

Inflammation and Coronary Artery Disease: Editorial

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Received: October 09, 2026; **Accepted:** October 22, 2026; **Published:** October 31, 2026

ABSTRACT

Growing evidence supports a central role for inflammation in the initiation, progression, and clinical manifestations of coronary artery disease (CAD). While traditional cardiovascular risk factors such as dyslipidemia, hypertension, diabetes mellitus, obesity, and smoking remain major contributors to atherosclerosis, many of their adverse effects are mediated through inflammatory pathways. This makes assessing inflammatory pathways crucial for accurately predicting risk of atherosclerosis and heart attacks. Despite the critical role of inflammation in cardiovascular health, routine physicals rely solely on basic lipid panels rather than specific inflammatory biomarkers. Recent clinical trials targeting inflammation, including CANTOS, COLCOT, and LoDoCo2, have demonstrated that modulation of inflammatory responses can reduce cardiovascular events independently of lipid lowering. These findings have strengthened the concept of CAD as a chronic inflammatory disease. Nevertheless, important uncertainties remain regarding the identification of causal inflammatory pathways, optimal biomarkers, patient selection, and long-term safety of anti-inflammatory therapies. These editorial reviews current evidence linking inflammation and CAD, highlights recent therapeutic advances, and discusses future directions for precision cardiovascular medicine.

Keywords: Inflammation, Atherosclerosis, Dyslipidemia, Hypertension, Diabetes, Cardiometabolic Diseases

Key Points

Atherosclerosis remains a multifactorial disorder involving lipid accumulation, endothelial dysfunction, thrombosis, oxidative stress, genetic susceptibility, and environmental influences; inflammation appears to be a critical amplifier throughout the disease process. Inflammation plays a central role in the development, progression, and complications of coronary artery disease. Evidence from major clinical trials (CANTOS, COLCOT, LoDoCo2) demonstrates that targeting inflammatory pathways can reduce cardiovascular events independent of lipid-lowering.

Introduction

Interest in the role of inflammation in cardiovascular disease has increased substantially during the last decade. In a recent commentary, Topol highlighted inflammation as one of the most significant yet historically underappreciated factors in the prevention and management of coronary artery disease (CAD). More than two decades earlier, the American Heart Association had already recognized the importance of inflammatory markers in cardiovascular disease and questioned whether atherosclerosis should be viewed fundamentally as an inflammatory disorder

[1,2]. Accumulating experimental, epidemiological, and clinical evidence suggests that vascular inflammation contributes to every stage of atherosclerosis, from endothelial dysfunction and fatty streak formation to plaque instability, plaque rupture, and thrombosis. This evolving understanding of cellular and molecular mechanisms leading to thrombosis has shifted the perception of CAD from a condition driven solely by cholesterol accumulation to a multifactorial disease involving complex interactions among lipid and glucose metabolism, vascular biology, immune responses, and environmental influences. Unlike previous reviews that primarily focus on individual inflammatory pathways or specific clinical trials, this editorial presents a broader perspective by integrating inflammation with oxidative stress, endothelial dysfunction, metabolic dysregulation, thrombosis, and ageing within the evolving concept of cardiometabolic disease. It argues that inflammation should not be viewed solely as a trigger of plaque rupture but as a continuous biological process that influences every stage of vascular disease—from endothelial injury and metabolic dysfunction to plaque instability, activation of platelet and coagulation pathways, and thrombosis. This broader framework provides a rationale for earlier diagnosis, personalized risk assessment, and integrated anti-inflammatory strategies [3-19].

Citation: Gundu H Rao. Inflammation and Coronary Artery Disease: Editorial. J Cardiovas Cardiol. 2026. 4(4): 1-5. DOI: doi.org/10.61440/JCC.2026.v4.71

Inflammation and Atherosclerotic Disease

Atherosclerosis is initiated by injury or dysfunction of the vascular endothelium (Figure 1). Traditional cardiovascular risk factors, including hypertension, diabetes mellitus, obesity, dyslipidemia, smoking, and sedentary lifestyle, promote chronic low-grade inflammation within the arterial wall.³⁻¹⁸ Endothelial cell activation leads to the expression of adhesion molecules and chemotactic factors that recruit circulating monocytes and other inflammatory cells into the vascular intima. These cells subsequently differentiate into macrophages, internalize modified lipoproteins, and form foam cells, which constitute the earliest visible lesions of atherosclerosis.¹⁹ As lesions progress, inflammatory mediators contribute to plaque growth, extracellular matrix degradation, and fibrous cap weakening. Persistent vascular inflammation is therefore increasingly recognized as a key determinant of plaque vulnerability and acute coronary events.

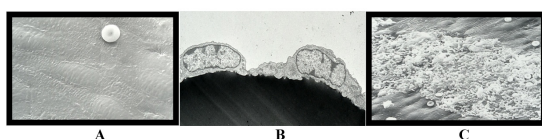


Figure 1: (Electron micrographs (EM) of healthy endothelium (A), Endothelial cells (B), and damaged vessel wall (C). EM's courtesy of Late Professor Jame G White, my associate at the University of Minnesota).

Legend for Figure 1: Circulating blood cells do not adhere to the healthy endothelium (A). A monolayer of healthy endothelial cells cover vessel walls. Vasodilators and vasoconstrictors secreted by blood cells maintain a non-reactive endothelial surface (B). A damaged vascular surface attracts blood cells and initiates the vessel wall repair process or promotes atherosclerosis (C).

The recognition of atherosclerosis as a chronic inflammatory disease has transformed preventive cardiology in both the United States and Europe. Beyond aggressive LDL-cholesterol reduction, increasing emphasis is being placed on identifying and treating residual inflammatory risk. Measurement of hs-CRP, use of low-dose colchicine in selected high-risk patients, and investigation of targeted cytokine inhibition strategies represent important advances toward reducing plaque vulnerability, recurrent coronary events, and cardiovascular mortality. The future of atherosclerosis management is likely to involve simultaneous control of both lipid burden and vascular inflammation.

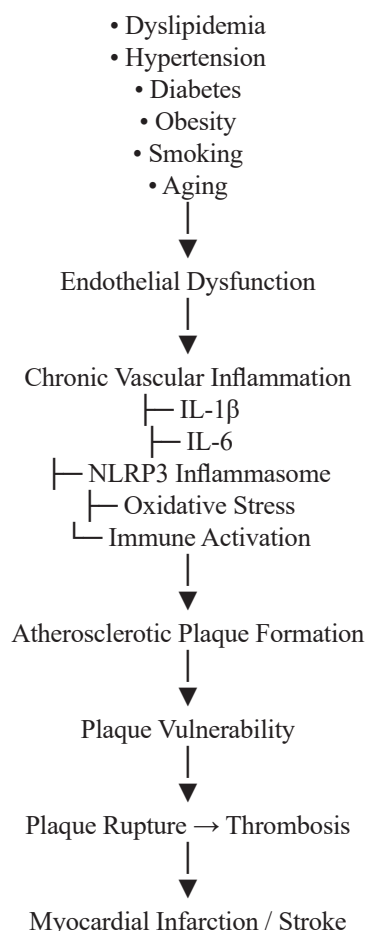
Biomarkers of Inflammation

Among the numerous inflammatory biomarkers evaluated in cardiovascular medicine, high-sensitivity C-reactive protein (hs-CRP) remains the most extensively studied and clinically validated. Elevated hs-CRP concentrations have been associated with increased risk of myocardial infarction, stroke, and cardiovascular mortality independent of traditional risk factors [20].

Additional biomarkers, including interleukin-6, tumor necrosis factor- α , fibrinogen, myeloperoxidase, and lipoprotein-associated phospholipase A₂, have also demonstrated associations with adverse cardiovascular outcomes [21]. Although these markers provide valuable insights into inflammatory activity, their clinical utility remains limited by variability, lack of specificity, and incomplete understanding of their causal role in disease

progression. Cleveland HeartLab (Cleveland Clinic, USA) offers unique inflammation testing which provides additional and complementary insight into cardiovascular risk beyond cholesterol testing alone. The group of tests cover a patients' biomarker profile which may result from lifestyle concerns (F2-IsoPs, OxLDL) to the development of metabolic or cardiovascular disease (ADMA/SDMA, Microalbumin, hsCRP) and formation of vulnerable plaque and increased risk for an adverse event (LP-PLA2 activity, MPO) (Figure 2).

Inflammation as a Central Driver of Coronary Artery Disease Traditional Risk Factors



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- Current Therapies
- Statins
 - PCSK9 inhibitors
 - Colchicine
 - Canakinumab
- Future Therapies
- IL-6 inhibitors
 - NLRP3 inhibitors
 - Precision immunotherapy
 - Multi-omics
 - AI-guided risk prediction
 - Gene editing

Figure 2: Inflammation as the Central Driver of Coronary Artery Disease (Schematics Developed by OpenAI)

Anti-inflammatory Therapies: Proof of Concept

Perhaps the strongest evidence supporting the inflammatory hypothesis of atherosclerosis comes from recent therapeutic trials. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) demonstrated that selective inhibition of interleukin-1 β reduced recurrent cardiovascular events without altering lipid concentrations. These findings provided the first direct evidence that targeting inflammation alone could improve cardiovascular outcomes [22].

Subsequent studies, including COLCOT and LoDoCo2, reported reductions in cardiovascular events among patients receiving low-dose colchicine [23]. Collectively, these investigations have established inflammation as a modifiable therapeutic target and have expanded the traditional framework of cardiovascular risk prevention beyond cholesterol lowering and blood pressure control. Recent advances suggest that cardiovascular inflammation can be modulated through multiple complementary approaches beyond cytokine inhibition. Novel agents targeting the IL-6 signaling pathway, NLRP3 inflammasome, chemokine networks, and innate immune activation are currently under investigation. Parallel advances in lipid biology, RNA therapeutics, and gene-editing technologies indicate that future cardiovascular prevention may combine aggressive lipid lowering with selective modulation of inflammatory pathways. These developments support the transition from generalized anti-inflammatory therapy toward precision immunomodulation tailored to individual biological risk profiles. Emerging concepts increasingly recognize that vascular inflammation is influenced by interactions among immune cells, metabolic tissues, the gut microbiome, clonal hematopoiesis, cellular senescence, and immunometabolism [24]. Multi-omics technologies—including genomics, transcriptomics, proteomics, metabolomics, and spatial biology—combined with artificial intelligence are expected to identify distinct inflammatory endotypes that may guide personalized therapeutic strategies. Such advances could enable clinicians to identify patients with residual inflammatory risk before irreversible vascular damage occurs [21-27].

Challenges and Remaining Questions

Despite substantial advances, several important challenges remain. Inflammation encompasses multiple interconnected biological pathways, many of which exert both protective and pathological effects [24,25]. Determining which pathways should be targeted therapeutically remains an area of active investigation. Furthermore, anti-inflammatory therapies may be associated with adverse effects, including increased susceptibility to infection and concerns regarding long-term safety [26]. Cost-effectiveness and broad implementation of such therapies also require further evaluation. Another unresolved issue involves the early detection of subclinical atherosclerosis. Emerging imaging modalities and biomarker-based approaches may facilitate earlier identification of high-risk individuals; however, definitive evidence demonstrating reductions in population-level mortality through widespread screening remains limited [27].

Future Perspectives

The growing recognition of interactions among inflammation, metabolic dysfunction, thrombosis, and ageing has led to the broader concept of cardiometabolic disease. Future research should focus on identifying inflammatory signatures associated

with oxidative stress, endothelial dysfunction, altered lipid and glucose metabolism, narrowing of the artery, plaque vulnerability, and molecular mechanisms that promote platelet and coagulation pathways. Better understanding of the cellular and molecular mechanisms will help develop safer and more selective anti-inflammatory therapies, as well as integrating advanced imaging with molecular biomarkers for personalized risk assessment [28].

Although substantial evidence demonstrates that inflammation contributes to the initiation and progression of virtually all major cardiovascular risk factors and disease processes—including oxidative stress, endothelial dysfunction, arterial stiffness, hypertension, diabetes, obesity, and coronary artery disease—most clinical trials have concentrated on preventing plaque rupture and thrombosis [3-19]. Future anti-inflammatory strategies should adopt a more comprehensive approach, emphasizing early diagnosis and targeted intervention across the entire spectrum of cardiovascular risk, from the earliest stages of vascular dysfunction to advanced atherosclerotic disease and its thrombotic complications. Advances in genomics, proteomics, metabolomics, artificial intelligence, and gene-editing technologies may further enhance precision cardiovascular medicine and identify individuals most likely to benefit from targeted interventions [29-31]. The clinical implications of these developments extend beyond secondary prevention following myocardial infarction. As evidence accumulates, assessment of residual inflammatory risk may become an integral component of cardiovascular risk stratification alongside traditional lipid measurements. Future clinical practice may incorporate inflammatory biomarkers, molecular imaging, and precision therapeutics to identify patients most likely to benefit from targeted anti-inflammatory interventions. Rather than replacing conventional therapies, anti-inflammatory approaches are likely to complement lipid-lowering agents, antihypertensive therapy, glucose control, and lifestyle modification, resulting in a more comprehensive strategy for cardiovascular prevention.

Conclusion

Accumulating evidence has firmly established inflammation as a pivotal contributor to the initiation, progression, and destabilization of atherosclerotic plaques. While coronary artery disease remains, a complex multifactorial disorder involving lipid abnormalities, endothelial dysfunction, oxidative stress, thrombosis, genetic predisposition, and environmental factors, vascular inflammation is now recognized as a key determinant of disease activity, progression and clinical outcomes. This evolving understanding has expanded the therapeutic paradigm beyond lipid lowering alone to include targeted modulation of inflammatory pathways. The integration of anti-inflammatory strategies with conventional cardiovascular therapies represents an important advance in future preventive cardiology. Continued translational research aimed at elucidating the cellular and molecular mechanisms underlying vascular inflammation will be essential for developing safe, effective, and affordable interventions that can further reduce the global burden of cardiovascular disease and improve long-term patient outcomes.

The understanding of coronary artery disease has evolved from a predominantly lipid-centered disorder to one characterized by complex interactions among oxidative stress, endothelial injury, inflammation, altered metabolism, and alterations

in cellular and molecular mechanisms modulating vascular biology and thrombosis. Evidence from experimental studies and major clinical trials has firmly established inflammation as a modifiable therapeutic target. The next decade is likely to witness the emergence of precision cardiovascular medicine, integrating inflammatory biomarkers, advanced imaging, artificial intelligence, and targeted immunomodulatory therapies to improve individualized prevention and treatment. Continued translational research will be essential for identifying safe, effective, and affordable interventions capable of reducing the global burden of cardiovascular disease.

Acknowledgements

The author acknowledges the longstanding support of the National Heart, Lung, and Blood Institute, National Institutes of Health, USA, for research activities related to thrombosis and cardiovascular disease. The author also thanks the Division of Laboratory Medicine and Pathology, University of Minnesota, for the generous support for these studies.

Funding

No external funding was received for preparation of this editorial.

Conflicts of Interest

The author declares no conflicts of interest.

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