Cinti *et al. Cardiovascular Diabetology* (2025) 24:208
https://doi.org/10.1186/s12933-025-02767-9

Cardiovascular Diabetology

REVIEW Open Access

The effects of SGLT2i on cardiac metabolism in patients with HFpEF: Fact or fiction?

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Abstract

The rising prevalence of Type 2 diabetes (T2D) has been closely associated with an increased incidence of cardiovascular diseases, particularly heart failure with preserved ejection fraction (HFpEF). Cardiometabolic disturbances in T2D, such as insulin resistance, hyperglycemia, and dyslipidemia, contribute to both microvascular and macrovascular complications, thereby intensifying the risk of heart failure. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), initially developed as glucose-lowering agents for T2D, have demonstrated promising cardiovascular benefits in patients with heart failure, including those with preserved ejection fraction (HFpEF), regardless of T2D status. These benefits include reduced heart failure hospitalization rates and improvements in various metabolic parameters. This review aims to critically examine the effects of SGLT2i on cardiac metabolism in HFpEF, evaluating whether the observed benefits can truly be attributed to their impact on myocardial energy regulation or whether they represent other, potentially confounding, mechanisms. We will focus on the key metabolic processes possibly modulated by SGLT2i, including myocardial glucose utilization, fatty acid oxidation, and mitochondrial function, and explore their effects on heart failure pathophysiology. Additionally, we will address the role of SGLT2i in other pathogenetic factors involved in HFpEF, such as sodium and fluid balance, inflammation, and fibrosis, and question the extent to which these mechanisms contribute to the observed clinical benefits. By synthesizing the current evidence, this review will provide an in-depth analysis of the mechanisms through which SGLT2i may influence cardiac metabolism in HFpEF, assessing whether their effects are supported by robust scientific data or remain speculative. We will also discuss the potential for personalized treatment strategies, based on individual patient characteristics, to optimize the therapeutic benefits of SGLT2i in managing both T2D and cardiovascular risk. This review seeks to clarify the true clinical utility of SGLT2i in the management of cardiometabolic diseases and HFpEF, offering insights into their role in improving long-term cardiovascular outcomes.

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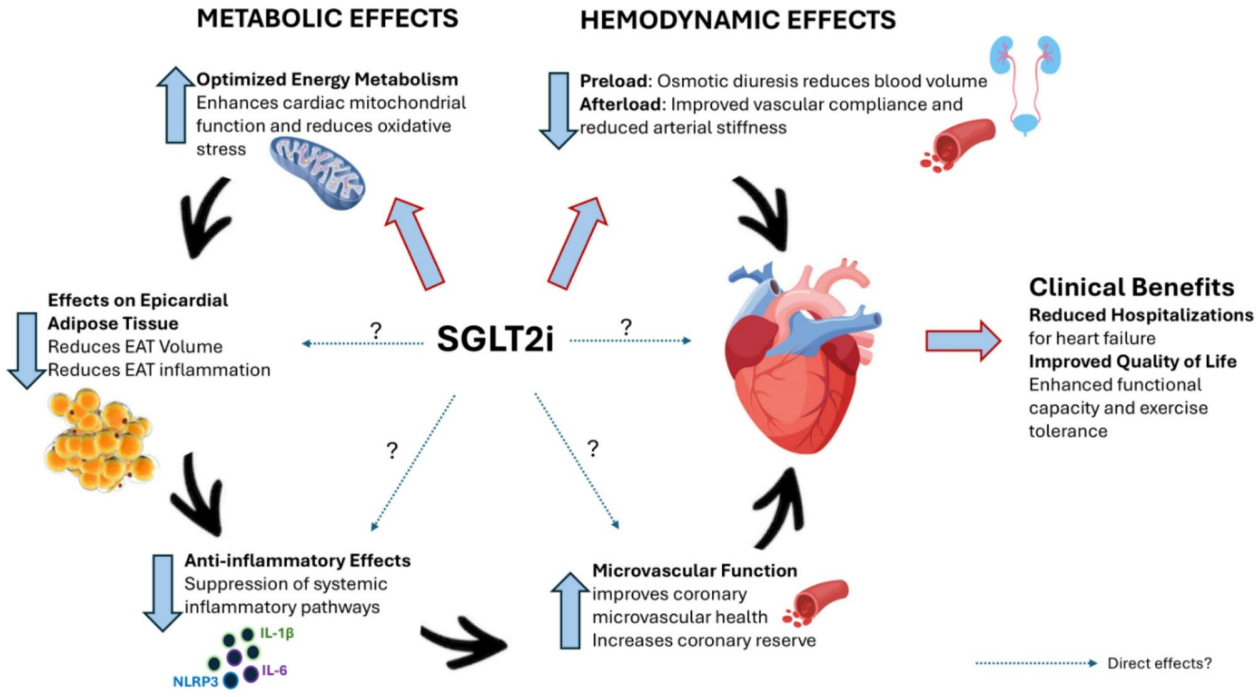
Keywords Diabetes, Heart failure, Metabolism, SGLT2i, Precision medicine, Microvascular dysfunction, Coronary reserve, Inflammation

Graphical abstract



Introduction

Type 2 diabetes (T2D) is a metabolic disorder and a significant risk factor for cardiovascular disease (CVD) [1]. Research has shown that individuals with diabetes, whether type 1 or type 2, have a twofold increased risk of developing CVD compared to those without diabetes [2].

In the last 10 years, the introduction of sodium-glucose co-transporter 2 inhibitors (SGLT2i) in clinical practice has profoundly changed the CVD risk scenario in T2D. While this class of drugs was originally used only as a glucose-lowering therapy, randomized clinical trials with cardiovascular outcomes (CVOTs) have in fact demonstrated that SGLT2i are able to significantly reduce the incidence of major adverse cardiovascular events (MACEs) and/or hospitalization for heart failure (HF) [1]. Interestingly, these striking results in HF patients have been observed irrespective of the presence of diabetes itself [2, 3].

Despite the introduction of this (and other) classes of drugs, T2D remains the most relevant risk factor for HF and, in particular, for HF with preserved ejection fraction [4, 5].

HF with preserved ejection fraction (HFpEF) is defined by the following criteria: a left ventricle (LV) ejection fraction (EF) ≥ 50%, along with evidence of LV diastolic dysfunction or elevated LV filling pressures, due to structural and/or functional cardiac abnormalities [6]. Patients with HFpEF are usually of advanced age and predominantly women, with multiple comorbidities including T2D, hypertension, obesity, hyperlipidemia, and sleep apnea [7, 8].

Although both the conditions are characterized by impaired cardiac metabolic flexibility with an over-reliance on fatty acids for ATP production, the pathophysiological mechanisms causing HFpEF differ from those of HF with reduced EF (HFrEF) with a more prevalent lipotoxicity in HFpEF [9], together with a prevalent microvascular dysfunction (MVD) determined by systemic inflammation [7, 10]. Both of these pathological processes are, moreover, predominant in T2D patients [11].

As a consequence, the "classical" therapeutic approaches focused on the blockade of the noradrenergic and renin-angiotensin-aldosterone system (RAAS), are often less effective in HFpEF and T2D patients, while drugs with effects on cardiac metabolism and small vessel physiology, such as SGLT2i, could open new frontiers in improving symptoms and prognosis in these diseases [12].

This review, therefore, aims to provide a state-of-the-art overview of the cardiometabolic changes in individuals with T2D, highlighting the effects of the use of SGLT2i, and exploring the specific pathogenetic

mechanisms of HFpEF targeted by these drugs in order to offer a personalized therapeutic approach.

HFpEF in T2D: pathophysiology and available treatments

Heart failure with preserved ejection fraction (HFpEF) in type 2 diabetes (T2D) represents a growing challenge in clinical cardiology as its prevalence has surged with the increasing global burden of diabetes [13]. The pathophysiological mechanisms linking T2D to HFpEF are multifactorial and involve intricate disruptions in metabolic, vascular, and myocardial function. One of the core contributors to the development of HFpEF in T2D is insulin resistance, which impairs glucose uptake and utilization in peripheral tissues, thereby driving hyperglycemia [14]. This chronic hyperglycemic state accelerates a cascade of metabolic abnormalities, including increased production of advanced glycation end-products (AGEs), which, through their interaction with the receptor for AGEs (RAGE), promote oxidative stress, inflammation, and fibrosis in both the myocardium and the vasculature [15, 16]. These changes promote myocardial stiffening, a hallmark of HFpEF, and impair diastolic function by disrupting the normal relaxation and compliance of the left ventricle [17].

In addition to altered metabolic pathways, T2D is associated with increased adiposity, particularly the accumulation of epicardial fat around the heart, which has been implicated in the pathogenesis of HFpEF. In pathological conditions such as T2D, epicardial fat is not only a source of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), but it also directly influences myocardial function through the secretion of adipokines, such as leptin and adiponectin, that alter cardiac metabolism and exacerbate myocardial fibrosis [18]. Increased epicardial fat contributes to the mechanical stiffness of the left ventricle, which impairs diastolic filling and increases the risk of developing HFpEF in diabetic patients. Furthermore, epicardial fat secretes a variety of bioactive molecules that can induce endothelial dysfunction and promote vascular stiffness, both significant contributors to the clinical syndrome of HFpEF [19].

Another critical aspect of HFpEF in T2D is endothelial dysfunction. In T2D, chronic hyperglycemia leads to reduced bioavailability of nitric oxide (NO), a key vasodilator that maintains vascular tone and flexibility [20]. The reduction in NO production contributes to endothelial dysfunction, which, in turn, promotes arterial stiffness and increases systemic vascular resistance. This elevated afterload places an added burden on the heart, further exacerbating diastolic dysfunction in HFpEF. Furthermore, endothelial dysfunction is closely linked to inflammation, with increased levels of inflammatory markers such as C-reactive protein (CRP) and high-sensitivity CRP (hs-CRP), which are known to correlate with adverse cardiovascular outcomes in individuals with T2D [16].

Changes in myocardial metabolism also play a pivotal role in the development of HFpEF in T2D. In the context of insulin resistance, the reduced ability of the heart to use glucose increases myocardial fatty acid oxidation leading to increased reactive oxygen species (ROS) production [21–23]. This change in metabolism leads to the accumulation of intracellular lipids, which contribute to myocardial lipotoxicity and impair cardiac contractility and relaxation [24]. Additionally, mitochondrial dysfunction, a key feature of insulin resistance, exacerbates oxidative stress and further impairs the heart's ability to handle the metabolic demands required during diastole [25, 26]. This results in myocardial stiffening and reduced compliance leading to the hallmark clinical features of HFpEF, including exercise intolerance, dyspnea, and fluid retention. [27].

The pathogenesis of HFpEF in T2D is also influenced by autonomic nervous system dysregulation. Diabetes-related neuropathy can impair the balance between sympathetic and parasympathetic activity, leading to an exaggerated sympathetic response and reduced parasympathetic tone [28]. This dysregulation can exacerbate vascular stiffness and elevate cardiac workload, which in turn worsens diastolic dysfunction [29, 30]. Additionally, the autonomic imbalance increases inflammatory responses, endothelial dysfunction, and myocardial fibrosis, thereby perpetuating the cycle of heart failure [31].

Despite a growing understanding of the pathophysiological mechanisms linking T2D to HFpEF, therapeutic options remain limited, and treatment remains primarily symptomatic. Recent pharmacological advances have shown promise in improving outcomes for patients with HFpEF, with sodium-glucose co-transporter 2 inhibitors (SGLT2i) emerging as a particularly effective treatment, especially for those with diabetes. These drugs not only improve glycemic control but also reduce hospitalization for heart failure and enhance diastolic function by improving vascular stiffness and reducing myocardial inflammation [17]. Additionally, mineralocorticoid receptor antagonists (MRAs) have demonstrated efficacy in reducing symptoms and improving functional capacity in HFpEF, likely through their effects on fibrosis and inflammation [32–34]. Neprilysin inhibitors, such as sacubitril, have also shown potential in this setting, as they reduce myocardial fibrosis and improve vasodilation through increased levels of natriuretic peptides, although more research is necessary to fully elucidate their role in the diabetic HFpEF population [35].

In summary, the pathophysiology of HFpEF in T2D involves a multifaceted interplay of metabolic changes,

myocardial and vascular remodeling, inflammation, and autonomic dysfunction. While current therapies, mostly SGLT2 inhibitors, offer promising benefits, further research is required to optimize treatment strategies and address the unique pathophysiological mechanisms that contribute to the significant burden of HFpEF in individuals with T2D.

SGLT2 inhibitors and the heart

SGLTs represent a family of six isoforms that act as a cellular cotransporter reabsorbing filtered glucose from the tubular lumen [36]. Among these, SGLT1 and SGLT2 have been extensively studied due to their key roles in the transport of glucose and sodium across the renal cell membrane and the intestinal barrier [37]. While the expression of SGLT2 has been observed in the myocardium in both animal models and humans, it is less abundant compared to the kidneys, where it plays a primary role in glucose reabsorption.

SGLT2i exert their glucose-lowering effect by selectively targeting SGLT2 in the proximal renal tubules, blocking glucose reabsorption and promoting glucosuria. [38] This mechanism effectively reduces plasma glucose levels, alleviating hyperglycemia and improving glycemic control, as evidenced by reductions in HbA1c levels. [39, 40] Furthermore, the excretion of glucose through urine leads to caloric loss, contributing to weight reduction, a particularly beneficial outcome in individuals with T2D. [41] Unlike other glucose-lowering agents, the action of SGLT2i is independent of insulin secretion or sensitivity. [42] This enables them to remain effective even in advanced stages of T2D, when β-cell function is significantly impaired. [43] Additionally, the osmotic diuresis induced by SGLT2i reduces glucotoxicity and indirectly enhances insulin sensitivity in peripheral tissues. [44–46] These effects, coupled with reductions in visceral fat, [47] underscore the multifaceted benefits of SGLT2i in managing glycemic levels and addressing metabolic abnormalities in T2D [48].

The following is a breakdown of the current understanding.

Expression of SGLT2 in the heart and epicardium

Although the topic remains controversial, several studies have demonstrated that SGLT2 is expressed in the myocardium and epicardial fat. SGLT2 expression in the heart is primarily localized to cardiac myocytes [47], vascular smooth muscle cells [49], and epicardial adipocytes [50]. Notably, there is evidence suggesting that SGLT2 expression in the myocardium may be transient, particularly during myocardial injury. This transient expression could help explain some of the discrepancies in the literature, as it may be induced by pathological conditions, such as ischemic injury, and may not be present in normal physiological states. This phenomenon may partially reconcile the observed inconsistencies regarding SGLT2 expression in the heart.

Studies have explored various cardiac cell types, including cardiomyocytes, endothelial cells, fibroblasts, and smooth muscle cells, as potential targets for the observed cardiovascular benefits of SGLT2 inhibitors [51]. While SGLT1 is highly expressed in cardiac tissue and its expression is altered under pathological conditions, there is ongoing debate regarding the cardiac expression of SGLT2 [52–54].

The sodium-hydrogen exchanger (NHE)-1 is an antiporter that regulates pH and intracellular volume by coupling proton extrusion with sodium entry [55]. The increased activity of this exchanger, in the heart and coronary vasculature, promotes Na^+ and Ca^{2+} enhancement, leading to increased cardiomyocyte damage and contributing to functional inefficiency and structural remodeling of the heart [56–58]. SGLT2i influence ion homeostasis in cardiomyocytes. In healthy rabbit cardiomyocytes, incubation with empagliflozin reduces cytosolic Na + and Ca2+, providing the first evidence of direct inhibition of NHE1, which plays a key role in preventing ion overload [57]. This inhibitory effect on NHE1 by SGLT2i has also been confirmed in human atrial cells [59].

Pathological conditions mediated by NHE-1 overexpression and activity involve inflammation, and endothelial dysfunction. Ventricular remodeling, partially mediated by oxidative or nitrosative stress is a classical sign of HF and is generally characterized by wall stress, inflammatory cytokines, and neurohormone dysregulation together with increased stiffness, cardiomyocyte hypertrophy and differentiation of fibroblasts into myofibroblasts [60]. All this highlights the importance of inflammation and cytokine release as being causal in the onset and progression of cardiac dysfunction [61].

In the failing heart, SGLT2i promote a reduction in inflammatory processes through the inhibition of the nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome, a complex network of regulatory proteins that initiate an inflammatory response leading to the secretion and release of proinflammatory cytokines, such as interleukin (IL)-1β and IL-18, also in the absence of diabetes [62–64]. SGLT2i have been reported to decrease expression of adhesion molecules, such as VCAM-1 and e-selectin, by preventing cytokine expression in endothelial cells [65].

Mechanisms of action of SGLT2i in patients with HFpEF: fact or fiction?

SGLT2i have shown significant cardiovascular benefits, particularly in patients with HF and T2D. While their beneficial effects on the heart have been documented, the precise mechanisms by which SGLT2i exert these

beneficial effects are subject to ongoing investigation. Several hypotheses have been proposed to explain the cardiovascular and myocardial benefits of SGLT2 inhibitors, some of which are widely accepted, while others remain controversial or are still under debate.

It is therefore important to assess how much is real (and clinically relevant) and how much is fiction (still a matter of debate and with uncertain evidence).

Current evidence from clinical trials on the use of SGLT2i in HFpEF

The two main SGLT2 inhibitors (SGLT2i), empagliflozin and dapagliflozin, have been extensively investigated in clinical trials and have demonstrated clear benefits for heart failure (HF) patients, including those with HF with preserved ejection fraction (HFpEF). The EMPERIAL trial [66] (and the PRESERVED-HF trial) [67] assessed the effects of SGLT2i on symptoms and functional capacity in HFpEF patients after 12 weeks of treatment. While the EMPERIAL trial did not show a significant improvement in the primary endpoint of the 6-minute walk distance (6MWD) for patients treated with empagliflozin, the PRESERVED-HF trial demonstrated a notable improvement in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS) (+5.8 points; $P=0.001$) and 6MWD (+20.1 m; $P=0.007$) for the dapagliflozin arm.

It is important to note that differences may exist between the two SGLT2i, which could be influenced by their varying selectivity for the SGLT2 receptor. Empagliflozin and dapagliflozin, while both targeting the SGLT2 receptor, may differ in their pharmacokinetic properties, receptor affinity, and tissue distribution. Such differences could lead to distinct therapeutic outcomes in clinical trials, which may explain the varying results observed in symptom improvement and functional capacity.

Furthermore, two large-scale trials have evaluated the impact of SGLT2i on major adverse cardiovascular events (MACEs) in HFpEF patients, both with and without diabetes. In the EMPEROR-PRESERVED trial [68], empagliflozin reduced the risk of cardiovascular death or HF hospitalization by 21% (HR 0.79; $P<0.001$). Similarly, in the DELIVER trial [69], dapagliflozin reduced the risk of worsening HF or cardiovascular death by 18% (HR 0.82; $P<0.001$). These findings underline the potential benefits of SGLT2i in improving HFpEF outcomes, though the differences in selectivity for the SGLT2 receptor between the two agents warrant further investigation to better understand the clinical implications. The main results and characteristics of these studies are summarized in Table 1.

These findings highlight that the cardiovascular benefits of SGLT2 inhibitors extend across all heart failure subgroups, including those with and without T2D, and regardless of left ventricular ejection fraction.

Hemodynamic effects: reduction of preload and afterload

One of the most widely accepted mechanisms by which SGLT2i benefit the myocardium is through the improvement of hemodynamics. SGLT2i promote glucosuria and osmotic diuresis, which leads to a reduction in circulating blood volume. This effect decreases preload (the volume of blood entering the heart), which can alleviate symptoms of fluid overload in patients with heart failure, including those with HFpEF. Additionally, by lowering blood pressure through diuresis and enhanced natriuresis, SGLT2i reduce afterload, which may improve myocardial efficiency and reduce cardiac workload [48].

Furthermore, there is evidence that SGLT2i can decrease arterial stiffness and improve vascular compliance, which may reduce systemic vascular resistance and thus afterload [70, 71]. This effect is particularly important in heart failure, where high afterload and poor myocardial relaxation are major contributors to diastolic dysfunction (Fig. 1).

Reduction in myocardial fibrosis and inflammation

SGLT2i improve heart function by exerting anti-inflammatory and antifibrotic effects, which are especially relevant in HFpEF, in which chronic inflammation and fibrosis play key roles. Research in both animal models and human trials has shown that SGLT2i reduce pro-inflammatory cytokines and fibrosis markers, such as myocardial collagen deposition [66], helping to mitigate fibrotic remodeling—a key contributor to diastolic dysfunction in HFpEF.

A study by Kolijn et al. [72] explored the mechanisms by which empagliflozin improves heart function in HFpEF. Using human myocardial samples and a murine model, they found that empagliflozin significantly reduced pro-inflammatory markers (e.g., TNF-α, IL-6, ICAM-1, VCAM-1) and oxidative stress markers (e.g., hydrogen peroxide, 3-nitrotyrosine). Additionally, empagliflozin improved nitric oxide (NO) signaling, which is impaired in HFpEF. Specifically, it prevented PKGIα oxidation, preserving its activity and restoring NO–sGC–cGMP signaling, thereby enhancing protein kinase G (PKG) activity and reducing oxidative stress. This, in turn, prevents titin hypo-phosphorylation, which is associated with increased cardiomyocyte stiffness.

SGLT2i also lower inflammatory biomarkers, including IL-6 and C-reactive protein (CRP) [73], possibly through effects on adiposity, metabolic homeostasis, and oxidative stress (Fig. 1). In patients with a history of myocardial infarction (MI), SGLT2i—especially when combined with GLP-1ra —are linked to improved cardiovascular

Table 1 Main characteristics of RCTs investigating SGLT2i in HFpEF. CI: confidence interval; CHQ-SAS: chronic heart failure questionnaire Self-Administered standardized format dyspnoea score EF: ejection fraction; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HR: hazard ratio; KCCQ-CS: Kansas City cardiomyopathy questionnaire-Clinical summary score; KCCQ-OS: KCCQ-Overall summary score; KCCQ-TSS: KCCQ-total system score; RCTs: randomized clinical trials; SGLT2i: sodium-glucose transporter 2 inhibitors; 6MWT: 6 min walking test

Trial (year of pubblication)	Study design	Duration of follow-up	n° of pts (mean age)	Setting	Primary endpoint (SGLT2i vs. placebo)	Secondary endpoints (SGLT2i vs. placebo)	Refs
EMPERIAL- Preserved (2021)	Multicentre, randomized, double-blind, placebo-controlled	12 weeks	312 (74)	Empagliflozin vs. placebo for 12 weeks in pts with HF signs/symptoms and EF > 40%	+ 10 m vs. + 5 m median increase at 6MWT ($P = 0.37$)	+ 4.17 vs. + 2.08 median increase in KCCQ-TSS + 0.10 vs. + 0.20 median increase in CHQ-SAS	[66]
PRESERVED-HF (2021)	Multicentre, randomized, double-blind, placebo-controlled	12 weeks	324 (70)	Dapagliflozin vs. placebo for 12 weeks in pts with HF signs/symptoms and EF ≥ 45%	+ 5.2 vs. + 1.00 median increase in KCCQ-CS ($P = 0.001$)	+ 18 m vs. -2 m median increase at 6MWT ($P = 0.007$) + 5.7 vs. + 2.2 median increase in KCCQ-OS ($P = 0.009$)	[67]
EMPEROR-Preserved (2021)	Multicentre, randomized, double blind, parallel-group, placebo-controlled, event-driven trial	26.2 months	5988 (71.8)	Empagliflozin vs. placebo in pts with HF signs/symptoms and EF > 40%	13.8% vs. 17.1% in composite of death from cardiovascular causes or hospitalization for HF (HR, 0.79; 95% CI, 0.69–0.90; $P < 0.001$)	8.6% vs. 11.8% hospitalization for HF (HR, 0.71; 95% CI, 0.60–0.83) −1.25 vs. − 2.62 ml per minute per 1.73 m2 per year in rate of decline in the eGFR ($P < 0.001$)	[68]
DELIVER (2022)	Multicentre, randomized, double blind, parallel-group, placebo-controlled, event-driven trial	27.6 months	6263 (71.6)	Dapagliflozin vs. placebo in pts with HF signs/symptoms and EF > 40%	16.4% vs. 19.5% in composite of worsening HF or death from cardiovascular causes (HR, 0.82; 95% CI, 0.73–0.92; $P = 0.009$)	815 vs. 1057 total no. of worsening heart failure events and cardiovascular deaths (HR 0.77, 95% CI 0.67–0.89; $P < 0.001$) 15.9% vs. 16.8% in death from any cause (HR, 0.94; 95% CI, 0.83–1.07)	[69]

outcomes, further enhancing their antifibrotic and anti-inflammatory effects [74]. However, the clinical relevance of these effects in patients without pre-existing heart disease remains uncertain, with some studies showing only modest benefits on myocardial fibrosis. While SGLT2i have been shown to improve HFpEF outcomes, the synergistic effects of SGLT2i and GLP-1 receptor agonists in this context warrant further investigation [75, 76–78].

Improvement in endothelial function and microvascular health

It has also been hypothesized that SGLT2i improve endothelial function, which is often impaired in both diabetes and heart failure. The endothelium plays a crucial role in regulating vascular tone and perfusion, and dysfunction here can contribute to increased afterload and inadequate coronary perfusion. SGLT2i have been shown to improve endothelial NO production, which can help dilate blood vessels and improve blood flow [79]. By enhancing NO availability, SGLT2i may help alleviate both macrovascular and microvascular dysfunction, improving coronary blood flow and reducing the ischemic burden on the heart. (Fig. 1)

Furthermore, studies in animal models have demonstrated that SGLT2i can reduce capillary rarefaction (a decrease in capillary density).This is a phenomenon commonly seen in heart failure and diabetes, which impairs myocardial oxygenation. By promoting better microvascular health, SGLT2i may reduce the myocardial ischemia that contributes to heart failure symptoms [80]. This hypothesis aligns with clinical observations of improved exercise capacity and reduced heart failure symptoms in patients taking SGLT2i (Fig. 1).

Metabolic effects

Improved myocardial energy utilization

Although the reduction in blood pressure and intravascular volume through the glycosuric effect can explain, at least in part, the improved cardiac function observed with SGLT2i [48, 81], the cardiometabolic benefits they provide extend beyond the purely mechanical function and may help account for the long-term advantages seen with their use [40, 44, 48].

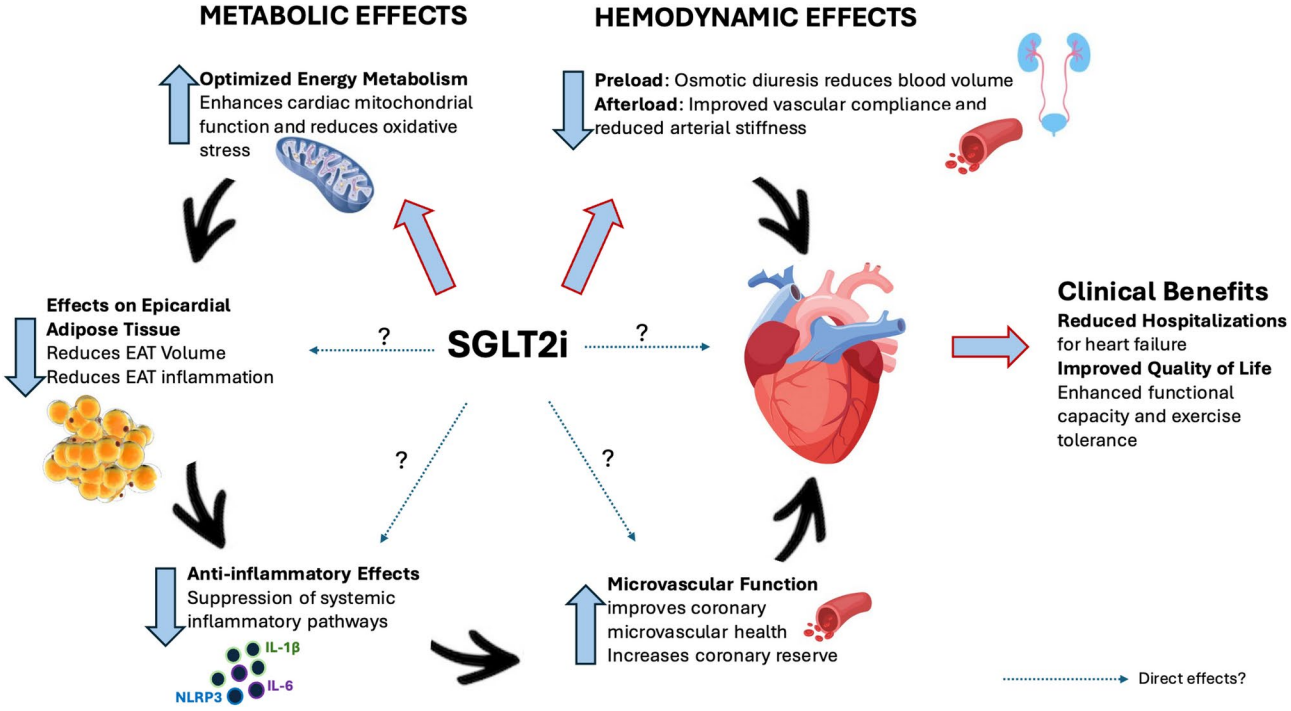


Fig. 1 Metabolic and Hemodynamic SGLT2i effects: schematic overview of SGLT2i metabolic and hemodynamic effects that positively impact cardiac function. Dotted arrows indicate potential SGLT2i direct effects that are still subject of ongoing debate

SGLT2i have been shown to cause beneficial shifts in myocardial metabolism. Under normal circumstances, the heart primarily utilizes fatty acids for energy production, but in heart failure and diabetes, the heart often becomes less efficient due to impaired glucose utilization and fatty acid oxidation. SGLT2i have been hypothesized to promote increased ketone body production [23, 44]. Ketones, particularly β-hydroxybutyrate, are a more efficient fuel for the heart, especially in the setting of myocardial stress or metabolic dysregulation [82] (Fig. 1).

By shifting cardiac substrate from fatty acids to ketones, SGLT2i may help the heart to function more efficiently, especially in conditions of high metabolic demand, like HFpEF. This has led to the hypothesis that SGLT2i may enhance cardiac mitochondrial function and reduce oxidative stress, improving overall myocardial performance. However, the precise nature of these metabolic changes in the human heart remains somewhat controversial, as the long-term effects of sustained ketone body utilization on cardiac health are not yet fully understood [83].

In the recently published EMPA-VISION trial [84], Hundertmark et al. showed that treatment with empagliflozin in 72 patients with HFrEF or HFpEF did not affect cardiac energetics (assessed as phosphocreatine: ATP ratioPCr/ATP). The authors concluded that it is unlikely that the enhancement of cardiac energy metabolism mediates the beneficial effects of SGLT2i in HF. Further studies are therefore warranted to better clarify the role of SGLT2i in improving myocardial energy utilization.

While the role of ketones as direct enhancers of cardiac function remains debated, their anti-inflammatory properties appear more clinically relevant. Recent evidence suggests that the substrate shift towards ketones and free fatty acids modulates key nutrient-sensing pathways, including mTOR and the inflammasome. [85, 86] These pathways are implicated in chronic low-grade inflammation, a central mechanism in HFpEF pathogenesis. Furthermore, ketogenesis induced by SGLT2i has been shown to suppress inflammasome activation and reduce pro-inflammatory cytokine secretion. Additionally, reductions in insulin and uric acid levels mediated by SGLT-2i contribute significantly to their anti-inflammatory effects, as these molecules are known to exacerbate inflammation. [87].

At the core of these metabolic effects and anti-inflammatory benefits there are epigenetic mechanisms. By modulating key regulators of gene expression, such as histone deacetylases (HDACs) and DNA methyltransferases, SGLT2i may induce sustained changes in inflammatory and metabolic pathways. Such epigenetic modifications, similar to those observed in caloric restriction, may partially explain the long-term CV and renal benefits associated with this class of drugs. [85, 88].

The impact on epicardial adipose tissue

As already mentioned, T2D is one of the main risk factors for the development of HF [4, 5],with insulin resistance, an essential condition in the pathogenesis of T2D, acting as the principal driver of HF in individuals with T2D [8, 14, 89, 90]. Recent studies suggest that CV benefits may stem from their impact on insulin resistance, although the effect on myocardial insulin sensitivity remains a topic of debate. [45, 46]This has led to a shift in focus toward the broader cardiometabolic effects of SGLT2i, extending beyond mere glycemic control [43]. In this context, current studies on animals and humans are centering on the direct/indirect effect of SGLT2i on the epicardial adipose tissue (EAT) [91]. Due to the absence of muscle fascia separating the two, epicardial adipose tissue shares the same microcirculation with the myocardium [91–93], an anatomical characteristic that explains the metabolic cross-talk between them [91, 94]. In healthy individuals, epicardial adipose tissue has an anti-inflammatory effect on the myocardium due to its dynamic, brown fat-like thermogenic function [93]. However, in metabolic disorders like obesity and T2D, EAT has harmful effects, secreting proinflammatory adipokines that can lead to atrial and ventricular fibrosis and dysfunction, and contributing to heart failure with preserved ejection fraction (HFpEF) [91, 95, 96]. For this reason, it has been defined as a cardiovascular risk factor and has become a target for strategies aimed at preventing or treating cardiovascular diseases.

Recent human studies have shown that SGLT2i treatment is associated with a significant reduction EAT thickness [97–103]. These data suggest that the cardiometabolic effects of SGLT2i may be partially mediated through their impact on EAT. The reduction in EAT thickness can be interpreted as an indirect sign of the reacquisition of brown fat-like properties, leading to the restoration of EAT anti-inflammatory properties. In fact, with the DAPAHEART trial, in which patients with T2D with stable coronary artery disease were randomized to dapagliflozin or placebo for 4 weeks, we recently demonstrated that SGLT2i treatment is associated with a reduction in EAT glucose uptake suggesting a reduction of EAT inflammation [99].

As mentioned above, the shared microcirculation between the EAT and the myocardium underlies the crosstalk between the two organs. Indeed, the increase in EAT thickness (i.e. inflammation) has been independently associated with coronary microvascular dysfunction, thus supporting the hypothesis that epicardial fat modulation of local inflammation is involved in the development of coronary microvascular dysfunction [104]. It has been demonstrated that coronary microvascular dysfunction impairs coronary physiology and myocardial blood flow in subjects with risk factors, contributing to myocardial ischemia in coronary artery diseases and cardiomyopathy [105]. In the DAPAHEART trial, we observed a significant 30% increase in coronary flow reserve after dapagliflozin treatment and interpreted this result as an improvement in coronary microvascular dysfunction due to the restoration of EAT anti-inflammatory properties [45] (Fig. 1). Contrary to our expectations, however, we did not observe a significant change in myocardial insulin sensitivity [46, 106]. Further studies are needed to clarify this point.

The metabolic effects of SGLT2 inhibitors appear to justify the cardiovascular benefits observed in CVOTs, establishing them as a key treatment option for HFpEF compared to other available therapies.

Impact on visceral and subcutaneous adipose tissue

Recent evidence has expanded our understanding of how SGLT2i impact fat depots beyond epicardial adipose tissue (EAT), [99] including visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). [107] VAT, a metabolically active depot closely linked to systemic inflammation and CV risk, [108] is significantly reduced by SGLT2i, as demonstrated in both preclinical and clinical studies [107]. This reduction in VAT is associated with decreased levels of pro-inflammatory cytokines, improved lipid profiles, and enhanced insulin sensitivity. [42, 46] Moreover, VAT reduction correlates with lower circulating levels of key inflammatory markers such as IL-6 and CRP, contributing to an overall reduction in CV risk. [109, 110] In parallel, SGLT2i positively influence SAT, a depot traditionally considered less metabolically harmful. These drugs promote the conversion of white SAT into brown SAT, [111] characterized by increased expression of uncoupling protein 1 (UCP1) [112] and enhanced mitochondrial activity, thus leading to a shift into a metabolically active adipose tissue. [113] In fact, this process promotes glucose homeostasis. The combined effects on VAT and SAT suggest that SGLT2i not only reduce fat depots but also improve the metabolic quality of adipose tissue, [114] highlighting their multifaceted role in reshaping the adipose organ. [108] Interestingly, the dual impact on VAT and SAT aligns with the systemic metabolic benefits observed with SGLT2i, including improved glycemic control, reduced oxidative stress, and attenuation of chronic low-grade inflammation. [107, 115].

SGLT2i versus other available treatments for HFpEF

As previously stated, the pathological processes responsible for HFpEF are different from those of HFrEF and, therefore, treatment options developed for the latter are usually ineffective in patients with a normal left ventricular ejection fraction. Before the latest update to the guidelines on the diagnosis and management of heart failure,

diuretics were the only recommended treatment for relieving symptoms of HFpEF, primarily aimed at reducing congestion [6]. The treatment of comorbidities and other cardiovascular risk factors was also recommended but, based on the available trials at the time, the use of SGLT2is was permitted only in patients with T2D at high risk of/with already established CV disease [116, 117]. Following the publication of the positive results of two large trials on the use of SGLT2i in patients with HFpEF, with or without T2D [68, 69], the 2023 guideline update acknowledged dapagliflozin and empagliflozin as the first disease-modifying drugs for patients with HFpEF [118]. In both trials, the use of SGLT2 inhibitors led to a reduction in the composite endpoint of death and hospitalization due to worsening heart failure, with the primary driver of this effect being a decrease in hospitalizations.

The use of SGLT2i in HFpEF, especially in patients with T2D, has represented a paradigm shift for the management of this disease. None of the other drugs previously tested in large randomized clinical trials in HFpEF, including renin-angiotensin-aldosterone system (RAAS) inhibitors, mineralocorticoid-receptor antagonists, digoxin and the most recent valsartan/sacubitril, were successful in reducing the incidence of major adverse cardiovascular events [119–124].

The mechanisms behind the remarkable superiority of SGLT2 inhibitors compared to other medications in HFpEF and T2D are not yet fully understood. While several hypothesis-generating studies have been conducted in recent years, the underlying mechanisms remain unidentified to this day.

Other, still controversial hypotheses

Potential effects on autophagy and cardiac remodeling

A more speculative hypothesis involves the role of SGLT2 inhibitors in modulating autophagy, a cellular process by which damaged proteins and organelles are degraded and recycled. There is growing interest in the role of autophagy in maintaining myocardial health, as impaired autophagic function is thought to contribute to myocardial remodeling, fibrosis, and contractile dysfunction. Some animal studies have suggested that SGLT2i may enhance autophagy, helping to clear dysfunctional mitochondria and reduce cellular stress in cardiomyocytes [82]. However, the evidence supporting this hypothesis in humans is still limited and requires further investigation.

Off-target effects or pathophysiological uncertainties

While the above mechanisms are generally supported by preclinical and clinical data, some hypotheses regarding SGLT2i remain controversial. One such hypothesis involves the potential for off-target effects related to SGLT2 inhibition in the kidney and other tissues, particularly concerning its effects on sodium balance and neurohormonal activation. For example, initial evidence suggested that SGLT2i might directly affect the sympathetic nervous system or the renin-angiotensin-aldosterone system (RAAS), both of which play a significant role in heart failure. Although SGLT2 inhibitors reduce blood pressure and improve fluid balance, the precise mechanisms through which these effects are mediated are not fully understood, and there are concerns that long-term effects on renal sodium handling could lead to unintended consequences, particularly in patients with advanced renal disease [125].

Another area of debate concerns the differential effects of SGLT2i in different subtypes of heart failure (e.g., HFrEF vs. HFpEF). While SGLT2i have been shown to improve outcomes in patients with HFrEF, the mechanisms underlying their efficacy in HFpEF, particularly in the absence of significant fluid overload or reduced ejection fraction, remain unclear. Some argue that their effects are more related to metabolic or vascular improvements rather than fluid management, while others suggest that the improvements in exercise tolerance and clinical outcomes may be due to as yet unidentified mechanisms.

Conclusion

In conclusion, SGLT2i exert beneficial effects on the myocardium through a combination of hemodynamic, metabolic, anti-inflammatory, and vascular mechanisms. These drugs improve myocardial efficiency, reduce fibrosis, enhance endothelial function, and promote a shift toward more efficient energy utilization. However, the full spectrum of their effects remains to be fully understood, and some proposed mechanisms remain controversial or yet unsubstantiated by clinical trials. Ongoing research into the molecular and cellular pathways affected by SGLT2i will be crucial for refining our understanding of their therapeutic potential in heart failure and other cardiovascular diseases.

Abbreviations

CAD	Coronary artery disease
EAT	Epicardial adipose tissue
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
SGLT2i	Sodium-glucose cotransporter-2 inhibitors
SGLT1i	Sodium-glucose cotransporter-1 inhibitors
LV	Left ventricle
T2D	Type 2 diabetes
CV	Cardiovascular
CVD	Cardiovascular disease
CFR	Coronary flow reserve
AGEs	Advanced glycation end-products
RAGE	Receptor for AGEs
NO	Nitric oxide
eGFR	Estimated glomerular filtration rate
MVD	Microvascular dysfunction
EF	Ejection fraction
CVOTs	Cardiovascular outcomes

CRP	C-reactive protein
NLRP3	Nucleotide-binding domain-like receptor protein 3
MACEs	Major adverse cardiovascular events
RAAS	Renin-angiotensin-aldosterone system
TNF-α	Tumor necrosis factor-alpha
Il-6	Interleukin-6
AGEs	Advanced glycation end-products
NHE-1	Sodium-hydrogen exchanger-1
HDACs	Histone deacetylases
MI	Myocardial infarction
VAT	Visceral adipose tissue
SAT	Subcutaneous adipose tissue

Acknowledgements
The authors thank Serena Rotunno for editorial assistance in the writing of this article.

Author contributions
All the authors drafted and review the manuscript. DDA, FC and AG made the final adjustments and drafting.

Funding
Not applicable.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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Received: 11 December 2024 / Accepted: 29 April 2025
Published online: 14 May 2025

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