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Use of disease-modifying drugs in diabetic patients with heart failure with reduced ejection fraction

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Abstract
Type 2 diabetes mellitus and heart failure are closely related, patients with type 2 diabetes mellitus have a higher risk of developing heart failure, and those with heart failure are at increased risk of developing type 2 diabetes. Although no specific randomized clinical trials have been conducted to test the effect of cardiovascular therapies (drugs and/or devices) in diabetic patients with heart failure, a lot of evidence shows that all interventions effective in improving prognosis in patients with heart failure reduced ejection fraction are equally beneficial in patients with and without diabetes. However, the use of disease-modifying drugs in patients with diabetes and heart failure reduced ejection fraction is a clinical challenge due to the increased risk of adverse effects. For example, β-blockers are underutilized in diabetic patients due to the theoretical unfavorable effects on glucose metabolism as well as the use of drugs that interact with the renin-angiotensin system can be challenged in patients with diabetic nephropathy because of the risk of hyperkalemia. This review outlines the current use of disease-modifying drugs in diabetic patients with heart failure reduced ejection fraction. In addition, the role of novel pharmacologic agents as type 2 sodium-glucose co-transporter inhibitors (SGLT2ii) is discussed.

Keywords Heart failure reduced ejection fraction · Type II diabetes mellitus · β-blockers · Sacubitril/valsartan · Sodium-glucose co-transporter inhibitors

Introduction

Heart failure (HF) remains a significant challenge for healthcare systems in Western countries [1]. Although therapies that improve the survival of patients with HF with reduced ejection fraction (HFrEF; so-called disease-modifying drugs) have been identified since the 1990s, HF remains one of the most common causes of hospitalization and death in individuals older than 65 years [2].

Type 2 diabetes mellitus (T2DM), whose prevalence has been steadily increasing in recent years because of the obesity epidemic [3], is associated with at least a doubled risk of cardiovascular disease. T2DM and HF share several characteristics: they are both common, chronic, and increasing. Worldwide, an estimated 10% of the adult population has diabetes, an established risk factor for coronary artery disease, which is a leading cause of HF [4]. In addition, diabetes alone can produce diabetic cardiomyopathy [5], and 6% of patients with new-onset diabetes will develop HF within 5 years [6]. As a result, up to 30% of patients with HF have diabetes, making it one of the most common chronic comorbid conditions an HF specialist will face [7].

Considering the similarities in the efficacy and safety of renin–angiotensin–aldosterone axis blockade and β-blockers in patients with or without T2DM, diabetic patients with HFrEF should be treated with the same pharmacologic options as those without diabetes [8].

This review summarizes the existing evidence regarding the use of disease-modifying drugs in patients with T2DM.

The rationale for the use of disease-modifying drugs in HFrEF

The cardinal principle underlying the treatment of HFrEF is the antagonization of the neurohormonal systems implicated in disease progression [9]. Both the activation of the renin–angiotensin–aldosterone system (RAAS) and the

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increase in sympathetic nervous activity have an initial compensatory role in the presence of reduced stroke volume and cardiac output [10–12]. This leads to increased peripheral vascular resistance and blood volume through fluid and salt retention [13]. However, in the long term, activation of these systems results in altered myocyte function [14], extracellular matrix remodelling [15], and gene expression, causing left ventricular remodelling [16].

Given this pathophysiological background, randomized controlled clinical trials with large populations have demonstrated that angiotensin-converting enzyme inhibitors (ACE-i) [17], angiotensin II receptor blockers (ARBs) [18], β-blockers [19], mineralocorticoid receptor antagonists (MRAs) [20], and more recently sacubitril/valsartan [21], a progenitor of the neprilysin inhibitor/ARBs (ARNIs), have significant clinical and pathophysiological benefits in patients with HFrEF (Fig. 1).

A novel therapeutic approach in patients with HFrEF, not based on neurohormonal modulation, is based on type 2 sodium-glucose co-transporter (SGLT2) inhibitors (SGLT2i) [22]. Initially evaluated as hypoglycemic drugs in T2DM, these drugs have subsequently demonstrated the extraordinary ability to reduce mortality and hospitalizations in patients with HFrEF [23].

The mechanisms by which SGLT2i can confer myocardial protection are numerous (Table 2) and not yet wholly known. The primary mechanism of myocardial protection is likely based on changes in energy substrates [24]. SGLT2i changes the cardiac fuel supply from fatty acids and glucose to ketone, increasing overall cardiac adenosine triphosphate production [25].

Use of disease-modifying drugs in HFrEF patients with T2DM

Although none of the trials based on the use of disease-modifying for HFrEF patients exclusively encompassed a diabetic patient population, the incidence of T2DM among participants ranged from 20 to nearly 50%, with the proportion of diabetic patients gradually increasing over the past two decades.

The following sections analyze the specific use of disease-modifying drugs in patients with diabetes.

β-Blockers

β-Blockers are the central component of standard therapy in patients with HFrEF; however, their use in patients with T2DM has been historically controversial [26]. The main reason for this concern is the adverse effect of β-blockers on glucose metabolism (Fig. 2). β-Blockers are thought to contribute to the development of hyperglycemia by impairing insulin release from pancreatic β-cells [27]. Interestingly, carvedilol and nebivolol are not associated with the development of hyperglycemia or new-onset diabetes [28].

Another concern is that β-blockers may mask the symptoms of hypoglycemia [29]. Neurogenic catecholamine-mediated hypoglycemic symptoms hidden by this class of drugs include hunger, tremors, irritability, and palpitations [30].

However, the positive effects that β-blockers exert in patients with HF and the improvement in prognosis that they also determine in patients with T2DM are certainly more significant than the hypothetical disadvantages.

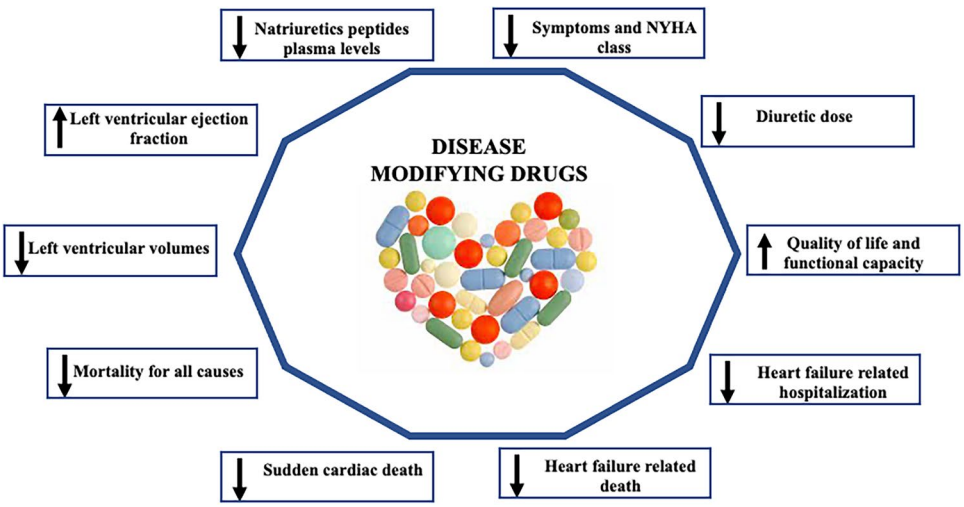

Fig. 1 Clinical and pathophysiological effects of disease-modifying drugs in HFrEF patients

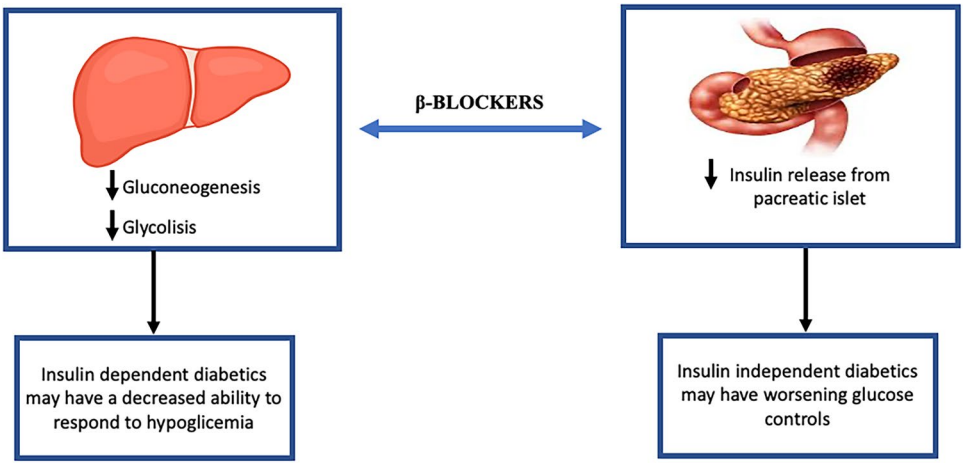

Fig. 2 Effects of β-blockers on glucose metabolism in patients with T2DM

Therefore, β-blockers represent the drugs of choice for treating HFrEF also in diabetic patients [31].

The landmark Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) that investigated the effects of extended-release metoprolol showed not only that the risk of hospitalization for HF was more significant in diabetic patients (who represented 25% of the population) than non-diabetics but also that treatment with the β-blocker resulted in a 37% reduction in hospitalizations for HF, similar to that observed in the group without diabetes [32, 33].

Pooling of mortality data from several β-blockers trials, notably the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), MERIT-HF, and the Carvedilol Prospective Randomized Cumulative Survival trial (COPERNICUS), showed that therapy resulted in similar survival benefits in patients with and without T2DM [34]. Furthermore, the latter meta-analysis of six pivotal β-blocker studies, including 3230 patients with T2DM, showed that β-blockers significantly reduced mortality in individuals with (relative risk 0.84 [95% CI 0.73–0.91]) and without (relative risk 0.72 [95% CI 0.65–0.79]) diabetes [35]. However, the magnitude of the reduction was more significant in patients without diabetes ($P = 0.023$).

In addition, concerns related to worse glycemic control in T2DM patients treated with β-Blockers seem unfounded; in a recent study in which 125 diabetic patients were enrolled, the use of carvedilol or bisoprolol did not worsen glycemic control or albuminuria status in diabetic patients with HFrEF [36].

In summary, β-blocker therapy in patients with HFrEF and T2DM significantly reduce morbidity and mortality. These benefits far outweigh the theoretical risks associated with hypoglycemia and poor glycemic control.

Therefore, the use of β-blockers should not be avoided in patients with HFrEF and T2DM, carvedilol and bisoprolol preferred [37], which have been shown not to adversely affect the glycemic profile.

ACE-i and ARBs

Following international guidelines for diagnosing and treating HFrEF, ACE-i, or ARBs are indicated as first-line therapy in patients with HFrEF with or without symptoms, in the absence of contraindications [38]. The clinical benefit includes reduced mortality, rehospitalizations, and progression of HF and has been observed independently of the presence of diabetes [39].

In the trials Studies of Left Ventricular Dysfunction Treatment (SOLVD) [40], Survival and Ventricular Enlargement (SAVE) [41], Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) [42], and Vasodilator Heart Failure Trial II (VHEFTII) [43], the use of ACE-i resulted in improved survival in patients with HFrEF. The designs of these studies did not include specific analyses for the subgroup of patients with T2DM. However, the Heart Outcomes Prevention Evaluation (HOPE) trial, which included patients at high risk for cardiovascular events but with ejection fraction values > 40% without signs and symptoms of HF, use of ramipril was associated with a marked reduction in the risk of myocardial infarction, death, and stroke, as well as a 22% reduction in the incidence of HFrEF [44]. These effects were most pronounced in patients with T2DM [45]. Similarly, in the Trandolapril Cardiac Evaluation (TRACE) trial, which enrolled patients with prior myocardial infarction and left ventricular dysfunction, trandolapril use resulted in a 27% increase in life expectancy [46]. Specifically, in patients with T2DM, reductions occurred in cardiovascular death (44%), sudden cardiac death (54%), and progression to HF (62%) with trandolapril. Therefore, in that study, in patients with diabetes (regardless of type and insulin use) and left ventricular systolic dysfunction secondary to coronary artery

disease, trandolapril use resulted in anti-ischemic and anti-remodelling effects that appear interrelated [47].

The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial evaluated the efficacy of candesartan therapy in patients with HFrEF [48]. The trial enrolled 4576 patients randomized to candesartan (2289) or placebo (2287). This trial showed that candesartan use resulted in a significant reduction in cardiovascular mortality and HF-related hospitalizations, regardless of the presence of diabetes [49].

Furthermore, in the Valsartan Heart Failure Trial (ValHeFT), treatment with valsartan resulted in a significant relative risk reduction in the primary composite endpoint (HF-related deaths and HF-related hospitalizations), regardless of the presence of diabetes [50].

Finally, the Effects of High-Dose versus Low-Dose Losartan on Clinical Outcomes in Patients with Heart Failure (HEAAL) trial showed that 150 mg daily of losartan was superior to 50 mg daily in reducing the risk of death or HF hospitalizations [51, 52]. Also, in this trial, the treatment effect was not different in the subgroup of patients with T2DM compared with those without diabetes (HR 0.96; interaction $P = 0.35$).

Although both ACE-i and ARBs are drugs capable of modifying the course of HFrEF and T2DM patients, the significant advantage conferred by ARNIs justifies their use only in patients intolerant to the latter.

MRAs

The MRAs spironolactone and eplerenone are recommended as first-line therapy for patients with symptomatic HFrEF. In the RandomizedRandomized Aldactone Evaluation Study (RALES) trial, spironolactone was compared with placebo in patients with a left ventricular ejection fraction < 35% and NYHA class III/IV [53]. In the spironolactone group, a reduction was documented in all-cause mortality (relative risk of death 0.70 [95% CI 0.60–0.82]; $P < 0.001$) and hospitalizations for worsening HF (relative risk of hospitalization 0.65 [95% CI 0.54–0.77]; $P < 0.001$). However, it should be noted that in this study, the population of patients treated with β-blockers was very low (around 10% of the total population). In the more recent Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, the use of eplerenone in patients with left ventricular ejection fraction < 30% (or < 35% in patients with a QRS duration > 130 ms) and NYHA class II resulted in reduced cardiovascular mortality (hazard ratio 0. 76 [95% CI 0.61–0.94]; $P = 0.01$) and HF-related hospitalizations (hazard ratio 0.77 [95% CI 0.67–0.88]; $P < 0.001$) [54]. Notably, in the EMPHASIS- HF trial, conducted 12 years after the RALES trial, the percentage of patients on β-blockers was significantly higher (> 85% of the overall population).

Although the beneficial effects of MRAs are also evident in diabetic patients with HFrEF, these drugs are underutilized in patients with HFrEF and T2DM due to the increased risk of hyperkalemia [55]. The advent of finerenone, a third-generation MRA, expands the therapeutic possibilities in patients with T2DM and HFrEF [56]. In the Mineralocorticoid Receptor Antagonist Tolerability Study—Heart Failure (ARTS-HF) trial, finerenone demonstrated similar efficacy to eplerenone in causing a > 30% reduction in NT-proBNP [57]. Top-line results from the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIDELIO-DKD) trial indicated that the study met its primary renal endpoint and achieved a secondary cardiovascular endpoint [58].

Specific effects on HFrEF patients have not been reported.

Although the use of MRAs in patients with HFrEF and T2DM is currently suboptimal in large part because of the fear of inducing hyperkalemia, it can be expected that in the coming years, the use of newer MRAs (such as finerenone) and newer potassium-lowering agents (such as patiromer and sodium zirconium cyclosilicate) will allow for increased use of these drugs to decrease cardiovascular mortality and HF hospitalizations further and improve patient wellbeing.

Sacubitril/valsartan

A significant advance in neurohormonal modulation was the advent of sacubitril/valsartan, the parent drug of ARNIs [21], which can simultaneously block angiotensin receptors and inhibit neprilysin (an enzyme involved in the degradation of natriuretic peptides).

In the prospective trial Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF), sacubitril/valsartan was superior to enalapril in reducing the composite endpoint of death and HF-related hospitalizations in more than 8,000 HFrEF patients with NYHA class II-IV [59]. In the subgroup with T2DM (35% of the total population), a trend was found toward reduced mortality in the sacubitril/valsartan group, with a statistically significant reduction in HF-related hospitalizations of 21% compared with the enalapril group.

In the post hoc analysis, treatment with sacubitril/valsartan was associated with a more significant reduction in HbA1c and a lower initiation rate of insulin or other diabetes medications than enalapril [60].

The mechanisms by which sacubitril/valsartan results in improved glycemic control are not known [61], but much of the experimental evidence shows that these are essentially related to the action of sacubitrilat (the active metabolite of sacubitril) rather than of valsartan (Table 1). A recent post hoc analysis of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF)

Table 1 Potential mechanism of beneficial effect of sacubitril/valsartan on glycemic control

Type of mechanism	Pathophysiology of mechanism
Increased lipid mobilizationmobilization from adipose tissue	Increased natriuretic peptide activity due to neprilysin inhibition
Increased postprandial lipid oxidation	Increased natriuretic peptide activity due to neprilysin inhibition
Increased adiponectin synthesis	Increased natriuretic peptide activity due to neprilysin inhibition
Improved insulin sensitivity	Increased bradykinin activity due to neprilysin inhibition
Increased insulin secretion	Increased glucagon-like peptide 1 activity due to neprilysin inhibition
Reduction hunger and food intake	Increased glucagon-like peptide 1 activity due to neprilysin inhibition
Improved insulin sensitivity	Blockade of angiotensin receptor type II

trial showed that effects of sacubitril/valsartan on reverse cardiac remodelling (reduction of left ventricular volumes and increased of left ventricular ejection fraction), biomarker concentrations (reduction of NT-proBNP plasma levels), and health status (increased Kansas City Cardiomyopathy Questionnaire-23 Overall Summary scores) were extended to patients with T2DM, who represented 45% of the overall trial population [62].

Finally, a secondary analysis of PARADIGM-HF [63] showed that compared with patients treated with enalapril, those treated with sacubitril/valsartan had a slower rate of decline in estimated glomerular filtration rate (− 1.3 ml/min/1.73 m^2 vs − 1.8 ml/min/1.73m^2 per year; $P < 0{\cdot}0001$), and the magnitude of the benefit was more significant in patients with versus those without diabetes (0.6 mL/min/1.73 m^2 per year [95% CI 0.4–0.8] in patients with diabetes vs 0.3 mL/min/1.73 m^2 per year [CI 0.2–0.5] in those without diabetes; $P = 0.038$).

Considering the evidence described, ARNIs represent the first-line disease-modifying drugs for patients with HFrEF and T2DM.

SGLT2i

This new class of antidiabetic drugs,with a pleiotropic cardioprotective effect (Table 2), has been shown in recent randomized clinical trials to reduce hospitalizations for HF and, although not universally, mortality from cardiovascular causes [64, 65].

In the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial [66], which enrolled 7020 patients with diabetes and established cardiovascular disease, the use of empagliflozin was associated with reduced cardiovascular mortality (38% relative risk reduction), hospitalization for HF (35% relative risk reduction), and death from any cause (32% relative risk reduction).

In the subsequent Canagliflozin Cardiovascular Assessment Study (CANVAS) [67] and Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) trial [68], the use of SGLT2i was associated with a lower risk of cardiovascular events, including the risk of hospitalizations for HF.

Finally, in the more recent ERTugliflozin CardioVascular Outcomes trial (VERTIS-CV), the use of ertugliflozin also resulted in a significant reduction in hospitalizations for HF (30% relative risk reduction) [69]. Based on these results, a new series of trials have been designed to document the efficacy of these pharmacological agents in patients with HFrEF in the absence of diabetes.

The Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial examined the SGLT2i dapagliflozin in patients with and without diabetes with an HFrEF [70]. The primary endpoint was a combination of cardiovascular death and worsening HF (hospitalizations or outpatient visits for unplanned HF with a need for intravenous diuretic or inotropic therapy). The primary endpoint was significantly reduced in patients on dapagliflozin therapy (relative risk reduction 26%), regardless of the presence of diabetes.

Also, a post hoc analysis of DAPA-HF showed that dapagliflozin reduces the risk of a composite endpoint of serious ventricular arrhythmia, resuscitated cardiac arrest, or sudden death. In fact, 140/2373 patients (5.9%) of participants assigned to dapagliflozin experienced the composite outcome vs 175/2371 patients (7.4%) in the placebo group

Table 2 Molecular mechanism of myocardial protection of SGLT2i

Myocardial effects	Systemic effects
Reduction sodium/hydrogen exchanger activity	Improved renal function
Reduction calmodulin-dependent protein kinase II activity	Improved energetics
Reduction nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 activity	Reduction sympathetic nervous system activity
Increased autophagy	Increase erythropoietin activity

[hazard ratio 0.79 (95% confidence interval 0.63–0.99), $P = 0.037$] [71].

Regarding renal outcomes, a secondary analysis of DAPA-HF, the rate of decline of estimated glomerular filtration rate between day 14 and 720 was less with dapagliflozin versus placebo (− 1.09 ml/min/1.73 m^2 versus placebo − 2.85 ml/min/1.73 m^2, $P < 0.001$) [72].

In the recent Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure (EMPERORReduced) trial [73], the use of empagliflozin resulted in a 25% reduction in the primary endpoint (cardiovascular death or hospitalizations for HF). These results are similar to those of DAPA-HF; however, in EMPEROReduced, no reduction occurred in cardiovascular mortality (HR 0.92 [95% CI 0.75–1.12]).

In the Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF) enrolled 105 patients with HFrEF and diabetes or prediabetes, randomized to (empagliflozin (52 patients) and placebo (53 patients) [74]. At 36 weeks of follow-up patients in the empagliflozin group have a greater reduction left ventricular end-systolic volume index (assessed by cardiac magnetic resonance) respect patients in placebo group (− 7.9 ml/m2 vs − 1.5 ml/m^2; $P = 0.015$).

So the reverse remodelling of the left ventricle may represent a mechanism by which SGLT2i reduce HF hospitalizations and cardiovascular deaths.

Similar to dapagliflozin, empagliflozin also has favourable effects on renal outcomes in patients with HFrEF.

In fact, in the EMPERORReduced trial, the rate of the decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (− 0.55 ml/min/1.73 m^2 per year vs − 2.28 ml/min/1.73 m^2 per year), for a between-group difference of 1.73 ml/min/1.73 m^2 per year (95% CI, 1.10 to 2.37; $P < 0.001$).

Based on these data and following the most recent international guidelines on the management of HF [75], we recommend using SGLT2i, such as dapagliflozin and empagliflozin, in association with other disease-modifying drugs in all HFrEF patients with or without T2DM.

Conclusion

The presence of comorbidities often complicates the treatment of patients with HFrEF. Among these, T2DM has recently gained more attention because of the pathophysiological link between the two diseases and the increasing prevalence of HFrEF and T2DM. The coexistence of the two conditions imposes the need for a multidisciplinary approach tailored to the needs of individual patients. In this sense, the combined use of drugs with innovative mechanisms of action such as ARNIs and SGLT2i can have complimentary benefits in both chronic disease states, which is not surprising considering their pathophysiologic overlap.

Although initial observations are encouraging, ad hoc clinical trials are needed to confirm the safety and efficacy of ARNI/SGLT2i combination therapy in high-risk patients such as those with T2DM.

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