

STATE-OF-THE-ART PAPER

High-Sensitivity C-Reactive Protein and Cardiovascular Disease

A Resolute Belief or an Elusive Link?

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The role of inflammation in the propagation of atherosclerosis and susceptibility to cardiovascular (CV) events is well established. Of the wide array of inflammatory biomarkers that have been studied, high-sensitivity C-reactive protein (hsCRP) has received the most attention for its use in screening and risk reclassification and as a predictor of clinical response to statin therapy. Although CRP is involved in the immunologic process that triggers vascular remodeling and plaque deposition and is associated with increased CV disease (CVD) risk, definitive randomized evidence for its role as a causative factor in atherothrombosis is lacking. Whether measurement of hsCRP levels provides consistent, clinically meaningful incremental predictive value in risk prediction and reclassification beyond conventional factors remains debated. Despite publication of guidelines on the use of hsCRP in CVD risk prediction by several leading professional organizations, there is a lack of clear consensus regarding the optimal clinical use of hsCRP. This article reviews 4 distinct points from the literature to better understand the current state and application of hsCRP in clinical practice: 1) the biology of hsCRP and its role in atherosclerosis; 2) the epidemiological association of hsCRP with CVD; 3) the quality of hsCRP as a biomarker of risk; and 4) the use of hsCRP as a tool to initiate or tailor statin therapy. Furthermore, we highlight recommendations from societies and important considerations when using hsCRP to guide treatment decisions in the primary prevention setting. (J Am Coll Cardiol 2013;62:397–408) © 2013 by the American College of Cardiology Foundation

Inflammation is central to the initiation and progression of atherothrombosis and to triggering cardiovascular disease (CVD) events (1). Advances in vascular biology have established the interaction of the innate immune system with atherosclerosis (2). Clinical studies have linked chronic inflammation to future CV events (3,4), and emerging biomarkers of inflammation have been postulated to improve identification of at-risk asymptomatic patients.

Conventional risk factors in the Framingham risk score (FRS), such as age, male sex, hypercholesterolemia, hypertension, and smoking, account for most of the risk of coronary heart disease (CHD) and have been the bedrock of risk assessment for decades. However, approximately one-third of

individuals with 0 or 1 risk factor develop CHD (5,6) and up to 40% of individuals with cholesterol levels below the population average die from CHD (7). Furthermore, many CV events occur in patients treated with statin therapy. As such, a wide array of biomarkers—high-sensitivity assays detecting low levels of C-reactive protein (CRP), genetic polymorphism arrays, and direct imaging of subclinical atherosclerosis with coronary artery calcium (CAC) or carotid intima-media thickness—have been investigated for refinement of risk assessment and preventive therapy allocation (Fig. 1).

This paper reviews 4 distinct points from the literature to better understand the current state and application of high-sensitivity C-reactive protein (hsCRP) in clinical practice: 1) the biology of CRP and its role in atherosclerosis; 2) the epidemiological association of hsCRP with CVD; 3) the quality of hsCRP level as a biomarker of risk; and 4) the use of hsCRP as a tool to initiate or tailor statin therapy. Furthermore, we highlight recommendations from societies and important considerations when using hsCRP to guide treatment decisions in primary prevention.

Is hsCRP a Maker or Marker of CVD?

CRP was first discovered in 1930 through a reaction with the somatic C polysaccharide of *Streptococcus pneumoniae* in patients

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Abbreviations and Acronyms

- CAC** = coronary artery calcium
- CHD** = coronary heart disease
- CVD** = cardiovascular disease
- FRS** = Framingham risk score
- hsCRP** = high-sensitivity C-reactive protein
- LDL-C** = low-density lipoprotein cholesterol
- MI** = myocardial infarction
- NRI** = net reclassification improvement
- RRS** = Reynolds risk score

afflicted with pneumonia (8). Its link to CHD was reported more than 60 years later (9). CRP has been prodigiously investigated, largely facilitated by its relative stability as a frozen sample, long plasma half-life of 19 h, and ease of testing with a standardized assay (10).

CRP is an acute-phase reactant and nonspecific marker of inflammation, produced predominantly in hepatocytes as a pentamer of identical subunits in response to several cytokines (11). Interleukin (IL)-6, one of the most potent drivers of CRP production, is released from activated leukocytes in response to

infection or trauma and from vascular smooth muscle cells in response to atherosclerosis. CRP directly binds highly atherogenic oxidized low-density lipoprotein cholesterol (LDL-C) and is present within lipid-laden plaques (2).

The possible mechanistic role of CRP in plaque deposition is highly complex, exerting proatherogenic effects in many cells involved in atherosclerosis (12). CRP may facilitate monocyte adhesion and transmigration into the vessel wall—a critical early step in the atherosclerotic process (13). Furthermore, M1 macrophage polarization, catalyzed by CRP, is a proinflammatory trigger in plaque deposition, leading to macrophage infiltration of both adipose tissue and atherosclerotic lesions (14).

Beyond its role in triggering immunity in plaque deposition, *in vitro* studies have also shown an association among CRP, inhibition of endothelial nitric oxide synthase, and impaired vasoreactivity (15,16). An isoform of CRP, monomeric CRP, is stimulated by platelet activation and has prothrombotic and inflammatory properties of its own (17). Monomeric CRP has also been found in plaques, particularly in regions of monocyte-mediated inflammatory activity, and within lipid microdomains of endothelial cells (18).

In humans, treatment with statin therapy reduces levels of both LDL-C and CRP, and concurrently there is a reduction in the number of CV events (19–22). The earliest evidence stems from the CARE (Cholesterol and Recurrent Events) trial, a secondary prevention trial of patients with post-myocardial infarction (MI) in which pravastatin reduced CRP levels independently of the magnitude of LDL-C reduction (22). Early interpretations of such evidence have suggested that statins have pleiotropic effects that might contest a potential causal role of CRP in atherosclerotic CV events (20–22).

Challenging a causative role of CRP in atherothrombosis. A meta-regression analysis of nearly 82,000 patients that compared clinical outcomes of lowering LDL-C levels from 10 statin trials versus 9 nonstatin trials showed a 1:1 relationship between LDL-C lowering and CHD and stroke reduction during 5 years of treatment (23). This challenges the idea that pleiotropic effects of statins contribute additional CV risk reduction benefit beyond that expected from the degree of LDL-C lowering. Indeed, some evidence suggests that the previously described proatherogenic effects of CRP may have been overstated because of contamination from endotoxins and use of preservatives in

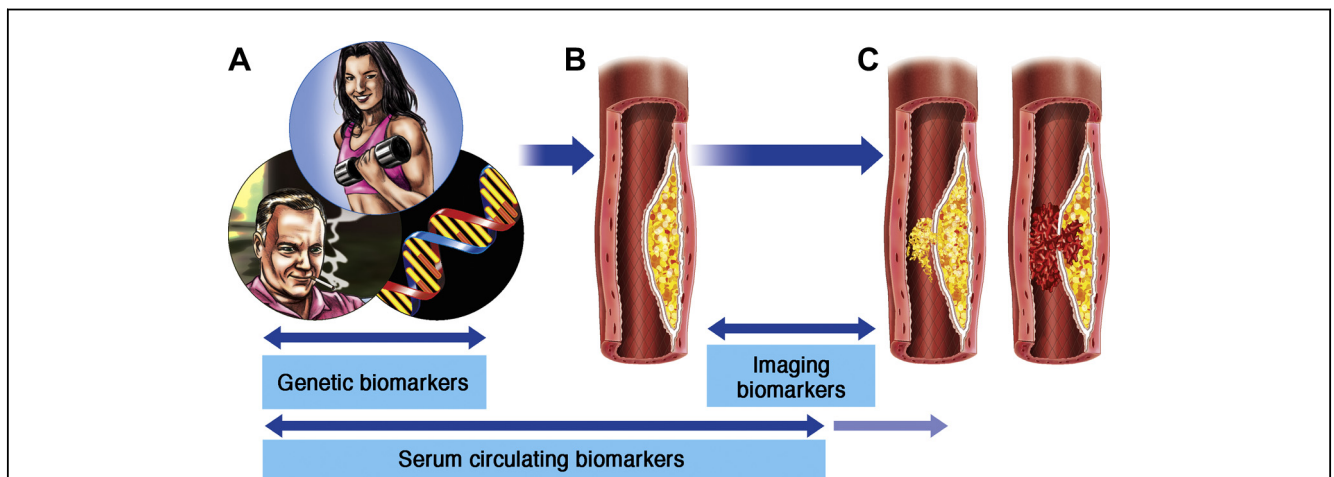


Figure 1 Utility of Biomarkers in the Lifelong Prevention of Cardiovascular Disease

A dynamic set of genetic, circulating, and imaging biomarkers may be used in the lifelong prevention of atherosclerosis. Genetic and serum biomarkers may be useful in detecting those with early risk factor exposure and genetic predisposition (A) Imaging biomarkers may be useful in detecting subclinical disease. (B) Circulating biomarkers may be most informative in detecting earlier stages of atherosclerosis before the presence of cardiovascular disease, although high-sensitivity C-reactive protein has been shown to predict coronary heart disease in patients with unstable angina (C). Figure illustration by Craig Skaggs.

commercial CRP assays (24). Additionally, some basic science research disputes the direct atherogenic effects of CRP. Transgenic overexpression of CRP in mice and in vivo injection of large doses of human CRP have minimal effect on inflammation and atherosclerosis (25–29). In another study, transgenic rabbits with low and high CRP expression fed a high-cholesterol diet experienced similar coronary and aortic atherosclerosis (30).

Furthermore, large-scale Mendelian randomization analyses of polymorphisms in the *CRP* gene have shown marked elevations in CRP concentrations without an increased risk of CHD (31–33). A genome-wide association analysis of more than 66,000 participants identified 18 loci associated with CRP levels and involved in pathways of metabolic syndrome, immune response, and chronic inflammation (34). Using a weighted genetic risk score, which explained approximately 5% of the variation in CRP levels, the researchers found marked differences in CRP levels but no association with CHD. This study is the latest and largest genome-wide association study failing to demonstrate a significant association between genetically elevated CRP levels and risk of CHD.

Last, a recent meta-analysis of 46,557 patients with CHD and 147,861 controls demonstrated a null association among CRP-related genotypes, traditional risk factors, and risk of CHD (33). These animal and human genetic data indicate a lack of causal relationship between CRP and CHD. In contrast, similar Mendelian analyses of LDL-C and lipoprotein(a) are compatible with causal effects in CHD (35,36).

Association Between hsCRP and Risk for CVD

hsCRP and CVD risk in men. An association of hsCRP with risk for CVD has been described in many studies (37). The MRFIT (Multiple Risk Factor Intervention Trial) was the first of many primary prevention, prospective epidemiological studies to show a strong relationship between levels of hsCRP and mortality from CHD in high-risk middle-aged men (9). A similar association between increasing hsCRP levels and subsequent rate of MI and stroke was found in an analysis of apparently healthy men (38).

hsCRP and CVD risk in women. In the WHS (Women's Health Study), LDL-C—an established causative biological marker of atherosclerosis—was compared with hsCRP in 27,939 healthy women who were followed for an average of 8 years for MI, ischemic stroke, coronary revascularization, or CV death. After adjustment for age and conventional risk factors, hsCRP was a stronger predictor of CV events than LDL-C. The primary endpoint was twice as likely in those with hsCRP in the fourth quintile between 2.10 and 4.19 mg/l as compared with levels of 0.49 mg/l (relative risk [RR]: 2.0; 95% CI: 1.3 to 3.0). LDL-C levels in the fourth quintile (132 to 154 mg/dl) had a 30% excess risk of CV events as compared with those with LDL-C <96 mg/dl (RR: 1.3; 95% CI: 1.0 to 1.7).

The RR of CV events with each increasing quintile of hsCRP was greater as compared with LDL-C. Women in

the high hsCRP and low LDL-C group were at greater absolute risk than the subgroup with low hsCRP and high LDL-C levels. Screening for both biological markers provided better prognostication than either alone (39).

Early expert opinions on hsCRP testing in primary prevention. In 2002, an expert panel recommended against routine testing of hsCRP in primary prevention but supported selective screening in individuals at an intermediate (10% to 20%) risk for mortality from CHD or nonfatal MI in 10 years. A literature-based meta-analysis of 22 studies was performed on behalf of the U.S. Preventive Services Task Force to determine whether hsCRP testing should be incorporated into current guidelines as an adjunctive screening tool for CHD. An hsCRP level >3 mg/l was independently associated with a 60% excess risk in incident CHD as compared with levels <1 mg/l (RR: 1.60; 95% CI: 1.43 to 1.78) after adjustment for all Framingham risk variables (40). Based on the available evidence at that time, the panel concluded that the effects of intensive treatment in those stratified as high risk on the basis of hsCRP testing were uncertain and recommended against routine testing (41).

Quality of hsCRP as a Biomarker

Standard hsCRP assays suffice in settings of active infection, tissue injury, or acute inflammation, which are known to cause marked elevations. However, in the chronic setting, the variability of standard hsCRP assays remains about as consistent as systolic blood pressure (SBP) and total cholesterol on a year-to-year basis (42). CV risk assessment requires a more sensitive assay, hsCRP, which can accurately detect very low levels of CRP in healthy individuals.

Variability among individuals. The interplay of *CRP* genetic polymorphisms, influence of genetic loci mediating CRP response, and lifestyle factors contributes to individual, ethnic, and sex-related variation in hsCRP concentration. A uniform cut point for hsCRP based on a single value should not be applied universally among all individuals. Body mass index, metabolic syndrome, diabetes mellitus, hypertension, oral contraceptive use, physical exercise, moderate alcohol consumption, periodontal disease, dietary patterns, environmental pollutant burden, and smoking cause significant baseline variation (43).

Furthermore, there is great variability in hsCRP levels among ethnicities, with the highest levels generally found in African Americans, followed by Hispanics, South Asians, whites, and East Asians, respectively. An analysis of 8,874 patients from the National Health and Nutrition Examination Survey (NHANES) database demonstrated hsCRP levels that ranged from 0.1 to 296 mg/l (mean 4.3; median 2.1). hsCRP levels are higher among women than men and increase with age. The mean hsCRP level was 3.5 mg/l in 20- to 29-year-old versus 5.7 mg/l in 70- to 79-year-old individuals (44).

There is also significant heterogeneity between sexes in the association of hsCRP with CVD. The magnitude of

hsCRP's association with CHD may be less in women compared with men (45). In the largest analysis to date, discrimination by hsCRP in at-risk individuals was limited to men. Furthermore, the net improvement in risk reclassification with the use of hsCRP was 1.24% for men and only 0.38% for women (45).

Technical and biological variability. A recent examination of a subset of the NHANES database showed significant short-term intraindividual variation in hsCRP levels (46). A high coefficient of variation of 46.2% (95% CI: 42.9% to 49.3%) was seen between the 2 hsCRP measurements 19 days apart. Nearly 32% of patients who were initially categorized as having elevated hsCRP levels were reclassified as having normal levels after the second check (46). In another recent analysis from the MESA (Multi-Ethnic Study of Atherosclerosis) trial, 54% of individuals in the middle tertile of hsCRP values had discordant levels on follow-up. Additionally, 69% of individuals with baseline hsCRP >3 mg/l were reclassified into a lower risk category on subsequent measurements (47). Use of single hsCRP measurements to risk-stratify patients may misclassify a significant number of individuals.

Phenotypes that portend accelerated atherosclerosis, including metabolic syndrome, obesity, and insulin resistance, are associated with elevated levels of hsCRP. In addition to cells in atherosclerotic plaques, adipose tissue is a significant source of IL-6, which may explain the robust association between hsCRP and obesity (40,48). In the Dallas Heart Study, obesity modified the association between hsCRP and atherosclerosis, such that increasing levels of hsCRP were no longer associated with CAC, aortic wall thickness, and plaque burden in obese patients (49). Analyses from the MESA trial also suggested that the biological association between hsCRP and coronary atherosclerosis is largely accounted for by obesity (50).

Is there an ideal level of hsCRP to define increased CV risk? Analyses from large-scale clinical trials have used a hsCRP cut point of 2 mg/l for defining increased CV risk (21,51). A MESA analysis of 6,722 individuals demonstrated a mean hsCRP level of 3.76 mg/l, which did significantly differ between those with and without future coronary events (52). Even among those with LDL-C <130 mg/dl, for whom the use of hsCRP has been advocated by some, there was no association between hsCRP levels and CVD (53). Similarly, in the St. Francis Heart Study, hsCRP was not a predictor of CV events (median 1.8 mg/l) (54). More than 50% of all adults and 41% of 20-year-olds in the United States have hsCRP levels >2 mg (44).

On the other hand, studies have more consistently shown hsCRP's association with CV events above levels of 3 mg/l compared with reference values of <1 mg/l (55–57). In the MESA trial, in which an hsCRP threshold of 2 mg/l performs poorly, there is still an approximately 50% increase in risk comparing values of >3 mg/l with those <1 mg/l (55–57). Thus, an hsCRP threshold of 2 mg/l to inform risk assessment—as advocated by some—may be misguided.

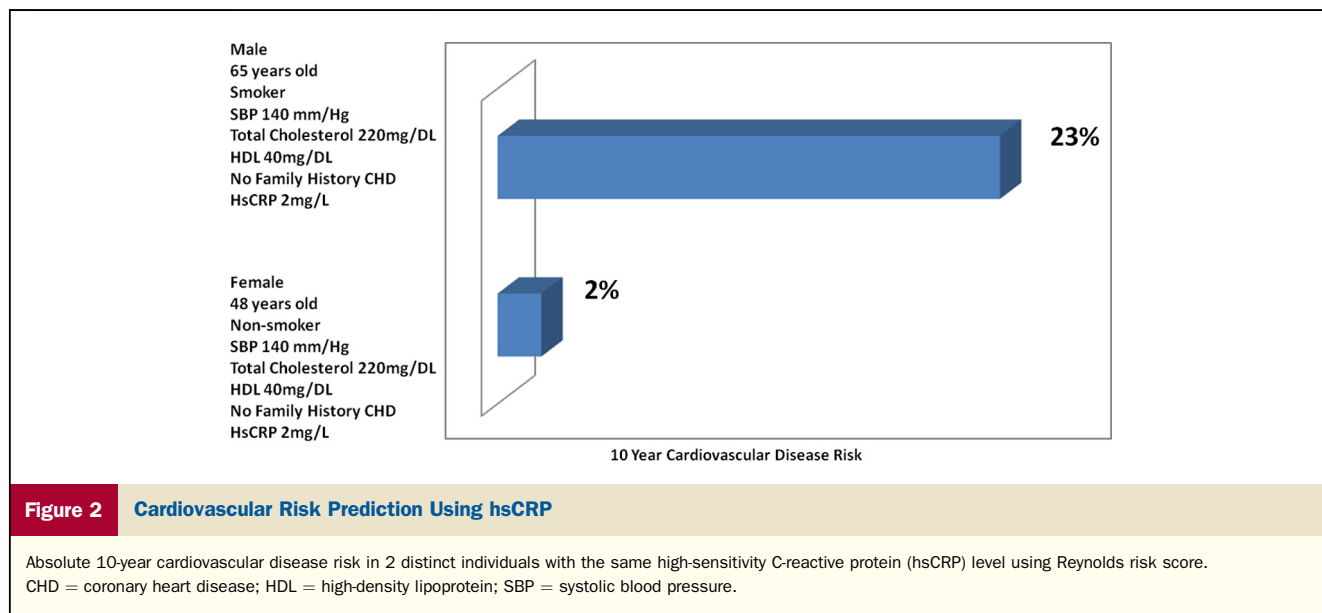
hsCRP in the context of other markers of inflammation and risk for CVD events. The Emerging Risk Factor Collaboration (ERFC) reviewed the association among hsCRP levels, CV risk factors, and vascular risk in 160,309 individuals from 54 prospective studies (48). In a total of 27,769 patients who suffered fatal or nonfatal events, hsCRP concentration was associated with increased risk to a similar magnitude across outcomes, including CHD (RR: 1.68; 95% CI: 1.59 to 1.78), ischemic stroke (RR: 1.46; 95% CI: 1.32 to 1.61), and death from vascular (RR: 1.82; 95% CI: 1.66 to 2.00) and nonvascular causes, such as cancer, chronic lung disease, and injury (RR: 1.55; 95% CI: 1.46 to 1.66) (48). This risk is similar to that seen for hyperlipidemia.

Not surprisingly, hsCRP levels were also associated with a number of other inflammatory markers, including fibrinogen levels, leukocyte count, albumin levels, and erythrocyte sedimentation rate. After adjustment for conventional risk factors and fibrinogen levels, the association with risk-attenuated hsCRP levels was modestly associated with CHD (RR: 1.23; 95% CI: 1.07 to 1.42), ischemic stroke (RR: 1.32; 95% CI: 1.18 to 1.49), and vascular mortality (RR: 1.34; 95% CI: 1.18 to 1.52).

Incremental value of hsCRP in risk prediction. A biomarker capable of discriminating events independent of conventional risk assessment would require a robust correlation with CVD and marked heterogeneity (less collinearity) with FRS variables. hsCRP's association with CVD is likely, in part, a function of its strong correlation with traditional risk factors, such as smoking, diabetes, visceral obesity (58), and markers of inflammation (59,60). The same hsCRP concentration in 2 individuals with distinct risk factors can predict a markedly different absolute risk of CVD (Fig. 2).

There are conflicting data regarding the incremental value of hsCRP for the prediction of first CV events. Although some studies have shown modest improvement in predictive ability (61,62), others have found little or no incremental value of adding hsCRP to conventional risk factors (39,42,63–70). Most recent studies have applied the C-statistic or area under the receiver-operating curve (AUC) as metrics of discrimination. To significantly improve predictive accuracy, an increase in the C-statistic or AUC with the addition of hsCRP to traditional risk factors may require an odds ratio of 7 between the high and low quartiles of hsCRP (68). A moderate improvement in predictive ability requires an increase in the C-statistic by 0.05 (68). No biomarker to date has achieved a RR of this magnitude except CAC (71).

The largest C-statistic improvement was seen in a study of 3,435 middle-aged European men, in whom the addition of hsCRP level to the FRS increased the C-statistic by 0.015 (67). Recently, investigators from the ERFC performed an analysis of 246,669 individuals from 52 studies. The addition of hsCRP and fibrinogen levels to a prediction model that included age, smoking status, total and high-density lipoprotein cholesterol, and history of diabetes increased



the C-statistic by 0.0039 and 0.0027, respectively (45). Furthermore, upon exploratory analysis, hsCRP's discriminatory benefit was limited to men.

A recent report of 1,330 intermediate-risk patients from the MESA cohort showed that among various novel laboratory and imaging biomarkers—CAC, carotid intima media thickness, ankle-brachial index, brachial flow-mediated dilation, hsCRP, and family history of CHD—CAC had the strongest association with CHD (hazard ratio [HR]: 2.60; 95% CI: 1.94 to 3.50; $p < 0.01$) and risk discrimination over FRS (AUC improved from 0.623 to 0.784) in at-risk individuals (71). In comparison, hsCRP's association was of borderline statistical significance (HR: 1.28; 95% CI: 1.00 to 1.64; $p = 0.05$) and showed the least increment in CHD risk prediction, with an AUC improvement from 0.623 to 0.640 (71).

In another recent analysis comparing several novel risk markers, investigators from the Rotterdam Study found that the addition of CAC scores to FRS provided the most robust improvement in discrimination, with an increase in the C-statistic by 0.05. Conversely, the addition of CRP did not change the C-statistic (72).

The Reynolds risk score (RRS) adds hsCRP level and family history to conventional parameters considered in the FRS. Although both scores are predictive of disease risk, the RRS has been shown in the MESA cohort to add additional predictive power for predicting atherosclerosis progression when discordance exists between the two scoring systems (73). Moreover, this difference was largely driven by recalibration of the traditional risk variables in RRS. Family history contributed a small amount and hsCRP even less. In the original validation study of RRS, hsCRP was also one of the smallest contributors to the risk stratification algorithm behind other factors such as age, glycated hemoglobin A_{1c}, smoking, SBP, and cholesterol (74). A doubling of hsCRP

level from the population mean leads to equivalent increase in risk as a rise in SBP of approximately 3 mm Hg in the RRS equation.

Reclassification of risk with hsCRP. Ultimately, the most clinically relevant factors may be those that reclassify patients into a more accurate risk category, presumably leading to more appropriate treatment decisions. Classically, those with the highest risk (i.e., 10-year risk $>20\%$) are treated to aggressive LDL-C goals, with lipid-lowering therapy in addition to lifestyle modifications, whereas those with lower risk (i.e., 10-year risk $<10\%$) are not treated as aggressively.

In patients at low 10-year risk, elevated hsCRP levels do not significantly increase the CV risk above that predicted by risk factors alone (39,63,67). Likewise, a low hsCRP level in patients at high risk does not markedly reduce risk, given its poor sensitivity (and thus low negative predictive value) (39). Although there is some modulation of risk in those with low or high 10-year risk, it often does not translate into a meaningful change in clinical management (68). Clinicians are left to struggle with intermediate-risk patients because there is no clear consensus on the use of statins in this group. A biomarker is most valuable if it reclassifies intermediate-risk patients who remain free of events into lower-risk categories and those who will suffer events into higher-risk groups.

Performance of hsCRP in reclassifying intermediate-risk patients. When hsCRP level is added to FRS, the totality of evidence suggests a modest benefit in reclassification of risk for initially intermediate-risk patients. In the WHS, of the 20% of intermediate-risk individuals, nearly 75% of them were reclassified into a lower-risk cohort and 4% ($<0.5\%$ of the total population) into higher-risk (75)—a transition that is most likely to alter clinical management in those not on statin therapy. In a study of German men with CRP >3.0 mg/l, individuals with an initial 10-year FRS of 15% to 19%

were meaningfully reclassified to high risk based on their CRP levels. However, CRP level did not reclassify those with a 10-year predicted risk of 10% to 14% (67).

Net reclassification improvement with hsCRP testing. Using hsCRP level in the Framingham Heart Study (65), the net reclassification improvement (NRI)—an index of the net number of correct reclassifications—was 11.8% ($p = 0.009$) for CHD and 5.6% ($p = 0.014$) for total CVD (76). Similarly, an analysis of the WHS yielded an NRI of 5.7% (75).

Incorporating both hsCRP level and family history into the RRS reclassified 7.6% of initially intermediate-risk men into a higher-risk category (74). Similar findings have also been shown in women (61). Investigators from the Swedish Malmö Diet and Cancer Study demonstrated reclassification of 16% of intermediate-risk individuals; correct reclassification was almost entirely attributed to down-classification into the low-risk category. The NRI was not significant for CV and coronary events (70). In the largest analysis of screening with hsCRP in preventing first CV events, the ERFC reclassified 1.52% of intermediate-risk individuals (45).

Two recent reports—from the Rotterdam Study and the MESA cohort—comparing several laboratory and imaging biomarkers, demonstrated an NRI of 2% (with no change in C-statistic) and 7.9% with the addition of hsCRP, respectively (71,72). As a comparison, the NRI was 19.3% and 65.9% with the addition of CAC to FRS, respectively.

hsCRP as a Tool to Target Therapy: Initiation and Intensification

Beyond use as an adjunctive tool in risk prediction and reclassification, there is interest in using hsCRP levels to select patients for statin initiation and to tailor the intensity of therapy.

Use of hsCRP in statin initiation. In a post hoc analysis of the AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention) primary prevention trial (77), individuals with “low” LDL-C (<149 mg/dl) and elevated hsCRP (>1.6 mg/l) had a 42% RR reduction (RRR [$p = 0.04$]) with lovastatin compared with placebo. In contrast, individuals with LDL-C <149 mg/dl and hsCRP <1.6 mg/l had a very low event rate and no benefit to lovastatin over placebo ($p = 0.74$). It was concluded that high hsCRP level unmasked a group of individuals that would be responsive to lipid-lowering therapy. These results thus gave rise to the use of 2 mg/l as the hsCRP threshold of risk and bolstered the rationale for no low hsCRP arm in the subsequent JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial (51). However, analysis using preferred statistical tests for a treatment-subgroup interaction in the AFCAPS/TexCAPS trial did not corroborate the initial findings (chi-square heterogeneity = 6.01; $p = 0.305$) (24). Similarly, in the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) analysis of 5,804 elderly individuals, a CRP

group by treatment interaction was not present. hsCRP levels minimally enhanced risk prediction (3.64 mg/l in those who had a CV event vs. 3.01 mg/l in those who remained event free). Moreover, hsCRP did not predict response to therapy with pravastatin (78).

Interpreting the JUPITER trial. It was not until the JUPITER trial that hsCRP’s potential role in CVD prevention became more recognized. The JUPITER trial randomized 17,802 middle-aged to elderly low to intermediate risk patients with LDL-C <130 mg/dl and hsCRP >2 mg/l to rosuvastatin 20 mg versus placebo (51). The trial was stopped early due to a robust 44% RRR (95% CI: 31% to 54%; $p < 0.00001$) in the primary endpoint of MI, stroke, revascularization, hospitalization for unstable angina, or death. There were 50% and 37% reductions in LDL-C and hsCRP levels in the rosuvastatin arm, respectively.

A pre-specified analysis showed that the lowest number of CV events were in those who achieved both a low LDL-C and low hsCRP level. This was consistent with observational data from the ARIC (Atherosclerosis Risk in Communities) study, in which JUPITER-eligible patients with hsCRP >2 mg/l had a higher risk of CV events than individuals with low hsCRP level (79).

JUPITER is often categorized as a biomarker or screening trial; however, it is still controversial whether an elevated hsCRP level is sufficient to identify individuals who may benefit from statin therapy (80–82). A lack of a low LDL-C/low hsCRP arm makes it impossible to exclude rosuvastatin’s benefit among at-risk middle-aged and elderly adults, irrespective of the hsCRP level. The average individual in the JUPITER trial had an FRS of 11% and a mean LDL-C of 104 mg/dl. A prior meta-analysis of statin trials showed that statins produce a similar proportional reduction in CV risk across all levels of the absolute risk, even in those with LDL-C as low as 80 mg/dl (83).

Indeed, hsCRP did not seem necessary for treatment benefit in a post hoc analysis from the HPS (Heart Protection Study) of 20,536 individuals at risk for vascular events who were randomized to simvastatin 40 mg versus placebo. Statin treatment was associated with a proportional reduction in the number of CV events, irrespective of hsCRP levels. Even among those with hsCRP levels <1.25 mg/l, there was a 29% reduction in the number of major vascular events (84).

A post-hoc Food and Drug Administration (FDA) analysis of the JUPITER data performed by Kaul et al. (80) demonstrated an inverse relationship between hsCRP levels and clinical response to statin therapy. There was a modestly greater relative benefit from rosuvastatin in those with hsCRP below the median cut point of 4.2 mg/l versus above 4.2 mg/l (RRR: 58% vs. 29%, respectively; $p = 0.015$) (Fig. 3) (80). Similar findings were observed in a post hoc analysis by the JUPITER investigators (85). There was a 37% RRR with rosuvastatin in the primary outcome in men with hsCRP >5.4 mg/l versus 57% ($p = 0.02$) in those with hsCRP between 2.0 and 3.1 mg/l ($p = 0.003$) (Fig. 3).

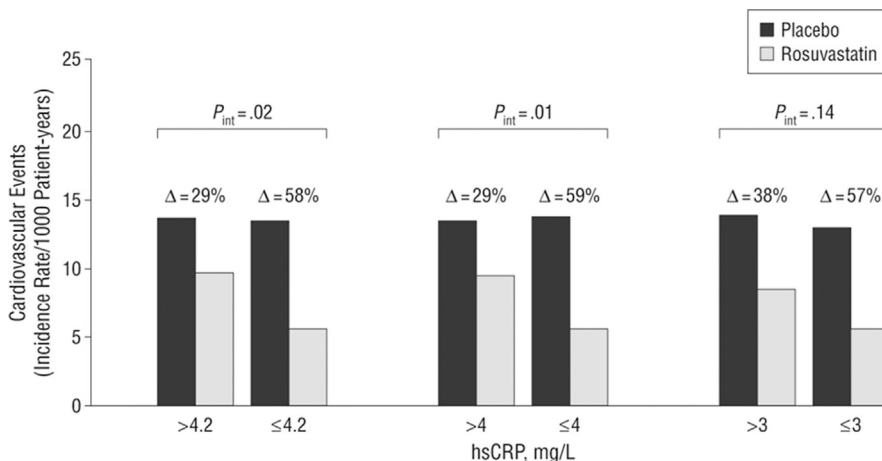


Figure 3 Treatment Effect by hsCRP in the JUPITER Trial

Treatment effect by hsCRP categories in the JUPITER trial. Compared with placebo, rosuvastatin reduced cardiovascular events in all hsCRP categories. Reprinted with permission from Kaul *et al.* (80). Abbreviation as in Figure 2.

Further analysis by the FDA with hsCRP cut points above and below 4 mg/l and 3 mg/l demonstrated a consistent RRR with rosuvastatin across the 3 hsCRP cut points and no change in event rates in the placebo arm (Fig. 3) (80). An elevated hsCRP concentration did not independently predict a preferential benefit to statin therapy. No significant interaction between hsCRP and treatment with statin was observed in the JUPITER trial on the basis of this analysis ($p = 0.15$).

The post hoc analysis by the JUPITER investigators demonstrated a linear relationship between increasing entry hsCRP thresholds and absolute risk of the combined endpoint of primary outcome and mortality (Fig. 4) (85). However, rosuvastatin-treated men with hsCRP ≥ 4 , ≥ 6 , and ≥ 10 mg/l all had very similar occurrences in the primary outcome (Fig. 5).

The JUPITER investigators concluded that the high background event rate seen in the trial was attributable to elevated hsCRP levels and not underlying traditional risk factors. However, data analyzed by the FDA found that the treatment response was only present in those with elevated hsCRP levels and at least 1 traditional risk factor (HR: 0.51; 95% CI: 0.41 to 0.64) and not in those with an elevated hsCRP level alone (HR: 0.91; 95% CI: 0.56 to 1.46; $p_{int} = 0.03$) (80)—corroborating the significance of global risk factors and the robust link between absolute risk and benefit from statins. Moreover, hsCRP levels have been shown to increase with age, and thus, JUPITER may be an applicable primary prevention trial of older adults (mean age 66 years) with metabolic syndrome traits.

Fueling this debate further, a recent analysis of the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcome Trial-Lipid Lowering Arm) study of atorvastatin 10 mg

versus placebo for primary prevention demonstrated that the addition of hsCRP level to the traditional FRS only minimally improved prediction of CV events (86). Although baseline hsCRP and LDL-C levels were significantly predictive of CV events (odds ratio: 1.19 and 1.31, respectively), baseline hsCRP levels did not predict the magnitude of the atorvastatin response in reducing the number of CV events (86).

Intensifying treatment: using hsCRP as a therapeutic target. Inflammation substudies from 2 secondary prevention trials—PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) (21) and REVERSAL (Reversing Atherosclerosis with Aggressive Lipid Lowering) (20)—have shown that intensive therapy with atorvastatin 80 mg compared with pravastatin 40 mg achieved a greater reduction in LDL-C and hsCRP levels, and together, they are associated with a greater reduction in the number of clinical events and progression of atherosclerotic plaque burden. Patients who had LDL-C < 70 mg/dl and hsCRP < 1 mg/l on atorvastatin had the lowest rate of adverse CV events. Atorvastatin reduced hsCRP and LDL-C levels by 38% and 35%, respectively (21). These findings were confirmed, albeit to a lower magnitude, in the Z phase of the A to Z trial, in which on-treatment hsCRP levels were independently associated with long-term survival (87).

At the population level, on-treatment hsCRP levels were reduced by 26% and 37% in the ASCOT and JUPITER trials, respectively. In the ASCOT trial, lower on-statin LDL-C level at 6 months had nearly a 60% reduction in the number of subsequent CV events compared with those above and below the median. In contrast, hsCRP levels above and below the median of 1.8 mg/l was not predictive

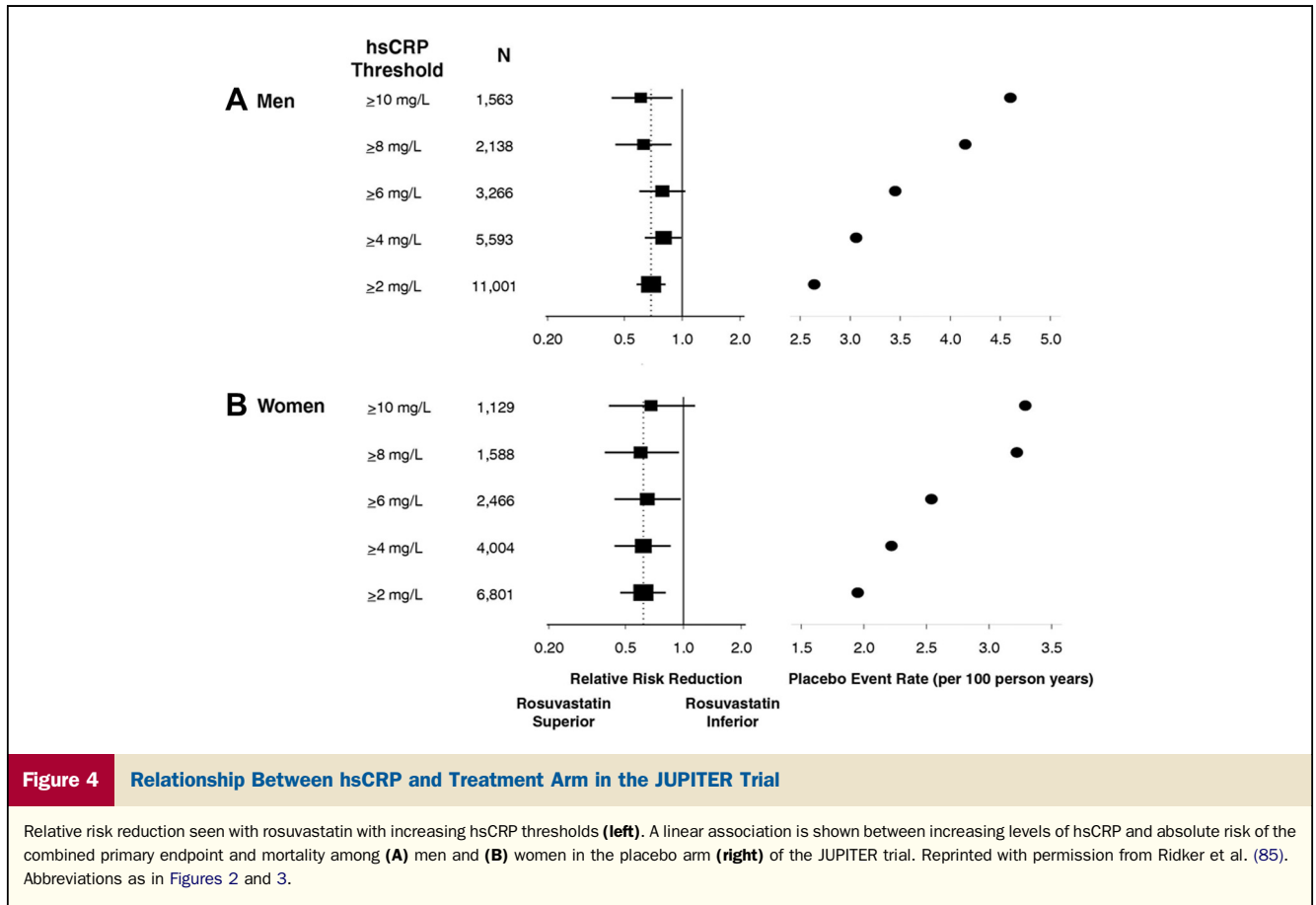


Figure 4 Relationship Between hsCRP and Treatment Arm in the JUPITER Trial

Relative risk reduction seen with rosuvastatin with increasing hsCRP thresholds (left). A linear association is shown between increasing levels of hsCRP and absolute risk of the combined primary endpoint and mortality among (A) men and (B) women in the placebo arm (right) of the JUPITER trial. Reprinted with permission from Ridker *et al.* (85). Abbreviations as in Figures 2 and 3.

of events. Adding hsCRP to LDL-C did not improve prediction in response to statin therapy (86). As many as 30% to 40% of patients may see no change or an increase in on-treatment hsCRP levels (88).

Is hsCRP a Deal Maker or Breaker in Clinical Practice?

In the quest for individualized medicine, biomarkers have emerged as a tool for improved risk prediction. Various statistical measures of risk prediction improvement and risk reclassification indices have been used; however, no single index tells the whole story. The American Heart Association has laid out a framework for the comprehensive evaluation of a novel biomarker (89). An ideal biomarker should demonstrate quantitative differences in patients with and without disease. Further, it should have predictive value in prospective studies and incremental benefit over standard clinical risk markers. The goal of measuring a biomarker should not only be risk assessment but rather ascertaining information that would alter the threshold of the pre-test risk to change clinical management in a cost-effective manner. The ideal risk marker should demonstrate these features with rigorous evidence and independence (89).

hsCRP continues to be tested routinely, despite its difficult and controversial value in guiding treatment

decisions. The association between elevated hsCRP levels and CVD is well established. Further, the literature also modestly supports the incremental value that hsCRP may have to current risk prediction models. However, reclassification of intermediate-risk patients with the addition of hsCRP to existing FRS variables does not meaningfully alter clinical management. Last, there is inconclusive evidence that reducing hsCRP levels prevents CHD.

Proponents of hsCRP justify its use as a screening tool based on the findings of the JUPITER study. However, JUPITER was not a true biomarker trial because there was no low hsCRP arm. It is unclear whether randomly selected intermediate-risk patients benefit from intensive treatment on the basis of elevated hsCRP levels. Despite the abundance of literature, there are no randomized data to confirm that intensifying therapy with or without hsCRP testing changes outcomes.

Patients with LDL-C levels <130 mg/dl most likely will have a net benefit to statin therapy with or without elevated hsCRP levels. Treating everyone with statins meeting JUPITER criteria may not precisely match clinical risk with therapy (90). Although the cost of hsCRP testing is approximately \$20 (91), which is similar to standard lipid evaluations and less than other potential biomarkers, models have suggested that risk-based treatment without hsCRP testing would prove more cost effective than the addition of

A Men							
hs-CRP (mg/L)	Patients (n)	Incidence Rate per 100 Person-Years			RR	95% CI	p Value
		Total Cohort	Rosuvastatin	Placebo			
Primary end point							
2	11,001	1.21	0.88	1.54	0.58	0.45–0.73	<0.0001
4	5,593	1.38	1.16	1.59	0.73	0.53–1.00	0.047
6	3,266	1.42	1.10	1.72	0.64	0.42–0.96	0.03
8	2,138	1.47	0.90	2.03	0.44	0.26–0.75	0.002
10	1,563	1.57	1.07	2.06	0.52	0.29–0.93	0.02
B Women							
Primary end point							
2	6,801	0.80	0.56	1.04	0.54	0.37–0.80	0.002
4	4,004	0.80	0.62	0.98	0.63	0.38–1.04	0.07
6	2,466	0.90	0.70	1.11	0.63	0.35–1.16	0.1
8	1,588	1.09	0.70	1.49	0.47	0.23–0.96	0.03
10	1,129	1.23	0.93	1.51	0.62	0.28–1.34	0.2

Figure 5 Rate of Primary Endpoint in the JUPITER Trial

Incidence rate of the primary endpoint among (A) men and (B) women in the rosuvastatin and placebo arm of the JUPITER trial. Adapted and modified with permission from Ridker *et al.* (85). Abbreviations as in Figures 2 and 3.

another test, given the increasing availability of low-cost statins and recent patent expirations (92).

Although hsCRP is commonly used clinically to raise risk estimates, it cannot be used to rule out disease because of its poor sensitivity and low negative predictive value. Recommendations for routine biomarker measurement may benefit from meticulous appropriate use criteria as those that have recently emerged for noninvasive and invasive imaging.

Ultimately, to test the inflammatory hypothesis of atherosclerosis, without reducing LDL-C is to directly randomize patients to targeted anti-inflammatory therapies. Two clinical trials that will test this hypothesis are underway—one using methotrexate and another using an IL-1 β inhibitor, canakinumab (Table 1) (93,94).

Guideline Recommendations

A number of professional organizations and agencies have published guidelines and recommendations on use of hsCRP in the primary prevention of CHD (Table 2) (41,95–98). The guidelines emphasize the lack of definitive data establishing a causal relationship and the loss of predictive power of CVD endpoints when standard CVD risk factors are accounted for. The 2010 American Heart Association guidelines are the most favorable, giving a class IIa designation for measurement of hsCRP in asymptomatic individuals. In the absence of true statin effect modification by hsCRP level, the ultimate benefit from statin therapy must depend on absolute risk, to which

Table 1 Ongoing Trials of Anti-Inflammatory Therapies for Atherosclerosis

Clinical Trial (#)	Study Population	Study Arms	Phase	Primary Endpoint	Secondary Endpoints
CANTOS (NCT01327846)	17,200 patients with history of MI on statins with hsCRP \geq 2 mg/l	Randomized to 3 distinct doses of quarterly subcutaneous canakinumab or placebo	III	MI, stroke, or CV death at 3 years	MI, stroke, CV death, revascularization for UA Total mortality Diabetes
CIRT (NCT01594333)	7,000 patients with history of MI and persistent elevation of hsCRP with type 2 diabetes mellitus or metabolic syndrome	Randomized to methotrexate 10 mg weekly or placebo on a background of folate therapy	III	Recurrent MI, stroke, or CV death at 4 years	All-cause mortality, hospitalization for heart failure, incidence of venous thromboembolism, atrial fibrillation, diabetes, or coronary revascularization

CANTOS = Cardiovascular Risk Reduction Study Reduction in Recurrent Major CV Disease Events; CIRT = Cardiovascular Inflammation Reduction Trial; CV = cardiovascular; hsCRP = high-sensitivity C-reactive protein; MI = myocardial infarction; UA = unstable angina.

Table 2 Professional Society Recommendations for hsCRP Testing

Professional Society	Year	Author, Journal	Designation	Recommendation for CRP screening
USPSTF	2009	USPSTF-AHRQ, <i>Ann Intern Med</i>	Grade insufficient (I)	Insufficient evidence to support the role of hsCRP in preventive screening of asymptomatic patients
CCS	2009	Genest et al., <i>Can J Cardiol</i>	Class IIa, Level B	Men >50 years and women >60 years who are intermediate risk by Framingham criteria and would not otherwise qualify for lipid-lowering therapy (LDL-C <135 mg/dl)
ESC	2012	Perk et al., <i>Eur Heart J</i>	Class IIb, Level B	Patients with moderate or unusual CVD risk profile Asymptomatic low-risk and high-risk patients to assess 10-year risk of CVD Patients with hypertension categorized as intermediate risk by Framingham criteria
	2009	Mancia et al., <i>J Hypertens</i>	Class III, Level B	
ACC/AHA	2010	Greenland et al., <i>J Am Coll Cardiol</i>	Class IIa, Level B Class IIb, Level B Class III, Level B	Men >50 years and women >60 years with LDL-C <130 mg/dl, not on lipid-lowering therapy and without chronic kidney disease, diabetes, or hormone replacement therapy Reasonable to test in asymptomatic intermediate-risk patients. No benefit in asymptomatic high-risk or younger low-risk patients

ACC/AHA = American College of Cardiology/American Heart Association; AHRQ = Agency for Healthcare Research and Quality; CCS = Canadian Cardiovascular Society; CVD = cardiovascular disease; ESC = European Society of Cardiology; USPSTF = U.S. Preventive Services Task Force; LDL-C = low-density lipoprotein cholesterol; other abbreviation as in Table 1.

hsCRP only modestly adds over traditional clinical metrics already in use. The lack of a unified recommendation speaks to the plethora of compelling but ultimately inconclusive data regarding the clinical utility of hsCRP at this time.

Conclusions

During the last decade, a number of biomarkers have been considered in the assessment of risk for prevention of CVD. The costs and risks of screening and potentially treating large populations are substantial. Therefore, considerable scrutiny has been applied to determining a candidate that materially adds to established models of risk assessment and modification. hsCRP, an inflammatory factor with wide variability among various ages, sexes, and ethnicities, is modestly associated with CVD. The addition of hsCRP level to FRS results in mild improvement in risk discrimination and reclassification largely because of the high correlation of hsCRP with the risk factors already in the model. Its long-term predictive capacity is likely a reflection of the inflammatory process associated with atherosclerotic risk.

Careful review of the available data from experimental research, epidemiological studies, and large clinical trials does not provide conclusive evidence for the routine testing of hsCRP in risk prediction and as a tool to initiate statin therapy. Statins are likely to mutually benefit individuals with or without elevated hsCRP levels. Further, the use of achieved hsCRP level to guide the intensity of lipid-modifying therapy is a hypothesis that is as yet unproven as a strategy. At this time, the existing evidence remains insufficient to justify widespread use of hsCRP in clinical practice. It may be time to remove hsCRP from the list of potential bandits of atherosclerosis. Further investigation with anti-inflammatory therapies may help bring vascular

inflammation closer to the bedside and refine the role of hsCRP as a therapeutic target in preventing CVD.

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