Physiological Basis of Cardiovascular Protection by SGLT2 Inhibitors in Diabetic Ischemic Heart Disease

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Abstract

Background: Diabetes mellitus is a major global health problem and represents a leading contributor to cardiovascular morbidity and mortality. Among the various cardiovascular complications associated with diabetes, ischemic heart disease remains the most prevalent and life-threatening condition. Chronic hyperglycemia, insulin resistance, dyslipidemia, and systemic inflammation contribute to structural and functional abnormalities within the cardiovascular system. The diabetic myocardium is particularly vulnerable to ischemic injury due to impaired metabolic flexibility, mitochondrial dysfunction, oxidative stress, endothelial dysfunction, and microvascular impairment. These alterations not only increase the risk of myocardial infarction but also worsen post-ischemic cardiac recovery and promote adverse cardiac remodeling. Sodium–glucose cotransporter-2 (SGLT2) inhibitors were originally developed as glucose-lowering agents that reduce renal glucose reabsorption in the proximal renal tubules. However, accumulating clinical and experimental evidence has demonstrated that the cardiovascular benefits of these agents extend beyond glycemic control. Large cardiovascular outcome trials have shown that SGLT2 inhibitors significantly reduce hospitalization for heart failure and improve cardiovascular outcomes in patients with type 2 diabetes, highlighting their potential role in cardioprotection. This review aims to explore the physiological mechanisms underlying the cardiovascular protective effects of SGLT2 inhibitors in diabetic ischemic heart disease. The article focuses on the metabolic, hemodynamic, cellular, and molecular pathways through which SGLT2 inhibition may influence myocardial susceptibility to ischemic injury. Particular attention is given to their effects on myocardial energy metabolism, endothelial function, oxidative stress, inflammatory signaling pathways, mitochondrial integrity, and cardiac remodeling. Additionally, the review integrates insights from experimental studies and major clinical trials to provide a comprehensive understanding of how SGLT2 inhibitors contribute to improved cardiovascular outcomes in patients with diabetes.

Conclusion: SGLT2 inhibitors exert multiple cardioprotective actions that extend well beyond their glucose-lowering properties. These agents improve myocardial energy efficiency, promote beneficial metabolic substrate utilization, reduce oxidative stress and inflammation, and preserve mitochondrial function within cardiomyocytes. In addition, favorable hemodynamic effects such as reductions in blood pressure, plasma volume, and cardiac workload contribute to improved cardiac performance. Emerging evidence also suggests that SGLT2 inhibitors may attenuate ischemia–reperfusion injury and limit adverse myocardial remodeling following infarction. Collectively, these physiological and molecular mechanisms provide a strong foundation for the cardiovascular benefits observed in clinical studies. A deeper understanding of these pathways may further support the therapeutic use of SGLT2 inhibitors in patients with diabetic ischemic heart disease and may guide future strategies aimed at improving cardiovascular outcomes in this high-risk population.

Keywords: Cardiovascular Protection, SGLT2 Inhibitors, Diabetic Ischemic Heart Disease

Introduction

Diabetes mellitus is a major global health challenge and a well-established risk factor for cardiovascular disease, particularly ischemic heart disease. Patients with diabetes have a significantly higher risk of developing coronary artery disease, myocardial infarction, and heart failure compared with non-diabetic individuals. Chronic hyperglycemia, insulin resistance, and dyslipidemia contribute to a complex pathophysiological environment that promotes vascular inflammation, endothelial dysfunction, and accelerated atherosclerosis. In addition to macrovascular complications, diabetes also induces profound alterations in myocardial structure and function, a condition often referred to as diabetic cardiomyopathy. These abnormalities increase the susceptibility of the diabetic myocardium to ischemic

injury and worsen clinical outcomes following myocardial infarction. Consequently, cardiovascular disease remains the leading cause of mortality among individuals with diabetes, highlighting the urgent need for therapeutic strategies that address both metabolic and cardiovascular abnormalities. [1] The pathophysiology of diabetic ischemic heart disease involves multiple interconnected mechanisms including impaired myocardial energy metabolism, mitochondrial dysfunction, increased oxidative stress, and chronic low-grade inflammation. In the diabetic heart, metabolic inflexibility leads to excessive reliance on fatty acid oxidation and reduced glucose utilization, resulting in decreased cardiac efficiency and increased oxygen consumption. Moreover, endothelial dysfunction and microvascular abnormalities further compromise myocardial perfusion during ischemic events. These metabolic and vascular disturbances exacerbate ischemia–reperfusion injury and contribute to adverse cardiac remodeling following myocardial infarction. Traditional glucose-lowering therapies primarily focus on glycemic control but have historically shown limited ability to significantly reduce cardiovascular mortality or prevent ischemic cardiac events, underscoring a major gap in the management of diabetic cardiovascular complications. [2]

Sodium–glucose cotransporter-2 (SGLT2) inhibitors have emerged as a novel class of antidiabetic agents that not only improve glycemic control but also demonstrate substantial cardiovascular benefits. Initially developed to reduce renal glucose reabsorption in the proximal renal tubules, these agents promote glycosuria and improve metabolic parameters in patients with type 2 diabetes. However, large- scale cardiovascular outcome trials have revealed that SGLT2 inhibitors significantly reduce hospitalization for heart failure, cardiovascular mortality, and adverse cardiovascular events. These findings suggest that the cardioprotective effects of SGLT2 inhibitors extend beyond their glucose- lowering actions and may involve multiple physiological mechanisms affecting cardiac metabolism, hemodynamics, inflammation, and cellular signaling pathways. Despite the growing clinical evidence, the precise physiological basis of these cardioprotective effects remains an area of active investigation.
[3]

Therefore, the aim of this review is to explore the physiological and molecular mechanisms through which SGLT2 inhibitors exert cardiovascular protective effects in diabetic ischemic heart disease. Particular emphasis is placed on the interaction between metabolic modulation, hemodynamic regulation, mitochondrial function, oxidative stress, inflammatory pathways, and myocardial remodeling. By integrating findings from experimental studies and clinical trials, this review seeks to provide a comprehensive understanding of how SGLT2 inhibition influences myocardial susceptibility to ischemic injury and contributes to improved cardiovascular outcomes in patients with diabetes. [4]

Pathophysiology of Diabetic Ischemic Heart Disease

Diabetic ischemic heart disease is characterized by a complex interplay of metabolic, vascular, and cellular abnormalities that significantly increase myocardial susceptibility to ischemic injury. Chronic hyperglycemia promotes the formation of advanced glycation end products (AGEs), activation of protein kinase C pathways, and increased production of reactive oxygen species. These processes lead to endothelial dysfunction, impaired nitric oxide bioavailability, and vascular inflammation, which collectively accelerate the development of atherosclerosis within the coronary arteries. In addition, diabetes is associated with dyslipidemia and prothrombotic states that further contribute to plaque formation and instability. These mechanisms increase the likelihood of coronary artery occlusion and myocardial infarction, making ischemic heart disease one of the most severe complications of diabetes mellitus. [5]

Another critical component of diabetic ischemic heart disease is the alteration in myocardial energy metabolism. Under normal physiological conditions, the heart demonstrates metabolic flexibility,

utilizing both glucose and fatty acids as energy substrates depending on availability and metabolic demand. However, in the diabetic state, insulin resistance and impaired glucose uptake lead to a marked shift toward increased fatty acid oxidation. Although fatty acid metabolism provides substantial energy, it is less oxygen-efficient compared with glucose oxidation and results in greater oxygen consumption for the same amount of ATP produced. This metabolic imbalance increases myocardial oxygen demand during ischemic conditions and reduces cardiac efficiency, thereby exacerbating ischemic injury and impairing functional recovery following myocardial infarction. [6]

Mitochondrial dysfunction also plays a central role in the pathogenesis of diabetic myocardial ischemia. Mitochondria are responsible for the majority of ATP production in cardiomyocytes, and their proper function is essential for maintaining myocardial contractility and cellular viability. In diabetes, excessive fatty acid oxidation and oxidative stress disrupt mitochondrial bioenergetics, leading to impaired ATP synthesis and increased generation of reactive oxygen species. These alterations contribute to cellular damage, activation of apoptotic pathways, and increased susceptibility to ischemia–reperfusion injury. Furthermore, mitochondrial dysfunction promotes calcium handling abnormalities and disrupts cardiomyocyte homeostasis, which can ultimately lead to contractile dysfunction and adverse cardiac remodeling following ischemic events. [7]

Endothelial dysfunction and coronary microvascular impairment further exacerbate ischemic injury in the diabetic heart. Hyperglycemia and oxidative stress impair endothelial nitric oxide production, reducing vasodilation and increasing vascular stiffness. Additionally, inflammation and endothelial activation promote leukocyte adhesion and microvascular obstruction, which limit myocardial perfusion even in the absence of significant epicardial coronary artery disease. This phenomenon, often referred to as coronary microvascular dysfunction, contributes to impaired oxygen delivery to the myocardium and worsens outcomes during ischemic episodes. Together, these metabolic, mitochondrial, and vascular abnormalities create a pathophysiological environment in which the diabetic heart becomes highly vulnerable to ischemic damage and subsequent heart failure. [8]

SGLT2 Inhibitors: Pharmacological Mechanisms and Systemic Metabolic Effects

Sodium–glucose cotransporter-2 (SGLT2) inhibitors represent a relatively new class of antidiabetic medications that act primarily by inhibiting glucose reabsorption in the proximal renal tubules. Under normal physiological conditions, approximately 90% of filtered glucose is reabsorbed in the kidneys through SGLT2 transporters located in the S1 segment of the proximal tubule. By blocking this transporter, SGLT2 inhibitors promote urinary glucose excretion, thereby lowering plasma glucose levels independently of insulin secretion or insulin sensitivity. This insulin-independent mechanism is particularly advantageous in patients with type 2 diabetes who often exhibit significant insulin resistance and progressive β-cell dysfunction. In addition to improving glycemic control, SGLT2 inhibition leads to modest weight reduction and decreased plasma glucose variability, both of which contribute to improved metabolic stability in diabetic patients. [9]

Beyond their glucose-lowering effects, SGLT2 inhibitors induce several systemic metabolic changes that may contribute to cardiovascular protection. One notable effect is the promotion of mild osmotic diuresis and natriuresis, which results from increased urinary glucose and sodium excretion. This process leads to reductions in plasma volume and interstitial fluid, ultimately lowering cardiac preload and systemic blood pressure. Furthermore, the loss of glucose through urine results in a negative caloric balance, which can promote weight loss and improvements in insulin sensitivity. SGLT2 inhibitors have also been associated with favorable changes in lipid metabolism and reductions in visceral adiposity, factors that may indirectly influence cardiovascular risk in patients with diabetes. Collectively, these metabolic

adaptations suggest that the therapeutic benefits of SGLT2 inhibitors extend beyond glycemic regulation to include broader cardiometabolic improvements. [10]

Another important systemic effect of SGLT2 inhibitors is their ability to influence energy substrate utilization and metabolic homeostasis. By promoting glycosuria and reducing circulating glucose levels, these agents trigger a metabolic shift characterized by increased lipolysis and enhanced production of ketone bodies in the liver. Ketone bodies, particularly β-hydroxybutyrate, may serve as an efficient alternative fuel source for the myocardium, providing more energy per unit of oxygen consumed compared with fatty acids. This metabolic reprogramming has been proposed as one of the mechanisms through which SGLT2 inhibitors improve myocardial energy efficiency, especially under conditions of metabolic stress or ischemia. Additionally, improvements in renal hemodynamics and reductions in intraglomerular pressure may contribute to the well-documented cardiorenal protective effects observed in patients treated with these agents. [11]

Hemodynamic and Cardiorenal Mechanisms of Cardiovascular Protection

One of the most important physiological effects of SGLT2 inhibitors is their ability to induce mild osmotic diuresis and natriuresis, which contributes to significant hemodynamic changes beneficial for cardiovascular function. By inhibiting glucose and sodium reabsorption in the proximal renal tubule, these agents increase urinary excretion of both glucose and sodium, resulting in a reduction in plasma volume and interstitial fluid. This volume reduction decreases cardiac preload, thereby lowering ventricular filling pressures and reducing myocardial wall stress. Such effects are particularly beneficial in patients with diabetes who frequently exhibit fluid retention and increased cardiac workload. The reduction in intravascular volume also contributes to improved ventricular performance and may partially explain the rapid reduction in heart failure hospitalization observed in major clinical trials involving SGLT2 inhibitors. [12]

In addition to reducing preload, SGLT2 inhibitors exert favorable effects on systemic blood pressure and vascular resistance. Clinical studies have demonstrated that treatment with SGLT2 inhibitors leads to modest but consistent reductions in both systolic and diastolic blood pressure, independent of their glucose-lowering actions. These blood pressure–lowering effects are thought to result from multiple mechanisms, including natriuresis, reduced arterial stiffness, and improved endothelial function. Lower systemic blood pressure reduces cardiac afterload, which decreases myocardial oxygen demand and improves cardiac efficiency, particularly under ischemic conditions. Furthermore, improvements in vascular function may enhance coronary perfusion and contribute to the overall cardioprotective profile of SGLT2 inhibitors in patients with diabetic ischemic heart disease. [13]

Another critical aspect of the cardiovascular benefits associated with SGLT2 inhibitors is their influence on the cardiorenal axis. The heart and kidneys are closely interconnected organs, and dysfunction in one often exacerbates pathology in the other. SGLT2 inhibitors improve renal hemodynamics by reducing intraglomerular pressure through enhanced tubuloglomerular feedback, which helps preserve kidney function in patients with diabetes. Improved renal function reduces neurohormonal activation, including the renin–angiotensin–aldosterone system and sympathetic nervous system, both of which are major contributors to cardiovascular disease progression. By stabilizing renal function and reducing neurohormonal stress on the cardiovascular system, SGLT2 inhibitors provide integrated cardiorenal protection that ultimately contributes to improved outcomes in patients with diabetic cardiovascular disease. [14]

Metabolic Reprogramming of the Diabetic Myocardium

Metabolic inflexibility is a hallmark feature of the diabetic myocardium and plays a central role in the development and progression of ischemic heart disease. Under physiological conditions, the heart

possesses the ability to utilize multiple energy substrates, including glucose, fatty acids, lactate, and ketone bodies, allowing it to adapt to varying metabolic demands. However, in diabetes, insulin resistance and impaired glucose uptake shift myocardial metabolism toward excessive fatty acid oxidation. This metabolic shift results in increased oxygen consumption for ATP generation, reduced cardiac efficiency, and accumulation of toxic lipid intermediates within cardiomyocytes. These alterations not only impair myocardial contractile function but also increase susceptibility to ischemic injury during episodes of reduced coronary blood flow. SGLT2 inhibitors appear to counteract some of these metabolic disturbances by promoting more efficient substrate utilization within the myocardium. [15]

One of the proposed mechanisms through which SGLT2 inhibitors improve cardiac metabolism is the promotion of ketone body production and utilization. By inducing glycosuria and reducing circulating glucose levels, SGLT2 inhibitors stimulate hepatic ketogenesis, leading to modest increases in circulating ketone bodies such as β-hydroxybutyrate. Ketone bodies represent a highly efficient fuel source for the heart because they generate more ATP per unit of oxygen consumed compared with fatty acids. This improved energetic efficiency may be particularly beneficial during ischemic conditions, when oxygen availability is limited. Enhanced myocardial uptake and oxidation of ketone bodies may therefore provide an alternative energy substrate that supports cardiac function and reduces metabolic stress in the diabetic heart. [16]

In addition to promoting ketone utilization, SGLT2 inhibitors may enhance overall myocardial energy efficiency by improving mitochondrial oxidative capacity and reducing metabolic overload. The reduction in circulating glucose and insulin levels associated with SGLT2 inhibitor therapy may decrease lipotoxicity and improve cellular metabolic signaling pathways involved in energy regulation. Experimental studies have also suggested that SGLT2 inhibition may activate pathways related to cellular energy sensing, such as AMP-activated protein kinase (AMPK), which plays a crucial role in maintaining metabolic homeostasis within cardiomyocytes. Activation of these metabolic regulatory pathways can improve mitochondrial function, reduce oxidative stress, and enhance ATP production, thereby supporting myocardial resilience during ischemic stress and contributing to improved cardiac outcomes in patients with diabetes. [17]

Cellular and Molecular Cardioprotective Mechanisms of SGLT2 Inhibitors

At the cellular level, SGLT2 inhibitors exert multiple protective effects that enhance cardiomyocyte survival and improve myocardial resilience during ischemic stress. One of the most important mechanisms involves the preservation of mitochondrial function. Mitochondria play a central role in cardiac energy production, and their dysfunction is a major contributor to myocardial injury in diabetes. Experimental studies have demonstrated that SGLT2 inhibitors improve mitochondrial efficiency, enhance oxidative phosphorylation, and reduce mitochondrial swelling and structural damage during ischemic conditions. Improved mitochondrial integrity helps maintain ATP production, which is essential for sustaining myocardial contractility and preventing cardiomyocyte apoptosis during ischemic events. By stabilizing mitochondrial bioenergetics, SGLT2 inhibitors may significantly enhance the ability of the diabetic heart to tolerate ischemic stress. [18]

Another key mechanism underlying the cardioprotective effects of SGLT2 inhibitors is the reduction of oxidative stress. Diabetes is associated with excessive production of reactive oxygen species (ROS) within cardiomyocytes, primarily due to mitochondrial dysfunction and increased fatty acid oxidation. Elevated ROS levels lead to lipid peroxidation, protein damage, and DNA injury, all of which contribute to cellular dysfunction and myocardial damage. SGLT2 inhibitors have been shown to reduce oxidative stress by improving mitochondrial efficiency and decreasing the generation of reactive oxygen species.

Additionally, these agents may enhance endogenous antioxidant defenses, including the activity of superoxide dismutase and other antioxidant enzymes. Through these mechanisms, SGLT2 inhibitors help protect cardiomyocytes from oxidative damage and limit the progression of ischemic injury. [19] Inflammation also plays a significant role in the pathogenesis of diabetic cardiovascular disease, particularly in the development of atherosclerosis and myocardial injury. Chronic hyperglycemia and metabolic dysregulation promote activation of pro-inflammatory signaling pathways such as nuclear factor kappa B (NF-κB), which leads to increased production of inflammatory cytokines including tumor necrosis factor-α and interleukin-6. These inflammatory mediators contribute to endothelial dysfunction, vascular damage, and cardiomyocyte injury. Evidence suggests that SGLT2 inhibitors may exert anti-inflammatory effects by suppressing pro-inflammatory signaling pathways and reducing circulating levels of inflammatory cytokines. By attenuating inflammatory responses, these agents may help limit myocardial injury and improve cardiac function in patients with diabetic ischemic heart disease. [20] Another important cellular mechanism involves the modulation of intracellular ion homeostasis, particularly through inhibition of the myocardial sodium–hydrogen exchanger (NHE1). Overactivation of NHE1 in the diabetic heart leads to increased intracellular sodium concentrations, which subsequently promote calcium overload through the sodium–calcium exchanger. Elevated intracellular calcium can impair mitochondrial function, promote oxidative stress, and trigger cardiomyocyte apoptosis. SGLT2 inhibitors have been proposed to indirectly inhibit NHE1 activity, thereby reducing intracellular sodium and calcium accumulation. This effect helps preserve cardiomyocyte ionic balance, improves mitochondrial function, and enhances myocardial contractility. The regulation of intracellular ion homeostasis may therefore represent an important mechanism contributing to the cardioprotective actions of SGLT2 inhibitors in ischemic heart disease. [21]

Effects of SGLT2 Inhibitors on Myocardial Remodeling and Ischemia–Reperfusion Injury

Myocardial remodeling is a critical pathological process that occurs following ischemic injury and myocardial infarction, particularly in patients with diabetes. This process involves structural and functional alterations in the myocardium, including cardiomyocyte hypertrophy, interstitial fibrosis, and ventricular dilation, all of which contribute to progressive cardiac dysfunction and the development of heart failure. Diabetes accelerates adverse cardiac remodeling through mechanisms such as chronic inflammation, oxidative stress, and activation of profibrotic signaling pathways. Emerging experimental evidence suggests that SGLT2 inhibitors may attenuate these pathological changes by modulating molecular pathways involved in myocardial fibrosis and cellular stress responses. By reducing inflammatory signaling and oxidative damage, these agents may limit excessive extracellular matrix deposition and preserve myocardial structural integrity after ischemic injury. [22]

In addition to limiting structural remodeling, SGLT2 inhibitors may also reduce the severity of ischemia–reperfusion injury, a phenomenon that occurs when blood supply returns to the myocardium after a period of ischemia. Although reperfusion is essential for myocardial survival, it can paradoxically exacerbate tissue injury through mechanisms involving oxidative stress, mitochondrial dysfunction, calcium overload, and inflammatory activation. Experimental studies have demonstrated that treatment with SGLT2 inhibitors can reduce infarct size and improve functional recovery of the myocardium following ischemia–reperfusion events. These beneficial effects are believed to result from improved mitochondrial stability, reduced oxidative stress, and enhanced myocardial energy metabolism. By mitigating ischemia–reperfusion injury and limiting adverse ventricular remodeling, SGLT2 inhibitors may contribute to improved cardiac function and better long-term outcomes in patients with diabetic ischemic heart disease. [23]

Clinical Evidence Supporting Cardiovascular Protection

Large-scale cardiovascular outcome trials have provided strong clinical evidence supporting the cardioprotective effects of SGLT2 inhibitors in patients with type 2 diabetes. One of the landmark trials in this field was the EMPA-REG OUTCOME study, which evaluated the cardiovascular safety and efficacy of empagliflozin in patients with type 2 diabetes and established cardiovascular disease. The trial demonstrated a significant reduction in major adverse cardiovascular events, including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Notably, empagliflozin therapy was associated with a substantial reduction in cardiovascular mortality and hospitalization for heart failure compared with placebo. These findings represented one of the first demonstrations that a glucose-lowering medication could provide significant cardiovascular benefits beyond glycemic control, highlighting the potential of SGLT2 inhibitors as cardioprotective agents in high-risk diabetic populations. [24]

Subsequent trials have confirmed and expanded these observations across different SGLT2 inhibitors and patient populations. The CANVAS Program, which evaluated canagliflozin, demonstrated a reduction in major cardiovascular events and hospitalization for heart failure in patients with type 2 diabetes who were at high cardiovascular risk. Similarly, the DECLARE–TIMI 58 trial assessed dapagliflozin and reported significant reductions in hospitalization for heart failure and favorable effects on renal outcomes. In addition, the DAPA-HF trial extended the benefits of SGLT2 inhibition to patients with heart failure with reduced ejection fraction, including those without diabetes, suggesting that the cardioprotective effects of these agents may involve mechanisms independent of glucose lowering. Collectively, these clinical trials provide compelling evidence that SGLT2 inhibitors significantly improve cardiovascular outcomes and support their role as an important therapeutic strategy in patients with diabetic cardiovascular disease. [25]

Future Perspectives and Therapeutic Implications

The growing body of experimental and clinical evidence supporting the cardioprotective effects of SGLT2 inhibitors has significantly reshaped the therapeutic landscape of diabetic cardiovascular disease. While these agents were initially introduced as glucose-lowering drugs, their ability to influence multiple physiological pathways—including myocardial metabolism, hemodynamic regulation, mitochondrial function, oxidative stress reduction, and anti-inflammatory signaling—has highlighted their broader role in cardiometabolic therapy. Future research should aim to further clarify the precise molecular mechanisms through which SGLT2 inhibitors confer myocardial protection, particularly in the context of ischemia–reperfusion injury and long-term cardiac remodeling. Additionally, emerging studies are exploring the potential benefits of SGLT2 inhibitors in patients without diabetes, suggesting that their cardiovascular effects may extend beyond glycemic control. Understanding these mechanisms may open new avenues for therapeutic strategies targeting metabolic and cellular pathways involved in ischemic heart disease. Furthermore, integrating SGLT2 inhibitors into comprehensive cardiovascular management strategies may offer substantial benefits in reducing the burden of ischemic heart disease and improving long-term outcomes in patients with diabetes. [26]

Conclusion

Diabetic ischemic heart disease represents a major contributor to cardiovascular morbidity and mortality worldwide, largely due to the complex metabolic, vascular, and cellular disturbances associated with diabetes mellitus. The diabetic myocardium is particularly vulnerable to ischemic injury because of impaired metabolic flexibility, mitochondrial dysfunction, increased oxidative stress, endothelial abnormalities, and chronic low-grade inflammation. These pathological alterations not only increase the risk of myocardial infarction but also worsen post-ischemic recovery and promote adverse ventricular

remodeling. Consequently, identifying therapeutic strategies that address both metabolic dysregulation and cardiovascular dysfunction has become a critical priority in the management of patients with diabetes.

Sodium–glucose cotransporter-2 inhibitors have emerged as an important therapeutic class that provides cardiovascular benefits extending beyond glucose lowering. By promoting glycosuria and natriuresis, these agents produce favorable hemodynamic effects including reductions in plasma volume, blood pressure, and cardiac workload. In addition, SGLT2 inhibitors improve myocardial metabolic efficiency by promoting the utilization of alternative energy substrates such as ketone bodies, which may enhance ATP production under conditions of limited oxygen availability. At the cellular level, these agents contribute to mitochondrial preservation, reduction of oxidative stress, suppression of inflammatory signaling pathways, and improvement of intracellular ion homeostasis within cardiomyocytes. Collectively, these mechanisms enhance myocardial resilience to ischemic stress and may reduce the severity of myocardial injury.

Another important aspect of SGLT2 inhibitor therapy is its potential to attenuate adverse cardiac remodeling following ischemic injury. By limiting inflammation, oxidative damage, and fibrotic signaling, these agents may help preserve myocardial structure and function after ischemic events. The ability to reduce ischemia–reperfusion injury and improve myocardial recovery further supports their role as cardioprotective agents in diabetic patients. Clinical trials have also demonstrated consistent reductions in heart failure hospitalization and cardiovascular mortality, reinforcing the clinical significance of the physiological mechanisms described.

In summary, SGLT2 inhibitors exert multifaceted cardioprotective actions that target several key pathophysiological processes involved in diabetic ischemic heart disease. Their combined metabolic, hemodynamic, and cellular effects contribute to improved myocardial function and reduced cardiovascular risk. Continued research into the mechanisms of action of these agents may further enhance our understanding of cardiometabolic interactions and support the development of new therapeutic strategies aimed at reducing the burden of cardiovascular disease in patients with diabetes.

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