Journal of Pharmaceutical and Sciences
Electronic ISSN: 2656-3088 DOI: https://doi.org/10.36490/journal-jps.com
Homepage: https://journal-jps.com
REVIEW ARTICLE JPS. 2025, 8(4), 2339-2347

Dapagliflozin in Heart Failure with Reduced Ejection Fraction (HFrEF): A Systematic Review of Its Mechanisms and Clinical Effectiveness

Dapagliflozin pada Gagal Jantung dengan Fraksi Ejeksi Rendah (HFrEF): Tinjauan Sistematis Mekanisme dan Efektivitas Klinis

Zalfa Nadia Prasasti Karmawan[a,*], Rahel Lambok Yohana Simorangkir[a], Jef Gishard Kristo Kalalo[a]

[a]*Department of Pharmacy, Faculty of Health Science, University of Singaperbangsa Karawang, Kawarang, West Java, Indonesia.*

**Corresponding Authors: 2310631210023@student.unsika.ac.id*

Abstract

Background: Heart failure with reduced ejection fraction (HFrEF) is a serious condition associated with high morbidity and mortality. Dapagliflozin has demonstrated cardioprotective effects in patients with HFrEF. **Objective:** This review explores the mechanisms underlying the clinical benefits of dapagliflozin and summarizes current evidence from the DAPA-HF trial and its sub-analyses regarding its effectiveness in patients with HFrEF. **Methods:** Relevant literature was systematically searched in PubMed, Google Scholar, and Scopus. Eligible studies were analyzed using a narrative approach to summarize the drug's mechanisms of action and clinical outcomes. **Results:** Dapagliflozin improves cardiac energy efficiency, stimulates erythropoiesis, reduces myocardial fibrosis, and lowers oxidative stress and NT-proBNP levels. Clinically, 10 mg/day therapy reduces heart failure hospitalizations and cardiovascular mortality by 26% (HR: 0.74), with recently hospitalized patients experiencing benefits up to 49% (HR: 0.51), consistent across subpopulations and providing added advantages to standard therapy. **Conclusion:** Dapagliflozin serves as an effective adjunct therapy for HFrEF, offering rapid and sustained benefits, reducing morbidity and mortality, and improving patients' quality of life. Further research is warranted to expand its clinical application.

***Keywords*: Dapagliflozin; HFrEF; Mechanism of Action; Clinical Effectiveness.**

Abstrak

Latar Belakang: Gagal jantung dengan fraksi ejeksi rendah (HFrEF) merupakan kondisi serius dengan morbiditas dan mortalitas tinggi. Dapagliflozin menunjukkan efek kardioprotektif pada pasien HFrEF. **Tujuan:** Tinjauan ini mengeksplorasi mekanisme yang mendasari manfaat klinis dapagliflozin dan merangkum bukti terkini dari DAPA-HF serta sub-analisisnya mengenai efektivitasnya pada pasien dengan HFrEF. **Metode:** Literatur dicari secara sistematis di PubMed, Google Scholar, dan Scopus. Data dari studi yang memenuhi kriteria dianalisis secara naratif untuk merangkum mekanisme aksi dan outcome klinis. **Hasil:** Dapagliflozin meningkatkan efisiensi energi jantung, merangsang eritropoiesis, mengurangi fibrosis miokard, dan menurunkan stres oksidatif serta NT-proBNP. Secara klinis, terapi 10 mg/hari mengurangi rawat inap akibat gagal jantung dan kematian kardiovaskular dengan penurunan risiko relatif 26% (HR: 0.74), sementara pasien yang baru dirawat menunjukkan manfaat hingga 49% (HR: 0.51), konsisten di berbagai subpopulasi dan menambah keuntungan dari terapi standar. **Kesimpulan:** Dapagliflozin merupakan terapi tambahan efektif untuk HFrEF, memberikan manfaat cepat dan berkelanjutan, menurunkan morbiditas dan mortalitas, serta meningkatkan kualitas hidup pasien. Penelitian lebih lanjut diperlukan untuk memperluas penerapan klinis.

***Kata Kunci*: Dapagliflozin; HFrEF; Mekanisme Aksi; Efektivitas Klinis.**

Article History:
Received: 02/09/2025,
Revisi: 26/10/2025,
Accepted: 27/10/2025,
Available Online: 27/10/2025.
QR access this Article

https://doi.org/10.36490/journal-jps.com.com.v8i4.1121

Introduction

Heart failure remains a major global health issue with high morbidity and mortality rates. This condition occurs when the heart is unable to pump blood effectively to meet the body's metabolic demands [1]. One of the most common forms is heart failure with reduced ejection fraction (HFrEF), defined as a left ventricular ejection fraction (LVEF) ≤40% [2]. Globally, heart failure affects more than 64 million individuals, with incidence increasing with age and comorbid cardiovascular conditions such as hypertension and coronary artery disease [3]. HFrEF is characterized by left ventricular systolic dysfunction, causing symptoms like dyspnea, peripheral edema, and reduced exercise tolerance, which impair quality of life and increase healthcare costs due to frequent hospitalizations [1]. For decades, the standard therapy for HFrEF has included angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor–neprilysin inhibitors (ARNIs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) [4]. Although these interventions have been shown to reduce mortality and hospitalizations, the rates of relapse and disease progression remain high [5]. This has prompted the development of novel therapeutic strategies that provide additional benefits beyond conventional neurohormonal modulation.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i), originally developed for the treatment of type 2 diabetes mellitus, have demonstrated significant cardioprotective effects in several large-scale clinical trials. Currently, SGLT2 inhibitors are recommended in the 2022 AHA/ACC/HFSA Guidelines for the Management of Heart Failure as a Class I therapy with Level A evidence for patients with HFrEF [6]. Among these, dapagliflozin is one of the most extensively studied agents. The landmark DAPA-HF trial showed that dapagliflozin significantly reduced the risk of heart failure hospitalization and cardiovascular mortality, in both diabetic and non-diabetic patients [7]. These findings have been further supported by subsequent analyses demonstrating improvements in symptoms, quality of life, renal function, and heart failure–related biomarkers. Despite these established clinical benefits, the mechanisms underlying dapagliflozin's cardioprotective effects remain incompletely understood. This systematic review therefore aims to provide a comprehensive synthesis of both mechanistic insights and clinical outcomes, consolidating evidence from the DAPA-HF trial and its sub-analyses to inform future clinical practice.

Methods

Study Design

This study is a systematic review aiming to analyze the mechanism of action and clinical effectiveness of dapagliflozin in patients with Heart Failure with Reduced Ejection Fraction (HFrEF). consolidating evidence from the DAPA-HF trial and its sub-analyses. The primary focus was to evaluate mechanistic insights underlying cardioprotective effects and clinical outcomes related to morbidity and mortality.

Literature Search

Relevant research articles and scientific publications were retrieved from PubMed, Google Scholar, and Scopus databases using the Publish or Perish software to ensure systematic and reproducible searches. The following Boolean search string was applied across all databases: *("dapagliflozin") AND ("heart failure with reduced ejection fraction" OR HFrEF) AND ("mechanism" OR "mechanism of action" OR "mechanism findings") AND ("clinical effectiveness" OR "mortality" OR "hospitalization")*. The search was limited to articles published between 2019 and 2025, reflecting the period after the publication of the pivotal DAPA-HF trial (2019). Only

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

English-language studies involving adult patients with HFrEF treated with dapagliflozin were included. Boolean operators (AND, OR) were applied to refine the results, focusing on studies addressing both the mechanistic and clinical aspects of dapagliflozin therapy.

Table 1. PICO Framework

Component	Description
Population	Patients with HFrEF
Intervention	Dapagliflozin (10 mg/day)
Comparison	Placebo or standard therapy (as reported in the source trials)
Outcome	Reduction in hospitalization and cardiovascular mortality; improvement in cardiac symptoms and function

Data Collection Technique

The literature search identified a total of 889 articles (199 from PubMed, 490 from Google Scholar, and 200 from Scopus). All records were imported into Zotero reference management software to detect and remove duplicates automatically, followed by manual verification.

Screening was conducted in three stages: (1) title screening for relevance, (2) abstract screening for eligibility, and (3) full-text review for inclusion. Inclusion criteria consisted of Randomized Controlled Trials (RCTs) or other clinical studies published in English between 2019 and 2025 involving adult patients with HFrEF who received dapagliflozin therapy. Exclusion criteria included studies not reporting heart failure outcomes or focusing exclusively on other comorbidities.

After removing duplicates and applying the inclusion/exclusion criteria, 13 studies were selected for analysis, comprising 3 mechanistic studies and 10 clinical effectiveness studies evaluating morbidity and mortality outcomes.

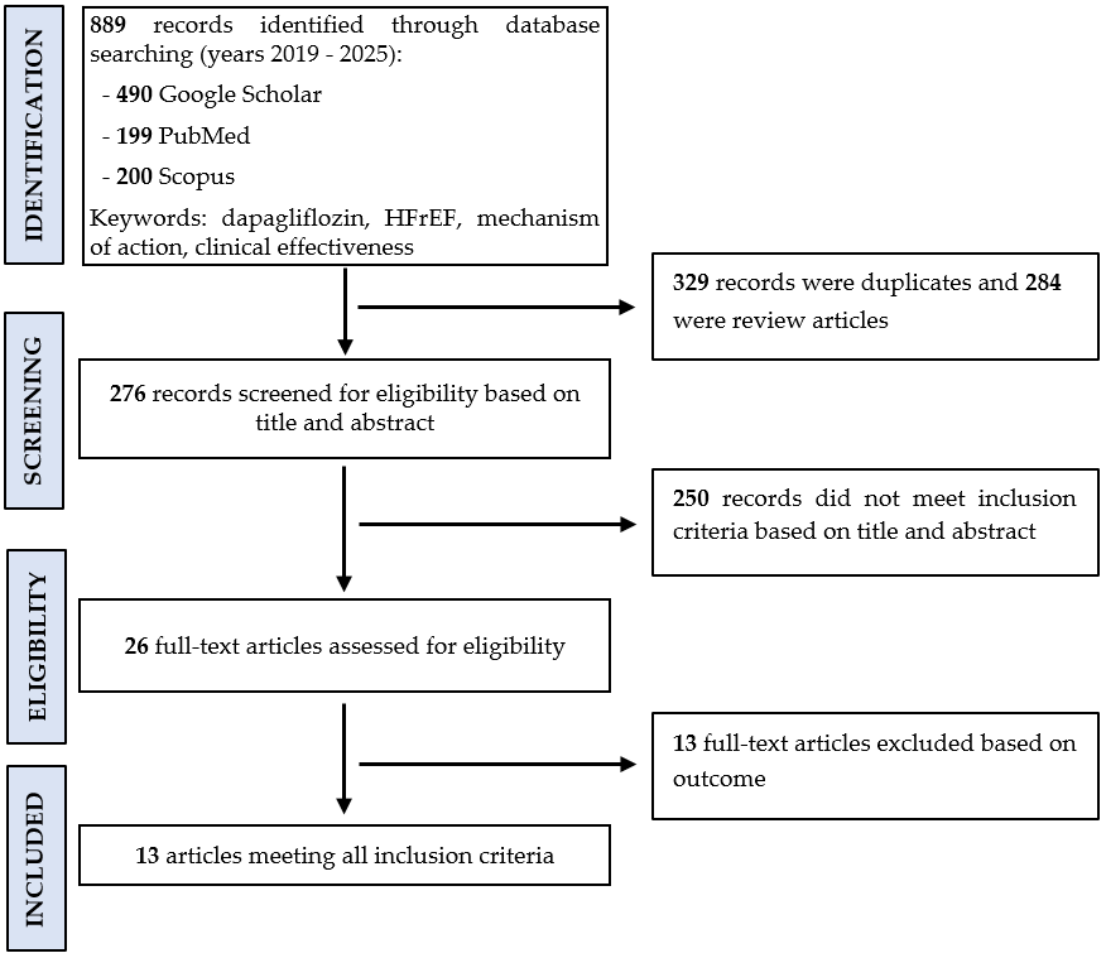

Figure 1. PRISMA Flow Diagram

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

Data Analysis Technique

Data were analyzed using a narrative synthesis approach. Eligible studies were categorized into two main groups: (1) mechanistic studies, which reported secondary parameters to support understanding of dapagliflozin's mechanisms in HFrEF, and (2) clinical studies, which reported primary outcomes such as cardiovascular mortality, heart failure hospitalization, or composite outcomes. Extracted data included study design, sample size, and effect measures such as hazard ratio (HR).

Results

A total of 13 studies met the inclusion criteria, consisting of three mechanistic investigations and ten clinical analyses derived from the DAPA-HF trial and its subsequent substudies. Table 2 summarizes the characteristics of all included studies, while Tables 3 and 4 present detailed findings on mechanisms and clinical effectiveness, respectively.

Table 2. Characteristics of Included Studies

No	Author (Year)	Title / Focus	Study Design	Population / Sample	Intervention	Main Outcome
1	Selvaraj et al. (2022)	Mechanistic insights of SGLT2i on myocardial metabolism	Experimental / mechanistic	Preclinical & HFrEF samples	Dapagliflozin 10 mg	↑ Ketone oxidation, ↑ energy efficiency
2	Aberle et al. (2020)	Effect on erythropoiesis	Mechanistic	Clinical data subset	Dapagliflozin 10 mg	↑ Hematocrit, EPO-mediated erythropoiesis
3	Ortega-Paz et al. (2025)	Anti-fibrotic and AMPK activation	Mechanistic	Experimental models	Dapagliflozin 10 mg	↓ Myocardial fibrosis, improved remodeling
4	McMurray et al. (2019)	DAPA-HF trial: Dapagliflozin in Patients with HFrEF	Randomized, double-blind, placebo-controlled	4,744 HFrEF patients	Dapagliflozin 10 mg/day	↓ CV death or HF hospitalization
5	Butt et al. (2021a)	Effect of dapagliflozin by diabetes status: DAPA-HF subgroup	Prespecified subgroup analysis	4,744 HFrEF patients (55% non-diabetic)	Dapagliflozin 10 mg/day	↓ Composite CV death/HF hospitalization
6	Butt et al. (2021b)	Impact of dapagliflozin by ischemic vs non-ischemic etiology	Prespecified subgroup analysis	4,744 HFrEF patients	Dapagliflozin 10 mg/day	↓ Composite CV death/HF hospitalization
7	Butt et al. (2022)	Effect of dapagliflozin in patients with atrial fibrillation	Prespecified subgroup analysis	4,744 HFrEF patients	Dapagliflozin 10 mg/day	↓ Composite CV death/HF hospitalization in AF and non-AF
8	Jhund et al. (2021a)	Renal outcomes with dapagliflozin in HFrEF	Post hoc analysis	4,744 HFrEF with CKD or eGFR <60	Dapagliflozin 10 mg/day	↓ Renal decline, ↓ CV death/HF hospitalization
9	Dewan et al. (2021)	Dapagliflozin in patients with COPD	Post hoc analysis	4,744 HFrEF patients, 12% COPD	Dapagliflozin 10 mg/day	↓ Composite CV death/HF hospitalization

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

10	Solomon et al. (2020)	Dapagliflozin in patients on sacubitril/valsartan	Subgroup analysis	4,744 HFrEF patients	Dapagliflozin 10 mg/day	↓ CV death/HF hospitalization regardless of ARNI use
11	Berg et al. (2021)	Time-to-benefit with dapagliflozin in HFrEF	Post hoc analysis	4,744 HFrEF	Dapagliflozin 10 mg/day	↓ CV death/HF hospitalization within 28 days
12	Petrie et al. (2020)	Dapagliflozin effects on quality of life (KCCQ)	Prespecified subgroup	4,744 HFrEF	Dapagliflozin 10 mg/day	↑ KCCQ total score
13	Jhund et al. (2021b)	Dapagliflozin in patients with previous HF hospitalization	Post hoc	4,744 HFrEF	Dapagliflozin 10 mg/day	↓ Recurrent hospitalization

The mechanistic studies aimed to elucidate the cardioprotective mechanisms of dapagliflozin in heart failure with reduced ejection fraction (HFrEF). These studies explored pathways involving myocardial energy metabolism, hematologic regulation, and myocardial remodeling. Collectively, they suggest that dapagliflozin exerts its benefits through improved myocardial energetics, enhanced erythropoiesis, and attenuation of fibrosis and oxidative stress. Table 3 summarizes the main mechanistic pathways and experimental findings.

Table 3. Mechanistic Findings

Study	Mechanism	Findings
[8]	Enhances the shift from glucose metabolism to fatty acid and ketone body oxidation, which helps increase myocardial energy in patients with HFrEF.	Dapagliflozin increases short-chain ketone and acylcarnitine metabolites, improving myocardial function and cardiac energy production. These changes also lower NT-proBNP levels and improve symptoms and function in patients with HFrEF.
[9]	Increases hematocrit, red blood cells (RBC), and reticulocytes, possibly due to EPO release, enhancing erythropoiesis and improving oxygen distribution.	Dapagliflozin increases hematocrit and RBC counts in a dose-dependent manner, improving oxygen transport and reducing cardiovascular risk by regulating body fluid volume and decreasing fluid overload.
[10]	Reduces extracellular matrix turnover and myocardial fibrosis by activating the AMPK pathway, which suppresses mitochondrial stress and inflammation.	Dapagliflozin exerts antifibrotic effects, reduces oxidative stress, and improves left ventricular remodeling, thereby enhancing cardiac function and energy metabolism efficiency.

Clinical analyses from the DAPA-HF trial and its subgroups consistently demonstrated that dapagliflozin reduces the composite endpoint of cardiovascular death or heart failure hospitalization in patients with HFrEF. The benefits were observed across multiple patient subgroups, regardless of diabetes status, heart failure etiology, comorbid conditions, or concomitant therapies. Table 4 presents the clinical outcomes and hazard ratios for each subgroup, highlighting the consistent efficacy of dapagliflozin in improving heart failure-related outcomes.

Table 4. Clinical Effectiveness of Dapagliflozin

Subpopulation / Analysis	Outcome Measured	Hazard Ratio (95% CI)	Key Findings
Overall DAPA-HF population [7]	Composite of CV death or HF hospitalization	0.74 (0.65–0.85)	Significant reduction in primary composite outcome regardless of diabetes status.
Diabetic & non-diabetic [11], [12], [13]	CV death or HF hospitalization	0.75 (0.63–0.90) & 0.73 (0.60–0.88)	Benefits consistent in both groups.

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

Ischemic & non-ischemic [14]	CV death or HF hospitalization	0.77 (0.65–0.92) & 0.71 (0.58–0.87)	Effect maintained across HF etiologies.
With & without atrial fibrillation (AF) [15]	CV death or HF hospitalization	0.75 (0.62–0.92) & 0.74 (0.62–0.88)	Effect consistent regardless of AF status.
With prior HF hospitalization [16]	CV death or HF hospitalization (within 28 days)	0.51 (0.28–0.94)	Early benefit observed after initiation.
With COPD [17]	CV death or HF hospitalization	0.67 (0.48–0.93)	Reduced HF events even in COPD subgroup
With CKD (eGFR <60) [18]	CV death or HF hospitalization	0.71 (0.59–0.86)	Consistent benefit in patients with renal impairment.
With & without sacubitril/valsartan [19]	CV death or HF hospitalization	0.75 (0.50–1.13) & 0.74 (0.65–0.86)	Consistent efficacy regardless of concomitant therapy

Discussion

Mechanism of Action of Dapagliflozin in Patients with HFrEF

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor initially developed for the treatment of type 2 diabetes mellitus. It works by inhibiting glucose reabsorption in the renal proximal tubules, thereby increasing glucose excretion through urine and lowering blood glucose levels. Interestingly, several clinical studies have shown that the effects of dapagliflozin extend beyond glycemic control alone. In patients with heart failure, particularly those with HFrEF, dapagliflozin provides significant cardioprotective benefits. These effects are believed to be associated with various non-glycemic mechanisms, such as improvement of myocardial function, modulation of energy metabolism, reduction of oxidative stress, as well as diuretic and hemodynamic effects that support cardiac performance (**Table 3**).

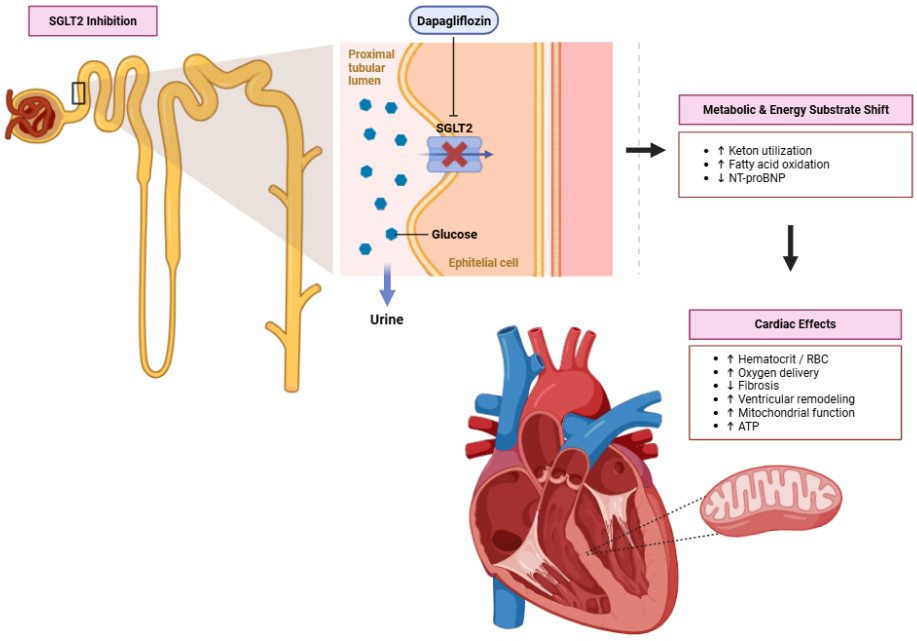

Figure 2. Mechanism of Action and Effects of Dapagliflozin

a. Improved Cardiac Energy Efficiency

In HFrEF, the heart experiences disturbances in energy metabolism, leading to an increased energy demand to maintain contraction, while glucose utilization as the primary energy source becomes inefficient. Dapagliflozin corrects this imbalance by shifting energy metabolism toward enhanced oxidation of fatty acids and ketone bodies as the main energy substrates [8]. Physiologically, a healthy heart uses a combination of glucose and fatty acids, however, in HFrEF, glucose utilization becomes inefficient due to mitochondrial dysfunction and metabolic stress.

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

Fatty acids and ketone bodies are more efficiently metabolized by mitochondria to generate adenosine triphosphate (ATP), which is required for myocardial contraction. By increasing the utilization of ketone bodies, a weakened heart can produce a greater amount of energy with lower oxidative stress. This mechanism contributes to improved myocardial function and cardiac pumping capacity in patients with HFrEF.

b. Increased Erythropoiesis

Hypoxia commonly accompanies heart failure and worsens its symptoms. Erythropoietin (EPO), a hormone produced by the kidneys, stimulates the formation of red blood cells (RBCs) in the bone marrow. RBCs play a crucial role in delivering oxygen throughout the body, including to the myocardium, which has a high oxygen demand. Dapagliflozin has been shown to increase EPO secretion, thereby raising RBC count [9]. This elevation enhances oxygen transport capacity, reduces cardiac workload, and supports optimal myocardial function under hypoxic conditions.

c. Inhibition of Myocardial Fibrosis and Ventricular Remodeling

In patients with heart failure, myocardial fibrosis (the formation of scar tissue in cardiac muscle) often occurs as a response to chronic stress and repetitive injury. Fibrosis reduces myocardial elasticity and contractile ability, worsening the progression of heart failure. Dapagliflozin activates AMP-activated protein kinase (AMPK), an enzyme that functions as an intracellular energy sensor [10]. Upon activation, AMPK decreases oxidative stress and inflammation, two key factors that drive myocardial fibrosis. By mitigating these processes, dapagliflozin prevents fibrotic tissue formation in the myocardium and improves ventricular remodeling, which refers to changes in the shape and size of the ventricles during heart failure. This leads to better recovery of cardiac function and improved pumping efficiency.

d. Reduction of Oxidative Stress and Inflammation

Oxidative stress occurs when free radicals damage cells, including cardiomyocytes. In heart failure, oxidative stress plays a major role in mitochondrial dysfunction and decreased cellular energy production. Dapagliflozin reduces the generation of reactive oxygen species, thereby minimizing mitochondrial damage in cardiac cells [10]. Healthier mitochondria can produce more energy, which is essential for a weakened heart. Furthermore, dapagliflozin alleviates cardiac inflammation. Chronic inflammation contributes to myocardial injury and accelerates the progression of heart failure. By reducing inflammation, dapagliflozin creates a more favorable metabolic environment for the heart, enhancing overall cardiac function.

e. Reduction of NT-proBNP Levels

NT-proBNP (*N-terminal pro B-type natriuretic peptide*) is a biomarker used to assess the severity of heart failure. It is released by the heart in response to increased cardiac pressure, which is commonly observed in heart failure patients. Dapagliflozin has been shown to lower NT-proBNP levels in such patients [8]. This reduction indicates decreased cardiac stress and improved heart function, reflecting a reduction in cardiac workload, an essential factor in the management of HFrEF.

Clinical Effectiveness of Dapagliflozin in Patients with HFrEF

A relative risk reduction of approximately 23% to 49% in heart failure hospitalizations and cardiovascular deaths represents a clinically meaningful outcome, particularly given the high morbidity and mortality rates in patients with HFrEF. This reduction has strong clinical relevance, as it helps alleviate the healthcare burden associated with worsening heart failure. Therefore, dapagliflozin can be considered a substantial therapeutic intervention for mitigating adverse outcomes in patients with HFrEF.

Dapagliflozin 10 mg/day has demonstrated clear clinical benefits in patients with HFrEF, primarily by reducing heart failure hospitalization, cardiovascular mortality, and improving cardiac function. In the DAPA-HF trial, the composite outcome of cardiovascular death or heart failure hospitalization was reduced by 26% in the overall population (HR: 0.74), with a stronger effect in patients recently hospitalized for heart failure (49%, HR: 0.51) [7,12,13]. Subgroup analyses confirmed consistent benefits across age groups, etiology (ischemic vs. non-ischemic), presence or absence of atrial fibrillation, and diabetes status. Importantly, these effects were observed in patients receiving background HFrEF therapy, including β-blockers, ACE inhibitors, ARNIs, or MRAs [11,17,18]. The trial also showed early onset of benefit within 28 days of therapy, which persisted throughout follow-up, indicating both rapid and durable effects [12,16].

Comparatively, the EMPEROR-Reduced trial with empagliflozin reported a 25% reduction in the composite of cardiovascular death or heart failure hospitalization (HR: 0.75). The primary driver of benefit was heart failure hospitalization, whereas reduction in cardiovascular mortality alone did not reach statistical

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

significance [20]. Similarly, sotagliflozin, evaluated in the SOLOIST-WHF trial, decreased the risk of a composite endpoint including cardiovascular death, heart failure hospitalization, and urgent heart failure visits by 26% (HR: 0.74), although the trial was terminated early, and the sample size was relatively small [21]. These comparisons indicate that the reduction in heart failure hospitalization is a consistent class effect of SGLT2 inhibitors, while dapagliflozin uniquely demonstrated statistically significant reduction in the composite cardiovascular mortality outcome, reinforcing its clinical value.

In terms of symptoms and cardiac function, DAPA-HF reported improvements in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, NT-proBNP reduction, and modest increases in ejection fraction, further supporting the benefits of dapagliflozin beyond hospitalization and mortality outcomes [7,12]. These clinical effects align with current guideline recommendations: the 2022 AHA/ACC/HFSA guidelines endorse SGLT2 inhibitors, including dapagliflozin and empagliflozin, as Class I add-on therapy for HFrEF patients to reduce heart failure hospitalizations and cardiovascular death [6]. The consistency of these results across trials and patient subgroups supports the generalizability of dapagliflozin's clinical benefits.

Overall, dapagliflozin 10 mg/day provides early, sustained, and generalizable improvements in hospitalization rates, cardiovascular mortality, and functional outcomes in HFrEF patients. Comparisons with other SGLT2 inhibitor trials reinforce a class effect, and further research should investigate long-term outcomes, specific mechanisms, and effects in underrepresented patient populations.

Limitations

This review has several limitations. Most of the clinical evidence comes from DAPA-HF and its sub-analyses, which could limit how widely the results apply. The narrative approach, while helpful, doesn't provide the statistical strength of a meta-analysis. The literature search was restricted to a few databases and didn't include extensive manual searches, so some relevant studies might have been missed. Finally, the review didn't formally assess publication bias, which could influence the interpretation of the outcomes.

Conclusions

Dapagliflozin improves heart function by enhancing cardiac energy use, reducing myocardial fibrosis and ventricular remodeling, lowering oxidative stress and inflammation, and stimulating erythropoiesis. Clinically, 10 mg/day reduces heart failure hospitalizations and cardiovascular deaths, with relative risk reductions ranging from 26% in the overall population to 49% in high-risk subgroups, including patients with ischemic or non-ischemic etiology and those with or without atrial fibrillation. Benefits appear early, within the first month, and are sustained over time, even in patients already receiving guideline-directed standard HFrEF therapy. As an add-on therapy, dapagliflozin provides meaningful reductions in morbidity and mortality while improving quality of life. Future research should focus on clarifying the precise mechanisms of cardioprotection, assessing long-term outcomes, and evaluating efficacy in underrepresented populations, such as frail elderly patients, those with severe renal impairment, or individuals with multiple comorbidities.

Conflict of Interest

The authors declare no conflict of interest in conducting this review.

References

[1] Corneanu LE, Sîngeap MS, Mutruc V, Petriș OR, Toma TP, Șorodoc V, et al. The Complex Relationship Between Heart Failure and Chronic Obstructive Pulmonary Disease: A Comprehensive Review. J Clin Med 2025;14:4774. https://doi.org/10.3390/jcm14134774.

[2] Shang Z, Wang X, Gao W. Heart failure with mildly reduced ejection fraction: Emerging frontiers in clinical characteristics, prognosis, and treatment. Rev Cardiovasc Med 2022;23. https://doi.org/10.31083/j.rcm2301030.

[3] Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res 2022;118:3272–87. https://doi.org/10.1093/cvr/cvac013.

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

[4] Kerr B, Pharithi RB, Barrett M, Halley C, Gallagher J, Ledwidge M, et al. Angiotensin Receptor Neprilysin Inhibitors in HFrEF: Is This the First Disease Modifying Therapy Drug Class Leading to a Substantial Reduction in Diuretic Need? International Journal of Heart Failure 2021;3:106–16. https://doi.org/10.36628/ijhf.2020.0043.

[5] Wirtz HS, Sheer R, Honarpour N, Casebeer AW, Simmons JD, Kurtz CE, et al. Real-world analysis of guideline-based therapy after hospitalization for heart failure. J Am Heart Assoc 2020;9. https://doi.org/10.1161/JAHA.119.015042.

[6] Maddox TM, Januzzi JL, Allen LA, Breathett K, Brouse S, Butler J, et al. 2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2024;83:1444–88. https://doi.org/10.1016/j.jacc.2023.12.024.

[7] McMurray JJ V, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, et al. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. Eur J Heart Fail 2019;21:1402–11. https://doi.org/10.1002/ejhf.1548.

[8] Selvaraj S, Fu Z, Jones P, Kwee LC, Windsor SL, Ilkayeva O, et al. Metabolomic Profiling of the Effects of Dapagliflozin in Heart Failure With Reduced Ejection Fraction: DEFINE-HF. Circulation 2022;146:808–18. https://doi.org/10.1161/CIRCULATIONAHA.122.060402.

[9] Aberle J, Menzen M, Schmid SM, Terkamp C, Jaeckel E, Rohwedder K, et al. Dapagliflozin effects on haematocrit, red blood cell count and reticulocytes in insulin-treated patients with type 2 diabetes. Sci Rep 2020;10. https://doi.org/10.1038/s41598-020-78734-z.

[10] Ortega-Paz L, Laudani C, Sionis A, Vidal-Cales P, Arevalos V, Andrea R, et al. Effect of DAPAgliflozin on Myocardial Fibrosis and Ventricular Function in Patients with ST-Segment Elevation Myocardial Infarction—DAPA-STEMI Trial. J Cardiovasc Dev Dis 2025;12. https://doi.org/10.3390/jcdd12060220.

[11] Butt JH, Docherty KF, Petrie MC, Schou M, Kosiborod MN, O'Meara E, et al. Efficacy and Safety of Dapagliflozin in Men and Women with Heart Failure with Reduced Ejection Fraction: A Prespecified Analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure Trial. JAMA Cardiol 2021;6:678–89. https://doi.org/10.1001/jamacardio.2021.0379.

[12] Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, Bělohlávek J, et al. Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients with Heart Failure with and Without Diabetes. JAMA - Journal of the American Medical Association 2020;323:1353–68. https://doi.org/10.1001/jama.2020.1906.

[13] Jhund PS, Ponikowski P, Docherty KF, Gasparyan SB, Böhm M, Chiang CE, et al. Dapagliflozin and Recurrent Heart Failure Hospitalizations in Heart Failure with Reduced Ejection Fraction: An Analysis of DAPA-HF. Circulation 2021;143:1962–72. https://doi.org/10.1161/CIRCULATIONAHA.121.053659.

[14] Butt JH, Nicolau JC, Verma S, Docherty KF, Petrie MC, Inzucchi SE, et al. Efficacy and safety of dapagliflozin according to aetiology in heart failure with reduced ejection fraction: insights from the DAPA-HF trial. Eur J Heart Fail 2021;23:601–13. https://doi.org/10.1002/ejhf.2124.

[15] Butt JH, Docherty KF, Jhund PS, de Boer RA, Böhm M, Desai AS, et al. Dapagliflozin and atrial fibrillation in heart failure with reduced ejection fraction: insights from DAPA-HF. Eur J Heart Fail 2022;24:513–25. https://doi.org/10.1002/ejhf.2381.

[16] Berg DD, Jhund PS, Docherty KF, Murphy SA, Verma S, Inzucchi SE, et al. Time to Clinical Benefit of Dapagliflozin and Significance of Prior Heart Failure Hospitalization in Patients with Heart Failure with Reduced Ejection Fraction. JAMA Cardiol 2021;6:499–507. https://doi.org/10.1001/jamacardio.2020.7585.

[17] Dewan P, Docherty KF, Bengtsson O, de Boer RA, Desai AS, Drozdz J, et al. Effects of dapagliflozin in heart failure with reduced ejection fraction and chronic obstructive pulmonary disease: an analysis of DAPA-HF. Eur J Heart Fail 2021;23:632–43. https://doi.org/10.1002/ejhf.2083.

[18] 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;143:298–309. https://doi.org/10.1161/CIRCULATIONAHA.120.050391.

[19] 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;8:811–8. https://doi.org/10.1016/j.jchf.2020.04.008.

[20] Ansar F, Azzam A, Zafar U, Ahmed S, Ghauri FK, Khan AM, et al. Empagliflozin and Cardiovascular Outcomes: A Systematic Review of Randomized Controlled Trials in Populations With Diabetes and Heart Failure. Cureus 2025. https://doi.org/10.7759/cureus.90150.

[21] Docherty KF, McMurray JJV. SOLOIST-WHF and updated meta-analysis: sodium–glucose co-transporter 2 inhibitors should be initiated in patients hospitalized with worsening heart failure. Eur J Heart Fail 2021;23:27–30. https://doi.org/10.1002/ejhf.2075.

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com