

EMERGING INSIGHTS INTO INFLAMMATION AS A THERAPEUTIC TARGET IN ISCHEMIC HEART DISEASE: MECHANISMS, RISKS, AND INNOVATIVE STRATEGIES

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Abstract

This review explores the pivotal role of inflammation in the pathophysiology of ischemic heart disease (IHD), particularly following acute myocardial infarction (AMI). Since the mid-20th century, the inflammatory response has been increasingly linked to cardiovascular events, with biomarkers such as C-reactive protein (CRP) gaining prominence for their prognostic value. Recent clinical trials, including CANTOS and COLCOT, underscore the potential of targeting inflammation to mitigate residual cardiovascular risk, revealing that anti-inflammatory therapies can reduce major adverse cardiac events (MACE) independently of traditional lipid-lowering strategies. We examine the mechanisms by which inflammation contributes to atherosclerosis and the interplay with risk factors, emphasizing the complexity of inflammatory pathways and their systemic implications. Additionally, we discuss both established and novel pharmacological interventions, including low-dose aspirin, statins, canakinumab, colchicine, and emerging agents like Ziltivekimab, assessing their efficacy and safety profiles. The review highlights the necessity for personalized treatment approaches to optimize outcomes in diverse patient populations, particularly among elderly individuals who may benefit from tailored anti-inflammatory strategies. As inflammation remains a significant, albeit underexplored, contributor to IHD, this article advocates for its recognition as a key therapeutic target in contemporary cardiovascular care.

Keywords: ischemic heart disease, therapeutic target, inflammatory response, inflammation, cardiovascular disease, biomarkers

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Introduction

Since the 1940s and 1950s, it has been recognized that an inflammatory response occurs following an acute myocardial infarction (AMI), evidenced by elevated erythrocyte sedimentation rate (ESR), C-reactive

protein (CRP) levels, and serum complement (C') activity [1,2]. In a study conducted by Boltax and Fischel in 1956 [3], which involved serial measurements of ESR, C', and CRP in sixty-one cases of AMI, it was found that these indicators were

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positive in more than 90% of the patients by the third day after the the initial phase of a disease [4,5].

In 1943, Lofstrom [6] observed that individuals suffering from myocardial infarction also exhibited "non-specific capsular swelling in pneumococci," which was later linked to the detection of CRP. Subsequent research has consistently found CRP in cases of myocardial infarction and other non-infectious inflammatory conditions [7-9]. Interestingly, a comprehensive review of literature from the 1960s through the 1980s showed a significant decline in the emphasis on inflammation's role in AMI, with it almost disappearing from scholarly discussions. However, the 1990s saw a resurgence in interest, driven by studies focusing on cytokines, marking a significant shift back towards the importance of inflammation in AMI [10-11].

Hence, given the critical role of inflammation in the development of ischemic heart disease (IHD), this article seeks to provide a comprehensive overview of the underlying concepts with the goal of investigating strategies to mitigate the inflammation linked to myocardial infarction [12].

In recent years, the concept of inflammation as a crucial factor has expanded beyond the acute response following myocardial infarction to also encompass its roles during the early stages of atherosclerosis. Studies suggest that inflammatory processes may initiate endothelial dysfunction, promote lipid accumulation in arterial walls, and contribute to plaque formation and instability [13].

Inflammation as a risk factor for heart disease

The link between inflammation and cardiovascular disease (CVD) has led to the growing consideration of inflammation as either a risk marker or a risk factor in recent years. CRP has played a crucial role in shedding light on this relationship [13-16]. Produced primarily by liver cells, CRP's production is driven by the influence of IL-6 and IL-1 β on its mRNA transcription. It is released in response to various stimuli, including infections and physical injuries, as part of the body's general innate defense system [17-19]. The production rate of CRP is the sole factor determining its concentration in the blood, making it a valuable biomarker for gauging the intensity of the stimuli triggering its production. However, CRP is considered a downstream marker, which likely does not have a direct role in the process of atherogenesis [20].

The evaluation of cardiovascular (CV) risk associated with inflammation has prominently featured C-reactive protein (CRP), a marker widely used in monitoring systemic inflammatory conditions such as rheumatoid arthritis and other inflammatory disorders. CRP, a key member of the short pentraxin family, is

produced in response to pro-inflammatory cytokines, notably IL-6, as well as IL-1 β and TNF- α [7]. While CRP plays a significant role in the immune response by binding to microbial ligands and damaged cells, thereby activating complement pathways and assisting in the clearance of apoptotic cells, the debate over its causal relationship with coronary heart disease risk persists. Although many studies identify elevated CRP levels as a useful risk marker for cardiovascular disease, Mendelian randomization studies have consistently failed to establish a direct causal link between genetically determined CRP levels and coronary heart disease. This contrasts with findings related to IL-6, which has shown more consistent links to cardiovascular risk, albeit with practical limitations for routine clinical measurement due to its unstable nature and variability. Moreover, while high-sensitivity (hs)CRP assays provide a standardized approach to measuring CRP levels, the predictive utility of hsCRP as a sole marker in assessing coronary artery disease remains contentious. Investigative data suggest that the relationship between hsCRP and plaque characteristics is variable and that hsCRP's prognostic value in patients post-acute coronary syndrome on optimal medical treatment may be limited. Therefore, while CRP and hsCRP levels may hold some relevance in identifying patients at risk for adverse cardiovascular events, further research is needed to clarify their roles in establishing causal pathways in coronary heart disease.

Despite this, assays for high-sensitivity C-reactive protein (hs-CRP), capable of detecting lower CRP levels linked to mild inflammation, have become crucial supplementary methods for exploring the link between inflammation and ischemic incidents [21]. Numerous research findings indicate that hs-CRP concentrations can forecast cardiovascular (CV) events in both the general populace and those with a history of CVD. Various studies have demonstrated that hs-CRP levels can independently assess CV risk apart from lipid measures, underscoring its potential as a risk indicator [22-24].

Research has increasingly clarified the link between various CV risk factors and inflammation. A pivotal study in this area, the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), examined the impact of rosuvastatin on people without CVD who had low LDL cholesterol (LDL-C) levels (<130 mg/dl) but high hs-CRP levels (≥ 2 mg/l) [25,26]. This trial revealed that rosuvastatin significantly lowered the primary composite endpoint and all-cause mortality, alongside notable reductions in both LDL-C and hs-CRP levels. Following this, studies on proprotein convertase subtilisin/kexin type 9 inhibitors, which lower LDL-C beyond what is achievable with statins

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without significantly affecting hs-CRP, demonstrated substantial decreases in CV events [27-29]. Conversely, the groundbreaking CANTOS trial showed that canakinumab, which reduces hs-CRP without altering LDL-C levels, also led to fewer CV events. This underscores the potential benefits of targeting inflammation in CV prevention. Thus, current evidence highlights the synergistic role of inflammation and traditional CV risk factors in atherosclerosis, moving beyond the previously perceived divide between these elements [30-31].

Lastly, the role of hs-CRP in refining CV risk assessment is acknowledged differently across guidelines. The current US guidelines for managing blood cholesterol recognize hs-CRP as a potential risk enhancer for certain individuals in primary prevention therapeutic decision-making [32-34]. In contrast, European guidelines on CV prevention and dyslipidemias, while acknowledging studies on hs-CRP, stop short of offering explicit guidance on using this biomarker, especially concerning anti-inflammatory treatments due to the need for more evidence from randomized trials on CV event reduction. Despite widespread acknowledgment of inflammation's role in CVD, its precise contribution relative to other CV risk factors and their management remains unclear, as reflected in existing guidelines. However, recent advancements in secondary prevention offer fresh insights into this ongoing debate, suggesting the possibility of a reevaluation of this topic in the future [35-36]. (Table 1)

Chronic low-grade inflammation is now recognized as a critical contributor to the pathogenesis of atherosclerosis. Factors such as endothelial injury, often due to traditional cardiovascular risk factors including hyperlipidemia and hypertension, promote the expression of adhesion molecules on endothelial cells, facilitating the recruitment of inflammatory cells to the vessel wall. Key inflammatory mediators, such as IL-1 β and IL-6, play a role in the early stages of plaque development by promoting the uptake of lipids by macrophages and the formation of foam cells, which are hallmark features of atherosclerosis.

Inflammation plays a critical role in the development of atherosclerosis, and specific inflammatory mediators, particularly interleukin-6 (IL-6) and interleukin-1 β (IL-1 β), have garnered significant attention for their involvement in cardiovascular disease (CVD). IL-6 is produced primarily by T cells, macrophages, and adipocytes, and it promotes inflammatory responses by interacting with both membrane-bound and soluble forms of the interleukin-6 receptor (IL6R) on various cell types, including monocytes and endothelial cells [7]. Elevated levels of IL-6 have been associated with an increased risk of coronary heart disease (CHD) events in several

prospective studies, and targeting IL6R signaling presents a potential therapeutic approach for preventing CHD. On the other hand, IL-1 β is another pro-inflammatory cytokine that significantly contributes to atherogenesis. Its role in enhancing inflammation and promoting plaque instability aligns with findings from clinical studies showing that monoclonal antibodies targeting IL-1 β , such as canakinumab, can reduce cardiovascular events in patients with a history of myocardial infarction. The CANTOS trial illustrated the efficacy of canakinumab in lowering hsCRP levels and reducing adverse cardiovascular outcomes, suggesting a critical role for IL-1 β inhibition in mitigating inflammatory pathways linked to CVD. Together, the modulation of IL-6 and IL-1 β through targeted therapies underscores the importance of these cytokines in cardiovascular risk management and reinforces the potential of anti-inflammatory strategies in the prevention of coronary heart disease.

In addition to traditional markers, lipoprotein-associated phospholipase A2 (Lp-PLA2) has emerged as a significant biomarker in the assessment of coronary heart disease (CHD) risk. Studies, including the ARIC study, have demonstrated that elevated levels of Lp-PLA2, alongside high-sensitivity C-reactive protein (hs-CRP), predict subsequent CHD events in a diverse cohort of individuals, including both men and women of varied racial backgrounds. Lp-PLA2 is produced primarily by macrophages and plays a crucial role in the hydrolysis of oxidized phospholipids on low-density lipoproteins (LDL), contributing to the inflammatory processes that underlie atherosclerosis. Notably, Lp-PLA2 concentrations have been independently associated with both CHD incidence and ischemic strokes, reinforcing its potential as an independent predictor of cardiovascular events in the general population. Furthermore, recent meta-analyses have confirmed that both Lp-PLA2 activity and mass correlate with increased risk of CHD and ischemic stroke, highlighting its relevance as a complimentary marker in individuals with low LDL cholesterol levels who may not be adequately identified by conventional lipid profiles. These findings support the inclusion of Lp-PLA2 measurement in the risk stratification tools for patients at the intermediate risk of CHD, thereby enhancing the understanding of cardiovascular pathophysiology and aiding in the development of targeted therapeutic strategies.

Recent evidence suggests that statin therapy not only exerts lipid-lowering effects but also significantly impacts inflammatory biomarkers, including lipoprotein-associated phospholipase A2 (Lp-PLA2).

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Lp-PLA2 is an enzyme linked to atherogenesis and inflammation, predominantly produced by macrophages and lymphocytes, and is known to contribute to cardiovascular disease (CVD) risk. Studies indicate that intensive statin therapy, such as atorvastatin at a dose of 80 mg per day, leads to a mean reduction of approximately 20% in Lp-PLA2 activity and a 23% reduction in Lp-PLA2 mass, which suggests a direct effect of statins on this enzyme independent of their lipid-lowering properties. In contrast, moderate statin therapy, such as pravastatin at 40 mg per day, demonstrates a much smaller reduction in Lp-PLA2 activity and mass, highlighting differences in the potency and mechanisms of various statins. Importantly, these reductions in Lp-PLA2 levels may attenuate the inflammatory processes associated with atherogenesis, offering additional cardiovascular protection beyond LDL cholesterol reduction. This dual action of statins—lowering both lipid levels and inflammatory markers like Lp-PLA2—reinforces their role as essential therapeutic agents in cardiovascular risk management.

Recent studies have highlighted the significance of oxidized phospholipid/apoB (OxPL/apoB) levels and lipoprotein(a) [Lp(a)] as important predictors of future cardiovascular events. The OxPL/apoB ratio, which quantifies the amount of oxidized phospholipids associated with apolipoprotein B particles, has been shown to independently predict cardiovascular outcomes over a 10-year follow-up in general population cohorts, even when adjusting for traditional risk factors and high-sensitivity C-reactive protein (hsCRP) levels. Notably, OxPL/apoB levels were associated with increased cardiovascular risk, particularly in patients with elevated lipoprotein-associated phospholipase A2 (Lp-PLA2) activity. Lp(a), an atherogenic lipoprotein variant, is independently correlated with cardiovascular risk, especially at levels exceeding 30 mg/dL, and exhibits a particular association with pro-inflammatory oxidized phospholipids. Although OxPL/apoB and Lp(a) are related, they provide independent information regarding cardiovascular risk, further underscoring the potential for combined measurement strategies. Future investigations are warranted to clarify the mechanisms underlying the interactions between these biomarkers and their roles in cardiovascular pathology, particularly regarding how elevated OxPL/apoB levels and Lp(a) may interact to enhance atherogenic processes.

Platelet activating factor (PAF) has been identified as a critical mediator in the initiation and progression of atherosclerosis, particularly due to its multifaceted roles in inflammatory responses. As a potent proadhesive signaling molecule, PAF not only facilitates the aggregation of platelets but also

activates leukocytes, enhancing their capacity to release additional inflammatory mediators. This cascade of events significantly contributes to the development of atherosclerotic plaques within the coronary arteries. Elevated levels of PAF are associated with increased platelet reactivity, which is linked to thrombus formation, a key factor in acute myocardial ischemia. Furthermore, PAF interacts with other inflammatory mediators, intensifying the inflammatory milieu that promotes atherogenesis. In the context of acute coronary syndromes, the actions of PAF in enhancing cellular adhesion and promoting leukocyte infiltration into the arterial wall are pivotal in both the acute inflammatory response and the chronic progression of atherosclerosis. This underscores the potential of PAF as a target for therapeutic strategies aimed at mitigating cardiovascular disease risk by interrupting these pro-inflammatory pathways.

Recent evidence suggests that both colchicine and methotrexate play significant roles in modulating inflammatory responses in articular diseases by effectively preventing leukocyte adhesion and emigration in response to platelet-activating factor (PAF). The accumulation of leukocytes in synovial fluid is a hallmark of disorders like gout and rheumatoid arthritis, where leukocyte-endothelial cell interactions are crucial for inflammation. In experimental models, the administration of colchicine and methotrexate has been shown to blunt the adhesive interactions elicited by PAF, leading to a decrease in leukocyte rolling velocity and the number of adherent leukocytes. The mechanisms underlying these effects may involve alterations in the function of membrane receptors or the suppression of mediator-induced up-regulation of leukocyte adhesion molecules, thus desensitizing neutrophils to PAF. Additionally, both agents may limit the production of reactive oxygen species, which are known to promote leukocyte adhesion. Furthermore, methotrexate's ability to enhance adenosine release from endothelial cells may also contribute to its antiadhesive effects. Collectively, these findings highlight the potential of colchicine and methotrexate not only as anti-inflammatory agents but also as modulators of leukocyte-endothelial interactions, paving the way for their therapeutic application in managing acute inflammatory responses, particularly those mediated by PAF.

Table 1: Key Inflammatory Biomarkers and Their Role in Ischemic Heart Disease (IHD)

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Biomarker	Source	Role in Inflammation	Clinical Implications	References
C-reactive protein (CRP)	Liver	Acute phase response, reflects systemic inflammation	Prognostic indicator for cardiovascular risk	[13-20]
High-sensitivity CRP (hs-CRP)	Liver	Detects low-grade inflammation, risk marker for CVD	Assesses cardiovascular risk independent of lipid levels	[21-34]
Interleukin-6 (IL-6)	Various cells	Pro-inflammatory cytokine that stimulates CRP production	Target for anti-inflammatory therapies (e.g., IL-6 inhibitors)	[106-110, 114,115]
Interleukin-1 β (IL-1 β)	Macrophages	Promotes inflammation and plays a role in atherosclerosis	Focus of canakinumab in CANTOS trial	[17-19, 109,110]
Erythrocyte sedimentation rate (ESR)	Blood	Indicator of inflammation	Less specific, used alongside other markers	[4,5]
Neutrophil-to-lymphocyte ratio (NLR)	Blood	Reflects balance between inflammation and immune response	Associated with cardiovascular events	[48-50]

Inflammation and Heart Disease: understanding the pathophysiological mechanisms

The ways in which inflammation affects atherosclerosis are intricate and multifaceted, encompassing both local and systemic responses. These responses can be triggered by various factors including autoimmune diseases, infections, shifts in

the body's microbial communities, environmental pollution, smoking, medications, and other external influences [37,38]. Additionally, genetic factors play a role in how these mechanisms interact. Notably, research has highlighted a link between infectious agents and atherosclerosis across different scenarios, from periodontal disease to Chlamydia pneumoniae infection. However, it's not the direct impact of individual pathogens on atherosclerotic plaques that seems to drive this link, but rather the involvement of pathways associated with chronic inflammation [39-41]. Despite studies using anti-infective agents like macrolides not showing cardiovascular benefits, they have shed light on this intricate relationship. While delving into the detailed pathophysiology of these interactions is beyond this discussion, having a basic understanding is crucial for keeping up with recent developments in this field [42,43].

As noted previously, various triggers can initiate the activation of different cell types, including lymphocytes and mast cells, which then produce proinflammatory cytokines. These cytokines further influence the behavior of monocytes that move from the bloodstream to the vessel wall and affect other cells as well. Importantly, the dynamics of blood flow and shear stress are crucial in this process, with research indicating that specific flow patterns linked to areas prone to atherosclerosis can cause endothelial cells to differently express adhesion molecules [44-46]. As leukocytes move towards the site of an atheromatous plaque, they release substances like proteases, factors that promote coagulation, and inflammatory cytokines, which all contribute to the formation of thrombi and make the plaque more unstable. A critical aspect of this process involves a balance between cytokines that promote inflammation (such as IL-18, IL-1, and IL-6) and those that counteract it (like IL-10) [47]. The NLR family pyrin domain containing 3 (NLRP3) inflammasomes, part of the innate immune system, plays a significant role in this balance. NLRP3 can be triggered by various factors, including those associated with pathogens, cell damage, cholesterol buildup, lack of oxygen, or issues with autophagy, leading to an increase in proinflammatory cytokines and cell death through pyroptosis, a specific type of programmed cell death [48-50].

Another aspect to consider is the generation of autoantibodies, including those targeting the heart. These can stem from underlying autoimmune conditions, such as systemic lupus erythematosus, enhancing the immune response. They are also present in individuals with CVD and the wider population, highlighting the shared pathways between these conditions [51,52]. Moreover, evidence suggests alterations in the leukocyte composition in individuals

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with CVD. While the full implications of these alterations are yet to be determined, a shift towards a proinflammatory state, indicated by changes in the neutrophil-to-lymphocyte ratio, has been identified. This shift suggests an increase in inflammatory activity through neutrophils and a decrease in anti-inflammatory actions through lymphocytes, playing a role in the link between blood cell changes and CVD [53-55]. Additionally, the interaction between different cell types, driven by a proinflammatory imbalance in cytokines, alongside oxidative stress, plays a significant role. This stress impacts various cellular components, contributing to the progression of atherosclerosis. Mitochondrial dysfunction may activate the NLRP3 inflammasome via reactive oxygen species, with disrupted mitochondrial balance further exacerbating this issue [56-58].

Inflammation in Atherosclerosis Onset and Progression

Research has established that inflammation not only correlates with the presence of atherosclerosis but actively facilitates its development.[59-65] The initiation of atherosclerosis begins with endothelial cell injury, leading to endothelial dysfunction. This dysfunction triggers the expression of adhesion molecules that recruit circulating monocytes into the intima of blood vessels. Once within the arterial wall, monocytes differentiate into macrophages, which engulf oxidized low-density lipoprotein (LDL) particles, resulting in the formation of foam cells—a key early event in atherosclerotic plaque development [65-139].

Chronic inflammation is further perpetuated as these macrophages secrete proinflammatory cytokines, perpetuating the inflammatory cascade. The role of the NLRP3 inflammasome in this context is critical; its activation leads to the secretion of IL-1 β , a key proinflammatory cytokine that drives the inflammatory response and contributes to plaque progression. Consequently, the environment within the plaque evolves, leading to plaque instability and a heightened risk of rupture, precipitating acute cardiovascular events such as myocardial infarction [140,141].

Lipid Mediators of Inflammation and Specialized Pro-resolving Mediators in Cardiovascular Disease

Recent research has illuminated the critical roles of lipid mediators in the inflammatory response associated with ischemic heart disease (IHD). These mediators, derived from fatty acids, significantly influence the initiation, propagation, and resolution of inflammation within the cardiovascular system [142].

Lipid Mediators of Inflammation

Lipid mediators, such as prostaglandins and leukotrienes, are produced during the inflammatory

response and play pivotal roles in modulating vascular function, inflammation, and hemostasis. For instance:

- Prostaglandins (e.g., PGE2) contribute to the recruitment of inflammatory cells and the amplification of the inflammatory response in atherosclerosis. Elevated levels of these mediators have been observed in atherosclerotic lesions and are tied to vascular remodeling and instability [143,144].
- Leukotrienes, specifically leukotriene B4 (LTB4), are potent pro-inflammatory mediators that promote leukocyte recruitment to sites of inflammation, including atherosclerotic plaques. The actions of these lipid mediators are essential for the initial phases of plaque formation and progression [145,146].

Understanding how these lipid mediators function can offer insights into their potential as therapeutic targets. Inhibiting their synthesis or action may perturb the dangerous cycle of chronic inflammation in atherosclerosis, presenting a novel approach for therapeutic intervention.

Specialized Pro-resolving Mediators (SPMs)

In contrast to classical lipid mediators, specialized pro-resolving mediators, including resolvins, protectins, and maresins, play critical roles in resolving inflammation and restoring tissue homeostasis. These mediators are derived from omega-3 and omega-6 fatty acids:

- Resolvins, such as resolvin E1 (from EPA) and resolvin D1 (from DHA), actively promote the cessation of neutrophil recruitment and enhance macrophage clearance of apoptotic cells and debris in atherosclerotic plaques. Their application has demonstrated promise in reducing plaque formation and modifying the inflammatory response in cardiovascular diseases [147-149].
- Protectins can exert protective effects in vascular tissues by promoting the resolution of inflammation, enhancing endothelial function, and improving local blood flow. They have been associated with reductions in myocardial ischemia-reperfusion injury and stabilization of arterial plaques by modulating inflammatory cell activity and enhancing repair mechanisms [150-152].
- Maresins, similarly, have shown protective effects in models of atherosclerosis by promoting macrophage resolution of inflammation and tissue repair, highlighting their therapeutic potential [153,154].

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High-density lipoprotein (HDL) is widely recognized for its anti-atherogenic properties, which extend beyond its well-known role in reverse cholesterol transport. HDL actively protects endothelial cells and modulates several mechanisms crucial to maintaining vascular health. For instance, HDL promotes endothelial cell survival and proliferation, thereby supporting the integrity of the endothelium, which is essential for preventing atherosclerosis. Studies demonstrated that HDL enhances the production of nitric oxide (NO) from endothelial cells, facilitating vasodilation and reducing platelet aggregation, which collectively mitigate the risks of thrombosis and arterial occlusion [155-157]. Moreover, HDL inhibits the expression of adhesion molecules such as VCAM-1 and ICAM-1 on endothelial cells, reducing the recruitment of inflammatory leukocytes to the arterial wall—a key step in the formation of atherosclerotic plaques. HDL’s ability to antagonize oxidized low-density lipoprotein (OX-LDL) further highlights its protective effects, as it helps prevent the endothelial dysfunction often triggered by oxidized lipids. Additionally, HDL exhibits antioxidant properties, scavenging reactive oxygen species and limiting LDL oxidation, which is a critical factor in atherogenesis. Collectively, these actions illustrate HDL’s multifaceted role as an anti-atherogenic lipoprotein, supporting vascular health and stability in the face of inflammatory processes that drive atherosclerosis [158].

Clinical Implications and Future Research

The clinical implications of understanding lipid mediators and specialized pro-resolving mediators in IHD are significant. Targeting these pathways could lead to interventions that not only mitigate inflammation but also facilitate resolution, significantly improving cardiovascular outcomes [159,160].

Emerging research into the therapeutic use of SPMs in clinical settings is underway, with initial findings suggesting beneficial effects in reducing cardiovascular events and improving heart function. Clinical trials aimed at evaluating the safety and efficacy of these mediators in cardiovascular disease are needed to fully elucidate their potential roles [161]. Furthermore, the individual variability in lipid mediator production among patients might influence responses to anti-inflammatory therapies, suggesting a personalized approach to treatment could enhance efficacy. Investigating the interactions between these mediators and established therapeutic strategies, such as statins and anti-inflammatory agents, could yield new insights into combined treatment approaches for IHD [162].

Tactics for Reducing Inflammation in Ischemic Heart Disease

Lately, the importance of inflammation in the development of atherosclerosis and IHD has become more recognized due to new research that highlights the intricate relationship between inflammation and cardiovascular diseases. This recognition has led scientists and medical professionals to investigate specific treatments designed to counteract the inflammation process linked to IHD. As a result, recent studies have examined whether using anti-inflammatory medications can decrease the occurrence of major adverse cardiac events (MACE) in individuals with IHD [59-61]. (Table 2)

Pharmacological Anti-Inflammatory Therapy

Table 2: Summary of Clinical Trials Evaluating Anti-Inflammatory Therapies in IHD

Trial Name	Intervention	Population	Key Findings	Outcome Measure	References
CANTOS	Canakinumab (IL-1 β inhibitor)	Post-MI patients with elevated hs-CRP	Reduced cardiovascular events, higher infection risk	Nonfatal MI, stroke, cardiovascular death	[85-92]
COLCOT	Colchicine (0.5 mg/day)	Post-MI patients	Decreased MACE, especially in elderly	Composite of cardiovascular events	[111,112]
JUPITER	Rosuvastatin (20 mg)	High hs-CRP, no prior CVD	Significant reduction in MACE, LDL-C levels lowered	Composite of cardiovascular events	[25,26,75,76]
CARE	Pravastatin	Patients with prior events	Lowered CRP without significant LDL-C effect	Recurrent cardiovascular events	[72,73]

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Trial Name	Intervention	Population	Key Findings	Outcome Measure	References
CIRT	Methotrexate (low-dose)	IHD, diabetes/metabolic syndrome	No significant reduction in cardiovascular events	Composite of MI, stroke, cardiovascular death	[101,102]
LoDoCo2	Low-dose colchicine	Chronic coronary syndrome	Reduced complications and inflammation	Composite of cardiovascular events	[98,99,113]
ASSA IL-MI	Tocilizumab (IL-6 receptor blocker)	Patients post-MI with elevated hs-CRP	Under investigation; potential for reduced events	Cardiovascular and safety outcomes	[114,115]
CLEAR SYNERGY	Colchicine	High cardiovascular risk patients	Ongoing; examining reduction of MACE	Composite of cardiovascular events	[114,115]
ZEUS	Ziltivekimab (IL-6 inhibitor)	Patients with chronic kidney disease	Ongoing; evaluating safety and efficacy in CVD	Cardiovascular outcomes including MACE	[109,110]

Traditional Pharmacological Anti-Inflammatory Therapy

The effectiveness of low-dose aspirin (100 mg/day) in preventing MACE in patients with IHD is well established, owing partly to its ability to decrease proinflammatory markers. Notably, aspirin contributes to the production of specialized pro-resolving mediators (SPMs), including lipoxins, which play a crucial role in resolving inflammation. The predominant theories for its beneficial impact include its antiplatelet and anti-inflammatory

properties, with the former being more comprehensively understood than the latter [62-64]. However, numerous clinical trials have shown that low-dose aspirin use is linked to a reduction in proinflammatory biomarkers like IL-6, IL-1, and C-reactive protein in IHD patients. Furthermore, a detailed analysis from The Physicians' Health Study indicated that the risk reduction of experiencing a first myocardial infarction with aspirin usage correlates directly with levels of C-reactive protein [65,66]. In this particular study, healthy subjects were randomly assigned to either an aspirin or placebo group, and CRP levels were measured at the study's outset. Participants in the highest CRP quartile faced a greater risk of myocardial infarction or stroke compared to those in the lowest quartile. Aspirin use resulted in significant risk reductions for participants in the highest quartile (55% reduction) but only minor, statistically insignificant reductions for those in the lowest quartile (13.9% reduction) [67]. This finding suggests that the higher the initial risk, the more pronounced the protective effects of aspirin in cardiovascular prevention, with inflammation, as indicated by CRP levels, playing a key role in the development of atherosclerosis. This strategy of identifying high-risk individuals is further supported by the ASPREE trial outcomes, which showed that daily aspirin use did not lead to a benefit in the primary endpoint of disability-free survival among healthy older adults [68,69].

Cholesterol overload in macrophages plays a central role in driving inflammation within the vascular wall, contributing to the development and progression of atherosclerosis. This process highlights the intricate relationship between lipid metabolism, immune response, and cardiovascular health, emphasizing the need for therapeutic strategies targeting lipid accumulation and inflammation to prevent cardiovascular disease. Conversely, the advantages of lipid-lowering treatments like statins or the innovative PCSK9 inhibitors go beyond merely decreasing LDL cholesterol levels. The wide-ranging benefits of statins, particularly in IHD, are well-supported by evidence [70,71]. This includes their significant anti-inflammatory effects that are not solely tied to their ability to lower lipids. Studies from the CARE (Cholesterol and Recurrent Events) and PRINCE (Pravastatin Inflammation/CRP Evaluation) trials demonstrated that pravastatin administration could lower C-reactive protein levels without directly correlating to LDL-C levels [72,73]. This phenomenon was noted in both the primary prevention (PRINCE trial) and secondary prevention (CARE trial) scenarios. The PROVE IT-TIMI 22 study also highlighted the dual benefits of statin therapy, showing it not only reduces LDL levels but also exerts

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a direct anti-inflammatory effect, as evidenced by lowered high-sensitivity CRP levels [74]. The JUPITER trial, comparing rosuvastatin 20 mg with a placebo in patients without prior cardiovascular disease, LDL-C levels under 130 mg/dL, but with high-sensitivity CRP levels ≥ 2 mg/L, further confirmed the efficacy of statins. This trial was prematurely halted due to a significant reduction in MACE, including a 54% decrease in myocardial infarction, 48% in stroke, 46% in arterial revascularization needs, and 20% in overall mortality [75,76]. With a number needed to treat (NNT) of 32 for MACE, the findings underscore the substantial benefits of statin use in individuals with an inflammatory profile, beyond just lowering LDL cholesterol [77,78].

Given the crucial role that inflammation plays in cardiovascular health, the anti-inflammatory properties of statins may contribute to their ability to lower the incidence of MACE, alongside their well-known effect of reducing LDL cholesterol levels. Similarly, recent research has shown that PCSK9 inhibitors can decrease the risk of atherosclerosis by reducing vulnerable plaque buildup in patients who have experienced acute coronary syndrome (ACS) and those with familial hypercholesterolemia [79,80]. It's critical to note that the significant decrease in MACE seen in key studies of these drug classes is mainly attributed to their effectiveness in lowering LDL cholesterol. Nonetheless, further research is needed to fully understand the importance and impact of their anti-inflammatory actions [81-84].

Novel Pharmacological Anti-Inflammatory Therapy Canakinumab

The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) was a pivotal study designed to investigate the effects of canakinumab, a fully human monoclonal antibody targeting interleukin-1 β , on preventing recurrent vascular events in stable patients with a history of myocardial infarction who also exhibited a persistent proinflammatory response (high-sensitivity CRP ≥ 2 mg/L). Interleukin-1 β is known to play a significant role in the proinflammatory process that leads to atherosclerosis [85-88]. This trial marked the first investigation into the impact of direct anti-inflammatory therapy on cardiovascular events. The study enrolled 10,061 patients who were evenly randomized to receive either a placebo, 150 mg of canakinumab, or 300 mg of canakinumab. After a median follow-up period of 3.7 years, the primary outcome — which included nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death — occurred at rates of 4.50, 3.86, and 3.90 events per 100 person-years in the placebo, 150-mg canakinumab, and 300-mg canakinumab groups, respectively,

showing a statistically significant reduction in the canakinumab groups [89,90]. There was no observed difference in all-cause mortality between the canakinumab and placebo groups. However, the canakinumab groups experienced a higher incidence of fatal infections/sepsis compared to the placebo group (0.31 vs. 0.18 events per 100 person-years; $p = 0.02$), while cancer mortality was notably lower in those receiving canakinumab than in those receiving placebo [91].

In examining the impact of this treatment on elderly patients, a secondary analysis of the CANTOS trial assessed canakinumab's influence on frailty. The analysis involved calculating the baseline frailty index for 9,942 participants, with 13% being identified as frail [92]. This detailed examination confirmed that the primary outcomes of the CANTOS trial, which highlighted the reduction of cardiovascular events due to canakinumab, remained consistent even when considering patients' frailty levels at the start of the study. This demonstrates the efficacy and safety of the treatment for frail individuals. However, it was observed that there was an increased occurrence of fatal sepsis in older diabetic patients, suggesting the need for careful monitoring of neutropenia in these patients to avoid infections while undergoing treatment.

While the primary outcomes confirmed canakinumab's efficacy in reducing cardiovascular events, it is important to reframe discussions on its use in frail patients, as this therapy demonstrated a higher incidence of infections compared to placebo (0.31 vs. 0.18 events per 100 person-years; $p = 0.02$) [89-91]. Therefore, while canakinumab shows promise, its overall safety profile, particularly concerning infectious complications, necessitates cautious attention in clinical practice.

Colchicine

Colchicine, an immunomodulatory agent, works by reducing inflammation through the inhibition of neutrophil migration and degranulation, and it also encourages the breakdown of collagen by enhancing the activity of collagenase. It is sanctioned for use in various inflammatory conditions, including gout, familial Mediterranean fever, and pericarditis, among others [93-95]. Recently, there's been a growing interest in exploring its potential in CV disease, particularly in IHD. Colchicine's appeal for investigation in the context of IHD stems from its widespread availability, affordability, and generally well-tolerated side effects. Consequently, Colchicine has been recognized as a promising option for CV prevention. Numerous clinical trials have been conducted to assess its efficacy and safety in patients with various forms of IHD, including both acute and chronic coronary syndromes [96,97].

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In a predetermined analysis within the LoDoCo2 trial (Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease), it was found that patients over the age of 65 experienced more significant benefits from colchicine therapy compared to younger patients. This specific age group analysis is not available in other studies [98,99]. These investigations have shed light on the advantages of using colchicine for cardiovascular health, especially for its role in decreasing complications and inflammation in individuals with IHD. The latest guidelines from the European Society of Cardiology on cardiovascular prevention in clinical practice have indicated that patients at high risk of cardiovascular disease might see improvements with a daily dose of 0.5 mg colchicine for secondary prevention, particularly when other risk factors remain unmanaged. Nonetheless, these findings should be approached with caution due to the potential side effects of colchicine, including digestive issues, muscle pains, and pneumonia. Given the increased prevalence of coexisting conditions in older adults, the benefits and risks of colchicine treatment need to be carefully weighed on an individual basis [100].

Methotrexate

Following the outcomes of the CANTOS trial, researchers sought to identify additional drugs that shared its anti-inflammatory characteristics but were more affordable and widely accessible. Low-dose methotrexate emerged as a candidate and was subsequently tested in the Cardiovascular Inflammation Reduction Trial (CIRT) [101,102]. This trial was a randomized, double-blind, placebo-controlled study initiated by investigators. It enrolled participants who had a history of IHD and either type 2 diabetes mellitus or metabolic syndrome. These participants were randomly allocated to receive either low-dose methotrexate (starting at 15 mg) or a placebo. The study ultimately included 4,786 participants. After a median follow-up period of 2.3 years, the initial occurrence of a primary endpoint event (which included nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, or hospitalization for unstable angina necessitating urgent revascularization) was observed in 201 patients in the methotrexate group and 207 in the placebo group (incidence rate of 4.13 vs. 4.31 per 100 person-years; hazard ratio of 0.96; 95% confidence interval CI of 0.79 to 1.16; $p = 0.67$) [103,104]. There were no significant differences observed in any other predetermined cardiovascular endpoint or in any individual component of these endpoints. The rates of serious adverse events, including bleeding and infection, were comparable between the two groups. Therefore, low-dose methotrexate did not lead to a reduction in cardiovascular events among patients

with IHD during the follow-up period. Additionally, it did not result in decreased levels of interleukin-1 β , interleukin-6, or CRP [105].

Ziltivekimab

Ziltivekimab, an innovative inhibitor of the IL-6 ligand, has shown promise as a new treatment option for atherosclerotic conditions. IL-6 is a crucial cytokine in the body's innate immune response and plays a significant role in the NLRP3 inflammasome pathway, which is connected to both IL-1 and IL-6, leading to the production of the inflammatory marker CRP [106,107]. Ziltivekimab targets these inflammatory pathways, especially in the realm of cardiovascular health. In the RESCUE trial, a phase 2 study that was randomized, double-blind, and placebo-controlled, Ziltivekimab was effective in lowering inflammation and thrombosis markers, such as high-sensitivity CRP, fibrinogen, serum amyloid A, haptoglobin, secretory phospholipase A2, and lipoprotein (a) [108]. This trial, which involved participants with chronic kidney disease and high CRP levels, found that these biomarkers decreased in a dose-dependent manner over 24 weeks, without significant side effects. Notably, the reduction in high-sensitivity CRP was more substantial than that seen in the CANTOS trial, which used an IL-1 β inhibitor. These encouraging findings lead to the initiation of the ZEUS trial, a comprehensive cardiovascular outcome study that will examine the effects of Ziltivekimab on patients with chronic kidney disease, high high-sensitivity CRP, and pre-existing cardiovascular disease [109,110]. Should the results from larger, long-term studies confirm its safety and effectiveness, Ziltivekimab could stand out among available IL-6 inhibitors, representing a significant advance in managing residual inflammatory risk in patients with atherosclerotic cardiovascular disease.

Existing paradigms and future perspectives

Although the current guidelines do not yet emphasize specific anti-inflammatory treatments, the encouraging outcomes from the CANTOS, COLCOT, and LoDoCo2 studies underscore the potential importance of this approach. There are still numerous questions about these treatments, especially regarding how to customize therapy, ensure patient adherence, assess long-term safety, and evaluate cost-effectiveness [111-113]. However, the existing evidence clearly directs modern medical practice towards this innovative perspective, confirming the significance of the residual risk hypothesis.

The proposed ideas should be further refined because people can show different types of remaining risk, such as 'inflammatory', 'lipid', or 'thrombotic'. Identifying these patterns can help in customizing secondary prevention strategies for individuals. In this context, using hs-CRP might be beneficial for both

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initial screening and monitoring the effectiveness of treatment [8,32]. Still, it's important to remember the successful outcomes in the CANTOS and LoDoCo2 trials, where high hs-CRP levels were not a requirement for participation. These results highlight the need for additional methods to evaluate residual inflammatory risk and suggest that a wide range of individuals could benefit from such strategies.

Upcoming and continuing studies, including CLEAR SYNERGY, which involves colchicine, and ASSAIL-MI, which focuses on tocilizumab (an IL-6 receptor blocker), will offer additional insights into the importance and position of these treatments within the therapeutic toolkit for IHD [114,115].

Conclusion

In summary, this review highlights the integral role of inflammation in the development and progression of ischemic heart disease, particularly after acute myocardial infarction. The evidence points to inflammation not only as a contributor to atherosclerosis but also as a potential therapeutic target. Clinical trials have demonstrated that anti-inflammatory treatments can significantly reduce the risk of major cardiovascular events, providing a compelling argument for their integration into standard care protocols. However, the variability in patient responses emphasizes the need for personalized treatment approaches, especially in diverse populations. As research continues to unveil the complexities of inflammatory pathways, future studies should focus on optimizing anti-inflammatory strategies to enhance cardiovascular outcomes. By recognizing and addressing inflammation as a key player in ischemic heart disease, we can advance towards more effective prevention and management strategies in cardiovascular care.

In conclusion, this review underscores the multifaceted role of inflammation in ischemic heart disease. Evidence suggests that inflammation is not only a prominent factor following acute myocardial infarction but also plays a pivotal role in the early onset and progression of atherosclerosis. Recognizing inflammation as a dynamic participant throughout the entire spectrum of cardiovascular disease is essential. This insight emphasizes the need for anti-inflammatory strategies that target not only secondary prevention post-event but also the early stages of atherogenesis, potentially revolutionizing cardiovascular care.

In summary, this review delineates the multifaceted role of inflammation in ischemic heart disease, emphasizing not only its contribution post-myocardial infarction but also during the development and progression of atherosclerosis. The exploration of lipid mediators and specialized pro-resolving mediators elucidates new avenues for therapeutic intervention

that could revolutionize cardiovascular care. Recognizing the dynamic nature of inflammation throughout the spectrum of cardiovascular disease is essential. Future studies should focus on integrating these mediators into therapeutic frameworks, potentially leading to more effective prevention and management strategies in cardiovascular care.

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