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Rewriting the Script: How SGLT2 Inhibitors Are Transforming Heart Failure Care

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Abstract: Heart failure (HF) is a major worldwide health concern, with significant morbidity, death, and healthcare expenditures. Traditional therapy sometimes fall short of improving outcomes, particularly in patients with preserved ejection fraction (HFpEF) and concurrent type 2 diabetes mellitus. Sodium-glucose co-transporter 2 (SGLT2) inhibitors, which were first designed for glycaemic management in T2DM, have shown considerable cardiovascular and renal advantages irrespective of glucose reduction. This review examines the evolving role of SGLT2 inhibitors in heart failure care, drawing on key studies such as DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and SOLOIST-WHF. SGLT2 inhibitors, such as dapagliflozin, empagliflozin, and sotagliflozin, have consistently decreased the incidence of cardiovascular mortality and heart failure hospitalisations in patients with reduced and maintained ejection fractions, independent of diabetes status. These medicines enhance myocardial metabolism by improving ketone body utilisation, increasing cardiac efficiency, and decreasing fibrosis and inflammation. They also influence neurohormonal pathways such as the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), anti-diuretic hormone (ADH), and endothelin systems, which help to enhance haemodynamics and fluid balance. Clinical trials have shown benefits in quality of life, symptom load, and renal outcomes, with few adverse events such as hypoglycemia or ketoacidosis. Early usage of SGLT2 inhibitors during heart failure decompensation results in faster symptom alleviation and improved patient outcomes. Finally, SGLT2 inhibitors have emerged as a cornerstone treatment for heart failure, providing advantages to a wide range of individuals. Their inclusion in heart failure recommendations represents a significant change in the management of both HFrEF and HFpEF.

Key words: SGLT2 inhibitor, Heart failure, HFrEF, HFpEF, Dapagliflozin, Empagliflozin, Sotagliflozin, Cardiovascular outcomes, Ketone metabolism, RAAS modulation, Neurohormonal regulation, Kansas City Cardiomyopathy Questionnaire (KCCQ), Quality of life, Type 2 diabetes mellitus, Renal outcomes.

I. Introduction

Definition: Congestive heart failure (CHF) is a complex clinical illness in which the heart fails to pump enough blood to meet the body's metabolic needs. It is caused by structural or functional cardiac abnormalities that affect ventricular filling and ejection of blood. CHF is commonly defined according to the left ventricular ejection fraction (LVEF) as heart failure with decreased ejection fraction (HFrEF), preserved ejection fraction (HFpEF), or mildly reduced ejection fraction (HFmrEF). The illness causes symptoms such as dyspnoea, tiredness, fluid retention, and exercise intolerance, which have a substantial influence on patients' quality of life and survival.[1]

Original use of SGLT2 inhibitors for diabetes: SGLT2 inhibitors (SGLT2i) were initially introduced as oral anti-diabetic drugs to reduce blood glucose via inhibition of sodium glucose cotransporters in the kidney, but SGLT2i caused unexpected beneficial effects on cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM) in large clinical trials. These results were mostly related to a significant reduction in heart failure (HF) hospitalisations.[1]

Recent extensive clinical trials like DAPA-HF and EMPEROR-Reduced have shown that SGLT2 inhibitors greatly lower the rates of hospitalizations and cardiovascular deaths in individuals with heart failure with reduced ejection fraction (HFrEF), regardless of whether they have type 2 diabetes. Likewise, the EMPEROR-Preserved trial demonstrated that these advantages extend to patients with heart failure with preserved ejection fraction (HFpEF), establishing SGLT2 inhibitors as the first successful treatment for this group. Although they were primarily designed for managing blood sugar levels in diabetes, SGLT2 inhibitors provide heart failure benefits that seem to be independent of their effects on glycemia, blood pressure, and weight reduction. Their early and considerable improvements in cardiovascular outcomes imply that there are mechanisms at play beyond mere metabolic control, including reductions in plasma volume, natriuresis, and decreased pre-load due to their distinct renal actions. Furthermore, even in individuals with compromised renal function, where the diuretic effects may be limited, the cardiovascular advantages continue to be observed, indicating that non-diuretic mechanisms also play a role.[1]

Recent preclinical and clinical findings suggest that SGLT2 inhibitors have direct effects on the myocardium that are separate from their actions in the kidneys. Research utilizing ex vivo heart models and isolated cardiomyocytes has demonstrated that SGLT2 inhibitors influence intracellular sodium and calcium concentrations, diminish oxidative stress, and inhibit pro-inflammatory pathways. These actions enhance myocardial energy metabolism, decrease fibrosis, and improve cardiac function. Importantly, mechanisms involving ketone metabolism, mitochondrial activity, and ionic balance may clarify the noted enhancements in diastolic function, contractility, and reduction of arrhythmias in patients with heart failure. Consequently, SGLT2 inhibitors likely function

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through an interplay of renal, systemic, and direct cardiac effects, providing a comprehensive therapeutic strategy for heart failure that extends beyond merely lowering glucose levels.[1]

The aim of this review is to thoroughly evaluate the increasing role of sodium-glucose co-transporter 2 (SGLT2) inhibitors in the treatment of congestive heart failure (CHF), concentrating on both heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). This review compiles findings from recent large clinical trials assessing the effectiveness of SGLT2 inhibitors in decreasing heart failure-related morbidity and mortality, regardless of their impact on glycemic control. Additionally, it seeks to investigate the proposed mechanistic pathways, including renal, hemodynamic, metabolic, and direct myocardial effects, that could explain these cardiovascular advantages. By combining current clinical evidence with new mechanistic insights, this review aims to offer an in-depth understanding of the therapeutic promise of SGLT2 inhibitors in CHF and guide future clinical practice and research efforts.[1]

Clinical Pharmacokinetics

Absorption and bioavailability

Ertugliflozin has quick oral absorption, with a median Tmax of 1-2 hours after treatment. In both single- and multiple-dose experiments, steady-state concentrations were reached by Day 6. A two-period 14C-microtracer research demonstrated an oral bioavailability (F) of nearly 100% in humans. The dosage-proportional increase in Cmax and AUC over a broad dose range (0.5-300 mg) indicates linear pharmacokinetics. Food consumption delays Tmax by nearly an hour and reduces Cmax by 29%, but total drug exposure (AUC) is unaltered, rendering meal time clinically unimportant for efficacy.[2]

Distribution and Protein Binding

Ertugliflozin is strongly attached to plasma proteins (94-95%) and preferentially distributed in plasma over red blood cells. The steady-state volume of distribution (Vss) was estimated to be 85.5 L, indicating moderate extravascular tissue distribution. Its distribution features contribute to its systemic efficacy and minimal central volume dispersion. The medicine is also a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), however they have no major effect on its absorption due to its high oral bioavailability.[2]

Metabolism and Elimination

Ertugliflozin is primarily cleared by hepatic metabolism, including glucuronidation (86%) by UGT1A9 and UGT2B7 enzymes and limited oxidative metabolism (~12%) by CYP3A4, CYP3A5, and CYP2C8. M5a and M5c, the most common circulating metabolites, are glucuronides that have no pharmacological activity. Only 1.5% of the unmodified medication is eliminated in urine, and the overall radioactivity recovery after dosage is around 91%, with 33.8% showing as unchanged drug in feces—most likely due to enterohepatic circulation of glucuronide conjugates.[2]

Dosing Regimens and Clinical Considerations

Although ertugliflozin is licensed for once-daily use, studies comparing once-daily and twice-day dosing at equal total daily doses (e.g., 15 mg once daily vs. 7.5 mg twice daily) found bioequivalence in AUC and overall exposure, with no significant clinical changes. When used with immediate-release metformin, twice-daily treatment is advised to match metformin's pharmacokinetic profile. Ertugliflozin's efficacy is determined by total exposure (AUC), not peak concentration, making it adaptable to a variety of dosage regimens and appropriate for fixed combos. [2]

SGLT2 inhibitor	Approval year (US; EU)	SGLT2 IC_{50} (nM)	SGLT1 IC_{50} (nM)	Relative selectivity (SGLT2:SGLT1)
Canagliflozin	2013; 2013	2.7	710	~260-fold
Dapagliflozin	2014; 2012	1.2	1400	~1200-fold
Empagliflozin	2014; 2014	3.1	8300	~2700-fold
Ertugliflozin	2017; 2018	0.877	1960	~2200-fold

IC_{50} 50% inhibitory concentration, *SGLT1* sodium-glucose cotransporter 1, *SGLT2* sodium-glucose cotransporter 2

Table 1 Summary of SGLT2 inhibitors currently approved for use in the US and EU and their relative selectivity [2]

Pathophysiology of CHF

Neurohormonal activation

Neurohormonal activation is a key element in the evolution of heart failure, which is induced by decreasing cardiac output and effective arterial blood volume. Baroreceptors in the aortic arch and carotid sinus detect these changes and alert the central nervous system to increased sympathetic nervous system (SNS) activity. This causes vasoconstriction, higher heart rate, and increased

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myocardial contractility. Furthermore, in heart failure patients, chemoreceptor sensitivity to hypoxia and hypercapnia increases, as does ergoreflex activity. These aberrant reflexes further excite neurohormonal pathways, exacerbating symptoms, lowering exercise tolerance, and indicating a poor prognosis. Although initially compensatory, prolonged neurohormonal stimulation becomes maladaptive and contributes to poor heart function and remodelling. [3]

Evidence suggests that neurohormonal activation is more than just a measure of disease severity; it also drives heart failure progression. Elevated neurohormone levels, such as norepinephrine (NE), have been proven in both clinical and experimental contexts to directly decrease left ventricular performance. This understanding serves as the foundation for heart failure pharmacotherapy, in which drugs that block the renin-angiotensin-aldosterone system (RAAS) or SNS—such as beta-blockers, ACE inhibitors, and ARBs—have demonstrated considerable advantages in terms of morbidity and mortality. Persistent SNS activity harms the heart, kidneys, and vasculature, contributing to a vicious circle of poor haemodynamic and organ damage. [3]

Fluid retention and Remodeling

Oedema production in congestive heart failure (CHF) is influenced by variations in fluid flow across capillaries caused by hydrostatic and osmotic pressure gradients. Blood pressure, flow, and capillary resistance are all factors that contribute to this phenomenon. Venous pressure, influenced by right atrial pressure, blood volume, and venous capacity, is directly related to salt balance. Increased interstitial fluid pressure causes resistance to fluid flow into tissues. Elevated venous pressure in CHF disturbs microcirculatory dynamics, resulting in fluid retention, increased ECF volume, and generalised oedema.[4]

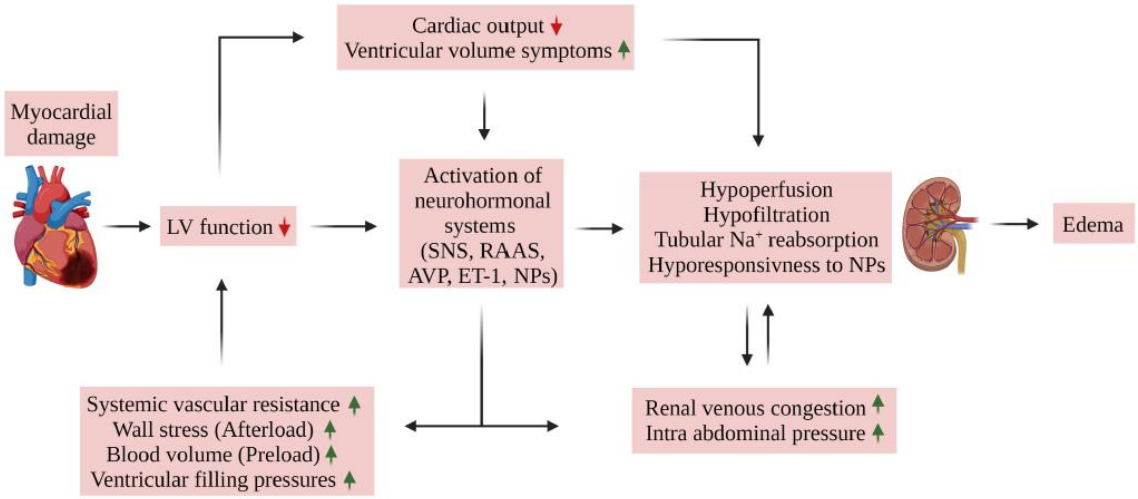

Fig – 1 Mechanisms of oedema formation in HFrEF [4]

Pathophysiological differences between HFpEF and HFrEF

Heart failure with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) differ significantly in their pathophysiology, which influences treatment outcomes—evidence-based therapies are effective in HFrEF but not HFpEF. HFpEF is mainly associated with impaired ventricular relaxation due to cardiomyocyte hypertrophy, fibrosis, inflammation, and endothelial dysfunction, often driven by comorbidities like hypertension, diabetes, obesity, and renal or pulmonary disease. Endothelial dysfunction, a key early event in HFpEF, can arise from oxidative stress, nitric oxide imbalance, or neurohormonal changes and may precede cardiac dysfunction. In contrast, HFrEF results from significant cardiomyocyte loss due to ischemic events (e.g., myocardial infarction), genetic mutations, or myocarditis, leading to systolic dysfunction and eccentric remodeling. Patients with HFrEF often present with elongated, fibrotic cardiomyocytes of lower myofibrillar density, while those with HFpEF typically show concentric hypertrophy. Gender and age also differ: HFpEF is more common in older women, whereas HFrEF predominates in men due to higher ischemic disease incidence. Additionally, variations in titin elasticity and calcium handling exist between the two types. HFmrEF (mid-range EF) can evolve into either form but shares characteristics with HFrEF. Genetic factors further influence the pathophysiology and management of heart failure, including inherited cardiomyopathies (e.g., DCM, HCM, RCM), where targeted genetic screening is recommended under current ESC guidelines, especially in cases with strong familial patterns or sudden cardiac death history.[5]

Clinical Evidence: Sglt2 Inhibitors in CHF

DAPA-HF Trial

The purpose of this trial was to determine the efficacy of dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, in patients with heart failure with reduced ejection fraction (HFrEF). The research was a multicenter, randomized, double-blind,

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placebo-controlled experiment that involved 4,744 patients with an ejection fraction (EF) of < 40%, classified as NYHA Class II-IV, and included both diabetic and non-diabetic persons.

In addition to their regular heart failure treatments, participants were given either dapagliflozin 10 mg once day or a comparable placebo. The median follow-up period was 18.2 months. The main outcome, a composite of worsening heart failure or cardiovascular (CV) mortality, was used to assess dapagliflozin's overall cardiovascular benefit in this high-risk cohort.

Dapagliflozin significantly reduced the risk of the main endpoint by 26% compared to placebo (HR 0.74; $p < 0.001$). This effect was consistent for diabetic and non-diabetic participants, highlighting dapagliflozin's cardiovascular benefits regardless of glycemic control. Furthermore, patients on dapagliflozin reported better quality of life, as shown by higher Kansas City Cardiomyopathy Questionnaire (KCCQ) symptom ratings.

Importantly, the safety profile of dapagliflozin has remained positive, with no substantial rise in adverse events such as hypoglycemia or ketoacidosis. In conclusion, the study firmly supports the use of dapagliflozin as an effective adjunct treatment in patients with HFrEF, leading to decreased rates of heart failure hospitalization and cardiovascular mortality, independent of diabetes status. [6]

EMPEROR-Reduced and EMPEROR-Preserved Trials

The EMPEROR-Reduced and EMPEROR-Preserved trials are two large-scale, phase III, randomized, double-blind, placebo-controlled studies that will evaluate the effectiveness and safety of empagliflozin (10 mg daily) in patients with heart failure (HF). The EMPEROR-decreased study addressed persons with heart failure with decreased ejection fraction (HFrEF, LVEF < 40%), whereas the EMPEROR-Preserved trial focused on patients with preserved ejection fraction (HFpEF, LVEF > 40%). Both trials recruited international, multicenter cohorts, with EMPEROR-Reduced recruiting 3,733 patients and EMPEROR-Preserved enrolling 5,988 patients, who were followed for 20-24 months.

Participants in both studies were randomly assigned to receive empagliflozin or a placebo, in addition to normal heart failure treatments. The primary outcome was the time until the first cardiovascular (CV) mortality or hospitalization for heart failure. The secondary outcomes were total HHF episodes, changes in estimated glomerular filtration rate (eGFR), start of chronic kidney disease and diabetes, all-cause mortality, and Kansas City Cardiomyopathy Questionnaire (KCCQ) symptom ratings to measure quality of life.

Adults over the age of 18 who were diagnosed as NYHA Class II-IV with increased NT-proBNP levels corrected for ejection fraction and atrial fibrillation were eligible to participate. Exclusion criteria were tight to ensure participant safety and data integrity, including recent MI, stroke, major surgery, acute decompensated HF, severe renal impairment (eGFR < 20 mL/min/1.73 m^2), recent use of SGLT2 inhibitors, and pregnancy.

The EMPEROR-Preserved experiment is particularly noteworthy since it is the first placebo-controlled trial to assess SGLT2 inhibitors in HFpEF, a group that has hitherto lacked effective treatments. Its favorable findings are likely to change therapy standards and provide hope to a subset of HF patients who previously had few pharmacologic alternatives. Meanwhile, the EMPEROR-Reduced study expands on the findings of DAPA-HF, establishing the efficacy of empagliflozin in HFrEF and allowing for comparative investigation of other SGLT2 inhibitors in this situation.

Beyond cardiovascular results, both studies provide valuable information about empagliflozin's renal protective effects. Changes in eGFR and delayed development of chronic kidney disease were detected in both diabetic and non-diabetic individuals, highlighting empagliflozin's potential as a dual action drug. Furthermore, findings from previous studies, such as DAPA-HF, show that SGLT2 inhibitors may lower the incidence of new-onset diabetes by up to 32%, and sub-analyses of the EMPEROR trials are expected to support this conclusion.

With approximately 10,000 participants, the EMPEROR studies are one of the most thorough examinations of empagliflozin's effect on cardiac, renal, and metabolic health. These convincing findings not only justify the significance of SGLT2 inhibitors in diverse types of heart failure, but also offer up new therapeutic options for controlling concomitant illnesses such as diabetes and chronic renal disease, hence encouraging their wider inclusion into cardiovascular care. [7]

SOLOIST-WHF Trials

The SOLOIST-WHF study was designed to assess the efficacy of sotagliflozin, a dual SGLT1/SGLT2 inhibitor, in improving outcomes for patients with type 2 diabetes who had recently been hospitalized for worsening heart failure. While the study's primary goal was to evaluate traditional cardiovascular endpoints, a key secondary objective was to look at changes in patient-reported health status using the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12), a validated tool for assessing heart failure symptoms, physical limitations, and quality of life.

This randomized, double-blind, placebo-controlled trial included 1,222 patients who were either hospitalized or recently released after receiving therapy for decompensated heart failure. Participants were randomly assigned to receive sotagliflozin or a placebo in addition to normal heart failure treatments. The KCCQ-12 was administered at baseline and every four months to monitor changes

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in health status. Of the total participants, 1,113 (91%) had complete KCCQ-12 data, which allowed for a thorough study of the treatment's influence on patient-centered outcomes.

At four months, sotagliflozin resulted in a statistically significant improvement in health status as compared to placebo. Patients who received sotagliflozin saw a mean increase of +4.1 points in their KCCQ-12 score (95% CI: 1.3-7.0; P=0.005). The sotagliflozin group had a 38% greater chance of achieving clinically significant improvement (a ≥5-point rise in KCCQ-12 score) (OR: 1.38; 95% CI: 1.06-1.80; P=0.017). These benefits were observed in all categories, including individuals with decreased or retained ejection fraction, and were independent of baseline health condition or clinical features.

The SOLOIST-WHF trial results indicate sotagliflozin's ability to rapidly improve health-related quality of life following an episode of heart failure decompensation. Within four months of starting therapy after being admitted to the hospital, symptoms, physical functioning, and general well-being improved. These findings show that sotagliflozin not only decreases the risk of hospitalization and death, but it also significantly improves patient-centered outcomes, making it a potential treatment choice for the post-exacerbation management of heart failure in type 2 diabetes patients. [8]

Trial	Drug	Population	EF Type	Primary Outcome	Key Findings	Duration
DAPA-HF	Dapagliflozin	4,744 HFrEF (EF ≤40%) patients	HFrEF	CV death or worsening HF (HHF or urgent HF visit)	↓ 26% risk of primary outcome (HR: 0.74, $p<0.001$); benefits in both diabetics & non-diabetics; improved KCCQ scores; no increase in adverse events	18.2 months
EMPEROR-Reduced	Empagliflozin	3,733 patients with EF <40%	HFrEF	Time to CV death or HHF	↓ 25% relative risk in primary endpoint; slowed eGFR decline; consistent benefit across subgroups; renal protection observed	~20 months
EMPEROR-Preserved	Empagliflozin	5,988 patients with EF >40%	HFpEF	Time to CV death or HHF	First trial showing benefit in HFpEF; ↓ risk of HF hospitalization ; modest effect on CV death; consistent renal and symptomatic benefits	~24 months
SOLOIST-WHF	Sotagliflozin	1,222 T2D patients post-HF hospitalization	Mixed (EF ≥/<50%)	CV death, HHF, or urgent HF visits	KCCQ-12 score ↑ by +4.1 points; 38% ↑ odds of ≥5-point	~4 months

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					KCCQ improvement (*P*=0.017); benefits regardless of EF; early initiation led to QoL improvement	

Table – 2 Overview of all the clinical trials [6,7,8]

Sglt2 Inhibitors Cardioprotective Mechanisms

Fig – 2 Main mechanisms of SGLT-2i on the heart

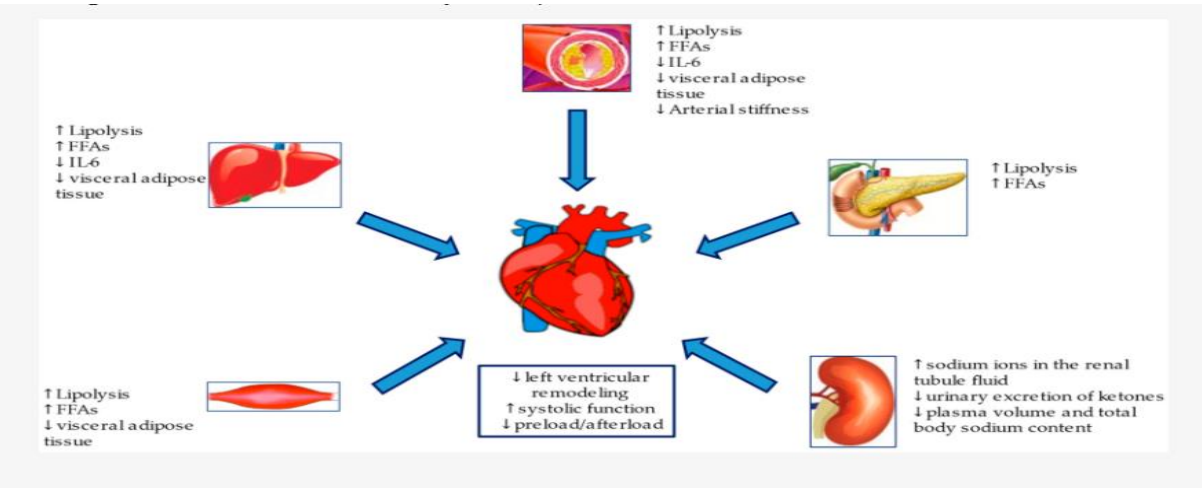

Fig – 3 Metabolic and haemodynamic protection mechanisms of SGLT2i

Hemodynamic Effects

Obesity and T2DM may also cause HFpEF by increasing cardiac preload in response to plasma volume expansion. In these patients, IR and proinflammatory cytokines generated by hypertrophic visceral adipocytes promote arterial stiffness, endothelial dysfunction in the arterioles, and a decrease in capillary density at the systemic and heart levels, increasing cardiac afterload.The direct cardiac effects of SGLT2i include an improvement in both the preload, secondary to natriuresis and osmotic diuresis, and the afterload, secondary to the reduction of sodium and circulating volume, through the reduction of both systolic and diastolic blood pressure (3-5 mmHg and 2 to 3 mmHg, respectively), without any increase in the HR and reducing arterial stiffness. A decrease in sodium reabsorption in the proximal renal tubule, which leads to an increase in diuresis, the improvement of vascular function in terms of stiffness and vascular resistance, and the reduction of bodyweight are some of the mechanisms that appear to be involved in the lowering of blood pressure (BP) caused by SGLT2i.

ISSN 2278-2540 | DOI: 10.51583/IJLTEMAS | Volume XIV, Issue VII, July 2025

SGLT2i's function as blood pressure-lowering medications was initially evaluated using the EMPAREG-OUTCOME data. Two meta-analyses have since validated this finding, demonstrating a decrease in 24-hour SBP and DBP of 3.76 mmHg and 1.83 mmHg, respectively, and in both SBP and DBP of 2.46 mmHg and 1.46 mmHg, respectively.

A meta-analysis's indirect data showed that canagliflozin 300 mg was more effective than other SGLT2i at lowering SBP, but there was no difference in DBP [98]. Empagliflozin is especially beneficial for high-risk Asian individuals with uncontrolled nocturnal hypertension. SGLT2i has also been proven to be more effective at night than during the day. Furthermore, in a small group of T2DM patients, the pulse wave velocity (PWV), a measure of arterial stiffness, dropped 48 hours after Dapagliflozin was administered. Additionally, the positive impact of dapagliflozin on endothelial function has been emphasised. Another study on Dapagliflozin and in vitro models also assessed the improvement of endothelial function the loop of Henle. Both empagliflozin and dapagliflozin have been investigated with good outcomes for several arterial stiffness measures, including central systolic blood pressure and forward and backward pulse wave amplitude. A double-blind, randomised trial found that after six weeks of Dapagliflozin medication, diabetes patients' tissue sodium levels drop. Gliflozins cause natriuresis and glucosuria by blocking SGLT2 in the proximal renal tube. Osmotic diuresis is triggered by the tubule's non-reabsorbed sodium and glucose. As a result, the tubular fluid has lower concentrations of sodium and chloride, which inhibits the NA-K-2Cl cotransporter and stops sodium reabsorption in the loop of henle. The left ventricular Franklin-Starling curve is positively impacted as a result of changes in the cardiac preload circumstances brought about by a decrease in the plasma volume and total body sodium content. However, two studies comparing Dapagliflozin vs. hydrochlorothiazide and bumetanide, respectively, found that other diuretics, such as thiazides and loop diuretics, did not improve the CV outcome. By influencing arterial stiffness and blood pressure, SGLT2i may also have an impact on afterload. Recent research indicates that the hemoconcentration brought on by the decrease in extracellular fluid volume and the improvement in diuresis is partially responsible for the rise in haematocrit linked to SGLT2. In people with type 2 diabetes, the natriuretic and diuretic effects of dapagliflozin cause a 7% drop in plasma volume, a 24-hour drop in blood pressure, and a 2.2% rise in haematocrit at week 12. However, the Dapagliflozin medication also raised reticulocyte counts and erythropoietin (EPO) concentrations, which raised haemoglobin and haematocrit levels. Additionally, a rise in erythropoietin has positive effects on angiogenesis, inflammation, cell proliferation, and the mitochondrial function of cardiomyocytes. Additionally, by raising the haematocrit, it protects the heart by boosting the oxygen flow to the tissues. Additionally, the exploratory analysis of the EMPA-REG research revealed a correlation between a decrease in the CV mortality rate and the observed link between higher haemoglobin and haematocrit levels and cardio protection following the administration of empagliflozin. The majority of recent research, however, indicates that it is more convincing to link the combined effects of the metabolic and haemodynamic pathways to the cardioprotective function of SGLT2i. [9]

Antiapoptic And Antifibrosis Effect

Increased ROS, inflammation, and apoptosis are additional factors that influence the heart damage brought on by hyperglycemia. The production of non-enzymatic glycation end products of proteins, lipids, and nucleic acids due to elevated glucose levels causes inflammation, which in turn triggers apoptosis and fibrosis. The production of adipokines is altered by epicardial fat hypertrophy, which leads to an increase in leptin levels instead of adiponectin. After nuclear factor-kappa B (NF-κB) is activated, leptin promotes the synthesis of proinflammatory cytokines and, as a result, the development of inducible NOS in cardiomyocytes. Research conducted on mice has demonstrated that SGLT2 inhibition lowers the levels of TNF-α, IL-6, and chemokine 2 in the blood. As with NF-κB and IL-6 in diabetic mice's kidneys and IL-6 and C-reactive protein (CRP) in the liver cells and adipocytes of obese mice fed a diet, similar results were also noted. Therefore, through a variety of molecular pathways, SGLT2i may alter the inflammatory responses in a number of kidney and other tissue cells, impacting oxidative stress, haemodynamics, cytokine production induced by hyperglycemia, RAAS activation, immune system function, and inflammation associated with obesity. Recent studies have looked into the molecular mechanisms behind the progression of HFpEF. Nitric oxide synthase (iNOS) overexpression reduces the activities of two proteins: the enzyme 1α and an isoform of the binding protein X-box 1 (XBP1). The protein response is inhibited, destabilised proteins accumulate in the heart, and cardiomyocyte apoptosis is elevated when XBP1 expression is decreased. Schiattarella et al. shown that in mice with HFpEF, either an overexpression of XBP1 or a deficit in iNOS expression improves the phenotype due to lower reduction of pulmonary congestion and left ventricular filling pressures. SGLT2i may increase titin phosphorylation and XBP1s expression in cardiac muscle by inhibiting iNOS production and activating eNOS.

Tne important aspect of cardiac remodelling that accelerates the development of heart failure (HF) is MYOCARDIAL FIBROSIS. Recent research has demonstrated the strong antifibrotic and cardioprotective benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i), including dapagliflozin and empagliflozin. In post-myocardial infarction rat models, Lee et al. showed that dapagliflozin decreases collagen synthesis by inducing M2 macrophages and preventing myofibroblast development. Empagliflozin also inhibits profibrotic indicators such matrix metalloproteinase-2, α-smooth muscle actin, type I collagen, and connective tissue growth factor, according to Kang et al. It also lessens the stimulation of fibroblasts caused by TGF-β1 The activation of AMP-activated protein kinase (AMPK), an enzyme involved in metabolic regulation, is a major mechanism underlying these effects. AMPK lowers inflammation, apoptosis, and fibrosis while promoting mitochondrial protection. Empagliflozin prevents mitochondrial damage by activating AMPK/Drp1 signalling in diabetic animal models. Additionally, it lessens endothelial damage and improves vascular barrier function through eNOS phosphorylation. Empagliflozin enhanced cardiac contractility and decreased infarct size via AMPK signalling in models of myocardial ischemia–reperfusion (I/R) injury and hypoxia/reoxygenation (H/R). Furthermore, the TGF-

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β/Smad pathway, which is crucial for the fibrotic transformation of heart tissue, is inhibited. Additionally, SGLT2i exhibits sympathetic inhibitory effects, which may reduce fibrosis and lower arrhythmogenic substrates. Despite the absence of clinical data explicitly connecting SGLT2i use to arrhythmia risk, their impact on autonomic nervous system (ANS) dysfunction is significant. Reducing insulin, glucose, and leptin levels, as well as improving insulin resistance, anaemia, and sodium volume management, can help diabetic patients with ANS problems. These actions further modulate cardiovascular autonomic regulation by suppressing the hypothalamus's activation of the carotid body (CB) and organum vasculosum of the lamina terminalis (OVLT). All things considered, SGLT2 inhibitors show encouraging antifibrotic and cardioprotective effects in both non-diabetic people and HF patients, including those with preserved (HFpEF) and reduced (HFrEF) ejection fraction. These results imply that SGLT2i may prove to be a useful therapy option in the management of HF, particularly in HFpEF, a condition for which there has been little success with current treatments.[9]

Metabolic Modulation

SGLT2 inhibitors lower blood glucose levels by inducing glucosuria, which reduces insulin and increases glucagon levels, particularly during fasting. These hormonal changes cause lipolysis in adipose tissue, favoring fat metabolism over carbohydrate utilization. This leads to a rise in circulating ketone bodies, including β-hydroxybutyrate (βOHB), acetoacetate (AcAc), and acetone. The liver produces these ketone bodies by fatty acid β-oxidation. A greater NADH/NAD^+ ratio promotes the conversion of AcAc to βOHB. Additionally, organs such as the kidneys and intestines contribute to ketone body homeostasis via sodium-dependent monocarboxylate transporters (SMCT1 and SMCT2).

The heart relies substantially on ATP for contraction, with fatty acid oxidation providing roughly 60% and carbohydrate metabolism providing the remainder. Under stress situations, such as hypoxia or pressure overload, fatty acid oxidation is reduced, and the heart switches to glucose metabolism, which is less efficient in terms of ATP production. Ketone bodies become advantageous under such conditions because they convert more easily into acetyl-CoA than fatty acids or glucose. This efficiency promotes ATP generation even when oxygen levels are low, making ketone bodies a more effective fuel supply for the failing heart.

In heart failure, cardiac energy metabolism shifts from fatty acids to ketone bodies. This adaptation is indicated by increased expression of ketone oxidation enzymes such BDH1 and enhanced levels of ketone-derived metabolites like C4OH-carnitine, βOHB-CoA, and acetyl-carnitine. These metabolic changes indicate the heart's requirement for a more oxygen-efficient energy source. Furthermore, transcriptional alterations encourage the use of ketones in energy synthesis, which may help to preserve cardiac output and cellular energy balance in heart failure patients.

Ketone bodies, in addition to providing energy, have protective benefits on the body. Research indicates that βOHB inhibits histone deacetylase activity, activating antioxidant genes such as FoxO3A and MT2. This reduces oxidative stress and may lengthen lifespan. Additionally, ketone bodies have anti-inflammatory properties, as evidenced by their capacity to inhibit the NLRP3 inflammasome, a crucial mediator in inflammation. Through these several mechanisms—enhancing energy efficiency, lowering oxidative damage, and dampening inflammation—SGLT2 inhibitor-induced ketone rise may provide varied benefits in the treatment of heart failure. [10]

Direct Myocardial Effects

Recent clinical trials have shown that SGLT2 inhibitors (SGLT2i) provide cardiovascular advantages in addition to their glucose-lowering effects. The DAPA-HF trial found that dapagliflozin reduced the composite risk of worsening heart failure (HF) or cardiovascular death by 27% in individuals with HFrEF, with no meaningful difference between diabetes and non-diabetic patients. Similarly, the DEFINE-HF trial showed significant improvements in heart failure-related health status and decreased natriuretic peptide levels, regardless of diabetes condition. These data lend support to the hypothesis that the heart advantages of SGLT2 inhibitors go beyond glucose management.

Preclinical research have confirmed the glucose-independent effects. Byrne et al. discovered that empagliflozin protected left ventricular (LV) systolic function in non-diabetic mice during pressure overload, even in the absence of ketones or hemodynamic abnormalities. Empagliflozin enhanced LV systolic function, decreased ventricular cavity size, and reduced cardiac fibrosis in a hypertensive rat heart failure model. Similarly, Zhang et al. found that dapagliflozin reduced blood pressure, reduced LV concentric remodeling, and decreased macrovascular inflammation in a pig model of HF with maintained ejection fraction (HFpEF).

According to the study, SGLT2 inhibitors improved LV function more significantly in diabetes patients with heart failure than in non-diabetic patients. This effect was detected regardless of the presence of other cardioprotective drugs such as ACE inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists. Many heart failure patients (notably those in groups 3 and 4) had their HF medications titrated to guideline-directed optimal doses throughout follow-up, which contributed to improved LV ejection fraction (LV-EF), particularly in diabetic patients.

Crucially, the positive effects of SGLT2i on LV function persisted even after accounting for changes in typical heart failure medications. The patterns of medication usage and adjustment during follow-up were not statistically different between the SGLT2i-treated and non-treated groups. This shows that the improvements in LV function observed with SGLT2i usage were not primarily

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owing to appropriate HF drug dose, but rather a direct result of the SGLT2i therapy itself. These findings underscore the therapeutic potential of SGLT2 inhibitors for the treatment of heart failure, particularly in diabetic patients. [11]

Neurohormonal And Renal Crosstalk

The RAAS is a key regulator of extracellular fluid (ECF) volume, salt balance, blood pressure, and heart function. It is triggered under hypovolemic or hypotensive conditions such as dehydration or bleeding. Angiotensin II (Ang II), the primary effector molecule of RAAS, produces vasoconstriction, increases salt reabsorption, stimulates thirst, and promotes aldosterone and ADH release. This cascade, while initially compensatory, exacerbates heart failure (HF) by increasing fibrosis, inflammation, and cardiac remodeling. While ACE inhibitors (ACEi) and Angiotensin receptor blockers (ARBs) suppress this damaging axis, new research suggests a beneficial "depressor arm" involving ACE2/Ang 1-7/Mas receptor, which counteracts the deleterious effects of Ang II by increasing vasodilation, natriuresis, and anti-inflammatory effects. This compensatory system may be crucial in preventing cardiac and renal damage in HF.

The renal sympathetic nerves control renal blood flow, salt absorption, and RAAS activation. In early HF, excessive sympathetic activity raises norepinephrine (NE) levels, which, while initially beneficial for perfusion, become deleterious as the illness progresses. SNS overactivity induces salt and water retention by increasing tubular reabsorption, renal vasoconstriction, and renin production. Experimental heart failure models suggest that renal denervation or β-blockers enhance renal and cardiac hemodynamics and reduce salt retention. This emphasizes the critical role of SNS in worsening HF and supports medicines that control sympathetic activity.

ADH (vasopressin) levels are high in HF patients, especially those with severe disease and hyponatremia. This increase is caused by non-osmotic stimuli such as decreased left atrial compliance and RAAS activation. ADH stimulates water reabsorption through V2 receptors and upregulates aquaporin-2 (AQP-2) channels in the kidney, resulting in dilutional hyponatremia. It also produces vasoconstriction through the V1a receptors. Though V2 antagonists (aquaretics) increase water excretion and congestion, they do not reliably improve clinical outcomes in post-acute heart failure conditions. Nonetheless, focusing on ADH remains a potential method for treating volume overload in HF.

The endothelin (ET) system, particularly ET-1, plays an important role in cardiovascular and renal disease. ET-1 promotes vasoconstriction, inflammation, and fibrosis, which impairs both heart and kidney function. ET-1 is increased in people with heart failure, contributing to renal hypoperfusion, salt retention, and cardiac remodeling. Animal trials using ET receptor antagonists (e.g., bosentan, tezosentan) revealed improvements in renal blood flow (RBF), glomerular filtration rate (GFR), and salt excretion. However, clinical trials have failed to show substantial mortality advantages, raising concerns about fluid retention and liver damage, particularly with non-selective medicines. While ET blockage has shown promise in preclinical models, its therapeutic use in HF warrants more exploration. [12]

II. Conclusion

A major global health burden, heart failure (HF) affects millions of people and contributes significantly to morbidity, mortality, and medical expenses. Heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) pose particular difficulties, particularly when combined with concomitant conditions such as type 2 diabetes mellitus (T2DM), which worsens the course and consequences of the disease. Despite improvements in guideline-directed therapy, interest in novel therapeutic classes, most notably SGLT2 (sodium-glucose co-transporter 2) inhibitors, has increased due to the unmet need for additional, more effective strategies, especially in HFpEF and diabetic heart failure.

Initially developed as glucose-lowering medicines for T2DM, SGLT2 inhibitors such as dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin have shown remarkable cardiovascular and renal beneficial benefits in addition to glycaemic management. These medicines work through a variety of methods, including producing glucosuria, moderate diuresis, and encouraging favourable metabolic changes. Their pharmacokinetic characteristics are usually safe and well tolerated, with adverse effects being treatable in the majority of patient groups.

The robust clinical evidence, highlighted by landmark trials—DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and SOLOIST-WHF—has firmly established SGLT2 inhibitors as effective therapies for reducing cardiovascular death and heart failure hospitalisations, as well as improving patients' quality of life as measured by validated tools such as the Kansas City Cardiomyopathy Questionnaire (KCCQ). These improvements were consistently reported in individuals with and without diabetes, as well as in patients with diverse heart failure characteristics. Meta-analyses and real-world observational data support their efficacy and usefulness in a broad range of patient demographics, prompting major cardiology societies (ACC/AHA, ESC) to issue a Class I recommendation for their usage in HFrEF therapy.

Mechanistically, the advantages of SGLT2 inhibitors go beyond haemodynamic unloading. Their cardioprotective properties include anti-inflammatory and anti-fibrotic effects, reduction of oxidative stress, improved myocardial energetics through enhanced ketone body utilisation, regulation of the Na^+/H^+ exchanger, and modification of mitochondrial activity and autophagy. Furthermore, their effect on neurohormonal regulation—reducing sympathetic overdrive and increasing renal salt handling—demonstrates their multi-system crosstalk, which contributes to cardiac and renal protection in HF patients.

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Importantly, the use of SGLT2 inhibitors is growing to include all types of HF, including HFrEF, HFmrEF, HFpEF, and acute decompensated HF. In particular, EMPEROR-Preserved revealed considerable outcome improvement in HFpEF—an area where earlier treatments had persistently failed—marking a watershed moment in treating this difficult-to-treat category. Furthermore, continuing research is looking at the use of these drugs in combination regimens with other HF therapies such as ARNI, beta-blockers, and MRAs, which might provide synergistic effects in complete HF management.

Nonetheless, some individuals should exercise caution, particularly those with chronic kidney disease (CKD), hypotension, advanced age, or a history of euglycemic ketoacidosis or genital infections. Long-term safety data are still being collected, and ongoing monitoring is required to monitor off-target effects and optimise patient selection. Future research should centre on precision medicine, discovering biomarkers or phenotypes that predict the best response to SGLT2 inhibitors, as well as mechanistic investigations that investigate their growing roles in vascular biology, inflammation, and fibrosis regulation.

To summarise, SGLT2 inhibitors have transformed the landscape of heart failure medicine, giving significant improvements in symptom alleviation, hospitalisation reduction, and death avoidance. Their wide applicability across HF phenotypes and diabetes state, together with their favourable safety profile, make them an essential component of modern HF therapy. As further research refines their location and combinations, SGLT2 inhibitors are expected to stay at the forefront of cardiovascular therapies for the foreseeable future.