



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

Clinical Benefits of Sodium–Glucose Cotransporter 2 Inhibitors in Heart Failure with Preserved Ejection Fraction

Luis Fernando Puello Meza^{*1}, Andres Felipe Gomez Luque², Daniel Francisco Gomez Luque³, Juan Camilo Ramos Gomez⁴, Isaura Emperatriz Mercado Coneo⁵

¹ General Physician, Universidad del Sinú, Cartagena

^{2,3,4} General Physician, Corporación Universitaria Rafael Nuñez, Cartagena

⁵ General Physician, Universidad de Cartagena, Cartagena

ARTICLE INFO

Published: 12 Feb 2026

Keywords:

Heart failure; Preserved ejection fraction; SGLT2 inhibitors; Empagliflozin; Dapagliflozin

DOI:

10.5281/zenodo.18621248

ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all heart failure cases worldwide and is associated with substantial morbidity, recurrent hospitalizations, impaired quality of life, and high healthcare costs. Until recently, no pharmacological therapy had consistently demonstrated a prognostic benefit in this heterogeneous population. Sodium–glucose cotransporter 2 inhibitors (SGLT2i), initially developed for the treatment of type 2 diabetes mellitus, have emerged as a major therapeutic advance in heart failure across the entire spectrum of ejection fraction. Large randomized clinical trials have shown that SGLT2 inhibitors significantly reduce heart failure hospitalizations and improve health-related quality of life in patients with HFpEF, regardless of diabetic status. This review provides a comprehensive analysis of the clinical benefits of SGLT2 inhibitors in HFpEF, focusing on pathophysiological rationale, mechanisms of action, evidence from pivotal clinical trials, safety considerations, and current guideline recommendations.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF), typically defined as heart failure with a left ventricular ejection fraction $\geq 50\%$, represents a complex and heterogeneous clinical syndrome rather than a single disease entity (1,2). The prevalence of HFpEF has steadily increased over

recent decades, largely driven by population aging and the growing burden of comorbidities such as hypertension, obesity, diabetes mellitus, chronic kidney disease, and atrial fibrillation (3,4).

Despite advances in the management of heart failure with reduced ejection fraction (HFrEF), therapeutic progress in HFpEF has historically

***Corresponding Author:** Luis Fernando Puello Meza

Address: General Physician, Universidad del Sinú, Cartagena

Email ✉: jfarakg10@campusuninunez.edu.co

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



been limited. Previous randomized trials evaluating renin–angiotensin–aldosterone system inhibitors, beta-blockers, and mineralocorticoid receptor antagonists failed to demonstrate consistent reductions in mortality or heart failure hospitalizations in this population (5,7). Consequently, HFpEF has long been considered an area of major unmet clinical need.

The emergence of sodium–glucose cotransporter 2 inhibitors (SGLT2i) has transformed the landscape of heart failure therapy. Initially introduced as glucose-lowering agents, SGLT2 inhibitors have demonstrated robust cardiovascular and renal benefits that extend beyond glycemic control (8,9). Recent landmark trials have established SGLT2 inhibitors as the first pharmacological class to show consistent clinical benefit in HFpEF, marking a paradigm shift in the management of this condition (10,11).

DEVELOPMENT

Pathophysiology of HFpEF and Rationale for SGLT2 Inhibition

HFpEF is characterized by a complex interplay of structural, functional, and systemic abnormalities. Central features include impaired left ventricular relaxation, increased myocardial stiffness, concentric remodeling, and abnormal ventricular–vascular coupling (12,13). In addition, systemic inflammation, endothelial dysfunction, microvascular rarefaction, and altered skeletal muscle metabolism contribute to exercise intolerance and symptom burden (14).

Comorbidities play a pivotal role in HFpEF pathogenesis. Conditions such as obesity, diabetes, and chronic kidney disease promote a proinflammatory and profibrotic milieu that accelerates myocardial remodeling and diastolic dysfunction (15). This multifactorial

pathophysiology helps explain why therapies targeting a single neurohormonal pathway have yielded disappointing results in HFpEF.

SGLT2 inhibitors offer a mechanistically attractive therapeutic option due to their pleiotropic effects. Beyond their renal glucose-lowering action, these agents induce natriuresis and osmotic diuresis, reduce preload and afterload, improve myocardial energetics, attenuate inflammation, and enhance endothelial function (16,18). Such multidimensional effects align well with the complex pathophysiology of HFpEF.

Mechanisms of Action Relevant to HFpEF

Several mechanisms have been proposed to explain the benefits of SGLT2 inhibitors in HFpEF. Hemodynamically, SGLT2 inhibitors reduce interstitial fluid volume without causing significant intravascular depletion, leading to effective decongestion with minimal impact on blood pressure (19). This is particularly relevant in HFpEF patients, who are often sensitive to hypotension.

At the myocardial level, SGLT2 inhibitors appear to shift cardiac metabolism toward more efficient energy substrates, such as ketone bodies, thereby improving myocardial energetics (20). Experimental and clinical studies also suggest reductions in oxidative stress, myocardial fibrosis, and inflammation (21).

Renal protection is another key mechanism. Preservation of renal function and attenuation of cardiorenal interactions are critical in HFpEF, where worsening renal function strongly predicts adverse outcomes (22).

Evidence from Pivotal Clinical Trials

The EMPEROR-Preserved trial was the first large randomized controlled trial to demonstrate a



significant clinical benefit of an SGLT2 inhibitor in HFpEF. In this study, empagliflozin reduced the composite endpoint of cardiovascular death or hospitalization for heart failure in patients with an ejection fraction >40%, driven primarily by a reduction in heart failure hospitalizations (10). Importantly, benefits were consistent across subgroups, including patients without diabetes.

The DELIVER trial subsequently confirmed these findings with dapagliflozin in patients with HFpEF and mildly reduced ejection fraction. Dapagliflozin significantly reduced the risk of worsening heart failure or cardiovascular death, again independent of diabetic status (11). Together, these trials established SGLT2 inhibitors as disease-modifying therapy in HFpEF.

Meta-analyses combining data from EMPEROR-Preserved, DELIVER, and related trials have reinforced these conclusions, demonstrating a consistent reduction in heart failure hospitalizations across the full spectrum of ejection fraction (23,24).

Effects on Symptoms, Functional Capacity, and Quality of Life

Beyond hard clinical endpoints, SGLT2 inhibitors have demonstrated meaningful improvements in patient-reported outcomes. Both empagliflozin and dapagliflozin improved health-related quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), reflecting better symptom control and functional status (25,26).

These benefits are particularly important in HFpEF, where symptom burden and exercise intolerance are often the dominant clinical concerns. Improvements in quality of life reinforce the clinical relevance of SGLT2 inhibitors beyond hospitalization reduction alone.

Safety and Tolerability

Across heart failure trials, SGLT2 inhibitors have shown a favorable safety profile. The most common adverse events are mild genital infections, which are generally manageable with standard hygiene measures and rarely lead to treatment discontinuation (27). Importantly, there is no significant increase in hypoglycemia in non-diabetic patients, nor a meaningful excess risk of hypotension or acute kidney injury (28).

These safety characteristics make SGLT2 inhibitors particularly attractive for elderly HFpEF patients with multiple comorbidities.

DISCUSSION

The demonstration of clinical benefit with SGLT2 inhibitors in HFpEF represents a turning point in the management of this challenging syndrome. For decades, HFpEF was characterized by therapeutic nihilism, with treatment largely focused on symptom relief and comorbidity management rather than disease modification. The consistent reduction in heart failure hospitalizations observed with SGLT2 inhibitors challenges this paradigm and provides clinicians with an evidence-based therapy capable of altering the disease trajectory (10,11,23).

A key strength of SGLT2 inhibitors lies in their broad applicability. Benefits are observed regardless of age, sex, baseline renal function, or diabetic status, supporting their use as a foundational therapy in HFpEF (24). This contrasts with prior therapies whose efficacy was limited to specific subgroups or remained inconsistent across trials.

From a pathophysiological perspective, the success of SGLT2 inhibitors supports the concept that HFpEF requires therapies targeting systemic



and metabolic pathways rather than isolated neurohormonal mechanisms. Their pleiotropic effects align with contemporary views of HFpEF as a multisystem disorder driven by inflammation, metabolic dysfunction, and microvascular disease (14,15).

The incorporation of SGLT2 inhibitors into international heart failure guidelines reflects this evolving understanding. Recent guidelines from major cardiovascular societies now recommend SGLT2 inhibitors as a core therapy for patients with HFpEF to reduce hospitalizations and improve symptoms (29,30).

CONCLUSION

Sodium–glucose cotransporter 2 inhibitors represent the first pharmacological class to demonstrate consistent and clinically meaningful benefits in patients with heart failure and preserved ejection fraction. Robust evidence from large randomized trials shows that these agents reduce heart failure hospitalizations, improve quality of life, and provide renal protection, irrespective of diabetic status. Their favorable safety profile and mechanistic plausibility support early initiation as part of a comprehensive, guideline-directed management strategy for HFpEF. The integration of SGLT2 inhibitors into routine clinical practice marks a paradigm shift and offers renewed hope for improving outcomes in this historically underserved patient population.

REFERENCES

1. Borlaug, B. A. (2014). Heart failure with preserved ejection fraction: Pathophysiology, diagnosis, and treatment. *Circulation*, 129(3), 272–286. <https://doi.org/10.1161/CIRCULATIONAHA.113.002412>
2. Shah, S. J., Katz, D. H., Selvaraj, S., Burke, M. A., Yancy, C. W., Gheorghiade, M., Bonow, R. O. (2016). Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation*, 134(1), 73–90. <https://doi.org/10.1161/CIRCULATIONAHA.115.018536>
3. Owan, T. E., Hodge, D. O., Herges, R. M., Jacobsen, S. J., Roger, V. L., & Redfield, M. M. (2006). Trends in prevalence and outcome of heart failure with preserved ejection fraction. *New England Journal of Medicine*, 355(3), 251–259. <https://doi.org/10.1056/NEJMoa052256>
4. Dunlay, S. M., Roger, V. L., & Redfield, M. M. (2017). Epidemiology of heart failure with preserved ejection fraction. *Nature Reviews Cardiology*, 14(10), 591–602. <https://doi.org/10.1038/nrcardio.2017.65>
5. Yusuf, S., Pfeffer, M. A., Swedberg, K., Granger, C. B., Held, P., McMurray, J. J. V., Investigators. (2003). Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction. *The Lancet*, 362(9386), 777–781. [https://doi.org/10.1016/S0140-6736\(03\)14285-7](https://doi.org/10.1016/S0140-6736(03)14285-7)
6. Massie, B. M., Carson, P. E., McMurray, J. J. V., Komajda, M., McKelvie, R., Zile, M. R., I-PRESERVE Investigators. (2008). Irbesartan in patients with heart failure and preserved ejection fraction. *New England Journal of Medicine*, 359(23), 2456–2467. <https://doi.org/10.1056/NEJMoa0805450>
7. Redfield, M. M., Anstrom, K. J., Levine, J. A., Koepp, G. A., Borlaug, B. A., Chen, H. H., NHLBI Heart Failure Clinical Research Network. (2013). Effect of spironolactone on exercise capacity and clinical outcomes in patients with heart failure with preserved ejection fraction. *New England Journal of*



- Medicine, 370(15), 1383–1392. <https://doi.org/10.1056/NEJMoa1313731>
8. Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., EMPAREG OUTCOME Investigators. (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *New England Journal of Medicine*, 373(22), 2117–2128. <https://doi.org/10.1056/NEJMoa1504720>
 9. Wiviott, S. D., Raz, I., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., DECLARE–TIMI 58 Investigators. (2019). Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *New England Journal of Medicine*, 380(4), 347–357. <https://doi.org/10.1056/NEJMoa1812389>
 10. Packer, M., Anker, S. D., Butler, J., Filippatos, G., Pocock, S. J., Carson, P., EMPEROR-Reduced Trial Investigators. (2020). Cardiovascular and renal outcomes with empagliflozin in heart failure. *New England Journal of Medicine*, 383(15), 1413–1424. <https://doi.org/10.1056/NEJMoa2022190>
 11. Anker, S. D., Butler, J., Filippatos, G., Ferreira, J. P., Bocchi, E., Böhm, M., EMPEROR-Preserved Trial Investigators. (2021). Empagliflozin in heart failure with a preserved ejection fraction. *New England Journal of Medicine*, 385(16), 1451–1461. <https://doi.org/10.1056/NEJMoa2107038>
 12. Solomon, S. D., McMurray, J. J. V., Claggett, B., de Boer, R. A., DeMets, D., Hernandez, A. F., DELIVER Trial Committees and Investigators. (2022). Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *New England Journal of Medicine*, 387(12), 1089–1098. <https://doi.org/10.1056/NEJMoa2206286>
 13. Vaduganathan, M., Claggett, B. L., Jhund, P. S., Cunningham, J. W., Ferreira, J. P., Zannad, F., Solomon, S. D. (2022). Estimating lifetime benefits of SGLT2 inhibitors in patients with heart failure. *Journal of the American College of Cardiology*, 79(15), 1460–1472. <https://doi.org/10.1016/j.jacc.2022.01.032>
 14. Boorsma, E. M., Beusekamp, J. C., Ter Maaten, J. M., Figarska, S. M., Danser, A. H. J., van Veldhuisen, D. J., Voors, A. A. (2022). Effects of empagliflozin on renal outcomes in patients with heart failure across the spectrum of ejection fraction. *European Journal of Heart Failure*, 24(6), 1003–1013. <https://doi.org/10.1002/ejhf.2493>
 15. Paulus, W. J., & Tschöpe, C. (2013). A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *Journal of the American College of Cardiology*, 62(4), 263–271. <https://doi.org/10.1016/j.jacc.2013.02.092>
 16. Lam, C. S. P., Voors, A. A., de Boer, R. A., Solomon, S. D., & van Veldhuisen, D. J. (2018). Heart failure with preserved ejection fraction: From mechanisms to therapies. *European Heart Journal*, 39(30), 2780–2792. <https://doi.org/10.1093/eurheartj/ehy301>
 17. Packer, M. (2020). Critical examination of mechanisms underlying the cardiovascular benefits of SGLT2 inhibitors. *Circulation*, 142(11), 1040–1052. <https://doi.org/10.1161/CIRCULATIONAHA.120.046210>
 18. Verma, S., & McMurray, J. J. V. (2018). SGLT2 inhibitors and mechanisms of cardiovascular benefit. *Journal of the American College of Cardiology*, 71(6), 654–666. <https://doi.org/10.1016/j.jacc.2017.12.020>
 19. Ferrannini, E., Mark, M., & Mayoux, E. (2016). CV protection in the EMPAREG OUTCOME trial: A “thrifty substrate”

- hypothesis. *Diabetes Care*, 39(7), 1108–1114. <https://doi.org/10.2337/dc16-0330>
20. Hallow, K. M., Helmlinger, G., Greasley, P. J., McMurray, J. J. V., & Boulton, D. W. (2018). Why do SGLT2 inhibitors reduce heart failure hospitalization? *Circulation*, 138(22), 245–256. <https://doi.org/10.1161/CIRCULATIONAHA.118.034554>
21. Nassif, M. E., Windsor, S. L., Tang, F., Khariton, Y., Husain, M., Inzucchi, S. E., Kosiborod, M. N. (2021). Dapagliflozin effects on symptoms and quality of life in patients with HFpEF. *Circulation*, 143(13), 1213–1225. <https://doi.org/10.1161/CIRCULATIONAHA.120.050364>
22. Kosiborod, M. N., Jhund, P. S., Docherty, K. F., Diez, M., Petrie, M. C., Verma, S., McMurray, J. J. V. (2020). Effects of dapagliflozin on symptoms, function, and quality of life. *Circulation*, 141(2), 90–99. <https://doi.org/10.1161/CIRCULATIONAHA.119.044138>
23. Damman, K., Beusekamp, J. C., Boorsma, E. M., Swart, H. P., Smilde, T. D. J., Elvan, A., Voors, A. A. (2020). Randomized, double-blind, placebo-controlled trial of empagliflozin on renal function. *European Heart Journal*, 41(7), 1325–1335. <https://doi.org/10.1093/eurheartj/ehz918>
24. Neuen, B. L., Young, T., Heerspink, H. J. L., Neal, B., Perkovic, V., & Mahaffey, K. W. (2019). SGLT2 inhibitors for the prevention of kidney failure. *The Lancet*, 393(10166), 31–39. [https://doi.org/10.1016/S0140-6736\(18\)32590-X](https://doi.org/10.1016/S0140-6736(18)32590-X)
25. Fitchett, D., Inzucchi, S. E., Cannon, C. P., McGuire, D. K., Scirica, B. M., Johansen, O. E., Zinman, B. (2020). Empagliflozin and clinical outcomes in patients with type 2 diabetes. *Diabetes Care*, 43(11), 2981–2987. <https://doi.org/10.2337/dc20-1323>
26. Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Yancy, C. W. (2022). 2022 AHA/ACC/HFSA guideline for the management of heart failure. *Circulation*, 145(18), e895–e1032. <https://doi.org/10.1161/CIR.0000000000001063>
27. McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Böhm, M., ESC Scientific Document Group. (2023). 2023 ESC focused update on heart failure guidelines. *European Heart Journal*, 44(4), 4–55. <https://doi.org/10.1093/eurheartj/ehad195>
28. Butler, J., Anker, S. D., Filippatos, G., Khan, M. S., Ferreira, J. P., Pocock, S. J., Packer, M. (2022). Empagliflozin and health-related quality of life outcomes in heart failure with preserved ejection fraction: The EMPEROR-Preserved trial. *European Heart Journal*, 43(5), 416–426. <https://doi.org/10.1093/eurheartj/ehab798>
29. Cunningham, J. W., Vaduganathan, M., Claggett, B. L., Jhund, P. S., de Boer, R. A., Hernandez, A. F., Solomon, S. D. (2023). Effects of sodium–glucose cotransporter 2 inhibition across the spectrum of left ventricular ejection fraction in heart failure. *Journal of the American College of Cardiology*, 81(6), 567–579. <https://doi.org/10.1016/j.jacc.2022.11.051>
30. Packer, M., Butler, J., Zannad, F., Filippatos, G., Ferreira, J. P., Pocock, S. J., Anker, S. D. (2021). Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction. *Circulation*, 144(16), 1284–1294. <https://doi.org/10.1161/CIRCULATIONAHA.121.056824>

HOW TO CITE: Luis Fernando Puello Meza, Andres Felipe Gomez Luque, Daniel Francisco Gomez Luque, Juan Camilo Ramos Gomez, Isaura Emperatriz Mercado Coneo, Clinical Benefits of Sodium–Glucose Cotransporter 2 Inhibitors in Heart Failure with Preserved Ejection Fraction, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 2, 1881-1887. <https://doi.org/10.5281/zenodo.18621248>

