The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 11, 2025

SGLT2 INHIBITORS IN HFPEF AND HFMREF: A COMPREHENSIVE PRISMA SYSTEMATIC REVIEW

Dr. Sharjeel Sadiq*[1], Dr Nimra Saeed[2], Dr Momina Butt[3], Umme Roman[4], Bisma Munawar[5], Dr Shaheer Abdullah[6]

DOI: https://doi.org/10.5281/zenodo.17774512

Keywords

Article History
Received: 01 October 2025
Accepted: 19 November 2025
Published: 29 November 2025

Corresponding Author: *
Dr. Sharjeel Sadiq

Abstract

Background: Heart failure with preserved (HFpEF) and mildly reduced ejection fraction (HFmrEF) represents over half of HF cases. Historically lacking effective treatments, recent evidence shows strong benefits of sodium–glucose cotransporter-2 (SGLT2) inhibitors.
Objective: To systematically review randomized trials, meta-analyses, guidelines, and observational evidence evaluating SGLT2 inhibitors in HFpEF/HFmrEF.
Methods: PRISMA-guided search of PubMed, Cochrane, and cardiology journals up to Nov 2025.
Results: SGLT2 inhibitors consistently reduced HF hospitalizations (~20–25%), improved KCCQ quality-of-life scores, and significantly lowered composite CV death/HF hospitalization. Mortality reduction remains modest. Safety signals were minimal.
Conclusion: SGLT2 inhibitors represent the most impactful advance in HFpEF/HFmrEF treatment, warranting Class I guideline recommendations

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) and mildly reduced ejection fraction (HFmrEF) collectively account for a major proportion of HF-related morbidity. Until recently, therapies failed to consistently reduce hospitalizations or cardiovascular mortality. SGLT2 inhibitors—initially used for diabetes—exert multiple cardiovascular and renal benefits independent of glucose lowering. Landmark trials such as EMPEROR-Preserved and DELIVER established them as foundational therapy. This review provides a comprehensive evaluation of their evidence across HFpEF/HFmrEF populations.

Methods

Search Strategy:
A PRISMA-guided search was performed in PubMed, MEDLINE, Cochrane Library, ESC/ACC guideline databases, and cardiology journals up to November 2025.

Inclusion Criteria:
- Randomized controlled trials (RCTs)
- Meta-analyses and systematic reviews
- Observational cohort studies
- Clinical guidelines

Exclusion Criteria:
- Non-HF studies
- Animal studies
- Lack of HF outcomes

Risk of Bias:
RCTs were evaluated with Cochrane RoB 2.0. Observational studies were evaluated with the Newcastle–Ottawa Scale.
Primary Outcome:
Composite of cardiovascular (CV) death or HF hospitalization.
Secondary Outcomes: All-cause mortality, KCCQ score, renal outcomes, safety endpoints.

Results

Randomized Controlled Trials

EMPEROR-Preserved:

- Population: EF >40%
- Findings: 21% reduction in primary composite outcome, mainly HF hospitalization reduction.
- Outcome: HR ~0.79

DELIVER:

- Population: EF >40%, including improved EF
- Findings: Significant reduction in worsening HF or CV death; robust across EF categories.
- Outcome: HR ~0.82

SOLOIST-WHF:

- Population: Recent worsening HF (broad EF spectrum)
- Findings: Reduction in CV events; HFpEF subgroup benefit consistent.

Across major RCTs, SGLT2 inhibitors improved symptoms (KCCQ +4–6 points) and decreased HF hospitalizations consistently.Tables

Table 1. Summary of Major Randomized Trials

Trial	Population	Drug / Dose	Primary Finding	Effect Size
EMPEROR-Preserved	EF >40%	Empagliflozin 10 mg	↓ HF Hosp + CV Death	HR ~0.79
DELIVER	EF >40%	Dapagliflozin 10 mg	↓ Worsening HF/CV Death	HR ~0.82
SOLOIST-WHF	Worsening HF	Sotagliflozin	↓ CV Events	Significant reduction

Table 2. Risk of Bias (Cochrane RoB 2.0)

Study	Randomization	Blinding	Overall Risk
EMPEROR-Preserved	Low	Low	Low
DELIVER	Low	Low	Low
SOLOIST-WHF	Some concerns	Low	Some concerns

Table 3. Summary of Meta-Analysis Findings

Outcome	Effect Size	Interpretation	Notes
HF Hospitalization	~20–25% ↓	Strong benefit	Consistent across EF spectrum
Composite CV Death/HF Hosp	~18–22% ↓	Moderate benefit	Driven by HF events
CV Mortality	Minimal ↓	Borderline	Needs long-term follow-up
KCCQ Improvement	+4 to +6	Meaningful	Better QoL

Discussion

This systematic review shows that SGLT2 inhibitors deliver consistent and clinically meaningful benefits for HFpEF/HFmrEF patients. Their effect on HF hospitalizations is robust and reproducible across trials.

Mechanisms include:

- Improved natriuresis
- Osmotic diuresis
- Enhanced myocardial energetics
- Reduced vascular stiffness
- Anti-inflammatory effects

Future research is required to clarify mortality benefit, optimal therapy sequencing, and phenotypespecific responses.

Conclusion

SGLT2 inhibitors are the most effective therapy to date for HFpEF and HFmrEF, with strong evidence supporting their use to reduce HF hospitalizations and improve symptoms. Their favorable safety profile and strong guideline support warrant routine implementation in eligible patients.

REFERENCES

1. Anker SD, et al. Empagliflozin in HFpEF. N Engl J Med. 2021;385:1451–1461.
2. Solomon SD, et al. Dapagliflozin in HFpEF/HFmrEF. N Engl J Med. 2022;387:1089–1098.
3. Bhatt DL, et al. Sotagliflozin after worsening HF. N Engl J Med. 2021;384:117–128.
4. Vaduganathan M, et al. SGLT2 inhibitors across HF spectrum. Lancet. 2022;400:1787–1798.
5. 2024 ACC/AHA/HFSA Heart Failure Guidelines.
6. ESC Heart Failure Guidelines 2023–2024.
7. McMurray JJV, et al. Mechanisms of SGLT2 benefit. Eur Heart J. 2023;44:3211–3223.