High-sensitivity C-reactive Protein in Atherosclerotic Cardiovascular Disease: To Measure or Not to Measure?

Adhya Mehta, MD [1], Roger S Blumenthal, MD [2], Ty J Gluckman, MD,[2,3] David I Feldman, MD, MPH,[4] and Payal Kohli, MD [5]

1. Department of Internal Medicine, Albert Einstein College of Medicine/Jacobi Medical Center, Bronx, NY; 2. Division of Cardiology, Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, MD; 3. Center for Cardiovascular Analytics, Research and Data Science (CARDS), Providence Heart Institute, Providence Joseph Health System, Portland, OR; 4. Massachusetts General Hospital, Harvard Medical School, Boston, MA; 5. Department of Cardiology, Johns Hopkins University, Baltimore, MD

Abstract

Inflammation and dyslipidemia are central to the pathogenesis of atherosclerotic cardiovascular disease (ASCVD). While lipid-lowering therapies are the cornerstone of ASCVD prevention and treatment, there are other emerging targets, including inflammation (which has been dubbed the 'residual inflammatory risk'), that can be addressed after LDL cholesterol thresholds have been reached. Research over the past 20 years has identified C-reactive protein (CRP) as a key marker of inflammation with atherosclerosis. The association of more sensitive measures of CRP (high-sensitivity C-reactive protein [hsCRP]) with ASCVD risk in epidemiological studies has also led to its incorporation as a risk enhancer in primary prevention guidelines and its incorporation into risk stratification tools. While there are no formal recommendations related to measurement of hsCRP in secondary prevention, consideration should be given to an individualized approach that addresses inflammatory risk in those with major adverse cardiovascular events, despite maximal lipid-lowering therapy and well-controlled LDL cholesterol levels. The aim of this review is to discuss the role of inflammation in ASCVD, the use of hsCRP as a tool to assess residual inflammatory risk to target upstream pathways such as glucose intolerance and obesity, and to consider use of additional anti-inflammatory medications for ASCVD risk reduction. The authors provide clinical context around when to measure hsCRP in clinical practice and how to address residual inflammatory risk in ASCVD.

Keywords

Atherosclerotic cardiovascular disease, high-sensitivity C-reactive protein, inflammation, residual inflammatory risk, residual cholesterol risk

Received: 10 May 2024 **Accepted:** 3 December 2024 **Citation:** *US Cardiology Review* 2025;19:e06. **DOI:** https://doi.org/10.15420/usc.2024.25

Disclosures: PK has received a grant from Lexicon Pharmaceuticals, consulting fees from Amarin, the American College of Cardiology, Family Heart, Grand Rounds/Included Health, Novartis, P-Value Communications, SecondMD, and Viz.ai, and honoraria from ACC/ABIM Question Writing, Amarin, Amgen, AstraZeneca, Boston Scientific, Bristol-Myers Squibb Company, Clinical Options, Esperion, Merck, and Zoll; and serves on advisory boards for Agepha Pharma, Amarin, Amgen, Doximity, Esperion, and Merck. All other authors have no conflicts of interest to declare.

Correspondence: Payal Kohli, Department of Cardiology, Johns Hopkins University, Baltimore, MD 21218. E: pkohli3@jh.edu

Atherosclerosis and its related complications (including MI and stroke) are leading causes of death worldwide, accounting for about half of all deaths in westernized society.[1,2] Importantly, dyslipidemia and inflammation have both been identified as major mediators of atherogenesis and the development of atherosclerotic cardiovascular disease (ASCVD).[3,4]

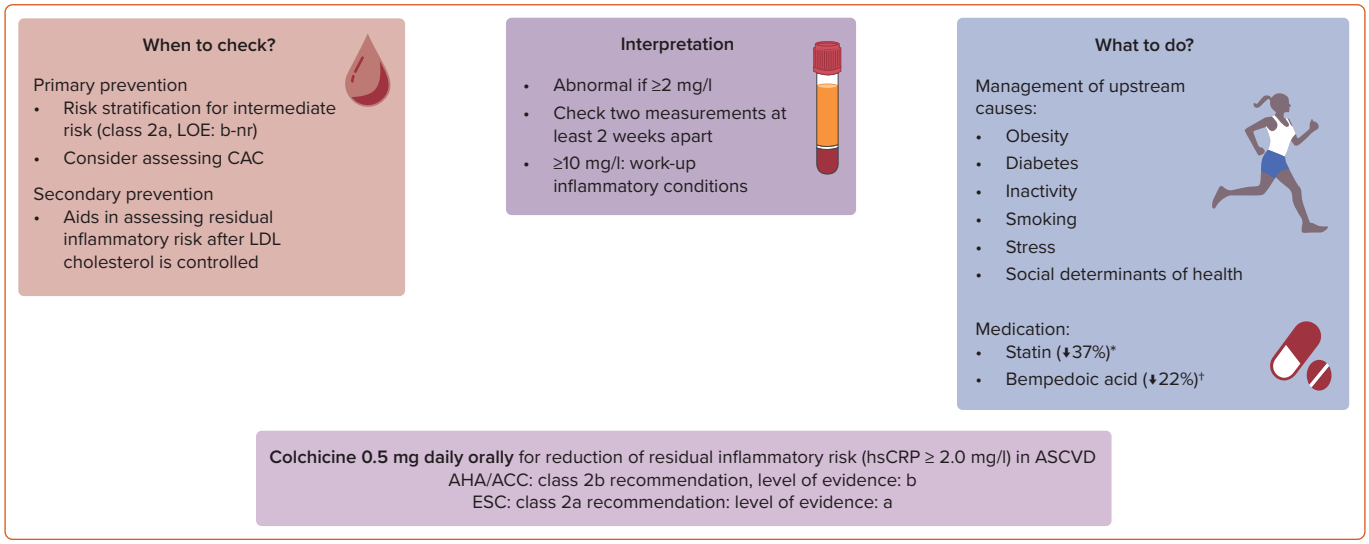
To date, lipid-lowering therapy has been prioritized to reduce cholesterol-associated risk.[5–7] Clinicians, however, have started to recognize the importance of inflammation as an additional target to reduce the risk of major adverse cardiovascular events (MACE). Herein, we discuss the role of inflammation in ASCVD, the use of high-sensitivity C-reactive protein (hsCRP) as a key biomarker of inflammation, and anti-inflammatory treatment options.

Plaque Formation

Atherosclerosis results from an inflammatory process that involves lipid deposition in arterial walls. Restriction of blood flow with demand–supply mismatch and plaque disruption resulting in MI or stroke can both ensue. Preventing the accumulation of atherogenic lipoproteins such as apolipoprotein B is critical, given that these particles penetrate the arterial wall to form and propagate atherosclerotic plaques.[8] Statins represent first-line lipid-lowering therapy for the treatment and prevention of atherosclerosis based on their ability to promote plaque stabilization and reduce MACE.[9–13]

Importantly, the role of inflammation in initiating and propagating ASCVD has been increasingly recognized. After formation of the initial atheroma, which involves lipid deposition in the arterial walls and the recruitment of inflammatory cells, such as T lymphocytes and monocytes/macrophages, atherosclerosis is propagated by excess cholesterol levels and inflammatory mediators including cytokines (i.e. interleukin [IL]-1, IL-6, tumor necrosis factor [TNF]-α) in addition to others, which play a key role in promoting the chronic inflammatory response that drives atherosclerotic progression (*Figure 1*).[14–16]

Central Illustration: High-sensitivity C-reactive Protein in ASCVD



**REGARDS;[35] †CLEAR Outcomes trial.[37] AHA/ACC = American Heart Association/American College of Cardiology; CAC = coronary artery calcium; ESC = European Society of Cardiology; hsCRP = high-sensitivity C-reactive protein; LOE = level of evidence. Created using images from Servier Medical Art, reproduced under a CC BY 4.0 License.*

Inflammation

Inflammation can be an important physiological immune response to injury, infection, or other irritants to fight infection or heal damaged tissue. When triggered by injury to the endothelium, it occurs locally and is mediated by cytokine release. When prolonged or persistent, it can become maladaptive. Importantly, epidemiological data suggest that the presence of persistent, low-grade systemic inflammation can be associated with a patient's likelihood of developing a life-threatening cardiac event.[4]

HsCRP is an acute phase reactant and an important biomarker of systemic inflammation, despite not being specific to cardiovascular inflammation. Elevated levels of hsCRP are associated with MACE, with some studies suggesting high prognostic value beyond LDL cholesterol.[3]

In the REGARDS study, which evaluated 6,136 participants at high risk for coronary events, there was a strong association between low levels of hsCRP and reduced risk of incident CHD, CHD death, and incident stroke. In contrast, low levels of LDL cholesterol, even <3.9 mmol/l (70 mg/dl), did not confer as much protective benefit as anticipated, emphasizing the important role of other factors such as inflammation.[17] In a 30-year follow-up study of women, increasing baseline levels of hsCRP, lipoprotein (a) (Lp(a)), and LDL cholesterol each independently predicted the 30-year risk of cardiovascular disease (CVD), with the maximum risk occurring when all three biomarkers were elevated. This underscores the importance of parallel risk pathways: cholesterol risk, thrombotic risk, and inflammatory risk in plaque formation and disruption.[18]

Thus, although lipid-lowering therapy has been a mainstay of ASCVD prevention (both primary and secondary), 'residual risk' persists. Multiple contributors have been implicated, including elevated Lp(a), hypertriglyceridemia, excess thrombotic risk, and systemic inflammation (*Figure 1*).[19] For maximum ASCVD risk reduction, all of these pathways should be targeted and optimized. This review will focus on the residual inflammatory risk pathway, while acknowledging that these pathways are interconnected and often overlap. For instance, conditions such as metabolic syndrome and obesity may elevate risk through multiple pathways, including thrombotic, inflammatory, and triglyceride-related mechanisms.

Given the role of inflammation in atherosclerosis initiation and propagation, assessing and targeting this process have become an emerging focus in addressing residual ASCVD risk. Inflammation is the common denominator across multiple chronic conditions including aging ('inflammaging'), obesity, diabetes, hepatic steatosis, metabolic syndrome, chronic kidney disease (CKD), neurodegenerative disorders, and even cancer. Inflammation can even predispose to the development of subclinical atherosclerosis and MACE. The presence of elevated inflammatory biomarkers (such as hsCRP) across these conditions supports the notion that inflammation should be routinely assessed when determining a treatment strategy.[20]

High-sensitivity C-reactive Protein as a Biomarker of ASCVD Risk

The NLRP3 inflammasome is a key mediator of inflammation during chronic low-grade inflammation, and its activation triggers the release of cytokines such as IL-1β, which subsequently stimulate the production of IL-6. IL-6 triggers hepatocytes, macrophages, and T-cells to produce and release CRP. CRP release is also induced in response to other inflammatory mediators, such as IL-18, infection, atheroma formation, and trauma.[21] CRP contributes to the inflammatory cascade, through its effect on endothelial function and fibrinolysis. Its direct role in the pathogenesis of ASCVD is unclear, given that CRP levels are not increased at sites of coronary occlusion.[4,21] While CRP is typically measured using standard sensitivity assays, hsCRP is a more sensitive marker, making it useful in individuals with low levels of elevation.[22] Traditionally, elevated levels of hsCRP (assessed on at least two distinct occasions) has been used for cardiovascular (CV) risk assessment in asymptomatic individuals.[4,22] Due to the widespread availability of standardized assays for hsCRP and strong evidence of associated risk with ASCVD, it has become a common and widely used inflammatory biomarker to assess inflammatory risk.[4]

Various other inflammatory biomarkers have also been evaluated (*Table 1*). GlycA is a novel biomarker of systemic inflammation.[23] IL-1, IL-6, and TNF-α are cytokines and key mediators of inflammation.[4] Myeloperoxidase is an enzyme abundant in activated neutrophils, reflecting oxidative stress.[24] Additional biomarkers include adhesion molecules (intracellular adhesion molecule-1 [ICAM-1], vascular cellular adhesion molecule-1

Figure 1: Atherosclerotic Cardiovascular Disease. Risk Pathways Beyond LDL Cholesterol

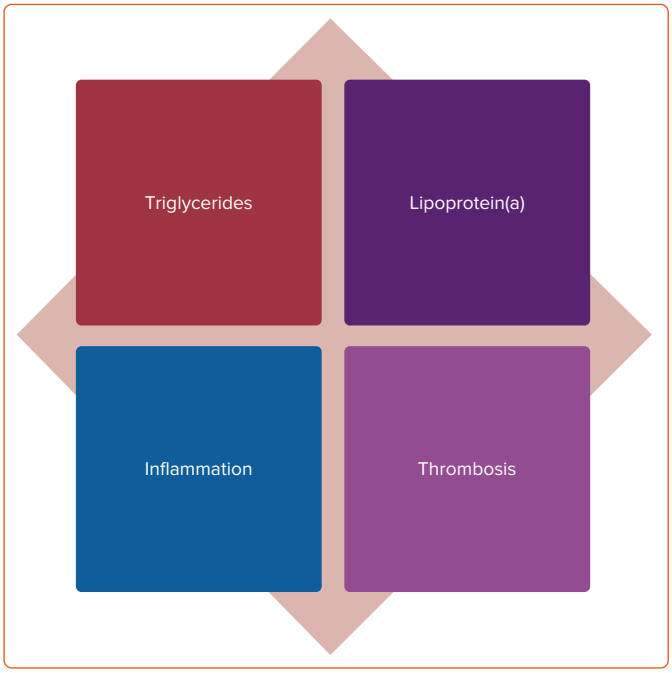


Table 1: Markers of Inflammation

Type	Markers
Biomarkers	Myeloperoxidase, lipoprotein-associated phospholipase A2, pentraxin-3, GlycA
Cytokines	Interleukin-1 and -6, tumor necrosis factor-α
Proteases	Matrix metalloproteinase 9
Adhesion molecules	Intracellular adhesion molecule-1, vascular cellular adhesion molecule-1
Acute phase reactants	C-reactive protein and fibrinogen

[VCAM-1], endothelial leukocyte adhesion molecule-1 [ELAM-1]) and acute phase reactants (CRP and fibrinogen; *Table 1*).[4]

In 2019, the American College of Cardiology (ACC) and American Heart Association (AHA) recommended that hsCRP ≥2 mg/l be used as a cut-off to identify the presence of CV risk.[5] Interindividual variability has remained a concern when interpreting hsCRP results, given that levels are influenced by various factors including sex (higher in women than men), age, race (African-American > Hispanic > Caucasian > Asian), ethnicity, smoking, alcohol use, concurrent infection, obesity, environmental factors, medications, comorbid chronic inflammatory states such as rheumatoid arthritis, and liver disease.[25] It is also limited by intraindividual variability, given that hsCRP can be nonspecifically elevated in the setting of infection or inflammation, which may be of greater concern with respect to accurate contextual interpretation.[26]

Interpreting hsCRP in an appropriate context is critical. As an acute phase reactant, levels of hsCRP can increase transiently with trauma and infection as well as with the use of certain medications; as such, it should not be measured during these times. To minimize intraindividual variability, it is recommended that two measurements be taken at least 2 weeks apart, irrespective of fasting status, to confirm elevation.[27] Moreover, levels of hsCRP ≥10 mg/l suggest other underlying inflammatory processes, with repeat testing and consideration of work-up for other underlying inflammatory conditions. HsCRP demonstrates measurement stability similar to cholesterol levels, hence serial measurements are not recommended.[28] Moreover, obtaining serial measurements (beyond verification of persistently elevated levels) is limited by cost-effectiveness, inconvenience, and lack of evidence-based guidelines about interventions based on serial measurements. Therefore, interpretation of hsCRP in the clinical context of individual patients and individual diseases is recommended.

Risk Assessment in Primary and Secondary Prevention Using hsCRP

Role in Primary Prevention of ASCVD Events

In primary prevention, hsCRP can further aid in risk stratification, particularly in individuals at intermediate risk based on the Reynolds risk score, which incorporates hsCRP.[29] Multiple epidemiological studies have linked high levels of hsCRP with increased risk of ASCVD events and prediction of incident CV events in individuals without known atherosclerosis.[30]

The Physicians' Health Study, which included 1,086 healthy male participants, highlighted the prognostic role of hsCRP in primary prevention. The study reported a strong association between incident CVD and elevated hsCRP, with levels ≥2.11 mg/l associated with an approximate threefold greater risk of MI ($p<0.001$) and twofold greater risk of stroke ($p=0.02$) compared with those in the lowest quartile, independent of traditional CV risk factors.[30]

Similarly, in the Women's Health Study, 27,939 healthy women were monitored for approximately 8 years to assess their risk of CV events, including MI, ischemic stroke, coronary revascularization, or CV death. In that study, hsCRP emerged as a stronger predictor for CV events than LDL cholesterol, with each quintile increase in hsCRP resulting in a 1.5-fold greater risk of CV events compared with similar increases in LDL cholesterol.[31]

The ACC/AHA 2019 primary guidelines recommend consideration of hsCRP testing in patients at intermediate risk for ASCVD as an option to help determine the need for pharmacological therapy of cholesterol or blood pressure (class 2a recommendation, level of evidence: b-nr). When hsCRP is ≥2 mg/l, it is considered a risk enhancer, which can further guide decisions for statin initiation and titration, including statin dose escalation or addition of another lipid-lowering agent.[5]

However, the question remains as to whether the measurement of hsCRP is sufficient for ASCVD risk assessment or whether additional tools are also necessary. To further help with this, a subset of 950 trial participants from the MESA study who met JUPITER trial inclusion criteria were evaluated with coronary artery calcium (CAC) scoring to assess incremental risk assessment. A considerable difference in numbers needed to screen over 5 years was noted among patients with CAC scores of 0 and 100 for CHD (549 versus 24) and CVD (124 versus 19), with nearly all events occurring in patients in whom moderate CAC was present irrespective of hsCRP levels.[32]

Similarly, in a report of MESA participants at intermediate risk of ASCVD, CAC, ankle–brachial index, hsCRP, and family history were all independent predictors of incident CHD/CVD, with CAC having the strongest association with CHD. CAC also provided superior discrimination and risk classification.[33] Thus, measurement of hsCRP can be helpful in patients

Table 2: Usage of hsCRP for Primary and Secondary Prevention of ASCVD

Prevention Type	Usage of hsCRP
Primary prevention	• In adults not on statin therapy with LDL cholesterol 3.9–10.5 mmol/l (70–189 mg/dl), without diabetes, and a 10-year ASCVD risk estimate of 5% to <7.5% or ≥7.5%, the risk discussion should consider ASCVD risk enhancers, including hsCRP ≥2 mg/l in selected individuals if measured[5] • In adults at intermediate risk (≥7.5% to <20%), the presence of risk enhancers favors initiation of moderate-intensity statin therapy to reduce LDL cholesterol by 30–49% (class 1 recommendation)[5] • In adults at borderline risk (5% to <7.5%), if a risk enhancer is present then a risk discussion regarding moderate-intensity statin therapy should be considered (class 2b recommendation)[5]
Secondary prevention	• For identification of residual inflammatory risk in patients with controlled LDL cholesterol • For prognostication, after a cardiac event

ASCVD = atherosclerotic cardiovascular disease; hsCRP = high-sensitivity C-reactive protein.

who need further risk stratification, especially in conjunction with CAC testing. However, it should be noted that the MESA-JUPITER study showed that hsCRP was not associated with CHD or CVD after multivariable adjustment.[32] Reasons for the failure of hsCRP to predict risk in MESA could include the multiethnic makeup of the cohort.

Disadvantages of CAC relative to hsCRP include radiation exposure and increased cost, whereas advantages include the direct measurement of atherosclerosis, which is a measure of disease rather than a risk factor, and more stability across ethnicities compared with hsCRP. While clinicians can consider checking hsCRP, CAC provides a superior risk reclassification.

In practice, clinicians can measure hsCRP to further refine CV risk assessment in patients at intermediate risk, or in cases when availability of additional prognostic markers helps guide decision-making (*Table 2*).

Role in Secondary Prevention of ASCVD Events

Apart from assessing inflammation to help predict an individual's risk for initial events in primary prevention, it is important to assess a patient's risk for recurrent events as well. To this end, measurement of hsCRP in secondary prevention is an area of ongoing research, with early data indicating significant, prognostic value.[34]

Measurement of hsCRP has prognostic value in individuals with coronary artery disease (CAD), including those who have undergone percutaneous coronary intervention (PCI), and coronary artery bypass graft surgery. In fact, residual inflammatory risk in this population is known to persist even after treatment with intensive lipid-lowering therapy, defined as an hsCRP level ≥2 mg/l in patients with LDL cholesterol <3.9 mmol/l (70 mg/dl). Among the one-third of individuals with known ASCVD in the PROVE-IT and IMPROVE-IT trials who had hsCRP ≥2 mg/l and LDL cholesterol <3.9 mmol/l (70 mg/dl), there was an increased risk of recurrent events (3.1 per 100 person-years and 33.7%, respectively).[34]

Similarly, in a collaborative analysis of 31,245 patients on statin therapy with either established ASCVD or at high risk for it, residual inflammatory risk was a strong predictor for MACE (highest hsCRP quartile versus lowest quartile: HR 1.31; 95% CI [1.20–1.43]), CV mortality (HR 2.68; 95% CI [2.22–3.23]), and all-cause mortality (HR 2.42; 95% CI [2.12–2.77]).[3]

Collectively, these findings suggest a possible role for measuring hsCRP in secondary prevention patients to assess inflammatory risk.

Clinical Outcomes in Patients with Inflammatory Risk

The landmark JUPITER trial was the first large-scale trial that sought to evaluate the role of inflammation as a modifiable risk factor for ASCVD.[35] In the study, 17,802 men and women with no known ASCVD, LDL cholesterol <7.2mmol/l (130 mg/dl; considered well controlled at that time) and hsCRP ≥2.0 mg/l were randomized to rosuvastatin 20 mg daily or placebo and followed for the combined primary endpoint of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CV causes. At the 12-month visit, individuals randomized to rosuvastatin had a 50% lower median LDL cholesterol concentration (mean difference, 1.2 mmol/l [47 mg/dl]), a 37% lower median hsCRP level, and a 17% lower median triglyceride level (p<0.001 for all 3 comparisons). These effects persisted throughout the study period. The trial was stopped prematurely after a median of 1.9 years because of differences in the CV event rate. Rates of the primary endpoint per 100 person-years were 0.77 and 1.36 in those receiving rosuvastatin and placebo, respectively (HR for rosuvastatin 0.56; 95% CI [0.46–0.69]; p<0.00001).[35] In a subanalysis of JUPITER, hsCRP was monitored in 8,901 participants randomized to the placebo arm (not on statin) over 4 years. Results revealed minimal variation in hsCRP levels over time (similar to LDL cholesterol and blood pressure), underscoring its reliability as a biomarker for CV risk assessment.[36]

Bempedoic acid, an adenosine triphosphate citrate lyase inhibitor that acts upstream and in the same pathway as statins, reduces both LDL cholesterol (21% greater than placebo) and hsCRP (22% greater than placebo) and therefore addresses both residual cholesterol and inflammatory risks. In the CLEAR-Outcomes trial, treatment with bempedoic acid was associated with a 13% relative reduction in the risk of first major CV disease event among patients with statin intolerance.[37] In a follow-up analysis, hsCRP was shown to be a stronger predictor of future CV events and death than hyperlipidemia. Compared with placebo, bempedoic acid had similar efficacy in reducing CV events across all levels of hsCRP and LDL cholesterol.[38]

The importance of targeting residual inflammation in patients with ASCVD is best illustrated by the CANTOS study. Canakinumab is a monoclonal antibody that targets IL-1β and slows the production of IL-6 and CRP, thereby reducing inflammation, with no effect on lipids. In 2017, CANTOS provided strong evidence that targeting inflammation even without lipid lowering can significantly reduce CV event rates and helped define the IL-1 to IL-6 to CRP pathway as a central target in CV disease.[39]

In the CANTOS study, 10,061 patients with previous MI and hsCRP ≥2 mg/l were randomized to subcutaneous canakinumab at one of three doses (50, 150, or 300 mg) or placebo every 3 months.[40] Median hsCRP levels were reduced by 26–41% in the canakinumab group compared with those receiving placebo. The hazard ratios for canakinumab compared with placebo at the 50, 150 and 300 mg doses were 0.93 (95% CI [0.80–1.07]; p=0.30), 0.85 (95% CI [0.74–0.98]; p=0.021), and 0.86 (95% CI [0.75–0.99]; p=0.031), respectively. Canakinumab significantly reduced recurrent vascular events (nonfatal MI, nonfatal stroke, or CVD death) proportionately to the reduction in hsCRP levels, with the greatest benefit derived by those who achieved hsCRP <2 mg/l. Treatment with canakinumab was, however, associated with a higher incidence of fatal infection and is not currently Food and Drug Administration (FDA) approved for ASCVD risk reduction.[40]

Additional support for targeting inflammation in combination with lipid-lowering is provided by the FOURIER and SPIRE-1/SPIRE-2 trials that reported residual inflammatory risk (hsCRP ≥2 mg/l) in patients treated with a statin and PCSK9 inhibitor. While treatment with evolocumab in the FOURIER trial was associated with a significant reduction in CV risk across hsCRP strata, the greatest absolute risk reduction, that is, 2.6% and 3% in the primary and secondary endpoints, respectively, was seen in patients with a higher baseline hsCRP (>3 mg/l).[41] After adjustment for confounders and achieved LDL cholesterol, a 13% increase in relative risk of MACE was observed with each doubling of the hsCRP level and a 62% relative increase in risk of future CV events after accounting for on-treatment LDL cholesterol was seen with an hsCRP >3 mg/l in the FOURIER and SPIRE-1/SPIRE-2 trials respectively.[41,42]

Current Anti-inflammatory Treatment Options for ASCVD and Ongoing Studies

Colchicine is the first anti-inflammatory agent approved by the FDA for use in patients with clinical ASCVD. Its approval was based upon observed CV risk reduction in patients with chronic coronary artery disease (based on the LoDoCo and LoDoCo2 trials), and patients with recent MI (based on the COLCOT trial).[43–45] Importantly, these studies did NOT measure hsCRP a priori to define patients eligible for study participation. As such, it is challenging to ascertain the extent to which benefits associated with colchicine use differ based on the level of background inflammation.

Compared with placebo, colchicine 0.5 mg once daily lowered MACE by 31% among those with stable atherosclerosis and by 23% after a recent MI on top of standard-of-care therapy, although there was a statistically significant increase in pneumonia in the COLCOT trial (recent acute coronary syndrome patients) and a trend for an increase in non-CV death in the LoDoCo2 trials (stable CAD).[44,45] Arguably, the benefit seen from colchicine 0.5 mg once daily is similar to that seen in many of the contemporary secondary prevention trials of adjunctive lipid-lowering agents; however, the narrow therapeutic window and the risk of increased infection and non-CV adverse events limited its use and FDA approval initially.[6] However, colchicine was FDA approved for secondary ASCVD prevention in 2023.

A subgroup of the COLCHICINE-PCI study did measure hsCRP levels and reported no significant reduction in the endpoints with colchicine in post-PCI patients despite a decrease in hsCRP levels.[46] Of note, colchicine was also discontinued in 15% of LoDoCo participants in the run-in phase of the trial because of varying side effects, including myalgias and gastrointestinal intolerance.

Ultimately, the 2023 AHA/ACC/Multisociety Chronic Coronary Disease Guideline notes that the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events (class 2b recommendation, level of evidence: b) and the 2024 European Society of Cardiology Chronic CAD guidelines also note that low-dose colchicine should be considered (class 2a recommendation, level of evidence: a), with the level of recommendation based partially on a narrow therapeutic window and increase in gastrointestinal and non-CV death events, warranting further investigation.[47,48]

However, the outcomes from the CLEAR SYNERGY (OASIS 9) trial found no benefit of colchicine in 7,062 patients post-MI and within 72 hours of their index PCI, contrary to prior studies. In that large, international 2×2 factorial, randomized controlled trial of low-dose colchicine 0.5 mg daily versus placebo and spironolactone 25 mg daily versus placebo, a greater reduction of CRP was noted in the colchicine arm, but no significant reduction of the primary outcome, which was a composite of CV death, MI, stroke, or ischemia-driven revascularization, was reported in the colchicine arm when compared with placebo at 5 years (9.1% versus 9.3%; HR 0.99; 95% CI [0.85–1.16]; p=0.93).[49,50] Moreover, a higher incidence of diarrhea was reported with colchicine use (10.2% versus 6.6%, p<0.001). In light of these findings, the benefit of colchicine in reducing MACE in secondary prevention has become debatable.

Therefore, we recommend that clinicians focus on assessing hsCRP and, when elevated, target this inflammation by going upstream with nonpharmacological measures that can reduce hsCRP: intensive lifestyle changes with improved dietary habits, weight loss, smoking cessation, increased exercise, and reduction in waist circumference.[20] If this fails, at that point one can consider prescribing colchicine to select patients with known atherosclerotic disease, in particular, those with residual inflammatory risk, defined as a hsCRP level ≥2 mg/l despite the use of statin therapy and those who are higher risk, as evidenced by recurrent vascular events with normal renal function and lower risk for infection.[45] Although the European Society of Cardiology guidelines recommend colchicine as a class 2b recommendation, they were updated prior to the CLEAR SYNERGY (OASIS 9) trial, and the use of colchicine may be lower now given the trial results.[51] In clinical studies, the rate of myotoxicity was similar in those treated with colchicine or placebo.[44,45]

Importantly, colchicine may have a narrow therapeutic window and should not be prescribed to individuals with clinically significant CKD (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2) or hepatic dysfunction and should not be used in combination with strong inhibitors of CYP3A4 or P-glycoprotein, such as clarithromycin, azole antifungal agents, and certain immunosuppressive medications.[6,52] In addition, colchicine should be temporarily discontinued for a week or two if any of these drugs are initiated in the short term. Even with mild renal impairment, some people can exceed the serum colchicine level upper safety limit of 3.0 µg/l on 0.6 mg colchicine, which poses the greatest risk among patients 65 years or older who may have declining liver or kidney function.[52]

Future Horizons

Additional studies evaluating alternative anti-inflammatory agents are underway, most notably IL-6 inhibitors. Despite the promise of directly targeting IL-6 to reduce the incidence of MACE, the safety and efficacy of IL-6 inhibition in individuals at high atherosclerotic risk has been uncertain.[53] The RESCUE trial addressed this issue with ziltivekimab, a fully human monoclonal antibody directed against the IL-6 ligand that is being specifically developed for atherothrombotic disease. RESCUE focused on individuals with elevated levels of hsCRP and CKD, a group with substantial cardiovascular risk for whom alternative proven anti-inflammatory agents such as renally excreted colchicine are contraindicated.

The RESCUE investigators randomly allocated 264 patients with residual inflammatory risk (hsCRP ≥2 mg/l) and stage 3–5 CKD to subcutaneous placebo or ziltivekimab 7.5 mg, 15 mg, or 30 mg once every 4 weeks over 24 weeks. Overall, the primary endpoint of median hsCRP change over time was −77%, −88%, and −92% across the ascending ziltivekimab doses as compared with −4% on placebo (all p-values <0.0001).[54] In follow-up studies, ziltivekimab is being tested in the ZEUS study. ZEUS will compare ziltivekimab with placebo in 6,200 patients with stage 3–4 CKD and elevated hsCRP to formally test whether reducing circulating IL-6 reduces

adverse cardiovascular events. Incident MACE inclusive of MI, stroke, and cardiovascular death is the trial's primary endpoint.[53]

Conclusion

Integration of hsCRP into clinical practice for risk assessment in primary prevention represents a potential means to stratify patients at risk for ASCVD while also identifying those who may benefit from additional risk-reducing therapies. Despite effective lipid-lowering options and attainment of low levels of LDL cholesterol in patients for secondary prevention, residual inflammatory risk persists, necessitating a multifaceted approach to CV prevention and management. Consideration can also be given to measurement of hsCRP in secondary prevention patients with recurrent CV events despite well-controlled LDL cholesterol as a way to identify those with residual inflammatory risk. It is strongly recommended to emphasize comprehensive lifestyle improvements to lower hsCRP before indefinitely committing the patient to anti-inflammatory therapy with its commensurate risks. Importantly, efforts are underway to identify anti-inflammatory treatments that are efficacious, well-tolerated, safe, and can serve as a complementary strategy to other CV risk-reducing therapies targeting cholesterol risk. Meanwhile, lifestyle modification including a heart-healthy diet, maintaining a healthy weight, smoking cessation, and regular exercise in addition to statin therapy remain the primary methods for addressing inflammatory risk and reducing the risk of MACE. ❑

1. Pahwa R, Jialal I. *Atherosclerosis*. Treasure Island, FL: StatPearls Publishing, 2024. PMID: 29939576.
2. Joynt Maddox KE, Elkind MSV, Aparicio HJ, et al. Forecasting the burden of cardiovascular disease and stroke in the United States through 2050 – prevalence of risk factors and disease: a Presidential Advisory from the American Heart Association. *Circulation* 2024;150:e65–88. https://doi.org/10.1161/CIR.0000000000001256; PMID: 38832505.
3. Ridker PM, Bhatt DL, Pradhan AD, et al. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. *Lancet* 2023;401:1293–301. https://doi.org/10.1016/S0140-6736(23)00215-5; PMID: 36893777.
4. Alfaddagh A, Martin SS, Leucker TM, et al. Inflammation and cardiovascular disease: from mechanisms to therapeutics. *Am J Prev Cardiol* 2020;4:100130. https://doi.org/10.1016/j.ajpc.2020.100130; PMID: 34327481.
5. Arnett DK, Blumenthal RS, Albert MA, 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* 2019;140:e596–646. https://doi.org/10.1161/CIR.0000000000000678; PMID: 30879355.
6. Nelson K, Fuster V, Ridker PM. Low-dose colchicine for secondary prevention of coronary artery disease: JACC review topic of the week. *J Am Coll Cardiol* 2023;82:648–60. https://doi.org/10.1016/j.jacc.2023.05.055; PMID: 37558377.
7. Aday AW, Ridker PM. Targeting residual inflammatory risk: a shifting paradigm for atherosclerotic disease. *Front Cardiovasc Med* 2019;6:16. https://doi.org/10.3389/fcvm.2019.00016; PMID: 30873416.
8. Shapiro MD, Fazio S. Apolipoprotein B-containing lipoproteins and atherosclerotic cardiovascular disease. *F1000Res* 2017;6:134. https://doi.org/10.12688/f1000research.9845.1; PMID: 28299190.
9. Abdul-Rahman T, Bukhari SMA, Herrera EC, et al. Lipid lowering therapy: an era beyond statins. *Curr Probl Cardiol* 2022;47:101342. https://doi.org/10.1016/j.cpcardiol.2022.101342; PMID: 35918009.
10. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–9. PMID: 7968073.
11. Tonelli M, Lloyd A, Clement F, et al. Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis. *CMAJ Can Med Assoc J* 2011;183:E1189–202. https://doi.org/10.1503/cmaj.101280; PMID: 21989464.
12. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013;2013:CD004816. https://doi.org/10.1002/14651858.CD004816.pub5; PMID: 23440795.
13. Tecson KM, Kluger AY, Cassidy-Bushrow AE, et al. Usefulness of statins as secondary prevention against recurrent and terminal major adverse cardiovascular events. *Am J Cardiol* 2022;176:37–42. https://doi.org/10.1016/j.amjcard.2022.04.018; PMID: 35606173.
14. Libby P. Inflammation and cardiovascular disease mechanisms. *Am J Clin Nutr* 2006;83:456S–60S. https://doi.org/10.1093/ajcn/83.2.456S; PMID: 16470012.
15. Libby P. Inflammation in atherosclerosis: no longer a theory. *Clin Chem* 2021;67:131–42. https://doi.org/10.1093/clinchem/hvaa275; PMID: 33393629.
16. Wolf D, Ley K. Immunity and inflammation in atherosclerosis. *Circ Res* 2019;124:315–27. https://doi.org/10.1161/CIRCRESAHA.118.313591; PMID: 30653442.
17. Penson PE, Long DL, Howard G, et al. Associations between very low concentrations of low density lipoprotein cholesterol, high sensitivity C-reactive protein, and health outcomes in the Reasons for Geographical and Racial Differences in Stroke (REGARDS) study. *Eur Heart J* 2018;39:3641–53. https://doi.org/10.1093/eurheartj/ehy533; PMID: 30165636.
18. Blumenthal RS, Martin SS. Prevention of cardiovascular disease – don't stop thinking about tomorrow. *N Engl J Med* 2024;391:2161–2. https://doi.org/10.1056/NEJMe2409080; PMID: 39216097.
19. Ding WY, Protty MB, Davies IG, Lip GYH. Relationship between lipoproteins, thrombosis, and atrial fibrillation. *Cardiovasc Res* 2022;118:716–31. https://doi.org/10.1093/cvr/cvab017; PMID: 33483737.
20. Ndumele CE, Nasir K, Conceiçao RD, et al. Hepatic steatosis, obesity, and the metabolic syndrome are independently and additively associated with increased systemic inflammation. *Arterioscler Thromb Vasc Biol* 2011;31:1927–32. https://doi.org/10.1161/ATVBAHA.111.228262; PMID: 21546603.
21. Shrivastava AK, Singh HV, Raizada A, Singh SK. C-reactive protein, inflammation and coronary heart disease. *Egypt Heart J* 2015;67:89–97. https://doi.org/10.1016/j.ehj.2014.11.005.
22. Banait T, Wanjari A, Danade V, et al. Role of high-sensitivity C-reactive protein (Hs-CRP) in non-communicable diseases: a review. *Cureus* 2022;14:e30225. https://doi.org/10.7759/cureus.30225; PMID: 36381804.
23. Connelly MA, Otvos JD, Shalaurova I, et al. GlycA, a novel biomarker of systemic inflammation and cardiovascular disease risk. *J Transl Med* 2017;15:219. https://doi.org/10.1186/s12967-017-1321-6; PMID: 29078787.
24. Khan AA, Alsahli MA, Rahmani AH. Myeloperoxidase as an active disease biomarker: recent biochemical and pathological perspectives. *Med Sci (Basel)* 2018;6:33. https://doi.org/10.3390/medsci6020033; PMID: 29669993.
25. Woloshin S, Schwartz LM. Distribution of C-reactive protein values in the United States. *N Engl J Med* 2005;352:1611–13. https://doi.org/10.1056/NEJM200504143521525; PMID: 15829550.
26. Bower JK, Lazo M, Juraschek SP, Selvin E. Within-person variability in high-sensitivity C-reactive protein. *Arch Intern Med* 2012;172:1519–21. https://doi.org/10.1001/archinternmed.2012.3712; PMID: 22945505.
27. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499–511. https://doi.org/10.1161/01.cir.0000052939.59093.45; PMID: 12551878.
28. Ockene IS, Matthews CE, Rifai N, et al. Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. *Clin Chem* 2001;47:444–50. https://doi.org/10.1093/clinchem/47.3.444; PMID: 11238295.
29. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;297:611–9. https://doi.org/10.1001/jama.297.6.611; PMID: 17299196.
30. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973–9. https://doi.org/10.1056/NEJM199704033361401; PMID: 9077376.
31. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347:1557–65. https://doi.org/10.1056/NEJMoa021993; PMID: 12432042.
32. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. *Lancet* 2011;378:684–92. https://doi.org/10.1016/S0140-6736(11)60784-8; PMID: 21856482.
33. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012;308:788–95. https://doi.org/10.1001/jama.2012.9624; PMID: 22910756.
34. Ridker PM. How common is residual inflammatory risk? *Circ Res* 2017;120:617–9. https://doi.org/10.1161/CIRCRESAHA.116.310527; PMID: 28209792.
35. Everett BM, Glynn RJ, MacFadyen JG, Ridker PM. Rosuvastatin in the prevention of stroke among men and women with elevated levels of C-reactive protein: Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). *Circulation* 2010;121:143–50. https://doi.org/10.1161/CIRCULATIONAHA.109.874834; PMID: 20026779.
36. Glynn RJ, MacFadyen JG, Ridker PM. Tracking of high-sensitivity C-reactive protein after an initially elevated concentration: the JUPITER study. *Clin Chem* 2009;55:305–12. https://doi.org/10.1373/clinchem.2008.120642; PMID: 19095726.
37. Nissen SE, Menon V, Nicholls SJ, et al. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. *JAMA* 2023;330:131–40. https://doi.org/10.1001/jama.2023.9696; PMID: 37354546.
38. Ridker PM, Lei L, Louie MJ, et al. Inflammation and cholesterol as predictors of cardiovascular events among 13 970 contemporary high-risk patients with statin intolerance. *Circulation* 2024;149:28–35. https://doi.org/10.1161/CIRCULATIONAHA.123.066213; PMID: 37929602.
39. Ridker PM. From CANTOS to CIRT to COLCOT to clinic: will all atherosclerosis patients soon be treated with combination lipid-lowering and inflammation-inhibiting agents? *Circulation* 2020;141:787–9. https://doi.org/10.1161/CIRCULATIONAHA.119.045256; PMID: 32150469.
40. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119–31. https://doi.org/10.1056/NEJMoa1707914; PMID: 28845751.
41. Bohula EA, Giugliano RP, Leiter LA, et al. Inflammatory and cholesterol risk in the FOURIER trial. *Circulation* 2018;138:131–40. https://doi.org/10.1161/CIRCULATIONAHA.118.034032; PMID: 29530884.
42. Pradhan AD, Aday AW, Rose LM, Ridker PM. Residual inflammatory risk on treatment with PCSK9 inhibition and statin therapy. *Circulation* 2018;138:141–9. https://doi.org/10.1161/CIRCULATIONAHA.118.034645; PMID: 29716940.
43. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;61:404–10. https://doi.org/10.1016/j.jacc.2012.10.027; PMID: 23265346.
44. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;383:1838–47. https://doi.org/10.1056/NEJMoa2021372; PMID: 32865380.
45. Tardif J-C, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;381:2497–505. https://doi.org/10.1056/NEJMoa1912388; PMID: 31733140.
46. Shah B, Pillinger M, Zhong H, et al. Effects of acute colchicine administration prior to percutaneous coronary intervention: COLCHICINE-PCI Randomized Trial. *Circ Cardiovasc Interv* 2020;13:e008717. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008717; PMID: 32295417.
47. Writing Committee Members, Virani SS, Newby LK, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the

management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2023;82:833–955. https://doi.org/10.1016/j.jacc.2023.04.003; PMID: 37480922.
48. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes: developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2024;45:3415–537. https://doi.org/10.1093/eurheartj/ehae177; PMID: 39210710.
49. d'Entremont M-A, Lee SF, Mian R, et al. Design and rationale of the CLEAR SYNERGY (OASIS 9) trial: a 2x2 factorial randomized controlled trial of colchicine versus placebo and spironolactone vs placebo in patients with myocardial infarction. *Am Heart J* 2024;275:173–82. https://doi.org/10.1016/j.ahj.2024.06.007; PMID: 38936755.
50. Jolly SS, d'Entremont M-A, Lee SF, et al. Colchicine in acute myocardial infarction. *N Engl J Med* 2024. https://doi.org/10.1056/NEJMoa2405922; PMID: 39555823; epub ahead of press.
51. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227–337. https://doi.org/10.1093/eurheartj/ehab484; PMID: 34458905.
52. Robinson PC, Terkeltaub R, Pillinger MH, et al. Consensus statement regarding the efficacy and safety of long-term low-dose colchicine in gout and cardiovascular disease. *Am J Med* 2022;135:32–8. https://doi.org/10.1016/j.amjmed.2021.07.025; PMID: 34416165.
53. Ridker PM. From RESCUE to ZEUS: will interleukin-6 inhibition with ziltivekimab prove effective for cardiovascular event reduction? *Cardiovasc Res* 2021;117:e138–40. https://doi.org/10.1093/cvr/cvab231; PMID: 34352102.
54. Ridker PM, Devalaraja M, Baeres FMM, et al. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* 2021;397:2060–9. https://doi.org/10.1016/S0140-6736(21)00520-1; PMID: 34015342.