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Review

Inflammasome-Driven Cardiac Fibrosis in Cardiometabolic Disease and Arrhythmias: Mechanisms, Biomarkers, and Therapeutic Targets

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Abstract

Chronic low-grade inflammation and maladaptive extracellular matrix remodeling co-evolve across atrial fibrillation, heart failure phenotypes, diabetic cardiomyopathy, and aortic valve stenosis. Emerging data implicate inflammasome signaling-particularly NOD-like receptor pyrin domain-containing protein 3 (NLRP3), caspase-1 activation, interleukin (IL)-1β/IL-18 maturation, and gasdermin-mediated pyroptosis-as a proximal driver of profibrotic programs. This narrative review synthesizes mechanistic and translational evidence linking pyroinflammation to myofibroblast transition, transforming growth factor β (TGF-β)/small mother against decapentaplegic (SMAD) and Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) activation, matrix deposition and cross-linking, and resultant electrical and mechanical heterogeneity. We emphasize multicellular crosstalk among immune cells, fibroblasts, cardiomyocytes, endothelium/pericytes, and epicardial adipose tissue, and outline organ-axis amplification from kidney and liver disease. We appraise candidate biomarkers and imaging readouts for enrichment, response assessment, and surrogate endpoint potential. The therapeutic landscape spans direct inflammasome inhibitors and IL-1/IL-18 blockade, modulators of upstream metabolic stress, and antifibrotic strategies. Finally, we propose trial frameworks integrating molecular and imaging phenotyping with rhythm and remodeling outcomes, and highlight priorities including assay standardization for pyroptosis and patient selection. By consolidating the inflammasome-fibrosis axis across cardiometabolic conditions, this review defines actionable diagnostic and therapeutic nodes to inform mechanism-guided clinical studies.

Keywords: inflammasome; NLRP3; cardiac fibrosis; cardiovascular diseases; innate immunity; pyroptosis

1. Introduction

Chronic low-grade inflammation and maladaptive extracellular matrix (ECM) remodeling represent converging pathophysiological processes across a wide spectrum of cardiovascular diseases (CVDs), including atrial fibrillation (AF), heart failure (HF), diabetic cardiomyopathy (DCM), and aortic valve stenosis (AVS). Traditionally these conditions are regarded as distinct clinical entities that appear to share a fibro-inflammatory substrate underlying structural, electrical, and metabolic abnormalities. Rather than passive sequelae of hemodynamic and metabolic stress, inflammation and fibrosis evolve in parallel through strictly coupled molecular and cellular interactions that enhance myocardial injury and dysfunction [1,2,3,4,5] (Fig. 1).

Inflammasomes detect pathogens and cellular stress and have emerged as a key mechanistic node of these processes. When activated, they promote cytokine maturation and pyroptosis, which is a form of lytic cell death that amplifies sterile inflammation. The release of cytokines sustains immune cell recruitment and fibroblast activation [6,7]. The elevated levels of interleukin (IL)-1β, IL-6, IL-18, and tumor necrosis factor-α (TNF-α) upregulate transforming growth factor β (TGF-β) receptor expression. The activated macrophages secrete TGF-β, which promotes the differentiation of fibroblasts into myofibroblasts and ultimately promoting extensive collagen deposition [8]. These processes create a substrate for arrhythmia and diastolic dysfunction through producing heterogeneous electrical conduction and mechanical compliance.

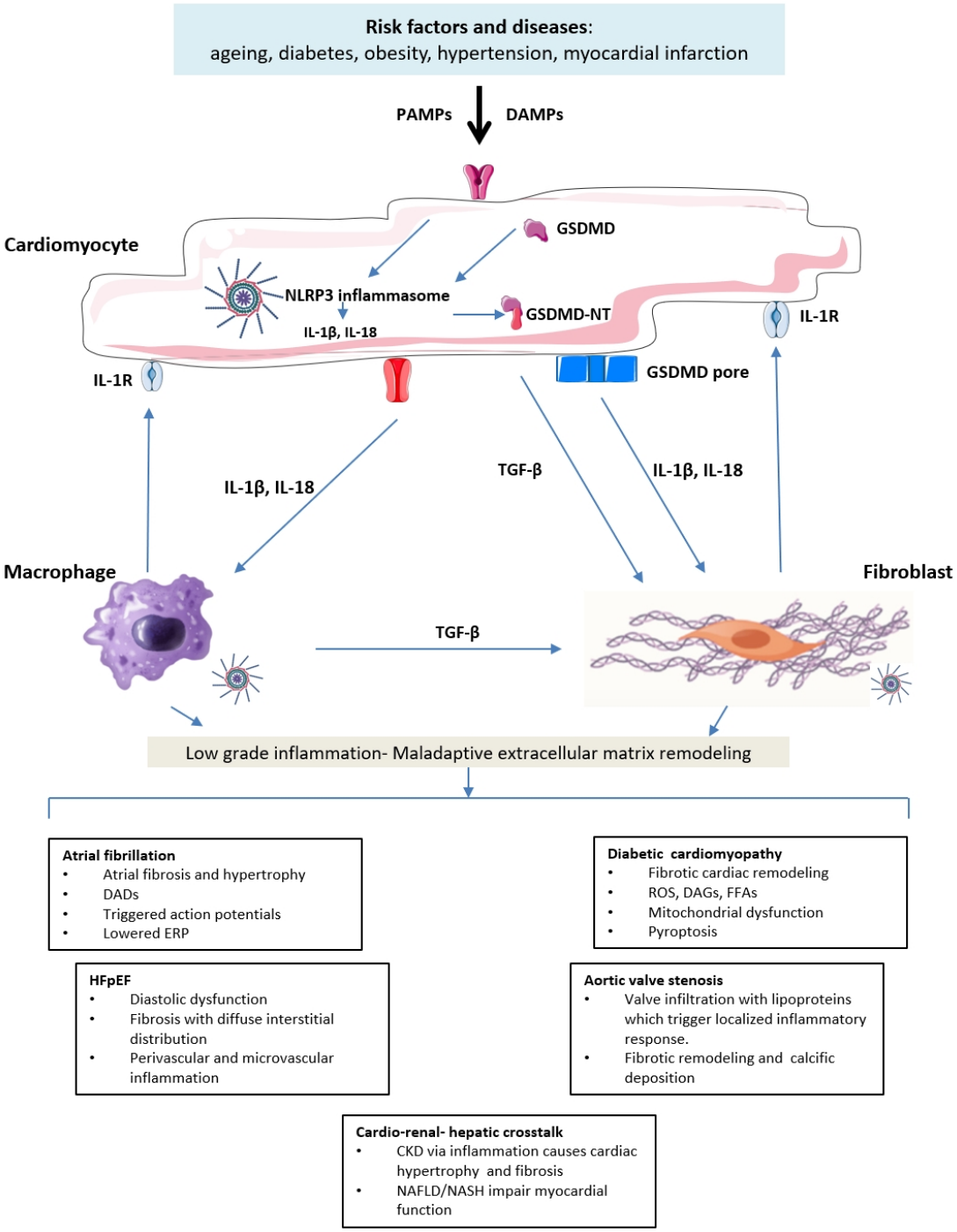

Fig. 1. The figure illustrates how interactions among cardiomyocytes, immune cells, and fibroblasts drive inflammasome-mediated cardiac inflammation and structural remodeling under common cardiovascular risk conditions. Activation of these pathways promotes persistent low-grade inflammation and maladaptive extracellular matrix remodeling, contributing to atrial fibrillation, heart failure, diabetic cardiomyopathy, and aortic valve disease. Systemic conditions such as chronic kidney disease further exacerbate myocardial inflammation and fibrosis, worsening cardiac dysfunction. DAMPs, damage-associated molecular patterns; PAMPs, pathogens associated with molecular patterns; GSDMD, gasdermin D; GSDMD-NT, gasdermin D N-terminal fragment; NLRP3, NOD-like receptor pyrin domain-containing protein 3; IL-1β, interleukin-1β; IL-18, interleukin-18; IL-1R, IL-1 receptor; TGF-β, transforming growth factor β; DADs, delayed afterdepolarizations; ERP, effective refractory period; HFpEF, heart failure with preserved ejection fraction; CKD, chronic kidney disease; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ROS, reactive oxygen species; DAGs, diacylglycerols; FFAs, free fatty acids.

The fibro-inflammatory response involves complex multicellular crosstalk among immune cells, fibroblasts, cardiomyocytes, endothelial and perivascular cells, and epicardial adipose tissue (EAT) [9,10]. Systemic metabolic and inflammatory disorders of the kidney and liver further amplify cardiac injury through circulating cytokines, lipotoxic intermediates, and mitochondrial stress signals [11,12]. These responses show the systemic nature of cardiac fibro-inflammation within the broader cardiometabolic network.

Despite expanding mechanistic understanding, current management is based on patients' phenotypes and does not adequately account for the underlying molecular pathology. Biomarkers that reflect inflammasome activation and matrix remodeling could prove to be useful in patient stratification and response assessment. Therapeutic innovation targeting the inflammasome–fibrosis axis through direct inhibitors, cytokine blockade, metabolic modulators, and antifibrotic agents may enable mechanism-guided interventions.

This narrative review analyses current mechanistic and translational evidence that links inflammasome-driven pyroinflammation to myocardial fibrosis across the whole range of cardiometabolic conditions. It aims to define common cellular and molecular pathways, evaluate emerging biomarkers and imaging modalities, assess therapeutic approaches targeting the inflammasome–fibrosis axis, and outline mechanism-guided clinical studies that encompass molecular profiling, imaging, and outcome-based endpoints.

2. Inflammasome Biology Primer

Inflammasomes serve as central components of the innate immune system and act as cytosolic pattern-recognition platforms [13,14]. They enable the detection of microbial pathogens and endogenous danger signals and identify pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). This process aims to eliminate harmful stimuli from the organism and preserves tissue homeostasis through inflammatory response [15]. Inflammasomes were initially associated only with immune cells such as macrophages and dendritic cells. However, inflammasome signaling has now also been described in non-immune cells reflecting its broader biological involvement in numerous other conditions [16].

Over the years, various inflammasome sensors have been described. These include absent in melanoma 2 (AIM2), interferon-γ–inducible protein 16 (IFI16), and members of the nucleotide-binding and leucine-rich repeat-containing (NLR) family, such as NLR family caspase recruitment domain (CARD)–containing protein 4 (NLRC4) [2,17,18]. Among them, the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome is the most extensively studied. Its activation has been associated with numerous cardiovascular (CV) disorders, including AF, HF, and post-infarction cardiac remodeling [2,19,20,21,22]. NLRP3 inflammasome activation occurs through two major mechanisms, canonical and non-canonical pathways. The canonical pathway follows a two-step process of priming and activation [13,23]. During the priming phase, engagement of toll-like receptors (TLRs) by PAMPs or DAMPs stimulates the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) signaling pathway, resulting in transcriptional upregulation of NLRP3 components [24,25]. After the activation phase, NLRP3 interacts with the adaptor apoptosis-associated speck-like protein containing a CARD (ASC) and pro-caspase-1, forming a multimeric complex that leads to autocatalytic cleavage of caspase-1 [24,26]. Once activated, caspase-1 converts pro-IL-1β and pro-IL-18 into their mature forms. Upon activation, the NLRP3 inflammasome also cuts the pore-forming protein gasdermin D (GSDMD), thereby enhancing pyroptosis, an inflammatory form of lytic programmed cell death [24,26].

The non-canonical pathway, bypasses caspase-1 and is usually recognized as a response to bacterial infection. It involves direct activation of murine caspase-11 (or human caspase-4 and -5) by cytosolic lipopolysaccharides (LPS) leading to GSDMD cleavage and thereby promoting pyroptosis [27]. The loss of potassium ions (K^+) can secondarily trigger the NLRP3 inflammasome and induce IL-1β secretion, a process that underlies the interactions between inflammasome-related canonical and non-canonical pathways [27,28,29].

NLRP3 inflammasome activation can be initiated by various cellular stimuli, which can be categorized into ion fluxes, reactive oxygen species (ROS), and organelle damage [30]. K^+ efflux is a common trigger of the inflammasome response and can be facilitated by activation of the purinergic receptor P2X7 induced by extracellular adenosine triphosphate (ATP) [30,31]. Calcium (Ca^{2+}) signaling is also a crucial modulator of the NLRP3 inflammasome activation as elevated cytosolic Ca^{2+} levels from extracellular influx and intracellular release, promote inflammasome assembly [2,32]. The calcium-sensing receptor (CaSR) activates phospholipase C (PLC) and generates inositol 1,4,5-trisphosphate (IP_3), which triggers Ca^{2+} release from the endoplasmic reticulum (ER) [33,34]. Other ions, including sodium (Na^+) and chloride (Cl^-), have complementary roles in the process and influence the osmotic balance and the NLRP3– NIMA-related kinase 7 (Nek7) interaction via Cl^- intracellular channels (CLICs) [30,35].

Accumulation of ROS, derived from the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) after mitochondrial damage, leads to oxidative stress and has emerged as a significant trigger of NLRP3 inflammasome activation [30,36]. Elevated cytosolic Ca^{2+} levels cause secondary increases in mitochondrial Ca^{2+} uptake, a process that also enhances the generation of mitochondrial ROS (mtROS) [37,38]. Redox stress not only initiates NLRP3 inflammasome activation but also

establishes a bidirectional feed-forward loop, whereby oxidative stress drives inflammasome signaling and NLRP3 activation that further amplifies ROS generation. This maladaptive cycle is a defining feature of ischemic heart disease, diabetes and other CV disorders [39]. Finally, lysosomal destabilization releases cathepsins into the cytosol, further promoting the activation of the NLRP3 inflammasome and IL-1β maturation [30,40,41].

3. Fibrosis Machinery and Where It Meets Pyroinflammation

Cardiac fibrosis is a key component of many CVDs and has been associated with adverse clinical outcomes [42]. The underlying mechanisms involve inflammation, pathological cellular proliferation, and excessive production of ECM proteins by myofibroblasts as part of the repair process after myocardial injury [42,43].

The destruction of parenchymal cells is mediated by pyroptosis, which contributes to fibrogenesis [44]. This critical pathogenic link between pyroinflammation and activation of the fibrotic mechanisms in the myocardium creates a feed-forward loop that plays a key role in adverse cardiac remodeling [45]. The process is triggered by pathological stress, such as ischemia/reperfusion injury (IRI) or chronic pressure overload, which leads to the activation of the NLRP3 inflammasome [46,47]. The cascade of events includes the activation of caspase-1 and the proteolytic cleavage of GSDMD, leading to the formation of cytomembrane pores, lysis, and leakage of cellular contents [45]. This process causes inflammation through the pyroptotic release of proinflammatory cytokines, such as IL-1β, IL-18, TNF-α, and high-mobility group box 1 (HMGB1) [8]. These inflammatory mediators also promote fibroblast activation, amplified mainly through the canonical transforming growth factor β (TGF-β)/small mother against decapentaplegic (SMAD) signaling pathway, which activates many profibrotic genes, including connective tissue growth factor (CTGF), and therefore enhances the production of ECM proteins [46].

Beyond its canonical inflammasome functions, NLRP3 also exerts inflammasome-independent roles that contribute to fibrosis. In cardiac fibroblasts, NLRP3 promotes TGF-β/SMAD signaling independently of ASC and caspase-1, driving fibroblast differentiation and ECM production through nucleotide-binding domain, Apaf-1, CIITA, HET-E, TP1 (NACHT) domain–dependent mtROS generation. Similar inflammasome-independent NLRP3–SMAD interactions have been described in renal epithelial and cancer models, supporting a broader role in profibrotic signaling. Moreover, NLRP3 can localize to mitochondria under hypoxic stress and regulate mitochondrial homeostasis independently of inflammasome activation, linking metabolic stress to tissue fibrosis [48].

Moreover, TGF-β promotes ECM accumulation by enhancing integrin expression, increasing inhibitors of proteases such as plasminogen activator inhibitor-1 (PAI-1) and tissue inhibitors of metalloproteinases (TIMPs), and reducing matrix metalloproteinase (MMP) activity, all of which create a matrix-preserving environment [49].

The excessive ECM deposition stiffens the myocardial tissue and alters the biophysical environment, which results in the engagement of mechanotransduction pathways [50]. Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) are the downstream effectors of the Hippo pathway and regulate cell proliferation and differentiation, and therefore tissue regeneration through their interactions with transcriptional enhanced associate domain (TEAD) proteins [51]. Myocardial stiffness mechano-activates the YAP/TAZ pathway in fibroblasts, which amplifies the transcription of profibrotic genes. This process results in more ECM being deposited, which makes the tissue even stiffer, thereby maintaining the activation of YAP/TAZ [51,52].

Lysyl oxidases (LOX) are key enzymes that facilitate collagen cross-linking, a process that enhances the structural stability of the ECM and supports the formation and accumulation of collagen fibers [53]. Among them, lysyl oxidase- like 2 (LOXL2) appear to have most significant effect in various diseases. Chronic injury and inflammation increase LOXL2 expression and activity, and promotes fibrosis [54].

4. Multicellular Crosstalk

Immune cells, cardiac fibroblasts, cardiomyocytes, endothelial cells (ECs), EAT, and platelets are all parts of a highly integrated signaling network that modulates the initiation and progression of cardiac fibrosis through multicellular crosstalk.

4.1 Immune-Fibroblast

Macrophages are a heterogeneous class of innate immune cells that have emerged as significant mediators in the process of fibrosis [55,56,57]. When activated naïve macrophages (M0) can be developed into two distinct functional phenotypes, M1 and M2 [58]. M1 macrophages are typically activated by LPS and interferon-gamma (IFN-γ) and enhance the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. In contrast, M2 macrophages are induced by IL-13 and IL-4 and secrete anti-inflammatory and reparative mediators, including IL-10 and TGF-β, which facilitate ECM synthesis and fibrosis. The dynamic balance between M1 and M2 macrophage polarization is critical for the transition from inflammation to tissue repair [59]. Following myocardial injury, M1 macrophages initiate inflammation, whereas a subsequent shift toward M2 macrophages lead to fibrotic remodeling [59,60]. In obesity, adipose tissue macrophages shift from an M2 to a pro-inflammatory M1 phenotype, releasing TNF-α and IL-6, which impair insulin signaling and promote the onset of diabetes [59].

Furthermore, M2 macrophages induce endothelial-to-mesenchymal transition (EndoMT) via TGF-β signaling, increasing fibroblast numbers [54,55]. In addition, bone marrow–derived macrophage–produced neuregulin 1 (Nrg1) engages erythroblastic leukemia viral oncogene homolog (ErbB) receptors on fibroblasts and activates the phosphatidylinositol 3′-kinase (PI3K)/Akt pathway to inhibit apoptosis, promote fibroblast proliferation, and accumulate ECM [59,61]. Following an acute myocardial infarction (MI) activation of the macrophage-related inflammasome can further induce cardiac fibrosis through the 15-hydroxy-5,8,11,13-eicosatetraenoic acid (15-HETE)–mediated pathway [62].

4.2 Cardiomyocyte-Fibroblast

The bidirectional crosstalk between cardiomyocytes and fibroblasts can maintain the cardiac structure and electrical stability across a wide range of heart diseases. This is mediated via both direct cell to cell communication through gap junctions and membrane nanotubes and indirectly via the ECM and the secretion of paracrine factors, including TGF-β, IL-6, and angiotensin II (AT-II) [63,64,65]. This crosstalk maintains structural and functional homeostasis in the healthy individual. However, under pathological conditions, this communication becomes maladaptive and leads the cardiomyocytes to release profibrotic mediators, with TGF-β playing a major role, which induces fibroblast differentiation into activated myofibroblasts [65]. In turn, myofibroblasts secrete paracrine factors that induce apoptosis and hypertrophy [12]. This pathological loop leads to myocardial stiffness, disrupts conduction, and contributes to arrhythmias and HF progression [65,66].

Cardiometabolic disorders can alter the crosstalk between cardiomyocytes and fibroblasts. In hypertension for example, left ventricular pressure overload causes mechanical stress that is sensed by resident cardiac fibroblasts through cell-surface receptors, which mediate mechanotransduction signaling and drive fibroblast activation and differentiation into myofibroblasts [67]. In diabetes and obesity metabolic dysregulation appears to drive myocardial fibrosis through distinct pathways, characterized not by fibrogenic conversion or pericyte activation, but by enhanced matrix-preserving activity of resident cardiac fibroblasts that occurs without myofibroblast differentiation [68]. High-glucose exposure also increases ROS production, which activates the NLRP3 inflammasome and enhances inflammasome-related IL-1 signaling, thereby promoting myocardial fibrotic remodeling [68,69].

4.3 Endothelium-Pericyte

Many factors can activate ECs, including TNF-α, TGF-β, IL-1β, activation of the NLRP3 inflammasome, endotoxins, and metabolic dysfunction such as elevated serum low-density lipoprotein (LDL) and glucose [70,71]. This activation leads to the loss of typical endothelial characteristics and the gain of mesenchymal characteristics, a process known as endothelial-to-mesenchymal transition (EndMT) [72]. EndMT contributes to endothelial dysfunction (ED) under both inflammatory and metabolic stress and is implicated in several postnatal pathological conditions, including fibrosis, pulmonary arterial hypertension (PAH), and metabolic syndrome [72,73,74].

Pericytes also contribute to cardiac fibrosis after MI [64]. Pericytes adopt a proinflammatory state and release cytokines and MMPs that increase vascular permeability [75,76]. They then induce ECM deposition, with some converting into fibroblast-like cells. In the maturation stage, TGF-β and platelet-derived growth factors (PDGFs) modulate pericytes to stabilize new blood vessels. Pressure overload, mechanical stress and neurohumoral activation stimulate pericytes to produce ECM proteins and fibroblast-activating factors and eventually promoting fibrotic remodeling [76].

The crosstalk between pericytes and the endothelium preserves vascular stability but often becomes dysregulated in aberrant fibrosis [77]. In response to injury, EC release factors, such as PDGF and various Vascular endothelial growth factor (VEGFs) isomers. This signaling leads pericytes to dissociate from the vessel wall and acquire an inflammatory and pro-fibrotic phenotype. The loss of this coverage simultaneously destabilizes the vessels and leads to capillary loss and tissue damage which further promotes the fibrotic response [76,77,78].

4.4 Adipose-Myocardium

EAT, situated adjacent to the myocardium and coronary arteries without a separating fascia, act as an important energy source and provides mechanical support to the heart. EAT has been found to also serve as an active paracrine and immunometabolic organ that, under pathological conditions, contributes to the development of cardiac fibrosis [79]. EAT can secrete proinflammatory cytokines such as IL-1β, IL-6, IL-8, IFN-γ and TNF-α, creating a localized inflammatory environment in the adjacent myocardium [80,81]. This promotes fibroblast activation and ECM deposition in the myocardium [2]. Recent evidence demonstrates that patients with hypertension and elevated systemic inflammatory response index (SIRI) exhibit significantly increased EAT volume, higher myocardial extracellular volume (ECV), elevated native T1 values, and impaired left ventricular multidirectional strain, suggesting a mechanistic link between systemic inflammation, EAT expansion, and myocardial fibrosis [82]. In metabolic disorders such as obesity and diabetes, EAT is also related to enhanced inflammatory activation and altered immune composition promoting myocardial inflammation [83]. Moreover, epicardial adipocytes disrupt electrical integrity that lead to conduction abnormalities and heterogeneity within the atrial substrate [2,84]. In addition, interactions between epicardial adipocytes and atrial car-

diomyocytes alter ionic currents, depolarize resting membrane potential, and increase cellular excitability, all of which contribute to the pathogenesis of electrical remodeling that underlies AF susceptibility [2,85,86,87]. Moreover, EAT-derived bioactive molecules, including profibrotic adipokines like activin A, enhance fibrogenic signaling which in turn reinforce the atrial structural remodeling process [88].

4.5 Platelet/Complement

The biological functions of platelets have important roles beyond hemostasis and thrombosis. Platelets release a diverse array of bioactive molecules that are involved in numerous processes associated with tissue repair, inflammation, angiogenesis, and fibrosis [89]. Platelets modulate inflammation and contribute to myocardial fibrosis through the secretion of immunomodulatory factors and direct interactions with leukocytes [89,90]. Notably, platelets exhibit the capability to de novo synthesize IL-1β and IL-18, cytokines primarily related with the activation of NLRP3 inflammasome, suggesting a potential new biological process requiring further investigation [91]. In line with this, platelets harbor inflammasome-related transcripts and key components such as ASC and GSDMD, enabling caspase-1 activation under inflammatory or thrombotic stress [91,92,93,94]. This inflammatory process is governed by megakaryocytes, which generate pro-inflammatory platelets in response to systemic cues including hyperlipidemia, infection, or cardiac injury. Upon activation, platelet NLRP3 drives IL-1β production and release, amplifying platelet activation and promoting endothelial activation, leukocyte recruitment, and neutrophil extracellular trap (NET) formation [95,96,97,98]. Table 1 (Ref. [20,46,53,60,62,99,100,101,102]) is summarizing the experimental models that have investigated the inflammasome-related molecular mechanisms of cardiac fibrosis.

5. Disease Modules

The following sections summarize major clinical contexts in which inflammasome activation and pyroptosis contribute to cardiac fibrosis and remodeling, highlighting shared mechanisms and disease-specific features across arrhythmias, heart failure, valvular disease, and systemic cardiometabolic conditions.

5.1 Atrial Fibrillation

Inflammation and fibrosis are two components that play a crucial role in the pathogenesis of AF [103,104]. The activation of the NLRP3 inflammasome is a key step triggered by the stimulation of pattern recognition receptors (PRRs) on atrial cardiomyocytes in response to AF-related risk factors. This leads to the maturation of IL-1β and IL-18, which, together with the downstream activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), ROS, and NF-κB signaling, drive maladaptive remodeling. These cytokines activate resident macrophages which in turn promote fibroblast activation and ECM deposition, which results to inflammation [2].

Electrical, structural, mechanical, and molecular alterations within the atrial myocardium often precede the onset of AF, a condition referred to as atrial cardiomyopathy (AtCM) [105,106]. A variety of pathophysiological contributors to AtCM including metabolic disturbances, EAT, oxidative stress, inflammation and activation of NLRP3 inflammasome, ageing, and sex-specific remodeling are implicated [99,107,108,109,110,111,112]. Extensive fibrosis contributes to the development of persistent AF. Once AF is established, it accelerates the progression of AtCM, creating a self-perpetuating cycle that exacerbates thromboembolic risk and contributes to HF and mortality [106].

5.2 Heart Failure

HF remains a leading cause of hospitalization, morbidity, and mortality worldwide [113]. Adverse cardiac remodeling is a complex process characterized by changes in heart size and shape driven by cell growth and death, inflammation, vascular rarefaction, and fibrosis [114]. Beyond atrial disease, inflammasome activation and pyroptosis are central to ventricular remodeling and HF across diverse etiologies.

The activation of the NLRP3 inflammasome and inflammation are key components in the development and progression of HF [115]. IL-18 generated from NLRP3 activation promotes TNF-α synthesis, which subsequently activates NF-κB signaling and enhances IL-1β expression, leading to myocardial inflammation [30]. IL-1β and IL-18 stimulate inducible nitric oxide (NO) synthase (iNOS), leading to the production of NO, which promotes cardiac injury and interactions between leukocytes and the endothelium [116]. Elevated iNOS also produces reactive nitrogen species (RNS), contributing to apoptosis and myocardial remodeling [117].

Hypoxia and ROS stimulate NLRP3 inflammasome activation in fibroblasts, promoting both inflammatory responses and a profibrotic phenotype, leading to progressive ventricular remodeling. NLRP3 also directly contributes to fibroblast differentiation via regulation of mtROS and activation of the R-SMAD signaling pathway highlighting a novel pathway for myocardial fibrosis [30].

Activation of the NLRP3 inflammasome and downstream caspase-1 signaling in cardiomyocytes impairs contractile function, stimulates fibroblast activation, and enhances ECM deposition. Experimental and clinical evidence further indicates that sustained, low-grade pyroptotic activity perpetuates sterile myocardial inflammation and fibrosis, thereby exacerbating adverse cardiac remodeling and accelerating the transition to overt HF [118].

The focus of HF research and therapeutic development has largely been on HF with reduced ejection fraction

Table 1. Experimental models investigating molecular mechanisms of inflammasome-related fibrosis.

Disease context	Species (model)	Age/sex	Experimental model	Molecular pathway	Fibrosis-related outcome	Reference
Cardiac fibrosis	Mouse	12–24 weeks old/male and female	Pressure overload and chronic allograft rejection	EndMT regulated by TGF-β signaling pathway and Smad-dependent signaling	Endothelial cells undergo transition into fibroblast-like cells contributing substantially to the population of cardiac fibroblasts, promoting fibrosis and adverse remodeling in the heart.	Zeisberg et al., 2007 [60]
Myocardial ischemia/reperfusion injury (cardiac injury)	Mouse	12–14 weeks old/male	Myocardial ischemia/reperfusion injury induced by transient coronary artery occlusion	NLRP3 inflammasome activation in cardiac fibroblasts leading to IL-1β secretion and inflammatory response	Activation of inflammasome in cardiac fibroblasts contributes to cardiac inflammation and subsequent fibrosis development post-injury.	Kawaguchi et al., 2011 [46]
Post-MI remodeling	Rat (Wistar rats)	Adult/male	Coronary ligation MI	NLRC4 inflammasome activation in cardiac tissue post-MI	Upregulation of NLRC4 inflammasome expression correlates with inflammation and fibrotic remodeling post-MI, contributing to cardiac fibrosis and adverse remodeling.	Borim et al., 2025 [20]
Acute myocardial infarction	Mouse	7–8 weeks old/male	Experimental AMI induced by coronary artery ligation	Macrophage-associated inflammasome activation via 15-HETE signaling pathway	Inflammasome activation in macrophages worsens myocardial fibrosis post-AMI through the 15-HETE pathway, increasing fibrotic tissue deposition and adverse cardiac remodeling.	Xu et al., 2024 [62]
β-adrenergic cardiac injury	Mouse	Adult/male	Chronic β-adrenergic stimulation via isoproterenol injection	IL-18 cleavage, inflammasome activation, cardiac inflammation	Inflammasome-dependent IL-18 activation in the myocardium during acute β-adrenergic overstimulation triggers cytokine release, macrophage infiltration, and pathological cardiac remodeling.	Xiao et al., 2018 [102]
Cardiac fibroblast activation	Human CFs	Not applicable	IL-18 stimulation (*in vitro*)	PI3K-Akt dependent NF-κB activation induced by IL-18	IL-18 and fibronectin mutually enhance each other's expression in human CFs, contributing to myocardial hypertrophy, remodeling, and fibrosis.	Reddy et al., 2008 [101]
Inflammatory cardiac fibrosis	Rat CFs	Adult/male	TNF-α exposure	TNF-α, TGF-β, PI3K	Increased lysyl oxidase expression promoting collagen cross-linking.	Voloshenyuk et al., 2011 [53]
Calcific aortic valve disease	Mouse	Adult/male and female	AS model	Platelet-derived TGF-β1	Platelet TGF-β1 drives valvular fibrosis.	Varshney et al., 2019 [100]
Age-related atrial fibrillation	Rat	Adult/male and female	Faecal microbiota transplantation	NLRP3 inflammasome activation	Promotes atrial fibrosis and AF susceptibility.	Zhang et al., 2022 [99]

EndMT, endothelial-to-mesenchymal transition; TGF-β, transforming growth factor β; NLRP3, NOD-like receptor pyrin domain-containing protein 3; IL-1β, interleukin-1β; MI, myocardial infarction; NLRC4, NLR family CARD domain-containing protein 4; AMI, acute myocardial infarction; 15-HETE, 15-hydroxyeicosatetraenoic acid; IL-18, interleukin-18; CFs, cardiac fibroblasts; PI3K-Akt, phosphatidylinositol 3′-kinase (PI3K)-Akt; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor-α; AS, aortic stenosis; AF, atrial fibrillation.

(HFrEF). However, HF with preserved ejection fraction (HFpEF) now accounts for approximately half of all HF cases and carries a high mortality risk [119]. Aging of the population living with chronic comorbidities, such as diabetes, obesity, arterial hypertension, chronic kidney disease (CKD), increases the prevalence of HFpEF that now accounts for approximately half of all HF cases [119,120]. Insulin resistance activates the renin–angiotensin–aldosterone system (RAAS), fostering vascular fibrosis and arterial stiffening and increasing the risk of HFpEF. Obesity further aggravates ED through chronic low-grade inflammation and adverse remodeling of perivascular adipose tissue, whereas hypertension induces endothelial injury via excess ROS production and endothelial nitric oxide synthase uncoupling. Central to these processes is NLRP3 inflammasome activation, which links oxidative stress and inflammation to ED and promotes vascular smooth muscle cell (VSMC) remodeling [121]. Therefore, there is an unmet need to intensify efforts to understand its pathogenesis and identify effective treatments.

New experimental studies and clinical trials have increasingly characterized HFpEF as a complex systemic inflammatory syndrome [122]. Preclinical models that replicate the phenotype of HFpEF have been successful to further investigating key pathogenic mechanisms, including inflammatory and cytokine signaling, cardiac fibroblast activation, ECM deposition, and posttranslational modifications of the sarcomeric protein Titin (Ttn). Therapies targeting cytokines or inflammatory mediators have largely been unsuccessful, and those aimed at cardiac fibroblasts remain largely unexplored [122]. Recent experimental studies combining pressure-overload models with single-cell RNA sequencing have identified myeloid cell–derived S100A8/A9 as a key mediator of myocardial inflammation, fibroblast activation, and fibrotic remodeling through NF-κB/NLRP3-dependent signaling, thereby promoting the transition from adaptive hypertrophy to HF [123].

In HFrEF, fibrosis is typically local and confined to subendocardial or transmural regions as a consequence of an acute myocardial infarction (AMI), whereas in HFpEF, fibrosis is characterized by a diffuse interstitial distribution, affecting the mid-wall and subepicardial myocardium. This results in increased myocardial stiffness and subsequently to diastolic dysfunction [124]. Perivascular and microvascular inflammation, largely arising from the cardiometabolic comorbidities that define and perpetuate the HFpEF phenotype, further promotes cardiac fibrosis [125].

5.3 Diabetic Cardiomyopathy

Among cardiometabolic disorders, diabetes represents a distinct clinical entity in which inflammasome activation directly drives myocardial injury and fibrosis.

DCM refers to myocardial structural and functional abnormalities that occur independently of other CV risk factors, such as arterial hypertension and coronary artery disease [126]. DCM is the leading cause of HF in patients with diabetes [127]. The underlying pathophysiological mechanisms of DCM are multifaceted and are only now beginning to be partially understood. Among these, the most significant contributors appear to involve abnormal cardiac metabolism, enhanced cardiomyocyte apoptosis, and progressive interstitial fibrosis, all of which are consequences of hyperglycemia and insulin resistance [128].

Fibrosis accompanies DCM. Prolonged hyperglycemia promotes the production of AGEs, which interact with ECM proteins and result in the development of cardiac fibrosis [129]. It also significantly activates the RAAS, which upregulates the expression of numerous fibrogenic factors in the myocardium, such as TGF-β1 and CTGF, further enhancing cardiac and vascular fibrosis [130]. Hyperglycemia generates excessive ROS, which leads to DNA damage and eventually triggers apoptotic signaling in cardiomyocytes [131]. Elevated circulating free fatty acids (FFAs), diacylglycerols (DAGs), and ceramides in diabetes induce cardiomyocyte lipotoxicity and amplify oxidative stress that drive fibrotic cardiac remodeling [132].

Activation of the NLRP3 inflammasome and pyroptosis contribute to the pathogenesis of DCM [30]. Elevated levels of ROS activate NF-κB and increases thioredoxin-interacting protein (TXNIP) which leads to inflammasome activation [133,134]. Hyperglycemia and lipotoxicity exacerbate mitochondrial oxidative stress and proinflammatory signaling, activating further the inflammasome. In parallel, cytosolic Ca^{2+} dysregulation, partly because of impaired SERCA2a function, facilitates NLRP3 activation and pyroptosis [30]. Experimental studies have demonstrated NLRP3–caspase-1–mediated cardiomyocyte pyroptosis in diabetic hearts, characterized by mitochondrial swelling and inflammatory injury, whereas pharmacological inhibition or genetic silencing of NLRP3 reduces inflammation, attenuates pyroptosis, and improves myocardial function. Moreover, emerging evidence indicates that dysregulated microRNAs (miRNA), such as miRNA 30d, modulate cardiomyocyte susceptibility to pyroptosis under hyperglycemic conditions, further implicating pyroptosis as a key driver of DCM progression [14].

5.4 Aortic Valve Stenosis

In AVS persistent hemodynamic overload and neurohormonal activation initiate various profibrotic signaling pathways including those involving TGF-β, galectin-3, and MMPs, that drive collagen accumulation and ECM expansion [100,135,136,137,138]. These structural alterations cause diastolic dysfunction and impair coronary flow reserve [139,140]. Simultaneously, microvascular dysfunction develops as a result of elevated wall stress and endothelial impairment, which aggravates myocardial ischemia and further enhances fibrotic remodeling. In advanced stages mitochondrial dysfunction and a metabolic shift from fatty

acid oxidation to glucose utilization, further impair contractile efficiency and make the myocardium more susceptible to injury [141,142].

At the valvular level, shear stress causes endothelial damage particularly on the fibrosa surface [143]. This promotes EndMT and facilitates the infiltration of lipoproteins (Lp), including Lp(a) and oxidized LDL [144,145]. Accumulated lipids trigger a localized inflammatory response, that attracts macrophages and T cells that secrete proinflammatory cytokines such as IL-6, TNF-α, and IL-1β, which in turn activate the NF-κB signaling pathway [146]. Accumulating evidence supports the involvement of the NLRP3 inflammasome in the pathogenesis of AVS. Experimental models demonstrate that NLRP3 inflammasome blockage reduces inflammation and alleviates valvular calcification [147,148,149]. Consequently, valvular interstitial cells (VICs) transform into myofibroblast- and osteoblast-like cells, driving fibrotic remodeling and calcific deposition [150]. Apoptotic bodies and extracellular vesicles derived from VICs and immune cells further act as nucleation centers for hydroxyapatite crystal formation [151,152]. Pyroptosis amplifies valvular inflammation, as reflected by increased expression of NLRP3 inflammasome components, activation of caspase-1, and elevated IL-1β and IL-18 in calcified aortic valve tissues. Dysregulation of the miRNA 29b-signal transducer and activator of transcription 3/suppressor of cytokine signaling 1 (miRNA 29b–STAT3/SOCS1) axis promotes inflammasome activation, osteogenic differentiation of aortic valve interstitial cells, and pyroptotic inflammation, thereby driving disease progression [153].

5.5 Cardio-Renal-Hepatic Crosstalk

Beyond primary cardiac diseases, systemic organ interactions further modulate inflammasome activation and fibrotic remodeling in the heart.

CVD represents the primary cause of mortality among patients with nonalcoholic fatty liver disease (NAFLD) [154]. Nonalcoholic steatohepatitis (NASH) is an advanced form of NAFLD and can progress to cirrhosis and hepatocellular carcinoma, with accumulating evidence suggesting that NLRP3 inflammasome activation plays a pivotal role in this progression [155]. Recent studies have increasingly focused on the role of pyroptosis in NAFLD, exploring its mechanisms, contributions to disease progression, and potential as a therapeutic target. While regulated pyroptosis can stimulate immune cell activity and protective host responses, excessive or dysregulated pyroptosis can amplify inflammation, cause cellular and tissue injury, impair the immune system, and negatively affect liver function [156].

NAFLD/NASH is linked with increased risk of coronary artery disease, HF, and valvulopathies [154]. It can be assumed that the association with CVDs is merely a consequence of comorbidities commonly linked to hepatic steatosis, such as obesity, diabetes, insulin resistance, and dyslipidemia. However, evidence suggests that hepatic steatosis itself may promote cardiac dysfunction independently of these factors. In a hepatocyte-specific PPARα knockout mouse model, excessive hepatic steatosis developed independently of obesity, insulin resistance, or dyslipidemia. Despite the absence of systemic metabolic disorders, these mice exhibited cardiac lipotoxicity, cardiomyocyte apoptosis, myocardial fibrosis, impaired contractility, reduced exercise capacity, and decreased D-β-hydroxybutyrate dehydrogenase I (BDH1) expression, all of which indicate that NAFLD/NASH can directly impair cardiac structure and function [157].

Patients with CKD are at increased risk of CVDs, including coronary artery disease, HF, and sudden cardiac death [158]. Prolonged low-grade inflammation is an important pathophysiological bridge between kidney dysfunction and CV pathology, which involves enhanced synthesis of proinflammatory cytokines and chemokines, C-reactive protein (CRP), and the activation of NF-κB signaling and the NLRP3 inflammasome, which contribute to cardiac hypertrophy and fibrosis [159]. CKD can further induce myocardial interstitial fibrosis through several additional mechanisms, including volume and pressure overload, RAAS activation, and increased production of fibroblast growth factor-23 (FGF-23), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and NO inhibitors [11].

Collectively, these clinical contexts highlight inflammasome activation, particularly NLRP3 signaling and pyroptosis, as a unifying mechanistic axis linking cardiometabolic stress, inflammation, and cardiac fibrosis across a broad spectrum of CVDs. Despite disease-specific triggers, including atrial electrical instability, pressure overload, metabolic derangements, valvular injury, and systemic organ dysfunction, convergent inflammasome-driven pathways promote cardiomyocyte injury, fibroblast activation, ECM expansion, and adverse structural remodeling. The integration of cardiac, vascular, renal, and hepatic inflammatory signals further amplifies this process, underscoring the systemic nature of inflammasome-mediated cardiac disease. Together, these observations position the NLRP3 inflammasome and pyroptosis as central drivers of maladaptive remodeling and compelling targets for future biomarker development and therapeutic intervention across diverse cardiovascular phenotypes.

6. Biomarkers and Imaging

6.1 Biomarkers

Myocardial injury and necrosis lead to inflammation that constitutes a significant component of the physiological healing process that ultimately leads to tissue repair through fibrosis. Throughout this process, a wide range of biologically active mediators are released, some of which may represent promising biomarkers for the early identification of inflammation-induced fibrosis.

Galectin-3 (Gal-3), a β-galactoside-binding lectin, has a significant role in both inflammatory and fibrotic pathways and seems to act as a valuable biomarker [160]. Gal-3 is mainly released by activated macrophages in response to cellular stress and promotes fibroblast activation and ECM deposition within the myocardium. Its high levels are associated with HF progression and worse cardiovascular outcomes, and they exhibit high predictive value for early fibrotic changes [161]. sST2, a soluble receptor from the IL-1 family, is released in response to cardiac stress and seems to a sensitive indicator of myocardial injury and fibrosis [162]. Because it reflects real-time changes in heart function and remodeling, it can help clinicians assess prognosis, guide short-term treatment decisions, and identify patients at higher risk for arrhythmias or adverse cardiac events [162,163,164]. Soluble urokinase plasminogen activator receptor (suPAR), the circulating form of membrane-bound uPAR, reflects the level of systemic inflammation and immune activity in numerous diseases [165]. Elevated suPAR levels are associated with the presence, severity, and prognosis of various CVDs, including coronary artery disease, MI, HF, AVS, pulmonary hypertension, and microvascular dysfunction, highlighting its potential as a valuable biomarker for risk stratification in inflammation-driven cardiac pathology, especially when combined with other inflammatory biomarkers, such as CRP [165,166].

As previously mentioned, NLRP3 inflammasome is a key mediator of fibrotic process in a variety of CVDs and tissue injuries. During NLRP3 inflammasome activation and pyroptosis, ASC specks are released. These active inflammasome complexes are resistant to proteases and can be internalized by smooth muscle cells and the endothelium which can cause ECM deposition [167,168]. Increased ASC speck levels have been positively associated with 30-day mortality in patients with cardiogenic shock [169]. Pro-inflammatory, inflammasome derived cytokines, such as IL-1 and IL-18, also contribute to the pathophysiology of cardiac fibrosis. Indeed, cardiac fibroblasts respond strongly to IL-1 and release an array of proinflammatory chemokines and cytokines which enhance MMPs activity and reduce collagen synthesis [169]. Moreover, IL-18 and its naturally circulating binding protein (IL-18BP) have been also linked to the development of myocardial hypertrophy and fibrosis [101,170]. *In vitro* studies indicate that IL-18 drive the proliferation and migration of fibroblast and smooth muscle cells by engaging the JNK and PI3-kinase signaling pathways [101,171]. Of note, activation of IL-18 within the myocardium upon acute β-AR over-activation stimulates cytokine cascades, macrophage infiltration and adverse cardiac remodeling [102]. IL-1 and IL-18 may serve as biomarkers of cardiac fibrosis, but their clinical utility remains unclear. Caspase-1, the most well-established pyroptosis promoter and inducer of IL-1β and IL-18 maturation, is involved in the pathogenesis of various CVDs, including ischemia/reperfusion (I/R) injury, HF caused by pressure overload and arrhythmia. A recent study showed that higher plasma caspase-1 levels were associated with an increased risk of CVD, with this association to be partially mediated by metabolic syndrome [172]. Last, Growth differentiation factor 15 (GDF-15) is a member of the TGF-β cytokine superfamily, with its elevated levels to be associated with adverse outcomes in patients with HFpEF. While GDF-15 has been emerged as an overall biomarker of cardiac dysfunction, its involvement in the fibrotic process seen in HFpEF remain less clear [173].

6.2 Imaging

Myocardial inflammation and fibrosis adversely affect the prognosis of patients with CVD. Early detection of these pathological processes is therefore essential in order to personalized treatment and predict disease progression and mortality. In line with this, current imaging modalities provide valuable tools for the detecting these changes early.

Commonly used echocardiography cannot directly detect cardiac fibrosis, but can evaluate its consequences. Advanced echocardiographic methods, such as tissue strain, have recently been validated and shown to correlate with the severity of cardiac fibrosis, adding prognostic insights [174]. Cardiac computed tomography (CT) provides accurate anatomical and functional analysis of the cardiac chambers and when used with a protocol for delayed enhancement, CT is also able to detect fibrotic areas in the myocardium [175,176]. Due to the excellent spatial resolution CT is now considered the most reliable technique for EAT quantification [177]. Studies using CT-based EAT measurements show that greater EAT thickness and volume independently predicts major adverse cardiovascular events (MACEs) [178].

Cardiac magnetic resonance (CMR) imaging is the most robust and extensively validated modality for assessing myocardial fibrosis, as it offers both diagnostic precision and prognostic value [179]. Late gadolinium enhancement (LGE) remains central for detecting fibrotic regions as gadolinium accumulates in areas of interstitial expansion which are caused by edema and/or infiltration [180]. Quantitative tissue characterization techniques, particularly T1 mapping and ECV measurement, provide sensitive markers of diffuse or interstitial fibrosis that may not be visible with conventional imaging [174,181]. T1 mapping, T2 mapping, and ECV have been described as reliable techniques for measuring both focal and diffuse edema [182].

Positron emission tomography (PET) provides an alternative, efficient approach to assess cardiac fibrosis by detecting activated fibroblasts rather than established structural changes [174]. Although nuclear imaging has traditionally focused on viability through reduced fluorodeoxyglucose (FDG) uptake, newer tracers such as 68Ga-labeled fibroblast activating protein inhibitors (68Ga-FAPI) enable direct visualization of activated myofibroblasts, offering a dynamic assessment of ongoing fibrotic activity [183,184]. FAPI imaging has gained substantial relevance

in CVD as it demonstrates utility in MI, HFpEF, non-ischemic cardiomyopathy, AVS, atherosclerosis, myocarditis, and AF, although it was originally developed for oncological surveillance [174].

A combination of imaging techniques holds significant potential. In particular, integrating data from FAPI-PET, which captures active remodeling, with magnetic resonance imaging (MRI)-based fibrosis quantification may offer a more tailored approach for improved monitoring and treatment.

7. Therapeutic Landscapes

7.1 NLRP3 Inhibitors

Several preclinical studies of inflammatory disease have been conducted to explore the efficacy of NLRP3-specific inhibitors, however only few have demonstrated promising results in the context of CVD.

A potential strategy to attenuate the activation of NLRP3 inflammasome is by suppressing toll-like receptor (TLR)-mediated upregulation. Agents that inhibit interleukin-1 receptor–associated kinase 4 (IRAK4), a central component of TLR-driven NF-κB signaling, are being developed and could indirectly mitigate NLRP3 inflammasome activation. Nevertheless, their lack of specificity raises concerns about broad immunosuppressive effects [185].

MCC950 acts as a selective inhibitor of NLRP3 inflammasome by targeting its NACHT domain [186]. MCC950 has demonstrated cardioprotective effects in preclinical models. These included reductions in atherosclerotic burden, infarct size, HF-related fibrosis and hypertrophy. However, these findings still require confirmation in clinical trials [187,188,189]. Another compound targeting the NACHT domain of NLRP3 is tranilast, also shown to have favorable effects on cardiac fibrosis and atherosclerosis [190,191]. Furthermore, oridonin suppresses NLRP3 inflammasome activation by creating a covalent bond with cysteine (Cys)279 in the NACHT domain [192]. Oridonin has proven to reduce ROS production and prevent cardiac hypertrophy by inducing P21-related autophagic lysosomal degradation [193]. CY-09, a novel NLRP3 inhibitor, directly targets the ATP-binding site of the NACHT domain to prevent NLRP3 assembly and adenosine triphosphatase (ATPase) activity. In preclinical models of diabetic ischemic stroke, CY-09 mitigates disease manifestations and prevents possible cardiac dysfunction [194].

NT-0796 is an oral, brain-penetrant NLRP3 inhibitor potentially useful in metabolic, neurodegenerative, and CVDs. Preclinical studies show it can reverse diet-induced obesity and inflammation, achieving weight loss similar to semaglutide and achieving enhancing effects when combined with it, while also reducing post-treatment weight regain [195,196]. NT-0796 is in Phase 2 trials for obesity: as monotherapy in RESOLVE-1 (NCT07055516) and with GLP-1 receptor agonists in RESOLVE-2 (NCT07220629).

Among compounds that inhibit NF-κB activation, BAY 11-7082 has demonstrated notable cardiovascular benefits. In preclinical I/R models, treatment with BAY 11-7082 reduced infarct size, myocardial apoptosis, fibrosis, and inflammatory responses, preserved cardiac function, and decreased pyroptosis [197,198,199].

7.2 ASC and Caspase-1

ASC acts as a key adaptor protein of the NLRP3 inflammasome, as it coordinates the recruitment and activation of caspase-1, making it an appealing, though challenging, therapeutic target [200]. OLT1177 is an oral beta-sulfonyl nitrile molecule that blocks ASC oligomerization without effecting AIM2 and NLRC4 inflammasomes [201]. In a murine myocardial I/R injury model, OLT1177 has been shown to confer cardioprotective properties by reducing infarct size and preserving contractile function [202]. Caspase-1 inhibition has also been achieved using peptidomimetic compounds such as VX-765 and VX-740, which are converted *in vivo* to their active metabolites (VRT-043198 and VRT-18858, respectively) by plasma esterases [203,204]. VX-765 has been shown to reduce infarct size in a mouse I/R injury model, and to prevent atherogenesis [205,206]. However, development of caspase-1 inhibitors was discontinued due to hepatotoxicity concerns and enhanced infection risk [207].

7.3 Targeting IL-1β

IL-1β is a proinflammatory cytokine generated downstream of NLRP3 inflammasome activation and poses as a therapeutic target for the management of NLRP3-mediated disorders [190]. However, blocking IL-1β signaling through its receptors (IL-1R) lacks specificity, and many of these receptors are not even linked to inflammasomes. Clinically available agents in this class include anakinra, a recombinant human IL-1R antagonist, canakinumab, a long-lasting monoclonal antibody that directly inhibits the action of IL-1β, and rilonacept, a fusion protein active against both IL-1α and IL-1β [208].

Anakinra has been widely investigated as a potential therapeutic option across a broad range of CVDs. In HFpEF, anakinra has been shown to reduce the systemic inflammatory response, as evidenced by the reduction of CRP, while producing mixed effects on cardiopulmonary parameters [209,210]. In the field of HFrEF, anakinra reduced CRP and N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels and improved exercise tolerance [211]. In the setting of non–ST-segment-elevation MI (NSTEMI), the MRC-ILA Heart Study demonstrated that although anakinra transiently reduced CRP and IL-6 levels compared with placebo, it was paradoxically associated with higher rates of MACEs at one year [212]. Conversely, in the VCU-ART3 trial, which enrolled patients with ST-segment-elevation MI (STEMI), anakinra led to a reduction in the incidence of death or new-onset HF, and of death or

hospitalization for HF, relative to placebo [213]. Its therapeutic potential in arrhythmias remains unexplored [2].

Canakinumab is an approved therapy for certain inflammasome-driven diseases such as rheumatoid arthritis, acute gout, and atherosclerosis [214,215]. The CANTOS study showed that inhibition of IL-1β with canakinumab significantly reduced the risk of CV events in patients with a history of MI and elevated levels of CRP. This IL-1β inhibitor in this study decreased the levels of CRP and IL-6 and increased the levels of total cholesterol and triglycerides. These findings provided the first robust clinical evidence that suppressing inflammation can improve CV outcomes independently of lipid lowering [214]. Furthermore, findings from a small prespecified secondary analysis of the CANTOS trial indicated that canakinumab, when used at a dose of 150 mg, improved left ventricular EF (LVEF) and exercise capacity in patients with HFrEF [216]. Despite its therapeutic value, the use of canakinumab is limited by adverse effects, such as injection-site reactions and a modest rise in fatal infections [215,217].

Rilonacept has been investigated in early studies for potential CV properties, though clinical evidence remains limited [30]. A small pilot trial in atherosclerosis and more recent data in recurrent pericarditis suggest potential benefits in reducing inflammation, but robust trials in broader CV populations are still lacking [218,219].

7.4 Gasdermin D Inhibitors

The inhibition of GSDMD-mediated pyroptosis represents a logical therapeutic target in our effort to mitigate inflammasome-driven pathology. At present, several GSDMD inhibitors are being investigating, aiming to improve outcomes in patients with CV and other inflammatory diseases [220]. Among these agents, disulfiram has been shown to reduce the development of aortic root atherosclerotic lesions in hyperlipidemic mouse models. This was achieved by promoting autophagy, enhancing efferocytosis, and modulating the gut microbiota [221]. In addition, disulfiram has shown potential in the treatment of cardiometabolic diseases, as preclinical models demonstrate anti-obesity effects and improvements in steatohepatitis [222,223].

GI-Y1 is a newly identified small-molecule selective inhibitor of GSDMD. A recent preclinical study showed that GI-Y1 prevents cardiomyocyte pyroptosis, exerts cardioprotective effects in myocardial I/R injury, and attenuates adverse cardiac remodeling, offering a potential therapeutic strategy for GSDMD-driven cardiac diseases [224].

7.5 Upstream Metabolic Modulators

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) were initially introduced as antihyperglycemic drugs and now are widely recognized as significant cardioprotective and renoprotective agents due to their pleiotropic effects. SGLT2is have anti-inflammatory, antifibrotic, and antioxidative actions, many of which converge on suppressing the NLRP3 inflammasome [225].

SGLT2is reduce inflammation through multiple interconnected mechanisms. These agents reduce the production of mtROS, which are well-known mediators of NLRP3 activation. They also promote a metabolic shift toward ketone utilization, which can directly inhibit inflammasome assembly [226]. Reduced levels of IL-1β and IL-6 have been observed in cardiac tissue and circulation [227]. SGLT2is enhance autophagy and improve intracellular Na^+ and Ca^{2+} balance stabilizing the mitochondrial function and mitigating downstream inflammatory signaling. Through these combined actions, SGLT2is effectively modulate cardiac inflammation and fibrosis that leads to favorable impacts on HF outcomes and arrhythmias [2,228].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are used in the management of type 2 diabetes, obesity, and CVD, due to their potent metabolic effects and broad cardio–renal–metabolic benefits [229]. GLP-1RAs exhibit significant anti-inflammatory and antifibrotic actions that improve cardiac energy utilization, and reduce oxidative stress [230,231,232,233]. Part of their anti-inflammatory activity arises from the suppression of the NLRP3 inflammasome, limiting NLRP3-related infiltration in atherosclerotic tissue. Mechanistically, they inhibit NLRP3 activation by enhancing mitophagy, lowering mtROS production, and shifting macrophage polarization from a pro-inflammatory M1 state toward an anti-inflammatory M2 profile [234].

Statins inhibit the activation of the NLRP3 inflammasome by blocking the mevalonate/isoprenoid pathway. This prevents the prenylation of small GTPases, which in turn mitigates the transcription of IL-1β and IL-18, which is mediated by NF-κB, and lowers ROS generation. Together, these effects suppress inflammasome assembly and downstream cytokine activation [235]. Nonetheless, emerging data suggest that in certain cellular or metabolic contexts, statins may paradoxically enhance NLRP3 inflammasome activity. This unintended activation has been associated with impaired insulin signaling in adipose tissue and macrophages, which may contribute to the small but consistent increase in new-onset diabetes, as well as with the development of statin-associated myopathy [236,237].

Colchicine is a plant-based alkaloid traditionally used for gout and pericarditis and is a promising therapeutic option for atherosclerotic CV disease and AF. Its anti-inflammatory effect is largely attributed to its nonselective inhibition of the NLRP3 inflammasome [30]. A recent meta-analysis showed that in patients with prior coronary disease or stroke, colchicine provides a 12% reduction in the composite outcome of CV death, MI, or stroke, in the setting of secondary prevention [238]. In AF, colchicine prevents adverse atrial remodeling because it inhibits profibrotic and proinflammatory pathways [2].

Mitochondria-targeted antioxidants, such as MitoTEMPO and MitoQ, confer cardioprotective effects by

Table 2. Summary of promising drugs and investigational compounds for the treatment of inflammasome-driven cardiac fibrosis.

Compound	Target	Proposed mechanism of action	Type of studies	Major effects
Anti-inflammatory compounds				
Anakinra	IL-1β	A recombinant human IL-1R antagonist.	Clinical (Phase III validated)	Lowers CRP and IL-6 across CVDs but shows mixed efficacy in HFpEF, improves inflammatory markers and exercise capacity in HFrEF, and yields divergent post-MI outcomes (increased MACEs in NSTEMI, reduced mortality/HF in STEMI); optimal dosing and timing remain to be defined [209,210,211,212,213].
Canakinumab	IL-1β	A monoclonal IL-1β neutralising antibody.	Clinical (Phase III validated)	Reduces CV events in post-MI patients with elevated inflammation and lowers CRP/IL-6 independent of lipid levels; potential benefits in HFrEF, but clinical use is limited by infection risk and injection reactions [214,216].
Rilonacept	IL-1α, IL-1β	Fusion protein active against both IL-1α and IL-1β.	Clinical (Phase III validated)	Shows potential anti-inflammatory benefits in atherosclerosis and recurrent pericarditis, but evidence in broader cardiovascular populations remains limited [218,219].
MCC950	NLRP3 inflammasome	Selective inhibitor of the NLRP3 inflammasome by targeting its NACHT domain.	Preclinical	Demonstrates broad cardioprotection in preclinical models, reducing atherosclerosis, infarct size, and heart-failure–associated fibrosis. Improves cardiac metabolism [187,188,189].
Tranilast	NLRP3 inflammasome	Inhibitor of the NLRP3 inflammasome by targeting its NACHT domain.	Preclinical	Improves cardiac fibrosis and atherosclerosis [190,191].
Oridonin	NLRP3 inflammasome	Creates a covalent bond with cysteine (Cys)279 in the NACHT domain.	Preclinical	Reduces ROS and prevents cardiac hypertrophy via p21-linked autophagic–lysosomal pathways [192,193].
CY-09	NLRP3 inflammasome	Inhibits NLRP3 oligomerization by binding to ATPase of the NACHT domain.	Preclinical	Improves outcomes in diabetic ischemic stroke models and limits secondary cardiac dysfunction [194].
NT-0796	NLRP3 inflammasome	Brain-penetrant NLRP3 inhibitor.	Preclinical	Reverses diet-induced obesity and inflammation in preclinical models, producing weight loss comparable to semaglutide; shows additive efficacy in combination with semaglutide and attenuates post-treatment weight regain [195,196].
BAY 11-7082	NF-κB	Prevents the nuclear translocation of NF-κB at the priming phase.	Preclinical	Reduces infarct size, apoptosis, fibrosis, and pyroptosis in preclinical models; off-target effects limit clinical applicability [197,198,199].
OLT1177	ASC	A beta-sulfonyl nitrile molecule that blocks ASC oligomerization.	Preclinical	Provides cardioprotection in myocardial I/R models by limiting infarct size and preserving contractile performance [202].
VX-765 and VX-740	Caspase-1	Peptidomimetic compounds that inhibit caspase-1.	Preclinical	Reduces infarct size and atherogenesis [205,206].
Disulfiram	GSDMD	Inhibitor of GSDMD-mediated pyroptosis.	Preclinical	Reduces atherosclerosis through autophagy, enhanced efferocytosis, and gut microbiota modulation, with additional cardiometabolic benefits [221,222,223].
GI-Y1	GSDMD	Selective inhibitor of GSDMD.	Preclinical	Prevents cardiomyocyte pyroptosis and limits myocardial I/R injury and adverse remodeling via inhibition of GSDMD-N pore formation; early-stage experimental compound [224].
Anti-fibrotic compounds				
Finerenone	TGF-β, Galectin-3, CTGF	Inhibit profibrotic signaling and prevent atrial remodeling.	Clinical (Phase III validated)	Reduces cardiac fibrosis, improves perfusion, and alleviates diastolic dysfunction in HFpEF; also lowers the risk of new-onset atrial fibrillation across cardio–renal–metabolic conditions [242].

Table 2. Continued.

Compound	Target	Proposed mechanism of action	Type of studies	Major effects
MCP	Galectin-3	Oligosaccharide which inhibits Galectin-3 by binding its carbohydrate recognition domain.	Preclinical	Reduces cardiac and renal fibrosis, improves cardio-renal function, and limits myocardial fibrosis in hyperaldosteronism; enhances anti-inflammatory and antifibrotic effects when combined with MRAs; lowers atherosclerotic plaque formation [245,246,247].
SNT-5382	LOXL2	LOXL2 inhibitor.	Preclinical	Reduces fibrosis and improves cardiac performance in MI models [249].
Mitochondria-targeted antioxidants				
MitoQ	Mitochondria	Antioxidant.	Clinical	Preserves mitochondrial function, normalizes electrical activity, and reduces atrial fibrosis; in hypertensive patients, combined with endurance training, improves cardiac function and lowers blood pressure via ROS reduction and modulation of microRNAs [2,229].
Mito-TEMPO	Mitochondria	Antioxidant.	Preclinical	Mitigates 5-fluorouracil–induced cardiotoxicity and reduces spontaneous and sustained arrhythmic episodes [2,240].
Upstream metabolic modulators				
SGLT2 inhibitors	SGLT2 protein/NLRP3 inflammasome	Exert anti-inflammatory, antifibrotic, antioxidant effect; preserves mitochondrial function, Ca^{2+} handling, and metabolic efficiency.	Clinical (Phase III validated)	Supported by robust Phase III evidence, these agents reduce cardiac inflammation and fibrosis by lowering mitochondrial ROS, enhancing ketone metabolism and autophagy, improving Na^{+}/Ca^{2+} handling, and decreasing IL-1β and IL-6, conferring benefits in HF and arrhythmias [226,227,228].
GLP-1 RAs	Glucagon-like peptide-1 receptor/NLRP3 inflammasome	Exert antifibrotic, anti-inflammatory, antioxidant, and metabolic modulation; improve mitochondrial function.	Clinical (Phase III validated)	Improve cardiac energy metabolism, and reduce oxidative stress; suppress NLRP3 inflammasome, limit macrophage-driven inflammation and foam cell formation, enhance mitophagy, lower mitochondrial ROS, and promote M2 macrophage polarization [230,231,232,233,234].
Statins	HMG-CoA/NLRP3 inflammasome	Inhibit the activation of the NLRP3 inflammasome by blocking the mevalonate/isoprenoid pathway. Pleiotropic effects.	Clinical (Phase III validated)	Primarily inhibit NLRP3 inflammasome by blocking the mevalonate pathway, reducing IL-1β/IL-18 production and ROS, and suppressing downstream inflammation; however, in certain contexts, they may paradoxically activate NLRP3, potentially impairing insulin signaling and contributing to new-onset diabetes and myopathy [235,236,237].
Colchicine	Chemotaxis/NLRP3 inflammasome	Inhibits β-tubulin polymerization into microtubules.	Clinical (Phase III validated)	Exerts anti-inflammatory effects via nonselective NLRP3 inhibition; reduces CV death, MI, or stroke by 12% in secondary prevention [238].

CRP, C-reactive protein; CVDs, cardiovascular diseases; HFrEF, HF with reduced ejection fraction; MACEs, major adverse cardiovascular events; NSTEMI, non–ST-segment-elevation MI; HF, heart failure; STEMI, ST-segment-elevation MI; CV, cardiovascular; NACHT, nucleotide-binding domain, Apaf-1, CIITA, HET-E, TP1; ASC, apoptosis-associated speck-like protein containing a CARD; I/R, ischemia/reperfusion; CTGF, connective tissue growth factor; MCP, modified citrus pectin; MRAs, mineralocorticoid receptor antagonists; LOXL2, lysyl oxidase- like 2; SGLT2, sodium–glucose cotransporter 2; GLP-1 Ras, glucagon-like peptide-1 receptor agonists; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

reducing mtROS, a key trigger for NLRP3 inflammasome activation. In preclinical models of AF, MitoTEMPO decreased spontaneous and sustained arrhythmic episodes, and MitoQ preserved mitochondrial function, normalized electrical activity, and limited atrial fibrosis [2]. In patients with hypertension, the combination of MitoQ and endurance training enhances cardiac function and lowers blood pressure, partly through modulation of miRNAs, such as miRNA 126 and miRNA 27a, and reduction of ROS [239]. In addition, Mito-TEMPO effectively alleviates the consequences of 5-fluorouracil–induced cardiotoxicity [240].

7.6 Antifibrotics

Currently, the primary therapeutic approach to managing cardiac fibrosis is based on inhibiting the RAAS with drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs). RAAS interacts with various pro-fibrotic signaling pathways. These involve factors such as TGF-β1, TNFα, PDGF, IL-6 and IL-13 which promote the proliferative phase of tissue repair and fibrosis [241]. In a preclinical model of HF-pEF, finerenone, a non-steroidal MRA with a more favorable benefit-risk profile compared to steroidal MRAs, was shown to reduce cardiac fibrosis, improve cardiac perfusion, and attenuate diastolic dysfunction. It has been also shown to reduce the risk of new-onset AF across the cardio–renal–metabolic spectrum [242].

The inhibition of TGF-β represents a logical strategy to mitigate cardiac fibrosis. However, translating this approach into clinical practice has been challenging because TGF-β also plays essential roles in tissue homeostasis [243]. Several therapeutic approaches have been investigated, however its broad biological functions and related safety concerns have made the development of anti–TGF-β therapies difficult. These include blocking the activation of latent TGF-β by integrins or proteases, directly inhibiting TGF-β with neutralizing antibodies or soluble TGF-β type II receptor, inhibiting ALK5, and targeting downstream mediators such as SMAD3. Each of these strategies carries its own risks. Direct inhibition may lead to excessive inflammation, whereas disrupting downstream pathways can impair tissue repair and structural integrity. Targeting regulators of latent TGF-β activation may offer a more selective and potentially safer method to attenuate TGF-β–driven fibrosis, as these mechanisms tend to be tissue- and context-specific [243].

Gal-3 inhibitors and antagonists, including small-molecule carbohydrates and larger natural compounds, are currently under development and being evaluated for clinical use. Modified citrus pectin (MCP), an oligosaccharide from fruit and vegetable peels, inhibits Gal-3 by binding its carbohydrate recognition domain [244]. In rodent models, MCP was shown to improve cardio-renal function by reducing cardiac and renal fibrosis [245]. Combined with MRAs, MCP enhance anti-inflammatory and antifibrotic effects [246]. Additionally, MCP decreased atherosclerotic plaque formation in high-cholesterol diet–fed ApoE mice, highlighting its potential in CVD management [247].

In a rat model of volume overload, lysyl oxidase (LOX) inhibition prevented increases in LV wall stress, attenuated ventricular hypertrophy, blocked accumulation of fibrotic proteins (collagens, MMPs, TIMPs), and preserved cardiac function [248]. Similarly, preclinical studies with the its isoform LOX-like 2 (LOXL2) inhibitor SNT-5382 in a MI model demonstrated reduced fibrosis and improved cardiac performance [249]. These findings highlight LOX and LOXL2 as key mediators of ECM remodeling and fibrosis, supporting their potential as therapeutic targets to prevent maladaptive cardiac remodeling.

Pharmacological or biological interventions that target inflammasome activation around the time of ablation may serve as promising adjunct therapies to minimize recurrence and enhance long-term procedural success. The acute tissue damage caused by catheter ablation generates a localized inflammatory milieu that can promote both structural and electrical remodeling of the atria, increasing the risk of AF recurrence [250]. By inhibiting NLRP3 during this critical window, the inflammatory cascade could potentially be limited leading to stabilization of the atrial substrate.

Table 2 (Ref. [2,187,188,189,190,191,192,193,194,195,196,197,198,199,202,205,206,209,210,211,212,213,214,216,218,219,221,222,223,224,226,227,228,229,230,231,232,233,234,235,236,237,238,240,242,245,246,247,249]) provides an overview of pharmacological agents that modulate inflammasome signaling pathways implicated in cardiac fibrosis. Fig. 2 summarizes the principal pharmacological strategies targeting the NLRP3 inflammasome and its downstream signaling pathways implicated in cardiac inflammation, pyroptosis, and fibrosis.

8. Trial Design and Endpoints

The design of robust clinical trials that aim to evaluate this crosstalk between activated inflammasomes and fibrosis and its potential reversal requires a methodical approach that reflects the complexity of the underlying pathophysiology and the heterogeneity of patient populations across CVDs.

The first step would be to create a clear definition of the study population. Patients differ widely in the degree of inflammatory activation and maladaptive ECM remodeling, and therefore it is essential to enrich study populations with individuals in whom the inflammasome–fibrosis axis is demonstrably active. We can use several complementary tools to achieve this. Many biomarkers mentioned in this review can identify patients with aberrant inflammasome activation [161,162,165,169,172,173]. Imaging can also provide additional information. For example, the status of EAT when assessed by CT or MRI, offers insight into

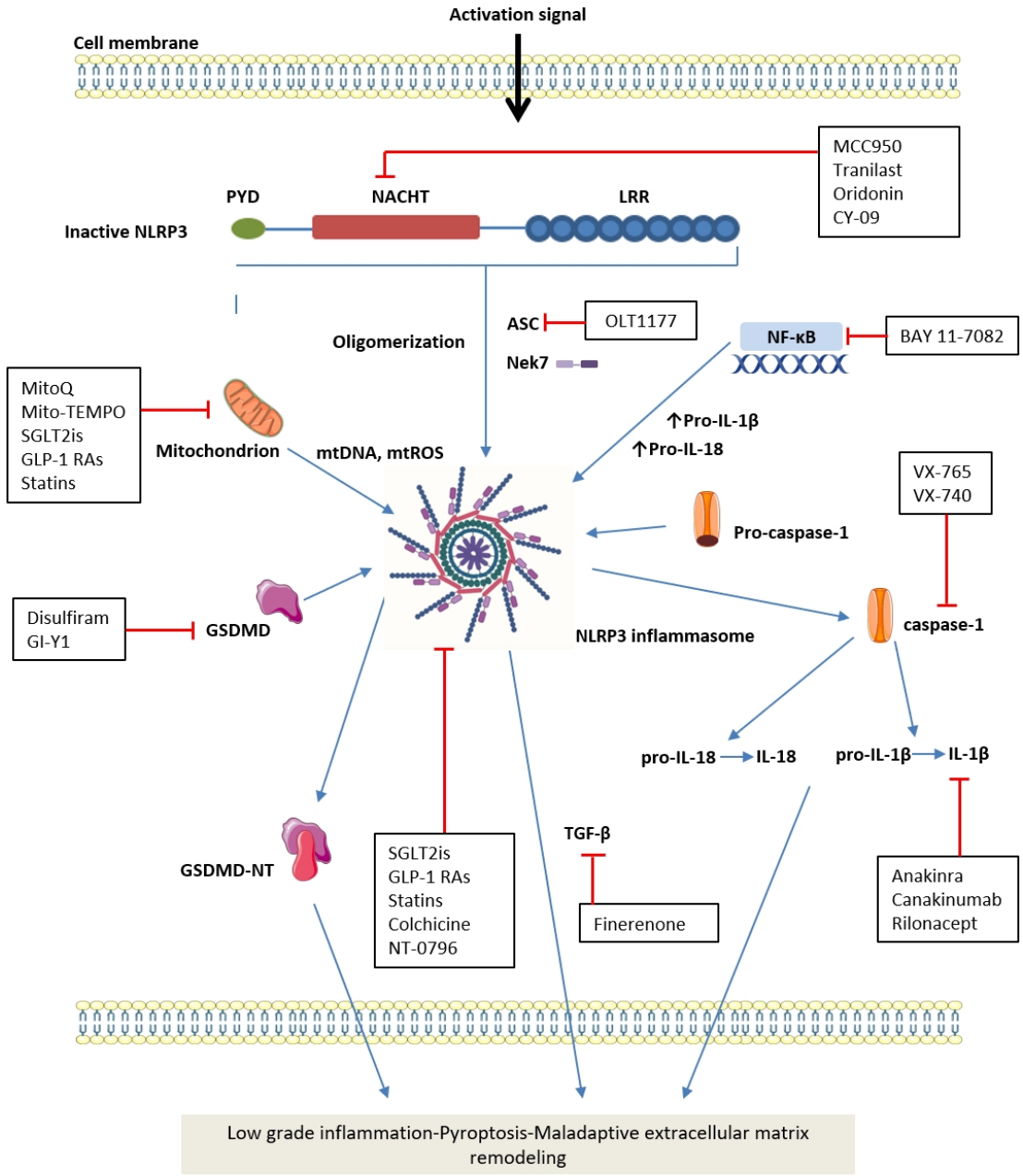

Fig. 2. Schematic overview of pharmacological compounds targeting the NLRP3 inflammasome and its downstream signaling pathways involved in inflammation, pyroptosis, and cardiac fibrosis. PYD, pyrin domain; NACHT, nucleotide-binding domain, Apaf-1, CIITA, HET-E, TP1; LRR, leucine-rich repeat; ASC, apoptosis-associated speck-like protein containing a CARD; NF-κB, nuclear factor-κB; Nek7, NIMA-related kinase 7; SGLT2is, sodium-glucose cotransporter 2 inhibitors; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; mtDNA, mitochondrial deoxyribonucleic acid; mtROS, mitochondrial reactive oxygen species; pro-IL-1β, pro-interleukin-1β; pro-IL-18, pro-interleukin-18; IL-1β, interleukin-1β; IL-18, interleukin-18; GSDMD, gasdermin D; GSDMD-NT, gasdermin D N-terminal fragment; NLRP3, NOD-like receptor pyrin domain-containing protein 3; TGF-β, transforming growth factor-β.

local inflammatory activity in both the atria and ventricles [177]. Combining these parameters with clinical factors related to cardiometabolic stress, can achieve a more precise selection of candidates and increase the likelihood of successful inflammasomes modulated therapies.

Despite these enrichment strategies, future trials should incorporate appropriate power calculations and patient stratification to account for disease heterogeneity, particularly in syndromes such as HFpEF and AF, where inflammasome activation may define distinct biological sub-

phenotypes. Adaptive and biomarker-guided trial designs may further optimize patient selection and therapeutic signal detection.

The next significant step for a clinical trial that aims to evaluate the efficacy of an inflammasome inhibitor is to ensure that the chosen mechanistic endpoints can adequately capture alterations in upstream inflammatory signaling and tissue remodeling. Indicators of inflammasome engagement, such as IL-1 and caspase-1 activation, can demonstrate if the intervention attenuates the inflammatory cascade [169,172]. In the same way, markers of fibroblast activation, including gal-3, sST2, and suPAR, can help to determine whether suppression of pyroinflammation translates into favorable effects on fibrogenic activity [160,162,165]. Once again imaging techniques can assist us to objectively identify and quantify myocardial fibrosis [174]. The combination of these endpoints may enhance our ability to identify true biological responses caused by inflammasome-directed therapy.

In the field of arrhythmias, the use of composite endpoints that combine arrhythmia burden with measures of tissue fibrosis can better capture the effects of targeting inflammasome activity. For instance, improvements in the incidence of AF together with reduced fibrosis on CMR may reflect the dual benefits of modulating inflammation on structural and electrical atrial remodeling.

9. Knowledge Gap and Future Directions

Significant progress has been made in understanding the role of inflammasome activation and fibrosis in cardiometabolic diseases and arrhythmias. However, important knowledge gaps persist.

Pyroptosis represents a distinct type of programmed cell death that connects inflammasome activation with maladaptive cardiac fibrosis [6,7]. Increasing data indicate that it significantly contributes to the development and progression of multiple CVDs, with its mechanisms now being progressively defined. Therefore, a key future direction in inflammasome and fibrosis research is standardizing pyroptosis assessment in CVD. To achieve this, precise biomarkers are needed. Among the biomarkers related to pyroptosis, GSDMD seems the most promising, as it may offer greater specificity for CV pathology than upstream cytokines.

There is a critical need for longitudinal coupling of molecular and imaging biomarkers in order to understand how inflammasome activation relates to ECM remodeling. Repeated measurements of blood markers (e.g., ASC specks, IL-1β/IL-18) combined with imaging modalities such as MRI, CT, and PET could be beneficial in disease progression monitoring, leading to identify key points for intervention, and improve endpoints identification for clinical trials.

The use of radiomics and multi-omics for patient selection in the inflammasome–fibrosis field is still largely unexplored. If we combine high-dimensional imaging features with molecular data, it could help us identify distinct inflammasome-high and fibrosis-dominant patient subgroups across various CVDs. Establishing standardized analytic methods, harmonizing imaging protocols, and validating these groups in diverse populations will be essential for precision enrollment and predicting responses to inflammasome-targeted therapies.

Finally, large clinical trials are warranted to evaluate the potential of the numerous promising drugs that have shown efficacy in preclinical studies for the treatment of inflammasome-driven fibrosis in CVD.

10. Conclusion

Inflammasome activation and fibrosis contribute to the development and progression of various CVDs through complex interactions among immune cells, cardiomyocytes, fibroblasts, adipose tissue, and endothelial cells.

Despite significant advances in understanding mechanisms, biomarkers, and imaging, challenges remain in accurately assessing inflammation, quantifying fibrosis, and determining its direct clinical significance. Integrating molecular and imaging biomarkers may improve diagnosis and patient stratification, while therapies aimed at inhibiting inflammasome signaling hold promise for limiting fibrotic progression. We are suggesting that future efforts should focus on precise evaluation and targeting of inflammasome-driven cardiac fibrosis. Large, well-designed clinical trials and reliable tools for fibrosis quantification will be essential to translate these strategies into meaningful clinical benefit.

Abbreviations

NLRP3, NOD-like receptor pyrin domain-containing protein 3; ROS, reactive oxygen species; ATPase, adenosine triphosphatase; NF-κB, nuclear factor-κB; ASC, apoptosis-associated speck-like protein containing a CARD; I/R, ischemia/reperfusion; IL-1β, interleukin-1β; IL-1R, interleukin-1 receptor; CVDs, cardiovascular diseases; CRP, c-reactive protein; IL-6, interleukin-6; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; MACE, major adverse cardiac event; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; CV, cardiovascular disease; LVEF, left ventricular ejection fraction; IL-1α, interleukin-1α; GSDMD, gasdermin D; TGF-β, transforming growth factor-β; CTGF, connective tissue growth factor; MCP, modified citrus pectin; LOXL2, lysyl oxidase- like 2; SGLT2, sodium-glucose cotransporter 2; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; Na^+, sodium; Ca^{2+}, calcium; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IL-18, interleukin-18; EndMT, endothelial to mesenchymal transition; NLRC4, NLR family CARD domain-containing protein 4; AMI, acute myocardial infarction; 15-HETE, 15-hydroxyeicosatetraenoic acid; CFs, cardiac fibrob-

lasts; PI3K-Akt, phosphatidylinositol 3′-kinase (PI3K)-Akt; TNF-α, tumor necrosis factor-α; AS, aortic stenosis; AF, atrial fibrillation.

Author Contributions

KG: Conceptualization, Methodology, Investigation, Visualization, Project administration, Writing—original draft, Writing—review & editing. VL: Investigation, Writing—original draft, Writing—review & editing. APA: Methodology, Investigation, Visualization, Writing—original draft, Writing—review & editing. PT: Investigation, Writing—original draft, Writing—review & editing. PI: Investigation, Writing—review & editing. NK: Investigation, Writing—review & editing. AA: Investigation, Writing—review & editing. AN: Writing—review & editing, Preparation of figures and tables. BF: Writing—review & editing, Preparation of figures and tables. EK: Writing—review & editing, Preparation of figures and tables. NF: Writing—review & editing, Supervision, Preparation of figures and tables. DP: Writing—review & editing, Supervision, Preparation of figures and tables. PK: Conceptualization, Methodology, Investigation, Writing—original draft, Writing—review & editing, Validation, Supervision. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

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