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Molecular aspects of SGLT2 inhibitor interactions in myocardial failure

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Abstract

Heart failure is a major public health issue and one of the leading causes of morbidity and mortality worldwide. Despite significant advances in heart failure treatment and improved patient prognosis, the effectiveness of standard therapies remains limited, prompting the search for new solutions. One of these are sodium-glucose co-transporter 2 inhibitors, initially introduced for the treatment of type 2 diabetes. They have demonstrated beneficial effects on the clinical course of heart failure, independent of the presence of carbohydrate metabolism disorders. Their mechanisms of action extend far beyond the hypoglycemic effect and involve multidimensional molecular processes. The most important include: modulation of cardiomyocyte energy metabolism, regulation of ionic homeostasis, effects on cardiac remodeling, and reduction of oxidative stress and inflammatory response. An increasing number of clinical studies confirm the role of these molecular effects in improving outcomes for HF patients. Understanding the complex mechanisms of sodium-glucose co-transporter 2 inhibitors provides new therapeutic opportunities and reinforces their position as a cornerstone of pharmacological heart failure management.

Running title: SGLT2 inhibitors: mechanistic overview

Keywords: heart failure, SGLT2i, empagliflozin, dapagliflozin, ertugliflozin, cardiac remodeling

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Introduction

Heart failure (HF) is a clinical syndrome resulting from structural or functional abnormalities of the heart muscle, leading to impaired ability to pump blood effectively and provide adequate perfusion to meet the body's metabolic demands [1]. Under physiological conditions, the heart functions as a dynamic pump whose performance adapts to the changing demands of the body. In HF, this mechanism is disrupted, leading to impaired organ perfusion and chronic activation of compensatory systems, which over time lose effectiveness and contribute to disease progression [2].

HF represents a growing challenge for healthcare systems, mainly due to an aging population, increasing prevalence of cardiovascular risk factors, and longer life expectancy. HF rarely occurs in isolation; comorbidities are common. In HF patients, diabetes is present in 43.7%, chronic obstructive pulmonary disease (COPD) in 39.7%, chronic kidney disease (CKD) in 21.1%, and anemia in 30.2%. Additionally, 40.6% have a history of stroke, obesity occurs in 21.0%, and depression affects 16.1% of patients. This comorbidity profile necessitates a comprehensive, multidisciplinary therapeutic approach and continuous medical or outpatient supervision [3,4].

Studies investigating HF pathophysiology have shown that HF causes hypoperfusion, which impairs the physiological function of other organs, such as the liver and kidneys. This leads to numerous complications—for the liver, elevated transaminase activity is a significant prognostic factor increasing mortality risk. HF is also closely associated with renal dysfunction, and albuminuria itself can induce HF. These alterations affect the renin-angiotensin-aldosterone (RAA) system, further disrupting cardiomyocyte function [5].

It is estimated that HF affects approximately 1–2% of the adult population in developed countries, with prevalence increasing sharply with age – exceeding 10% in individuals over 70 years [6]. In Poland alone, approximately 1.2 million people are diagnosed with HF, with nearly 150,000 deaths annually [3]. The average age at diagnosis is around 75 years, and 5-year mortality after the first HF hospitalization exceeds 50%, making HF prognosis worse than that of many malignant cancers [4].

Due to the high risk of hospitalization, symptom recurrence, and death, HF remains a leading cause of mortality in developed countries. Furthermore, according to the European Society of Cardiology (ESC), the total cost of HF treatment in Europe exceeds €29 billion annually, with hospitalizations accounting for the majority [1]. These figures highlight not only the clinical but also the economic importance of heart failure, underscoring its impact on both healthcare systems and patients' quality of life. Therefore, the present study aims to focus on the molecular aspects of SGLT2 inhibitors, with the expectation that a deeper exploration of these mechanisms may provide valuable insights into their therapeutic potential and contribute to a better understanding of their role in the management of myocardial failure.

History of heart failure pharmacotherapy

Pharmacotherapy remains the cornerstone of HF treatment and has evolved significantly over the past decades. Since the 1980s, drugs aimed at reducing fluid retention and improving cardiac contractility have been successfully introduced, leading to significant improvements in HF patient survival between 1980 and 2000 [1]. Initially, this was achieved using digoxin or digitoxin (cardiac glycosides) and diuretics, which relieved acute symptoms but did not improve long-term survival. Later, angiotensin-converting enzyme inhibitors (ACEi) and beta-blockers, and in ACEi-intolerant patients, angiotensin receptor blockers (ARB) were introduced [7].

Until recently, the pillars of HF pharmacotherapy included ACEi or ARB, beta-blockers, and mineralocorticoid receptor antagonists (MRA) [8]. These drugs are often supplemented with device-based interventions such as implantable cardioverter-defibrillators and cardiac resynchronization therapy. For end-stage HF, heart transplantation is the preferred treatment, although limited donor organ availability significantly restricts its use [9].

Currently, cardiac glycosides are rarely used in HF due to their toxicity and arrhythmogenic potential. A new class of drugs has emerged as a fourth cornerstone in first-line HF therapy – sodium-glucose co-transporter 2 inhibitors (SGLT2i). Originally developed to treat type 2 diabetes (T2D), a major HF risk factor, SGLT2i have been shown to reduce the risk of HF hospitalization and serious renal complications in diabetic patients. They exhibit properties suggesting cardioprotective and renoprotective effects [10,11].

Characteristics of SGLT2 inhibitors

Sodium-glucose co-transporters (SGLTs) are transport proteins that mediate the uptake of glucose and sodium ions into cells. Currently, six isoforms of SGLT proteins have been identified. SGLT1 is present in organs such as the brain, kidneys, and heart, and is highly expressed in the small intestine. Notably, in patients with HF, overexpression of SGLT1 in cardiomyocytes has been observed [12]. SGLT2 is primarily located in the renal cortex [13]. Special attention should be given to SGLT2, which is responsible for 90% of renal glucose reabsorption [14].

SGLT2 inhibitors (SGLT2i) selectively block SGLT2, thereby reducing glucose reabsorption and increasing urinary glucose excretion (glucosuria). Their hypoglycemic effect is insulin-independent, as the liver compensates by producing glucose, protecting against hypoglycemia. This allows SGLT2i to be used in patients without diabetes [15].

Clinical studies have shown that 2–3 years of SGLT2i therapy reduces the risk of kidney failure and other major renal events by 30–40% in patients with chronic kidney disease (CKD), regardless of diabetes status. Moreover, they reduce the likelihood of acute kidney injury (AKI) [16].

Results from the EMPEROR-Reduced and DAPA-HF trials indicate that SGLT2i use in patients with heart failure with reduced ejection fraction (HFrEF) can decrease the risk of cardiovascular death and worsening organ failure, independent of diabetes status [17].

The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have approved five SGLT2 inhibitors: empagliflozin, canagliflozin, ertugliflozin, dapagliflozin, and sotagliflozin [15,17].

Empagliflozin

Empagliflozin is highly selective for SGLT2 among all SGLT2 inhibitors and exhibits high selectivity toward SGLT1, 4, 5, and 6 [18]. Comparative studies evaluating empagliflozin versus liraglutide and sitagliptin demonstrated a more favorable impact of empagliflozin on cardiovascular events. Empagliflozin was associated with a lower risk of HF hospitalization (HHF) compared to liraglutide and a lower risk of major adverse cardiovascular events (MACE) and HHF compared to sitagliptin. Additionally, in patients with HF or atherosclerotic cardiovascular disease (ASCVD), empagliflozin more effectively reduced the risk of HHF and MACE than liraglutide [19].

The EMPEROR-Preserved trial showed that, regardless of diabetes status, empagliflozin reduced the risk of the composite endpoint (HHF and cardiovascular death) in patients with heart failure with preserved ejection fraction (HFpEF), primarily by reducing HF hospitalizations [20]. In the EMPULSE trial, patients received 10 mg of empagliflozin daily or placebo. Empagliflozin led to significant clinical benefits, including reductions in HF events and events leading to death. Notably, in hospitalized patients with acute HF, clinical benefits were observed as early as 15 days and persisted for 90 days [21].

Canagliflozin

Canagliflozin selectively inhibits SGLT2 and, to a lesser extent, SGLT1. It exhibits high plasma protein binding, particularly to albumin [22]. This contributes to reduced albuminuria and improved renal function [14].

The CREDENCE trial demonstrated that canagliflozin in patients with T2D and CKD reduced the risk of doubling serum creatinine, end-stage kidney disease, and death from cardiovascular or renal causes as part of a composite endpoint, confirming its effectiveness in this patient population [23]. The CANVAS trial showed that canagliflozin attenuated increases in high-sensitivity troponin I and NT-proBNP compared with placebo in older T2D patients. Additionally, canagliflozin reduced the risk of major cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death [24].

Ertugliflozin

VERTIS CV trial results confirmed that ertugliflozin reduces the likelihood of HF hospitalization and cardiovascular death (HHF/CV) as well as first and total HHF [25]. The EFFORT trial indicated that ertugliflozin favorably affects cardiac remodeling by reducing left atrial volume and improving global longitudinal strain (LV GLS) of the left ventricle, without significantly affecting ejection fraction, NT-proBNP levels, or left ventricular volume. Additionally, ertugliflozin reduces functional mitral regurgitation (MR) associated with HF [26].

Dapagliflozin

Meta-analyses from DELIVER and DAPA-HF indicate that dapagliflozin reduces the likelihood of HHF, HF-related visits, and cardiovascular death [27]. According to Peiker A. et al., DELIVER trial results show that dapagliflozin reduces HF events regardless of age in patients with HF with preserved or mildly reduced ejection fraction [28]. During approximately four years of follow-up in the DECLARE-TIMI 58 study, dapagliflozin reduced urine albumin-to-creatinine ratio (UACR) across all UACR and eGFR categories [29].

Sotagliflozin

Sotagliflozin is a dual SGLT1/2 inhibitor, with 20-fold higher inhibition of SGLT2 than SGLT1 [30,31]. By targeting glucose transport in both the intestines and kidneys, these inhibitors not only reduce blood glucose levels but also improve insulin sensitivity. Sotagliflozin limits postprandial glucose absorption, reducing the risk of hyperglycemia-related complications and hypoglycemia [30].

The SCORED trial demonstrated that in patients with CKD, T2D, and cardiovascular risk, sotagliflozin reduced MACE, with independent reductions in stroke and myocardial infarction [32]. The SOLOIST-WHF trial showed that initiating sotagliflozin therapy in hospitalized patients with worsening HF and T2D reduced cardiovascular death at 30 and 90 days post-discharge [33].

Molecular mechanisms of SGLT2 inhibitors in heart failure

Metabolic effects

The first group of mechanisms through which SGLT2 inhibitors (flozins) exert clinical benefits involves changes in specific cardiovascular risk factors. Notably, these include body weight reduction, which normalizes over a few months and averages 2–3 kg, primarily due to increased urinary glu-

cose excretion. Another important effect is a blood pressure reduction, resulting from enhanced sodium loss. Improvements in lipid profiles and reductions in ectopic fat deposits, which can negatively impact vital organs such as the heart and kidneys through paracrine effects and mechanical stress, have also been observed [34,35].

Studies suggest that improved ketone and glucose metabolism in the heart correlates with the degree of diastolic dysfunction [36]. A key aspect of flozins' action is the adaptive shift in energy substrate preference, including increased ketogenesis, modulation of lipolysis, support of mitochondrial biogenesis and autophagy, and attenuation of the renin-angiotensin-aldosterone (RAA) system [37].

SGLT2i therapy enhances ketone body production through several mechanisms. Reduced blood glucose levels increase glucagon secretion, promoting ketogenesis [38]. Importantly, the SGLT2 receptor has been identified in pancreatic α-cells, which may act as glucose sensors. Increased lipolysis supports hepatic ketone body formation. Ketone oxidation is more energy-efficient than fatty acid oxidation, yielding a higher ATP-to-oxygen ratio compared with other substrates [39].

SGLT2i induce moderate hyperketonemia, during which β-hydroxybutyrate is preferentially utilized by the heart instead of fatty acids or glucose. Thus, ketone bodies serve as an alternative and more efficient energy source, improving cardiac function and mechanical performance [40]. β-hydroxybutyrate also possesses antioxidant properties, inhibiting histone deacetylases and promoting mitochondrial biogenesis [41].

Metabolic flexibility refers to the heart's ability to switch between glucose and fatty acids based on substrate availability. In T2D, this mechanism is impaired due to excess fatty acid supply resulting from inadequate insulin response, which under normal conditions would inhibit lipolysis. Consequently, the heart becomes more reliant on fatty acid oxidation [42]. Conditions in which the heart derives a higher proportion of energy from fatty acid oxidation lead to lipotoxicity and reduced cardiac efficiency [43]. Hyperinsulinemia due to hyperglycemia further exacerbates cellular stress via increased reactive oxygen species production.

Ketone bodies are primarily produced in the liver when acetyl-CoA generation exceeds hepatic energy demand and free fatty acid levels are elevated [44,45]. They are then transported via the bloodstream to extrahepatic tissues, particularly the heart and kidneys, where they become a major energy source during fasting. Studies have shown that SGLT2i therapy moderately increases circulating ketone bodies. Skeletal muscles have limited ability to utilize this alternative energy source effectively, whereas the failing heart can adaptively increase ketone utilization, though the magnitude of this effect varies among patients [46,47].

It is important to note that euglycemic diabetic ketoacidosis is a rare but serious complication of SGLT2i therapy. Risk factors include cardiovascular events (stroke, myocardial infarction), infections, excessive alcohol intake, and fluid loss [48].

SGLT2i may also interact with other HF therapies, such as neprilysin inhibitors (ARNI) and mineralocorticoid receptor antagonists (MRA) [49]. Possible synergistic or antagonistic metabolic effects can influence combination therapy strategies. Recent data suggest that combined therapy with sacubitril/valsartan and SGLT2i may provide additional clinical benefits, including further reductions in hospitalization risk and improvements in hemodynamic parameters [50]. ARNI increase the availability of natriuretic peptides, supporting SGLT2i in maintaining fluid-electrolyte balance and reducing afterload [51,52].

MRA affect cardiac remodeling and sodium-potassium balance, which, when combined with the natriuretic properties of SGLT2i, may enhance renal protection but require careful electrolyte monitoring [53]. From a clinical perspective, identifying biomarkers to predict which patients will derive the greatest benefit from combination therapy is essential. Biomarkers such as NT-proBNP, hs-troponin, and oxidative stress markers have been associated with improved outcomes during SGLT2i therapy [54,55]. In the future, defining a comprehensive biomarker panel incorporating metabolic, inflammatory, and hemodynamic parameters may help personalize therapy and identify patients most likely to benefit from multi-drug regimens [56].

Ionic homeostasis

Initially, SGLT2i were developed to improve glycemic control in diabetes by increasing urinary glucose excretion and lowering blood glucose. It is now recognized that they also exert cardioprotective effects in both diabetic and non-diabetic patients [57].

Although SGLT2 is not expressed in cardiomyocytes, its inhibitors affect cellular metabolism, ionic homeostasis, and oxidative stress [58,59].

In HF patients with preserved ejection fraction (HFpEF), elevated glucose, TNF-α, or physical exertion can increase intracellular sodium and overactivate the NHE1 exchanger. Sodium overload disrupts the sodium-calcium exchanger (NCX), leading to intracellular sodium and calcium accumulation and triggering oxidative stress [60][Chen S., 2024]. Additionally, mitochondrial calcium decreases, activating apoptosis pathways and causing cardiomyocyte death, further worsening HF.

SGLT2i, exemplified by empagliflozin, inhibit overactive NHE1, lowering intracellular Na+ and Ca2+ and protecting against apoptosis [61]. Sodium and calcium overload in HF activates NCX, leading to delayed afterdepolarizations and triggered action potentials, which can precipitate life-threatening ventricular arrhythmias [62]. Normally, NCX exchanges

one Ca2+ out of the cell for three Na+ in; in pathological sodium overload, this direction reverses, increasing cytoplasmic calcium. SGLT2i-mediated modulation reduces calcium overload while enhancing nitric oxide synthesis and capillary dilation [63].

Hemodynamically, SGLT2i increase osmotic diuresis through urinary glucose excretion, reducing cardiac preload and, to a lesser extent, afterload by lowering arterial blood pressure. Unlike loop diuretics, SGLT2i minimally affect systemic electrolytes and preserve intracellular fluid clearance [64]. Empagliflozin also attenuates GFR decline and slows CKD progression in HF patients, independent of diabetes status [65].

Effects on cardiac remodeling

Pathological remodeling of the heart is one of the key mechanisms underlying the development and progression of heart failure. It occurs due to acute or chronic stress on the heart, therefore it is associated with conditions such as hypertension, diabetes, obesity and others, all of which may ultimately lead to HF [66–68]. It is a progressive process which may act as a predictive marker of outcome in chronic heart failure (CHF) patients [69]. The search for therapeutic agents targeting pathological remodeling of the cardiac tissue remains a vivid and crucial part of developing new strategies to combat heart failure [70].

Adverse cardiac remodeling comprises multiple processes such as: cardiomyocyte hypertrophy, myofibroblast activation and production of excess collagen fibers leading to fibrosis, endothelial dysfunction, tissue ischemia and inflammation [66,71–73]. On the subcellular level, the observed alterations include: mitochondrial injury related to disrupted Ca^{2+} homeostasis and excessive production of free radicals, metabolic dysfunction, apoptosis and autophagy [73,74].

SGLT2i's ability to reverse pathological remodeling was first examined on hearts altered by diabetes and metabolic syndrome. In a study on a mural model of diabetic cardiomyopathy, empagliflozin reduced cardiac fibrosis and alleviated oxidative stress, as well as hampered the activation of TGFβ/Smad pathway, a major regulator of fibrosis [75]. In a study on cell cultures, empagliflozin was shown to reduce oxidative stress and lipotoxicity, as well as Ca2+ accumulation in the cell, thus reducing cellular stress [76]. In another study on diabetic rats, empagliflozin attenuated fibrosis and cardiomyocyte hypertrophy in the left atria, in a dose-dependent manner [77].

There is a growing body of evidence of a positive effect of SGLTis on a failing heart in non-diabetic patients. Dapagliflozin was shown to reduce cardiac hypertrophy and fibrosis in a mural model of hypertension and left ventricular hypertrophy [78]. In a randomized study, which enrolled 88 non-diabetic patients with HFrEF or HFmrEF, dapagliflozin proved to be more effective in reversing pathological cardiac remodeling than optimal standard therapy [79]. In another study on human patients with chronic heart failure, dapagliflozin induced reverse remodelling of both the left atria and ventricles [80]. In a study on patients with HFrEF, empagliflozin proved to be efficient in reversing fibrotic changes, reducing adipose tissue deposition in the heart and curbing inflammation [81].

In a study on porcine non-diabetic model of HFrEF, during a two-month administration, empagliflozin improved diastolic function of the failing heart, reduced heart stiffness and fibrotic tissue content, as well as enhanced nitric oxide signalling pathway, thus limiting inflammation [82]. SGLT2is were also effective in reducing the size of injury and alleviating adverse remodeling of the heart following myocardial infarction [83,84].

Although there is conflicting evidence as to whether there are SGLT2 receptors on cardiomyocytes [85–87], it is agreed that the mechanism of action on cardiac remodeling remains independent of SGLT2 receptors and glucose metabolism [88–90]. The details of SGLT2i mechanism of action in this context remain to be elucidated, although some clues for agents involved have been unraveled. One of them is NHE1, a Na+/H+ exchange protein proved essential for lowering intracellular Na+ and Ca2+ [60,91,92]. An imbalance of Na+ and Ca2+ levels in the cardiomyocyte is an important factor in development of arrhythmia, impaired contractility, oxidative stress and mitochondrial dysfunction [93], the last two being directly associated with pathological cardiac remodeling [72,73,75,76].

By positively influencing the function of the aforementioned sodium/calcium exchanger, SGLTis also impact the expression of ALDH2, an enzyme which plays an important role in regulating fibrosis, scar formation, cardiomyocyte apoptosis and loss of function. In a 2024 study, it was shown that dapagliflozin wasn't able to inhibit pathological remodeling of the heart in ALDH2-knock out mice. The same study was able to prove the key role which NHE1 plays in ALDH2 function [92]. Another important factor seems to be the already mentioned TGFβ/Smad pathway, which has been shown to be influenced by empagliflozin [75,90] and dapagliflozin [94].

Angiotensin II, a well-known blood pressure regulator and important factor in the development of hypertension [95], was observed to be influencing cardiac fibrosis, and dapagliflozin was proven to alleviate this process [94]. In a study on a mural model of cardiac hypertrophy induced by administration of angiotensin II, dapagliflozin reduced cardiomyocyte size and tissue fibrosis by activating the SIRT/HIF-1α signalling pathway [96], Empagliflozin was also shown to ameliorate fibrotic changes in the hypertensive heart, as well as to reduce the production of TNFα, a molecule of great importance for the induction of apoptosis and inflammation [97].

It is also important to note that structural changes in the failing cardiac tissue might be closely related to alterations in cell metabolism – in a study on a rat model of HFpEF, dapagliflozin was shown to alleviate interstitial and perivascular fibrosis, as well as reduce hypertrophy of cardiomyocytes and hamper inflammation, an effect which was proven by the authors to be linked with increased activation of a Krebs cycle enzyme, citrate synthase [98]. Ertugliflozin was shown to reduce cardiac fibrosis and cell apoptosis by decreasing the activity of mTOR signalling pathway, thus also increasing ketone body metabolism and alleviating ER stress [99].

In a systematic review and meta-analysis conducted in 2023, out of 7 studies investigated, only 3 studies showed statistically significant improvement of reverse remodelling after administration of SGLTi. Small sample sizes and limited patient demographics could be reasons of the inconsistent results [100]. Another meta-analysis from 2024 which included 555 patients in total, proved SGLTis to be beneficial for reverse remodeling of the heart in patients with HFrEF [101]. Thus, a firm body evidence of efficacy of this drug class on reverse remodeling, as well as its underlying mechanisms, remain to be established, though SGLT2 inhibitors already pose an exciting new therapeutic prospect for treatment of pathological heart failure-associated cardiac remodeling.

Relationship with oxidative stress and inflammation

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have dual roles in the body. Under physiological conditions, they stimulate signaling pathways, support redox homeostasis, regulate cellular metabolism, and are produced by the immune system to neutralize pathogens [102,103].

Excess ROS/RNS, however, induces oxidative-nitrosative stress, arising from an imbalance between their production and the antioxidant defense capacity, leading to damage of key cellular components, including lipids, proteins, carbohydrates, and DNA. Mitochondria are both major sources and targets of these reactive molecules [104].

Physiologically, during mitochondrial oxidative phosphorylation, a small fraction of electrons (~0.1%) leak from the electron transport chain, particularly at the first three enzymatic complexes, where flavins and quinones act as single-electron donors. This results in the partial reduction of oxygen to superoxide anion, a type of ROS, which can also be generated by enzymes such as NADH/NADPH oxidases (NOX) and xanthine oxidoreductase [104–106]. Exogenous ROS sources include high-energy radiation, chemotherapy, heavy smoking, excessive alcohol intake, and other factors.

The antioxidant system becomes overwhelmed when oxidants exceed the enzymatic and non-enzymatic buffering capacity. Superoxide produced in mitochondria can be converted into hydrogen peroxide, a key signaling molecule, by superoxide dismutase (SOD). Hydrogen peroxide can further react with redox-active transition metals, such as iron or copper, forming highly reactive hydroxyl radicals via the Fenton reaction. These reactive molecules can damage biomolecules but are normally neutralized by enzymes including SOD, catalase, and glutathione peroxidase, which convert ROS into less toxic species [105,107,108].

Inflammation is a physiological process aimed at eliminating damaged cells and initiating tissue repair [109][Marwan Amara, 2025]. Pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides (LPS), and damage-associated molecular patterns (DAMPs), including HSP60, HMGB1, and mitochondrial components, activate pattern recognition receptors (PRRs), particularly TLR4. This triggers signaling pathways involving NF-κB and NLRP3 inflammasomes, leading to the secretion of proinflammatory cytokines (IL-6, IL-1β, IL-18, TNF-α) and adhesion molecules (ICAM-1), forming a feedback loop between inflammation and oxidative stress [107,110,111].

At rest, NF-κB is bound in the cytoplasm by IκBα. Upon stimulation, the IKK complex phosphorylates IκBα at Ser32 and Ser36, allowing NF-κB nuclear translocation and induction of inflammatory gene expression, simultaneously activating NLRP3 inflammasomes, which promote maturation and release of IL-1β and IL-18. Overexpression of these pathways is observed in many inflammatory diseases [111–113].

Inflammation in coronary vessels reduces nitric oxide (NO) bioavailability and increases ROS, suppressing PKG activity, leading to titin hyperphosphorylation, increased cardiomyocyte stiffness, and hypertrophy, thereby impairing diastolic function. HF is associated with inflammation and oxidative stress, which disrupt redox balance and induce apoptosis; ROS accumulation is a key pathogenic mechanism. Elevated proinflammatory cytokines (TNF-α, IL-1, IL-6, IL-8, IL-18, IL-1RA, IL-3) correlate with HF severity [109,112,114].

SGLT2 inhibitors reduce ROS and oxidative stress. Mechanisms include eNOS phosphorylation and deacetylation via SIRT1/eNOS activation. SIRT1 signaling enhances gluconeogenesis, ketogenesis, and mitigates oxidative stress [12,115]. SGLT2i also activate SIRT1 and AMPK while inhibiting Akt/mTOR, improving cardiac structure and microcirculation. AMPK activation increases NAD+, enhancing SIRT1 activity. This AMP:ATP shift contributes to SGLT2i benefits, as demonstrated in mouse models [113,116,117].

At the molecular level, empagliflozin decreases mRNA expression of IL-6, IL-1β, TNF-α, and MCP-1 in macrophages, prevents oxidative stress in HU-

VECs by inhibiting the Na+/H+ exchanger, reduces intracellular Na+, activates the Nrf2/HO-1 pathway, and decreases mitochondrial Ca2+ overload and ROS production, improving cell survival, mitochondrial biogenesis, and lowering inflammatory markers (MPO, ICAM-1, IL-6, NFκB), while increasing SOD1 and glutathione levels [110,118,119].

Nrf2 maintains cellular and mitochondrial redox homeostasis, supplying reduced glutathione (GSH) and mitochondrial antioxidant enzymes (GSH peroxidase, SOD, peroxiredoxin). Nrf2 deficiency impairs fatty acid oxidation, cellular respiration, and ATP production, weakening mitochondrial function. Nrf2 via Nrf2/HO-1 signaling regulates cardiomyocyte regeneration, oxidative stress, and apoptosis [118,120,121]. Empagliflozin activates Nrf2/ARE signaling, enhances antioxidant defenses, and inhibits TGF-β/SMAD, reducing NADPH oxidase activity and ROS, integrating antioxidant and anti-inflammatory effects [12,121].

By reducing ROS and increasing NO bioavailability, SGLT2i mitigate inflammation and lower proinflammatory cytokines such as TNF-α. Canagliflozin has been shown to enhance antioxidant and anti-inflammatory signaling via AMPK, Akt, eNOS, and Nrf2 [27,116]. Deficiency in antioxidant proteins (SOD, HO-1, glutathione peroxidases) combined with excess ROS (e.g., via NADPH oxidases) promotes an inflammatory phenotype, highlighting the close link between redox imbalance and inflammation. Modern SGLT2i modulate inflammation and have potent antioxidant properties, making them promising agents in heart disease associated with oxidative stress and inflammation [27,119].

Clinical evidence supporting molecular mechanisms

Recent clinical trials provide strong evidence that SGLT2i (e.g., dapagliflozin, empagliflozin) confer benefits in HF beyond glucose lowering. In DAPA-HF, adding dapagliflozin to standard therapy in HFrEF patients reduced cardiovascular death and HF hospitalization [122].

The "Lessons Learned" analysis highlighted that benefits were similar in diabetic and non-diabetic patients, suggesting that SGLT2i effects are not solely due to glycemic improvement. Modest changes in natriuretic peptides (e.g., NT-proBNP) indicate that effects are not primarily due to diuresis [123].

Additional trials demonstrate benefits in HF with preserved or mildly reduced EF. EMPEROR-Preserved showed that empagliflozin reduced HF hospitalization in patients with EF >40% [124], and improved structural heart parameters, such as LV mass index, suggesting regression of hypertrophy [125].

A meta-analysis of nine RCTs including 2,824 patients with acute HF showed that SGLT2i reduced mortality, HF rehospitalization, and combined CV death/HF hospitalization. Patients on SGLT2i had increased urine output and required lower loop diuretic doses, without worsening renal function [126].

In a study of 324 HFpEF patients, dapagliflozin improved quality of life and physical performance after 12 weeks, measured by the Kansas City Cardiomyopathy Questionnaire and 6-minute walk test, with modest weight loss [127].

Finally, a large meta-analysis of >421,000 T2D patients showed that SGLT2i reduce mortality, cardiovascular events, and HF hospitalizations, consistent with their molecular mechanisms: improving cardiomyocyte energy metabolism, reducing oxidative stress, and inhibiting myocardial fibrosis [128].

In summary, clinical data strongly support molecular hypotheses: SGLT2i protect the heart by reducing oxidative stress and inflammation, improving ionic and metabolic homeostasis, attenuating hypertrophy and fibrosis, and providing systemic effects including renal protection.

SGLT2 inhibitors: molecular effects in heart failure

The data reviewed depict SGLT2 inhibitors (SGLT2i) as multi-faceted agents in HF. Their clinical benefits – such as reduced hospitalizations, lower mortality, and improved cardiac structure – are consistent with molecular observations: improved ionic homeostasis, reduction of oxidative stress and inflammation, and attenuation of hypertrophy and fibrosis.

Molecular mechanisms explain how these drugs can exert long-term cardioprotective effects. For example, the cardioprotective action of empagliflozin in HF involves modulation of the NHE1–NO pathway, where inhibition of overactive sodium–hydrogen exchanger 1 (NHE1) in cardiomyocytes improves nitric oxide (NO) signaling, preventing both systolic and diastolic dysfunction and reducing oxidative stress [60]. Similarly, in an experimental swine model, dapagliflozin activated the NO–cGMP–PKG pathway, reducing inflammatory activity and inhibiting cardiac remodeling [129].

However, direct evidence in human myocardium remains limited. Imaging, echocardiography, and proteomic studies suggest significant effects, but it is challenging to clearly separate benefits from hemodynamic unloading versus direct cardiomyocyte actions [130]. Additionally, in HFpEF, effects may be less pronounced than in HFrEF due to complex pathophysiology, comorbidities, and microvascular dysfunction [131]. Another limitation is the duration of observation – processes such as fibrosis regression may require longer treatment than most studies provided [132].

Importantly, the literature increasingly supports multi-targeted actions of SGLT2i. Reviews and meta-analyses emphasize the role of ionic homeostasis, oxidative stress, and inflammation, noting that clinical benefits occur regardless of diabetes status [58,133].

Consequently, SGLT2i are already recommended in guidelines as standard therapy for HFrEF, even in non-diabetic patients [134]. Their use in HFpEF is gradually expanding, especially since EMPEROR--Preserved demonstrated benefits in HF hospitalizations [135].

Future research should focus on human myocardial tissue studies, including biopsies to confirm molecular mechanisms (e.g., gene expression changes, mitochondrial metabolism), as well as long--term trials to assess progression and remodeling (effects on fibrosis, hypertrophy, left ventricular geometry) and subpopulation analyses (HFpEF, various HF etiologies, different severity levels) to identify patients with maximal benefit [136].

In summary, clinical evidence strongly supports molecular mechanisms underlying SGLT2i in HF. Observed benefits – independent of diabetes, with reduced hospitalization and mortality – align with cellular effects: improved ionic homeostasis, reduced oxidative stress, and attenuation of remodeling. The future lies in direct human myocardial evidence and tailoring therapy to individual mechanistic profiles.

Limitations

Although we tried our hardest to cover the topic extensively and address the crucial details, we acknowledge our work bears some limitations. One of them is limited scope of sources we referenced in our our paper. We mostly cited open access articles and certainly in the limited access realm there's some exciting knowledge we did not include in this work. Moreover, the issue of SGLT2i's role in managing heart failure is now being researched extensively, making it almost impossible to reach all the data which might be of value.

Another limitation is the selection of sources – some of the research we cited had not been finished due to pandemic [26], some others were post-hoc analyses [33,55], small sample sizes were the limitations of other few [38,79,81]. Moreover, inclusion and exclusion criteria, specific to each study, sometimes limit the generalisability of the conclusions. We also acknowledge that animal model studies we cite may not fully reflect the effect of SGLTi on the human body, therefore further studies should be performed to enable us to understand this complex issue even better.

Conclusions

Heart failure remains one of the major contemporary medical challenges, and despite significant advances in pharmacotherapy, patient prognosis remains poor. SGLT2 inhibitors represent a breakthrough in HF management, exhibiting multi-targeted actions across patient physiology. Their molecular effects include enhanced energy metabolism, ionic homeostasis regulation, reduction of oxidative stress, and inhibition of maladaptive cardiac remodeling.

These well-characterized mechanisms contribute to meaningful improvements in patient outcomes, underscoring the importance of SGLT2i as a modern therapeutic strategy in heart failure.

Ethical approval
This study is not related to either human or animal use.

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Conflict of interest
The authors declare no conflict of interest.

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