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Review Article

SGLT2 Inhibitors Beyond Glycemic Control: Emerging Therapeutic Applications, Clinical Evidence, Safety and Future Perspectives

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ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors were initially developed as antihyperglycemic agents for the treatment of type 2 diabetes mellitus. However, accumulating evidence from large randomized controlled trials has transformed their therapeutic position from glucose-lowering medicines into important cardiorenal-metabolic agents. Pharmacological inhibition of SGLT2 decreases renal glucose and sodium reabsorption, resulting in glucosuria, natriuresis and osmotic diuresis. These effects are accompanied by alterations in tubuloglomerular feedback, intraglomerular pressure, systemic hemodynamics, myocardial metabolism, inflammatory pathways, oxidative stress and renal energy metabolism. Major cardiovascular outcome trials demonstrated reductions in hospitalization for heart failure and favorable renal outcomes in individuals with type 2 diabetes. Dedicated heart-failure trials subsequently established benefits in patients with heart failure with reduced, mildly reduced and preserved ejection fraction, including individuals without diabetes. Similarly, CREDENCE, DAPA-CKD and EMPA-KIDNEY demonstrated clinically important kidney protection and slowing of chronic kidney disease progression. These findings have substantially broadened the role of SGLT2 inhibitors in contemporary pharmacotherapy. Emerging evidence is also evaluating their potential applications in metabolic dysfunction-associated steatotic liver disease, obesity-related metabolic disorders, hyperuricemia, anemia, polycystic ovary syndrome and other conditions; however, these applications remain less established than their cardiovascular and renal indications. Despite their favorable benefit-risk profile, SGLT2 inhibitors require appropriate patient selection and monitoring because genital mycotic infections, volume depletion, hypotension and rare euglycemic diabetic ketoacidosis may occur. This review summarizes the pharmacological basis, mechanisms, established cardiovascular and renal applications, emerging therapeutic uses, major clinical evidence, safety profile, drug interactions, patient-counselling considerations, limitations and future perspectives of SGLT2 inhibitors.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), heart failure (HF) and chronic kidney disease (CKD) are closely interconnected chronic disorders that contribute substantially to morbidity, mortality and healthcare utilization worldwide. Traditionally, pharmacotherapy for T2DM focused primarily on achieving glycemic targets and preventing microvascular and macrovascular complications. However, the modern approach to diabetes pharmacotherapy increasingly emphasizes cardiovascular, renal, metabolic and weight-related outcomes in addition to glycemic control.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors represent one of the most important developments in this transition. The first members of this class were introduced as glucose-lowering drugs based on their ability to inhibit glucose reabsorption in the proximal renal tubule. By promoting urinary glucose excretion, these drugs reduce plasma glucose concentrations independently of insulin secretion or insulin sensitivity.

The initial cardiovascular outcome trials produced an unexpected and clinically important observation: SGLT2 inhibitors could reduce hospitalization for heart failure and influence renal outcomes beyond what would be expected from their modest glucose-lowering effects. Subsequent dedicated trials in heart failure and CKD populations confirmed that their therapeutic benefits extended beyond patients with diabetes.

DAPA-HF demonstrated that dapagliflozin reduced worsening heart failure or cardiovascular death in patients with heart failure with reduced ejection fraction (HFrEF), irrespective of diabetes status. EMPEROR-Reduced demonstrated similar benefits with empagliflozin in HFrEF.

Subsequently, EMPEROR-Preserved and DELIVER extended the evidence to patients with preserved or mildly reduced ejection fraction. [1–4]

The renal evidence has been equally transformative. CREDENCE established renal protection with canagliflozin in patients with diabetic kidney disease, while DAPA-CKD and EMPA-KIDNEY demonstrated benefits across broader CKD populations, including patients without diabetes. [5–7]

Current diabetes guidelines therefore recognize SGLT2 inhibitors as important agents for reduction of cardiovascular and renal risk. The 2026 American Diabetes Association Standards of Care recommend an SGLT2 inhibitor with demonstrated benefit for people with T2DM and CKD, with initiation at an estimated glomerular filtration rate (eGFR) of ≥ 20 mL/min/1.73 m² in appropriate patients. The same guidance recommends proven SGLT2 inhibitor therapy for individuals with T2DM and established heart failure with preserved or reduced ejection fraction. [8,9]

The therapeutic evolution of SGLT2 inhibitors raises an important pharmacotherapeutic question: how can a class initially developed to reduce blood glucose produce clinically meaningful benefits in the heart and kidney, including in people without diabetes?

This review therefore examines the pharmacological basis and mechanisms of SGLT2 inhibition, established cardiovascular and renal applications, emerging therapeutic areas, major clinical trials, safety considerations, patient counselling and future research directions.

2. Pharmacological Basis of SGLT2 Inhibition



Glucose is freely filtered through the glomerulus and is normally almost completely reabsorbed in the proximal renal tubule. SGLT2, expressed predominantly in the early proximal tubule, is responsible for the majority of filtered glucose reabsorption. SGLT1 contributes to glucose recovery in the more distal proximal tubule.

SGLT2 transports glucose together with sodium across the apical membrane of proximal tubular epithelial cells. Inhibition of this transporter reduces sodium-glucose reabsorption and increases urinary glucose and sodium excretion.

The resulting glucosuria contributes to a reduction in plasma glucose and glycated hemoglobin. Unlike insulin secretagogues, SGLT2 inhibitors do not directly stimulate pancreatic insulin secretion

and therefore have a relatively low intrinsic risk of hypoglycemia when used alone.

Several SGLT2 or SGLT-related inhibitors are used clinically, including dapagliflozin, empagliflozin and canagliflozin. Ertugliflozin is another selective SGLT2 inhibitor used for diabetes management. Sotagliflozin inhibits both SGLT1 and SGLT2 and has also generated important cardiovascular and heart-failure evidence.

The clinical evidence and regulatory indications vary between individual agents and jurisdictions. Therefore, class effects should not automatically be interpreted as identical regulatory indications for every drug.

Table 1. Major SGLT2/SGLT-related inhibitors

Drug	Principal target	Major established therapeutic areas
Dapagliflozin	SGLT2	T2DM, HF, CKD
Empagliflozin	SGLT2	T2DM, HF, CKD
Canagliflozin	SGLT2	T2DM, diabetic kidney disease
Ertugliflozin	SGLT2	T2DM
Sotagliflozin	SGLT1/SGLT2	Selected HF/cardiorenal applications

3. Mechanisms of Action Beyond Glycemic Control

The benefits of SGLT2 inhibitors cannot be explained solely by urinary glucose excretion. Multiple complementary mechanisms are proposed.

SGLT2 inhibition increases urinary sodium and glucose excretion. Increased osmotic diuresis promotes fluid loss, while natriuresis reduces sodium retention. These effects may decrease plasma volume and venous congestion, particularly relevant to heart failure.

In diabetes, increased proximal tubular sodium-glucose reabsorption reduces sodium delivery to the macula densa. This can alter tubuloglomerular

feedback and contribute to increased intraglomerular pressure. SGLT2 inhibition increases sodium delivery to the macula densa and restores tubuloglomerular feedback. The resulting afferent arteriolar response reduces intraglomerular pressure and may contribute substantially to renoprotection.

SGLT2 inhibition is associated with an initial modest decline in eGFR in many patients, followed by slower long-term loss of kidney function. This early change is generally interpreted as reflecting reduced intraglomerular pressure rather than structural kidney injury.

SGLT2 inhibitors generally produce modest reductions in blood pressure through combined natriuretic, diuretic and vascular mechanisms.



They also produce modest weight reduction through urinary glucose loss and altered energy balance.

SGLT2 inhibition may alter myocardial substrate utilization, increase ketone-body availability, influence cytosolic sodium and calcium handling,

and affect mitochondrial function. Experimental and clinical studies also suggest effects on oxidative stress and inflammatory signaling. SGLT2 inhibitors may increase urinary uric acid excretion and serum hematocrit through effects on urate handling and erythropoiesis/iron metabolism.

Table 2. Proposed mechanisms beyond glycemic control

Mechanism	Potential consequence
Glycosuria	Reduced plasma glucose and caloric loss
Natriuresis	Reduced sodium retention
Osmotic diuresis	Reduced volume overload
Restoration of tubuloglomerular feedback	Reduced intraglomerular pressure
Blood-pressure reduction	Reduced cardiovascular load
Altered myocardial metabolism	Potential improvement in energetic efficiency
Reduced oxidative stress	Potential tissue protection
Reduced inflammatory signaling	Potential cardiorenal protection
Increased uricosuria	Reduced serum uric acid
Effects on erythropoiesis/iron metabolism	Increased hematocrit and potential oxygen-delivery effects

4. Cardiovascular Applications

The cardiovascular benefits of SGLT2 inhibitors represent one of the most important developments in modern cardiorenal pharmacotherapy. Early cardiovascular outcome trials in T2DM demonstrated reductions in heart-failure hospitalization, leading to dedicated HF trials.

In DAPA-HF, dapagliflozin significantly reduced the composite of worsening heart failure or cardiovascular death in patients with HFrEF. The primary outcome occurred in 16.3% of patients receiving dapagliflozin compared with 21.2% receiving placebo, corresponding to a hazard ratio of 0.74. Benefits were consistent in patients with and without diabetes. [1]

EMPEROR-Reduced similarly demonstrated that empagliflozin reduced cardiovascular death or hospitalization for HF in HFrEF. [2]

EMPEROR-Preserved randomized 5,988 patients with HF and ejection fraction >40% to empagliflozin or placebo. The primary outcome occurred in 13.8% versus 17.1%, corresponding to a hazard ratio of 0.79. The effect was mainly driven by reduced hospitalization for HF and was consistent regardless of diabetes status. [3]

DELIVER subsequently evaluated dapagliflozin in patients with HF and ejection fraction >40% and demonstrated a reduction in the composite of worsening HF or cardiovascular death. [4]

These trials support the role of SGLT2 inhibitors across the heart-failure spectrum. Their benefits in patients without diabetes indicate that mechanisms beyond glucose lowering are clinically important.



Table 3. Major cardiovascular outcome trials

Trial	Drug	Population	Major finding
EMPA-REG OUTCOME	Empagliflozin	T2DM + high CV risk	Reduced CV death and HF hospitalization
CANVAS Program	Canagliflozin	T2DM + high CV risk	Reduced major CV events; reduced HF hospitalization
DECLARE-TIMI 58	Dapagliflozin	T2DM + established/ high CV risk	Reduced HF hospitalization/CV death composite
DAPA-HF	Dapagliflozin	HFrEF ± diabetes	Reduced worsening HF/CV death
EMPEROR-Reduced	Empagliflozin	HFrEF ± diabetes	Reduced HF/CV outcomes
EMPEROR-Preserved	Empagliflozin	HFpEF ± diabetes	Reduced CV death/HF hospitalization
DELIVER	Dapagliflozin	HFmrEF/HFpEF	Reduced worsening HF/CV death
SOLOIST-WHF	Sotagliflozin	Recent worsening HF	Reduced CV death/HF hospitalization

5. Renal Applications

Diabetic kidney disease is a major complication of T2DM and an important cause of CKD and kidney failure. SGLT2 inhibitors have added a major therapeutic pathway for renal protection.

The CREDENCE trial evaluated canagliflozin in patients with T2DM, CKD and substantial albuminuria receiving renin-angiotensin system blockade. Canagliflozin significantly reduced the primary composite of kidney failure, doubling of serum creatinine, or renal/cardiovascular death. [5]

DAPA-CKD enrolled patients with CKD with and without T2DM. Dapagliflozin significantly reduced the risk of the composite renal/cardiovascular outcome. The inclusion of patients without diabetes demonstrated that

renoprotection is not simply a consequence of improved glycemic control. [6]

EMPA-KIDNEY further expanded the evidence for empagliflozin in CKD, including patients without diabetes and those with lower levels of albuminuria. [7]

Current ADA 2026 guidance recommends an SGLT2 inhibitor with demonstrated benefit in people with T2DM and CKD at eGFR ≥ 20 mL/min/1.73 m² and recommends continuation when tolerated until kidney failure. [8]

The glucose-lowering effect decreases as kidney function declines; however, cardiovascular and renal benefits may persist at lower eGFR levels. This distinction is important in pharmacotherapy: reduced glucose-lowering efficacy does not imply loss of cardiorenal benefit.

Table 4. Major renal outcome trials

Trial	Drug	Population	Major contribution
CREDENCE	Canagliflozin	T2DM + albuminuric CKD	Demonstrated renal protection
DAPA-CKD	Dapagliflozin	CKD ± T2DM	Reduced renal/CV outcomes
EMPA-KIDNEY	Empagliflozin	Broad CKD population ± T2DM	Expanded evidence across CKD
EMPA-REG OUTCOME	Empagliflozin	T2DM + CV risk	Important secondary renal benefits
CANVAS	Canagliflozin	T2DM + CV risk	Slowed renal disease progression



6. Cardiorenal-Metabolic Therapeutic Role

The increasing convergence of diabetes, CKD, HF and obesity has led to the concept of cardiorenal-metabolic disease. SGLT2 inhibitors influence several components of this interconnected disease network.

In the kidney, they reduce intraglomerular pressure and slow CKD progression. Through natriuresis and osmotic diuresis, they modify volume status. In the heart, they reduce congestion and HF hospitalization. Metabolically, they produce glucosuria, modest weight reduction and altered substrate utilization. They may also influence blood pressure, uric acid, inflammation and oxidative stress.

This multidimensional activity distinguishes SGLT2 inhibitors from traditional glucose-lowering therapies.

7. Emerging Therapeutic Applications

Metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly associated with obesity, insulin resistance, T2DM and cardiovascular disease. SGLT2 inhibitors have demonstrated reductions in body weight, glycemic exposure and, in some studies, liver enzymes and measures of hepatic steatosis. Potential mechanisms include reduced caloric availability, improved insulin sensitivity, weight reduction and altered lipid metabolism. However, evidence for histological improvement and prevention of

clinically significant liver outcomes remains less definitive than evidence for HF and CKD.

SGLT2 inhibitors produce modest weight reduction but are substantially less potent than dedicated modern anti-obesity pharmacotherapies. Their role in obesity is therefore likely to be as part of comprehensive cardiometabolic management.

SGLT2 inhibitors may increase urinary uric acid excretion and reduce serum urate. This is of interest in metabolic syndrome, CKD and cardiovascular disease, although they should not currently be regarded as substitutes for established urate-lowering therapy.

SGLT2 inhibitors can increase hematocrit and may influence erythropoietin and iron metabolism. These effects are scientifically important but do not make SGLT2 inhibitors conventional treatments for anemia.

SGLT2 inhibitors have also been explored in polycystic ovary syndrome because of effects on weight, glucose metabolism and insulin resistance. Early studies are promising but limited, and pregnancy-related safety considerations are important.

Changes in urinary glucose, sodium, volume and uric acid handling have prompted investigation of SGLT2 inhibitors in nephrolithiasis. Evidence remains insufficient to recommend them specifically for kidney-stone prevention.

Table 5. Emerging applications

Potential application	Evidence status	Main rationale
MASLD	Emerging	Weight, metabolic and hepatic effects
Obesity	Adjunctive/emerging	Modest weight reduction
Hyperuricemia	Emerging	Increased uricosuria
Anemia/erythropoiesis	Mechanistic/emerging	Increased hematocrit
PCOS	Early clinical evidence	Metabolic effects
Kidney stones	Investigational	Changes in urinary composition
Hypomagnesemia	Emerging	Potential effects on magnesium handling



8. Safety and Adverse Effects

SGLT2 inhibitors are generally well tolerated, but their mechanism produces characteristic adverse effects. Genital mycotic infections are the most characteristic class effect. Patients should receive counselling regarding genital hygiene and early recognition of symptoms.

Volume depletion and hypotension may occur because of osmotic diuresis and natriuresis, particularly in older adults and patients taking loop diuretics. Assessment of volume status and concomitant therapy is important.

Diabetic ketoacidosis is uncommon but clinically important. SGLT2 inhibitors can produce DKA with only modestly elevated blood glucose. Risk factors include prolonged fasting, acute illness, severe carbohydrate restriction, dehydration,

alcohol intake, insulin deficiency and perioperative stress.

An early reduction in eGFR may occur after initiation and usually reflects hemodynamic changes. A large or persistent decline requires clinical evaluation.

Hypoglycemia risk is low when SGLT2 inhibitors are used alone but may increase with insulin or insulin secretagogues.

Fournier's gangrene is very rare but serious. Patients should seek urgent medical attention for severe genital or perineal pain, swelling, fever or systemic symptoms.

Early concerns regarding amputation and fracture risk were particularly associated with canagliflozin. Subsequent evidence has been more nuanced, and baseline patient characteristics should be considered.

Table 6. Adverse effects and management

Adverse effect	Clinical consideration	Management
Genital mycotic infection	Relatively common class effect	Hygiene, early treatment
Volume depletion	Higher risk with diuretics/older age	Assess volume status
Hypotension	May occur with diuretic effect	Review antihypertensives/diuretics
DKA	Rare, may be euglycemic	Recognize symptoms; stop during acute risk
Hypoglycemia	Mainly with insulin/secretagogues	Adjust concomitant therapy if required
UTI	Usually mild	Treat appropriately
Acute eGFR change	Early hemodynamic effect possible	Monitor renal function
Fournier's gangrene	Very rare	Urgent evaluation
Foot complications	Patient-dependent	Foot assessment and counselling

9. Drug Interactions and Clinical Considerations

SGLT2 inhibitors have relatively few classical pharmacokinetic drug interactions, but clinically important pharmacodynamic interactions exist.

Concurrent loop or thiazide diuretics may increase volume depletion. In patients who are clinically

euvolemic, diuretic requirements may need reassessment.

Combination with insulin or insulin secretagogues may increase hypoglycemia risk, and adjustment of concomitant therapy may be appropriate in selected patients.



The additional blood-pressure-lowering effect may require monitoring in patients receiving multiple antihypertensive agents.

SGLT2 inhibitors are frequently used alongside ACE inhibitors or ARBs in CKD. Their mechanisms are complementary, although renal function and volume status should be monitored.

Patients receiving medications that can impair renal perfusion, particularly in the presence of dehydration, require appropriate clinical assessment.

10. Perioperative and Acute-Illness Management

One of the most important practical issues is temporary interruption during situations associated with increased DKA risk.

SGLT2 inhibitors should generally be withheld before major surgery according to current local

prescribing guidance and restarted only when the patient is clinically stable, adequately hydrated and eating normally.

Temporary interruption may also be appropriate during severe acute illness, prolonged fasting or significant dehydration. Patients should receive clear sick-day counselling.

11. Patient Counselling

Patient education is essential for safe and effective therapy. Patients should understand administration, hydration requirements, genital hygiene, symptoms of DKA, sick-day instructions, perioperative interruption, foot care where relevant, and the increased hypoglycemia risk when SGLT2 inhibitors are combined with insulin or sulfonylureas.

Patients should also be instructed to report severe or persistent urinary or genital symptoms and symptoms suggestive of ketoacidosis.

Table 7. Patient-counselling checklist

Counselling point	Message to patient
Administration	Take exactly as prescribed
Hydration	Maintain adequate fluid intake unless fluid restriction is prescribed
Genital hygiene	Maintain hygiene and report symptoms early
DKA symptoms	Seek care for nausea, vomiting, abdominal pain or unusual breathing
Acute illness	Follow sick-day instructions
Surgery	Inform healthcare team before planned procedures
Foot care	Inspect feet regularly when appropriate
Hypoglycemia	Extra caution if using insulin/sulfonylurea
Urinary symptoms	Report severe or persistent symptoms
Pregnancy	Inform clinician if pregnancy occurs or is planned

12. Special Populations

Older adults may derive substantial cardiovascular and renal benefit but can be more vulnerable to volume depletion, hypotension and genitourinary adverse effects. Treatment should be individualized according to renal function, blood pressure, frailty and concomitant medications.

Patients with CKD may benefit even when glucose-lowering efficacy is reduced at lower eGFR. Patients with HF may receive SGLT2 inhibitor therapy irrespective of diabetes status when supported by the specific agent's approved indication and guidelines.



SGLT2 inhibitors are not routine therapies during pregnancy because of limited human safety data and concerns arising from developmental kidney biology. They should not be used casually in pregnancy.

Temporary discontinuation may be appropriate during severe illness, fasting, dehydration or other situations associated with increased DKA risk.

13. Major Clinical Trials and Evidence Synthesis

The clinical evidence for SGLT2 inhibitors is supported by a large body of randomized controlled trials. EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 established

cardiovascular and HF signals in T2DM. CREDENCE, DAPA-CKD and EMPA-KIDNEY established renal protection across diabetic and non-diabetic CKD populations. DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved and DELIVER established benefits across the HF spectrum.

A 2024 systematic review and meta-analysis across CKD populations found reductions in mortality, cardiovascular death, kidney failure and hospitalization for HF, with no credible subgroup interaction based on diabetes status, HF status, eGFR or albuminuria. Large meta-analyses across the cardiometabolic spectrum have also demonstrated consistent reductions in HF hospitalization.

Table 8. Landmark SGLT2 inhibitor trials

Trial	Drug	Population	Key outcome
EMPA-REG OUTCOME	Empagliflozin	T2DM/high CV risk	Major CV benefit
CANVAS	Canagliflozin	T2DM/high CV risk	CV and renal benefits
DECLARE-TIMI 58	Dapagliflozin	T2DM/high CV risk	HF/renal benefit
CREDENCE	Canagliflozin	T2DM + CKD	Renal protection
DAPA-HF	Dapagliflozin	HFrEF ± diabetes	Reduced worsening HF/CV death
EMPEROR-Reduced	Empagliflozin	HFrEF ± diabetes	Reduced HF/CV outcomes
DAPA-CKD	Dapagliflozin	CKD ± diabetes	Reduced renal/CV outcomes
EMPEROR-Preserved	Empagliflozin	HFpEF ± diabetes	Reduced HF/CV outcomes
DELIVER	Dapagliflozin	HFmrEF/HFpEF	Reduced worsening HF/CV death
EMPA-KIDNEY	Empagliflozin	CKD ± diabetes	Slower CKD progression
SOLOIST-WHF	Sotagliflozin	Recent worsening HF	Reduced CV death/HF hospitalization

14. Pharmacotherapeutic Positioning

The appropriate role of SGLT2 inhibitors depends on the patient's dominant clinical risk.

In T2DM with CKD, an SGLT2 inhibitor with demonstrated renal benefit should be considered as part of comprehensive CKD and cardiovascular risk reduction.

In T2DM with HF, an SGLT2 inhibitor with demonstrated HF benefit should be considered

independent of the need for additional glucose lowering.

In HF without diabetes, SGLT2 inhibitors can provide HF benefit when clinically indicated.

In CKD without diabetes, evidence from DAPA-CKD and EMPA-KIDNEY supports selected SGLT2 inhibitors.

In patients primarily seeking weight loss, SGLT2 inhibitors should not be regarded as first-line dedicated anti-obesity drugs.



Table 9. Practical pharmacotherapeutic positioning of SGLT2 inhibitors

Clinical setting	Evidence maturity	Main rationale	Key caution
T2DM + CKD	Established	Slow CKD progression and reduce cardiorenal events	Assess eGFR, volume status and sick-day risks
Heart failure across EF phenotypes	Established	Reduce worsening HF and HF hospitalization	Monitor volume status and renal function
CKD without diabetes	Established for selected agents	Renal and cardiovascular protection	Use agent-specific approved indication
Weight management	Adjunctive/emerging	Modest weight and metabolic effects	Not a substitute for dedicated anti-obesity therapy
MASLD	Emerging	Possible improvement in steatosis and metabolic measures	Hard hepatic outcomes remain uncertain
Hyperuricemia	Emerging	Increased urinary urate excretion	Not a substitute for urate-lowering therapy
PCOS	Early evidence	Potential metabolic and weight effects	Limited evidence; pregnancy considerations

15. Limitations and Unmet Needs

Clinical outcomes are not completely uniform across all SGLT2 inhibitors and all disease populations. Class effects should therefore be interpreted cautiously.

Cardiovascular benefits are particularly strong for HF outcomes, whereas effects on atherosclerotic events vary between trials. Evidence for emerging indications such as MASLD, PCOS and kidney stones remains less mature than evidence for HF and CKD.

Many trials have specific inclusion and exclusion criteria, limiting generalizability to very frail patients and populations underrepresented in clinical trials.

Real-world implementation remains suboptimal because of cost, clinician familiarity, concern about adverse effects, therapeutic inertia and fragmentation between diabetes, cardiology and nephrology care.

Finally, patient education is essential because rare but serious adverse effects such as euglycemic DKA can occur.

16. Future Perspectives

Future research will likely focus on identifying patients who derive the greatest absolute benefit from SGLT2 inhibition. Baseline kidney function, albuminuria, HF phenotype, congestion, diabetes status and cardiovascular risk may influence absolute benefit.

Combination pharmacotherapy is another important area. SGLT2 inhibitors may be combined with GLP-1 receptor agonists, mineralocorticoid receptor antagonists and renin-angiotensin system blockers because these therapies target different biological pathways.

Further research is required in MASLD, obesity, PCOS, hyperuricemia and other emerging indications. Trials should prioritize hard clinical outcomes rather than relying only on surrogate biomarkers.

Implementation science is also important because efficacy in randomized trials does not automatically translate into population-level benefit. Improving prescribing, adherence, patient



education and monitoring could substantially increase real-world impact.

Biomarkers capable of predicting response may eventually support more personalized use of SGLT2 inhibitors.

A further pharmacotherapeutic implication is that the value of SGLT2 inhibitors should be judged according to the patient's dominant risk rather than HbA1c alone. In a patient with T2DM and CKD or heart failure, the indication may persist even when additional glucose lowering is modest. Conversely, prescribing solely for weight loss or speculative metabolic benefits is difficult to justify when more effective indication-specific therapies are available. This risk-based positioning can help reduce therapeutic inertia while avoiding overextension of the evidence.

Taken together, the recent literature supports a hierarchy of evidence. Heart failure and chronic kidney disease represent the strongest non-glycemic therapeutic domains because they are supported by large randomized outcome trials and consistent meta-analytic evidence. Weight reduction, MASLD, urate lowering, anemia-related mechanisms and PCOS remain areas of scientific interest, but their clinical positioning should remain adjunctive or investigational until hard-outcome evidence and regulatory indications are sufficiently established.

The evidence for metabolic and hepatic indications remains promising but less mature. A 2025 systematic review and meta-analysis of 11 randomized studies involving 805 patients with nonalcoholic fatty liver disease reported improvements in liver enzymes, body weight, BMI and selected metabolic parameters. However, biochemical and imaging improvements should not be equated with proven reductions in cirrhosis, liver failure or hepatocellular carcinoma. [39]

MASLD should therefore currently be considered an emerging rather than an established primary indication.

Safety evidence continues to support a favorable overall benefit-risk profile when patients are appropriately selected. A network meta-analysis involving 85,997 participants found an increased risk of diabetic ketoacidosis compared with control, reinforcing the importance of temporary interruption during prolonged fasting, acute illness and perioperative periods. [37] A 2025 meta-analysis of 98 randomized controlled trials involving 91,756 participants found a clear increase in genital mycotic infections, whereas the association with urinary tract infection was less consistent. [38]

A 2024 meta-analysis of 15 trials involving more than 100,000 participants reported reductions in first hospitalization for heart failure across heart failure, diabetes, CKD and atherosclerotic cardiovascular disease populations. Cardiovascular mortality benefits were more variable across phenotypes, illustrating why SGLT2 inhibitors should not be described as producing identical effects on every cardiovascular endpoint. [36]

A broader systematic review and meta-analysis including 13 randomized trials and 29,614 patients with CKD found reductions in all-cause mortality, cardiovascular death, kidney failure and hospitalization for heart failure, without credible subgroup differences according to diabetes status, heart-failure status, eGFR or albuminuria. Importantly, the absolute benefit varied according to baseline risk, emphasizing that relative risk reduction should not be interpreted as identical absolute benefit for every patient. [35]

Recent evidence reinforces the central cardiorenal role of SGLT2 inhibitors while also clarifying the



limits of extrapolation to emerging indications. A 2024 systematic review and meta-analysis of 12 studies involving 89,191 participants with chronic kidney disease found a 32% relative reduction in heart-failure events with SGLT2 inhibition, with broadly consistent benefit across baseline eGFR strata. This supports the concept that heart-failure prevention is not dependent on the glucose-lowering effect of the class. [34]

CONCLUSION

SGLT2 inhibitors have undergone a remarkable therapeutic transformation. Initially developed as glucose-lowering agents for T2DM, they have evolved into important cardiorenal-metabolic therapies supported by large randomized clinical trials.

Their benefits extend beyond glycemic control and include reductions in hospitalization for HF, slowing of CKD progression and improvement in cardiovascular and renal outcomes. Importantly, dedicated HF and CKD trials demonstrate that many of these benefits occur in individuals without diabetes.

The pharmacological effects of SGLT2 inhibition are multifactorial and include glycosuria, natriuresis, osmotic diuresis, restoration of tubuloglomerular feedback, reduction of intraglomerular pressure, altered myocardial metabolism, modulation of inflammatory and oxidative pathways, and effects on erythropoiesis and uric acid handling.

DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved and DELIVER established an important role in HF across the ejection-fraction spectrum. CREDENCE, DAPA-CKD and EMPA-KIDNEY similarly established the importance of SGLT2 inhibitors in renal protection.

Emerging applications such as MASLD, obesity-related metabolic disease, hyperuricemia, anemia and PCOS are promising but require additional clinical evidence and should not yet be considered equivalent to established HF and CKD indications.

From a pharmacotherapeutic perspective, SGLT2 inhibitors represent a paradigm shift from disease-specific glucose lowering toward integrated cardiorenal-metabolic risk modification. Appropriate patient selection, renal-function assessment, monitoring, adverse-effect prevention and patient counselling are essential to maximize therapeutic benefit.

Future research should focus on personalized treatment strategies, combination therapy, emerging indications and implementation of evidence-based SGLT2 inhibitor therapy in routine clinical practice.

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