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REVIEW ARTICLE

Inflammation and cardiovascular disease – Part I: Mechanisms and biomarkers

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Abstract

Inflammation is a fundamental driver of atherosclerotic cardiovascular disease (ASCVD), orchestrating immune activation, endothelial dysfunction, and plaque instability. While lipid-lowering therapies can reduce the burden of ASCVD, persistent inflammation remains a critical determinant of residual cardiovascular risk, highlighting the need for deeper investigation into inflammatory pathways. Key mediators, including interleukin-6, high-sensitivity C-reactive protein, and myeloperoxidase, amplify immune cell infiltration, foam cell formation, and extracellular matrix degradation, exacerbating atherosclerotic progression. Beyond these well-established markers, emerging inflammatory biomarkers, such as cluster of differentiation (CD)47, serum and glucocorticoid-regulated kinase 1 (SGK1), P-selectin, and growth differentiation factor 15 (GDF15), provide novel insights into vascular inflammation and immune dysregulation. CD47 modulates macrophage-mediated immune evasion, allowing apoptotic debris to accumulate within plaques, while SGK1 enhances pro-inflammatory signaling and endothelial dysfunction. P-selectin facilitates leukocyte adhesion and platelet aggregation, contributing to plaque destabilization and thrombotic risk. GDF15, a stress-responsive cytokine, is associated with adverse cardiovascular outcomes, linking metabolic dysfunction to chronic inflammation. Likewise, inflammasome activation, particularly through NACHT, LRR, and PYD domains-containing protein 3 and absent in melanoma 2 pathways, triggers cytokine cascades that perpetuate vascular injury, while clonal hematopoiesis of indeterminate potential promotes myeloid-driven inflammation and atherosclerotic acceleration. The expanding role of these biomarkers underscores the complexity of inflammation in ASCVD and highlights their potential for refining cardiovascular risk assessment and elucidating novel mechanisms underlying plaque progression.

Keywords: Cardiovascular disease; Chronic kidney disease; Atherosclerotic cardiovascular disease; Inflammatory biomarkers; Vascular inflammation; Plaque instability and thrombosis

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1. Introduction

1.1. The prevalence of cardiovascular disease

Globally, cardiovascular disease (CVD) remains the leading cause of mortality and morbidity, accounting for over 20.6 million deaths and approximately 393 million disability-adjusted life years annually.[1,2] While high-income countries have achieved a 34.9% decline in CVD mortality from 1990 to 2022, reflecting the impact of preventive measures and advancements in treatment, low- and middle-income countries are experiencing a rising burden. These alarming statistics underscore the urgent need for comprehensive strategies that combine population-level prevention, risk factor management, and equitable access to healthcare to mitigate the profound impact of CVD on global health systems.

1.2. Reduction in cardiovascular disease inflammation through risk factor control

Reducing the global burden of CVD requires prioritizing the control of modifiable risk factors to decrease disease prevalence, mortality, and healthcare costs. The American Heart Association's Life's Essential 8 framework provides a comprehensive roadmap for achieving and maintaining cardiovascular health (CVH) across diverse populations (Figure 1). The framework is as follows:

i. Diet: Adherence to dietary patterns such as the Dietary Approaches to Stop Hypertension or the Mediterranean diet lowers hypertension, atherogenic lipids, and ischemic risk by emphasizing whole foods, healthy fats, and low sodium
ii. Physical activity: Regular exercise boosts endurance, lowers blood pressure, enhances insulin sensitivity, and reduces inflammation, reducing the risk of myocardial infarction and heart failure
iii. Nicotine exposure: Avoiding smoking and secondhand smoke prevents endothelial dysfunction and atherogenesis, lowering the risk of peripheral arterial disease and coronary events
iv. Sleep health: Adequate sleep (7 – 9 h) supports CVH by regulating metabolism, reducing sympathetic overactivity, and mitigating hypertension and obesity
v. Body mass index (BMI): Maintaining a healthy BMI lowers the prevalence of metabolic syndrome and reduces the risk of coronary artery disease and non-ischemic cardiomyopathy
vi. Blood lipids: Controlling non-high-density lipoprotein (HDL) cholesterol slows atherosclerosis progression and stabilizes plaques, especially in high-risk individuals
vii. Blood glucose: Optimized glucose control prevents diabetes-related vascular complications, including retinopathy, nephropathy, myocardial infarction, and stroke
viii. Blood pressure: Managing systolic and diastolic blood pressure prevents strokes, heart failure, and renal damage, reducing the overall CVD burden.

Studies indicate that achieving high scores across these domains reduces CVD risk by up to 80% and could prevent an estimated 2 million CVD events annually in the United States (U.S.) alone.[3] A recent analysis highlighted the significant impact of adhering to the updated Life's Essential 8 framework in improving CVH and reducing mortality, demonstrating a linear association between CVH scores and reductions in all-cause and CVD-specific mortality. Among a cohort of nearly 20,000 U.S. adults, those achieving high CVH scores (≥75) experienced a 58% reduced risk of all-cause mortality and a 64% reduced risk of CVD-specific mortality compared to those with low scores.[4] Physical activity emerged as the most significant contributor, with improvements linked to a 17.8% reduction in CVD-specific mortality. Similarly, optimal control of blood pressure and glucose were critical, accounting for 12.5% and 10.3% of preventable deaths, respectively.

2. Inflammation in atherosclerotic cardiovascular disease (ASCVD)

2.1. The inflammatory mechanisms underlying ASCVD pathogenesis

Inflammation is now recognized as a key driver of ASCVD, redefining it from a passive lipid accumulation process to a dynamic interplay of immune activation and vascular injury. Biomarkers such as high-sensitivity C-reactive protein (hs-CRP) highlight the residual inflammatory risk, even in patients with optimal low-density lipoprotein (LDL) levels on statins.

2.2. Plaque formation

The formation of atherosclerotic plaques is initiated by endothelial injury (Figure 2). Endothelial dysfunction promotes the retention of apolipoprotein B-containing lipoproteins, such as LDL, within the subendothelial space. These lipoproteins undergo oxidative modification, triggering the expression of adhesion molecules, such as vascular cell adhesion molecule 1 and intercellular adhesion molecule 1, which facilitate the recruitment of circulating monocytes.[5,6] On transmigration into the intima, monocytes differentiate into macrophages and engulf oxidized LDL, forming foam cells. Concurrently, smooth muscle cells migrate from the media to the intima and synthesize extracellular matrix components, such as collagen, which stabilize the nascent plaque. However,

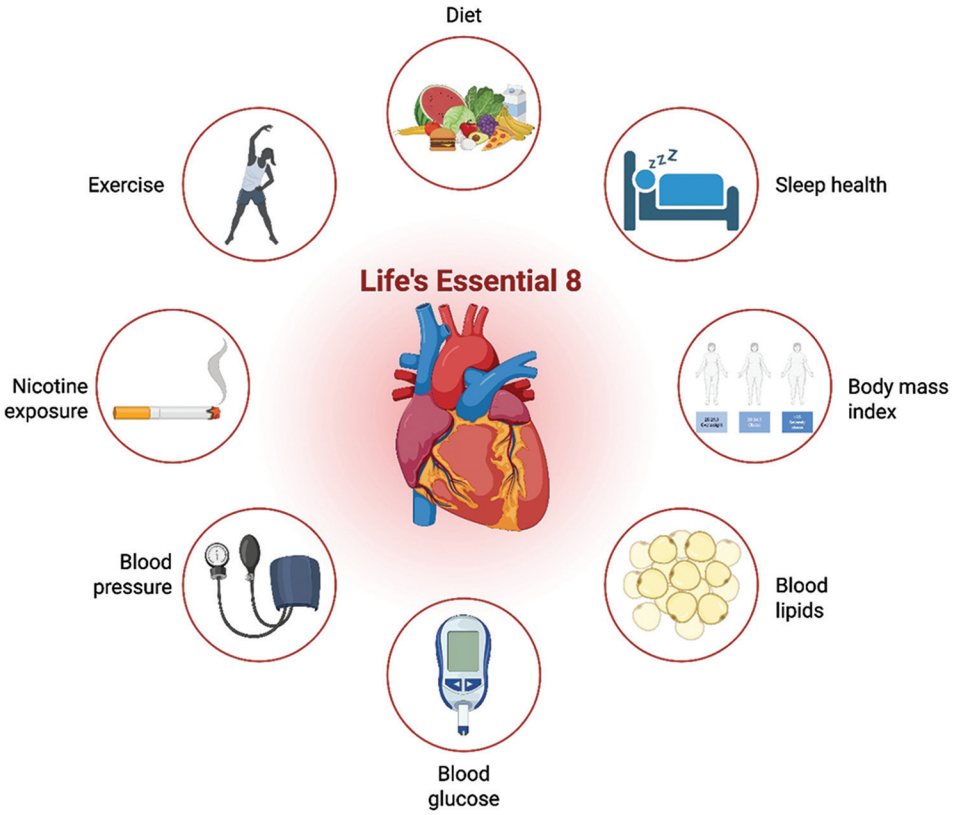

Figure 1. Life's Essential 8 for optimal cardiovascular health. These include a heart-healthy diet, engaging in regular physical activity, avoiding nicotine exposure, maintaining restorative sleep hygiene, achieving a healthy body mass index, optimizing blood pressure, controlling blood lipids, and managing blood glucose levels. Collectively, these factors form the foundation for reducing the burden of atherosclerotic cardiovascular disease and associated complications. Image was created using Biorender.

a chronic inflammatory environment leads to apoptotic cell death and necrosis, forming a lipid-rich necrotic core surrounded by calcified deposits.

2.3. Plaque rupture

Rupture occurs when the structural integrity of the fibrous cap is compromised, exposing the highly thrombogenic necrotic core to circulating blood. This event is predominantly driven by macrophage infiltration into the cap, where these cells release matrix metalloproteinases and other proteolytic enzymes that degrade collagen and weaken the extracellular matrix.[5,6] Simultaneously, the apoptosis of smooth muscle cells further reduces collagen synthesis, exacerbating cap thinning. Thin-cap fibroatheromas, characterized by fibrous caps <65 μm thick, large necrotic cores, and extensive macrophage infiltration, are particularly prone to rupture. The exposure to necrotic material activates platelets and the coagulation cascade, leading to thrombus formation that can occlude arterial blood flow, resulting in myocardial infarction.

2.4. The role of inflammatory markers

Inflammatory blood markers provide critical insights into ASCVD pathophysiology, reflecting systemic immune activation and its role in disease progression (Table 1). The interleukin (IL)-1 cytokine signaling, particularly through IL-1β, serves as a key upstream mediator of inflammation by activating nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase/protein kinase B pathways, leading to increased IL-6 transcription. This cascade amplifies systemic inflammation, with IL-6 stimulating the hepatic synthesis of hs-CRP, a widely studied biomarker of cardiovascular risk. Hs-CRP levels have been incorporated into risk stratification tools, such as the Reynolds Risk Score, and have been shown to improve the identification of individuals at heightened ASCVD risk, particularly those with low LDL levels but persistent low-grade inflammation.[5] Elevated IL-6 levels, a cytokine that contributes to atherogenesis by promoting endothelial activation and foam cell formation, have also been linked to a two-fold increase in cardiac events among individuals in the highest quartile of IL-6 levels.

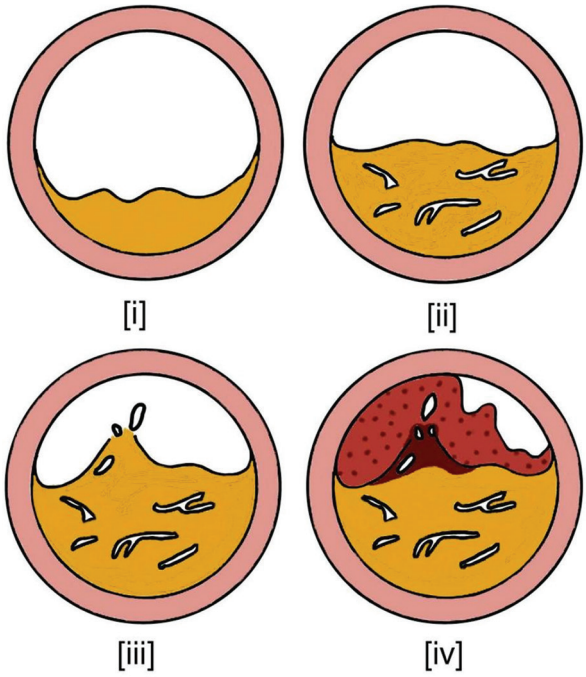

Figure 2. Four stages of atherosclerosis, from fatty deposition to plaque rupture: (i) Early fatty streak formation: Initial accumulation of lipids in the arterial wall. (ii) Plaque expansion: Increased lipid accumulation with inflammatory cell infiltration. (iii) Advanced plaque: Plaque enlargement with cholesterol deposits and immune cell involvement. (iv) Plaque rupture and thrombosis: Ulceration and rupture of the plaque, leading to potential clot formation and vessel occlusion. Image was created using Notability.

Additional biomarkers offer further insights into ASCVD pathophysiology. Myeloperoxidase (MPO) released by inflammatory cells catalyzes LDL and HDL oxidative modifications, impairing cholesterol efflux and contributing to plaque instability.[5] Lipoprotein-associated phospholipase A2 (Lp-PLA2), primarily associated with LDL particles, promotes oxidative stress and the progression of atherosclerotic plaques by releasing pro-inflammatory mediators. In large cohort studies, elevated plasma levels of Lp-PLA2 have been independently linked to coronary artery disease events.[5] Finally, trimethylamine-N-oxide, a gut microbiome-derived metabolite, exacerbates vascular inflammation by promoting cholesterol deposition and foam cell formation, correlating with adverse cardiovascular outcomes.

2.5. Emerging biomarkers in ASCVD

While established biomarkers, such as hs-CRP and IL-6, help assess systemic inflammation, emerging biomarkers provide deeper insight into disease mechanisms. These include cluster of differentiation (CD)47, serum and glucocorticoid-regulated kinase 1 (SGK1), P-selectin, and growth differentiation factor 15 (GDF15).

In immune regulation, CD47, widely expressed on vascular endothelial cells, macrophages, and platelets, plays a crucial role by interacting with signal regulatory protein-alpha (SIRPα) on phagocytes.[7] This interaction generates a "do not eat me" signal that suppresses macrophage-mediated clearance of apoptotic cells. In the context of ASCVD, increased CD47 expression within plaques promotes immune evasion, allowing damaged endothelial and lipid-laden foam cells to persist, fueling chronic inflammation and plaque progression.[7] Impaired efferocytosis leads to necrotic core expansion, further increasing the risk of plaque rupture and thrombosis. This dysfunction is mediated through the thrombospondin-1/CD47/SIRPα signaling, which limits apoptotic cell clearance and enhances IL-1β release through inflammasome activation, amplifying vascular immune responses.[7] Elevated CD47 levels correlate with plaque vulnerability, supporting its potential role in inflammatory risk stratification. Preclinical studies have demonstrated that CD47 blockade restores efferocytosis and reduces plaque burden, underscoring its emerging relevance as a prognostic biomarker and therapeutic target in ASCVD.

Besides, SGK1 is a serine/threonine kinase involved in ion transport, cellular survival, and inflammatory signaling. In ASCVD, it contributes to vascular remodeling by modulating endothelial function, promoting smooth muscle proliferation, and activating immune cells.[8] SGK1 enhances NF-κB signaling and NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome activation, leading to increased IL-6 and IL-1β production and subsequent leukocyte recruitment. It also disrupts endothelial nitric oxide synthase activity, promoting endothelial dysfunction and impaired vasodilation. In advanced plaques, SGK1-driven smooth muscle proliferation promotes neointimal thickening and arterial stiffening, exacerbating the hemodynamic burden of atherosclerosis. Inhibition of SGK1 in preclinical models has been shown to suppress NF-κB activity, reduce caspase-1 activation, and dampen downstream cytokine production, resulting in attenuation of cardiac inflammation and remodeling.[8] SGK1 expression is also elevated in thrombi from patients with acute myocardial infarction, suggesting potential utility in identifying high-risk inflammatory states. These findings highlight SGK1 as a mechanistic driver of vascular inflammation and a promising biomarker and therapeutic target in inflammation-mediated CVD.

Similarly, P-selectin, an adhesion molecule stored in the α-granules of platelets and Weibel–Palade bodies of endothelial cells, is rapidly translocated to the cell surface on activation, where it binds to P-selectin glycoprotein

Table 1. Pro-inflammatory markers and their mechanisms in atherosclerotic inflammation

Pro-inflammatory marker	Mechanisms in atherosclerotic inflammation
Interleukin (IL)-1α	IL-1α functions as an alarmin released upon necrotic cell death. It is constitutively expressed in endothelial and epithelial cells. It binds to IL-1 receptor type 1 (IL-1R1) to activate NF-κB, MAPK, and JNK pathways, promoting early local inflammation, leukocyte recruitment, and induction of IL-1β. It is central to initiating the IL-1-driven inflammatory loop in ASCVD.
IL-1β	The binding of IL-1β to IL-1R1 activates signal pathways such as NF-κB, JNK, and p38 MAPK and induces expressions of genes such as IL-6, IL-8, MCP-1, COX-2, IL-1α, and IL-1β.
IL-6	Multi-modal pathways are noted. IL-6 binds to membrane-bound IL-6 receptors present on hepatocytes, some leukocytes, and endothelial cells (classic signaling); to soluble forms of the IL-6 receptors, which allow signaling in most other cell types (trans-signaling); or through trans-presentation from dendritic cells to T cells (trans-presentation). All modes of signaling converge on the membrane signal-transducing receptor subunit glycoprotein 130 to activate the intracellular Janus kinase signal transducer and activator of transcription pathway.
Myeloperoxidase (MPO)	Released by inflammatory cells, MPO catalyzes oxidative modifications of LDL and HDL, impairing cholesterol efflux and destabilizing plaques.
High-sensitivity C-reactive protein (hs-CRP)	Synthesized in the liver in response to IL-6 activation, hs-CRP serves as a marker of systemic inflammation and cardiovascular risk.
Lipoprotein-associated phospholipase A2 (Lp-PLA2)	Lp-PLA2 is associated with LDL particles. It promotes oxidative stress and releases pro-inflammatory mediators, driving plaque progression.
Trimethylamine-N-oxide (TMAO)	Derived from the gut microbiome, TMAO enhances vascular inflammation by promoting cholesterol deposition and foam cell formation.

Abbreviations: ASCVD: Atherosclerotic cardiovascular disease; COX-2: Cyclo-oxygenase-2; JNK: c-Jun N-terminal kinase; MAPK: Mitogen-activated protein kinase; MCP-1: Monocyte chemoattractant protein-1; NF-κB: Nuclear factor-kappa B.

ligand-1 (PSGL-1) on monocytes and neutrophils.[9] This interaction facilitates leukocyte rolling, adhesion, and infiltration into the arterial intima, promoting local inflammation, foam cell formation, and plaque progression. Sustained P-selectin/PSGL-1 signaling activation amplifies cytokine release, fosters platelet–leukocyte aggregation, and contributes to both microvascular dysfunction and thrombotic instability. Genetic polymorphisms in the *SELP* gene have been associated with elevated soluble P-selectin levels and increased cardiovascular risk, suggesting a role in inflammatory risk stratification.[9] Furthermore, anti-P-selectin therapies, such as crizanlizumab and inclaclumab, have demonstrated early promise in reducing myocardial injury and dampening inflammatory thrombotic responses, underscoring the translational potential of this pathway in ASCVD.

Meanwhile, GDF15, a member of the transforming growth factor-beta superfamily, is a stress-responsive cytokine upregulated in response to ischemic injury, pressure overload, oxidative stress, and systemic inflammation. It integrates signals from cardiometabolic, inflammatory, and mechanical stress pathways, making it a broad cardiovascular risk marker. Persistently elevated GDF15 levels reflect maladaptive remodeling and are independently associated with adverse outcomes in coronary artery disease, heart failure, and atrial fibrillation – even after adjustment for natriuretic peptides and troponins.[10] Its prognostic value across large cohorts has positioned GDF15 as a promising tool for inflammatory risk stratification. In addition, the incorporation of GDF15 into multi-marker models improves the prediction of mortality and hospitalization, reinforcing its utility in identifying patients with high-risk, inflammation-driven CVD.

2.6. The role of adaptive immunity

The adaptive immune system plays a pivotal role in the pathogenesis of ASCVD, contributing to the progression and regulation of atherosclerotic plaques. The key components of this system include antigen-presenting cells, $CD4^+$ T-helper cells, and B lymphocytes, all of which orchestrate targeted immune responses within the arterial wall.

Antigen-presenting cells, such as dendritic cells and macrophages, process and present oxidized LDL and other atherogenic antigens through major histocompatibility complex molecules to naive T cells.[11,12] This interaction drives the differentiation of $CD4^+$ T cells into distinct subsets with varying impacts on atherogenesis. T helper

1 cells, the predominant subset in plaques, release pro-inflammatory cytokines, such as interferon-γ and tumor necrosis factor-alpha (TNF-α), which amplify vascular inflammation, recruit additional immune cells, and destabilize plaques by promoting matrix degradation and necrotic core expansion.

Meanwhile, B lymphocytes also play a pivotal role in the progression of ASCVD by amplifying inflammatory responses within atherosclerotic plaques. Adaptive B2 cells contribute to disease pathogenesis by producing IgG antibodies against atherogenic antigens, which form immune complexes and activate complement pathways, intensifying local vascular inflammation.[11,12] These cells secrete pro-inflammatory cytokines, such as IL-6 and TNF-α, further exacerbating endothelial dysfunction and promoting plaque instability. By interacting with other immune cells and perpetuating inflammatory cascades, B lymphocytes contribute significantly to the chronic immune activation that drives the progression and destabilization of atherosclerotic plaques in ASCVD.

The clonal expansion of T- and B-cells specific to atherogenic antigens sustains the immune activation within plaques, perpetuating a cycle of inflammation and vascular injury. The accumulation of immune complexes, activation of complement pathways, and engagement of cytotoxic $CD8^+$ T cells further contribute to plaque destabilization, emphasizing the multifaceted nature of active immunity in ASCVD.

3. The role of inflammasomes in ASCVD

3.1. Introduction to inflammasomes in ASCVD

Inflammasomes are multiprotein complexes within the cytoplasm that act as pivotal regulators of the inflammatory response. They link cellular stress and immune activation in the development and progression of ASCVD. The NLRP3 and absent in melanoma 2 (AIM2) inflammasomes are the most extensively studied inflammasomes implicated in ASCVD (Figure 3). Together, these inflammasomes destabilize atherosclerotic plaques, making them more prone to rupture and thrombosis.

3.2. Mechanisms of NLRP3 and AIM2 inflammasomes

The NLRP3 inflammasome is a central driver of inflammation in atherosclerosis and is activated through a well-characterized two-step process. The priming phase is initiated by pattern recognition receptors, such as toll-like receptors, which activate NF-κB and upregulate the transcription of NLRP3 and its downstream effectors, pro-IL-1β and pro-IL-18.[13,14] The subsequent activation phase is triggered by stimuli characteristic of the atherogenic environment, including extracellular cholesterol crystals, oxidized LDL, potassium efflux, lysosomal destabilization, and mitochondrial-derived reactive oxygen species. These signals converge to promote NLRP3 oligomerization and its interaction with the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC) and pro-caspase-1, forming the active inflammasome complex. Once assembled, this complex cleaves pro-caspase-1 into its active form, which subsequently processes pro-IL-1β and pro-IL-18 into their mature, secreted forms. These cytokines propagate vascular inflammation by inducing endothelial cell activation, upregulating adhesion molecules, and recruiting monocytes to the arterial intima. In vascular smooth muscle cells, inflammasome activity promotes apoptosis and extracellular matrix degradation, while in macrophages, inflammasome-driven IL-1β release enhances foam cell formation and necrotic core expansion. Together, these effects compromise fibrous cap integrity, reduce plaque stability, and increase susceptibility to rupture and thrombosis.

The AIM2 inflammasome operates through a distinct DNA-sensing mechanism, detecting cytoplasmic double-stranded DNA (dsDNA) derived from mitochondrial damage, necrotic cells, or neutrophil extracellular traps.[13,14] On binding dsDNA, AIM2 undergoes conformational changes that drive its oligomerization and subsequent recruitment of ASC and pro-caspase-1, leading to caspase-1 activation and downstream cytokine maturation. In macrophages and endothelial cells, AIM2 activation has been shown to induce pyroptotic cell death through gasdermin D pore formation, disrupting membrane integrity and releasing intracellular damage-associated molecular patterns (DAMPs), such as DNA fragments, ATP, and oxidized lipids.[13,14] These DAMPs perpetuate local inflammation and act as secondary triggers for additional inflammasome activation, creating a self-reinforcing inflammatory loop within the plaque. AIM2 has also been implicated in promoting plaque necrosis, expanding the necrotic core, and impairing resolution pathways such as efferocytosis – further destabilizing the plaque microenvironment. The combined activity of NLRP3 and AIM2 inflammasomes across multiple vascular cell types highlights their role as central orchestrators of atherosclerotic progression and potential therapeutic targets for inflammation-driven CVD.

3.3. The IL-1 cytokine signaling: Upstream initiator of inflammation

Before amplifying downstream mediators such as IL-6, the IL-1 family – particularly IL-1α and IL-1β – initiates

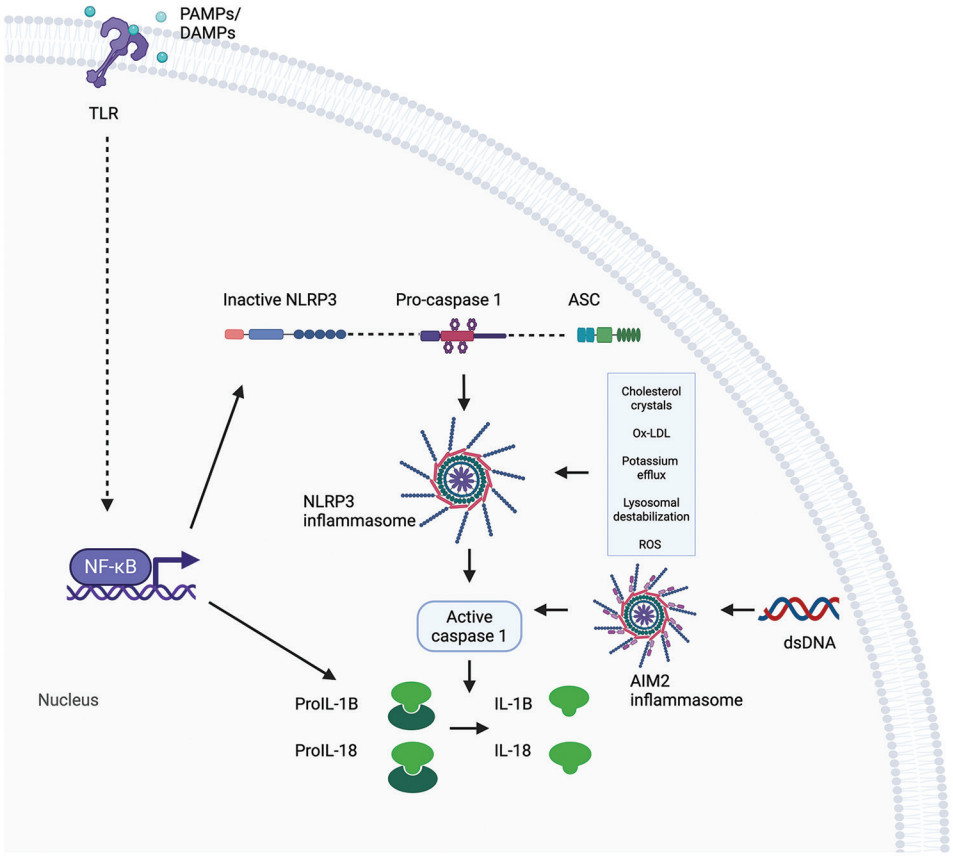

Figure 3. Inflammasome pathways in atherosclerosis. The NACHT, LRR, and PYD domains-containing protein 3 inflammasome activation involves toll-like receptor-mediated priming via nuclear factor-kappa B and triggering by stimuli such as cholesterol crystals, oxidized low-density lipoprotein, and reactive oxygen species. This leads to caspase-1 activation and interleukin (IL)-1β/IL-18 maturation. The absent in melanoma 2 inflammasome, activated by cytoplasmic double-stranded DNA, also promotes IL-1β/IL-18 release and pyroptosis. Together, these pathways drive chronic inflammation. Image was created using Biorender. Abbreviations: ASC: Apoptosis-associated speck-like protein containing a CARD; DAMPs: Damage-associated molecular patterns; PAMPs: Pathogen-associated molecular patterns.

vascular inflammation. IL-1α is constitutively expressed in endothelial and epithelial cells and is rapidly released in a biologically active form on cell necrosis, functioning as an alarmin that alerts surrounding immune cells to tissue injury.[15] In contrast, IL-1β is synthesized by activated myeloid cells and requires cleavage by the NLRP3 inflammasome to become active. Both forms engage the IL-1 receptor type 1, triggering NF-κB and MAPK signaling cascades that upregulate adhesion molecules, cytokines, and chemokines critical to monocyte recruitment and endothelial dysfunction. Experimental models demonstrate that IL-1α release precedes IL-1β activation, initiating an IL-1-driven loop in which dying vascular cells stimulate infiltrating macrophages to produce IL-1β, further amplifying local and systemic inflammation.[15] This interplay is crucial in atherosclerosis, where IL-1 signaling promotes foam cell formation, plaque destabilization, and thrombotic risk. Importantly, IL-1 directly induces hepatic IL-6 production, establishing a mechanistic bridge between early innate immune activation and downstream cytokine-mediated risk.

The upstream positioning of IL-1α and IL-1β in the inflammatory cascade has translational implications. Elevated IL-1 levels have been detected in patients with acute coronary syndromes, myocarditis, and inflammatory vascular conditions, supporting its role as a clinical biomarker of vascular inflammation. Moreover, targeted inhibition of IL-1 signaling with agents, such as anakinra, rilonacept, and canakinumab, has shown benefits across a range of cardiovascular and systemic inflammatory diseases. These findings underscore the diagnostic and therapeutic potential of IL-1 modulation in inflammation-driven cardiovascular pathology. With the upstream role of IL-1 established, attention now turns to IL-6, whose broad influence across cardiovascular, renal, and metabolic systems underscores its relevance as both a biomarker and a therapeutic target.

4. IL-6 inhibition in cardiac disease and chronic kidney disease (CKD): A multidimensional perspective

4.1. Introduction to IL-6 signaling

IL-6 is pivotal in immune regulation and inflammatory responses, acting through complex signaling pathways. It is secreted by various cell types, including macrophages, fibroblasts, and endothelial cells, often in response to upstream stimuli, such as IL-1 or tissue injury. IL-6 signals through three distinct mechanisms: (i) classic signaling, in which IL-6 binds to membrane-bound IL-6 receptors and activates glycoprotein 130 (gp130); (ii) trans-signaling, which uses soluble IL-6 receptors to broaden its effect to cells lacking IL-6 receptors; and (iii) trans-presentation, a specialized process involving dendritic cells and T cells.[16] All signaling modes converge on gp130 and activate the Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway, driving gene expression changes that promote inflammation, endothelial dysfunction, and disease progression. Beyond its mechanistic roles, IL-6 has emerged as a potent clinical biomarker and therapeutic target in inflammation-driven CVD. Elevated IL-6 levels are independently associated with adverse outcomes in coronary artery disease, heart failure, and CKD, even after adjusting for traditional risk markers. Genetic evidence supports a causal relationship between IL-6 signaling and ASCVD, while *post hoc* analyses from the CANTOS trial demonstrated that a reduction in IL-6 levels was closely tied to improved cardiovascular outcomes.[16] These insights have led to the development of IL-6-targeted therapies, such as ziltivekimab, which is currently being tested in the ZEUS trial (ClinicalTrials.gov ID: NCT05021835) to reduce cardiovascular events in patients with CKD and elevated inflammatory risk.

4.2. The role of IL-6 in acute coronary ischemia

Acute coronary ischemia, characterized by myocardial hypoxia and plaque rupture, is significantly affected by elevated IL-6 levels, which amplify systemic and local inflammation. In phase II trials, including the ASSAIL-MI and SOLID-TIMI 52[17] studies, a single administration of the IL-6 receptor antagonist tocilizumab in patients with ST-segment elevation myocardial infarction demonstrated reductions in microvascular obstruction and inflammatory markers, such as CRP. These improvements were evident during hospitalization and were particularly notable when treatment was initiated after a delay of more than 3 h from symptom onset. Mechanistically, IL-6 inhibition mitigates the acute-phase response by decreasing monocyte chemoattraction and neutrophil activation, thereby limiting inflammatory damage to myocardial tissue.

4.3. Integrative inflammatory networks in ASCVD

While each inflammatory pathway contributes uniquely to atherogenesis, their interactions form a tightly interconnected network that amplifies vascular injury and plaque progression. IL-1 signaling, often triggered by necrotic cell death or inflammasome activation, initiates a cascade that upregulates IL-6, bridging local tissue inflammation with systemic responses, such as hepatic hs-CRP production. IL-6, in turn, reinforces monocyte activation and endothelial dysfunction, enhancing the expression of adhesion molecules and facilitating leukocyte infiltration. Concurrently, SGK1 intensifies this pro-inflammatory signaling environment by promoting NF-κB activity and NLRP3 inflammasome assembly, further increasing IL-1β and IL-6 production. CD47 exacerbates this cycle by impairing efferocytosis, allowing apoptotic cells and inflammatory debris to accumulate within the plaque, thereby sustaining immune cell activation. In addition, MPO and Lp-PLA2 perpetuate oxidative stress, leading to destabilized plaques and amplified cytokine release. These interwoven pathways collectively fuel a feed-forward loop of inflammation, oxidative injury, and immune dysregulation – underpinning the pathophysiology of plaque instability and thrombotic events in ASCVD.

The downstream consequences of these overlapping inflammatory circuits become especially pronounced in chronic cardiovascular and renal conditions, where IL-6 drives maladaptive tissue remodeling, systemic immune activation, and end-organ dysfunction – hallmarks of both heart failure and CKD.

4.4. The role of IL-6 in heart failure

IL-6 plays a central role in heart failure, promoting adverse cardiac remodeling through inflammatory pathways. Elevated IL-6 levels have been consistently associated with higher rates of hospitalization, cardiovascular mortality, and worsening cardiac function. Findings from the BIOSTAT-CHF study revealed that IL-6 correlated with markers of disease severity, including elevated N-terminal pro-B-type natriuretic peptide and cardiac fibrosis.[16,17] Moreover, IL-6 stimulates hepcidin production, contributing to anemia – a common exacerbating factor in heart failure.[16,17] Clinical evidence from the CANTOS trial demonstrated that patients with the highest reductions in IL-6 following anti-inflammatory therapy exhibited the most significant declines in heart failure hospitalizations.

4.5. The role of IL-6 in CKD and hemodialysis

Patients with CKD and those undergoing hemodialysis experience elevated IL-6 levels due to persistent oxidative

stress, tissue hypoxia, and retention of uremic toxins.[16,17] IL-6 predicts vascular events and mortality more accurately than traditional lipid measures in prognostic accuracy. Elevated IL-6 levels contribute to systemic inflammation, exacerbating endothelial dysfunction and promoting atherosclerosis. In hemodialysis patients, IL-6 also affects anemia by modulating hepcidin levels, reducing iron bioavailability, and impairing erythropoiesis.[16,17] Data from the CANTOS trial and related studies suggest that targeting IL-6 pathways reduces inflammatory marker expression and may improve cardiovascular outcomes in CKD patients.

5. Clonal hematopoiesis as a risk factor for ASCVD

5.1. Clonal hematopoiesis of indeterminate potential (CHIP) and atherosclerosis

CHIP is characterized by somatic mutations in hematopoietic stem and progenitor cells (HSPCs), increasingly recognized as a key contributor to ASCVD. Frequently observed mutations – most commonly in *TET2*, *DNMT3A*, *ASXL1*, and *JAK2* – promote myeloid-biased differentiation and endow HSPCs with enhanced self-renewal and inflammatory potential. These mutations are not merely passenger events. They induce functional changes in immune cells that accelerate atherosclerosis. In murine models, the transplantation of *Tet2*-deficient bone marrow promotes plaque growth, enhanced macrophage accumulation, and increased IL-1β secretion, mainly through NLRP3 inflammasome activation, even when present in only 10% of donor marrow.[18-20] This indicates that minor clonal populations can exert outsized inflammatory effects. Similarly, *Jak2* V617F mutation increases monocyte recruitment, macrophage proliferation, and necrotic core formation in plaques, driven by dual activation of AIM2 and NLRP3 inflammasomes. CHIP-mutant macrophages exhibit a hyperinflammatory phenotype that compromises efferocytosis, destabilizes plaques, and enhances leukocyte recruitment. These effects are not limited to atherosclerosis alone but extend to impaired cardiac repair and increased fibrosis in heart failure models. Epidemiologically, CHIP carriers – especially those with high variant allele fractions – face a twofold increased risk of ASCVD, comparable to traditional risk factors and independent of lipid levels or smoking history.[18-20] Emerging evidence also links CHIP to epigenetic aging, suggesting an additional biomarker framework for risk stratification.

5.2. Gene variants associated with clonal hematopoiesis of indeterminate potential

The pathogenicity of CHIP is highly dependent on the specific mutated gene, each of which affects inflammatory pathways through distinct mechanisms. *TET2* mutations lead to the loss of its demethylase function, increasing histone acetylation at inflammatory gene promoters, such as those in *IL1B* and *NLRP3*. *Tet2*-deficient macrophages display enhanced inflammasome priming and IL-1β production in response to oxidized LDL and other danger signals.[18-20] Treatment with NLRP3 inhibitors in murine *Tet2*-CHIP models significantly attenuates plaque burden, underscoring the therapeutic potential of targeting upstream inflammatory pathways. *DNMT3A* mutations, while impairing epigenetic regulation, alter gene expression through distinct methylation patterns. Although they similarly skew hematopoiesis and promote a pro-inflammatory macrophage phenotype, *DNMT3A*-mutant cells show increased IL-6 and chemokine secretion with relatively less IL-1β production, suggesting partial divergence from Tet methylcytosine dioxygenase 2 (Tet2)-mediated pathways.[18-20] *JAK2* V617F mutation, a gain-of-function mutation, enhances cytokine signaling through STAT pathways and drives NLRP3 and AIM2 inflammasome activation. *Jak2*-mutant macrophages demonstrate metabolic reprogramming – elevated glycolysis and mitochondrial reactive oxygen species production – that promotes pyroptosis and plaque instability.[18-20] In contrast to TET2, AIM2 appears to play a more dominant role in JAK2-associated atherogenesis. DNA damage response gene mutations, such as *TP53* and *PPM1D*, also contribute by expanding inflammatory myeloid populations, though without consistent inflammasome activation, suggesting inflammasome-independent contributions to plaque growth.[18-20] Collectively, these mutation-specific pathways point to a nuanced immunoepigenetic landscape and support the development of tailored anti-inflammatory therapies targeting CHIP-associated atherosclerosis.

6. Conclusion

Inflammation drives ASCVD through complex immune pathways, including cytokine signalings, inflammasome activation, and clonal hematopoiesis. Biomarkers such as hs-CRP, IL-1, IL-6, and MPO, as well as emerging targets such as CD47 and SGK1, provide critical insights into disease progression and risk stratification. Understanding these mechanisms refines our ability to predict cardiovascular events and uncover novel pathogenic pathways. Future research should focus on integrating these biomarkers to enhance diagnostic precision and deepen our understanding of inflammatory drivers in CVD. As the first part of a two-part review, this article outlines the immunopathogenic mechanisms and biomarker landscape of inflammation in CVD, while Part II will focus on therapeutic strategies targeting inflammatory pathways.

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Conflict of interest

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Further disclosure

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References

1. Mensah GA, Fuster V, Murray CJL, Global Burden of Cardiovascular Diseases and Risks Collaborators. Global burden of cardiovascular diseases and risks, 1990-2022. *J Am Coll Cardiol*. 2023;82(25):2350-2473.

   doi: 10.1016/j.jacc.2023.11.007

2. Martin SS, Aday AW, Almarzooq ZI, *et al*. 2024 heart disease and stroke statistics: A report of US and global data from the American Heart Association. *Circulation*. 2024;149(8):e347-e913.

   doi: 10.1161/CIR.0000000000001209

3. Lloyd-Jones DM, Allen NB, Anderson CAM, *et al*. Life's essential 8: Updating and enhancing the American heart association's construct of cardiovascular health: A presidential advisory from the American heart association. *Circulation*. 2022;146(5):e18-e43.

   doi: 10.1161/CIR.0000000000001078

4. Sun J, Li Y, Zhao M, *et al*. Association of the American heart association's new "life's essential 8" with all-cause and cardiovascular disease-specific mortality: Prospective cohort study. *BMC Med*. 2023;21(1):116.

   doi: 10.1186/s12916-023-02824-8

5. Alfaddagh A, Martin SS, Leucker TM, *et al*. Inflammation and cardiovascular disease: From mechanisms to therapeutics. *Am J Prev Cardiol*. 2020;4:100130.

   doi: 10.1016/j.ajpc.2020.100130

6. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res*. 2014;114(12):1852-1866.

   doi: 10.1161/CIRCRESAHA.114.302721

7. Dou M, Chen Y, Hu J, Ma D, Xing Y. Recent advancements in CD47 signal transduction pathways involved in vascular diseases. *Biomed Res Int*. 2020;2020:4749135.

   doi: 10.1155/2020/4749135

8. Yarmohammadi F, Karimi G. Serum and glucocorticoid-regulated kinase 1 (SGK1) as an emerging therapeutic target for cardiac diseases. *Pharmacol Res*. 2024;208:107369.

   doi: 10.1016/j.phrs.2023.107369

9. Escopy S, Chaikof EL. Targeting the P-selectin/PSGL-1 pathway: Discovery of disease-modifying therapeutics for disorders of thromboinflammation. *Blood Vessels Thromb Hemost*. 2024;1(3):100015.

   doi: 10.1016/j.bvth.2024.100015

10. Di Candia AM, Avila DX, Moreira GR, Villacorta H, Maisel AS. Growth differentiation factor-15, a novel systemic biomarker of oxidative stress, inflammation, and cellular aging: Potential role in cardiovascular diseases. *Am Heart J Plus*. 2021;9:100046.

    doi: 10.1016/j.ahjo.2021.100046

11. Wolf D, Ley K. Immunity and inflammation in atherosclerosis. *Circ Res*. 2019;124(2):315-327.

    doi: 10.1161/CIRCRESAHA.118.313591

12. Hansson GK. Immune mechanisms in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2001;21:1876-1890.

    doi: 10.1161/hq1201.100220

13. Tall AR, Bornfeldt KE. Inflammasomes and atherosclerosis: A mixed picture. *Circ Res*. 2023;132(11):1505-1520.

    doi: 10.1161/CIRCRESAHA.123.321637

14. Sagulenko V, Thygesen SJ, Sester DP, *et al*. AIM2 and NLRP3 inflammasomes activate both apoptotic and pyroptotic death pathways via ASC. *Cell Death Differ*. 2013;20(9):1149-1160.

doi: 10.1038/cdd.2013.37

15. Cavalli G, Colafrancesco S, Emmi G, *et al*. Interleukin 1α: A comprehensive review on the role of IL-1α in the pathogenesis and treatment of autoimmune and inflammatory diseases. *Autoimmun Rev*. 2021;20(2):102763.

doi: 10.1016/j.autrev.2021.102763

16. Ridker PM, Rane M. Interleukin-6 signaling and anti-interleukin-6 therapeutics in cardiovascular disease. *Circ Res*. 2021;128(11):1728-1746.

doi: 10.1161/CIRCRESAHA.121.319077

17. Fanola CL, Morrow DA, Cannon CP, *et al*. Interleukin-6 and the risk of adverse outcomes in patients after an acute coronary syndrome: Observations from the SOLID-TIMI 52 (stabilization of plaque using darapladib-thrombolysis in myocardial infarction 52) trial. *J Am Heart Assoc*. 2017;6(10):e005637.

doi: 10.1161/JAHA.117.005637

18. Jaiswal S, Natarajan P, Silver AJ, *et al*. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N Engl J Med*. 2017;377(2):111-121.

doi: 10.1056/NEJMoa1701719

19. Khetarpal SA, Qamar A, Bick AG, *et al*. Clonal hematopoiesis of indeterminate potential reshapes age-related CVD: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74(4):578-586.

doi: 10.1016/j.jacc.2019.05.045

20. Tall AR, Fuster JJ. Clonal hematopoiesis in cardiovascular disease and therapeutic implications. *Nat Cardiovasc Res*. 2022;1(2):116-124.

doi: 10.1038/s44161-021-00015-3