Cardiovascular Disease Prevention and Control

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Review

Emerging Role of SGLT2 Inhibitors Beyond Glycemic Control: "Cardiovascular and Renal Benefits and Risks"

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Abstract

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as empagliflozin (EMPA) and dapagliflozin (DAPA), represent a significant advancement in the management of metabolic and cardiovascular disorders. Originally developed to enhance glycemic control in type 2 diabetes mellitus, their benefits now extend beyond glucose reduction, offering cardiovascular and renal protection. Accumulating clinical data highlight their effectiveness in reducing the risk of heart failure, slowing renal disease progression, and improving survival, independent of their glycemic effects. The pleiotropic actions of SGLT2 inhibitors, are attributed to a combination of mechanisms: improved hemodynamics, natriuresis, normalization of tubule glomerular feedback, reduction of oxidative stress, and inflammation. These agents have also shown positive effects on weight reduction, blood pressure, and metabolic homeostasis, further enhancing their therapeutic profiles in cardiorenal and metabolic disorders. Despite their well-established efficacy, SGLT2 inhibitors have anticipated adverse effects, such as vaginal infections, mild volume depletion, and, in rare cases, euglycemic diabetic ketoacidosis (DKA). However, these risks are generally manageable through appropriate patient selection, education, and monitoring. The overall safety profile remains favorable, with consistent outcomes across large-scale randomized controlled trials and real-world studies. This article aims to provide insight and analysis into the expanding role of SGLT2 inhibitors, focusing not only on their traditional role but also on their benefits and side effects on the kidneys and heart. In an effort to establish the benefits of these inhibitors in protecting both the heart and kidneys in diabetic and non-diabetic patients, this article seeks to present the latest studies on these inhibitors. Additionally, it aims to offer a balanced approach that physicians can leverage in the role of these inhibitors in treating both the heart and kidneys.

Keywords

SGLT2 inhibitors, Empagliflozin, Dapagliflozin, Cardiovascular protection, Heart failure with preserved ejection fraction

Article History

Received: 26 November 2025
Revised: 02 March 2026
Accepted: 05 March 2026
Available Online: 24 March 2026

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major global health concern. The International Diabetes Federation estimates that 537 million people worldwide had diabetes in 2021, and that number is expected to increase to 643 million by 2030 [1]. People with T2DM not only have chronic hyperglycemia but also a significantly increased risk of cardiovascular disease (CVD) and chronic kidney disease (CKD), which together account for the majority of morbidity and mortality in this population [2]. Advances in glucose-lowering medications notwithstanding, traditional treatments predominantly focused on glycemic management have thus far proven ineffective at reducing long-term cardiorenal outcomes, revealing a significant unmet clinical need. The treatment of type 2 diabetes using sodium-glucose cotransporter-2 (SGLT2) inhibitors has been a paradigm shift. Approximately 90% of filtered glucose is reabsorbed by SGLT2, which is largely expressed in the S1 segment of the proximal convoluted tubule (PCT). On the other hand, the rest of the reabsorption of glucose is mediated by SGLT1, which is mainly located in the intestinal epithelium and the distal part of the proximal tubule. SGLT2 inhibition is independent of insulin and inhibits the reabsorption of glucose by the kidneys, causing glucosuria, osmotic diuresis, and natriuresis. Empagliflozin (EMPA), dapagliflozin (DAPA), canagliflozin, and ertugliflozin are clinically approved SGLT2 inhibitors.

Although these compounds vary slightly in their chemistry, PK properties, and receptor affinity, they all selectively inhibit SGLT2. These drugs have a once-a-day dosage and an efficient route of absorption, contributing to their widespread use as therapeutic drugs. Most significantly, cardiovascular and renal outcome studies have recently identified their efficacy not only in glycemic regulation. In addition to the physiological aspects, the glomerular filtration rate (GFR) and metabolic clearance rate are directly associated with glucose filtration and reabsorption. A person normally filters 180 g of glucose daily with complete reabsorption. However, glucose hyperfiltration triggers nephron damage in patients with type 2 diabetes due to hyperglycemia. Although indices such as the homeostatic model assessment of insulin resistance (HOMA-IR) help understand metabolic disturbances, factors such as glycated hemoglobin (HbA1c) help understand cumulative exposure to glucose. SGLT2 inhibitors have beneficial effects on these pathophysiological processes. They reduce the load on the proximal tubules and restore tubuloglomerular feedback. SGLT2 inhibitors markedly reduce the risk of hospitalization due to heart failure, slow the progression of CKD, and decrease cardiovascular mortality among both diabetic and non-diabetic individuals, based on key randomized trials such as DAPA-CKD, EMPEROR, and EMPA-KIDNEY [3-7].

These benefits appear to be independently unaltered by the level of preexisting hyperglycemia, thus indicating the broader role of SGLT2 inhibitors in reducing cardiorenal risk. Their renoprotective effect can also be observed from the reduction in albuminuria, which serves as a surrogate marker for the progression of renal disease [8]. Although the tolerability profile of SGLT2 inhibitors is generally good, there are some safety concerns regarding their use, including hypotensive episodes, genital mycotic infections, volume depletion, and occasional cases of euglycemic diabetic ketoacidosis (DKA). However, the benefit-to-risk ratios are substantially in favor of administering these drugs [9] Inhibitors of SGLT2 are increasingly recognized as integral components of modern cardiorenal therapies and not solely agents for lowering blood glucose levels as a consequence of accumulating clinical and molecular evidence. The purpose of this review is to examine the available information on outcomes with respect to both CVD and renal effects and systematically discuss the mechanisms of action and related outlooks for therapies that use SGLT2 inhibitors as a means to control glycemia.

2. Methodology

A structured literature review was conducted using PubMed, Scopus, Web of Science, and Google Scholar to identify studies published between 2015 and 2025 that evaluated the cardiovascular and renal effects of SGLT2 inhibitors beyond glycemic control. Randomized controlled trials, observational studies, systematic reviews, and meta-analyses reporting cardiorenal outcomes were included. Studies focusing solely on glycemic endpoints were excluded. Relevant data were narratively synthesized, with emphasis on large outcome trials and guideline-supported evidence.

3. Mechanism of Action of SGLT2 Inhibitors

3.1 Renal Glucose Handling

Approximately 90% of glucose reabsorption is inhibited by SGLT2 inhibitors, primarily in the PCT. As a result of negative energy balance, this insulin-independent mechanism promotes glucosuria through the reduction of blood glucose levels and a small amount of weight loss [10]. The most well-known mechanism of SGLT2 inhibitors is their renal action.

3.2 Hemodynamic Effects

SGLT2 inhibitors have been clinically shown to have hemodynamic actions in addition to their glucose-lowering action. Their properties as osmotically acting diuretics and natriuretics lead to a small volume reduction of plasma and interstitial fluid quantities, resulting in a reduction in blood pressure without any compensation by tachycardia and

reductions in cardiac preload and afterload [11]. Enhanced sodium secretion at the macula densa at the renal level triggers the restoration of tubuloglomerular feedback with afferent vasoconstriction and reduced intraglomerular pressure, a very important action contributing to renal protection.

3.3 Metabolic Reprogramming

Recent studies have suggested a link between adaptive metabolic rewiring in cardiac and renal cells and SGLT2 inhibitors. Increased uptake of fatty acids and ketone bodies, which are considered more oxygen-efficient metabolites, could occur due to reduced glucose entry. Although this is believed to increase myocardial energy efficiency and reduce oxidative stress, this process is still under investigation and has not yet been validated in a clinical environment [12].

3.4 Erythropoiesis and Oxygen Delivery

Clinical trials have shown a positive impact of SGLT2 inhibitors on hematocrit and hemoglobin levels. The mechanism behind this action is assumed to be mediated, at least to some extent, through increased erythropoietin secretion and better renal oxygenation secondary to decreased tubular workload. Increased renal and, therefore, tissue oxygenation can also contribute to improvement through better perfusion and organ function, especially in patients with heart failure (HF) and CKD [13].

3.5 Endothelial and Mitochondrial Effects

Animal and early transitional studies have shown promise regarding the endothelial and mitochondrial effects of SGLT2 inhibitors. Experimental findings have shown increased biogenesis, reduced oxidative phosphorylation, and lower production of reactive oxygen species. Additionally, some emerging data suggest increased endothelial bioavailability of nitric oxide and reduced vascular inflammation. These potential mechanisms, while mostly investigational, have yet to be confirmed for their clinical relevance to cardiovascular risk reduction [14].

4. Cardiovascular Benefits of SGLT2 Inhibitors

SGLT2 inhibitors have proven substantial cardiovascular benefits not only in glycemic control but also in patients with heart failure and T2DM, have emerged as important adjuncts in the management of heart failure and cardiovascular disease because of their outstanding clinical efficacy. The use of SGLT2 inhibitors has consistently resulted in a substantial reduction in heart failure hospitalization, major adverse cardiovascular events (MACE), and CVD mortality, as established by various randomized studies and meta-analyses [15,16]. As discussed earlier, hemodynamic and metabolic changes are the primary contributing factors to the cardiovascular benefits observed in clinical studies. SGLT2 inhibitors reduce intravascular volume and afterload by promoting osmotic diuresis and natriuresis. Importantly, there is a reduction in blood pressure without compensatory tachycardia, which predisposes the patient to greater stability with less cardiac stress [16].

SGLT2 inhibitors also induce salutary myocardial metabolic remodeling independent of hemodynamic effects. These compounds enhance myocardial energy efficiency and reduce oxygen demand by promoting a shift in cardiac substrate utilization from glucose to fatty acids and ketone bodies. This enhanced metabolic flexibility is particularly advantageous in heart failure with reduced ejection fraction (HFrEF), in which impaired myocardial energetics play critical roles in systolic dysfunction and disease progression [17]. SGLT2 inhibitors may play a role in preventing detrimental cardiac remodeling, as recent studies established. The decrease in myocardial fibrosis and ventricular stiffness has been ascribed to anti-inflammatory and antifibrotic properties, in part explained by the inhibition of the NLRP3 inflammasome, reduction of oxidative stress, and suppression of pro-inflammatory cytokine signling [18]. As established by the findings concerning cardiac magnetic resonance imaging (CMR), there was an improvement in diastolic relaxation and a decrease in the left ventricular mass index, establishing a positive effect at the structural level, despite the lack of impact on systemic hemodynamics [19].

SGLT2 inhibitors have been shown to augment mitochondrial function and reduce oxidative injury to cardiomyocytes at the cellular level. Ischemia and oxidative resistance in the myocardium can be increased when the AMPK-PGC1α signaling pathway is stimulated because it stimulates mitochondrial biogenesis, thereby correcting energy dysfunction at the cellular level [20,21]. There are also some case reports showing augmentation of endothelial function, such as higher numbers of mobilized endothelial progenitor cells, which can collectively lead to increased cardiac perfusion. Recently, the potential role of SGLT2 inhibitors in heart failure with preserved ejection fraction (HFpEF) has received increasing attention. Although various trials have revealed a reduction in hospitalization events of Heart Failure, their overall efficacy remains ambiguous, and the mortality benefit has yet to be confirmed. Future studies are likely to elucidate the precise role of SGLT2 inhibitors in the treatment of HFpEF and provide more information about the target patients likely to gain the most benefits from their use [16,18].

5. Renal Protection of SGLT2 Inhibitors

SGLT2 inhibitors have become key disease-modifying drugs that exhibit considerable renoprotective benefits beyond

lowering blood glucose. Clinical and experimental evidence has demonstrated that these medications reduce the burden of kidney failure in both diabetic and nondiabetic populations, decrease albuminuria, and retard the progression of CKD [22].

5.1 Hemodynamics and Tubuloglomerular Feedback

SGLT2 inhibitors primarily act on the PCT to inhibit glucose and sodium reabsorption, thereby increasing the sodium supply to the macula densa. Restoration of tubuloglomerular feedback is associated with afferent arteriolar vasoconstriction and a reduction in intraglomerular pressure, as shown in Figure 1. This action dampens glomerular hyperfiltration, retarding the progression of CKD and preserving long-term renal function [23]. Experimental findings also suggest that enhanced renal cellular resilience is a consequence of increased tubular oxygenation and reduced stress [24].

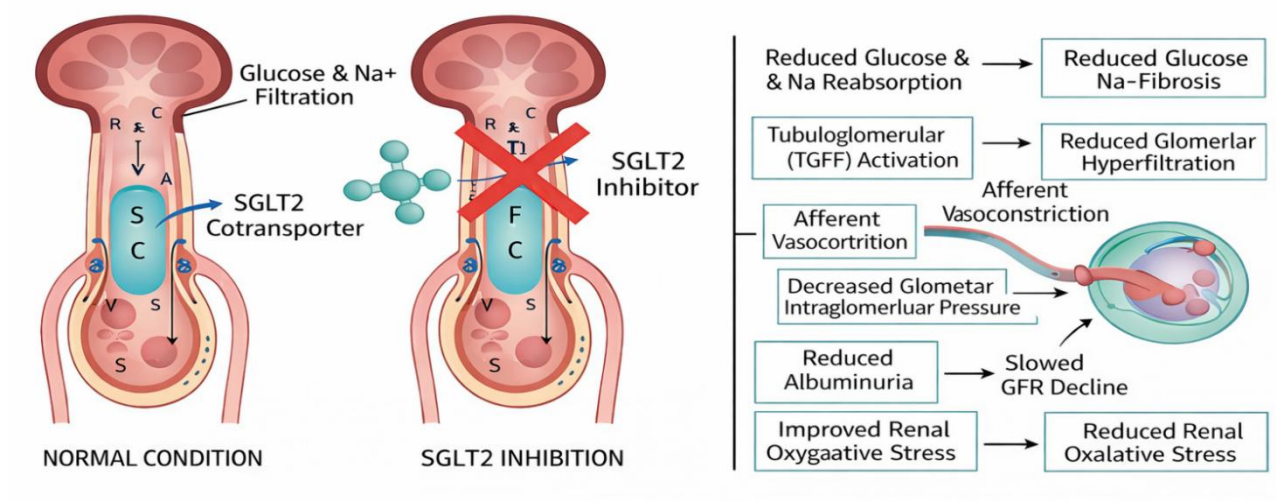

Figure 1. Renal hemodynamic and tubuloglomerular feedback effects of SGLT2 inhibitors. By inhibiting glucose and sodium reabsorption in the proximal tubule, these agents increase sodium delivery to the macula densa, thereby restoring tubuloglomerular feedback. This mechanism induces afferent arteriolar vasoconstriction, lowers intraglomerular pressure, and mitigates hyperfiltration. Collectively, these actions contribute to renal protection, improved oxygenation, and reduced progression of CKD.

5.2 Effects on Albuminuria and Estimated Glomerular Filtration Rate (eGFR) Decline

SGLT2 inhibitors have caused substantial reductions in albuminuria and slowed eGFR decline in randomized clinical trials. Compared with active therapy, both DAPA and canagliflozin reduced the risk of sustained eGFR decline, end-stage kidney disease (ESKD), and kidney death in the DAPA-CKD and CREDENCE trials [25,26]. Additionally, these benefits were observed in both diabetic and nondiabetic CKD patients, confirming an extrarenal mechanism of action.

5.3 Metabolic and Anti-Inflammatory Effects

SGLT2 inhibitors also exert additional kidney benefits via metabolic and inflammatory modulation and hemodynamic stabilization, in addition to their role in hemodynamic stabilization. They reduce oxidative stress, suppress the synthesis of pro-inflammatory cytokines, and reduce renal fibrosis based on preliminary studies and early clinical trials [3,27,28]. Furthermore, experimental evidence also supports an increase in the use of oxygen in the kidney and improved mitochondrial function that could lower hypoxia-related tubular injury [3,24,29]. Nevertheless, rather than playing a definitive role in therapy, these mechanisms are best viewed as supplementary mechanisms.

5.4 Clinical Trial Evidence and Guideline Implications

The renoprotective benefits of SGLT2 inhibitors have been confirmed through large, long-term outcome studies. In the key composite endpoint of sustained eGFR deterioration, ESKD, or renal or cardiovascular death, the risk reduction was 39% in the DAPA-CKD study [3]. In the EMPA-KIDNEY study, the risk reduction in kidney disease progression endpoints was confirmed in a broad CKD population, almost half of whom were not diabetic, showing the greatest benefits [30]. In light of the renoprotective efficacy of SGLT2 inhibitors, the kidney disease: Improving global outcomes (KDIGO) and American Diabetes Association (ADA) clinical practice guidelines recommend first-line disease-modifying treatment of CKD with albuminuria, regardless of the presence of diabetes.

In general, SGLT2 inhibitors are well-tolerated. However, rare cases of euglycemic ketoacidosis have been reported, although vaginal mycosis and mild volume depletion are more frequent adverse events. In advanced CKD, these potential issues can be prevented by patient selection, education, and adjusting the medication dosage.

6. Safety Profile and Risks

SGLT2 inhibitors are presumed to have a favorable safety profile in patients with metabolic, cardiovascular, and renal diseases. Nevertheless, their growing use has led to several common and uncommon adverse drug reactions that require careful patient selection, monitoring, and risk minimization strategies [31]. Long-term and uncommon safety issues are still being slowly understood through post-marketing surveillance studies. Vaginal infections are seen in 5% to 10% of patients, while the incidence of significant hypovolemia is mostly in the initial phase of the treatment

7. Specific Adverse Events

7.1 General Tolerability and Adverse Events

Most episodes of adverse effects are mild to moderate and transient; SGLT2 inhibitors are generally well tolerated. Genital mycotic infections, mild volume depletion, and transient elevation of blood creatinine concentration on the start of drug therapy are the three main adverse effects that could be encountered by patients taking SGLT2 inhibitors [32]. This could be attributed to osmotic diuresis and enhanced glucose excretion [33].

7.2 Risk of Genitourinary Infections

The most common source of side effects is genital mycotic infections, particularly in women and uncircumcised men. Fungal colonization is encouraged due to higher glucose levels in their urine [34]. Most of these infections can be effectively treated with standard antifungal therapy and rarely require drug discontinuation. Recurrences can be effectively reduced through preventive educational counseling on personal hygiene and early recognition of events [35]. Compared to placebo trials in large cardiovascular outcome studies such as DECLARE TIMI 58, no significant rise in pyelonephritis or serious urinary tract infections has been observed [36]. Occasionally, rare and severe infections like Fournier's gangrene have emerged. Although the absolute risk is extremely low, health practitioners must remain vigilant in patients at risk.

7.3 Volume Depletion and Hemodynamic Concerns

Through natriuresis and osmotic diuretic effects, SGLT2 inhibitors can induce slight intravascular volume reduction, especially in the elderly, in patients with pretreatment hypotension, or in the presence of concomitant loop diuretic therapy [37]. Hypotension, although infrequent, can be largely prevented by proper hydration, slow dosage escalation, and adjustment of concomitant antihypertensive drugs. A temporary reduction in eGFR also commonly occurs following the onset of treatment, which gradually normalizes with time and does not indicate any underlying kidney affection [38].

7.4 Metabolic Risks: Euglycemic DKA

The rare but serious adverse effect of SGLT2 inhibitor medicines is euglycemic diabetic ketoacidosis, also known as euDKA. Patients using insulin, those with serious illness, prolonged fasting, or sudden reduction in insulin intake are at greater risk [39]. The incidence rate, in most cases, is less than 0.1 percent. It is important to monitor gastrointestinal symptoms, discomfort, or inexplicable dyspnea early in the treatment. Education, temporary discontinuation in the presence of acute illness or during surgeries, and in patients prone to ketosis are examples of precautions to be taken [40].

7.5 Renal Safety and Other Rare Concerns

Large trials and meta-analyses have clarified that SGLT2 inhibitors reduce, instead of increasing, the likelihood of acute kidney injury (AKI), though initial concerns existed [41]. Recommendations include monitoring renal function, specifically for patients with hypovolemia, severe CKD, or co-administration of nephrotoxic agents. Reports of increased risks of fractures and below-knee amputations, particularly with the first trials of canagliflozin, have been reported. Although reassessments have revealed that these remain low with appropriate patient selection and are not inherent SGLT2 inhibitor class properties [42].

8. Clinical Applications and Prospects

SGLT2 inhibitors have developed from medications that reduce glucose levels to essential components of cardiovascular and renal treatment. Their growing involvement in various disease areas indicates that they may soon become vital elements of comprehensive metabolic care [43]. Future clinical applications will probably encompass patients who do not have diabetes, especially those with CKD and HFpEF. Recent studies such as EMPA- KIDNEY and DELIVER have shown renal and cardiac benefits regardless of glycemic status, confirming their pleiotropic potential [44]. These results suggest that the therapeutic window for SGLT2 inhibition extends beyond the conventional limits of diabetes management. Emerging research also supports their involvement in inflammatory and metabolic disorders. Preliminary findings indicate that SGLT2 inhibitors might ameliorate hepatic steatosis, decrease visceral adiposity, and

provide anti-inflammatory effects, positioning them as promising options for managing non- alcoholic fatty liver disease (NAFLD) and obesity [45].

As illustrated in Figure 2, SGLT2 inhibitors improve survival, reduce hospitalizations for heart failure and CKD, protect renal function, and exert pleiotropic effects, while their adverse events remain generally manageable. These agents improve survival and reduce hospitalizations for heart failure and CKD, protect renal function by slowing eGFR decline and reducing albuminuria, and exert pleiotropic effects via natriuresis, anti-inflammatory pathways, and metabolic reprogramming. Despite these benefits, risks such as genital infections, mild dehydration, rare euglycemic ketoacidosis, and occasional fractures or amputations remain; however, these risks are generally manageable with appropriate patient selection and monitoring. In addition, current research is investigating their effects on endothelial function, vascular remodeling, and oxidative stress, which may offer further protection against atherogenesis and fibrosis. From a translational standpoint, incorporating SGLT2 inhibitors into multifaceted treatment plans together with GLP- 1 receptor agonists, ACE inhibitors, and angiotensin receptor-neprilysin inhibitors (ARNI) therapies provides synergistic advantages for cardiorenal and metabolic outcomes [46]. It is anticipated that personalized medicine strategies will enhance therapy by considering patients' genetic, metabolic, and phenotypic differences. Future treatment standards for complex cardiometabolic conditions could be reshaped by the use of SGLT2 inhibitors in conjunction with other pathway-modulating drugs.

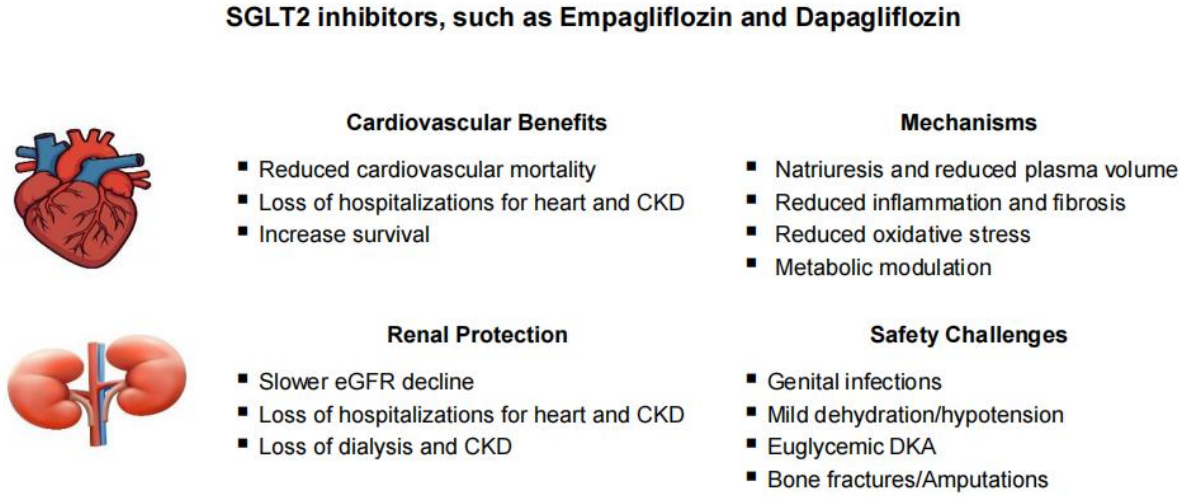

Figure 2. Emerging role of SGLT2 inhibitors beyond glycemic control: Cardiovascular and renal benefits and risks. These agents improve survival and reduce hospitalizations for heart failure and CKD, protect renal function by slowing eGFR decline and reducing albuminuria, and exert pleiotropic effects via natriuresis, anti-inflammatory pathways, and metabolic reprogramming. Despite these benefits, risks such as genital infections, mild dehydration, rare euglycemic ketoacidosis, and occasional fractures or amputations remain, but are generally manageable with appropriate patient selection and monitoring.

9. Future Research Direction

Future research should also focus on the use of SGLT2 inhibitors in acute situations such as myocardial infarction, ischemia-reperfusion injury, and postoperative heart failure, as adjusting cellular metabolism and inflammation may provide protective benefits in these cases [47]. Moreover, their possible neuroprotective functions achieved through enhanced cerebral glucose use and decreased neuroinflammation markers are being investigated. With the ongoing accumulation of evidence, regulatory bodies and clinical guidelines are anticipated to broaden indications, endorsing use beyond diabetes and heart failure. When integrated into population health strategies, it could lead to a decrease in cardiovascular events, CKD progression, and an improvement in global longevity. The ultimate aim is to establish them as an integrative treatment for metabolic, cardiovascular, and renal health, a paradigm of translational achievement in contemporary pharmacotherapy.

10. Safety Challenges and Risk-Mitigation Strategies

SGLT2 inhibitors are known to provide therapeutic benefits, their use poses several safety risks that require specific mitigation techniques. Genitourinary infections, volume depletion and hypotension, euglycemic diabetic ketoacidosis (euDKA), amputations or bone fractures (with certain medicines), and uncommon renal events are some of the most commonly reported side effects. To properly integrate SGLT2 inhibitors into clinical practice, it is critical to understand these dangers and implement preventive measures. The most common side effect associated with SGLT2 inhibitors is genital mycotic infection. This process enetial increased glucose excretion in urine, leading to glycosuria, which encourages the growth of fungi in the vaginal region. Compared to the placebo group, meta-analyses showed a three- to five-fold increase in genital infections [48]. Recurrent infections, although typically mild and manageable, can lead to the cessation of therapy, particularly in older or frail patients [49]. Patient education on genital hygiene, prompt

symptom identification, and a low threshold for topical antifungal treatment are practical mitigation strategies. Another category of safety issues is volume depletion and hypotension. SGLT2 inhibitors lower the intravascular volume by promoting osmotic diuresis and natriuresis. In susceptible patients such as those with autonomic dysfunction, those taking angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) or loop diuretics, and older individuals this may result in AKI, syncope, or symptomatic hypotension [50] To reduce these risks, clinicians should evaluate diuretic/vasodilator regimens used simultaneously, check baseline blood pressure and orthostatics, guarantee sufficient hydration, and contemplate lowering the dose for frail patients. A 'sick-day' rule that recommends a temporary halt during acute illness, vomiting, or decreased fluid intake is also suggested. The most severe but uncommon adverse event may be euDKA.

In contrast to typical DKA, euDKA can occur with normal or slightly elevated glucose levels, which can delay its diagnosis [51]. Case-series and meta-analyses indicate that SGLT2 inhibitor therapy is linked to approximately a twofold increase in the risk of DKA compared to control [52]. Insufficient insulin, fasting during surgery, extended vomiting or diarrhea, significant alcohol consumption, and extremely low carbohydrate intake are risk factors. Careful patient selection (avoid or use cautiously in insulin-deficient patients), halting the medication 24 to 48 hours before surgery, and monitoring ketone levels in high-risk circumstances are some mitigation techniques. The occurrence of euDKA can also be decreased by giving patients a clear sick-day card or guideline. Amputations and bone health outcomes have also been a source of concern, particularly with some SGLT2 inhibitors. Although the historic canagliflozin experiment revealed an increased risk of amputation, following empirical data and recent meta-analyses have produced contradictory findings [52].

However, the risk-benefit ratio should be carefully considered, and strict foot care should be implemented in individuals with peripheral vascular disease, neuropathy, or prior foot ulcers. Similarly, individuals with osteoporosis or other risk factors should have their bone mineral density evaluated. SGLT2 inhibitors may, paradoxically, increase renal safety; nonetheless, practitioners may occasionally be concerned about the initial temporary drop in eGFR, known as the "eGFR dip." Rarely, AKI has been documented, especially in situations involving hemodynamic instability or volume depletion [7]. Baseline renal function evaluation, repeated eGFR monitoring, avoiding initiation in cases of acute kidney damage or quickly changing renal status, and making sure there is sufficient perfusion and hydration are all examples of mitigation.

11. Biomarker Evidence

SGLT2 inhibitors have demonstrated significant benefits beyond glycemic control through their influence on cardiorenal biomarkers, neuroprotective pathways, and long-term clinical outcomes. Clinical trials have shown that these agents reduce biomarkers associated with cardiac stress and renal injury, including N-terminal pro-brain natriuretic peptide (NT-proBNP), albuminuria, inflammatory markers, and oxidative stress indicators, reflecting improved myocardial and renal function. Evidence from major randomized trials suggests that SGLT2 inhibitors significantly improve cardiac remodeling and renal hemodynamics, thereby reducing disease progression [53]. Emerging research also indicates potential neuroprotective effects mediated through improved cerebral perfusion, reduction in neuroinflammation, attenuation of oxidative stress, and enhancement of mitochondrial function, which may contribute to a reduced risk of cognitive decline and stroke in high-risk populations. Furthermore, long-term outcome studies have consistently demonstrated that SGLT2 inhibitors reduce hospitalization for heart failure, delay progression to end-stage renal disease, and improve overall survival in both diabetic and non-diabetic patients. These multifaceted benefits highlight the expanding therapeutic scope of SGLT2 inhibitors and reinforce their role as essential agents in the management of cardiorenal metabolic disorders.

12. Conclusion

SGLT2 inhibitors have emerged as transformative agents, extending beyond glycemic control to provide substantial cardiovascular and renal protection. Their mechanisms, including improved hemodynamics, reduced oxidative stress, and modulation of metabolic pathways, provide multidimensional benefits for patients with diabetes, heart failure, and CKD. These inhibitors significantly reduce hospitalizations for heart failure, slow the progression of kidney disease, and enhance overall survival, thereby reshaping modern therapeutic strategies. Although adverse effects, such as genital infections or mild dehydration, may occur, they are generally manageable with appropriate monitoring and education. The evolving body of evidence positions SGLT2 inhibitors as the cornerstone of cardiorenal-metabolic therapy. Future research should continue to investigate their expanding role in non-diabetic populations and additional disease contexts to maximize their therapeutic potential and improve long-term outcomes globally.

Conflict of Interest

The authors declare that they have no competing interests.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Abbreviations

ACE: angiotensin- converting enzyme

ADA: American Diabetes Association

AKI: acute kidney injury

ARBs: angiotensin receptor blockers

ARNI: angiotensin receptor-neprilysin inhibitors

CKD: chronic kidney disease

CMR: cardiac magnetic resonance imaging

DAPA: dapagliflozin

eGFR: estimated glomerular filtration rate

EMPA: empagliflozin

ESKD: end-stage kidney disease

euDKA: euglycemic diabetic ketoacidosis

GFR: glomerular filtration rate

HbA1c: glycated hemoglobin

HFpEF: heart failure with preserved ejection fraction

HFrEF: heart failure with reduced ejection fraction

HOMA-IR: homeostatic model assessment of insulin resistance

KDIGO: kidney disease: Improving global outcomes

MACE: major adverse cardiovascular events

NAFLD: non- alcoholic fatty liver disease

NT-proBNP: N-terminal pro- brain natriuretic peptide

PCT: proximal convoluted tubule

SGLT2: sodium-glucose cotransporter- 2

T2DM: type 2 diabetes mellitus

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