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Review Article

SGLT2 inhibitor, a new bullet in heart failure management

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ABSTRACT

The global health landscape is confronted with substantial challenges stemming from diabetes mellitus and heart failure (HF). The escalating incidence of diabetes mellitus (DM), in correlation with HF, underscores the imperative necessity for efficacious strategies in the realm of prevention and management. The most recent advancements in therapeutic approaches, specifically Sodium-glucose transporter 2 inhibitors (SGLT2i), present a promising prospect for enhancing outcomes and addressing the existing gaps in HF management. This paper aims to elucidate the significance of SGLT2i in the therapeutic management of both reduced and preserved heart failure, with or without the presence of DM. SGLT2i are new heart failure drugs. In trials, SGLT2i improved diastolic dysfunction, reduced oxidative stress, inflammation, fibrosis, and myofilament rigidity. The first SGLT2 inhibitor studies, EMPA-REG OUTCOME, DECLARE-TIMI 58, and CANVAS, showed that Empagliflozin and Canagliflozin reduced HF mortality and rehospitalization in type 2 diabetes mellitus (T2DM) patients. Dapagliflozin reduces HF hospitalizations without impacting T2DM mortality. Canagliflozin avoided creatinine rises, kidney disease deaths, and cardiovascular deaths in the CREDENCE Study. SGLT2i improve health in heart failure with preserved ejection fraction (HFpEF). SGLT2i improved health status statistically in the PRESERVED-HF and EMPEROR-Preserved investigations. SGLT2i became known as a promising therapeutic choice in the treatment of HF. The substantial evidence from prominent large-scale clinical trials has substantiated the cardiovascular and renal protective effects of SGLT2i. Furthermore, the benefits of these medications are relevant for individuals who have been diagnosed with heart failure with reduced ejection fraction (HFrEF), as well as those who are experiencing heart failure with preserved ejection fraction (HFpEF).

1. Introduction

Diabetes Mellitus (DM) is a significant health concern that has become unmanageable. DM is projected to have a global impact on approximately 537 million individuals in 2021, with this number expected to rise to 643 million by 2030 and further increase to 783 million by 2045. According to projections, the estimated number of individuals aged 20 to 79 who will succumb to diabetes-related causes in the year 2021 is approximately 6.7 million. According to the IDF Diabetes Atlas 2021, the incidence of DM in Southeast Asia is projected to affect approximately 90 million individuals in 2021. This figure is expected to experience a significant surge, reaching 152 million individuals by the year 2045. DM is a persistent medical condition characterized by elevated levels of glucose in the bloodstream. This condition arises due to the body's insufficient production or utilization of the hormone insulin. An insufficient production of insulin can lead to severe and potentially life-threatening health complications, causing damage to multiple bodily organs.[1] T2DM is widely recognized as a significant contributing factor to various cardiovascular (CV) complications, such as HF. In the context of T2DM, there exists a positive correlation between a 1% elevation in glycated hemoglobin A1c levels and an 8% augmentation in the risk of developing HF.[2]

Heart Failure (HF) is a major public health concern. It is estimated that there are approximately 26 million cases of cardiac failure worldwide.[3] HF is a progressive condition with a significant risk of mortality and rehospitalization.[4] All aspects of health are impacted by HF: mobility issues, discomfort, inability to perform routine tasks, difficulty taking care of oneself, anxiety, and depression. Consequently, enhancing HF symptoms and quality of life, such as through physical activity, remains an unmet medical need among patients with HF.[5] Diagnosis and intervention at an early stage are recommended to prevent disease progression.

The causes and treatment modalities for HF have undergone significant advancements within the last five decades. In the year 1950, hypertension and valvular heart disease (VHD) were identified as the prevailing factors contributing to HF in the United States and other Western countries. In contemporary times, the three most commonly observed cardiac conditions are ischemic heart disease (IHD), hypertensive heart disease (HHD), and idiopathic dilated cardiomyopathy. In 1950, HF was treated with bed rest, a sodium-restricted diet, the inotropic drug digitalis, and parenterally administered diuretics. Currently, medications that inhibit neurohormonal activation are frequently employed, and physical activity is advised.[6]

Several randomized controlled trials have been conducted to investigate the efficacy of pharmacological interventions in patients admitted to the hospital for acute HF. These studies have consistently demonstrated a lack of improvement in post-discharge outcomes,

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indicating a significant gap in current treatment strategies. SGLT2i represent a recent class of therapeutic agents for HF. These inhibitors have shown significant efficacy in reducing the likelihood of cardiovascular mortality or hospitalization due to HF in patients with chronic heart failure, regardless of whether they have a reduced or preserved LVEF.[7]

2. Discussion

2.1 Heart Failure

HF is a pathological condition characterized by impaired cardiac structure or function, resulting in inadequate oxygen delivery to various tissues and organs of the body. HF is a multifaceted condition that manifests through the aggregation of symptoms, which are distinguished by the presence of HF symptoms, HF specific characteristics, and objective indications of compromised cardiac structure or function. The American Heart Association (AHA), in conjunction with the American College of Cardiology, has delineated four distinct phases of HF. Based on the provided chart, it can be observed that Stage A is associated with a heightened susceptibility to heart failure, Stage B represents a preliminary stage preceding heart failure, Stage C denotes the presence of symptomatic HF, and Stage D signifies the occurrence of advanced HF (Table 1).[8]

Table 1. Stages of heart failure.[8]

Stage A: At risk for heart failure	People who are at risk for heart failure but do not yet have symptoms or structural or functional heart disease Risk factors for people in this stage include hypertension, coronary vascular disease, diabetes, obesity, exposure to cardiotoxic agents, genetic variants for cardiomyopathy and family history of cardiomyopathy
Stage B: Pre-heart failure	People without current or previous symptons of heart failure but with either structural heart disease, increased filling pressures in the heart or other risk factors
Stage C: Symptomatic heart failure	People with current or previous symptons of heart failure
Stage D: Advanced heart failure	People with heart failure symptons that interfere with daily life functions or lead to repeated hospitalizations

Patients diagnosed with HF were categorized into stages C and D based on the severity of their symptoms. The New York Heart Association (NYHA) Functional Classification is widely recognized as the most extensively utilized system for categorizing patients. This classification system assigns individuals to one of four distinct categories, which are determined by their respective limitations in physical activity. The table below presents the various classes of the New York Heart Association (NYHA) Functional Classification (Table 2).[9]

HF is classified based on the presence of decreased systolic function, specifically ejection fraction, and impaired diastolic function. The LVEF holds significance in the categorization of individuals diagnosed with HF owing to variations in prognosis and treatment outcomes. Moreover, a majority of clinical trials employ LVEF as a criterion for patient selection. Individuals who exhibit a substantially reduced left ventricular systolic function are classified as having a LVEF below 40%. This condition is commonly known as HFrEF. Individuals exhibiting a LVEF ranging from 41% to 49% are diagnosed with HF with mid-range ejection fraction (HFmrEF), denoting a condition characterized by a mildly impaired left ventricular systolic function. Patients who exhibit symptoms and signs of HF, demonstrate evidence of structural and/or functional abnormalities in the heart, and/or have elevated levels of natriuretic peptides alongside a LVEF greater than 50% are diagnosed with HFpEF.[9]

In order to diagnose HF, it is necessary to observe the manifestation of symptoms and/or signs of HF, as well as obtain objective evidence of cardiac dysfunction. Common symptoms often

Table 2. Functional classification based on severity of symptoms and physical activity

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain.
IV	Symptoms of heart failure at rest. Any physical activity causes further discomfort

observed in individuals include dyspnea, fatigue, and peripheral edema in the lower extremities. The diagnosis of HF cannot be solely based on symptoms. It is advisable to conduct the subsequent diagnostic examinations for patients who are suspected of experiencing HF. Diagnosing HF based solely on a normal electrocardiogram (ECG) is unlikely. Abnormalities that may be detected by the ECG include atrial fibrillation (Af), Q waves, left ventricular hypertrophy (LVH), and a widened QRS complex. These findings can enhance the probability of diagnosing HF and provide valuable guidance for therapeutic interventions. It is advisable to conduct measurements of nanoparticles if they are accessible. Plasma levels of B-type natriuretic peptide (BNP) at 35 pg/mL and N-terminal pro-B-type natriuretic peptide (NT-proBNP) at 125 pg/mL suggest a low probability of HF as a diagnosis. It is recommended to perform a chest X-ray in order to explore alternative etiologies for dyspnea, including pulmonary pathologies. Additionally, it can offer corroborating evidence of heart failure, such as pulmonary obstruction or cardiomegaly. Echocardiography is widely recommended as the primary diagnostic tool for assessing cardiac function. In addition to assessing the LVEF, echocardiography offers valuable insights into various aspects of cardiac health. These include the evaluation of chamber dimensions, identification of eccentric or concentric left ventricular hypertrophy (LVH), detection of regional wall motion abnormalities that may indicate underlying CAD, Takotsubo syndrome, or myocarditis. Furthermore, echocardiography allows for the assessment of right ventricular function, identification of pulmonary hypertension, evaluation of valvular function, and examination of markers associated with diastolic function.[9]

Pharmacotherapy plays a crucial role in the management of HFrEF and should be prioritised over device therapy, while also being used in conjunction with non-pharmaceutical interventions. There are three primary treatment objectives for patients with HFrEF. This intervention has three primary benefits: a reduction in mortality rates, a decrease in hospitalisations due to deteriorating heart failure, and an improvement in clinical status, functional capacity, and overall quality of life.10 It has been demonstrated that treatment with an ACE-I or an ARNI, BB, and MRA improves survival, reduces the risk of hospitalisations due to HF, and alleviates symptoms in patients with HFrEF. The HFrEF pharmacotherapy begins with these medications.[9]

ACE-I represent the initial category of pharmaceutical agents that have been proven to effectively decrease both mortality and morbidity in patients suffering from HFrEF. Furthermore, it has been shown that they can also mitigate symptoms. It is recommended that these medications be prescribed to all patients, unless there are specific contraindications or intolerable side effects. The dosage should be escalated to the maximum tolerable level as recommended. The guidelines established by the ESC suggest the utilization ARNI as a substitute for ACE-I in appropriate patients who continue to experience symptoms despite receiving ACE-I, BB, and MRA treatment. Nevertheless, ARNI could be contemplated as an initial treatment option instead of ACE-I. In the PARADIGM-HF trial, it was demonstrated that sacubitril/valsartan, classified as an ARNI, exhibited a higher level of efficacy compared to enalapril in the context of diminishing hospitalizations related to deteriorating HF, cardiovascular (CV) mortality, and mortality from all causes. This finding was observed specifically in ambulatory patients diagnosed

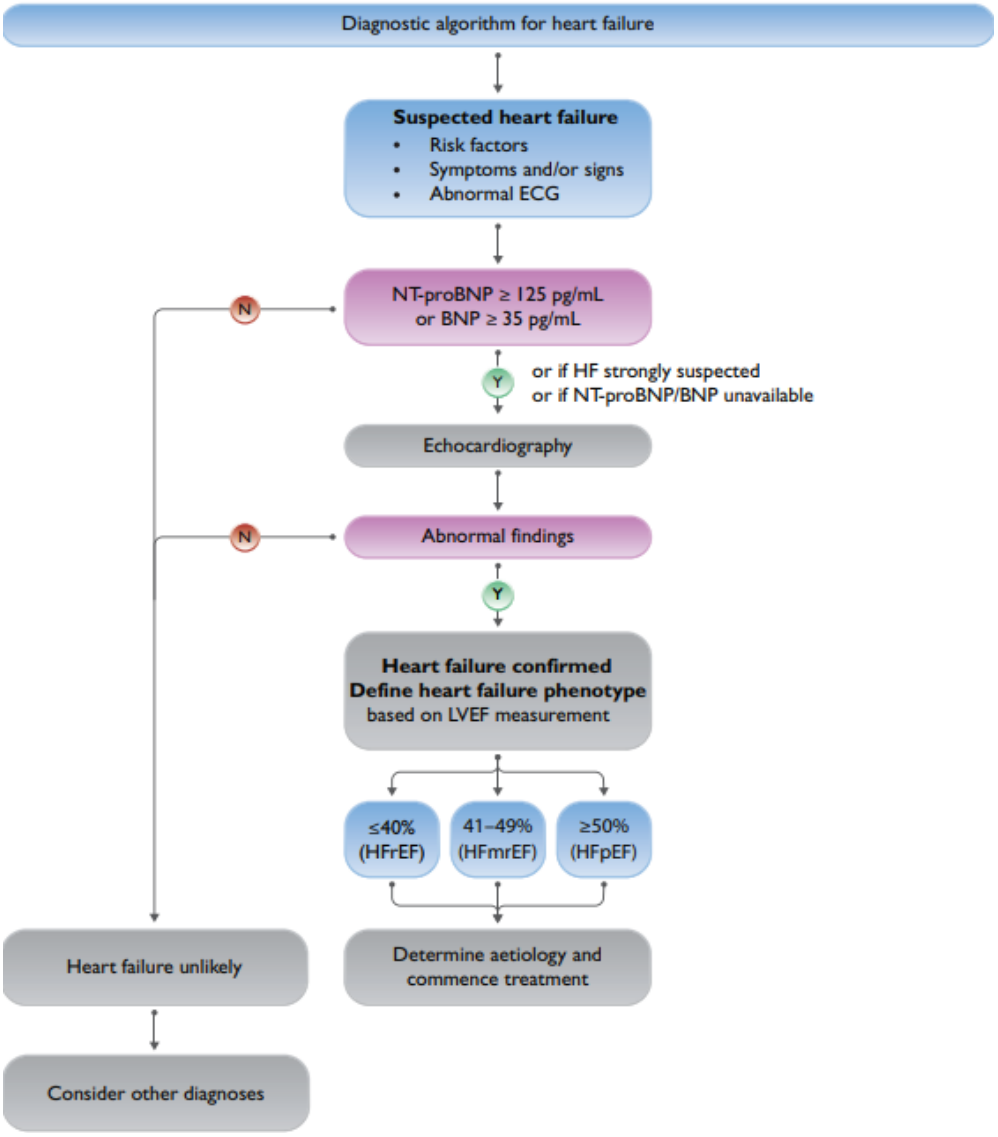

Figure 1. Diagnostic Algorithm for Heart Failure[9]

with HFrEF. The administration of ARNIs has demonstrated notable enhancements in symptomatology and overall well-being, as well as a decrease in the occurrence of diabetes necessitating insulin therapy, a deceleration in the deterioration of eGFR, and a reduction in the prevalence of hyperkalemia. In order for patients to be eligible for ARNI therapy, it is imperative that they possess sufficient blood pressure levels and an eGFR of 30 mL/min/1.73 m2 or higher. To mitigate the potential occurrence of angioedema, it is imperative to observe a washout period of no less than 36 hours subsequent to the administration of ACE-I therapy.[9]

Furthermore, it has been shown that BB, in conjunction with ACE-I and diuretics, can effectively decrease both mortality and morbidity in individuals suffering from HFrEF. Moreover, they mitigate symptoms. Once the diagnosis of symptomatic HFrEF is established, there is a consensus among experts that the administration of ACE-I and BB can be initiated simultaneously. There is a lack of empirical evidence substantiating the preferential administration of BB prior to ACE-I, or conversely, the administration of ACE-I before BB. In patients who are clinically stable and have normal fluid volume status, it is recommended to initiate beta-blockers at a low dosage and gradually increase it until the maximum tolerated dosage is reached. After achieving hemodynamic stability in patients with acute heart failure (AHF), it is advisable to exercise caution when administering beta blockers within a hospital setting. In conjunction with an ACE-I and a BB, MRAs are recommended for the treatment of all patients with HFrEF in order to mitigate mortality rates and decrease the likelihood of hospitalization due to heart failure. Individuals who have compromised kidney function and those who have serum potassium levels exceeding 5.0 mmol/L should exercise caution when utilizing MRAs.[9]

In conjunction with ACE-I, ARNI, BB, and MRA, the addition of SGLT2i, specifically dapagliflozin and empagliflozin, to the treatment regimen of patients with HFrEF has been associated with a reduction in the risk of cardiovascular mortality and worsening HF symptoms. Dapagliflozin or empagliflozin should be prescribed to all patients with HFrEF who are already receiving an ACE-I or ARNI, BB, and MRAs, regardless of their diabetes status, unless there are contraindications or intolerable adverse effects.[9]

2.2 SGLT2 Inhibitor

The introduction of SGLT2i has emerged as a therapeutic approach for managing diabetes mellitus. These inhibitors effectively reduce blood glucose levels by impeding the transportation of glucose into the proximal tubular cells of the kidney through the SGLT2 transporter. Consequently, this mechanism promotes an elevated excretion of glucose in the urine. In a state of euglycemia, the renal system exhibits a high degree of glucose reabsorption from the glomerular filtration through the utilization of two glucose transporters, namely SGLT1 and SGLT2. The SGLT2 protein is a glucose transporter that exhibits a high capacity and low affinity for glucose. It is primarily found in the apical membrane of the early S1/S2 segments of the proximal tubule. In this location, SGLT2 plays a crucial role in the reabsorption of glucose, accounting for the reabsorption of more than 90% of the filtered glucose. The gene SLC5A2 is responsible for encoding the protein SGLT2, which plays a crucial role in familial renal glycosuria. The luminal glucose that remains is subsequently transported to the downstream S2/S3 segments of the proximal tubule, where it is reabsorbed by the SGLT1 glucose transporter, which has a high affinity for glucose but a low capacity for transport.[11]

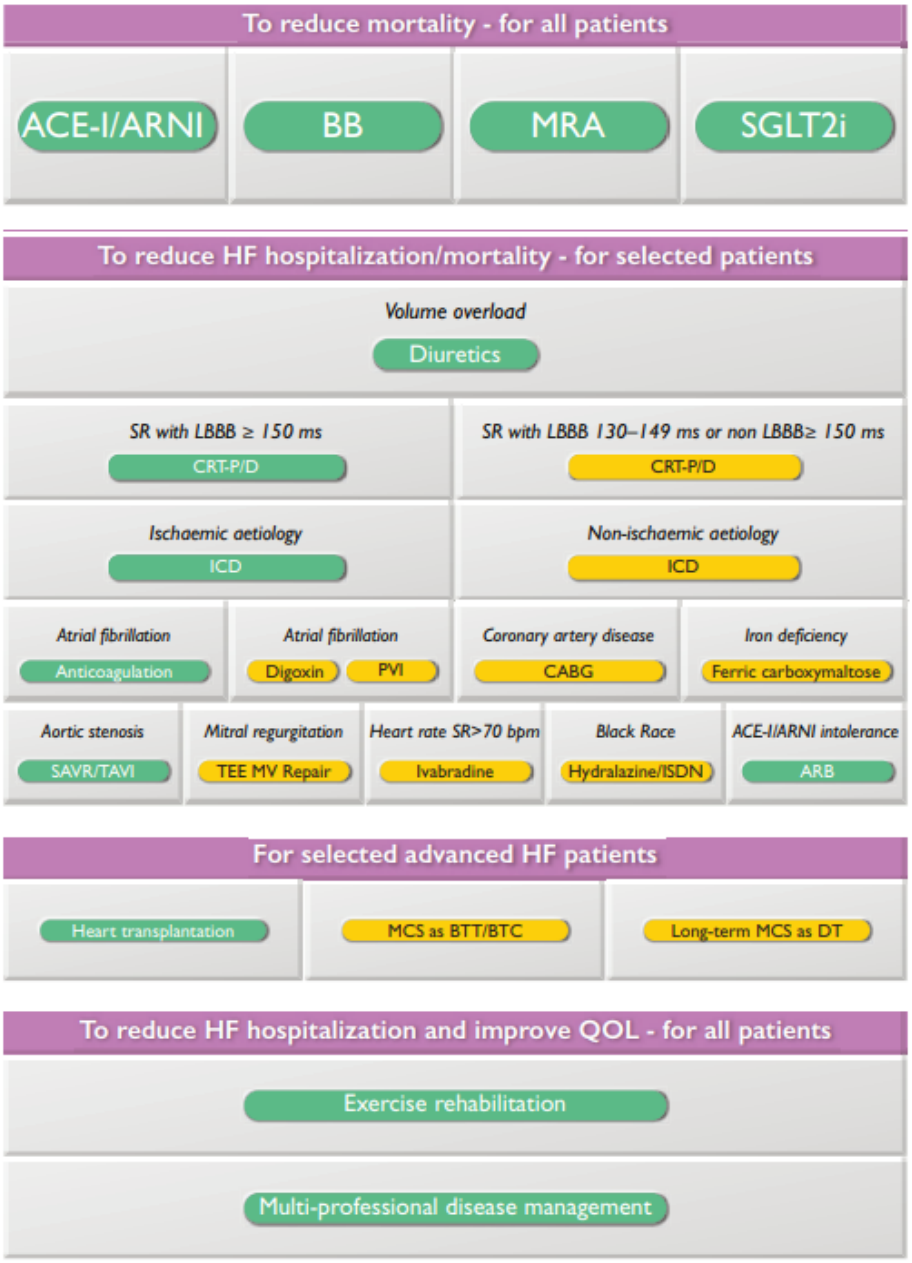

Figure 2. Management of HFrEF[9]

The gene SLC5A1 encodes for SGLT1, which is also observed in the mucosal lining of the small intestine. The process of glucose reabsorption via SGLT1 has been observed to exhibit heightened levels when SGLT2 is either absent due to the deletion of the SLC5A2 gene, inhibited by SGLT2 inhibitors, or when there is an elevated amount of filtered glucose in individuals with diabetes. The expression of SGLT2 is primarily observed in the proximal convoluted tubule of the renal system. The act of inhibiting it leads to a reduction in the renal threshold for glucose excretion and an elevation in the excretion of glucose in urine, leading to a mild increase in urine production and a net loss of calories. Therefore, the therapeutic targeting of both renal SGLT2 and SGLT1 presents a potential approach for reducing glycemia in individuals diagnosed with T2DM.[11]

The expression of the SGLT2 occurs in the proximal tubule of the renal nephron, where it plays a crucial role in facilitating the reabsorption of approximately 90 percent of the glucose that is filtered by the kidneys. SGLT2i facilitate the elimination of glucose through the kidneys, leading to a modest reduction in elevated blood glucose levels among individuals diagnosed with type 2 diabetes. The therapeutic efficacy of this treatment is constrained by the filtered glucose load and the resulting osmotic diuresis, which restricts the capacity to reduce blood glucose and glycated hemoglobin (A1C) levels. Furthermore, it should be noted that the existing SGLT2 inhibitors exhibit a high degree of inhibition in blocking the reabsorption of glucose in the proximal tubules. However, it is important to acknowledge that the level of inhibition observed is actually less than 50 percent, as determined by the measurement of glucose excretion in urine.

SGLT2i are also used in individuals without diabetes mellitus, with indications based on randomised controlled trials and broadly divided into the five categories below. This study evaluates glycemic control and metabolic risk, prevents atherosclerotic cardiovascular disease, manages heart failure, treats albuminuria diabetic renal disease, and treats nondiabetic CKD. SGLT-2 receptors, found only in the renal proximal convoluted tubules, reabsorb virtually all of the body's glucose and most of the glomerulus' salt. Diuretic receptor blockade eliminated sodium and glucose. This reduces hypoglycemia by lowering serum glucose without insulin.[12]

The administration of SGLT2i has been shown to result in the inhibition of proinflammatory and profibrotic pathways in various animal models. The majority of these studies have investigated the effects either in vitro or in vivo on kidney tissue. The preservation of renal function, encompassing the maintenance of salt and water balance throughout the body and the prevention of sympathetic nervous system

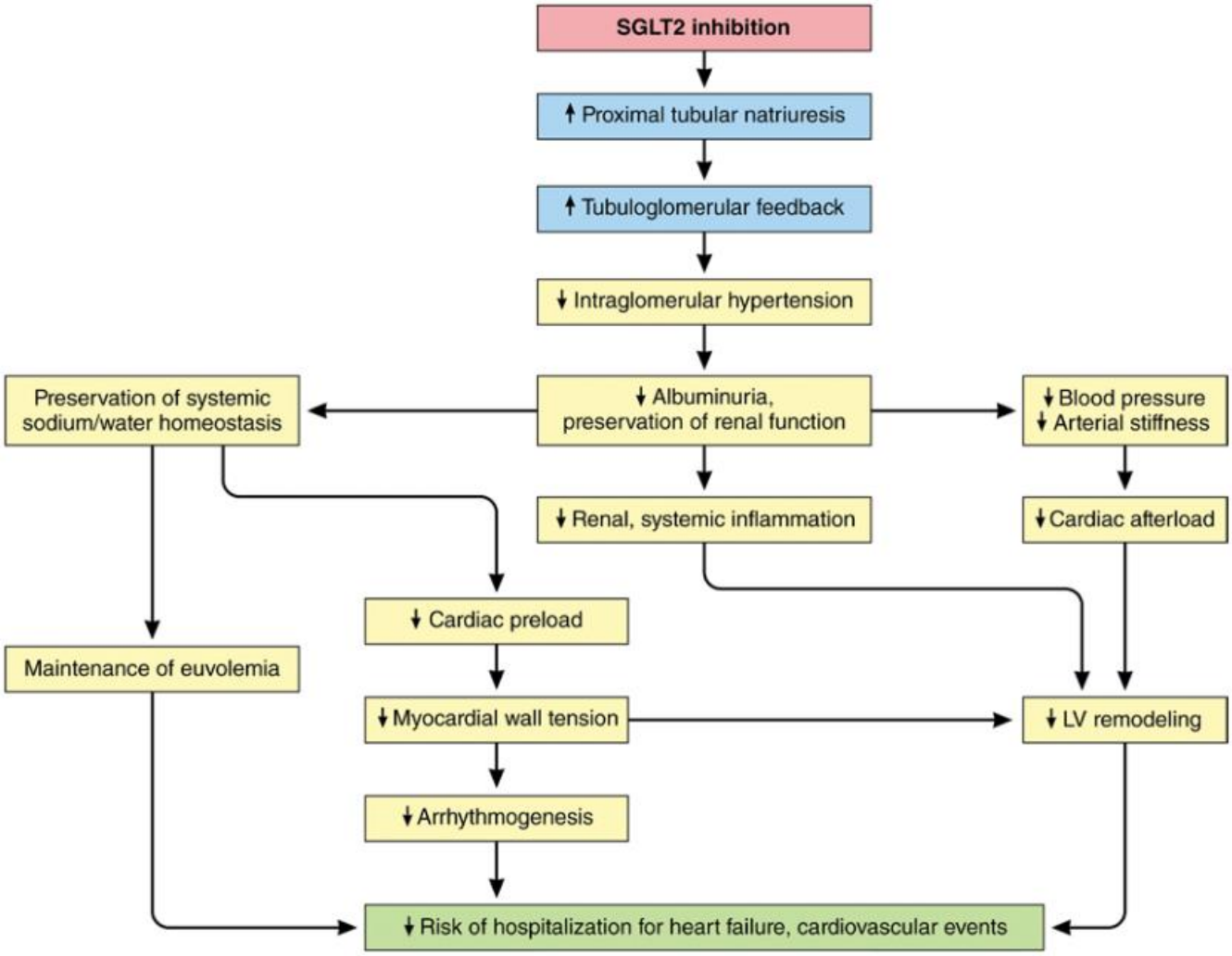

Figure 3. The renal-cardio hypothesis for cardiovascular protection with SGLT2 inhibition: a nephrocentric perspective[13]

activation and inflammation associated with diabetic nephropathy, may have led to a reduction in the risk of HF. (Figure 3).[13]

Obesity is considered to be a distinct and autonomous risk factor for cardiovascular diseases. The inhibition of SGLT2 leads to an elevated excretion of glucose through the urine. According to estimates, a daily loss of approximately 75 grams of glucose occurs through diuresis, which amounts to approximately 400 milliliters per day. The administration of these pharmaceutical compounds in clinical trials has yielded an aggregate reduction in body mass ranging from two to three kilograms. The process of weight loss initiates during the initial weeks of treatment, subsequently reaching a state of stability after a duration of six months, and continues to be maintained over a prolonged period. Nevertheless, it should be noted that the projected energy loss does not correspond to the projected weight loss, as the projected reduction in weight was more substantial. The difference between expected and observed weight loss suggests a progressive increase in caloric consumption, while SGLT2i have no effect on resting or postprandial energy expenditure.[14,15]

Researchers have discovered that SGLT2i reduce blood pressure by 2.46 mmHg in the systolic measurement and 1.46 mmHg in the diastolic measurement. These inhibitors have also been shown to reduce systolic blood pressure by 3.76 mmHg and diastolic blood pressure by 1.83 mmHg during the course of a 24-hour ambulatory measurement. Various pathophysiological mechanisms have been hypothesized to elucidate this phenomenon. At the outset, the suppression of co-transporters in the proximal tubule yields a modest elevation in sodium excretion in urine, while an escalation in glucose excretion further contributes to an osmotic diuretic impact. Furthermore, there exists a correlation between weight loss and a decrease in sympathetic nervous system activity, which in turn has been associated with a decline in blood pressure levels. Furthermore, SGLT2i have been found to have advantageous impacts on arterial rigidity.[14,15]

SGLT2i function by impeding the process of reabsorption of sodium and glucose from the tubule. As a result, a greater amount of sodium is transported to the macula dense, leading to the dilation of afferent arterioles. This dilation subsequently causes a reduction in intraglomerular pressure and a decrease in hyperfiltration. The clinical presentation of this condition is characterized by a decrease in estimated glomerular filtration rate (eGFR) of 4-5 mL/min/1.73 m2 within the initial weeks of treatment, with subsequent restoration to baseline levels observed within a period of 6-12 months. The process of diuresis leads to a reduction in plasma volume, causing a decrease of approximately 7% in the overall volume of plasma.[14,15]

Finally, SGLT2 inhibitors have exhibited significant advantages in terms of cardiovascular morbidity and mortality, along with other metabolic disorders that commonly accompany diabetes mellitus, such as obesity and arterial hypertension.

2.3 SGLT2 Inhibitor, A New Bullet in Heart Failure Management

The management of heart failure has been continuously evolving in order to decrease both mortality rates and rates of re-hospitalization. SGLT2i represent a recently developed pharmacological category of medications that have received regulatory approval for the management of heart failure. The findings of a meta-analysis indicate that the utilization of SGLT2i yields favorable outcomes in terms of reducing cardiovascular mortality and hospital readmissions.

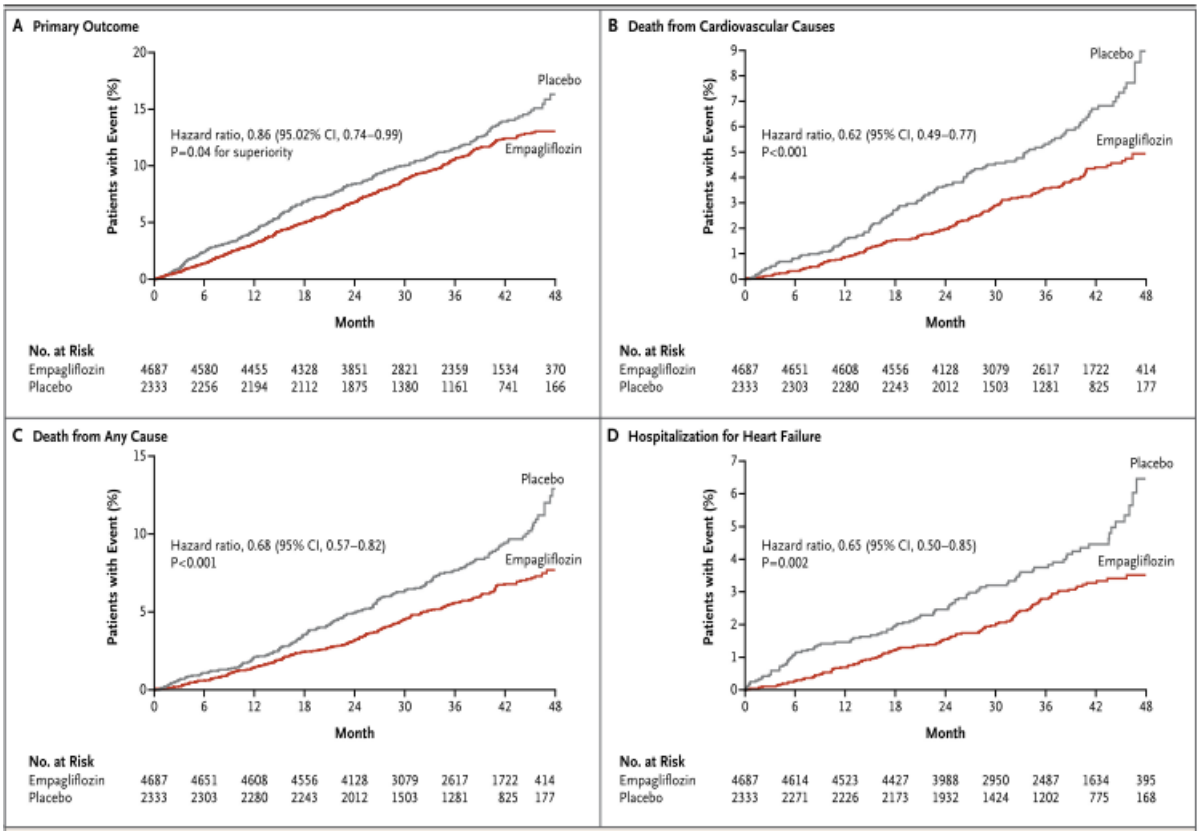

Figure 3. Cardiovascular Outcome and Death in EMPA-REG OUTCOME study

The cardiovascular effects of three SGLT2i (canagliflozin, empagliflozin, dapagliflozin) have been investigated in significant randomized clinical trials, including the DECLARE-TIMI 58, CANVAS, and EMPA-REG OUTCOME studies. The findings from these three studies demonstrate the efficacy of SGLT2 inhibitors in mitigating the occurrence of heart failure among individuals with type 2 diabetes. Consequently, this outcome forms the primary conjecture that this medication may be applicable for heart failure patients who do not have type 2 diabetes.[16]

In the EMPA-REG OUTCOME trial, 7020 patients with type 2 diabetes and preexisting cardiovascular disease were randomly assigned to one of three treatment groups: empagliflozin 10 mg, empagliflozin 25 mg, or placebo. Comparatively to the placebo group, the empagliflozin group demonstrated a statistically significant reduction in the incidence of cardiovascular mortality or hospitalisation for HF. The use of empagliflozin significantly reduced the incidence of a predetermined outcome, namely hospitalisation for HF that was adjudicated. The 95% confidence interval for the hazard ratio for this reduction ranged from 0.61 to 0.88. The observed benefit of empagliflozin was observed in patients with and without a documented history of HF, and was independent of initial renal function or traditional risk factors such as A1c, blood pressure, or lipid levels (Figure 3).[17]

The CANVAS Programme was the second significant investigation on SGLT2i to establish the cardiovascular benefits for type 2 diabetes patients. The primary objective of the CANVAS initiative was to evaluate the cardiovascular safety and efficacy of canagliflozin in a heterogeneous cohort of T2DM patients. This study included 10,142 individuals who were diagnosed with type 2 diabetes and had an eGFR greater than 30 mL/min/1.72 m2. These participants either had cardiovascular disease or were over the age of 50 with two cardiovascular disease risk factors. They were randomly assigned to one of three groups: placebo, 100 mg/d or 300 mg/d canagliflozin, or both. The canagliflozin group experienced cardiovascular mortality, myocardial infarction, or stroke at a rate of 26.9 per 1,000 patient-years, while the placebo group experienced a rate of 31.5 per 1,000 patient-years. Additionally, the CANVAS Programme demonstrated a 33% reduction in hospitalisations due to HF when canagliflozin therapy was administered. According to a subsequent study, this benefit was observed in patients with and without a history of atherosclerotic cardiovascular disease.[18]

The findings of the EMPA-REG OUTCOME and CANVAS trials demonstrate the efficacy of Empagliflozin and Canagliflozin in mitigating mortality and reducing re-hospitalization rates associated with HF among individuals diagnosed with T2DM. The EMPA-REG and CANVAS trials both demonstrated notable renal advantages. The participants in the CANVAS study observed a decrease of 27% in the incidence of albuminuria. The EMPA-REG study additionally exhibited a 38% decrease in the occurrence of macroalbuminuria and a 39% decrease in the frequency or progression of nephropathy.[19]

In a sample of 17,160 patients, the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-Thrombolysis in Myocardial Infarction (TIMI) 58 study compared dapagliflozin and placebo. 10 186 of these patients showed no symptoms of atherosclerotic cardiovascular disease. In addition, individuals with a minimum creatinine clearance of 60 mL per minute were enlisted in the study, in contrast to previous research. The primary effectiveness indicators included significant adverse cardiovascular events and the combination of cardiovascular mortality and hospitalisation HF. There were no observed statistically significant differences in MACE rates. The composite outcome of cardiovascular mortality or hospitalisation for HF, however, revealed a statistically significant difference. The relative benefits for patients with and without a history of atherosclerotic cardiovascular disease or HF were comparable. In a secondary analysis of the DECLARE study, it was determined that 671 patients had an LVEF of at least 45%, whereas 1316 patients had a documented history of HF without a reduced ejection fraction. In the present study, individuals with a LVEF of 45% who received dapagliflozin exhibited a more pronounced decrease in the occurrence of cardiovascular death or HF compared to those without a documented lower LVEF. This disparity can be attributed to a notable reduction in CV mortality. Furthermore, it was observed that individuals with a lower ejection fraction who underwent treatment with dapagliflozin exhibited a decrease in all-cause mortality.[20]

The initial clinical evaluation of the Canagliflozin and Renal Events in DM With Established Nephropathy (CREDENCE) trial has been documented. This trial concentrates on the use of a specific SGLT2 inhibitor for renal purposes. This study involved the random administration of a placebo or a daily dose of 100 mg canagliflozin to a total of 4,401 patients with T2DM and chronic albuminuria renal disease, with an eGFR between 30 and 90 mL/min/1.73 m2. It is of the utmost importance to observe that all participants were required to have taken ACE-I or ARBs consistently for at least 4 weeks. Due to its efficacy, the trial was terminated early after a median follow-up period of 2.6 years. The results demonstrated a 30% reduction in the incidence of renal progression or cardiovascular mortality. Additionally, there was a significant decline in the incidence of hospitalisation for HF. There was no statistically significant disparity observed among the groups in terms of the risk of cardiovascular mortality or overall mortality. The findings presented in this study provide further evidence supporting the positive effects on renal health that were previously observed in sub-analyses of earlier trials focused on prevention. Additionally, this study demonstrates that SGLT2i can also offer benefits for patients with CKD and albuminuria who are experiencing HF.[21]

The DAPA-HF trial is an important study that evaluated the effect of Dapagliflozin on the incidence of HF deterioration or cardiovascular mortality in patients with chronic HF. This study included 4744 patients with stable class II-IV HF with HFrEF, optimal medical therapy, a serum N-terminal pro-B-type natriuretic peptide level above 600 pg/mL, and an eGFR above 30 mL/min/1.73 m2. Patients were randomly assigned to receive either a placebo or 10 mg of dapagliflozin daily. At baseline, more than 90% of patients were taking /ARBs and BB, and approximately 70% were also taking mineralocorticoids. A substantial proportion of participants in the DAPA HF study did not exhibit diabetes symptoms. The administration of dapagliflozin led to a reduction in the primary outcome measure, which included the combined occurrence of the time required for heart failure to worsen or cardiovascular-related mortality. The present study provides novel evidence demonstrating that inhibiting SGLT2 with dapagliflozin significantly reduces morbidity and mortality in HFrEF patients without diabetes.[22]

The EMPEROR-Reduced study also investigated the use of SGLT2 inhibitors in patients without diabetes. This study included 3,730 chronic heart failure patients with an LVEF of 40% or less. The effect of empagliflozin on the primary outcome was consistent across all patients, irrespective of their diabetes status. Significantly fewer hospitalisations for HF occurred in the empagliflozin group compared to the placebo group. Compared to the placebo group, the empagliflozin group experienced a reduced annual decline in eGFR. In addition, patients treated with empagliflozin were less likely to experience severe renal outcomes. The meta-analyses of DAPA-HF and EMPEROR-Reduced have demonstrated the efficacy of Empagliflozin and Dapagliflozin in reducing hospitalisation rates for HF, cardiovascular mortality, all-cause mortality, and improving renal protection outcomes in HF patients without comorbid T2DM.[23,24]

The DETERMINE-Reduced study compared the effects of Dapagliflozin 10 mg on the quality of life and functional capacity of individuals following three months of treatment with a placebo. After 16 weeks of observation, the scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) indicate that the administration of Dapagliflozin improves the functional status, as indicated by the positive trends in the present study. Notably, the subgroup of participants with the most severe symptoms exhibited the greatest improvement. However, it is important to observe that Dapagliflozin administration did not significantly improve the 6-minute walking test in this study.[25]

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The DAPA-HF trial is an important study that evaluated the effect of Dapagliflozin on the incidence of HF deterioration or cardiovascular mortality in patients with chronic HF. This study included 4744 patients with stable class II-IV HF with HFrEF, optimal medical therapy, a serum N-terminal pro-B-type natriuretic peptide level above 600 pg/mL, and an eGFR above 30 mL/min/1.73 m2. Patients were randomly assigned to receive either a placebo or 10 mg of dapagliflozin daily. At baseline, more than 90% of patients were taking /ARBs and BB, and approximately 70% were also taking mineralocorticoids. A substantial proportion of participants in the DAPA HF study did not exhibit diabetes symptoms. The administration of dapagliflozin led to a reduction in the primary outcome measure, which included the combined occurrence of the time required for heart failure to worsen or cardiovascular-related mortality. The present study provides novel evidence demonstrating that inhibiting SGLT2 with dapagliflozin significantly reduces morbidity and mortality in HFrEF patients without diabetes.[22]

The EMPEROR-Reduced study also investigated the use of SGLT2 inhibitors in patients without diabetes. This study included 3,730 chronic heart failure patients with an LVEF of 40% or less. The effect of empagliflozin on the primary outcome was consistent across all patients, irrespective of their diabetes status. Significantly fewer hospitalisations for HF occurred in the empagliflozin group compared to the placebo group. Compared to the placebo group, the empagliflozin group experienced a reduced annual decline in eGFR. In addition, patients treated with empagliflozin were less likely to experience severe renal outcomes. The meta-analyses of DAPA-HF and EMPEROR-Reduced have demonstrated the efficacy of Empagliflozin and Dapagliflozin in reducing hospitalisation rates for HF, cardiovascular mortality, all-cause mortality, and improving renal protection outcomes in HF patients without comorbid T2DM.[23,24]

The DETERMINE-Reduced study compared the effects of Dapagliflozin 10 mg on the quality of life and functional capacity of individuals following three months of treatment with a placebo. After 16 weeks of observation, the scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) indicate that the administration of Dapagliflozin improves the functional status, as indicated by the positive trends in the present study. Notably, the subgroup of participants with the most severe symptoms exhibited the greatest improvement. However, it is important to observe that Dapagliflozin administration did not significantly improve the 6-minute walking test in this study.[25]

3. Conclusion

HF is a complex medical condition characterised by the heart's diminished ability to circulate blood and supply oxygen to the body's organs and tissues. Pharmacotherapy plays a crucial function in the management of HFrEF patients. Pharmaceutical agents that modulate the RAAS and sympathetic nervous system, such as ACE-I, ARNIs, BB, and MRAs, have shown efficacy in improving survival rates, reducing hospitalisations, and alleviating symptoms. ARNIs, such as sacubitril/valsartan, have demonstrated more favourable outcomes than conventional ACE-I.

SGLT2i have been identified as potentially valuable therapeutic agents in the management of HFrEF. The pharmaceuticals in question, initially formulated for the purpose of managing diabetes, have exhibited advantages that extend beyond their primary function of glucose regulation. These benefits encompass a decrease in cardiovascular mortality rates as well as enhancements in outcomes related to HF. These medications can be included as part of the

conventional pharmacotherapy for patients with HFrEF, regardless of their diabetes status.

The effectiveness of SGLT2i in lowering glucose levels is constrained by the filtered load of glucose and the occurrence of osmotic diuresis. Nevertheless, the capacity of these medications to reduce blood glucose and A1C levels, along with their beneficial impact on cardiovascular morbidity and mortality, renders them a valuable choice for managing T2DM. SGLT2i have demonstrated favorable results in diverse clinical contexts, such as mitigating the likelihood of atherosclerotic cardiovascular disease, effectively treating HF, addressing diabetic kidney disease characterized by albuminuria, and managing CKD with albuminuria in individuals without diabetes. The inhibitory effects of these substances on the reabsorption of sodium and glucose in the tubule result in a decrease in intraglomerular pressure and an increase in filtration rate, thereby conferring advantages to renal function in certain groups of patients.

The cardiovascular and renal protective effects of SGLT2i have been strongly supported by significant evidence from prominent large-scale clinical trials, including EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and EMPEROR trials. Furthermore, it should be noted that the advantages of these medications are not limited to patients suffering from HFrEF. The EMPEROR-Preserved trial has demonstrated that these drugs also offer benefits to individuals with heart failure and preserved ejection fraction. Although SGLT2i have exhibited notable therapeutic efficacy, it is imperative to persist in conducting research and diligently monitor their long-term safety and potential adverse reactions. Similar to any medical intervention, a thorough comprehension of the mechanisms of these drugs and their effects on various patient populations will persistently guide their optimal utilization in clinical settings.

In general, SGLT2i have demonstrated considerable therapeutic promise in addressing diverse facets of metabolic disorders and cardiovascular well-being. The broad range of applications and numerous advantages associated with their use render them a valuable adjunct in the management of patients, both with and without T2DM, in the context of reducing or preserving ejection fraction in HF and its related comorbidities.

4. Declaration

4.1 Ethics Approval and Consent to participate
Not applicable.

4.2. Consent for publication
Not applicable.

4.3 Availibility of data and materials
Data used in our study were presented in the main text.

4.4 Competing interests
Not applicable.

4.5 Funding Source
Not applicable.

4.6 Authors contributions
Idea/concept: ZS. Design: ZS. Control/supervision: SW. Data collection/processing: ZS. Analysis/interpretation: ZS, SW. Literature review: ZS. Writing the article: ZS. Critical review: SW. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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