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Protective Potential of Sodium-Glucose Cotransporter 2 Inhibitors in Internal Medicine (Part 1)

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Abstract
Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have emerged as a revolutionary class of drugs with far-reaching protective effects in multiple organs. The protective potential of SGLT2i is much broader than that of the classical concept of glucose control and consists of an entire conglomerate of associated pleiotropic effects. This study aims to provide a descriptive review of the pleiotropic therapeutic potential of SGLT2i. The first part of the literature review examined the use of SGLT2i in cardiology and nephrology. The use of SGLT2i represents an innovative approach to improving patients' quality of life and course of heart failure and chronic kidney disease, regardless of left ventricular ejection fraction and type 2 diabetes.
Keywords: SGLT2i, cardioprotection, nephroprotection, dapagliflozin, empagliflozin
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Протективный потенциал ингибиторов натрий-глюкозного котранспортера 2 типа в клинике внутренних болезней (часть 1)

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Резюме
Ингибиторы натрий-глюкозного котранспортера 2 типа (SGLT2i) вошли в клиническую практику как революционный класс пероральных сахароснижающих препаратов. По мере накопления клинических данных были обнаружены их долговременные защитные эффекты в отношении многих органов и тканей. Защитный потенциал SGLT2i гораздо шире, чем классическая концепция контроля глюкозы и состоит из целого конгломерата плейотропных эффектов.
Целью данной статьи является предоставление описательного обзора плейотропного терапевтического потенциала SGLT2i. В первой части обзора литературы рассматривается использование SGLT2i в кардиологии и нефрологии.
Таким образом, использование SGLT2i представляет собой инновационный подход к улучшению качества жизни пациентов и течения как сердечной недостаточности, так и хронической болезни почек, независимо от фракции выброса левого желудочка и наличия сахарного диабета 2 типа.
Ключевые слова: SGLT2i, кардиопротекция, нефропротекция, дапаглифлозин, эмпаглифлозин
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Introduction

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have emerged as a revolutionary class of drugs with far-reaching protective effects in many organ systems.[1] The protective potential of SGLT2i is much broader than that of the classical concept of glucose control and consists of an entire conglomerate of associated pleiotropic effects, leading to multisystem protection.[2-5] Developed as antidiabetic agents, SGLT2i have demonstrated cardioprotective properties; they significantly reduce the risk of heart failure after myocardial infarction, cardiovascular death, and major adverse cardiovascular events.[1,6,7]

In nephrology SGLT2i have shown promising results in slowing progression of chronic kidney disease and improving renal outcomes, even in patients without type 2 diabetes (T2D).[8] Interestingly, these drugs have also demonstrated potential neuroprotective effects, suggesting potential applications in neurology.[9] Emerging data indicate potential benefits of SGLT2i in ophthalmology and oncology.[10,11]

The multifaceted effects of SGLT2i in various medical specialties highlight their potential as versatile therapeutic agents. As new areas of application and mechanisms of action continue to be explored, SGLT2i may revolutionize management of internal medicine patients. However, further studies are required to fully elucidate the efficacy and safety profiles in these diverse areas.

This article aims to provide a descriptive review of the multiorgan (multisystem) pleiotropic therapeutic potential resulting from SGLT2 inhibition. The first part of the literature review examines the use of SGLT2i in cardiology and nephrology, and the second part observes their therapeutic potential in neurology, ophthalmology, hepatology, oncology, and other areas of clinical medicine.

Discussion

SGLT2i in Cardiology

Cardiovascular diseases (CVD) remain a global health problem.[12] Thus, development and continuous modernization of prevention and cardiac rehabilitation programs using evidence-based approaches is an urgent task in modern cardiology.[13,14]

In recent years, many studies have been published indicating a whole conglomerate of pleiotropic effects of SGLT2i, which made a breakthrough in heart failure (HF) treatment.[15,16] One of the modern approaches aimed at improving the efficacy of primary and secondary cardiovascular prevention programs is SGLT2i administration.[17]

The main mechanisms underlying the glucose-independent cardioprotective effects of SGLT2i are as follows:

1. Nuclear factor erythroid 2-related factor 2 (Nrf2) activity is regulated by cytoplasmic Kelch-like ECH-associated protein 1 (Keap1). Keap1 binds to Nrf2, leading to its ubiquitination by the CUL3/RBX1 complex and its subsequent degradation by the 26S proteasome.[18] Many proteins containing the BTB domain serve as substrate-specific adaptors for CUL3-based ubiquitin ligases.[19] The primary function of the BTB domain is to facilitate the interaction between Keap1 and Nrf2 and the subsequent degradation of Nrf2 through ubiquitination.[20] Under oxidative stress, Keap1 is inactivated, thereby halting Nrf2 ubiquitination and enabling the accumulation of newly synthesized Nrf2, which, in turn, activates the Keap1-Nrf2-ARE signaling pathway.[21] Keap1/Nrf2/ARE signaling is involved in the HF pathogenesis.[22] Simultaneously, SGLT2i stabilized the reduced activity of this cascade, exhibiting a pathogenetically significant antioxidant effect. SGLT2i also stabilize NADPH oxidase 4 in cardiomyocytes and reduce the level of methylglyoxal, a precursor of advanced glycation end products.[23]

2. TGF-1β/Smad cascade. Transforming growth factor β1 (TGF-β1) plays a critical role in the initiation of myocardial fibrosis and regulation of reactive oxygen species.[24] In an "inflammatory microenvironment," the binding of TGF-β1 to its membrane receptors leads to the activation of Smad proteins, which migrate to the nucleus and participate in the activation of target gene transcription responsible for proliferative activity.[25]

Activation of Smad2 and Smad3 has been extensively observed in fibroblasts infiltrating fibrotic and remodeled hearts, whereas Smad1/5/8 activation is less prominent. Smad3 plays a crucial role in regulating multiple functions of cardiac fibroblasts.[26,27] The basic principles of Smad3 activity are as follows:

1. Smad3 promotes the conversion of fibroblasts to myofibroblasts by upregulating α-SMA expression and facilitating its recruitment to stressed fibers. This process involves direct effects of Smad3 on α-SMA transcription, as well as indirect mechanisms such as upregulation of fibronectin expression and downregulation of FOXO3a.

2. Smad3 stimulates the transcription of structural and extracellular matrix proteins, including collagen types I and III, fibronectin, periostin, and tenascin C, and induces enzymes responsible for matrix cross-linking, such as lysyl oxidase and tissue transglutaminase.

3. Smad3 promotes a matrix preservation phenotype characterized by suppressed synthesis of extracellular matrix components, decreased activity of MMP-3 and MMP-8 matrix metalloproteinases, and induction of antiproteases such as tissue inhibitors of metalloproteinases (TIMP-1).

4. Smad3 stimulates the expression of integrins α2, α5, β3, and α11, facilitating interactions between fibroblasts and the extracellular matrix, which may be important for the formation of organized scar tissue.

5. Smad3 may exert antiapoptotic effects by increasing fibroblast viability under stressful conditions. Thus, SGLT2i-related inhibition of the TGF-β1/Smad cascade is one of the pathways with a cardiopreventive potential.

Moreover, SGLT2i increase the level of phosphorylated phospholamban (a key regulator of SERCA) and have a positive effect on hyperphosphorylated ryanodine-sensitive channels (RyR), which are responsible for the release of Ca^{2+} from the sarcoplasmic reticulum by reducing the activity of Ca^{2+}/calmodulin-dependent protein kinase II.[28]

It is noteworthy that SGLT2i stabilize AMP-activated protein kinase (AMPK) activity, normalizing the entire cascade of cellular bioenergetics restoration, leading to increased production and decreased consumption of ATP.[29] SGLT2i also suppress myofibroblast infiltration into the myocardium by adjusting polarizing macrophage maturation through the modulation of STAT3 signaling.[30]

SGLT2i significantly improve the function of the microvascular endothelium and have a beneficial effect on arterial stiffness, which is manifested by a decrease in the carotid-femoral pulse wave velocity and augmentation indices of the carotid artery and aorta.[31] Dapagliflozin reduced expression of adhesion molecules, such as ICAM-1 and VCAM-1, on the endothelium, thus stabilizing the endothelial cell-cardiomyocyte interaction.[32]

The key clinical trial data that underpin the efficacy of SGLT2i in CVD treatment are presented in the Table below.

Table

Main results of clinical studies of SGLT2i for CVD treatment

Таблица

Основные результаты клинических исследований по использованию SGLT2i в лечении сердечно-сосудистых заболеваний

Study	Sample size	Main results
DECLARE–TIMI 58 trial[33]	17 160	Compared with placebo, dapagliflozin reduced risks of HF by 27% (HR, 0.73; 95% CI, 0.61-0.88), kidney disease by 24% (HR, 0.76; 95% CI, 0.67-0.87). Dapagliflozin provided lower rate of CV death or hospitalization for HF (4.9% vs 5.8%; HR, 0.83; 95% CI, 0.73-0.95; *P*=.005).
DAPA-HF[34]	4744	Dapagliflozin reduced the risk of death from CV causes or HF exacerbation by 26% (16.3% vs 21.2%; HR, 0.74; 95% CI, 0.65-0.85; *P*<.001) and all-cause mortality (11.6% vs 13.9%; HR, 0.83; 95% CI, 0.71-0.97).
DELIVER[35]	6263	Dapagliflozin reduced the risk of HF exacerbation: 368 patients (11.8%) in the dapagliflozin group and 455 patients (14.5%) in the placebo group (HR, 0.79; 95% CI, 0.69-0.91). CV death was recorded in 231 (7.4%) and 261 patients (8.3%), respectively (HR, 0.88; 95% CI, 0.74-1.05). The number of CV events and symptom severity were lower in the dapagliflozin group. Dapagliflozin reduced the combined risk of HF exacerbation or CV death in patients with HF.
DAPA-CKD[36]	4304	Dapagliflozin improved the primary composite outcome of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or CV causes in 197 of 2152 participants (9.2%) compared with 312 of 2152 participants (14.5%) from the placebo group (HR, 0.61; 95% CI, 0.51-0.72; *P*<.001). Death occurred in 101 patients (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (HR, 0.69; 95% CI, 0.53-0.88; *P*=.004). The effects of dapagliflozin were similar in participants with and without type 2 diabetes.
CAMEO-DAPA[37]	38	Compared with placebo, dapagliflozin reduced the primary end point (change in pulmonary capillary wedge pressure) both at rest and during exercise (*P*<.001). Body weight was lower with dapagliflozin (ETD, −3.5 kg; 95% CI, −5.9 to −1.1; *P*=.006), as was plasma volume (ETD, −285 mL; 95% CI, −510 to −60; *P*=.014).
PRESERVED-HF[38]	162	Dapagliflozin increased walking distance by ≥15 m during the 6-minute walk test compared with placebo (n=64, 44% vs n=48, 34%). Dapagliflozin-treated patients with HFpEF experienced clinically significant improvement and less decline in exercise capacity over 12 weeks.
DAPASALT[39]	14	Dapagliflozin treatment is associated with a decrease in mean BP by 10 mm Hg (*P*<.05) and stabilizes endothelial function (*P*<.05).

Continued/Окончание таблицы

Study	Sample size	Main results
CREDENCE[40]	4401	The canagliflozin group had a lower risk of CV death, MI, or stroke (HR, 0.80; 95% CI, 0.67-0.95; *P*=.01) and of hospitalization for HF (HR, 0.61; 95% CI, 0.47-0.80; *P*=0.01). The RR of creatinine doubling or death from renal causes was lower by 34% (HR, 0.66; 95% CI, 0.53-0.81; *P*<.001), and the RR of end-stage kidney disease, by 32% (HR, 0.68; 95% CI, 0.54-0.86; *P*=.002).
EMPEROR-Reduced[41]	3730	The primary outcome occurred in 361 of 1863 patients (19.4%) from the empagliflozin group compared with 462 of 1867 patients (24.7%) from the placebo group (HR for CV death or hospitalization for HF, 0.75; 95% CI, 0.65-0.86; *P*<.001). The total number of hospitalizations for HF was lower in the empagliflozin group than in the placebo group (HR, 0.70; 95% CI, 0.58-0.85; *P*<.001).
EMPEROR-Preserved[42]	5988	The primary end point was achieved in 415 of 2997 patients (13.8%) from the empagliflozin group, compared with 511 of 2991 patients (17.1%) from the placebo group (HR, 0.79; 95% CI, 0.69-0.90; *P*<.001). This effect was mainly due to a lower risk of hospitalization for HF in the empagliflozin group. The total number of hospitalizations for HF was lower in the empagliflozin group than in the placebo group (407 vs 541; HR, 0.73; 95% CI, 0.61-0.88; *P*<.001).
SOLOIST-WHF[43]	1222	The rate of primary end-point events was lower in the sotagliflozin group than in the placebo group (51.0 vs 76.3; HR, 0.67; 95% CI, 0.52-0.85; *P*<.001). The rate of CV death was 10.6 in the sotagliflozin group and 12.5 in the placebo group (HR, 0.84; 95% CI, 0.58-1.22); the rate of all-cause death, 13.5 in the sotagliflozin group and 16.3 in the placebo group (HR, 0.82; 95% CI, 0.59-1.14).
CANVAS[44]	15 494	The rate of the primary outcomes was lower with canagliflozin than with placebo (26.9 vs 31.5/1000 patient-years; HR, 0.86; 95% CI, 0.75-0.97; *P*<.001 for noninferiority; *P*=.02 for superiority). The results showed a possible benefit of canagliflozin on albuminuria progression (HR, 0.73; 95% CI, 0.67-0.79) and the composite outcome of a sustained 40% reduction in estimated GFR, need for renal replacement therapy, or death from renal causes (HR, 0.60; 95% CI, 0.47-0.77).
EMPA-REG OUTCOME[45]	7020	The primary outcome occurred in 490 of 4687 patients (10.5%) in the combined empagliflozin group and 282 of 2333 patients (12.1%) in the placebo group (HR in the empagliflozin group, 0.86; 95.02% CI, 0.74-0.99; *P*=.04). The empagliflozin group had lower rates of CV death (3.7% vs 5.9%; 38% RRR), hospitalization for HF (2.7% vs 4.1%), and all-cause death (5.7% vs 8.3%; 32% RRR) compared with the placebo group.
VERTIS CV[46]	8246	A major adverse CV event occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and 327 of 2745 patients (11.9%) in the placebo group (HR, 0.97; 95.6% CI, 0.85-1.11; *P*<.001 for non-inferiority).
SCORED[47]	10 584	The rate of primary end-point events was 5.6 events/100 patient-years in the sotagliflozin group and 7.5 events/100 patient-years in the placebo group (*P*<.001). The rate of CV deaths per 100 patient-years was 2.2 with sotagliflozin and 2.4 with placebo (*P*=.35). In patients with diabetes and CKD, with or without albuminuria, sotagliflozin administration resulted in a lower risk of the composite outcome comprising CV mortality, hospitalizations for HF, and urgent visits for HF compared with placebo.
EMPT-ANGINA[48]	75	Empagliflozin-treated patients showed improvement in both the primary end point, SAQ total score (192.73±20.70 vs 224±25.36, *P*<.001). Exercise testing components (time to onset of 1 mm ST-segment depression and heart rate recovery) were significantly improved in the empagliflozin group.
DAHOS [49]	107	Significant improvements in sleep parameters, including AHI, HI, longest rest time, ODI, time spent at SpO_2 <90%, and mean SpO_2, were observed in the dapagliflozin group. There was an improvement in ESS, MLHFQ, and EQ-5D-3L scores, as well as a significant decrease in CRP and IL-6 levels, while CRP and IL-6 levels did not change in the controls.
DAPA-MI[50]	4017	Dapagliflozin improved cardiometabolic parameters by 34% compared with placebo. However, after approximately 1 year of treatment, there was no effect on cumulative CV mortality or hospitalization for HF compared with placebo.

Note: AHI, apnea-hypopnea index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CV, cardiovascular; ESS, Epworth Sleepiness Scale; ETD, estimated treatment difference; GFR, glomerular filtration rate; HF, heart failure; HFpEF, heart failure and preserved ejection fraction; HI, hypopnea index; HR, hazard ratio; MI, myocardial infarction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; ODI, oxygen desaturation index; RR, relative risk; RRR, relative risk reduction; SAQ, Seattle Angina Questionnaire

Прим.: AHI – индекс апноэ-гипопноэ; BP – артериальное давление; CI – доверительный интервал; CKD – хроническая болезнь почек; CRP – С-реактивный белок; CV – сердечно-сосудистый; ESS – шкала сонливости Эпворта; ETD – предполагаемая разница в лечении; GFR – скорость клубочковой фильтрации; HF – сердечная недостаточность; HFpEF – сердечная недостаточность с сохраненной фракцией выброса; HI – индекс гипопноэ; HR – отношение рисков; MI – инфаркт миокарда; MLHFQ – Миннесотский опросник качества жизни у больных с сердечной недостаточностью; ODI – индекс десатурации кислородом; RR – относительный риск; RRR – снижение относительного риска; SAQ – Сиэтлский опросник качества жизни при стенокардии

Thus, the results of future clinical studies and experience with the use of SGLT2i in cardiological practice will provide an innovative approach to improve the quality of life and course of HF, regardless of left ventricular ejection fraction and T2D.[51] Impressively, there was a reduction in the risk of cardiovascular death and death from all causes, as well as a reduction in the number of hospitalizations for HF across the entire range of left ventricular ejection fraction.

SGLT2i in Nephrology

Since their introduction as antidiabetic agents, SGLT2i have shown significant progress, demonstrating positive effects on renal outcomes regardless of diabetic status.[52] These mechanisms include the activation of tubuloglomerular feedback, leading to a reduction in glomerular hyperfiltration, alleviation of hypoxia, and oxidative stress in the renal cortex.[53] The most observed alterations associated with diabetic nephropathy involve thickening of various kidney compartments, such as the glomerular, capillary, tubular, and basement membranes, which is associated with metabolic changes that contribute to inflammation and fibrosis.[54,55] SGLT2i can preserve kidney function by mitigating glomerular hypertension through tubuloglomerular feedback, regardless of its effects on glycemic control.[56] It is important to note that SGLT2i may initially cause a temporary decrease in the glomerular filtration rate due to reduced glomerular hypertension.[57-59]

SGLT2i-induced nephroprotection may act either directly or indirectly both locally and systemically. For instance, SGLT2i not only promote glycosuria but also improve glucose metabolism in the liver and reduce insulin resistance in muscles.[60,61]

Similar to the DAPA-HF, EMPEROR, CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials, SGLT2i have been proven to effectively enhance renal and cardiovascular outcomes in individuals with T2D and chronic kidney disease, despite their limited impact on blood glucose levels.[62] Deeper insights into the renoprotective effects of SGLT2i have been gained through experimental research and clinical studies uncovering both blood glucose-dependent and -independent pathways.

SGLT2i can influence the activation of tubuloglomerular feedback by increasing sodium delivery to the macula densa. This mechanism reduces glomerular hypertension and albuminuria.[63,64] Recent meta-analyses have demonstrated that SGLT2i are associated with a notable and consistent reduction in acute kidney injury.[65]

By inhibiting SGLT2, the distribution of the transport workload across tubular segments becomes more equitable. These effects of SGLT2i may contribute to the preservation of mitochondrial function and metabolism of tubular cells, which are expected to sustain their function.[66,67] A recent study conducted on patients with T2D and albuminuria revealed that dapagliflozin treatment resulted in an increase in urinary metabolites linked to mitochondrial metabolism compared with placebo, suggesting that dapagliflozin may crucially improve mitochondrial function in patients with T2D.[68]

Empagliflozin treatment stabilized mitochondrial function and autophagy activity in renal proximal tubular cells under elevated glucose conditions in a streptozotocin-based mouse model of diabetes.[69] This effect may involve the AMPK and mammalian target of rapamycin (mTOR) signaling pathways, ultimately leading to reduced apoptosis and tubulointerstitial fibrosis. Similarly, the SGLT2i ipragliflozin reversed tubular and mitochondrial damage induced by a high-fat diet in mice, regardless of blood glucose levels.[70] Therefore, SGLT2i may provide renoprotection and maintain kidney integrity by enhancing mitochondrial function and regulating autophagy.[71]

In summary, the primary mechanisms of SGLT2i-induced nephroprotection can be divided as follows. The first mechanism involves a reduction in glomerular hyperfiltration, which is linked to diabetic glomerular injury, although it has also been suggested that this may occur independently of glucose levels. The second mechanism pertains to a decrease in energy consumption leading to hypoxia adaptation, which is inherently glucose-dependent and significantly exacerbated under diabetic conditions. The third mechanism involves the suppression of inflammatory, fibrotic, and proapoptotic responses, which largely operate independently of T2D. This highlights the extensive direct effects of SGLT2i on kidney function and elucidates their efficacy in treating chronic kidney disease in patients with and without T2D.[72]

A randomized placebo-controlled clinical trial on the effects of canagliflozin, involving 10 142 participants with T2D and a high risk of cardiovascular events showed that renal outcomes were statistically insignificant. However, the occurrence of increased albuminuria was significantly lower in the canagliflozin group.[73] In a double-blind placebo-controlled clinical trial (3730 patients), analysis showed a significant decrease in the rate of eGFR decline in the empagliflozin group.[74] Dapagliflozin improves kidney function in mice with ischemia-reperfusion injury. Dapagliflozin induces the expression of hypoxia-inducible factor-1α (HIF-1α) and reduces the Bax/Bcl2 ratio in ischemic renal tissues and hypoxia-cultured tubular cells. Dapagliflozin elevated the levels of phosphorylated AMPK and extracellular signal-regulated kinase (ERK) in hypoxia-cultured HK-2 cells. Elevated phosphorylation of AMPK and ERK may also induce HIF-1α expression. In addition, dapagliflozin treatment resulted in decreased glucose uptake and SGLT2 expression in hypoxia-cultured HK-2 cells.[75] Furthermore, luseogliflozin was effective in preventing rarefaction of renal capillaries and fibrosis in a mouse model of renal ischemia-reperfusion.[76]

Conclusions

The use of SGLT2i is an innovative approach to improve the quality of life and slow the progression of CVD and kidney diseases in patients with or without T2D.

Author contributions
Concept and design: All authors
Acquisition, analysis, or interpretation of data: All authors
Manuscript drafting: All authors
Manuscript revising: Pogosova, Urazova, Sarrafzadegan

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