Assessment & Treatment of Inflammation in Atherosclerosis

A Clinical Proceedings White Paper

July 2024

IAS

Table of Contents

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

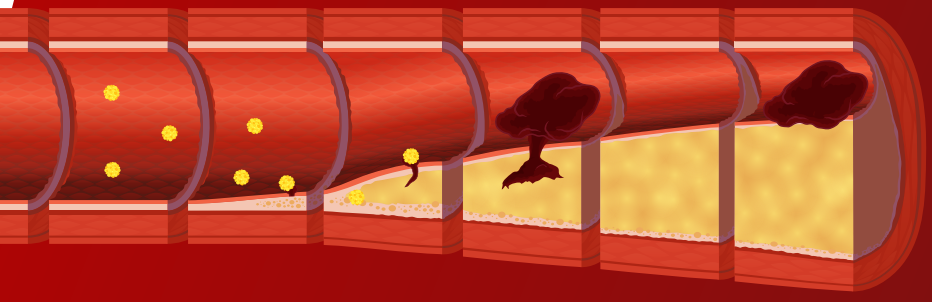
Cytokines are signaling proteins that are released by cells that regulate inflammatory and immune responses. Most engender inflammation, but others can dampen inflammatory responses or promote resolution of inflammation and tissue repair.

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.

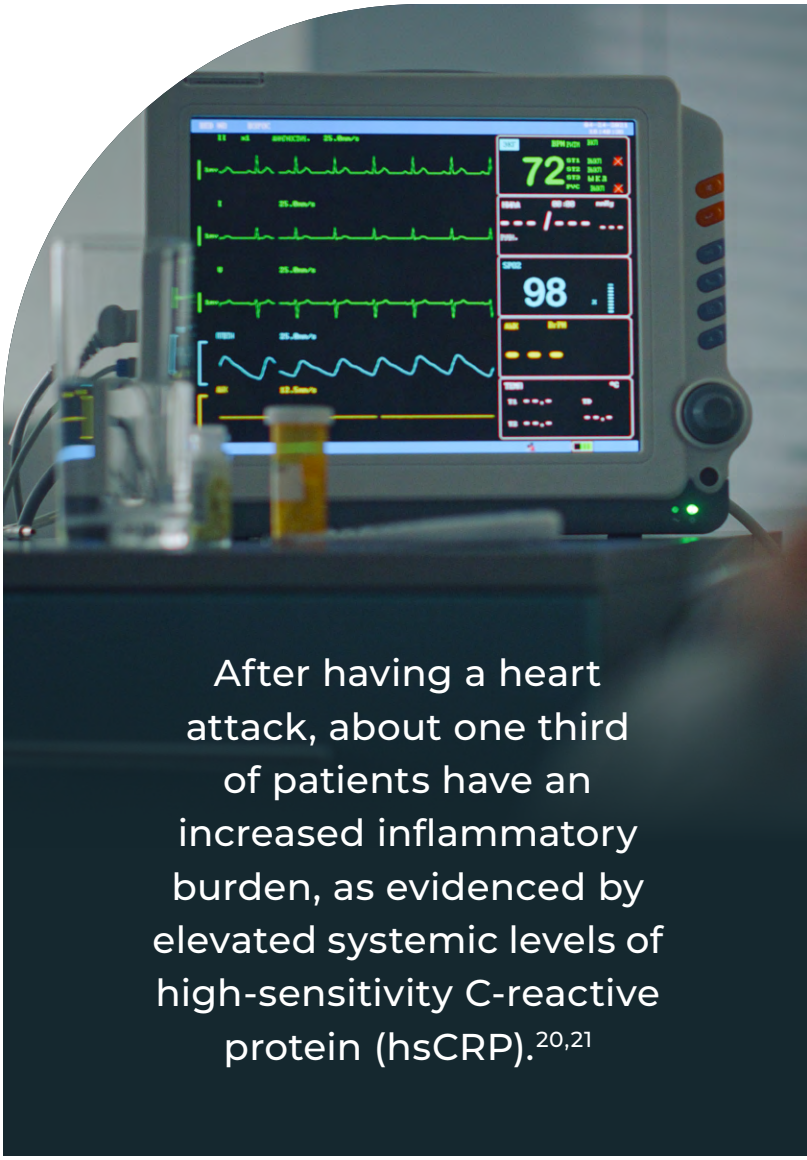
Blood clots can form, as shown on the right side of this image of the evolving atheroma, due to a rupture of the plaque or erosion on its surface.

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]

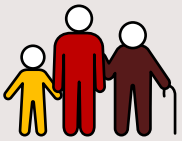
While local inflammation in the artery wall participates directly in the development of atherosclerosis, systemic, chronic inflammation can also promote the advancement of atherosclerosis and increase the risk of developing cardiovascular diseases.[16] Indeed, many epidemiological[17] and clinical studies[18] 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]

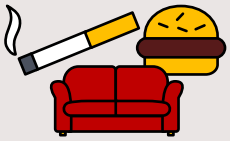
A more complete understanding of the role of inflammation in atherosclerosis progression, how to identify such inflammation, and how to mitigate the inflammation-associated risk of adverse cardiovascular events is of utmost importance for the development of effective treatment strategies.

> “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

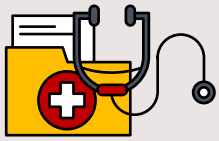


Age



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**

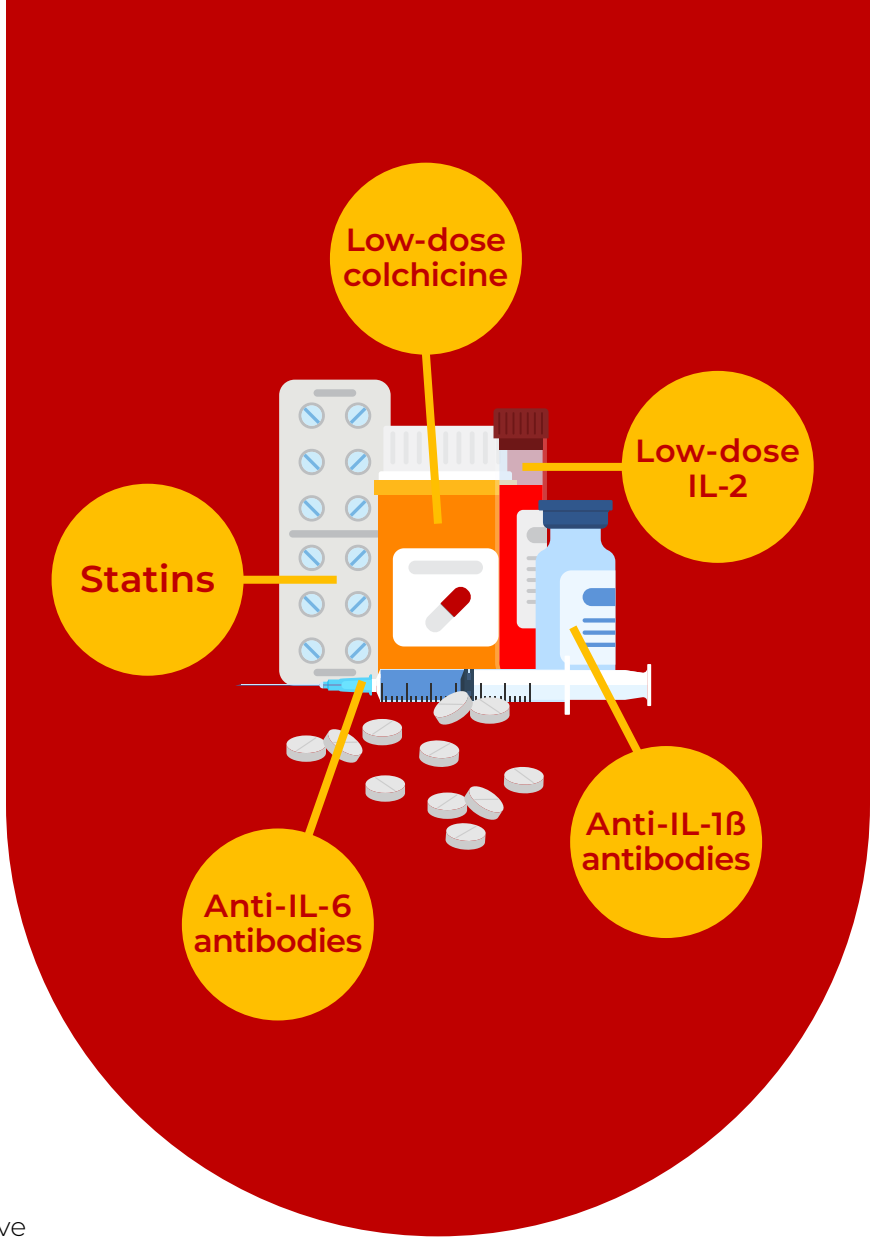
> It is always going to be a challenge to get people who feel well to take multiple preventive medications."
>
> **~Jessica M. Peña, MD**

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

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.

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

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

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

IAS acknowledges the professional writing assistance of Amy Sullivan, PhD, with Obrizus Communications, in the preparation of this document. This Clinical Proceedings white paper was supported in part with a grant from Novo Nordisk.

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

athero.org

References

1. World Health Organization. Cardiovascular diseases (CVDs). https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
2. Roth, G. A. *et al.* Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019. *J. Am. Coll. Cardiol.* **76**, 2982–3021 (2020).
3. Vaduganathan, M., Mensah, G. A., Turco, J. V., Fuster, V. & Roth, G. A. The Global Burden of Cardiovascular Diseases and Risk. *J. Am. Coll. Cardiol.* **80**, 2361–2371 (2022).
4. Pahwa, R. & Jialal, I. Atherosclerosis. in *StatPearls* (StatPearls Publishing, Treasure Island (FL), 2023).
5. Gimbrone, M. A. & García-Cardeña, G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ. Res.* **118**, 620–636 (2016).
6. Libby, P. The changing landscape of atherosclerosis. *Nature* **592**, 524–533 (2021).
7. Libby, P. Inflammation and the pathogenesis of atherosclerosis. *Vascul. Pharmacol.* **154**, 107255 (2023).
8. Saigusa, R., Winkels, H. & Ley, K. T cell subsets and functions in atherosclerosis. *Nat. Rev. Cardiol.* **17**, 387–401 (2020).
9. Miteva, K., Madonna, R., De Caterina, R. & Van Linthout, S. Innate and adaptive immunity in atherosclerosis. *Vascul. Pharmacol.* S1537-1891(17)30464–0 (2018) doi:10.1016/j.vph.2018.04.006.
10. Libby, P. & Hansson, G. K. From Focal Lipid Storage to Systemic Inflammation: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* **74**, 1594–1607 (2019).
11. Libby, P., Pasterkamp, G., Crea, F. & Jang, I.-K. Reassessing the Mechanisms of Acute Coronary Syndromes. *Circ. Res.* **124**, 150–160 (2019).
12. Asada, Y., Yamashita, A., Sato, Y. & Hatakeyama, K. Pathophysiology of atherothrombosis: Mechanisms of thrombus formation on disrupted atherosclerotic plaques. *Pathol. Int.* **70**, 309–322 (2020).
13. Loftus, I. Mechanisms of Plaque Rupture. in *Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists* (eds. Fitridge, R. & Thompson, M.) (University of Adelaide Press, Adelaide (AU), 2011).
14. Nishimiya, K. et al. Mechanisms of Coronary Artery Spasm. *Eur. Cardiol.* Rev. **18**, e39 (2023).
15. Mohanta, S. K. et al. Neuroimmune cardiovascular interfaces control atherosclerosis. *Nature* **605**, 152–159 (2022).
16. Furman, D. et al. Chronic inflammation in the etiology of disease across the life span. *Nat. Med.* **25**, 1822–1832 (2019).
17. Ernst, E., Hammerschmidt, D. E., Bagge, U., Matrai, A. & Dormandy, J. A. Leukocytes and the Risk of Ischemic Diseases. *JAMA* **257**, 2318–2324 (1987).
18. Ono, M. *et al.* Impact of white blood cell count on clinical outcomes in patients treated with aspirin-free ticagrelor monotherapy after percutaneous coronary intervention: insights from the GLOBAL LEADERS trial. *Eur. Heart J. Cardiovasc. Pharmacother.* **8**, 39–47 (2022).
19. Madjid, M., Awan, I., Willerson, J. T. & Casscells, S. W. Leukocyte count and coronary heart disease: Implications for risk assessment. *J. Am. Coll. Cardiol.* **44**, 1945–1956 (2004).
20. Ridker, P. M. How Common Is Residual Inflammatory Risk? *Circ. Res.* **120**, 617–619 (2017).
21. Ridker, P. M. Clinician's Guide to Reducing Inflammation to Reduce Atherothrombotic Risk: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* **72**, 3320–3331 (2018).
22. Khafagy, R. & Dash, S. Obesity and Cardiovascular Disease: The Emerging Role of Inflammation. *Front. Cardiovasc. Med.* **8**, (2021).
23. Jukema, R. A., Ahmed, T. A. N. & Tardif, J.-C. Does low-density lipoprotein cholesterol induce inflammation? If so, does it matter? Current insights and future perspectives for novel therapies. *BMC Med.* **17**, 197 (2019).
24. American Diabetes Association. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2019. *Diabetes Care* **42**, S103–S123 (2018).
25. Kearns, A., Gordon, J., Burdo, T. H. & Qin, X. HIV-1–Associated Atherosclerosis: Unraveling the Missing Link. *J. Am. Coll. Cardiol.* **69**, 3084–3098 (2017).
26. Pothineni, N. V. K. et al. Infections, atherosclerosis, and coronary heart disease. *Eur. Heart J.* **38**, 3195–3201 (2017).
27. Dahdah, A. *et al.* Immunological Insights into Cigarette Smoking-Induced Cardiovascular Disease Risk. *Cells* **11**, 3190 (2022).
28. Li, J. *et al.* Dietary Inflammatory Potential and Risk of Cardiovascular Disease Among Men and Women in the U.S. *J. Am. Coll. Cardiol.* **76**, 2181–2193 (2020).
29. Jankowski, J., Floege, J., Fliser, D., Böhm, M. & Marx, N. Cardiovascular Disease in Chronic Kidney Disease. *Circulation* **143**, 1157–1172 (2021).
30. Hansildaar, R. *et al.* Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. *Lancet Rheumatol.* **3**, e58–e70 (2021).
31. Leon, B. M. & Maddox, T. M. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World J. Diabetes* **6**, 1246–1258 (2015).
32. Libby, P. *et al.* Inflammation, Immunity, and Infection in Atherothrombosis: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* **72**, 2071 (2018).
33. Westcott, S. K., Lewis, T. T. & Albert, M. A. Tackling Adversity and Cardiovascular Health: It is About Time. *Circulation* **147**, e1–e3 (2023).
34. Zaman, M., Muslim, M. & Jehangir, A. Environmental noise-induced cardiovascular, metabolic and mental health disorders: a brief review. *Environ. Sci. Pollut. Res.* **29**, 76485–76500 (2022).
35. Netea, M. G. et al. Defining trained immunity and its role in health and disease. *Nat. Rev. Immunol.* **20**, 375–388 (2020).
36. Soehnlein, O. & Libby, P. Targeting inflammation in atherosclerosis — from experimental insights to the clinic. *Nat. Rev. Drug Discov.* **20**, 589–610 (2021).
37. Hoogeveen, R. M. et al. Monocyte and haematopoietic progenitor reprogramming as common mechanism underlying chronic inflammatory and cardiovascular diseases. *Eur. Heart J.* **39**, 3521–3527 (2018).
38. Ridker, P. M., Hennekens, C. H., Buring, J. E. & Rifai, N. C-Reactive Protein and Other Markers of Inflammation in the Prediction of Cardiovascular Disease in Women. *N. Engl. J. Med.* **342**, 836–843 (2000).
39. Kobiyama, K. & Ley, K. Atherosclerosis: A Chronic Inflammatory Disease with an Autoimmune Component. *Circ. Res.* **123**, 1118–1120 (2018).
40. U.S. Food & Drug Administration. The BEST Resource: Harmonizing Biomarker Technology (2016). https://www.fda.gov/media/99221/download
41. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin. Pharmacol. Ther.* **69**, 89–95 (2001).

42. Ridker, P. M., Cushman, M., Stampfer, M. J., Tracy, R. P. & Hennekens, C. H. Inflammation, Aspirin, and the Risk of Cardiovascular Disease in Apparently Healthy Men. *N. Engl. J. Med.* **336**, 973–979 (1997).

43. Koenig, W. *et al.* C-Reactive Protein, a Sensitive Marker of Inflammation, Predicts Future Risk of Coronary Heart Disease in Initially Healthy Middle-Aged Men. *Circulation* **99**, 237–242 (1999).

44. Albert, C. M., Ma, J., Rifai, N., Stampfer, M. J. & Ridker, P. M. Prospective Study of C-Reactive Protein, Homocysteine, and Plasma Lipid Levels as Predictors of Sudden Cardiac Death. *Circulation* **105**, 2595–2599 (2002).

45. Ridker, P. M., Stampfer, M. J. & Rifai, N. Novel Risk Factors for Systemic AtherosclerosisA Comparison of C-Reactive Protein, Fibrinogen, Homocysteine, Lipoprotein(a), and Standard Cholesterol Screening as Predictors of Peripheral Arterial Disease. *JAMA* **285**, 2481–2485 (2001).

46. Rost, N. S. *et al.* Plasma Concentration of C-Reactive Protein and Risk of Ischemic Stroke and Transient Ischemic Attack. *Stroke* **32**, 2575–2579 (2001).

47. Burger, P. M. *et al.* C-Reactive Protein and Risk of Cardiovascular Events and Mortality in Patients with Various Cardiovascular Disease Locations. *Am. J. Cardiol.* **197**, 13–23 (2023).

48. Ledue, T. B. & Rifai, N. Preanalytic and Analytic Sources of Variations in C-reactive Protein Measurement: Implications for Cardiovascular Disease Risk Assessment. *Clin. Chem.* **49**, 1258–1271 (2003).

49. Plebani, M. Why C-reactive protein is one of the most requested tests in clinical laboratories? *Clin. Chem. Lab. Med. CCLM* **61**, 1540–1545 (2023).

50. The Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* **375**, 132–140 (2010).

51. Ridker, P. M. Clinical Application of C-Reactive Protein for Cardiovascular Disease Detection and Prevention. *Circulation* **107**, 363–369 (2003).

52. Bargiel, W. *et al.* Recognized and Potentially New Biomarkers—Their Role in Diagnosis and Prognosis of Cardiovascular Disease. *Medicina (Mex.)* **57**, 701 (2021).

53. Yamada, S. *et al.* Distribution of Serum C-Reactive Protein and Its Association with Atherosclerotic Risk Factors in a Japanese Population: Jichi Medical School Cohort Study. *Am. J. Epidemiol.* **153**, 1183–1190 (2001).

54. Wyczalkowska-Tomasik, A., Czarkowska-Paczek, B., Zielenkiewicz, M. & Paczek, L. Inflammatory Markers Change with Age, but do not Fall Beyond Reported Normal Ranges. *Arch. Immunol. Ther. Exp. (Warsz.)* **64**, 249–254 (2016).

55. Ferrucci, L. *et al.* The origins of age-related proinflammatory state. *Blood* **105**, 2294–2299 (2005).

56. Hutchinson, W. L. *et al.* Immunoradiometric Assay of Circulating C-Reactive Protein: Age-related Values in the Adult General Population. *Clin. Chem.* **46**, 934–938 (2000).

57. Lakoski, S. G. *et al.* Gender and C-reactive protein: Data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *Am. Heart J.* **152**, 593–598 (2006).

58. Albert, M. A. & Ridker, P. M. C-Reactive Protein as a Risk Predictor. *Circulation* **114**, e67–e74 (2006).

59. Nazmi, A. & Victora, C. G. Socioeconomic and racial/ethnic differentials of C-reactive protein levels: a systematic review of population-based studies. *BMC Public Health* **7**, 212 (2007).

60. Kamath, D. Y., Xavier, D., Sigamani, A. & Pais, P. High sensitivity C-reactive protein (hsCRP) & cardiovascular disease: An Indian perspective. *Indian J. Med. Res.* **142**, 261–268 (2015).

61. Arnett, D. K. *et al.* 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **140**, e596–e646 (2019).

62. Chinese Guideline on the Primary Prevention of Cardiovascular Diseases. *Cardiol. Discov.* **1**, 70 (2021).

63. Kinoshita, M. *et al.* Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017. *J. Atheroscler. Thromb.* **25**, 846–984 (2018).

64. Dinwiddie, G. Y., Zambrana, R. E., Doamekpor, L. A. & Lopez, L. The Impact of Educational Attainment on Observed Race/Ethnic Disparities in Inflammatory Risk in the 2001–2008 National Health and Nutrition Examination Survey. *Int. J. Environ. Res. Public. Health* **13**, 42 (2016).

65. Koster, A. *et al.* Association of Inflammatory Markers With Socioeconomic Status. *J. Gerontol. Ser.* A **61**, 284–290 (2006).

66. Pollitt, R. A. *et al.* Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. *Eur. J. Epidemiol.* **22**, 55–66 (2007).

67. Janicki-Deverts, D., Cohen, S., Kalra, P. & Matthews, K. A. The Prospective Association of Socioeconomic Status with C-Reactive Protein Levels in the CARDIA Study. *Brain. Behav. Immun.* **26**, 1128–1135 (2012).

68. Gor, S., Kim, S.-H., Yein, K., Michael, J. & Price, E. C-Reactive protein rise in rheumatology patients following COVID-19 vaccination. *Rheumatol. Adv. Pract.* **7**, i2–i5 (2023).

69. Terentes-Printzios, D. *et al.* The effect of an mRNA vaccine against COVID-19 on endothelial function and arterial stiffness. *Hypertens. Res.* **45**, 846–855 (2022).

70. Sattar, N. *et al.* C-Reactive Protein and Prediction of Coronary Heart Disease and Global Vascular Events in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). *Circulation* **115**, 981–989 (2007).

71. Cainzos-Achirica, M. *et al.* The Prognostic Value of High Sensitivity C-Reactive Protein in a Multi-Ethnic Population After More Than 10 Years of Follow-Up: The Multi-Ethnic Study of Atherosclerosis (MESA). *Int. J. Cardiol.* **264**, 158–164 (2018).

72. Visseren, F. L. J. *et al.* 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur. Heart J.* **42**, 3227–3337 (2021).

73. Chomistek, A. K. *et al.* Healthy Lifestyle in the Primordial Prevention of Cardiovascular Disease Among Young *Women. J. Am. Coll. Cardiol.* **65**, 43–51 (2015).

74. Akesson, A., Larsson, S. C., Discacciati, A. & Wolk, A. Low-risk diet and lifestyle habits in the primary prevention of myocardial infarction in men: a population-based prospective cohort study. *J. Am. Coll. Cardiol.* **64**, 1299–1306 (2014).

75. Frodermann, V. *et al.* Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. *Nat. Med.* **25**, 1761–1771 (2019).

76. Lee, D. *et al.* Leisure-Time Running Reduces All-Cause and Cardiovascular Mortality Risk. *J. Am. Coll. Cardiol.* **64**, 472–481 (2014).

77. Noz, M. P. *et al.* Sixteen-Week Physical Activity Intervention in Subjects With Increased Cardiometabolic Risk Shifts Innate Immune Function Towards a Less Proinflammatory State. *J. Am. Heart Assoc. Cardiovasc. Cerebrovasc. Dis.* **8**, e013764 (2019).

78. Panagiotakos, D. B. *et al.* Mediterranean diet and inflammatory response in myocardial infarction survivors. *Int. J. Epidemiol.* **38**, 856–866 (2009).

79. Lahoz, C. *et al.* Relationship of the Adherence to a Mediterranean Diet and Its Main Components with CRP Levels in the Spanish Population. *Nutrients* **10**, 379 (2018).

80. Schwingshackl, L. & Hoffmann, G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. *Nutr. Metab. Cardiovasc. Dis. NMCD* **24**, 929–939 (2014).

81. Trichopoulou, A., Costacou, T., Bamia, C. & Trichopoulos, D. Adherence to a Mediterranean Diet and Survival in a Greek Population. *N. Engl. J. Med.* **348**, 2599–2608 (2003).

82. Ahmad, S. *et al.* Assessment of Risk Factors and Biomarkers Associated With Risk of Cardiovascular Disease Among Women Consuming a Mediterranean Diet. *JAMA Netw. Open* **1**, e185708 (2018).

83. Pant, A. *et al.* Primary prevention of cardiovascular disease in women with a Mediterranean diet: systematic review and meta-analysis. *Heart* **109**, 1208–1215 (2023).

84. Martínez-González, M. A. *et al.* Mediterranean diet and the incidence of cardiovascular disease: a Spanish cohort. *Nutr. Metab. Cardiovasc. Dis. NMCD* **21**, 237–244 (2011).

85. Selvin, E., Paynter, N. P. & Erlinger, T. P. The effect of weight loss on C-reactive protein: a systematic review. *Arch. Intern. Med.* **167**, 31–39 (2007).

86. Nicklas, J. M. *et al.* Effect of Dietary Composition of Weight Loss Diets on High Sensitivity C-Reactive Protein: The Randomized POUNDS LOST Trial. *Obes. Silver Spring Md* **21**, 681–689 (2013).

87. World Health Organization. Tobacco responsible for 20% of deaths from coronary heart disease. https://www.who.int/news/item/22-09-2020-tobacco-responsible-for-20-of-deaths-from-coronary-heart-disease.

88. Tonstad, S. & Cowan, J. L. C-reactive protein as a predictor of disease in smokers and former smokers: a review. *Int. J. Clin. Pract.* **63**, 1634–1641 (2009).

89. Kawada, T. Relationships between the smoking status and plasma fibrinogen, white blood cell count and serum C-reactive protein in Japanese workers. *Diabetes Metab. Syndr. Clin. Res. Rev.* **9**, 180–182 (2015).

90. Gallus, S. *et al.* Effect of Tobacco Smoking Cessation on C-Reactive Protein Levels in A Cohort of Low-Dose Computed Tomography Screening Participants. *Sci. Rep.* **8**, 12908 (2018).

91. Jao, N. C., Martinez-Cardoso, A., Vahora, M. & Tan, M. M. The role of smoking history in longitudinal changes in C-reactive protein between Black and White older adults in the US. *Prev. Med. Rep.* **28**, 101885 (2022).

92. Ambrose, J. A. *et al.* Reducing Tobacco-Related Disability in Chronic Smokers. *Am. J. Med.* **133**, 908–915 (2020).

93. Valdivielso, J. M. *et al.* Atherosclerosis in Chronic Kidney Disease. *Arterioscler. Thromb. Vasc. Biol.* **39**, 1938–1966 (2019).

94. Bowry, A. D. K., Lewey, J., Dugani, S. B. & Choudhry, N. K. The Burden of Cardiovascular Disease in Low- and Middle-Income Countries: Epidemiology and Management. *Can. J. Cardiol.* **31**, 1151–1159 (2015).

95. Bąk-Sosnowska, M., Gruszczyńska, M., Wyszomirska, J. & Daniel-Sielańczyk, A. The Influence of Selected Psychological Factors on Medication Adherence in Patients with Chronic Diseases. *Healthcare* **10**, 426 (2022).

96. Khera, R. *et al.* Cost-Related Medication Nonadherence in Adults With Atherosclerotic Cardiovascular Disease in the United States, 2013 to 2017. *Circulation* **140**, 2067–2075 (2019).

97. McQuaid, E. L. & Landier, W. Cultural Issues in Medication Adherence: Disparities and Directions. *J. Gen. Intern. Med.* **33**, 200–206 (2018).

98. Yap, A. F., Thirumoorthy, T. & Kwan, Y. H. Medication adherence in the elderly. *J. Clin. Gerontol. Geriatr.* **7**, 64–67 (2016).

99. Moise, N. *et al.* Leveraging Implementation Science for Cardiovascular Health Equity: A Scientific Statement From the American Heart Association. *Circulation* **146**, e260–e278 (2022).

100. Smith, L. E., Webster, R. K. & Rubin, G. J. A systematic review of factors associated with side-effect expectations from medical interventions. *Health Expect. Int. J. Public Particip. Health Care Health Policy* **23**, 731–758 (2020).

101. Albert, M. A., Danielson, E., Rifai, N., Ridker, P. M., & for the PRINCE Investigators. Effect of Statin Therapy on C-Reactive Protein Levels: The Pravastatin Inflammation/CRP Evaluation (PRINCE): A Randomized Trial and Cohort Study. *JAMA* **286**, 64–70 (2001).

102. Ridker, P. M. *et al.* Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *N. Engl. J. Med.* **359**, 2195–2207 (2008).

103. Bohula, E. A. *et al.* Achievement of Dual Low-Density Lipoprotein Cholesterol and High-Sensitivity C-Reactive Protein Targets More Frequent With the Addition of Ezetimibe to Simvastatin and Associated With Better Outcomes in IMPROVE-IT. *Circulation* **132**, 1224–1233 (2015).

104. Tardif, J.-C. *et al.* Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N. Engl. J. Med.* **381**, 2497–2505 (2019).

105. Leung, Y. Y., Hui, L. L. Y. & Kraus, V. B. Colchicine --- update on mechanisms of action and therapeutic uses. *Semin. Arthritis Rheum.* **45**, 341–350 (2015).

106. Nidorf, S. M. *et al.* Colchicine in Patients with Chronic Coronary Disease. *N. Engl. J. Med.* **383**, 1838–1847 (2020).

107. Nidorf, S. M., Eikelboom, J. W., Budgeon, C. A. & Thompson, P. L. Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease. *J. Am. Coll. Cardiol.* **61**, 404–410 (2013).

108. Winslow, R. A New Way to Protect Against Heart Attacks. *The Wall Street Journal* https://www.wsj.com/health/wellness/heart-attack-health-inflammation-drug-353dabf5 (2023).

109. Dunleavy, K. Agepha Pharma gets ancient gout remedy colchicine across FDA finish line for heart disease. *Fierce Pharma* https://www.fiercepharma.com/pharma/agepha-pharma-gets-ancient-gout-remedy-colchicine-across-fda-finish-line-heart-disease (2023).

110. Ridker, P. M. *et al.* Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N. Engl. J. Med.* **377**, 1119–1131 (2017).

111. Thompson, P. L. & Nidorf, S. M. Anti-inflammatory therapy with canakinumab for atherosclerotic disease: lessons from the CANTOS trial. *J. Thorac. Dis.* **10**, 695–698 (2018).

112. Wada, Y., Jensen, C., Meyer, A. S. P., Zonoozi, A. A. M. & Honda, H. Efficacy and safety of interleukin-6 inhibition with ziltivekimab in patients at high risk of atherosclerotic events in Japan (RESCUE-2): A randomized, double-blind, placebo-controlled, phase 2 trial. *J. Cardiol.* **82**, 279–285 (2023).

113. Ridker, P. M. *et al.* IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. *The Lancet* **397**, 2060–2069 (2021).

114 Novo Nordisk A/S. *ZEUS - Effects of Ziltivekimab Versus Placebo on Cardiovascular Outcomes in Participants With Established Atherosclerotic Cardiovascular Disease, Chronic Kidney Disease and Systemic Inflammation.* https://clinicaltrials.gov/study/NCT05021835 (2023).

115. Ito, S. *et al.* Ultra-low dose interleukin-2 promotes immune-modulating function of regulatory T cells and natural killer cells in healthy volunteers. *Mol. Ther. J. Am. Soc. Gene Ther.* **22**, 1388–1395 (2014).

116. Ito, S. *et al.* Ultra-Low Dose IL-2 Safely Expands Regulatory T Cells and CD56bright NK Cells in Healthy Volunteers: Towards Safer Stem Cell Donors? *Blood* **120**, 3283 (2012).

117. Koreth, J. *et al.* Interleukin-2 and Regulatory T Cells in Graft-versus-Host Disease. *N. Engl. J. Med.* **365**, 2055–2066 (2011).

118. Matsuoka, K. *et al.* Low-Dose Interleukin-2 Therapy Restores Regulatory T Cell Homeostasis in Patients with Chronic Graft-Versus-Host Disease. *Sci. Transl. Med.* **5**, 179ra43-179ra43 (2013).

119. Saadoun, D. *et al.* Regulatory T-Cell Responses to Low-Dose Interleukin-2 in HCV-Induced Vasculitis. *N. Engl. J. Med.* **365**, 2067–2077 (2011).

120. Hartemann, A. *et al.* Low-dose interleukin 2 in patients with type 1 diabetes: a phase 1/2 randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol.* **1**, 295–305 (2013).

121. Zhao, T. X. *et al.* Low-dose interleukin-2 in patients with stable ischaemic heart disease and acute coronary syndromes (LILACS): protocol and study rationale for a randomised, double-blind, placebo-controlled, phase I/II clinical trial. *BMJ Open* **8**, e022452 (2018).

122. Zhao, T. X. *et al.* Low dose interleukin-2 in patients with stable ischaemic heart disease and acute coronary syndrome (LILACS). *Eur. Heart J.* **41**, ehaa946.1735 (2020).

123. Sriranjan, R. *et al.* Low-dose interleukin 2 for the reduction of vascular inflammation in acute coronary syndromes (IVORY): protocol and study rationale for a randomised, double-blind, placebo-controlled, phase II clinical trial. *BMJ Open* **12**, e062602 (2022).

124. Elbarbary, M. *et al.* Systemic Inflammation (C-Reactive Protein) in Older Chinese Adults Is Associated with Long-Term Exposure to Ambient Air Pollution. *Int. J. Environ. Res. Public. Health* **18**, 3258 (2021).

125. Peters, A. *et al.* Particulate air pollution is associated with an acute phase response in men. Results from the MONICA–Augsburg Study. *Eur. Heart J.* **22**, 1198–1204 (2001).

126. Guo, L.-H. *et al.* Influence of Air Pollution Exposures on Cardiometabolic Risk Factors: a Review. Curr. Environ. *Health Rep.* **10**, 501–507 (2023).

127. Li, Y., Rittenhouse-Olson, K., Scheider, W. L. & Mu, L. Effect of particulate matter air pollution on C-reactive protein: a review of epidemiologic studies. *Rev. Environ. Health* **27**, 133–149 (2012).

128. Brandt, E. J., Myerson, R., Perraillon, M. C. & Polonsky, T. S. Hospital Admissions for Myocardial Infarction and Stroke Before and After the Trans-Fatty Acid Restrictions in New York. *JAMA Cardiol.* **2**, 627–634 (2017).

129. Brownell, K. D. *et al.* The Public Health and Economic Benefits of Taxing Sugar-Sweetened Beverages. *N. Engl. J. Med.* **361**, 1599–1605 (2009).

130. Anand, S., Bradshaw, C. & Prabhakaran, D. Prevention and management of CVD in LMICs: why do ethnicity, culture, and context matter? *BMC Med.* **18**, 7 (2020).

131. Gheorghe, A. *et al.* The economic burden of cardiovascular disease and hypertension in low- and middle-income countries: a systematic review. *BMC Public Health* **18**, 975 (2018).

132. Mensah, G. A. *et al.* Global Burden of Cardiovascular Diseases and Risks, 1990-2022. *J. Am. Coll. Cardiol.* **82**, 2350–2473 (2023).

133. Owolabi, M., Miranda, J. J., Yaria, J. & Ovbiagele, B. Controlling cardiovascular diseases in low and middle income countries by placing proof in pragmatism. *BMJ Glob. Health* **1**, e000105 (2016).

134. Miranda, J. J. & Zaman, M. J. Exporting 'failure': why research from rich countries may not benefit the developing world. *Rev. Saúde Pública* **44**, 185–189 (2010).

135. Carlsson, K., Nilsson, K., Wolden, M. L. & Faurby, M. Economic burden of atherosclerotic cardiovascular disease: costs related to healthcare and loss of productivity; a matched case-control study in more than 450,000 Swedish individuals. *Eur. Heart J.* **43**, ehac544.2849 (2022).

136. Khera, R., Valero-Elizondo, J. & Nasir, K. Financial Toxicity in Atherosclerotic Cardiovascular Disease in the United States: Current State and Future Directions. *J. Am. Heart Assoc.* **9**, e017793 (2020).

137. Annapureddy, A. *et al.* Association Between Financial Burden, Quality of Life, and Mental Health Among Those With Atherosclerotic Cardiovascular Disease in the United States. *Circ. Cardiovasc. Qual. Outcomes* **11**, e005180 (2018).

138. Schofield, D. *et al.* The indirect costs of ischemic heart disease through lost productive life years for Australia from 2015 to 2030: results from a microsimulation model. *BMC Public Health* **19**, 802 (2019).

139. Health Systems Innovation Lab at Harvard University & Rifat, A. The State of Cardiovascular Disease in G20+ Countries. *HPHR J.* **HSIL**, (2022).

140. Martin, S. S. *et al.* 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. *Circulation* **149**, e347–e913 (2024).

141. Ekinci, G. Economic Impacts of Cardiovascular Diseases: An Econometric Evaluation in Turkey. *Iran. J. Public Health* **52**, 118–127 (2023).

142. Savira, F. *et al.* The impact of coronary heart disease prevention on work productivity: a 10-year analysis. *Eur. J. Prev. Cardiol.* **28**, 418–425 (2021).