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Review Article **Cardiology**

The Use of Oral Antidiabetics in Heart Failure: A Promising Therapeutic Approach

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Abstract

This article examines the use of oral antidiabetic agents in the treatment of heart failure. Heart failure is a serious condition that is often associated with diabetes mellitus, which worsens the prognosis for patients. Oral antidiabetic agents, such as SGLT2 inhibitors and GLP-1 receptor agonists, have recently gained increasing interest due to their potential beneficial effects on cardiac function. Clinical studies have shown that these medications reduce cardiovascular morbidity and mortality, decrease hospitalizations for heart failure, and improve cardiac function in patients with heart failure, whether they are diabetic or not. The mechanisms of action of these medications include blood pressure reduction, improvement in endothelial function, modulation of cardiac energy metabolism, and reduction of oxidative stress and inflammation. While these findings are promising, further research is needed to better understand the long-term effectiveness and optimization of the use of these medications in the context of heart failure.

Keywords: Sglt2 Inhibitors, Heart Failure, Diabetes Mellitus, Cardiovascular Outcomes, Hospitalization For Heart Failure.

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I. INTRODUCTION

Heart failure (HF) is a serious medical condition characterized by the heart's inability to pump enough blood to meet the body's needs. It is often associated with comorbidities such as diabetes mellitus, which significantly worsens the prognosis of patients [1]. Oral antidiabetic drugs have long been a controversial class of medications in the treatment of heart failure due to their potential adverse effects on the cardiovascular system. However, recent research has highlighted potential benefits of certain oral antidiabetic agents in patients with heart failure [2, 3, 4].

II. Diabetes and Heart Failure Relationship

Independent of the presence of coronary lesions, there is a direct relationship between diabetes and HF. A term coined to describe this is diabetic cardiomyopathy. Its pathophysiological basis involves the presence of microvascular disease, fibrosis, inflammation, and myocardial metabolic disorders [5].

The percentage of diabetic individuals among HF patients is increasing more rapidly than diabetes in the general population. The risk of heart failure (HF) is multiplied by two to three in diabetics. The role of glycemic imbalance is demonstrated, with an increased risk of HF ranging from 8% to 30% according to studies, for a 1% increase in HbA1c levels [1].

The recommendations regarding glycemic control are becoming increasingly stringent, with HbA1c targets that should be <7% or even 6.5%, aiming to prevent micro- and macrovascular complications of diabetes. This often requires combining two or three oral antidiabetic agents, possibly in combination with insulin, in type 2 diabetics. Therapeutic strategies and medications need to be well tolerated in the long term, especially from a cardiac perspective. Precautions should be taken into account, even if the levels of evidence are not very high [1].

III. Novel Classes of Oral Antidiabetic Drugs

1- **Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors:** SGLT2 inhibitors, such as dapagliflozin and empagliflozin, are oral antidiabetic drugs that reduce renal glucose reabsorption and promote glucose excretion in the urine. Recent clinical trials have demonstrated that these medications improve

clinical outcomes in patients with heart failure, regardless of their diabetic status. They reduce cardiovascular morbidity and mortality, decrease hospitalizations for heart failure, and slow disease progression [1, 2, 3, 4].

2- **Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists:**GLP-1 receptor agonists, such as liraglutide and exenatide, are also oral antidiabetic drugs used to treat type 2 diabetes. They act by increasing insulin secretion and reducing glucagon secretion. Recent studies have shown that these medications reduce hospitalizations for heart failure and improve cardiac function in patients with heart failure, regardless of their diabetic status. They also offer benefits in terms of weight loss and blood pressure control [1, 6, 7].

IV. Mechanisms Of Action And Beneficial Effects Of Oral Antidiabetic Drugs In Heart Failure With Reduced Ejection Fraction (Hfref)

Oral antidiabetic drugs, particularly SGLT2 inhibitors and GLP-1 receptor agonists, exert beneficial effects in heart failure through several mechanisms. These medications reduce blood pressure, decrease cardiac preload and afterload, improve endothelial function, reduce cardiac remodeling, decrease oxidative stress and inflammation, and modulate cardiac energy metabolism. These combined effects contribute to an overall improvement in cardiac function and a reduction in adverse cardiovascular events. SGLT2 inhibitors, in particular, have beneficial cardio-renal effects. The rapid onset of these effects suggests a mechanism of action independent of glycemic control. Although the exact mechanisms of action of SGLT2 inhibitors are unknown, osmotic diuresis due to glycosuria and concomitant natriuresis appears to be essential [8].

V. Integration of SGLT2 Inhibitors in the Treatment of Heart Failure :

After many years of stability, the therapeutic strategy for HFrEF is evolving with the introduction of several first- and second-line medications. The newcomers mainly consist of two therapeutic classes that have recently demonstrated their benefits in heart failure: SGLT2 inhibitors, recommended as first-line therapy, and guanylate cyclase stimulators, recommended as second-line therapy in worsening patients [5, 8].

Significant reduction in a composite endpoint of hospitalization for heart failure and cardiovascular death has been observed in patients treated with SGLT2 inhibitors [1].

The beneficial effects of SGLT2 inhibitors on heart failure in patients with type 2 diabetes have led to the creation of the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) trials. These trials were the first to demonstrate a significant beneficial effect of SGLT2 inhibitors on HFrEF in patients without diabetes [1, 2, 3, 4].

SGLT2 inhibitors have also been shown to reduce the risk of worsening renal function in diabetic and non-diabetic patients with chronic kidney disease. This is an important finding, as chronic kidney disease is present in one-third of patients with heart failure and is associated with increased mortality. Preventing the progression of chronic kidney disease may be beneficial for patients with heart failure [1].

- SGLT2 inhibitors can be prescribed to HFrEF patients in addition to angiotensin-neprilysin inhibitors, mineralocorticoid receptor antagonists, and beta-blockers.
- SGLT2 inhibitors can be prescribed both in an outpatient setting and during hospitalization (e.g., during a hospital stay for decompensated acute heart failure).
- Common side effects of SGLT2 inhibitors include genital infections and volume depletion. Diuretic doses may need to be adjusted in patients predisposed to hypovolemia.

VI. Role Of SGLT2 Inhibitors In Heart Failure With Preserved Ejection Fraction (Hfpef) :

In large previous clinical trials (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58), it has been demonstrated that SGLT2 inhibitors attenuate HF progression by reducing the risk of hospitalizations for HF in patients with type 2 diabetes, primarily without HF at baseline. This benefit has further been supported by positive outcomes on HF-related endpoints (cardiovascular mortality and hospitalizations for HF) in HF patients with preserved ejection fraction (HFpEF) in the EMPEROR-Preserved (empagliflozin) and DELIVER (dapagliflozin) trials. Several biological mechanisms beyond glycosuria are attributed to these agents in this context, including anti-inflammatory effects, reduction of fibrosis and apoptosis, improvement of myocardial metabolism, optimization of mitochondrial function, and protection against oxidative stress. Furthermore, SGLT2 inhibitors may also improve ventricular loading conditions by promoting diuresis and natriuresis and improving vascular and renal function. Additionally, they may reduce passive myocardial stiffness (diastolic function) by enhancing the phosphorylation of myofilament modulatory proteins [9].

VII. CONCLUSION

Oral antidiabetic drugs, particularly SGLT2 inhibitors and GLP-1 receptor agonists, represent a promising new therapeutic avenue in the treatment of heart failure. Their beneficial effects on cardiovascular morbidity and mortality, regardless of diabetic status,

make them attractive treatment options. However, it is important to emphasize that these medications should be used with caution, taking into account individual patient characteristics. Further research is needed to better understand the mechanisms of action and long-term efficacy of these drugs in heart failure.

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