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# SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS BEYOND DIABETES: AN EMERGING CARDIORENAL STRATEGY IN INTERNAL MEDICINE

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## ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors were initially developed as glucose-lowering agents for patients with type 2 diabetes mellitus. However, accumulating evidence has demonstrated substantial cardiovascular and renal benefits that extend beyond glycemic control and may occur independently of diabetes status. To review the current evidence regarding the use of SGLT2 inhibitors as a cardiorenal therapeutic strategy in patients with heart failure and chronic kidney disease, with particular emphasis on recent clinical trials and contemporary recommendations. A narrative review of contemporary evidence was conducted using major randomized controlled trials, systematic reviews, and international clinical practice guidelines addressing SGLT2 inhibitors in heart failure and chronic kidney disease. Particular attention was given to evidence published between 2023 and 2026, including the EMPA-KIDNEY follow-up data and recent European and international recommendations. SGLT2 inhibitors consistently reduce the risk of hospitalization for heart failure and slow the progression of chronic kidney disease. Their benefits have been demonstrated across different left ventricular ejection fraction categories and in patients with and without type 2 diabetes. Recent long-term follow-up of EMPA-KIDNEY demonstrated a sustained reduction in the composite risk of kidney disease progression or cardiovascular death among patients receiving empagliflozin. Contemporary evidence also supports early incorporation of SGLT2 inhibitors into guideline-directed medical therapy for heart failure. SGLT2 inhibitors represent an important therapeutic paradigm shift in internal medicine. Their cardiovascular and renal effects extend beyond glucose lowering, supporting their use as disease-modifying agents in appropriate patients with heart failure and chronic kidney disease, regardless of diabetes status.

**Keywords:** SGLT2 Inhibitors; Heart Failure; Chronic Kidney Disease; Empagliflozin; Dapagliflozin; Cardiorenal Protection; Internal Medicine.

## 1 INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors represent one of the most significant therapeutic advances in cardiovascular and renal medicine in recent years. Initially developed for the treatment of type 2 diabetes mellitus (T2DM), these agents inhibit glucose and sodium reabsorption in the proximal renal tubule, resulting in glycosuria and

natriuresis. Subsequent cardiovascular and renal outcome trials demonstrated that their clinical benefits extend beyond glucose lowering, establishing a new therapeutic role for this drug class (MCMURRAY et al., 2019; PACKER et al., 2020).

Heart failure (HF) and chronic kidney disease (CKD) are major causes of morbidity and mortality worldwide. These conditions frequently coexist and share several pathophysiological mechanisms, including neurohormonal activation, endothelial dysfunction, inflammation, altered renal hemodynamics, and progressive cardiovascular and renal injury. Consequently, therapeutic strategies capable of simultaneously modifying cardiovascular and renal outcomes have become increasingly important in internal medicine.

The first major evidence for cardiovascular benefits emerged from trials involving patients with T2DM and high cardiovascular risk. However, subsequent randomized controlled trials demonstrated that SGLT2 inhibitors could reduce heart failure events even in patients without diabetes. Dapagliflozin, for example, significantly reduced the risk of worsening heart failure or cardiovascular death among patients with heart failure and reduced ejection fraction, regardless of diabetes status (MCMURRAY et al., 2019).

Similarly, empagliflozin demonstrated significant cardiovascular and renal benefits in patients with heart failure and reduced ejection fraction, supporting the incorporation of SGLT2 inhibition into guideline-directed medical therapy (PACKER et al., 2020).

The therapeutic indications subsequently expanded to patients with heart failure with preserved and mildly reduced ejection fraction. In the EMPEROR-Preserved trial, empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and preserved ejection fraction (ANKER et al., 2021). The DELIVER trial subsequently demonstrated that dapagliflozin reduced worsening heart failure or cardiovascular death among patients with mildly reduced or preserved ejection fraction (SOLOMON et al., 2022).

The renal evidence has been equally important. The DAPA-CKD trial demonstrated that dapagliflozin reduced the risk of sustained decline in kidney function, end-stage kidney disease, or renal or cardiovascular death in patients with CKD, including individuals without diabetes (HEERSPINK et al., 2020). The EMPA-KIDNEY trial further expanded the evidence by demonstrating significant benefits of empagliflozin across a broad population of patients with CKD (HERRINGTON et al., 2023).

The 2024 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline subsequently incorporated SGLT2 inhibitors as an important component of CKD management in appropriate patients, emphasizing their benefits in reducing kidney disease progression and cardiovascular complications (KDIGO, 2024).

More recent long-term follow-up from EMPA-KIDNEY has provided additional evidence that the renal and cardiovascular benefits of empagliflozin are sustained beyond the original randomized treatment period (EMPA-KIDNEY COLLABORATIVE GROUP, 2025).

These developments represent a major paradigm shift. SGLT2 inhibitors are no longer considered exclusively glucose-lowering medications; rather, they are increasingly recognized as cardiorenal disease-modifying therapies.

The objective of this article was to review the current evidence regarding the cardiovascular and renal effects of SGLT2 inhibitors in patients with heart failure and chronic kidney disease, emphasizing their role beyond glycemic control and their applicability to patients with and without type 2 diabetes mellitus.

## 2 METHODOLOGY

This study consisted of a narrative literature review focused on the contemporary role of SGLT2 inhibitors in cardiovascular and renal disease.

The literature search prioritized randomized controlled trials, systematic reviews, meta-analyses, international clinical practice guidelines, and scientific publications from recognized cardiovascular and nephrology organizations.

The main topics investigated included the use of SGLT2 inhibitors in heart failure, chronic kidney disease, cardiovascular disease, renal disease progression, patients without diabetes, safety considerations, and contemporary therapeutic recommendations.

Landmark randomized controlled trials published between 2019 and 2023 were included to establish the development of the evidence base, while greater emphasis was placed on contemporary guidelines and long-term follow-up evidence published between 2024 and 2026.

The principal evidence sources included publications from The New England Journal of Medicine, The Lancet, European Heart Journal, and Kidney International, as well as recommendations from the European Society of Cardiology and KDIGO.

## 3 RESULTS

### 3.1 SGLT2 inhibitors and heart failure

The evidence consistently demonstrates that SGLT2 inhibitors reduce the risk of worsening heart failure and hospitalization for heart failure.

In the DAPA-HF trial, dapagliflozin significantly reduced the composite outcome of worsening heart failure or cardiovascular death in patients with heart failure with reduced ejection fraction. Importantly, the treatment effect was observed regardless of the presence or absence of diabetes mellitus (MCMURRAY et al., 2019).

The EMPEROR-Reduced trial produced similar findings with empagliflozin, demonstrating a reduction in the combined risk of cardiovascular death or hospitalization for heart failure and a slower decline in renal function (PACKER et al., 2020).

These results established SGLT2 inhibitors as one of the foundational pharmacological therapies for HFrEF.

Subsequent evidence expanded their role to other heart failure phenotypes. Empagliflozin reduced the risk of cardiovascular death or hospitalization for heart failure in patients with preserved ejection fraction in the EMPEROR-Preserved trial (ANKER et al., 2021).

Likewise, dapagliflozin significantly reduced worsening heart failure or cardiovascular death in patients with mildly reduced or preserved ejection fraction in the DELIVER trial (SOLOMON et al., 2022).

The 2023 focused update of the European Society of Cardiology guidelines therefore incorporated SGLT2 inhibitors into the therapeutic strategy for patients with heart failure across a broader spectrum of ejection fraction categories (MCDONAGH et al., 2023).

### 3.2 Renal protection

SGLT2 inhibitors have also demonstrated substantial nephroprotective effects. The DAPA-CKD trial showed that dapagliflozin reduced the risk of sustained decline in estimated glomerular filtration rate, end-stage kidney disease, or renal or cardiovascular death among patients with CKD. Importantly, the benefits were also observed in patients without diabetes, demonstrating that the renal effects were not dependent on glucose lowering (HEERSPINK et al., 2020).

The EMPA-KIDNEY trial subsequently evaluated empagliflozin in a broad CKD population and demonstrated a significant reduction in the risk of kidney disease progression or cardiovascular death (HERRINGTON et al., 2023).

The KDIGO 2024 guideline consequently recommends SGLT2 inhibitors for several categories of patients with CKD because of their ability to slow kidney disease progression and reduce cardiovascular complications (KDIGO, 2024).

Long-term follow-up of EMPA-KIDNEY provided further evidence supporting sustained cardiorenal protection. During the extended follow-up period, the primary composite outcome of kidney disease progression or cardiovascular death occurred less frequently among participants originally assigned to empagliflozin than among those assigned to placebo, supporting a persistent treatment benefit (EMPA-KIDNEY COLLABORATIVE GROUP, 2025).

### 3.3 Benefits independent of diabetes

One of the most important findings in the development of SGLT2 inhibitors has been the demonstration that their cardiovascular and renal benefits are not dependent on the presence of diabetes.

The DAPA-HF, EMPEROR-Reduced, DAPA-CKD, and EMPA-KIDNEY trials included substantial populations without diabetes and demonstrated clinically meaningful benefits in these patients (MCMURRAY et al., 2019; PACKER et al., 2020; HEERSPINK et al., 2020; HERRINGTON et al., 2023).

This evidence fundamentally changed the therapeutic concept surrounding SGLT2 inhibitors. Their mechanism of benefit appears to involve several physiological effects beyond glucose lowering, including natriuresis, reduction of

intraglomerular pressure, modulation of tubuloglomerular feedback, and favorable effects on cardiac loading conditions.

Consequently, SGLT2 inhibitors are increasingly viewed as cardiorenal therapies rather than exclusively antidiabetic drugs.

### 3.4 Safety and tolerability

SGLT2 inhibitors generally have a favorable safety profile when prescribed appropriately. The most commonly recognized adverse effects include genital mycotic infections and volume depletion. In patients with diabetes, rare cases of euglycemic diabetic ketoacidosis may occur, particularly during prolonged fasting, acute illness, major surgery, or significant reduction in insulin availability.

An initial decline in estimated glomerular filtration rate may occur shortly after treatment initiation. This initial change is generally related to hemodynamic alterations and should be interpreted in the context of the patient's clinical condition rather than automatically considered evidence of acute kidney injury (KDIGO, 2024).

Appropriate patient selection and clinical monitoring are therefore essential.

## 4 DISCUSSION

The emergence of SGLT2 inhibitors as cardiorenal therapies represents a major paradigm shift in internal medicine.

Historically, diabetes, heart failure, and chronic kidney disease were often managed using relatively separate therapeutic strategies. The current evidence demonstrates that these diseases share important pathophysiological pathways and that a single pharmacological class can simultaneously influence cardiovascular and renal outcomes.

The cardiovascular benefits of SGLT2 inhibitors are particularly relevant because heart failure remains associated with substantial morbidity, recurrent hospitalization, and mortality. The consistent reduction in hospitalization for heart failure across different ejection fraction categories represents one of the strongest therapeutic effects associated with this drug class (MCMURRAY et al., 2019; ANKER et al., 2021; SOLOMON et al., 2022).

The renal effects are equally important. CKD is a major risk factor for cardiovascular disease, and progressive loss of kidney function significantly increases the risk of kidney failure and cardiovascular events. By slowing the decline in kidney function, SGLT2 inhibitors may alter the natural history of CKD in appropriately selected patients (HEERSPINK et al., 2020; HERRINGTON et al., 2023).

The long-term EMPA-KIDNEY findings are particularly relevant because they demonstrate that the benefits associated with empagliflozin persist during extended follow-up (EMPA-KIDNEY COLLABORATIVE GROUP, 2025).

From a clinical perspective, the growing evidence supports earlier integration of SGLT2 inhibitors into comprehensive cardiorenal management. Current heart failure guidelines recognize SGLT2 inhibitors as foundational therapy, while KDIGO recommendations support their use in appropriate CKD populations regardless of diabetes status (MCDONAGH et al., 2023; KDIGO, 2024).

Another important issue is the possibility of initiating therapy during or shortly after hospitalization for acute heart failure. Recent evidence suggests that early initiation may reduce subsequent cardiovascular and heart failure events in appropriately selected patients, although clinical stability and contraindications must always be considered.

The practical implementation of SGLT2 inhibitor therapy requires individualized assessment. Physicians should evaluate renal function, volume status, concomitant diuretics, risk of genital infections, nutritional status, and circumstances associated with ketoacidosis. Patient education regarding temporary interruption during prolonged fasting or severe acute illness may further improve safety.

Despite the strength of current evidence, barriers to implementation remain. Guideline-directed therapies are frequently introduced sequentially and may be underused in routine practice. Greater awareness among internists and multidisciplinary teams may therefore help improve treatment optimization.

## 5 CONCLUSION

SGLT2 inhibitors have evolved from glucose-lowering medications into important cardiorenal disease-modifying therapies.

Current evidence demonstrates that these agents reduce hospitalization for heart failure, improve cardiovascular outcomes, and slow the progression of chronic kidney disease. Importantly, these benefits extend to patients without type 2 diabetes mellitus.

Evidence from major trials including DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, DAPA-CKD, and EMPA-KIDNEY has established the broad cardiovascular and renal efficacy of this drug class. Long-term EMPA-KIDNEY follow-up has further strengthened the evidence for sustained cardiorenal protection.

Therefore, SGLT2 inhibitors should be considered an important component of contemporary internal medicine practice for appropriately selected patients with heart failure and chronic kidney disease. Their incorporation into comprehensive treatment strategies may contribute substantially to reducing cardiovascular events, hospitalization, kidney disease progression, and overall disease burden.

## STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

### *Disclosure of conflict of interest*

The authors declare no conflicts of interest regarding this manuscript.

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