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Review

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Comprehensive Benefits of Sodium-Glucose Cotransporter 2 Inhibitors in Heart Failure With Reduced Ejection Fraction: A Literature Review

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, initially developed for type 2 diabetes, have emerged as a promising treatment for heart failure with reduced ejection fraction (HFrEF). They show significant cardiovascular benefits, including reduced cardiovascular mortality and heart failure hospitalizations. This review consolidates knowledge on the efficacy of SGLT2 inhibitors in HFrEF, focusing on their mechanisms of action, clinical benefits, and patient outcomes. To consolidate existing knowledge on the efficacy of SGLT2 inhibitors in reducing cardiovascular mortality in HFrEF, with an emphasis on pathophysiology, clinical benefits, and patient outcomes, major medical databases such as PubMed, Scopus, and Web of Science were reviewed, prioritizing research published from 2020 to 2024. Key studies and clinical trials, including DAPA-HF and EMPEROR-Reduced, were analyzed to understand the impacts of SGLT2 inhibitors on HFrEF management. The review highlights the multifaceted mechanisms by which SGLT2 inhibitors exert their cardiovascular benefits, including osmotic diuresis, natriuresis, improved myocardial energetics, and anti-inflammatory and antifibrotic effects. Clinical trials have consistently demonstrated significant reductions in cardiovascular mortality and hospitalizations among HFrEF patients treated with SGLT2 inhibitors. These benefits are observed across diverse demographic and clinical subgroups, indicating their broad applicability in clinical practice. SGLT2 inhibitors significantly advance HFrEF management, reducing cardiovascular mortality and hospitalizations. However, gaps remain in long-term outcomes, early diagnostic indicators, and mechanisms of action. Future research should address these gaps and explore personalized medicine to optimize treatment. Integrating SGLT2 inhibitors into standard HFrEF management guidelines, supported by updated policies and educational initiatives for healthcare providers, will be crucial to maximize their therapeutic potential and improve patient outcomes.

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Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have recently gained significant recognition within cardiology for their transformative impact on heart failure management, particularly in patients with heart failure with reduced ejection fraction (HFrEF) [1]. Initially developed for managing type 2 diabetes, these agents have demonstrated considerable cardiovascular benefits, markedly reducing both cardiovascular mortality and hospitalizations for heart failure [2].

SGLT2 inhibitors, such as empagliflozin, dapagliflozin, and canagliflozin, represent a groundbreaking advancement in the treatment of HFrEF. These drugs were originally introduced to improve glycemic control by inhibiting glucose reabsorption in the kidneys, thereby promoting glucose excretion through urine. Beyond their primary glucose-lowering effects, SGLT2 inhibitors exhibit several mechanisms that contribute to cardiovascular protection, including osmotic diuresis, natriuresis, improved myocardial energetics, and anti-inflammatory and antifibrotic properties [3].

The pathogenesis of HFrEF involves a complex interplay of mechanisms leading to impaired cardiac output and heart failure symptoms. HFrEF is characterized by reduced myocardial contractility, which compromises the heart's ability to pump blood effectively, resulting in decreased tissue perfusion. This triggers the activation of neurohormonal systems, notably the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). These systems exacerbate heart failure through vasoconstriction, fluid retention, and adverse cardiac remodeling, ultimately worsening the condition [4]. Chronic inflammation and oxidative stress further damage myocardial tissue and promote fibrosis, contributing to the progressive decline in cardiac function. SGLT2 inhibitors intervene in these processes by improving myocardial metabolism, reducing neurohormonal activation, and alleviating inflammation and oxidative stress, thereby enhancing overall cardiac function and reducing mortality [5].

Epidemiologically, HFrEF is a significant global health

Table 1. Summary of Pivotal Clinical Trials of SGLT2 Inhibitors in HFrEF

Study name	Population characteristics	Intervention details	Primary outcomes
DAPA-HF	4,744 patients with HFrEF; mean age: 66 years; 23% female	Dapagliflozin 10 mg daily; median follow-up: 18.2 months	26% RRR in CV death or worsening HF (HR: 0.74, 95% CI: 0.65 - 0.85); 16% RRR in all-cause mortality (HR: 0.84, 95% CI: 0.72 - 0.99)
EMPEROR-Reduced	3,730 patients with HFrEF; mean age: 67 years; 24% female	Empagliflozin 10 mg daily; median follow-up: 16 months	25% RRR in CV death or HF hospitalization (HR: 0.75, 95% CI: 0.65 - 0.86); 13% RRR in all-cause mortality (HR: 0.87, 95% CI: 0.77 - 0.98)

SGLT2: sodium-glucose cotransporter 2; HFrEF: heart failure with reduced ejection fraction; RRR: relative risk reduction; CV: cardiovascular; HR: hazard ratio; CI: confidence interval.

concern, with its prevalence and incidence influenced by various demographic factors, including age, sex, and ethnicity. The condition is notably more prevalent in older populations, with higher rates of heart failure events observed as age increases [6]. Moreover, socio-economic factors, healthcare access, and comorbid conditions such as hypertension and diabetes significantly affect the distribution and outcomes of HFrEF. Despite these variations, SGLT2 inhibitors have shown consistent efficacy in reducing cardiovascular death and hospitalizations for heart failure across diverse patient populations, regardless of age, sex, or baseline renal function. However, the underrepresentation of certain demographic groups, such as Black populations, in clinical trials necessitates further research to ensure the broad applicability of these benefits [7].

The clinical significance of HFrEF is profound, given its substantial impact on patient morbidity, mortality, and quality of life. HFrEF leads to frequent hospitalizations and high healthcare costs, placing a considerable burden on patients and healthcare systems alike. The introduction of SGLT2 inhibitors has provided a new therapeutic avenue that not only improves survival rates but also enhances health-related quality of life. Patients treated with SGLT2 inhibitors report better outcomes on measures such as the Kansas City Cardiomyopathy Questionnaire, indicating significant improvements in their daily functioning and well-being [8].

Recent clinical trials, such as DAPA-HF and EMPEROR-Reduced, have provided robust evidence supporting the efficacy of SGLT2 inhibitors in managing HFrEF. These trials have demonstrated significant reductions in cardiovascular mortality and heart failure hospitalizations, reinforcing the importance of these inhibitors in clinical practice. To provide a more detailed understanding, we have summarized the key aspects of these pivotal studies, including the characteristics of the study subjects, the details of the interventions (drug dosage and duration), and the primary outcomes with specific numerical values. These findings highlight the potential of SGLT2 inhibitors to revolutionize heart failure management, offering hope for improved outcomes in a condition that has historically been challenging to treat (Table 1) [9, 10].

Despite these advancements, several gaps in the literature remain. Long-term studies are needed to fully understand the sustained impact of SGLT2 inhibitors on cardiovascular outcomes and overall health. Additionally, research should focus on identifying early diagnostic indicators to predict which patients will benefit most from SGLT2 inhibitor therapy, thus enabling more personalized treatment approaches. Furthermore, a deeper understanding of the precise mechanisms of action of SGLT2 inhibitors will help refine treatment strategies and may lead to the development of even more effective therapeutic options [11].

In conclusion, SGLT2 inhibitors have emerged as a cornerstone in the management of HFrEF, offering significant reductions in cardiovascular mortality and hospitalizations. Their multifaceted benefits, which extend beyond glycemic control, underscore their importance in contemporary cardiology. Future research should aim to address the existing gaps in knowledge, ensuring that the full potential of these innovative therapies is realized, ultimately improving patient outcomes and reducing the burden of HFrEF.

Methodology

In conducting this literature review on the comprehensive benefits of SGLT2 inhibitors in HFrEF, a thorough and systematic approach was employed to ensure a comprehensive synthesis of existing knowledge. The review focused on understanding the efficacy, mechanisms of action, clinical benefits, and patient outcomes associated with SGLT2 inhibitors in the context of HFrEF.

The initial step involved identifying relevant medical databases, including PubMed, Scopus, and Web of Science, which are well-regarded for their extensive repositories of biomedical literature. The search strategy was meticulously designed to capture articles published from January 2020 to April 2024, ensuring the inclusion of the most current and pertinent research. Keywords such as “SGLT2 inhibitors”, “heart failure with reduced ejection fraction”, “cardiovascular mortality”, “clinical outcomes”, and “mechanisms of action” were utilized in various combinations to maximize the retrieval of relevant studies.

Inclusion criteria were defined to select studies that specifically addressed the impact of SGLT2 inhibitors on cardiovascular outcomes in HFrEF. These criteria encompassed randomized controlled trials (RCTs), observational studies, and review articles that provided significant insights into the therapeutic effects and underlying mechanisms of these agents. Articles that focused solely on glycemic control without addressing cardiovascular outcomes or those related to heart failure with preserved ejection fraction (HFpEF) were excluded to maintain the review’s focus on HFrEF.

To ensure the quality and reliability of the included stud-

ies, each article was subjected to a rigorous evaluation process. This involved assessing the methodological robustness, sample size, statistical analyses, and the relevance of the findings to the objectives of this review. Key studies, such as the DAPA-HF and EMPEROR-Reduced trials, which have significantly contributed to the understanding of SGLT2 inhibitors in HFrEF, were prioritized for detailed analysis.

The synthesis of the literature was conducted in a manner that consolidated findings on the multifaceted benefits of SGLT2 inhibitors. Particular emphasis was placed on their cardiovascular effects, including reductions in cardiovascular mortality and heart failure hospitalizations. Mechanisms of action such as osmotic diuresis, natriuresis, improved myocardial energetics, and anti-inflammatory and antifibrotic properties were explored to provide a comprehensive understanding of how these agents exert their therapeutic effects.

Additionally, the review considered the applicability of SGLT2 inhibitors across diverse demographic and clinical subgroups, highlighting the consistency of benefits observed in different populations. The implications of these findings for clinical practice were discussed, with recommendations for integrating SGLT2 inhibitors into standard HFrEF management protocols.

The review also identified existing gaps in the literature, such as the need for long-term outcome data, early diagnostic indicators, and further elucidation of the mechanisms of action. These gaps were framed within the context of future research directions to optimize the use of SGLT2 inhibitors in HFrEF management.

In conclusion, this literature review employed a structured and methodical approach to collate and synthesize current evidence on the benefits of SGLT2 inhibitors in HFrEF, providing a comprehensive overview that can inform clinical practice and guide future research endeavors.

Epidemiology

HFrEF is a substantial global health concern, characterized by the heart's inability to pump blood effectively. SGLT2 inhibitors have gained prominence as a therapeutic intervention for HFrEF, demonstrating significant potential in reducing cardiovascular mortality and hospitalizations. The epidemiology of HFrEF is influenced by various demographic, geographic, genetic, lifestyle, and environmental factors, which play critical roles in its prevalence, incidence, and outcomes [12].

HFrEF is widely prevalent across the globe, contributing to high mortality rates and frequent hospitalizations. The efficacy of SGLT2 inhibitors in reducing cardiovascular mortality and hospitalizations in HFrEF patients is well documented. These inhibitors significantly decrease the composite risk of cardiovascular death or hospitalization for heart failure, with combined therapy involving angiotensin receptor-neprilysin inhibitors (ARNI) further enhancing these outcomes. Notably, SGLT2 inhibitors are associated with a 13% reduction in all-cause death and a 14% reduction in cardiovascular death among HFrEF patients [13].

The prevalence of HFrEF varies significantly across different geographic regions, influenced by factors such as healthcare access, socioeconomic status, and the prevalence of risk factors like hypertension and diabetes. SGLT2 inhibitors, including dapagliflozin and empagliflozin, have been shown to reduce the risk of cardiovascular death and hospitalizations for heart failure consistently across various subgroups, including different ages, sexes, and baseline renal functions. Real-world studies corroborate the efficacy of these inhibitors in reducing hospitalizations for heart failure, particularly in patients with a history of cardiovascular disease, thereby improving health-related quality of life. These findings support the approval of SGLT2 inhibitors for treating HFrEF patients regardless of gender or diabetes status [14].

The incidence and prevalence of HFrEF increase with age, with older populations showing higher rates of heart failure events. SGLT2 inhibitors effectively reduce the risk of cardiovascular death and hospitalizations for heart failure across all age groups, demonstrating consistent benefits regardless of age. Additionally, demographic variations reveal that SGLT2 inhibitors show cardiovascular benefits in White and Asian populations, with less pronounced effects in Black populations, potentially due to underrepresentation in clinical trials or variations in drug response. Differences in the prevalence and incidence of HFrEF among various ethnic and racial groups highlight the importance of tailored treatment approaches, underscoring the importance of these inhibitors in managing HFrEF across diverse demographic groups [15].

Genetic mutations and hereditary conditions significantly predispose individuals to HFrEF. Common mutations include those in genes encoding sarcomeric proteins (e.g., *MYH7*, *MYBPC3*) and ion channel proteins (e.g., *SCN5A*). Hereditary conditions such as familial dilated cardiomyopathy, often linked to *TTN* gene mutations, further contribute to HFrEF risk [16].

Lifestyle choices such as diet, physical activity, smoking, and alcohol consumption significantly influence the development, progression, and management of HFrEF. High sodium intake, unhealthy diets, sedentary lifestyles, smoking, and excessive alcohol consumption exacerbate heart failure symptoms. SGLT2 inhibitors help mitigate these negative impacts by improving glucose control, promoting weight loss, enhancing exercise capacity, and offering cardiovascular protection [17].

Comorbidities such as diabetes, hypertension, and obesity are common in HFrEF patients and contribute to worse cardiovascular outcomes. Effective management of these conditions can lead to improved renal outcomes and benefits beyond glycemic control, including hemodynamic changes, natriuresis, osmotic diuresis, and weight loss [18].

Environmental influences, including air pollution, socioeconomic status, access to healthcare, and exposure to toxins, play significant roles in the development and progression of HFrEF. SGLT2 inhibitors reduce systemic inflammation and oxidative stress, improve hemodynamics, enhance cardiac function, and preserve kidney function, thereby mitigating the adverse effects of environmental stressors [19].

The consistent and significant benefits of SGLT2 inhibitors across various subgroups underscore their extensive applicability in clinical practice, particularly in the management

Table 2. Key Impacts of SGLT2 Inhibitors in HFrEF

Aspect	Details	Impact of SGLT2 inhibitors
Demographic influence	Age, sex, ethnicity	14% reduction in cardiovascular death; significant benefits in Whites and Asians
Geographic/environmental factors	Healthcare access, socioeconomic status, pollution	25% reduction in HF hospitalizations across diverse regions
Genetic factors	*MYH7*, *MYBPC3*, *SCN5A*, *TTN* mutations	Effective despite genetic predispositions
Comorbidities/lifestyle	Diabetes, hypertension, obesity, unhealthy habits	13% reduction in all-cause mortality; improved weight and blood pressure
Clinical outcomes	Cardiovascular death, all-cause mortality, HF hospitalizations	14% CV death, 13% all-cause mortality, 25% HF hospitalizations reduction

SGLT2: sodium-glucose cotransporter 2; HFrEF: heart failure with reduced ejection fraction; HF: heart failure; CV: cardiovascular.

of HFrEF. Both dapagliflozin and empagliflozin have demonstrated similar efficacy in reducing cardiovascular mortality and the risk of hospitalization for heart failure, with additional improvements in renal outcomes and right ventricular function. Meta-analyses from pivotal trials like DAPA-HF and EMPEROR-Reduced confirmed that these agents offer comparable therapeutic effects, without significant differences in their impact on cardiac function or clinical outcomes. These benefits persist across diverse patient populations, regardless of age, sex, or baseline renal function, with minor variations noted in response based on New York Heart Association (NYHA) functional class and race. Integrating SGLT2 inhibitors with ARNI further enhances outcomes, emphasizing the critical role of these drugs in a comprehensive, multifaceted approach to HFrEF management (Table 2) [20].

Pathophysiology

HFrEF is a complex clinical syndrome characterized by significant alterations in cardiac structure and function, resulting from intricate biochemical and molecular pathways. The pathophysiology of HFrEF encompasses a cascade of maladaptive responses initiated by cardiac injury or stress, which progressively impair the heart's ability to pump blood effectively [21].

At the core of HFrEF pathophysiology is the activation of neurohormonal systems, particularly the RAAS and the SNS. The RAAS, when activated, leads to the release of angiotensin II and aldosterone. Angiotensin II promotes vasoconstriction, sodium and water retention, and myocardial fibrosis, contributing to increased blood pressure and cardiac workload. Aldosterone exacerbates these effects by further promoting sodium retention and fibrosis, leading to volume overload and detrimental remodeling of the myocardium. The chronic activation of the SNS results in elevated levels of catecholamines like norepinephrine, which increase heart rate and myocardial contractility. However, prolonged SNS activation causes direct myocardial toxicity, promotes arrhythmogenesis, and contributes to adverse cardiac remodeling [22].

Inflammatory and oxidative stress pathways are also pivotal in HFrEF development and progression. Elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6 play a crucial role in myocardial injury and fibrosis. These cytokines promote apoptosis and necrosis of cardiomyocytes, leading to a loss of functional cardiac muscle and contributing to reduced ejection fraction. Additionally, the overproduction of reactive oxygen species (ROS) results in oxidative damage to cellular structures, including proteins, lipids, and DNA, exacerbating myocardial dysfunction and remodeling [23].

Cardiac remodeling in HFrEF involves significant structural changes, including hypertrophy and fibrosis. Chronic pressure and volume overload stimulate the heart to undergo hypertrophy in an attempt to maintain cardiac output. However, this hypertrophy is often maladaptive, leading to increased myocardial stiffness and impaired relaxation. Fibrosis further stiffens the myocardium, reducing its compliance and contributing to diastolic dysfunction. Over time, these structural changes result in a more spherical shape of the left ventricle, decreasing the efficiency of cardiac contraction and exacerbating systolic dysfunction [24].

Metabolic dysregulation is another critical aspect of HFrEF pathophysiology. The failing heart shifts from predominantly using glucose as an energy source to relying more on fatty acid oxidation. This metabolic shift is less efficient, leading to inadequate adenosine triphosphate (ATP) production and further compromising cardiac function. Additionally, impaired mitochondrial function in HFrEF results in reduced energy production and increased oxidative stress, contributing to the progression of heart failure [25].

SGLT2 inhibitors have emerged as a promising therapeutic option for HFrEF, primarily through their multifaceted mechanisms of action that target various aspects of the disease's pathophysiology. One of the primary benefits of SGLT2 inhibitors is their diuretic and natriuretic effects, which reduce plasma volume and decrease preload and afterload on the heart. This alleviates volume overload, lowers blood pressure, and reduces ventricular wall stress [26].

Furthermore, SGLT2 inhibitors improve myocardial energy metabolism by enhancing the utilization of ketone bodies, which are more efficient energy substrates compared to glucose and fatty acids. This metabolic shift reduces oxidative stress and improves mitochondrial function, thereby supporting overall myocardial efficiency and function. By reducing the activation of the RAAS and SNS, SGLT2 inhibitors miti-

Table 3. Mechanisms of Action of SGLT2 Inhibitors in HFrEF

Mechanism	Effect
Diuretic and natriuretic	Reduced plasma volume, decreased preload and afterload
Improved myocardial energetics	Enhanced ketone body utilization, reduced oxidative stress
Reduced RAAS activation	Decreased fibrosis and hypertrophy
Reduced SNS activation	Lower incidence of arrhythmias, improved myocardial function

SGLT2: sodium-glucose cotransporter 2; HFrEF: heart failure with reduced ejection fraction; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system.

gate the harmful effects of neurohormonal overactivation, including fibrosis, hypertrophy, and arrhythmias (Table 3) [27].

The anti-inflammatory and antifibrotic properties of SGLT2 inhibitors further contribute to their cardioprotective effects. By lowering levels of pro-inflammatory cytokines and oxidative stress markers, these drugs reduce myocardial inflammation and fibrosis, improving cardiac structure and function. Additionally, SGLT2 inhibitors enhance endothelial function by promoting vasodilation and improving microcirculatory perfusion, which reduces cardiac workload and enhances oxygen delivery to tissues [28].

Genetic factors also play a significant role in HFrEF. Mutations in genes encoding sarcomeric proteins (e.g., *MYH7*, *TNNT2*, *TTN*), cytoskeletal proteins (e.g., *LMNA*), ion channels (e.g., *SCN5A*), and mitochondrial genes (e.g., *MT-TL1*) can predispose individuals to HFrEF. SGLT2 inhibitors interact with these genetic factors by improving cardiac metabolism, reducing oxidative stress and inflammation, and enhancing myocardial efficiency. This interaction helps mitigate the detrimental impacts of genetic mutations on cardiac function [29].

In summary, the pathophysiology of HFrEF is multifactorial, involving neurohormonal activation, inflammatory and oxidative stress pathways, structural and metabolic changes, and genetic predispositions. SGLT2 inhibitors address these pathophysiological mechanisms through diuresis, improved myocardial energy metabolism, reduced neurohormonal activation, anti-inflammatory and antifibrotic effects, and enhanced endothelial function. These multifaceted benefits make SGLT2 inhibitors a crucial component in the management of HFrEF, significantly reducing cardiovascular mortality and improving clinical outcomes for patients.

Clinical Manifestations

HFrEF presents with a range of clinical manifestations that are crucial for diagnosis, management, and prognostication. The primary symptoms of HFrEF include dyspnea, fatigue, and fluid retention. These symptoms are the direct consequence of the heart's diminished capacity to maintain adequate circulation, leading to systemic and pulmonary congestion as well as insufficient perfusion of peripheral tissues [30].

Dyspnea, or shortness of breath, is one of the hallmark symptoms of HFrEF. It occurs due to elevated pressures in the left atrium and pulmonary veins, leading to pulmonary congestion and edema. This symptom is often exacerbated by physical activity and can progress to orthopnea, where patients experience difficulty breathing while lying flat, and paroxysmal nocturnal dyspnea, which involves sudden episodes of severe breathlessness at night. These nighttime symptoms are particularly distressing and significantly impact patients' quality of life [30].

Fatigue in HFrEF results from decreased cardiac output and poor perfusion of skeletal muscles, leading to reduced exercise tolerance and a general sense of tiredness. This symptom is often one of the earliest signs of heart failure and tends to worsen as the disease progresses. Patients with severe fatigue may find even basic daily activities challenging, which further diminishes their quality of life [31].

Fluid retention is another critical manifestation of HFrEF, manifesting as peripheral edema, ascites, and weight gain. This occurs due to the activation of neurohormonal systems, particularly the RAAS, which promotes sodium and water retention. The resulting volume overload leads to increased venous pressures and subsequent leakage of fluid into the interstitial spaces [31].

In addition to these common symptoms, HFrEF can also present with less typical manifestations. For instance, nocturia, the need to urinate frequently at night, occurs due to the mobilization of interstitial fluid when lying down. Cachexia, a wasting syndrome characterized by significant weight loss and muscle atrophy, is seen in advanced heart failure and is associated with poor prognosis. Gastrointestinal symptoms like nausea, abdominal discomfort, and early satiety can occur due to congestion of the gastrointestinal tract [32].

Major clinical syndromes associated with HFrEF include heart failure symptoms and arrhythmias. Arrhythmias, such as atrial fibrillation (AF) and ventricular tachycardia (VT), are common in HFrEF and significantly impact morbidity and mortality. AF exacerbates heart failure symptoms by impairing atrial contraction and leading to an irregular and often rapid ventricular response. VT and other ventricular arrhythmias increase the risk of sudden cardiac death, a leading cause of mortality in heart failure patients [33].

The prevalence and impact of arrhythmias in HFrEF are substantial. AF is particularly prevalent and is associated with worsened heart failure symptoms and increased hospitalizations. Ventricular arrhythmias, including VT and ventricular fibrillation, are critical due to their potential to cause sudden cardiac death. The management of these arrhythmias is a crucial aspect of HFrEF treatment, aiming to improve symptoms and reduce mortality [33].

SGLT2 inhibitors have shown significant benefits in

Table 4. Clinical Manifestations and Management in HFrEF

Clinical manifestation	Description	Impact on patient	Management approach
Dyspnea	Shortness of breath due to pulmonary congestion	Decreased quality of life, impaired exercise tolerance	Diuretics, SGLT2 inhibitors
Fatigue	General sense of tiredness due to reduced cardiac output	Difficulty in daily activities	Optimize heart failure therapy, SGLT2 inhibitors
Fluid retention	Peripheral edema, ascites, weight gain due to volume overload	Discomfort, swelling	Diuretics, SGLT2 inhibitors
Nocturia	Frequent urination at night due to fluid mobilization	Disrupted sleep	Fluid management, SGLT2 inhibitors
Cachexia	Weight loss and muscle atrophy in advanced stages	Poor prognosis	Nutritional support, SGLT2 inhibitors
Gastrointestinal symptoms	Nausea, abdominal discomfort due to gastrointestinal congestion	Decreased appetite, discomfort	Symptom management, SGLT2 inhibitors
Arrhythmias	Atrial fibrillation and ventricular tachycardia	Increased risk of morbidity and mortality	Antiarrhythmic medications, SGLT2 inhibitors

SGLT2: sodium-glucose cotransporter 2; HFrEF: heart failure with reduced ejection fraction.

modifying the clinical manifestations of HFrEF. They promote diuresis and natriuresis, reduce plasma volume, and thereby reduce cardiac preload and afterload. This alleviates symptoms of dyspnea and fluid retention, leading to significant symptomatic relief and improved quality of life.

Patients treated with SGLT2 inhibitors often report less dyspnea and fatigue, reflecting enhanced functional status. These improvements are likely due to the drugs' effects on reducing cardiac congestion and improving cardiac output [33].

In terms of arrhythmias, SGLT2 inhibitors have shown potential benefits in reducing the incidence and severity of both atrial and ventricular arrhythmias. By reducing atrial stretch and fibrosis, these drugs decrease the risk of AF. Furthermore, their positive effects on myocardial energy metabolism and reduction of oxidative stress may help mitigate ventricular arrhythmias, contributing to overall cardiovascular protection [34].

Initial diagnostic tests in HFrEF patients typically include echocardiography, electrocardiography (ECG), and biomarker analysis. Echocardiography often reveals reduced left ventricular ejection fraction (LVEF), ventricular dilation, and wall motion abnormalities. Common ECG findings in HFrEF include left bundle branch block (LBBB), AF, and nonspecific ST-T wave changes. Elevated levels of natriuretic peptides, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP), are also typical, reflecting increased cardiac wall stress [34].

SGLT2 inhibitors significantly impact these diagnostic findings. They improve LVEF and reduce left ventricular volumes, indicating better myocardial contractility and reduced adverse remodeling. These drugs also lead to normalization of some ECG abnormalities, such as reducing QRS duration and improving T-wave changes, which are indicative of better myocardial electrical stability. Biomarker levels, including NT-proBNP and BNP, decrease with SGLT2 inhibitor therapy, correlating with reduced cardiac stress and improved hemodynamics [35].

Early initiation of SGLT2 inhibitors can lead to rapid and meaningful reductions in clinical events, making them a valuable addition to the therapeutic regimen for newly diagnosed HFrEF patients or those hospitalized with heart failure (Table 4) [35].

In summary, the clinical manifestations of HFrEF are varied and impactful, affecting patients' quality of life and prognosis. SGLT2 inhibitors offer significant improvements in these symptoms, leading to better clinical outcomes and enhanced quality of life for patients with HFrEF. Their role in reducing cardiovascular mortality and hospitalizations underscores their importance in the comprehensive management of heart failure.

Diagnostic Criteria and Challenges

HFrEF presents a significant diagnostic challenge due to its multifaceted clinical presentation and the need for a comprehensive evaluation to confirm the diagnosis and guide treatment. The identification of HFrEF requires an integration of clinical symptoms, physical examination findings, and diagnostic tests, each contributing vital information to ensure an accurate diagnosis (Table 5) [36].

The primary clinical indicators of HFrEF include dyspnea, fatigue, and fluid retention. Dyspnea, or shortness of breath, is a cardinal symptom and can manifest during exertion (exertional dyspnea) or at rest. Orthopnea, which occurs when the patient is lying flat, and paroxysmal nocturnal dyspnea, characterized by sudden breathlessness at night, are particularly indicative of advanced heart failure. Fatigue results from the heart's inability to pump sufficient blood, leading to inadequate oxygen delivery to tissues and muscles, thereby reducing the patient's capacity for physical activity. Fluid retention, evident as peripheral edema, ascites, and rapid weight gain, arises from sodium and water retention driven by neurohormonal activation [36].

Physical examination findings that are critical in diagnos-

Table 5. Diagnostic Criteria and Challenges in HFrEF

Diagnostic tool	Key findings
Clinical symptoms	Dyspnea, fatigue, fluid retention
Physical examination	Jugular venous distension, pulmonary crackles, peripheral edema, S3 heart sound
Laboratory tests	Elevated BNP/NT-proBNP levels
Echocardiography	Reduced LVEF, ventricular dilation, wall motion abnormalities
Electrocardiography (ECG)	QRS prolongation, T-wave abnormalities, left ventricular hypertrophy or atrial enlargement
Advanced imaging	CMR for myocardial fibrosis, structural abnormalities

HFrEF: heart failure with reduced ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; BNP: B-type natriuretic peptide; LVEF: left ventricular ejection fraction; CMR: cardiovascular magnetic resonance.

ing HFrEF include jugular venous distension (JVD), pulmonary crackles, peripheral edema, and an S3 heart sound. JVD, visible as distended jugular veins, indicates elevated central venous pressure, a common sign of right-sided heart failure. Pulmonary crackles, heard during lung auscultation, suggest pulmonary congestion due to left-sided heart failure. The presence of an S3 heart sound, indicative of increased left ventricular filling pressures, often correlates with severe heart failure and poor prognosis. Physical examination should meticulously assess signs of fluid overload and evaluate heart sounds for abnormalities. Regular monitoring of blood pressure and renal function is crucial, especially since SGLT2 inhibitors, used in HFrEF management, have renal protective effects and can mitigate hyperkalemia risk [37].

Laboratory tests are essential for the diagnosis of HFrEF, and BNP and NT-proBNP levels are key biomarkers. Elevated levels of these peptides directly correlate with increased cardiac wall stress and are highly sensitive and specific for diagnosing heart failure. These biomarkers not only aid in the initial diagnosis but also in monitoring disease progression and treatment response, making them essential in the management of HFrEF. SGLT2 inhibitors have been shown to modestly reduce these biomarker levels, contributing to their overall cardiovascular benefits by reducing cardiac wall stress and improving hemodynamics [37].

Echocardiography is the cornerstone imaging modality for HFrEF, providing detailed information about LVEF, ventricular dimensions, wall motion, and valvular function. A reduced LVEF, typically below 40%, confirms the diagnosis of HFrEF. Echocardiography can also reveal ventricular dilation and wall motion abnormalities, both indicative of structural heart disease. In addition, it assesses diastolic function, which can be impaired in heart failure, providing a comprehensive evaluation of the heart's pumping and filling capacities [38].

ECG is another critical diagnostic tool. Common ECG findings in HFrEF include QRS prolongation, T-wave abnormalities, and signs of left ventricular hypertrophy or atrial enlargement. These abnormalities can provide insights into the electrical and structural remodeling of the heart associated with HFrEF [38].

A systematic diagnostic approach involves a thorough patient history, including details of previous cardiovascular events, hospitalizations, and comorbid conditions like diabetes and hypertension. Family history is also important, as genetic predispositions can significantly impact the risk of developing HFrEF. Medication history, including current and past medications, is vital to identify potential contributors to the patient's condition and to guide appropriate therapy [39].

Risk factors such as hypertension and diabetes are critical in the diagnostic process, given their significant role in the pathogenesis of HFrEF. SGLT2 inhibitors have shown particular benefits in patients with these conditions, improving cardiovascular outcomes and reducing adverse events. Lifestyle factors, including smoking, alcohol consumption, and physical activity levels, should also be evaluated to provide a comprehensive risk assessment [39].

Advanced imaging techniques, such as cardiovascular magnetic resonance (CMR), are invaluable for assessing myocardial fibrosis, structural abnormalities, and precise measurements of ventricular volumes and function. CMR can detect myocardial fibrosis and structural abnormalities with high sensitivity and specificity, providing detailed images that are crucial for diagnosing and managing HFrEF [40].

Molecular and genetic testing can identify underlying etiologies of HFrEF, such as mutations in genes associated with cardiomyopathies. Identifying these mutations helps tailor specific treatments and management strategies, including the use of SGLT2 inhibitors, which have demonstrated efficacy in reducing cardiovascular death and hospitalization for heart failure [41].

Endomyocardial biopsy may be considered in cases of unexplained heart failure or suspected infiltrative diseases when other diagnostic methods are inconclusive. This invasive procedure can provide definitive histological evidence, guiding treatment decisions and confirming diagnoses that are challenging to establish through noninvasive means [42].

In conclusion, diagnosing HFrEF involves a multifaceted approach, integrating clinical indicators, patient history, physical examination, and a range of diagnostic tests. SGLT2 inhibitors play a crucial role in modifying these diagnostic findings and improving patient outcomes, emphasizing their importance in the comprehensive management of heart failure.

Prognosis

HFrEF presents a significant challenge in clinical management due to its complex pathophysiology and variable prognosis. Prognosis in HFrEF patients treated with SGLT2 inhibitors is

influenced by multiple factors including baseline ejection fraction, comorbid conditions, biomarkers, and patient adherence to therapy. Understanding these variables is crucial for optimizing treatment strategies and improving patient outcomes [42].

Baseline ejection fraction is a critical determinant of prognosis in HFrEF. A lower ejection fraction typically indicates more severe myocardial damage and a poorer prognosis. SGLT2 inhibitors have demonstrated efficacy in improving outcomes across a range of ejection fraction levels, offering significant benefits even in patients with severely reduced ejection fraction. This suggests that the protective mechanisms of SGLT2 inhibitors are effective regardless of the degree of systolic dysfunction. Furthermore, these benefits are consistent across both ischemic and non-ischemic etiologies of HFrEF, indicating the broad applicability of SGLT2 inhibitors [43].

The presence of comorbid conditions such as diabetes and hypertension significantly impact the prognosis of HFrEF patients. Diabetes exacerbates cardiovascular risk and is associated with worse outcomes in heart failure. SGLT2 inhibitors, initially developed for glucose lowering, have shown robust cardiovascular benefits in both diabetic and non-diabetic HFrEF patients. They reduce cardiovascular death and hospitalizations for heart failure, making them an essential component of therapy for patients with these comorbidities. Similarly, effective management of hypertension with SGLT2 inhibitors helps reduce cardiac workload and prevent adverse cardiac remodeling, further improving outcomes [43].

Biomarkers such as NT-proBNP are critical in assessing the severity of heart failure and predicting outcomes. Elevated NT-proBNP levels correlate with increased cardiac stress and poorer prognosis. SGLT2 inhibitors have been shown to reduce NT-proBNP levels, reflecting reduced cardiac stress and improved clinical outcomes. The effectiveness of these inhibitors is evident across a range of baseline NT-proBNP levels, with higher levels typically indicating a greater need for intensive therapy. Monitoring NT-proBNP levels can help assess response to treatment and guide adjustments in therapy. In addition, biomarker analysis, including high-sensitivity troponin, provides further insight into the severity of heart failure and the effectiveness of therapy [44].

Adherence to SGLT2 inhibitor therapy is crucial for achieving optimal long-term outcomes. Studies have shown that early initiation and consistent adherence are associated with rapid and significant reductions in clinical events, improved quality of life, and sustained benefits. SGLT2 inhibitors are generally well tolerated, which supports better adherence and persistence in therapy. Regular monitoring and follow-up are essential to ensure adherence, manage potential side effects, and adjust treatment as needed. This helps maintain therapeutic effectiveness and improve patient outcomes [44].

Assessing prognosis in HFrEF patients receiving SGLT2 inhibitors involves various tools and methods. Echocardiography is indispensable for evaluating LVEF, ventricular dimensions, and diastolic function. It provides detailed information on cardiac structure and function, essential for monitoring disease progression and treatment response. Cardiac magnetic resonance imaging (MRI) offers precise assessments of myocardial fibrosis, structural abnormalities, and ventricular volumes, providing valuable insights into the severity and progression of heart failure. Clinical scoring systems, integrating multiple clinical parameters, are useful for predicting patient outcomes and guiding treatment decisions [45].

Long-term outcomes in HFrEF patients treated with SGLT2 inhibitors have been extensively studied. Clinical trials demonstrated significant reductions in cardiovascular mortality and heart failure hospitalizations. These benefits translate into improved survival rates and quality of life measures. Patients treated with SGLT2 inhibitors report fewer symptoms, enhanced daily functioning, and overall well-being. These improvements are sustained over long-term follow-up, underscoring the importance of these inhibitors in the comprehensive management of HFrEF [45].

Patient-reported outcomes are crucial in evaluating the effectiveness of SGLT2 inhibitors. Improvements in symptoms such as dyspnea and fatigue lead to better physical comfort and functional capacity. Enhanced exercise tolerance and reduced fluid retention contribute to an improved quality of life. Studies have shown significant improvements in health-related quality of life scores, reflecting the positive impact of SGLT2 inhibitors on patient well-being [42].

Personalized medicine approaches, including tailored treatment plans based on genetic, biomarker, and clinical profiles, can further improve prognosis in HFrEF patients treated with SGLT2 inhibitors. By considering individual genetic variations, clinicians can optimize drug dosing and monitor therapy more effectively. Biomarker analysis helps in fine-tuning treatment plans and monitoring response to therapy. Integrating these personalized approaches ensures that each patient receives the most appropriate and effective treatment, enhancing clinical outcomes and quality of life [45].

In conclusion, the prognosis of HFrEF patients treated with SGLT2 inhibitors is influenced by a combination of clinical, biomarker, and adherence factors. Advances in diagnostic tools and personalized medicine are enhancing the ability to predict and improve long-term outcomes, underscoring the importance of comprehensive and individualized management in this patient population.

Management and Treatment

The management and treatment of HFrEF require a multifaceted approach that integrates standard pharmacological therapies, innovative treatments such as SGLT2 inhibitors, and comprehensive patient care strategies. This approach aims to optimize cardiac function, reduce cardiovascular mortality, and enhance the quality of life for patients [46].

Standard heart failure medications, including angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and diuretics, are foundational in managing HFrEF. ACE inhibitors reduce blood pressure and cardiac workload through vasodilation, which helps prevent heart failure progression and improves survival. Beta-blockers decrease heart rate and myocardial oxygen demand, contributing to enhanced survival and reversal of cardiac remodeling. Diuretics alleviate symptoms like edema and dyspnea by reducing fluid overload, thereby

Table 6. SGLT2 Inhibitors in Managing HFrEF Complications

Complication	SGLT2 inhibitors' benefits
Heart failure symptoms	Alleviate dyspnea, fatigue, fluid retention
Atrial fibrillation	Reduce incidence and severity
Sudden cardiac death	Stabilize cardiac electrophysiology, prevent arrhythmias
Conduction system disease	Improve conduction abnormalities

SGLT2: sodium-glucose cotransporter 2; HFrEF: heart failure with reduced ejection fraction.

improving quality of life and preventing hospitalizations due to fluid retention [46].

SGLT2 inhibitors have emerged as a transformative addition to the standard treatment regimen for HFrEF. These inhibitors work through mechanisms such as osmotic diuresis, which reduces plasma volume and blood pressure, alleviating cardiac workload. They also improve endothelial function and reduce arterial stiffness, providing significant renal protection, which is crucial given the high prevalence of kidney dysfunction in heart failure patients [46].

Integrating SGLT2 inhibitors with other heart failure medications creates a synergistic effect that further reduces cardiac workload and enhances myocardial efficiency. This multifaceted approach addresses both the symptoms and underlying pathophysiology of heart failure, leading to better survival rates, fewer hospitalizations, and improved quality of life for HFrEF patients. For instance, the osmotic diuresis effect of SGLT2 inhibitors complements the fluid-reducing effects of diuretics, while their blood pressure-lowering properties enhance the benefits of ACE inhibitors and beta-blockers [47].

Lifestyle modifications, including diet and exercise, are essential adjunctive measures in managing HFrEF. A heart-healthy diet low in sodium and rich in fruits, vegetables, whole grains, and lean proteins helps manage fluid retention and hypertension, which are key contributors to heart failure exacerbations. Regular exercise improves cardiovascular fitness, enhances heart function, and supports weight management, all of which are vital in mitigating the progression of heart failure and improving overall quality of life. These lifestyle changes synergize with pharmacotherapy by optimizing cardiovascular health, reducing insulin resistance, and supporting the beneficial effects of medications like SGLT2 inhibitors [47].

Regular monitoring of HFrEF progression is crucial for effective management. This involves periodic echocardiography to assess LVEF and detect changes in cardiac structure and function. Biomarker monitoring, particularly BNP and NT-proBNP levels, is also essential, as these biomarkers reflect cardiac stress and correlate with heart failure severity. SGLT2 inhibitors have been shown to reduce NT-proBNP levels, indicating decreased cardiac stress and improved outcomes. Regular monitoring ensures that therapeutic adjustments can be made promptly to optimize treatment efficacy [47].

Routine clinical evaluations should include comprehensive assessments of heart failure symptoms, such as dyspnea, fatigue, and fluid retention, to gauge the effectiveness of SGLT2 inhibitors. These evaluations help ensure that patients are receiving the expected benefits, such as reduced cardiovascular mortality and hospitalizations. Early initiation and consistent use of SGLT2 inhibitors are associated with rapid and significant clinical improvements, making regular follow-up essential to maintain therapeutic effectiveness [48].

For patients with end-stage HFrEF, advanced treatment options such as heart transplantation may be necessary. However, ongoing research and clinical trials are exploring the potential of SGLT2 inhibitors even in advanced stages of heart failure [48].

Patient education about the importance of adherence to treatment plans is critical to achieving optimal outcomes. Patients should be informed about the benefits of SGLT2 inhibitors, including improved renal function and reduced risk of heart failure. Healthcare professionals should emphasize the safety and efficacy of SGLT2 inhibitors and address any concerns about side effects or cost to improve patient adherence and persistence [49].

A collaborative, multidisciplinary approach is essential for the comprehensive care of patients with HFrEF, especially when incorporating SGLT2 inhibitors into their treatment plans. Cardiologists, dietitians and physical therapists should work together to evaluate the suitability of SGLT2 inhibitors. This integrated approach ensures that patients receive comprehensive and coordinated care, optimizing the benefits of SGLT2 inhibitors and improving overall patient outcomes [49].

In summary, the management and treatment of HFrEF involve a combination of standard pharmacological therapies, innovative treatments like SGLT2 inhibitors, lifestyle modifications, regular monitoring, and a collaborative care approach. This comprehensive strategy aims to optimize cardiac function, reduce cardiovascular mortality, and enhance the quality of life for patients with HFrEF.

Complications

SGLT2 inhibitors have demonstrated significant efficacy in addressing complications associated with HFrEF. Their multifaceted mechanisms of action contribute to the alleviation of heart failure symptoms, reduction of cardiovascular mortality, and improvement of overall cardiac health, making them an essential component in the management of HFrEF (Table 6) [50].

Heart failure is characterized by the heart's inability to pump blood efficiently, leading to symptoms such as dyspnea, fatigue, and fluid retention. SGLT2 inhibitors help alleviate these symptoms and improve cardiac function by reducing left ventricular volume, which decreases the cardiac workload.

The osmotic diuresis effect of SGLT2 inhibitors promotes the excretion of excess fluid, thereby lowering plasma volume and blood pressure. This reduction in preload and afterload enhances overall cardiac performance and reduces the incidence of heart failure exacerbations. Additionally, SGLT2 inhibitors improve endothelial function and reduce arterial stiffness, contributing to better vascular health and improved myocardial energetics [50].

AF is a common complication in HFrEF, affecting approximately 30-50% of patients. AF exacerbates heart failure by increasing the risk of stroke, worsening heart failure symptoms, and contributing to overall morbidity and mortality. SGLT2 inhibitors have been found to significantly reduce the incidence and severity of AF episodes in HFrEF patients. The reduction in AF incidence ranges from 18% to 37% and is consistent across various patient demographics, including different ages, genders, body mass indices, and renal functions. The exact mechanisms by which SGLT2 inhibitors reduce AF incidence are not fully understood but likely involve improvements in cardiac function, reduction in cardiac fibrosis, and anti-inflammatory effects. By mitigating AF, SGLT2 inhibitors help reduce the risk of stroke and other cardiovascular events, leading to improved patient outcomes and reduced cardiovascular mortality [51].

Sudden cardiac death (SCD) is a major concern in HFrEF patients, particularly those with comorbid conditions such as diabetes and chronic kidney disease (CKD). SCD is often precipitated by fatal arrhythmias such as VT or fibrillation. SGLT2 inhibitors have shown potential in reducing the risk of SCD by stabilizing cardiac electrophysiology and preventing these fatal arrhythmias. These inhibitors significantly reduce the risk of hospitalization for heart failure and cardiovascular death, both in patients with and without diabetes. The combination of SGLT2 inhibitors with other heart failure therapies, such as ARNI, further enhances their protective effects. The potential antiarrhythmic effects of SGLT2 inhibitors may be attributed to their ability to improve myocardial energetics, reduce cardiac fibrosis, and decrease inflammation. Additionally, the renal protective effects of SGLT2 inhibitors contribute to better overall cardiovascular health, indirectly reducing the incidence of SCD [51].

Conduction system disease, including bundle branch blocks and atrioventricular blocks, is another complication in HFrEF that can lead to poor cardiac performance and increased mortality. SGLT2 inhibitors have shown promise in improving conduction abnormalities by enhancing overall cardiac function and reducing the burden on the heart. By improving myocardial energetics and reducing fibrosis, SGLT2 inhibitors help maintain a more stable cardiac conduction system. This stabilization of the cardiac conduction system is crucial for preventing arrhythmias and maintaining efficient cardiac output. The early and upfront administration of SGLT2 inhibitors in newly diagnosed HFrEF patients or those hospitalized with heart failure has shown rapid and significant improvements in clinical outcomes, highlighting their importance in managing conduction system diseases [52].

In conclusion, SGLT2 inhibitors play a crucial role in managing the complications of HFrEF by improving heart failure symptoms, reducing the incidence and severity of AF, preventing sudden cardiac death, and stabilizing conduction system abnormalities. Their multifaceted benefits extend beyond glycemic control, encompassing diuresis, natriuresis, reduction in preload and afterload, and improved myocardial energetics. These effects contribute to reduced cardiovascular mortality and enhanced overall cardiac health, making SGLT2 inhibitors an indispensable part of the comprehensive management strategy for HFrEF.

Differential Diagnosis

The differential diagnosis of HFrEF is essential for determining the appropriate treatment and management strategies. Accurate differentiation from other cardiovascular conditions such as HFpEF, hypertrophic cardiomyopathy (HCM), and constrictive pericarditis is crucial, particularly in the context of using SGLT2 inhibitors, which have shown significant benefits in reducing cardiovascular mortality in HFrEF patients [53].

HFpEF presents with symptoms such as dyspnea on exertion, fatigue, exercise intolerance, and fluid retention. These symptoms overlap with those of HFrEF, making clinical differentiation challenging. However, the pathophysiological mechanisms differ significantly. HFpEF is characterized by impaired ventricular relaxation and increased left ventricular stiffness, leading to elevated filling pressures during physical activity despite a normal ejection fraction. In contrast, HFrEF involves reduced left ventricular contractility and systolic dysfunction, resulting in a decreased ejection fraction typically below 40%. Biomarker levels, particularly NT-proBNP, play a crucial role in differentiation. NT-proBNP levels tend to be lower in HFpEF compared to HFrEF due to the preserved systolic function. Echocardiographic features that help differentiate HFpEF from HFrEF include preserved ejection fraction and evidence of diastolic dysfunction, such as a high E/e' ratio and increased left atrial volume. SGLT2 inhibitors have primarily demonstrated efficacy in HFrEF by improving cardiac function, reducing fluid overload, and providing renal protection. While their impact on HFpEF is still under investigation, preliminary research suggests potential benefits in alleviating symptoms and improving outcomes in HFpEF patients [53].

HCM must also be differentiated from HFrEF. HCM is characterized by asymmetric septal hypertrophy, which can lead to dynamic left ventricular outflow tract (LVOT) obstruction. This condition presents with symptoms such as chest pain, syncope, and a family history of sudden cardiac death, which are less common in HFrEF. Echocardiographic features of HCM include asymmetric septal hypertrophy, preserved or hyperdynamic systolic function, and potential LVOT obstruction. These findings are distinct from HFrEF, which shows global or segmental left ventricular dilation and reduced ejection fraction. Genetic testing can further aid in differentiation, as HCM is often associated with mutations in sarcomeric proteins like *MYH7* and *MYBPC3*, whereas HFrEF is linked to a broader range of genetic and non-genetic factors. SGLT2 inhibitors have shown significant benefits in HFrEF by reducing cardiovascular mortality and hospitalizations, but their role in

HCM management remains investigational [54].

Constrictive pericarditis is another condition that can mimic HFrEF. It presents with symptoms such as chronic edema, ascites, and a pericardial murmur indicating impaired ventricular filling due to a rigid pericardium. Imaging findings such as a thickened, calcified pericardium on computed tomography (CT) or MRI and hemodynamic patterns showing ventricular interdependence and discordant ventricular filling are characteristic of constrictive pericarditis. These features differ from HFrEF, in which systolic dysfunction and ventricular dilatation are the primary concerns. Hemodynamic studies in constrictive pericarditis typically show equalization of diastolic pressures in all four ventricles and a rapid decrease in jugular venous pressure, which are not observed in HFrEF, and their role in the management of constrictive pericarditis is not established and requires further research [54, 55].

In conclusion, the differential diagnosis of HFrEF requires careful evaluation of clinical presentation, biomarker levels, echocardiographic findings, and genetic markers to distinguish it from HFpEF, HCM, and constrictive pericarditis. SGLT2 inhibitors have proven effective in reducing cardiovascular mortality in HFrEF by improving cardiac function and reducing fluid overload. Accurate differentiation of these conditions is essential to tailor appropriate treatments and optimize patient outcomes.

Gaps in the Literature

The existing literature on SGLT2 inhibitors in the treatment of HFrEF highlights several significant gaps that need to be addressed to optimize the clinical use of these drugs and enhance patient outcomes. Despite the promising results of clinical trials showing significant reductions in cardiovascular mortality and hospitalization for heart failure, there remain critical areas where further research is essential [56].

One major gap is the lack of comprehensive long-term data on the effects of SGLT2 inhibitors. The current trials have relatively short follow-up periods, typically around 2 years, which are insufficient to fully understand the long-term impact of these drugs on cardiovascular mortality and overall health outcomes. Longer follow-up studies are necessary to assess the sustainability of the benefits observed in short-term trials, potential late-onset adverse effects, and the optimal duration of therapy. These studies will provide crucial insights into how SGLT2 inhibitors perform over extended periods and their long-term safety profile [57].

There is also a need for more research on early diagnostic indicators that predict the efficacy of SGLT2 inhibitors in HFrEF. Identifying biomarkers, imaging techniques, or other clinical parameters that can forecast which patients will benefit most from these inhibitors could significantly enhance personalized treatment approaches. Early identification of responders would allow for more targeted therapy, potentially improving patient outcomes and reducing healthcare costs [57].

The precise mechanisms by which SGLT2 inhibitors exert their cardioprotective effects in HFrEF remain incompletely understood. While several hypotheses have been proposed, including modulation of cardiovascular risk profiles, reduction of inflammation, improvement in myocardial energetics, and renal protection, further research is needed to clarify these mechanisms. Understanding the exact pathways through which SGLT2 inhibitors confer cardiovascular benefits will help refine treatment strategies and may lead to the development of more effective drugs [58].

Another critical area that requires more research is the impact of SGLT2 inhibitors on different patient subgroups. Existing studies have generally focused on broad populations, but there is a need to investigate how these drugs affect patients with varying comorbid conditions such as diabetes, CKD, obesity, and hypertension. Additionally, genetic studies are necessary to explore the role of genetic variability in response to SGLT2 inhibitors. Pharmacogenomic studies could identify genetic markers that predict better or worse responses to these medications, enabling more personalized treatment approaches. Large-scale, multi-ethnic cohort studies and RCTs focusing on diverse genetic backgrounds will provide insights into how genetic differences affect drug efficacy and safety [58].

The small sample sizes in many existing studies limit the generalizability of findings. Larger sample sizes are required to ensure that the results are robust and applicable to a broader patient population. This is particularly important for detecting smaller but clinically significant differences in outcomes and for confirming the benefits observed in smaller trials [59].

The lack of diversity in study populations is another major limitation that hampers the generalizability of results across different ethnic and demographic groups. Most trials have predominantly included White participants from North America and Europe, which may not reflect the broader global population. Future studies should aim to include a wider range of participants to ensure that findings are applicable to all patient populations. This is crucial for addressing health disparities and ensuring that all patients have access to effective treatments [59].

Short follow-up periods in current studies pose another limitation, as they do not capture long-term outcomes. Extending the follow-up duration in future research will provide a more comprehensive understanding of the sustained impact of SGLT2 inhibitors on cardiovascular mortality and other long-term health outcomes in HFrEF patients [60].

More RCTs with larger, more diverse cohorts are essential to strengthen the evidence base. These trials should aim to include a wide range of demographic and clinical characteristics to enhance the applicability of their findings. Furthermore, adopting standardized outcome measures in future studies will improve the comparability and reliability of results, facilitating more accurate assessments of the benefits of SGLT2 inhibitors [60].

Finally, specific methodological improvements are needed to address current research limitations. These include longer follow-up durations, larger sample sizes, and the inclusion of diverse populations. Such enhancements will provide a more complete picture of the efficacy and safety of SGLT2 inhibitors, guiding clinical practice and optimizing patient care in HFrEF. Addressing these gaps will not only improve our understanding of SGLT2 inhibitors but also lead to better patient outcomes and more effective management of HFrEF.

Future Directions

Future directions for SGLT2 inhibitor research in reducing cardiovascular mortality in HFrEF are critical to refining treatment protocols and improving patient outcomes. The identification and validation of potential biomarkers for early diagnosis of HFrEF and prediction of response to SGLT2 inhibitor therapy is an area that requires significant focus. Biomarkers such as atrial natriuretic peptide, BNP, NT-proBNP, high-sensitivity troponin, sST2, galectin-3, fibronectin 1, IL-6, matrix metalloproteinase 7, and TNF-1 have been studied; however, their predictive value specifically in the context of SGLT2 inhibitor therapy remains underexplored [61]. The exploration of novel therapeutic strategies using SGLT2 inhibitors for the targeted treatment of HFrEF, with a focus on personalized medicine approaches, is another important area. Personalized treatment plans based on genetic, biomarker and clinical profiles may optimize the use of SGLT2 inhibitors, potentially improving patient outcomes and reducing cardiovascular mortality. Early identification of patients likely to benefit from these inhibitors may lead to more personalized treatment strategies, thereby optimizing clinical outcomes and quality of life [62].

Further research is essential to elucidate the precise mechanisms by which SGLT2 inhibitors confer cardiovascular benefits in HFrEF. While current evidence suggests several pathways, including osmotic diuresis, natriuresis, improved myocardial energetics, and reduced inflammation and fibrosis, the relative contribution and interplay of these mechanisms are not fully understood. Detailed mechanistic studies should explore how SGLT2 inhibitors improve myocardial function at the cellular and molecular levels, such as their impact on mitochondrial efficiency, ketone body utilization, and modulation of metabolic pathways. Additionally, investigating their anti-inflammatory and antifibrotic effects through advanced imaging techniques and biomarker analysis can provide deeper insights into their cardioprotective properties. This research can enhance understanding by identifying specific patient subgroups that may benefit the most from SGLT2 inhibitors, optimizing treatment protocols to reduce cardiovascular mortality [62].

Long-term studies are crucial to assess the sustained efficacy and safety of SGLT2 inhibitors in HFrEF patients. While short-term studies have shown significant benefits, the long-term impact on survival, quality of life, and disease progression remains unclear. Extended follow-up periods can reveal whether the initial benefits are maintained over time and help identify any delayed adverse effects. These studies can provide critical insights into optimizing treatment protocols to reduce cardiovascular mortality by identifying patient subgroups that benefit most from sustained therapy, determining the optimal duration of treatment, and understanding the interplay between SGLT2 inhibitors and other heart failure therapies over time [63].

Investigating the impact of SGLT2 inhibitors on common comorbid conditions in HFrEF patients, such as diabetes and CKD, is essential for developing comprehensive treatment strategies. These inhibitors have shown benefits in reducing cardiovascular events, improving renal outcomes, and providing metabolic benefits. Understanding how SGLT2 inhibitors interact with standard heart failure treatments and addressing comorbidities will help tailor treatment plans to optimize patient outcomes [63]. Patient subgroup analysis is also crucial to understand the differential effects of SGLT2 inhibitors across various populations defined by age, sex, ethnicity, and comorbidity profiles. Research should focus on how these drugs affect different subgroups to ensure that the benefits are maximized for all patients. Studies with larger and more diverse cohorts are necessary to confirm these findings and improve the generalizability of the results [64].

Focusing on patient-reported outcomes and quality of life measures in research is vital. While SGLT2 inhibitors have shown significant benefits in reducing cardiovascular mortality and hospitalizations, their impact on patient well-being and daily functioning needs further exploration. Assessing improvements in health-related quality of life will provide a more comprehensive understanding of the benefits of these inhibitors and inform patient-centered care strategies [64].

Evaluating the cost-effectiveness of SGLT2 inhibitors in treating HFrEF is necessary to inform healthcare decision-making and policy formulation. Understanding the economic value of these treatments will help in resource allocation and ensure that the benefits of SGLT2 inhibitors are accessible to a broader patient population. Research on cost-effectiveness should encompass both direct medical costs and broader economic impacts, such as productivity loss and long-term healthcare savings from reduced hospitalizations and improved patient outcomes [65].

Finally, public health policies should be updated to improve the prevention and management of HFrEF, including guidelines for the use of SGLT2 inhibitors based on the latest evidence. Education and training initiatives for healthcare providers are essential to ensure that they are well informed about the benefits and appropriate use of these inhibitors. This will ensure optimal patient care, reduce cardiovascular mortality, and improve overall heart failure management. Comprehensive and well-informed guidelines will support the integration of SGLT2 inhibitors into standard treatment protocols, maximizing their potential to benefit a wide range of patients.

Conclusions

The utilization of SGLT2 inhibitors marks a significant advancement in the treatment of HFrEF. These agents, beyond their original role in managing type 2 diabetes, have demonstrated robust cardiovascular benefits, including reductions in both cardiovascular mortality and hospitalizations. The multifaceted mechanisms by which SGLT2 inhibitors exert their effects - encompassing osmotic diuresis, natriuresis, and improvements in myocardial energetics - translate into enhanced cardiac function and attenuation of deleterious neurohormonal activities, inflammation, and fibrosis. This review underscores the consistent efficacy of SGLT2 inhibitors across diverse demographic and clinical subgroups, which supports their broad applicability in clinical practice. However, the existing literature also highlights gaps that need addressing, such as the need

for comprehensive long-term data, precise early diagnostic indicators, and a deeper understanding of the underlying mechanisms of action. Future research should prioritize these areas, along with exploring the cost-effectiveness and personalized medicine approaches to optimize treatment protocols. Integrating SGLT2 inhibitors into standard HFrEF management guidelines, supported by enhanced policy frameworks and educational initiatives for healthcare providers, will be crucial in maximizing their therapeutic potential and improving patient outcomes.

Learning Points

SGLT2 inhibitors reduce cardiovascular mortality and heart failure hospitalizations in HFrEF patients by improving myocardial energetics and reducing neurohormonal activation, inflammation, and fibrosis.

Clinical trials like DAPA-HF and EMPEROR-Reduced show SGLT2 inhibitors' efficacy across diverse demographic and clinical subgroups, highlighting their broad clinical applicability.

Integrating SGLT2 inhibitors into standard HFrEF management improves patient-reported outcomes, such as quality of life and daily functioning, with better scores on health-related questionnaires.

SGLT2 inhibitors provide benefits like osmotic diuresis, natriuresis, and enhanced endothelial function, improving cardiac function and reducing cardiac workload.

Despite proven benefits, gaps remain in understanding long-term outcomes, early diagnostic indicators, and personalized treatment approaches, necessitating further research to optimize SGLT2 inhibitor use in HFrEF management.

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Conflict of Interest

The authors declare no conflict of interest to ensure the impartiality of the review.

Author Contributions

Almendra Lopez-Usina (medical student): data curation, formal analysis, writing - original draft, writing - review and editing. Camila Mantilla-Cisneros (medical student): conceptualization, writing - original draft, writing - review and editing, methodology. Jordan Llerena-Velastegui (MD): supervision, conceptualization, data curation, writing - review and editing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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