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Cardiovascular Mechanisms and Clinical Implications of SGLT2 Inhibitors in Heart Failure: A Narrative Review

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Abstract

This narrative review aims to synthesize contemporary evidence on the cardiorenal mechanisms, clinical efficacy, safety, and practical implementation of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in heart failure (HF). A focused narrative literature search was conducted using PubMed/MEDLINE and major international professional society guideline repositories, primarily covering publications from January 2019 to September 1, 2026. Priority was given to randomized controlled trials, prespecified trial analyses, meta-analyses, human mechanistic studies, and contemporary international clinical practice guidelines. Major randomized controlled trials consistently demonstrated the cardiovascular and renal benefits of SGLT2 inhibition across the HF spectrum, although the magnitude and certainty of renal benefits varied across populations and outcomes. The DAPA-HF and EMPEROR-Reduced trials established reductions in worsening HF events and HF hospitalizations among patients with heart failure with reduced ejection fraction (HFrEF), whereas the EMPEROR-Preserved and DELIVER trials extended these benefits to patients with heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF). The EMPULSE trial supported the initiation of empagliflozin following clinical stabilization during hospitalization for acute HF, while dedicated renal outcome trials demonstrated clinically meaningful kidney protection. Mechanistically, SGLT2 inhibition reduces sodium and glucose reabsorption in the renal proximal tubule, restores tubuloglomerular feedback, lowers intraglomerular pressure, and promotes modest natriuresis and osmotic diuresis. Additional mechanisms involving erythropoiesis, metabolic regulation, mitochondrial function, and anti-inflammatory and antifibrotic effects may contribute to cardiovascular protection, although several pathways remain supported primarily by preclinical and translational evidence rather than definitive human studies. Important safety considerations include genital mycotic infections, volume depletion, and the rare but clinically significant risk of euglycemic diabetic ketoacidosis.

INTRODUCTION

Heart failure (HF) is a heterogeneous clinical syndrome in which cardiac dysfunction, renal impairment, neurohormonal activation, inflammation, and metabolic dysregulation reinforce one another. Although advances in guideline-directed medical therapy (GDMT) have

improved clinical outcomes, substantial residual risks of hospitalization, progressive kidney dysfunction, impaired health status, and mortality remain (Alvi et al., 2026; Krasińska et al., 2026). The emergence of sodium–glucose cotransporter 2 inhibitors (SGLT2i) has transformed this therapeutic landscape. Initially developed to lower plasma glucose levels by increasing urinary glucose excretion, these agents demonstrated unexpectedly substantial and early reductions in HF hospitalization in cardiovascular outcome trials. Subsequent dedicated HF trials demonstrated clinical benefits in patients with and without type 2 diabetes mellitus and across the spectrum of left ventricular ejection fraction (LVEF) (Anker et al., 2021; Bhatt et al., 2021; McMurray et al., 2019; Packer et al., 2020; Peikert et al., 2022; Solomon et al., 2022; Voors et al., 2022).

In contemporary clinical guidelines, dapagliflozin and empagliflozin are established components of therapy for symptomatic heart failure with reduced ejection fraction (HFrEF) and are recommended to reduce HF-related events in patients with heart failure with mildly reduced ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF) (Heidenreich et al., 2022; McDonagh et al., 2023; Ndumele et al., 2026). Their practical advantages include fixed once-daily dosing, no requirement for routine dose titration, minimal direct effects on heart rate, generally modest blood pressure reduction, and compatibility with renin–angiotensin system inhibitors, beta-blockers, and mineralocorticoid receptor antagonists. However, the relative simplicity of prescribing these agents should not obscure important clinical considerations, including volume depletion in susceptible patients, genital mycotic infections, rare cases of euglycemic diabetic ketoacidosis (eDKA), and the need to distinguish an expected initial decline in estimated glomerular filtration rate (eGFR) from true acute kidney injury (AKI).

This narrative review examines the cardiovascular and renal mechanisms that may explain the clinical benefits of SGLT2i, summarizes key evidence of efficacy across HF phenotypes and vulnerable patient populations, and translates these findings into practical principles for treatment initiation and monitoring. It also identifies unresolved questions that remain relevant to future research and real-world clinical implementation. Despite robust evidence from randomized controlled trials supporting the use of SGLT2i in HF, important uncertainties persist regarding the mechanisms underlying their cardiorenal benefits, particularly the relative contributions of renal hemodynamic, metabolic, erythropoietic, anti-inflammatory, and direct myocardial pathways. Furthermore, evidence remains limited in specific populations, including patients receiving dialysis, those experiencing cardiogenic shock, and frail older adults. The clinical importance of this review lies in the need to synthesize evidence from diverse sources and provide practical guidance for integrating SGLT2i into routine clinical practice, particularly given the complexities of managing patients with HF and concomitant renal and metabolic comorbidities. The distinctive contribution of this review is its integration of cardiorenal mechanisms with practical clinical implications, including proposed algorithms for treatment initiation and monitoring that may support clinical decision-making. Accordingly, this review aims to provide a comprehensive synthesis of the cardiovascular mechanisms and clinical implications of SGLT2i in HF, emphasizing evidence from major randomized controlled trials, safety considerations, and practical implementation strategies. By integrating mechanistic insights with clinical evidence, this review seeks to advance the understanding of SGLT2i mechanisms of action while providing clinically relevant recommendations to optimize HF management.Heart failure is a heterogeneous clinical syndrome in which cardiac dysfunction, kidney impairment, neurohormonal activation,

inflammation, and metabolic dysregulation reinforce one another. Although advances in guideline-directed medical therapy (GDMT) have improved outcomes, residual risks of hospitalization, progressive kidney dysfunction, impaired health status, and death remain substantial. The emergence of SGLT2i has changed this therapeutic landscape.

METHOD

Review Design

This study employed a focused narrative review approach to examine the contemporary role of sodium–glucose cotransporter 2 (SGLT2) inhibitors across the spectrum of heart failure and cardiorenal disease. The review integrated evidence from major clinical trials, secondary and prespecified trial analyses, meta-analyses, mechanistic studies, and international clinical practice guidelines. Rather than conducting an exhaustive systematic synthesis, the review critically evaluated and synthesized clinically relevant evidence concerning therapeutic efficacy, underlying mechanisms, patient selection, safety considerations, and the clinical implementation of SGLT2 inhibitor therapy.

Information Sources and Search Strategy

A focused literature search was conducted using PubMed/MEDLINE and major international society guideline repositories. The primary search period covered publications from January 2019 through 1 September 2026, reflecting the period during which SGLT2 inhibitors became increasingly established as cardiorenal therapies beyond their original glucose-lowering indication. Earlier publications were additionally considered when they represented landmark cardiovascular outcome trials, foundational mechanistic studies, or other evidence necessary to contextualize subsequent developments.

Search concepts included combinations of terms related to the intervention, clinical conditions, relevant populations, outcomes, mechanisms, and safety. These included “SGLT2 inhibitor,” “sodium-glucose cotransporter 2 inhibitor,” “dapagliflozin,” “empagliflozin,” “sotagliflozin,” “heart failure,” “heart failure with reduced ejection fraction,” “heart failure with preserved ejection fraction,” “cardiorenal,” “kidney,” “chronic kidney disease,” “acute heart failure,” “hospitalization,” “frailty,” “elderly,” “ketoacidosis,” “safety,” and “mechanism.” Search terms were combined as appropriate to identify literature addressing the major themes of this review.

Guideline repositories and publications from major professional societies were additionally examined to identify contemporary recommendations concerning the use of SGLT2 inhibitors in heart failure, chronic kidney disease, and related cardiorenal conditions.

Evidence Selection and Prioritization

Evidence was selected according to its relevance to the clinical and mechanistic questions addressed in this review. Priority was given to randomized controlled trials, particularly landmark cardiovascular, heart failure, and kidney outcome trials; prespecified and clinically relevant secondary analyses of major trials; meta-analyses of randomized trials; mechanistic studies involving human participants; and contemporary international clinical practice guidelines or consensus documents.

Observational studies and other relevant clinical reports were considered when randomized evidence was limited or when they provided complementary information regarding safety, treatment implementation, or populations underrepresented in randomized trials, including older or frail patients. Preclinical evidence was used selectively when required to

explain proposed biological mechanisms and was distinguished from evidence directly demonstrated in humans.

Studies were considered particularly relevant when they addressed cardiovascular death, heart failure hospitalization or worsening heart failure events, kidney outcomes, changes in symptoms or health status, treatment initiation during or shortly after hospitalization, effects across left ventricular ejection fraction categories, and clinically important adverse events.

Evidence Synthesis

The identified evidence was synthesized narratively and organized according to clinically relevant themes rather than pooled quantitatively. Findings from individual trials were interpreted in the context of the broader evidence base, with emphasis on consistency across studies, clinically relevant differences in study populations and trial design, and the distinction between established clinical effects and proposed biological mechanisms.

Where appropriate, evidence was examined across heart failure phenotypes and clinical settings, including heart failure with reduced, mildly reduced, and preserved ejection fraction, as well as acute or recently hospitalized heart failure. Particular attention was also given to cardiorenal interactions, kidney function, older and frail populations, and practical considerations regarding treatment initiation and safety.

Mechanistic explanations were interpreted according to the level of available evidence. Mechanisms directly demonstrated in human studies were distinguished from hypotheses primarily supported by experimental or translational data. Similarly, conclusions derived from subgroup or secondary analyses were interpreted more cautiously than findings from prespecified primary outcomes of randomized trials.

Methodological Considerations

This review represents a narrative rather than a systematic evidence synthesis. Accordingly, study identification and selection were guided by relevance to the predefined clinical themes and the strength of available evidence rather than by a formally registered systematic-review protocol. No formal risk-of-bias assessment, duplicate independent screening, or quantitative meta-analysis was performed. Consequently, the review does not claim exhaustive capture of all eligible publications, and the possibility of selection bias inherent to narrative reviews should be acknowledged. Nevertheless, emphasis on major randomized trials, meta-analyses, human mechanistic studies, and contemporary international guidelines was intended to provide a balanced and clinically relevant synthesis of the available evidence.

RESULT AND DISCUSSION

Overview of the Evidence Base

The literature search identified a substantial body of randomized and secondary evidence supporting the cardiovascular and renal effects of SGLT2 inhibition across the heart failure spectrum. The principal evidence base was derived from large randomized controlled trials evaluating dapagliflozin and empagliflozin in chronic heart failure, complemented by trials of treatment initiation during or shortly after hospitalization for worsening heart failure and by dedicated chronic kidney disease outcome trials. Relevant meta-analyses, prespecified subgroup analyses, mechanistic studies, and contemporary clinical practice guidelines were used to contextualize these findings.

Across the major randomized trials, the clinical effects of SGLT2 inhibitors were generally consistent across diabetes status and extended across a broad range of left ventricular

ejection fraction (LVEF). In HFrEF, the strongest evidence was provided by DAPA-HF and EMPEROR-Reduced, whereas EMPEROR-Preserved and DELIVER extended the evidence to patients with mildly reduced or preserved LVEF. EMPULSE and SOLOIST-WHF provided complementary evidence regarding initiation during or shortly after an episode of worsening heart failure. Dedicated kidney outcome trials, particularly DAPA-CKD and EMPA-KIDNEY, further demonstrated that the therapeutic effects of SGLT2 inhibition extend beyond heart failure outcomes to clinically important kidney endpoints (Group, 2023; Heerspink et al., 2020).

Heart failure with reduced ejection fraction

DAPA-HF randomized 4,744 patients with symptomatic HFrEF (LVEF ≤40%) to dapagliflozin or placebo on top of recommended therapy. Dapagliflozin reduced the primary composite of worsening HF or cardiovascular death by 26% (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.65–0.85), with similar benefit in patients with and without diabetes.5 EMPEROR-Reduced enrolled 3,730 patients with HFrEF and showed that empagliflozin reduced cardiovascular death or HF hospitalization by 25% (HR 0.75, 95% CI 0.65–0.86), lowered total HF hospitalizations, and slowed eGFR decline.4 A pooled analysis of both trials supported consistent reductions in HF hospitalization and favorable renal outcomes (Zannad et al., 2020).

These findings established SGLT2i as one of the four foundational drug classes for HFrEF. Because benefit appears within weeks and the class has minimal effect on blood pressure in most patients, therapy should generally be introduced early rather than deferred until full titration of other agents. Sequencing should remain individualized according to blood pressure, congestion, kidney function, potassium, and access, but unnecessary therapeutic inertia forfeits early preventable events (Greene et al., 2021) .

Mildly reduced and preserved ejection fraction

EMPEROR-Preserved randomized 5,988 patients with symptomatic HF and LVEF >40%. Empagliflozin reduced the composite of cardiovascular death or HF hospitalization by 21% (HR 0.79, 95% CI 0.69–0.90), principally through fewer HF hospitalizations.6 DELIVER enrolled 6,263 patients with LVEF >40%, including individuals with improved LVEF, and showed an 18% reduction in worsening HF or cardiovascular death with dapagliflozin (HR 0.82, 95% CI 0.73–0.92).3 A prespecified meta-analysis of DELIVER and EMPEROR-Preserved yielded an HR of 0.80 for cardiovascular death or first HF hospitalization and supported benefit across the LVEF continuum.9

The magnitude of benefit in HFpEF is driven mainly by fewer worsening-HF events rather than a clearly established reduction in cardiovascular mortality in each individual trial. This distinction should be communicated accurately. Nevertheless, prevention of recurrent hospitalization and deterioration in health status is clinically meaningful in a population historically lacking broadly effective disease-modifying therapy. SGLT2i do not substitute for careful phenotyping or management of obesity, hypertension, atrial fibrillation, ischemia, valvular disease, amyloidosis, sleep-disordered breathing, and congestion (Cox et al., 2021; Damman et al., 2020; Fonseca et al., 2025).

Hospitalized and recently worsening heart failure

Hospitalization is a high-risk transition and a key opportunity to initiate disease-modifying therapy. In EMPULSE, 530 patients hospitalized for acute HF were randomized after clinical stabilization at a median of three days. Empagliflozin produced greater 90-day clinical benefit using a hierarchical composite of all-cause death, HF events, and health status,

with a win ratio of 1.36 (95% CI 1.09–1.68). Benefits occurred regardless of LVEF or diabetes, and adverse events were acceptable.7 A decongestion analysis suggested greater weight loss and diuretic efficiency.19

SOLOIST-WHF, conducted in patients with type 2 diabetes and recent worsening HF, showed that sotagliflozin initiated before or shortly after discharge reduced the total number of cardiovascular deaths and HF hospitalizations or urgent visits.8 Smaller acute-HF studies and DICTATE-AHF add evidence that early initiation can augment decongestion, although they do not establish SGLT2i as a replacement for intravenous loop diuretics. In practice, initiation is reasonable once the patient is hemodynamically stable, eating and drinking, not in shock, and without active ketoacidosis or rapidly progressive kidney injury.10,20,21

Summary of Landmark Randomized Evidence

The major randomized trials identified in this narrative synthesis demonstrate complementary cardiovascular and renal effects of SGLT2 inhibition across different clinical settings. Their key characteristics and principal findings are summarized in Table 1.

Table 1. Landmark randomized evidence for SGLT2 inhibition in heart failure and chronic kidney disease.

Trial	Population	Intervention and primary endpoint	Main result	Clinical interpretation
DAPA-HF [5]	HFrEF; n=4,744	Dapagliflozin; worsening HF or CV death	HR 0.74 (95% CI 0.65–0.85)	Benefit with or without diabetes
EMPEROR-Reduced [4]	HFrEF; n=3,730	Empagliflozin; CV death or HF hospitalization	HR 0.75 (95% CI 0.65–0.86)	Fewer HF events and slower eGFR decline
EMPEROR-Preserved [6]	LVEF >40%; n=5,988	Empagliflozin; CV death or HF hospitalization	HR 0.79 (95% CI 0.69–0.90)	Benefit mainly through fewer HF hospitalizations
DELIVER [3]	LVEF >40%; n=6,263	Dapagliflozin; worsening HF or CV death	HR 0.82 (95% CI 0.73–0.92)	Consistent across EF and glycemic subgroups
EMPULSE [7]	Stabilized acute HF; n=530	Empagliflozin; hierarchical 90-day clinical benefit	Win ratio 1.36 (95% CI 1.09–1.68)	Supports in-hospital initiation after stabilization
SOLOIST-WHF [8]	T2D and recent worsening HF; n=1,222	Sotagliflozin; total CV death and HF events	HR 0.67 (95% CI 0.52–0.85)	Supports initiation around discharge in T2D
DAPA-CKD [13]	CKD; n=4,304	Dapagliflozin; kidney/CV composite	HR 0.61 (95% CI 0.51–0.72)	Kidney protection with or without diabetes
EMPA-KIDNEY [14]	CKD; n=6,609	Empagliflozin; kidney progression or CV death	HR 0.72 (95% CI 0.64–0.82)	Broad CKD benefit down to eGFR 20

From Proximal Tubule Inhibition to Multiorgan Protection

Renal hemodynamics and tubuloglomerular feedback

SGLT2 is expressed predominantly in the S1 and S2 segments of the proximal tubule and normally reabsorbs most filtered glucose together with sodium. In diabetes, hyperfiltration and

increased proximal sodium–glucose reabsorption reduce sodium chloride delivery to the macula densa. SGLT2 inhibition increases distal sodium delivery, enhances adenosine-mediated tubuloglomerular feedback, and reduces intraglomerular pressure. Depending on the underlying hemodynamic state, this response may involve afferent vasoconstriction and changes in efferent tone. Clinically, it often appears as a small, earlyeGFR decline followed by a slower chronic rate of kidney-function loss.

The early eGFR change is therefore best interpreted in context. In a clinically stable patient without marked hypotension, severe congestion, nephrotoxin exposure, or progressive creatinine elevation, a modest dip can be compatible with the intended hemodynamic effect. By contrast, a large or continuing decline requires evaluation for hypovolemia, sepsis, urinary obstruction, nephrotoxic medication, or another cause of acute kidney injury. This distinction prevents premature discontinuation of a therapy that provides long-term cardiorenal protection.

Natriuresis, osmotic diuresis, and interstitial decongestion

By limiting proximal sodium and glucose reabsorption, SGLT2i induce glycosuria, osmotic diuresis, and a modest natriuretic effect. The resulting reduction in plasma and interstitial volume can lower ventricular preload and filling pressures without the intense neurohormonal activation associated with rapid high-dose loop diuresis. SGLT2i are not replacements for loop diuretics in overt pulmonary or systemic congestion; their diuretic effect is smaller and depends on filtered glucose and kidney function. Instead, they complement conventional diuresis and may improve diuretic efficiency in selected patients.19,20,24

Hemoconcentration and increases in hematocrit are not explained solely by volume contraction. SGLT2 inhibition may improve renal cortical oxygenation, suppress hepcidin, and stimulate erythropoietin-mediated erythropoiesis. Mediation analyses from earlier cardiovascular outcome studies suggest that changes in hematocrit may track with cardiovascular benefit, although such analyses cannot establish a single causal pathway.25,26

Myocardial energetics and the fuel-shift hypothesis

The failing myocardium is metabolically inflexible and has impaired capacity to generate adenosine triphosphate. SGLT2i lower the insulin-to-glucagon ratio and promote lipolysis and mild ketogenesis, potentially increasing circulating beta-hydroxybutyrate. Ketone bodies can provide an additional oxidative substrate for the failing heart, and experimental studies demonstrate improved myocardial energetics under selected conditions.[27–29] Nevertheless, the "thrifty substrate" or fuel-shift hypothesis remains one component of a broader network. Human evidence does not justify describing ketone use as the exclusive or definitively dominant mechanism of clinical benefit.

Cellular sodium, mitochondrial function, inflammation, and remodeling

Proposed direct cardiac effects include inhibition of myocardial sodium–hydrogen exchanger activity, lower cytosolic sodium and calcium overload, improved mitochondrial calcium handling, reduced reactive oxygen species, and enhanced autophagy. SGLT2i may also reduce NLRP3 inflammasome activation, endothelial dysfunction, and profibrotic signaling. These effects could improve diastolic relaxation and limit adverse remodeling, particularly in HFpEF, where systemic inflammation, microvascular dysfunction, and myocardial stiffness are prominent. Most direct myocardial mechanisms are supported mainly by preclinical or translational data because cardiomyocytes express little or no SGLT2. They should therefore be framed as biologically plausible contributors rather than proven receptor-level cardiac actions.30–33

Integrated cardiorenal mechanism

The rapid separation of event curves in clinical trials suggests that early hemodynamic and renal effects are important, whereas sustained benefits likely reflect slower changes in kidney preservation, erythropoiesis, metabolism, inflammation, and tissue remodeling. The most defensible model is integrated: proximal tubular inhibition alters sodium and glucose handling; this improves renal autoregulation and volume distribution; systemic consequences reduce cardiac loading conditions and improve oxygen delivery; and parallel cellular adaptations may increase energetic resilience and reduce fibrosis. No single pathway fully accounts for the consistency of benefit across diabetic status and LVEF.

Taken together, the cardiovascular and renal benefits of SGLT2 inhibitors are best understood as the result of interconnected rather than isolated mechanisms. As summarized in Figure 1, proximal tubular SGLT2 inhibition modifies sodium and glucose handling, restores tubuloglomerular feedback, and promotes modest osmotic diuresis and natriuresis. These effects may improve renal hemodynamics and interstitial decongestion, while parallel changes in metabolic, erythropoietic, inflammatory, and fibrotic signaling may enhance myocardial resilience. The convergence of these pathways provides a plausible mechanistic framework for the early reduction in heart failure events and improvement in health status observed in clinical trials.

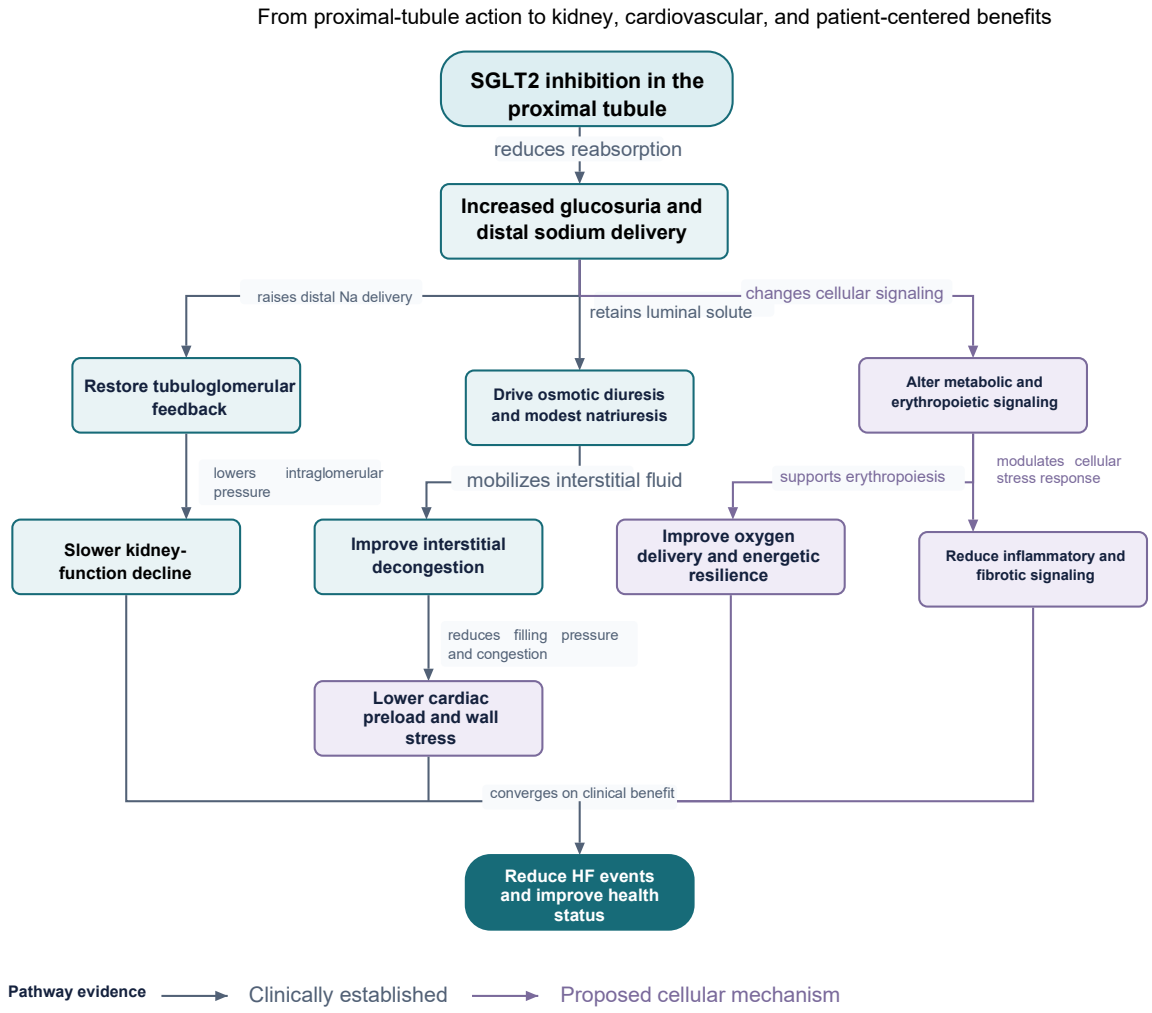


Figure 1. Integrated cardiorenal mechanisms and clinical effects of sodium–glucose cotransporter 2 inhibition in heart failure.

Inhibition of SGLT2 in the proximal tubule increases urinary glucose and sodium delivery, thereby restoring tubuloglomerular feedback and reducing intraglomerular pressure while promoting modest natriuresis and osmotic diuresis. These clinically established renal and hemodynamic effects may slow kidney-function decline, improve interstitial decongestion, and reduce cardiac preload and wall stress. Additional proposed mechanisms include altered metabolic and erythropoietic signaling, improved oxygen delivery and myocardial energetic resilience, and attenuation of inflammatory and fibrotic pathways. Together, these complementary effects may contribute to fewer heart failure events and improved health status. Solid blue-gray pathways represent mechanisms supported by clinical evidence, whereas purple pathways indicate proposed cellular mechanisms. HF, heart failure; Na, sodium; SGLT2, sodium–glucose cotransporter 2.

Special and Vulnerable Populations

Chronic kidney disease

Kidney disease is common in HF and increases the risks of death, hospitalization, hyperkalemia, and treatment underuse. In EMPEROR-Reduced, empagliflozin benefit was consistent in patients with and without CKD and down to an eGFR of 20 mL/min/1.73 m^2; it also slowed chronic eGFR decline.23 DAPA-CKD and EMPA-KIDNEY independently established kidney protection in CKD populations with and without diabetes.13,14 These trials support a cardiorenal approach rather than withholding therapy solely because glucose-lowering efficacy diminishes at low eGFR.

Initiation thresholds should follow the locally approved product label and current guideline, because indications differ by molecule and jurisdiction. Evidence in maintenance dialysis and after kidney transplantation remains limited. During initiation in advanced CKD, clinicians should document baseline creatinine/eGFR, potassium, blood pressure, congestion, and concomitant diuretics; arrange early review when clinical instability is likely; and interpret the initial eGFR trajectory alongside volume status.

Older adults and frailty

Subgroup analyses of DAPA-HF and DELIVER indicate consistent efficacy and acceptable safety in older adults, including those aged 75 years or older.[38,39] Chronological age alone should not exclude treatment. Frailty, however, changes implementation: low oral intake, orthostatic symptoms, urinary incontinence, recurrent genital infection, cognitive impairment, and polypharmacy can increase treatment burden. Baseline functional assessment, medication reconciliation, hygiene counseling, and early follow-up are therefore more informative than age cutoffs. Evidence remains thinner in the very old, nursing-home residents, and patients with severe frailty, so shared decision-making should emphasize goals, competing risks, and feasibility.

Diabetes status and glycemic therapy

HF benefits occur in normoglycemia, prediabetes, and type 2 diabetesHypoglycemia is uncommon when an SGLT2i is used without insulin or an insulin secretagogue. In patients receiving insulin or sulfonylureas, glucose monitoring and selective adjustment of those agents may be necessary, but insulin should not be abruptly or excessively reduced because relative insulin deficiency increases ketoacidosis risk. SGLT2i are not indicated for routine HF treatment in type 1 diabetes because of ketoacidosis risk.[40]

Safety Boundaries and Practical Risk Management

Euglycemic diabetic ketoacidosis

SGLT2i-associated ketoacidosis is uncommon but potentially life-threatening. Because glucosuria lowers plasma glucose, ketoacidosis may occur with glucose below the usual hyperglycemic range. Precipitating factors include prolonged fasting, major surgery, acute infection, dehydration, excessive alcohol intake, ketogenic diets, and abrupt insulin reduction. Symptoms—nausea, vomiting, abdominal pain, malaise, or unexplained tachypnea—should trigger measurement of blood ketones and acid–base status even when capillary glucose is not markedly elevated. Urine glucose reflects pharmacologic exposure but cannot reliably distinguish eDKA from starvation ketosis; diagnosis requires ketonemia and metabolic acidosis in the appropriate clinical context.

Patients should receive written sick-day advice: temporarily stop the SGLT2i during significant vomiting, inability to maintain oral intake, severe acute illness, or dehydration; maintain appropriate hydration and carbohydrate intake; continue insulin unless specifically advised otherwise; and seek urgent assessment when ketoacidosis symptoms occur. For scheduled surgery, commonly used guidance recommends withholding dapagliflozin, empagliflozin, and canagliflozin for at least three days and ertugliflozin for four days, with restart only after clinical stability and adequate oral intake. Local perioperative protocols should prevail.

Genital and urinary infections

Genital mycotic infection is the most consistent class-specific adverse effect and is usually mild and treatable. Risk is higher in individuals with prior infection, poor glycemic control, uncircumcised men, and those unable to maintain perineal hygiene. Counseling about symptoms and hygiene improves early recognition. Routine discontinuation is usually unnecessary after an uncomplicated episode. Randomized trials have not shown a large consistent excess of serious urinary tract infection, but dysuria, fever, flank pain, or systemic illness requires prompt evaluation. Recurrent or severe infection warrants individualized reassessment.

Volume status, hypotension, and concomitant diuretics

Before initiation, clinicians should determine whether the patient is congested, euvolemic, or intravascularly depleted. Routine pre-emptive loop-diuretic reduction is not required for every patient. A modest reduction may be appropriate in a euvolemic patient with low blood pressure, orthostasis, or a history of volume depletion; conversely, a congested patient may benefit from unchanged or intensified loop diuresis with close reassessment. Monitoring should focus on symptoms, weight, blood pressure, renal function when clinically indicated, and the dynamic need for loop diuretics.

Kidney function and acute illness

A modest early eGFR decrease should prompt clinical assessment rather than reflex discontinuation. Temporary interruption is appropriate during shock, severe hypovolemia, active ketoacidosis, prolonged fasting, or critical illness. Routine “renal protection” by stopping therapy for every minor creatinine fluctuation may deprive patients of benefit. The decision should integrate magnitude and trajectory of change, hemodynamics, urine output, nephrotoxin exposure, and congestion.[47]

Practical Integration Into Guideline Directed Therapy

For an eligible ambulatory patient with HF, dapagliflozin 10 mg once daily or empagliflozin 10 mg once daily can usually be started without titration. Baseline assessment

should include indication, eGFR, blood pressure, volume status, diabetes therapy, infection history, pregnancy status where relevant, and factors that predispose to ketoacidosis. The patient should understand expected increased urination, genital symptoms, warning signs of volume depletion or ketoacidosis, and when to pause treatment. Laboratory follow-up can be individualized: early testing is prudent in advanced CKD, recent acute kidney injury, borderline blood pressure, high-dose diuretic use, or frailty, whereas stable lower-risk patients may follow routine HF monitoring.

SGLT2i should be integrated with, not positioned against, other foundational therapies. In HFrEF, simultaneous or rapid-sequence initiation of renin–angiotensin receptor–neprilysin inhibition or an alternative renin–angiotensin system blocker, an evidence-based beta-blocker, a mineralocorticoid receptor antagonist, and an SGLT2i can provide early multidimensional risk reduction. In HFpEF, treatment combines SGLT2 inhibition with meticulous control of congestion and comorbidities. Cost, availability, literacy, and continuity of follow-up are implementation determinants, particularly in resource-variable settings.

The practical use of SGLT2 inhibitors requires more than confirmation of a heart failure indication. Before initiation, clinicians should assess hemodynamic stability, oral intake, volume status, kidney function, and factors that increase the risk of ketoacidosis. Treatment should be accompanied by clear counseling regarding genital infections, volume depletion, sick-day management, and perioperative interruption. As outlined in Figure 3, follow-up should distinguish an expected modest and stable early decline in eGFR from progressive kidney injury or clinical instability requiring temporary treatment interruption.[4,5,12,48,50,51]

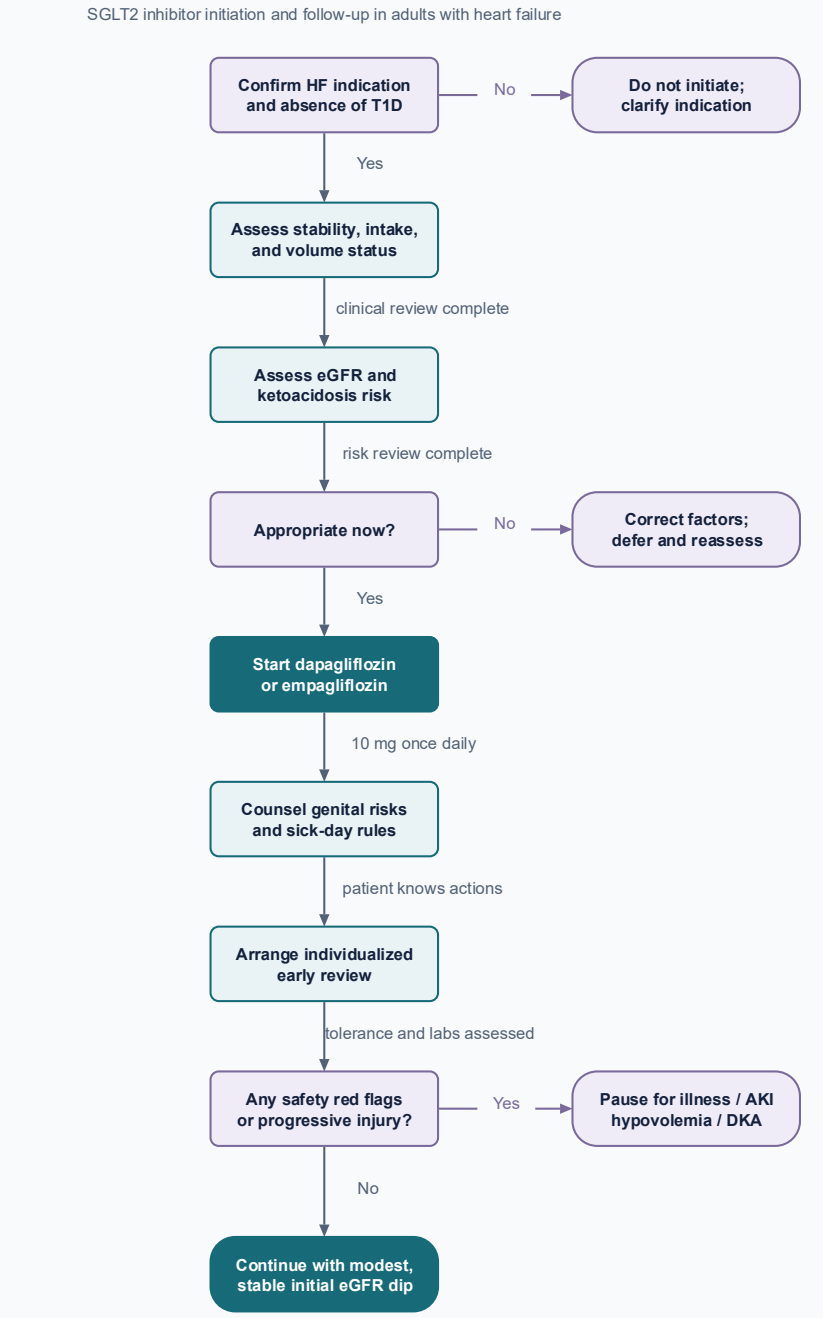


Figure 2. Practical algorithm for initiation and safety monitoring of sodium–glucose cotransporter 2 inhibitors in adults with heart failure.

After confirming an appropriate heart failure indication and excluding type 1 diabetes, treatment readiness should be assessed according to hemodynamic stability, oral intake, volume status, kidney function, and ketoacidosis risk. Dapagliflozin or empagliflozin may generally be initiated at 10 mg once daily without dose titration when no temporary contraindication is present. Patient education should include genital infection risk, maintenance of hydration, sick-day rules, and circumstances requiring temporary treatment interruption. A modest and stable initial decrease in estimated glomerular filtration rate is generally compatible with the expected hemodynamic response and does not independently require discontinuation. Treatment should be paused and the patient evaluated when severe acute illness, marked hypovolemia, progressive kidney injury, or suspected diabetic ketoacidosis occurs. AKI, acute

kidney injury; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HF, heart failure; SGLT2, sodium–glucose cotransporter 2; T1D, type 1 diabetes.4,5,12,48,50,51

Evidence Gaps and Future Directions

Several uncertainties remain. First, the relative contribution of renal hemodynamic, metabolic, erythropoietic, anti-inflammatory, and direct myocardial pathways has not been quantified in humans. Mechanistic studies that incorporate serial imaging, invasive hemodynamics, metabolomics, kidney biomarkers, and mediation analyses could clarify causal pathways. Second, evidence remains limited in patients receiving maintenance dialysis, those with cardiogenic shock, active myocarditis, advanced valvular disease awaiting intervention, and the severely frail or institutionalized elderly. Third, pragmatic studies are needed to determine how best to sustain adherence, coordinate sick-day rules, and prevent therapeutic discontinuation after minor adverse events.

Future research should also address sex-specific effects, regional differences, affordability, combination therapy in cardiovascular–kidney–metabolic disease, and implementation in low- and middle-income health systems. Longer follow-up will be important to establish whether early reductions in HF events translate into durable effects on myocardial remodeling, disability, kidney replacement therapy, and survival. The 2026 cardiovascular–kidney–metabolic guideline framework reinforces the need to treat HF, CKD, obesity, and diabetes as interacting conditions rather than isolated diagnoses.12

CONCLUSION

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have transformed heart failure (HF) management by reducing worsening HF events across the spectrum of left ventricular ejection fraction (LVEF), regardless of diabetes status, while providing renal protection in a broad range of patients. Their therapeutic benefits appear to result from integrated cardiorenal mechanisms originating in the renal proximal tubule and extending to volume regulation, renal hemodynamics, erythropoiesis, metabolic regulation, inflammation, and tissue remodeling. The strongest clinical evidence supports reductions in HF-related events; however, the precise contributions of individual mechanisms remain uncertain, and no single pathway fully explains the observed therapeutic benefits.

Optimal clinical outcomes depend on the early initiation of SGLT2i therapy in eligible patients and careful adherence to established safety precautions. Clinicians should assess volume status, kidney function, acute illness, prolonged fasting, infection risk, and concomitant diabetes medications; provide clear instructions regarding temporary medication interruption during acute illness and before surgery; and avoid unnecessary discontinuation in response to a modest, expected initial decline in estimated glomerular filtration rate (eGFR). Within this clinical framework, SGLT2i should be regarded not merely as glucose-lowering agents or adjunctive diuretics but as foundational components of comprehensive cardiorenal therapy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this research, and are free from any commercial or financial relationships that could potentially pose a conflict of interest.

AUTHOR CONTRIBUTIONS

In this research, the contributions of each author are detailed as follows. Author 1 was

responsible for the conceptualization and drafting of the manuscript, while Author 2 was responsible for the data analysis.

STATEMENT ON THE USE OF AI

In the preparation of this manuscript, the authors used artificial intelligence (AI), the use of which was limited solely to grammar improvement and language checking.

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