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Review Article

SGLT2 Inhibitors Beyond Glycemic Control: Emerging Pharmacological and Cardiovascular Applications A Narrative Review

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Sodium-glucose cotransporter-2 (SGLT2) inhibitors were introduced as antihyperglycemic medicines that increase urinary glucose loss by limiting glucose and sodium uptake in the proximal renal tubule. Their clinical significance has since expanded considerably. Cardiovascular and kidney outcome trials have shown that agents in this class can reduce heart-failure events and slow kidney disease progression, including in many patients who do not have diabetes. These observations have shifted the pharmacological concept of SGLT2 inhibition from isolated glucose lowering toward integrated cardiorenal and metabolic protection. The benefits appear to arise from several interacting processes rather than from a single mechanism. These include altered proximal tubular sodium handling, restoration of tubuloglomerular feedback, lower intraglomerular pressure, modest changes in plasma and interstitial fluid volume, improved ventricular loading conditions, metabolic adaptation, and possible effects on inflammation, oxidative stress, vascular function, and myocardial remodeling. The strongest clinical evidence currently concerns heart failure across the ejection-fraction spectrum and chronic kidney disease. Additional research is examining possible roles in coronary syndromes, myocardial infarction, arrhythmias, cardiomyopathies, cerebrovascular disease, and cardio-oncology. This review discusses the pharmacological basis of SGLT2 inhibition, mechanisms that may explain benefits beyond glycemic control, established cardiovascular and renal applications, major clinical-trial evidence, safety considerations, and emerging therapeutic directions.

Keywords: SGLT2 inhibitors; dapagliflozin; empagliflozin; canagliflozin; heart failure; cardiovascular protection; chronic kidney disease; cardiorenal medicine; pharmacology; natriuresis.

INTRODUCTION

SGLT2 inhibitors have become an important example of how the therapeutic identity of a drug class can change after cardiovascular and renal outcomes are carefully studied. Dapagliflozin, empagliflozin, canagliflozin and other agents were developed principally to improve glycemic control in type 2 diabetes mellitus (T2DM). Their renal mechanism is straightforward: inhibition of sodium-glucose cotransport in the proximal tubule reduces glucose reabsorption and increases urinary glucose excretion. The subsequent increase in distal sodium delivery also produces a series of renal and systemic effects. The unexpected cardiovascular findings from early outcome trials prompted a major expansion of research. Later randomized trials specifically enrolled patients with heart failure or chronic kidney disease and demonstrated benefits that were not dependent on diabetes. A 2024 systematic review and meta-analysis of 15 large trials involving more than 100,000 participants found a consistent reduction in first heart-failure hospitalization across populations with heart failure, T2DM, CKD and atherosclerotic cardiovascular disease. These findings support the view that the class has effects extending well beyond glucose lowering. [1] Current clinical guidance reflects this change. KDIGO 2024 recommends SGLT2 inhibitors for adults with T2DM and CKD at appropriate eGFR levels and also recommends them for selected adults with CKD and heart failure irrespective of albuminuria. The guideline also recognizes that the early reversible fall in eGFR after initiation is generally not, by itself, a reason to discontinue treatment. [2] The objective of this review is to examine the pharmacological mechanisms and clinical evidence supporting the cardiovascular and renal effects of SGLT2 inhibitors, while distinguishing established indications from promising but still investigational applications.

2. Pharmacological Basis of SGLT2 Inhibition

SGLT2 is a high-capacity transporter expressed mainly in the early proximal renal tubule. Under physiological conditions, it contributes substantially to reabsorption of filtered glucose together with sodium. Pharmacological blockade reduces proximal tubular sodium and glucose uptake. Glucose consequently remains in the tubular fluid and is excreted in urine, producing an insulin-independent reduction in circulating glucose. The same renal action changes sodium handling. Greater sodium delivery to the distal nephron enhances signaling at the macula densa and helps restore tubuloglomerular feedback. This is particularly relevant in diabetes and hyperfiltration states, in which excessive proximal reabsorption can reduce macula-densa sodium sensing. The resulting hemodynamic adjustment can lower intraglomerular pressure. The class also produces osmotic diuresis and modest natriuresis. These effects differ from those of high-dose conventional diuretics because SGLT2 inhibitors act predominantly in the proximal tubule and have relatively modest effects on total fluid loss. Their clinical benefit in heart failure is therefore unlikely to be explained by simple volume depletion alone.

3. Mechanisms Underlying Benefits Beyond Glycemic Control

3.1 Renal hemodynamics and tubuloglomerular feedback

The renal effects of SGLT2 inhibition are central to its cardiorenal profile. By increasing sodium delivery to the macula densa, these agents enhance tubuloglomerular feedback and reduce the hyperfiltration state that can occur with diabetes and CKD. Lower intraglomerular pressure may reduce mechanical stress on the glomerular filtration barrier and help preserve kidney function over time. [2,3]

3.2 Natriuresis and fluid redistribution

SGLT2 inhibition promotes urinary sodium and glucose loss. The accompanying osmotic diuresis can decrease extracellular fluid and venous congestion, while the modest nature of the diuretic effect may permit use alongside standard heart-failure diuretics. Reduction in filling pressures is a plausible contributor to the lower rate of heart-failure hospitalization observed in trials.

3.3 Neurohumoral and vascular effects

Cardiorenal disease is associated with activation of sympathetic and other neurohumoral pathways. Experimental and clinical literature suggests that SGLT2 inhibition may influence sympathetic activity and vascular function. Proposed vascular actions include improved endothelial responsiveness and reduced vascular oxidative stress. These mechanisms remain active areas of investigation rather than fully established explanations for clinical outcomes. [4,5]

3.4 Myocardial metabolism

SGLT2 inhibitors may alter myocardial substrate availability and energy handling. Increased fatty-acid utilization and ketone-body availability have been proposed as possible components of a more energy-efficient metabolic state in the failing heart. Mitochondrial effects and changes in cellular energetics have also been described experimentally. Because these mechanisms are complex and may differ between disease states, they should be regarded as complementary hypotheses rather than a single definitive pathway. [5,6]

3.5 Inflammation, oxidative stress and remodeling

Chronic inflammation and oxidative stress contribute to endothelial dysfunction, myocardial fibrosis and adverse ventricular remodeling. Preclinical and translational studies suggest that SGLT2 inhibitors can influence inflammatory signaling, oxidative pathways and fibrotic processes. A 2025 pharmacology review emphasized that the cardiovascular effects of the class are likely multifactorial, involving hemodynamic, metabolic, vascular and cellular mechanisms. [5]

3.6 Erythropoiesis, uric acid and systemic metabolism

Additional proposed mechanisms include changes in erythropoietic signaling, iron handling, uric-acid excretion and whole-body metabolic adaptation. These effects may be relevant to cardiorenal physiology, although their independent contribution to clinical outcomes is not yet established. [6]

4. Cardiovascular Applications

4.1 Heart failure with reduced ejection fraction

Dapagliflozin and empagliflozin demonstrated that SGLT2 inhibition can improve outcomes in HFrEF regardless of diabetes status. DAPA-HF showed a reduction in the composite of worsening heart failure or cardiovascular death with dapagliflozin, while EMPEROR-Reduced demonstrated a similar reduction in heart-failure events with empagliflozin. These findings established SGLT2 inhibitors as an important component of contemporary HFrEF therapy. [7,8]

4.2 Heart failure with mildly reduced and preserved ejection fraction

The benefits were subsequently extended to patients with higher ejection fractions. EMPEROR-Preserved showed a reduction in the composite of cardiovascular death or heart-failure hospitalization with empagliflozin in HFpEF, while DELIVER demonstrated benefit with dapagliflozin in HFmrEF and HFpEF. These studies were particularly important because pharmacological options for HFpEF had historically been limited. [9,10]

4.3 Hospitalized and acute heart failure

The EMPULSE trial evaluated empagliflozin started during hospitalization for acute heart failure and provided evidence supporting early treatment in clinically stable patients. The results have increased interest in beginning SGLT2 inhibition before discharge rather than routinely delaying treatment until outpatient follow-up. [11]

4.4 Atherosclerotic cardiovascular disease and myocardial infarction

SGLT2 inhibitors consistently reduce heart-failure events, but their effects on atherosclerotic outcomes such as myocardial infarction and stroke are less uniform. A large 2024 meta-analysis found substantial reductions in heart-failure hospitalization across several cardiometabolic populations, while effects on cardiovascular death and other outcomes varied by disease setting. [1] The class should therefore complement, rather than replace, established therapies directed at atherosclerotic risk.

5. Renal Applications

SGLT2 inhibitors have become central to contemporary CKD management. DAPA-CKD demonstrated kidney and cardiovascular benefits with dapagliflozin in patients with CKD, including participants without diabetes. EMPA-KIDNEY subsequently expanded the evidence for empagliflozin across a broad CKD population. [12,13] The renal benefits include slower loss of filtration capacity, reduction in albuminuria, and lower risk of clinically important kidney outcomes. The early fall in eGFR after starting therapy reflects a hemodynamic response in many patients and generally stabilizes with continued treatment. KDIGO 2024 recommends SGLT2 inhibition for adults with CKD and specified levels of albuminuria or heart failure and permits continuation after eGFR falls below 20 mL/min/1.73 m² when tolerated and kidney replacement therapy has not begun. [2] An important development is the recognition that kidney protection is not simply a consequence of improved glycemia. The effects on proximal tubular workload, sodium handling and glomerular pressure provide a pharmacological rationale for benefit in non-diabetic CKD.

6. Major Clinical Evidence

The clinical development of SGLT2 inhibitors can be understood as three overlapping phases. First, cardiovascular outcome trials in T2DM identified unexpected heart-failure and renal signals. Second, dedicated heart-failure trials confirmed benefit independently of diabetes. Third, kidney trials established renoprotection in broader populations. EMPA-REG OUTCOME evaluated empagliflozin in T2DM with established cardiovascular disease and reported a marked reduction in cardiovascular death and hospitalization for heart failure. [14] The CANVAS Program provided cardiovascular and renal evidence for canagliflozin. [15] DECLARE-TIMI 58 showed a strong reduction in heart-failure hospitalization with dapagliflozin in a broad T2DM population. [16] DAPA-HF and EMPEROR-Reduced established the efficacy of dapagliflozin and empagliflozin in HFrEF, while EMPEROR-Preserved and DELIVER extended evidence into HFpEF and HFmrEF. [7-10] DAPA-CKD and EMPA-KIDNEY then demonstrated important kidney benefits in CKD. [12,13] Taken together, these trials changed the pharmacological positioning of SGLT2 inhibitors from glucose-lowering drugs with cardiovascular safety data to therapies with direct cardiorenal outcome indications.

7. Comparison of Major SGLT2 Inhibitors

Dapagliflozin has particularly extensive evidence in heart failure and CKD. Empagliflozin has strong cardiovascular, heart-failure and renal outcome evidence. Canagliflozin has major evidence in diabetic kidney disease and cardiovascular-risk populations. Ertugliflozin has established cardiovascular safety, while its evidence base for broader cardiorenal indications is less extensive. Sotagliflozin differs pharmacologically because it inhibits both SGLT1 and SGLT2 and has generated cardiovascular and heart-failure outcome data. The drugs share the class mechanism but should not automatically be assumed to have identical evidence for every clinical indication. Prescribing should follow the approved indication, renal-function requirements and current guideline recommendations for the individual agent.

Table 1. Major Clinical Trials of SGLT2 Inhibitors

Trial	Agent	Population	Principal clinical finding
EMPA-REG OUTCOME	Empagliflozin	T2DM + established CVD	Reduced CV death and HF hospitalization
CANVAS	Canagliflozin	T2DM + high CV risk	Reduced CV events and HF hospitalization
DECLARE-TIMI 58	Dapagliflozin	T2DM + CV risk/ASCVD	Reduced HF hospitalization and renal outcomes
DAPA-HF	Dapagliflozin	HFrEF ± diabetes	Reduced worsening HF/CV death
EMPEROR-Reduced	Empagliflozin	HFrEF ± diabetes	Reduced HF hospitalization and renal outcomes
EMPEROR-Preserved	Empagliflozin	HFpEF	Reduced HF events
DELIVER	Dapagliflozin	HFmrEF/HFpEF	Reduced worsening HF/CV outcomes
DAPA-CKD	Dapagliflozin	CKD ± diabetes	Reduced kidney and HF outcomes
EMPA-KIDNEY	Empagliflozin	CKD ± diabetes	Slowed CKD progression
EMPULSE	Empagliflozin	Hospitalized acute HF	Supported early initiation in stable patients

8. Emerging Cardiovascular Applications

The expanding evidence base has prompted investigation into cardiovascular applications beyond established heart failure.

8.1 Coronary syndromes and myocardial infarction

Potential mechanisms include improved endothelial function, reduced oxidative stress, altered myocardial metabolism and attenuation of ischemia-reperfusion injury. However, the evidence for routine use specifically to prevent recurrent coronary events is less mature than the evidence for heart failure. Recent reviews describe myocardial-infarction findings as encouraging but not yet equivalent in strength to the heart-failure evidence. [5,17]

8.2 Cardiomyopathies

SGLT2 inhibition may influence ventricular loading, fibrosis, cellular energetics and remodeling. These mechanisms provide a rationale for research in specific cardiomyopathies, but dedicated clinical evidence remains limited.

8.3 Arrhythmias

Potential antiarrhythmic effects may arise indirectly through reduced ventricular stress, improved remodeling, metabolic effects and changes in autonomic signaling. Whether these translate into meaningful reductions in clinically important arrhythmias remains uncertain.

8.4 Cerebrovascular disease

The vascular and metabolic effects of SGLT2 inhibitors have stimulated interest in cerebrovascular protection. However, stroke prevention is not currently the principal therapeutic rationale for this drug class.

8.5 Cardio-oncology and other cardiovascular settings

Experimental and early clinical work is exploring whether SGLT2 inhibitors may protect against cardiovascular injury associated with cancer therapy and other systemic disorders. These indications remain investigational.

Table 2. Established and Emerging Applications

Clinical area	Evidence status	Key pharmacological rationale
HFrEF	Established	Hemodynamic, renal and metabolic effects
HFmrEF/HFpEF	Established	Reduced congestion and cardiorenal stress
CKD	Established	Tubuloglomerular feedback and lower intraglomerular pressure
T2DM with CV risk	Established	HF and selected cardiovascular protection
Myocardial infarction	Emerging	Metabolic, vascular and ischemia-reperfusion mechanisms
Coronary syndromes	Emerging	Endothelial and metabolic effects
Arrhythmias	Investigational	Remodeling and autonomic/metabolic effects
Cardiomyopathies	Investigational	Potential antifibrotic and metabolic effects
Cardio-oncology	Investigational	Potential cardioprotective mechanisms

9. Safety, Contraindications and Practical Considerations

The favorable benefit-risk profile of SGLT2 inhibitors does not eliminate the need for careful patient selection. Genital mycotic infections are among the most characteristic adverse effects. Increased urination, volume depletion and hypotension can occur, particularly in patients receiving other diuretics or with limited oral intake. Euglycemic diabetic ketoacidosis is uncommon but clinically important, especially in people with diabetes during prolonged fasting, acute illness, major surgery or marked insulin deficiency. KDIGO advises withholding SGLT2 inhibitors during prolonged fasting, surgery or critical illness when ketosis risk is increased. [2] A small reversible fall in eGFR commonly occurs soon after initiation and is usually a hemodynamic effect rather than progressive kidney injury. Monitoring remains appropriate when clinically indicated, particularly in patients at risk of volume depletion. Patient counseling should cover genital hygiene, hydration, recognition of symptoms suggestive of ketoacidosis, and temporary interruption during major illness or prolonged fasting. The balance between cardiovascular and renal benefit and adverse-event risk should be individualized.

10. Current Limitations and Evidence Gaps

Although the clinical evidence is extensive, several questions remain. First, no single mechanism fully explains the cardiovascular effects of SGLT2 inhibition. Renal hemodynamics, fluid handling, metabolic changes, vascular effects and direct myocardial pathways probably interact.

Second, evidence is strongest for heart failure and CKD. Claims regarding coronary disease, arrhythmias, cardiomyopathies and cerebrovascular protection should therefore be presented cautiously until supported by dedicated outcome trials.

Third, the optimal integration of SGLT2 inhibitors with other cardiometabolic therapies remains an evolving field. Combination strategies involving GLP-1 receptor agonists, mineralocorticoid receptor antagonists and other guideline-directed treatments may provide complementary benefits, but treatment sequencing and patient selection require continued study.

Finally, although emerging evidence supports efficacy in advanced CKD populations, prescribing at very low kidney function and in patients receiving dialysis requires careful interpretation of the specific drug label and available trial evidence.

FUTURE PERSPECTIVES

The future of SGLT2 pharmacology is likely to focus less on glucose lowering and more on targeted cardiorenal-metabolic protection. Research priorities include identifying patients who derive the greatest benefit, understanding direct myocardial mechanisms, defining optimal combinations with other cardiometabolic therapies, and evaluating possible roles in coronary syndromes, cardiomyopathies, arrhythmias and cardio-oncology. The field is also moving toward a broader cardiovascular-kidney-metabolic framework in which treatment decisions are based on organ protection rather than a single biochemical target. Recent reviews describe SGLT2 inhibitors as a bridge between metabolic, renal and cardiovascular pharmacology. [5,18]

CONCLUSION

SGLT2 inhibitors have undergone a major therapeutic transition. Initially developed to increase urinary glucose excretion in T2DM, they are now established cardiorenal therapies with clinically meaningful benefits that frequently occur independently of diabetes. Their most firmly supported cardiovascular applications are across the heart-failure spectrum, while their renal benefits extend to diabetic and selected non-diabetic CKD. The pharmacology of SGLT2 inhibition is multifaceted. Changes in sodium handling and tubuloglomerular feedback, lower intraglomerular pressure, modest fluid redistribution, metabolic adaptation and possible vascular, inflammatory and myocardial effects together provide a plausible explanation for the observed outcomes. Nevertheless, several mechanistic questions remain unresolved. Future research should distinguish established therapeutic indications from emerging hypotheses and should prioritize high-quality outcome trials. The continuing expansion of SGLT2 research illustrates a broader principle of pharmacotherapy: manipulation of a renal transport pathway can generate clinically important effects across multiple organ systems. SGLT2 inhibitors therefore represent a distinctive example of modern cardiorenal-metabolic pharmacology.

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