



Understanding inflammatory pathways in cardiovascular diseases: A step toward targeted anti-inflammatory therapies

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Abstract

Inflammation is a key factor in the development of cardiovascular diseases (CVDs), contributing to atherosclerosis, myocardial infarction, and heart failure. This study analyses critical inflammatory pathways in cardiovascular diseases, including the NLRP3 inflammasome, cytokines, and chemokines that regulate the inflammatory response. Recent clinical trials have demonstrated that addressing inflammation can reduce cardiovascular events, with the CANTOS trial validating the concept of IL-1 β suppression, and additional studies indicating the benefits of colchicine in secondary prevention. Novel medicines targeting specific inflammatory pathways, such as NLRP3 inhibitors, IL-6 antagonists, and SGLT2 inhibitors, show promise for cardiovascular protection. Future directions encompass the advancement of precision medicine strategies to identify patients most likely to benefit from anti-inflammatory treatments, achieving a balance between efficacy and safety through selective pathway inhibition, and investigating innovative therapeutic targets, including gene editing and immunomodulatory vaccines. As our comprehension of inflammatory pathways advances, targeted anti-inflammatory medicines may emerge as a fundamental aspect of cardiovascular disease care.

Keywords

Cardiovascular diseases; Chronic inflammation; IL-6 (Interleukin-6); TNF- α (Tumor Necrosis Factor-alpha); NF- κ B pathway; mTOR signaling

Introduction

1. Background on cardiovascular diseases (CVDs)

Cardiovascular diseases (CVDs) remain the primary cause of morbidity and mortality worldwide, accounting for around 17.9 million deaths per year [1, 2]. Even with major advancements in preventative and curative methods, the prevalence of CVDs is still rising worldwide [3]. Conventional risk factors such as hypertension, dyslipidaemia, diabetes mellitus, and smoking account for a significant share of cardiovascular risk [4]. However, these traditional risk factors are absent in about half of individuals with CVDs, indicating the participation of other pathophysiological mechanisms.

Atherosclerosis, the fundamental aetiology of coronary artery disease, cerebrovascular disease, and peripheral arterial disease, entails a multifaceted interaction of lipid deposition, endothelial impairment, and vascular inflammation [5]. Myocardial infarction, caused by the rupture of atherosclerotic plaque and ensuing thrombosis, results in cardiomyocyte necrosis and detrimental ventricular remodelling [6]. Inflammation is a key factor in the development of heart failure, which is characterized by the heart's inability to meet the body's metabolic needs. Myocardial infarction or other cardiac injuries can cause heart failure [7, 8].

2. The role of inflammation in CVD pathogenesis

The discovery of inflammation as a significant factor in cardiovascular pathology marks a paradigm change in our understanding of CVDs [9, 10]. The inflammation hypothesis of atherosclerosis has grown from a theoretical idea to an established treatment framework. Early findings linking infections to atherosclerosis motivated investigations into inflammatory markers as indicators of cardiovascular risk [11]. Further studies have shown that increased concentrations of high-sensitivity C-reactive protein (hs-CRP) independently predict cardiovascular incidents, even in individuals who appear healthy [12]. Both the innate and adaptive immune systems play a role in every phase of cardiovascular disease, ranging from the initial dysfunction of endothelial cells to the formation, development, and rupture of plaques [13]. Innate immune cells, specifically monocytes, macrophages, and neutrophils, initiate and enhance the inflammatory response. Adaptive immune cells, comprising different T cell subsets and B cells, regulate the inflammatory setting and affect disease progression. This persistent, low-grade inflammation increases the risk of atherosclerotic plaque and cardiovascular disease by encouraging endothelial dysfunction, vascular smooth muscle cell proliferation, and extracellular matrix disintegration [14-16].

The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial established conclusive evidence that addressing inflammation, particularly the interleukin-1 β (IL-1 β) pathway, diminishes cardiovascular events irrespective of lipid-lowering effects [17]. This important study confirmed inflammation as a therapeutic target in cardiovascular diseases and facilitated

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the further study of anti-inflammatory strategies in cardiovascular therapy [18].

3. Objectives of the review

This study aims to provide a thorough analysis of inflammatory pathways in cardiovascular disorders, emphasising mechanisms that may serve as prospective therapeutic targets. Specifically, we will:

1. Summarise the principal inflammatory pathways involved in diverse cardiovascular disorders, encompassing the NLRP3 inflammasome, cytokine/chemokine networks, and adaptive immune responses.
2. Assess the clinical evidence on anti-inflammatory therapy in cardiovascular disease, emphasising the positive outcomes and limits of existing strategies.
3. Examine novel targeted medicines that specifically regulate distinct inflammatory pathways, aiming for enhanced efficacy and safety profiles.
4. Address obstacles in the implementation of anti-inflammatory treatments for cardiovascular disease, encompassing patient selection, the equilibrium of efficacy and safety, and the identification of innovative therapeutic targets.

Key inflammatory pathways in cardiovascular diseases

1. Innate immune activation in CVD

NLRP3 inflammasome: Structure and activation

In cardiovascular disorders, the NLRP3 (NOD-like receptor, LRR-, and pyrin domain-containing protein 3) inflammasome has become a key mediator of inflammation [19, 20]. The adapter protein ASC, the effector protein procaspase-1, and the sensor protein NLRP3 make up this multiprotein complex. Upon activation, the NLRP3 oligomerizes and binds to ASC, which in turn recruits procaspase-1, resulting in the activation of caspase-1. The inflammatory response is spread by active caspase-1, which cleaves pro-interleukin-1 β (pro-IL-1 β) and pro-IL-18 into their mature forms [21, 22].

NLRP3 inflammasome activation normally requires two signals: a priming signal that stimulates expression of NLRP3 and pro-IL-1 β through NF- κ B activation, and an activation signal that initiates inflammasome assembly [23, 24]. The activation of pattern recognition receptors by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) is an example of priming signals in cardiovascular disorders. Crystals of cholesterol, reactive oxygen species (ROS) in the mitochondria, and ATP released from dying cells are examples of activation signals [25, 26]. The NLRP3 inflammasome contributes to cardiovascular disease in several ways. IL-1 β and IL-18 accelerate the development of atherosclerosis by promoting endothelial dysfunction, vascular smooth muscle cell proliferation, and the activation of macrophages. Furthermore, inflammasome activation causes pyroptosis, a type of inflammatory cell death that releases cellular contents and exacerbates inflammation [27, 28].

2. Cytokines and chemokines in CVD

IL-1 family cytokines (IL-1 β , IL-18)

Cardiovascular inflammation is heavily influenced by the IL-1 family of cytokines, particularly IL-1 β and IL-18. Endothelial activation, adhesion molecule upregulation, vascular smooth muscle cell proliferation, and the synthesis of additional pro-inflammatory cytokines are all induced by IL-1 β [10]. By promoting the recruitment of macrophages, the generation of foam cells, and the synthesis of matrix metalloproteinase, IL-1 β plays a role in the development and destabilisation of plaque in atherosclerosis. IL-1 β worsens tissue damage after myocardial infarction and has a role in the development of heart failure and unfavourable ventricular remodelling [29]. Another inflammasome-dependent cytokine, IL-18, primarily promotes a Th1-dominant immune response that facilitates the progression of atherosclerosis by stimulating T cells and natural killer cells to produce interferon-gamma (IFN- γ). Furthermore, IL-18 promotes plaque instability and cardiovascular problems by upregulating the expression of adhesion molecules, matrix metalloproteinases, and pro-inflammatory cytokines [30].

IL-6 and TNF- α signaling

In cardiovascular disorders, TNF- α and IL-6 are important downstream mediators of the inflammatory cascade [31]. C-reactive protein (CRP) and other acute-phase proteins are produced when IL-6 activates the JAK-STAT pathway by sending signals through the IL-6 receptor complex [32]. Furthermore, IL-6 directly contributes to the advancement of atherosclerosis by encouraging endothelial dysfunction, vascular smooth muscle cell proliferation, and macrophage activation [33]. TNF- α signals trigger mitogen-activated protein kinase (MAPK) and NF- κ B pathways via TNF receptor 1 (TNFR1) and TNFR2. TNF- α facilitates the onset and progression of atherosclerosis in cardiovascular disorders by promoting arterial permeability, leukocyte recruitment, and endothelial activation. TNF- α promotes the progression of heart failure after myocardial infarction by causing cardiomyocyte death, matrix degradation, and unfavourable ventricular remodelling [34, 35].

Chemokines and leukocyte recruitment

Chemokines create concentration gradients that direct cell migration, which helps to coordinate leukocyte trafficking in cardiovascular disorders [36]. A crucial stage in the development of atherosclerosis is the migration of monocytes to the arterial wall, which is facilitated by the CC chemokine ligand 2 (CCL2), also referred to as monocyte chemoattractant protein-1 (MCP-1). Atherosclerosis is significantly decreased in animal models when CCL2 or its receptor, CCR2, is genetically deleted or pharmacologically inhibited. The chemokines CCL5 (RANTES), CXCL1, and CX3CL1 (fractalkine) are also associated with cardiovascular disorders [37, 38]. They attract different leukocyte subsets to areas of vascular inflammation. Together with adhesion molecules, these chemokines work in concert to enable leukocytes to be sequentially captured, rolled, firmly adhered to, and transmigrated across the endothelium [39].

Table 1 - Clinical Trials Summary: CANTOS, COLCOT, and LoDoCo2 with Statistical Results.

Trial Name	Target/Intervention	Study Population	Primary Endpoint	Key Findings	Statistical Results
CANTOS	Canakinumab (IL-1 β inhibitor)	Post-MI patients with elevated hs-CRP (>2 mg/L)	MACE (CV death, MI, stroke)	Reduced MACE independent of lipid levels; no LDL-C change; $\uparrow$ infection risk	HR = 0.85; 95% CI: 0.74–0.98; p = 0.021
COLCOT	Low-dose Colchicine (0.5 mg/day)	Patients within 30 days post-MI	Composite CV death, cardiac arrest, MI, stroke, angina, hospitalization	23% relative risk reduction in the primary endpoint	HR = 0.77; 95% CI: 0.61–0.96; p = 0.02
LoDoCo2	Low-dose Colchicine (0.5 mg/day)	Stable coronary artery disease patients	Composite CV death, MI, stroke, or ischemia-driven revascularization	31% relative risk reduction in the primary endpoint	HR = 0.69; 95% CI: 0.57–0.83; p < 0.001

3. Adaptive immunity in CVD

T cell subsets and their roles

T lymphocytes, particularly CD4⁺ helper T cells, regulate cardiovascular inflammation by producing cytokines and interacting with other cells [40]. IFN- γ -producing Th1 cells typically exacerbate atherosclerosis by enhancing antigen presentation, promoting pro-inflammatory cytokine production, and stimulating macrophage activation. On the other hand, regulatory T cells (Tregs) directly decrease effector T cell responses and produce anti-inflammatory cytokines (IL-10, TGF- β) to have atheroprotective effects [41]. Th17 cells have intricate and context-dependent functions in cardiovascular disorders and are distinguished by their production of IL-17. By directly cytotoxically attacking cells that express particular antigens and by generating pro-inflammatory cytokines, CD8⁺ cytotoxic T cells contribute to cardiovascular inflammation [42, 43].

B cells and antibody responses

By presenting antigens, secreting cytokines, and producing antibodies, B lymphocytes contribute to cardiovascular disease [44]. B2 cells typically cause atherosclerosis by presenting antigens to T cells, secreting pro-inflammatory cytokines, and producing pathogenic antibodies against changed lipoproteins and other antigens [45]. On the other hand, B1 cells, and specifically the B1a subset, produce natural IgM antibodies that aid in the removal of changed lipoproteins and apoptotic cells, exhibiting atheroprotective properties [46, 47]. Furthermore, regulatory B cells (Bregs) reduce inflammation by directly modulating T cell responses and producing the anti-inflammatory cytokine IL-10.

4. Inflammatory mechanisms in specific CVDs

Atherosclerosis: From initiation to plaque rupture

Endothelial dysfunction causes atherosclerosis. The increased production of chemokines and adhesion molecules resulting from endothelial activation facilitates the attraction of monocytes to the subendothelial region. Monocytes develop into macrophages inside the artery wall, which then internalise modified lipoproteins via scavenger receptors to produce foam cells [9]. Plaque formation and remodelling are the result of a complex interaction between immune cells, vascular smooth muscle cells, and extracellular matrix components as atherosclerosis progresses. Plaque instability is

exacerbated by the production of matrix-degrading enzymes, reactive oxygen species, and pro-inflammatory cytokines by macrophages within the plaque [48]. The fibrous cap covering the lipid-rich necrotic core weakens and fractures, leading to plaque rupture —the initial event in the majority of acute coronary syndromes. Collagen and other extracellular matrix components are broken down by matrix metalloproteinases produced by inflammatory cells, especially macrophages, which increases plaque susceptibility [49].

Myocardial infarction: Inflammatory response to cardiac injury

A strong inflammatory response is triggered by myocardial infarction and progresses through different time phases. Necrotic cardiomyocytes emit DAMPs during the acute phase, which triggers the production of pro-inflammatory cytokines and the recruitment of neutrophils by activating pattern recognition receptors on native cardiac cells and invading leukocytes [50]. In addition to causing tissue damage, neutrophils release neutrophil extracellular traps (NETs), reactive oxygen species, and proteolytic enzymes. Monocytes and macrophages take the role of neutrophils as the predominant leukocyte population as the inflammatory response worsens, with various subsets of macrophages coordinating various elements of heart repair [51]. Active resolution of inflammation is necessary for the heart repair process to move from the inflammatory to the proliferative phase. Negative ventricular remodelling, poor heart repair, and ongoing inflammatory activation can result from an inability to resolve inflammation [52].

Heart failure: Inflammation in HFrEF vs. HFpEF

Heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) are two distinct clinical syndromes that share similar inflammatory processes but exhibit different behaviors. Inflammation plays a role in the pathophysiology of HFrEF by directly affecting the survival and function of cardiomyocytes and by encouraging unfavourable ventricular remodelling. Pro-inflammatory cytokines decrease contractile performance by causing oxidative stress, promoting cardiomyocyte death, and impairing calcium handling [53, 54]. On the other hand, coronary microvascular inflammation is the focal point of a unique inflammatory paradigm in HFpEF [55]. Common comorbidities in individuals with HFpEF include systemic inflammation that affects

NLRP3 Inflammasome Activation in Cardiovascular Disease

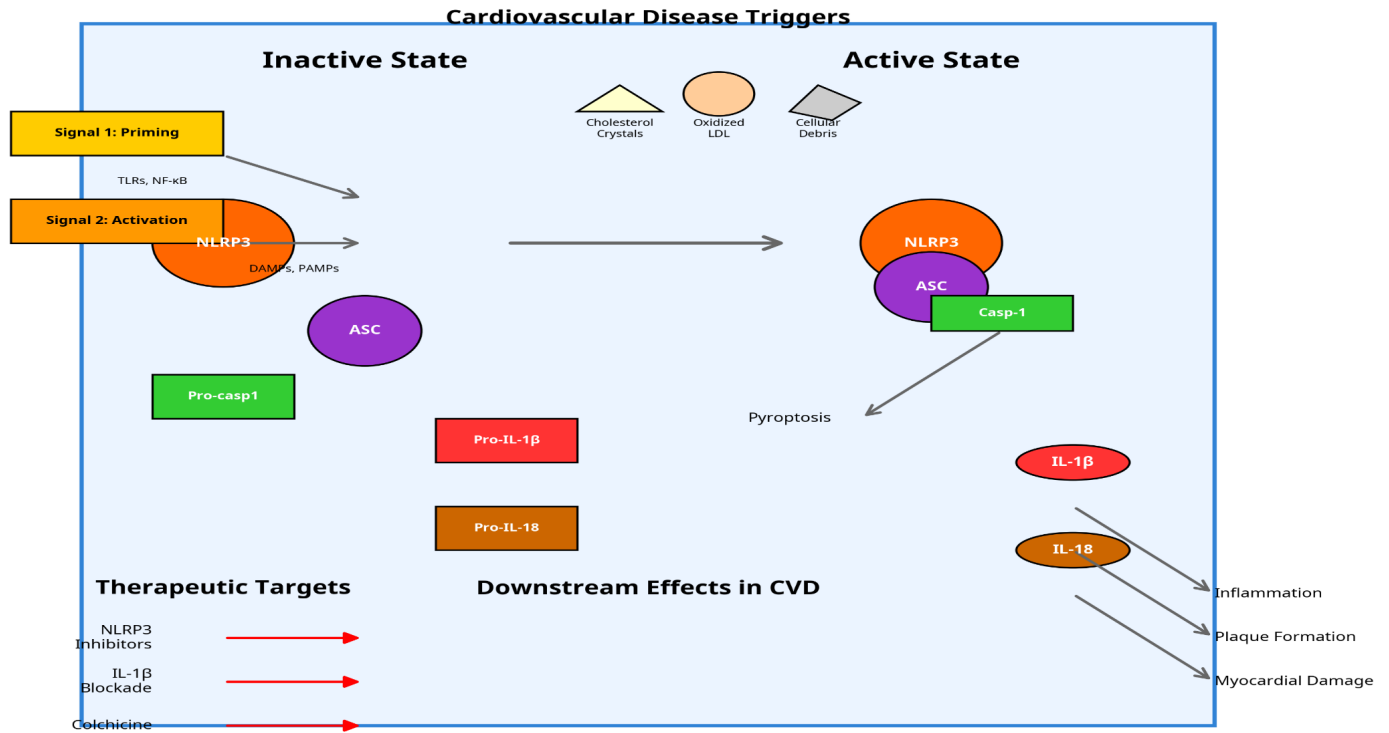


Figure 1 - Detailed illustration of the NLRP3 inflammasome activation in cardiovascular disease, showing both inactive and active states, activation signals, cardiovascular disease triggers, downstream effects, and therapeutic targets.

Inflammatory Pathways in Atherosclerosis

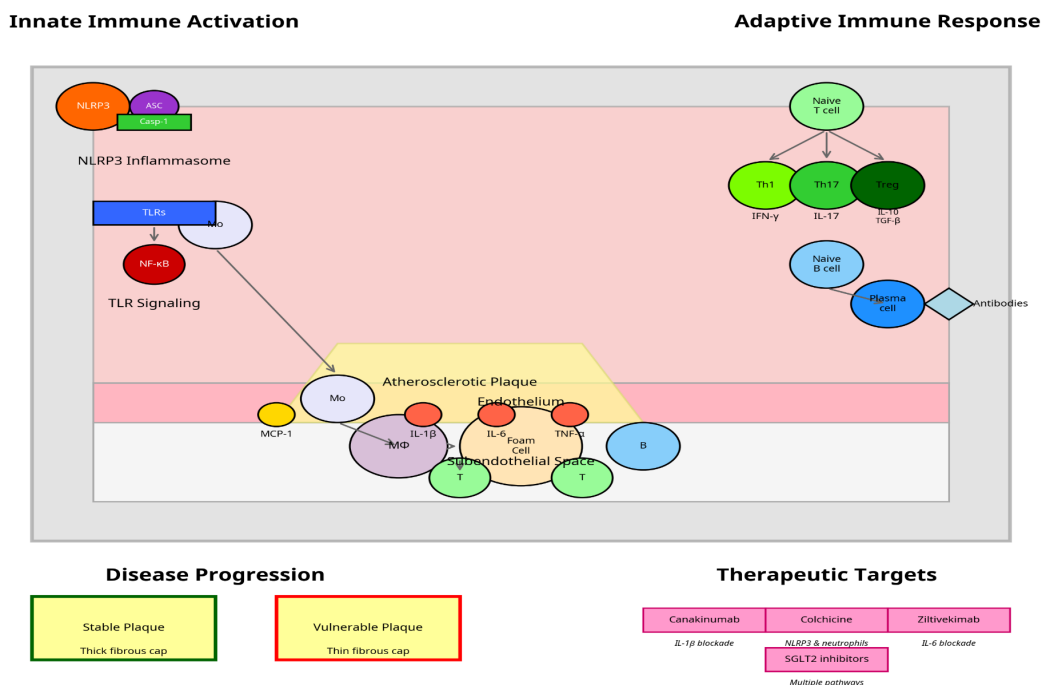
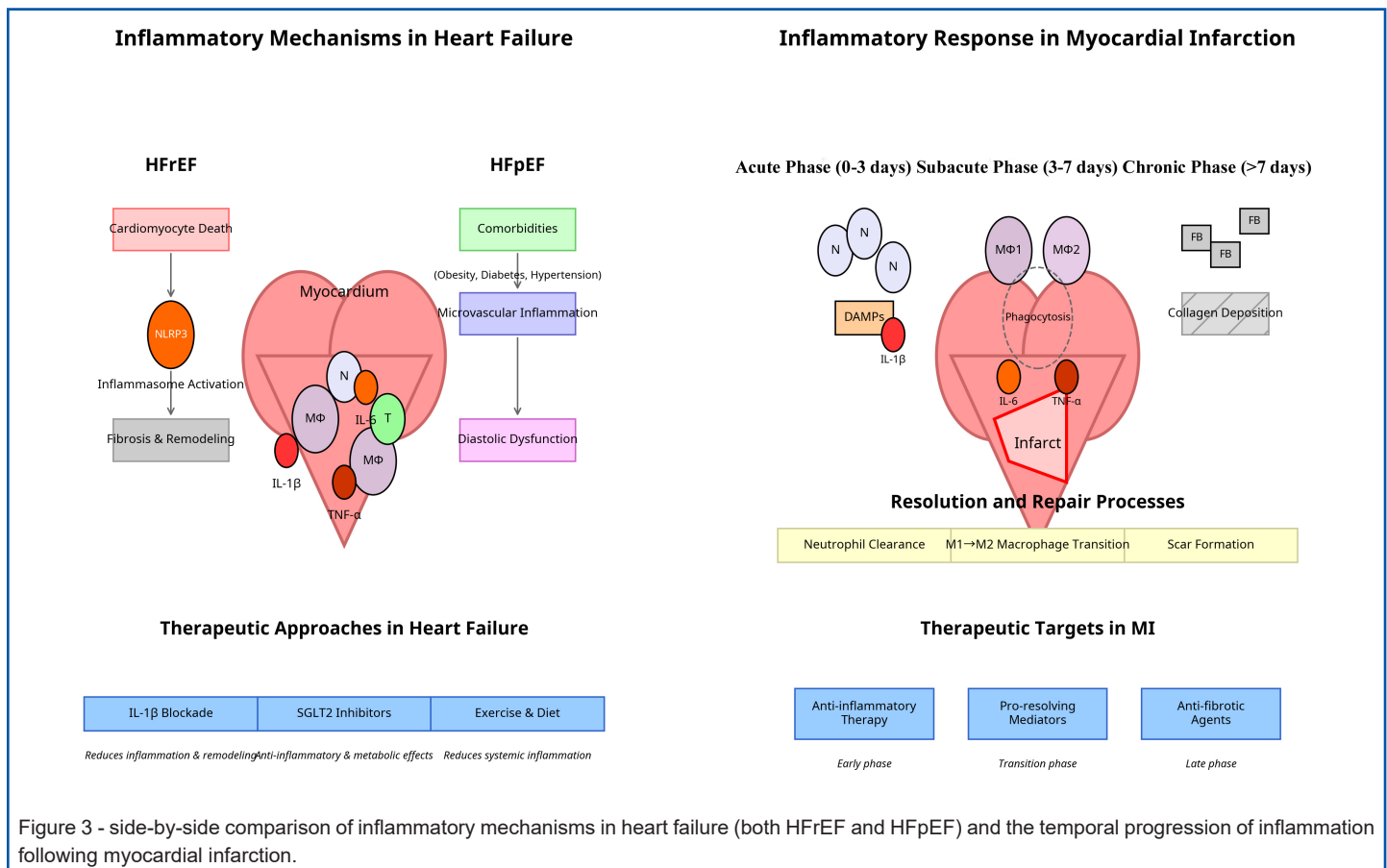


Figure 2 - Visual representation of the complex inflammatory processes in atherosclerosis, including endothelial dysfunction, monocyte recruitment, foam cell formation, adaptive immune responses, and potential therapeutic interventions.



the coronary microcirculation, leading to an increased generation of reactive oxygen species, decreased nitric oxide bioavailability, and endothelial dysfunction. Diastolic function is further compromised by these alterations, which further impede cardiomyocyte relaxation and encourage interstitial fibrosis [56].

Current and emerging anti-inflammatory therapies

1. Clinical evidence from trials

CANTOS trial: Canakinumab (anti-IL-1 β) and reduced CVD events

The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) included 10,061 individuals with prior myocardial infarction and elevated high-sensitivity C-reactive protein (hs-CRP) levels (≥ 2 mg/L). Every three months, participants were randomly assigned to receive either a placebo or one of three subcutaneous doses of canakinumab (50 mg, 150 mg, or 300 mg) [57, 58].

At a dose of 150 mg, canakinumab significantly decreased the primary endpoint (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular mortality) by 15% compared to a placebo after a median follow-up of 3.7 years (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.74-0.98, $p = 0.021$). It was confirmed that anti-inflammatory mechanisms mediated the cardiovascular protection, as this benefit was observed even when there was no discernible

change in LDL cholesterol levels. Canakinumab's cardiovascular effect was directly related to the degree of inflammation decrease. Major adverse cardiovascular events were 30% lower in patients who achieved hs-CRP levels < 2 mg/L following the first dosage of canakinumab (responders) than in those with hs-CRP ≥ 2 mg/L (nonresponders) [59].

Nonetheless, a slight rise in lethal infections was linked to therapy (incidence rate 0.31 vs. 0.18 per 100 person-years, $p = 0.02$), underscoring the significance of cautious patient selection for anti-inflammatory treatments [17, 60].

COLCOT & LoDoCo2: Colchicine in secondary prevention

In the Colchicine Cardiovascular Outcomes Trial (COLCOT), 4,745 patients who had recently experienced a myocardial infarction were assessed for secondary prevention using low-dose colchicine (0.5 mg daily). Colchicine significantly decreased the primary endpoint by 23% compared to a placebo (HR 0.77, 95% CI 0.61-0.96, $p = 0.02$), with 74% reductions in stroke and a 50% reduction in urgent hospitalizations for angina that resulted in myocardial revascularization [61]. Colchicine decreased the primary endpoint by 31% compared to a placebo in the Low-Dose Colchicine 2 (LoDoCo2) trial, which assessed colchicine in 5,522 patients with chronic coronary disease (HR 0.69, 95% CI 0.57-0.83, $p < 0.001$). All elements of the main endpoint and the different subgroups showed a similar benefit [62]. Colchicine inhibits the NLRP3 inflammasome and tubulin polymerisation, which interferes with neutrophil adherence,

extravasation, and chemotaxis. Colchicine offers several benefits over canakinumab, including being an oral medication with high bioavailability, a proven safety record, and a lower cost [63].

2. Targeted therapies under investigation

Direct suppression of the NLRP3 inflammasome is a viable therapeutic approach because of its pivotal role in the pathophysiology of cardiovascular disease. In preclinical models of cardiovascular disease, MCC950, a strong and selective small-molecule inhibitor of the NLRP3 inflammasome, has demonstrated potential by improving plaque stability, decreasing macrophage infiltration, and reducing plaque formation in atherosclerosis models, as well as decreasing infarct size and improving cardiac function in myocardial infarction models [64]. In comparison to IL-1 β blockade, NLRP3 inhibitors may have broader anti-inflammatory effects by inhibiting multiple inflammasome-dependent cytokines, be able to be administered orally, and potentially have a better safety profile because they target pathogenic inflammation more specifically [65].

IL-6 blockade (Ziltivekimab)

Ziltivekimab is a completely human monoclonal antibody that specifically binds to the IL-6 ligand, inhibiting its interaction with the IL-6 receptor and subsequent signalling [66]. Ziltivekimab is being studied in the Cardiovascular Inflammation Reduction Trial of IL-6 Inhibition (CIRT-IL6) to determine if it can reduce cardiovascular events in individuals with chronic renal disease and established cardiovascular disease who have elevated high-sensitivity C-reactive protein (hs-CRP) levels. Clinical studies that show IL-6 inhibition improves endothelial function and minimises arterial stiffness in rheumatoid arthritis patients, genetic studies that show variations in the IL-6 receptor gene that result in reduced IL-6 signalling are linked with lower risk of coronary heart disease. Epidemiological studies that suggest a strong link between elevated IL-6 levels and a higher risk of cardiovascular disease all support the rationale for targeting IL-6 [67, 68].

SGLT2 inhibitors: Anti-inflammatory effects beyond glucose control

SGLT2 inhibitors have shown impressive cardiovascular effects in numerous large-scale clinical trials [69-71]. While the kidneys' suppression of glucose reabsorption is the main mechanism of action, new research indicates that these medicines may also have anti-inflammatory actions that help protect the cardiovascular system [72]. SGLT2 inhibitors enhance endothelial function, reduce vascular inflammation, and decrease macrophage infiltration in animal models of atherosclerosis. Regardless of alterations in glycemic control, SGLT2 inhibitors lower blood levels of inflammatory markers such as hs-CRP, IL-6, and TNF- α in individuals with type 2 diabetes. SGLT2 inhibitors' anti-inflammatory effects are mediated via inhibition of the NLRP3 inflammasome, reduction of oxidative stress, modification of immune cell function, and indirect effects via improvements in metabolic parameters [73].

3. Non-pharmacological approaches

Lifestyle interventions (exercise, mediterranean diet)

Physical activity lowers inflammation through multiple pathways. Skeletal muscle contraction during acute exercise causes a brief rise in circulating IL-6, which in turn promotes the synthesis of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (IL-1Ra) [74, 75]. Frequent exercise also increases insulin sensitivity, reduces oxidative stress, enhances endothelial function, and minimizes inflammation in adipose tissue. Lower levels of inflammatory markers and a lower risk of cardiovascular disease have been repeatedly linked to the Mediterranean diet. In people at high cardiovascular risk, the PREDIMED study showed that a Mediterranean diet supplemented with nuts or extra-virgin olive oil decreased the incidence of major cardiovascular events by almost 30% when compared to a low-fat diet [76]. The Mediterranean diet's anti-inflammatory benefits can be attributed to omega-3 fatty acids, polyphenols, and fiber [77]. A Mediterranean diet, combined with regular exercise, provides complementary cardiovascular and anti-inflammatory benefits.

Gut microbiome modulation and its impact on systemic inflammation

The gut microbiota is essential for controlling inflammation, immunity, and host metabolism. Several inflammatory diseases, such as atherosclerosis, hypertension, and heart failure, have been linked to changes in the composition and function of the gut microbiota [78]. When the intestinal barrier is compromised by gut dysbiosis, bacterial compounds can enter the bloodstream and cause inflammatory reactions, which can result in systemic inflammation [79]. On the other hand, good gut bacteria provide anti-inflammatory metabolites, such as short-chain fatty acids (SCFAs), which decrease NLRP3 inflammasome activation, suppress NF κ B activation, and encourage the development of regulatory T cells [80].

Challenges and future directions

1. Identifying the right patients

Biomarkers for patient stratification (hs-CRP, IL-18, genetic profiling)

The most widely used inflammatory biomarker for determining cardiovascular risk is high-sensitivity C-reactive protein (hs-CRP) [81]. Elevated hs-CRP (≥ 2 mg/L) was used as an inclusion criterion in the CANTOS study, and the extent of hs-CRP reduction with canakinumab predicted the degree of cardiovascular benefit [58]. Nevertheless, hs-CRP has drawbacks, including nonspecificity, substantial intra-individual variability, and a lack of knowledge regarding the precise inflammatory pathways triggered in different patients. More specialised inflammatory biomarkers, like IL-18, could help choose a treatment and offer more precise information regarding inflammasome activation [82].

Genetic profiling is another promising method for identifying patients who may benefit from anti-inflammatory treatments.

Changes in cardiovascular outcomes and inflammatory responses have been linked to variations in genes encoding inflammatory mediators or their receptors, which may help identify patients who may benefit from particular targeted treatments [83].

Precision medicine approaches

Precision medicine seeks to tailor therapies to the precise pathophysiological pathways causing disease in individual patients [84]. This could entail a thorough characterization of inflammatory pathways in the context of inflammatory cardiovascular disease, aiming to identify the primary inflammatory mechanisms and inform the selection of targeted anti-inflammatory treatments. To create complex risk prediction models and treatment algorithms, artificial intelligence and machine learning techniques can combine various data sources [85]. This could improve patient classification for anti-inflammatory treatments [86]. Despite its potential, several obstacles hinder the implementation of precision medicine approaches for anti-inflammatory therapy in cardiovascular disease, including the need for prospective trials to assess biomarker-guided treatment options, infrastructure development, and cost considerations.

2. Balancing efficacy and safety

Risk of immunosuppression (infections, impaired wound healing)

Anti-inflammatory therapy for cardiovascular disease must strike a balance between lowering pathogenic inflammation and protecting important immune functioning [87]. This issue was discovered by the CANTOS trial, which revealed that canakinumab increased the risk of deadly infections [88]. Different anti-inflammatory strategies carry varying risks of infection; in general, broad-spectrum medications carry higher risks than specialised treatments. Immunosuppressive effects may be amplified by comorbidities such as diabetes, chronic renal disease, and advanced age.

In addition to increasing the risk of infection, anti-inflammatory medications may hinder the healing of wounds and the repair of damaged tissue [89]. They may also disrupt the positive effects of inflammation in cardiovascular disease, such as the acute inflammatory reactions required to remove necrotic debris and start the healing process after myocardial infarction.

3. Novel therapeutic targets

Specific therapies for inflammasomes

Inflammasome-specific therapies seek to prevent the construction and activation of the inflammasome complex itself, which may provide broader anti-inflammatory effects than targeting downstream cytokines [90]. MCC950 is one of several small-molecule NLRP3 inhibitors under development that have shown potential in cardiovascular disease preclinical models [91].

Other strategies for pathway-specific modulation include treatments that target particular elements of the inflammasome activation pathway, including NEK7 or ASC, or inhibitors of particular upstream activators, in addition to direct NLRP3 suppression [92].

RNA-based interventions and gene editing

Gene-editing technologies, particularly CRISPR-Cas9, provide unparalleled precision in targeting inflammatory pathways. Preclinical studies have shown that CRISPR-Cas9-mediated gene deletion or alteration of inflammatory mediator-encoding genes is effective in lowering inflammation and enhancing cardiovascular outcomes [93].

Targeting inflammatory pathways with great specificity can also be accomplished with RNA-based therapies, such as small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs) [94]. By binding to messenger RNA that codes for inflammatory mediators or their receptors, these treatments effectively silence gene expression and stop protein translation.

Although their pleiotropic effects require careful consideration of potential off-target implications, microRNAs (miRNAs) that regulate inflammatory pathways important to cardiovascular disease constitute another potential target for RNA-based therapies [95].

Immunomodulatory vaccines for CVD

Inducing immune responses that reduce harmful inflammation while maintaining protective immunity against infections is the goal of immunomodulatory vaccines for cardiovascular disease [96, 97]. Some strategies include vaccines that target pro-inflammatory cytokines to achieve long-term neutralisation, vaccines that target oxidised LDL to aid in the removal of changed lipoproteins, and vaccines that target and activate regulatory T cells that are specific to cardiovascular antigens [98].

Conclusion

One of the most significant paradigm shifts in cardiovascular medicine over the last three decades has been the recognition of inflammation as a major factor in the pathophysiology of cardiovascular diseases. The intricate inflammatory pathways underlying various cardiovascular disorders are examined in this review, along with the data supporting anti-inflammatory treatments and the challenges and potential paths forward in this rapidly evolving field. A key player in cardiovascular pathology, the NLRP3 inflammasome coordinates the synthesis of pro-inflammatory cytokines IL-1 β and IL-18, which intensify the inflammatory response and aid in the progression of the disease. Pro-inflammatory cytokines, including TNF- α , IL-1 β , and IL-6, stimulate macrophage activation, vascular smooth muscle cell proliferation, and endothelial dysfunction, all of which contribute to the development of atherosclerosis and plaque instability. Another level of complexity is introduced by the adaptive immune system, in which different subsets of T and B cells can have either protective or pathogenic effects depending on the situation.

The CANTOS trial provided the first conclusive evidence that reducing inflammation, particularly the IL-1 β pathway, can reduce cardiovascular risk without lowering cholesterol. Colchicine has been shown in later studies to dramatically lower cardiovascular events in people with coronary artery disease. Through anti-inflammatory mechanisms, emerging treatments such as SGLT2 inhibitors, NLRP3 inhibitors, and IL-6 inhibition offer promise for cardiovascular protection.

Finding the right patients using biomarkers and precision medicine techniques, striking a balance between safety and efficacy to reduce the risks associated with immunosuppression, and creating novel therapeutic targets, such as inflammasome-specific treatments, gene-editing, and RNA-based interventions, as well as immunomodulatory vaccines, are some of the challenges in implementing anti-inflammatory therapies. We are on the cusp of an era of innovation in cardiovascular medicine, where controlling inflammation may become a key component of prevention and treatment as our understanding of inflammatory pathways continues to grow and new therapeutic methods emerge. Although there are many obstacles to overcome, the possibility of reducing the worldwide burden of cardiovascular disease by utilizing targeted anti-inflammatory therapies provides a strong motivation for further study and clinical advancement in this area.

Conflicts of interest

The authors declare no conflicts of interest

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Ethics Compliance

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