Review Article

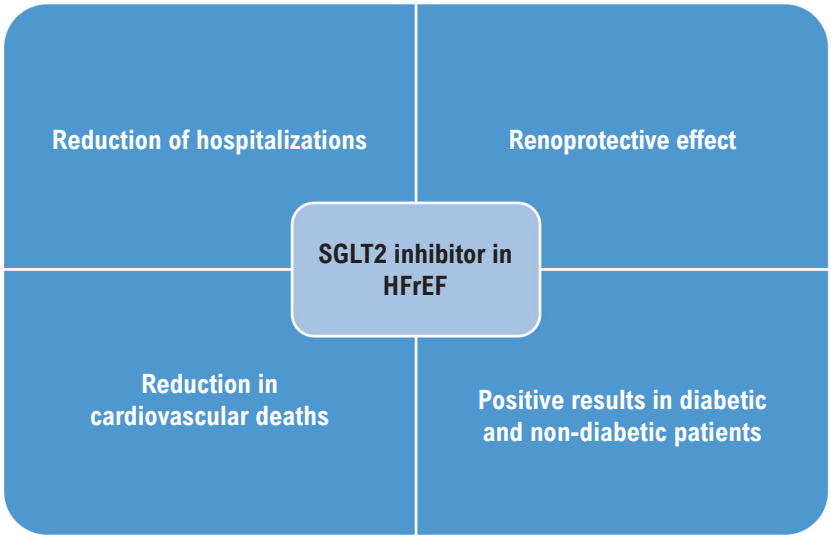
The Use of Sodium-Glucose Cotransporter2 (SGLT2) Inhibitors in Patients with Reduced Ejection Fraction: An Integrative Review

Irving Gabriel Araújo Bispo,[1] *Guilherme Martins Chaves,*[2] *Mariana Gonçalves Fernandes,*[2] *Larissa Hiromi Yamamoto,*[2] *Giulia Amorim Almeida*[2]

Universidade Federal de São Paulo (UNIFESP),[1] *São Paulo, SP – Brazil*

Universidade Municipal de São Caetano do Sul (USCS),[2] *São Caetano do Sul, SP – Brazil*

Central Illustration: The Use of Sodium-Glucose Cotransporter2 (SGLT2) Inhibitors in Patients with Reduced Ejection Fraction: An Integrative Review



ABC Heart Fail Cardiomyop. 2025; 5(1):20240048

Abstract

Heart failure (HF) is characterized as a clinical syndrome comprised of different etiologies. HF can be classified according to the left ventricular ejection fraction (LVEF) in heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). Studies have shown that sodium-glucose cotransporter2 (SGLT2) inhibitors can collaborate in the treatment of HF.

Keywords

Diabetes Mellitus; Heart Failure; Systolic Heart Failure; Sodium-Glucose Transporter 2 Inhibitors.

Mailing Address: Irving Gabriel Araújo Bispo •
Universidade Municipal de São Caetano do Sul - Rua Santo Antônio, 50. Postal Code 09550-051, Centro, Sao Caetano do Sul, SP - Brazil
E-mail: irvingbispo@yahoo.com.br
Manuscript received August 22, 2024, revised manuscript November 10, 2024, accepted December 08, 2024
Editor responsible for the review: Luis Beck-da-Silva

DOI: https://doi.org/10.36660/abchf.20240048i

To conduct a bibliographic survey in the form of an integrative qualitative review on the use of SGLT2 inhibitors in the treatment of heart failure.

This study was carried out through the elaboration of an integrative literature review. Articles published in the last five years were selected from the PubMed, SciELO, LILACS, and Cochrane Library databases, using the following descriptors: "Diabetes Mellitus", "Heart Failure", "Heart Failure with Reduced Ejection Fraction" and "Sodium-Glucose Transporter 2 Inhibitors"

A total of 1,504 articles, published in the PubMed, SciELO, Cochrane Library, and LILACS databases, were found. After analysis, in accordance with the inclusion and exclusion criteria; reading of the abstracts or full text; and exclusion of duplicate articles, 17 studies were selected,

In the past five years, there has been a lack of conclusive studies on the use of SGLT2 inhibitors. Studies, such as DAPA-HF, have shown that dapagliflozin reduces hospitalizations and cardiovascular deaths in patients with HF, regardless of their glycemic status. Recent guidelines have already incorporated SGLT2 inhibitors for the treatment of HFrEF due to strong scientific evidence.

Introduction

Heart failure (HF) is a growing global health concern. It is defined, according to the American Heart Failure Society, the European Society of Cardiology, and the Japanese Heart Failure Society, as a clinical syndrome with different etiologies, causing multiple structural and functional dysfunctions that result in the inability of the ventricle to fill and eject sufficient blood volume to meet tissue metabolic demands.[1] The main clinical manifestations include dyspnea, fatigue, and peripheral edema, which can directly impact exercise tolerance and the practice of daily activities, resulting in frequent hospitalizations and substantial overload of the health system.

These changes, present in HF, are related to the activation of neurohormonal regulatory systems, such as the sympathetic nervous system and the renin-angiotensin-aldosterone system, as well as by the dysfunction of endogenous natriuretic mechanisms. At first, this activation acts to maintain blood pressure and kidney function. However, in the chronic activation scenario, deleterious effects are observed that contribute to the progression of HF, causing an increase in afterload and vascular and cardiac remodeling.[2]

The prevalence of HF is closely linked to an improved treatment of causative events, such as acute myocardial infarction. In Brazil, HF caused 252,000 deaths between 2008 and 2018, costing the health system approximately R$3 billion.[3,4]

HF can be classified according to the left ventricular ejection fraction (LVEF) as follows: heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), and heart failure with mid-range ejection fraction (HFmrEF), the latter being a recently established term. In this classification, HFpEF is defined as LVEF ≥50%. HFrEF presents LVEF <40% and HFmrEF is defined as between 41% and 49%.[5]

Another form of assessment is the New York Heart Association's (NYHA) functional classification. It stratifies HF into four classes based on the manifestation of symptoms related to daily activities and exercise tolerance. In simplified terms, class I is defined as the absence of symptoms; class II presents mild limitation; Class III is characterized by significant limitation, with moderate symptoms; and Class IV is marked by the presence of severe symptoms, in which there is an inability to perform simple daily activities.[6]

The third form of assessment of HF is known as the stage classification, developed by the American College of Cardiology (ACC) / American Heart Association (AHA), and is based on the development and progression of the disease. HF occurs in four stages: stage A, in which there is a risk of developing HF; stage B, which consists of the presence of structural heart disease and the absence of HF symptoms; stage C, which presents structural heart disease associated with previous or current HF symptoms; and, finally, stage D, in which HF is refractory to clinical treatment.[6]

The main causes of HF include ischemic heart disease, arterial hypertension, and valvular heart disease. Other related etiologies include genetic cardiomyopathies, amyloidosis, cardiotoxicity associated with cancer treatment, alcohol abuse, tachycardia, myocarditis, autoimmune diseases, among others.[7]

Pharmacological treatment for HF is already well established in medical practice and has some common pillars for HFrEF and HFpEF, such as the use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists, and beta-blockers. Specifically for HFrEF, the updated Brazilian Guideline for Heart Failure (2021) recommends the use of sacubitril-valsartan (recommendation IB) and SGLT2 inhibitors (recommendation IA), the latter being associated with a reduction in cardiovascular death and hospitalization for HF. BY contrast, specific treatment for HFpEF has not advanced as much as that for HFrEF; therefore, the current recommendation is based on the administration of diuretics to reduce congestion and improve symptoms, according to the ACC/AHA guidelines.[7,8]

SGLT2 inhibitors were initially studied for the treatment of type 2 diabetes mellitus (T2DM). However, studies have shown that their effects can also contribute to the treatment of HF. The exact mechanism of action of this drug is still uncertain, but studies show that it inhibits glucose reabsorption, inducing glycosuria, reducing the insulin/glucagon ratio and promoting lipolysis through the oxidation of free fatty acids. As a consequence, there is an increase in the hepatic production of ketone bodies. These, in turn, are considered superfuels for the myocardium, leading to greater availability of beta-hydroxybutyrate to the cardiomyocyte, thus providing an improvement in cardiac function.[9]

Furthermore, it appears to promote osmotic diuresis and natriuresis in patients with or without T2DM. It also serves to induce glycosuria, thereby reducing preload, and to improve endothelial function, thus decreasing afterload. Some theories about its actions have been highlighted: 1) the improvement of myocardial metabolism, increasing cardiac energy reserve through myocardial substrate exchange; 2) the inhibition of sodium-hydrogen transporter isoform 1, increasing mitochondrial calcium levels; 3) the reduction of cardiac fibrosis; 4) the reduction of cytokine and adipokine production; and 5) the reduction of the risk of developing atrial arrhythmias.[2,10]

In this context, considering the scientific evidence referent to the impact of drug treatment with SGLT2 inhibitors in reducing mortality and hospitalization for HF, the difference in the effects of their applicability in patients with HFrEF has been questioned.

Objective

To conduct a qualitative integrative literature review on the use of SGLT2 inhibitors in heart failure and identify the impact of medication use on heart failure with reduced ejection fraction (HFrEF), demonstrating the main differences in cardiovascular impacts in the most recent clinical trials and meta-analyses (Central Illustration).

Methods

This study was conducted through a qualitative integrative review of national and international literature in order to establish a synthesis of scientific production on the use of SGLT2 inhibitors in the context of heart failure.

Initially, the theme of the study was defined and the guiding question was developed, following the PICO format (Figure 1), as well as the definition of the search strategy, descriptors, and databases that would be used.

Next, the inclusion and exclusion criteria were defined; articles were searched in the databases and pre-selected; and selected studies were identified, based on reading the abstract, keywords, and title of the publications in order to assess whether or not the study was relevant to the guiding question. When the information contained in the abstract was not sufficient, the full text was read.

The criteria used after a careful reading of the abstracts or full texts were based on the type of study, excluding those with little scientific relevance and those in which there was no correlation with the use of the drug analyzed for heart failure, given that many of them presented analyses directly related to other associated comorbidities and were therefore excluded from the research.

In the next stage, the selected studies were categorized according to the degree of recommendation and strength of evidence into: 1) Degree of recommendation A: experimental or observational studies with better consistency (comprised of meta-analyses or randomized clinical trials) and 2) Degree of recommendation B: experimental or observational studies with less consistency (comprised of other non-randomized clinical trials or observational studies or case-control studies), as recommended by the Brazilian Medical Association (*Associação Médica Brasileira* – AMB). Studies related to degrees C and D were not included.

The limitation of the chosen articles was essential in order to highlight the scientific rigor that supports the research and to provide a clear understanding of the robustness of the analyzed data, thus reinforcing the credibility of the conclusions and the relevance of the discussions presented.

The studies were then arranged in a table using a synthesis matrix for critical analysis of the selected studies (Table 1). Based on the interpretation and synthesis of the results, the findings were compared with the theoretical framework in a descriptive manner, enabling the assessment of the applicability of the integrative review and formulation of the discussion in order to achieve the objective of this study. Finally, a document was created to summarize the evidence found in the study and prepare the integrative review.

The inclusion criteria were studies published in Portuguese and English, in the PubMed, Cochrane Library, SciELO, and LILACS databases, according to the MeSH descriptors contained in the DeCS platform: "diabetes mellitus", "heart failure", "heart failure with reduced ejection fraction" and "sodium-glucose transporter 2 inhibitors", published in the last 5 years. The consultation period took place from September 2023 to February 2024. The following characteristics were considered exclusion criteria: experimental articles, editorials, communications from reviewers, and articles published in duplicate in the databases.

Results

A total of 1,504 articles published in the PubMed, SciELO, Cochrane Library, and LILACS databases were found. After analysis according to the inclusion and exclusion criteria, 17 studies were selected, 11 from PubMed, 3 from SciELO, 2 from the Cochrane Library, and 1 from LILACS, which fully met the inclusion and exclusion criteria (Figure 2). Among the selected articles were literature reviews, meta-analyses, systematic reviews, double-blind randomized clinical trials, and prospective cohort studies (Figure 3).

Table 1 presents a summary of the main articles selected in this integrative literature review, containing the title of the work, year of publication, database, and relevant topics of the article.

Among the studies analyzed for HFrEF (LVEF < 40%) in the last five years, most analyzed two large trials (DAPA-HF and EMPEROR), which concluded that SGLT2 inhibitors significantly benefited patients with chronic HFrEF. In addition, the studies recommend early initiation for those with chronic and symptomatic HFrEF, with dapagliflozin or empagliflozin, whether diabetic or not, as the studies found that there was an improvement in the rate of hospitalization for HF, mortality, clinical conditions, and decline in renal function.

Finally, among the selected articles, few adverse effects were noted due to the use of SGLT2 inhibitors. Furthermore, only one study emphasized that the use of the medication in anemic patients led to an increase in hematocrit and improvement in clinical conditions. However, another study addressed the high cost of the medication, and its cost-benefit advantages if there were a near 43% reduction, possibly improving the analyzed outcomes.

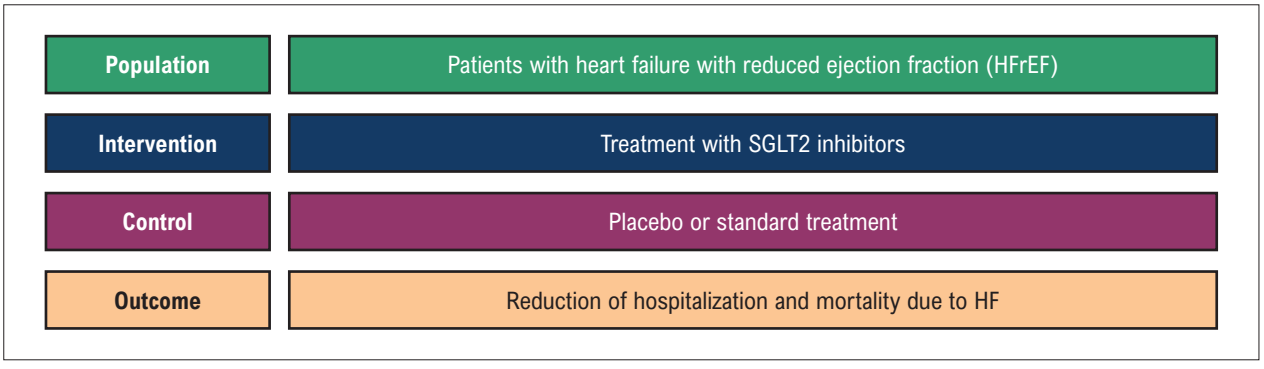


Figure 1 – *PICO strategy applied to define the guiding question.*

Table 1 – Core characteristics of the main studies included in the integrative review

Article Title	Year of publication / database	Number of patients in the study / included studies	Relevant topics
Diabetes and heart failure. Are type two sodium-glucose cotransporter inhibitors the future of treatment?[11]	2022 Scielo	EMPAREG-OUTCOME: 7020 DECLARE-TIMI 58: 17160 DAPA-HF: 4744 CANVAS R: 10142	Reduction in the rate of cardiovascular death or hospitalization for HF. Reduction in the risk of major adverse cardiovascular events. Reduction in HbA1c levels.
Diabetes and cardiovascular disease[12]	2021 Scielo	EMPAREG-OUTCOME: 7020 DECLARE-TIMI 58: 17160 DAPA-HF: 4744 CREDENCE: 4401	DM therapy is constantly advancing, including new drugs that act as an additional tool to reduce blood glucose levels and major cardiovascular events.
Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction Results of DAPA-HF[13]	2021 PubMed	DAPA-HF: 4744	Mortality, morbidity, and symptoms were improved by dapagliflozin in patients with HFrEF compared with placebo, regardless of baseline renal function.
SGLT2 inhibitors in heart failure with reduced ejection fraction: a paradigm shift towards dual cardio-renal protection[14]	2022 PubMed	DAPA-HF: 4744 EMPEROR-Reduced: 3730 SOLOIST-WHF: 1222 EMPULSE-HF: 530 EMPIRE-HF: 190	Considered together, the studies suggest that the early administration of SGLT2 inhibitors in patients hospitalized for acute HF may reduce hospitalization and mortality. DAPA-HF and EMPEROR-Reduced were associated with similar risk reduction, regardless of advanced age, etiology, and duration of HF, as well as the presence of COPD, DM, and impaired renal function. The renal protective effect is an important development in the treatment of HFrEF.
SGLT2 Inhibitors and Heart Failure – A Review of the State of the Art[15]	2023 Scielo	EMPAREG: 7020 CANVAS: 10.142 DECLARE-TIMI 58: 17.160 DAPA-HF: 4744 EMPEROR-Reduced: 3730 EMPEROR-Preserved: 5988 DELIVER Trial: 6263	SGLT2 inhibitors have shown significant benefits in reducing cardiovascular mortality and hospitalizations for HF, regardless of the presence or absence of T2DM and the HF phenotype based on left ventricular ejection fraction (LVEF).
SGLT2 inhibitors in heart failure with mildly reduced or preserved ejection fraction: an updated systematic review and meta-analysis[16]	2022 PubMed	EMPEROR-Preserved: 5988 SOLOIST-WHF: 256 DELIVER Trial: 6263 DECLARE-TIMI 58: 808 VERTIS-CV: 1007 SCORED: 1667	This meta-analysis of patients with heart failure and LVEF <40% showed that SGLT2 inhibitors significantly reduced the risk of the combination of cardiovascular death and hospitalization due to heart failure but not cardiovascular death and all-cause death. However, given that SGLT2 inhibitors can reduce the risk of hospitalization due to heart failure, they should be considered the mainstay of treatment for all patients with HFrEF.
Efficacy of sacubitril valsartan and SGLT2 inhibitors in heart failure with reduced ejection fraction: A systematic review and meta-analysis[17]	2023 PubMed	DAPA-HF: 4744 EMPEROR-Reduced: 3730 EMPIRE-HF: 190 Hsiao et al: 2312 Jiang et al: 136 Karabulut et al: 244	The combination of sacubitril-valsartan (SV) and SGLT2 inhibitors may have a greater cardiovascular protective effect and minimize the risk of death or hospitalization due to HFrEF. An improvement wsa also observed in LVEF. The combination was even more effective when compared to treatment with SV alone.
Evaluation of the effect of SGLT2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial[18]	2019 PubMed	EMPA-REG OUTCOME trial and EMPEROR-Reduced trial	Empagliflozin may significantly contribute to current approaches that have established benefits in the treatment of chronic heart failure with left ventricular systolic dysfunction.
The dawn of the four-drug era? SGLT2 inhibition in heart failure with reduced ejection fraction[19]	2021 PubMed	EMPAREG: 7020 CANVAS: 10.142 DECLARE-TIMI 58: 17.160 DAPA-HF: 4744 EMPEROR-Reduced: 3730 VERTIS-CV: 1007	Publication approval of cardiovascular outcome data for three of these agents (canagliflozin, empagliflozin, and dapagliflozin) showed an unexpected improvement in cardiovascular outcomes, including hospitalization due to heart failure and mortality, among patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease or risk factors.

Effect of Empagliflozin on the Clinical Stability of Patients with Heart Failure and a Reduced Ejection Fraction[20]	2020 Cochrane	EMPEROR-Reduced Trial: 3730	In patients with heart failure and reduced ejection fraction, empagliflozin reduced the risk and total number of inpatient and outpatient worsening of heart failure events, with benefits observed shortly after onset of treatment and maintained during double-blind therapy.
Effect of Dapagliflozin in Patients With HFrEF Treated With Sacubitril/Valsartan[21]	2020 Cochrane	DAPA-HF Trial: 4744	Dapagliflozin was equally effective and safe in patients who were and were not taking sacubitril/valsartan in the DAPA-HF trial, which suggested that using both agents together could further reduce morbidity and mortality in patients with HFrEF. (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure).
Effects of SGLT2 inhibitors on nutritional status in heart failure with reduced ejection fraction[22]	2022 PubMed	153	In patients with heart failure with reduced ejection fraction who are symptomatic despite optimal medical treatment, the addition of a SGLT2 inhibitors for treatment can significantly improve nutritional and functional status.

Discussion

SGLT2 inhibitors are a relatively new class of antihyperglycemic medications with similar effects on glucose control, body weight, and blood pressure. Emerging evidence now suggests that these medications may have a beneficial effect on outcomes in HFrEF.

Post-approval cardiovascular outcome data for three of these agents (canagliflozin, empagliflozin, and dapagliflozin) have shown unexpected improvements in cardiovascular outcomes, including hospitalization for heart failure and mortality, among patients with or without T2DM and established cardiovascular disease or risk factors. This context is related to the EMPEROR-Reduced study, which included 3,730 symptomatic patients with HFrEF (EF ≤ 40%), who were randomly assigned to receive empagliflozin or placebo. After a median of 16 months, empagliflozin showed a 25% reduction in combined cardiovascular death or hospitalization for heart failure, highlighting the beneficial effect of such medications in patients with HFrEF. As for canagliflozin, the same research cites that, in CANVAS, canagliflozin caused a 14% reduction in the combined outcome of cardiovascular events of cardiovascular death, myocardial infarction or stroke over 3.6 years of follow-up.[10,23,24]

The exact mechanism for the cardiovascular benefit of SGLT2 inhibitors, which reduce sodium and glucose reabsorption in the proximal tubule of the kidney, remains unknown, although diuretic properties and favorable changes in cardiac metabolism by altering cardiac substrate use have been postulated. Although the exact mechanism of SGLT2 inhibitors leading to cardiovascular benefit is unknown, one study demonstrated that "sodium-glucose transporter (SGLT-)2 inhibitors prevent incident hospitalization for HF in patients with diabetes. Dapagliflozin recently proved to reduce the combination of cardiovascular death or worsening HF in patients with HFrEF in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial."[2,25,26]

In addition, in the EMPAREG OUTCOME trial, empagliflozin reduced the risk of sudden myocardial infarction and sudden death. In none of the three studies could the benefits of SGLT2 inhibitors in heart failure be explained by the actions of these drugs when used as diuretics or antihyperglycemic agents. These observations raise the possibility that SGLT2 inhibitors may reduce morbidity and mortality in patients with established heart failure, including those without diabetes.[7,27]

The selected studies definitively demonstrated that empagliflozin and dapagliflozin, respectively, reduce the risk and total number of inpatients and outpatients with worsening HF events, with benefits observed soon after beginning treatment and maintained during double-blind therapy.[28,29]

The DAPA-HF study followed 4,744 patients, comparing the effect of dapagliflozin with placebo on the incidence of worsening HF and mortality in patients with chronic HF.

As with other SGLT2 inhibitors, dapagliflozin causes small reductions in blood pressure and weight, a small initial increase in creatinine (although long-term treatment with SGLT2 inhibitors appears to be renoprotective in T2DM), and an increased risk of genital fungal infection.[22,30,31]

What mechanisms could possibly be responsible for such a marked cardioprotective effect of SGLT2 inhibitors in HFrEF?

SGLT2 inhibitors increase fasting ketone body levels and have therefore been hypothesized to improve the use of this efficient metabolic fuel in HF. However, results from experimental studies have provided inconsistent support for this hypothesis. Instead, it has been proposed that SGLT2 inhibitors may slow the course of cardiomyocyte injury and loss by inhibiting sodium-hydrogen exchanger-1 (NHE-1) in the myocardium, the overactivity of which can lead to increases in intracellular sodium and calcium, which may impair cardiomyocyte function and viability. Interestingly, empagliflozin has also proven to inhibit the activation of Ca++/calmodulin-dependent kinase II, which contributes to NHE-1 activation in the heart. Empagliflozin's actions to prevent calcium overload may explain why the drug prevents the time-dependent decline in systolic cardiac function observed in experimental pressure-overload-induced heart failure.[20,32,33] Regardless of the mechanisms that may be at play, the EMPEROR-Reduced trial is well positioned to determine

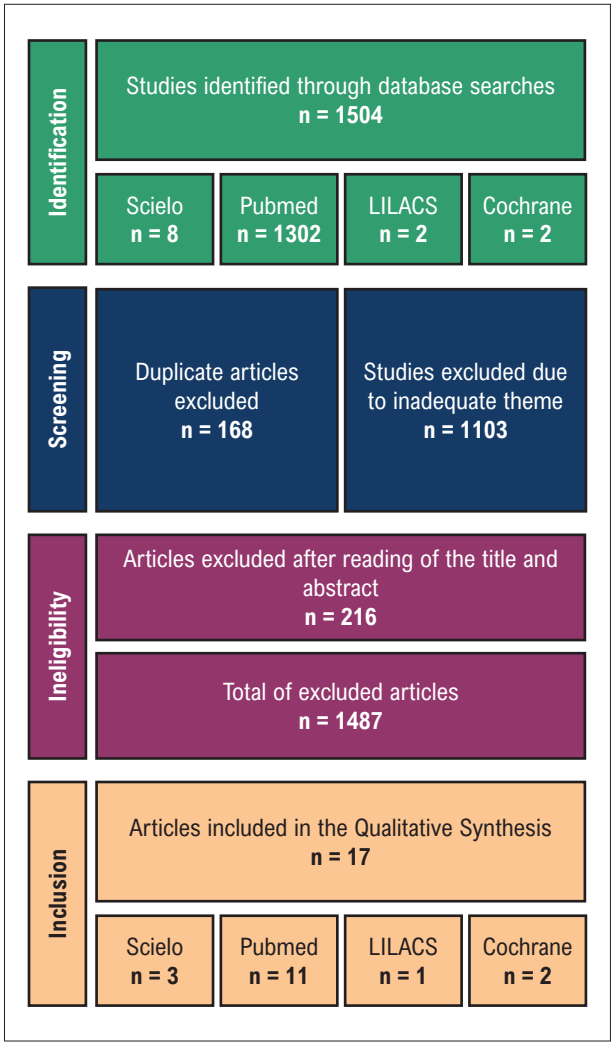


Figure 2 – *Flowchart of the selection of included articles.*

whether the addition of SGLT2 inhibitors could meaningfully add to current approaches that have established benefits in the treatment of chronic HF. The findings from the trial are likely to advance both our understanding of the disease and our treatment options.[34-36]

Limitations

This study has a bias in selecting more recent articles on the subject that have only ratified previous studies on the use of SGLT2 inhibitors. There is also a lack of standardization of the selected studies, with a greater number of articles from systematic reviews and meta-analyses. New randomized studies with the use of SGLT2 inhibitors in HFrEF contexts in different scenarios, such as Acute HF or HF in patients with improved ejection fraction, are necessary.

Conclusion

It can therefore be concluded that SGLT2 inhibitors have obtained significant benefits for patients with HFrEF. Studies, such as DAPA-HF, have shown that dapagliflozin reduces hospitalizations and cardiovascular deaths in patients with HF, regardless of their glycemic status. Recent guidelines already incorporate SGLT2 inhibitors for the treatment of HFrEF due to strong scientific evidence. Therefore, it is understood that the drug has had a positive impact on quality of life and morbidity and mortality, and is currently considered an essential part of the treatment for HF.

Author Contributions

Conception and design of the research: Bispo IGA, Chaves GM; Acquisition of data: Chaves GM, Amorim G; Analysis and interpretation of the data: Fernandes MG, Yamamoto LH; Writing of the manuscript: Bispo IGA, Chaves GM, Fernandes MG, Yamamoto LH, Amorim G; Critical revision of the manuscript for content: Bispo IGA.

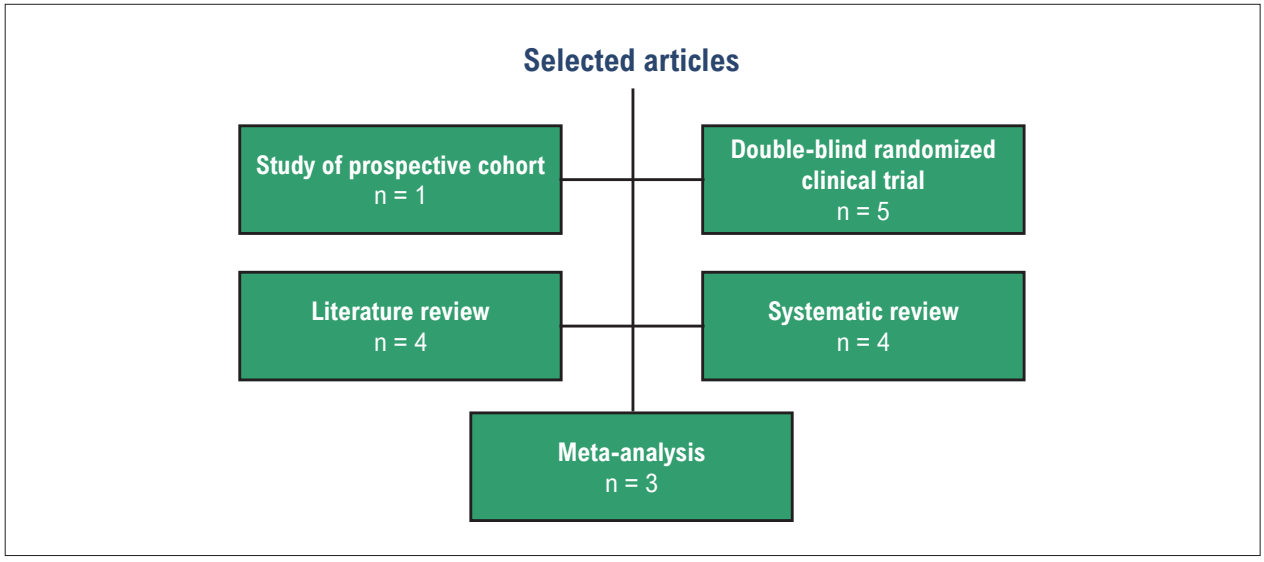


Figure 3 – *Categorization of the analyzed articles according to type of study.*

Potential conflict of interest

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

Sources of funding

There were no external funding sources for this study.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

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

References

1. Alexsander R, Bessa LLC, Silveira AVD, Souza IG, Ferreira GFS, Souza GP, et al. Análise Epidemiológica por Insuficiência Cardíaca no Brasil. Braz Med Students. 2022;6(9):1-8. doi: 10.53843/bms.v6i9.224.
2. Bocchi EA, Biolo A, Moura LZ, Figueiredo Neto JA, Montenegro CEL, Albuquerque DC. Emerging Topics in Heart Failure: Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2i) in HF. Arq Bras Cardiol. 2021;116(2):355-8. doi: 10.36660/abc.20210031.
3. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021;S1071-9164(21):00050-6. doi: 10.1016/j.cardfail.2021.01.022.
4. Hundertmark MJ, Adler A, Antoniades C, Coleman R, Griffin JL, Holman RR, et al. Assessment of Cardiac Energy Metabolism, Function, and Physiology in Patients with Heart Failure Taking Empagliflozin: The Randomized, Controlled EMPA-VISION Trial. Circulation. 2023;147(22):1654-69. doi: 10.1161/CIRCULATIONAHA.122.062021.
5. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. J Card Fail. 2022;28(5):e1-e167. doi: 10.1016/j.cardfail.2022.02.010.
6. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium Glucose Cotransporter-2 Inhibition in Heart Failure: Potential Mechanisms, Clinical Applications, and Summary of Clinical Trials. Circulation. 2017;136(17):1643-58. doi: 10.1161/CIRCULATIONAHA.117.030012.
7. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. The SGLT2 Inhibitor Dapagliflozin in Heart Failure with Preserved Ejection Fraction: A Multicenter Randomized Trial. Nat Med. 2021;27(11):1954-60. doi: 10.1038/s41591-021-01536-x.
8. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: 10.5935/abc.20180190.
9. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008. doi: 10.1056/NEJMoa1911303.
10. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med. 2020;383(15):1425-35. doi: 10.1056/NEJMoa2004967.
11. Almero-Ballesteros B, Tarraga-Marcos L, Madrona-Marcos F, Romero-de-Avila JM, Tárraga-López J. Diabetes and Heart Failure. Are Type Two Sodium-Glucose Cotransporter Inhibitors the Future of Treatment? J Negat No Posit Results. 2022; 7(2):209-34. doi: 10.19230/jonnpr.4443.
12. Guamán C, Acosta W, Alvarez C, Hasbum B. Diabetes y Enfermedad Cardiovascular. Rev Urug Cardiol. 2021;36(1):7-18. doi: 10.29277/cardio.36.1.4.
13. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, et al. Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients with Heart Failure with Reduced Ejection Fraction: Results of DAPA-HF. Circulation. 2021;143(4):298-309. doi: 10.1161/CIRCULATIONAHA.120.050391.
14. Rastogi T, Girerd N. SGLT2 Inhibitors in Heart Failure with Reduced Ejection Fraction: A Paradigm Shift Toward Dual Cardio-Renal Protection. Heart Fail Clin. 2022;18(4):561-77. doi: 10.1016/j.hfc.2022.03.006.
15. Meza-González YA, Alfonso-Arrieta N, Salas-Solorzano S, Florez-Garcia V. Sodium-Glucose Co-Transporter Type 2 Inhibitors and Heart Failure: A Review of the State of the Art. Iberoam J Med. 2023;5(2):68-77. doi: 10.53986/ibjm.2023.0009
16. Wang Y, Gao T, Meng C, Li S, Bi L, Geng Y, et al. Sodium-Glucose Co-Transporter 2 Inhibitors in Heart Failure with Mildly Reduced or Preserved Ejection Fraction: An Updated Systematic Review and Meta-Analysis. Eur J Med Res. 2022;(1):314. doi: 10.1186/s40001-022-00945-z.
17. Mo X, Lu P, Yang X. Efficacy of Sacubitril-Valsartan and SGLT2 Inhibitors in Heart Failure with Reduced Ejection Fraction: A Systematic Review and Meta-Analysis. Clin Cardiol. 2023;46(10):1137-45. doi: 10.1002/clc.24085.
18. Packer M, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al. Evaluation of the Effect of Sodium-Glucose Co-Transporter 2 Inhibition with Empagliflozin on Morbidity and Mortality of Patients with Chronic Heart Failure and a Reduced Ejection Fraction: Rationale for and Design of the EMPEROR-Reduced Trial. Eur J Heart Fail. 2019;21(10):1270-78. doi: 10.1002/ejhf.1536.
19. Genuardi MV, Mather PJ. The Dawn of the Four-Drug Era? SGLT2 Inhibition in Heart Failure with Reduced Ejection Fraction. Ther Adv Cardiovasc Dis. 2021;15:17539447211002678. doi: 10.1177/17539447211002678.
20. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of Empagliflozin on the Clinical Stability of Patients with Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. Circulation. 2021;143(4):326-36. doi: 10.1161/CIRCULATIONAHA.120.051783.
21. Solomon SD, Jhund PS, Claggett BL, Dewan P, Køber L, Kosiborod MN, et al. Effect of Dapagliflozin in Patients with HFrEF Treated with Sacubitril/Valsartan: The DAPA-HF Trial. JACC Heart Fail. 2020;8(10):811-8. doi: 10.1016/j.jchf.2020.04.008
22. Arslan K, Yılmaz E, Aydın E. Effects of Sodium-Glucose Cotransporter-2 Inhibitors on Nutritional Status in Heart Failure with Reduced Ejection Fraction. Rev Assoc Med Bras. 2022;68(11):1576-81. doi: 10.1590/1806-9282.20220737.
23. Botelho LLR, Cunha CCR, Macedo M. O Método da Revisão Integrativa nos Estudos Organizacionais. Gest Soci. 2011;5(11):121-36. doi: 10.21171/ges.v5i11.1220.
24. Anker SD, Butler J, Packer M. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. Reply. N Engl J Med. 2022;386(21):e57. doi: 10.1056/NEJMc2118470.
25. Filippatos G, Butler J, Farmakis D, Zannad F, Ofstad AP, Ferreira JP, et al. Empagliflozin for Heart Failure with Preserved Left Ventricular Ejection Fraction with and Without Diabetes. Circulation. 2022;146(9):676-86. doi: 10.1161/CIRCULATIONAHA.122.059785.
26. Kanie T, Mizuno A, Takaoka Y, Suzuki T, Yoneoka D, Nishikawa Y, et al. Dipeptidyl Peptidase-4 Inhibitors, Glucagon-Like Peptide 1 Receptor Agonists and Sodium-Glucose Co-Transporter-2 Inhibitors for People with Cardiovascular Disease: A Network Meta-Analysis. Cochrane Database Syst Rev. 2021;10(10):CD013650. doi: 10.1002/14651858.CD013650.pub2.

27. Lin Y, Cai Z, Yuan J, Liu H, Pang X, Chen Q, et al. Effect of Pharmacological Treatment on Outcomes of Heart Failure with Preserved Ejection Fraction: An Updated Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Cardiovasc Diabetol. 2022;21(1):237. doi: 10.1186/s12933-022-01679-2.

28. Lorenzi AB, Kaplinsky E, Zambrano MR, Chaume LT, Rosas JM. Emerging Concepts in Heart Failure Management and Treatment: Focus on SGLT2 Inhibitors in Heart Failure with Preserved Ejection Fraction. Drugs Context. 2023;12:2022-7-1. doi: 10.7573/dic.2022-7-1.

29. Pandey AK, Bhatt DL, Pandey A, Marx N, Cosentino F, Pandey A, et al. Mechanisms of Benefits of Sodium-Glucose Cotransporter 2 Inhibitors in Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2023;44(37):3640-51. doi: 10.1093/eurheartj/ehad389.

30. Solomon SD, McMurray JJV, Claggett B, Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022;387(12):1089-98. doi: 10.1056/NEJMoa2206286.

31. Tsampasian V, Elghazaly H, Chattopadhyay R, Ali O, Corballis N, Chousou PA, et al. Sodium Glucose Co-Transporter 2 Inhibitors in Heart Failure with Preserved Ejection Fraction: A Systematic Review and Meta-Analysis. Eur J Prev Cardiol. 2022;29(6):e227-9. doi: 10.1093/eurjpc/zwab189.

32. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, et al. A Trial to Evaluate the Effect of the Sodium-Glucose Co-Transporter 2 Inhibitor Dapagliflozin on Morbidity and Mortality in Patients with Heart Failure and Reduced Left Ventricular Ejection Fraction (DAPA-HF). Eur J Heart Fail. 2019;21(5):665-75. doi: 10.1002/ejhf.1432.

33. Parizo JT, Goldhaber-Fiebert JD, Salomon JA, Khush KK, Spertus JA, Heidenreich PA, et al. Cost-Effectiveness of Dapagliflozin for Treatment of Patients with Heart Failure with Reduced Ejection Fraction. JAMA Cardiol. 2021;6(8):926-35. doi: 10.1001/jamacardio.2021.1437.

34. Ferreira JP, Anker SD, Butler J, Filippatos G, Iwata T, Salsali A, et al. Impact of Anaemia and the Effect of Empagliflozin in Heart Failure with Reduced Ejection Fraction: Findings from EMPEROR-Reduced. Eur J Heart Fail. 2022;24(4):708-15. doi: 10.1002/ejhf.2409.

35. Monzo L, Ferrari I, Cicogna F, Tota C, Calò L. Sodium-Glucose Co-Transporter-2 Inhibitors Eligibility in Patients with Heart Failure with Reduced Ejection Fraction. Int J Cardiol. 2021;341:56-9. doi: 10.1016/j.ijcard.2021.08.035.

36. Clark KAA. The Use of Sodium-Glucose Cotransporter 2 Inhibitors in Heart Failure with Reduced or Preserved Ejection Fraction: New Guidelines Hot off the Press and Directly into Guidelines! Postgrad Med J. 2023;99(1176):1052-7. doi: 10.1093/postmj/qgad022.