Review Article

New Perspectives in the Treatment of Heart Failure with Preserved Ejection Fraction with SGLT-2 Inhibitors

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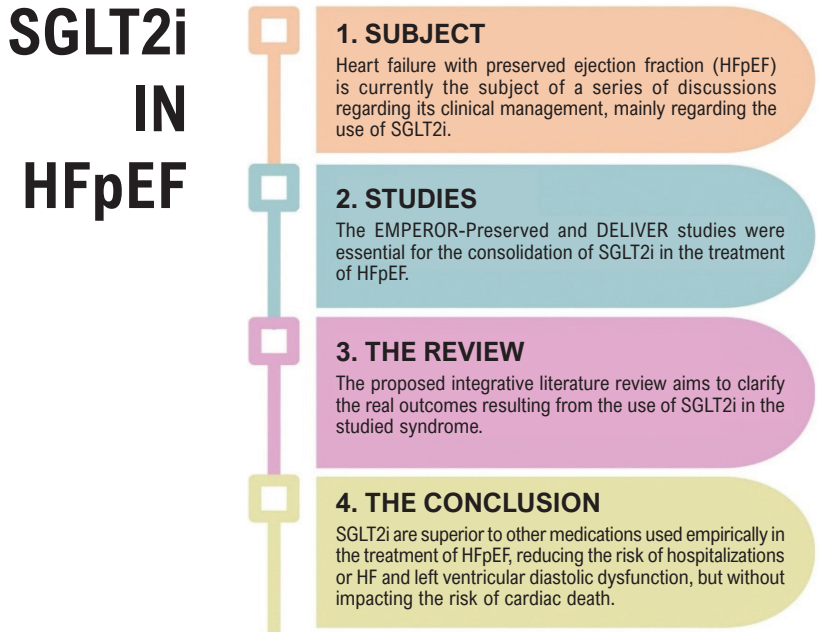
Central Illustration: New Perspectives in the Treatment of Heart Failure with Preserved Ejection Fraction with SGLT-2 Inhibitors



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New perspectives in the treatment of heart failure with preserved ejection fraction with SGLT-2 inhibitors.

Keywords

Diastolic Heart Failure; Sodium-Glucose Transporter 2 Inhibitors; Drug Therapy; Efficacy

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Abstract

The treatment of heart failure with preserved ejection fraction (HFpEF) has always represented a challenge in clinical management. The discovery of sodium-glucose cotransporter 2 inhibitors (SGLT2i) as efficient cardiac protectors brought the possibility of treating HFpEF, a topic driven by robust studies such as EMPEROR-Preserved and DELIVER. The present work aims to identify the main studies on SGLT2i and primary outcomes in HFpEF.

The qualified search was carried out in the BVS and Pubmed indexed databases, with the inclusion criteria

being randomized clinical trials, meta-analyses and analyses of clinical trials, full text available, and publication in the last 5 years.

11 articles were selected to compose the review.

SGLT2i shows efficacy in the treatment of HFpEF, reducing hospitalization for heart failure in this population and improving ventricular diastolic function in these patients, but not altering the risk of cardiac death alone.

Introduction

Heart failure (HF) is a clinical syndrome characterized by symptoms and/or signs caused by structural and/or functional cardiac abnormality and corroborated by elevated levels of natriuretic peptides and/or evidence of pulmonary or systemic congestion.[1] The classification of HF refers to the ejection fraction (EF) of the left ventricle (LV). When this is less than 40%, it is categorized as HF with reduced EF (HFrEF), and when the EF is above 50%, it is classified as HF with preserved EF (HFpEF). On the other hand, since the EF has a value between 40% and 50%, it characterizes HF with slightly reduced EF (HFpEF).[2]

Standard therapy for HFpEF includes control of comorbidities, self-care education, regular exercise, weight loss, and diuretics (usually loop diuretics) for those with evident symptoms of pulmonary and/or systemic congestion.[3] However, the treatment of HFpEF has shown gaps, as studies have shown that the drug arsenal has not significantly reduced mortality.[4]

SGLT2 inhibitors have a hypoglycemic effect mediated by glycosuria, preventing tubular reabsorption of glucose in the nephrons, a mechanism that triggers few side effects and is highly effective in glycemic control. Previously restricted to their function as antidiabetogenic agents, they have demonstrated positive effects in the clinical management of HF.[2,5]

The introduction of this class as cardioprotective was driven by the randomized clinical trial EMPA-REG OUTCOME in 2015, in which empagliflozin showed a 14% reduction in the risk of cardiovascular death in patients over 18 years of age with Diabetes Mellitus (DM) and atherosclerotic cardiovascular disease, compared to the placebo group.[6] Subsequently, the EMPEROR-Reduced and DAPA-HF studies made clear the role of SGLT2 inhibitors as useful and safe in the clinical management of HFREF regardless of the presence of DM, thus solidifying the recommendation of this drug in the latest guidelines.[7]

This review aims to identify the main studies on SGLT2i and primary outcomes in HFpEF.

Methods

This study consists of an integrative literature review, whose qualified search was performed only by the main author in the indexed databases Virtual Health Library (BVS) and PubMed. The descriptors used for the search, according to DeCS/MeSH, were "Insuficiência Cardíaca Diastólica", "Inibidores do cotransportador de sódio-glicose 2", "Tratamento Farmacológico" and "Eficácia". It is worth mentioning that "Insuficiência Cardíaca Diastólica" was the only descriptor found in the search to refer to the entity HFpEF.

In the search performed in Pubmed, the above-mentioned descriptors were written in such a way that the Boolean operator "AND" was applied between them. In the qualified search in the BVS, the descriptors in English and Spanish were also included. The descriptors translated into English and included in DeCS/MeSH were: "Heart Failure, Diastolic", "Sodium-Glucose Transporter 2 Inhibitors", "Drug Therapy" and Efficacy. The descriptors in Spanish were: "Insuficiencia Cardíaca Diastólica", "Inhibidores del Cotransportador de Sodio-Glucosa 2", Quimioterapia, and Eficacia. For the search, the equivalent descriptors were typed separated by the Boolean operator "OR", while the four trios of different descriptors were separated by the Boolean operator "AND".

The inclusion criteria for selecting studies were full-text available, articles in English, randomized clinical trials, meta-analyses, and analyses of clinical trials published in the last 5 years. A total of 70 articles were found, of which 1 duplicate was excluded. After reading the titles and abstracts, 11 articles remained for the review. The evaluation of the articles, as well as the search, was performed only by the main author. Figure 1, presented below, summarizes the steps of the article search.

Results

The final sample of this study consisted of 11 articles, including 2 meta-analyses, 3 randomized clinical trials, and 6 analyses of clinical trials. All participants had HF and included individuals with preserved EF, with or without type 2 DM. The drugs used in the interventions were dapagliflozin, empagliflozin, luseogliflozin, canagliflozin, ertugliflozin, and sotagliflozin. Table 1 summarizes the analysis of the results of the studies.

Discussion

The studies in this review mostly indicate the beneficial effects of SGLT2 inhibitors in the clinical management of patients with HFpEF, thus corroborating their use in this clinical syndrome, evaluated mainly by the EMPEROR-Preserved and DELIVER studies (Central Illustration). EMPEROR-Preserved consisted of a clinical trial with 5,988 individuals who exhibited LVEF ≥40%, subjecting randomized individuals to intervention with empagliflozin, demonstrating a 21% reduction in the primary outcome composed of cardiovascular death and first hospitalization for HF in the group that received the medication.[17] DELIVER, evaluating dapagliflozin, included 6,263 individuals with LVEF ≥40% and demonstrated an 18% reduction in its primary composite outcome of cardiovascular death, hospitalization for HF, or urgent visit for HF through the intervention.[18] These results allowed the guidelines regarding the clinical management of HFpEF to be updated. In 2022, the update of the American Heart

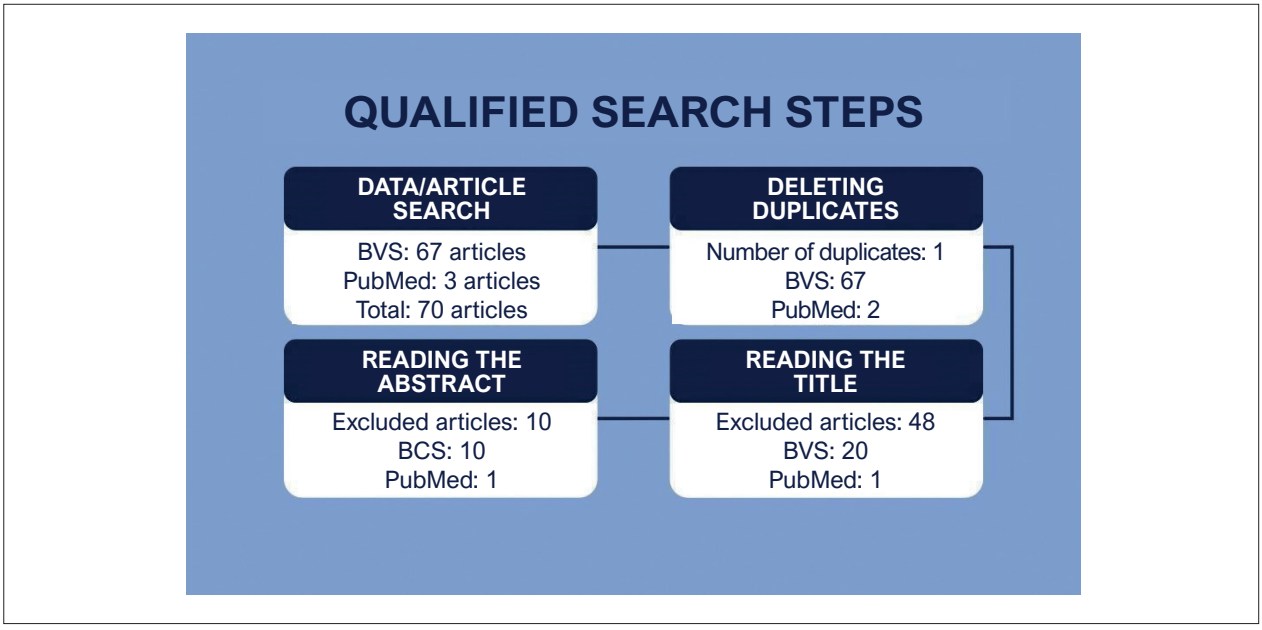

Figure 1 – *Flow of Search Steps. Source: Author (2024).*

Failure Guideline addressed, for the first time, the use of dapagliflozin and empagliflozin in the treatment of HFpEF as a class IIa recommendation.[19] The following year, the update of the European guideline established SGLT2i as a class I recommendation in the treatment of HFpEF.[3] Figure 2 shows the flowchart showing the timeline of the studies that constituted the validation of SGLT2i as useful in the treatment of HF.

It is worth mentioning that the EMPEROR-Preserved and DELIVER studies included individuals with HFrEF and HFpEF. A pre-specified analysis of EMPEROR-Preserved compared the effects of empagliflozin in individuals with preserved and intermediate EFs in the study, resulting in a 17% reduction in the primary composite outcome of cardiovascular death and hospitalization for HF in patients with HFpEF (who totaled 4,005 among the 5,988 in the study), with a 22% reduction in hospitalization for HF alone in this group. These studies endorse the updates in the latest guidelines on the clinical management of HFpEF.[7]

A subanalysis of the CANVAS (Canagliflozin Cardiovascular Assessment Study) program was performed, which involved patients with T2DM and Coronary Artery Disease (CAD), identifying those who had HFpEF and HFrEF, aiming to define the effects of canagliflozin among such individuals. It was reported that, among the 10,142 people involved in CANVAS, 101 patients had events related to HFpEF and, at the end of the program, there was a reduction in the risk rate of fatal HF events or hospitalization for HF that was quite similar among individuals with HFpEF and HFrEF.[8]

HFpEF can also cause other cardiovascular repercussions, including the development of atrial arrhythmias. A study with obese rats subjected to intervention with sotagliflozin demonstrated an improvement in left atrial remodeling, assessed by echocardiography, and in the metabolic HFpEF condition, in addition to a reduction in the intensity of arrhythmic events, but without influencing their frequency. Furthermore, sotagliflozin is an SGLT1 and SGLT2 inhibitor, but it is important to note that, for the most part, there are no SGLT1 inhibitors because they reduce carbohydrate absorption, increasing the risk of diarrhea.[11]

In addition to the primary outcome results of the main studies elucidated, other variables were analyzed, as was done in a substudy of EMPEROR-Preserved, which assessed health-related quality of life using the Kansas City Cardiomyopathy Questionnaire (KCCQ). Patients were divided into initial tertiles of the KCCQ Clinical Summary Score (CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) in individuals with HFpEF undergoing intervention with empagliflozin. There was clinical improvement in all tertiles of individuals at 12 weeks, which was sustained for at least one year.[14]

The pre-specified analysis sought to assess differences in the effect of SGLT2 inhibitors in men and women, performing a pooled analysis of the DAPA-HF and DELIVER studies. No significant difference was found in the effect of this pharmacological class regarding sex.[12] The variables described among the individuals by the authors, such as gender, did not appear to bias the result. It was observed, for example, that although women had higher LVEF at the beginning of the study, they had worse KCCQ-CSS scores than men.[14]

Left ventricular diastolic dysfunction is proposed to be an underlying condition in individuals with HFpEF.[10] Analysis of the EmDia study, which included 144 diabetic patients with elevated left ventricular E/E' ratio (a predictor of cardiac remodeling), 21 of whom had HFpEF,

Table 1 – Summary of Results

Title	Authors	Year of Publication	Type of Study	Objectives	Results
Effects of Canagliflozin on Heart Failure Outcomes Associated With Preserved and Reduced Ejection Fraction in Type 2 Diabetes Mellitus.	Figtree et al.[8]	2019	Analysis of randomized clinical trial	To clarify possible distinct effects of canagloflozin on events in HFpEF versus HFrEF in the CANVAS (Canagliflozin Cardiovascular Assessment Study) population.	Among the 10,142 participants in the CANVAS study, 1,461 had a prior history of HF. During the 188.2 weeks of the study, 101 patients had a first event of HFpEF, 122 had HFrEF, and 61 had no known ejection fraction. Canagliflozin, compared with placebo, reduced fatal HF events or hospitalization in patients with DM and high cardiovascular risk, with no clear difference in effects on HFrEF versus HFpEF events.
Effect of Luseogliflozin on Heart Failure With Preserved Ejection Fraction in Patients With Diabetes Mellitus.	Ejiri et al.[9]	2020	Multicenter, open, randomized, controlled trial	To evaluate the effectiveness of luseogliflozin in the treatment of HFpEF in individuals with DM2.	From the randomization of 169 individuals, 86 received intervention with luseogliflozin and 83 with voglibose; there was no significant reduction in BNP concentration among patients treated with both drugs in 12 weeks.
Positive effect of dapagliflozin on left ventricular longitudinal function for type 2 diabetic mellitus patients with chronic heart failure.	Tanaka et al.[10]	2020	Analysis of a prospective multicenter study	To investigate the effect of dapagliflozin on LV diastolic function in patients with T2DM and stable HF.	In a study involving 53 individuals, dapagliflozin promoted improvement in LV longitudinal myocardial function and, consequently, improvement in LV diastolic function. Hhear decrease in E/e′ significantly increased from 9.3 to 8.5 cm/s at 6 months after dapagliflozin administration (p = 0.020),
Dual SGLT-1 and SGLT-2 inhibition improves left atrial dysfunction in HFpEF.	Bode et al.[11]	2021	Clinical trial	To elucidate the effects of treatment with sotagliflozin on left atrial remodeling and cellular arrhythmogenesis based on a study with rats with HFpEF.	The left atrial volume of the rats, obtained by echocardiography, was increased. Sotagliflozin contained the atrial increase and decreased the intensity of the arrhythmogenic events in the animals.
Effects of canagliflozin on NT-proBNP stratified by left ventricular diastolic function in patients with type 2 diabetes and chronic heart failure: a sub analysis of the CANDLE trial.	Kusunose et al.[12]	2021	Analysis of randomized clinical trial	To evaluate the effects of canagliflozin and glimepiride on NT-pro BNP levels in individuals participating in the CANDLE study.	Among the 233 individuals in the CANDLE study, 133 were randomized to the drug intervention with canagliflozin and 120 to glimepiride. In the group with greater impairment of diastolic function, canagliflozin appeared to reduce NT-proBNP levels more compared with those observed in the glimepiride group, although this did not reach statistical significance.
Benefit of sodium-glucose cotransporter-2 inhibitors on survival outcome is related to the type of heart failure: A meta-analysis.	Zhao et al.[13]	2022	Meta-analysis	To evaluate the efficacy of SGLT2i across the spectrum of HF ejection fractions from 13 studies.	Among the studies, seven had a primary composite outcome of cardiac death or hospitalization for HF, eight reported the outcome of cardiac death, and nine had hospitalization for HF as the primary outcome. Two studies included individuals with HFpEF, six studies with HFrEF, and four included HFpEF and HFrEF. In patients with HFpEF, SGLT2i reduced the composite outcome of cardiac death or readmission for HF, but not cardiac death alone, a result found only in patients with HFrEF.

Efficacy of empagliflozin in heart failure with preserved versus mid-range ejection fraction: a pre-specified analysis of EMPEROR-Preserved.	Anker et al.[4]	2022	Pre-specified analysis of the randomized	To evaluate the effect of empagliflozin in individuals from the EMPEROR-Preserved trial (n=5988) according to division into two categories: preserved ejection fraction (≥ 50%) and intermediate ejection fraction (41-49%).	Among the individuals involved, 4005 individuals (66.9%) had HFpEF, while 1983 (33.1%) had HF with intermediate ejection fraction. There was a reduction in the primary composite outcome of risk of cardiovascular death or hospitalization for HF in a similar way in both categories of ejection fraction evaluated. Empagliflozin reduced the primary outcome of cardiac death and first hospitalization for HF by 22% compared with the placebo group, analyzing the subgroup with HFpEF separately. In comparison, the reduction of the same outcome was 29% for patients with intermediate LVEF. In both groups, empagliflozin did not promote a reduction in cardiac death alone.
Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial.	Butler et al.[14]	2022	Analysis of randomized clinical trial	To assess the health-related quality of life of individuals involved in the EMPEROR-Preserved study using the Kansas City Cardiomyopathy Questionnaire (KCCQ).	The 5942 individuals involved were divided into three groups according to the initial KCCQA score: <62.5, 62.5-83.3, and ≥83.3. Empagliflozin improved health-related quality of life, which was sustained for at least 1 year.
Effects of empagliflozin on left ventricular diastolic function in addition to usual care in individuals with type 2 diabetes mellitus-results from the randomized, double-blind, placebo-controlled EmDia trial.	Prochaska et al.[6]	2023	Randomized, double-masked, controlled clinical trial	Evaluation of the effectiveness of empagliflozin compared to the placebo group on left ventricular diastolic function in patients with type 2 Diabetes Mellitus and elevated left ventricular end-diastolic pressure covered by the EmDia clinical trial.	A total of 144 patients with T2DM and an elevated left ventricular E/e' ratio. After 12 weeks of intervention, empagliflozin resulted in a significantly greater decrease in the E/e' ratio compared to placebo.
Efficacy of SGLT2-inhibitors across different definitions of heart failure with preserved ejection fraction.	De Marzo et al.[15]	2023	Meta-analysis	To evaluate the efficacy of SGLT2i in patients who participated in phase 3 randomized clinical trials with HFpEF (EF>40%) based on clinical, biochemical, and echocardiographic criteria.	The studies included were EMPEROR-Preserved, DELIVER, SOLOIST-WHF and four CVOTs, EMPA-REG OUTCOME, DECLARE-TIMI 58, VERTIS-CV and SCORED, thus including 14,034 individuals. SGLT2i reduced the risk of cardiovascular death and hospitalization for HF in all randomized clinical trials, regardless of how HFpEF was diagnosed.
Sex Differences in Characteristics, Outcomes, and Treatment Response With Dapagliflozin Across the Range of Ejection Fraction in Patients With Heart Failure: Insights From DAPA-HF and DELIVER.	Wang et al.[16]	2023	Pre-specified pooled analysis.	To elucidate possible differences in the safety and efficacy of SGLT2 inhibitors in each sex in HFrEF and HFpEF.	In the DAPA-HF (n= 4744) and DELIVER (n= 6263) trials, sex did not modify the effect of dapagliflozin across the ejection fraction spectrum.

Source: Author (2024). HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LV: left ventricle; LVEF: left ventricler ejection fraction.

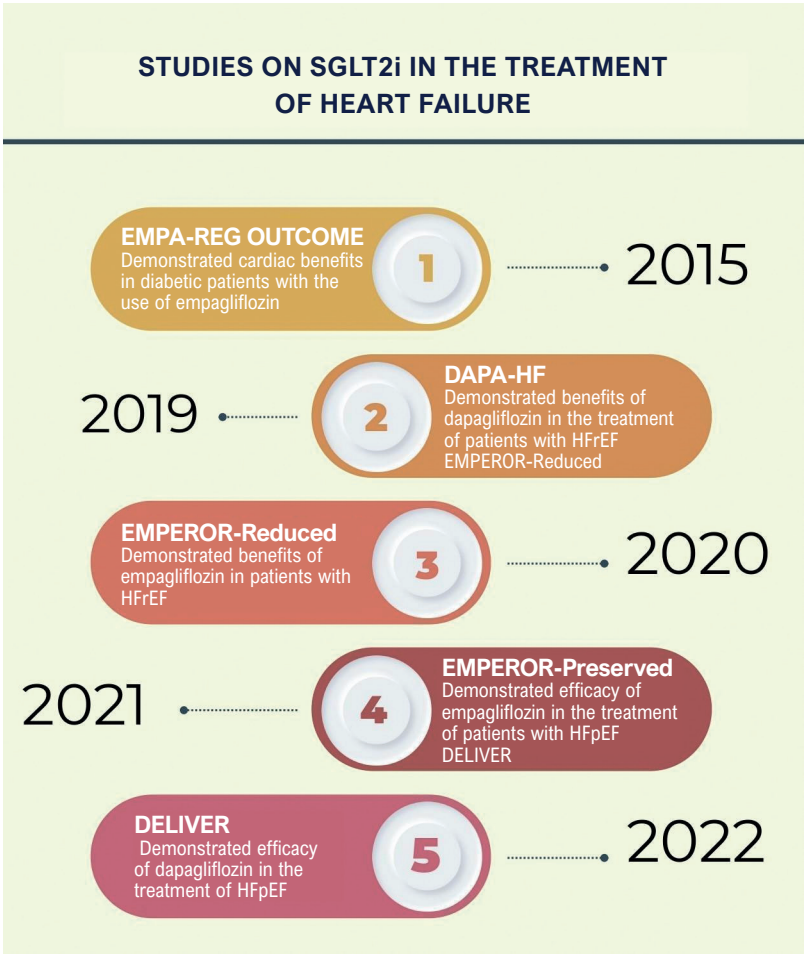

Figure 2 – *Timeline of the main studies that constituted the validation of SGLT2i as useful in the treatment of HF. Source: Author (2024). HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction.*

demonstrated a positive result in its primary outcome, which consisted of a change in this predictor after 12 weeks of intervention with empagliflozin, indicating an improvement in diastolic function.[5] Similarly, analysis of a prospective multicenter study including individuals with HFrEF and HFpEF demonstrated the efficacy of dapagliflozin in reducing the predictor of myocardial function E/e', which consists of the ratio between mitral flow and mitral annular velocities. The result was more significant in patients with HFpEF.[10]

Furthermore, knowledge about the effect of SGLT2 inhibitors on the levels of natriuretic peptides, such as NT-proBNP and BNP, is also important to clarify the mechanisms of these antidiabetogenic agents in the syndrome studied. Brain natriuretic peptide (BNP) is produced as a result of high pressures and volumes in the cardiac chambers and is the gold standard for the diagnosis and prognosis of HF, while NT-proBNP is an inactive peptide formed by the N-terminal portion of the prohormone proBNP, also giving rise to BNP.[20] A CANVAS substudy, considering diabetic patients with diastolic dysfunction, demonstrated a tendency for a reduction in NT-proBNP levels with the use of canagliflozin in 12 weeks. The authors also showed that the effect of this SGLT2i on the biochemical marker in question is more evident in individuals with higher levels of diastolic dysfunction.[12] In contrast, another randomized multicenter trial, including patients with HFpEF and diabetics, demonstrated no significant differences in BNP levels with the use of luseogliflozin or voglibose in 12 weeks.[9]

Furthermore, there are some gaps regarding the use of SGLT2 inhibitors in HFpEF. The EMPEROR-Reduced and DELIVER studies had positive results for composite but not isolated outcomes. A meta-analysis that included 7 robust studies using SGLT2 inhibitors showed that empagliflozin, dapagliflozin, sotagliflozin, and ertugliflozin reduced the risk of cardiovascular death or hospitalization for HF in randomized clinical trials of HF and cardiovascular outcomes trials. However, SGLT2 inhibitors were not superior to placebo for cardiovascular death or all-cause

death in any of these studies.[15] Similarly, another meta-analysis, through the pooled analysis of 13 randomized clinical trials, aimed to clarify the real impact of SGLT2 inhibitors on cardiovascular death in individuals with HFpEF and HFrEF. The authors addressed the fact that most studies on SGLT2 inhibitors selected cardiac death as a secondary outcome and reduced the statistical power of this analysis. Among the study components, 8 studies addressed cardiac death as a simple primary outcome, while 7 of them defined a composite primary outcome as cardiac death or hospitalization for HF. As a result, it was observed that the group of individuals with HFpEF undergoing intervention with SGLT2i had no reduction in the risk of cardiac death compared to placebo.[13]

It should be noted that studies with SGLT2 inhibitors in the context of HFpEF have demonstrated a reduction in hospitalizations due to HF as well as an improvement in quality of life, with no reduction in mortality. However, when analyzing the subgroups, the predominant benefit of the studies occurred in the group of patients with an EF between 40 and 50%, that is, the group with a slightly reduced EF.[21]

There is still no clear data in the literature showing the mechanism responsible for the benefit to the heart. However, studies, such as EMPA VISION, generate the hypothesis that the increase in ketone bodies by the drug causes an increase in inotropism, as well as improving mitochondrial function by optimizing intramyocardial ATP.[22] It is important to highlight the role of SGLT2 inhibitors in the current clinical management of Chronic Kidney Disease (CKD). This condition shares risk factors with HFpEF, thus highlighting the large EMPA-KIDNEY study, which showed that empagliflozin was able to delay the decline in the glomerular filtration rate by 50% over 2 years.[23]

Conclusion

Patients with HFpEF benefit from the integration of SGLT2 inhibitors into clinical management, presenting positive results in relation to other medications used empirically. There was a reduction in the risk of hospitalization due to HF and an improvement in left ventricular diastolic function, but there was no significant outcome in the risk of cardiac death in isolation.

Author Contributions

Conception and design of the research and Acquisition of data: Gomes JNA; Analysis and interpretation of the data: Gomes JNA, Campos MSB; Writing of the manuscript and Critical revision of the manuscript for content: Gomes JNA, Campos MSB, Aragão CAS, Sousa AC.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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