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Review Paper

Cardiovascular And Renal Benefits of Sodium–Glucose Cotransporter 2 Inhibitors in Patients Without Diabetes: A Review of Current Evidence

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ABSTRACT

Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) were initially developed for the treatment of type 2 diabetes mellitus. However, recent clinical trials have demonstrated cardiovascular and renal benefits that extend to patients without diabetes, expanding their potential therapeutic role in conditions such as heart failure and chronic kidney disease. Objective: To review the available evidence regarding the role of SGLT2 inhibitors in reducing cardiovascular and renal events in patients without diabetes mellitus, with particular emphasis on major clinical trials and the mechanisms underlying these effects. Methods: A literature review will be conducted using major biomedical databases, prioritizing randomized controlled trials, systematic reviews, metaanalyses, and clinical practice guidelines. Particular attention will be given to studies evaluating dapagliflozin, empagliflozin, and other SGLT2 inhibitors in patients with heart failure or chronic kidney disease without diabetes mellitus. Results: Evidence from major randomized clinical trials indicates that SGLT2 inhibitors reduce the risk of hospitalization for heart failure and selected outcomes related to kidney disease progression, including among patients without diabetes mellitus. These benefits appear to involve hemodynamic, renal, and metabolic mechanisms that are largely independent of glucose lowering. The magnitude of benefit varies according to the clinical population, heart failure phenotype, baseline kidney function, and specific

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outcome evaluated. Conclusions: SGLT2 inhibitors have evolved from primarily glucose-lowering agents into an important cardiorenal therapeutic strategy for selected patients without diabetes mellitus. Current evidence supports their use in specific clinical settings involving heart failure and chronic kidney disease, although the magnitude of benefit depends on the underlying clinical context and should be interpreted according to evidence specifically derived from non diabetic populations.

INTRODUCTION

Cardiovascular disease and chronic kidney disease (CKD) are closely interconnected conditions that substantially contribute to morbidity and mortality worldwide. CKD is associated with an increased risk of cardiovascular events, heart failure, and premature death, with this risk persisting across different levels of kidney function and albuminuria. Current clinical guidelines therefore emphasize strategies aimed not only at slowing kidney disease progression but also at reducing cardiovascular complications in patients with CKD.¹

Heart failure represents another major component of the cardiorenal disease spectrum. Despite advances in pharmacological treatment, patients with heart failure remain at substantial risk of hospitalization and cardiovascular death. The therapeutic landscape has progressively evolved from treatments focused predominantly on neurohormonal modulation toward multidimensional approaches targeting both cardiac and renal pathophysiology. In this context, sodium–glucose cotransporter 2 (SGLT2) inhibitors have emerged as an important therapeutic class with effects that extend beyond their original glucose-lowering indication.²

SGLT2 inhibitors were initially developed as antihyperglycemic agents for patients with type 2 diabetes mellitus (T2DM). Their inhibition of glucose and sodium reabsorption in the proximal renal tubule produces glycosuria and natriuresis, while also influencing intraglomerular

hemodynamics and renal tubular glomerular signaling. Increasing evidence suggests that their cardiovascular and renal effects cannot be explained solely by improved glycemic control. Proposed mechanisms include restoration of tubuloglomerular feedback, reduction of intraglomerular pressure, modulation of plasma volume, improvement of cardiac loading conditions, and metabolic and cellular effects that may influence myocardial and renal function.³

The transition from a diabetes-centered therapeutic strategy to a broader cardiorenal indication was supported by randomized clinical trials conducted specifically in patients with heart failure, including individuals without diabetes. In DAPA-HF, dapagliflozin significantly reduced the composite of worsening heart failure or cardiovascular death in patients with heart failure with reduced ejection fraction (HFrEF), with consistent effects in participants with and without diabetes.⁴ Similarly, EMPEROR-Reduced demonstrated that empagliflozin reduced the risk of cardiovascular death or hospitalization for heart failure in patients with HFrEF, and the treatment effect was consistent irrespective of baseline diabetes status.⁵

Subsequent trials expanded the evidence to patients with heart failure and mildly reduced or preserved ejection fraction. EMPEROR-Preserved demonstrated a significant reduction in the composite of cardiovascular death or hospitalization for heart failure with empagliflozin in patients with left ventricular ejection fraction greater than 40%, while DELIVER showed a comparable reduction in worsening heart failure or cardiovascular death with dapagliflozin. Importantly, both trials included substantial proportions of participants without diabetes, and treatment effects were generally consistent according to diabetes status.^{6,7} These findings contributed to the incorporation of SGLT2 inhibitors into contemporary heart failure

treatment strategies across a broad range of left ventricular ejection fractions.⁸

The renal evidence has followed a similar trajectory. In the DAPA-CKD trial, dapagliflozin reduced the risk of a composite kidney and cardiovascular outcome in patients with CKD, with benefits that were consistent among participants with and without diabetes.⁹ The EMPA-KIDNEY trial subsequently broadened the evidence base by enrolling a large population with CKD across a wider range of estimated glomerular filtration rates and albuminuria levels. Empagliflozin significantly reduced the risk of kidney disease progression or cardiovascular death, with consistent effects in participants with and without diabetes.¹⁰ These findings have contributed to a fundamental shift in the perception of SGLT2 inhibitors, from glucose-lowering medications with secondary cardiovascular effects to therapies with clinically relevant cardiorenal benefits that may be applicable independently of diabetes status.

The growing body of evidence has consequently led international guidelines to incorporate SGLT2 inhibitors into the management of heart failure and CKD beyond their traditional role in diabetes. The 2023 focused update of the European Society of Cardiology heart failure guidelines expanded recommendations for dapagliflozin and empagliflozin across the spectrum of left ventricular ejection fraction, while the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guideline recognizes SGLT2 inhibitors as an important component of CKD management in appropriate patients.^{1,8}

Nevertheless, important questions remain regarding the magnitude and consistency of cardiovascular and renal benefit specifically in patients without diabetes. The available evidence derives from populations with different baseline cardiovascular risk, degrees of kidney dysfunction, albuminuria, heart failure

phenotypes, and background therapies. Furthermore, reductions in heart failure hospitalization and kidney disease progression appear more consistent than reductions in cardiovascular mortality, emphasizing the importance of distinguishing individual clinical outcomes rather than considering “cardiorenal protection” as a uniform endpoint.^{4,10}

Therefore, this review aims to critically evaluate the current evidence regarding the cardiovascular and renal effects of SGLT2 inhibitors in patients without diabetes mellitus, focusing on the major randomized clinical trials, proposed glucose independent mechanisms of benefit, clinically relevant cardiovascular and renal outcomes, safety considerations, and the implications of these findings for contemporary clinical practice.

METHODS

Study design

A narrative review of the current scientific literature was conducted to evaluate the cardiovascular and renal effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors in adults without diabetes mellitus. The review was designed to integrate evidence from randomized controlled trials, systematic reviews, meta-analyses, mechanistic studies, and international clinical practice guidelines, with particular emphasis on cardiovascular and renal outcomes in populations without diabetes.

Literature search strategy

A comprehensive literature search was performed in PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library. Additional relevant publications were identified through manual screening of the reference lists of key articles and major clinical practice guidelines.



The search strategy combined controlled vocabulary and free text terms related to SGLT2 inhibitors, cardiovascular disease, heart failure, chronic kidney disease, renal outcomes, and absence of diabetes. The principal search terms included: “SGLT2 inhibitors,” “sodium-glucose cotransporter 2 inhibitors,” “dapagliflozin,” “empagliflozin,” “canagliflozin,” “ertugliflozin,” “heart failure,” “cardiovascular outcomes,” “cardiovascular death,” “hospitalization for heart failure,” “chronic kidney disease,” “renal outcomes,” “kidney disease progression,” “non diabetic,” and “without diabetes.”

The search included publications available from database inception through October 5, 2026, allowing the incorporation of the most recent evidence available at the time of preparation of this review.

Eligibility criteria

Studies were considered eligible when they met the following criteria:

Inclusion criteria:

- Studies conducted in adults aged ≥ 18 years.
- Studies evaluating an SGLT2 inhibitor, including dapagliflozin, empagliflozin, canagliflozin, or ertugliflozin.
- Studies including patients without diabetes mellitus or reporting prespecified cardiovascular or renal outcomes according to diabetes status.
- Randomized controlled trials, systematic reviews, meta analyses, mechanistic studies, and international clinical practice guidelines.
- Studies reporting cardiovascular outcomes, renal outcomes, or both.
- Publications available in English.
- Studies providing sufficient methodological and outcome information for interpretation.

Exclusion criteria:

Studies were excluded when they focused exclusively on glycemic control in patients with diabetes without reporting relevant cardiovascular or renal outcomes; observational studies with insufficient methodological information; duplicate publications; conference abstracts without complete peer reviewed data; case reports; case series; editorials; letters without original data; and publications whose full text was unavailable.

Study selection

The selection process was performed in successive stages. Initially, titles and abstracts were screened according to the predefined eligibility criteria. Potentially relevant publications were subsequently evaluated through full text assessment. Duplicate records were removed before final selection.

Because the objective of this work was to provide a clinically focused and comprehensive narrative synthesis rather than to perform a de novo quantitative meta analysis, study selection emphasized the methodological quality, clinical relevance, originality, and applicability of the available evidence to patients without diabetes.

Evidence included in the review

A total of 32 publications were selected for inclusion in the final reference set of this review. These publications comprise the complete bibliographic corpus used throughout the manuscript.

The selected evidence includes pivotal randomized controlled trials evaluating SGLT2 inhibitors in heart failure and chronic kidney disease, prespecified and post hoc analyses according to diabetes status, systematic reviews and meta analyses evaluating cardiovascular and renal outcomes, studies addressing the mechanisms of cardiorenal protection, and

contemporary international clinical practice guidelines.

Particular emphasis was placed on the DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, DAPA-CKD, and EMPA-KIDNEY trials, as these studies provide the principal evidence supporting the use of SGLT2 inhibitors in cardiovascular and renal disease irrespective of diabetes status.

Recent evidence published through 2026 was incorporated when it provided clinically relevant information beyond that available from the pivotal trials, including contemporary systematic reviews and meta analyses specifically addressing outcomes according to diabetes status. Recent analyses have continued to demonstrate cardiovascular and renal benefits across populations with and without diabetes, although the magnitude of benefit may vary according to baseline cardiovascular and kidney risk.^{1,4}

DEVELOPMENT

Pharmacological rationale and mechanisms of cardiorenal protection

Sodium–glucose cotransporter 2 (SGLT2) inhibitors act primarily in the early proximal renal tubule, where SGLT2 is responsible for the majority of filtered glucose and sodium reabsorption. Pharmacological inhibition of this transporter increases urinary glucose and sodium excretion, producing osmotic diuresis and natriuresis. Although these effects were initially considered primarily relevant to glycemic control, subsequent physiological and clinical evidence has demonstrated that the consequences of SGLT2 inhibition extend to renal hemodynamics, cardiac loading conditions, vascular function, and cellular metabolism.^{3,11,12}

One of the principal mechanisms proposed to explain renal protection is restoration of tubuloglomerular feedback. By reducing proximal

sodium reabsorption, SGLT2 inhibitors increase sodium chloride delivery to the macula densa, enhancing tubuloglomerular feedback and promoting afferent arteriolar vasoconstriction. This reduces intraglomerular pressure and filtration stress, thereby decreasing mechanical injury to the glomerular filtration barrier. The resulting hemodynamic adaptation is particularly relevant because it occurs independently of the glucose lowering effect and can therefore operate in patients without diabetes.^{11,12}

SGLT2 inhibition also produces sustained natriuresis and osmotic diuresis, although the magnitude of these effects may vary according to volume status and concomitant diuretic therapy. The reduction in plasma volume and interstitial congestion may decrease cardiac preload and ventricular filling pressures, providing a plausible mechanism for the rapid reduction in heart failure events observed in clinical trials. Additional effects on blood pressure, vascular stiffness, tissue sodium, and neurohumoral activation may further contribute to cardiovascular benefit.^{11,13}

Metabolic effects may also contribute to cardiorenal protection. SGLT2 inhibition induces a modest shift in substrate utilization toward fatty acids and ketone bodies and has been associated with changes in energy metabolism, erythropoiesis, uric acid handling, and cellular stress responses. These effects may improve myocardial and renal energetic efficiency and reduce oxidative and inflammatory stress. Nevertheless, the available evidence does not support a single mechanism as sufficient to explain the clinical effects of the drug class; rather, the observed benefits appear to result from the interaction of multiple renal, hemodynamic, metabolic, and cellular pathways.^{12,14}

Importantly, recent physiological research continues to support the concept that the initial renal action of SGLT2 inhibition triggers a broader systemic response. In individuals with and without



diabetes, inhibition of proximal sodium and glucose transport modifies distal sodium delivery, renal oxygen requirements, plasma volume, and metabolic substrate availability. This integrated physiological response provides a plausible explanation for why clinical benefits can occur in the absence of hyperglycemia.^{15, 16}

SGLT2 inhibitors in heart failure without diabetes

The strongest evidence for cardiovascular benefit in patients without diabetes comes from randomized clinical trials of chronic heart failure. DAPA-HF was one of the first pivotal studies to directly demonstrate that an SGLT2 inhibitor could improve clinically relevant outcomes in patients with heart failure with reduced ejection fraction (HFrEF) irrespective of diabetes status. The trial included 4744 patients with symptomatic heart failure and a left ventricular ejection fraction of 40% or less. Dapagliflozin reduced the composite outcome of worsening heart failure or cardiovascular death compared with placebo (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.65–0.85). Importantly, the treatment effect was consistent in patients with and without diabetes.¹⁷

A prespecified analysis according to diabetes status provided particularly relevant evidence for the present review. Among the 2605 participants without diabetes, the primary outcome occurred in 13.2% of patients receiving dapagliflozin compared with 17.7% receiving placebo, corresponding to an HR of 0.73 (95% CI, 0.60–0.88). The absence of significant interaction between diabetes status and treatment effect supported the interpretation that the cardiovascular benefit of dapagliflozin was not dependent on the presence of diabetes.¹⁸

The EMPEROR-Reduced trial independently confirmed these findings with empagliflozin. Among 3730 patients with HFrEF, empagliflozin

reduced the risk of cardiovascular death or hospitalization for heart failure. Importantly, the prespecified analysis according to diabetes status showed a consistent treatment effect among patients with diabetes and those without diabetes, with HRs of 0.72 and 0.78, respectively, and no significant interaction. The effects on heart failure hospitalization and renal outcomes were also generally consistent across glycemic categories.¹⁹ The evidence was subsequently extended to patients with heart failure and preserved or mildly reduced ejection fraction. EMPEROR-Preserved enrolled patients with a left ventricular ejection fraction greater than 40% and demonstrated that empagliflozin reduced the composite of cardiovascular death or hospitalization for heart failure, primarily through a reduction in heart failure hospitalization. The treatment effect was consistent regardless of diabetes status.²⁰ A prespecified analysis demonstrated an HR of 0.78 (95% CI, 0.64–0.95) among participants without diabetes, compared with an HR of 0.79 (95% CI, 0.67–0.94) among those with diabetes.²¹

The DELIVER trial further reinforced this evidence in patients with heart failure and mildly reduced or preserved ejection fraction. Dapagliflozin reduced the risk of worsening heart failure or cardiovascular death compared with placebo, with an overall HR of 0.82 (95% CI, 0.73–0.92). The benefit was consistent across prespecified subgroups, including patients with and without diabetes.²² A subsequent analysis according to baseline glycemic status similarly demonstrated that the cardiovascular benefit of dapagliflozin was maintained across glycemic categories, supporting the concept of a glucose independent therapeutic effect.²³

Taken together, the major heart failure trials demonstrate a remarkably consistent pattern: SGLT2 inhibitors reduce worsening heart failure and hospitalization across the spectrum of left ventricular ejection fraction, and this effect is



maintained in individuals without diabetes. The consistency across dapagliflozin and empagliflozin, as well as across HFrEF, mildly reduced ejection fraction, and preserved ejection fraction, strengthens the argument that the cardiovascular effects of this drug class are not primarily mediated by glucose lowering.^{17, 23}

Effects on chronic kidney disease in patients without diabetes

The renal evidence represents a second major pillar supporting the use of SGLT2 inhibitors in patients without diabetes. DAPA-CKD was specifically designed to evaluate whether dapagliflozin could slow CKD progression in patients with substantial albuminuria, including individuals without diabetes. The trial enrolled 4304 participants with an estimated glomerular filtration rate of 25–75 mL/min/1.73 m² and urinary albumin-to-creatinine ratios of 200–5000 mg/g. Dapagliflozin significantly reduced the risk of the primary composite endpoint consisting of sustained decline in estimated glomerular filtration rate of at least 50%, end-stage kidney disease, or kidney-related or cardiovascular death.²⁴

The prespecified analysis according to diabetes status was particularly relevant. The relative risk reduction was consistent in participants with diabetes (HR, 0.64; 95% CI, 0.52–0.79) and those without diabetes (HR, 0.50; 95% CI, 0.35–0.72), without evidence of a significant interaction. Similar consistency was observed for the kidney specific composite outcome and other secondary endpoints.²⁵ These findings demonstrated that the nephroprotective effect of dapagliflozin was not dependent on the presence of diabetic kidney disease.

The EMPA-KIDNEY trial subsequently broadened the applicability of SGLT2 inhibition to a wider spectrum of CKD. Empagliflozin significantly reduced the risk of kidney disease progression or cardiovascular death compared

with placebo, including in a population with and without diabetes and across a broad range of baseline kidney function.²⁶ Secondary analyses demonstrated that the relative reduction in kidney disease progression was consistent across different underlying causes of CKD, supporting the concept that the renal effects of SGLT2 inhibition extend beyond diabetic nephropathy.²⁷

The importance of these findings is particularly evident in patients with CKD who do not have diabetes. Historically, pharmacological strategies for slowing CKD progression were strongly influenced by the underlying etiology, particularly diabetes and hypertension. The demonstration that SGLT2 inhibitors reduce kidney disease progression in non diabetic CKD represents a substantial change in the therapeutic paradigm and supports their consideration as disease-modifying agents rather than exclusively glucose-lowering drugs.^{24, 27}

Cardiovascular outcomes

Across clinical trials involving patients without diabetes, the most reproducible cardiovascular benefit associated with SGLT2 inhibition is a reduction in heart failure events, particularly hospitalization for heart failure. This effect has been demonstrated in patients with reduced, mildly reduced, and preserved ejection fraction and appears relatively independent of baseline glycemic status.^{18, 2, 3}

The magnitude of the effect on cardiovascular mortality is less consistent. DAPA-HF demonstrated a reduction in cardiovascular death as a component of the overall treatment effect, whereas other heart failure trials have shown that the principal driver of the composite endpoint was a reduction in hospitalization for heart failure.^{17, 20, 22} Therefore, the available evidence supports a distinction between the robust reduction in heart failure events and the less certain effect on cardiovascular mortality.



The cardiovascular benefit may reflect several complementary mechanisms. Reduction of sodium and water retention may decrease ventricular filling pressures and congestion, while modest reductions in blood pressure and plasma volume can reduce cardiac workload. In addition, changes in myocardial substrate utilization, improved metabolic efficiency, attenuation of oxidative stress, and potential effects on myocardial remodeling have been proposed as contributors.^{12, 16}

Importantly, these mechanisms do not require the presence of hyperglycemia. The preservation of cardiovascular benefit in participants with normal glycemic indices or without diabetes provides clinical support for the hypothesis that SGLT2 inhibitors exert effects that extend beyond glucose lowering.^{18, 23}

Renal outcomes

Renal protection is characterized by two complementary phenomena: an early hemodynamic reduction in estimated glomerular filtration rate followed by a slower chronic decline in kidney function. The initial fall in estimated glomerular filtration rate is generally interpreted as a consequence of reduced intraglomerular pressure rather than structural kidney injury. Over longer follow-up, this is followed by attenuation of the chronic decline in renal function.^{11, 12, 24, 27}

In DAPA-CKD, the renal benefit of dapagliflozin was evident in participants without diabetes, demonstrating that the effect was not restricted to diabetic nephropathy.²⁵ EMPA-KIDNEY provided complementary evidence by demonstrating slower progression of kidney disease across a broad range of CKD etiologies and kidney function.^{26, 27}

The clinical relevance of this effect extends beyond changes in estimated glomerular filtration rate. Slowing CKD progression may delay the onset of kidney failure and reduce the subsequent cardiovascular burden associated with advanced

kidney disease. The simultaneous reduction in heart failure events further supports the concept of SGLT2 inhibitors as therapies acting across the interconnected cardiovascular and renal systems rather than as isolated organ specific treatments.

Safety profile in patients without diabetes

The safety profile of SGLT2 inhibitors in patients without diabetes is an important component of their expanding clinical use. Because these drugs were initially developed as antihyperglycemic therapies, hypoglycemia has been a particular concern when considering their use in individuals with normal glucose metabolism. However, randomized clinical trials have not demonstrated a clinically important increase in hypoglycemia attributable to SGLT2 inhibition in patients without diabetes who are not receiving glucose lowering agents.^{18, 19}

Genital mycotic infections and, to a lesser extent, urinary tract infections represent recognized adverse effects associated with glucosuria. In EMPEROR-Preserved, uncomplicated genital and urinary tract infections occurred more frequently with empagliflozin, as did hypotension.²⁰ Volume depletion is another clinically relevant consideration, particularly in patients receiving concomitant diuretic therapy, although major trials have generally not demonstrated substantial excess risk of serious volume-related adverse events.^{18, 20}

Euglycemic diabetic ketoacidosis is a recognized class related adverse effect, but its absolute risk is substantially lower in individuals without diabetes than in patients with diabetes, particularly in the absence of severe insulin deficiency. Nevertheless, clinicians should exercise caution during prolonged fasting, acute severe illness, major surgery, or other circumstances associated with reduced oral intake or increased ketogenesis.

Overall, the major randomized trials indicate that SGLT2 inhibitors have an acceptable safety profile



in patients without diabetes when used in appropriately selected populations. The balance between cardiovascular and renal benefits and potential adverse effects therefore appears favorable in patients with established heart failure or CKD who meet evidence based treatment criteria.^{18, 27}

DISCUSSION

The evidence reviewed in this study supports a fundamental change in the therapeutic concept of sodium–glucose cotransporter 2 (SGLT2) inhibitors. Although these agents were initially developed as glucose lowering medications for patients with type 2 diabetes mellitus, the accumulated clinical evidence demonstrates that their cardiovascular and renal effects extend substantially beyond glycemic control. In patients without diabetes, the benefits observed across heart failure and chronic kidney disease (CKD) trials indicate that SGLT2 inhibition should be considered a cardiorenal therapeutic strategy rather than exclusively an antidiabetic intervention.^{17, 27}

One of the most important findings is the consistency of cardiovascular benefit across different heart failure phenotypes. DAPA-HF and EMPEROR-Reduced demonstrated that dapagliflozin and empagliflozin reduce the risk of worsening heart failure or cardiovascular death in patients with reduced ejection fraction, with comparable treatment effects in individuals with and without diabetes.^{17, 19} This finding was subsequently reproduced in patients with preserved and mildly reduced ejection fraction in EMPEROR-Preserved and DELIVER.^{20, 23} The consistency of these findings is clinically important because it suggests that diabetes status should not be regarded as a prerequisite for the cardiovascular efficacy of SGLT2 inhibitors.

The magnitude of benefit appears particularly robust for heart failure hospitalization. A

prespecified meta-analysis combining DAPA-HF and EMPEROR-Reduced showed a 26% relative reduction in the composite of cardiovascular death or first hospitalization for heart failure and a 25% reduction in recurrent heart failure hospitalizations or cardiovascular death. The analysis also demonstrated a reduction in the composite renal outcome, with no significant heterogeneity according to diabetes status.²⁸ These findings reinforce the interpretation that the principal cardiovascular effect of SGLT2 inhibition is not dependent on glucose lowering and is reproducible across different molecules within the drug class.

The evidence in heart failure with mildly reduced and preserved ejection fraction is particularly relevant because therapeutic options historically differed according to left ventricular ejection fraction. Meta-analytic evidence has demonstrated that SGLT2 inhibitors significantly reduce the risk of cardiovascular death or hospitalization for heart failure in patients with HFmrEF and HFpEF, including those without diabetes.²⁹ This supports the concept that the therapeutic effect of SGLT2 inhibition is relatively independent of left ventricular ejection fraction and that these agents occupy a broader role in contemporary heart failure management.

The renal findings are similarly important. DAPA-CKD provided direct evidence that dapagliflozin slows CKD progression in patients without diabetes, while EMPA-KIDNEY expanded the evidence to patients with a wider range of kidney function and underlying renal disease.^{24, 27} The magnitude and consistency of these effects suggest that SGLT2 inhibitors modify fundamental pathways involved in CKD progression rather than acting specifically on diabetic kidney disease.

Recent systematic evidence further supports this interpretation. A meta-analysis of randomized trials involving patients without diabetes reported reductions in cardiovascular outcomes, cardiovascular death, hospitalization for heart



failure, and composite renal outcomes, while also demonstrating a slower decline in estimated glomerular filtration rate.³⁰ Importantly, the same analysis did not identify a significant increase in hypoglycemia, ketoacidosis, acute renal failure, or treatment discontinuation because of adverse events, although genital and urinary tract infections remained relevant safety considerations.³⁰ These findings are consistent with the major individual trials and strengthen the external validity of the cardiorenal benefits observed in non diabetic populations.

An important consideration when interpreting the renal evidence is that the population studied in clinical trials is heterogeneous. DAPA-CKD required substantial albuminuria, whereas EMPA-KIDNEY included patients with lower levels of albuminuria and a broader range of CKD etiologies.^{24,26} Consequently, the evidence cannot necessarily be extrapolated uniformly to every patient with CKD without diabetes. Nevertheless, the progressive expansion of trial inclusion criteria has substantially increased the generalizability of SGLT2 inhibitor therapy beyond diabetic kidney disease.

The mechanisms underlying these effects are likely multifactorial. Restoration of tubuloglomerular feedback and reduction of intraglomerular pressure provide a biologically plausible explanation for the early hemodynamic changes in estimated glomerular filtration rate and the subsequent slowing of chronic kidney function decline.^{11,12} The associated natriuresis, reduction in plasma volume, and improvement in congestion may explain part of the rapid reduction in heart failure events. Additional effects involving myocardial energetics, erythropoiesis, vascular function, inflammation, oxidative stress, and neurohormonal signaling may contribute to the broader cardiorenal phenotype.^{12,16}

The distinction between cardiovascular mortality and heart failure hospitalization deserves

particular emphasis. Although several analyses suggest a favorable effect on cardiovascular and all cause mortality, the most consistent endpoint across individual trials is hospitalization for heart failure.^{17,23} A systematic review specifically evaluating patients without diabetes found reductions in cardiovascular outcomes and cardiovascular death, but the certainty of evidence for some mortality outcomes was lower than that for hospitalization and renal outcomes.³⁰ Therefore, the available evidence supports strong confidence in reduction of heart failure events, whereas conclusions regarding mortality should remain more cautious.

Another relevant issue is whether the benefits observed in non diabetic patients can be considered a class effect. The available evidence includes dapagliflozin and empagliflozin across several large randomized trials, with consistent findings in both cardiovascular and renal populations.^{17,27} This convergence strongly supports a class effect, although extrapolation to every SGLT2 inhibitor should still consider the fact that the most robust evidence in non-diabetic cardiorenal disease has been generated with these two agents.

The safety profile also influences the clinical applicability of this therapeutic strategy. The absence of a substantial increase in hypoglycemia in individuals without diabetes is expected because SGLT2 inhibitors do not directly stimulate insulin secretion.³⁰ Nevertheless, genital mycotic infections, volume depletion, hypotension, and transient changes in renal function remain clinically relevant. The risk of euglycemic diabetic ketoacidosis is considerably more relevant in patients with diabetes, but clinicians should nevertheless consider temporary discontinuation during prolonged fasting, major surgery, severe acute illness, or conditions associated with reduced carbohydrate intake.

An additional consideration is the interaction between SGLT2 inhibitors and other guideline directed therapies. In HFrEF, SGLT2 inhibitors are generally incorporated into multidrug therapeutic strategies rather than used as isolated interventions. Evidence from subgroup analyses suggests that their benefits are maintained alongside other established heart failure therapies, including renin–angiotensin system inhibition, mineralocorticoid receptor antagonists, beta-blockers, and angiotensin receptor neprilysin inhibition.²⁸ This is particularly relevant because the clinical benefit of SGLT2 inhibition should be understood within the context of comprehensive cardiorenal risk reduction rather than as a replacement for established therapies.

Recent evidence also raises an important question concerning the breadth of renal protection across different CKD phenotypes. A contemporary systematic review and meta-analysis demonstrated that SGLT2 inhibitors improve kidney outcomes across populations with CKD, heart failure, and diabetes, although the magnitude of benefit varies according to the underlying clinical phenotype.³¹ These findings suggest that the absolute benefit of treatment may be greatest among individuals with higher baseline cardiorenal risk. Consequently, treatment decisions should incorporate kidney function, albuminuria, heart failure status, cardiovascular risk, volume status, and concomitant medications rather than diabetes status alone.

The evolving evidence therefore supports a paradigm in which diabetes status becomes less central to the decision to use SGLT2 inhibitors. Instead, the presence of heart failure or CKD and the patient's overall cardiorenal risk profile become increasingly important determinants of treatment eligibility. This shift is particularly relevant in clinical practice because a substantial proportion of patients with heart failure or CKD do not have diabetes, yet historically many

pharmacological interventions were evaluated primarily through a diabetic framework.

Nevertheless, several limitations should be acknowledged. First, much of the evidence in non-diabetic populations comes from prespecified subgroup analyses rather than trials exclusively designed for individuals without diabetes. Although the consistency of treatment effects is reassuring, subgroup analyses may have lower statistical power than dedicated trials. Second, individual CKD trials have differed in inclusion criteria, particularly with respect to albuminuria and baseline kidney function, limiting direct comparisons between studies. Third, the majority of available evidence concerns dapagliflozin and empagliflozin, and therefore the extent to which all class members provide equivalent cardiorenal benefits in non diabetic populations remains less certain.

Finally, the evidence base continues to evolve. A 2026 drug and dose specific meta-analysis including 31 randomized controlled trials and more than 98,000 participants further evaluated the influence of diabetes status on renal outcomes and reported persistent kidney benefits across populations, although heterogeneity according to drug, dose, kidney function, and CKD stage highlights the importance of individualized interpretation.³² These data reinforce the direction of the current evidence while also demonstrating that the clinical role of SGLT2 inhibitors continues to expand.

Overall, the available evidence indicates that SGLT2 inhibitors provide clinically meaningful cardiovascular and renal protection in selected patients without diabetes. The strongest and most consistent benefits are reductions in heart failure hospitalization and slowing of CKD progression, while effects on cardiovascular and all cause mortality appear favorable but comparatively less uniform. The convergence of physiological, randomized clinical trial, and meta-analytic



evidence supports the interpretation that these benefits are fundamentally independent of glucose lowering. SGLT2 inhibitors should therefore be regarded as cardiorenal disease modifying therapies whose therapeutic value extends well beyond the treatment of diabetes.

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