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Review Article

Cardiovascular Protection with SGLT2 Inhibitors: Systemic Mechanisms Beyond Glycemic Control

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ABSTRACT

Sodium–glucose cotransporter-2 (SGLT2) inhibitors were initially developed as glucose-lowering agents but have evolved into therapies with significant cardiovascular impact after outcome trials demonstrated reductions in heart failure hospitalization and cardiovascular mortality that could not be attributed solely to glycemic control. Subsequent studies confirmed consistent benefits across both reduced and preserved ejection fraction, including in patients without diabetes, highlighting mechanisms beyond metabolic regulation. This review outlines the integrated pathways underlying these effects, including restoration of tubuloglomerular feedback with reduction of intraglomerular pressure and improved cardiorenal interaction, mild natriuresis leading to favorable preload reduction without neurohormonal activation, and improvements in arterial compliance and systemic hemodynamics. At the myocardial level, SGLT2 inhibition promotes metabolic reprogramming toward more efficient substrate utilization, enhances mitochondrial function, reduces lipotoxic stress, and attenuates maladaptive neurohormonal signaling. Additional structural and vascular effects include reductions in myocardial fibrosis and hypertrophy, improved endothelial function, and suppression of inflammatory and oxidative stress pathways. Together, these coordinated systemic and myocardial actions provide a mechanistic basis for the rapid and sustained reductions in heart failure events observed in clinical trials and support the positioning of SGLT2 inhibitors as disease-modifying therapies across the cardiovascular spectrum.

Keywords: SGLT2 inhibitors; Heart failure; Cardiorenal interaction; Myocardial energetics; Cardiovascular outcomes

INTRODUCTION

Sodium–glucose cotransporter-2 (SGLT2) inhibitors were initially developed as antihyperglycemic agents targeting renal glucose reabsorption in patients with type 2 diabetes mellitus. By promoting glycosuria through inhibition of proximal tubular sodium–glucose transport, these agents offered an insulin-independent mechanism for glycemic control. However, cardiovascular outcome trials (CVOTs) conducted over the past decade revealed that the benefits of SGLT2 inhibitors extend far beyond glucose lowering. Unexpected reductions in heart failure hospitalization and cardiovascular mortality were observed early after treatment initiation, often preceding meaningful changes in glycemic parameters. This temporal dissociation raised important mechanistic questions and shifted the perception of this drug class from purely metabolic therapy toward a pleiotropic cardiovascular intervention [1].

The EMPA-REG OUTCOME trial provided the first major signal of cardiovascular protection, demonstrating a significant reduction in cardiovascular death and heart failure hospitalization among high-risk patients with type 2 diabetes treated with empagliflozin[2]. These findings were subsequently reinforced by the CANVAS program, which showed similar reductions in heart failure outcomes with canagliflozin[3]. Importantly, the DECLARE-TIMI 58 trial expanded these observations to a broader population with lower baseline cardiovascular risk, confirming that SGLT2 inhibition consistently reduces heart failure events regardless of atherosclerotic burden[4].

Subsequent trials focused specifically on heart failure populations, including those without diabetes, further challenged the traditional paradigm linking metabolic control to cardiovascular benefit. The DAPA-HF trial demonstrated that dapagliflozin significantly reduced worsening heart failure and cardiovascular death in patients with reduced ejection fraction irrespective of diabetic status[5]. Similar benefits were later confirmed in EMPEROR-Reduced and EMPEROR-Preserved trials, extending the therapeutic scope of SGLT2 inhibitors across the heart failure spectrum[6,7].

Collectively, these studies suggest that the cardiovascular advantages of SGLT2 inhibitors cannot be fully explained by improvements in glycemic control alone. Instead, a range of physiologic effects, including hemodynamic modulation, metabolic reprogramming, neurohormonal regulation, and direct myocardial influences, likely contribute to their clinical efficacy. Understanding these mechanisms is essential for interpreting the expanding role of SGLT2 inhibitors in cardiovascular medicine and for integrating them into treatment strategies beyond diabetes management.

To provide a comprehensive overview of the systemic mechanisms underlying the cardiovascular effects of SGLT2 inhibitors, a narrative literature search was conducted across multiple databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Relevant studies published between 2000 and 2025 were identified using combinations of predefined keywords such as "SGLT2 inhibitors," "cardiovascular outcomes," "heart failure," "cardiorenal interaction," "endothelial function," "myocardial metabolism," and "mechanisms." Emphasis was placed on randomized controlled trials, major cardiovascular outcome trials, mechanistic experimental studies, meta-analyses, and contemporary guideline documents. The selected literature was synthesized qualitatively to summarize current evidence regarding the systemic pathways contributing to cardiovascular protection with SGLT2 inhibition.

The aim of this review is to provide a comprehensive overview of the systemic mechanisms through which SGLT2 inhibitors confer cardiovascular protection beyond glycemic control. By integrating evidence from clinical trials, experimental studies, and contemporary guidelines, this article seeks to clarify how renal, hemodynamic, metabolic, neurohormonal, vascular, and myocardial pathways collectively contribute to improved cardiovascular outcomes. Understanding these interconnected mechanisms may help to better position SGLT2 inhibitors within cardiovascular therapy and support their role as disease-modifying agents across the spectrum of heart failure.

RENAL HEMODYNAMIC AND CARDIORENAL COUPLING

A substantial proportion of the cardiovascular benefits associated with SGLT2 inhibitors is mediated through their effects on renal hemodynamics. By reducing sodium and glucose reabsorption in the proximal tubule, these agents increase sodium delivery to the distal nephron. This activates the tubuloglomerular feedback mechanism, leading to afferent arteriolar vasoconstriction and a subsequent reduction in intraglomerular pressure[8]. As a result, glomerular hyperfiltration is attenuated, alleviating stress on both the renal and cardiovascular systems.

This mechanism plays a particularly important role in correcting maladaptive hyperfiltration observed in diabetic nephropathy. The reduction in intraglomerular pressure not only preserves renal function but also contributes to systemic hemodynamic stability. Decreased renal venous congestion may improve heart–kidney interaction and contribute to lowering cardiac filling pressures[9].

The natriuretic effect of SGLT2 inhibitors differs from that of conventional diuretics. These agents predominantly promote mobilization of interstitial fluid without causing abrupt intravascular volume depletion [10]. This property is advantageous in heart failure, where relief of venous congestion and tissue edema is required without provoking hemodynamic instability. Compared with loop diuretics, SGLT2 inhibitors induce a more physiologic redistribution of body fluid.

Additionally, SGLT2 inhibition has been shown to reduce renal oxygen consumption and alleviate cortical and medullary hypoxia[11]. By decreasing tubular workload, these agents improve renal metabolic efficiency and may limit systemic inflammatory activation. This represents an important pathophysiological mechanism within the framework of cardiorenal syndrome.

Clinical studies have demonstrated that these physiological effects translate into meaningful outcomes. The CREDENCE trial showed that SGLT2 inhibition not only slows renal disease progression but also reduces cardiovascular events[12]. These findings support the concept that renal hemodynamic modulation plays a central role in the cardiovascular protective profile of SGLT2 inhibitors. The major mechanistic pathways contributing to cardiovascular protection with SGLT2 inhibitors are summarized in Table 1.

Table 1: Major Mechanistic Pathways of Cardiovascular Protection with SGLT2 Inhibitors

Mechanistic Domain	Primary Physiological Effect	Downstream Impact	Clinical Relevance
Renal Hemodynamics	Restoration of tubuloglomerular feedback	↓ Intraglomerular pressure	Cardiorenal protection
Volume Regulation	Mild natriuresis & osmotic diuresis	↓ Preload without RAAS activation	Decongestion without instability
Vascular Function	Improved endothelial function	↓ Arterial stiffness	↓ Afterload
Myocardial Metabolism	Shift toward ketone utilization	↑ Energetic efficiency	Improved contractile reserve
Neurohormonal Modulation	↓ Sympathetic & RAAS activity	↓ Wall stress	Slower HF progression
Structural Effects	↓ Fibrosis & LV mass	Reverse remodeling	Improved compliance
Anti-inflammatory Actions	↓ Cytokines & inflammasome activity	Reduced tissue injury	Stabilized myocardium
Oxidative Stress Reduction	↓ ROS production	Preserved cellular function	Improved myocardial integrity

Abbreviations: RAAS: Renin–Angiotensin–Aldosterone System, LV: Left Ventricular, HF: Heart Failure, ROS: Reactive Oxygen Species

HEMODYNAMIC MODULATION

Beyond their renal effects, SGLT2 inhibitors exert significant influence on systemic hemodynamics, contributing to their cardiovascular benefits. One of the primary mechanisms involves sustained reductions in cardiac preload. Through mild but persistent natriuresis and osmotic diuresis, these agents facilitate gradual volume reduction without abrupt intravascular depletion[13]. This allows for improvement in cardiac filling pressures while maintaining hemodynamic stability, a feature that distinguishes them from conventional diuretics.

In addition to preload modulation, SGLT2 inhibitors also influence afterload. Clinical studies have demonstrated modest but consistent reductions in systolic blood pressure that occur independently of glycemic control[14]. These reductions are not typically accompanied by compensatory increases in heart rate, suggesting a favorable hemodynamic profile. Lower systemic vascular resistance may contribute to decreased left ventricular wall stress and improved cardiac efficiency.

Arterial stiffness is another key determinant of cardiovascular load. Evidence suggests that SGLT2 inhibition improves vascular compliance, leading to reductions in pulse wave velocity and enhancement of arterial elasticity[15]. These effects may reflect improvements in endothelial function and reductions in oxidative stress, both of which are known contributors to vascular rigidity.

Furthermore, SGLT2 inhibitors may positively influence the microcirculation. Improved endothelial responsiveness and reduced vascular resistance at the microvascular level may enhance tissue perfusion, particularly in the myocardium[16]. This is of particular importance in patients with heart failure, where impaired microvascular flow contributes to functional decline.

Together, these hemodynamic effects, such as reduced preload, improved afterload, enhanced arterial compliance, and better microvascular function, provide a physiological basis for the observed reductions in heart failure events in clinical trials[17]. These benefits appear to occur independently of glycemic changes, reinforcing the concept that SGLT2 inhibitors act through integrated cardiovascular mechanisms.

MYOCARDIAL ENERGETICS AND METABOLIC REPROGRAMMING

SGLT2 inhibitors influence myocardial energy metabolism in ways that extend beyond their renal and hemodynamic actions. One of the proposed mechanisms involves a shift in cardiac substrate utilization toward ketone bodies. Treatment with SGLT2 inhibitors has been associated with mild increases in circulating ketone levels, particularly β-hydroxybutyrate, which can serve as an efficient myocardial fuel[18]. Compared with glucose and free fatty acids, ketone oxidation yields more adenosine triphosphate per molecule of oxygen consumed, potentially improving cardiac energetic efficiency in conditions characterized by impaired myocardial metabolism.

In addition to promoting ketone utilization, SGLT2 inhibition may reduce myocardial lipotoxicity. Excessive reliance on free fatty acid oxidation has been linked to mitochondrial dysfunction and accumulation of toxic lipid intermediates in cardiomyocytes. By modulating systemic metabolic balance and reducing glucotoxic and lipotoxic stress, these agents may improve mitochondrial function and cellular energy production[19].

Experimental studies suggest that SGLT2 inhibitors may enhance mitochondrial efficiency by improving oxidative phosphorylation and reducing reactive oxygen species generation[20]. These effects may preserve myocardial contractile function and limit progressive structural damage. Improved mitochondrial dynamics may also contribute to better tolerance of ischemic or metabolic stress.

Another important aspect of metabolic reprogramming involves increased flexibility in substrate use. In heart failure, the myocardium often loses its ability to adapt fuel selection to changing physiologic demands. SGLT2 inhibition may restore this adaptability by promoting balanced utilization of glucose, fatty acids, and ketone bodies[21]. Such metabolic flexibility is essential for maintaining contractile performance under varying energetic conditions.

Collectively, these metabolic adaptations provide a plausible explanation for the rapid and sustained cardiovascular benefits observed in clinical trials[22]. By improving myocardial efficiency and reducing metabolic stress, SGLT2 inhibitors may contribute to both functional and structural cardiac preservation.

NEUROHORMONAL REGULATION

SGLT2 inhibitors also exert important effects on neurohormonal pathways that are central to the progression of cardiovascular disease, particularly heart failure. One of the key systems influenced by these agents is the renin–angiotensin–aldosterone system. By reducing intraglomerular pressure and improving sodium handling, SGLT2 inhibition may attenuate maladaptive activation of this pathway without causing the compensatory neurohormonal stimulation typically observed with conventional diuretics[23]. This contributes to improved circulatory stability and reduced cardiac workload.

In parallel, evidence suggests that SGLT2 inhibitors may modulate sympathetic nervous system activity. Excess sympathetic activation plays a major role in the progression of heart failure by promoting vasoconstriction, sodium retention, and adverse myocardial remodeling. Experimental and clinical observations indicate that treatment with SGLT2 inhibitors may reduce sympathetic tone, potentially reflected by stabilization of heart rate and improved vascular regulation[24]. This effect may further contribute to reductions in arrhythmic risk and myocardial stress.

Another important neurohormonal pathway involves natriuretic peptides. Clinical studies have demonstrated reductions in circulating BNP and NT-proBNP levels following SGLT2 inhibitor therapy[25]. These changes likely reflect decreased ventricular wall stress and improved hemodynamic conditions rather than direct pharmacologic suppression of peptide synthesis.

In addition, SGLT2 inhibitors may influence arginine vasopressin signaling through effects on osmotic balance and plasma volume regulation[26]. Modulation of this pathway may further support cardiovascular stability, particularly in states of fluid overload.

Taken together, these neurohormonal effects suggest that SGLT2 inhibitors provide a more balanced modulation of circulatory regulation compared with traditional diuretic strategies. By attenuating maladaptive activation of key neurohormonal systems, these agents may slow disease progression and improve clinical outcomes in patients with cardiovascular dysfunction[27].

DIRECT MYOCARDIAL STRUCTURAL EFFECTS

In addition to systemic and neurohormonal influences, SGLT2 inhibitors appear to exert direct effects on myocardial structure. One of the most consistently observed changes involves attenuation of myocardial fibrosis. Experimental data suggest that SGLT2 inhibition may suppress profibrotic signaling pathways, including those mediated by transforming growth factor beta, thereby limiting extracellular matrix deposition within the myocardium[28]. Reduced fibrotic burden may improve ventricular compliance and contribute to enhanced diastolic performance.

Another structural benefit relates to regression of myocardial hypertrophy. Chronic pressure and metabolic stress often lead to increased left ventricular mass, which is associated with adverse cardiovascular outcomes. Clinical imaging studies have demonstrated reductions in left ventricular mass index following treatment with SGLT2 inhibitors, indicating a potential role in reverse remodeling[29]. These changes may be partly mediated by reductions in wall stress and improvements in myocardial energetics.

SGLT2 inhibition has also been associated with improvements in diastolic function. By lowering filling pressures and improving myocardial relaxation, these agents may alleviate stiffness of the ventricular wall[30]. Improved diastolic mechanics are particularly relevant in patients with heart failure with preserved ejection fraction, where structural abnormalities often predominate.

Beyond these effects, evidence suggests that SGLT2 inhibitors may promote overall reverse remodeling of the myocardium. Structural improvements in chamber geometry and wall thickness have been observed in imaging-based studies, supporting the concept that these agents influence myocardial architecture in addition to functional parameters[31].

The cumulative impact of reduced fibrosis, regression of hypertrophy, improved diastolic properties, and structural remodeling may help explain the sustained reductions in heart failure events observed in outcome trials (32). These findings reinforce the view that SGLT2 inhibitors act not only through systemic mechanisms but also through direct myocardial pathways.

VASCULAR AND ENDOTHELIAL FUNCTION

SGLT2 inhibitors exert meaningful effects on vascular biology that may contribute to their cardiovascular benefits. One of the central mechanisms involves improvement in endothelial function. Experimental and clinical data indicate that SGLT2 inhibition enhances nitric oxide bioavailability, thereby promoting endothelium-dependent vasodilation[33]. Improved endothelial responsiveness may translate into better regulation of vascular tone and reduced peripheral resistance.

In addition to facilitating nitric oxide signaling, SGLT2 inhibitors appear to reduce oxidative stress within the vascular wall. Hyperglycemia and metabolic dysfunction are known to increase reactive oxygen species production, which impairs endothelial function and accelerates vascular aging. By mitigating oxidative stress pathways, these agents may preserve endothelial integrity and support vascular homeostasis[34].
Another important effect relates to arterial stiffness. Increased vascular rigidity contributes to elevated systolic pressure and greater cardiac workload. Clinical observations have shown that treatment with SGLT2 inhibitors is associated with reductions in pulse wave velocity, reflecting improved arterial elasticity[15]. These changes may improve ventricular–vascular coupling and reduce afterload.

SGLT2 inhibition may also influence the microvasculature. Improved endothelial function at the level of small resistance vessels may enhance tissue perfusion, including in the myocardium[16]. Enhanced microvascular flow is particularly relevant in patients with heart failure, where impaired perfusion contributes to functional limitation.

Collectively, these vascular effects suggest that SGLT2 inhibitors support cardiovascular health through modulation of endothelial biology and arterial function. Improved vasodilatory capacity, reduced oxidative stress, enhanced arterial compliance, and better microvascular perfusion may all contribute to the observed reductions in cardiovascular events in clinical trials[35].

ANTI-INFLAMMATORY AND ANTI-OXIDATIVE MECHANISMS

Chronic low-grade inflammation and oxidative stress play central roles in the pathogenesis of cardiovascular disease and heart failure. Emerging evidence suggests that SGLT2 inhibitors may exert anti-inflammatory effects that contribute to their cardioprotective profile. Treatment with these agents has been associated with reductions in circulating inflammatory markers such as interleukin-6, tumor necrosis factor alpha, and C-reactive protein[36]. These changes may reflect improvements in metabolic and hemodynamic status as well as direct modulation of inflammatory signaling pathways.

In addition to systemic inflammation, SGLT2 inhibition may influence intracellular inflammatory processes. Experimental studies indicate that these agents can suppress activation of the NLRP3 inflammasome, a key mediator of innate immune responses and myocardial injury[37]. Inhibition of this pathway may limit inflammatory cell recruitment and reduce downstream tissue damage.

Oxidative stress is closely linked to inflammatory activation and contributes to endothelial dysfunction, myocardial fibrosis, and progressive cardiac remodeling. SGLT2 inhibitors have been shown to reduce reactive oxygen species production and improve mitochondrial redox balance[38]. These effects may help preserve cellular integrity within both vascular and myocardial tissues.

The combined reduction of inflammation and oxidative stress may have important implications for cardiovascular outcomes. By attenuating these pathophysiological drivers, SGLT2 inhibitors may slow structural deterioration and functional decline in the heart[39]. This integrated anti-inflammatory and antioxidative profile provides further insight into the mechanisms underlying their benefits beyond glycemic control.

ELECTROPHYSIOLOGICAL AND ARRHYTHMIC IMPLICATIONS

Arrhythmias represent a major source of morbidity and sudden death in patients with diabetes and heart failure, and several lines of evidence suggest that SGLT2 inhibitors may have a favorable electrophysiological profile. From a safety standpoint, dedicated thorough QT evaluation demonstrated that empagliflozin does not produce clinically relevant QT prolongation, supporting electrical neutrality with respect to ventricular repolarization in controlled conditions[40]. This is clinically important because drug induced QT prolongation and repolarization heterogeneity can increase vulnerability to malignant ventricular arrhythmias, particularly in patients with structural heart disease and electrolyte instability.

Beyond neutrality, emerging clinical studies suggest that SGLT2 inhibitors may improve repolarization markers associated with ventricular arrhythmogenic risk. In a recent clinical study in type 2 diabetes, dapagliflozin therapy was associated with shortening of QTc and Tp Te related indices, a pattern interpreted as reduced dispersion of ventricular repolarization[41]. Although such surrogate markers cannot be equated with definitive antiarrhythmic efficacy, they are directionally consistent with a reduction in electrical remodeling and with a mechanistic framework that links SGLT2 inhibition to improved myocardial energetics, reduced oxidative stress, and attenuation of adverse remodeling.

Outcome oriented data provide more direct support for arrhythmic benefit in high risk heart failure. A post hoc analysis of the DAPA HF trial reported that dapagliflozin reduced the composite risk of serious ventricular arrhythmias, resuscitated cardiac arrest, or sudden death when added to guideline directed therapy in patients with heart failure and reduced ejection fraction[42]. This observation aligns with the concept that reductions in wall stress, neurohormonal activation, congestion, and myocardial fibrosis may collectively lower the substrate for ventricular tachyarrhythmias and sudden death, even if the drug does not act as a classical ion channel modulator.

Atrial arrhythmias are also clinically relevant because atrial fibrillation frequently coexists with heart failure and is associated with worse outcomes. Meta analytic evidence in type 2 diabetes populations suggests that SGLT2 inhibitors may reduce the incidence of atrial fibrillation or atrial flutter compared with control, indicating a potential class effect in susceptible patients[43]. More contemporary comparative analyses across randomized trial data have reported that dapagliflozin in particular is associated with a significant reduction in atrial fibrillation risk versus placebo, whereas estimates for other agents have been less consistent across networks and populations[44]. These signals are biologically plausible given that atrial fibrillation risk is influenced by atrial stretch and pressure, inflammation, autonomic tone, and metabolic milieu, all of which may improve under SGLT2 inhibition.

Overall, the current evidence supports two practical conclusions. First, SGLT2 inhibitors appear electrically safe with respect to QT liability in controlled evaluations. Second, a growing body of clinical data suggests potential reductions in both atrial and ventricular arrhythmic events, particularly in heart failure, although the strength of evidence varies by endpoint definition, ascertainment methods, and agent. These considerations position electrophysiological effects as a plausible contributor to the broader cardiovascular benefit profile observed with SGLT2 inhibitors. The integrated cardiovascular effects across different physiological systems are outlined in Table 2.

Table 2: Cardiovascular Effects of SGLT2 Inhibitors Across Physiological Systems

System	Mechanism	Functional Effect	Clinical Outcome
Kidney	Reduced proximal sodium reabsorption	Improved cardiorenal coupling	↓ HF hospitalization
Hemodynamic	Gradual plasma volume reduction	Stable preload reduction	Symptom improvement
Vascular	Enhanced nitric oxide bioavailability	Improved vasodilation	↓ Systemic resistance
Myocardial	Improved mitochondrial function	↑ ATP efficiency	Better performance
Neurohormonal	Reduced sympathetic tone	Stabilized circulation	↓ Arrhythmic risk
Structural	Reduced myocardial stiffness	Improved diastolic function	Benefit in HFpEF
Inflammatory	Suppressed NLRP3 pathway	↓ Tissue inflammation	Slower remodeling
Electrophysiologic	Neutral QT effect	Improved repolarization indices	↓ Arrhythmia burden

Abbreviations: ATP: Adenosine Triphosphate, RAAS: Renin–Angiotensin–Aldosterone System, HF: Heart Failure, HFpEF: Heart Failure with Preserved Ejection Fraction, QT: QT Interval , NLRP3: NOD-like receptor family pyrin domain containing 3

EFFECTS ACROSS THE HEART FAILURE SPECTRUM

SGLT2 inhibitors have demonstrated consistent clinical benefits across the spectrum of heart failure, extending beyond traditional metabolic indications. In patients with heart failure and reduced ejection fraction, treatment with these agents has been associated with significant reductions in cardiovascular death and hospitalization for worsening heart failure[5]. These findings suggest that their effects are not limited to volume modulation but involve broader physiological improvements.

Importantly, these benefits are not restricted to patients with diabetes. Clinical trials have shown that SGLT2 inhibitors improve outcomes in heart failure populations regardless of glycemic status[6]. This observation reinforces the concept that their cardioprotective actions are mediated through mechanisms independent of glucose lowering.

In heart failure with preserved ejection fraction, where therapeutic options have historically been limited, SGLT2 inhibitors have also demonstrated meaningful clinical effects. Treatment has been associated with reductions in heart failure hospitalization and improvements in symptom burden[7]. These findings are particularly relevant given the complex pathophysiology of this condition, which involves structural, hemodynamic, and metabolic abnormalities.

The beneficial impact of SGLT2 inhibition in both reduced and preserved ejection fraction suggests a unifying mechanism that targets shared pathophysiological pathways such as congestion, myocardial stiffness, and neurohormonal activation[45]. By improving these underlying processes, these agents may influence disease trajectory across diverse heart failure phenotypes.

In heart failure with preserved ejection fraction, myocardial stiffness rather than systolic impairment represents the dominant pathophysiologic abnormality. SGLT2 inhibitors may influence this process by reducing interstitial fibrosis and improving cardiomyocyte mechanical properties, thereby lowering passive ventricular stiffness. Beyond their preload-reducing effects, these agents may directly modify intrinsic myocardial compliance through anti-inflammatory and anti-remodeling actions[43].

Microvascular dysfunction also plays a central role in HFpEF pathogenesis. Endothelial inflammation leads to reduced nitric oxide bioavailability and downstream impairment of the cGMP–PKG signaling pathway, which contributes to increased titin stiffness within cardiomyocytes. By improving endothelial function and attenuating inflammatory signaling, SGLT2 inhibition may help restore this pathway and enhance titin phosphorylation, ultimately improving myocardial elasticity[19]. These mechanisms provide a plausible biological explanation for the clinical benefits observed in HFpEF beyond simple hemodynamic modulation.

Overall, the consistent reduction in heart failure events observed in large randomized trials supports the role of SGLT2 inhibitors as disease-modifying therapies in heart failure management[46]. Their effects appear to transcend traditional classifications based on glycemic status or ejection fraction.

ATHEROSCLEROTIC AND ISCHEMIC CARDIOVASCULAR MODULATION

Beyond their established benefits in heart failure, SGLT2 inhibitors may exert clinically relevant effects on atherosclerotic cardiovascular disease through modulation of vascular biology. Although reductions in major atherosclerotic events such as myocardial infarction have been less prominent compared with their impact on heart failure outcomes, mechanistic and clinical data suggest that these agents influence pathways involved in endothelial dysfunction and vascular inflammation[47].

One proposed mechanism involves attenuation of endothelial inflammatory activation. Experimental studies have demonstrated that SGLT2 inhibition may reduce the expression of adhesion molecules such as ICAM-1 and VCAM-1, which play key roles in leukocyte recruitment and vascular inflammation[48]. By limiting monocyte adhesion and migration into the vascular wall, these agents may slow the progression of early atherogenesis and reduce inflammatory activity within established plaques.

SGLT2 inhibitors may also contribute to plaque stabilization through indirect metabolic and anti-inflammatory effects. Improvements in oxidative stress profiles and reductions in systemic inflammatory signaling may promote stabilization of the fibrous cap and limit lipid core expansion, thereby reducing plaque vulnerability [49].

Another relevant pathway involves the reduction of serum uric acid levels consistently observed with SGLT2 inhibitor therapy. Elevated uric acid has been associated with endothelial dysfunction and vascular inflammation. Clinical analyses have shown that SGLT2 inhibitors lower serum uric acid concentrations, which may translate into improved vascular health and reduced pro-atherogenic signaling[50].

Finally, improvements in microvascular function and myocardial metabolic efficiency may enhance tolerance to ischemia. Enhanced tissue perfusion and reduced metabolic stress may allow the myocardium to better withstand periods of reduced oxygen supply, providing a potential explanation for trends toward reduced ischemic events observed in outcome trials[25].

Collectively, these mechanisms suggest that SGLT2 inhibitors may influence atherosclerotic disease progression and ischemic resilience through pathways distinct from traditional lipid-lowering or antithrombotic therapies.

CLINICAL INTEGRATION

The translation of SGLT2 inhibitors into routine cardiovascular practice has accelerated because multiple guideline bodies now position them as foundational therapy for heart failure rather than adjunctive treatment contingent on glycemic status. The 2022 AHA/ACC/HFSA heart failure guideline recommends SGLT2 inhibitors as part of core disease-modifying therapy in heart failure with reduced ejection fraction, reflecting robust outcome data and the class's favorable benefit to risk profile[51]. The 2023 ESC focused update further strengthened this position by expanding and reinforcing recommendations across ejection-fraction categories, emphasizing that the clinical benefits are consistent and clinically meaningful even when baseline diabetes is absent[52]. In practical terms, this shift means that eligibility is primarily driven by cardiovascular phenotype and safety considerations, not by the presence of hyperglycemia.

Initiation strategies in chronic heart failure are generally straightforward because SGLT2 inhibitors have minimal effects on heart rate and only modest effects on blood pressure. In stable outpatients, initiation can be integrated early alongside other foundation therapies, with attention to baseline volume status, renal function, and concomitant diuretic dosing. Because these agents can contribute to decongestion, clinicians commonly consider modest loop diuretic dose reduction in patients who are borderline euvolemic or prone to orthostatic symptoms, while monitoring congestion markers and renal indices after initiation. Importantly, an early, small decline in estimated glomerular filtration rate may occur, consistent with hemodynamic adjustment rather than intrinsic renal injury, and this pattern is explicitly addressed in kidney-focused guidance.

Renal thresholds and continuation principles are particularly relevant when SGLT2 inhibitors are used for cardiorenal protection. The KDIGO 2022 guideline positions SGLT2 inhibitors as a key therapy for patients with type 2 diabetes and chronic kidney disease, including those with reduced eGFR, with an emphasis on maintaining therapy when feasible because long-term kidney and cardiovascular benefits outweigh the predictable early hemodynamic eGFR dip in most patients[53]. A joint ADA and KDIGO consensus report similarly supports early use of SGLT2 inhibitors in appropriate patients with diabetes and CKD, aligning glycemic management with organ protection goals and clarifying practical limitations related to kidney function and monitoring[54]. Although heart failure indications are not identical to CKD indications, the practical framework overlaps in day-to-day care because both domains require the same vigilance for volume status, renal function trends, and intercurrent illness. The clinical implications of these systemic mechanisms in real-world practice are summarized in Table 3.

Table 3: Clinical Implications of Systemic SGLT2 Inhibitor Effects

Pathophysiological Target	**Mechanistic Action**	**Clinical Translation**
Congestion	Interstitial fluid mobilization	Reduced edema
Elevated Filling Pressure	Preload reduction	Improved symptoms
Vascular Rigidity	Improved arterial compliance	Reduced LV workload
Metabolic Inefficiency	Ketone-based fuel utilization	Enhanced myocardial efficiency
Neurohormonal Activation	RAAS & SNS attenuation	Disease stabilization
Myocardial Remodeling	Anti-fibrotic effects	Reverse remodeling
Oxidative Injury	ROS suppression	Cellular protection
Electrical Instability	Improved repolarization	Reduced AF/VAs risk
Systemic Inflammation	Cytokine reduction	Improved vascular health

Abbreviations: LV: Left Ventricular, RAAS: Renin–Angiotensin–Aldosterone System, SNS: Sympathetic Nervous System, ROS: Reactive Oxygen Species, AF: Atrial Fibrillation, VAs: Ventricular Arrhythmias

In-hospital initiation has become another key integration point. The EMPULSE trial demonstrated that starting empagliflozin in stabilized patients hospitalized for acute heart failure was feasible and associated with clinically meaningful benefit over short-term follow-up, supporting early initiation rather than deferral to post-discharge care[55]. This matters because the early post-discharge phase carries high vulnerability for recurrent congestion and readmission. In practical protocols, initiation during hospitalization is typically considered once patients are hemodynamically stable, not requiring escalating intravenous diuretics or vasoactive support, and able to maintain oral intake.

Safety integration should be explicit in the clinical workflow. The main issues are volume depletion, genital mycotic infections, and rare ketoacidosis, with particular caution during prolonged fasting, acute illness, or perioperative periods when temporary withholding is often appropriate. For patients with diabetes using insulin or insulin secretagogues, hypoglycemia risk is generally not increased by SGLT2 inhibitors alone, but regimen adjustments may be needed when overall glycemic control improves or when caloric intake is reduced. With these precautions, contemporary guideline positioning reflects an overall conclusion that SGLT2 inhibitors can be implemented early, across a wide heart failure population, and coordinated effectively with cardiorenal management strategies.

SAFETY CONSIDERATIONS

SGLT2 inhibitors are generally well tolerated, but several safety aspects should be considered in routine clinical practice. Volume depletion may occur due to their natriuretic and osmotic diuretic effects, particularly in elderly patients or those receiving concomitant diuretic therapy. Careful assessment of baseline volume status and gradual adjustment of loop diuretics may help reduce the risk of hypotension or dizziness. Genital mycotic infections are among the most commonly reported adverse effects and are typically mild and manageable with standard antifungal therapy. Although urinary tract infections have been reported, most studies suggest that the overall increase in risk is modest and does not usually necessitate discontinuation of therapy [23].

Another important consideration is the rare occurrence of diabetic ketoacidosis, which may present with only mildly elevated glucose levels. This risk is most relevant in situations of prolonged fasting, acute illness, perioperative stress, or significant insulin dose reduction. Temporary discontinuation during such conditions may be appropriate to minimize risk. SGLT2 inhibitors have minimal intrinsic hypoglycemic potential; however, in patients treated with insulin or insulin secretagogues, dose adjustment may be required to prevent hypoglycemia as glycemic control improves. With appropriate patient selection and monitoring, these safety considerations do not outweigh the established cardiovascular and renal benefits observed with this class of therapy[51-53].

FUTURE PERSPECTIVES

Despite substantial advances in understanding the cardiovascular effects of SGLT2 inhibitors, several areas remain open for further investigation. One important direction involves clarifying the relative contribution of individual physiological mechanisms to clinical benefit. While current evidence supports a multifactorial model involving hemodynamic, metabolic, neurohormonal, and structural pathways, the precise interplay between these mechanisms is not fully defined[56]. Improved mechanistic insight may allow more targeted therapeutic use in specific cardiovascular phenotypes.

Another evolving area concerns combination therapy. The integration of SGLT2 inhibitors with other disease-modifying agents such as angiotensin receptor–neprilysin inhibitors or mineralocorticoid receptor antagonists may produce additive or synergistic effects[57]. Understanding how these therapies interact at a physiological level may help optimize treatment strategies and improve outcomes.

There is also growing interest in the role of SGLT2 inhibitors beyond traditional heart failure populations. Ongoing studies are exploring their potential benefits in conditions such as acute myocardial infarction, cardiometabolic syndrome, and even non-cardiac disorders characterized by systemic inflammation and metabolic stress[58]. Expanding indications may further broaden the therapeutic scope of this drug class.
Future research will likely focus on identifying patient subgroups most likely to benefit from early initiation of therapy. Biomarker-guided approaches and advanced imaging may help refine treatment selection and improve precision in clinical decision-making[59].

Overall, continued investigation into the mechanistic and clinical implications of SGLT2 inhibition will be essential for fully realizing the therapeutic potential of these agents in cardiovascular medicine[60].

CONCLUSION

SGLT2 inhibitors have emerged as a therapeutic class with substantial cardiovascular relevance that extends well beyond their original role in glucose lowering. The consistency of clinical benefits observed across diverse patient populations indicates that their impact is mediated through integrated physiological mechanisms rather than through metabolic control alone. These agents influence multiple systems simultaneously, including renal hemodynamics, vascular function, myocardial metabolism, neurohormonal balance, and structural cardiac remodeling.
By promoting favorable shifts in volume status without provoking maladaptive neurohormonal activation, SGLT2 inhibitors improve cardiac loading conditions in a manner that supports long-term stability. Their influence on myocardial energetics enhances metabolic efficiency, while anti-inflammatory and antioxidative effects contribute to preservation of cellular integrity. Structural adaptations such as reductions in fibrosis and hypertrophy further support functional improvement across the spectrum of heart failure.

The observed reductions in arrhythmic risk and improvements in endothelial function suggest that the benefits of SGLT2 inhibition extend into domains traditionally considered outside metabolic therapy. These multidimensional effects provide a coherent explanation for the rapid and sustained reductions in cardiovascular events documented in clinical trials.

Taken together, SGLT2 inhibitors represent a shift in therapeutic perspective from disease-specific intervention toward systemic physiological modulation. Their expanding role in cardiovascular care reflects the recognition that targeting interconnected pathways may offer more durable protection than strategies focused on isolated risk factors. As clinical experience continues to evolve, these agents are likely to remain central to integrated approaches in cardiovascular medicine.

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