REVIEW ARTICLE

CONTENTS

Mechanisms of nephroprotective action of sodium–glucose cotransporter type 2 inhibitors

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ABSTRACT

Aim: To study the potential mechanisms underlying the beneficial nephroprotective effects of sodium-glucose cotransporter 2 (SGLT-2) inhibitors.

Materials and Methods: An analysis of literature sources was conducted regarding the clinical, epidemiological, and fundamental aspects of the nephroprotective effects of SGLT-2 inhibitors. For this purpose, articles were searched for and selected in the PubMed database using the following keywords: "sodium-glucose cotransporter-2 inhibitors," "heart failure," "chronic kidney disease," and "cardiorenal syndrome," with a primary focus on studies published in the last 5 years. To provide context and explain the underlying mechanisms, several classical and fundamental studies relevant to the aim of the review were also included.

Conclusions: SGLT-2 inhibitors exert nephroprotective effects through a complex of interrelated hemodynamic, metabolic, and cellular-molecular mechanisms that are largely independent of their hypoglycemic action. The combination of these mechanisms explains the clinically proven nephroprotective effect of SGLT-2 inhibitors in both patients with and without DM and justifies considering them not only as glucose-lowering agents but also as fundamental agents of pathogenetic therapy for chronic kidney disease.

KEY WORDS: sodium-glucose cotransporter 2 (SGLT-2) inhibitors, chronic kidney disease, nephroprotection, cardiorenal syndrome

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INTRODUCTION

Currently, chronic kidney disease and heart failure are epidemics of chronic diseases that may coexist and are based on shared risk factors, causing the development of systemic disorders. The presence of one disease accelerates the onset and progression of the other. Conversely, coexistence of both conditions increases the risk of primary and recurrent hospitalizations, the need for therapy intensification, progression to end-stage kidney disease, and death [1-3]. The spread of CKD has increased significantly over recent decades, mainly due to the substantial rise in DM, which has become the leading cause of CKD. When CKD develops in the presence of cardiovascular diseases (CVD), chronic HF occurs more frequently and has a more severe course. The incidence of newly diagnosed HF in patients with established CKD ranges from 17% to 21% [4]. A decrease in glomerular filtration rate (GFR) is associated with an increased risk of all-cause mortality, cardiovascular mortality, and hospitalization in patients with HF [5-7]. It should also be noted that elevated urinary albumin levels are a prognostic factor for adverse HF outcomes [8].

In recent years, the arsenal of medications for HF treatment has expanded significantly, and therapeutic options for CKD have also increased, particularly due to the introduction of SGLT-2 inhibitors into routine clinical practice. Their effectiveness in patients with HF and CKD is of particular scientific interest. These medications, which entered clinical practice relatively recently and were originally developed for the treatment of type 2 DM, have demonstrated significant benefits in reducing cardiovascular mortality in patients with carbohydrate metabolism disorders in several studies, while also positively affecting the decline in renal function in this patient group [9-13]. Furthermore, several randomized controlled trials subsequently demonstrated significant efficiency of SGLT-2 inhibitors in the treatment of HF and CKD regardless of the presence of type 2 DM [14-17]. These studies reported a substantial nephroprotective effect of SGLT-2 inhibitors, manifested through combined secondary renal endpoints and determining the frequency of renal outcomes in these patients. These unexpected and surprisingly favorable renal effects proved to be highly significant. According to the conducted studies, SGLT-2 inhibitors significantly slowed CKD progression and reduced the risk of acute

kidney injury. Although some differences in endpoint definitions prevent demonstration of absolute identity of results among different representatives of gliflozins, overall outcomes were similar and very promising. The results regarding the risk of onset and progression of albuminuria were also particularly impressive [18-20].

Owing to these striking results, SGLT-2 inhibitors have evolved from a class of glucose-lowering agents into a cornerstone therapeutic option for the prevention, slowing of progression, and improvement of prognosis in cardiorenal syndrome. The mechanisms underlying the nephroprotective effects of gliflozins are therefore of exceptional interest for thorough investigation.

AIM

The aim is to investigate the potential mechanisms underlying the beneficial nephroprotective effects of SGLT-2 inhibitors.

MATERIALS AND METHODS

An analysis of literature sources was conducted regarding the clinical, epidemiological, and fundamental aspects of the nephroprotective effects of SGLT-2 inhibitors. For this purpose, articles were searched for and selected in the PubMed database using the following keywords: "sodium-glucose cotransporter-2 inhibitors," "heart failure,""chronic kidney disease," and "cardiorenal syndrome," with a primary focus on studies published in the last 5 years. To provide context and explain the underlying mechanisms, several classical and fundamental studies relevant to the aim of the review were also included.

ETHICS

All sources used in this literature review are publicly available.

REVIEW AND DISCUSSION

The primary mechanism of the hypoglycemic action of gliflozins in humans is inhibition of sodium–glucose cotransporter 2 (SGLT-2), which is localized in the early segments of the proximal renal tubules and is responsible for the reabsorption of more than 90% of glucose filtered by the glomeruli. The remaining glucose is reabsorbed in the terminal segments of the proximal tubules by another sodium-glucose cotransporter, SGLT-1. SGLT-2 inhibitors reduce glucose reabsorption by approximately 30-50%, resulting in decreased blood glucose levels, glucosuria, and osmotic diuresis [21]. A distinctive feature of these agents is that their glucose-lowering effect is independent of insulin secretion or pancreatic β-cell function; therefore, they do not increase the risk of hypoglycemia. Consequently, SGLT-2 inhibitors provide a mild reduction in both fasting and postprandial glycemia [22].

Under physiological conditions, SGLT-2 is also responsible for the reabsorption of approximately 5% of sodium in tubular fluid. In the presence of diabetes mellitus, sodium reabsorption increases due to upregulation of SGLT-2 and SGLT-1 expression in the proximal tubular epithelium. Accordingly, SGLT-2 blockade is accompanied by natriuresis [23, 24]. It should be noted that another sodium reabsorption mechanism is present in the proximal tubules – the sodium-hydrogen exchanger isoform 3 (NHE3), which mediates reabsorption of up to 30% of filtered sodium [25]. Experimental knockout of NHE3 has been shown to suppress SGLT-2 activity, while inhibition of SGLT-2 also affects NHE3 function [25-27]. As a result, one of the earliest effects of gliflozins observed in clinical studies is increased natriuresis due to inhibition of SGLT-2 activity in the proximal renal tubules. In addition, SGLT-2 inhibitors have been shown to inhibit sodium reabsorption through direct suppression of NHE3 in this nephron segment, likely via phosphorylation mechanisms [28, 29].

Unreabsorbed glucose, which reaches the distal nephron, induces moderate osmotic diuresis. Diuresis associated with SGLT-2 inhibitors occurs both under euglycemic conditions and, to a greater extent, during hyperglycemia, and remains enhanced even in patients with CKD stages 3-4, as well as in chronic and acute heart failure [30, 31]. Notably, the natriuretic and diuretic effects of gliflozins differ substantially from those of conventional diuretics. The diuretic effect of SGLT-2 inhibitors is more short-lived, not accompanied by significant changes in plasma electrolyte concentrations, and does not disturb acid-base balance [32-34]. Moreover, the long-term use of gliflozins does not lead to severe metabolic disturbances such as hyperglycemia or hyperuricemia and, importantly, does not activate the sympathetic nervous system (SNS). The commonly used diuretics, such as loop and thiazide diuretics, act on more distal nephron segments by inhibiting electrolyte reabsorption in the loop of Henle and distal convoluted tubules, respectively. Gliflozins act in the proximal tubule, where sodium reabsorption is coupled with the reabsorption of glucose, uric acid, and other metabolites. By directly inhibiting their reabsorption, SGLT-2 inhibitors induce glucosuria and uricosuria, thereby reducing hyperglycemia and hyperuricemia, unlike other diuretics [35]. This combined diuretic effect – osmotic diuresis due to glucosuria and moderate natriuresis – promotes redistribution of fluid

between intracellular and extracellular, as well as intravascular and extravascular compartments, unlike the effects of thiazide and loop diuretics. Thus, gliflozins primarily reduce interstitial rather than intravascular fluid volume. On the one hand, it contributes to a reduction in sodium content within internal organs, which may be beneficial in cardiovascular diseases, including heart failure and arterial hypertension. Indirect evidence supporting this hypothesis is the ability of dapagliflozin to significantly reduce skin sodium concentration in patients with type 2 DM during long-term use [36]. Earlier studies demonstrated that sodium concentration in the skin and muscles positively correlates with cardiovascular risk in patients with CKD [37, 38]. On the other hand, the absence of significant changes in intravascular volume prevents abrupt alterations in organ perfusion and limits activation of the SNS and the renin–angiotensin system (RAS) [39-42]. Finally, traditional diuretics do not exhibit the pronounced cardioprotective effects observed with SGLT-2 inhibitors and displayed in reduced cardiovascular mortality and fewer hospitalizations for heart failure [43].

One of the key effects of SGLT-2 inhibitors explaining their nephroprotective action is their influence on glomerular filtration and restoration of tubuloglomerular feedback within the nephron [44]. According to the hyperfiltration theory formulated by B. Brenner et al. in 1996 to explain the development and progression of CKD [45], agents that reduce intraglomerular pressure should exhibit nephroprotective properties. The theory posits that a universal renal response to nephron loss, regardless of its etiology, is increased pressure and hyperfiltration in the remaining intact nephrons, allowing temporary maintenance of filtration capacity. Indeed, in early stages, this mechanism normalizes or even increases GFR. Although the pathogenesis of hypertension and hyperfiltration is complex and varies among different diseases, in most cases it is driven by afferent arteriole dilation and efferent arteriole constriction via tubuloglomerular feedback and activation of the RAS [45, 46]. However, prolonged maintenance of renal excretory function through nephron overload is detrimental. Hyperfiltration increases mechanical stress on glomerular capillaries and enhances filtration of tubulotoxic factors such as albumin, growth hormones, and advanced glycation end products. Their interaction with the tubular system increases energy demand, promotes hypoxia, impairs autophagy, and triggers oxidative stress, inflammation, and fibrosis. Over time, nephron loss progresses, and despite single-nephron hyperfiltration, global renal function declines [44].

As noted above, SGLT-2 mediates reabsorption of both glucose and sodium. Therefore, SGLT-2 blockade increases sodium concentration in the tubular fluid by reducing proximal sodium reabsorption, thereby stimulating the juxtaglomerular apparatus (macula densa) in the distal tubule. This leads to adenosine triphosphate (ATP) release from juxtaglomerular cells, which is subsequently degraded to adenosine. Activation of A1 adenosine receptors causes afferent arteriole constriction, resulting in reduced intraglomerular pressure and suppression of hyperfiltration [47, 48]. An additional mechanism increasing sodium delivery in distal parts of the nephron (near the macula densa) is the inhibitory effect of gliflozins on NHE3 activity [49]. To a lesser extent, adenosine also affects A2 receptors in efferent arterioles, leading to the vasodilation [47-49].

It should be emphasized that while a reduction in intraglomerular pressure confers long-term benefits, the initiation of SGLT-2 inhibitors may be associated with a transient increase in serum creatinine or a decrease in GFR. However, GFR gradually recovers within 3-9 months and subsequently remains significantly higher in patients receiving SGLT-2 inhibitors compared with the placebo group. Interestingly, early GFR responses vary. A recent subanalysis of the EMPA-REG OUTCOME trial (patients with type 2 DM and established atherosclerosis) identified three patient subgroups based on GFR dynamics during the first 4 weeks of therapy [50]: those with a significant (>10%) decline in estimated GFR ("dippers," 28%), those with a mild decline (0-10%, 41%), and those with no decline or even an increase in estimated GFR (31%). Multivariate analysis showed that predictors of significant early estimated GFR decline included concomitant diuretic therapy and higher KDIGO risk category (CKD stage/proteinuria degree). Importantly, the magnitude of early estimated GFR decline did not affect long-term safety or efficacy in preventing cardiovascular and renal outcomes. Recent studies further indicate that nephroprotective effects are independent of the extent of initial GFR reduction at therapy initiation [50, 51]. Thus, transient suppression of hyperfiltration is a class effect of gliflozins, followed by a slower long-term decline in GFR compared with placebo. The initial reduction in GFR during SGLT-2 inhibitor initiation is transient and fully reversible. Reduction in albuminuria following decreased intraglomerular pressure is a critically important beneficial effect that lowers the risk of end-stage kidney disease. Long-term SGLT-2 inhibitor therapy reduces the risk of developing microalbuminuria and progression to more severe albuminuria, while increasing the likelihood of regression of established albuminuria during treatment with gliflozins. Accordingly, the urinary albumin-to-creatinine ratio (UACR) significantly decreases in patients with both micro- and macroalbuminuria [18, 52-54]. A meta-analysis of 48 randomized clinical trials involving

more than 50,000 patients treated with gliflozins for over 12 weeks demonstrated a significant reduction in UACR (weighted mean difference – 14.6 mg/g, p = 0.006), with a more pronounced effect in patients with higher baseline UACR [52]. Specifically, the risk of microalbuminuria (RR 0.69, p = 0.032), macroalbuminuria (RR 0.49, p < 0.001), nephropathy progression (RR 0.73, p = 0.012), and end-stage kidney disease (RR 0.70, p = 0.001) was significantly reduced. Thus, SGLT-2 inhibitors exert a beneficial renal effect by reducing the risk of development or progression of albuminuria and lowering the risk of end-stage renal disease compared with placebo or other antidiabetic agents [52].

Under SGLT-2 inhibitor therapy, reabsorptive workload increases in downstream tubular segments, which traditionally receive less oxygen supply. Together with a metabolic shift from glucose to free fatty acids induced by gliflozins, this state mimics renal ischemia. Consequently, hypoxia-inducible factor (HIF)-dependent adaptive mechanisms are activated, leading to increased erythropoietin production and improved oxygen delivery to renal tissue. This represents an indirect antihypoxic mechanism of gliflozins [55, 56]. SGLT-2 inhibitors also increase nitric oxide bioavailability, further contributing to their antihypoxic properties [57]. A direct nephroprotective effect on tubular epithelium has also been demonstrated, manifested by inhibition of mitochondrial lipid peroxidation in proximal tubular epithelial cells. Therapy is associated with reduced markers of inflammation and fibrosis [58-60]. However, distinguishing direct anti-inflammatory and antifibrotic effects from secondary effects mediated by hemodynamic changes and improved carbohydrate metabolism remains challenging and requires further investigation.

Beyond their effects on glomerular hemodynamics, SGLT-2 inhibitors possess additional properties that explain their beneficial impact on CKD development and progression. One key mechanism is metabolic reprogramming: SGLT-2 inhibitors promote lipolysis, induce a negative energy balance, and stimulate ketogenesis by increasing free fatty acid delivery to the liver and lowering the insulin-to-glucagon ratio in systemic circulation. Ketone bodies serve as an efficient energy source for tissues under ischemic conditions. The kidneys and heart exhibit the greatest capacity to utilize ketone bodies (particularly β-hydroxybutyrate) under oxidative stress, which is crucial for maintaining adequate energy supply during impaired perfusion. Beyond energetic benefits, this shift reduces lipotoxic cellular injury and prevents fibrosis [61].

Treatment with SGLT-2 inhibitors leads to weight loss. The body-weight-reducing effect of SGLT-2 inhibitor therapy may be explained by the fact that inhibition of SGLT-2 induces renal glucose excretion, and glucose is a high-calorie substrate. Therapy with SGLT-2 inhibitors is accompanied by reduced leptin production and decreased fat deposition in the perivisceral, pericardial, and perivascular spaces, which contributes to a reduction in insulin resistance, may play a role in improving metabolic processes, has a positive effect on renal function, and is critically important for reducing cardiometabolic risk [61-65].

The use of SGLT-2 inhibitors is also associated with a reduction in serum uric acid levels by an average of 5.9-17.8%, due to decreased urate reabsorption by the epithelium of the proximal tubules via GLUT9b [20, 65]. In particular, a meta-analysis (43 studies, 31,921 patients) demonstrated that SGLT-2 inhibitor therapy is associated with a reduction in uric acid levels both in patients with diabetes mellitus [-31.48 μmol/L; 95% confidence interval (CI): -37.35 to -25.60] and in those without diabetes [-91.38 μmol/L; 95% CI: -126.53 to -56.24]. At the same time, the uricosuric effect of these drugs decreases with the progression of renal dysfunction [66]. The exact mechanism of the hypouricemic effect of gliflozins is unknown. It is assumed that the reduction in serum uric acid occurs in the setting of pronounced glucosuria due to activation of the type 2 isoform of the cotransporter, GLUT9, which increases uric acid excretion into the tubular lumen. Notably, the uricosuric effect of SGLT-2 inhibitors is not accompanied by an increased incidence of nephrolithiasis [67]. Hyperuricemia, through the induction of inflammation, oxidative stress, endothelial dysfunction, and activation of the renin-angiotensin system (RAS), contributes to the progression of tubulointerstitial fibrosis. Therefore, by lowering serum uric acid levels, SGLT-2 inhibitors may indirectly promote protection of the renal tubules.

Numerous studies and meta-analyses have demonstrated a beneficial effect of gliflozins on blood pressure levels, which is not accompanied by an effect on heart rate (HR). On average, these drugs reduce systolic blood pressure by 2-4 mmHg [20]. Moreover, this effect is fully preserved in patients despite reduced renal function. Possible mechanisms underlying this effect include a reduction in plasma volume, weight loss, improved glycemic control (in patients with diabetes or prediabetes), reduced plasma renin production and inhibition of the systemic RAS, decreased inflammation and arterial stiffness, and improved endothelial function. The most important mechanism is considered to be the reduction in plasma volume due to a combined diuretic effect (osmotic diuresis and natriuresis) [61, 68-71].

An important advantage of SGLT-2 inhibitors is the reduction in systolic blood pressure without an increase in

heart rate (HR), which contradicts the conventional concept linking natriuresis with tachycardia [61]. This observation led to the hypothesis that, in addition to natriuresis, SGLT-2 inhibitors may attenuate aberrant SNS stimulation, since a low HR is associated with low sympathetic tone. Evidence supporting this assumption comes from animal studies in which SGLT-2 inhibitors reduced levels of SNS activity markers – norepinephrine, neuropeptide Y, and tyrosine hydroxylase [72]. These data indicate that drugs of this class may contribute to cardioprotective and renoprotective effects by attenuating sympathetic hyperactivity.

Recently, the theory of nutrient deprivation signaling, or the autophagy hypothesis formulated by M. Parker [73], has gained popularity in explaining the mechanisms of action of SGLT-2 inhibitors (including their nephroprotective effects). This theory is based on the assumption that the loss of some calories due to urinary glucose excretion induced by SGLT-2 inhibitors triggers a universal cellular response similar to that observed during fasting, namely activation of autophagy processes (the process by which a cell digests its own organelles and cytoplasmic components via lysosomes to eliminate old and damaged structures) [73-75]. At the cellular level, autophagy results in enhancement of antioxidant mechanisms, reduction of endoplasmic reticulum stress, restoration of mitochondrial function, and an increase in mitochondrial number; at the tissue level it prevents apoptosis and cellular aging, and reduces inflammation and fibrosis. Studies in recent years have shown that similar cellular reprogramming during treatment with gliflozins is also observed in isolated cell cultures, indicating a direct (glucosuria-independent) effect of these drugs [73-75].

Thus, at present, the following are considered the main probable mechanisms of the nephroprotective action of SGLT-2 inhibitors: reduction of hyperfiltration and intraglomerular pressure through constriction of the afferent and dilation of the efferent arterioles, reduction of albuminuria, an antihypoxic effect (both direct, mediated by decreased oxygen demand, and indirect, mediated by increased erythropoietin production), anti-inflammatory and antifibrotic effects, a metabolic shift with stimulation of ketogenesis, leading to increased energy efficiency and reduced lipotoxic cellular damage, reduction of pressure and volume overload, and other pleiotropic effects, including lowering of glycemia, uric acid levels, and body weight, among others. It is likely that the use of gliflozins induces a universal cellular response (autophagy) that improves energy efficiency, reduces cellular stress, and increases cellular resistance to overload in the development of type 2 diabetes mellitus, chronic HF, and CKD. The realization of these mechanisms makes it possible to prevent the development and progression of renal failure and prolong patients' lives. Since patient management focused on cardiorenal protection is crucial for prognosis and quality of life, SGLT-2 inhibitors may contribute to improved treatment strategies for a vast number of patients with cardiorenal-metabolic syndrome. Further studies are needed to evaluate the use of this drug class in patients without carbohydrate metabolism disorders and with various spectra of cardiovascular diseases, as well as CKD, particularly to assess the efficacy and safety of SGLT-2 inhibitors in populations excluded from previous randomized clinical trials, such as very elderly individuals (age >85 years) and/or very frail patients.

The significant nephroprotective effect of gliflozins identified in clinical trials has led to updated CKD guidelines that, for the first time, stipulate the possibility of using SGLT-2 inhibitors (dapagliflozin and empagliflozin) in patients without concomitant diabetes mellitus as an adjunct to therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, in order to reduce the risk of CKD progression, prevent the development of acute kidney injury, and decrease cardiovascular mortality [76].

CONCLUSIONS

SGLT-2 inhibitors exert nephroprotective effects through a complex of interrelated hemodynamic, metabolic, and cellular-molecular mechanisms that are largely independent of their hypoglycemic action. The combination of these mechanisms explains the clinically proven nephroprotective effect of SGLT-2 inhibitors in patients both with and without diabetes mellitus and justifies their consideration not only as glucose-lowering agents but also as fundamental agents of pathogenetic therapy for chronic kidney disease.

REFERENCES

1. Kadowaki T, Maegawa H, Watada H, et al. Interconnection between cardiovascular, renal and metabolic disorders: A narrative review with a focus on Japan. Diabetes Obes Metab. 2022;24(12):2283-96. doi: 10.1111/dom.14829. DOI
2. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709-733. doi: 10.1016/S0140-6736(20)30045-3. DOI
3. Provenzano M, Coppolino G, Faga T et al. Epidemiology of cardiovascular risk in chronic kidney disease patients: the real silent killer. Rev Cardiovasc Med. 2019;20(4):209-220. doi: 10.31083/j.rcm.2019.04.548. DOI

4. Xanthopoulos A, Papamichail A, Briasoulis A et al. Heart Failure in Patients with Chronic Kidney Disease. J Clin Med. 2023;12 (18):6105. doi:10.3390/jcm12186105. DOI
5. Chen Z, Lin Q, Li J et al. Estimated Glomerular Filtration Rate Is Associated With an Increased Risk of Death in Heart Failure Patients With Preserved Ejection Fraction. Front Cardiovasc Med. 2021;8:643358. doi: 10.3389/fcvm.2021.643358. DOI
6. Patel R, Dawit W, Cheng A et al. Long-term prognostic impact of estimated glomerular filtration rate on admission in patients hospitalized for acute heart failure. Cardiorenal Medicine. 2022;12(4):179-188. doi:10.1159/000527147. DOI
7. Birkeland KI, Bodegard J, Eriksson JW et al. Heart failure and chronic kidney disease manifestation and mortality risk associations in type 2 diabetes: A Large multinational cohort study. Diabetes Obes Metab. 2020; 22(9):1607-18. doi: 10.1111/dom.14074. DOI
8. Boorsma EM, Ter Maaten JM, Damman K et al. Albuminuria as a marker of systemic congestion in patients with heart failure. Eur Heart J. 2023;44(5):368-380. doi: 10.1093/eurheartj/ehac528. DOI
9. Verma S, Leiter LA, Zinman B et al. Time to cardiovascular benefits of empagliflozin: a post hoc observation from the EMPA-REG outcome trial. ESC Heart Fail. 2021;8(4):2603-2607 doi: 10.1002/ehf2.13374. DOI
10. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644-57. doi: 10.1056/NEJMoa1611925 16. DOI
11. Wiviott SD, Raz I, Bonaca MP et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347-57. doi: 10.1056/ NEJMoa1812389. DOI
12. O'Hara DV, Lam CSP, McMurray JJV et al. Applications of SGLT2 inhibitors beyond glycaemic control. Nat Rev Nephrol. 2024;20(8):513-529. doi: 10.1038/s41581-024-00836-y. DOI
13. Preda A, Montecucco F, Carbone F et al. SGLT2 inhibitors: from glucose-lowering to cardiovascular benefits. Cardiovasc Res. 2024;120(5):443-460. doi: 10.1093/cvr/cvae047. DOI
14. Packer M, Anker SD, Butler J et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413-1424. doi: 10.1056/NEJMoa2022190. DOI
15. Heerspink HJL, Stefansson BV, Correa-Rotter R et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436-46. doi: 10.1056/NEJMoa2024816. DOI
16. Anker SD, Butler J, Filippatos G et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451-61.doi: 10.1056/NEJMoa2107038.
17. Solomon SD, McMurray JJV, Claggett B et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387(12):1089-98. doi: 10.1056/NEJMoa2206286. DOI
18. Barutta F, Bernardi S, Gargiulo G et al. SGLT2 inhibition to address the unmet needs in diabetic nephropathy. Diabetic Metab Res Rev. 2019;35(7):e3171. doi: 10.1002/dmrr.3171. DOI
19. Mosenzon O, Wiviott SD, Cahn A et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol. 2019;7(8):606-617. doi: 10.1016/S2213-8587(19)30180-9. DOI
20. Bonora BM, Avogaro A, Fadini GP. Extraglycemic effects of SGLT2 inhibitors: a review of evidence. Diabetes Metab Syndr Obes. 2020;13:161-174. doi: 10.2147/DMSO.S233538. DOI
21. Brown E, Heerspink HJL, Cuthbertson DJ et al. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet. 2021;398(10296):262-276. doi: 10.1016/S0140-6736(21)00536-5. DOI
22. Rieg T, Vallon V. Development of SGLT1 and SGLT2 inhibitors. Diabetologia. 2018;61(10):2079-2086. doi: 10.1007/s00125-018-4654-7. DOI
23. Tang J, Ye L, Yan Q et al. Effects of sodium-glucose cotransporter 2 inhibitors on water and sodium metabolism. Front Pharmacol. 2022;23;13:800490. doi: 10.3389/fphar.2022.800490. DOI
24. Grempler R, Thomas L, Eckhardt M et al. Empagliflozin a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes Metab. 2012;14(1):83-90. doi: 10.1111/j.1463-1326.2011.01517.x. DOI
25. Pessoa TD, Campos LC, Carraro-Lacroix L et al. Functional role of glucose metabolism, osmotic stress, and sodium-glucose cotransporter isoform-mediated transport on Na+/H+ exchanger isoform 3 activity in the renal proximal tubule. J Am Soc Nephrol. 2014;25(9):2028-2039. doi: 10.1681/ASN.2013060588. DOI
26. Onishi A, Fu Y, Darshi M et al. Effect of renal tubule-specific knockdown of the Na+/H+ exchanger NHE3 in Akita diabetic mice. Am J Physiol Renal Physiol. 2019;317(2):F419-F434. doi: 10.1152/ajprenal.00497.2018. DOI
27. Silva Dos Santos D, Polidoro JZ, Borges-Junior FA, Girardi ACC. Cardioprotection conferred by sodium-glucose cotransporter 2 inhibitors: a renal proximal tubule perspective. Am J Physiol Cell Physiol. 2020;318(2):328-36. doi:10.1152/ajpcell.00275.2019. DOI
28. Fu Y, Gerasimova M, Mayoux E et al. SGLT2 inhibitor empagliflozin increases renal NHE3 phosphorilation in diabetic Akita mice: possible implications for the prevention of glomerular hyperfiltration. Diabetes. 2014;63(1):A132.
29. Packer M. Activation and inhibition of sodiumhydrogen exchanger is a mechanism that links the pathophysiology and treatment of diabetes mellitus with that of heart failure. Circulation. 2017;136(16):1548-1559. doi: 10.1161/CIRCULA TIONAHA.117.030408. DOI

30. Rosul MM, Bletskan MM, Ivano NV, et al. Priorities of anti-hyperglycaemic drug therapy in patients with type 2 diabetes and heart failure. Wiad Lek. 2020;73(3):609-613. doi: 10.36740/WLek202003139. DOI
31. Wilcox CS. Antihypertensive and renal mechanisms of SGLT2 (sodium-glucose linked transporter 2) inhibitors. Hypertension. 2020;75(4):894-901. doi:10.1161/hypertensionaha.119.11684. DOI
32. Packer M. Lack of durable natriuresis and objective decongestion following SGLT2 inhibition in randomized controlled trials of patients with heart failure. Cardiovasc Diabetol. 2023;22:197. doi:10.1186/s12933-023-01946-w. DOI
33. Wilcox CS, Shen W, Boulton DW et al. Interaction Between the Sodium-Glucose-Linked Transporter 2 Inhibitor Dapagliflozin and the Loop Diuretic Bumetanide in Normal Human Subjects. J Am Heart Assoc. 2018;10;7(4):e007046. doi: 10.1161/JAHA.117.007046. DOI
34. Amani-Beni R, Darouei B, Shafie D et al. The impact of sodium-glucose co-transporter-2 inhibitors on serum sodium and potassium in patients with Heart Failure: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2025;25(1):252. doi: 10.1186/s12872-025-04704-w. DOI
33. Layton AT, Vallon V, Edwards A. Predicted consequences of diabetes and SGLT2 inhibition on transport and oxygen consumption along a rat nephron. Am J Renal Physiol. 2016;310(12):F1269-F1283. doi: 10.1152/ajprenal.00543.2015. DOI
34. Mima A. Renal protection by sodium-glucose cotransporter 2 inhibitors and its underlying mechanisms in diabetic kidney disease. J Diabetes Complications. 2018;32:720-725. doi: 10.1016/j.jdiacomp.2018.04.011. DOI
35. Suijk DLS, van Baar MJB, van Bommel EJM et al. SGLT2 Inhibition and Uric Acid Excretion in Patients with Type 2 Diabetes and Normal Kidney Function. Clin J Am Soc Nephrol. 2022;17(5):663-671. doi: 10.2215/CJN.11480821. DOI
36. Karg MV, Bosch A, Kannenkeri D et al. SGLT2-inhibition with dapagliflozin reduces tissue sodium content: A randomised controlled trial. Cardiovasc Diabetol. 2018;17(1):5. doi: 10.1186/ s12933-017-0654-z. DOI
37. Titze J. A different view on sodium balance. Curr Opin Nephrol Hypertens. 2015;24(1):14-20. doi: 10.1097/MNH.0000000000000085. DOI
38. Schneider MP, Raff U, Kopp C et al. Skin sodium concentration correlates with left ventricular hypertrophy in CKD. J Am Soc Nephrol. 2017;28:1867-1876. doi: 10.1681/ASN.2016060662. DOI
39. Griffin M, Rao VS, Ivey-Miranda J et al. Empagliflozin in heart failure: diuretic and cardiorenal effects. Circulation. 2020;142(11):1028-39 doi:10.1161/CIRCULATIONAHA.120.045691. DOI
40. Mordi NA, Mordi IR, Singh JS et al. Renal and cardiovascular effects of SGLT2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure: the RECEDE-CHF trial. Circulation. 2020;142(18):1713-24. doi:10.1161/CIRCULATIONAHA.120.048739. DOI

A complete list of references can be requested from the authors

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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