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Review Article

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 (SGLT2) inhibitors were initially developed to improve glycemic control in type 2 diabetes. Large cardiovascular and kidney outcome trials subsequently demonstrated benefits that extend beyond glucose lowering, including among participants without diabetes. This evidence has changed the treatment of heart failure and chronic kidney disease (CKD), but the magnitude and clinical meaning of benefit vary by disease phenotype and outcome. **Objective:** To summarize the clinical evidence for cardiovascular and renal effects of SGLT2 inhibitors in adults without diabetes, emphasizing heart failure across the ejection-fraction spectrum, CKD progression, potential mechanisms, safety, and implications for practice. **Methods :** This narrative review synthesizes landmark randomized controlled trials, prespecified and post hoc analyses by glycemic status, and major clinical practice guidelines. The discussion prioritizes trials that enrolled participants without diabetes or reported treatment effects by diabetes status. This document is a narrative synthesis rather than a completed systematic review; no exhaustive database search, duplicate screening, formal risk-of-bias assessment, or PRISMA study-flow count is claimed. **Results :** In heart failure with reduced ejection fraction, DAPA-HF demonstrated that dapagliflozin reduced worsening heart failure or cardiovascular death, with consistent effects in participants with and without diabetes. EMPEROR-Preserved and DELIVER extended evidence to patients with mildly reduced or preserved ejection fraction, with benefits driven predominantly by fewer worsening-heart-failure events. In CKD, DAPA-CKD and EMPA-KIDNEY showed slower kidney disease progression in populations that included people without diabetes, with broadly consistent relative effects across glycemic subgroups.

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Proposed mechanisms include altered renal hemodynamics, natriuresis, changes in tubuloglomerular feedback, and broader cardiorenal effects that are not dependent on lowering blood glucose. Important risks include genital mycotic infection, volume depletion in susceptible patients, and rare ketoacidosis, including euglycemic presentations. Conclusions: : Evidence supports the use of selected SGLT2 inhibitors for eligible patients with heart failure or CKD regardless of diabetes status. Treatment decisions should be based on the relevant indication, kidney function, volume status, concomitant therapy, contraindications, and current local prescribing information. Benefits should not be generalized to every cardiovascular outcome or every patient subgroup.

INTRODUCTION

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have reshaped cardiovascular and kidney medicine. Their original role was glucose lowering in type 2 diabetes mellitus, through inhibition of glucose and sodium reabsorption in the proximal renal tubule. Clinical outcome trials, however, identified reductions in heart-failure events and slower progression of kidney disease that could not be explained solely by changes in glycated hemoglobin. The clinical relevance of these findings is particularly clear in patients who do not have diabetes, for whom SGLT2 inhibitors can be considered for cardiorenal indications rather than glycemic control [1,5].

Heart failure and CKD frequently coexist and amplify each other's risks. Congestion, altered renal perfusion, neurohormonal activation, inflammation, and structural cardiac or renal disease contribute to recurrent admissions and progressive organ dysfunction. Historically, treatment options for these conditions were often selected according to left ventricular ejection fraction, albuminuria, diabetes status, and estimated glomerular filtration rate (eGFR). The SGLT2 inhibitor trials challenged the assumption that the cardiorenal benefits of this drug class require diabetes, and they provided evidence across a wider range of heart-failure phenotypes and kidney function levels [1,8].

The phrase “benefit without diabetes” should nevertheless be interpreted precisely. It means that randomized trials enrolled participants without diabetes and observed treatment effects consistent with those in

participants with diabetes. It does not mean that every outcome improved significantly in every subgroup, that the absolute benefit is identical for all patients, or that treatment is appropriate regardless of clinical stability or contraindications. Absolute benefit depends on baseline risk, disease phenotype, competing risks, and the endpoint being considered.

This review therefore examines the evidence through three linked questions: (1) do SGLT2 inhibitors reduce heart-failure events in people without diabetes across the ejection-fraction spectrum (2) do they slow CKD progression in the absence of diabetes? and (3) how should efficacy, mechanism, safety, and evidence limitations shape clinical use?

2. Review approach

This manuscript was prepared as a narrative review focused on randomized clinical trials and guideline documents relevant to SGLT2 inhibitor treatment in adults without diabetes. Priority was given to DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, DAPA-CKD, and EMPA-KIDNEY, together with glycemic-status analyses and major heart-failure and kidney guidelines [1,12]. The clinical evidence was interpreted by indication and outcome rather than pooled quantitatively.

Important methodological limitation: this is not presented as a systematic review. The current draft does not report a reproducible, exhaustive search across all databases, a prespecified protocol, dual-reviewer screening, a complete record count, or a formal risk-of-bias assessment. Those procedures must be completed and documented if the target journal requires a systematic or PRISMA-compliant review. No new statistical meta-analysis was performed.

The principal evidence domains were: heart failure with reduced ejection fraction (HFrEF); heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF); CKD progression; proposed biological mechanisms; safety and practical prescribing considerations; and gaps in the evidence. Guideline recommendations are described as recommendations of the cited organizations and should be checked against the latest local guidance before clinical implementation.



3. Biological rationale for effects beyond glucose lowering

3.1 Renal sodium handling and tubuloglomerular feedback

SGLT2 is expressed in the proximal tubule and mediates reabsorption of filtered glucose together with sodium. Its inhibition increases urinary glucose excretion and modifies sodium delivery to the distal nephron. The resulting changes in tubuloglomerular feedback can reduce intraglomerular pressure and contribute to an early, usually modest decline in eGFR after treatment initiation. This initial hemodynamic change differs conceptually from progressive structural kidney injury, although an eGFR decline in an individual patient must still be interpreted in the context of blood pressure, volume status, concurrent medications, and the overall clinical picture [13,16].

3.2 Hemodynamic and congestion-related effects

SGLT2 inhibitors can produce modest osmotic diuresis and natriuresis. In heart failure, these effects may complement conventional diuretics and alter the distribution of extracellular fluid. The clinical benefit is not adequately described as simple fluid removal alone: randomized trials have shown fewer worsening-heart-failure events over months to years, suggesting that effects on renal hemodynamics, cardiac loading conditions, metabolism, and other pathways may contribute. The relative importance of each proposed mechanism in humans remains incompletely resolved [13,14,17].

3.3 Metabolic, cellular, and inflammatory hypotheses

Additional mechanisms under investigation include changes in myocardial energy utilization, erythropoiesis and hematocrit, uric-acid handling, oxidative stress, inflammation, and cellular ion transport. These hypotheses may help explain why effects extend to people without diabetes, but mechanistic plausibility should not be mistaken for proof that any single pathway mediates the observed outcome reductions. Clinical recommendations are primarily supported by randomized outcome trials rather than by one definitive mechanistic model [13,17].

4. Evidence in heart failure

4.1 Heart failure with reduced ejection fraction

DAPA-HF randomized 4,744 patients with symptomatic HFrEF and a left ventricular ejection fraction of 40% or less to dapagliflozin or placebo on top of recommended therapy. The primary composite of worsening heart failure or cardiovascular death was reduced with dapagliflozin. Prespecified analyses found a consistent effect in participants with and without diabetes, supporting a treatment role independent of glucose-lowering needs ^{1,2}.

EMPEROR-Reduced evaluated empagliflozin in patients with HFrEF and likewise demonstrated a reduction in the composite of cardiovascular death or hospitalization for heart failure. Benefits were observed irrespective of diabetes status, while the trial also contributed evidence on kidney-function trajectories in a population at substantial risk of cardiorenal deterioration ^{3,4}. Taken together, DAPA-HF and EMPEROR-Reduced established SGLT2 inhibition as a foundational component of contemporary HFrEF therapy, alongside other evidence-based treatments.

These trials should not be interpreted as proof that SGLT2 inhibitors replace renin-angiotensin system inhibitors/ARNI, beta-blockers, or mineralocorticoid receptor antagonists. Their role is complementary. In patients without diabetes, the rationale for treatment is reduction of heart-failure events and related cardiorenal risk, not an expectation of meaningful glucose lowering.

4.2 Heart failure with mildly reduced or preserved ejection fraction

The evidence base was extended to patients with a left ventricular ejection fraction above 40%. In EMPEROR-Preserved, 5,988 patients were assigned to empagliflozin or placebo. The primary composite of cardiovascular death or hospitalization for heart failure was reduced, with the difference driven mainly by fewer hospitalizations for heart failure. Treatment effects appeared consistent in participants with and without diabetes ⁵.

DELIVER randomized 6,263 patients with heart failure and an ejection fraction above 40% to dapagliflozin or

placebo. Dapagliflozin reduced the composite of worsening heart failure or cardiovascular death, with consistency across glycemic-status categories. These findings are clinically important because HFpEF and HFmrEF have historically had fewer therapies with consistent outcome benefits than HFrEF ^{6,7}.

The principal nuance is that the composite benefit should not be equated with a proven reduction in cardiovascular mortality alone. Across EMPEROR-Preserved and DELIVER, fewer worsening-heart-failure events were the major contributor to the overall effect. For patients without diabetes, this supports an expectation of fewer heart-failure events rather than a promise of mortality reduction in every subgroup.

4.3 Symptoms, health status, and functional burden

Beyond hard clinical endpoints, analyses of the major heart-failure trials have evaluated health status, symptoms, and functional limitations. Improvements in patient-reported outcomes can be relevant because heart failure affects daily activity and quality of life even when hospitalization is avoided. These outcomes should be interpreted alongside the primary trial endpoints and not substituted for them. The size of symptomatic improvement varies among patients and does not eliminate the need for diuretics, rehabilitation, management of comorbidities, or follow-up [5,8].

5. Evidence in chronic kidney disease

5.1 DAPA-CKD: kidney protection with and without diabetes

DAPA-CKD enrolled 4,304 participants with CKD, an eGFR of 25–75 mL/min/1.73 m², and urinary albumin-to-creatinine ratio of 200–5,000 mg/g. The trial included participants with and without type 2 diabetes. Dapagliflozin reduced the primary composite of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. The relative treatment effect was consistent by diabetes status ⁹.

The result established that kidney protection with dapagliflozin is not restricted to diabetic kidney disease. However, DAPA-CKD selected a population with albuminuric CKD and therefore should not be treated as a direct estimate of benefit for every CKD

phenotype, especially people with low albuminuria or a different cause of kidney disease.

5.2 EMPA-KIDNEY: a broader CKD population

EMPA-KIDNEY randomized 6,609 participants with CKD to empagliflozin or placebo. Eligibility included an eGFR of 20 to below 45 mL/min/1.73 m², or an eGFR of 45 to below 90 mL/min/1.73 m² with albuminuria meeting the trial threshold. The primary outcome of kidney disease progression or cardiovascular death occurred less frequently with empagliflozin, and the results were consistent in participants with and without diabetes ¹⁰.

EMPA-KIDNEY broadened the evidence by including a wide range of eGFR values and diverse causes of CKD. The primary result supports a kidney-protective effect beyond diabetes, while secondary outcomes should be read individually: not every cardiovascular or mortality endpoint showed a statistically significant difference during the trial. This distinction is important when translating a composite primary endpoint into patient counselling.

5.3 Interpreting early eGFR changes

A small early eGFR reduction can occur after initiation of an SGLT2 inhibitor. In trial populations, this pattern was generally followed by a slower chronic decline in kidney function. The early change is often hemodynamic, but clinicians should not automatically dismiss a large or progressive fall in eGFR. Assessment should consider volume depletion, hypotension, intercurrent illness, nephrotoxic exposures, and concurrent diuretic or renin–angiotensin system therapy. Follow-up testing should be individualized according to baseline kidney function and clinical risk [9,12,15,16].

6. Safety and practical prescribing

6.1 Genital infections and volume depletion

Genital mycotic infections occur more often with SGLT2 inhibitors than with placebo and should be discussed before treatment. Volume depletion, dizziness, or hypotension may occur, particularly in patients with low blood pressure, frailty, poor oral intake, or intensive diuretic therapy. The risk profile is not identical for every patient; assessment of volume status



and medication review are central to safe prescribing
5,9,10,18

6.2 Ketoacidosis and acute illness

Diabetic ketoacidosis is uncommon but potentially serious and may occur with only modest elevations in blood glucose. The risk is most established in diabetes, especially in the setting of insulin deficiency, fasting, surgery, severe illness, or marked carbohydrate restriction. Ketoacidosis in people without diabetes is rare but has been reported; therefore, the absence of diabetes does not justify ignoring symptoms or acute-illness precautions. Current product information and local protocols should guide temporary withholding during prolonged fasting, major surgery, or critical illness^{18,19}.

6.3 Kidney function, concomitant treatment, and eligibility

SGLT2 inhibitors are not interchangeable with respect to every licensed indication, eGFR threshold, or jurisdiction-specific label. Prescribers should consult current product information and applicable guidelines rather than rely on a single class-wide threshold. Treatment should be considered in the context of the patient's heart-failure or CKD indication, renal function, blood pressure, volume status, pregnancy status where relevant, and concurrent medications. Initiation during acute decompensation requires clinical judgment and should follow evidence and local protocols for patient stabilization.

6.4 Hypoglycemia in people without diabetes

Because SGLT2 inhibitors do not directly stimulate insulin secretion, clinically significant hypoglycemia is generally not expected when they are used without insulin or insulin secretagogues. In people without diabetes, glucose lowering is not the therapeutic objective. This does not remove the need to review the full medication list or recognize that the overall safety profile depends on the patient's comorbidities and clinical circumstances^{18,19}.

7. Clinical interpretation and guideline implications

The most defensible clinical conclusion is indication-specific. For eligible patients with HFrEF, randomized

evidence supports dapagliflozin or empagliflozin as part of foundational therapy regardless of diabetes status. For symptomatic HFmrEF and HFpEF, EMPEROR-Preserved and DELIVER support SGLT2 inhibitor treatment primarily to reduce worsening-heart-failure events. For CKD, DAPA-CKD and EMPA-KIDNEY demonstrate kidney protection in populations that included people without diabetes [1,10].

Guidelines have incorporated these results. The 2023 focused update of the European Society of Cardiology heart-failure guideline recommends dapagliflozin or empagliflozin for symptomatic HFmrEF and HFpEF to reduce the risk of heart-failure hospitalization or cardiovascular death. Kidney guidelines also support SGLT2 inhibitor use in defined CKD populations, with recommendations depending on eGFR, albuminuria, heart failure, and other clinical criteria^{11,12}. Recommendations may differ by region and are updated over time; the latest local guideline and product label should be checked.

For shared decision-making, patients should be told that the strongest and most consistent effect is prevention of worsening heart failure and slowing CKD progression in appropriate populations. The evidence does not imply that treatment will reverse established structural disease, eliminate all future admissions, or provide the same absolute benefit to every person. Cost, access, adherence, monitoring, and the patient's treatment goals also influence real-world effectiveness.

8. Limitations of the evidence

Several limitations qualify the interpretation. First, most pivotal trials were not designed exclusively for people without diabetes; conclusions for this group rely on prespecified or post hoc subgroup analyses and consistency of treatment effects. Second, subgroup analyses generally have less statistical power than the overall trial, so the absence of a statistically significant interaction should be interpreted as evidence of consistency rather than proof of identical effects. Third, trial populations had defined eligibility criteria and may not represent patients with severe hemodynamic instability, very advanced multimorbidity, or uncommon CKD causes.



Fourth, composite outcomes combine events of different clinical importance. A reduction in a composite driven largely by heart-failure hospitalization does not establish a separate reduction in cardiovascular death. Similarly, a kidney composite can demonstrate overall disease-modifying benefit even when individual components have different event rates. Fifth, class effects should be inferred carefully: dapagliflozin and empagliflozin have the most directly relevant evidence across the conditions discussed, but not every molecule has the same breadth of outcome-trial evidence or regulatory indication.

Finally, this document is a narrative review draft and does not claim a systematic, exhaustive search. It has not undergone duplicate screening, formal risk-of-bias grading, or a complete audit of all potentially eligible literature. Before submission, the authors should verify every reference against the publisher or PubMed record, check the journal's article type and reference style, and decide whether a formal systematic-review methodology is required.

9. Future research directions

Further research should refine estimates of absolute benefit among people without diabetes across age, sex, race and ethnicity, baseline eGFR, albuminuria, heart-failure phenotype, and frailty. Although relative treatment effects have generally been consistent across glycemic categories, absolute benefit is shaped by baseline event risk. Trials and individual-participant meta-analyses could better identify which patients derive the largest net benefit and how outcomes vary with competing risks.

Additional work is needed to understand the mechanisms that connect SGLT2 inhibition to heart and kidney protection. Mechanistic studies should be linked to clinical outcomes rather than treated as substitutes for them. Research should also examine implementation: initiation in routine care, persistence after discharge, affordability, adherence, patient education, and equitable access. Safety surveillance should continue to characterize rare events, particularly ketoacidosis during acute illness and the management of treatment around surgery or prolonged fasting.

Finally, the evidence base should continue to evolve as newer trials, longer follow-up, and updated guidelines become available. Future reviews should prespecify their questions, document a reproducible database search, use independent screening and extraction, assess risk of bias, and distinguish direct randomized evidence from indirect or mechanistic inference.

CONCLUSION

SGLT2 inhibitors have established a role in cardiorenal medicine that extends beyond glucose lowering. In adults without diabetes, randomized evidence supports their use in eligible patients with heart failure across the ejection-fraction spectrum and in defined populations with chronic kidney disease. DAPA-HF and EMPEROR-Reduced demonstrated benefit in HFrEF; EMPEROR-Preserved and DELIVER extended the evidence to HFmrEF and HFpEF; and DAPA-CKD and EMPA-KIDNEY demonstrated kidney protection in CKD populations that included participants without diabetes [1,10].

The clinical interpretation should remain anchored to the outcomes actually demonstrated. In heart failure with mildly reduced or preserved ejection fraction, the overall benefit was driven predominantly by fewer worsening-heart-failure events; a separate mortality benefit should not be assumed for every subgroup. In CKD, the evidence supports slower disease progression, but the degree of benefit depends on baseline risk and the population studied. These distinctions matter for informed consent, expectation-setting, and guideline-based prescribing.

The absence of diabetes should not, by itself, exclude a patient from receiving an SGLT2 inhibitor when an evidence-based heart-failure or kidney indication is present. Safe use requires confirmation of the relevant indication, review of kidney function and volume status, attention to genital infections and rare ketoacidosis, and adherence to current product information and clinical guidance. The next stage for this manuscript is a final reference audit and, if a systematic review is intended, completion of a reproducible search and transparent study-selection process.



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