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# NLRP3 Inflammasome in Cardiovascular Disease: Mechanisms, Pharmacological Targets and Therapeutic Perspectives

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**ABSTRACT:**

Cardiovascular disease remains a major cause of morbidity and mortality worldwide, with inflammation contributing substantially to atherosclerosis, myocardial injury, ventricular remodeling, and heart failure. The NLRP3 inflammasome has emerged as an important molecular link between metabolic stress, mitochondrial dysfunction, oxidative stress, ionic disturbances, and cardiovascular inflammation. Its activation promotes caspase-1 activation, maturation of interleukin-1β and interleukin-18, and gasdermin D-mediated pyroptosis, thereby amplifying cardiovascular injury. This review examines the role of NLRP3 inflammasome activation in major cardiovascular disorders and evaluates its potential as a pharmacological target for cardioprotection. Particular emphasis is placed on direct NLRP3 inhibitors, including MCC950 and dapansutrile, emerging agents, indirect modulators, and downstream anti-inflammatory strategies. Experimental evidence supports therapeutic targeting of NLRP3, while early clinical studies indicate pharmacological feasibility. However, challenges involving safety, treatment timing, patient selection, target engagement, and cardiovascular outcome validation remain. NLRP3-directed therapy represents a promising emerging strategy for mechanism-based cardioprotection.

**Keywords:** NLRP3 inflammasome; cardiovascular disease; cardioprotection; atherosclerosis; myocardial infarction; ischemia–reperfusion injury; heart failure; pyroptosis; IL-1β; inflammasome inhibitors; MCC950; cardiovascular inflammation.

## 1. INTRODUCTION

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide despite major advances in pharmacological prevention and treatment. Statins, antiplatelet agents, renin–angiotensin system blockers, β-blockers, and sodium–glucose cotransporter 2 (SGLT2) inhibitors have substantially improved cardiovascular outcomes; however, significant residual risk persists in many patients receiving guideline-directed therapy. Increasing evidence indicates that inflammation is an active contributor to atherosclerosis, myocardial injury, ventricular remodeling, and heart failure rather than merely a consequence of cardiovascular damage. A major clinical milestone supporting this concept was the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), in which inhibition of interleukin (IL)-1β reduced recurrent cardiovascular events in patients with previous myocardial infarction and elevated high-sensitivity C-reactive protein without lowering low-density lipoprotein cholesterol. These findings provided clinical evidence for the inflammatory hypothesis of atherosclerotic disease while also highlighting the limitations of systemic cytokine inhibition. [1]

The nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3) inflammasome has subsequently emerged as an important molecular target linking cellular stress to cardiovascular inflammation. Inflammasomes are intracellular multiprotein complexes that regulate inflammatory caspase activation and cytokine maturation. NLRP3 is particularly significant because it responds to diverse danger-associated signals, including extracellular ATP, potassium efflux, mitochondrial dysfunction, reactive oxygen species, lysosomal injury, metabolic stress, and cholesterol crystals. Following activation, NLRP3 recruits apoptosis-associated speck-like protein containing a CARD (ASC) and pro-caspase-1, resulting in caspase-1 activation, maturation of IL-1β and IL-18, and gasdermin D-mediated pyroptosis. [2]

These mechanisms have direct relevance to cardiovascular pathology. Cholesterol crystals within atherosclerotic plaques can activate NLRP3 and promote inflammatory progression, while ischemia–reperfusion injury generates mitochondrial dysfunction, oxidative stress, ATP release, and other danger signals capable of activating the inflammasome. Importantly, pharmacological inhibition of NLRP3 with MCC950 reduced infarct size and preserved cardiac function in a porcine model of myocardial infarction, supporting its potential as a cardioprotective target.[3]

This review critically examines the molecular mechanisms and cardiovascular significance of NLRP3 inflammasome activation, evaluates current and emerging pharmacological inhibitors, and discusses their efficacy, safety, target engagement, and translational potential. Particular emphasis is placed on the prospects and challenges of developing selective NLRP3 inhibition as a novel strategy for cardioprotection.

## 2. NLRP3 INFLAMMASOME BIOLOGY AND MECHANISMS OF CARDIOVASCULAR INJURY:

The nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3) is a member of the nucleotide-binding domain and leucine-rich repeat-containing receptor family and contains three principal structural domains: an N-terminal pyrin domain (PYD), a central NACHT domain with ATPase activity, and a C-terminal leucine-rich repeat (LRR) domain. The PYD mediates interaction with the adaptor apoptosis-associated speck-like protein containing a CARD (ASC), whereas the NACHT domain facilitates oligomerization and the LRR region contributes to conformational regulation. Following activation, NLRP3 oligomerizes and recruits ASC through PYD–PYD interactions. ASC subsequently forms filamentous structures that recruit pro-caspase-1, enabling proximity-induced caspase-1 activation. Active caspase-1 cleaves pro-interleukin (IL)-1β and pro-IL-18 into their biologically active forms and cleaves gasdermin D (GSDMD), releasing its pore-forming N-terminal fragment. GSDMD pores facilitate cytokine release and, when membrane-repair mechanisms are overwhelmed, produce inflammatory lytic cell death known as pyroptosis. [4-6]

Canonical NLRP3 activation is generally conceptualized as a two-stage process involving priming and activation. Priming is commonly initiated by Toll-like receptors, tumor necrosis factor or IL-1 receptors, leading to nuclear factor-κB (NF-κB)-dependent transcription of NLRP3 and pro-IL-1β. Post-translational modifications, including phosphorylation and ubiquitination, further regulate the activation threshold. The activation stage is induced by diverse cellular disturbances, including extracellular ATP, potassium efflux, calcium and chloride fluxes, mitochondrial dysfunction, reactive oxygen species (ROS), lysosomal damage, and particulate or crystalline material. Because these stimuli are structurally unrelated, NLRP3 is thought to function primarily as a sensor of disturbed cellular homeostasis rather than as a receptor for individual activating ligands. Potassium efflux is one of the most consistently observed proximal events, and the identification of NIMA-related kinase 7 (NEK7) as an essential mediator established an important mechanistic link between ionic disturbance and inflammasome assembly. NEK7 interacts with NLRP3 and stabilizes the oligomeric inflammasome complex following potassium depletion.

Mitochondrial dysfunction provides another major link between cellular stress and NLRP3 activation. Excess mitochondrial ROS, mitochondrial DNA release, cardiolipin exposure, and impaired mitochondrial quality control can promote inflammasome activation, while inflammasome-driven inflammation may further aggravate mitochondrial injury, establishing a self-amplifying cycle of oxidative stress and inflammation. Lysosomal destabilization following uptake of crystalline or particulate material can release cathepsins into the cytosol and is particularly relevant to atherosclerosis, where cholesterol crystals activate NLRP3 in macrophages and promote plaque inflammation (Duewell et al., 2010; Rajamäki et al., 2010). In cardiovascular tissues, these mechanisms are especially important because ischemia, reperfusion, metabolic stress, lipid accumulation, and tissue injury generate multiple endogenous danger-associated molecular patterns.

The cardiovascular consequences of NLRP3 activation are therefore diverse. In atherosclerosis, macrophages represent an important source of inflammasome-derived IL-1β, while endothelial cells, vascular smooth muscle cells, and other inflammatory cells may also contribute. NLRP3 activation promotes endothelial activation, leukocyte recruitment, macrophage inflammation, and progression of plaque-associated inflammation. Within the myocardium, ischemia and reperfusion generate ATP depletion, ionic imbalance, mitochondrial dysfunction, ROS, and release of damage-associated molecular patterns from injured cardiomyocytes. These signals can activate NLRP3 and amplify inflammatory cell recruitment, cardiomyocyte injury, extracellular matrix remodeling, and fibrosis. Experimental studies have demonstrated that pharmacological inhibition of NLRP3 can reduce cardiac injury and preserve ventricular function following ischemic and nonischemic insults. [7]

Pyroptosis further amplifies cardiovascular injury by causing inflammatory cell death and release of intracellular danger signals, thereby sustaining local inflammation. Although macrophages are prominent inflammasome-responsive cells, NLRP3 components have also been detected in cardiomyocytes, cardiac fibroblasts, endothelial cells, and infiltrating myeloid populations. The relative contribution of these cell types varies with disease context and remains incompletely defined. Non-canonical inflammasome pathways involving human caspases-4 and -5, or murine caspase-11, can additionally promote GSDMD cleavage and secondary NLRP3 activation, particularly during intracellular lipopolysaccharide exposure. Conversely, autophagy, mitophagy, nitric oxide signaling, type I interferon pathways, and metabolic regulators such as β-hydroxybutyrate can restrain NLRP3 activity, highlighting the importance of endogenous mechanisms that maintain inflammatory homeostasis.

The pharmacological tractability of NLRP3 was substantially advanced by the discovery of MCC950 (CRID3/CP-456,773), a selective inhibitor that acts on the NACHT domain and prevents inflammasome activation without directly inhibiting AIM2, NLRC4, or NLRP1 inflammasomes. Subsequent structural studies demonstrated that MCC950 stabilizes an inactive NLRP3 conformation, establishing the inflammasome as a druggable target. Other compounds, including dapansutrile (OLT1177), oridonin, and tranilast, have demonstrated NLRP3-inhibitory activity through distinct molecular mechanisms. Collectively, these findings establish NLRP3 as a central molecular convergence point linking metabolic, oxidative, ionic, infectious, and tissue-injury signals to cardiovascular inflammation and provide a mechanistic foundation for developing selective inflammasome-directed cardioprotective therapies. [8]

## 3. NLRP3 INFLAMMASOME IN CARDIOVASCULAR DISEASE

NLRP3 inflammasome activation has been implicated across a spectrum of cardiovascular disorders, including atherosclerosis, myocardial infarction, ischemia–reperfusion injury, heart failure, hypertension, atrial fibrillation, metabolic cardiomyopathy, and treatment-associated cardiotoxicity. Although the magnitude and quality of evidence vary among these conditions, a common mechanistic theme is the convergence of metabolic stress, oxidative injury, mitochondrial dysfunction, lipid accumulation, and tissue damage on NLRP3 activation, resulting in IL-1β and IL-18 maturation, pyroptosis, and amplification of local and systemic inflammation.

Atherosclerosis is one of the most extensively studied cardiovascular conditions associated with NLRP3 inflammasome activation. Lipid accumulation within the arterial wall promotes innate immune activation, while cholesterol crystals can cause lysosomal injury and activate NLRP3 in macrophages. Oxidized low-density lipoprotein may further enhance inflammasome activation, contributing to persistent vascular inflammation. Experimental studies indicate that disruption of NLRP3 signaling can reduce atherosclerotic lesion development, while pharmacological inhibition may improve plaque characteristics. Increased expression of NLRP3, ASC, caspase-1, and IL-1β has also been observed in advanced human atherosclerotic plaques, supporting the clinical relevance of this pathway. However, experimental findings are not entirely consistent, as some genetic models have shown continued atherosclerotic progression despite disruption of NLRP3-related pathways. Such differences may reflect variations in experimental models, dietary conditions, disease stage, compensatory inflammatory mechanisms, and the distinction between lifelong genetic deficiency and therapeutic inhibition after disease establishment. Mechanistically, NLRP3-derived IL-1β promotes endothelial activation, monocyte recruitment, vascular inflammation, and downstream inflammatory signaling, while macrophage pyroptosis may contribute to necrotic-core formation and plaque instability. Clinical evidence from IL-1β inhibition further supports the importance of inflammation in recurrent cardiovascular events. However, these findings establish the relevance of IL-1 signaling rather than confirming that direct NLRP3 inhibition will produce equivalent cardiovascular benefits. [9]

Myocardial infarction and ischemia–reperfusion injury represent important conditions in which NLRP3 contributes to cardiovascular damage. Acute coronary occlusion causes cardiomyocyte death and initiates a sterile inflammatory response that is essential for tissue clearance and repair but can become harmful when excessive or prolonged. Ischemia followed by reperfusion generates ATP release, mitochondrial reactive oxygen species, calcium overload, acidosis, and cellular debris, providing multiple signals that activate the NLRP3 inflammasome. Activation within cardiac fibroblasts and other myocardial cells can promote infarct expansion, inflammation, and adverse ventricular remodeling, whereas pharmacological suppression of NLRP3 has been associated with reduced myocardial injury. The selective inhibitor MCC950 has also reduced infarct size and improved cardiac function in experimental myocardial infarction models, supporting the therapeutic potential of this pathway. The timing of intervention is particularly important because early inhibition during reperfusion may limit excessive inflammatory injury, whereas prolonged suppression could potentially interfere with macrophage-mediated clearance and tissue repair. Clinical studies targeting the downstream IL-1 pathway provide indirect support for this concept, with anakinra reducing inflammatory responses after myocardial infarction and showing potential effects on ventricular remodeling. Colchicine has likewise demonstrated anti-inflammatory effects in selected post-infarction settings, although its nonspecific mechanism and variable clinical outcomes highlight the importance of treatment timing, patient selection, and pathway specificity. These findings support NLRP3 as a potential therapeutic target for limiting myocardial injury and adverse remodeling following ischemic events. [10]

Heart failure is a chronic cardiovascular condition in which NLRP3 inflammasome activation contributes to myocardial inflammation, remodeling, fibrosis, and ventricular dysfunction. Pressure overload, neurohormonal activation, metabolic disturbances, mitochondrial dysfunction, and oxidative stress can sustain NLRP3 signaling, with experimental inhibition showing beneficial effects in ischemic, pressure-overload, and diabetic cardiomyopathy. NLRP3 activation in cardiomyocytes and cardiac fibroblasts may also contribute to atrial remodeling and susceptibility to atrial fibrillation, particularly postoperative atrial fibrillation, although direct clinical evidence remains limited. This pathway may be relevant to both heart failure with reduced and preserved ejection fraction, despite their distinct pathophysiological characteristics. Early clinical evidence with the oral NLRP3 inhibitor dapansutrile has demonstrated acceptable tolerability and exploratory improvements in ventricular function and exercise capacity in systolic Heart failure. However, larger studies are required to determine whether NLRP3 inhibition can reduce adverse remodeling, prevent arrhythmias, and improve long-term outcomes across different Heart failure phenotypes.[11]

Hypertension is another cardiovascular condition in which NLRP3 inflammasome activation may contribute to vascular inflammation and remodeling. Angiotensin II, oxidative stress, endothelial dysfunction, and immune-cell activation can stimulate NLRP3 signaling, potentially promoting vascular stiffness and structural changes during chronic blood-pressure elevation. However, the relationship is bidirectional, as hypertension itself can promote inflammatory activation, making NLRP3 more likely to function as an inflammatory amplifier rather than an isolated primary driver. [12]

Metabolic cardiovascular disease is also closely associated with NLRP3 activation. Obesity, insulin resistance, hyperglycemia, dyslipidemia, and ectopic lipid accumulation generate mitochondrial stress and inflammatory signals that can promote inflammasome activation. In diabetic cardiomyopathy, sustained NLRP3 signaling may contribute to cardiomyocyte dysfunction, fibrosis, and impaired ventricular relaxation. Although SGLT2 inhibitors and GLP-1 receptor agonists may indirectly influence inflammatory and metabolic pathways, their cardiovascular benefits should not be interpreted as evidence of direct NLRP3 inhibition.

Anticancer therapy-associated cardiotoxicity represents another emerging area of interest. Doxorubicin-induced mitochondrial dysfunction, oxidative stress, DNA damage, and cardiomyocyte injury may activate NLRP3-associated inflammatory and pyroptotic pathways, contributing to cardiac dysfunction. Natural compounds such as resveratrol, curcumin, and honokiol have demonstrated NLRP3-modulating and cardioprotective effects in experimental models, although limited bioavailability and the predominantly preclinical nature of current evidence restrict their clinical translation.

Pericardial inflammation may also involve NLRP3-dependent inflammatory signaling. Experimental and clinical observations, together with the efficacy

of IL-1-directed therapies in recurrent pericarditis, support a role for inflammasome-related mechanisms. The development of direct NLRP3 inhibitors for recurrent pericarditis further illustrates the progression from downstream cytokine blockade toward more selective inflammasome-directed therapy. [13,14]

Collectively, NLRP3 appears to function as an inflammatory amplifier across multiple cardiovascular disorders. However, evidence is strongest for atherosclerosis and myocardial injury, whereas hypertension, metabolic cardiomyopathy, heart failure, cardiotoxicity, and pericardial inflammation require further clinical validation of NLRP3 as a therapeutic target.

## 4. PHARMACOLOGICAL STRATEGIES FOR TARGETING THE NLRP3 INFLAMMASOME

Pharmacological intervention within the NLRP3 pathway can theoretically occur at multiple levels, including suppression of priming, modulation of upstream metabolic and oxidative triggers, inhibition of NLRP3 assembly or NLRP3–NEK7 interaction, inhibition of caspase-1, neutralization of downstream cytokines, and blockade of gasdermin D-mediated pyroptosis. From a drug-development perspective, direct NLRP3 inhibition is particularly attractive because it has the potential to simultaneously attenuate IL-1β and IL-18 maturation and pyroptotic cell death while preserving signaling mediated by other inflammasome sensors. However, indirect and downstream approaches provide important pharmacological precedents and clinical validation of inflammatory targeting. [15-17]

Indirect and upstream modulation includes agents that influence cellular events required for NLRP3 activation. Colchicine is the most clinically established example. By binding tubulin and interfering with microtubule polymerization, colchicine can disrupt cellular trafficking and organelle repositioning involved in NLRP3 assembly, while also suppressing neutrophil chemotaxis and inflammatory oxidant production. Low-dose colchicine reduced cardiovascular events in patients with recent myocardial infarction in COLCOT and in patients with chronic coronary disease in LoDoCo2 . Nevertheless, colchicine is not selective for NLRP3, and gastrointestinal intolerance, drug interactions, and concerns regarding toxicity remain relevant. Moreover, failure to reduce major cardiovascular outcomes in a large acute myocardial infarction trial despite lowering C-reactive protein illustrates that biomarker suppression does not necessarily translate into clinical benefit. Thus, colchicine is best regarded as clinical evidence supporting modulation of inflammation rather than as a precision NLRP3 inhibitor.

Established cardioprotective therapies may also influence NLRP3 indirectly. Sodium–glucose cotransporter-2 (SGLT2) inhibitors have demonstrated anti-inflammatory effects in experimental cardiovascular models, with proposed mechanisms involving metabolic reprogramming, oxidative-stress reduction, and increased β-hydroxybutyrate availability. Because β-hydroxybutyrate can suppress NLRP3 activation, this pathway has been proposed as one possible contributor to the cardiovascular effects of SGLT2 inhibition. However, whether NLRP3 modulation materially contributes to their established clinical benefits remains unresolved. Other experimental strategies include P2X7 receptor antagonism, inhibition of NF-κB-dependent priming, mitochondrial ROS suppression, and enhancement of autophagy or mitophagy. Their major limitation is that these pathways participate in numerous physiological processes, making both efficacy and adverse effects difficult to attribute specifically to NLRP3.

Direct NLRP3 inhibition provides greater molecular specificity. MCC950 (CRID3) remains the prototypical selective NLRP3 inhibitor and has demonstrated efficacy across numerous inflammatory models, including atherosclerosis and myocardial infarction. Structural studies subsequently identified its interaction with the NACHT domain and provided an important foundation for structure-guided development of newer compounds. Although clinical development of MCC950 was limited by toxicity and pharmacokinetic concerns, these limitations are generally interpreted as compound-specific rather than evidence that NLRP3 itself is an unsuitable target.

Dapansutrile (OLT1177) represents an important advancement because it is an orally available NLRP3 inhibitor that has progressed into human studies. Its investigation in patients with heart failure with reduced ejection fraction provided early evidence that systemic NLRP3 inhibition is pharmacologically feasible in cardiovascular disease. More recently, newer agents have expanded the clinical development landscape. Ruvonoflast (NT-0796), an orally administered NLRP3 inhibitor, has demonstrated pharmacodynamic suppression of inflammatory biomarkers, including high-sensitivity C-reactive protein, IL-6, and fibrinogen, in individuals with elevated cardiovascular risk. However, these findings demonstrate biological activity rather than cardiovascular outcome efficacy and require confirmation in larger, longer-duration trials. VTX2735 represents another investigational direct NLRP3 inhibitor being explored in cardiovascular inflammatory conditions, including recurrent pericarditis.

Natural-product and repurposed compounds provide additional chemical diversity. Oridonin has been reported to directly modify NLRP3 and disrupt the NLRP3–NEK7 interaction, whereas tranilast has been associated with inhibition of NLRP3 oligomerization. Resveratrol, curcumin, quercetin, honokiol, berberine, and related phytochemicals have also demonstrated NLRP3-modulating effects through reduction of oxidative stress, NF-κBinhibition, mitochondrial stabilization, and regulation of inflammasome assembly. However, the term “NLRP3 inhibitor” should be applied cautiously because many natural compounds suppress inflammasome-associated inflammation indirectly without demonstrated direct binding to NLRP3. Their poor bioavailability, variable pharmacokinetics, metabolic instability, and limited clinical evidence remain important barriers to cardiovascular development.

Downstream strategies include inhibition of caspase-1, IL-1 signaling, and pyroptosis. Canakinumab provides the strongest clinical proof of concept for targeting an inflammasome-associated cytokine, as selective IL-1β neutralization reduced recurrent cardiovascular events in appropriately selected patients with residual inflammatory risk . Anakinra, an IL-1 receptor antagonist, has similarly demonstrated anti-inflammatory and exploratory functional benefits in myocardial infarction and heart failure. However, downstream cytokine blockade may suppress IL-1 signaling irrespective of its cellular source

and can increase susceptibility to infection. In contrast, direct NLRP3 inhibition may additionally influence IL-18 maturation and pyroptosis while potentially preserving signaling mediated by other innate immune sensors. Gasdermin D inhibition is another emerging strategy, but cardiovascular evidence remains predominantly preclinical.

## 5. Translational Challenges and Future Perspectives

Despite strong mechanistic evidence, several scientific, pharmacological, and clinical challenges must be addressed before NLRP3 inhibition can be established as a cardioprotective strategy. [18-21]

- Long-term safety and target specificity are major concerns because NLRP3 contributes to innate immune defense. Excessive inhibition could potentially impair protective inflammatory responses and increase susceptibility to infection. Although direct NLRP3 inhibitors may selectively target inflammasome signaling while preserving other immune pathways, their long-term safety in humans remains uncertain. Careful monitoring of infections, hepatic and hematological effects, and other immune-related adverse events will therefore be essential.

- Treatment timing is particularly important because inflammation has both beneficial and detrimental effects during cardiovascular injury. Following myocardial infarction, early inflammation facilitates removal of damaged tissue and repair, whereas persistent activation can promote infarct expansion, fibrosis, and adverse remodeling. Thus, the therapeutic window for NLRP3 inhibition may differ between acute ischemia, reperfusion, early remodeling, and chronic heart failure. Treatment duration and dose should consequently be adapted to disease stage rather than uniformly applied across cardiovascular disorders.

- Patient selection and biological heterogeneity represent additional challenges. NLRP3 activation is unlikely to contribute equally to cardiovascular disease in all patients. Although high-sensitivity C-reactive protein may identify individuals with residual inflammatory risk, it is not specific for NLRP3. Future studies may therefore incorporate IL-1β, IL-18, caspase-1 activity, gasdermin D fragments, ASC specks, inflammatory transcriptomic signatures, and relevant genetic characteristics to identify patients most likely to benefit.

- Reliable pharmacodynamic biomarkers and target-engagement measures will be essential for clinical development. Conventional markers such as hsCRP and IL-6 indicate systemic inflammation but cannot confirm direct NLRP3 inhibition. Ex vivo NLRP3-stimulated IL-1β release, circulating IL-18, caspase-1 activity, ASC specks, and gasdermin D-derived products may provide more specific evidence. Single-cell sequencing and spatial transcriptomic or proteomic approaches may further identify the cardiovascular cell populations most relevant to NLRP3-mediated pathology.

- Preclinical-to-clinical translation remains difficult because animal models do not completely reproduce human cardiovascular disease. Differences in lipid metabolism, immune responses, comorbidities, and disease duration can influence therapeutic outcomes. Large-animal models and human-based systems, including induced pluripotent stem cell-derived cardiomyocytes, macrophages, engineered cardiac tissues, and ex vivo human plaques, may improve translational relevance.

- The cellular complexity of NLRP3 signaling also requires further clarification. Its contribution may differ among macrophages, cardiomyocytes, endothelial cells, and cardiac fibroblasts depending on disease stage and tissue environment. NLRP3 may additionally participate in mitochondrial and fibrotic signaling beyond classical inflammasome assembly. Advanced cell-specific and spatial approaches may therefore help identify appropriate therapeutic targets.

- Because NLRP3 is an intracellular target, adequate tissue penetration and pharmacokinetic optimization are essential. Structure-based drug design may facilitate development of compounds that stabilize inactive NLRP3 conformations, inhibit ATPase-dependent activation, or disrupt oligomerization. Combination therapy may also be valuable, with NLRP3 inhibitors potentially complementing established lipid-lowering, antiplatelet, renin–angiotensin system, SGLT2 inhibitor, and GLP-1 receptor agonist therapies. Targeted delivery using nanoparticle-based systems could further improve tissue specificity, although these approaches remain experimental.

- Lastly, clinical trial design must progress beyond demonstration of pathway inhibition toward evidence of meaningful cardiovascular benefit. Early studies should establish pharmacokinetics and target engagement, followed by evaluation of inflammatory biomarkers, plaque characteristics, infarct size, and ventricular remodeling. Definitive trials must assess major cardiovascular outcomes in biologically selected populations with appropriate treatment windows and follow-up. The emergence of oral direct NLRP3 inhibitors such as dapansutrile, ruvonoflast, and VTX2735 demonstrates increasing clinical feasibility, but their ability to provide durable cardioprotection remains to be established.

## 6. CONCLUSION:

In conclusion, the NLRP3 inflammasome represents a mechanistically important link between cardiometabolic stress, sterile inflammation, cytokine signaling, and pyroptotic cardiovascular injury, with experimental studies and emerging clinical evidence supporting its potential as a therapeutic target. Although challenges related to long-term safety, treatment timing, patient selection, and definitive cardiovascular outcome evidence remain, advances in

selective inhibitors, biomarker-guided therapy, and precision pharmacology may establish NLRP3-directed strategies as a future component of mechanism-based cardioprotection.

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