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The SGLT-2 Inhibitors and their Role in the Treatment of Heart Failure – a Review of Literature

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ABSTRACT

The purpose of research: Heart failure (HF) is an important global health concern. Despite advancements in treatment, HF remains the leading cause of hospitalization among the elderly. The development of sodium-glucose cotransporter 2 (SGLT2) inhibitors has shown promising cardiovascular and renal benefits beyond glucose control. This study aims to explore the potential mechanisms by which SGLT2 inhibitors provide cardiovascular protection, regardless of type 2 diabetes mellitus (T2DM).

Research materials and methods: A comprehensive literature review was conducted, analyzing clinical trials, guideline documents, and mechanistic studies on SGLT2 inhibitors. Definitions and classifications of HF, risk factors, and cardiovascular effects of SGLT2 inhibitors were reviewed. Key studies such as EMPA-REG OUTCOME, DAPA-HF, and others were analyzed to identify mechanisms contributing to cardiovascular protection.

Results: SGLT2 inhibitors provide cardiovascular benefits in HF patients, regardless of T2DM status. Key mechanisms include natriuresis, improved cardiac metabolism, reduced inflammation, prevention of cardiac remodeling, sympathetic inhibition, enhanced vascular health, and better kidney function.

Conclusions: The benefits of SGLT2 inhibitors extend beyond glucose control. They provide various effects, including improved hemodynamics, reduced inflammation, and enhanced cardiac energy metabolism. While several mechanisms have been proposed, further research is necessary to rule which are most critical. The benefits observed with SGLT2 inhibitors stress their potential as a cornerstone in HF management, regardless of a patient's diabetes status.
Keywords: SGLT-2 inhibitors, Heart failure, Benefits, Cardiovascular effects

Introduction

Heart failure (HF) is one of the most severe health problems worldwide affecting over 50 million people. (1,2) Even though over the years noteworthy progress has been made in therapy for this disease it remains the most common reason for hospitalization in older patients. (1) Since the development of SGLT2 inhibitors as diabetes mellitus 2 treatment many studies have shown promising results in therapy for the T2DM in patients with established vascular disease, multiple cardiovascular risk factors, or renal insufficiency and in those with established heart failure and reduced ejection fraction (with and without type 2 diabetes). (3–6) Numerous hypotheses were presented in efforts to explain the potential mechanism of SGLT2 inhibitors resulting in cardiovascular benefits. (7–10) It is however still not determined which if any are most accurate. In the following sections, we highlight the definition and describe select classifications of HF as well as risk factors, summarize the proposed mechanisms of action of the SGLT2 inhibitors, and synthesize which mechanisms are likely the most significant in explaining the observed clinical results.

Definition of heart failure

The definitions of heart failure (HF) as a condition are qualified based on a variety of factors and lack standardization. (11) Heart failure was traditionally characterized as 'condition in which the heart cannot pump enough blood to meet the body's needs' (12) or an abnormality in the structure or function of the heart that results in its inability to deliver oxygen at a rate sufficient to meet the needs of metabolizing tissues. (13) Aforementioned definitions are too complex and

usually, cannot be established in clinical practice (11). The most frequently used definitions provided by the American College of Cardiology/American Heart Association (ACC/AHA) (14), HFA/ESC ((15) include three key elements: evidence of structural heart disease, a history of symptoms commonly associated with HF, and objective signs typically observed in HF. (11)

Table 1. HF definitions in clinical practice guidelines

ACC/AHA (2013)	Heart failure (HF) is a complex clinical syndrome caused by structural or functional impairments affecting ventricular filling or blood ejection. The primary manifestations of HF include dyspnea and fatigue, which can limit exercise tolerance, as well as fluid retention, leading to pulmonary, splanchnic congestion, and/or peripheral oedema. Some patients experience exercise intolerance with minimal fluid retention, while others present with oedema, dyspnea, or fatigue. (14)
HFA/ESC (2023)	Heart failure (HF) is a clinical syndrome defined by typical symptoms, such as breathlessness, ankle swelling, and fatigue, often accompanied by signs like elevated jugular venous pressure, pulmonary crackles, and peripheral oedema. These manifestations are caused by structural and/or functional cardiac abnormalities, leading to reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. (15)

The classifications of heart failure

There is a big assortment of different classifications of HF presently in use (11) in an attempt to create definite subsets of HF. Some, such as NYHA class (16) based on the severity of

symptoms and is the most common tool to determine mortality risk and clinical trial eligibility (16). There are 4 NYHA heart failure classes:

1. Class I: asymptomatic
2. Class II: symptomatic with moderate activity
3. Class III: symptomatic with mild activity
4. Class IV: symptomatic at rest. (17).

Others classify patients by HF etiology (18), e.g. ischemic/non-ischemic, valvular, hypertensive, infiltrative cardiomyopathy such as cardiac amyloidosis, peripartum cardiomyopathy, viral myocarditis, chemotherapy-induced cardiomyopathy or the classification released by the ACC, AHA, and Heart Failure Society of America (HFSA)(19) that divides heart failure by ejection fraction of the left ventricle (LVEF) (19,20).

1. Heart Failure with Reduced Ejection Fraction (HFrEF): patients with an LVEF ≤40%
2. Heart Failure with Improved Ejection Fraction (HFimpEF): patients with a previous LVEF ≤40% and a subsequent measurement of LVEF >40%
3. Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF): patients with an LVEF 41% to 49%, characterized by elevated natriuretic peptides or hemodynamic measurements.
4. Heart Failure with Preserved Ejection Fraction (HFpEF): patients with an LVEF ≥50%, characterized by elevated natriuretic peptides or hemodynamic measurements.

Moreover, there is also a TNM-like classification (MOGE(S)) for HF staging based on the cancer staging system (21,22). It allows for better disease understanding, easier communication among physicians, and helps develop multicenter registries for research. The MOGE(S) classification is a systematic nomenclature for cardiomyopathies that consists of 5 key attributes:

M - Morphofunctional characteristic (describes the phenotype and functional characteristics)
O - Organ involvement (indicates whether only the heart or other organs are affected, using notations like OH for heart, OHM for skeletal muscle involvement)
G - Genetic inheritance pattern
E - Etiologic annotation (provides description of specific disease genes and mutations)
S - Functional Status (incorporates ACC/AHA stage and NYHA functional class). (23)

The American College of Cardiology and American Heart Association (ACC/AHA) have also outlined the following stages of heart failure (19):

1. Stage A: At Risk for Heart Failure – This stage includes patients who are at risk for heart failure but do not exhibit symptoms, structural heart disease, or cardiac biomarkers indicative of ventricular stretch or injury. Treatment focuses on modifying underlying risk factors to prevent the development of heart failure.
2. Stage B: Pre-Heart Failure – Patients in this stage show evidence of increased filling pressures (detected through invasive or noninvasive methods) or have risk factors accompanied by elevated biomarkers of stretch or cardiac injury, not attributable to other conditions. The goal of treatment is to address risk factors and structural heart disease to prevent progression to heart failure.
3. Stage C: Symptomatic Heart Failure – This stage applies to patients with structural heart disease who currently have or have previously experienced symptoms of heart failure. Management aims to alleviate symptoms, reduce morbidity, and decrease mortality.
4. Stage D: Advanced Heart Failure – Patients in this stage experience severe symptoms that significantly impact daily life, often requiring recurrent hospitalizations despite optimized guideline-directed medical therapy. Treatment efforts are directed at minimizing symptoms, morbidity, and mortality.

Most common HF risk factors

1. Hypertension is a significant risk factor globally, with a particularly high prevalence in Eastern and Central Europe and Sub-Saharan Africa. (24) It is the most common risk factor in many populations, affecting up to 66% of heart failure cases. (25)
2. Ischemic Heart Disease (IHD) is a prevalent risk factor, especially in Europe and North America, where it affects over 50% of heart failure patients. (24)
3. Diabetes is a strong predictor of HF, especially when insufficiently controlled or accompanied by obesity or renal insufficiency. It is associated with a high incidence of HF hospitalizations. (26–28)
4. Obesity and Metabolic Syndrome are increasingly recognized as important contributors to HF, with obesity being a significant risk factor, particularly in younger populations. (26,29)
5. Smoking is a frequent risk factor, contributing significantly to heart failure cases, especially in younger patients. (29)

   Renal insufficiency: lower estimated glomerular filtration rate (eGFR) and higher albuminuria are strong predictors of HF in patients with chronic kidney disease (30), moreover mild renal insufficiency, even in the absence of severe kidney disease, is associated with an increased risk of congestive heart failure (CHF) in the elderly. (31)

Potential mechanisms of cardiovascular protection of the SGLT-2 inhibitors

The Sodium–glucose cotransporter (SGLT) 2 inhibitors have achieved unparalleled cardiorenal benefits in clinical trials of people who have type 2 diabetes and either established cardiovascular disease or multiple cardiovascular risk factors. (2,10,32) The beneficial effects of SGLT2 inhibition include: 1) lowering of blood pressure; 2) increasing diuresis/natriuresis; 3) improving cardiac energy metabolism; 4) preventing inflammation; 5) inhibiting the sympathetic nervous system; 6) preventing adverse cardiac remodeling; 7) increasing autophagy and lysosomal degradation; 8) decreasing epicardial fat mass; 9) increasing erythropoietin (EPO) levels; 10) increasing circulating provascular progenitor cells; and 11) improving vascular function. (2,7–10).

Blood pressure lowering

One of the most common and preventable risk factors for developing HF is hypertension. The SGLT2 inhibitors lower blood pressure (33), therefore, contribute to their heart failure benefits through improved cardiac energetics. Their antihypertensive effects likely result from increased sodium excretion due to inhibited sodium reabsorption in kidney tubules, leading to osmotic and diuretic effects. This effect, stronger than that of thiazide diuretics in certain combinations (e.g. ß-blockers or calcium antagonists) (34,35), may reduce cardiac afterload and improve heart efficiency. However, the modest blood pressure reduction alone cannot fully explain the cardiovascular and kidney benefits of SGLT2 inhibitors, nor their significant impact on heart failure outcomes observed in trials like EMPA-REG OUTCOME (36) and DAPA-HF. (3)

Increasing diuresis/natriuresis

SGLT2 inhibitors have been shown to bolster natriuresis and glucosuria, and it has been considered that the resultant osmotic diuresis may improve heart failure outcomes. In fact, mediation analyses from the EMPA-REG OUTCOME trial suggested that hemoconcentration (presumed to be less important than volume contraction) accounted for about 50% of the cardiovascular benefit detected. (36) It is unlikely that the benefits of SGLT2 inhibitors are only depended on diuresis, because trials with other diuretics per se have not been associated with an improvement in event reduction in HF studies. It has been implied that SGLT2 inhibitors have different mechanism of action from classical diuretics. In a study comparing dapagliflozin and hydrochlorothiazide, a decline in plasma volume and gain in erythrocyte mass was present with dapagliflozin but not with hydrochlorothiazide. (37) When correlated with a loop diuretic (bumetanide), dapagliflozin was linked to a grater reduction in interstitial versus intravascular

volume. (38) It has been suggested that SGLT2 inhibitors may preferentially regulate interstitial fluid rather than intravascular volume, potentially reducing reflex neurohumoral activation typically triggered by intravascular volume contraction seen with traditional diuretics. (2,10)

Improving cardiac energy metabolism

Heart failure leads to a decline in mitochondrial oxidative metabolism and increased reliance on glycolysis, reducing energy production and efficiency. Reduced mitochondrial glucose oxidation and increased proton production contribute to lower cardiac efficiency, affecting both heart failure with reduced and preserved ejection fraction. (39) SGLT2 inhibitors increase circulating ketone levels by mobilizing adipose tissue fatty acids, which are then used by the liver for ketogenesis (40,41) in patients with or without T2DM. Increased ketone oxidation provides supplemental energy to the "energy-starved" heart, improving cardiac performance and potentially reducing adverse remodeling. (42,43) SGLT2 inhibitors may enhance mitochondrial respiratory function, contributing to better energy production in the heart. Benefits of SGLT2 inhibitors likely stem from providing extra energy to the failing heart rather than improving the efficiency of energy use. These effects result in overall increased ATP production without reducing glucose or fatty acid oxidation. (44)

Preventing inflammation

Inflammation substantially contributes to the severity of heart failure. Elevated pro-inflammatory biomarkers correlate with disease severity in both reduced and preserved ejection fraction heart failure. (45–47) Inflammatory cytokines cause endothelial dysfunction, increase extracellular matrix turnover, and promote fibrosis. SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) reduce inflammatory profiles in diabetic patients. (48–50) These effects can potentially decrease extracellular matrix turnover and fibrosis, as shown by studies showing antifibrotic effects in animal models and attenuation of collagen remodeling. (51)The potential mechanisms may involve: 1) reduced glucose levels, leading to decreased macrophage inflammatory responses since macrophages rely on glucose for energy, 2) direct targeting of inflammatory pathways, independent of glucose lowering, 3) the nucleotide-binding oligomerization domain-like receptor protein (NLRP3) inflammasome contributes to chronic inflammation in heart failure, 4) evidence suggests empagliflozin can inhibit the NLRP3 inflammasome in various tissues, including the heart, independently of glucose lowering, 5) the ketone ß-hydroxybutyrate, elevated by SGLT2 inhibitors, is a known inhibitor of the NLRP3 inflammasome, which may partially explain the anti-inflammatory benefits.

(52,53) Anti-inflammatory effects may stem from a combination of glucose reduction, direct inflammasome inhibition, and ketone-mediated processes.

Inhibition of the sympathetic nervous system

It has been observed that the SGLT2 inhibitors lower blood pressure without then increase of the heart rate. Previously conducted research implies that these agents might reduce the activity of the sympathetic nervous system (SNS), inhibit norepinephrine turnover in brown adipose tissue, and reduce tyrosine hydroxylase production. These sympathoinhibitory effects seem to be present in both animal models of diabetes as well as those with obesity (without diabetes). (54–56)

Preventing adverse cardiac remodeling

Adverse cardiac remodeling includes development of cardiac hypertrophy, fibrosis, inflammation, and cardiomyocyte cell death and contributes to heart failure severity. It has been detected that the SGLT2 inhibitors have a positive effect on cardiac remodeling. A 6-month randomized trial in people with type 2 diabetes and coronary artery disease showed that empagliflozin significantly reduced LV mass index compared to placebo, (57) suggesting that SGLT2 inhibitors can promote cardiac reverse remodeling even with short-term use. This effect may be linked to inhibiting the mammalian target of rapamycin (mTOR) pathway, which drives cardiac hypertrophy, and reducing fibrosis through anti-inflammatory actions. (58) These changes can help decrease LV wall stress and improve heart function in heart failure.

Increasing autophagy and lysosomal degradation

Cardiac autophagy and lysosomal degradation are commonly harmed in diabetes and heart failure. By driving catabolic rates because of perpetual glycosuria, it has been proposed that SGLT2 inhibition can promote autophagy and lysosomal degradation, thereby improving the morphology and function of the mitochondria. (59) SGLT2 inhibition of the mammalian target of rapamycin may enhance autophagy and lysosomal degradation, promoting the breakdown of dysfunctional organelles. Thus, some benefits of SGLT2 inhibitors in heart failure could stem from their role in stimulating autophagy.

Decreasing epicardial fat mass

High buildup of the epicardial adipose tissue increases risk of cardiovascular events. SGLT2 inhibitors reduce the aggregation and inflammation of perivascular adipose tissue. In this way

they minimize the secretion of leptin and its paracrine actions on the heart to promote fibrosis (60). In patients with diabetes and coronary artery disease, SGLT2 inhibitors reduce epicardial adipose tissue and bioactive molecules like TNF-α and PAI-1, potentially limiting adverse heart remodeling. (61)

Increasing erythropoietin (EPO) levels

SGLT2 inhibitors raise the hematocrit (62), even in those without diabetes (as seen in DAPA-HF). That has led to the hypothesis that these agents may bolster erythropoiesis by enhancing EPO secretion in the kidney. An increase in EPO may positively impact cardiomyocyte mitochondrial function, angiogenesis, cell proliferation, inflammation, and oxygen delivery to heart tissue. The EMPA-Heart CardioLink-6 trial by Mazer et al. (63) showed a significant rise in EPO levels after 1 month of empagliflozin treatment in patients with type 2 diabetes and coronary artery disease, along with increased hematocrit, reduced ferritin, and lower red blood cell hemoglobin concentration. It remains unclear if similar effects occur in non-diabetic patients. (63)

Increasing circulating provascular progenitor cells

Prior evidence in humans aims toward an effect of SGLT2 inhibitors on the restoration of provascular progenitor cells in people with T2DM. Hess et al. (64) noted that empagliflozin treatment was connected with a simultaneous reduction in the number of proinflammatory M1 cells and increase of the number M2 polarized, anti-inflammatory cells. Using the Aldeflour assay (STEMCELL Technologies, Cambridge, Massachusetts), the researchers discovered that inhibiting SGLT2 reduced the systemic burden of granulocytes in individuals with T2DM, while also increasing the number of circulating ALDHhiSSCmid monocytes. Additionally, they observed a shift from M1 to M2 polarization, which aligns with the development of collateral blood vessels during arteriogenesis. The researchers concluded that SGLT2 inhibition could be a unique approach to support the recovery of circulating provascular cells in T2DM. However, it remains unclear if this effect occurs in individuals without T2DM.

Improving vascular function

Patients suffering from the vascular smooth muscle and endothelial dysfunction have increased risk of morbidity and mortality of heart failure. (65) It has been proved that SGLT2 inhibitors enhance vascular health by reducing endothelial cell activation, promoting direct vasodilation, improving endothelial function, and mitigating early molecular processes linked to

atherosclerosis. Additionally, they help lower arterial stiffness and decrease vascular resistance. (66,67) Several mechanisms may explain the positive effects of SGLT2 inhibitors, such as reducing inflammation and enhancing mitochondrial function. (66) Another suggested pathway involves promoting vasodilation through the activation of protein kinase G and voltage-gated potassium channels. (68) Additionally, the combination of direct vascular effects and the diuretic-like action of SGLT2 inhibitors, which promotes sodium excretion, likely contributes to the favorable hemodynamic outcomes observed with their use.

What mechanisms most likely explain the cardiovascular benefits of the SGLT2 inhibitors?
The SGLT2 inhibitors have major beneficial effects in patients with heart failure regardless of T2DM. The mechanisms of action are yet to be precisely described, but they exceed simply lowering of glucose levels in blood. Potential ways in which the SGLT2 inhibitors improve the severity of heart failure are protection of the kidneys, by reducing inflammation, inhibiting the sympathetic nervous system, and reducing oxidative stress. Better kidney function results in increased EPO levels, which help improve hematocrit. SGLT2 inhibitors also exert an early hemodynamic effect at the level of the renal tubules, leading to sodium and water loss and a reduction in intraglomerular pressure. Other possible cardioprotective mechanisms of the SGLT2 inhibition are preventing adverse cardiac remodeling, preventing inflammation in the heart muscle, improving cardiac energy metabolism. There are needed further investigations into the SGLT2 inhibitors' cardioprotective mechanisms. The key characteristics of the strategy must take into account the kidneys protection, rapid onset of action, operation regardless of glucose levels in blood or application of alternative heart failure strategies.

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