Yoo *et al. Cardiovascular Diabetology* (2025) 24:227
https://doi.org/10.1186/s12933-025-02777-7

Cardiovascular Diabetology

REVIEW Open Access

Impact of sodium–glucose transport protein-2 (SGLT2) inhibitors on the inflammasome pathway in acute myocardial infarction in type 2 diabetes mellitus: a comprehensive review

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Abstract
Sodium–glucose transport protein-2 (SGLT2) inhibitors, initially developed for glycemic control in type 2 diabetes mellitus (T2DM), have emerged as potential cardioprotective agents, reducing cardiovascular mortality and improving heart failure outcomes. Recent evidence suggests that SGLT2 inhibitors exert anti-inflammatory effects, particularly through modulating the inflammasome pathway. This review explores the role of the inflammasome in acute myocardial infarction (AMI) in T2DM and discusses the mechanisms by which SGLT2 inhibitors influence this pathway. We evaluate current studies on the impact of SGLT2 inhibitors on key inflammatory mediators, particularly the NLRP3 inflammasome, and discuss their potential therapeutic implications for reducing inflammation and myocardial injury in patients with T2DM experiencing AMI. In summary, the key novelties in this review lie in its *focused mechanistic approach* on the inflammasome pathway, its integration of *diabetes and cardiovascular research*, and its potential to influence *future therapeutic strategies* for AMI in T2DM patients. It offers a novel angle by tying together molecular mechanisms of inflammation with clinical implications in a specific patient population that faces high cardiovascular risk.

Keywords Sodium–glucose transport protein-2 inhibitor, Inflammation, Diabetes, Myocardial infarction

Introduction

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular diseases, including acute myocardial infarction (AMI). Chronic hyperglycemia, insulin resistance, and systemic inflammation exacerbate cardiovascular complications, leading to poorer outcomes following AMI. The inflammasome pathway, specifically the NLRP3 (nucleotide-binding domain, leukocyte-rich-containing family, pyrin domain-containing-3) inflammasome, has been implicated in the inflammatory response during AMI. This multiprotein complex triggers the release of pro-inflammatory cytokines such as IL-1β and IL-18 [1], contributing to myocardial damage during ischemia–reperfusion injury [2, 3]. Sodium–glucose transport protein-2 (SGLT2)

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inhibitors, widely prescribed for controlling hyperglycemia in T2DM, have demonstrated cardioprotective effects beyond their glucose-lowering properties, including potential modulation of the inflammasome pathway [4] (Fig. 1. Central Diagram). In this review, we explore the role of the inflammasome in AMI, the impact of SGLT2 inhibitors on this pathway, and their potential therapeutic benefits in reducing inflammation and improving cardiovascular outcomes in T2DM patients.

Mechanisms of SGLT2 inhibitors in cardiovascular protection

Glycemic control and cardiovascular benefits

SGLT2 inhibitors reduce blood glucose levels by inhibiting glucose reabsorption in the renal proximal tubules, leading to increased urinary glucose excretion [5]. Clinical trials, such as EMPA-REG OUTCOME [6], DECLARE-TIMI 58 [7], and CANVAS program [8] have demonstrated that SGLT2 inhibitors significantly reduce major cardiovascular events, including hospitalization for heart failure (HHF) and cardiovascular mortality in T2DM patients. These benefits extend beyond glycemic control, suggesting additional protective mechanisms explored in subsequent sections.

Anti-inflammatory and myocardial protective effects of SGLT2 inhibitors

Beyond their metabolic benefits, SGLT2 inhibitors have been shown to exhibit anti-inflammatory properties and confer myocardial protection particularly in acute myocardial infarction (AMI) (Figs. 1 and 2) [9, 10]. These inhibitors have been shown to lower circulating levels of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α [2, 11–17] as demonstrated in preclinical models and clinical studies [18–22] with drugs like canagliflozin and empagliflozin [2]. This cytokine suppression correlates with decreased myocardial inflammation [20], smaller infarct sizes [18, 19], and improved cardiac function [19], highlighting their cardioprotective potential—especially in AMI, where inflammation exacerbates myocardial injury [21–23].

The beneficial actions of SGLT2 inhibitors stem from their ability to modulate inflammatory signaling pathways, notably the NLRP3 inflammasome [2, 21, 22] in

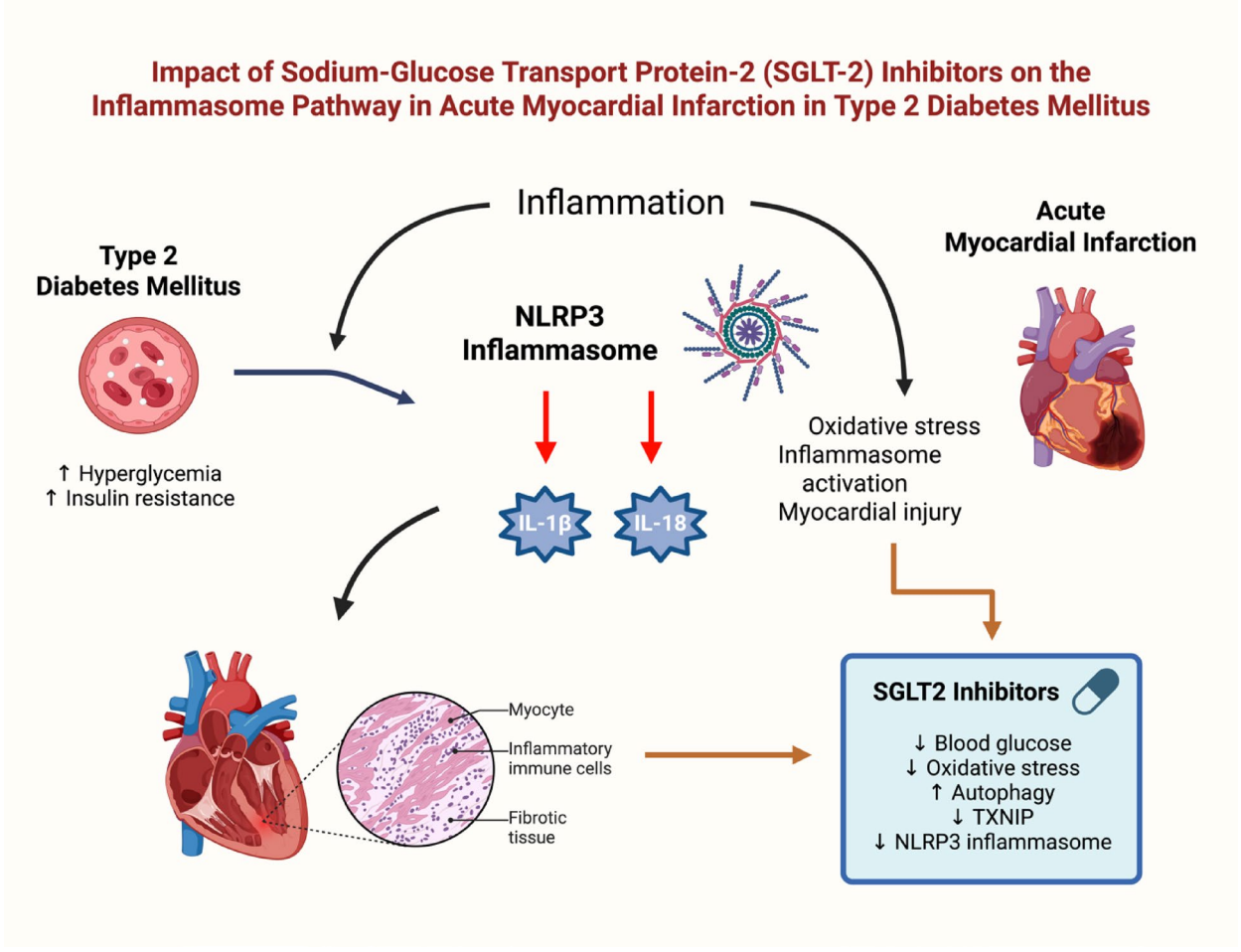

Fig. 1 Central diagram

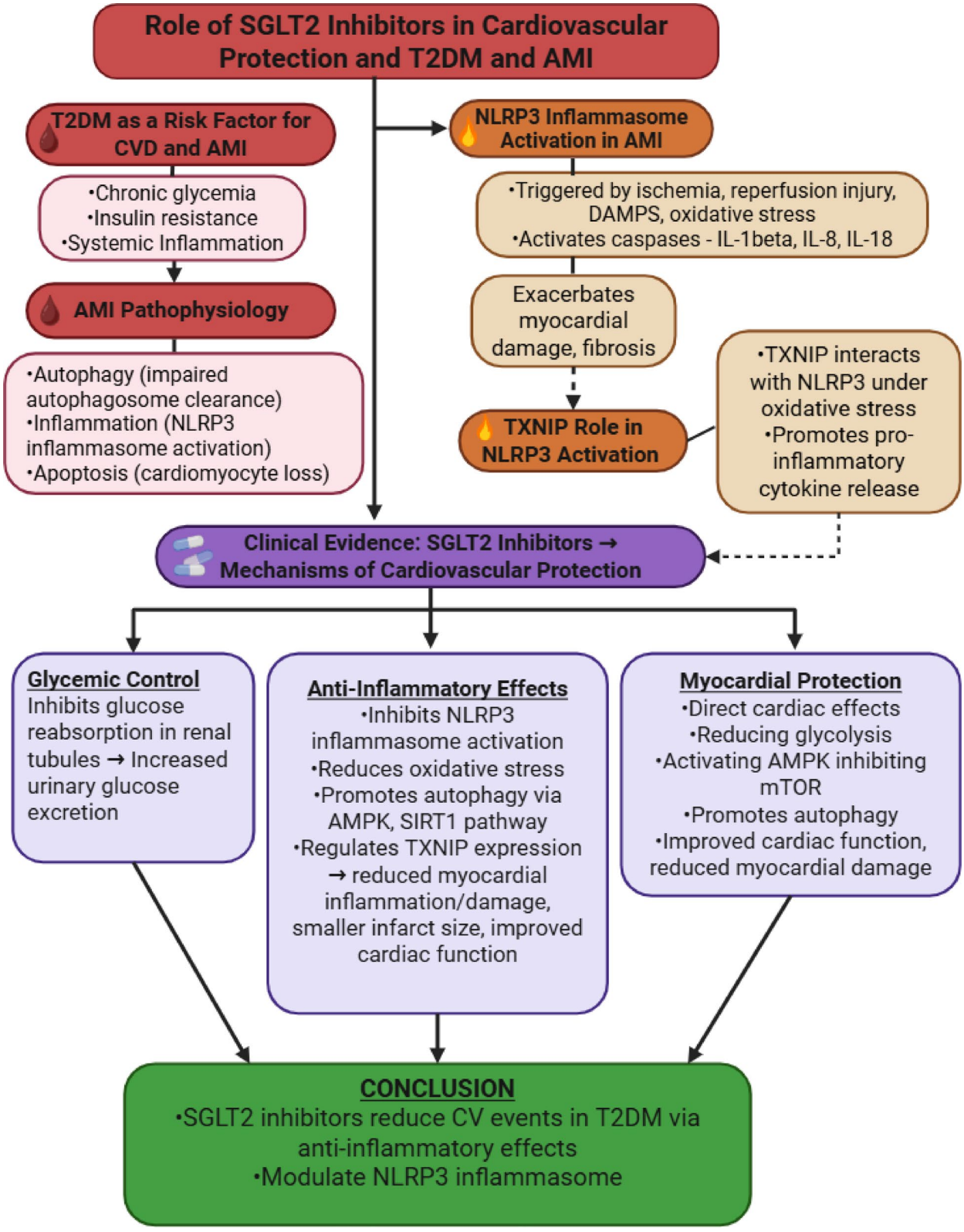

Fig. 2 Summary diagram

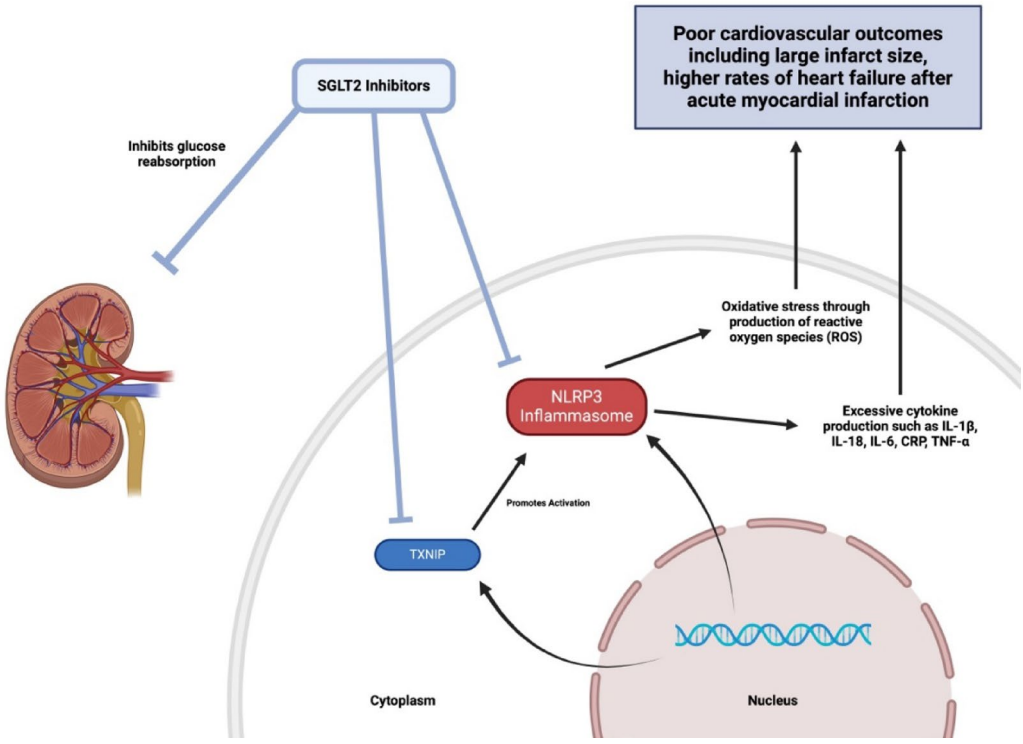

Fig. 3 Mechanism of SGLT2 inhibitors in the inhibition of TXNIP and NLRP3

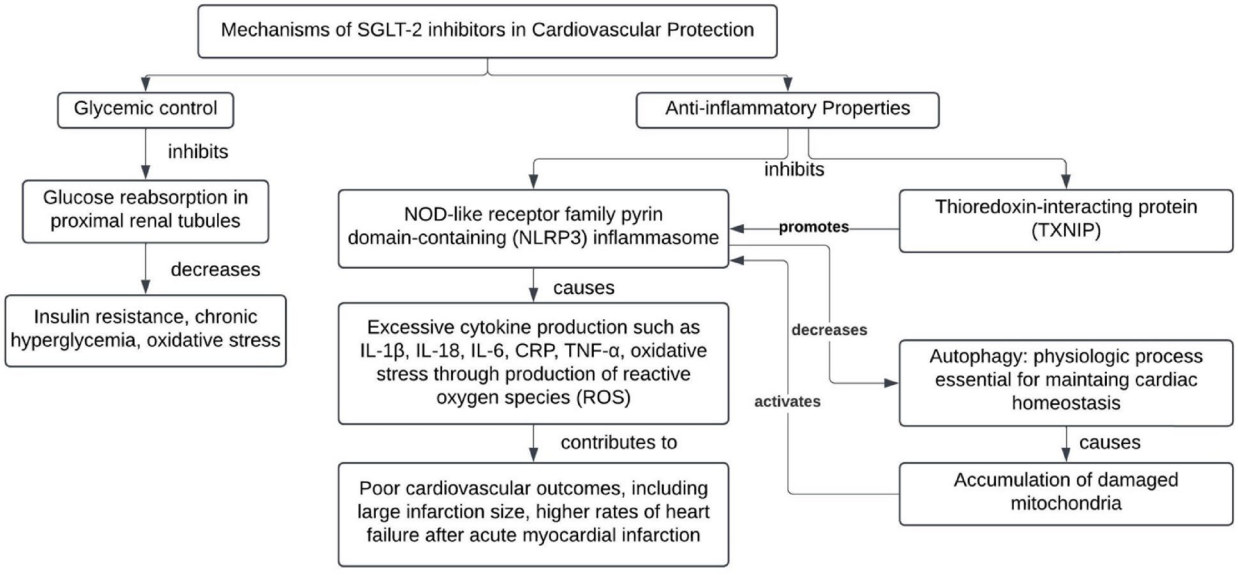

Fig. 4 Mechanisms of SGLT2 inhibitors in cardiovascular protection

various models of cardiovascular, including myocardial ischemia–reperfusion injury (Fig. 3). These inhibitors, such as empagliflozin and dapagliflozin, achieve this by reducing oxidative stress and improving mitochondrial function, key triggers for the activation of the NLRP3 inflammasome [24–27], which attenuate the release of pro-inflammatory cytokines that drive myocardial damage during ischemic events (Fig. 4) [2, 22, 28–35].

By targeting these pathways, SGLT2 inhibitors decrease the expression and plasma concentrations of key inflammatory markers (e.g., IL-1β [2, 15], IL-6 [13, 16], TNF-α [13, 15]) mitigating the inflammatory processes associated with cardiovascular diseases and diabetes [9].

These mechanisms, detailed further in Sect. "Impact of SGLT2 inhibitors on the inflammasome pathway in AMI", underscore their role in reducing infarct size and

preserving cardiac function, offering a multifaceted approach to cardioprotection in AMI.

Core mechanisms underlying cardioprotection

SGLT2 inhibitors may inhibit NLRP3 inflammasome activation through multiple mechanisms, including:

- Reduction of oxidative stress: SGLT2 inhibitors improve mitochondrial function and reduce reactive oxygen species (ROS) production, which are key triggers of NLRP3 activation [22, 24]. These drugs enhance mitochondrial efficiency and limit the excessive generation of ROS, thereby preventing oxidative stress-induced activation of the NLRP3 inflammasome pathway, which is implicated in various inflammatory and cardiovascular conditions. SGLT2 inhibitors have also been shown to lower NOX2 (NADPH oxidase 2)-related oxidative stress therefore reducing platelet activation and thrombus formation [36]. By targeting mitochondrial dysfunction and ROS, SGLT2 inhibitors provide protective effects against inflammation and ischemic injury in the heart.
- Promotion of autophagy: Preclinical studies suggest that SGLT2 inhibitors can enhance autophagy, a crucial cellular process responsible for clearing damaged organelles, including mitochondria [29, 37, 38]. This effect plays a key role in preventing the activation of the NLRP3 inflammasome, a major driver of inflammatory responses. By promoting autophagic activity, SGLT2 inhibitors mitigate oxidative stress and the accumulation of damaged mitochondria, thereby preventing inflammasome activation [39, 40]. This reduction in cellular stress and inflammation helps protect against myocardial injury, making autophagy a vital mechanism in their cardioprotective effects.

Multiple studies have demonstrated that SGLT2 inhibitors, increase autophagy in various tissues [41], including the heart and kidneys, by modulating signaling pathways like AMP-activated protein kinase (AMPK) [42, 43] and SIRT1, which regulate cellular energy and stress responses [44–46]. These findings are particularly significant in conditions like diabetes and cardiovascular diseases, where enhanced autophagy reduces organ damage and improves cardiac function.

Regulation of thioredoxin-interacting protein (TXNIP): Thioredoxin-interacting protein (TXNIP) is a key regulator of oxidative stress and has been implicated in the activation of the NLRP3 inflammasome [47]. Under conditions of elevated ROS, TXNIP dissociates from thioredoxin (TRX) and binds directly to NLRP3, triggering its activation [48]. This activation pathway is associated with various inflammatory [47] and cardiovascular diseases [49]. SGLT2 inhibitors, such as empagliflozin, have been shown to modulate TXNIP expression, thereby reducing oxidative stress and preventing NLRP3 inflammasome activation [49, 50]. By doing so, these inhibitors help attenuate inflammation and protect against further cardiovascular damage, such as myocardial injury [49].

It is also important to note that oxidative stress is known to impair nitric oxide (NO) bioavailability, leading to decreased soluble guanylate cyclase (sGC) activity, reduced protein kinase G (PKG) activity, hypophosphorylation of titin, and cardiomyocyte stiffness and interstitial fibrosis, thus causing HFpEF [51]. SGLT2 inhibitors reduce oxidative stress and improve NO signaling and availability [52]. Thus, it is plausible that the clinical benefits observed with SGLT2 inhibitors in HFpEF (EMPEROR-Preserved trial) may be partly mediated through modulation of oxidative stress and inflammasome pathways.

In addition to their cardiometabolic effects, SGLT2 inhibitors also improve anemia by reducing hepcidin levels and improving functional iron deficiency [53, 54]. This is particularly relevant given the high prevalence of anemia among patients with heart failure and acute coronary syndromes (ACS) [55–60], in which anemia is independently associated with increased mortality in patients with heart failure or MI [61–63].

SGLT2 expression in human cardiomyocytes and its association with inflammation, oxidative stress, and metabolic pathways

The expression of SGLT1 and SGLT 2 is upregulated in the context of T2DM [64] and MI [65]. In human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), exposure to a high-glucose, insulin-free environment significantly increased the expression of both SGLT1 and SGLT2 [66]. Treatment with an SGLT2 inhibitor led to a reduction in the expression of both transporters, independent of insulin presence. Moreover, elevated gene expression has been associated with molecular signatures of myocardial fibrosis, inflammation, oxidative stress, and altered cardiac metabolism [67].

The role of the inflammasome pathway in acute myocardial infarction

Myocardial infarction—autophagy, inflammation, apoptosis

Myocardial infarction (MI) initiates a complex interplay of cellular responses including autophagy [68, 69], inflammation pathways [70], and apoptosis [70, 71], each crucial in determining the extent of myocardial damage and subsequent cardiac function. Autophagy, a cellular process essential for maintaining cardiac homeostasis, has been implicated both in promoting cardiomyocyte

survival through the removal of damaged organelles and in contributing to cell death under pathological conditions like MI [72]. Ischemia and reperfusion injury impairs autophagosome clearance contributing to increased cardiomyocyte death [73]. Inflammation plays a pivotal role post-MI, with the NLRP3 inflammasome pathway highlighted as a key mediator of inflammatory responses leading to myocardial injury and adverse remodeling [33]. The activation of pro-inflammatory cytokines exacerbates tissue damage and promotes fibrosis, impacting overall cardiac function. Concurrently, apoptosis, a programmed cell death mechanism, contributes significantly to cardiomyocyte loss post-MI, further impairing cardiac contractility and structural integrity [74].

NLRP3 inflammasome activation

The NLRP3 inflammasome is a key component of the innate immune system that is activated in response to cellular stress, including ischemia and reperfusion injury, which are hallmarks of AMI [75]. Upon activation, NLRP3 forms a complex that activates caspase-1, leading to the cleavage and maturation of pro-inflammatory cytokines, particularly IL-1β [76, 77] and IL-18 [77]. These cytokines drive the inflammatory response in the myocardium, exacerbating cell death, oxidative stress, and tissue damage during AMI.

This inflammasome activation is particularly triggered by damage-associated molecular patterns (DAMPs) released during cellular injury [78], and the oxidative stress commonly associated with reperfusion injury. Research has shown that targeting the NLRP3 inflammasome can significantly reduce the extent of inflammation and subsequent tissue damage in ischemic conditions, highlighting its potential as a therapeutic target in reducing myocardial injury in AMI [33].

TXNIP and NLRP3 inflammasome pathway

Thioredoxin-interacting protein (TXNIP), also known as thioredoxin-binding protein 2 (TBP2), is a key protein in the cellular stress response pathway [79]. TXNIP contributes to various pathophysiological states such as the nervous system inflammation seen in Alzheimer's disease [80] and premature death of insulin-secreting cells in patients with diabetes [65].

TXNIP is a major regulator of the NLRP3 inflammasome, a multiprotein complex that plays a pivotal role in the innate immune response. Under conditions of oxidative stress or cellular damage, TXNIP interacts with the NLRP3 inflammasome to promote its activation. This leads to the secretion of pro-inflammatory cytokines contributing to chronic inflammation and various inflammatory diseases [47].

Inflammasome activation in T2DM and AMI

Patients with T2DM exhibit heightened inflammasome activation due to hyperglycemia, insulin resistance, and oxidative stress, which predispose them to exaggerated inflammatory responses during AMI [81]. The persistent activation of the NLRP3 inflammasome in T2DM leads to excessive cytokine production (Fig. 2) and contributes to poor cardiovascular outcomes, including larger infarct sizes, worse cardiac function, and higher rates of heart failure (HF) following AMI [81–83].

The enhanced oxidative stress seen in T2DM, driven by mitochondrial dysfunction and excessive ROS production, plays a pivotal role in NLRP3 inflammasome activation [84]. This chronic inflammation not only worsens the inflammatory environment during AMI but also exacerbates overall cardiovascular outcomes in diabetic patients, leading to more severe cardiac dysfunction and elevated heart failure rates [81–83, 85, 86].

Inflammation in cardiovascular diseases

Among patients with heart failure, elevated levels of interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) have been independently associated with an increased risk of heart failure progression, cardiovascular death, and adverse renal outcomes [87, 88]. Moreover, higher concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) have been linked to an elevated risk of both heart failure and renal outcomes [89].

Impact of SGLT2 inhibitors on the inflammasome pathway in AMI

Inhibition of NLRP3 inflammasome activation

Preclinical studies have demonstrated that SGLT2 inhibitors can effectively inhibit the activation of the NLRP3 inflammasome (Fig. 3) in various models of cardiovascular injury [2, 22, 90] including myocardial ischemia–reperfusion injury [38] by leveraging the mechanisms outlined in Sect. "Core mechanisms underlying cardioprotection". These inhibitors, such as empagliflozin and dapagliflozin, reduce mitochondrial dysfunction and suppress the production of ROS, which are known to be key triggers for the activation of the NLRP3 inflammasome [24–27]. By preventing this activation, SGLT2 inhibitors reduce the release of pro-inflammatory cytokines, particularly IL-1β [2, 32, 38] and IL-18 (Fig. 4). This inhibition of the inflammasome-mediated inflammatory response is crucial in limiting myocardial damage and preserving cardiac function during and after AMI [33–35].

SGLT2 inhibitors also contribute to improved mitochondrial function and autophagy [29, 91], thereby reducing oxidative stress and supporting cardiovascular health. These effects play a significant role in minimizing the extent of ischemic injury and inflammation in the

heart, offering potential therapeutic benefits for managing cardiovascular complications in both diabetic and non-diabetic patients.

Although a post-hoc analysis of the EMMY trial found no significant changes in certain inflammatory biomarkers—including IL-6, neutrophil count, leukocyte count, and the neutrophil-to-lymphocyte ratio (NLR) [92]—it is important to note that key components of the inflammasome pathway were not assessed. Specifically, the study did not evaluate levels of nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP)-3 inflammasome, IL-1β or IL-18. As such, the impact of empagliflozin on these critical inflammasome-related mediators in the EMMY trial population remains unclear.

Additional cardiac mechanisms of SGLT2 inhibitors

Molecular docking studies and experiments with isolated perfused hearts reveal that empagliflozin binds directly to glucose transporters, leading to several key metabolic improvements in failing hearts. This binding reduces glycolysis and rebalances the relationship between glycolysis and oxidative phosphorylation. Empagliflozin also influences the adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin complex 1 (mTORC1) pathways. AMPK activation inhibits the mTOR pathway, thereby reducing protein synthesis and promoting autophagy—a cellular cleanup process triggered under stress or nutrient deprivation. Furthermore, AMPK stimulates fatty acid catabolism through the activation of adipose triglyceride lipase (ATGL) and inhibits fatty acid and cholesterol synthesis by downregulating acetyl-CoA carboxylase (ACC) and HMG-CoA reductase. Additionally, AMPK facilitates glucose uptake by promoting GLUT4 translocation to the cell membrane and inhibits glycogen synthesis [93]. Overall, these actions collectively enhance cardiac function by improving glucose utilization and fatty acid metabolism.

Clinical evidence: SGLT2 inhibitors in AMI and T2DM

Clinical trials demonstrating cardiovascular benefits

Large-scale clinical trials such as EMPA-REG OUTCOME and CANVAS (Fig. 5) have demonstrated the ability of SGLT2 inhibitors to reduce the risk of cardiovascular events in T2DM patients [6, 8]. Although these trials primarily focus on macrovascular outcomes, secondary analyses suggest that the anti-inflammatory effects of SGLT2 inhibitors may contribute to their cardioprotective benefits, particularly in patients at high risk for AMI. Furthermore, studies have demonstrated the impact of SGLT2 inhibitors among patients with T2DM, chronic kidney disease (CKD), MI, and HF (Table 1).

In patients with T2DM and high cardiovascular risk, the 2015 EMPA-REG OUTCOME trial and 2017 CANVAS Program integrated study from two trials (CANVAS and CANVAS-R) demonstrated improved primary outcome of CV death, nonfatal MI, or nonfatal stroke with empagliflozin and canagliflozin [6, 8]. The 2018 DECLARE-TIMI 58 trial found that while dapagliflozin did not change the rates of major adverse cardiovascular events (MACE) compared to placebo, it did lower cardiovascular death (CVD) or HHF among patients with Type 2 DM and established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD [7]. The 2019 CREDENCE trial demonstrated a marked reduction in the incidence of CVD, HHF, MI, or cerebrovascular accident (CVA) among patients with T2DM and kidney disease treated with canagliflozin [94]. A meta-analysis by Zou et al. in 2019 revealed that SGLT2 inhibitors are associated with a decreased risk of major adverse cardiovascular events (MACE) and mortality in type 2 diabetes [95]. In DAPA-CKD trial 2020 among patients with CKD, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50% end-stage kidney disease, or death from renal or cardiovascular causes

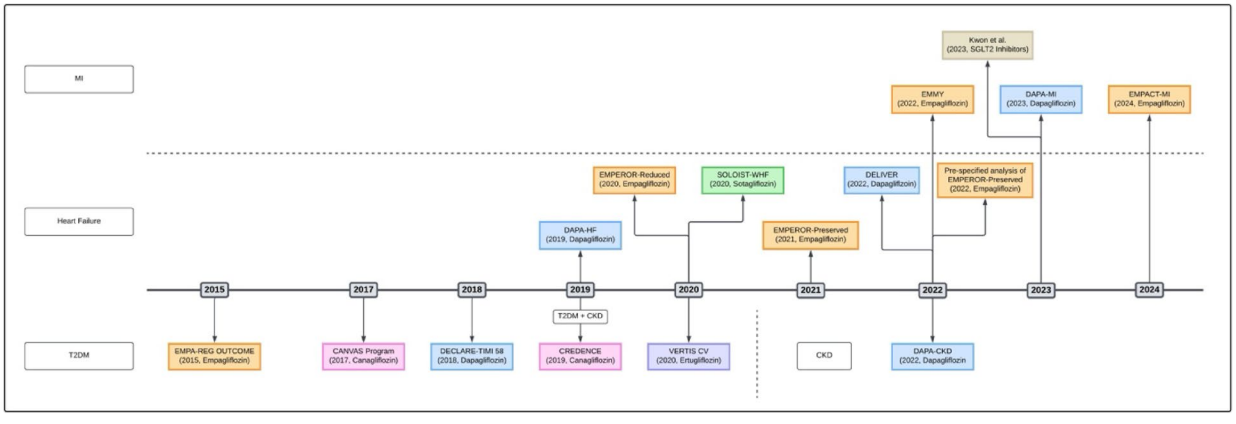

Fig. 5 Timeline of major studies

Table 1 Summary of major clinical trials

Year	Trial	Population	Medication	Outcome
Heart failure				
2019	DAPA-HF	Patients with heart failure and a reduced ejection fraction, regardless of presence or absence of diabetes	Dapagliflozin	Risk of worsening HF or death from CV causes was lower
2020	EMPEROR-reduced	Patients with heart failure and a reduced ejection fraction, regardless of presence or absence of diabetes	Empagliflozin	Lower risk of CV death or HHF
2020	SOLOIST-WHF	Patients with T2DM and recent hospitalization for worsening heart failure	Sotagliflozin	Lower total number of deaths from CV causes and hospitalizations and urgent visits far heart failure
2021	EMPEROR-preserved	Patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes	Empagliflozin	Reduced the combined risk of CV death or HHF
2022	Pre-specified analysis of EMPEROR-preserved 2022	Patients with preserved LVEF or mid-range LVEF (41–49%)	Empagliflozin	Reduced the combined risk of CV death or HHF
2022	DELIVER	Patients with heart failure with midly reduced or preserved EF	Dapagliflozin	Reduced the combined risk of worsening heart failure or CV death
T2DM				
2015	EMPA-REG OUTCOME	T2DM and high CV risk	Empagliflozin	Lower rate of primary composite CV outcome and death from any cause
2017	CANVAS program	T2DM and high CV risk	Canagliflozin	Improved primary outcome of CV death, nonfatal MI, or nonfatal stroke
2018	DECLARE-TIMI 58	T2DM and established ASCVD or multiple risk factors for ASCVD	Dapagliflozin	No change in the rates of major adverse CV events (MACE), however, lowered CV death or HHF
2020	VERTI5 CV	T2DM and ASCVD	Ertugliflozin	Non-inferiority in major adverse CV events; however, did not show superiority in composite of death from CV causes or HHF
T2DM and CKD				
2020	DAPA-CKD	CKD, regardless of the presence or absence of diabetes	Dapagliflozin	Significant reduction in the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or CV causes
T2DM and CKD				
2019	CREDENCE	T2DM + CKD	Canagliflozin	Marked reduction in the incidence of CV death, HHF, MI, or CVA
Myocardial infarction				
2022	EMMY	Patients with acute MI and large creatine kinase elevation; within 72 h of PCI	Empagliflozin	Significantly reduced NT-proBNP levels and improved both echocardiography functional and structural parameters
2023	Kwon et al	Patients with T2DM who received PCI for acute MI	SGLT2 inhibitors	Early use of SGLT2 inhibitors in patients with diabetes treated with PCI for acute MI was associated with reduced rates of CV events, including all-cause mortality and fewer hospitalizations for heart failure
2023	DAPA-MI	Patients without prior diabets or chronic HF, presenting with acute MI and impaired LV systolic function	Dapagliflozin	Improved cardiometabolic outcomes; did not significantly affect the composite rates of cardiovascular death or HHF
2024	EMPACT-MI	Patients who had been hospitalized for acute MI and were at risk for HF	Empagliflozin	No significant difference in the rates of first HHF or death from any cause

HF, heart failure; CV, cardiovascular; HHF, hospitalization for heart failure; T2DM, type 2 diabetes mellitus; LVEF, Left ventricular ejection fraction; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; CVA, cerebrovascular accident; PCI, percutaneous coronary intervention; SGLT2, sodium–glucose cotransporter 2; MI, myocardial infarction

was significantly lower with dapagliflozin than with placebo [96]. Conversely, the VERTIS CV trial 2020 demonstrated noninferiority of ertugliflozin among patients with Type 2 DM and ASCVD in major adverse cardiovascular events compared to placebo, however, did not show superiority in composite of death from cardiovascular causes or HHF [97]. In 2020 meta-analysis by McGuire et al., SGLT2 inhibitors were associated with a reduced risk of major CV events and HHF among patients with T2DM and ASCVD [98].

The role of SGLT2 inhibitors in patients with AMI has been investigated through several key studies. The 2017

EMMY trial demonstrated that empagliflozin, administered within 72 h of percutaneous coronary intervention, significantly reduced NT-proBNP levels and improved both echocardiographic functional and structural parameters in patients with large creatine kinase elevation [99]. A 2023 population-based study by Kwon et al. showed that early initiation of SGLT2 inhibitors post-MI was linked to reduced rates of cardiovascular events, including lower all-cause mortality and fewer HHF [100]. A nationwide observation registry study from SWEDEHEART (2024) also showed that SGLT2 inhibitor use was associated with lower rates of the composite outcome of death and first hospitalization for heart failure after one year [101]. In a multicenter international registry with diabetic AMI patients undergoing percutaneous coronary intervention (PCI), SGLT2 inhibitor use was associated with lower risk of contrast-induced acute kidney injury (AKI) [102], in-hospital CVD and long-term cardiovascular mortality and HHF [103]. Additionally, SGLT2 inhibitor use in T2DM patients was associated with lower risk of arrhythmic events during hospitalization for AMI [103, 104]. In meta-analysis of patients with recent or previous MI, SGLT2 inhibitor was associated with lower rates of HHF [105], and early and delayed treatment with SGLT2 inhibitors following MI was associated with a significant reduction in all-cause mortality with greater reduction in T2DM patients [106]. However, the EMPACT-MI trial (2020) found no significant difference in the rates of first HHF or death from any cause between empagliflozin and placebo groups, suggesting limited impact on these specific outcomes [107]. Similarly, the DAPA-MI trial (2020) indicated that while dapagliflozin improved cardiometabolic outcomes, it did not significantly affect the composite rates of CVD or HHF compared to placebo approximately 1 year after treatment [108].

While numerous trials have demonstrated robust cardiovascular benefits of SGLT2 inhibitors, particularly in reducing heart failure hospitalizations and cardiovascular mortality in patients with heart failure or T2DM, a more nuanced understanding is necessary when evaluating their efficacy across diverse cardiovascular contexts. The general enthusiasm for SGLT2 inhibitors is largely driven by trials such as EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, DAPA-HF, and EMPEROR-Reduced, which have consistently shown favorable outcomes in populations with established ASCVD or heart failure with reduced ejection fraction (HfrEF). However, more recent studies aimed at extending the benefits of SGLT2 inhibitors to post-AMI populations have yielded less conclusive results. Notably, the DAPA-MI and EMPACT-MI trials did not demonstrate significant reductions in their primary endpoints. These studies raise important questions about the timing, patient selection, and mechanistic underpinnings of SGLT2 inhibitor efficacy in acute ischemic settings. For instance, DAPA-MI, which enrolled post-AMI without prior diabetes or chronic symptomatic HF, failed to show a statistically significant benefit in reducing the composite of CVD or HHF [108]. Similarly, EMPACT-MI did not meet its primary endpoint [107]. These findings suggest that the cardioprotective effects observed in chronic disease settings may not readily translate to the acute post-infarction setting, possibly due to differences in myocardial stress, remodeling dynamics, or underlying metabolic conditions. These negative or neutral results are sometimes underrepresented in reviews that highlight the broader cardiovascular benefits of SGLT2 inhibitors, potentially leading to an overly optimistic portrayal of their role in all cardiovascular contexts. A balanced interpretation must recognize that while SGLT2 inhibitors represent a transformative advance in cardio-renal medicine, their utility may be context-specific and should not be presumed uniformly effective across all stages of cardiovascular disease. Further research is needed to delineate the optimal timing, patient phenotypes, and adjunctive therapies that may influence outcomes post-AMI.

Improved outcomes with SGLT2 inhibitor were more consistent among patients with heart failure (HF). In DAPA-HF trial 2019, patients with heart failure and a reduced ejection fraction, the risk of worsening HF or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence of absence of diabetes [109]. In EMPEROR-Reduced trial 2020, patients who received empagliflozin had a lower risk of CV death or HHF than those in the placebo group, regardless of presence or absence of diabetes [110]. In SOLOIST-WHF trial 2020, patients with Type 2 DM and recent hospitalization for worsening HF treated with sotagliflozin therapy had lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure [111]. In EMPEROR-Preserved trial 2021, empagliflozin reduced the combined risk of CV death or HHF in patients with heart failure and a preserved ejection fraction, regardless of the presence of absence of diabetes [112]. In a pre-specified analysis of EMPEROR-Preserved 2022, empagliflozin reduced the risk of CV death or HHF for preserved LVEF patients and mid-range LVEF (41–49%) patients [113]. Furthermore, in DELIVER trial 2022, dapagliflozin reduced the combined risk of worsening heart failure or CV death among patients with HF with mildly reduced or preserved ejection fraction [114].

Combinational therapeutics of SGLT2 inhibitors

SGLT2 inhibitors may have either additive benefits or adverse effects when used alongside common cardiovascular medications such as statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), diuretics, and antiplatelets.

Conflicting findings have been reported regarding the interaction between statins and SGLT2 inhibitors [115–119]. A recent large pharmacovigilance study analyzing 456 reports of myopathy and 77 reports of rhabdomyolysis found no increased risk of myotoxicity with concomitant use of SGLT2 inhibitors and statins [120], a finding supported across studies [121]. Additionally, no clinically relevant drug-drug interactions have been observed and pharmacokinetic studies suggest dose adjustments were not necessary when empagliflozin and simvastatin are co-administered [122]. Meta-analyses have demonstrated significant increases in both low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels with SGLT2 inhibitor use [123, 124], highlighting the need for lipid profile monitoring and underscoring the importance of further investigation into these metabolic effects when SGLT2 inhibitors are administered concomitantly with statins.

When SGLT2 inhibitors are used in conjunction with ACE inhibitors or ARBs, there may be an initial reduction in estimated glomerular filtration rate (eGFR) and increased risk of hypoglycemia [125]. Additionally, combined SGLT2 and ACE inhibition upregulate plasma renin activity and angiotensin I levels, which may counteract some of the effects of ACE inhibitors [126]. However, this combination also demonstrates beneficial effects, including decreased albuminuria, lowered hemoglobin A1c (HbA1c) levels, reduced oxidative stress makers, and an additive decline in blood pressure and total peripheral resistance [127, 128], which have also been shown in meta-analyses [125, 129]. Notably, long-term eGFR and kidney injury outcomes were similar, despite the initial decrease in eGFR observed with SGLT2 inhibitor treatment [130, 131]. In fact, the EMPA-REG OUTCOME trial demonstrated an improvement in eGFR after 12 weeks of treatment from initial decrease [6]. Collectively, these findings support drug interactions between SGLT2 inhibitors and ACE inhibitors are beneficial for cardiorenal risk reduction.

SGLT2 inhibitor in combination with Entresto (Sacubitril/Valsartan) has been shown to provide an additional benefit on improving the heart function in rat study [132]. This combination was superior to either treatment alone in protecting the heart from ischemia–reperfusion injury. Additionally, a meta-analysis of seven trials by Mo et al. demonstrated this superior cardiovascular protective effect [133].

The combination of SGLT2 inhibitors and diuretics may lead to volume depletion, increasing the risk of hypotension, syncope, and falls particularly in the elderly patients [134, 135]. As a result, diuretic dose adjustment is often necessary upon initiation of SGLT2 inhibitors [136, 137]. Notably, while neither agent alone significantly increased urinary volume, their combination resulted in a marked rise in diuresis [138]. Additionally, SGLT2 inhibitor use with a diuretic can have natriuretic synergy [139, 140], which may offer therapeutic benefit when used together. Furthermore, SGLT2 inhibitors have been shown to mitigate bumetanide-induced hyperuricemia [139, 140], potentially enhancing the metabolic profile of diuretic therapy. However, co-administration also elevates plasma renin and aldosterone levels [138], indicating that concurrent use of renin–angiotensin–aldosterone system (RAAS) blockers may be warranted to counteract this compensatory activation.

Canagliflozin has demonstrated its effect on blood pressure in the CREDENCE trial, which showed reduction in systolic blood pressure (SBP) decreasing the necessity for additional antihypertensive medications [141]. This may indicate the need to adjust commonly used blood pressure medications when taken concurrently with SGLT2 inhibitor.

In the analysis of DAPA-HF, dapagliflozin demonstrated comparable efficacy and safety in patients with HFrEF, regardless of whether they were also taking a mineralocorticoid receptor antagonist, which supports the combined use of both medications [142].

In the EDGE trial, dapagliflozin significantly reduced platelet reactivity and achieved a greater antiplatelet effect in patients with stable coronary artery disease (CAD) and T2DM who were receiving dual antiplatelet therapy (DAPT) [143].

When combined with metformin in diabetic patients with AMI, SGLT2 inhibitor improved left ventricular ejection fraction (LVEF) compared with dipeptidyl peptidase-4 (DPP-4) inhibitor but did not show difference in the rate of MACEs [144]. However, combination therapy with metformin and SGLT2 inhibitors have shown reduced risk of all-cause mortality and kidney disease progression [145]. Additionally, the combination of SGLT2 inhibitor and glucagon-like peptide-1 receptor agonists (GLP-1RA) had lower incidence of MACE compared to either alone [146].

Potential risks and limitations of using SGLT2 inhibitors in AMI patients

While SGLT2 inhibitors have demonstrated benefits in heart failure outcomes and glycemic control, their use in patients with AMI presents potential risks and limitations. These include hypotension, an increased risk of diabetic ketoacidosis (DKA), which can present atypically

and may be difficult to detect in the acute setting, and AKI, which may be exacerbated by concurrent renal hypoperfusion or contrast exposure during PCI [107].

SGLT2 inhibitors can lead to volume depletion, resulting in hypotension. This effect is particularly concerning with AMI patients, who may already experience hemodynamic instability. However, dapagliflozin had a small effect on SBP in patients with HFrEF and was well tolerated across the range of SBP included in DAPA-HF [147]. Similarly, empagliflozin has been associated with small reduction in SBP and diastolic blood pressure (DBP) [6] without significant long-term effects on SBP [148]. Nonetheless, the impact of SGLT2 inhibitors on hemodynamics in AMI remains inadequately understood, warranting further research.

The use of SGTL2 inhibitors in patients with AMI is associated with a potential risk of DKA. Notably, SGLT2 inhibitor-induced DKA can present atypically as euglycemic DKA (EDKA), characterized by normal or only mildly elevated blood glucose levels, which can make clinical recognition challenging [149]. In light of this, heightened clinical vigilance is required when initiating SGLT2 inhibitors in AMI patients. Careful assessment of patient suitability and close monitoring for early signs of DKA are imperative to ensure safe therapeutic use in this population.

Concerns have been raised regarding the risk of AKI with SGLT2 inhibitor use. However, SGLT2 inhibitor use was associated with lower risk of incident AKI after PCI therapy in AMI patients [150] and lower risk of contrast-induced AKI [102].

Clinicians should carefully monitor hemodynamics, for DKA, and renal function with SGLT2 use in patients with AMI.

Potential pharmacodynamic interactions with anticoagulants and dual antiplatelet therapy

Potential pharmacodynamic interactions of SGLT2 inhibitors with anticoagulants and dual antiplatelet therapy (DAPT)—both cornerstones of AMI management—may influence bleeding risk or drug metabolism. SGLT2 inhibitors have been shown to reduce platelet activation and thrombus formation [36, 151, 152], raising concerns regarding a possible increase in bleeding risk when used concomitantly with DAPT. Dapagliflozin had no clinically meaningful pharmacokinetic interactions with warfarin, a commonly used anticoagulant, indicating that co-administration is generally safe from a pharmacokinetic perspective. Additionally, the pharmacodynamics of warfarin were unaffected by dapagliflozin, suggesting no significant impact on anticoagulant efficacy [153]. Currently, there is no direct evidence suggesting that SGLT2 inhibitors significantly alter the pharmacodynamics of direct oral anticoagulants (DOACs). Considering the complex polypharmacy often required in AMI patients, the initiation of SGLT2 inhibitors necessitates careful patient selection and close monitoring.

Inflammatory marker reduction in clinical studies

While much of the mechanistic insight into inflammasome modulation by SGLT2 inhibitors has been derived from preclinical research, emerging clinical and translational data suggest plausible link between SGLT2 inhibition and suppression of the NLRP3 inflammasome in the setting of AMI (Table 2).

For instance, registry-based data from the AMI Protect registry demonstrated that diabetic patients treated with SGLT2 inhibitors after AMI exhibit significantly lower levels of inflammatory markers, including C-reactive protein (CRP) [21]. Similarly, other clinical studies involving patients with T2DM and CVD have reported reductions in circulating CRP [157] and IL-6 [158] following treatment with SGLT2 inhibitors (Table 3). Although these studies did not directly measure inflammasome-specific components such as IL-1β and IL-18, the observed anti-inflammatory effects are consistent with NLRP3 inflammasome inhibition. In the study by Kim et al. (2020), SGLT2 inhibitor use was associated with decreased levels of IL-1β, IL-18, TNF-α, and attenuation of NLRP3 inflammasome activation in isolated macrophages from patients with diabetes and high cardiovascular risk [2]. Additional clinical studies and meta-analysis involving diabetic patients across various cardiovascular conditions have similarly reported reductions in inflammatory markers with SGLT2 inhibitor use [13, 154–156].

Despite these findings, the specific pathways by which SGLT2 inhibitors modulate inflammasome activity in MI remain inadequately explored. This underscores a critical gap in the field and highlights the need for future studies to validate these mechanistic links.

Potential therapeutic implications

Early intervention in AMI

The ability of SGLT2 inhibitors to reduce inflammasome activation and inflammation in the setting of AMI [21] suggests that these agents may be beneficial as early intervention strategies for patients with T2DM experiencing AMI. Early administration of SGLT2 inhibitors could limit myocardial damage, reduce infarct size, and improve long-term outcomes by targeting key inflammatory pathways [19, 21, 22] as inflammasome inhibition ameliorates myocardial ischemia/reperfusion (I/R) injury and reduces MI size [160]. Importantly, pretreatment SGLT2 inhibitor improved myocardial I/R injury and reduced MI size [161]. These findings raise possibility that cardioprotective effects of SGLT2 inhibitor in the context of I/R injury may be mediated, at least in part, through inhibition of inflammasome.

Table 2 Table summarizing clinical studies on anti-inflammatory effects of SGLT2 inhibitors

Study/Trial name	Year	SGLT2 inhibitor	Population	Inflammation markers measured	Main findings	References
Sachiko Hattori	2018	Empagliflozin	T2DM with high CV risk	hsCRP, remnant-like particle cholesterol (RLP-C)	Reduced hsCRP and RLP-C levels	Hattori et al. [154]
Sato et al.	2018	Dapagliflozin	Diabetic patients with CAD	TNF-α, PAI-1	Reduced TNF-α and PAI-1 levels	Sato et al. [17]
Bray et al. a systematic review	2020	Unspecified	T2DM	CRP, IL-6, TNF-α, 8-iso-PGF2α, 8-OHdG	Consistent reductions observed for CRP, IL-6, TNF-α, 8-*iso*-PGF2α, 8-OHdG	Bray et al. [13]
Kim et al.	2020	Empagliflozin	T2DM with high CV risk	IL-1β, IL-18, TNF-α levels, NLRP3 inflammasome activation	Significant reduction in IL-1β, IL-18, TNF-α levels, and attenuation of NLRP3 inflammasome activation (in isolated macrophages with inflammasome stimulation by palmitate)	Kim et al. [20]
EMPEROR-reduced (NT-proBNP)	2021	Empagliflozin	HFrEF with/without T2DM	NT-proBNP	Reduced risk of heart failure or renal outcomes regardless of baseline NT-proBNP concentration. Empagliflozin treatment significantly reduced NT-proBNP at all timepoints	Januzzi [89]
AMI PROTECT registry	2022	Unspecified	Diabetic AMI patients undergoing PCI	CRP, NLR, PLR, NPR, lymphocyte level, neutrophil level	CRP, NLR, PLR, NPR, lymphocyte and neutrophil levels (at 24 h) were significantly lower with SGLT2 inhibitors	Paolisso et al. [103]
New insights from CANVAS	2022	Canagliflozin	T2DM with high CV risk	IL-6	Canaglifiozin modestly attenuated the IL-6 increase	Koshino et al. [88]
Post-hoc analysis of the EMMY trial	2023	Empagliflozin	AMI patients	IL-6, hsCRP, neutrophils, leukocytes, NLR, PLR	No significant difference between Empagliflozin and placebo treatment in levels of IL-6, hsCRP, neutrophils, leukocytes, NLR, PLR	Benedikt et al. [92]
Gotzmann et al.	2023	Empagliflozin	HFrEF with T2DM	IL-6	Significant reduction in IL-6 levels	Gotzmann et al. [155]
Dihoum et al.	2024	Dapagliflozin	T2DM with LVH	CRP, TNF-α, IL-1β, IL-6. IL-10, NLR	Significant reduction in CRP levels but no significant statistical changes in other inflammatory markers	Dihoum et al. [156]
DAPA-HF: an exploratory analysis	2025	Dapagliflozin	HFrEF with/without T2DM	IL-6, hs-CRP	Elevated IL-6 and hs-CRP levels associated with risk of worsening HF or CVD. Dapgliflozin reduced the risk of adverse outcomes regardless of baseline IL-6 or hsCRP	Docherty et al. [87]

T2DM, type 2 diabetes mellitus; CV, cardiovascular; hsCRP, high sensitivity c-reactive protein; TNF-α, tumor necrosis factor alpha; PAI-1, plasminogen activator inhibitor-1; CRP, c-reactive protein; IL-6, interleukin-6; 8-*iso*-PGF2a, 8-iso-prostaglandin F2a; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; IL-1β, interleukin-1 beta; IL-18, interleukin-18; NLRP3, nucleotide-binding domain, leukocyte-rich-containing family, pyrin domain-containing-3; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NLR, neutrophil–lymphocyte ratio; PLR, platelet-lymphocyte ratio; NPR, neutrophil-platelet ratio; IL-10, interleukin-10

SGLT2 inhibitors in non-diabetic patients with AMI

SGLT2 inhibitors have shown significant benefits in patients with HF and T2DM, but their role in non-diabetic patients with AMI is still being explored. Recent studies have provided insights into their potential benefits and limitations in this context.

The EMPACT-MI trial evaluate the effect of empagliflozin in patients with AMI and found no significant reduction in the composite primary endpoint of hospitalization for heart failure or death from any cause compared to placebo [107]. Similarly, the DAPA-MI trial, which focused on dapagliflozin in non-diabetic patients post-AMI, did not demonstrate a significant reduction in CVD or HHF [108].

A meta-analysis by Zhang et al., included both diabetic and non-diabetic patients with AMI and found that SGLT2 inhibitors significantly reduced the rate of hospitalization for heart failure and all-cause mortality [162]. The analysis also reported improvements in LVEF and reductions in NT-proBNP levels, supporting the potential cardioprotective effects of SGLT2 inhibitors in this setting.

The DACAMI trial specifically investigated dapagliflozin in non-diabetic patients with anterior ST-elevation myocardial infarction (STEMI) and found significant improvements in cardiac function, including reductions in NT-proBNP levels and left ventricular (LV) mass index, further supporting the potential benefits of SGLT2 inhibitors in improving cardiac outcomes post-AMI [163].

Despite these promising findings, the overall evidence remains mixed, and large-scale randomized controlled trials are needed to confirm the efficacy and safety of SGLT2 inhibitors in non-diabetic patients with AMI.

Table 3 Anti-inflammatory effects of SGLT2 inhibitors, clinical and pre-clinical data

SGLT2 inhibitor	Anti-inflammatory effects
Empagliflozin	Reduces hsCRP and RLP-C levels [154] Reduces IL-1β, IL-18, TNF-α levels and attenuates NLRP3 inflammasome activation (in isolated macrophages) [2] Reduces IL-6 levels [155] Conflicting evidence: No significant change in IL-6, hsCRP, neutrophil, and leukocyte levels, or NLR and PLR [92] Reduces NT-proBNP levels [89] Inhibits ROS generation [159]
Dapagliflozin	Reduces TNF-α and PAI-1 levels [17] Reduces CRP levels [156] Inhibits ROS generation [159]
Canagliflozin	Attenuates IL-6 increase [88]

hsCRP, high sensitivity c-reactive protein; RLP-C, remnant-like particle cholesterol; IL-1β, interleukin-1 beta; IL-18, interleukin-18; TNF-α, tumor necrosis factor alpha; NLRP3, nucleotide-binding domain, leukocyte-rich-containing family, pyrin domain-containing-3; IL-6, interleukin-6; NLR, neutrophil–lymphocyte ratio; PLR, platelet-lymphocyte ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ROS, reactive oxygen species; PAI-1, plasminogen activator inhibitor-1; CRP, c-reactive protein

Current data suggest that while SGLT2 inhibitors may improve certain cardiac parameters, their impact on clinical outcomes such as mortality and hospitalization for HF requires further investigation [164–166].

Combination therapy with anti-inflammatory agents

SGLT2 inhibitors may be used in combination with other anti-inflammatory agents, such as IL-1β inhibitors, to enhance their cardioprotective effects in AMI. This combination approach could further attenuate the inflammatory response and improve myocardial healing in high-risk patients.

Future perspectives and emerging indications

Beyond their established role in T2DM and HF, SGLT2 inhibitors are gaining interest as potential therapeutic agents in other cardiovascular conditions. Emerging data suggest a broader spectrum of cardioprotective effects that may extend to valvular heart diseases such as aortic stenosis (AS) and mitral regurgitation (MR).

In the 2024 BIO-AS study, patients with low-flow, low-gradient (LF-LG) AS exhibited significantly elevated expression of SGLT2 gene and protein in cardiomyocytes. This upregulation was closely associated with increased markers of myocardial fibrosis, oxidative stress, and inflammation, indicating a pathophysiologic link between SGLT2 signaling and disease progression in AS [67]. Further supporting this, a clinical study involving diabetic patients with severe AS, reduced LVEF, and evidence of extra-valvular cardiac damage undergoing transcatheter aortic valve implantation (TAVI) demonstrated that SGLT2 inhibitor use was associated with improved cardiac remodeling and a reduced risk of MACE, all-cause death, and HF-hospitalization at 2-year follow-up [167]. Additionally, preclinical data from a rat model of MR-induced HF revealed that SGLT2 inhibition attenuated cardiac fibrosis, recued endoplasmic reticulum stress, and improved hemodynamic parameters—highlighting a novel therapeutic strategy for MR-induced HF [168].

Collectively, these findings suggest a promising expansion of the clinical indications for SGLT2 inhibitors. Their mechanistic benefits—targeting inflammation, oxidative stress, and myocardial remodeling—may be leveraged in various forms of non-ischemic heart disease. However, robust validation through larger, prospective clinical trials is essential to confirm these preliminary benefits and define their optimal role in these emerging indications.

Conclusion

SGLT2 inhibitors have emerged as promising agents for reducing cardiovascular events in T2DM patients, with growing evidence supporting their anti-inflammatory effects. By modulating the NLRP3 inflammasome pathway, SGLT2 inhibitors reduce the release of pro-inflammatory cytokines and mitigate myocardial injury in the context of AMI. While preclinical data provide strong support for the anti-inflammatory role of SGLT2 inhibitors, further clinical studies are needed to confirm their impact on the inflammasome in human patients. Understanding the molecular mechanisms by which SGLT2 inhibitors modulate inflammation will help optimize their therapeutic use and improve outcomes for T2DM patients with cardiovascular disease.

Author contributions

TY did literature review, investigation, visualization and writing—original draft; IHB: writing—riginal draft, figure preparation; LS and AS: provided critical revisions and analysis of the literature, ensuring a comprehensive discussion of the topic. LS and AS: provided expert input on therapeutic strategies and assisted in finalizing the manuscript; AH: conceptualization, project administration and supervision; DD: conceptualization, supervision, validation and writing—review and editing. LS, AH, AS: final approval of the manuscript.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Received: 6 March 2025 / Accepted: 6 May 2025
Published online: 26 May 2025

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