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THE EFFICACY OF SGLT2 (sodium–glucose cotransporter 2) INHIBITORS IN THE TREATMENT OF HEART FAILURE

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Background

Heart failure (HF (heart failure)) continues to be an important cause of hospitalization, disability, and cardiovascular mortality. Sodium–glucose cotransporter 2 (SGLT2) inhibitors, initially developed as glucose-lowering agents, are now regarded as disease-modifying treatment across the spectrum of left ventricular ejection fraction (LVEF (left ventricular ejection fraction)). Objective: To review the mechanisms of action, therapeutic efficacy, cardiovascular and kidney outcomes, safety profile, and contemporary clinical role of SGLT2 inhibitors in heart failure. Methods: A narrative, non-systematic synthesis of pivotal randomized trials including DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, and EMPULSE, together with contemporary ESC (European Society of Cardiology) guidance and recent scientific statements. Results: In HFrEF (heart failure with reduced ejection fraction), dapagliflozin and empagliflozin lowered the risk of worsening HF or cardiovascular death by approximately one quarter in pivotal trials. In HF with LVEF >40%, empagliflozin in EMPEROR-Preserved reduced cardiovascular death or HF hospitalization (HR (hazard ratio) 0.79), while dapagliflozin in DELIVER reduced cardiovascular death or worsening HF (HR 0.82). The observed benefits were largely unrelated to the presence or absence of diabetes and were also associated with fewer HF hospitalizations and favorable renal effects. Conclusions: Dapagliflozin and empagliflozin represent effective foundational treatments for HF across the LVEF spectrum. Their clearest and most reproducible benefit is prevention of worsening HF and hospitalization, with additional cardiorenal advantages and a generally favorable safety profile.

Keywords: SGLT2 inhibitors; heart failure; dapagliflozin; empagliflozin; HFrEF; HFmrEF (heart failure with mildly reduced ejection fraction); HFpEF (heart failure with preserved ejection fraction); cardiovascular outcomes; hospitalization.

Introduction

Heart failure is a clinical syndrome arising from structural or functional cardiac abnormalities that lead to elevated intracardiac pressures, inadequate cardiac output, or both. Despite major advances in pharmacological and device therapy, patients with HF

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remain at risk of recurrent hospitalization, impaired quality of life, progressive renal dysfunction, and premature death. This burden is amplified because HF commonly coexists with chronic kidney disease, type 2 diabetes mellitus, obesity, hypertension, and atherosclerotic cardiovascular disease.

SGLT2 inhibitors were originally developed as glucose-lowering agents because blockade of sodium–glucose cotransporter 2 in the proximal renal tubule increases urinary glucose and sodium excretion. Cardiovascular outcome trials in diabetes subsequently revealed a rapid and reproducible reduction in HF hospitalization. These findings led to dedicated HF trials in patients both with and without diabetes and eventually expanded the therapeutic role of this drug class.

The most extensive dedicated HF evidence is available for dapagliflozin and empagliflozin. Their clinical effects cannot be attributed to glucose lowering alone. Natriuresis, osmotic diuresis, improved renal hemodynamics, reduction of interstitial congestion, changes in myocardial energetics, lower inflammatory signaling, and favorable effects on cardiorenal interactions have each been proposed. No individual mechanism appears to explain the entire clinical effect, and the rapid separation of event curves suggests that several mechanisms act together.

Modern HF classification uses LVEF to describe HFrEF, HFmrEF, and HFpEF. Historically, therapies that clearly reduced mortality in HFrEF often failed to show equally convincing benefits in HFpEF. SGLT2 inhibitors are therefore notable because randomized evidence demonstrates clinically important benefit across a broad LVEF range. This review aims to examine the efficacy demonstrated in the major outcome trials, distinguish effects on hospitalization from effects on mortality, discuss renal and safety considerations, and describe the current place of SGLT2 inhibitors in HF treatment.

Materials and Methods

This article is a narrative, non-systematic literature review and does not include a newly recruited patient cohort, original intervention, or pooled patient-level analysis. The main evidence base includes pivotal randomized controlled HF trials of dapagliflozin and empagliflozin, particularly DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, and EMPULSE. Contemporary European Society of Cardiology guidance and recent scientific statements were used to interpret the trial findings within current clinical practice.

The evidence was summarized descriptively with attention to study population, LVEF category, diabetes status, treatment dose, primary composite endpoint, HF hospitalization or worsening HF, cardiovascular death, renal outcomes, symptom burden, and major safety considerations. Trial results were kept within their original populations and follow-up periods. No indirect head-to-head efficacy comparison between dapagliflozin and empagliflozin was undertaken because the studies differed in eligibility criteria, endpoint definitions, background treatment, and duration of follow-up.

The review concentrates on SGLT2 inhibitors with dedicated HF outcome evidence. A reduction in a composite endpoint should not be interpreted as evidence that every

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component was reduced to the same extent. Relative measures such as hazard ratios are discussed together with the clinical context, because relative risk reduction and absolute patient benefit are not interchangeable. The evidence is also separated by HFrEF and HF with mildly reduced or preserved EF where appropriate.

This methodology has several limitations. There was no prespecified database protocol, PRISMA flow diagram, independent duplicate screening, formal risk-of-bias instrument, or meta-analysis performed for this paper. Therefore, this article is best regarded as an explanatory synthesis of major high-quality evidence rather than a systematic review.

Results

Mechanism and early clinical effect. SGLT2 inhibition causes glycosuria and modest natriuresis through inhibition of proximal tubular reabsorption of glucose and sodium. In HF, the therapeutic effect extends well beyond glycemic control. Treatment can reduce congestion without the same neurohormonal activation expected from aggressive conventional diuresis, lower intraglomerular pressure, and preserve kidney function over time. A small early fall in eGFR (estimated glomerular filtration rate) can occur soon after treatment begins, although this hemodynamic response is generally followed by a slower long-term decline in renal function.

HFrEF: DAPA-HF. DAPA-HF demonstrated that dapagliflozin functions as an HF treatment, not simply as an antidiabetic agent. Symptomatic patients with reduced LVEF received dapagliflozin 10 mg once daily or placebo in addition to recommended HF therapy. Dapagliflozin produced a significant reduction in the primary composite of worsening HF or cardiovascular death. Notably, benefit was demonstrated in patients with and without type 2 diabetes, demonstrating that the HF effect is not dependent on hyperglycemia.

HFrEF: EMPEROR-Reduced. EMPEROR-Reduced supplied complementary evidence supporting empagliflozin 10 mg once daily in symptomatic HFrEF. Empagliflozin reduced the composite risk of cardiovascular death or HF hospitalization, with an especially consistent reduction in HF hospitalization. Renal outcomes also favored treatment, supporting the view that SGLT2 inhibition modifies both cardiac and renal trajectories in patients with HF.

HFmrEF and HFpEF: EMPEROR-Preserved. In EMPEROR-Preserved, 5,988 patients with symptomatic HF and LVEF above 40% were randomized to empagliflozin or placebo. Over a median follow-up of 26.2 months, empagliflozin reduced the primary composite of cardiovascular death or HF hospitalization (HR 0.79; 95% CI (confidence interval) 0.69–0.90; P<0.001). Most of the observed effect reflected fewer HF hospitalizations, whereas cardiovascular death considered alone did not decline significantly. Benefit was present regardless of diabetes status.

HFmrEF and HFpEF: DELIVER. DELIVER randomized 6,263 patients with symptomatic HF and LVEF above 40% to dapagliflozin 10 mg once daily or placebo. Dapagliflozin reduced the composite of cardiovascular death or worsening HF (HR 0.82; 95% CI 0.73–0.92; P<0.001). The principal contribution was a reduction in worsening HF.

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The treatment effect remained consistent across the LVEF range studied, in patients with and without diabetes, and in patients whose previously reduced EF had improved.

Across the LVEF spectrum. Collectively, these trials challenged the earlier concept that disease-modifying pharmacotherapy must be sharply separated by EF category. A meta-analysis of EMPEROR-Preserved and DELIVER reported an approximately 20% reduction in cardiovascular death or first HF hospitalization and an approximately 26% reduction in HF hospitalization. The consistency of benefit across LVEF supports the use of dapagliflozin or empagliflozin from reduced through preserved EF, although the magnitude of effect on individual endpoints differs.

Hospitalization versus mortality. The most consistently reproduced clinical effect of SGLT2 inhibitors is prevention of worsening HF and HF hospitalization. This distinction is clinically important. In HFrEF, the overall evidence supports reductions in major HF outcomes and cardiovascular events, whereas in trials enrolling LVEF above 40%, the composite benefit was predominantly driven by fewer worsening-HF events rather than a statistically definitive reduction in cardiovascular death within each individual trial. This difference should be maintained when the evidence is communicated clinically.

Symptoms and functional status. In addition to preventing clinical events, SGLT2 inhibitors can improve patient-reported health status and clinical stability. These outcomes matter because HF treatment is intended not only to prolong life but also to reduce congestion, exercise limitation, and recurrent episodes that impair daily functioning. Improvements are not uniform in every individual, so symptoms, volume status, blood pressure, renal function, and adherence still require follow-up.

Renal effects. HF and CKD (chronic kidney disease) often worsen one another. SGLT2 inhibitors reduce intraglomerular pressure and slow chronic eGFR decline in many cardiorenal populations. The early eGFR dip after treatment initiation should not automatically be regarded as evidence of kidney injury. However, marked volume depletion, hypotension, acute illness, or an unexpectedly large creatinine rise warrants clinical reassessment.

Use in patients without diabetes. Dedicated HF trials are especially informative because they enrolled large numbers of participants without diabetes. Similar relative benefits in diabetic and non-diabetic subgroups demonstrate that dapagliflozin and empagliflozin should not be considered merely glucose-lowering medications when prescribed for HF. Their indication in HF is based on cardiovascular and renal outcome evidence.

Administration. In HF care, dapagliflozin and empagliflozin are commonly prescribed at 10 mg once daily without the dose titration required for several other foundational HF medicines. Their modest blood-pressure effect can be useful in patients in whom hypotension limits intensification of other therapies. However, renal function, volume status, concomitant diuretics, and acute illness should be reviewed at initiation and follow-up.

Safety. Important practical safety concerns include genital mycotic infection and volume depletion. Euglycemic diabetic ketoacidosis is rare but potentially serious,

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especially during prolonged fasting, major surgery, severe acute illness, or marked insulin deficiency. Patients should be given appropriate sick-day and perioperative advice. SGLT2 inhibitors are not conventional loop diuretics, and an excessive reduction in circulating volume can still occur when they are combined with high-dose diuretic therapy.

Trial	Agent	HF population	Main efficacy finding
DAPA-HF	Dapagliflozin 10 mg once daily	Symptomatic HFrEF	Significantly reduced worsening HF or cardiovascular death; benefit was present with and without type 2 diabetes.
EMPEROR-Reduced	Empagliflozin 10 mg once daily	Symptomatic HFrEF	Reduced cardiovascular death or HF hospitalization, with a particularly consistent reduction in HF hospitalization.
EMPEROR-Preserved	Empagliflozin	Symptomatic HF with LVEF >40%	Reduced cardiovascular death or HF hospitalization (HR 0.79; 95% CI 0.69-0.90); effect was driven mainly by fewer HF hospitalizations.
DELIVER	Dapagliflozin 10 mg once daily	Symptomatic HF with LVEF >40%	Reduced cardiovascular death or worsening HF (HR 0.82; 95% CI 0.73-0.92); the principal contribution was fewer worsening-HF events.
EMPEROR-Preserved + DELIVER meta-analysis	Empagliflozin / Dapagliflozin	HF across LVEF >40% populations	Approximately 20% reduction in cardiovascular death or first HF hospitalization and approximately 26% reduction in HF hospitalization.

Table 1. Comparative summary of pivotal SGLT2 inhibitor trials in heart failure

Discussion

The pivotal HF trials establish SGLT2 inhibition as an important disease-modifying strategy. In HFrEF, dapagliflozin and empagliflozin add to established neurohormonal therapies rather than replacing them. Contemporary management therefore considers an SGLT2 inhibitor alongside an ARNI (angiotensin receptor–neprilysin inhibitor) or ACE (angiotensin-converting enzyme) inhibitor/ARB (angiotensin receptor blocker), an evidence-based beta-blocker, and a mineralocorticoid receptor antagonist as foundational therapy when tolerated and appropriate.

The clinical importance of this class is particularly evident in HFmrEF and HFpEF. The 2023 ESC focused update recommends dapagliflozin or empagliflozin in HFmrEF and

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HFpEF to reduce HF hospitalization or cardiovascular death, with a Class I, Level A recommendation. This recommendation reflects the EMPEROR-Preserved and DELIVER evidence and marks a substantial change from earlier treatment eras when convincing disease-modifying options for HFpEF were limited.

Clinical benefit can emerge soon after therapy is started. This characteristic has supported earlier initiation, including during or soon after hospitalization for acute HF once the patient is clinically stable. The EMPULSE program and subsequent scientific statements support the feasibility and benefit of initiating empagliflozin in stabilized hospitalized patients. Early initiation may reduce the period during which a high-risk patient remains without an effective therapy after decompensation.

The relationship between SGLT2 inhibitors and diuretics requires individualized clinical judgment. Both can reduce congestion, but their mechanisms and long-term purposes differ. A patient already receiving a large loop-diuretic dose may develop excessive volume loss after additional natriuretic therapy, particularly if oral intake is poor. Conversely, many stable patients do not require an automatic reduction in loop-diuretic dose. Clinical examination, body weight, blood pressure, renal function, and symptoms should guide adjustment.

Renal function also requires careful interpretation. An early modest eGFR decline reflects altered glomerular hemodynamics and can occur even when long-term renal preservation is favorable. Stopping therapy solely because of a small expected early change may unnecessarily deprive a patient of benefit. At the same time, clinicians must distinguish this expected pattern from true acute kidney injury caused by dehydration, infection, nephrotoxic exposure, or severe hemodynamic compromise.

Diabetes status should not by itself determine whether an otherwise eligible HF patient receives therapy. The dedicated HF trials repeatedly showed benefit in participants without diabetes. In patients with diabetes, however, additional precautions are required because ketoacidosis can occur with only modest blood glucose elevation. Temporary interruption is appropriate in clinical situations associated with prolonged fasting, major surgery, or severe acute illness according to product-specific and local guidance.

The magnitude of benefit needs to be communicated precisely. A hazard ratio around 0.8 does not mean that one fifth of every treated patient's personal risk is eliminated in an absolute sense. Absolute benefit is determined in part by baseline risk. A recently hospitalized patient with advanced HF may avoid more events per number treated than a clinically stable lower-risk patient even if the relative treatment effect is similar. This is one reason recurrent hospitalization history and comorbidity burden remain important.

HFpEF is a heterogeneous syndrome. Patients may have obesity, hypertension, atrial fibrillation, CKD, pulmonary vascular disease, ischemia, or infiltrative disease. SGLT2 inhibitors provide an evidence-based treatment for the HF syndrome, but they do not eliminate the need to identify and manage these underlying contributors. Blood-pressure control, management of atrial fibrillation and ischemia, appropriate diuresis, weight management, exercise and rehabilitation, and treatment of comorbidities remain central.

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A similar principle applies to HFrEF. SGLT2 inhibition should not be considered a replacement for the other foundational therapies with proven outcome benefit. Because dapagliflozin and empagliflozin require no HF dose titration and usually have little effect on blood pressure, they can often be introduced rapidly while other medicines are being initiated and titrated. A sequencing strategy should aim to establish all indicated foundational therapies promptly rather than maximize one drug before starting the next.

Safety monitoring should be tailored to the individual level of risk. Genital fungal infections are generally manageable but should be recognized early. Symptoms of hypotension or dehydration require assessment of fluid intake and concomitant diuretic therapy. Patients with diabetes should know the warning features of ketoacidosis. Routine counseling about hygiene, hydration, acute illness, and medication interruption around selected procedures can reduce avoidable complications.

Current evidence also favors a broader cardiorenal perspective of HF treatment. Kidney dysfunction is not merely a comorbidity but an important determinant of prognosis and medication tolerance. By reducing HF events while slowing renal deterioration in appropriate populations, SGLT2 inhibitors can help preserve the ability to continue other evidence-based therapies. This combined cardiac and renal effect is a major reason the class has become central to contemporary HF care.

However, not every SGLT2 inhibitor can automatically be assumed to have identical supporting evidence for every HF indication. The strongest HF outcome data and guideline positioning are for dapagliflozin and empagliflozin. Drug-specific labeling, kidney-function thresholds, local regulatory approvals, and patient characteristics should therefore be checked rather than extrapolating all findings to the entire pharmacological class.

An additional clinically relevant question concerns treatment after improvement in LVEF. DELIVER included patients whose EF had previously been reduced and later improved above 40%, and the treatment effect remained consistent. This supports the broader concept that improvement in EF does not necessarily indicate resolution of the HF substrate or elimination of future risk. Patients with HF with improved EF generally require continued evidence-based disease-modifying therapy unless a specific clinical reason dictates otherwise.

Acute HF represents a particularly vulnerable phase. The risk of death and rehospitalization is high soon after discharge. Contemporary HF strategies therefore prioritize initiation and rapid optimization of evidence-based therapies before discharge and during close early follow-up. SGLT2 inhibitors are attractive in this setting because of their rapid onset of clinical benefit, fixed dosing, and relatively small blood-pressure effect, provided the patient is hemodynamically stable.

From the patient-centered perspective, fewer HF admissions can be as meaningful as changes in mortality statistics. Hospitalization disrupts independence, accelerates deconditioning, exposes patients to iatrogenic complications, and predicts subsequent events. The consistent reduction in worsening-HF events across trials therefore represents a clinically substantial outcome even where an individual preserved-EF trial does not show a significant reduction in cardiovascular death.

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Several limitations of this review should be acknowledged. It is narrative rather than systematic, focuses mainly on landmark randomized trials and major guidance, and does not provide a formal network comparison of agents. Trial participants may differ from frail, very elderly, severely hypotensive, or highly multimorbid patients seen in routine practice. Long-term adherence, affordability, local access, and implementation can modify the real-world effectiveness of treatment.

Future studies should clarify optimal sequencing with other HF therapies, treatment in underrepresented populations, implementation after acute hospitalization, and mechanisms that account for benefit across such diverse EF phenotypes. Real-world registries can complement randomized trials by describing adherence, safety, renal trajectories, and outcomes in populations excluded or sparsely represented in pivotal studies.

Overall, the evidence is robust but should be interpreted specifically. SGLT2 inhibitors meaningfully reduce worsening HF and HF hospitalization across the EF spectrum, and in HFrEF they form part of foundational outcome-modifying therapy. Their role should be understood as part of comprehensive HF management rather than as isolated glucose-lowering treatment.

Conclusion

Dapagliflozin and empagliflozin have established SGLT2 inhibition as an effective therapeutic strategy for heart failure across the LVEF spectrum. The most consistent benefit is a reduction in worsening HF and HF hospitalization, with important cardiorenal advantages and efficacy that is independent of diabetes status. In HFrEF, SGLT2 inhibitors are foundational therapy in combination with other evidence-based medicines; in HFmrEF and HFpEF, contemporary ESC guidance recommends dapagliflozin or empagliflozin to reduce HF hospitalization or cardiovascular death. Safe prescribing requires attention to volume status, renal function, genital infections, and the uncommon risk of ketoacidosis. Treatment decisions should combine the trial evidence with individual risk, comorbidities, kidney function, background therapy, and patient preferences.

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