REVIEW ARTICLE

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Dapagliflozin and empagliflozin – a new perspective for patients with heart failure with preserved ejection fraction (HFpEF)

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Abstract

Introduction and Objective. The aim of this review is to analyze and evaluate the results of studies from the last six years regarding the therapeutic efficacy of SGLT-2 inhibitors – dapagliflozin and empagliflozin – in patients with heart failure with preserved left ventricular ejection fraction (HFpEF). The review includes a detailed discussion of the key studies in this field – DELIVER and EMPEROR-Preserved, Also described are new research directions that focus on understanding the metabolic effects of SGLT-2 inhibitors on the myocardium, and their impact on microcirculation.

Review Methods. A literature search was conducted in the PubMed and Web of Science databases, using the inclusion criteria of 'free full text' and articles in English published between 2020 – 2025. A total of 139 records were found, of which 35 publications were ultimately included in the review.

Brief description of the state of knowledge. Sodium-glucose cotransporter (SGLT-2) inhibitors are anti-diabetic medications that also exhibit beneficial cardioprotective and nephroprotective effects. In 2023, the European Society of Cardiology (ECS) guidelines for HFpEF recommended dapagliflozin and empagliflozin as first-line treatments for this group of patients. Numerous randomized trials have confirmed that these medications reduce the risk of hospitalization for heart failure and cardiovascular death.

Summary. Dapagliflozin and empagliflozin are drugs that have recently revolutionized the treatment of HFpEF, benefitting a group of patients with previously limited therapeutic options. The positive impact of these drugs on the cardiovascular system opens up new therapeutic perspectives and is a current and important topic in the context of the development of modern cardiology.

Key words

heart failure, sglt-2 inhibitors, HFpEF, empagliflozin, dapagliflozin

INTRODUCTION

According to the 2021 definition provided by the European Society of Cardiology (ESC), heart failure (HF) is a set of clinical features resulting from a variety of diseases. As there are no pathognomonic features, it is necessary to perform comprehensive diagnostics in order to make an accurate diagnosis [1]. Patients with HF are divided into three groups: with reduced ejection fraction (≤40%), with minimally reduced ejection fraction (41–49%), and with preserved ejection fraction (≥50%) [2, 3]. Heart failure with preserved ejection fraction (HFpEF) is estimated to account for approximately half of the cases in Europe and North America. Aging populations contribute to the increasing incidence of HFpEF, and comorbidities such as hypertension, obesity and diabetes, are common in this group of patients [4]. Treatment options for patients with HFpEF remain limited [5, 6]. Heart failure is a significant public health problem and it is estimated that 26 million people worldwide suffer from the condition. Hospitalizations due to this condition significantly burden healthcare systems and the economies of many countries [6, 7].

In the past decade, SGLT-2 inhibitors were first approved for the treatment of type 2 diabetes. Their primary mechanism of action is inhibiting glucose re-absorption in the proximal renal tubules which results in lower blood glucose levels and increased urinary glucose excretion [8, 9]. Additionally, SGLT-2 inhibitors have been shown to have pleiotropic effects and may improve cardiovascular parameters in cardiac patients [8]. The recently published DELIVER (dapagliflozin) [2] and EMPEROR-Preserved (empagliflozin) [10] trials were groundbreaking, providing a strong argument for changes in treatment recommendations for patients with HFpEF.

OBJECTIVE

The aim of this review is to summarize the latest research and guidelines regarding sodium-glucose co-transporter 2 (SGLT-2) inhibitors, empagliflozin, and dapagliflozin in the treatment of heart failure with preserved ejection fraction (HFpEF).

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REVIEW METHODS

A literature review was conducted in the Pubmed and Web of Science databases. Articles published from 2020 – 2025 were selected. Articles written in English with free full-text access were included in the review. Case reports, studies with incomplete data, and letters to the editor were excluded. Article searches were conducted using the terms 'heart failure', 'SGLT-2 inhibitors', 'HFpEF', 'empagliflozin', and 'dapagliflozin'.

STATE OF KNOWLEDGE

Pathophysiology. Heart failure with preserved ejection fraction (HFpEF) results primarily from left ventricular diastolic dysfunction, leading to impaired cardiac filling with a preserved left ventricular ejection fraction (≥ 50%) [11]. Diagnosis of this condition is difficult, but according to the 2021 ESC guidelines, is based on symptoms of heart failure, a left ventricular ejection fraction (LVEF) ≥ 50%, and objective evidence of structural or functional cardiac abnormalities [1]. The pathophysiology of HFpEF is multi-factorial and not fully understood, which complicates causal treatment of the disease [12]. Due to increased stiffness and impaired ventricular relaxation, the left ventricle is unable to accommodate an adequate amount of blood during diastole, despite preserved systolic volume [13]. A significant factor contributing to diastolic dysfunction is endothelial dysfunction, which leads to microcirculation disorders [14]. Typical symptoms of heart failure include shortness of breath (dyspnoea) and limited exercise tolerance, which significantly reduce the quality of life of patients [15]. Additionally, heart failure (HF) is associated with numerous co-morbidities. Chronic inflammation associated with the release of inflammatory cytokines and oxidative stress contribute to cardiac remodelling, a process which results in myocardial fibrosis and increased ventricular wall stiffness [16]. An analysis published in 2023 presents the results of the prevalence of co-morbidities in patients with HF. The study used data from 20,159 people with HFrEF and 6,563 with HFpEF. The group of patients with HFpEF had a significantly higher burden, as 79.8% of this group had three or more co-morbidities, compared to 59.7% in the HFrEF group [17] (Tab. 1).

SGLT-2 Inhibitors – a pharmacological review. SGLT-2 inhibitors are new anti-diabetic medications. The primary site of action of this class of drugs is sodium-glucose co-transporters, located in the proximal convoluted tubules of the kidney. The drug binds to the SGLT-2 transport protein and inhibits renal glucose reabsorption. This process results in glucosuria and a decrease in blood glucose levels. The mechanism is independent of insulin action, and compared to other anti-diabetic medications, it therefore has a low risk of hypoglycemia [6, 12]. Furthermore, SGLT-2 inhibitors exhibit diuretic and natiuretic effects, reducing plasma volume and left ventricular filling pressure. This mechanism protects against excessive fluid retention and the exacerbation of heart failure [18]. Additionally, SGLT-2 inhibitors exhibit anti-inflammatory and anti-fibrotic effects, favourably reducing pro-inflammatory cytokines (TNF-α, IL-6), oxidative stress, and markers of fibrosis. This contributes to slowing fibrotic cardiac remodelling, which is one of the main causes of HFpEF development [16]. Empagliflozin and dapagliflozin are representatives of this group of drugs that demonstrate benefits in cardiac patients, regardless of the presence of diabetes [19, 20].

Table 1. The most common diseases occurring in patients depending on the type of HF with preserved or reduced ejection fraction [17]

Co-morbidity	HFpEF (n = 6563)	HFrEF (n = 20159)
Hypertension	94.1%	68.4%
Atrial Fibrillation (AF)	54.0%	36.2%
Obesity	53.3%	31.4%
Chronic Kidney Disease (CKD)	48.7%	33.9%
Diabetes Mellitus (DM)	43.4%	33.9%

Empagliflozin and dapagliflozin comparison. Two large, recently published studies, EMPEROR-Preserved and DELIVER, have proven to be breakthroughs in the treatment of patients with HFpEF [21]. Both studies were conducted in multi-centre, double-blind, randomized designs. Eligible patients were those who met the criteria for HF with minimally reduced (HFmrEF) or preserved ejection fraction (HFpEF). The primary endpoint in both studies was a composite outcome of worsening heart failure, which included hospitalization for heart failure, or cardiovascular death. Both studies met their objectives. A significant difference ($p < 0.001$) was observed for the endpoint. EMPEROR-Preserved demonstrated a 21% risk reduction (HR = 0.79), while DELIVER demonstrated an 18% risk reduction (HR = 0.82) for the primary composite endpoint. Approximately half of the participants in both studies were diabetic.

The EMPEROR-Preserved and DELIVER studies demonstrated the efficacy of SGLT-2 inhibitors in the treatment of heart failure (HF) with minimally reduced and preserved ejection fraction. Additionally, a statistically significant secondary endpoint was achieved in the EMPEROR-Preserved study. The overall number of hospitalizations for HF was 13.6% (407 of 2,997 individuals) in the empagliflozin group and 18.1% in the placebo group. This translated into a 27% reduction in the risk of HF hospitalization (HR = 0.73%). In the DELIVER study, patients were divided into three subgroups based on left ventricular ejection fraction (LVEF). The first group consisted of patients with a fraction of less than 40%, the second group consisted of patients with a fraction of 50–59%, and the third group consisted of patients with a fraction of greater than or equal to 60%. Interestingly, the risk reduction for the primary composite endpoint was greatest in the group of patients with an ejection fraction ≥60% (HR = 0.78). In patients with an ejection fraction in the range of 50–59% (HR = 0.79), the effect was smallest in the group with the lowest studied ejection fraction of 40–49% (HR = 0.87) [2, 10, 22, 23]. Table 2 summarizes the

Table 3. Comparison of results of the EMPEROR-Preserved and EMPEROR-Reduced studies

EMPEROR trail	LVEF (%)	Follow-up time (months)	Composite primary endpoint [HR]	Hospitalization for heart failure [HR]
Reduced [29]	≤40%	16	0.75	0.70
Preserved [10]	>40%	26	0.79	0.73

data, allowing for a more detailed comparative analysis of the studies.

Clinical Data – dapagliflozin in HFpEF. Dapagliflozin has previously been shown to be effective in reducing the risk of worsening heart failure in patients with reduced ejection fraction [24]. In recent years, attempts have been made to assess whether SGLT-2 inhibitor therapy would be equally effective in patients with preserved left ventricular ejection fraction. The previously described RCT DELIVER study proved groundbreaking in this regard, demonstrating the efficacy of dapagliflozin in patients with this type of HF [2]. Data obtained from patients from this study could form the basis for further analyses. Among other things, a correlation was sought between baseline NT-proBNP concentration and the degree of improvement in the composite endpoint. The analysis did not observe an association; the improvement occurred regardless of baseline NT-pro-BNP concentration [25]. PRESERVED-HF is a multicentre, randomized trial, the results of which were published in 2021. Patients with HFpEF who took dapagliflozin as an adjunct to primary therapy, regardless of diabetes, experienced an improved quality of life as measured by the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS). This group of patients also experienced significant improvements in physical fitness. The initial median distance covered in the six-minute walk test (6MWT) was 244 m in both the dapagliflozin and placebo groups. The mean increase in distance was 20.1 m ($p = 0.007$) after 12 weeks of SGLT-2 inhibitor therapy [26].

The CAMEO-DAPA study published in 2023, provides valuable data on the effects of dapagliflozin. Patients with HFpEF were randomized; one group received 10 mg of dapagliflozin and the other received placebo. After a 24-week follow-up period, patients receiving the SGLT-2 inhibitor had a statistically significant reduction in pulmonary capillary wedge pressure (PCWP) compared to the placebo group, at rest (-3.5 mm Hg) and during exercise (-5.7 mm Hg). Additionally, the dapagliflozin group experienced a mean reduction in body weight (-3.5 kg) and a mean reduction in plasma volume (-285 ml) [27].

One of the primary indications for SGLT-2 inhibitors is the treatment of type 2 diabetes [8]. Interesting results were presented in a study published in 2025. The study enrolled 100 patients with HFpEF and type 2 diabetes. Randomization was performed in a 1:1 ratio. Patients in the study group received 10 mg of dapagliflozin, and those in the control group received placebo for 12 months. Baseline extracellular volume (ECV) was measured using magnetic resonance imaging to determine the degree of myocardial fibrosis. After 12 months of follow-up, a mean decrease from baseline in ECV of -3.5% was observed in the dapagliflozin group and -0.8% in the placebo group. In addition to the significant effect on myocardial fibrosis, there was an improvement in the 6MWT. The mean increase in distance was 45 m in the dapagliflozin group and 10 m in the placebo group [28].

Clinical data – empagliflozin in HFpEF. In 2020, the results of the large EMPEROR-Reduced study were published, assessing the effect of empagliflozin (10 mg/day) on prognosis in patients with left ventricular ejection fraction (LVEF) below 40%. Empagliflozin effectively reduced the risk of cardiovascular death and hospitalization for heart failure, regardless of diabetes. Additionally, the drug slowed the rate of decline of renal function: the mean annual decline in GFR in the empagliflozin group was -0.55 ml/min/1.73 m², compared to -2.28 ml/min/1.73 m² in the placebo group [29]. The results of the previously-described EMPEROR-Preserved study were published in 2021. In the population with a LVEF greater than 40%, empagliflozin also proved effective [10]. Table 3 presents the results of studies assessing the effects of empagliflozin across the full LVEF range.

Table 2. Data from key trials of SGLT-2 inhibitors in HFpEF

Study	EMPEROR-Preserved [10, 22]	DELIVER [2]
Drug, dose	Empagliflozin (10 mg/day)	Dapagliflozin (10 mg/day)
Year	2021	2022
Number of participants	5,988	6,263
Follow-up time (median)	2.2 years	2.3 years
Primary endpoint results	Empagliflozin group: 415/2997 (13.8%)	Dapagliflozin group: 512/3,131 (16.4%)
	Placebo group: 511/2,991 (17.1%)	Placebo group: 610/3,132 (19.5%)
HR endpoint	0.79 ($p < 0.001$)	0.82 ($p < 0.001$)
Patients without diabetes	Empagliflozin group: 1,531 (51.1%)	Dapagliflozin group: 1,730 (55.3%)
	Placebo group: 1,519 (50.8%)	Placebo group: 1,727 (55.1%)

The EMPULSE study demonstrated that in patients hospitalized with an acute episode of heart failure, regardless of baseline phenotype, empagliflozin (10 mg/day) significantly reduced mortality within 90 days of the episode. The HFpEF group included 115 patients. Participants were randomized, with 50 receiving empagliflozin and 65 receiving placebo. All-cause mortality was 4% (2 deaths) in the empagliflozin group and 12.3% (8 deaths) in the placebo group [5]. Furthermore, six months of empagliflozin treatment in patients with HFpEF and type 2 diabetes resulted in improved six-minute walk distance; on average, patients could walk 13 meters further than patients in the placebo group. One of the secondary endpoints was exercise duration on a stationary bicycle. In the group treated with empagliflozin, the test results improved by an average of 66 seconds, while in the placebo group only by nine seconds. Both results of the performance tests reached statistical significance and constitute a strong argument for the beneficial effect of empagliflozin on improving cardiac exercise capacity [31].

Current recommendations and guidelines. The ESC Guidelines published in 2021 recommend the prophylactic use of SGLT2 inhibitors in patients with diabetes at high risk of cardiovascular disease or with cardiovascular disease, to prevent hospitalization due to HF [1]. In the 2022 American Heart Association (AHA) guidelines, SGLT2 inhibitors were given a Class IIA recommendation in patients with LVEF ≥ 50% to reduce the risk of hospitalization for heart failure and cardiovascular death [32]. The positive results of the DELIVER (dapagliflozin) and EMPEROR-Preserved (empagliflozin) trials allowed the ESC expert group to update the recommendations in 2023 [2, 10]. According to these recommendations, dapagliflozin and empagliflozin are

recommended in patients with symptomatic HFpEF to reduce the risk of hospitalization due to HF and cardiovascular death. They received a class I recommendation, level of evidence A [33].

Perspectives and directions for future research. The metabolic effects of empagliflozin on the heart are still not fully understood. The results of a 2025 study indicate that a significant increase in citrulline levels was observed in patients with HFpEF following empagliflozin therapy. Future studies should focus on assessing the correlation between elevated citrulline levels and cardioprotective effects and be conducted on a larger group of patients [34]. An interventional study published in 2025 analyzed the effect of empagliflozin on cardiac microcirculation flow induced by vasodilators (acetylcholine, insulin, sodium nitroprusside). Flow was measured before and after empagliflozin therapy (10 mg/day). After three months, a statistically significant improvement in insulin-induced flow was observed, while the response to acetylcholine was attenuated and to nitroprusside remained unchanged. The results obtained in this study may suggest a potential mechanism of action of SGLT-2 inhibitors, the selective effect of empagliflozin on improving insulin vasodilatory action. The study was limited due to the small study group (26 patients) and the lack of a control group; therefore, future studies should be conducted on larger and more diverse groups of patients [35]. Studies from 2021 [26] and 2025 [28] demonstrated the effectiveness of dapagliflozin in improving functional capacity, as measured by the 6WTM test, but the patient follow-up period was 12 weeks and 12 months, respectively. Further studies with longer follow-up periods are necessary to assess the long-term effects of the drug.

SUMMARY

Heart failure with preserved ejection fraction is a significant public health problem. Due to the aging population, the number of patients with HFpEF will steadily increase. SGLT-2 inhibitors, such as dapagliflozin and empagliflozin, are recommended by the AHA (2022) and the ESC (2023) for the treatment of HFpEF. Numerous clinical trials have shown that the use of these medications significantly reduces the risk of hospitalization for heart failure and cardiovascular death in this group of patients. Additionally, they improve functional test results, including the six-minute walk (6MWT) and the exercise bicycle ergometer test, demonstrating their impact on improving cardiac exercise capacity. Furthermore, SGLT-2 inhibitors contribute to a reduction in body weight and plasma volume, and have been shown to be effective in reducing myocardial fibrosis. The described drugs have successfully filled the therapeutic gap for this group of patients, but further research is needed to understand the exact cardio-protective mechanisms and long-term effects of use.

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