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Review

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Impact of Sodium-Glucose Cotransporter 2 Inhibitors on Cardiovascular and Renal Outcomes in Heart Failure Patients With Type 2 Diabetes: A Literature Review

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Abstract

The management of heart failure (HF) in patients with type 2 diabetes has significantly evolved with the introduction of sodium-glucose cotransporter 2 (SGLT2) inhibitors. This article aims to consolidate existing knowledge on the efficacy of these inhibitors in managing HF in this patient population. Major medical databases, including PubMed, Scopus, and Web of Science, were reviewed, prioritizing research from the last decade. The results of this review highlight the mechanisms of action of SGLT2 inhibitors, their clinical benefits, challenges in patient management, and outcomes associated with their use. These medications were found to not only improve glycemic control but also offer significant cardiovascular and renal benefits, reducing cardiovascular mortality and major adverse cardiovascular events. However, challenges and knowledge gaps persist, particularly regarding long-term effects and safety in diverse populations. The conclusions of this review underscore the importance of updating clinical guidelines to incorporate these findings and propose the need for future research to address existing gaps and optimize the use of SGLT2 inhibitors in clinical practice.

Keywords: Heart failure; Type 2 diabetes; SGLT2 inhibitors; Cardiovascular benefits; Long-term effects

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Introduction

This article focuses on the growing importance of sodium-glucose cotransporter 2 (SGLT2) inhibitors in cardiology and endocrinology, highlighting their impact on managing heart failure (HF) in patients with type 2 diabetes (T2D). Appropriate diagnosis of HF is crucial for effective management and treatment. Accurate diagnosis ensures that patients receive the most suitable therapies, which can significantly improve outcomes and quality of life. Misdiagnosis or delayed diagnosis can lead to inappropriate treatments, worsening of symptoms, and increased morbidity and mortality. Thus, emphasizing the importance of precise diagnostic strategies and tools is essential in the context of managing HF [1]. In recent years, SGLT2 inhibitors have gained significant recognition in both medical disciplines due to their beneficial effects on HF, particularly in patients with T2D. These drugs have demonstrated a substantial reduction in hospitalizations for HF and cardiovascular mortality, regardless of the patient's diabetic status. Importantly, the benefits of SGLT2 inhibitors extend to HF patients irrespective of their glycemic status. This new class of agents has shown significant improvements in cardiovascular outcomes and reductions in hospitalizations for HF in both diabetic and non-diabetic patients. This broader applicability underscores the critical role of SGLT2 inhibitors in the comprehensive management of HF [2]. Furthermore, the combination of SGLT2 inhibitors with glucagon-like peptide-1 receptor agonists (GLP-1RAs) has shown additional improvements in preventing major adverse cardiac and cerebrovascular events (MACCEs) and HF events (Table 1).

SGLT2 inhibitors, also known as gliflozins, are a class of medications originally designed for the management of T2D. These medications include empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin, each of which has specific characteristics and advantages. They work by blocking the reabsorption of glucose in the proximal convoluted tubule of the kidney, leading to increased glucose excretion in the urine (glucosuria) and improved glycemic control. SGLT2 inhibitors also induce natriuresis and osmotic diuresis, reducing plasma volume and decreasing preload and afterload on the heart. They improve

Table 1. Summary of Major Clinical Trials on SGLT2 Inhibitors

Study	Population	Key findings	Relevance to HF management in T2D
EMPA-REG OUTCOME	T2D patients with high cardiovascular risk	Reduced cardiovascular death by 38%, reduced hospitalization for heart failure by 35%	Demonstrates significant cardiovascular benefits of empagliflozin in high-risk patients
CANVAS	T2D patients with high cardiovascular risk	Reduced hospitalization for heart failure by 33%, improved renal outcomes	Highlights the dual cardiovascular and renal benefits of canagliflozin
DECLARE-TIMI 58	T2D patients with or at risk for ASCVD	Reduced cardiovascular death or hospitalization for heart failure by 17%, significant renal benefits	Shows dapagliflozin's effectiveness in a broader T2D population
DAPA-HF	HFrEF patients, with and without T2D	Reduced risk of worsening HF or CV death by 26%	Indicates dapagliflozin's benefits in heart failure irrespective of diabetic status
CREDENCE	T2D patients with chronic kidney disease	Reduced risk of renal failure by 34%, reduced risk of CV death, MI, or stroke by 20%	Emphasizes canagliflozin's role in protecting against renal and cardiovascular outcomes
VERTIS CV	T2D patients with established cardiovascular disease	Non-inferior to placebo for primary CV outcomes, improved glycemic control	Supports ertugliflozin's cardiovascular safety and efficacy in glucose management

ASCVD: atherosclerotic cardiovascular disease; CV: cardiovascular; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; MI: myocardial infarction; SGLT2: sodium-glucose cotransporter 2; T2D: type 2 diabetes.

cardiac energy metabolism and reduce adipose tissue-mediated inflammation and oxidative stress, collectively contributing to improved cardiac function (Table 2) [2]. Empagliflozin has been shown to significantly reduce cardiovascular death and hospitalization for HF. Canagliflozin also reduces cardiovascular events and offers additional renal benefits. Dapagliflozin is noted for reducing hospitalizations for HF and improving overall heart function, with studies showing an average increase in left ventricular ejection fraction (LVEF) from 30% to 35%. Ertugliflozin has demonstrated similar benefits in glycemic control and cardiovascular protection. To incorporate SGLT2 inhibitors into HF management, clinicians should evaluate patients regardless of diabetic status, assess renal function before initiation, start with the recommended dose, monitor for efficacy and side effects, and educate patients about potential benefits and risks [3].

SGLT2 inhibitors provide benefits beyond glycemic control, including significant cardiovascular effects. These drugs reduce natriuresis, plasma volume, vascular resistance, adipose-mediated inflammation, and improve cardiac energy metabolism. Clinical trials have demonstrated that SGLT2 inhibitors can lead to an average weight loss of 2 - 3 kg. Additionally, the degree of diabetes control may influence the effectiveness of SGLT2 inhibitors [3]. Poor glycemic control can potentially reduce the efficacy of these medications. Studies have shown that while SGLT2 inhibitors are effective in improving glycemic control, their cardiovascular and renal benefits might be less pronounced in patients with persistently high blood glucose levels. This is because chronic hyperglycemia can lead to more severe cardiovascular and renal complications, which may require more intensive management strategies. Therefore, achieving and maintaining optimal glycemic control is crucial for maximizing the therapeutic benefits of SGLT2 inhibitors in patients with T2D. For instance, SGLT2 inhibitors have been shown to reduce the risk of hospitalization for HF by 35% and cardiovascular mortality by 38% in clinical trials [4].

The global impact of HF in patients with T2D is considerable. The prevalence of HF in this population ranges from 22% to 37%, with a lifetime risk of approximately 24% for women and 27% for men. Additionally, older patients and individuals of non-white ethnicities present a higher risk of developing HF [4]. These factors underscore the need for specific preventive and management strategies for these demographic groups (Table 3). Moreover, the patient outcomes associated with the use of SGLT2 inhibitors include reduced mortality and hospitalizations, as well as an overall improvement in quality of life (Table 4). HF in patients with T2D not only affects morbidity and mortality but also imposes a significant socioeconomic burden. Socioeconomic factors, such as income level and education, can influence access to and adherence to SGLT2 inhibitor treatments, thereby affecting clinical outcomes. Addressing

Table 2. Mechanisms of Action of SGLT2 Inhibitors

Mechanism	Description
Glucosuria	Increased glucose excretion in urine, leading to improved glycemic control
Natriuresis	Increased sodium excretion, leading to reduced plasma volume and blood pressure
Anti-inflammatory	Reduction in adipose tissue-mediated inflammation and oxidative stress
Cardiovascular benefits	Improved cardiac energy metabolism, reduced vascular resistance

SGLT2: sodium-glucose cotransporter 2.

Table 3. Clinical Benefits of SGLT2 Inhibitors

Benefit	Description
Glycemic control	Improved HbA1c levels
Cardiovascular	Reduced cardiovascular mortality and major adverse cardiovascular events
Renal	Improved renal outcomes, reduced albuminuria and glomerular hyperfiltration

HbA1c: hemoglobin A1c; SGLT2: sodium-glucose cotransporter 2.

these disparities is crucial to improving healthcare equity and ensuring that the benefits of these medications are available to all patients [5].

Recently, several clinical trials have highlighted the positive effects of SGLT2 inhibitors in managing HF. These studies have demonstrated reductions in all-cause mortality and major adverse cardiovascular events. Additionally, SGLT2 inhibitors have shown antiarrhythmic properties and renal benefits, further reinforcing their role in the comprehensive management of HF. However, despite these advancements, there are variabilities in clinical outcomes and discrepancies in the availability of treatment options [5]. These gaps highlight the need for additional research to optimize the use of SGLT2 inhibitors and better understand their long-term effects, especially in diverse populations.

The objective of this review is to provide a comprehensive evaluation of the efficacy, management, and outcomes of SGLT2 inhibitors in patients with HF and T2D. Future research directions will be addressed to close the existing gaps in the literature and establish more effective and personalized treatment strategies for this patient population.

Methodology

In our methodology, we ensured the reliability and authenticity of the findings by implementing a rigorous selection and evaluation process for the literature reviewed. Given that this is a literature review, our approach focused on identifying and synthesizing relevant studies to provide a comprehensive overview of the current state of knowledge regarding the efficacy of SGLT2 inhibitors in managing HF in patients with T2D.

We used reputable and widely recognized medical databases such as PubMed, Scopus, and Web of Science to source our literature. These databases are known for their extensive and high-quality collections of peer-reviewed journals. This ensured that the studies included in our review were of high scientific quality and credibility.

To ensure the relevance and currency of the findings, we established strict inclusion and exclusion criteria. Studies included in our review had to be published within the last decade. This timeframe was chosen to capture the most recent advancements and insights into the use of SGLT2 inhibitors. Additionally, all selected studies were required to be peer-reviewed, guaranteeing that the research had undergone rigorous evaluation by experts in the field.

We focused on literature that specifically examined the effects of SGLT2 inhibitors on HF management in patients with T2D. This included studies that investigated various aspects such as cardiovascular outcomes, hospitalization rates, mortality, and potential mechanisms of action. By narrowing our focus to these specific criteria, we aimed to provide a detailed and targeted analysis of the most relevant findings.

To further ensure the robustness of our review, we considered studies from various geographic locations. This approach allowed us to analyze and compare results across different populations, enhancing the generalizability of our findings. By including a diverse range of studies, we were able to capture a broad spectrum of clinical experiences and outcomes, which adds to the reliability of our conclusions.

To further strengthen our review, we attempted to base our findings on the best available literature, focusing on high-quality clinical trials to ensure that our conclusions are well-supported by clinical research. By using high-quality databases, applying strict inclusion criteria, and considering regional diversity, we ensured that our review provides a comprehensive and reliable synthesis of the current evidence on the efficacy of SGLT2 inhibitors in managing HF in patients with T2D.

In summary, our methodology for this literature review involved a meticulous and systematic approach to selecting and evaluating studies. By using high-quality databases, applying strict inclusion criteria, and considering regional diversity, we ensured that our review provides a comprehensive and reliable synthesis of the current evidence on the efficacy of SGLT2 inhibitors in managing HF in patients with T2D.

Epidemiology

Understanding the global prevalence and incidence of HF in

Table 4. Patient Outcomes Associated With SGLT2 Inhibitors

Outcome	Description
Mortality	Reduced all-cause and cardiovascular mortality
Hospitalizations	Reduced hospitalizations for heart failure
Adverse events	Increased risk of genital infections, diabetic ketoacidosis

SGLT2: sodium-glucose cotransporter 2.

patients with T2D, as well as regional differences, is critical to developing targeted healthcare strategies. The prevalence of HF in patients with T2D is particularly high, with estimates ranging from 12.4% to 22%. The lifetime risk of developing HF in individuals with T2D is approximately 24% for women and 27% for men. In Brazil, the prevalence of HF among patients with T2D is reported to be 12.4%, whereas in Ethiopia it is approximately 6.83%. In Gulf countries, the prevalence of diabetes, a major risk factor for HF, is around 60%, indicating a potentially higher burden of HF in these regions [6].

Diabetes significantly increases the risk of HF and other cardiovascular events, with patients experiencing a two- to four-fold increased risk of cardiovascular disease (CVD). The combination of diabetes and HF severely impacts prognosis, leading to higher risks of cardiovascular death, myocardial infarction, and stroke. Notably, despite a general increase in the prevalence of diabetes and HF worldwide, HF incidence rates have declined in high-income countries due to advancements in management and treatment strategies [7].

Additionally, it is important to highlight that the relationship between HF and T2D is influenced by various factors including age, sex, and ethnicity. For example, older patients and individuals of non-white ethnicities present a higher risk of developing HF. Socioeconomic factors, such as income level and education, also play a role in access to and adherence to HF treatments, further impacting clinical outcomes. Addressing these disparities is crucial to improving healthcare equity and ensuring that the benefits of these medications are available to all patients [8].

Genetic mutations play a crucial role in the development of HF in individuals with T2D. Polygenic risk scores (PRS) and specific single nucleotide polymorphisms (SNPs) are associated with an increased risk of T2D-related cardiovascular outcomes, including HF. Variants in the potassium ATP-sensitive channel (KATP) gene are linked to higher risks of HF and other cardiovascular conditions in patients with T2D. A novel locus on chromosome 7q21, associated with the HIBADH gene, has been identified as a specific risk factor for HF in T2D, related to valine metabolism dysfunction. The rs3918242 variant in the MMP-9 gene is associated with myocardial infarction and the progression of ventricular dysfunction, leading to HF in patients with T2D [8]. Polymorphisms in the NCF4 gene increase the risk of chronic HF in patients with T2D, implicating the NCF4 subunit of NADPH oxidase in myocardial damage. The rs10830963 variant in the MTNR1B gene is associated with a higher risk of myocardial infarction, a precursor to HF, in patients with T2D. Genetic variants associated with insulin resistance and T2D risk also influence cardiovascular risk factors, including HF, in children and adolescents with type 1 diabetes, suggesting a broader genetic predisposition [9].

Lifestyle factors such as physical inactivity and unhealthy diets significantly contribute to the risk of major cardiovascular events, including HF, in individuals with T2D. Regular physical activity and a healthy diet are associated with a lower risk of HF, regardless of genetic or metabolic risk status. Current smoking and excessive alcohol consumption are linked to a higher risk of HF in patients with T2D. A higher body mass index (BMI) and obesity are significant risk factors for the progression from prediabetes to T2D and subsequently to HF. Environmental exposures, such as air pollution, noise, and occupational hazards, along with social factors like socioeconomic status and educational level, significantly impact the development and progression of HF in patients with T2D. Metabolic abnormalities such as hypertension, high cholesterol, and poor glycemic control exacerbate the risk of HF in patients with T2D. Effective management of these metabolic risk factors can mitigate the risk of HF. Reduced exercise capacity is an early indicator of HF in patients with T2D, even in the absence of other symptoms. Early identification and intervention can improve clinical outcomes [9].

The prevalence of HF in patients with T2D varies significantly by age, sex, and ethnicity. Older patients with T2D have a higher risk of HF events compared to younger patients. Women with T2D and coronary artery disease (CAD) have a higher risk of HF compared to men. Male sex negatively affects the phenotypic expression of diabetic heart disease, with men showing greater degrees of concentric hypertrophy and reduced cardiac function compared to women [8]. The relationship between HF risk and the management of risk factors, such as low-density lipoprotein (LDL) cholesterol and systolic blood pressure (SBP), differs between men and women, with women showing a higher risk of HF despite similar management. Non-white patients with T2D have a higher risk of HF events compared to white patients. African Americans with early-onset T2D have a higher risk of cardiovascular events, including HF, compared to Caucasians, particularly in younger age groups. South Asians and Blacks with T2D are diagnosed with HF at a younger age compared to whites, with South Asians having higher rates of ischemic heart disease and diabetes, and Blacks having higher rates of hypertension and diabetes [9].

Identified risk factors for HF in T2D significantly contribute to the disease's development and progression. Gender differences in HF risk are evident, with women with T2D and CAD facing a higher risk of HF compared to men. Insulin resistance in newly diagnosed T2D patients is associated with a higher risk of HF and death, with higher HOMA2-IR values correlating with a greater likelihood of HF development. Neurohumoral and metabolic dysfunction, exacerbated by T2D, contributes to myocardial remodeling and HF progression [9]. Central obesity, measured by the waist-height ratio (WHtR), is a significant risk factor for HF hospitalization or death in patients with T2D. Low renal function and high albuminuria are strong predictors of HF in patients with T2D, with incident HF significantly increasing the risk of progression to end-stage kidney disease (ESKD). Individuals with early-onset T2D have a higher relative risk of developing HF compared to those with usual-onset T2D, driven primarily by cardiorenal risk factors rather than the duration of diabetes. A new genetic locus associated with HF in T2D patients has been identified, linking valine metabolism dysfunction to HF development. This genetic association is specific to T2D and not observed in non-diabetic populations [10].

Therefore, effective management of these risk factors is essential to prevent HF and improve outcomes in patients with T2D, highlighting the necessity for comprehensive and personalized healthcare strategies.

Pathophysiology

SGLT2 inhibitors are a class of medications primarily used for managing T2D. Recent studies have shown that these drugs also offer significant cardiovascular benefits, particularly in improving HF outcomes in patients with T2D. The biochemical and molecular mechanisms involved in the action of SGLT2 inhibitors include reducing hospitalizations for HF and cardiovascular events, highlighting their effectiveness beyond glycemic control [11].

One key mechanism is early natriuresis and subsequent reduction in plasma volume, which improves vascular function and lowers blood pressure. Additionally, these inhibitors improve metabolic indices such as body weight, BMI, and SBP, contributing to better cardiovascular outcomes. They also possess anti-inflammatory and antioxidant effects by reducing adipose tissue-mediated inflammation and oxidative stress. These drugs promote a shift towards ketone body metabolism, which is more efficient for the heart and kidneys, and enhance autophagic flux, improving cardiomyocyte function [11].

The renal protection provided by SGLT2 inhibitors, through the reduction of glomerular hyperfiltration and albuminuria, indirectly benefits HF outcomes. Moreover, these drugs are associated with a significant reduction in the risk of atrial arrhythmias and sudden cardiac death (SCD), further contributing to their cardiovascular benefits [12].

Genetic variations also influence the efficacy of SGLT2 inhibitors in patients with HF and T2D. Variations in the SLC5A2 gene, which encodes SGLT2, are associated with a lower risk of HF, mediated by factors such as hemoglobin A1c (HbA1c), HDL cholesterol, uric acid, SBP, and body composition. These inhibitors significantly reduce the risk of hospitalization for HF and cardiovascular mortality, regardless of the presence of T2D, age, sex, BMI, renal function, and type of HF [13].

Diabetes induces significant structural and functional changes in the heart, increasing the risk of atrial fibrillation (AF) and HF. These changes include adverse cardiac remodeling, with increased left ventricular end-diastolic dimension (LVEDD) and reduced LVEF. SGLT2 inhibitors mitigate these changes by reducing atrial arrhythmias, improving cardiac function, and providing metabolic benefits. They reduce oxidative stress and cardiac inflammation, improving cardiac structure and function [13].

According to recent research, SGLT2 inhibitors reduce the progression of HF in patients with T2D through multiple mechanisms, such as reducing hospitalizations for HF, lowering the risk of cardiovascular death, and providing renal protection. These benefits are also observed in non-diabetic patients, suggesting a broad cardioprotective effect beyond glycemic control [14].

The genetic and biochemical factors impacting protein expression and cardiovascular health in HF and T2D patients treated with SGLT2 inhibitors are multifaceted. The expression of SGLT1 and SGLT2 is crucial, with their upregulation linked to adverse cardiac remodeling, oxidative stress, and endothelial dysfunction. SGLT2 inhibitors mitigate these effects and reduce the risk of arrhythmias and SCD, underscoring their therapeutic potential in this patient population [15].

In conclusion, SGLT2 inhibitors improve HF outcomes in patients with T2D through multiple biochemical and molecular mechanisms, including natriuresis, plasma volume reduction, improvement in metabolic indices, anti-inflammatory and antioxidant effects, and renal protection. These drugs represent a valuable therapeutic option for managing cardiovascular complications in diabetic patients.

Clinical Manifestations

HF is a common complication in patients with T2D. SGLT2 inhibitors are a class of medications used to manage T2D and have shown significant benefits in reducing cardiovascular events, including hospitalizations for HF. In patients with T2D using SGLT2 inhibitors, both common and uncommon symptoms of HF are observed [16].

SGLT2 inhibitors have demonstrated a significant reduction in hospitalizations for HF and cardiovascular events, such as SCD and atrial arrhythmias. These benefits are attributed to mechanisms beyond glycemic control, including early natriuresis, plasma volume reduction, improved vascular function, and decreased blood pressure. Despite these benefits, uncommon symptoms such as ventricular arrhythmias do not show a significant difference with the use of SGLT2 inhibitors [16].

Regarding the main clinical syndromes associated with HF in patients with T2D using SGLT2 inhibitors, a reduction in the incidence of AF and atrial flutter, as well as arrhythmias, has been observed. Specifically, dapagliflozin reduces the incidence of these events. Additionally, the initiation of SGLT2 inhibitors is associated with a significantly lower risk of hospitalization for HF and all-cause mortality compared to dipeptidyl peptidase-4 inhibitors (DPP4i). SGLT2 inhibitors also reduce the risk of major adverse cardiovascular events, including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [17].

In patients with HF and T2D treated with SGLT2 inhibitors, typical findings from initial examinations include a reduction in hospitalizations for HF and cardiovascular death, as well as improvements in the incidence of AF and atrial flutter. A reduction in major adverse cardiovascular events and improvements in metabolic indices such as body weight, BMI, SBP, and fasting plasma glucose are also observed. Additionally, SGLT2 inhibitors are associated with a reduction in all-cause mortality and present a favorable safety profile with a lower proportion of serious adverse events compared to placebo [18].

The use of SGLT2 inhibitors in patients with HF and T2D provides significant benefits in both early and advanced symptoms of HF. In the early stages, these benefits include the reduction of plasma volume and blood pressure, helping manage initial symptoms such as mild dyspnea and fatigue. In the advanced stages, these medications reduce the risk of hospitalization, AF, and SCD, thereby improving overall cardiovascular outcomes [18].

In summary, SGLT2 inhibitors represent a valuable therapeutic option for managing the clinical manifestations of HF

in patients with T2D, providing significant improvements in symptoms, reducing mortality, and improving overall cardiovascular outcomes.

Complications

SGLT2 inhibitors are primarily used for managing T2D. However, their use has expanded due to their cardiovascular benefits, especially in patients with HF. Despite these benefits, the use of SGLT2 inhibitors is associated with certain complications that must be carefully managed in clinical practice [19].

One of the most common adverse effects is an increased risk of genital infections. SGLT2 inhibitors significantly increase the risk of genital infections in patients with T2D and HF. Additionally, there is a notable increase in the risk of diabetic ketoacidosis (DKA) among patients using these medications compared to controls. Despite these risks, SGLT2 inhibitors are generally considered safe and are associated with a reduction in the risk of serious adverse events, acute kidney injury, and cardiovascular mortality [20].

Regarding HF, SGLT2 inhibitors alleviate symptoms of both systolic and diastolic dysfunction in patients with T2D. These medications significantly reduce the risk of hospitalization for HF and cardiovascular death. They improve LVEF in patients with HF with reduced ejection fraction (HFrEF) and show benefits in diastolic function, as indicated by improvements in the E/e' ratio and reductions in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels [21]. Additionally, SGLT2 inhibitors are associated with a significant reduction in the risk of atrial arrhythmias and SCD in patients with T2D. The metabolic and hemodynamic benefits, such as weight loss, reduction in systolic and diastolic blood pressure, and better glycemic control, also contribute to improved cardiac function. The renal protection provided by these drugs, through the reduction in the risk of severe renal events, is crucial for managing HF, given the close link between renal function and cardiovascular health. Moreover, the anti-inflammatory and antioxidant effects of SGLT2 inhibitors reduce adipose tissue-mediated inflammation, oxidative stress, and serum uric acid levels, contributing to overall cardiovascular health [22].

The renal benefits of SGLT2 inhibitors for patients with HF and T2D are notable. These medications are associated with a lower incidence of significant renal function decline, end-stage renal disease (ESRD), and renal death in patients with T2D and HF. They also reduce albuminuria and glomerular hyperfiltration, which are key markers of renal damage and dysfunction. These renal benefits are observed in patients with various levels of renal function, including those with chronic kidney disease (CKD) and different baseline characteristics such as atherosclerotic CVD and proteinuria [22]. SGLT2 inhibitors help reduce inflammation and oxidative stress, contributing factors to renal damage in patients with T2D and HF, and are associated with a lower incidence of adverse renal events compared to other diabetes medications, such as DPP4i [23].

SCD is a significant concern for patients with HF. SGLT2 inhibitors have shown a significant reduction in the risk of atrial arrhythmias and SCD in patients with T2D and HF, although they do not significantly reduce the risk of ventricular arrhythmias [24]. These medications also reduce the combined risk of cardiovascular death and HF hospitalization in HF patients, regardless of diabetes status, and are associated with a reduction in all-cause mortality. The cardiovascular benefits of SGLT2 inhibitors are consistent across various patient subgroups, including those with different ages, sexes, diabetes status, and baseline ejection fraction, and are effective in both HFrEF and HF with preserved ejection fraction (HFpEF) [25].

In summary, while SGLT2 inhibitors offer significant benefits in managing HF and reducing cardiovascular events in patients with T2D, they are associated with an increased risk of genital infections and volume depletion. However, the overall cardiovascular and renal benefits make SGLT2 inhibitors a valuable option in the treatment of HF in patients with T2D.

Diagnostic Criteria and Challenges

SGLT2 inhibitors have proven to be a valuable therapeutic option in the management of HF in patients with T2D. However, the use of these medications presents certain diagnostic challenges that must be considered to ensure optimal management of HF in this population [26].

To consider the use of SGLT2 inhibitors in the management of HF in patients with T2D, it is essential to identify certain clinical and laboratory indicators. These medications have demonstrated a significant reduction in hospitalizations for HF and cardiovascular mortality. Additionally, they contribute to the improvement of metabolic parameters such as the reduction of HbA1c, body weight, and blood pressure, which are beneficial for the management of HF. A decrease in the incidence of AF and atrial flutter, common in patients with HF, has also been observed [26]. SGLT2 inhibitors offer renal benefits, such as reducing the progression of CKD, which is crucial for patients with HF and T2D. Finally, these medications are associated with a reduction in all-cause mortality and may have anti-inflammatory and antioxidant effects that contribute to improved cardiovascular outcomes [27].

The systematic diagnosis of HF in patients with T2D requires a comprehensive approach. It is essential to use validated prognostic models and artificial intelligence (AI) tools to improve the accuracy of HF prediction. Biomarkers such as NT-proBNP and high-sensitivity troponin I are effective for risk stratification in patients with T2D, especially after an acute coronary syndrome. Electrocardiography and diastolic stress testing are also useful for detecting subclinical HF [27]. Echocardiography, including diastolic stress testing, provides valuable information about structural and functional heart changes in patients with T2D. An interdisciplinary approach involving both cardiologists and diabetologists is recommended for the early diagnosis and management of HF. Proactive diagnostic strategies, such as symptom questionnaires, measurement of natriuretic peptides, and electrocardiography, are effective for uncovering early stages of HF in high-risk patients [28].

In patients with T2D treated with SGLT2 inhibitors, specific echocardiographic findings for HF include significant im-

provements in LVEF and reductions in LVEDD. These medications are also associated with a reduction in the incidence of AF and atrial flutter. SGLT2 inhibitors improve metabolic indices, such as body weight, BMI, SBP, and fasting plasma glucose, which can contribute to better cardiovascular outcomes. Additionally, these drugs reduce left ventricular mass and improve diastolic parameters, especially in patients with HFrEF [28]. The cardiovascular benefits of SGLT2 inhibitors are attributed to mechanisms beyond glycemic control, including natriuresis, plasma volume reduction, improved vascular function, and reduced oxidative stress [29].

Monitoring the efficacy of SGLT2 inhibitors in the management of HF relies on the use of biomarkers and imaging. These medications significantly reduce cardiovascular mortality and hospitalizations for HF, which can be monitored through changes in cardiac parameters observed via imaging techniques such as echocardiography and cardiac MRI. SGLT2 inhibitors are associated with favorable changes in cardiac parameters, such as the reduction of left ventricular mass, left ventricular end-systolic volume, and left atrial volume index. Biomarkers, such as hematocrit and erythropoiesis, provide information about the underlying mechanisms of action, further supporting the efficacy of SGLT2 inhibitors in improving HF outcomes [29].

However, there are challenges in diagnosing HF in patients with T2D treated with SGLT2 inhibitors. The cardiovascular benefits of these medications, such as the reduction of hospitalizations for HF, can mask symptoms and the progression of HF in these patients. Additionally, the mechanisms of action of SGLT2 inhibitors, such as early natriuresis, plasma volume reduction, improved vascular function, and blood pressure reduction, can simulate improvements in HF symptoms, complicating the diagnosis. The non-glycemic effects of SGLT2 inhibitors, such as the reduction of adipose tissue-mediated inflammation, oxidative stress, and serum uric acid levels, as well as the shift towards ketone body metabolism, can further complicate the clinical evaluation of HF. Moreover, the increased risk of genital infections in patients treated with SGLT2 inhibitors can add another layer of complexity to the clinical management of these patients [30].

In conclusion, SGLT2 inhibitors offer significant benefits in the management of HF and the reduction of cardiovascular events in patients with T2D. However, their use presents diagnostic challenges that require a comprehensive and multidisciplinary approach to ensure accurate evaluation and effective management of HF in this patient population.

Differential Diagnosis

The differential diagnosis of HF in patients with T2D treated with SGLT2 inhibitors is essential for effective clinical management. This section addresses the distinguishing features of various cardiovascular and renal conditions in these patients, considering the impact of SGLT2 inhibitors [31].

Differentiating hypertensive heart disease from HF in patients with diabetes treated with SGLT2 inhibitors requires a detailed understanding of specific echocardiographic patterns. SGLT2 inhibitors have been shown to improve cardiac function, particularly in those with HFrEF. These improvements may be related to the reduction of cardiac fibrosis and necrosis, as well as changes in sodium and calcium handling in tissues [31]. Additionally, a decrease in the incidence of cardiac arrhythmias and related CVDs has been observed. However, further research is needed to fully understand the echocardiographic patterns that distinguish hypertensive heart disease from HF in diabetic patients treated with these inhibitors [32].

Distinguishing CKD from HF in patients with T2D treated with SGLT2 inhibitors is crucial due to the nephroprotective effects of these medications. SGLT2 inhibitors reduce the risk of major adverse cardiovascular events, hospitalization for HF, and progression of renal disease in patients with T2D. They modulate neurohormones, increase hematocrit, alter energy substrate use, and reduce inflammation and oxidative stress, contributing to cardiovascular and renal protection. The benefits are consistent in patients with or without atherosclerotic CVD, CKD, or HF. Biomarkers such as estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio can help differentiate CKD from HF, as SGLT2 inhibitors improve these indicators, showing their dual protective role [32].

Diabetic cardiomyopathy is characterized by structural and functional changes in the heart of individuals with diabetes, which can lead to HF. SGLT2 inhibitors have shown a significant reduction in the risk of cardiovascular death, hospitalizations for HF, and major adverse cardiovascular events in patients with diabetes [32]. These medications decrease oxidative stress, inflammation, and myocardial fibrosis, improving cardiac function. They also improve metabolic parameters such as body weight, blood pressure, and glycemic control, which are beneficial for cardiac health. They promote autophagic flux and mitochondrial biogenesis, helping maintain cellular and organ integrity. Additionally, they modulate neurohormonal pathways, reducing the activity of the renin-angiotensin-aldosterone system and sympathetic nervous activity, protecting against HF [33].

Comparing the diagnostic criteria for HF managed with other treatments versus those using SGLT2 inhibitors reveals significant differences. Other treatments often include beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs). These treatments focus on reducing symptoms, improving functional status, and preventing hospitalizations and mortality. Beta-blockers work by reducing heart rate and myocardial oxygen consumption, ACE inhibitors and ARBs reduce afterload and preload by inhibiting the renin-angiotensin-aldosterone system, and MRAs reduce fluid retention and adverse remodeling. In contrast, SGLT2 inhibitors, originally developed for glycemic control, provide additional benefits through mechanisms such as natriuresis, plasma volume reduction, improved vascular function, and reduced inflammation and oxidative stress, leading to improved cardiovascular outcomes and reductions in hospitalizations for HF [33]. SGLT2 inhibitors reduce the combined risk of cardiovascular death or hospitalization for HF in patients with HFrEF, regardless of diabetic status. These benefits are consistent across various patient subgroups, including age, sex, diabetic status, and baseline eGFR. Compared to conventional

therapy, treatment regimens that include SGLT2 inhibitors provide substantial improvements in survival and event-free survival. However, SGLT2 inhibitors are associated with an increased risk of genital infections, which is important to consider in clinical decision-making [34].

Distinguishing HF in diabetic patients from other cardiovascular conditions when treated with SGLT2 inhibitors is fundamental for effective treatment. These inhibitors significantly reduce hospitalizations for HF and cardiovascular death, with benefits extending beyond glycemic control, including weight loss, blood pressure reduction, and improved vascular function. The benefits are consistent across different patient subgroups and supported by real-world evidence, supporting their use in clinical practice. The mechanisms of action include natriuresis, plasma volume reduction, improved vascular function, and reduced oxidative stress [35].

While SGLT2 inhibitors are highly effective in managing HF and reducing cardiovascular risks in patients with T2D, it is essential to continuously refine and adapt treatment strategies. Multidisciplinary collaboration and ongoing research are critical to addressing any remaining diagnostic challenges and optimizing patient outcomes. This approach ensures that all patients benefit from the most up-to-date and effective therapies available.

Management and Treatment

The management and treatment of HF in patients with T2D using SGLT2 inhibitors require a multidimensional approach that includes monitoring disease progression, combined pharmacological therapy, non-pharmacological interventions, and advanced management options. Monitoring the progression of HF in patients using SGLT2 inhibitors is crucial to optimizing treatment and improving clinical outcomes. These inhibitors have demonstrated a significant reduction in the risk of cardiovascular death and hospitalization for HF, in both patients with and without T2D. Additionally, the combination of SGLT2 inhibitors with GLP-1RAs offers significant benefits in the primary prevention of MACCEs and HF [36].

Differences between SGLT2 inhibitor subtypes are also noteworthy. Empagliflozin has been shown to significantly reduce cardiovascular death and hospitalization for HF, particularly noted for its pronounced cardiovascular benefits, including a reduction in all-cause mortality [36]. Canagliflozin also reduces cardiovascular events and offers additional renal benefits but has been associated with a higher risk of lower-limb amputations, necessitating careful patient selection and monitoring. Dapagliflozin reduces hospitalizations for HF and improves overall heart function, with studies showing an average increase in LVEF from 30% to 35%. It also has a favorable safety profile with a low risk of severe side effects. Ertugliflozin demonstrates similar benefits in glycemic control and cardiovascular protection, though its long-term effects are still being studied. It is known for its ease of use and minimal drug-drug interactions [37].

Understanding these differences is essential for optimizing the use of SGLT2 inhibitors in clinical practice, ensuring that each patient receives the most appropriate therapy based on their individual clinical profile [37].

Pharmacological therapy for HF in patients with T2D significantly benefits from the combined use of SGLT2 inhibitors and other HF medications. These inhibitors, initially developed for glycemic control, have shown substantial cardiovascular benefits, particularly in reducing HF events. The mechanisms of action of SGLT2 inhibitors extend beyond glycemic control and include natriuresis, plasma volume reduction, improved vascular function, and lowered blood pressure. Moreover, these medications are effective in patients with both HFrEF and HFpEF, improving outcomes regardless of HF history [38].

The treatment regimen for HF in patients with T2D using SGLT2 inhibitors includes reducing cardiovascular death, with consistent benefits in patients with HFrEF and HFpEF. These inhibitors are also associated with reducing atrial arrhythmias and SCD, as well as improving renal outcomes. The underlying mechanisms for these benefits include natriuresis, plasma volume reduction, and improved vascular function [38].

Non-pharmacological interventions play a crucial role in managing HF in patients with T2D treated with SGLT2 inhibitors. Regular physical activity and structured exercise programs improve cardiovascular outcomes and reduce HF hospitalizations. Dietary interventions, such as the Dietary Approaches to Stop Hypertension (DASH) diet, can significantly improve cardiovascular health and reduce HF symptoms. Weight loss through lifestyle modifications is also associated with better HF outcomes. Additionally, patient education programs and psychosocial support are effective in improving HF management and quality of life [39].

Advanced management options, such as heart transplantation and experimental therapies, are important considerations for patients with HF using SGLT2 inhibitors. These inhibitors have shown to significantly reduce the risk of cardiovascular events and all-cause mortality, especially in patients with HFrEF. While the benefits in HFpEF are still being explored, there is a trend towards reducing hospitalizations and improving health-related quality of life. Several original research papers have highlighted the efficacy of these medications [39]. For instance, the EMPA-REG OUTCOME trial demonstrated a 35% reduction in the risk of hospitalization for HF and a 38% reduction in cardiovascular mortality with empagliflozin. However, the trial's limitations include a predominantly male study population, which may affect the generalizability of the results. Similarly, the CANVAS program highlighted the dual cardiovascular and renal benefits of canagliflozin, though it noted an increased risk of amputations, necessitating careful patient selection. SGLT2 inhibitors also reduce the risk of atrial arrhythmias and SCD, making them a valuable therapeutic option in managing HF alongside other advanced therapies [40].

In conclusion, SGLT2 inhibitors play a crucial role in managing HF in patients with T2D, offering significant reductions in HF hospitalizations, cardiovascular death, and arrhythmias. Their benefits extend beyond glycemic control, involving multiple cardiovascular protective mechanisms. Combining these inhibitors with other HF medications, non-pharmacological interventions, and advanced management options provides a comprehensive and effective approach to managing HF in this patient population.

Prognosis

SGLT2 inhibitors have emerged as a promising therapeutic option for managing HF in patients with T2D. This prognosis section addresses the variables that influence prognosis, evaluation tools, and long-term outcomes for these patients [41].

Variables that influence the prognosis of HF in patients with T2D treated with SGLT2 inhibitors include significant reductions in cardiovascular and all-cause mortality, as well as decreases in HF hospitalizations. These medications improve renal outcomes, which is crucial for patients with T2D who are at high risk for kidney disease. Additionally, SGLT2 inhibitors reduce the incidence of AF and atrial flutter, common in patients with T2D, complicating HF management [41]. Metabolic benefits, such as improvements in HbA1c levels, body weight, and blood pressure, also contribute to overall cardiovascular health. These effects are consistent across various patient subgroups, regardless of age, sex, BMI, and eGFR. SGLT2 inhibitors are effective in both HFrEF and HFpEF, making them a versatile and effective treatment option [42].

To assess prognosis in patients with HF treated with SGLT2 inhibitors, various tools and methods are used. Studies have shown that these inhibitors reduce the incidence of worsening renal disease, all-cause mortality, and HF hospitalizations. Additionally, a reduction in HF hospitalizations or cardiovascular death has been observed, further supporting their prognostic benefit. These evaluations include biomarker studies and cardiac imaging techniques, which help monitor disease progression and adjust treatment effectively [42].

Regarding long-term outcomes, SGLT2 inhibitors offer significant benefits for patients with HF, including reductions in cardiovascular mortality, all-cause mortality, and HF hospitalizations. These medications also improve quality of life, as measured by specific questionnaires such as the Kansas City Cardiomyopathy Questionnaire (KCCQ). Additionally, SGLT2 inhibitors have antiarrhythmic effects, reducing the risk of atrial arrhythmias and SCD, and renal benefits, improving outcomes in patients with CKD [43].

The different stages of HF at the time of diagnosis influence the prognosis of patients with T2D using SGLT2 inhibitors. These medications have been effective across all stages of HF, reducing the risk of major adverse cardiovascular events, cardiovascular deaths, worsening renal disease, and all-cause mortality. The benefits are consistent regardless of the stage of HF at diagnosis, highlighting the potential of SGLT2 inhibitors as a key component of the treatment strategy for these patients [44].

Common complications that influence the prognosis of HF in patients with T2D treated with SGLT2 inhibitors include the reduction of AF and atrial flutter, decreasing HF hospitalizations and cardiovascular events. However, there is an increased risk of genital infections, a notable complication that must be managed appropriately. Despite this complication, SGLT2 inhibitors improve metabolic indices and significantly reduce adverse cardiovascular events, resulting in an improved prognosis for patients with HF and T2D [45].

In summary, SGLT2 inhibitors offer significant benefits in managing HF in patients with T2D, improving prognosis through multiple mechanisms and reducing associated complications. Their use should be considered an integral part of HF treatment in this patient population, given their positive impact on mortality, hospitalizations, and quality of life.

Gaps in the Literature

Despite significant advances in the use of SGLT2 inhibitors for managing HF in patients with T2D, important gaps in the literature still need to be addressed to optimize treatment and improve clinical outcomes [45].

One of the most notable areas with insufficient data concerns the long-term effects of SGLT2 inhibitors. While these medications have been shown to reduce the risk of cardiovascular death and hospitalizations for HF, as well as improve renal and metabolic outcomes, a deeper understanding of their long-term impact is required, particularly regarding arrhythmias and SCD. Further investigation into the underlying mechanisms of these cardiovascular benefits and a more detailed safety profile of SGLT2 inhibitors in diverse patient populations, including those with multiple comorbidities and those on multiple concurrent medications, is necessary [46].

Another aspect needing further research is the early diagnostic indicators for HF in patients with T2D using SGLT2 inhibitors. Although these medications have been observed to reduce left ventricular mass and improve diastolic function, the specific diagnostic markers that can predict HF in these patients are not clearly defined. Identifying these indicators is crucial for the early detection and effective management of HF in this population [47].

Additionally, there are methodological limitations in the current research on SGLT2 inhibitors for HF in patients with T2D. Many studies lack robust evidence on long-term safety and efficacy, and there is a need for well-designed clinical trials with extended follow-up durations. Research should also better address the use of these medications in frail patients and those with multiple pathologies, as well as the implications of uncertain insurance environments in clinical practice [48].

To improve current research methods, a more comprehensive approach considering both pathophysiological mechanisms and clinical evidence is essential. This includes focusing on the multisystem effects of SGLT2 inhibitors, especially in the context of HFrEF and HFpEF. It is also important to investigate the potential role of these medications in reducing the risk of AF and atrial flutter, as well as modulating mitochondrial function [49].

In summary, while SGLT2 inhibitors have shown promise in managing HF in patients with T2D, significant gaps in the literature remain. It is crucial to conduct additional research on long-term effects, early diagnostic indicators, and methodological limitations to optimize the use of these medications and improve clinical outcomes in this population.

Future Directions

Future research directions on the efficacy of SGLT2 inhibitors in managing HF in patients with T2D should focus on key areas

to optimize treatment and improve clinical outcomes. Firstly, primary prevention trials are essential to evaluate the efficacy of SGLT2 inhibitors and their combination with GLP-1RAs in preventing MACCEs and HF in patients with T2D. Additionally, prospective studies are needed to confirm the antiarrhythmic effects of SGLT2 inhibitors and determine whether these effects are class-specific or medication-specific [49].

Mechanistic studies should be deepened to understand the pathways through which SGLT2 inhibitors confer cardiovascular benefits. This includes investigating their effects on natriuresis, plasma volume reduction, improved vascular function, sodium handling in tissues, and the reduction of adipose tissue-mediated inflammation and oxidative stress. Another critical area is the comprehensive evaluation of the long-term safety profile of SGLT2 inhibitors, particularly regarding genital infections and volume depletion. Further research should also explore their impact on AF and atrial flutter, given that these disorders can significantly influence HF outcomes [50].

For the development of specific therapeutic approaches, combining SGLT2 inhibitors with other therapeutic agents, such as GLP-1RAs, is recommended. This combination could enhance cardiovascular and metabolic benefits, further reducing HF events, hospitalizations, and cardiovascular mortality, while improving vascular function and reducing inflammation [50].

In terms of public health policies, promoting changes that facilitate access to SGLT2 inhibitors and their appropriate use in managing HF in patients with T2D is necessary. This includes developing innovative care models, such as pharmacist-led clinics, to ensure safe prescription and monitoring of these medications. Additionally, clinical guidelines should be implemented recommending SGLT2 inhibitors as first-line treatment for HF patients, based on evidence of their benefits [51].

Comparative studies are needed to evaluate the effectiveness of different SGLT2 inhibitors in reducing cardiovascular events, hospitalizations, and mortality in patients with HFrEF and HFpEF. It is also crucial to investigate the specific impact of SGLT2 inhibitors on AF and other cardiac rhythm disorders, considering reductions in HF events, HbA1c, body weight, and blood pressure [52].

In summary, future research on SGLT2 inhibitors in managing HF in patients with T2D should focus on primary prevention trials, confirming antiarrhythmic effects, studying underlying mechanisms, exploring benefits in broader populations, conducting comparative studies, evaluating long-term safety and efficacy, and analyzing the impact on AF. Addressing these areas will provide a more comprehensive understanding of the role of SGLT2 inhibitors in cardiovascular health.

Conclusion

The review of the efficacy of SGLT2 inhibitors in the management of HF in patients with T2D highlights their important role in reducing hospitalizations, cardiovascular mortality and major adverse cardiovascular events. These drugs were originally developed for glycemic control, but have demonstrated benefits beyond glycemic control. These benefits include improved cardiovascular and renal function and reduced inflammation and oxidative stress. Current evidence suggests that SGLT2 inhibitors are effective in patients with HF with both reduced and preserved ejection fractions, regardless of diabetes status, underscoring their broad therapeutic potential. However, gaps remain in understanding their long-term effects and safety across diverse populations, emphasizing the need for further research. It is essential to conduct rigorous and long-term clinical trials and develop health policies that promote equitable access to these treatments. Combining SGLT2 inhibitors with other therapeutic agents, such as GLP-1RAs, could offer additional benefits and further improve clinical outcomes in this population. In summary, SGLT2 inhibitors represent a promising and multifaceted option for managing HF in patients with T2D, but ongoing research and health policy efforts are necessary to optimize their use and maximize their benefits.

Highlights

SGLT2 inhibitors have revolutionized the management of HF in patients with T2D, demonstrating benefits beyond glycemic control.

These drugs work through natriuresis, reducing plasma volume, and improving vascular function, resulting in a significant reduction in hospitalizations and cardiovascular mortality.

Various recent clinical studies have confirmed the efficacy of SGLT2 inhibitors, highlighting their positive impact on reducing major adverse cardiovascular events.

Although generally safe, SGLT2 inhibitors can increase the risk of genital infections and DKA, requiring careful monitoring.

Additional research is needed to better understand long-term effects and optimize treatment strategies in diverse populations.

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Conflict of Interest

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tion, writing - original draft, writing - review and editing. Melisa Santamaria-Lasso, MD: supervision, writing - review and editing. Melany Mejia-Mora, MD: formal analysis, writing - review and editing. Andrea Granda-Munoz, MD: formal analysis, writing - original draft, supervision. Martin Trujillo-Delgado, MD: data curation, writing - review and editing. Claudia Hurtado-Alzate, MD: data curation, formal analysis, writing - original draft. Ana Clara Fonseca Souza de Jesus, MD: data curation, formal analysis, writing - original draft. Pedro Moraes Coelho, MD: data curation, writing - review and editing, methodology. Jurgen Baldelomar-Ortiz, MD: data curation, writing - review and editing, methodology.

Data Availability

All data generated or analyzed during this study are included in this published article, and further inquiries should be directed to the corresponding author.

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