Assessment & Treatment of Inflammation
in Atherosclerosis

A Clinical Proceedings White Paper

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IAS

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Introduction

Cardiovascular diseases, primarily ischemic heart disease and stroke, lead as causes of death worldwide. Collectively, cardiovascular diseases account for a third of all deaths and contribute to both declines in health and increasing health care costs.[1-3]

Atherosclerosis is a primary cause of cardiovascular diseases.[4] Atherogenesis, a complex, chronic inflammatory process, involves the formation of deposits called plaques inside the inner walls of arteries. Plaques contain fatty substances called lipids and inflammatory cells that accumulate over time. As they grow, plaques can block blood flow, either directly or due to the formation of a blood clot following plaque disruption. Blocked blood flow in the heart or brain can cause heart attacks (myocardial infarctions) or strokes that may result in serious disability or death.

Recognizing inflammation and understanding its role in atherosclerosis is key for instituting early interventions to lower cardiovascular risk and prevent life-threatening cardiac events, ultimately improving health outcomes.

The Role of Inflammation

Atherosclerotic plaques develop in large- and medium-sized arteries in places with disturbed blood flow, such as branch points or curves. In these areas, the disturbed blood flow activates the cells of the inner lining of the artery (endothelial cells), resulting in the expression of surface adhesion molecules that capture inflammatory cells from the blood.

Endothelial cell activation also triggers the release of chemokines and pro-inflammatory cytokines, protein mediators that promote the recruitment of innate and adaptive immune cells, including monocytes and T lymphocytes, into the artery wall. Local cytokines stimulate recruited monocytes to mature into macrophages that can then proliferate and accumulate lipids derived from lipoproteins, including low-density lipoprotein (LDL) and triglyceride-rich lipoproteins (TGRLs), taking on a foamy appearance under the microscope. Such "foam cells" characterize atherosclerotic lesions and, early in the disease process, form "fatty streaks" on the artery wall.[4–7]

Cytokines

Cytokines are signaling proteins that are released by cells that regulate inflammatory and immune responses. Most engender inflammation, but others can dampen inflammatory responses or promote resolution of inflammation and tissue repair.

Chemokines

Chemokines (or chemotactic cytokines) are small proteins that stimulate the directed migration of cells, particularly immune cells, from one place to another.

Development of a Lesion

The evolution of an atherosclerotic plaque and its complications
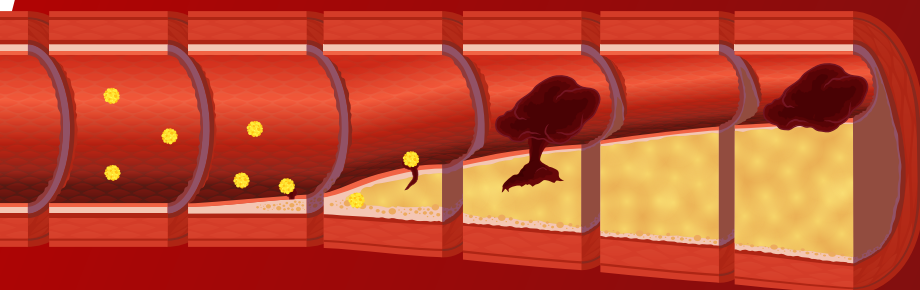
▸ Over time - from left to right - the fatty plaque develops while the artery wall actually enlarges to accommodate growth of the lesion for much of the history of the plaque.

Blood clots can form, as shown on the right side of this image of the evolving atheroma, due to a rupture of the plaque or erosion on its surface.

The artery does not have to be critically narrowed for a blood clot to form that causes a heart attack.

As the plaque develops, smooth muscle cells in the artery wall form a fibrous layer or cap over the top, protecting it from rupture. During this time, additional immune cells, particularly inflammatory T cell subtypes, also enter the lesion, promoting regional sustained or chronic inflammation.[8–10] As the lipoproteins and immune cells continue to accumulate, the foam cells that form can undergo apoptosis (programmed cell death) or die by other means. Plaques then accrue additional monocytes/macrophages by local proliferation or further recruitment from the blood. These cells can clear the dead cells (efferocytosis), but this process may fail, thus perpetuating a vicious cycle of inflammation, monocyte/macrophage recruitment, and cell death.

As these processes persist, generally over decades, a necrotic core full of lipids and dead cells forms within the artery wall. The impaired clearance of injured or dead cells in the lesion's core also contributes to the growth of this structure. With time, the plaque continues to grow and may even partially or fully block blood flow through the artery. The lesion may also disrupt and provoke local blood clotting (thrombosis), which may block downstream blood flow. Such clots most often cause heart attacks and strokes.[11–13] Moreover, the endothelial cells that form the inner lining of blood vessels can lose their usual properties that maintain arterial caliber and promote narrowing or spasm that can also impair blood flow and cause chest discomfort (angina) or heart attacks.[14] The outer layer of arteries (adventitia) surrounding plaques can also become inflamed, grow connections with the nervous system, and contribute to plaque growth and complication.[15]

> Molecular biology has taught us that inflammation in the vascular wall is present throughout all stages of the disease process, from endothelial dysfunction to plaque rupture.
>
> **~Wolfgang Koenig, MD, PhD**
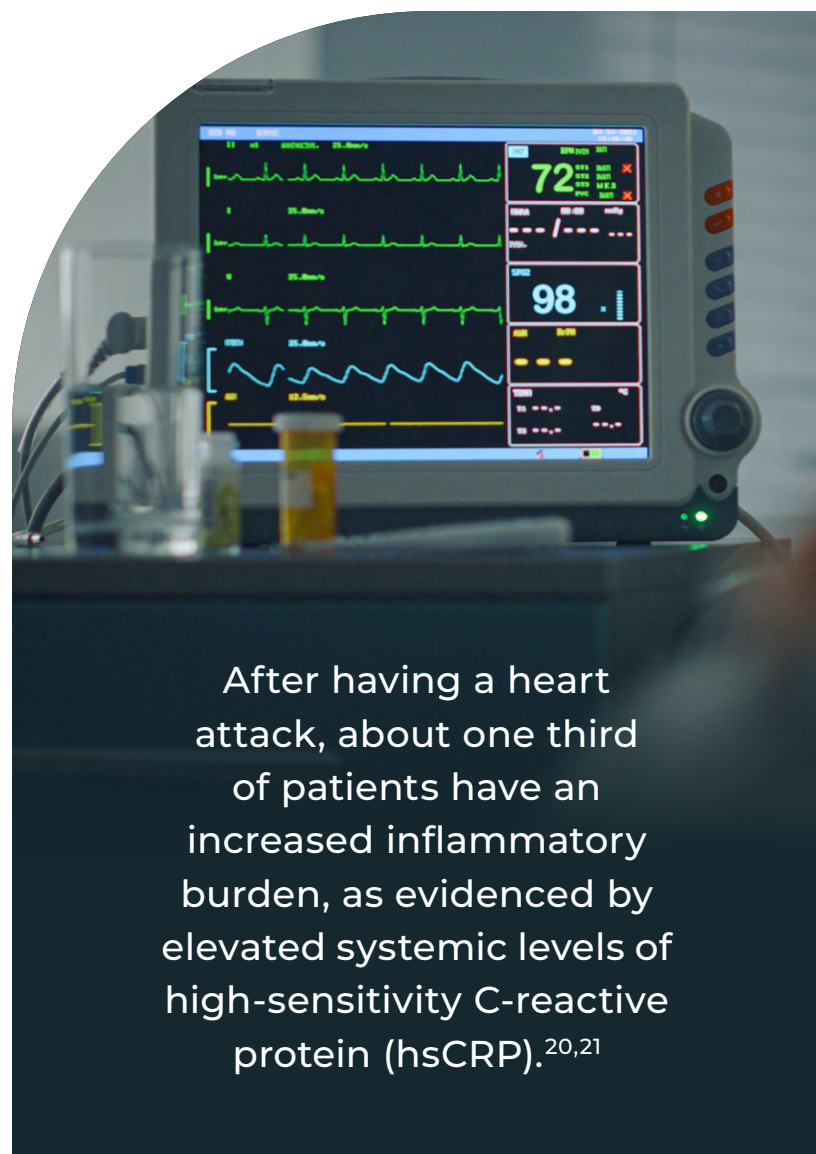
After having a heart attack, about one third of patients have an increased inflammatory burden, as evidenced by elevated systemic levels of high-sensitivity C-reactive protein (hsCRP).[20,21]

While local inflammation in the artery wall participates directly in the development of atherosclerosis, systemic, chronic inflammation can also promote the advancement of atherosclerosis and increase the risk of developing cardiovascular diseases.[16] Indeed, many epidemiological[17] and clinical studies[18] have found that circulating white blood cell counts, an indicator of systemic inflammation, as well as biomarkers of inflammation correlate with increased risk of future cardiovascular events both in patients with and without an existing cardiovascular disease.[19]

Environmental and physiological factors, such as smoking, obesity, air pollution, noise, and diabetes, that increase inflammation can increase the risk of developing cardiovascular diseases.[16,22–34] Indeed, chronic inflammation caused by such factors may cause long-term cellular reprogramming of immune cells called trained immunity.[35] This reprogramming can both increase the sensitivity of these cells to additional inflammatory stimuli and amplify their inflammatory responses, making people more susceptible to the development of additional chronic inflammatory diseases, including atherosclerosis.[23,36,37]

A more complete understanding of the role of inflammation in atherosclerosis progression, how to identify such inflammation, and how to mitigate the inflammation-associated risk of adverse cardiovascular events is of utmost importance for the development of effective treatment strategies.

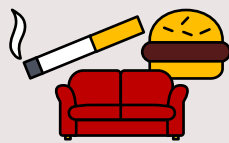> Patients often ask about the root cause of detrimental inflammation. They want to know where it comes from."
>
> **~Jessica M. Peña, MD**

Environmental & Physiological Factors that Increase Inflammation
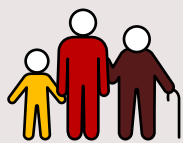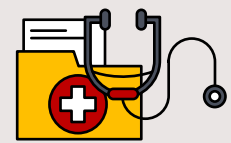

Age

Lifestyle Behaviors
smoking, physical inactivity, Western diet

Social Factors
stress, adversity

Other Health Conditions
diabetes, obesity, HIV chronic kidney disease, rheumatoid arthritis

Using Biomarkers to Identify Inflammatory Risk

LDL promotes atherosclerosis, and LDL-cholesterol (LDL-C) lowering medications can reduce the risk of having cardiovascular events by 25–45%.[37] However, around half of all heart attacks occur in people who have plasma lipid levels traditionally considered normal, suggesting that factors beyond circulating LDL-C drive atherosclerosis and its complications. Lipid-lowering medications alone do not suffice to control the full risk of an atherosclerotic event.[38]

Even with LDL-C levels under control, inflammation has emerged as a primary trigger of major cardiovascular events.[39] For this reason, recognizing inflammation is a key step toward early detection and prevention of such events.[7]

> More than 50% of cardiovascular events are explained by 5 risk factors, including systolic blood pressure, non-high-density lipoprotein-cholesterol, current smoking, diabetes, and body mass index. Thus, a large proportion of cardiovascular disease remains unexplained. The residual inflammatory burden might cover a significant proportion of the remaining risk."
>
> **~Wolfgang Koenig, MD, PhD**

> Now that there are so many ways to effectively treat high cholesterol, we can broaden our focus to address other sources of residual risk, such as inflammation, to further lower overall cardiovascular risk."
>
> **~Jessica M. Peña, MD**

Measuring the concentrations of inflammatory biomarkers circulating in the blood provides a clinically useful approach to assessing inflammatory risk. Such biomarkers can help predict the risk of an individual experiencing a major cardiac event as well as help identify therapeutic approaches that may reduce this risk.

While numerous inflammatory factors have been explored as biomarkers for atherosclerotic events, C-reactive protein (CRP) has proven, over decades of investigation, to be the most reliable, consistent, and clinically useful marker of cardiovascular risk.[38,42–47] The liver synthesizes CRP and releases it into the circulation in response to stimulation by pro-inflammatory cytokines, particularly IL-6.[48,49]

CRP itself does not likely contribute causally to atherosclerosis, but it serves as an easily measured, standardized, stable, and high-fidelity marker of inflammation. In the case of serious infections or major tissue injury, CRP levels can increase up to 10,000-fold. However, under baseline conditions – in the absence of acute infection or injury or an underlying inflammatory disease such as rheumatoid arthritis – CRP levels remain constant, with no more fluctuation than that seen in repeated measurements of total cholesterol or systolic blood pressure.[48–50] Thus, CRP concentration serves as an important, validated, and clinically useful indicator of the presence of inflammatory risk for atherosclerosis.

Biomarker

A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how a patient feels, functions, or survives.[40,41]

> For the last 25 years, no other biomarker has superseded high-sensitivity CRP. It is still the best validated biomarker that we have, despite thorough searches for a better, clinically useful inflammatory biomarker. None of the other markers that have been rigorously evaluated have withstood the test of time and shown additional value.
>
> **~Peter Libby, MD**

Besides its strong association with risk of major cardiac events, CRP is also an effective biomarker because it is easy to measure. CRP is a stable protein, and its levels can be measured from either fresh or previously frozen blood samples.[51] Furthermore, inexpensive, standardized, high-sensitivity CRP (hsCRP) assays are already available internationally on several commercial platforms, allowing for broad diagnostic use.[49,52]

Levels of hsCRP can vary due to various biological factors, including age, sex, and race/ethnicity. For example, hsCRP levels generally increase with age.[53–56] Sex may also affect hsCRP levels, with one study showing that in those without known vascular disease, women had higher median hsCRP levels than men.[57] However, such sex-dependent differences may depend on whether or not hormone therapy is involved.[48,58]

Race/ethnicity may also affect hsCRP levels. Indeed, a systematic review of population-based studies, primarily done in high-income countries, found that Black, Hispanic, and South Asian populations had the highest levels of hsCRP.[59] Similarly, an analysis of multiple small studies suggested that Asian Indian populations have higher baseline hsCRP values than those observed in Western populations.[60] In contrast, a study of more than 6000 Japanese men and women found that their hsCRP levels tended to be lower than what is observed in US and European populations.[53,58]

Despite the reported influence of biological factors on hsCRP levels, clinical practice guidelines simply classify hsCRP levels over a threshold of >= 2 mg/L as indicative of increased risk.[61–63]

> " In the 2019 prevention guidelines, the American Heart Association/American College of Cardiology recommended an hsCRP threshold of 2 mg/L when using this biomarker for risk assessment, which is consistent with entry criteria in the JUPITER trial. "
>
> **~Jessica M. Peña, MD**

> " Despite such differences, the association between elevated hsCRP levels and the incidence of non-fatal and fatal cardiovascular events holds true in almost all populations. "
>
> **~Wolfgang Koenig, MD, PhD**

Lifestyle and environmental factors can also affect circulating hsCRP levels. For example, sedentary people and those who smoke have higher hsCRP concentrations than non-smokers or those who engage in physical activity.[50] Many analyses have also identified links between socioeconomic status and hsCRP levels, with lower socioeconomic status associating with higher levels of hsCRP and other inflammatory markers.[59,64–67] This association may arise from differences in living situation (ambient environmental pollution), lifestyle behaviors, and/or stress and adversity experienced by different socioeconomic groups. Moreover, considering the role of hsCRP in the innate immune

response, acute inflammatory conditions, such as infections or injuries, and medical interventions, such as vaccinations or surgery, also raise circulating hsCRP levels.[49,68,69]

> " Since recent vaccinations or illnesses raise hsCRP levels, it is helpful to ask about such history at visits and avoid measuring hsCRP in these scenarios. "
>
> ~Jessica M. Peña, MD

Overall, while a few studies did not see a strong positive association between hsCRP levels and cardiovascular risk,[70,71] the preponderance of data support the practical utility of hsCRP as an inflammatory biomarker that, when applied in a thoughtful way, reliably augments cardiovascular risk prediction beyond traditional risk factors. Accordingly, clinical practice guidelines published by various organizations worldwide recognize that hsCRP levels can enhance estimation of cardiovascular disease risk, when considered in conjunction with conventional risk prediction models.[61–63] Yet, such use of hsCRP is not universally advised[72], indicating that work is still required to ensure the translation of existing clinical evidence into clinical guidelines.

> " CRP is recognized in the ACC/AHA guidelines as a risk-enhancing factor, which implies that primary care physicians would measure hsCRP along with other biomarkers in people who are at intermediate risk for cardiovascular disease. "
>
> ~Jessica M. Peña, MD

> " When it comes to biomarkers in general, it should be mentioned that hsCRP is the only one that has been able to prospectively identify a high-risk population in a randomized trial setting and has been used to successfully determine whether or not anti-inflammatory treatment is beneficial. "
>
> ~Wolfgang Koenig, MD, PhD

> " In Japan, CRP levels are routinely measured as part of primary care, in addition to blood pressure and LDL levels. However, the results of imaging data, such as the carotid intima/media ratio and coronary calcium score, provide more direct evidence of atherosclerosis. "
>
> ~Hiroaki Shimokawa, MD, PhD

Interventions That May Help Mitigate Inflammatory Risk

Several lifestyle, pharmaceutical, and policy interventions merit consideration to combat the deleterious effects of inflammation on atherosclerosis and hence decrease cardiovascular risk.

Lifestyle Modifications

A healthy lifestyle can contribute to mitigation of cardiovascular risk. Two prospective observational studies found an almost 80% reduction in the incidence of heart attack when subjects adhered to a healthy lifestyle.[73,74] Engaging in moderate physical activity, for example, can reduce inflammation, decrease the number of circulating leukocytes, and lower the risk of cardiovascular events.[75–77] Consuming a Mediterranean diet composed of primarily fruits, vegetables, whole grains, nuts, fish, and olive oil can also decrease markers of inflammation, including hsCRP, and lower the risk of cardiovascular disease.[78–84] Consistent with these findings, hsCRP levels decline with weight loss.[85,86]

> Adipocytes from the visceral fat depot represent a major source of pro-inflammatory cytokines and, consequently, elevated CRP.
>
> **~Wolfgang Koenig, MD, PhD**

Smoking drives some 20% of all deaths due to coronary heart disease worldwide, which equates to 1.9 million deaths each year.[87] Smoking tobacco likely promotes inflammation via inhalation of toxic or irritative smoke constituents. Consequently, smokers display increased markers of inflammation, including higher white blood cell counts as well as increased cytokine and hsCRP levels, than non-smokers.[88,89] Over the long term, hsCRP levels decrease following smoking cessation;[90,91] thus, smoking status is another important lifestyle factor whose management can help mitigate the risk of developing atherothrombosis.[92]

> Some people are motivated by having a measure to follow — something that helps them know that the lifestyle changes they are making are doing something beneficial for their health and longevity.
>
> **~Jessica M. Peña, MD**

Treatment Adherence

In addition to embracing a healthier lifestyle to reduce inflammation and improve overall health, appropriate medication use is important for effectively treating atherosclerosis. Such measures have particular relevance when co-morbid inflammatory conditions accompany atherosclerosis, including diabetes, chronic kidney disease, rheumatoid arthritis, or HIV, each of which can further increase systemic inflammation and amplify the risk of cardiovascular disease.[23,24,37,93]

Ensuring appropriate treatment adherence presents challenges, however, and can be affected by overall psychological wellness, cost, cultural factors, age, and socioeconomic status.[94–99] Fear of side effects and the burden of the treatment regimen can also affect treatment adherence.[98,100] Strategies to help improve adherence include public health education and communication with health providers, motivational interviewing, and increased provider knowledge of population-specific mental health and cultural factors. Continued research and development of treatments that are accessible and simple, have utmost importance for decreasing the overall global impact of atherosclerosis and cardiovascular disease.

> Non-adherence is extremely frequent for varied reasons. Some patients are just sick of pills and others don't want to have to take pills at all. Regardless, it is a major problem. We recently did an adherence study and found that three years after starting statin treatment, only 20% of patients were still on the drug. This is painful.
>
> **~Wolfgang Koenig, MD, PhD**

> A major challenge with all preventive therapies is that people are reluctant to take a drug to which they attribute perceived side effects when it doesn't make them feel noticeably better.
>
> **~Peter Libby, MD**

> It is always going to be a challenge to get people who feel well to take multiple preventive medications.
>
> **~Jessica M. Peña, MD**

Pharmaceutical Interventions

Statins

Statins lower the level of LDL-C in the blood. They inhibit the enzyme HMG CoA reductase, which catalyzes the rate limiting step in the pathway that produces cholesterol in the body. While the direct effects of statins on atherosclerosis via the reduction of circulating cholesterol stand out, statins also exert anti-inflammatory effects independent of LDL lowering that contribute to improved cardiovascular outcomes.

The Pravastatin Inflammation/CRP Evaluation (PRINCE) trial showed that pravastatin treatment decreased hsCRP levels in a manner that was largely independent of LDL.[101] Moreover, JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) found that men and women with then acceptable LDL-C concentrations but above median levels of hsCRP who took rosuvastatin experienced significantly reduced first-ever major cardiovascular events and had a lower incidence of death compared with placebo.[102] Analyses of these and other studies[103] indicate that statins indeed have anti-inflammatory capabilities beyond their lipid-lowering effects.

Low-dose colchicine

As an extract from the autumn crocus plant, colchicine has had medicinal use for centuries. In modern times, however, it is mostly used for the treatment of gout, Familial Mediterranean Fever, and pericarditis.[104] Mechanistically, colchicine primarily inhibits microtubular function in innate immune cells (macrophages and neutrophils), preventing these cells from

migrating to and proliferating at sites of inflammation. It also prevents phagocytosis as well as the release of cytokines and other regulatory factors, thus suppressing the inflammatory response.[105]

Colchicine's anti-inflammatory capabilities spurred large scale randomized studies (COLCOT and LoDoCo2) to investigate its ability to reduce the risk of cardiovascular events in patients with stable coronary artery disease. The results of these studies showed that a low dose (0.5 mg/day) lowered the risk of acute cardiovascular events when compared to treatment with placebo.[104,106,107] In light of these positive results, colchicine became the first drug approved

Low-dose colchicine

Low-dose IL-2

Statins

Anti-IL-1ß antibodies

Anti-IL-6 antibodies
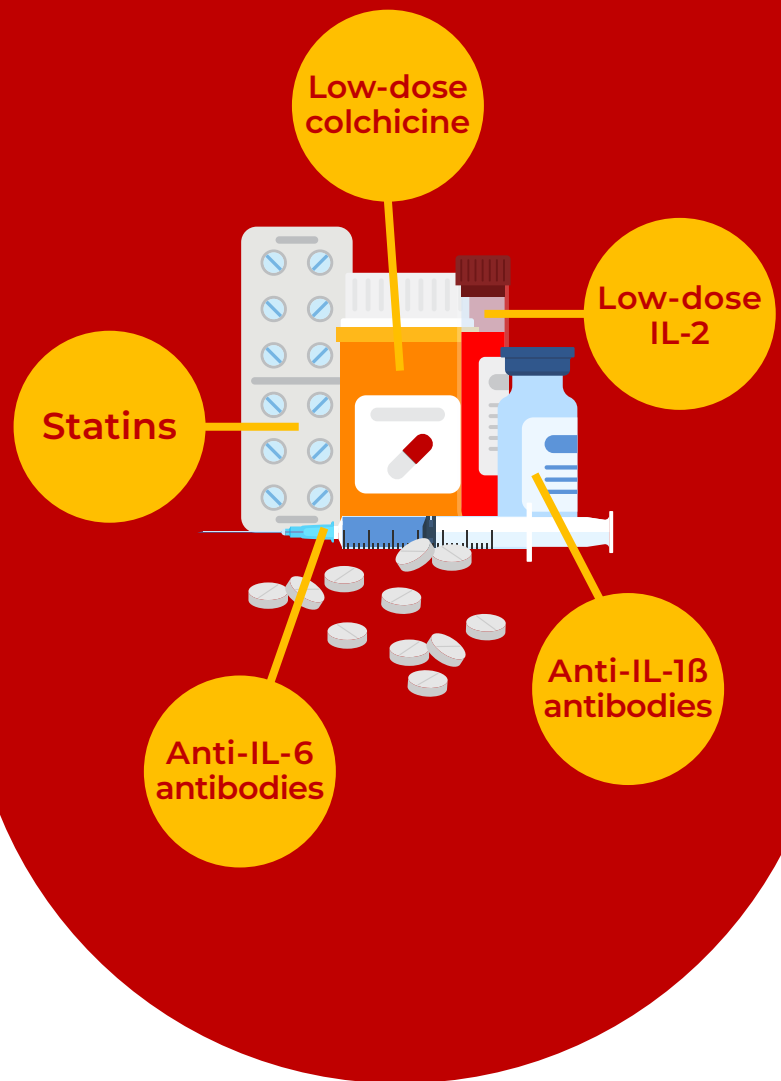
by the Food and Drug Administration for the treatment of cardiovascular inflammation in the US in June of 2023.[94,95]

Anti-IL-1ß antibodies

In the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) trial, participants who had previously had a myocardial infarction and had hsCRP levels ≥2 mg/L received either canakinumab, a high-affinity antibody that neutralizes the pro-inflammatory cytokine IL-1ß, or a control antibody every three months.[110] IL-1ß activates pro-inflammatory signaling, including the production of IL-6, which, in turn, stimulates CRP expression. Treatment with canakinumab significantly reduced the levels of plasma IL-6 and hsCRP but did not alter cholesterol concentrations.[110]

After a median follow-up of 3.7 years, patients who received canakinumab had experienced fewer major cardiac events, including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death.[110] While canakinumab has been approved for periodic fever syndromes and juvenile arthritis in Europe and the US, and additionally for acute gout and Still's disease in Europe,[111] it is not indicated for the treatment of inflammation associated with atherosclerosis.

Anti-IL-6 antibodies

Not surprisingly, since IL-6 signaling occurs downstream of IL-1ß, IL-6 has also emerged as a target for the treatment of atherosclerosis. To determine whether inhibiting IL-6 could safely and effectively reduce the levels of inflammatory biomarkers, such as hsCRP, clinical trials (RESCUE and RESCUE-2) were conducted in which individuals in the US and Japan who had a high risk of developing atherosclerotic cardiovascular disease (those with chronic kidney disease) were treated with

either a human monoclonal antibody against IL-6 (ziltivekimab) or a placebo.[112,113]

These studies showed that ziltivekimab was well-tolerated and profoundly lowered the levels of inflammatory biomarkers compared to placebo. Based on these results, a phase 3 trial (ZEUS) is currently in progress to test whether treatment with ziltivekimab can lower the incidence of major cardiovascular events (heart attacks, strokes or cardiovascular death) in individuals with chronic kidney disease and inflammation.[114] This study will determine whether inhibiting IL-6 can reduce inflammation and lower the risk of atherosclerotic complications.

Low-dose IL-2

T cells play a key role in the progression of atherosclerosis. As such, modulation of T cell subsets has potential for treating ischemic heart disease.

One specific mediator of interest is the cytokine IL-2, which, in low doses, selectively increases the number of anti-inflammatory regulatory T cells (Tregs) in healthy volunteers[101,102] as well as in those with the autoimmune syndrome graft-versus-host disease,[117,118] hepatitis C virus-induced vasculitis,[119] or type 1 diabetes.[120] In a clinical trial called LILACS, researchers examined the safety of low-dose IL-2 (aldesleukin) treatment and its ability to increase the number of Tregs in those with ischemic heart disease/atherosclerosis.[121] They found that aldesleukin was well-tolerated and that the number of Tregs in the participants rose, without similar increases in pro-inflammatory effector T cells (Teffs).[122] Due to the encouraging data recovered from this trial, a follow-up study called IVORY, currently in progress, will determine whether low-dose IL-2 can reduce vascular inflammation in patients with acute coronary syndromes.[123]

Policy Interventions

In addition to adopting a healthy lifestyle and taking appropriate medications, changes in public policy may also mitigate the inflammatory risk of atherosclerosis. Similar to those who smoke, people who live in areas with high levels of air pollution have elevated risk of sustaining major adverse cardiac events. In fact, in 2021, 4.75 million cardiovascular disease deaths globally were attributable to air pollution, making it the leading environmental risk factor for premature cardiovascular disease mortality and the fourth highest risk factor for cardiovascular disease overall.[3]

Furthermore, increased air particulate levels associate with higher levels of hsCRP.[124–127] Thus, changes in public policy that result in cleaner air, particularly in areas with poor air quality, might decrease inflammation and overall cardiovascular risk.

Finally, due to the strong association between atherosclerosis and conditions that are heavily influenced by diet, such as obesity and diabetes, instituting policies that attempt to moderate the consumption of unhealthy foods, such as trans-fats and sugar-sweetened beverages, could also limit inflammation and thus, atherothrombosis.[128,129]

> It is easy to focus on the individual; however, we must remember the powerful systems and policies in place that put people at risk in the first place."
>
> **~Jessica M. Peña, MD**

> We are just beginning to realize the enormous impact of environmental risk factors like air pollution on human health, with inflammation being one particular mechanism of action."
>
> **~Wolfgang Koenig, MD, PhD**

The Burdens of Disease

Atherosclerosis is a great burden on patients as well as their families and society at large. It results in significant loss of life and has substantial impacts on household finances as well as economies worldwide.

Loss of Life

In 2019, the World Health Organization estimated that cardiovascular diseases were the cause of 17.9 million deaths, making it the leading cause of death worldwide.[1] While high-income countries have made progress in reducing their numbers of cardiovascular disease-related deaths, the same cannot be said for low- and middle-income countries who bear the burden of over 80% of the deaths due to cardiovascular diseases.[130–132]

This difference may be explained by an "epidemiologic transition" in which industrialization, urbanization, changes in lifestyle, and advancements in medical knowledge and innovation have resulted in a shift from deaths being caused by infectious diseases to deaths being caused by non-communicable diseases. As this transition takes place, gaps in public knowledge regarding the risk factors of cardiovascular disease, including diet, lifestyle aspects, and co-morbid conditions, impede mitigating disease risk. This lack of knowledge can be compounded by limited access to preventive and diagnostic medical care, including the availability of effective medications.[6,94,133] Furthermore, given that both biological and cultural factors affect cardiovascular disease risk, effectively decreasing cardiovascular disease mortality in low- and middle-income countries will require the development of culturally-sensitive, customized, regional, and multi-dimensional approaches.[94,130,133,134]

> Many countries have realized that successfully treating the epidemic of atherosclerosis and its complications requires more investment into targeted prevention."
>
> **~Wolfgang Koenig, MD, PhD**

Economic Costs

Health care expenditures associated with the treatment of atherosclerosis represent a significant burden of the disease on patients and their families. In a recent study that included over 450,000 individuals in Sweden, the average annual total direct (inpatient, outpatient, and drug expenses) and indirect (lost productivity/work wages) costs incurred by people with atherosclerotic cardiovascular disease were 2.5 times higher than what was incurred by those who did not have this disease.[135]

Additional studies done in the US found that nearly 1 in 8 families who had a member with atherosclerotic cardiovascular disease reported financial hardship related to their care, with this hardship being more pronounced among low-income and uninsured families.[136] Such hardships associate with poor mental and physical quality of life as well as medication nonadherence, delaying or foregoing medical care, food insecurity, and early retirement,[135–137] further hindering the overall stability, financial and otherwise, of patients and their families.

Disease-related expenses extend beyond individuals to government systems. Such governmental costs include contributions for the direct care of its citizens as well as indirect expenses, such as more welfare payments and lost income tax revenue from those unable to work due to poor health.[138] Of the G20+ countries, the total annual economic costs (direct and indirect; in USD) incurred due to cardiovascular diseases were highest for the US ($402.2 billion), followed by Japan ($109.6 billion), the United Kingdom ($29.1 billion), Brazil ($17.3 billion), and Mexico ($6.1 billion).[139,140]

In line with these findings, cardiovascular disease burden was one of the reasons cited for the decrease in gross domestic product (GDP) in Turkey, and similar losses have been projected to occur in Australia through 2030.[138,141,142] The economies of low- and middle-income countries are also affected

TOTAL ANNUAL ECONOMIC COSTS
Due to Cardiovascular Disease *(in billions)*

UNITED STATES
$402.2

JAPAN
$109.6

UNITED KINGDOM
$29.1

BRAZIL
$17.3

MEXICO
$6.1

substantially, with disease-related losses estimated to be $3.7 trillion in 2010, representing 2% of their GDP.[131] Thus, finding ways to screen for and treat atherosclerosis effectively in a variety of populations to reduce the incidence of cardiovascular diseases would have considerable economic benefits for individuals, families, and societies across the globe.

> Given the staggering societal costs associated with ASCVD, policymakers should prioritize primordial prevention.
>
> **~Jessica M. Peña, MD**

Conclusion

Atherosclerosis is a primary cause of cardiovascular diseases, which comprise the leading cause of death worldwide and represent a significant economic hardship for patients, their families, and society. Early identification and treatment of atherosclerosis is an important aspect of mitigating the ravages of cardiovascular diseases across the globe that disproportionately affect certain minority groups, those of low socioeconomic status, and inhabitants of low- and middle-income countries.

Along with circulating atherogenic lipoproteins, inflammation is a key driver of the development and progression of atherosclerosis. Therefore, identifying effective strategies for recognizing inflammatory risk and treating inflammation has compelling importance in combatting cardiovascular diseases.

While other inflammatory factors might serve as biomarkers of inflammation in relation to atherosclerosis, hsCRP has proven, in the long-term, to be the leading and most consistently reliable, scalable, and validated indicator of inflammatory cardiovascular disease risk. Although hsCRP has a continuous relationship with first or recurrent atherosclerotic events, different categorical cut points have proven practical for clinical actionability and design of clinical trials.

Moreover, the recent approval of colchicine in several jurisdictions and the evaluation of additional promising pharmaceutical treatments offer new avenues to reduce inflammatory risk in atherosclerosis and mortality. Such measures, in conjunction with lifestyle modification, continued public health education, and the institution of policies to combat inflammation, have great potential to alleviate the burdens that cardiovascular diseases place on patients, families, health systems, and governments worldwide.

IAS' Clinical Proceedings

Established in 1979, the International Atherosclerosis Society is a global network of the world's leading atherosclerotic cardiovascular disease experts who collaborate to develop mission centered programming that spans geographical and generational boundaries. IAS' Clinical Proceedings — a white paper series — are informational resources intended to raise awareness and address unmet needs in atherosclerosis.

IAS recognizes the expert panel members who contributed to the development of this white paper.

Peter Libby, MD
Chair

Wolfgang Koenig, MD, FRCP, FESC, FACC, FAHA

Jessica M. Peña, MD, MPH, FACC, FNLA

Hiroaki Shimokawa, MD, PhD

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

athero.org

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