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NEW HORIZONS IN HEART FAILURE MANAGEMENT: IMPLICATIONS OF THE 2022 GUIDELINES

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Abstract: Goal: Analyze the impact of adding SGLT2 inhibitors, as recommended by the 2022 heart failure guidelines, in treating patients with heart failure with preserved ejection fraction (HFpEF), highlighting changes in treatment practices and potential benefits for patients. Methods: Bibliographic review using the PubMed database using the strategy search query: ("Sodium Glucose Transporter 2 Inhibitors") AND ("Preserved Ejection Fraction Heart Failure") AND ("prognosis") OR ("efficacy") OR ("treatment"). Resulting in 355 articles, 18 of which were chosen to compose the present study after analyzing the selection criteria. Revision: the benefits of sodium-glucose cotransporter type 2 (SGLT2) inhibitors in the treatment of heart failure with preserved ejection fraction (HFpEF) are discussed. Studies indicate that medications such as empagliflozin and dapagliflozin significantly reduce the risk of cardiovascular death and hospitalizations, in addition to improving kidney function and patients' quality of life. Despite some adverse effects, such as genital infections and hypotension, SGLT2 inhibitors have a satisfactory safety profile and are recommended as first-line therapy in the 2022 guidelines, representing a significant advance in the management of HFpEF. **Final considerations:** The treatment of HFpEF has advanced significantly with the inclusion of SGLT2 inhibitors, showing robust clinical benefits, such as reducing hospitalizations and mortality, in addition to improving heart and kidney function, with few adverse effects. However, more research is still needed to understand its mechanisms of action, evaluate long-term effects and their effectiveness in specific subgroups.

Keywords: Sodium-Glucose Cotransporter 2 Inhibitors; Heart Failure with Preserved Ejection Fraction; Efficiency; Prognosis.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome resulting from abnormalities in cardiac structure or function, impacting ventricular filling or blood ejection. Globally, the prevalence of HF is increasing, in parallel with the aging of the population, representing a growing challenge for health systems (Liang; Liang; Gu, 2022; Clark, 2023). Among HF subtypes, heart failure with preserved ejection fraction (HFpEF) is particularly challenging due to its complex pathological features, such as systemic inflammation, accumulation of epicardial adipose tissue, myocardial fibrosis, and vascular stiffness, which lead to morbidity. significant mortality (Anker et al., 2019; Nassif et al., 2021).

Recently, the addition of sodium-glucose cotransporter type 2 (SGLT2) inhibitors in the treatment of patients with HFrEF has shown promise. These agents are known for their multiple beneficial effects, which include reducing cardiac inflammation, improving glomerular function, and reducing sodium retention, thus contributing to the management of this complex condition (Anker et al., 2021). Emerging evidence suggests that SGLT2 inhibitors can alter cardiac morphofunctional patterns and mitigate central sympathetic hyperactivity, promoting a substantial cardioprotective effect (Panico et al., 2023; Rao, 2022). Therefore, this study aims to analyze the impact of including SGLT2 inhibitors, according to the 2022 heart failure guidelines, in the treatment of patients with HFrEF. It is intended to highlight changes in treatment practices and explore the potential benefits of this therapeutic approach for this vulnerable population.

METHODOLOGY

Literature review structured according to the criteria of the PVO strategy (population or research problem, variables and outcome), focused on the guiding question: "How can sodium-glucose cotransporter 2 (SGLT2) inhibitors be included in the 2022 guidelines for insufficiency heart failure, based on the EMPEROR-Preserved study, does it change treatment for patients with heart failure with preserved ejection fraction (HFpEF)?". The searches were carried out in PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online), using a combination of specific terms with Boolean operators "AND" and "OR": ("Sodium Glucose Transporter 2 Inhibitors") AND ("Preserved Ejection Fraction Heart Failure") AND ("prognosis") OR ("efficacy") OR ("treatment"). From this initial search, 355 articles were identified. The inclusion criteria applied were: articles in English, published between 2019 and 2024, addressing topics relevant to this research, including reviews, clinical trials and observational studies, and available in full. The exclusion criteria were: duplicate articles, publications available only in summary format, and works that were not directly related to the proposed topic or that did not meet other inclusion criteria. After rigorous filtering, 18 articles were selected to compose the present study.

REVISION

According to a study by Anker et al. (2021), empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure by 21% compared to placebo. This benefit extended to both patients with and without diabetes, demonstrating the applicability of the treatment to a broad spectrum of heart failure patients. Despite reported side effects, such as genital infections and hypotension, the safety profile of empagliflozin was considered satisfactory, especially when compared to the positive results on cardiovascular outcomes.

Nassif et al. (2021) also highlighted the potential of SGLT2 inhibitors in the management of heart failure with preserved ejection fraction (ICCFp), noticing improvements in patients' symptoms and functional capacity. Dapagliflozin, specifically, was associated with a significant increase in six-minute walk test (6MWT) distance covered, as well as contributing to modest weight loss and an increase in quality of life, as indicated by the Quality of Life Questionnaire. Related to Cardiovascular Health (KCCQ).

The study by Packer et al. (2021) corroborated these findings, observing a 29% reduction in hospitalizations for heart failure, including those requiring intensive care and the use of advanced therapies such as intravenous diuretics and inotropic agents. Additionally, patients treated with empagliflozin were more likely to improve their New York Heart Association (NYHA) functional class, demonstrating sustained improvements in their quality of life and cardiac function over two years. These results highlight empagliflozin not only as an effective strategy in improving function and reducing cardiovascular risks, but also as a promising advance in the complex treatment of ICCFp, providing lasting benefits to patients.

Anker et al. (2019) also describe how empagliflozin can significantly benefit kidney function by improving glomerular function, slowing the progression of kidney disease, and reducing kidney inflammation and fibrosis. These effects contribute to the conservation of renal function, offering a promising therapeutic approach for patients with heart failure with preserved ejection fraction (HFPEF).

Furthermore, empagliflozin acts on systemic inflammatory states that contribute to inflammation of epicardial and perivascular adipose tissue. This negatively affects the myocardium and aorta, interrupting microvascular supply and causing fibrosis and compromised distension of the heart chambers and great vessels. The regulation of these pathological processes by empagliflozin has the potential to reduce cardiovascular mortality and hospitalizations, as indicated by Böhm et al. (2022), who observed significant benefits across all age groups, including elderly patients, who often face more treatment challenges due to comorbidities and greater vulnerability to side effects.

Specifically, severe acute renal complications were less frequent in patients under 65 years of age and in those between 65 and 74 years of age treated with empagliflozin, showing particular renal protection in these groups, with sustained efficacy in the elderly. In terms of adverse effects, empagliflozin generally shows a safe profile. Genital infections were the most common adverse effect, presenting in almost 2 in 100 users compared to almost 1 in 100 placebo users. Urinary infections were also slightly more common, affecting almost 10% of users compared to 8.1% of those taking placebo. Hypotensive episodes occurred in about 10% of empagliflozin users, slightly more than the 8.6% observed in the placebo group (Zannad; Macari, 2023). Such data reinforce empagliflozin as a valuable therapeutic option not only for the treatment of HFPEF, but also as a means of renal protection and control of cardiovascular complications in a diverse population of patients.

Empagliflozin is generally well tolerated, with few adverse effects. The most common adverse effect compared to placebo is genital infection, which occurs in almost 2 in 100 users, compared to almost 1 in 100 placebo users. Bladder infections and other urinary infections are also slightly more common, affecting almost 9.9% of empagliflozin users compared with 8.1% of those taking a placebo. Hypotensive episodes occurred in approximately 10.4% of empagliflozin users, compared to 8.6% of those using placebo, as reported by Zannad and Macari (2023).

The SGLT-2 inhibitors emerge as a promising approach for the treatment of heart failure with preserved ejection fraction (HFpEF), offering benefits beyond glycemic control in diabetics. The inclusion of these medications in treatment guidelines represents a significant evolution in the approach to heart failure, a field previously lacking robust therapeutic options, as highlighted by Salazar, Stroud and DeFilippis (2023).

The SGLT-2 inhibitors such as empagliflozin, dapagliflozin, canagliflozin, and sotagliflozin have shown remarkable efficacy in multiple facets of treating patients with type 2 diabetes (T2D) and heart failure, both with reduced (rHFrEF) and preserved (pHFrEF) ejection fraction). Empagliflozin, for example, demonstrated a 21% decrease in the primary outcome in patients with HFrEF and a 35% reduction in hospitalizations in patients with diabetes in the EMPA-REG study, while dapagliflozin, in the DAPA-HF study, showed a decrease in 21.1% in the primary outcome and a 30% reduction in hospitalizations (Muscoli et al., 2022).

Furthermore, iSGLT2 improves diastolic dysfunction by reducing oxidative stress, inflammation, fibrosis and stiffness of cardiac myocytes. The 2022 American Heart Association (AHA) guidelines recommend iSGLT2 as first-line therapy in patients with heart failure with reduced ejection fraction (HFrEF) and provide a high level of evidence for their use also in patients with HFrEF and heart failure. with slightly reduced ejection fraction, as reported by Muscoli et al. (2022). Although more research is needed to fully

explore the potential of SGLT-2 inhibitors, especially in populations with HFrEF and in other clinical settings, current data strongly support the inclusion of these medications as part of a comprehensive treatment strategy to improve outcomes in patients with heart failure and type 2 diabetes.

Ultimately, the use of SGLT2 inhibitors, such as empagliflozin and dapagliflozin, has shown promising results in the management of HFpEF. According to Nassif et al. (2021), empagliflozin significantly reduced the need for hospitalization for heart failure and cardiovascular death in patients with HFpEF (Nassif et al., 2021).

The preserved study highlighted by Anker et al. (2019), reinforces that empagliflozin not only improves clinical outcomes but also provides beneficial effects on renal function, a critical and important aspect in the management of patients with HFpEF (Anker et al., 2019).

Furthermore, recent studies indicate that SGLT2 inhibitors are safe, with a manageable adverse effect profile and rarely leading to treatment discontinuation. Böhm et al. (2022) highlight long-term cardiovascular safety and mainly the improvement in quality of life in patients treated with such medications (Böhm et al., 2022).

The incorporation of SGLT2 inhibitors as a standard recommendation in the 2022 guidelines for the treatment of HFpEF reflects a significant change in treatment practices for this pathology. Salazar, Stroud, and DeFilippis (2023) analyze the practical implementation of these guidelines, highlighting the need for careful monitoring of patients, particularly regarding the risk of urogenital infections, an important consideration in therapy with SGLT2 inhibitors (Salazar; Stroud; DeFilippis, 2023). Muscoli et al. (2022) explore the potential benefits of SGLT2 inhibitors also in reducing the risk of progression to more severe heart failure, proposing that these medications may play a crucial role in highly favorable cardiac remodeling in patients with HFpEF (Muscoli et al., 2022).

FINAL CONSIDERATIONS

The current panorama of knowledge about the treatment of heart failure with preserved ejection fraction (HFpEF) shows a significant evolution with the inclusion of sodium-glucose cotransporter type 2 (SGLT2) inhibitors in treatment guidelines. These medications have demonstrated achievements in reducing adverse cardiovascular events and inflammatory states, improving cardiac function and patients' quality of life, in addition to providing beneficial effects on renal function, filling a significant gap in the treatment of this condition. Improvements achieved through research include robust evidence of its clinical benefits, such as a 29% reduction in hospitalizations and a 21% reduction in the risk of death from heart failure. Furthermore, the studies also provided a positive perspective on the safety of these medications, as they have few adverse effects, such as urogenital infections and hypotension, and their effectiveness, enabling the recommendation of SGLT2 inhibitors as first-line therapy in HFpEF treatment guidelines. reflecting a significant change in treatment practices and offering a new horizon in the management of this condition. Although significant advances have been made, there are still areas that require investigation.

For example, it is necessary to better understand the mechanisms of action of SGLT2 inhibitors, aiming to fully elucidate their cardioprotective and renoprotective effects.

Furthermore, additional studies are needed to evaluate the long-term effects of SGLT2 inhibitors on the morbidity and mortality of patients with HFpEF and the efficacy of these medications in specific subgroups of patients, such as those with additional comorbidities or

at different stages of the disease. Furthermore, investigate strategies for monitoring and managing adverse effects associated with the use of SGLT2 inhibitors, with a special focus on the prevention of genital and urinary infections. In view of the above, the inclusion of sodium-glucose cotransporter 2 (SGLT2) inhibitors in the 2022 guidelines for heart failure, based on the EMPEROR-Preserved study, modifies the treatment for patients with HFpEF due to the multifaceted efficacy that stands out in relation to adverse effects, which are minimized because they are manageable and establish a favorable safety profile.

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