

## **Heart failure and treatment with Sodium-glucose Co-transporter Inhibitor (SGLT2): dapagliflozin and its effects on the cardiac system**

### **Insuficiência cardíaca e o tratamento com Inibidor do Co-transportador Sódio-glicose (SGLT2): dapagliflozina e seus efeitos no sistema cardíaco**

### **Insuficiencia cardíaca y el tratamiento con Inhibidor del Co-transportador Sodio-Glucosa (SGLT2): dapagliflozina y sus efectos en el sistema cardíaco**

DOI:10.34119/bjhrv7n2-302

Originals received: 03/08/2024

Acceptance for publication: 03/29/2024

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**ABSTRACT**

This article thoroughly examines the effectiveness of treatment with dapagliflozin, a sodium-glucose co-transporter inhibitor, in the context of heart failure. The primary focus of this analysis lies in evaluating patients' clinical condition, the diagnostic procedures employed, and the various medications used as part of the treatment regimen. The objective of this investigation is based on a meticulous analysis of relevant scientific articles. Classified as documentary research within the field of Applied Linguistics, this study draws upon research covering classification, pathophysiology, clinical presentation, diagnosis, pharmacological treatment, and the role of SGLT2 inhibitors in heart failure as its primary theoretical framework. The findings indicate dapagliflozin's efficacy in reducing the heart's ejection fraction, regardless of the presence of diabetes. However, it emphasizes the importance of a comprehensive medical assessment before initiating the use of this medication, highlighting the need for caution and appropriate professional supervision.

**Keywords:** heart , SGLT2, dapagliflozin, insufficiency, treatment.

**RESUMO**

Este artigo analisa detalhadamente a eficácia do tratamento com dapagliflozina, um inibidor do co-transportador sódio-glicose, no contexto da insuficiência cardíaca. O foco principal desta análise é a avaliação da condição clínica dos pacientes, os procedimentos diagnósticos utilizados e as diversas medicações empregadas como parte do regime de tratamento. O objetivo desta investigação baseia-se em uma análise cuidadosa de artigos científicos relevantes. Classificado como pesquisa documental no campo da Linguística Aplicada, o estudo utiliza estudos sobre classificação, fisiopatologia, apresentação clínica, diagnóstico, tratamento farmacológico e o papel dos inibidores do SGLT2 na insuficiência cardíaca como referencial teórico. Os resultados indicam a eficácia da dapagliflozina na redução da fração de ejeção do

coração, independentemente da presença de diabetes. No entanto, destaca-se a importância de uma avaliação médica completa antes do início do uso deste medicamento, enfatizando a necessidade de cuidado e supervisão profissional adequada.

**Palavras-chave:** coração, SGLT2, dapagliflozina, insuficiência, tratamento.

## RESUMEN

Este artículo examina detalladamente la eficacia del tratamiento con dapagliflozina, un inhibidor del cotransportador sodio-glucosa, en el contexto de la insuficiencia cardíaca. El enfoque principal de este análisis se centra en evaluar la condición clínica de los pacientes, los procedimientos diagnósticos empleados y los diversos medicamentos utilizados como parte del régimen de tratamiento. El objetivo de esta investigación se basa en un análisis minucioso de artículos científicos relevantes. Clasificado como investigación documental dentro del campo de la Lingüística Aplicada, este estudio se basa en investigaciones que abarcan clasificación, fisiopatología, presentación clínica, diagnóstico, tratamiento farmacológico y el papel de los inhibidores de SGLT2 en la insuficiencia cardíaca como su marco teórico principal. Los hallazgos indican la eficacia de la dapagliflozina en la reducción de la fracción de eyección del corazón, independentemente de la presencia de diabetes. Sin embargo, se enfatiza la importancia de una evaluación médica exhaustiva antes de iniciar el uso de este medicamento, resaltando la necesidad de precaución y supervisión profesional adecuada.

**Palabras clave:** corazón, SGLT2, dapagliflozina, insuficiencia, tratamiento.

## 1 INTRODUCTION

Over time, various paradigms have guided the understanding of the pathophysiological process of heart failure (HF) and directed therapeutic approaches. In the distant past, the cardiorenal model delineated HF as a condition resulting from volume expansion due to salt and water retention. This condition was characterized as a dysfunction affecting both the heart and kidneys, and as a result, the recommended treatment involved the use of digitalis to enhance contractility and diuretics to mitigate edema (MANN, 1999).

In the late 1970s, researchers elucidated the role of the peripheral circulatory system in maintaining homeostasis in the presence of cardiac dysfunction. The cardiocirculatory model explained HF as a situation of decreased cardiac output (CO) due to inadequate contractility and peripheral vasoconstriction. Consequently, inotropes were initially recommended to enhance inotropism, followed by vasodilators, aiming to act on peripheral vascular resistance (MOREIRA, 2007).

In the 1980s, the neuro-hormonal model emerged, recognizing that initial events such as myocardial infarction (MI) or systemic arterial hypertension (SAH) result in the reduction of left ventricular ejection fraction (LVEF) and CO, triggering the HF syndrome. The

development of HF activates various crucial neuro-hormonal systems, such as the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), playing a central role in pathophysiology. These activated systems are responsible for the progressive nature of the disease and the high mortality rate of patients (MOREIRA, 2007).

## 2 OBJECTIVE

The aim of the article is to investigate the effectiveness of dapagliflozin in treating heart failure, evaluating its effects on the cardiac system, including its influence on ventricular function, ejection fraction, and cardiac remodeling. Additionally, it seeks to analyze the mechanisms of action of dapagliflozin and how they may contribute to improving symptoms and prognosis in patients with heart failure. Finally, it discusses the clinical and therapeutic implications of the results obtained with the use of dapagliflozin, including considerations about its clinical applicability and potential impact on treatment guidelines.

## 3 CARDIAC INSUFFICIENCY

According to Rohde *et al.* (2018) the complex clinical syndrome known as heart failure occurs when the heart cannot pump blood effectively to meet the metabolic needs of the tissues, or does so only through high filling pressures. This condition can be caused by structural or functional changes in the heart, manifesting itself through characteristic signs and symptoms resulting from reduced cardiac output and/or high filling pressures, both at rest and during exertion. The term "chronic heart failure" reflects the progressive and persistent nature of the disease, while "acute heart failure" is reserved for rapid or gradual changes in signs and symptoms resulting in the need for urgent therapy. Although many diseases that lead to HF are marked by the presence of low cardiac output (often compensated) at rest or during exertion (low-output HF), some high-output clinical conditions, such as thyrotoxicosis, anemia, arteriovenous fistulas and beriberi (HF high output), can also result in heart failure.

In recent years, there has been considerable progress in understanding heart failure. We now have a deeper understanding of its pathophysiology and natural history, along with new therapeutic options that allow for altering its course. Despite technological advances and the increase in pharmacological resources, the incidence of HF is on the rise. This increase is partly attributed to the aging population, as HF is more prevalent in the elderly. Additionally, the reduction in deaths related to underlying heart disease implies prolonged coexistence with

illnesses, with HF being the common final manifestation of cardiac diseases, making it more frequent (FREITAS and CIRINO, 2017).

Heart failure remains a syndrome of malignant character, with high mortality rates in advanced forms. Several studies have demonstrated mortality rates of up to 50% within one year, especially in patients classified as New York Heart Association functional class (NYHA FC) IV, and even higher in those requiring inotropic support for compensation. On the other hand, patients with mild symptoms show a favorable prognosis, even with significantly reduced ejection fraction (EF). The natural history of the disease can be altered through correction of the heart disease, control of aggravating factors, or through the use of certain medications. However, it is important to highlight that the use of certain drugs can worsen the situation, making it more severe (BARRETO and RAMIRES, 1998).

This condition is identified by characteristic symptoms such as dyspnea, edema in the lower limbs, or fatigue, and may be accompanied by signs such as elevated jugular venous pressure, pulmonary crackles, and peripheral edema. Although the definition is limited to stages where clinical symptoms are evident, patients may exhibit asymptomatic functional and/or structural cardiac abnormalities (FREITAS and CIRINO, 2017).

### 3.1 CLASSIFICATION

Several ways of categorizing heart failure exist; however, the most practically applicable ones, especially in the context of outpatient disease management, will be described.

The American College of Cardiology (ACC) and the American Heart Association (AHA) emphasize the importance of considering heart failure as a continuum composed of four interconnected stages. Stage A encompasses patients at high risk of developing heart failure but without evidence of structural heart disease or symptoms, such as hypertensive or diabetic patients. In stage B, patients with structural heart changes are found but remain asymptomatic, such as those with previous myocardial infarction (MI) or asymptomatic left ventricular (LV) dysfunction. Stage C includes individuals with structural heart changes who have developed heart failure symptoms, such as dyspnea or fatigue, exemplified by patients with a history of previous MI. Finally, stage D includes patients resistant to treatment, requiring special interventions, such as those awaiting heart transplantation (MANN *et al.*, 2015) (Sociedade Brasileira de Cardiologia, 2009).

Another way to categorize heart failure is based on the exercise capacity of patients already diagnosed with the condition. From this perspective, the New York Heart Association (NYHA) divides these patients into functional classes (FC), as follows:

- FC I: Absence of symptoms (fatigue, palpitation, or dyspnea) during daily activities. Limitation for efforts is comparable to that expected for normal individuals.
- FC II: Symptoms triggered by daily activities.
- FC III: Symptoms triggered by activities less intense than daily activities or moderate efforts.
- FC IV: Symptoms triggered by minimal efforts or even at rest.

Although it is a subjective assessment, this classification can be used to guide therapeutic interventions and assess treatment response (Sociedade Brasileira de Cardiologia, 2009).

Additionally, there is a third categorization based on the evaluation of the left ventricular ejection fraction (LVEF). Individuals with an LVEF  $\geq 50\%$  are identified as having heart failure with preserved ejection fraction (HFpEF). Those with an LVEF  $< 40\%$  are classified as having heart failure with reduced ejection fraction (HFrEF). Patients with an LVEF in the range of 40 to 49% are placed in a "gray area," recently designated as heart failure with mid-range ejection fraction (HFmrEF) (Sociedade Brasileira de Cardiologia, 2009) (PONIKOWSKI *et al.*, 2016).

This distinction is crucial as epidemiological characteristics, etiology, comorbidities, and therapeutic approaches vary among these categories. Moreover, only patients with HFrEF have demonstrated benefits in terms of reducing morbidity and mortality with treatment (PONIKOWSKI *et al.*, 2016).

### 3.2 PATHOPHYSIOLOGY OF CARDIAC INSUFFICIENCY

The pathophysiology is complex and still lacks full understanding. Regarding heart failure with reduced ejection fraction (HFrEF), patients in this category generally present distinct characteristics, being older, predominantly female, and associated with various cardiovascular comorbidities, such as arterial hypertension, atrial fibrillation, coronary artery disease, pulmonary hypertension, as well as non-cardiovascular conditions such as diabetes mellitus, chronic kidney disease, anemia, chronic obstructive pulmonary disease, among others. Additionally, there is a higher proportion of non-cardiovascular pathologies, with significant impact on morbidity and mortality, and a reduced incidence of acute myocardial infarction, as well as cases of sudden death or death related to heart failure (ZAKERI & COWIE, 2018).

Historically, heart failure with preserved ejection fraction (HFpEF) was exclusively linked to diastolic dysfunction, in contrast to heart failure with reduced ejection fraction (HFrEF), associated with systolic dysfunction. Currently, it is understood that this relationship is not as linear, as both types of heart failure can involve impairment in both systolic and diastolic function, with multiple mechanisms implicated in HFpEF. It is believed that this condition results from a complex variety of dysfunctions at cardiac, vascular, and systemic levels, with the contribution of various comorbidities (KIRALI, ALTAY, & PEHLIVANOGLU, 2017).

Diastolic dysfunction is commonly present and results from structural changes (fibrosis, hypertrophy, and cardiac remodeling), microvascular dysfunction, and metabolic abnormalities, resulting in increased stiffness and reduced cardiac compliance. This scenario not only causes elevation of left ventricular filling pressures but can also induce structural and functional changes at the atrial, pulmonary, and right ventricular levels, through increased upstream pressures. Furthermore, there is impairment of systolic reserve, mainly through alterations in the ventricular-vascular coupling (KIRALI, ALTAY, & PEHLIVANOGLU, 2017).

Another involved mechanism is chronotropic incompetence, which implies inadequate variations in heart rate in response to needs, possibly resulting from dysfunctions in the autonomic nervous system. Electrical and/or mechanical asynchrony, both in systolic and diastolic terms, has also been identified in some patients. The magnitude of this phenomenon is related to the extent of diastolic dysfunction and exercise capacity (SENNI *et al.*, 2014).

Many of these modifications are not visible nor result in impairment during rest, consisting of limitations in functional reserve that only become evident during physical or emotional exertion. Neuro-hormonal alterations, such as autonomic dysfunction and activation of the renin-angiotensin-aldosterone system, also represent significant mechanisms involved.

In the vascular realm, endothelial dysfunction, systemic inflammation, increased vascular stiffness, and impaired vasodilation are observed. A possible underlying mechanism would be the dysregulation of the NO-sGC-cGMP-PKG pathway (nitric oxide, soluble guanylate cyclase, cyclic guanosine monophosphate, and protein kinase G), responsible for smooth muscle relaxation, cardiac protection, gene transcription, endothelial permeability, and platelet inhibition. In the peripheral scenario, musculoskeletal modifications seem to contribute to decreased aerobic capacity, resulting in reduced effort tolerance (BORLAUG, 2014).

Both advancing age and the presence of various comorbidities intensify these mechanisms and contribute to disease progression. The interaction between the various

pathophysiological factors and comorbidities, as well as the relative predominance of each of them, make this condition intricate and heterogeneous, complicating diagnosis and treatment. Subdivision into subgroups, with specific phenotypes, can optimize this process by enabling a more precise and targeted approach (KIRALI, ALTAY, & PEHLIVANOGLU, 2017).

### 3.3 DIAGNOSIS

The conduct of a comprehensive evaluation assumes great importance to identify possible related causes, determine the stage of the disease and the patient's functional class, and to facilitate the formulation of a personalized therapeutic plan, as well as to estimate prognosis. The likelihood of heart failure should be assessed based on history, physical examination, and resting electrocardiogram. If all these aspects yield normal results, heart failure becomes highly unlikely, and consideration of an alternative diagnosis is warranted. However, if at least one of these aspects shows abnormalities, measurement of plasma natriuretic peptide should be performed, when available, to identify patients who will require further investigation (PONIKOWSKI *et al.*, 2016).

Over the past decade, the measurement of innovative biomarkers, combined with routine laboratory tests, has emerged as one of the most crucial parameters in the diagnostic, therapeutic, and prognostic evaluation of individuals with suspected or confirmed heart failure (PONIKOWSKI *et al.*, 2016). Currently, these markers are regularly employed to differentiate heart failure from other conditions and to determine disease severity. Increased levels of these biomarkers may indicate various pathophysiological aspects of heart failure, including myocardial wall stress, hemodynamic abnormalities, inflammation, myocyte injury, neurohormonal activation, and myocardial remodeling, as well as alterations in the extracellular matrix (YANCY *et al.*, 2013).

The most frequently evaluated natriuretic peptides are brain natriuretic peptide (BNP) and its inactive derivative, N-terminal pro-BNP (NT-pro-BNP), both secreted by cardiomyocytes in response to cardiac wall stress (PONIKOWSKI *et al.*, 2016).

Natriuretic peptide levels tend to increase progressively with deterioration of functional class (NYHA) and to be higher in HF-REF than HF-PEF, as well as tend to decrease with treatment, and may correlate with better clinical outcomes. Patients with acute decompensation of HF generally present higher levels of BNP and NT-pro-BNP when compared to those with stable chronic HF. It is important to remember that the levels of these biomarkers vary in various cardiac and non-cardiac conditions. For example, levels are higher in patients with



valvular heart disease, pulmonary hypertension, ischemic heart disease, atrial arrhythmias, pericardial diseases, and pulmonary embolism (MANN *et al.*, 2015).

### 3.4 PHARMACOLOGICAL TREATMENTS

For patients with HFpEF (Heart Failure with Preserved Ejection Fraction), therapeutic goals aim to alleviate heart failure symptoms, improve functional status, and reduce the risk of hospitalization. There is no conclusive evidence indicating that pharmacological approaches, diet, or other therapies impact mortality reduction in individuals with HFpEF. However, engaging in physical activity, participating in cardiac rehabilitation programs, and dietary interventions are safe and may result in small improvements in exercise tolerance (INA, 2021). Conditions frequently associated with HFpEF include hypertension, atrial fibrillation, coronary artery disease, hyperlipidemia, obesity, anemia, diabetes mellitus, chronic kidney disease (CKD), and sleep-disordered breathing. In general, the treatment of these conditions follows similar approaches applied to the general population or other forms of heart failure (OLUCCI & BORLAUG, 2022). Patients with volume overload initiate treatment with diuretic therapy before considering other pharmacological interventions. The choice of loop diuretics type and dose depends on the severity of volume overload. After optimizing symptom and volume control, a plan for continuous diuretic therapy is established (MARTUCHELI *et al.*, 2022). Renin-angiotensin system inhibitors are not routinely used, although they may be considered as initial therapy for patients with diabetes and CKD. Beta-blockers are not the first-line treatment for HFpEF but may be employed in the management of chronic coronary syndromes, heart rate control in atrial fibrillation, or hypertension treatment (INA, 2021). Organic nitrates, phosphodiesterase-5 inhibitors, and digoxin are ineffective in treating HFpEF and are more appropriate for other conditions, such as angina in chronic coronary syndrome or rate control in atrial fibrillation (MARTUCHELI *et al.*, 2022).

Unlike heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), there are no dedicated clinical studies specifically for patients with mildly reduced ejection fraction heart failure (HFmrEF). Generally, the available evidence indicates that patients with HFmrEF respond to medical therapy more similarly to HFrEF than HFpEF. Given the scarcity of evidence, the initial and target doses for these initial agents are the same as those used for HFrEF (BOURLAUG, 2020).

Treatment goals for HFrEF encompass reducing symptoms, improving health-related quality of life and functional status, and decreasing hospitalization rates, with additional

promotion of mortality reduction. Therapeutic approach involves managing the underlying causes of heart failure (such as interventions for coronary artery disease, treatment for symptomatic valvular disease, and therapy for treatable causes of cardiomyopathy) and associated conditions (such as hypertension, diabetes mellitus, and thyroid dysfunction) (COLUCCI, 2022). Initial pharmacological therapy includes a combination of diuretic therapy, a renin-angiotensin system inhibitor (angiotensin receptor-neprilysin inhibitors [ARNI], angiotensin-converting enzyme inhibitors [ACEIs], or angiotensin II receptor blockers [ARBs]), and a beta-blocker. Diuretic therapy aims to relieve symptoms and signs of volume overload, while renin-angiotensin system blockers are chosen based on considerations of effectiveness, accessibility (considering costs, especially for ARNI), and risk of side effects (highlighting the higher risk of hypotension with ARNI) (MARTUCHELI *et al.*, 2022).

In stable patients with NYHA class II to III heart failure, sacubitril-valsartan has shown reduction in the risk of mortality or rehospitalization. As for less stable patients who initiated sacubitril-valsartan during hospitalization, a possible reduction in the risk of rehospitalization was observed. Patients with HFrEF without current or minimal evidence of volume overload should receive one of the three beta-blockers: carvedilol, metoprolol, or bisoprolol. Beta-blockers are generally initiated after starting an angiotensin system blocker (MEYER, 2022).

Patients with mild heart failure and left ventricular ejection fraction less than 35% should receive statin therapy as per standard indications. Supplementation with polyunsaturated fatty acids is not recommended in patients with HFrEF, based on evidence indicating minimal or no benefit (MARTUCHELI *et al.*, 2022). Pharmacological therapy for HFrEF treatment, including renin-angiotensin system blocker and beta-blocker, is generally maintained indefinitely, even in patients with recovery of systolic function, although there is limited data on the optimal duration of therapy and the risk of drug withdrawal (MEYER, 2022).

### 3.5 ROLE AND INNOVATION OF SGLT2 IN HEART FAILURE

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a groundbreaking therapeutic approach in the management of heart failure (HF). These agents, originally developed for the treatment of diabetes mellitus, have demonstrated remarkable benefits beyond glycemic control, particularly in reducing the risk of hospitalization for HF and improving cardiovascular outcomes in patients with both HF and type 2 diabetes mellitus (T2DM).

The mechanism underlying the beneficial effects of SGLT2 inhibitors in HF extends beyond glucose-lowering properties. These drugs act by inhibiting SGLT2 in the proximal tubules of the kidney, thereby promoting glycosuria and natriuresis, leading to osmotic diuresis and subsequent reduction in blood volume and intravascular pressure. Additionally, SGLT2 inhibition is associated with favorable effects on cardiac metabolism, including increased myocardial ketone utilization, improved myocardial energetics, and reduced oxidative stress and inflammation within the myocardium.

Moreover, SGLT2 inhibitors have been shown to elicit cardiorenal protective effects independent of their glucose-lowering actions. They attenuate cardiac remodeling, reduce myocardial fibrosis, and improve endothelial function. These drugs also exert renoprotective effects by reducing glomerular hyperfiltration, decreasing albuminuria, and preventing renal tubular injury and fibrosis.

The landmark clinical trials, such as EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58, have demonstrated significant reductions in the risk of hospitalization for HF and cardiovascular death with SGLT2 inhibitors, regardless of the presence of diabetes. These findings have led to the incorporation of SGLT2 inhibitors into the treatment algorithms for HF, representing a paradigm shift in the management of this complex syndrome.

The introduction of SGLT2 inhibitors in HF therapy has paved the way for novel treatment strategies targeting cardiometabolic pathways beyond traditional neurohormonal blockade. Ongoing research is exploring the potential synergistic effects of combining SGLT2 inhibitors with existing HF therapies, such as renin-angiotensin-aldosterone system inhibitors and beta-blockers, to further optimize outcomes in patients with HF.

In conclusion, the emergence of SGLT2 inhibitors represents a transformative advance in the field of HF management, offering new therapeutic avenues and hope for improved clinical outcomes in this challenging patient population.

#### **4 MATERIALS AND METHODS**

This is a qualitative exploratory study aimed at identifying literature on the treatment with a sodium-glucose co-transporter inhibitor (dapagliflozin) in heart failure. A literature review was conducted as it contributes to the process of systematizing and analyzing the results of other publications, aiming to understand the topic from other independent studies. The strategy for identifying and selecting articles will involve searching for publications indexed in freely accessible databases available on the internet, such as Scielo, PubMed, and Google

Scholar, during the months of February and March 2024. The criteria adopted for selecting articles will include those with abstracts and full texts available for analysis, published in Portuguese, English, or Spanish, between the years 1998 and 2024, and articles containing the following Health Sciences Descriptors (DeCS) in their titles and/or abstracts: 'Heart Failure'; 'SGLT2'; 'Dapagliflozin'; 'Ejection Fraction'; and 'Treatment'. Articles that do not meet the inclusion criteria mentioned above will be excluded. Based on this survey, an article for discussion will be produced after a careful analysis and comparison with existing literature on the topic. The articles obtained in the survey were analyzed through meticulous reading, highlighting those that addressed the objective proposed by this study, in order to organize and tabulate the data.

## 5 INTEGRATIVE REVIEW ON SGLT2 AND DISCUSSION OF RESULTS

For the elaboration of the theoretical framework of the study, 21 articles were used, according to the selection criteria presented in the previous section. Among these articles, 10 were selected to compose the integrative review and are presented in Table 1.

Table 1 - Results and conclusions of selected articles.

Authors/year	Title of the article	Results	Conclusions
REDFIELD e BORLAUG, 2023.	Heart Failure With Preserved Ejection Fraction: A Review	ICFEP carries risks such as age, hypertension, and diabetes. Diagnosis includes dyspnea, H2FPEF, and exams. Dapagliflozin may reduce hospitalizations by 20%. Exercise, weight loss improve quality of life. Diuretics, education are essential.	Sodium-glucose co-transporter 2 inhibitors, such as dapagliflozin, lead the therapy, reducing hospitalizations for heart failure or death by about 20%. Physical training and diet, compared to usual care, significantly improve functional capacity and quality of life. Diuretics, especially loop diuretics, are recommended to treat congestion symptoms.
ALI <i>et al.</i> , 2023.	Effect of Dapagliflozin in Patients with Heart Failure: A Systematic Review and Meta-Analysis	The overall risk of all-cause mortality favored the dapagliflozin group compared to the placebo/conventional therapy group, and pooled studies showed no heterogeneity. Additionally, dapagliflozin demonstrated a significant reduction in hospitalizations for heart failure, cardiovascular deaths, and their combined outcomes.	Dapagliflozin reduces the risk of death from any cause, hospitalizations due to heart failure, and cardiovascular-related death in a wide range of heart failure patients.
BORLAUG <i>et al.</i> , 2023.	Cardiac and Metabolic Effects of Dapagliflozin in Heart	Out of 38 evaluated (mean age 68 years; 66% women; 71% obese), 37 completed the study. Dapagliflozin reduced PCWP at rest and exercise at 24 weeks compared to placebo, with lower PCWP at rest and maximal	In individuals diagnosed with HFpEF, the use of dapagliflozin reduces PCWP at rest and during physical activities, accompanied by beneficial impacts on plasma volume and body mass. These

	Failure With Preserved Ejection Fraction: The CAMEO-DAPA Trial	exercise. Weight and plasma volume decreased, with no impact on red blood cells. There was no difference in oxygen consumption at 20 W or at peak exercise, but dapagliflozin reduced arterial lactate at 20 W.	findings provide a new perspective on the positive hemodynamic mechanisms associated with sodium-glucose cotransporter-2 inhibitors in HFpEF.
PASCUAL-FIGAL <i>et al.</i> , 2023.	Impact of dapagliflozin on cardiac remodelling in patients with chronic heart failure: The DAPA-MODA study	In the beginning, there was identified left atrial dilation and similar parameters in phenotypes based on left ventricular ejection fraction. At 180 days, there was a significant reduction in left ventricular mass index, end-diastolic volume, and end-systolic volume, with a decrease in reservoir volume highlighted, resulting in an improvement in left ventricular geometry. The N-terminal pro-brain natriuretic peptide also showed a significant reduction during this period, while Doppler filling measurements remained unchanged.	The use of dapagliflozin in stable, optimally treated patients with chronic heart failure induces a global reverse remodeling of cardiac structure. This includes a decrease in left atrial volumes and improvement in left ventricular geometry, as well as a reduction in NT-proBNP concentrations.
BUTT <i>et al.</i> , 2023.	Dapagliflozin in Black and White Patients With Heart Failure Across the Ejection Fraction Spectrum	Out of 3,526 patients in the Americas, 74.5% were white and 10.8% were black. The primary outcome occurred at a rate of 16.8 in blacks and 11.6 per 100 person-years in whites. Dapagliflozin reduced the risk of the primary endpoint similarly in both ethnicities. The number needed to treat was 17 in whites and 12 in blacks. The benefits and safety profile of dapagliflozin were consistent across different left ventricular ejection fractions in both ethnic groups.	The benefits provided by dapagliflozin were consistent across individuals from different ethnic groups, encompassing various ranges of left ventricular ejection fraction. Significantly, more substantial advantages were observed among black patients.
PEIKERT <i>et al.</i> , 2023.	Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction According to Polypharmacy Status	About 60.6% of the 3,795 patients met criteria for polypharmacy, and 30.1% met criteria for hyperpolypharmacy. Dapagliflozin similarly reduced the risk of the primary outcome compared to placebo, regardless of polypharmacy status. The benefits of dapagliflozin were consistent across the spectrum of total medication use. Despite an increase in adverse events with more medications, dapagliflozin did not increase their frequency, regardless of polypharmacy status.	In the DELIVER trial, dapagliflozin safely reduced the worsening of heart failure or cardiovascular death, encompassing various medication regimens, including those with polypharmacy (Dapagliflozin Evaluation to Improve the Lives of Patients with Heart Failure and Preserved Ejection Fraction study).
NASSIF <i>et al.</i> , 2023.	Dapagliflozin Improves Heart Failure Symptoms and Physical Limitations Across the Full Range of Ejection Fraction: Pooled Patient-Level Analysis From	Out of a total of 587 randomized patients, the ejection fraction (EF) was $\leq 40\%$ , $>40\%$ – $\leq 60\%$ , and $>60\%$ in 262 (45%), 199 (34%), and 126 (21%) patients, respectively. Dapagliflozin improved the KCCQ-CSS score at 12 weeks. This improvement was observed in participants with both EF $\leq 40\%$ and $>60\%$ . The benefits of dapagliflozin on KCCQ-CSS also remained consistent when EF was considered continuously. In response analyses, fewer patients treated with dapagliflozin experienced deterioration, while more showed small, moderate, and	In patients with heart failure (HF), dapagliflozin promotes substantial improvements in symptoms and physical limitations over 12 weeks of treatment, showing persistent and clinically relevant benefits across the entire range of ejection fraction (EF).

	DEFINE-HF and PRESERVED-HF Trials	large improvements in KCCQ-CSS compared to placebo; these results were also consistent regardless of EF.	
KONDO <i>et al.</i> , 2023.	Efficacy of Dapagliflozin According to Heart Rate: A Patient-Level Pooled Analysis of DAPA-HF and DELIVER	Among patients with sinus rhythm, the rate of the primary outcome was higher in individuals with higher heart rate (HR): 16.8 compared to 7.7 per 100 person-years for HR $\geq 80$ bpm versus $< 60$ bpm. The relationship between HR and risk was more pronounced in heart failure with reduced ejection fraction (HFrEF) compared to heart failure with mildly reduced/preserved ejection fraction (HFmrEF/HFpEF). HR showed no association with outcomes in patients with atrial fibrillation (AF) for both heart failure phenotypes. The benefit of dapagliflozin on the primary outcome was consistent across the range of HR, both in sinus rhythm and in AF. This benefit was consistent in both heart failure groups, whether with reduced or mildly reduced/preserved ejection fraction.	The risk of worsening heart failure or occurrence of cardiovascular death increased as the initial heart rate (HR) rose among patients in sinus rhythm (SR). However, this relationship was not identified in patients with atrial fibrillation (AF), regardless of the left ventricular ejection fraction. The benefits provided by dapagliflozin remained consistent across the entire range of HR, irrespective of left ventricular ejection fraction or rhythm.
KONDO <i>et al.</i> , 2023.	Efficacy of Dapagliflozin According to Geographic Location of Patients With Heart Failure	Among 11,007 patients, 46.9% were registered in Europe, 13.9% in North America, 18.2% in South America, and 21.1% in Asia. The incidence of the primary outcome (per 100 person-years) was higher in North America compared to other regions. The efficacy of dapagliflozin on the primary outcome was not altered by region: dapagliflozin vs placebo HR: Europe, 0.85; North America, 0.75; South America, 0.72; and Asia, 0.74. This trend persisted when separately analyzing ICFer.	The effectiveness and safety of dapagliflozin remained consistent across all global regions, even in the face of geographical disparities in patient characteristics, prior therapies, and incidence of events.
NGUYEN <i>et al.</i> , 2023.	Cost-effectiveness of dapagliflozin and empagliflozin for treatment of heart failure with reduced ejection fraction	The dapagliflozin-SoC was the most advantageous strategy among the three, comprehensively outperforming empagliflozin-SoC. The ICER for dapagliflozin-SoC and empagliflozin-SoC, compared to SoC alone, was \$56,782 and \$89,258 per QALY, respectively. Dapagliflozin-SoC cost \$5,524 more but resulted in a gain of 0.20 QALYs compared to empagliflozin-SoC, with an ICER of \$27,861 per QALY. The cost-effectiveness ratio of the strategies did not vary with diabetic status. However, the empagliflozin SoC was not more cost-effective compared to SoC alone in patients with ICFer without CKD, and dapagliflozin SoC was not cost-effective versus empagliflozin SoC in patients with ICFer and CKD.	It can be inferred that in terms of cost-effectiveness, the use of dapagliflozin as part of standard treatment was considered more advantageous than empagliflozin in the same condition (HFrEF) or standard treatment alone. Therefore, dapagliflozin, when incorporated into standard treatment, has been shown to be a more efficient and affordable option compared to empagliflozin or standard treatment alone for patients with HFrEF.

Source: Compiled by the authors

After analyzing the selected articles, it has been demonstrated that dapagliflozin, a

sodium-glucose co-transporter 2 (SGLT2) inhibitor, has been recognized for its benefits in heart failure through various mechanisms. The improvements can be exemplified in the following aspects: Reduction in morbidity and mortality (dapagliflozin substantially reduces the risk of hospitalization for heart failure and cardiovascular mortality in patients with heart failure); Symptom improvement (relief of heart failure symptoms such as dyspnea and fatigue, providing a better quality of life for patients); Reduction in intravascular volume (promotes osmotic diuresis, which contributes to the reduction of intravascular volume and stress on the heart); Reduction in blood pressure (studies indicate the ability to lower blood pressure, which is particularly beneficial for patients with heart failure); Renal protection (in addition to its cardiac benefits, dapagliflozin offers renal protection by delaying the progression of chronic kidney disease in patients with heart failure). Therefore, the use of dapagliflozin in heart failure provides significant benefits both in terms of morbidity and mortality and quality of life for patients.

## **6 CONCLUSION**

Heart failure is characterized by the heart's inability to pump blood properly. Treatment involves lifestyle changes, administration of medications (such as angiotensin-converting enzyme inhibitors, beta-blockers, diuretics), and in some situations, surgical procedures such as device implantation or heart transplantation. The drug dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, according to studies, has been approved to treat heart failure with reduced ejection fraction, regardless of diabetes mellitus. The suggested dose is 10 mg once daily for this condition. Dapagliflozin is available in film-coated tablets containing 10 mg for oral administration. Prescription of this medication needs to be tailored, taking into account individual clinical characteristics, drug interactions, and contraindications, and should be performed by a physician after appropriate assessment of the patient's clinical situation.

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