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EFFICACY AND SAFETY OF SGLT2 INHIBITORS IN THE TREATMENT OF HEART FAILURE: A COMPREHENSIVE REVIEW

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Abstract: Objective: To evaluate the efficacy and safety of sodium-glucose cotransporter type 2 inhibitors (SGLT2 inhibitors) in the treatment of heart failure. **Method:** Bibliographic review carried out in the PubMed database based on the PVO strategy using the terms "SGLT2 inhibitors", "heart failure", "efficacy" and "safety", combined with the Boolean operators AND and OR. After screening, 15 articles were selected for critical analysis. **Discussion:** SGLT2 inhibitors have demonstrated efficacy and safety in the management of heart failure, resulting in significant clinical improvement and a reduction in adverse outcomes, including cardiovascular mortality and heart failure-related hospitalizations. **Final considerations:** Despite the benefits observed, more studies are needed to elucidate the precise mechanisms of action of these drugs and optimize their application in specific subgroups of patients.
Keywords: SGLT2 inhibitors; Heart failure; Efficacy.

INTRODUCTION

Heart failure (HF) is one of the leading causes of morbidity and mortality worldwide, affecting around 26 million people globally. The condition is triggered by structural and/or functional changes in the heart, which result in ventricular systolic and/or diastolic dysfunction. Characteristic symptoms include dyspnea, fatigue and fluid retention, which significantly impair patients' quality of life (Dong *et al*., 2021). The classification of HF is based on the ejection fraction (EF) of the left ventricle, and three main types are identified: HF with reduced ejection fraction (HFrEF), HF with slightly reduced ejection fraction (HFmEF) and HF with preserved ejection fraction (HFpEF) (Wagdy *et al*., 2021).

While the prevalence of HFpEF has stabilized in developed countries, HFpEF and HFpEF are continuously increasing, espe-

cially in emerging countries and in elderly populations. This increase can be attributed to population aging and the high prevalence of cardiovascular risk factors, such as hypertension, obesity, dyslipidemia and type 2 diabetes mellitus (DMT2) (Stachteas *et al*., 2024). In addition, HFpEF is prevalent in women and elderly patients, and is exacerbated in the presence of type 2 diabetes mellitus (T2DM) (Scheen; Bonnet, 2023).

The increase in the prevalence of HF also entails a significant increase in the medical costs associated with managing the disease. In countries such as the United States, it is projected that costs related to HF will grow from US$ 30.7 billion to US$ 69.8 billion by 2030 (Fang *et al*., 2024). In addition, mortality rates remain alarming: studies such as the Framingham Heart Study have shown that around 50% of patients diagnosed with HF die within five years of their initial diagnosis, while readmission rates exceed 80% (Dong *et al*., 2021).

Conventional treatments for HF, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers and digitalis, have improved the management of the disease, but still have significant limitations, especially in terms of reducing mortality and recurrent hospitalizations (Dong *et al*., 2021). In this context, new therapeutic approaches are essential to optimize treatment and clinical outcomes.

Inhibitors of the sodium-glucose cotransporter type 2 (iSGLT2) have emerged as an innovative and promising class of drugs initially developed for the management of diabetes mellitus. These agents have demonstrated significant cardioprotective and renoprotective effects in clinical trials, including a reduction in hospitalizations for HF and cardiovascular mortality (Wagdy *et al*., 2021). The mechanism of action involves inhibiting glucose reabsorption by the proximal renal tubules, which concomitantly increases sodium and water excretion, generating beneficial hemodynamic effects (Scheen; Bonnet, 2023).

However, the use of iSGLT2 is also associated with adverse events such as volume depletion, hypotension, hypoglycemia, genitourinary infections and, in rarer cases, acute kidney injury. These adverse effects tend to be more frequent in elderly patients. Recent studies highlight that although adverse events such as volume depletion are more common in the elderly, the cardiovascular and renal benefits of iSGLT2 remain consistent in this population.

According to Waijer *et al.* (2022), the positive effects on kidney function and cardiovascular outcomes outweigh the associated risks, even in high-risk patients. Similarly, Butt *et al*. (2021) showed that the use of dapagliflozin significantly reduces NT-proBNP levels, markers of myocardial dysfunction, without a substantial increase in serious adverse events. In populations with HFpEF, studies such as Dewan *et* al. (2020) and Chatur *et al*. (2023) corroborate the safety of the class in the elderly, with consistent results in reducing hospitalizations and cardiovascular mortality, promoting a safe and effective approach to HF management.

Despite these limitations, there is consistent evidence that SGLT-2 inhibitors offer substantial benefits for patients with HFrEF, including a reduction in hospitalizations and cardiovascular mortality. However, the efficacy and safety of these drugs in patients with HFpEF are still areas of intense investigation, with controversial and heterogeneous results (Dong *et al*., 2021; Li *et al.*, 2023).

With this in mind, the aim of this study is to evaluate the efficacy and safety of iSGLT2 (such as dapagliflozin and empagliflozin) in the treatment of heart failure, covering both HFrEF and HFpEF. The objective is to investigate the effects of these drugs on clinical ou-

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tcomes, such as reduction in hospitalizations, cardiovascular death, improvement in symptoms and quality of life, as well as the risks and adverse effects associated with their use.

METHODOLOGY

This study is characterized as a literature review based on the PVO strategy, which represents the elements: population or research problem, variables and outcome. This approach was used to formulate the following research question: "What is the efficacy and safety of iSGLT2 in the treatment of heart failure, both with reduced and preserved ejection fraction, in relation to clinical outcomes such as hospitalizations, cardiovascular mortality, quality of life and adverse effects?"

The searches were carried out in the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) database, using a structured search strategy using descriptors and Boolean operators "AND", "OR" and "NOT". The search strategy used was: ("efficacies"[All Fields] OR "efficacious"[All Fields] OR "efficaciously"[All Fields] OR "efficaciousness"[All Fields] OR "efficacy"[All Fields]) AND ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields]) AND ("sodium glucose transporter 2 inhibitors"[Pharmacological Action] OR "sodium glucose transporter 2 inhibitors"[MeSH Terms] OR "sodium glucose transporter 2 inhibitors"[All Fields] OR ("sglt2"[All Fields] AND "inhibitors"[All Fields]) OR "sglt2 inhibitors"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]).

The application of this strategy initially resulted in a total of 335 articles, which were subjected to the previously established inclusion and exclusion criteria. The inclusion criteria adopted were: articles published in English; in the period from 2019 to 2024; and which directly addressed the proposed themes, including review-type studies, meta-analyses, observational studies, experimental studies and clinical studies. On the other hand, the exclusion criteria were defined as: duplicate articles; studies available only in abstract form; publications that did not directly address the central theme of the study; and those that did not meet the inclusion criteria described.

After initial screening to remove duplicates, the 335 articles were reduced to 291 publications. The inclusion and exclusion criteria were then carefully applied, resulting in the selection of 15 articles considered eligible to make up the database for this literature review.

This methodology was designed to ensure the selection of relevant, up-to-date and high-quality studies, providing a solid basis for the critical analysis of clinical outcomes related to the efficacy and safety of iSGLT2 in the treatment of heart failure.

DISCUSSION

CLINICAL EVIDENCE ON DAPAGLIFLOZIN IN HEART FAILURE

According to Waijer *et al.* (2022), this drug has been shown to be effective in slowing the progression of chronic kidney disease (CKD), regardless of initial severity or the presence of diabetes. In addition, dapagliflozin contributes to a significant reduction in HF-related hospitalizations, strengthening its role in the management of patients at high risk of kidney failure and cardiovascular disease. This evidence suggests that the early use of iSGLT2 can be considered even in patients without diabetes, promoting a preventive and comprehensive approach.

In the DAPA-HF study described by Jackson and McMurray (2021), dapagliflozin significantly reduced the risk of worsening HF and cardiovascular death, regardless of the use of diuretics. This benefit was consistent

in several subgroups, indicating the medication's applicability in high morbidity scenarios. In addition, strategies that expand access to dapagliflozin could prevent serious complications such as renal failure and recurrent hospitalizations, generating considerable long-term savings for health systems.

Another relevant aspect is the impact of dapagliflozin on improving biomarkers and clinical outcomes. Butt *et al.* (2020) point out that the use of dapagliflozin is associated with a significant reduction, within six months, in levels of NT-proBNP, a biomarker of myocardial dysfunction. This reduction reflects an improvement in cardiac function, with a reduction in the risk of cardiovascular death and relief of HF symptoms. These findings reinforce the usefulness of dapagliflozin as an essential intervention to improve prognosis in patients with HF.

THERAPEUTIC BENEFITS OF iSGLT2 IN DIFFERENT PATIENT PROFILES

The iSGLT2 have shown consistent efficacy in improving clinical outcomes in HF, regardless of left ventricular ejection fraction (LVEF), age or the presence of diabetes. According to Dewan *et al.* (2020), these drugs are effective in patients with both HFrEF and HFpEF, demonstrating their broad applicability. Dapagliflozin, in particular, significantly reduced the risk of cardiovascular death and hospitalizations, offering a promising alternative for patients with metabolic conditions and multiple comorbidities. These findings highlight the relevance of iSGLT2 in complex patient subgroups, including those with greater clinical vulnerability, such as the elderly and individuals with severe metabolic dysfunctions.

The benefits of iSGLT2 in elderly patients have been consistently reinforced by recent studies. The results of the DELIVER study, described by Peikert *et al.* (2022, 2024), confirmed the robust efficacy of dapagliflozin in this population, showing not only a significant improvement in cardiovascular outcomes, but also no increase in the incidence of serious adverse events such as hypoglycemia or volume depletion. This evidence suggests that dapagliflozin is a safe and effective option for the management of HF in more vulnerable groups, such as older individuals and those with a greater burden of comorbidities, promoting cardiovascular and renal benefits without compromising safety.

In the context of post-hospitalization management, Salah *et al.* (2022) observed that the introduction of iSGLT2 during or shortly after hospital discharge contributes significantly to reducing the risk of readmissions and improving patient-reported outcomes. These benefits are attributed not only to diuretic effects, but also to cardioprotective mechanisms that include optimization of cardiac energy metabolism and anti-inflammatory actions. These mechanisms, when added to the improvement in symptoms and reduction in mortality rates, consolidate iSGLT2 as an essential intervention for HF patients in high morbidity contexts.

In addition, Chatur *et al.* (2023) highlighted that the benefits of iSGLT2 are widely applicable to patients with multiple comorbidities, such as renal failure associated with HF and metabolic conditions. Their studies showed that iSGLT2s, such as dapagliflozin and empagliflozin, maintain a consistent safety and efficacy profile across different risk profiles, even in populations with significant vulnerabilities. This data reinforces the need to consider these drugs as a standard therapeutic approach for HF, prioritizing their integration into clinical management guidelines.

LIMITATIONS AND CHALLENGES IN USING iSGLT2

Although iSGLT2s are widely recognized for their benefits in the management of HF, some important limitations and clinical challenges remain. According to Sharma *et al.* (2020), one of the main restrictions of this pharmacological class is related to its contraindication in patients with a glomerular filtration rate (GFR) of less than 45 mL/min/1.73m². This limitation is due to the mechanism of action of iSGLT2, which promotes natriuresis and early diuresis, which can cause complications such as dehydration and electrolyte imbalances in patients with advanced renal failure. This restriction reduces the therapeutic reach of the class and reinforces the need for alternative approaches or adapted strategies for patients with significant renal impairment.

In addition, recent studies have hypothesized that there are differences in terms of efficacy and safety between the various iSGLT2s, such as dapagliflozin, empagliflozin and canagliflozin. Although the general benefits of these drugs in the management of HF are well established, comparative studies are limited, making it difficult to identify the most effective and safe option for different subgroups of patients. This knowledge gap highlights the need for additional studies that can provide a clearer picture of the particularities of each iSGLT2, including potential differences in cardiovascular and renal outcomes and overall safety (Patel; Kaye, 2022).

Another challenging aspect is the heterogeneity of the evidence on the efficacy of iSGLT2 in the management of diuretic resistance, as pointed out by Stachteas *et al.* (2024). Although these drugs have proved useful in mitigating diuretic resistance in HF patients, their diuretic effect alone may not be powerful enough to relieve signs of congestion in cases of severe heart failure. This may limit its applicability in more complex clinical contexts, where the management of fluid overload is crucial. However, the introduction of iSGLT2 in combination with other diuretic treatments may offer an effective and safe strategy, although more studies are needed to validate this approach and clarify the mechanisms involved.

Finally, the data available on the mechanisms of action underlying the cardiovascular and renal benefits of iSGLT2 are still limited. While theories suggest that ketogenesis, modulation of inflammatory cytokines and improved cardiac metabolism play important roles, the specific contribution of each mechanism remains uncertain (Sharma *et al.*, 2020; Stachteas *et al.*, 2024). This lack of detailed understanding reinforces the need for additional mechanistic studies that can not only elucidate the physiological processes involved, but also guide the development of new therapeutic strategies based on the modulation of these systems.

FINAL CONSIDERATIONS

The iSGLT2s stand out as an innovative and effective therapeutic class in the management of HF, covering both patients with reduced and preserved ejection fraction. The use of dapagliflozin, in particular, demonstrates consistent benefits in contexts of high morbidity, contributing to improved cardiac function, symptom relief and a reduction in serious adverse events, such as hospitalizations and cardiovascular mortality. These results reinforce its role in optimizing the quality of life and prognosis of these patients. In addition, future research should focus on elucidating the pathophysiological mechanisms underlying the beneficial effects of iSGLT2 and identifying personalized therapeutic strategies, ensuring more comprehensive and safer use in specific populations.

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