CRP/hs-CRP lowering by statins and other drugs used to treat dyslipidemia

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Purpose of review
Atherosclerosis is recognized as a chronic inflammatory disease, with high-sensitivity C-reactive protein (hs-CRP) serving as a biomarker of cardiovascular risk that persists despite optimal control of traditional risk factors. Landmark trials, like JUPITER (Justification for the Use of Statins in Prevention) and PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy), demonstrate the effect of lipid-lowering medications on inflammation. This can have further implications for comprehensive cardiovascular risk reduction.

Recent findings
Statins lower hs-CRP alongside low-density lipoprotein cholesterol (LDL-C), with greater effects from high-intensity regimens. Nonstatin medications have variable effects; for example, the addition of ezetimibe to statin therapy enhances hs-CRP reduction. Bempedoic acid exerts direct anti-inflammatory effects, producing significant hs-CRP lowering. Omega-3 fatty acids also demonstrate favorable effects on inflammatory markers. However, fibrates offer only marginal benefits, and PCSK9 inhibitors (Proprotein Convertase Subtilisin/Kexin type 9) have minimal impact. Residual inflammatory risk persists despite LDL-C control, supporting dual-target strategies.

Summary
The evidence supports therapeutic strategies targeting both lipid and inflammatory pathways, with hs-CRP serving as a complementary marker to refine cardiovascular risk stratification and guide treatment intensification in primary and secondary prevention. Future studies should evaluate inflammation-targeted adjunctive therapies to address discordance between lipid control and residual inflammatory risk.

Keywords
atherosclerosis, high-sensitivity C-reactive protein, inflammation, lipid-lowering therapy, statins

INTRODUCTION

Atherosclerosis, the root cause behind most acute coronary events, is now considered a chronic inflammatory condition of the arterial walls [1]. Risk factors (dyslipidemia, hypertension, diabetes, and smoking) induce damage in the innermost layer of arteries, the intima [1]. Lipoprotein accumulation and oxidation follow, which attracts circulating monocytes to the intima. These cells differentiate into macrophages and engulf lipoprotein, forming foam cells [1]. T lymphocytes and vascular smooth muscle cells later, along with foam cells, secrete proteolytic enzymes and pro-inflammatory cytokines, causing the above fibrous cap to destabilize and rupture. This process, involving inflammation and various inflammatory cytokines, predisposes patients to acute coronary events [2].

Within this inflammatory cascade, C-reactive protein (CRP) has gained considerable attention. It is synthesized by the liver in response to cytokines such as interleukin-6 (IL-6), which are released during acute-phase reactions, such as infection, trauma, or inflammation [3]. Traditional assays detect CRP in clinical ranges associated with significant inflammation; however, the emergence of high-sensitivity methods such as high-sensitivity C-reactive protein (hs-CRP) has enabled quantification of subtle elevations characteristic of low-grade inflammation, such as atherosclerosis. This enables assessment of atherosclerotic burden and its application for stratifying cardiovascular risk in apparently healthy populations [3].

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Curr Opin Cardiol 2026, 41:298–303

DOI:10.1097/HCO.0000000000001307

KEY POINTS

- Evidence of the anti-inflammatory effects of lipid-lowering pharmacotherapies is growing.
- Persistently elevated CRP despite optimal LDL-C levels can signify residual inflammatory risk highlighting the need to integrate inflammatory risk in ASCVD assessment.
- Future research will clarify whether hs-CRP evolves from a risk-stratification marker to a treatment target in defined subgroups.

While it lacks specificity, elevated hs-CRP has consistently been associated with future cardiovascular events across numerous prospective studies. This association has been present even after adjusting for various established risk factors like dyslipidemia. All this data support the hypothesis that hs-CRP captures the residual risk not reflected by conventional risk factors [4▪].

Multiple trials have demonstrated that lipid-lowering medications not only help regulate low-density lipoprotein-cholesterol (LDL-C) levels but also lower hs-CRP concentrations. Landmark trials like Justification for Use of statin in Prevention (JUPITER) demonstrated a 37% reduction in hs-CRP, and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) showed that a higher statin dose led to a greater reduction than lower doses [5]. Bempedoic acid reduced hs-CRP by 22% in CLEAR Outcomes (Cholesterol Lowering via Empedoic acid, an ACL-inhibiting Regimen), while PCSK9 inhibitors (proprotein convertase subtilisin/kexin type 9) in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk/SPIRE Study of PCSK9 Inhibition and the Reduction of vascular Events (FOURIER/SPIRE) study spare hs-CRP despite considerable LDL-C lowering, with residual hs-CRP at least 2 mg/l predicting higher risk [4▪,6].

REVIEW

Traditional CRP assays detect high concentrations typical of acute infection but cannot reliably distinguish the low-grade inflammation relevant to atherosclerosis [7]. hs-CRP assays, using refined immunonephelometric or immunoturbidimetric methods, quantify CRP between 0.1 and 10 mg/l, making them suitable for cardiovascular risk assessment in stable individuals [8]. Both measure the same analyte; the distinction is analytic sensitivity [7,8]. For risk stratification, hs-CRP thresholds of less than 1, 1–3 mg/l, and greater than 3 mg/l define low, intermediate, and high cardiovascular risk, respectively, when measured in the absence of acute illness. Values at least 10 mg/l indicate nonatherosclerotic inflammation (infection, trauma, sepsis) and warrant repeat testing after excluding acute causes [7]. Meta-analyses show 1.5–2 times higher major adverse cardiovascular event rates in the highest vs. the lowest hs-CRP categories after adjustment for traditional risk factors [4▪,8]. Residual inflammatory risk indicates the persistent cardiovascular risk (present despite controlling LDL-C) from ongoing vascular inflammation [4▪].

Major society guidelines consider hs-CRP as adjunctive rather than primary. American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) recommend measuring it in individuals with borderline/intermediate 10-year risk to refine estimates and guide statin decisions, but not universal screening or 'treat-to-CRP' targets [4▪,7].

Statins

Statins decrease CRP levels through anti-inflammatory effects, independent of their ability to lower LDL-C levels. The primary mechanism is direct inhibition of IL-6 signaling, which triggers CRP production in hepatocytes [9]. By blocking HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase), they decrease intermediates in the mevalonate pathway, which are needed for protein geranylgeranylation [9]. This decreases Rac-1-dependent signaling (Ras-related C3 botulinum toxin substrate 1), which leads to decreased STAT3 (Signal Transducer and Activator of Transcription 3) serine phosphorylation, which then lowers gene transcription for CRP [9]. Statins have also been shown to lower CRP by upregulating IκBα (inhibitor of B alpha), which suppresses NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) nuclear signaling which decreases CRP gene transcription [10]. In a meta-analysis of 53 placebo-controlled randomized controlled trials, statins were found to significantly lower CRP by –0.65 mg/l (–0.87 to –0.4.3) the greatest significant reduction compared with other lipid-lowering therapies [11]. A meta-regression analysis also found no significant association between the changes in CRP vs. LDL-C; this shows that statins can lower CRP partly independently of lipid lowering [11]. Statins have also been found to have a dose-potency effect with high-intensity statins producing greater reduction in CRP/hs-CRP compared with low or moderate statin therapy. In the PROVE-IT TIMI 22 study (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22), after

acute coronary syndrome (ACS) atorvastatin 80 mg lowered CRP more than pravastatin 40 mg (38 vs. 27%), similarly the REVERSAL (Reversal of Atherosclerosis with Aggressive lipid lowering) study showed 30–40% greater reduction in CRP with atorvastatin 80 mg compared with pravastatin 40 mg [12,13].

The clinical significance of statin-mediated reduction in CRP levels is supported by analyses that showed targeted CRP levels may stratify residual risk. In PROVE-IT TIMI 22, 3745 patients with ACS treated with either atorvastatin or pravastatin, achieving an LDL-C less than 70 mg/dl was associated with lower recurrent event rates (2.7 vs. 4 events/100 person-years, $P=0.008$), and achieving CRP less than 2 mg/l provided similar results (2.8 vs. 3.9 events/100 person-years, $P=0.006$) across all LDL-C levels. Patients who reached both low LDL-C and very low CRP (<1 mg/l) had the lowest event rates (1.9 events/100 person-years). This indicates that a 'dual target' approach, reducing both lipid levels and inflammation (CRP) may have better outcomes [12]. The JUPITER trial showed that rosuvastatin 20 mg daily reduced hs-CRP by 37% and LDL-C by 50% resulting in a 44% reduction in major cardiovascular events among healthy individuals with elevated hs-CRP (≥2 mg/l) but normal LDL-C (<130 mg/dl, median 108 mg/dl). This trial demonstrated that among healthy individuals with elevated CRP but normal LDL-C, rosuvastatin was able to significantly lower risk for major adverse cardiovascular events and reduced all-cause mortality; this reinforces use of CRP as marker to stratify individuals who may benefit from statin therapy for primary prevention [14]. However, it is important to note that baseline hs-CRP levels showed an inverse relationship with the relative treatment benefit. Patients with hs-CRP 2.0–3.1 mg/l had a 57% relative risk reduction, and those with hs-CRP greater than 5.4 mg/l had a 37% reduction ($P=0.02$). The overall cardiovascular risk was higher at higher hs-CRP levels, the absolute number of events prevented was greatest in the group with the highest baseline hs-CRP level [15].

With regards to differences between hydrophilic and lipophilic statins in lowering CRP, a meta-analysis of randomized controlled trials in patients with kidney disease found that both hydrophilic and lipophilic statins significantly lowered hs-CRP levels [16]. Furthermore, a randomized double-blind cross over trial comparing pravastatin, simvastatin, and atorvastatin found that they all significantly lowered hs-CRP levels, median baseline 2.6 mg/l reduced to 1.7–1.9 mg/l, reduction was similar despite differences in lipophilicity, however, the study did not specifically investigate whether more potent statins or higher doses would produce greater hs-CRP reduction [17].

The fall in CRP levels after initiation of statin therapy occurs rapidly. A study showed that simvastatin 40 mg significantly reduced hs-CRP levels within 14 days after initiation and independent of LDL-C changes [18]. The Pravastatin Inflammation/CRP Evaluation study (PRINCE trial) showed that pravastatin 40 mg reduced CRP levels by 14.7% at 12 weeks and 16.9% in 24 weeks [7]. Another study showed that atorvastatin was able to significantly reduce CRP levels by 22–40% within a month and 32–36% after 3 months compared with baseline, independent of LDL-C changes [19].

Overall evidence supports inflammation as a driver for atherosclerotic cardiovascular disease (ASCVD) risk, CRP is a useful marker to determine residual inflammation. Statins remain the foundation of therapy as they not only decrease LDL-C but also CRP, even in individuals with normal LDL-C. Importantly, persistently elevated CRP despite optimal LDL-C levels can signify residual inflammatory risk highlighting the need to integrate inflammatory risk in ASCVD assessment and investigate other therapies that can lower CRP and baseline inflammation [20▪].

Nonstatins

Ezetimibe inhibits intestinal absorption of cholesterol by impeding cholesterol transport across the intestinal wall [21]. According to the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT trial), significantly more patients treated with a combination of simvastatin and ezetimibe met the hs-CRP goal than those treated with simvastatin alone [22]. In a pooled analysis, the addition of ezetimibe to statin provided a significant reduction in CRP levels, over and above those of statin monotherapy; however, the effects of ezetimibe monotherapy were not well defined [23]. In another randomized controlled trial, a combination of atorvastatin and ezetimibe decreased CRP, but ezetimibe alone did not decrease it [24].

Bempedoic acid works by inhibiting ATP citrate lyase enzyme, which in turn decreases cholesterol synthesis. Additionally, it targets the AMP-activated protein kinase pathway, resulting in potent anti-inflammatory effects [11]. In a meta-analysis, patients treated with bempedoic acid experienced a 13.2% decrease in CRP levels compared with placebo [25]. Pooled data from four phase 3 clinical trials showed bempedoic acid significantly reduced hs-CRP levels irrespective of background statin therapy and independent of the LDL-C lowering [26]. A secondary biomarker analysis of the Evaluation of Long-Term Safety and Tolerability of ETC-1002 in High-Risk Patients With Hyperlipidemia and High CV Risk (CLEAR Harmony trial) demonstrated that

the pattern of inflammation inhibition with bempedoic acid is almost identical to what is observed with statin therapy [27].

A recent meta-analysis on omega-3 fatty acids showed a considerable reduction in CRP levels compared with placebo [–0.27 mg/l (–0.52 to –0.01)] [11]. A randomized placebo-controlled clinical trial of 60 patients showed that omega-3 fatty acids decreased hs-CRP in patients postacute myocardial infarction [1,28▪]. An umbrella meta-analysis of 32 meta-analyses showed that supplementation with poly-unsaturated fatty acids (n-3 PUFAs) can improve various inflammatory markers, including CRP [29].

A case–control study demonstrated that fenofibrate reduced the CRP levels in patients with elevated triglycerides and a high CRP without severe overweight [30], whereas another meta-analysis showed that fibrates reduced CRP levels and the change in CRP was correlated with the change in high-density lipoprotein cholesterol but not with triglyceride levels [31]. However, another meta-analysis [11] showed that the effect of fibrate on CRP was limited, as they showed only a marginal, nonsignificant reduction in CRP levels. In multiple meta-analyses, PCSK9i and Cholesteryl Ester Transfer Protein inhibitor (CETPi) showed slight or no effect on CRP levels [11,32].

CONCLUSION

Atherosclerosis is a disease defined by vascular plaque deposition, primarily driven by dyslipidemia and often associated with vascular inflammation. CRP and hs-CRP are biomarkers of systemic inflammation that is commonly elevated in atherosclerotic patients and used to predict vascular risk [33]. Traditionally, inflammation has been viewed as a downstream effect of vascular lipid deposition, where CRP elevations were considered a consequence, rather than a driver, of atherosclerosis [34]. Statins have been observed to significantly reduce CRP levels in both primary and secondary prevention studies [7]. However, the mechanism by which statins decrease CRP levels is not entirely clear. Statins may reduce CRP levels by reducing plaque-causing lipoproteins, thereby attenuating lipid-driven inflammation, but lipid-independent anti-inflammatory mechanisms have also been proposed [13]. In the REVERSAL trial, patients treated with moderate-intensity or high-intensity statin therapy had a weak yet significant correlation between reductions in LDL-C and CRP levels ($r=0.13$, $P=0.005$) [13]. This weak coupling supports the concept of residual inflammatory risk, signaling that lipid lowering alone may not fully address vascular inflammation. The clinical relevance of this observation is demonstrated in the JUPITER study, where patients with elevated hs-CRP levels, with normal LDL-C levels, treated with rosuvastatin had a significant reduction in major cardiovascular events [14]. PROVE IT-TIMI 22 found that the lowest cardiovascular event rates occurred when both LDL-C and CRP levels are reduced, indicating that optimal clinical benefit is achieved when both lipid burden and inflammatory activity are addressed [12].

Clinical implications and future directions

In primary prevention, low hs-CRP correlates with reduced coronary events and stroke incidences (sometimes more strongly than low LDL-C itself) [4▪,8]. In secondary prevention, elevated hs-CRP identifies patients with higher recurrent event risk despite guideline-directed therapy, while low hs-CRP confers better outcomes [8,35]. This helps to further stratify patients with intermediate baseline risks, and it is used in risk assessment tools like the Reynold risk score [4▪,8].

Major statin trials analyses show that patients achieving both low LDL-C and low hs-CRP have the lowest event rates [8,35]. Patients with hs-CRP at least 2 mg/l despite optimal LDL-C represent residual inflammatory risk and may benefit from intensified lifestyle, high-intensity statins, or adjunctive therapies [4▪]. Statins used alongside IL-1β/IL-6 inhibitors demonstrate further CRP reduction alongside lipid lowering and reduce cardiovascular events in selected high-risk groups [36,37]. Statin plus ezetimibe (lowers LDL-C by an additional 15–25% + hs-CRP by 10–20%) reinforces the dual-target concept despite the absence of direct cytokine modulation [22]. Similarly, statins plus bempedoic acid (lowers LDL-C + hs-CRP 22%) offers a practical dual-pathway targeting [4▪,36].

Ongoing trials enroll patients with elevated hs-CRP to test anti-inflammatory strategies beyond current standard care (LDL-C lowering). Precision medicine uses hs-CRP to phenotype 'cholesterol-predominant' vs. 'inflammation-predominant' risk, tailoring therapy intensity [36,37]. Dual-pathway discordance (low LDL-C/high hs-CRP) identifies patients needing closer monitoring or inflammation-targeted approaches beyond cholesterol control alone [4▪,8,36].

Future research will clarify whether hs-CRP evolves from a risk-stratification marker to a treatment target in defined subgroups. It will also help determine optimal repeat measurement intervals and the cost-effectiveness of such inflammation-focused therapies.

Limitations of current evidence

Several limitations limit widespread hs-CRP-guided therapy. hs-CRP is a nonspecific acute-phase reactant

that is affected by infection, obesity, and chronic inflammatory diseases [38]. Isolated elevations, therefore, require clinical context and often repeated measurement [4▪,7]. Heterogeneity in assay platforms, calibration, and use of standard vs. high-sensitivity methods complicates comparison of absolute thresholds across studies and may contribute to variability in reported effect sizes [7,8]. Much of the evidence relating hs-CRP reduction to outcome benefit is observational or derived from post-hoc analyses, so hs-CRP currently functions mainly as a surrogate marker rather than a validated causal target [4▪,36]. Trials of anti-inflammatory agents show variable efficacy and raise concerns about safety, cost, and patient selection [36,37]. Publication bias and selective reporting may further exaggerate the apparent prognostic value of hs-CRP if negative or neutral studies are under-represented [4▪,37]. These uncertainties underpin current recommendations that hs-CRP be used selectively and adjunctively, rather than as a stand-alone determinant of therapy [4▪,7].

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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