Beyond Glycemic Control: SGLT2 Inhibitors as Modulators of Post-Infarction Myocardial Remodeling

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Abstract

Background: Acute myocardial infarction initiates a dynamic process of structural, functional, metabolic, and molecular adaptation that may culminate in adverse left ventricular remodeling and subsequent heart failure despite successful contemporary reperfusion. Sodium–glucose cotransporter-2 inhibitors were originally introduced as glucose-lowering agents; however, their consistent cardiovascular and renal benefits in populations with heart failure and chronic kidney disease have generated substantial interest in their potential role during the vulnerable post-infarction period. This review examines the biological rationale and clinical evidence supporting SGLT2 inhibition as a potential modulator of post-myocardial infarction remodeling. Proposed mechanisms extend well beyond glycemic control and include natriuresis and optimization of ventricular loading conditions, improved myocardial energetics, modulation of sodium and calcium homeostasis, attenuation of oxidative stress and inflammation, antifibrotic signaling, preservation of renal function, and favorable effects on autonomic balance. Early mechanistic and imaging studies have demonstrated improvements in natriuretic peptides, ventricular volumes, myocardial deformation, and selected remodeling indices. Nevertheless, contemporary randomized evidence is more heterogeneous. While the EMMY trial demonstrated favorable biomarker and echocardiographic changes with early empagliflozin, EMPRESS-MI did not demonstrate additional cardiovascular magnetic resonance-defined reverse remodeling, and the larger DAPA-MI and EMPACT-MI trials have not established a reduction in mortality after myocardial infarction. The most consistent emerging clinical signal is a reduction in subsequent heart failure events. SGLT2 inhibitors therefore represent a biologically plausible and clinically promising component of post-infarction cardioprotection, although their specific role as direct anti-remodeling therapy requires further phenotypically targeted investigation.

Keywords: SGLT2 inhibitors, myocardial infarction, ventricular remodeling, heart failure

Introduction

Survival after acute myocardial infarction (AMI) has improved substantially through rapid reperfusion, potent antithrombotic treatment, intensive lipid lowering, and evidence-based neurohormonal therapy. Nevertheless, restoration of epicardial coronary flow does not invariably restore myocardial integrity. A clinically important proportion of survivors subsequently undergo adverse left ventricular (LV) remodeling, characterized by progressive changes in chamber size, geometry, wall thickness, myocardial mechanics, and systolic or diastolic performance. These structural alterations provide an important substrate for chronic heart failure, ventricular arrhythmias, functional mitral regurgitation, and late cardiovascular morbidity. Prevention of post-infarction remodeling consequently remains an important therapeutic objective even in the modern primary percutaneous coronary intervention (PCI) era. [1]

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) represent one of the most important recent developments in cardiovascular therapeutics. Initially developed to lower plasma glucose by reducing proximal tubular glucose reabsorption, these drugs subsequently demonstrated substantial reductions in heart failure events and preservation of kidney function that could not be adequately explained by their modest glucose-lowering effects. Benefits observed in patients without diabetes and across a broad spectrum of LV ejection fraction (LVEF) further shifted the conceptual framework surrounding these agents from antihyperglycemic drugs toward cardiorenal therapies. [2]

The post-MI setting is therefore particularly attractive for SGLT2 inhibition. Myocardial infarction simultaneously activates hemodynamic overload, neurohormonal signaling, inflammation, oxidative injury, energetic disturbance, renal stress, extracellular matrix turnover, and maladaptive hypertrophy—several processes potentially influenced by SGLT2i. However, the key research gap is whether these biologically plausible mechanisms translate into clinically meaningful prevention of post-infarction remodeling when SGLT2 inhibitors are initiated early in patients already receiving contemporary reperfusion and guideline-directed therapy. This review critically evaluates the pathophysiological rationale, myocardial and systemic mechanisms, imaging evidence, randomized trial data, and future role of SGLT2 inhibitors as modulators of post-infarction myocardial remodeling. [3]

Post-Infarction Remodeling: From Myocyte Loss to Ventricular Failure

Post-infarction remodeling begins within hours of coronary occlusion. Prolonged ischemia depletes adenosine triphosphate, disrupts membrane ion gradients, impairs mitochondrial function, and ultimately produces irreversible cardiomyocyte injury. Necrotic myocardium releases damage-associated molecular signals that activate innate immunity and recruit neutrophils and monocyte-derived macrophages. This inflammatory phase is indispensable for removal of cellular debris and initiation of repair, but excessive or persistent inflammation may increase extracellular matrix degradation and extend injury into the peri-infarct region. The quality and temporal regulation of this transition from inflammation to repair critically influence scar formation and subsequent ventricular architecture. [4]

Reperfusion limits infarct size and remains the most effective anti-remodeling intervention after STEMI, yet reperfusion itself may generate additional oxidative and metabolic injury. Sudden restoration of oxygen availability promotes reactive oxygen species formation, mitochondrial permeability transition, calcium overload, and endothelial dysfunction. Microvascular obstruction can therefore persist despite successful restoration of epicardial coronary flow. Larger infarcts, anterior location, extensive microvascular obstruction, and reduced myocardial salvage are consequently associated with a greater propensity for adverse LV remodeling and subsequent heart failure. [5]

The early mechanical phase of remodeling is dominated by infarct expansion. Necrotic myocardium loses tensile strength, while degradation and reorganization of intercellular collagen allow myofiber slippage. The infarcted region becomes thinner and may elongate circumferentially without additional cardiomyocyte necrosis. According to Laplace principles, progressive chamber enlargement and reduced wall thickness increase regional wall stress. Increased wall stress then promotes further dilation

and stimulates adaptive hypertrophy in surviving myocardium, establishing a self-perpetuating cycle that can eventually transform the normally elliptical LV into a more spherical and mechanically inefficient chamber. [6]

Late remodeling extends beyond the original infarct zone. Surviving cardiomyocytes develop hypertrophy in response to increased loading conditions, whereas fibroblasts and myofibroblasts regulate deposition and turnover of extracellular matrix. Activation of the renin–angiotensin–aldosterone system and sympathetic nervous system initially supports blood pressure and cardiac output but subsequently promotes vasoconstriction, sodium retention, hypertrophy, fibrosis, oxidative stress, and apoptosis. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists reduce post-MI morbidity partly by attenuating these maladaptive processes, providing proof that ventricular remodeling is therapeutically modifiable. [7]

Importantly, remodeling is not synonymous with a reduction in LVEF. A patient may maintain a seemingly normal or mildly impaired ejection fraction while developing regional wall thinning, worsening myocardial deformation, altered ventricular geometry, or increased filling pressures. Conversely, substantial improvement in LVEF may occur through recovery of stunned myocardium without complete normalization of tissue mechanics. Modern assessment of therapeutic effects after MI therefore requires a multidimensional approach rather than reliance on LVEF alone. [8]

Why SGLT2 Inhibition May Influence the Post-Infarction Heart

The cardiovascular effects of SGLT2 inhibitors became apparent during outcome trials in type 2 diabetes. EMPA-REG OUTCOME demonstrated an unexpectedly prominent reduction in hospitalization for heart failure with empagliflozin, stimulating intense investigation into mechanisms independent of glucose lowering. Subsequent heart failure trials confirmed that SGLT2i improve clinical outcomes even in patients without diabetes, establishing that their principal cardiovascular actions cannot be interpreted simply as a consequence of improved glycemic control. [9]

DAPA-HF and EMPEROR-Reduced established dapagliflozin and empagliflozin as fundamental therapies for heart failure with reduced ejection fraction, while subsequent trials extended benefit to patients with mildly reduced or preserved LVEF. The consistency and rapid onset of reductions in worsening heart failure suggested that SGLT2i influence pathways operating earlier than conventional structural reverse remodeling alone. These observations provide the translational rationale for testing the drugs immediately after myocardial infarction, before chronic heart failure is established. [10]

A major conceptual advantage of SGLT2 inhibition is the simultaneous modification of cardiac and renal physiology. Renal dysfunction after MI may intensify neurohormonal activation, congestion, diuretic resistance, and vulnerability to heart failure. SGLT2 inhibition produces glycosuria and natriuresis while restoring tubuloglomerular feedback, lowering intraglomerular pressure, and preserving kidney function over time. Because cardiorenal interactions materially influence ventricular loading conditions and post-MI recovery, renal protection may indirectly contribute to a more favorable remodeling environment. [11]

Hemodynamic Unloading and Reduction of Wall Stress

SGLT2 inhibitors increase urinary glucose and sodium excretion, producing modest osmotic diuresis and natriuresis. Unlike aggressive loop-diuretic therapy, the resulting volume effect is generally accompanied by relatively limited activation of counter-regulatory neurohormonal pathways. Reduction in plasma and interstitial volume can decrease ventricular preload and filling pressure, while modest reductions in systemic blood pressure may decrease afterload. In a recently infarcted ventricle, where regional wall stress is already elevated, even moderate optimization of loading conditions may reduce the mechanical forces that contribute to infarct expansion and progressive chamber dilation. [12]

Hemoconcentration observed during SGLT2 treatment has also been linked to increased hematocrit and erythropoietin signaling. Improved oxygen delivery has been proposed as another potentially favorable mechanism, although the contribution of erythropoiesis relative to plasma-volume contraction remains debated. The rapid clinical benefits of SGLT2 inhibition in heart failure are probably therefore generated by several overlapping physiological changes rather than a single diuretic mechanism. [2]

Myocardial Energetics and Metabolic Reprogramming

The healthy myocardium is metabolically flexible and derives energy predominantly from fatty acids while retaining the capacity to oxidize glucose, lactate, amino acids, and ketone bodies. Ischemia and subsequent heart failure disrupt this flexibility, impair mitochondrial oxidative phosphorylation, and reduce energetic efficiency. SGLT2 inhibition induces a metabolic state resembling mild fasting through glycosuria, reduced insulin-to-glucagon signaling, enhanced lipolysis, and increased circulating ketone bodies. Ketones such as β-hydroxybutyrate can serve as an efficient oxidative substrate for stressed myocardium and may improve the relationship between ATP production and oxygen utilization. [13]

The "thrifty substrate" hypothesis should nevertheless not be interpreted as established proof that ketone oxidation is the dominant cardioprotective mechanism. Contemporary data suggest broader metabolic reprogramming involving mitochondrial function, autophagy, nutrient-sensing pathways, adipose-tissue metabolism, and insulin sensitivity. These adaptations may collectively increase cellular resilience during the metabolically vulnerable period following ischemia-reperfusion. Thus, the importance of SGLT2 inhibition may lie less in supplying one preferred fuel and more in restoring metabolic flexibility to injured myocardium. [14]

Sodium–Calcium Homeostasis, Mitochondria, and Oxidative Stress

Intracellular sodium and calcium overload are important contributors to ischemic and reperfusion injury. Increased activity of the myocardial sodium–hydrogen exchanger can elevate cytosolic sodium, promote reverse-mode sodium–calcium exchange, increase calcium loading, and impair mitochondrial energetics. Experimental work has suggested that SGLT2 inhibitors may reduce pathological sodium accumulation and favor more physiological cytosolic and mitochondrial calcium handling. Because cardiac expression of SGLT2 itself is minimal, these effects appear to involve indirect or off-target mechanisms rather than conventional inhibition of myocardial SGLT2. [15]

Improved ionic homeostasis may additionally reduce mitochondrial reactive oxygen species production and prevent activation of calcium-dependent hypertrophic and arrhythmogenic pathways. This provides a plausible connection between SGLT2 inhibition, preservation of cardiomyocyte viability, reduced hypertrophic signaling, and electrical stability. However, direct inhibition of myocardial sodium–hydrogen exchange by individual SGLT2 inhibitors remains mechanistically debated, and it should be regarded as a plausible contributory pathway rather than an established class mechanism in humans. [15]

Inflammation, Fibrosis, and Extracellular Matrix Remodeling

A successful post-infarction repair response requires carefully timed inflammation followed by resolution and scar maturation. Persistent activation of the NLRP3 inflammasome, nuclear factor-κB pathways, and pro-inflammatory cytokines may amplify tissue injury and promote adverse fibrosis. Experimental studies suggest that SGLT2 inhibition can attenuate oxidative-inflammatory signaling and favor a shift from pro-inflammatory macrophage phenotypes toward reparative states. These actions may potentially restrict excessive inflammation while preserving necessary scar formation. [16]

Fibrosis represents another potential therapeutic target. Transforming growth factor-β signaling stimulates fibroblast activation and collagen deposition, whereas matrix metalloproteinases contribute to extracellular matrix turnover and infarct expansion. Preclinical studies have associated SGLT2 inhibition with reduced profibrotic signaling, collagen deposition, and myocardial stiffness. The resulting hypothesis is attractive: SGLT2i may promote sufficient scar integrity while reducing excessive interstitial fibrosis in remote myocardium. Nevertheless, direct demonstration that these agents alter human post-infarction scar architecture remains limited, particularly when assessed with serial cardiovascular magnetic resonance tissue characterization. [17]

Autonomic and Electrophysiological Effects

Sympathetic activation following myocardial infarction is adaptive in the immediate period but becomes harmful when sustained. Excess adrenergic signaling increases myocardial oxygen demand, promotes hypertrophy and apoptosis, and contributes to ventricular arrhythmogenesis. Experimental and clinical observations suggest that SGLT2 inhibition may reduce sympathetic activity and improve autonomic

balance, providing an additional pathway through which ventricular workload and arrhythmic vulnerability might be modified. [18]

The SGLT2-I AMI PROTECT registry provided hypothesis-generating clinical support for an anti-arrhythmic association. Among patients with diabetes hospitalized with AMI, prior SGLT2 inhibitor treatment was associated with fewer new-onset arrhythmias, including a lower ventricular arrhythmic burden. Because the study was observational, residual confounding and treatment-selection effects cannot be excluded. Nevertheless, the findings complement mechanistic data concerning sodium-calcium homeostasis, oxidative stress, fibrosis, and autonomic modulation and justify further prospective evaluation of arrhythmic endpoints after MI. [19]

Imaging the Remodeling Response: Beyond Ejection Fraction

Two-dimensional echocardiography remains the principal clinical method for serial assessment after myocardial infarction because it is widely available, repeatable, and capable of evaluating ventricular dimensions, regional wall motion, systolic function, filling pressure, and mechanical complications. LV end-diastolic and end-systolic volumes provide more direct information about remodeling than LVEF alone. Adverse remodeling has commonly been defined by a substantial increase in LV end-diastolic volume during follow-up, although thresholds and imaging modalities vary among studies. [20]

Three-dimensional echocardiography reduces geometric assumptions and improves reproducibility of serial volumetric assessment, while cardiovascular magnetic resonance (CMR) represents the reference standard for chamber volumes and tissue characterization. CMR can identify infarct size, transmurality, microvascular obstruction, intramyocardial hemorrhage, and scar distribution—all important determinants of remodeling. Consequently, a therapy capable of genuinely modifying post-infarction biology should ideally be evaluated not only by changes in LVEF but also by serial volumes and, where feasible, tissue-level CMR endpoints. [21]

Speckle-tracking echocardiography provides a complementary perspective through quantification of myocardial deformation. Global longitudinal strain (GLS) is particularly sensitive to subclinical impairment of longitudinal fibers and can detect abnormalities when LVEF remains preserved. Following MI, GLS correlates with infarct burden and provides prognostic information regarding ventricular recovery and adverse events. Changes in strain may therefore reveal treatment effects earlier than conventional global volumetric measures, an issue of particular relevance in low-risk or preserved-EF populations where substantial changes in LVEF may never occur. [22]

Regional indices such as infarct-wall thinning and expansion may also provide valuable information. Infarct expansion reflects disproportionate regional dilatation and elongation of noncontractile myocardium, whereas a declining ratio between infarcted and remote wall thickness indicates loss of structural integrity. Although these parameters are less standardized than LV volumes or GLS, they conceptually link myocardial tissue integrity to the mechanical process of remodeling and may be especially informative after large anterior infarctions. Their future utility depends on standardized acquisition, reproducibility, and validation against CMR-derived scar characteristics and clinical outcomes. [6]

Evidence for SGLT2 Inhibition and Reverse Remodeling Outside Acute MI

Imaging studies in established diabetes and heart failure provided the initial evidence that SGLT2 inhibition may favor reverse remodeling. In a prospective observational study, Gamaza-Chulián and colleagues reported improvement in longitudinal strain and indices of LV remodeling among patients receiving SGLT2 inhibitors. Although observational data cannot establish causality, the findings supported the hypothesis that myocardial mechanics may respond to therapy beyond changes in conventional ejection fraction. [23]

A subsequent meta-analysis of randomized heart failure studies strengthened this concept. Carluccio and colleagues found that SGLT2 inhibitor treatment was associated with reductions in LV end-diastolic and end-systolic volumes and LV mass, together with a modest improvement in LVEF. Importantly, these data predominantly represented patients with established heart failure rather than patients in the immediate post-MI phase. Extrapolating these findings directly to acute infarction therefore requires

caution because spontaneous recovery, reperfusion-related myocardial salvage, and contemporary post-MI therapy create a fundamentally different remodeling environment. [24]

Early Post-MI Evidence: The EMMY Trial

The EMMY trial provided the clearest early randomized mechanistic signal supporting SGLT2 inhibition following acute MI. In 476 patients with a large recent myocardial infarction, empagliflozin 10 mg daily was initiated within 72 hours after PCI. At 26 weeks, empagliflozin produced a significantly greater reduction in NT-proBNP than placebo. Echocardiographic secondary endpoints were also favorable: LV end-systolic and end-diastolic volumes were lower, E/e′ was reduced, and improvement in LVEF was modestly greater with empagliflozin. Importantly, early treatment was well tolerated without a significant excess of serious safety events. [25]

EMMY was not powered for hard cardiovascular outcomes, and its structural endpoints should therefore be interpreted primarily as mechanistic evidence. Nevertheless, the combination of lower NT-proBNP, reduced chamber volumes, and improved filling-pressure indices created a coherent biological signal consistent with attenuation of remodeling. These results substantially strengthened the rationale for larger post-MI trials while simultaneously illustrating why biomarkers and imaging endpoints may be important for understanding an intervention whose clinical effects may not be captured by mortality alone. [25]

DAPA-MI: Cardiometabolic Benefit Without Definitive Heart Failure Prevention

DAPA-MI evaluated dapagliflozin after myocardial infarction in patients without previously established diabetes or chronic heart failure. The trial demonstrated superiority for a hierarchical cardiometabolic composite outcome, largely reflecting prevention of new diabetes and favorable weight-related metabolic outcomes. However, conventional cardiovascular endpoints were uncommon, and dapagliflozin did not establish a significant reduction in cardiovascular death or hospitalization for heart failure. The trial therefore demonstrated that SGLT2 inhibition can be initiated safely in a comparatively low-risk post-MI population but did not provide definitive evidence for prevention of clinical heart failure in such patients. [26]

The DAPA-MI experience also illustrates an important principle of post-MI trial design. Contemporary reperfusion and secondary prevention have reduced event rates substantially, particularly in patients without established heart failure or diabetes. Detecting an incremental anti-remodeling effect in such populations may consequently require either very large sample sizes, more selective recruitment of patients with biological evidence of remodeling risk, or sensitive imaging and biomarker endpoints rather than conventional clinical outcomes alone. [26]

EMPACT-MI: A Heart Failure Signal Without Reduction in the Primary Endpoint

EMPACT-MI addressed a higher-risk population by enrolling more than 6500 patients hospitalized with acute MI who had newly reduced LVEF, signs or symptoms of congestion, or both. Empagliflozin was initiated within 14 days of admission. The primary composite of first hospitalization for heart failure or death from any cause was not significantly reduced compared with placebo. Mortality was also not significantly different between treatment groups. Therefore, EMPACT-MI did not establish routine empagliflozin therapy after MI as a mortality-reducing intervention. [27]

A clinically important signal nevertheless emerged for heart failure hospitalization. First hospitalization for heart failure occurred less frequently with empagliflozin, and subsequent analyses similarly supported reduction in recurrent heart failure events. This distinction is central to interpretation of the SGLT2 post-MI literature. The available evidence is more compatible with attenuation of subsequent heart failure vulnerability than with a broad effect on all mechanisms responsible for post-MI mortality. Such a pattern is consistent with the established pharmacological profile of SGLT2 inhibitors across the heart failure spectrum. [27]

EMPRESS-MI and the Limits of the Remodeling Hypothesis

EMPRESS-MI adds an important counterbalance to earlier mechanistic optimism. This randomized, placebo-controlled CMR study recruited patients with LVEF below 45% after recent MI and evaluated empagliflozin over approximately 24 weeks. Both treatment groups demonstrated substantial

spontaneous improvement in systolic function following contemporary MI care. Empagliflozin did not produce an additional reduction in indexed LV end-systolic volume, nor did it significantly alter LV end-diastolic volume, LVEF, LV mass, or NT-proBNP compared with placebo. [28]

These neutral CMR findings should not be interpreted as evidence that SGLT2 inhibition lacks post-MI cardiovascular value. Instead, they challenge the simplistic assumption that reduction in heart failure events must be mediated by large measurable changes in LV chamber geometry. Modern reperfusion itself can produce considerable reverse remodeling, potentially leaving limited room for an additional treatment effect. SGLT2 inhibitors may also influence congestion, renal reserve, metabolic resilience, microvascular physiology, or cellular function without necessarily producing major differences in conventional CMR volumes. [28]

Reconciling Apparently Conflicting Evidence

The apparent divergence between EMMY, EMPACT-MI, and EMPRESS-MI is scientifically informative rather than contradictory. EMMY demonstrated favorable biomarker and echocardiographic changes; EMPACT-MI demonstrated a reduction in heart failure hospitalization despite a neutral primary composite endpoint; and EMPRESS-MI failed to demonstrate incremental CMR reverse remodeling. Differences in baseline risk, infarct characteristics, timing of treatment, LVEF, imaging methods, background therapy, follow-up duration, and spontaneous recovery after reperfusion can plausibly explain part of this heterogeneity. [25,27,28]

Meta-analyses incorporating randomized post-MI data increasingly suggest that the most reproducible clinical effect is reduction in hospitalization for heart failure, whereas convincing reductions in all-cause or cardiovascular mortality have not been demonstrated. This is a more defensible interpretation than describing SGLT2 inhibitors as established post-MI "reverse-remodeling drugs." They may instead modify the transition from myocardial injury to clinically overt heart failure through several structural and nonstructural pathways, with the relative contribution of each mechanism varying according to the phenotype of the individual patient. [29]

Which Patients May Benefit Most?

The patients most likely to demonstrate measurable benefit may be those with substantial residual remodeling risk despite successful PCI: large anterior infarction, reduced LVEF, clinical or radiographic congestion, elevated natriuretic peptides, impaired GLS, extensive infarct burden or microvascular obstruction on CMR, diabetes, chronic kidney disease, or early increases in LV volumes. Conversely, low-risk patients with small reperfused infarcts and rapid spontaneous recovery may have little residual structural remodeling for an additional pharmacological intervention to modify. This concept argues for phenotype-driven rather than indiscriminate post-MI remodeling trials. [21]

Patients with preserved LVEF deserve particular attention. A normal ejection fraction does not exclude regional mechanical impairment or subsequent heart failure risk. GLS and other deformation indices may identify subtle abnormalities before conventional LV volumes change. If SGLT2 inhibitors primarily preserve myocardial mechanics or prevent deterioration rather than generate dramatic reverse remodeling, studies limited to LVEF could underestimate their effect. Future trials should therefore combine conventional volumetric outcomes with strain, biomarkers, CMR tissue characterization, and clinical heart failure events. [22]

Timing of Initiation and Integration With Contemporary Therapy

The early post-infarction period provides a biologically attractive therapeutic window because inflammatory activation, infarct expansion, neurohormonal signaling, and metabolic stress are maximal before mature scar formation. EMMY demonstrated that empagliflozin can be initiated within days of PCI in appropriately stabilized patients, whereas DAPA-MI and EMPACT-MI extended evaluation into the early post-discharge period. These studies collectively support the feasibility of early initiation in hemodynamically stable patients who do not have contraindications. [25-27]

Importantly, SGLT2 inhibitors should be viewed as potential additions to, rather than substitutes for, established post-MI therapy. Revascularization, antiplatelet therapy, intensive lipid lowering, renin–angiotensin system inhibition where indicated, beta-blockade in appropriate patients, mineralocorticoid

receptor antagonism in selected LV dysfunction, smoking cessation, rehabilitation, and management of diabetes and blood pressure remain fundamental. Current acute coronary syndrome guidance recognizes the established indications for SGLT2 inhibitors in diabetes, chronic kidney disease, and heart failure while acknowledging that the dedicated post-MI trials have not demonstrated a reduction in mortality or the primary composite clinical outcomes. [30]

Safety Considerations in the Post-Infarction Setting

Early SGLT2 inhibition has generally been well tolerated in contemporary post-MI trials. Nevertheless, patient selection remains important. Osmotic diuresis can contribute to volume depletion or symptomatic hypotension, particularly in individuals receiving multiple diuretics or with marginal blood pressure. Renal function may show a small early hemodynamic decline before longer-term stabilization, and clinicians should consider volume status and kidney function when initiating therapy. Genital mycotic infections are recognized adverse effects, while severe hypoglycemia is uncommon in the absence of insulin or insulin-secretagogue therapy. [30]

Euglycemic diabetic ketoacidosis, although uncommon, is potentially serious and becomes more relevant during prolonged fasting, severe acute illness, or perioperative states. SGLT2 inhibitors should therefore be withheld when ketoacidosis risk is increased and around major surgery according to contemporary recommendations. Initiation immediately after MI should be reserved for clinically stable patients rather than individuals with ongoing shock, severe metabolic instability, or marked volume depletion. The reassuring safety profiles of EMMY, DAPA-MI, and EMPACT-MI support early use when a conventional indication is present but do not eliminate the need for appropriate clinical screening. [25-27]

Remaining Research Gaps and Future Directions

Several fundamental questions remain unresolved. First, the optimal biological phenotype for post-MI SGLT2 therapy has not been identified. Trials based predominantly on LVEF may combine patients with very different infarct sizes, scar burdens, microvascular injury, strain abnormalities, and remodeling trajectories. Integration of CMR tissue characterization, GLS, NT-proBNP trajectories, and potentially circulating markers of fibrosis and inflammation could identify patients in whom an anti-remodeling intervention has the greatest opportunity to produce measurable benefit. [21]

Second, the mechanistic hierarchy remains uncertain. Natriuresis, renal protection, metabolic reprogramming, inflammation, fibrosis, ionic homeostasis, mitochondrial function, autonomic balance, and vascular effects are all plausible contributors, yet their relative importance in humans after MI is unknown. Future mechanistic trials should therefore evaluate multiple domains simultaneously rather than attributing observed clinical benefits to a single pathway. Serial imaging combined with metabolomic, inflammatory, renal, and fibrosis biomarkers may help distinguish direct myocardial actions from systemic cardiorenal effects. [14]

Third, future trials should distinguish prevention of adverse remodeling from induction of reverse remodeling. In a patient whose LV geometry remains stable after a large infarction, absence of deterioration may itself represent therapeutic success even without a reduction in chamber volume. This distinction is especially important when standard therapy already produces spontaneous reverse remodeling. Time-to-event outcomes, longitudinal trajectories of LV volumes and GLS, recurrent heart failure events, functional capacity, and quality of life may therefore provide a more comprehensive assessment than a single follow-up LVEF measurement. [28]

Finally, adequately powered studies should determine whether treatment effects vary according to infarct location, diabetes status, baseline renal function, preserved versus reduced LVEF, or timing of initiation. Large anterior infarctions are particularly suitable for mechanistic investigation because the magnitude of myocardial injury and propensity for regional expansion increase the likelihood of detecting a treatment signal. Personalized application of SGLT2 inhibition based on remodeling risk may ultimately prove more informative than universal administration to an unselected post-MI population. [29]

Conclusion

SGLT2 inhibitors have evolved from glucose-lowering drugs into multidimensional cardiorenal therapies with several biologically plausible mechanisms capable of influencing the post-infarction myocardium. Experimental, biomarker, echocardiographic, and clinical evidence supports favorable effects on myocardial loading, energetics, renal function, cellular stress, and subsequent heart failure vulnerability; however, contemporary randomized data do not establish a uniform direct reverse-remodeling effect or a mortality benefit after myocardial infarction. The strongest emerging clinical signal is prevention of heart failure hospitalization. Future phenotype-directed trials integrating advanced imaging and myocardial mechanics are needed to determine which patients derive genuine structural benefit and whether early SGLT2 inhibition can meaningfully alter the transition from successfully reperfused myocardial infarction to chronic heart failure.

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