresis and enhanced diuresis due to an osmotic effect dependent on glycosuria, resulting in blood pressure decrease. The exclusive peculiarity of these "diuretics", which distinguishes them from loop and thiazide diuretics, lies also in the activation of the tubule-glomerular feedback.
Conclusions: This mechanism, resulting in modulation of arterioles' tone and renin secretion, contributes to the favorable outcomes, suggesting a wider use of SGLT2i in internal medicine, nephrology and cardiology.

Abbreviations: A1AR, A1 adenosine receptor; A2AR, A2 adenosine receptor; ABPM, 24-h ambulatory blood pressure monitoring; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACEi, angiotensin converting enzyme inhibitors; AKI, acute kidney injury; ANP, atrial natriuretic peptide; ARB, angiotensin II type 1 receptor blockers; ATP, adenosine triphosphate; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GFR, glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City cardiomyopathy questionnaire; NNT, number-needed-to-treat; NPRC, natriuretic peptide clearance receptor; NPs, natriuretic peptides; PRA, plasma renin activity; RAAS, renin–angiotensin–aldosterone system; RCTs, randomized clinical trials; SGLT2i, sodium-glucose co-transporter-2 inhibitors; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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Introduction

Blood pressure (BP) reduction in patients with diabetes has a primary role in preventing cardiovascular diseases (CVD) [1]. Recently, glucose-lowering therapy has been enriched by drugs that are also able to reduce CV events in patients with diabetes: the glucagon-like-peptide 1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 inhibitors (SGLT2i) [2]. Regarding SGLT2i, two main findings clearly emerged from the first (EMPA-REG OUTCOME) [3] to the last (CANVAS Program and DECLARE-TIMI 58) [4,5] outcome trials: 1) the significant reduction in CV events including heart failure (HF); 2) the central role of kidney and the renal protection. Furthermore, the long-term positive effects on CV outcomes are unlikely to be related to glycemic control, while a more relevant effect could be played by the reduction of blood volume, body sodium, and, therefore, BP. Moreover, their mechanism of action exerts specific intrarenal hemodynamic changes, leading to renal protection [6], that are not completely reproducible by thiazide-like diuretics even in combination with angiotensin converting enzyme inhibitors (ACEi) or angiotensin II type 1 receptor blockers (ARB). This review describes the main mechanisms of action and clinical aspects of the SGLT2i, focusing on their peculiar diuretic properties.

Mechanism of action of SGLT2i and kidney

Osmotic diuresis, natriuresis and glomerular hemodynamics

SGLT2 is a low-affinity high-capacity co-transporter distributed mainly along the early segments of the proximal renal tubule and therefore leads to peculiar renal effects of SGLT2i. Glucose reabsorption is increased in diabetic patients. Human studies have shown conflicting evidence regarding the expression of SGLT2 in diabetic patients. An increased expression of SGLT2 in tubular cells was reported in some studies [7], whereas other studies reported the opposite [8]. The inhibition of this mechanism to increase glucose excretion, lower blood glucose and glycated hemoglobin levels is the original reason for these agents to be classified as “antidiabetic drugs”. However, these drugs lead to natriuresis and osmotic diuresis dependent on glycosuria and can, therefore, be considered diuretics with a “hybrid” mechanism. A slightly lower osmotic effect is seen in non-diabetic individuals, due to their lower plasma glucose levels (estimated average glycosuria is 75 g and 45–72 g per day for diabetic and non-diabetic subjects, respectively) [9,10]. SGLT2 is responsible for up to 97% of glucose reabsorption and for about 5% of total renal Na^+ reabsorption. The latter can likely increase to 14% in patients with diabetes. SGLT2i therefore lead to reduced sodium reabsorption, which might even be greater due to a functional interaction with the Na^+/H^+ exchanger isoform 3, that mediates most of the sodium reabsorption in the proximal tubule [11]. Up to now, only few studies have compared the diuretic effects of SGLT2i with those of classic diuretics, such as hydrochlorothiazide, in small and heterogeneous samples. The study with the longest follow-up (12 weeks) showed a persistent decrease in circulating volume of 7.3% with dapagliflozin, estimated using radioisotope techniques, not reported with hydrochlorothiazide [12]. After treatment initiation with SGLT2i, there is an increased urinary output (ranging from approximately 110 ml/day to 470 ml/day) that returns to normal within 12 weeks [13], when natriuresis is attenuated through compensatory mechanisms and a new stable state is achieved, similarly to other diuretics. Furthermore, an increased vasopressin-induced solute-free water reabsorption has been recently found in rats treated with SGLT2i, in order to maintain body fluid volume [14]. The proximal tubular action of SGLT2i increases the quantity of sodium, together with water and glucose, reaching the lower parts of the renal tubule, resulting in increased natriuresis, glycosuria and diuresis. The macula densa adjusts the glomerular filtration rate (GFR) to the tubular salt load. The increased sodium in the renal tubule is sensed by the Na–K–2Cl co-transporter of the macula densa, that promptly releases adenosine, thus inducing vasoconstriction of the afferent arteriole (tubule-glomerular feedback) and a reduction in the GFR (see mechanisms detailed below). Patients with diabetes are usually obese with a volume-overload due to the dietary sodium excess and the hyper-reabsorption of sodium/glucose via SGLT2. This leads to glomerular hyperfiltration, because of the consequent reduction of the tubule-glomerular feedback. Empagliflozin was found to increase urine adenosine excretion in patients with type 1 diabetes mellitus (T1DM), documenting the increased activity of the macula densa in the regulation of renal hemodynamics, when SGLT2 is inhibited [15]. This results in a reduction of glomerular capillary pressure and BP-dependent hyperfiltration. Indeed, previous studies with SGLT2i on T1DM subjects had found a 7 mmHg [16] and a 19% [17] reduction in intraglomerular pressure regardless of the reduced serum glucose levels or the increased glycosuria. Now, if we take into account that most type 2 diabetes mellitus (T2DM) patients are already taking ARB or ACEi (81% in the EMPA-REG OUTCOME trial) [3], which reduce glomerular capillary pressure by relaxing the efferent arteriole, we can hypothesize how SGLT2i and renin–angiotensin–aldosterone system (RAAS) blockers could be complementary in reducing intraglomerular pressure and hyperfiltration, cooperating in glomerular and therefore nephron protection. Studying and understanding the exact interaction between SGLT2i and other drugs that alter intrarenal hemodynamics (included RAAS blockers) in clinical practice is not easy, given that their individual renal hemodynamic effects are predominantly conceptual and derived from animal studies or small and heterogeneous clinical studies [18]. Most of the evidence on renal hemodynamics with SGLT2i comes from studies on animal models or T1DM patients and remains speculative in T2DM [15–19]. A recent small clinical study on patients with T2DM evaluated indirect measurements of glomerular pressures and relative reciprocal contractile

state of afferent (preglomerular) vs. efferent (postglomerular) arterioles [20]. By indirect estimates of intrarenal hemodynamics, this study suggests a role of efferent arteriole dilatation rather than of afferent arteriole constriction, when patients, mostly treated with RAAS antagonists (75%), are also treated with SGLT2i. The authors confirm the increase in renal/urinary adenosine, following the activation of the tubule-glomerular feedback, previously found in T1DM subjects [15]. However, they hypothesize a vasodilatory action of adenosine on the efferent (postglomerular) arteriole through A2 adenosine receptor (A2AR), when the potential for preglomerular vasoconstriction is limited, such as in T2DM patients in which a much higher renal vascular resistance is already present. Their data could be interpreted also as the result of an enhanced efficacy of RAAS antagonists, due to the macula densa adenosine-mediated reduction of renin secretion (see below), that is previously increased by the usual concomitant ACEi/ARB therapy [21]. Therefore, in the presence of the well-documented tubule-glomerular feedback, which avoids, at least in part hyperfiltration, glomerular intracapillary pressure could be further reduced by this mechanism. However, further investigations on the renal hemodynamics in T2DM are needed. Up to now, although speculative, the increased vasoconstrictor tone of afferent arteriole, driven by the release of adenosine following the activation of tubule-glomerular feedback, as previously described, remains the more diffuse hypothesis.

SGLT2i and renin–angiotensin–aldosterone system

The increased sodium delivery to the macula densa theoretically leads to lower renin levels *per se*. Adenosine is critical for the inhibition of renin release. Macula densa cells release adenosine triphosphate (ATP) in response to a high extracellular Na^+Cl^- concentration. ATP can be rapidly degraded into adenosine in the interstitium of the juxtaglomerular apparatus, acting mainly on the afferent arteriole. Smooth muscle contraction and suppression of renin release is induced via activation of A1 adenosine receptor (A1AR) by adenosine. In the early stages of treatment, the natriuresis and the transient polyuria potentially activate the RAAS, leading to an initial increase in renin levels in the first month after starting SGLT2i, but not after 3–6 months [22]. In fact, in chronic SGLT2i administration, the effects on blood volume are slightly reduced and the urinary output returns to normal [23], because a new steady state is reached thanks to counter-regulatory mechanisms, similarly to what happens for classic diuretics [24]. This new steady state is believed to be one with slightly lower total body sodium and blood volume. The complex interaction of these mechanisms led to mixed results regarding the consequences (activation/inhibition) on the systemic RAAS, although an activation of the intrarenal RAAS has been excluded in chronic SGLT2i treatment [25]. Inversely, experimental models with inhibited SGLT2 activity showed lower intrarenal RAAS activation [25–27].

Comparison with the "traditional" diuretics

These "hybrid" diuretics show a major advantage compared to thiazides and thiazide-like diuretics, that act on the Na^+Cl^- co-transporter in the distal convoluted tubule (located after the macula densa), or loop diuretics, that block the Na–K–2Cl co-transporter of both the Henle loop and the macula densa, making the macula insensitive to the increased tubular sodium coming from the Henle loop. In fact, loop diuretics do not activate the tubule-glomerular feedback and sharply stimulate RAAS. The blockade of Na–K–2Cl co-transporter on the macula densa by loop diuretics counterbalances the suppression of renin release by high tubular Na^+Cl^- concentrations. In addition they indirectly stimulate renin release due to the reduction of blood volume and BP. Higher renin release is among the well-documented pathophysiological mechanisms underlying diuretic resistance in HF patients [28]. Therefore, loop and thiazide/thiazide-like diuretics, when used without a RAAS antagonists, do not protect glomeruli from the increased pressure and hyperfiltration, maintaining GFR at the expenses of increased workload with glomerular chronic damage. This being said, the concomitant use of loop diuretics did not appear to affect the renal benefit of SGLT2i, despite some Na–K–2Cl channel inhibition on macula densa by loop diuretics, thus suggesting that the tubule-glomerular feedback activated by SGLT2i is not impaired by loop diuretics [29]. Moreover, it is important to remember that SGLT2i, unlike loop and thiazide diuretics, are not associated to a systemic sympathetic hyperactivity [30]. Studies on animal models showed that dapagliflozin reduced markers of sympathetic nervous system such as tyrosine hydroxylase and noradrenaline in kidney and heart [31], therefore leading to a decreased inappropriate activation of sympathetic activity typically found in obesity, hypertension and diabetes.

The "hybrid" diuretic effect of SGLT2i on the proximal tubule and the changes in glomerular hemodynamics resemble at least in part those found with sacubitril/valsartan, a drug that enhances natriuretic peptides (NPs) activity and is effective in HF patients with reduced (HFrEF) or mid-range ejection fraction [32]. Both SGLT2i and sacubitril/valsartan exert direct effects on proximal tubular reabsorption of sodium and therefore stimulate tubule-glomerular feedback. NPs, especially atrial natriuretic peptide (ANP), significantly decrease sodium reabsorption in the proximal tubule, through the activation of NPR-A/cGMP/PKG pathway, thus increasing sodium delivery to the distal nephron segment [33]. Glomeruli are therefore protected from hyperfiltration, given the increased afferent constriction mediated by the adenosine from the macula densa, not burdened by the long-term fall in GFR thanks to the bland efferent vasodilation arteriole that is a main target of angiotensin II. Not by chance, sacubitril/valsartan was found to maintain or even improve renal function in HF patients [34]. The main renal hemodynamic actions of SGLT2i in comparison with sacubitril/valsartan and loop diuretics are summarized in Fig. 1.

Pathophysiological and clinical benefits of SGLT2i

On blood volume and blood pressure

SGLT2i reduce plasma volume by 7% [12] and increase sodium excretion. The resulting reduction of blood volume is associated with BP lowering, consistent in all the randomized clinical trials (RCTs) on SGLT2i [3–5]. Recent meta-analyses of available RCTs showed a significant reduction of approximately 2–4 mmHg for systolic BP and 1–2 mmHg for diastolic BP [35], a decrease, which could contribute to CV benefits of SGLT2i [36]. The BP reduction has been confirmed in smaller studies and sub-studies with 24-h ambulatory BP monitoring (ABPM), reporting significant reduction in 24 h BP, daytime BP and night-time BP [37]. No significant differences were found between the various SGLT2i of interest. Moreover, this effect was found to be independent of concomitant use of other anti-hypertensive drugs [38,39]. Although not as important as daytime BP reduction, a significant night-time BP reduction has also been described, likely due to the decreased diuresis for lower glucose levels during night-time, to the circadian regulation of renal function, and also to the increased RAAS activity [39]. Higher night-time BP is typical of the salt-sensitive phenotype, where higher BP is required to excrete sodium from the body, and is strongly predictive of CVD and hypertension-mediated organ damage [40,41]. A very recent meta-analysis comparing SGLT2i with low-dose hydrochlorothiazide, described a greater night-time BP-lowering with SGLT2i, likely also due to the shorter half-life of hydrochlorothiazide [42]. Furthermore, empagliflozin led to a significant daytime and night-time BP reduction after 24 weeks, with a magnitude comparable to diuretics or calcium channel blockers, in a recent study on 150 T2DM African Americans [43]. These are salt-sensitive patients in which the BP response to diuretics is generally greater compared to RAAS blockers. Interestingly, BP lowering, together with weight lowering, is partially independent of renal function, while the decrease of glycated hemoglobin is reduced with increasing renal damage [44].

The SGLT2i “hybrid” diuretic activity, which couples osmotic diuresis with natriuresis and a negative salt balance, likely plays a key role in the anti-hypertensive potential of this drug class. In clinical settings, a correlation between the decrease in systolic BP and the increase in

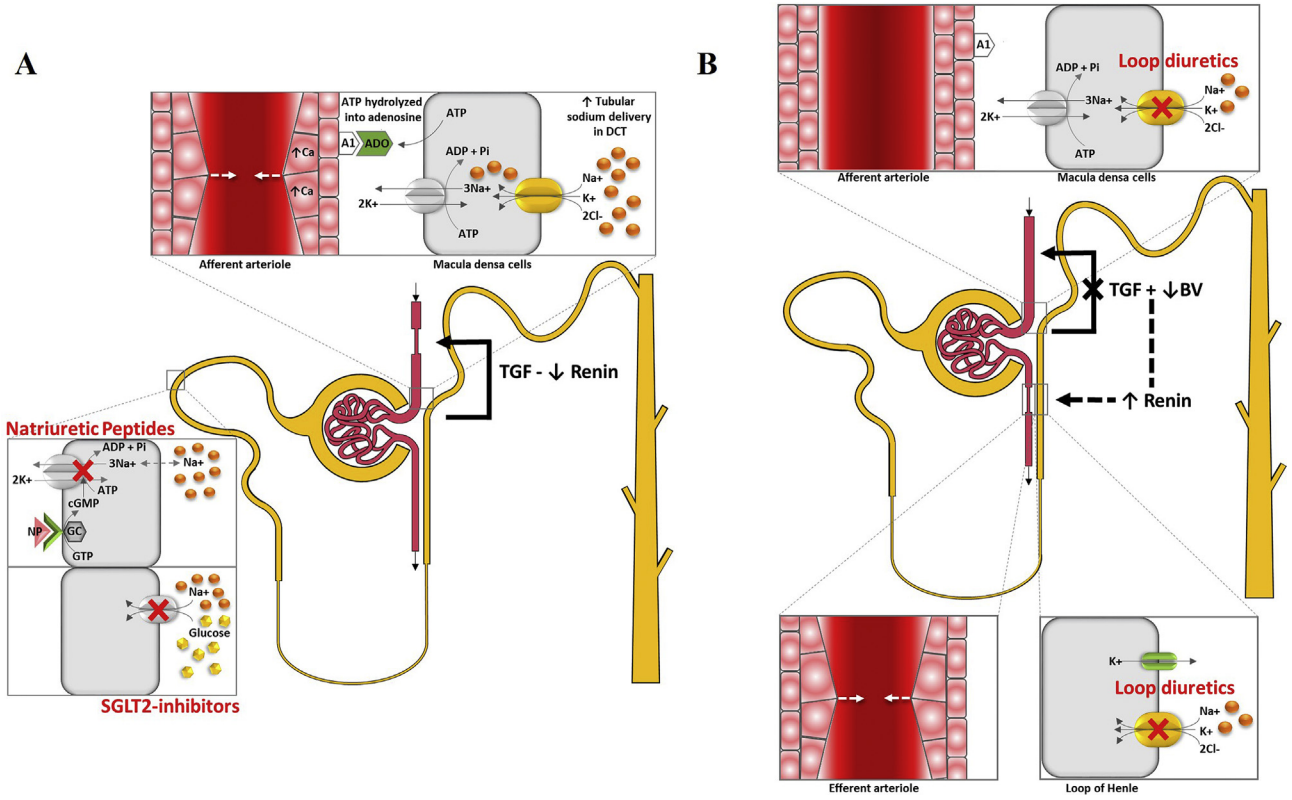

Figure 1 Renal actions of SGLT2 inhibitors in comparison with sacubitril/valsartan and loop diuretics. Panel A. Natriuretic peptides and SGLT2 inhibitors effects on proximal convoluted tubule and macula densa. Both natriuretic peptides and SGLT2 inhibitors decrease sodium reabsorption in the proximal tubule cells. The enhanced sodium delivery in the distal convoluted tubule (DCT) is sensed by the Na^+-K^+-$2Cl^-$ co-transporter of the macula densa that releases adenosine triphosphate (ATP). ATP is rapidly hydrolyzed into adenosine (ADO) in the interstitium of the juxtaglomerular apparatus, thus inducing vasoconstriction of the afferent arteriole (tubule-glomerular feedback, TGF) and suppressing renin release via activation of A1 adenosine receptor (A1). Panel B. Loop diuretics effect on the loop of Henle and macula densa. The blockade of Na^+-K^+-$2Cl^-$ co-transporter on loop of Henle and macula densa, mediated by loop diuretics, abrogates the suppression of renin release by high tubular Na^+ concentrations, in addition to the indirect stimulus of renin release due to the reduction of blood volume (BV) and blood pressure. Loop diuretics do not activate the TGF. ADP: adenosine diphosphate; Pi: phosphate; cGMP: cyclic guanosine monophosphate; GC: guanylate cyclase; GTP: guanosine triphosphate; ATP: adenosine triphosphate; A1: adenosine receptor 1.

urinary sodium excretion was also reported up to 6 months after administration of SGLT2i [45]. In addition to the natriuretic and osmotic diuretic effects, other mechanisms have been proposed to explain the lower BP profile secondary to treatment with SGLT2i. The BP reduction induced by SGLT2i is not accompanied by a significant increase in heart rate in T2DM patients, as expected after an increase in urine volume in the short-term. As previously discussed, this suggests that SGLT2i likely affect the sympathetic nervous system, that could contribute to BP lowering, although the precise mechanisms are still unclear [30]. Experimental studies showed how sodium balance can affect the activity of sympathetic nervous system [46], and the acute lowering of body sodium (natriuresis) could reset it to a reduced activity. This mechanism, together with the BP lowering without an increase in heart rate, contributes to the reduced cardiac afterload and heart protection. Moreover, SGLT2i administration has been associated with a reduction in body weight (and body adipose depots). A weight loss of 2–3 kg in about 6 months has been reported and likely attributable to a loss of adipose tissue mass rather than extracellular fluids [22]. In addition to the energy loss linked to glycosuria (about 300 kcal/d), partly offset by the increased caloric intake, SGLT2 inhibition modulates multiple metabolic pathways. For example, insulin levels are reduced, while glucagon levels are increased, resulting in hepatic glycogenolysis and gluconeogenesis [9]. Moreover, insulin in the presence of high glycaemic levels is a potent inducer of the NPs clearance receptor (NPRC) [47]. Therefore, SGLT2i could enhance NPs activity by reducing insulin levels. Furthermore, lipolysis is stimulated leading to higher levels of circulating free fatty acids for lipid oxidation and ketogenesis [9], a metabolic change that can have a role in CV benefits, especially improving the cardiac metabolism [48]. Finally, several studies showed also a reduction in arterial stiffness, likely due to a direct effect of SGLT2i on the arterial vessel and oxidative stress, although not all evidences are in agreement [49,50].

On renal function

Up to now, RAAS blockers were the only drugs recommended to prevent and slow the progression of renal damage in patients with T2DM and hypertension [51]. However, all the major published RCTs found that SGLT2i are able to protect the kidney, even though most of the participants had a baseline estimated GFR (eGFR) $>$ 60 ml/min/1.73 m^2 and normal albuminuria [52,53]. In addition to these, the CREDENCE trial tested the renal and CV effects of canagliflozin in patients who were already taking RAAS blockers and who suffered from T2DM and chronic kidney disease (CKD), defined by an eGFR between 30 and 89 ml/min/1.73 m^2 and a urine albumin-to-creatinine ratio between 300 and 5000 mg/g. Authors found a 30% reduction in the primary composite outcome (end-stage kidney disease, doubling of serum creatinine, or death from renal or CV causes) [54]. Additionally, similar results were found in patients with more advanced renal impairment (eGFR 30–45 ml/min/1.73 m^2) at baseline and across all levels of baseline HbA1c, including 650 patients with HbA1c levels below 7% [55]. The results translate into a number-needed-to-treat (NNT) of 19, which is lower than that reported in previous studies with ARB alone [56]. All the RCTs have been included in a very recent meta-analysis that confirmed the beneficial effects on both the progression of renal damage (35% reduction compared to placebo) and risk of acute kidney injury (AKI) (25% reduction compared to placebo), regardless of CKD stages, levels of albuminuria and treatment with RAAS blockers [6]. Recently, the lower rate of eGFR decline with SGLT2i was also confirmed in a real-world observational cohort study, involving more than 65,000 patients with T2DM [57]. The changes in glomerular hemodynamics explain the eGFR trend and the reduction in albuminuria after inhibition of SGLT2, similarly to the RAAS blockade. In fact, the early eGFR fall after SGLT2i (3–5 ml/min/1.73 m^2) is followed by a long-term decrease in the eGFR slope with a slower progression of kidney disease compared to placebo [6,53]. The initial transient drop in eGFR and the long-term eGFR stabilization were also confirmed in T2DM patients with moderate renal impairment (eGFR: 45–59 ml/min/1.73 m^2) [58]. In terms of albuminuria, RCTs showed a reduction in urinary albumin-to-creatinine ratio (the higher the baseline urinary albumin excretion, the greater the reduction), after only few weeks of treatment, which was then maintained during the long-term treatment [59]. Concomitant therapy with SGLT2i and RAAS inhibitors may provide additional benefits on albuminuria reduction [29], without increased risk of AKI, volume depletion or hyperkalemia, as observed in the CREDENCE trial [54]. The activation of the tubule-glomerular feedback with the positive direct effects on renal hemodynamics, together with the improvement of cardiac function, have been proposed to be the key factors involved in renal protection. However, other possible direct non-hemodynamic mechanisms are emerging, such as improvement of inflammation, tubular fibrosis and mitochondrial function (Table 1) [60,61]. To this date, these findings are mainly focused on patients with diabetes, but other RCTs are exploring the renal outcome, outside of the diabetic kidney disease, even in advanced renal disease (eGFR $<$ 20 ml/min/1.73 m^2) [62,63].

On major adverse cardiovascular events and mortality

In the CV outcome trials on patients with T2DM, SGLT2i led to a significant reduction in major adverse CV events (11%) and all-cause death (15%), showing greater benefits in patients with known atherosclerotic CVD, but without significant effects on stroke [64]. The reasons for this unexpected result on cerebrovascular events are still the subject of debate and need future studies. A possible role could be played by the mild elevation in hematocrit and blood viscosity, linked to volume depletion, which could counteract the effects of BP lowering [65]. However, current data are insufficient to confirm or disprove this hypothesis. Interestingly, sub-analyses of RCTs showed a positive effect of SGLT2i on stroke in Afro-Americans, in

Table 1 Possible favorable mechanisms of SGLT2 inhibitors beyond diuretic effects and blood pressure lowering.

Heart protection
- Improved oxygen delivery (stimulation of renal erythropoietin secretion) [70]
- Reduced sympathetic nervous system activity [31]
- Improved mitochondrial respiration and coronary vasodilation (inhibition of sodium/hydrogen exchanger 1) [97]
- Reduced inflammation and oxidative stress (improved mitochondrial function) [98] leading to reduced fibrosis
- Improved contractility (inhibition of calcium/calmodulin-dependent kinase II activity) [99]
- Improved myocardial efficiency (utilization of fatty substrates) [100]
- Epigenetic modifications [101]
- Improved metabolism and slowed kidney disease progression [102]
Vascular protection
- Reduced low-grade tissue inflammation [103]
- Reduced oxidative stress and improved endothelial function [104]
- Reduced epicardial fat deposition and modulation of leptin and renin-angiotensin-aldosterone system [105]
- Reduced vascular stiffness [49]
- Increased vascular progenitor cells [106]
- Improved metabolism and cardiorenal health [102]
Renal protection
- Reduced tubular senescence and glomerular loss [107]
- Reduced renal inflammation, oxidative stress and fibrosis [108,109]
- Reduced energy demand (ATP production) [70]
- Reduced uric acid levels [110]
- Improved metabolism and cardiovascular health [102]
Metabolic protection
- Reduced glycated hemoglobin levels [111]
- Reduced body weight and adiposity [112]
- Reduced uric acid levels [110]
- Reduced liver fat [113]

ATP: adenosine triphosphate.

whom overweight and high sodium intake are prevalent and a greater BP reduction may be conferred by these drugs [65]. Furthermore, the positive effects of SGLT2i were also present for hemorrhagic stroke, which is likely to be more strongly associated with higher BP than ischemic stroke [66]. On the other hand, when major adverse CV events (MACE) were combined, the benefits of SGLT2i were found to be reduced or even absent in Afro-American T2DM patients [67].

In the EMPA-REG OUTCOME trial on 7020 patients with T2DM at high CV risk, a reduction of 38% on CV death and 32% on all-cause death was found with empagliflozin compared to placebo after only 3.1 years of median observation time [3]. It should be noted that most patients in these trials were already taking both anti-hypertensive and lipid-lowering drugs [3,5]. This highlights the advantage of SGLT2i on top of an already adequate CV therapy. The results of the CREDENCE trial were stratified by presence/absence of known CVD [68]. The cumulative risk for MACE was 32% lower in the primary prevention group (those without known CVD at study entry) and 15% lower in the secondary prevention group. Reductions in CV death or hospitalization for HF were 26% in the primary prevention group and 34% in the secondary prevention group. However, the reduction of MACE in primary prevention patients was not confirmed in the sub-analysis of DECLARE-TIMI 58 Trial with dapagliflozin [5,69], thus still leaving doubts about the benefits in this specific subpopulation.

An increase in hematocrit was found across all outcome trials up to day and has been proposed as an indicator of the effective diuretic action of SGLT2i, as a consequence of the natriuretic and the glycosuria-driven osmotic effect, at least in the initial period of treatment. On the contrary, a reduction in both metabolic stress and hypoxia in the microenvironment around the proximal tubules is probably involved with an increased erythropoiesis through the enhanced erythropoietin production by fibroblasts in the long period [70,71]. The suppression of circulating hepcidin was recently described in T2DM subjects treated with dapagliflozin [72]. A mediation analysis from the EMPA-REG Outcome trial found that changes in hematocrit and hemoglobin, as expression of the volume status, were the most important mediators of the risk reduction of CV death by empagliflozin and its diuretic properties have certainly played a role in changing these markers of hemoconcentration [73].

Besides these multiple CV benefits, potential side effects of these drugs also emerged from RCTs. More specifically, in addition to the potential risk of AKI linked to the volume depletion in susceptible individuals with an inadequate fluid intake, an increased risk of genital mycotic infections has been reported in RCTs, while the risk of urinary tract infections did not increase significantly [74]. Even though the several RCTs have provided a well-defined safety profile, few other rare and debated potential side effects have been reported [75]: euglycaemic ketoacidosis, especially in T1DM or during acute illness, bone fractures, Fournier's gangrene, lower limb amputations, the latter three without agreement between RCTs and not confirmed in real-world evidence [76].

On heart failure

In a comparative study between SGLT2i and GLP-1 receptor agonists, the other newer class of antidiabetic agents, both drugs reduced atherosclerotic CV events to a similar degree in patients with established atherosclerotic CVD, but SGLT2i had an increased effect on preventing hospitalization for HF and progression of kidney disease [77]. It is very important to note that hospitalizations for HF showed a greater decrease in patients with worse baseline renal function [54,64]. However, few patients in the aforementioned trials had HF at baseline (10%–14.8%) and only patients with diabetes were included. Moreover, HF was not included as part of the primary endpoint and there was an incomplete identification and characterization of HF, both at baseline and during the course of follow-up [78].

The growing interest on the possible role of SGLT2i in HF has led to ad-hoc RCTs. More specifically, the first SGLT2i trial (DAPA-HF), recruiting also non-diabetic patients with HF and reduced ejection fraction (EF $\leq$ 40%), was recently published [79]. The primary outcome was a composite of worsening HF or death from CV causes. After enrolling 4744 symptomatic HF patients, who were followed for a median of 18.2 months, authors found a 26% lower relative risk of primary outcome (NNT = 21), with a split between curves that emerged in favor of patients on dapagliflozin compared with placebo since the first months. Interestingly, these advantages occurred in patients already taking standard HF therapy, and the primary outcome was reached regardless the concomitant therapy with sacubitril/valsartan (about 10% of the studied population) or the presence/absence of T2DM. This supports the concept that the cardiac positive effect of SGLT2i is independent of diabetic condition. Furthermore, a slight reduction in NT-proBNP levels was also found (−303 pg/ml) in DAPA-HF and was partly confirmed in the DEFINE-HF [79,80]. In these patients, dapagliflozin improved symptoms and quality of life, evaluated through the Kansas City Cardiomyopathy Questionnaire (KCCQ) when compared to placebo [80,81]. This improvement was even greater than that shown with sacubitril/valsartan [82], and it was early and amplified over time [81]. These trials also demonstrated a good safety profile of SGLT2i in non-diabetic HF patients taking concomitant high doses of loop diuretics, in term of hypoglycemia and volume depletion risk, which did not differ between active group and placebo, even in older adults [83]. The hypoglycemic risk in non-diabetic subjects is prevented thanks to the changes in both glycemic/lipid metabolism and energy balance, and the residual transport capacity of SGLT1 that compensates when blood glucose levels decline [9,84]. The reduction in HF events and symptoms was consistent across all age groups and associated with a minor rate of renal adverse events in favor of the dapagliflozin group in patients aged $\geq$75 [80]. This is an important finding given the several comorbidities in the older adults, which can make it difficult to administer and uptitrate standard HF treatment [85]. Both experimental models and small human samples with cardiac damage showed improvement of left ventricular diastolic function and reduction of left ventricular mass, most likely driven by the reduced preload and afterload [86–88]. Additionally, SGLT2i-mediated natriuresis and glycosuria can reduce pulmonary congestion and systemic edema [89]. These effects can at least partially explain the reduction in hospitalizations for HF. A further advantage could be given by their peculiar glycosuric effect, not present in classic diuretics. This property likely results in greater electrolyte-free water clearance and in greater fluid clearance from the interstitial fluid space than from the circulation, providing better control of congestion without reducing arterial filling [90]. Moreover, SGLT2i have been shown to significantly reduce the Na^+ content of the skin, which positively correlates with left ventricular remodeling [91].

Next to the renoprotection and the peculiar “hybrid” diuretic effects, other additional hypotheses have been proposed such as the increase in myocardial energy efficiency, the improvement in mitochondrial function through direct inhibition of Na^+/Hydrogen exchanger 1 (NHE1) in the myocardium, the reduction in oxygen-reactive stress, the increase in hematocrit with improved oxygen delivery, the direct anti-fibrotic and antiarrhythmic properties, mechanisms that remain speculative in the absence of published and reproduced data in humans [92,93] (see Table 1).

Therefore, SGLT2i could provide significant benefit also in HF patients with preserved EF (HFpEF). A sub-analysis of the DECLARE-TIMI 58, a trial with detailed baseline information on EF, showed similar reductions in hospitalization for HF between patients with HFrEF and HFpEF, while a reduction in CV death and all-cause mortality was found only in patients with HFrEF [94]. Up to now, the evidence in HF is limited to dapagliflozin in HFrEF patients, but several RCTs with other SGLT2i are ongoing and are also enrolling HFpEF non-diabetic patients (i.e. EMPEROR HF-Preserved, DELIVER, PRESERVED-HF). The main RCTs on the CV and renal outcomes of SGLT2i are summarized in the Supplementary material (see Table S1).

While we await the development of further innovative drugs [95], consistent evidence supports SGLT2i as a valid new treatment option for patients with HFrEF. A very recent consensus document of the European Society of Cardiology on HF management, stated that both dapagliflozin and canagliflozin should also be considered for patients with T2DM and either established CVD or at high CV risk in order to prevent or delay the onset of and hospitalizations for HF [96]. The association of SGLT2i with sacubitril/valsartan will also be interesting to study in different HF phenotypes.

Conclusion and perspectives

In conclusion, SGLT2i act mainly as “hybrid” diuretics. Natriuresis and glycosuria are key determinants of their clinical benefits, leading to blood volume reduction and decreased BP, thereby reducing cardiac overload, which is

particularly important in HF. Their peculiar site of action, that differentiates them from thiazide and loop diuretics, provides a reduction of intraglomerular pressure restoring the physiologic tubule-glomerular feedback, which is a key factor in renal protection, especially in common conditions of hyperfiltration such as diabetes, obesity and hypertension. If you reduce hyperfiltration, you reduce progressive glomerular damage and loss, and this is one important reason why SGLT2i are “winning” drugs. Among the large number of mechanisms, mostly metabolically-centered, proposed to explain the observed CV effects of SGLT2i, to this day the “hybrid” diuretic activity appears to be the most important. Several issues need to be further clarified, such as the net role of long-term treatment with SGLT2i, loop diuretics and RAAS inhibitors on renal hemodynamics of HF patients, or the role of sodium intake in affecting SGLT2i efficacy.

SGLT2i are likely to become a key drug class in the hands of internists, nephrologists and cardiologists rather than remaining a drug class for diabetologists only. The recent findings on HFrEF non-diabetic patients represent the first step to unmask the true nature of SGLT2i and the number of patients who could benefit from this drug class could be much higher than expected. A bright future for this drug class will be in the prevention of CVD and renal damage, improving CV outcomes, regardless of the presence of diabetes. The “hybrid” diuretic activity of this novel “king” drug class among the antidiabetic drugs, imposes a reconsideration of their main clinical pharmacological effect. This story reminds of a famous sentence from the short tale of Hans Christian Andersen “The Emperor's New Clothes” in which, at the end, a child cried out: “ … But he isn't wearing anything at all!”.

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Declaration of Competing Interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2020.05.030.

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