

Effectiveness of sodium-glucose cotransporter 2 inhibitors in the treatment of chronic heart failure

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Chronic heart failure (CHF) is one of the outcomes of cardiovascular diseases (CVDs) that significantly worsens patient prognosis. For this reason, research has been ongoing for decades to find effective drugs that can improve the prognosis for patients with CHF.

Methods. The article was prepared based on a review of literature published in peer-reviewed journals available on PubMed, eLIBRARY.RU, CyberLeninka, and other research platforms over the last 10 years.

Results. Despite significant progress in understanding the pathogenesis and treatment of CHF, the search for effective therapies continues. One of the discoveries of recent years has been drugs from the class of sodium-glucose cotransporter 2 inhibitors (SGLT2i), the efficacy of which in CHF has been demonstrated in a number of major clinical trials.

Conclusion. SGLT2i are antidiabetic drugs that hold an important place in the management of type 2 diabetes mellitus. They have been shown to favorably influence the

course of CHF, thereby reducing cardiovascular risks and mortality from CHF.

Keywords: sodium-glucose cotransporter 2 inhibitors, chronic heart failure, diabetes mellitus, left ventricular ejection fraction, blood volume, cardiovascular diseases.

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Introduction

Chronic heart failure (CHF) is a condition that represents one of the outcomes of cardiovascular disease (CVD). Its global prevalence ranges from 0.3% (India) to 5.3% (Australia) [1]. Mortality from CHF in various forms of coronary heart disease (CHD) in Russia is 35%. The most common causes of CHF development are arterial hypertension and CHD [1]. The overall prognosis for patients with CHF is unfavorable. According to the EPOKHA study, the average life expectancy for patients with CHF of functional class (FC) 1–2 is 8.4 years (95% confidence interval [CI]: 7.8–9.1 years), while for CHF FC 3–4 it is 3.8 years (95% CI: 3.4–4.2 years) [2].

Research has been ongoing for many decades to find effective drugs capable of improving the prognosis for patients with CHF.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated a favorable effect on the course and outcomes of CHF based on the results of numerous large studies; however, the extent of this effectiveness remains a subject of debate.

SGLT2i are drugs that inhibit sodium-glucose cotransporter-2 (SGLT2) proteins, located predomi-

Results

Potential mechanisms of action of SGLT2i

As mentioned above, SGLT2i inhibit the reabsorption of glucose in the proximal renal tubules, inducing glucosuria and thereby lowering plasma glucose levels. This occurs when the glucose transport proteins become fully saturated, reaching maximum glucose reabsorption capacity, and the excess glucose begins to be excreted in the urine [3].

Results from clinical studies indicate that SGLT2i reduce body weight by 1 to 4 kg [4]. For instance, according to completed randomized clinical trials (RCTs), monotherapy with ipragliflozin was associated with an average body weight reduction of 2.33 kg ($p < 0.001$) and a waist circumference reduction of 1.61 cm over 16 weeks [5]. Furthermore, the weight loss is attributed to a reduction in visceral fat, not just a decrease in intravascular volume due to reduced blood volume (BV) from increased diuresis [4].

SGLT2i also possess a modest antihypertensive effect, reducing both systolic blood pressure (SBP) and diastolic blood pressure (DBP). This is related to their diuretic, osmotic diuretic, and natriuretic ef-

fects in the epithelial cells of the early proximal tubules of the kidneys. Under normal conditions, these transporters reabsorb glucose and sodium into the bloodstream [3]. Thus, drugs in the SGLT2i group inhibit the reabsorption of glucose and sodium in the proximal renal tubules by blocking the sodium-glucose cotransporters. To date, known representatives of this drug class include canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, and luseogliflozin.

Methods

The materials for this review article were gathered from peer-reviewed publications indexed in PubMed, eLIBRARY.RU, CyberLeninka, and other research platforms over the last 10 years. This timeframe encompasses the publication of pivotal clinical trials relevant to the subject. The literature search employed the following key terms: SGLT2 inhibitors, cardiometabolic disorders, chronic heart failure, cardiovascular complications, and type 2 diabetes mellitus.

Studies or articles that did not meet quality standards were excluded from the analysis.

fects, which lead to a reduction in BV, decrease cardiac preload, and thereby improve cardiac function [3, 6]. Additionally, SGLT2i therapy has been shown to reduce arterial stiffness and BP, i.e., myocardial afterload, which can be explained by their positive effect on endothelial function through increased nitric oxide (NO) production, released in response to reduced oxidative stress [7].

SGLT2i therapy has been associated with increased serum erythropoietin levels. This is because SGLT2i suppress sodium reabsorption, thereby reducing adenosine triphosphate (ATP) consumption by Na^+/K^+ -ATPase. Consequently, hypoxic conditions in epithelial cells improve, potentially leading to the conversion of myofibroblasts into erythropoietin-producing fibroblasts [8].

There is a viewpoint that SGLT2i improve myocardial metabolism by shifting energy substrate utilization to ketone bodies, the levels of which increase during SGLT2i therapy [6, 9].

Various studies have observed that dapagliflozin and empagliflozin can reduce left ventricular myocar-

dial mass [7]. Furthermore, it has been demonstrated that dapagliflozin can attenuate myocardial fibrotic changes by suppressing collagen synthesis through increased macrophage activity and inhibition of myofibroblast differentiation [10–12].

SGLT2i have been found to reduce levels of reactive oxygen species (ROS), which have damage the myocardium, causing electrophysiological and contractile dysfunction of cardiomyocytes, mitochondrial dysfunction, and enhanced myocardial fibrosis. ROS contribute to endothelial dysfunction associated with heart failure (HF) by accelerating NO degradation, converting it into peroxynitrite [13].

It has been demonstrated that SGLT2i lower blood leptin levels and increase the concentration of adiponectin, which has a cardioprotective effect, including reducing myocardial infarct size [14].

Numerous studies have established that these drugs inhibit NHE1 (sodium-hydrogen exchanger type 1), widely expressed in the cell membrane of all tissues, especially in the myocardium. This leads to reduced intracellular sodium and calcium levels, improving mitochondrial function and enhancing cardiomyocyte viability [6]. Inhibition of NHE3 (sodium-hydrogen exchanger type 3) by SGLT2i in the proximal tubules reduces sodium reabsorption [15]. Dysregulation of sodium handling plays a crucial role in the development and progression of CHF, as intracellular sodium concentration in cardiomyocytes is critical for cardiac electromechanical coupling and contractility. In CHF, cytosolic sodium concentration in cardiomyocytes increases due to an imbalance between ion influx and efflux. Sodium-calcium exchange in cardiomyocytes regulates cardiac contractility, and disruption in the homeostasis of these ions contributes to the contractile dysfunction present in CHF [16].

It has been established that empagliflozin can reduce pulse pressure, which may increase with greater vascular wall stiffness. Furthermore, empagliflozin was found to lower markers of arterial stiffness [17]. Empagliflozin treatment is associated with a 14.4% reduction in carotid-femoral pulse wave velocity and a 7.8% reduction in central pulse pressure.

Treatment with SGLT2i leads to a reduction in levels of proinflammatory cytokines, namely CRP, TNF- α , IL-6, and MCP-1. Another mechanism for reducing inflammation is decreasing renal urate reabsorption, thereby lowering blood levels of the proinflammatory

uric acid. Moreover, SGLT2i increase NO bioavailability by suppressing its degradation pathway. Reducing inflammation is significant because enhanced systemic inflammation markedly increases the risk of atherosclerotic cardiovascular disease [18].

Adverse effects of SGLT2i

It has been found that SGLT2i therapy leads to a slight increase in LDL cholesterol and a 10% reduction in 1,25-dihydroxyvitamin D levels [19]. Additionally, frequent occurrences of vulvovaginal candidiasis and lower urinary tract infections have been noted with SGLT2i use [20].

Contraindications for SGLT2i include: type 1 diabetes mellitus, diabetic ketoacidosis, severe liver failure, renal failure with a glomerular filtration rate (GFR) < 45 mL/min/1.73 m², pregnancy, and breastfeeding. SGLT2 inhibitors are also contraindicated in patients undergoing hemodialysis¹.

Evidence base for the efficacy of SGLT2i in CHF treatment

One of the studies that proved the efficacy of SGLT2 inhibitors in treating CHF is the SOLOIST-WHF trial (Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure), conducted from 2018 to 2021. It investigated the effect of sotagliflozin on cardiovascular outcomes in patients with type 2 diabetes following an episode of worsening heart failure. This study included 1,222 patients randomized into two groups (608 received sotagliflozin and 614 received placebo). During the follow-up, it was found that the group receiving sotagliflozin had a significantly lower total number of cardiovascular deaths, hospitalizations, and urgent visits for heart failure compared to the placebo group — 51.0 vs. 76.3 events (relative risk [RR] = 0.67; 95% CI: 0.52–0.85; $p < 0.001$). The rate of cardiovascular death was 10.6 events per 100 patient-years in the sotagliflozin group and 12.5 events per 100 patient-years in the placebo group (RR=0.84; 95% CI: 0.58–1.22) [21].

Another study demonstrating the efficacy of SGLT2i was the EMPEROR-REDUCED trial (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction), conducted in 2020. This trial included 3,730 patients with CHF of NYHA class 2–4 and a left ventricular ejection fraction

¹ Vidal drug database. <https://www.vidal.ru/>

(LVEF) $\leq 40\%$, who received either empagliflozin (10 mg daily) or placebo in addition to recommended therapy. Over 1 year and 4 months, the number of cardiovascular deaths or hospitalizations due to worsening HF was higher in the placebo group (462 (24.7%) out of 1,867 patients), than in the empagliflozin group (361 (19.4%) out of 1,863 patients). The effect of empagliflozin was also found to be similar in patients with and without diabetes [22].

In the DAPA-HF trial, which studied 4,744 patients with CHF of NYHA class 2-4 and LVEF $\leq 40\%$, divided into groups receiving either dapagliflozin (10 mg daily) or placebo in addition to prescribed therapy, it was found that the likelihood of cardiovascular death was lower in the dapagliflozin group (8.2%) compared to the placebo group (9.6%), regardless of the presence of diabetes (95% CI: 0.66–1.04). The risk of hospitalization for heart failure was also reduced in the dapagliflozin group (13.7%) compared to placebo (18.2%) (95% CI: 0.63–0.85) [23].

The EMPEROR-Preserved trial involved 5,988 individuals with heart failure and LVEF $\geq 40\%$. Participants were divided into two groups in a 1:1 ratio, with one group receiving empagliflozin (10 mg daily) and the other receiving placebo. The study results established that empagliflozin reduces the risk of cardiovascular death or hospitalization for heart failure by 21% compared to placebo. Empagliflozin was effective for all types of CHF, regardless of the presence or absence of diabetes [24].

Research has shown that in patients with stable CHF and LVEF, switching from renin-angiotensin-aldosterone system blockers to angiotensin receptor-neprilysin inhibitors and adding SGLT2i reduces the one-year mortality rate from 12.2% to 8.9% [25].

It has been established that dapagliflozin promotes reverse myocardial remodeling and improves cardiac contractility. One study included patients with CHF who were prescribed dapagliflozin and patients with atrial fibrillation who served as a comparison group. During dapagliflozin therapy, a statistically significant increase in LVEF was observed from $29 \pm 6\%$ (27–31) to $37 \pm 9\%$ (33–40), $p < 0.001$, along with a reduction in the volumetric and linear dimensions of the left ventricle and left atrium. Specifically, end-diastolic dimension decreased from 70 (64–73) to 63 (60–70) mm ($p < 0.001$), end-systolic dimension from 55 ± 7 (52–58) to 50 ± 7 (47–52) mm ($p < 0.003$), end-diastolic volume

from 239 ± 50 (220–258) to 207 ± 43 mL/m² (191–223) ($p < 0.001$), end-systolic volume from 170 ± 40 (155–185) to 140 ± 33 mL/m² ($p < 0.001$), left atrial dimension from 48 ± 5 (46–49) to 44 ± 6 (42–46) mm ($p < 0.001$), and left ventricular myocardial mass from 156.5 (130–180) to 109 (98–145) g ($p = 0.001$) [26].

In a clinical study of patients with CHF and iron-deficiency anemia, an increase in hemoglobin concentration and hematocrit was observed after treatment with dapagliflozin — from 13.4 ± 0.3 to 13.9 ± 0.4 g/dL ($p = 0.02$) and from $41.3 \pm 0.9\%$ to $43.5 \pm 1.0\%$ ($p = 0.01$), respectively. The therapy also reduced hepcidin and ferritin concentrations by $24 \pm 3\%$ and $32 \pm 7\%$ respectively, while increasing levels of the hepcidin inhibitor erythroferrone by $71 \pm 22\%$ and causing a transient $21 \pm 7\%$ increase in erythropoietin levels after 6 weeks of treatment. Additionally, dapagliflozin increased plasma transferrin levels by $11 \pm 3\%$ and the expression of transferrin receptors 1 and 2 in blood mononuclear cells by $59 \pm 14\%$, with no changes observed in the expression of the cellular iron exporter ferroportin. Thus, it was shown that dapagliflozin positively influences erythropoietin synthesis in patients with CHF and anemia [27].

It has been established that empagliflozin significantly improves parameters of diastolic function after 6 months. This study included 84 patients with CHF of NYHA class 2–3, LVEF $> 50\%$, signs of diastolic dysfunction, and elevated NT-pro-BNP levels (> 125 pg/mL). They were randomized into two equal groups: one group received empagliflozin (10 mg) in addition to standard therapy, while the other received standard therapy alone. All patients underwent transthoracic echocardiography before the study and after 6 months of therapy to assess standard parameters of systolic and diastolic LV function. Key efficacy parameters included the E/e' ratio (average of septal and lateral positions), left atrial volume index, and left ventricular mass index. In the empagliflozin group, a statistically significant reduction in the E/e' ratio and left atrial volume index was observed. In the control group, no significant changes in these parameters were found. The effect on the left ventricular mass index was statistically insignificant in both groups [28]. To date, there is no data on whether genetic population diversity affects SGLT2i therapy. Thus, it can be concluded that SGLT2i therapy provides the same effect in all patients [29].

Conclusion

Nowadays, clinicians have a wide range of drugs of various classes with different mechanisms of action at their disposal, the efficacy of which has been proven in the treatment of patients with CHF. However, the prognosis for these patients remains unfavorable, which drives the ongoing search for new medications capable of improving life expectancy and slowing the progression of CHF.

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