International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

Check for updates

From bench to bedside: A systematic review of empagliflozin's cardioprotective mechanisms and clinical outcomes in heart failure

Sahasyaa Adalarasan [1], M. S. Govind Krishna [1], Rakhesh Varshan R B [1], Prasanthini S [1], Shalini P [1], Yogesh S [2, 3, *] and Hariharan C [3]

[1] *MBBS, Institute of Internal Medicine, Madras Medical College, Chennai, IND.*
[2] *Master in Health Profession Education (MHPE SCHOLAR), Sri Balaji Vidyapeeth university, Pondicherry, IND.*
[3] *Internal Medicine, Madras Medical college and Rajiv Gandhi Government General Hospital, Chennai, IND.*

International Journal of Science and Research Archive, 2026, 19(01), 758-769

Publication history: Received on 01 March 2026; revised on 11 April 2026; accepted on 14 April 2026

Article DOI: https://doi.org/10.30574/ijsra.2026.19.1.0749

Abstract

Empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, has demonstrated robust benefits in heart failure (HF), but existing reviews often examine either molecular mechanisms or clinical outcomes in isolation. This systematic review integrates evidence from both preclinical and clinical studies to provide a unified evaluation of empagliflozin's cardioprotective role. Following PRISMA 2020 guidelines and a PROSPERO-registered protocol (CRD420251186611), major biomedical databases were searched for mechanistic, translational, and clinical studies of empagliflozin in HF. Thirty four studies met inclusion criteria. Preclinical studies consistently showed that empagliflozin attenuates inflammation, oxidative stress, mitochondrial dysfunction, and myocardial fibrosis. In clinical studies, empagliflozin significantly improved natriuretic peptide levels, ventricular loading conditions, and structural remodeling, with reductions in left ventricular (LV) volumes and fibrosis markers. Across major trials (EMPEROR-Reduced, EMPEROR-Preserved, EMPA-REG OUTCOME, EMPA-AHF-RESPONSE, EMPULSE), empagliflozin reduced the risk of cardiovascular death or HF hospitalization by 24-35%, lowered total HF events, improved diuretic efficiency, slowed renal function decline, and enhanced quality of life (Kansas City Cardiomyopathy Questionnaire (KCCQ) scores) . Integrating mechanistic and clinical evidence provides a cohesive understanding of empagliflozin's therapeutic potential and supports its widespread adoption in HF management.

Categories: Cardiology, Pharmacology, Internal Medicine

Keywords: Empagliflozin; Emperor trial; Heart failure with preserved ejection fraction; HF; India

1. Introduction

Heart failure represents the final common pathway of diverse cardiovascular insults, including ischemic injury, long-standing hypertension, valvular disorders, and cardiomyopathies. Its etiopathogenesis reflects a complex interplay of structural remodeling, neurohormonal activation, mitochondrial dysfunction, and progressive decline in myocardial contractile reserve [1].

The global burden of heart failure continues to rise, driven by aging populations and improved survival after acute cardiac events [2]. Low- and middle-income countries face the steepest ascent in prevalence, with India shouldering a disproportionate load due to high rates of uncontrolled hypertension, diabetes, ischemic heart disease, and delayed access to care [2]. The resulting clinical and economic strain on the healthcare system underscores the urgent need for therapies that offer meaningful improvements in morbidity and mortality.

* Corresponding author: Yogesh S

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, originally developed for glycemic control, have emerged as a major therapeutic class in heart failure [3]. Empagliflozin reduces renal glucose reabsorption in the proximal tubule, promoting glycosuria and modest natriuresis [3]. Beyond these actions, it favorably modulates cardiac preload and afterload, improves myocardial energetics through ketone shift, attenuates inflammation and oxidative stress, and suppresses maladaptive neurohormonal pathways. These pleiotropic effects form a strong mechanistic rationale for its use across the spectrum of heart failure phenotypes, irrespective of diabetic status.

Empagliflozin is an especially attractive candidate because of its predictable pharmacokinetic profile, once- daily dosing, fewer clinically significant drug interactions, and a comparatively favorable safety spectrum [4]. Its cost-effectiveness in chronic therapy further reinforces its suitability for resource-constrained settings, including large segments of the Indian population.

The novelty of this project lies in its integrated approach: A systematic review that synthesizes evidence.

1.1. How to cite this article

from both experimental rat models and human clinical studies. By spanning molecular mechanisms, tissue- level effects, and real-world clinical outcomes, this work aims to bridge preclinical insights with bedside implications. No previous review has combined these dimensions into a unified framework, positioning this study to provide a more comprehensive understanding of empagliflozin's cardioprotective potential.

1.2. Adherence to Reporting Standards

The present systematic review was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All methodological steps, including the identification of studies, screening, assessment of eligibility, and extraction of data, followed the PRISMA 2020 framework to ensure methodological transparency and reproducibility [5]. The review process was undertaken by two independent researchers who worked in parallel during all stages of the study, with disagreements resolved through discussion and, when required, arbitration by a third reviewer. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251186611.

1.3. Data Sources and Search Strategy

A comprehensive literature search was conducted across five electronic databases-PubMed/MEDLINE (n = 9), Embase (n = 7), Scopus (n = 6), Web of Science (n = 4), and the Cochrane Library (n = 4). The search combined controlled vocabulary (MeSH/Emtree) and free-text terms using Boolean operators, including: "empagliflozin," "SGLT2 inhibitor," "sodium-glucose cotransporter-2," "heart failure," "HFrEF," "HFpEF," "cardiomyopathy," "cardiorenal," "cardiovascular outcomes," and "clinical trial." Search strings were adapted to the indexing of each database. No language or publication-year restrictions were applied. In addition to database searching, multiple supplementary strategies were used: screening of reference lists of all included studies, forward and backward citation tracking, review of relevant websites, and manual search of clinical trial registries and conference proceedings. These additional methods yielded 20 records (10 from websites and 10 from citation searching). Reasons for exclusion were because of not meeting the eligibility criteria (n = 5) or overlapping data (n = 5). The PRISMA flowchart for the present review is given blow [Figure 1].

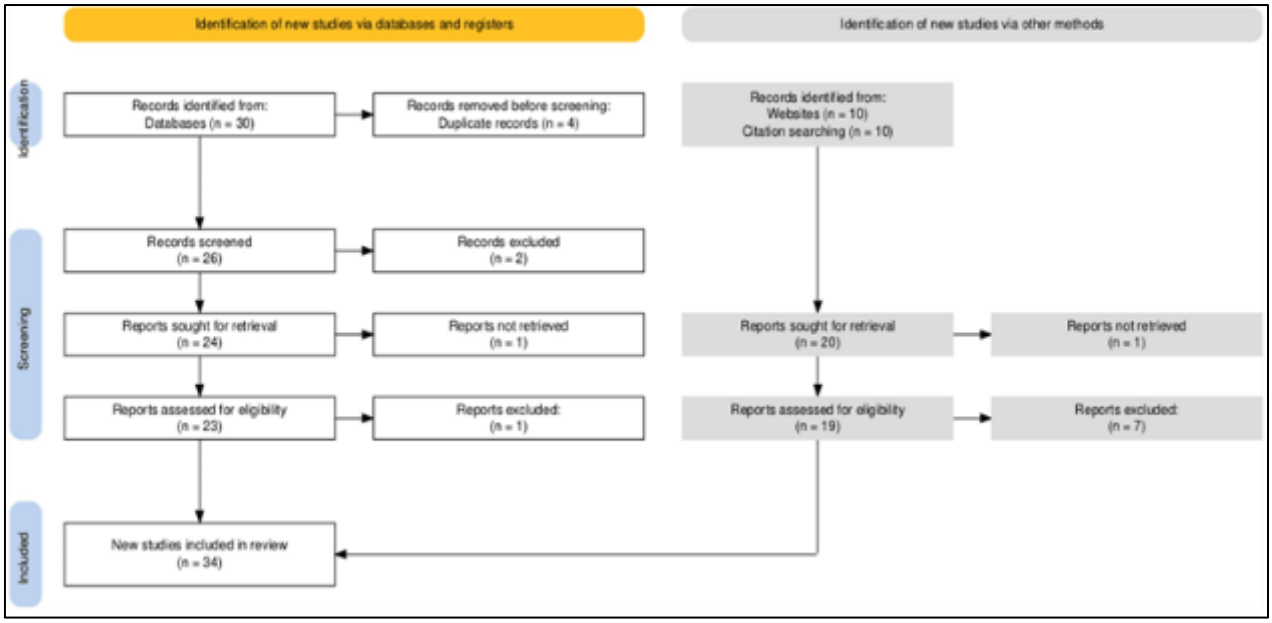

Figure 1 PRISMA flowchart

1.4. Eligibility Criteria

Eligibility criteria were predefined to include randomized controlled trials and robust clinical studies involving adult patients with heart failure receiving empagliflozin. Included studies were required to report at least one clinically or mechanistically relevant endpoint, including left ventricular ejection fraction, natriuretic peptide levels, echocardiographic or structural indices, markers of remodeling or inflammation, renal parameters pertinent to heart failure pathophysiology, or major clinical outcomes such as hospitalizations, mortality, and changes in New York Heart Association (NYHA) grading functional class.

Patient-reported outcomes such as Kansas City Cardiomyopathy Questionnaire scores and data on adverse events were also considered essential. Key clinical trials, such as EMPEROR-Reduced, EMPEROR-Preserved, and EMPA-AHF response studies, met these criteria and were evaluated accordingly. Non-clinical research, case reports, reviews, commentaries, and studies demonstrating high risk of bias were excluded from synthesis.

1.5. Outcomes of Interest

The outcomes assessed in this review reflected the multidimensional profile of empagliflozin's cardioprotective influence. Extracted data included variations in natriuretic peptide concentrations, improvements in Kansas City Cardiomyopathy Questionnaire scores, transitions in NYHA class, echocardiographic changes in systolic and structural parameters, shifts in biomarkers of remodeling and inflammation, and alterations in renal indices associated with clinical progression. In addition, clinical endpoints such as heart-failure-related hospitalization, cardiovascular mortality, composite outcome measures, and adverse-event profiles were systematically recorded to provide a comprehensive understanding of treatment effects.

1.6. Data Extraction

Data extraction was performed independently by two reviewers using a standardized template to ensure consistency. Extracted fields included study characteristics, patient demographics, intervention details, duration of follow-up, endpoints evaluated, and reported outcomes. Discrepancies between reviewers were resolved through consensus-based discussion, and attempts were made to communicate with study authors when clarification of data was necessary.

1.7. Risk of Bias Assessment

Risk of bias (RoB) for randomized controlled trials was evaluated using the revised Cochrane Risk of Bias Tool (RoB 2), while observational studies were assessed using methodological criteria aligned with contemporary Cochrane principles [6]. Studies identified as demonstrating high risk of bias in critical domains were excluded from the evidence synthesis to preserve internal validity and reduce methodological distortion.

1.8. Statistical Analysis

Statistical analysis was done on the IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA) statistical software. It focused on extracting effect estimates appropriate to each outcome.

Dichotomous variables such as cardiovascular mortality, heart failure hospitalizations, composite cardiovascular endpoints, and adverse events were summarized using risk ratios or hazard ratios with corresponding 95% confidence intervals. Continuous outcomes including changes in left ventricular ejection fraction, natriuretic peptide concentrations, echocardiographic indices, inflammatory and remodeling markers, renal parameters, and patient-reported symptom scores were analyzed using mean differences or standardized mean differences depending on whether measurement scales were consistent across studies.

Time-to-event outcomes were preferably extracted as hazard ratios, and when only raw event data were available, risk ratios were calculated.

2. Review

2.1. Molecular and cellular mechanisms of cardioprotection by empagliflozin

In diabetic rats, the left atrium enlarged, interstitial fibrosis increased, and atrial fibrillation became easier to induce compared with healthy controls. Their atrial mitochondria showed weaker respiration, reduced membrane potential, and poorer biogenesis. Empagliflozin largely prevented these diabetes-related defects, most likely through activation of the PGC-1α/NRF-1/Tfam pathway [7].

When NRK-52P cells were exposed to p-Cresol , the LC3-BII/LC3-BI ratio, a marker of autophagy, rose sharply at 24 hours and increased further at 48 hours. Empagliflozin significantly blunted this rise at both time points [8].

In rats with chronic heart failure, empagliflozin improved cardiac performance, enhanced mitochondrial membrane potential, reduced cellular swelling on Hematoxylin and Eosin (HE) staining, promoted more organized tissue architecture, and suppressed Inducible Nitric Oxide Synthase (iNOS) expression. These benefits likely came from reduced inflammation, lower oxidative stress, and mitigation of myocardial fibrosis [9].

2.2. Key biomarker changes associated with empagliflozin

In a rat model of cardiorenal syndrome, levels of TNF-α, NF-κB, IL-1β, and MMP-9 were markedly elevated compared with sham controls and were significantly reduced by empagliflozin. Angiotensin II type 2 receptor (AT2R) expression and Brain Natriuretic peptide (BNP) levels showed the same pattern, tracking with the inflammatory response across groups [7].

Diabetic ventricular myocytes generated far more cytosolic reactive oxygen species (126 ± 5 F/F0) than either control cells or diabetic cells treated with empagliflozin, which showed comparable Reactive Oxygen Species (ROS) levels. Mitochondrial ROS was also higher in diabetic myocytes (41 ± 1 F/F0) than in controls and empagliflozin-treated cells. Intracellular sodium followed the same trend, being highest in untreated diabetic myocytes. Empagliflozin significantly lowered all three abnormalities [10].

2.3. In additional rat studies, empagliflozin produced better cardiac function, increased Matrix

Metalloproteinase (MMP), lowered intracellular ROS, and reduced Neurotransmitter-proBNP (NT- proBNP) and high sensitivity-C reactive protein (hs-CRP). Tissue sections showed less edema, cleaner cellular arrangement, and decreased iNOS expression. The overall cardiac improvement likely stems from anti-inflammatory, antioxidative, and antifibrotic effects [9].

n humans, pooled EMPEROR data showed baseline NT-proBNP closely mirrored heart failure severity and outcomes. Patients in the top NT-proBNP quartile had a 4-6-fold higher rate of major endpoints and 2-3-fold more total HF hospitalizations than those in the lowest quartile [10]. Empagliflozin consistently lowered NT- proBNP at all follow-ups, with a 13% adjusted reduction at week 52. Achieving NT-proBNP under 1,115 pg/mL by week 12 substantially decreased later risk of cardiovascular death or HF hospitalization, and empagliflozin increased the chance of reaching this target by 27% compared with placebo [10].

Subgroup analyses showed that patients with high baseline NT-proBNP or high-sensitivity cardiac troponin T (hs-cTnT) had more comorbidities and worse disease, translating into 2-5-times higher event rates [10]. Even in these high-risk categories, empagliflozin reduced major cardiovascular outcomes and slowed estimated glomerular filtration rate (eGFR) decline. Over about 100 weeks, empagliflozin maintained a modest 7% reduction in NT-proBNP. Rising NT-proBNP from baseline to week 12 strongly predicted later cardiovascular death or HF hospitalizations, even in those receiving empagliflozin [11].

2.4. Cardiac structural and functional changes with empagliflozin

In hypertensive diabetic rats, empagliflozin provided both cardiac and renal protection without altering plasma glucose. It normalized end-systolic and end-diastolic volumes and restored systolic function, reflected by improved maximal pressure rise and a normalized end-systolic pressure-volume relationship. Histology revealed significantly reduced fibrosis in atrial and ventricular tissue [12].

In another rat model, baseline ejection fractions near 70-76% dropped to around 40% in both empagliflozin and control groups, but empagliflozin-treated hearts showed markedly less collagen accumulation. Collagen volume fraction in scar and remote myocardium was lower in the empagliflozin group (53.8 ± 5.4% and 2.5 ± 1.3%) than in controls (79.1 ± 6.2% and 4.6 ± 2.5%). Hydroxyproline levels trended lower as well. Expression of TGF-β1 and Smad3 fell significantly in empagliflozin-treated animals, demonstrating attenuation of profibrotic signaling [13].

Table 1 Effects of empagliflozin in rat studies

Study Type	Measure	Control	Empagliflozin	Effect
Rat – Remodeling [12]	LV volumes	Higher	Normalized	Reverse remodeling
	Cardiac fibrosis	Higher	Lower	Significant reduction in fibrosis
Rat – MI model [13]	Scar collagen	79.10%	53.80%	P<0.05
	Remote collagen	4.60%	2.50%	P<0.05
	TGF-β1/Smad3	Higher	Lower	P<0.05

In the SUGAR-DM-HF study, empagliflozin led to clear improvements in cardiac remodeling. It lowered the left ventricular end-systolic volume index by 6.0 mL/m^2 (95% CI −10.8 to −1.2; p = 0.015) and reduced the end-diastolic volume index by 8.2 mL/m^2 (95% CI −13.7 to −2.6; p = 0.0042). Global longitudinal strain didn't show a measurable change, but there was a meaningful 28 percent drop in NT-proBNP (95% CI 2%-47%; p = 0.038), suggesting better ventricular loading conditions and less myocardial stress [14].

Findings from the EMPEROR-Reduced and EMPEROR-Preserved trials strengthened this picture across a wide span of ejection fractions. In the combined analysis, the hazard ratio for the composite of heart failure hospitalization or cardiovascular death steadily declined as baseline Left Ventricular Ejection Fraction (LVEF) increased: 0.75 (95% CI 0.61-0.91) at 25-34%, 0.54 (0.42-0.68) at 35-44%, 0.42 (0.34-0.52) at 45-54%,

0.34 (0.27-0.42) at 55-64%, and 0.29 (0.21-0.39) at 65 percent or higher (p < 0.001 for trend) [15]. First and recurrent heart failure hospitalizations followed the same pattern, confirming that empagliflozin provides consistent clinical benefit in both reduced and preserved LVEF groups [Table 2].

Table 2 Structural and functional cardiac changes in humans

Trial	Measure	Empagliflozin Effect	Effect Size
SUGAR-DM-HF [14]	LVESV	reduction of 6.0 mL/m^2	95% CI −10.8 to −1.2; P=0.015
	LVEDV	reduction of 8.2 mL/m^2	95% CI −13.7 to −2.6; P=0.0042
	NT-proBNP	decrease in 28%	95% CI 2–47%; P=0.038
EMPEROR pooled [15]	HF hospitalization/CV death	Benefit across all EF ranges	HR 0.75 → 0.29 from EF 25% → ≥65%

LVESV - Left ventricular end systolic volume LVEDV - Left ventricular end diastolic volume; NT-pro-BNP - Neurotransmitter pro-Brain natriuretic peptide HF - Heart failure, CV - Cardiovascular

2.5. Histopathological evidence of tissue protection and radiological evidence of remodeling reversal

In obese ZSF1 rats, empagliflozin lowered blood glucose by about 28 percent and improved endothelial function as well as cardiac remodeling. It also reduced markers of cellular aging and atherothrombosis in arterial regions prone to injury, but this reduction was seen only in lean ZSF1 controls, not in the obese animals [16].

Masson's trichrome staining showed a clear gradient of myocardial fibrosis: Chronic Restraint Stress (CRS) rats had the largest fibrotic area, CRS animals treated with empagliflozin had less, and sham controls had the least. Sirius red staining confirmed the same graded pattern of collagen deposition across the three groups [8].

Microscopy revealed that Connexin-43, a protein marking healthy gap-junction structure, was lowest in CRS rats, higher in CRS rats treated with empagliflozin, and highest in sham controls. TUNEL staining showed the reverse trend, with the most apoptotic nuclei in CRS animals, fewer in CRS-Empa, and the fewest in sham controls [8].

Single-strand DNA damage, assessed by γ-H2AX, followed the same escalating pattern as fibrosis, with CRS rats showing the highest levels, CRS-Empa an intermediate level, and sham animals the lowest. Double- strand DNA damage, identified by XRCC1+CD90+ expression, mirrored this pattern exactly [8].

Echocardiography showed no differences among the groups in LVEF, left ventricular end-diastolic diameter (LVEDd), or left ventricular end-systolic diameter (LVESd) before induction of CRS or at day 14 afterward. By days 28 and 42, LVEDd increased significantly in both CRS and CRS-Empa groups compared with sham but did not differ between those two disease groups. LVESd rose in CRS and CRS-Empa compared with sham, but CRS animals had a larger increase than CRS-Empa. LVEF showed the opposite behavior, remaining highest in sham animals and lowest in CRS animals, with the CRS-Empa group in between [8].

2.6. Composite of cardiovascular death or hospitalization for heart failure

The EMPA-REG OUTCOME trial was the first large clinical study to show that empagliflozin provides cardiovascular protection in people with type 2 diabetes and established cardiovascular disease [Table 3]. It reduced major cardiovascular events and hospitalizations for heart failure by roughly 35 percent compared with placebo, and these benefits occurred independently of glucose lowering [17, 18].

Among 7020 participants either living with or at risk for heart failure (10.1%), empagliflozin reduced the combined outcome of heart failure hospitalization or cardiovascular death to 5.7 percent compared with 8.5 percent in the placebo arm (HR 0.66, 95% CI 0.55-0.79, $P < 0.001$). The composite of heart-failure hospitalization or death specifically due to heart failure also occurred less often with empagliflozin (2.8% vs. 4.5%; HR 0.61, 95% CI 0.47-0.79, $P < 0.001$) [18]. These benefits were similar regardless of whether patients already had heart failure [19].

Across predefined heart-failure risk strata, including low-average (67.2%), high (24.2%), and very high (5.1%) risk, empagliflozin continued to show protection against cardiovascular death and heart-failure hospitalization, even in the most vulnerable group [17]. It also lowered heart-failure hospitalization rates in people with previous myocardial infarction or stroke (9.4% vs. 14.5%) [20], and its effect did not differ between those with or without atrial fibrillation [HR 0.58 (0.36-0.92) vs. 0.67 (0.55-0.82); P_interaction = 0.56] [21]. Early signs of worsening heart failure, such as edema or new diuretic use, predicted higher events, but empagliflozin softened these risks [20].

Altogether, EMPA-REG OUTCOME established empagliflozin (10 or 25 mg) as a reliable agent for cutting cardiovascular death and heart-failure hospitalizations in people with or without pre-existing heart failure or atherosclerotic disease [19-22].

In the EMPA-RESPONSE-AHF pilot trial, which enrolled patients with acute heart failure irrespective of diabetes status, empagliflozin 10 mg daily for 30 days significantly reduced the combined outcome of in- hospital worsening heart failure, rehospitalization for heart failure, or death at 60 days (10% vs. 33%; $P = 0.014$) [23]. Cumulative urine output by day 4 was also markedly higher with empagliflozin (difference 3449 mL; $P < 0.01$), pointing to improved diuretic responsiveness. These results suggest that starting empagliflozin early in acute heart failure is feasible and potentially beneficial, pending confirmation from larger trials [23].

In the EMPEROR-Reduced trial of 3730 patients with heart failure with reduced ejection fraction (HFrEF), the main endpoint of cardiovascular death or heart-failure hospitalization occurred significantly less often in the empagliflozin group (19.4% vs. 24.7%; HR 0.75, 95% CI 0.65-0.86, $P < 0.001$). Heart-failure hospitalization alone also decreased

(13.2% vs. 18.3%; HR 0.69, 95% CI 0.59-0.81) [24]. Overall, empagliflozin cut the composite risk by 24 percent (HR 0.76, 95% CI 0.67-0.87, P < 0.0001).

Further analyses showed fewer total heart-failure admissions (HR 0.70, 95% CI 0.58-0.85, P = 0.0003), fewer cardiovascular hospitalizations (HR 0.78, 95% CI 0.67-0.91, P < 0.0001), and reduced all-cause hospitalizations (HR 0.85, 95% CI 0.75-0.95, P = 0.007). Emergency or urgent visits for worsening heart failure dropped by 34 percent (HR 0.66, 95% CI 0.53-0.83, P = 0.0004), and the total number of such visits fell by 37 percent (HR 0.63, 95% CI 0.49-0.83, P = 0.0004) [25].

Table 3 Hospitalization compared between two groups

Study	Population	Outcome	Empagliflozin Result	Comparator	Effect Size
EMPA-REG OUTCOME [19]	T2DM + established ASCVD	CV death or hHF	5.70%	8.50%	HR 0.66 (95% CI 0.55–0.79), P<0.001
	Subgroup: HF or HF risk (10.1%)	hHF or death due to HF	2.80%	4.50%	HR 0.61 (95% CI 0.47–0.79), P<0.001
HF-risk categories	Low/avg, high, very high	CV death + hHF	HRs: 0.71, 0.52, 0.55; very high: 0.67	—	Significant benefit across all categories
Prior MI/stroke subgroup	T2DM + prior MI/stroke	hHF	9.40%	14.50%	—
AF subgroup	With AF	CV death + hHF	—	—	HR 0.58 vs 0.67 (P_interaction=0.56)
EMPA-RESPONSE- AHF [23]	Acute HF (DM & non- DM)	Worsening HF/rehospitalization/death at 60 d	10%	33%	P=0.014
	Acute HF	Cumulative urine output (day 4)	increase in 3449 mL	—	P<0.01
EMPEROR-Reduced [22]	HFrEF (n=3730)	CV death + hHF	19.40%	24.70%	HR 0.75 (95% CI 0.65–0.86), P<0.001
	HFrEF	hHF alone	13.20%	18.30%	HR 0.69 (95% CI 0.59–0.81)
	Total HF hospitalizations	—	—	—	HR 0.70 (95% CI 0.58–0.85)
	Urgent HF visits	—	—	—	HR 0.66 (first), HR 0.63 (total)
Sacubitril/valsartan subgroup	HFrEF +/– ARNI	CV death + hHF	HR 0.64 vs 0.77	—	p_interaction=0.31

HF - Heart failure; hHF - Hospitalized heart failure; HFrEF - Heart failure with reduced ejection fraction T2DM - Type 2 diabetes mellitus; MI - Myocardial infarction AF - Atrial fibrillation; HR - Hazard ratio CV - Cardiovascular

Patients taking empagliflozin needed fewer increases in diuretic doses (297 vs. 414) and had fewer visits tied to diuretic escalation (380 vs. 564). Meanwhile, visits associated with reducing diuretic doses were more common in the empagliflozin arm (334 vs. 291; 281 vs. 246 patients) [25].

Crucially, empagliflozin lowered the risk of cardiovascular death or heart-failure hospitalization regardless of whether patients were also receiving sacubitril/valsartan. Hazard ratios were 0.64 (95% CI 0.45-0.89, P = 0.009) with sacubitril/valsartan and 0.77 (95% CI 0.66-0.90, P = 0.0008) without it (interaction P = 0.31) [26].

2.7. Change in KCCQ score influenced by empagliflozin

In EMPEROR-Preserved, empagliflozin's ability to reduce cardiovascular death or heart-failure hospitalization did not vary across baseline tertiles of the KCCQ Clinical Summary Score (CSS): HR 0.83 (95% CI 0.69-1.00), 0.70 (0.55-0.88), and 0.82 (0.62-1.08) for <62.5, 62.5-83.3, and ≥83.3, respectively (P for trend = 0.77). It also showed similar consistency for total HF hospitalizations. Empagliflozin improved KCCQ-CSS relative to placebo at 12, 32, and 52 weeks by +1.03, +1.24, and +1.50 points (all P < 0.01) [27].

In the EMPULSE trial (n = 530), baseline KCCQ-CSS averaged 40.8 ± 24.0 [Table 4]. Empagliflozin delivered greater overall clinical benefit across all tertiles of baseline functional status (win ratios 1.49 [1.01-2.20], 1.37 [0.94-1.99], and 1.48 [1.00-2.20]; interaction P = 0.94). Symptomatic and quality-of-life improvements emerged by day 15 and continued through day 90 [28].

Table 4 Changes in KCCQ score

Study	Score Measure	Empagliflozin	Comparator	Effect Size
EMPEROR-Preserved [27]	KCCQ-CSS	+1.03, +1.24, +1.50 at 12/32/52 wks	—	P<0.01
	≥5-point improvement	OR 1.23	—	—
	Avoiding ≥5-point deterioration	OR 0.85	—	—
EMPULSE [28]	KCCQ scores at 90 days	+4.40 to +4.85	—	All P≤0.05
EMPATROPISM [29]	KCCQ change	22	2	Large KCCQ benefit

KCCQ - Kansas City Cardiomyopathy Questionnaire

In the EMPATROPISM trial, empagliflozin created a marked improvement of 22 points (on average) in KCCQ compared with only 2 a point increase in the placebo group. A higher proportion of patients on empagliflozin achieved improvements, with the greatest benefit observed in those starting with the lowest baseline KCCQ scores [29].

2.8. Changes brought to the renal and systemic metabolic parameters by empagliflozin

Empagliflozin shifts several renal stress pathways back toward normal, especially in diabetic models that love going haywire. In Akita/+ mice, the G1-arrest markers p21 and p27, along with the stress protein HO-1, were all elevated compared with Wilms tumor (WT) kidneys. Empagliflozin brought these levels down, though not perfectly to baseline, and-sensibly-it didn't suppress them in WT animals where nothing needed fixing [30].

Empagliflozin also improved broader renal injury markers. It lowered serum creatinine and urea, reduced the kidney weight-to-tibia length ratio, minimized tubular damage, blunted renal pro-inflammatory cytokine expression, and cut down apoptosis in damaged kidneys. It increased phosphorylation of GSK-3β, and artificial inhibition of this kinase reproduced the same effects, suggesting that modulation of GSK-3β is one of the key mechanisms behind its renal protection [31].

In diabetic kidneys treated for four weeks, empagliflozin improved hyperglycemia and HbA1c and reduced oxidative-stress markers such as dvanced Glycation End-products (AGEs), its receptors, 8- hydroxydeoxyguanosine, and the macrophage marker F4/80. It also suppressed the usual inflammatory and fibrotic gene upregulation seen in diabetic nephropathy, including MCP-1, ICAM-1, PAI-1, TGF-β, and CTGF. Preventing glucose overload in proximal tubular cells appears to be the central reason for this protective profile [32].

2.9. Incidence of adverse events in empagliflozin and comparison with other SGLT2i

Across human studies, empagliflozin has shown the kind of tolerability profile that makes regulators sleep well at night. A systematic review of ten trials with 6,203 participants showed HbA1c reductions of −0.62 percent (10 mg) and −0.66 percent (25 mg), with the higher dose performing similarly to metformin or sitagliptin. It consistently reduced weight and mildly improved blood pressure. Hypoglycemia rates didn't differ from placebo, but genital tract infections were predictably more common, which is the classic SGLT2i tax everyone already knows about [33].

A larger umbrella review across 31 systematic reviews and 48 different adverse events showed that only 17 percent of all point estimates reached statistical significance. Genital infections remained the most consistent safety signal across comparisons with placebo and active drugs. A small uptick in urinary tract infection (UTI) risk versus dapagliflozin appeared, but only a tiny fraction of comparisons showed significance, so it's hardly catastrophic [34].

Table 5 Adverse effects of empagliflozin [34]

Category	Finding	Effect Size
Hypoglycemia	No increase vs placebo	OR 1.10 (95% CI 0.87–1.39)
Genital infections	Increased	OR 3.31 (95% CI 1.55–7.09)
UTI	Slightly higher vs dapagliflozin	Only 4% significant
Renal protection	Lesser renal composite events	6/9 point estimates
Cancer signals	Rare: bladder/GI in some analyses	Low evidence
Weight loss	−1.84 kg	—
HbA1c reduction	−0.62% (10 mg), −0.66% (25 mg)	—

UTI - Urinary tract infection

Empagliflozin showed a higher incidence of hypoglycemia versus canagliflozin in some analyses but a lower risk relative to placebo in others. Empagliflozin also demonstrated a significant reduction in acute renal injury or other renal impairment compared with placebo and active comparators [34].

Increased rates of pollakiuria, polydipsia, and mild elevations in serum magnesium and sodium were reported in empagliflozin [34]. A potential association with bladder cancer was identified in two of eight point estimates, and one network meta-analysis indicated a possible increase in gastrointestinal malignancy compared with canagliflozin [34].

2.10. Risk of bias assessment

The risk of bias for the included randomized controlled trials was evaluated using the Cochrane Risk of Bias

2.0 tool across its five domains. All these studies demonstrated a low risk of bias, regarding the randomization process, allocation concealment, and handling of missing outcome data.

3. Conclusions

Empagliflozin demonstrates multifaceted cardioprotective effects that span molecular regulation, structural remodeling, ventricular function, renal physiology, and clinical outcomes. By targeting central pathways involved in inflammation, oxidative stress, mitochondrial dysfunction, fibrosis, and neurohormonal activation, empagliflozin provides benefits that align closely with improvements observed in clinical trials across the spectrum of HF phenotypes.

This systematic review shows that the alignment between preclinical and clinical data is striking: molecular and structural improvements consistently translate into reductions in hospitalizations, cardiovascular death, and symptom burden. Given its safety, affordability, and applicability to both diabetic and non- diabetic patients, empagliflozin should be regarded as a foundational pillar of HF management. Future research should focus on long-term remodeling dynamics, optimal timing of initiation in acute HF, and potential synergistic mechanisms with other guideline-directed therapies.

Compliance with ethical standards

Disclosure of conflict of interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

- Concept and design: M.S.Govind Krishna, Sahasyaa Adalarasan, Yogesh S, Hariharan C
- Acquisition, analysis, or interpretation of data: M.S.Govind Krishna, Sahasyaa Adalarasan, Yogesh S, Hariharan C
- Drafting of the manuscript: M.S.Govind Krishna, Sahasyaa Adalarasan, Yogesh S, Hariharan C
- Critical review of the manuscript for important intellectual content: M.S.Govind Krishna, Sahasyaa
- Adalarasan, Yogesh S, Hariharan C
- **Supervision:** M.S.Govind Krishna, Sahasyaa Adalarasan, Yogesh S

References

[1] Bernatova I, Liskova S, Bartekova M: Hypertension and cardiovascular diseases: from etiopathogenesis to potential therapeutic targets. International Journal of Molecular Sciences. 2022, 13:7742. 10.3390/ijms23147742

[2] Savarese G, Lund LH: Global public health burden of heart failure. Cardiac failure review . 2017, 2016:25-2. 10.15420/cfr.2016:25:2

[3] Palmiero G, Cesaro A, Vetrano E: Impact of SGLT2 inhibitors on heart failure: from pathophysiology to clinical effects. International Journal of Molecular Sciences. 2021, 30:5863. 10.3390/ijms22115863

[4] Grempler R, Thomas L, Eckhardt M: Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-

[5] 2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. Diabetes, Obesity and Metabolism. 2012, 14:83-90. 10.1111/j.1463-1326.2011.01517.x

[6] Page MJ, McKenzie JE, Bossuyt PM: The PRISMA. 20202021, 29:372. 10.1016/j.jclinepi.2021.02.003

[7] Corbett MS, Higgins JP, Woolacott NF: Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. Research Synthesis Methods. 2014, 5:79-85. 10.1002/jrsm.1090

[8] Shao Q, Meng L, Lee S: Empagliflozin, a sodium glucose co-transporter-2 inhibitor, alleviates atrial remodeling and improves mitochondrial function in high-fat diet/streptozotocin-induced diabetic rats. Cardiovascular diabetology. 2019, 28:165. 10.1186/s12933-019-0964-4

[9] Yang CC, Chen YT, Wallace CG: Early administration of empagliflozin preserved heart function in cardiorenal syndrome in rat. Biomedicine & Pharmacotherapy. 20191, 109:658-70. 10.1016/j.biopha.2018.10.095

[10] Wang Z, Liu Q, Wang X: Empagliflozin improves cardiac function in rats with chronic heart failure . Naunyn-Schmiedeberg's Archives of Pharmacology. 2024, 397:1037-44. 10.1007/s00210-023-02655-7

[11] Lee TI, Chen YC, Lin YK: Empagliflozin attenuates myocardial sodium and calcium dysregulation and reverses cardiac remodeling in streptozotocin-induced diabetic rats. International journal of molecular sciences. 2019, 4:1680. 10.3390/ijms20071680

[12] Januzzi Jr JL, Zannad F, Anker SD: Prognostic importance of NT-proBNP and effect of empagliflozin in the EMPEROR-reduced trial. Journal of the American College of Cardiology. 2021, 28:1321-32. 10.1016/j.jacc.2021.07.046

[13] Lee HC, Shiou YL, Jhuo SJ: The sodium-glucose co-transporter 2 inhibitor empagliflozin attenuates cardiac fibrosis and improves ventricular hemodynamics in hypertensive heart failure rats. Cardiovascular diabetology. 20191, 18:45. 10.1186/s12933-019-0849-6

[14] Seefeldt JM, Lassen TR, Hjortbak MV: Cardioprotective effects of empagliflozin after ischemia and reperfusion in rats. Scientific Reports. 2021, 5:9544. 10.1038/s41598-021-89149-9

[15] Lee MM, Brooksbank KJ, Wetherall K: Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). Circulation. 2021, 9:516-25. 10.1161/circulationaha.120.052186

[16] Butler J, Packer M, Filippatos G: Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. European Heart Journal. 20221, 43:416-24. 10.1093/eurheartj/ehab798

[17] Park SH, Farooq MA, Gaertner S: Empagliflozin improved systolic blood pressure, endothelial dysfunction and heart remodeling in the metabolic syndrome ZSF1 rat. Cardiovascular diabetology. 2020, 18:19. 10.1186/s12933-020-00997-7

[18] Fitchett D, Butler J, van de Borne P: Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. Eur Heart J. 2018, 39:363-70. 10.1093/eurheartj/ehx511

[19] Zinman B, Wanner C, Lachin JM: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes . N Engl J Med. 2015, 373:2117-28. 10.1056/nejmoa1504720

[20] Fitchett D, Zinman B, Wanner C: Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME® trial. Eur Heart J. 2016, 37:1526-34. 10.1093/eurheartj/ehv728

[21] Fitchett D, Inzucchi SE, Cannon CP: Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the EMPA-REG OUTCOME trial. Circulation. 2019, 139:1384-

[22] 95. 10.1161/circulationaha.118.037778

[23] Böhm M, Slawik J, Brueckmann M: Efficacy of empagliflozin on heart failure and renal outcomes in patients with atrial fibrillation: Data from the EMPA-REG. OUTCOME trial Eur J Heart Fail. 2020, 22:126-35. 10.1002/ejhf.1663

[24] Packer M, Butler J, Filippatos GS: 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, 21:1270-8. 10.1002/ejhf.1536

[25] Damman K, Beusekamp JC, Boorsma EM: Randomized double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail. 2020, 22:713-22. 10.1002/ejhf.1713

[26] Kumbhani DJ, Bhatt DL: Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction - EMPEROR-Reduced Available from https://www.acc.org/sitecore/content/Sites/ACC/Home/Latest-in-Cardiology/Clinical-Trials/2020/08/28/16/12/EMPEROR-Reduced#references-for-article.

[27] Packer M, Anker SD, Butler J: Effect of Empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: The EMPEROR-reduced trial. Circulation. 2021, 143:326-36. 10.1161/circulationaha.120.051783

[28] Packer M, Anker SD, Butler J: Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: The EMPEROR-Reduced trial. Eur Heart J. 2021, 42:671-80. 10.1093/eurheartj/ehaa968

[29] Butler J, Filippatos G, Jamal Siddiqi T: Empagliflozin, health status, and quality of life in patients with heart failure and preserved ejection fraction: the EMPEROR-Preserved trial. Circulation. 2022, 18:184-93. 10.1161/circulationaha.121.057812

[30] Kosiborod MN, Angermann CE, Collins SP: Effects of empagliflozin on symptoms, physical limitations, and quality of life in patients hospitalized for acute heart failure: results from the EMPULSE trial. Circulation. 2022, 26:279-88. 10.1161/circulationaha.122.059725

[31] Requena-Ibáñez JA, Santos-Gallego CG, Rodriguez-Cordero A: Empagliflozin improves quality of life in nondiabetic HFrEF patients. Sub-analysis of the EMPATROPISM trial. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2022, 1:102417-10. 10.1016/j.dsx.2022.102417

[32] Vallon V, Gerasimova M, Rose MA: SGLT2 inhibitor empagliflozin reduces renal growth and albuminuria in proportion to hyperglycemia and prevents glomerular hyperfiltration in diabetic Akita mice. American Journal of Physiology-Renal Physiology. 2014, 15:194-204. 10.1152/ajprenal.00520.2013

[33] Wang Q, Ju F, Li J: Empagliflozin protects against renal ischemia/reperfusion injury in mice . Scientific reports. 2022, 11:19323. 10.1038/s41598-022-24103-x

[34] Ojima A, Matsui T, Nishino Y: Empagliflozin, an inhibitor of sodium-glucose cotransporter 2 exerts anti-inflammatory and antifibrotic effects on experimental diabetic nephropathy partly by suppressing AGEs-receptor axis. Hormone and Metabolic Research. 2015, 47:686-92. 10.1055/s-0034-1395609

[35] Liakos A, Karagiannis T, Athanasiadou E: Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2014, 16:984-93. 10.1111/dom.12307

[36] Pelletier R, Ng K, Alkabbani W: Adverse events associated with sodium glucose co-transporter 2 inhibitors: an overview of quantitative systematic reviews. Therapeutic Advances in Drug Safety. 2021, 12:2042098621989134. 10.1177/2042098621989134