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C-Reactive Protein and the Prediction of Cardiovascular Events Among Those at Intermediate Risk

Moving an Inflammatory Hypothesis Toward Consensus

Paul M Ridker, MD, MPH, FACC

Boston, Massachusetts

Over 20 large-scale prospective studies show that the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) is an independent predictor of future cardiovascular events that additionally predicts risk of incident hypertension and diabetes. In many studies, the relative impact of hsCRP is at least as large as that individually of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood pressure, or smoking, and knowledge of hsCRP correctly reclassifies a substantial proportion of "intermediate-risk" individuals into clinically relevant higher- or lower-risk categories. Other studies show the relative benefit of statins to be greater among those with increased hsCRP and that achieved hsCRP levels after statin therapy predict recurrent event rates as much as achieved levels of low-density lipoprotein cholesterol. Nonetheless, it remains controversial whether the time has come to modify traditional algorithms used for global risk detection. As described here, 6 areas of controversy regarding hsCRP are resolvable with a consensus position that focuses in primary prevention on selective use among individuals with 5% to 20% 10-year risk as estimated by Adult Treatment Panel III, and focuses in secondary prevention on high-risk patients being treated with statin therapy. Forthcoming trial data could expand or contract this "screen selectively" policy, and investigators should be open to the possibility that second-generation inflammatory biomarkers may be developed that supplant hsCRP altogether. In the meantime, however, this consensus position on hsCRP should be one to which both advocates and critics of the inflammatory hypothesis of atherosclerosis can adhere because it is one that can immediately improve patient care.
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Exactly 10 years ago it was reported that the inflammatory biomarker C-reactive protein, when measured in blood with a high-sensitivity assay (hsCRP), is a strong, independent predictor of future myocardial infarction and stroke among apparently healthy asymptomatic men, and that the magnitude of this effect was similar to that of cholesterol and blood pressure (1,2). That work showed that inflammation, as reflected in the concentration of hsCRP, preceded the onset of cardiovascular events rather than being a result of ischemia or smoking as previously assumed (3–6), and thus provided evidence confirming the hypothesis that atherothrombosis was, in part, an inflammatory disorder (7–9).

Since that report from the Physicians Health Study in 1997, the ability of hsCRP to predict myocardial infarction, ischemic stroke, and vascular death has been confirmed in more than 20 diverse population cohorts including the Women's Health Study (10–12), a general population cohort from Britain (13), the WHI (Women's Health Initiative)-observational cohort (14), the Honolulu Heart Study (15), the NHS (Nurses Health Study) (16), the HPFUS (Health Professionals Follow-Up Study) (16), the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease)-Augsberg cohort (17,18), the ARIC (Atherosclerosis Risk in Communities) study (19), the CHS (Cardiovascular Health Study) (20), the SHS (Strong Heart Study) (21), the Kuopio Ischemic Heart Disease Risk Factor Study (22), and the EPIC (Evaluation for Prevention of Ischemic Complications)-Norfolk cohort (23). Further work has shown elevated hsCRP to modify risk associated with metabolic syndrome (24–26) and to predict incident type 2 diabetes (27–29) as well as hypertension (30,31). In 2002, on the basis of data from 27,939 initially healthy women followed up over a decade, plasma levels of hsCRP <1 mg/l, 1 to 3 mg/l, and >3 mg/l were established as

From the Center for Cardiovascular Disease Prevention, the Divisions of Preventive Medicine and Cardiovascular Diseases, Brigham and Women's Hospital, the Harvard Medical School, and the Harvard School of Public Health, Boston, Massachusetts. Supported by grants from the National Heart, Lung, and Blood Institute, the Donald W. Reynolds Foundation (Las Vegas, Nevada), the Doris Duke Charitable Foundation (New York, New York), and the Leducq Foundation (Paris, France). Dr. Ridker is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes.

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Abbreviations and Acronyms

ATP = Adult Treatment Panel III

HDL = high-density lipoprotein

hsCRP = high-sensitivity C-reactive protein

LDL = low-density lipoprotein

ROC = receiver-operator characteristic

representing lower, average, or higher relative vascular risk when added to traditional risk factors (12). After a comprehensive assay standardization program was completed by the Centers for Disease Control and Prevention, a panel of prevention experts presented in 2003 the first guidelines for use of commercial hsCRP tests as an adjunct to global risk prediction (32).

More recently, the addition of hsCRP to traditional risk factors has been shown to reclassify up to 30% of individuals at "intermediate risk" into clinically relevant higher- or lower-risk categories, and that the relative impact of hsCRP on prediction is at least as large as that individually of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, or smoking (33). In fact, as shown in the recently published Reynolds Risk Score (34), 2 key biomarkers, hsCRP (reflecting inflammation) and family history (reflecting genetic predisposition), not only reclassify nearly 50% of all women with Adult Treatment Panel III (ATP-III) estimated 5% to 10% and 10% to 20% 10-year risk into higher- or lower-risk categories, but do so with markedly improved accuracy (35). Other data show that hsCRP is effective at predicting incident peripheral arterial disease in the general population (36,37) as well as vascular complications among diabetic patients (38,39), those undergoing hemodialysis and peritoneal dialysis (40–42), and those undergoing bypass surgery or percutaneous coronary angioplasty (43,44). Many additional studies confirm the utility of hsCRP for prediction of ischemic stroke, a condition in which lipid levels are less effective (15,45–48). Because hsCRP has been implicated in progression of carotid and cortical small vessel disease (49,50), these observations suggest an even larger role for inflammation in the cerebral vasculature. Finally, hsCRP levels track with abdominal obesity, insulin resistance, and the number of components of the metabolic syndrome that are present. Yet, despite this concordance, multiple studies show that individuals formally qualifying for metabolic syndrome by current criteria who have hsCRP >3 mg/l are at higher risk for future cardiovascular events and diabetes compared with those with metabolic syndrome who have hsCRP <1 mg/l, a risk relationship almost identical to that for hsCRP among individuals without metabolic syndrome (24–26).

Based on this consistent body of evidence, many physicians measure hsCRP as an adjunct to global cardiovascular risk prediction, and an intensive search has been initiated for targeted vascular anti-inflammatory agents that might have efficacy in the treatment and prevention of coronary disease. However, there is ongoing debate regarding whether or not the time has come to modify traditional algorithms used for the global detection of vascular risk (51). Over the past decade, 6 areas of controversy have framed much of this debate. As will be described, these controversies are largely resolvable such that a consensus position on hsCRP can be reached that both advocates and critics of the inflammation hypothesis can adhere to and will ultimately improve patient care.

Resolving the Framingham Heart Study and Reykjavik Heart Study Controversies

Figure 1 shows the predictive value in 14 apparently healthy populations with baseline hsCRP levels of <1 mg/l, 1 to 3 mg/l, and >3 mg/l after adjustment for traditional risk factors. All show similar efficacy with no evidence of heterogeneity. Nonetheless, reports from 2 of these cohorts generated controversy because they did not seem to affirm these data, at least as initially published. Of these, the Framingham Heart Study data are the most important because they represent a cohort that is the basis for most global risk prediction models.

Three presentations from the Framingham investigators are highlighted here. In the first, Rost et al. (46) published Framingham data in which risk of stroke or transient ischemic attack for men and women with baseline CRP levels in the top quartile were 2.0 and 2.7 times higher, respectively, when compared with those in the lowest quartile, effects that remained significant for both genders after adjustment for smoking, total:HDL cholesterol, systolic blood pressure, and diabetes. This article was followed in 2005 by a second Framingham manuscript that again found CRP to be an important predictor of cardiovascular risk in age- and gender-adjusted models, but was interpreted less optimistically because these effects were attenuated and no longer significant after full multivariate adjustment (52). Although often cited as a null paper, that analysis unfortunately was performed with a non–high-sensitivity assay for CRP, and thus a true test of the inflammation hypothesis in Framingham required repeat testing with an appropriate hsCRP assay. That re-analysis was presented as an abstract at the November 2006 meeting of the American Heart Association. As reported, the age- and gender-adjusted relative risks in Framingham for hard cardiovascular events among individuals with baseline blood levels of hsCRP <1 mg/l, 1 to 3 mg/l, and >3 mg/l were 1.0 (referent), 1.5, and 2.9, highly significant observations entirely consistent with earlier work. Moreover, this re-analysis showed that the fully adjusted relative risks among those with increasing levels of hsCRP were 1.0 (referent), 1.2, and 1.7, again a highly significant finding (53). Thus, had an appropriate high-sensitivity assay been used originally, there would never have been any controversy between data from the Framingham Heart Study and data presented by earlier investigators.

A second cohort that generated controversy at the time of its publication was the Reykjavik Heart Study (54). This

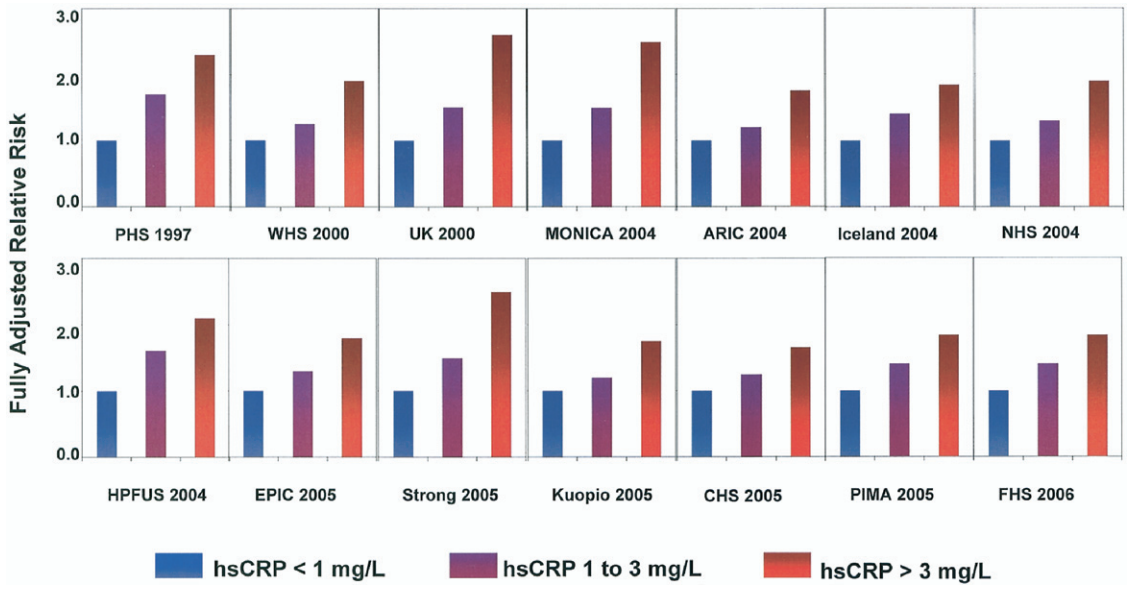

Figure 1 **Independent Impact of hsCRP on Cardiovascular Risk**

Multivariate adjusted relative risks of future cardiovascular events according to baseline levels of high-sensitivity C-reactive protein (hsCRP) <1 mg/l, 1 to 3 mg/l, and >3 mg/l in 14 major prospective cohort studies. Data adapted from references 1,11–13,16–20,22,23,51–54. ARIC = Atherosclerosis Risk in Communities study; CHS = Cardiovascular Health Study; EPIC = Evaluation for Prevention of Ischemic Complications-Norfolk study; FHS = Framingham Heart Study; HPFUS = Health Professionals Follow-Up Study; Iceland = Reykjavik Heart Study data; Kuopio = Kuopio Heart Study; MONICA = Monitoring Trends and Development in Cardiovascular Disease study; NHS = Nurses Health Study; PHS = Physicians Health Study; PIMA = Pima Indian study; Strong = Strong Heart Study; UK = British general practice cohort; WHS = Women's Health Study.

Icelandic cohort began in 1967 in a population with high lipid levels and thus is a comparison of hsCRP with usual risk factors in an era that preceded effective public health recommendations to reduce fat intake. The investigators of the Reykjavik Heart Study did not report outcomes by hsCRP levels of <1 mg/l, 1 to 3 mg/l, and >3 mg/l, but did report multivariate adjusted evidence showing that individuals with hsCRP in the highest tertile were significantly more likely to suffer future vascular events when compared with those in the lowest tertile (relative odds 1.5, 95% confidence interval [CI] 1.3 to 1.7). Despite this statistically significant result, the Reykjavik report concluded that hsCRP was not clinically meaningful as this effect was "modest" in magnitude. However, in the same report, the multivariate adjusted odds ratio for systolic blood pressure was also 1.5 (95% CI 1.3 to 1.7). Further, for those with hsCRP in the top fifth of the distribution (a level that should correlate closely with hsCRP >3 mg/l), the multivariate adjusted odds ratio for hsCRP was 1.7 with 95% CIs completely overlapping the risk associated with smoking (1.4 to 2.0). Thus, the impact of hsCRP in the Reykjavik data is in fact identical in magnitude to the impact of hypertension and smoking in that population.

Subsequent to the Reykjavik data, 2 other European cohorts presented prospective data on hsCRP in populations with more contemporary lipid levels, and both reported affirmative data. In the EPIC-Norfolk prospective population (23), the fully adjusted odds ratio for future vascular events among those with baseline hsCRP levels >3 mg/l was 1.8 (95% CI 1.4 to 2.3), whereas the Kuopio Ischemic Heart Disease Risk Factor Study of vascular mortality reported a fully adjusted odds ratio of 2.9 (95% CI 1.5 to 5.9) (22). Both of these contemporary European cohorts found the impact of hsCRP to be at least as large as that of most usual risk factors, data fully consistent with other reports (55).

Resolving the C-Statistic Controversy

Despite the data in Figure 1, the impact of adding hsCRP to model fit as measured by area under the receiver-operator characteristic (ROC) curve (and summarized by the C-statistic) is small, an observation that has led some to conclude that hsCRP (and potentially other novel risk factors for that matter) has little role in vascular disease prediction (56–58). However, a careful analysis of the C-statistic and its role in prediction modeling suggests that this is an incorrect conclusion and that the use of the C-statistic as a method of selecting variables for risk prediction models may be ill advised (59).

The C-statistic is a technique designed to discriminate between cases and noncases in the setting of diagnostic testing where disease already exists and where sensitivity and specificity are of clinical importance. The C-statistic,

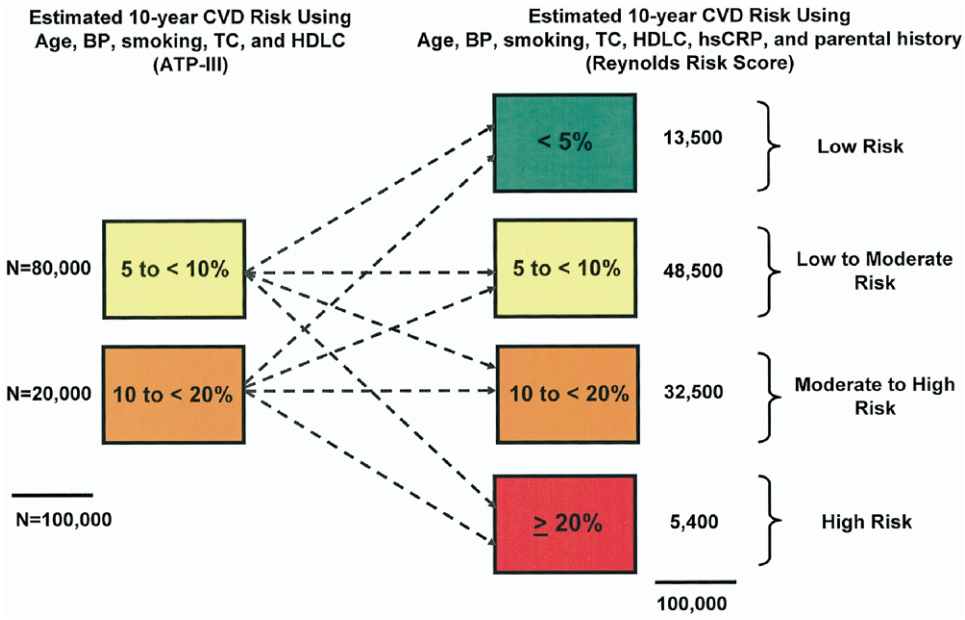

Figure 2 Risk Reclassification Using hsCRP and Parental History

Impact of high-sensitivity C-reactive protein (hsCRP) (representing inflammation) and family history (representing genetics) on estimates of global cardiovascular risk for a representative population of 100,000 U.S. women at 5% to 10% and 10% to 20% 10-year risk according to the Adult Treatment Panel III (ATP-III). Data adapted from references 34 and 35. BP = blood pressure; CVD = cardiovascular disease; HDLC = high-density lipoprotein cholesterol; TC = total cholesterol.

however, is a far less effective tool for selecting prediction variables when faced with a healthy population in which the task is to identify future disease where none currently exists. As Cook (59) has recently shown, this technique can lead to erroneous conclusions when applied to risk prediction in prospective cohort data, particularly those involving healthy individuals at risk for common disorders such as myocardial infarction or stroke.

By way of example, for an individual risk factor to provide adequate discrimination on its own as judged by the C-statistic, it must have a hazard ratio of 16.0 or greater (60). This fact, however, should not be construed to imply that biomarkers with smaller hazard ratios are without clinical utility. For example, a biomarker with an adjusted hazard ratio of 3.0 may be incapable of moving the C-statistic, yet that same biomarker could in theory increase a specific individual's estimated 10-year risk from 8% to 24%, a reclassification of risk with major implications for treatment decisions. Moreover, other than age, no component of the Framingham risk score has an adjusted hazard ratio >3.0 (most, in fact, are between 1.6 and 2.0). As such, proponents of the C-statistic as the sole basis for selecting risk factors would, by necessity, also eliminate lipids, blood pressure, and perhaps even smoking from consideration as clinically important. This paradox is particularly true for cholesterol, the core basis for pharmacologic interventions proven to lower cardiovascular risk; were the same criteria applied to total, LDL, and HDL cholesterol that are now being applied to hsCRP, each of these would have erroneously been eliminated as a risk factor for heart disease.

A more tenable position would be to acknowledge that the C-statistic is an insensitive tool for selecting variables to be included in risk prediction models based on prospective cohort data of currently healthy individuals. Statisticians have suggested that additional methods can be used to evaluate model fit in this setting, including global measures such as the Bayes Information Criteria, Brier score, Yates slope, and entropy (59,61). They also have emphasized that more attention should be paid in this setting to calibration and to reclassification (59,62–64).

Using these techniques, large and clinically important differences between prediction models with and without hsCRP have been found, despite minimal effects on the C-statistic (33,35,53). This turns out to be of greatest importance for reclassifying individuals at intermediate global risk using ATP-III criteria. For example, as shown in Figure 2, for a representative population of 100,000 U.S. women without diabetes (80,000 at 5% to <10% 10-year risk and 20,000 at 10% to <20% 10-year risk by ATP-III), additional knowledge of hsCRP and family history would place 13,500 of these women at low risk, 48,500 at low to moderate risk, 32,500 at moderate to high risk, and 5,400 at high risk. Moreover, in a direct comparison of estimated to actual event rates, this reclassification of risk has been shown to be correct for well over 95% of those reclassified, despite only marginal effects on the C-statistic (35).

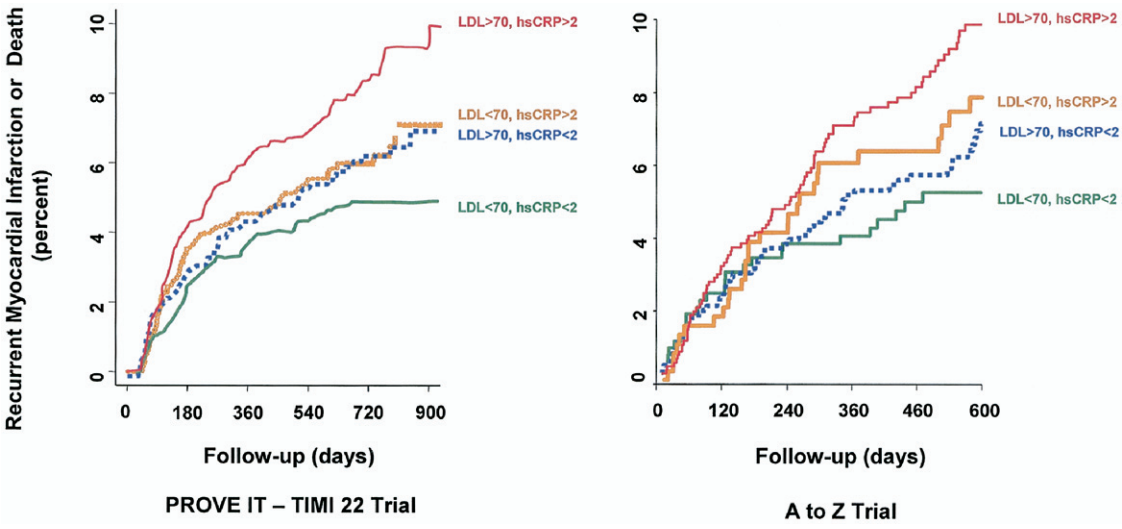

Figure 3 **LDL Cholesterol, hsCRP, and Clinical Outcomes on Statin Therapy**

Cumulative rates of recurrent myocardial infarction or cardiovascular death among statin-treated patients according to achieved levels of LDL cholesterol in mg/dl and achieved levels of hsCRP in mg/l in the PROVE-IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction-22) trial **(left)** and in the A to Z (Aggrastat to Zocor) trial **(right)**. Data adapted from references 77 and 80. hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

Resolving the Statin Controversy

In collaboration with the CARE (Cholesterol And Recurrent Events) Investigators, it was reported in 1998 that post-MI patients with elevated hsCRP levels had a greater relative clinical benefit from statin therapy in secondary prevention when compared with those with lower hsCRP levels (65). Soon thereafter, it was reported that statins reduce plasma levels of hsCRP in a manner largely independent of LDL reduction (66–68). Further, in collaboration with the AFCAPS/TexCAPs (Air Force/Texas Coronary Atherosclerosis Prevention Study) Investigators, the observation was made in primary prevention that individuals with elevated levels of hsCRP seemed to benefit from statin therapy even when LDL cholesterol levels were not elevated (69).

Although initially controversial, the observation that statins lower hsCRP has been confirmed by multiple investigators (70–74) and provides clinical support for the hypothesis that in addition to lowering LDL cholesterol, statins might also have clinically relevant anti-inflammatory effects (75,76). On this basis, many physicians use hsCRP as a "tie-breaker" method to decide on statin use among patient groups in which lipid-lowering therapy is considered optional by current ATP-III guidelines. In primary prevention, such patients typically include those with LDL cholesterol between 130 and 160 mg/dl who also have 10% to 20% 10-year risks and are not diabetic. The use of hsCRP for this purpose seems to provide a method of better targeting statins to the most appropriate higher-risk individuals, an effect that would both maximize benefit and minimize risk.

A second statin controversy was raised when investigators in the PROVE-IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction-22) trial presented a prespecified analysis addressing whether best clinical outcomes were obtained among acute coronary syndrome patients treated with statins who had LDL cholesterol reduced below 70 mg/dl or who had hsCRP levels reduced below 2 mg/l, the approximate median values for both variables after 30 days of therapy (77). In that analysis of 3,745 patients, rates of recurrent myocardial infarction or cardiovascular death were lowest when both of these target goals was achieved (Fig. 3, left). However, when only the LDL cholesterol <70 mg/dl target or only the hsCRP <2 mg/l target was achieved, risk reductions were less impressive (and the worst outcomes were observed when neither target was attained). These effects were independent of other determinants of outcome including age, gender, smoking, diabetes, hypertension, obesity, HDL cholesterol, peak creatine kinase leak, Killip class, use of early revascularization, and left ventricular ejection fraction. On this basis, it was hypothesized that among very-high-risk patients undergoing statin therapy, the dual goals of LDL and hsCRP reduction should be considered a new clinical target for therapy (78). In a follow-up analysis of PROVE-IT–TIMI-22, achieving low levels of hsCRP after initiation of statin therapy was further found to be associated with reduced risks of stroke (79).

As with any controversial hypothesis, these data required independent confirmation. Recently, the A to Z (Aggrastat to Zocor) Investigators also found that achieving the dual goal of LDL cholesterol <70 mg/dl and hsCRP <2 mg/l was associated with the best clinical outcomes among 3,813 acute coronary syndrome patients initiating statin therapy (80); as shown in Figure 3 (right), this effect in the A to Z trial was virtually identical to that found in PROVE-IT–TIMI-22. Moreover, in an analysis of the REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering Therapy) trial that used intravascular ultrasound to measure disease progression over 18 months of statin therapy, individuals who achieved below median levels of both LDL and hsCRP achieved the greatest coronary atheroma regression (81). This surrogate biomarker data supports hard end point data from PROVE-IT–TIMI-22 and A to Z, as well as data showing that those in whom both LDL cholesterol and hsCRP are reduced on statin therapy are also those with the least progression of carotid intimal medial thickness (82). These confirmations show that initial observations regarding statins and hsCRP are reproducible and consistent (83). Not all LDL-lowering therapies reduce hsCRP. For example, ezetimibe given as monotherapy has no impact on hsCRP, although when given concomitantly with a statin it seems to augment CRP reduction.

For primary prevention patients with LDL cholesterol below 130 mg/dl who are at increased risk on the basis of elevated hsCRP, it remains unproven whether statin therapy will effectively reduce vascular event rates. To address this issue, the multinational JUPITER (Justification for the Use of statins in Primary prevention: an International Trial Evaluating Rosuvastatin) trial was launched in 2003 comparing rosuvastatin with placebo among 17,800 primary prevention patients with LDL cholesterol <130 mg/dl who also have hsCRP >2 mg/l (84). This trial has completed enrollment and is designed to complete after approximately 500 end points have accrued.

Resolving the Biological Variation Controversy

Plasma levels of hsCRP acutely increase during stress, whether ischemic or because of major trauma or infection. This biological variance has led some critics to suggest that hsCRP measurement cannot be an effective clinical tool. Below is a summary of evidence addressing this concern.

First, marked variation in hsCRP levels would have imposed a major bias toward the null hypothesis in all of the aforementioned early epidemiologic studies in which only a single baseline hsCRP measure was obtained. As such, the observed relative risks consistently seen in these studies will, if anything, be underestimates of the true relative risk associated with inflammation in the vascular disease process. Moreover, as suggested in the 2003 American College of Cardiology/American Heart Association guidelines for inflammatory biomarker use (32), evaluating hsCRP on 2 occasions separated by a few weeks (as is also recommended for lipids) greatly reduces any such variation in usual clinical practice.

Second, hsCRP levels are stable over long periods of time. In the CARE trial, the age-adjusted correlation coefficient for hsCRP measured at baseline and after 5 years of follow-up among individuals allocated to placebo was 0.60, a level of correlation greater than that of total cholesterol, LDL cholesterol, or triglycerides (66). Similarly, for 2,834 participants in the AFCAPS/TexCAPs trial treated with placebo, there was no difference between median hsCRP levels at baseline and after 1 year of follow-up (69). Finally, among 379 participants in the Reykjavik Heart Study who provided paired samples over a decade apart, the within-person correlation coefficient for hsCRP was 0.59, identical to that of total cholesterol (0.60) (54). In all of these studies, the reported correlation coefficients for repeated hsCRP levels were similar to if not superior to that of repeated blood pressure measurements, another risk marker commonly used in global prediction models.

Despite this consistency of hsCRP levels over time, the potential for biologic variation has led to misunderstanding regarding the predictive value of chronically high levels of hsCRP. Published data indicate that individuals with very high levels of hsCRP (ranging between 10 and 60 mg/l on a chronic basis) are in fact at markedly high risk for future vascular events, and that the impact of hsCRP on risk is linear across a full range of hsCRP levels in a manner analogous to that of LDL cholesterol (85). Thus, although it is appropriate to repeat hsCRP testing for values in excess of 5 mg/l (and to use the lower of the 2 measurements for clinical decision making), individuals with substantially increased levels on a chronic basis should not be considered false-positive because they are at high risk for future cardiovascular events.

Resolving the "Marker or Mechanism" Controversy

Controversy exists regarding whether CRP is only a clinically useful determinant of disease, or whether it also may play a causal role in the atherothrombotic process (86,87). Those who have proposed a causal role for CRP note that CRP promotes endothelial cell activation and dysfunction, has substantive effects on vascular smooth muscle cells and neointimal formation, and directly affects monocyte and macrophage activity as well as matrix metalloproteinase function (88–93). Further, human CRP infusion studies show both proinflammatory and prothrombotic effects (94), whereas in transgenic mouse models, CRP seems to increase thrombosis rates after vascular injury (95). From a genetic perspective, CHS investigators have found that specific polymorphisms in the CRP gene associate with plasma levels of CRP and predict future events, data suggesting a potentially causal link between CRP and atherothrombosis

(96). The CRP also may block the effect of leptin on satiety and weight gain, suggesting a novel mechanism for leptin resistance (97). Some of these findings are controversial, however, and those who argue that CRP is not a causal determinant of atherothrombosis correctly note that no data directly showing that CRP reduction reduces vascular risk are yet available. Further, because the liver is a major source of CRP production and because CRP levels will increase with secretion of cytokines such as interleukin-6 from several tissues including adipocytes, CRP may only be a secondary messenger of the inflammatory process.

The "marker versus mechanism" debate remains open and is an area with a need for more research. Most importantly, there is a need to develop novel CRP inhibitors that can be used to test directly whether CRP reduction results in reduced event rates. One such agent has been described and, at least in animal models, has shown promise (98).

That being said, it is not necessary for any particular biomarker to fulfill the Koch postulates before being useful in a clinical setting. Even if CRP proves not to be causally related to atherothrombosis, it could remain a highly effective adjunctive method for the detection of cardiovascular risk, particularly when LDL cholesterol levels are normal or low. By way of example, physicians routinely measure HDL cholesterol to assist in risk detection despite a lack of evidence that increasing HDL improves clinical outcomes. Debate concerning mechanistic properties of CRP should have little bearing on its utility as a clinically effective biomarker for risk detection.

Moving Toward a Consensus: Resolving the "Screen Everyone" Versus "Screen Those at Intermediate Risk" Controversy

Half of all heart attacks and strokes in the U.S. occur among those without hyperlipidemia, and between 15% and 20% occur among individuals who additionally do not smoke or suffer from hypertension or diabetes (99). These data, along with the observation that higher levels of hsCRP predict vascular risk even when lipid levels are low, have led to an additional controversy in the hsCRP literature that relates to the selection of whom to screen. In essence, that controversy can be summarized as "screen everyone" versus "screen selectively" focusing on those at intermediate global risk.

Those who advocate a "screen everyone" position note that because current guidelines suggest screening all individuals for total cholesterol and HDL cholesterol as well as blood pressure, the same should hold for hsCRP because the magnitude of risk is similar and equally independent. Further, the finding of an isolated but persistently marked elevation of hsCRP should raise clinical concern regarding vascular risk in a manner analogous to that of isolated hyperlipidemia or hypertension. A "screen everyone" approach may also be cost-effective because the test itself is far less expensive than a return physician visit to review initial lipid findings (100). From a patient perspective, this approach would eliminate the need for a second phlebotomy (and third physician contact) before risk level is computed. Because risk assessment should ultimately occur in the primary care physician's office, these issues have spurred interest in on-site finger stick evaluation for hsCRP analogous to that currently available for total cholesterol and HDL cholesterol.

A more conservative view that I favor is a "screen selectively" policy for hsCRP that focuses on primary prevention for those at 5% to 20% 10-year risk as estimated by ATP-III risk factors, and focuses on secondary prevention for high-risk patients being treated with statins when achievement of low hsCRP levels along with low levels of LDL cholesterol portend best outcomes. Each of these positions has the advantage of being fully evidence based, and they are modest extensions of the intermediate-risk and high-risk recommendations made in 2003 by the American Heart Association/Centers for Disease Control and Prevention panel at a time when far less data were available (32). Forthcoming data such as that from the JUPITER trial could expand or contract a "screen selectively" policy. Investigators should also be open to the possibility that second-generation inflammatory biomarkers may be developed that supplant hsCRP altogether.

Clear policy statements endorsing selective hsCRP use among these intermediate-risk and high-risk groups would contribute to consensus building in the epidemiology and clinical community, as critics of the "screen everyone" approach have agreed that selective screening of intermediate-risk individuals is an evidence-based position (101). After all, if the primary purpose of risk prediction is to better inform our patients about their respective needs for dietary discretion, smoking cessation, exercise, and appropriate pharmacologic intervention, a more accurate scoring system should not be objectionable as long as it is inexpensive and leaves the locus of control in the hands of the primary care physician. Because those with 5% to 20% 10-year risk by current ATP-III algorithms represent the group in which clinical decision making is most complex, both patients and primary care providers stand to benefit from such a middle-ground position at this time.

Reprint requests and correspondence: Dr. Paul M Ridker, Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, Massachusetts 02215. E-mail: pridker@partners.org.

REFERENCES

1. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–9.
2. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation 1998;97:2007–11.

3. Berk BC, Weintraub WS, Alexander RW. Elevation of C-reactive protein in "active" coronary artery disease. Am J Cardiol 1990;65: 168–72.
4. Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994;331:417–24.
5. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Am J Epidemiol 1996;144:537–47.
6. Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Lancet 1997;349: 462–6.
7. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685–95.
8. Libby P, Ridker PM. Inflammation and atherothrombosis from population biology and bench research to clinical practice. J Am Coll Cardiol 2006;48:A33–46.
9. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999;340:15–26.
10. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation 1998;98:731–3.
11. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836–43.
12. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. 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.
13. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 2000;321:199–204.
14. Pradhan AD, Manson JE, Rossouw JE, et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. JAMA 2002;288:980–7.
15. Curb JD, Abbott RD, Rodriguez BL, et al. C-reactive protein and the future risk of thromboembolic stroke in healthy men. Circulation 2003;107:2016–20.
16. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 2004;351: 2599–610.
17. Koenig W, Sund M, Frohlich M, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 1999;99:237–42.
18. Koenig W, Lowel H, Baumert J, Meisinger C. C-reactive protein modulates risk prediction based on the Framingham Score: implications for future risk assessment: results from a large cohort study in southern Germany. Circulation 2004;109:1349–53.
19. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2004;109:837–42.
20. Cushman M, Arnold AM, Psaty BM, et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. Circulation 2005;112:25–31.
21. Best LG, Zhang Y, Lee ET, et al. C-reactive protein as a predictor of cardiovascular risk in a population with a high prevalence of diabetes. The Strong Heart Study. Circulation 2005;112:1289–95.
22. Laaksonen DE, Niskanen L, Nyyssonen K, Punnonen K, Tuomainen TP, Salonen JT. C-reactive protein in the prediction of cardiovascular and overall mortality in middle-aged men: a population-based cohort study. Eur Heart J 2005;26:1783–9.
23. Boekholdt SM, Hack CE, Sandhu MS, et al. C-reactive protein levels and coronary artery disease incidence and mortality in apparently healthy men and women: the EPIC-Norfolk prospective population study 1993–2003. Atherosclerosis 2006;187:415–22.
24. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. Circulation 2003;107:391–7.
25. Rutter MK, Meigs JB, Sullivan LM Sr., Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004;110: 380–5.
26. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation 2003;108:414–9.
27. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin-6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327–34.
28. Freeman DJ, Norrie J, Caslake MJ, et al. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes 2002;51: 1596–600.
29. Laaksonen DE, Niskanen L, Nyyssonen K, et al. C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. Diabetologia 2004;47:1403–10.
30. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. JAMA 2003;290:2945–51.
31. Niskanen L, Laaksonen DE, Nyyssonen K, et al. Inflammation, abdominal obesity, and smoking as predictors of hypertension. Hypertension 2004;44:859–65.
32. 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.
33. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. Ann Intern Med 2006;145:21–9.
34. Reynolds Risk Score: Calculating Heart and Stroke Risk for Women. Available at: http://www.ReynoldsRiskScore.org. Accessed February 15, 2007.
35. 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.
36. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation 1998;97:425–8.
37. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 2001;285:2481–5.
38. Malik S, Wong ND, Franklin S, Pio J, Fairchild C, Chen R. Cardiovascular disease in U.S. patients with metabolic syndrome, diabetes, and elevated C-reactive protein. Diabetes Care 2005;28: 690–3.
39. Schulze MB, Rimm EB, Li T, Rifai N, Stampfer MJ, Hu FB. C-reactive protein and incident cardiovascular events among men with diabetes. Diabetes Care 2004;27:889–94.
40. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 1999;55:648–58.
41. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 2000;35:469–76.
42. deFilippi C, Wasserman S, Rosanio S, et al. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. JAMA 2003;290:353–9.
43. Mueller C, Buettner HJ, Hodgson JM, et al. Inflammation and long-term mortality after non-ST elevation acute coronary syndrome treated with a very early invasive strategy in 1042 consecutive patients. Circulation 2002;105:1412–5.
44. Walter DH, Fichtlscherer S, Sellwig M, Auch-Schwelk W, Schachinger V, Zeiher AM. Preprocedural C-reactive protein levels and cardiovascular events after coronary stent implantation. J Am Coll Cardiol 2001;37:839–46.

45. Ford ES, Giles WH. Serum C-reactive protein and self-reported stroke: findings from the Third National Health and Nutrition Examination Survey. Arterioscler Thromb Vasc Biol 2000;20: 1052–6.
46. Rost NS, Wolf PA, Kase CS, et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham Study. Stroke 2001;32:2575–9.
47. Cao JJ, Thach C, Manolio TA, et al. C-reactive protein, carotid intima-media thickness, and incidence of ischemic stroke in the elderly: the Cardiovascular Health Study. Circulation 2003;108:166–70.
48. Everett BM, Kurth T, Buring JE, Ridker PM. The relative strength of C-reactive protein and lipid levels as determinants of ischemic stroke compared with coronary heart disease in women. J Am Coll Cardiol 2006;48:2235–42.
49. Schillinger M, Exner M, Mlekusch W, et al. Inflammation and carotid artery risk for atherosclerosis study (ICARAS). Circulation 2005;111:2203–9.
50. vanDijk EJ, Prins ND, Vermeer SE, et al. C-reactive protein and cerebral small-vessel disease: the Rotterdam Scan Study. Circulation 2005;112:900–5.
51. Ridker PM, Wilson PWF, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation 2004;109:2818–25.
52. Wilson PW, Nam BH, Pencina M Sr., Benjamin EJ, O'Donnell CJ. C-reactive protein and risk of cardiovascular disease in men and women from the Framingham Heart Study. Arch Intern Med 2005;165:2473–8.
53. Wilson PW, D'Agostino RB, Sullivan L, O'Donnell CJ. Increased CRP and long term risk for cardiovascular events in middle age men and women. Circulation 2006;114 Suppl II:II-877.
54. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350:1387–97.
55. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA 2005;294:326–33.
56. van der Meer IM, de Maat MP, Kiliaan AJ, van der Kuip DA, Hofman A, Witteman JC. The value of C-reactive protein in cardiovascular risk prediction: the Rotterdam Study. Arch Intern Med 2003;163:1323–8.
57. Folsom AR, Chambless LE, Ballantyne CM, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. Arch Intern Med 2006;166:1368–73.
58. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006;355:2631–9.
59. Cook NR. Use and misuse of the ROC curve in the medical literature. Circulation 2007;115:928–35.
60. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. Am J Epidemiol 2004; 159:882–90.
61. Gail, MH, Pfeiffer RM. On criteria for evaluating models of absolute risk. Biostat 2005;6:227–39.
62. D'Agostino RB, Griffith JL, Schmidt CH, Terrin N. Measures for evaluating model performance. Proc Biom Section. Presented at: American Statistical Association, Biom Section: Alexandria, VA, 1997;253–8.
63. Moons KGM, van Es G-A, Deckers JW, Habbema J, Dik F, Grobbee DE. Limitations of sensitivity, specificity, likelihood ratio, and Bayes' theorem in assessing diagnostic probabilities: a clinical example. Epidemiology 1997;8:12–7.
64. Diamond GA. What price perfection? Calibration and discrimination of clinical prediction models. J Clin Epidemiol 1992;45:85–9.
65. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. Circulation 1998;98:839–44.
66. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. Circulation 1999;100:230–5.
67. Ridker PM, Rifai N, Lowenthal SP. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. Circulation 2001;103:1191–3.
68. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the Pravastatin Inflammation/CRP Evaluation (PRINCE), a randomized trial and cohort study. JAMA 2001;286:64–70.
69. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001;344:1959–65.
70. Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S. Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. Circulation 2001;103:1933–5.
71. Balk EM, Lau J, Goudas LC, et al. Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. Ann Intern Med 2003;139:670–82.
72. Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003;107:2409–15.
73. Bays HE, Stein EA, Shah AK, Maccubbin DL, Mitchel YB, Mercuri M. Effects of simvastatin on C-reactive protein in mixed hyperlipidemic and hypertriglyceridemic patients. Am J Cardiol 2002;90: 942–6.
74. Plenge JK, Hernandez TL, Weil KM, et al. Simvastatin lowers C-reactive protein within 14 days: an effect independent of low-density lipoprotein cholesterol reduction. Circulation 2002;106: 1447–52.
75. Schonbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? Circulation 2004;109:II18–26.
76. Bonetti PO, Lerman LO, Napoli C, Lerman A. Statin effects beyond lipid lowering—are they clinically relevant? Eur Heart J 2003;24: 225–48.
77. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352: 20–8.
78. Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol <70 mg/dl and C-reactive protein <2 mg/l: an analysis of the PROVE-IT TIMI-22 trial. J Am Coll Cardiol 2005;45:1644–8.
79. Mega JL, Morrow DA, Cannon CP, et al. Cholesterol, C-reactive protein, and cerebrovascular events after intensive and moderate statin therapy. J Thromb Thrombolysis 2006;22:71–6.
80. Morrow DA, deLemos JA, Sabatine MS, et al. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. Circulation 2006;114: 281–8.
81. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29–38.
82. Kent SM, Taylor AJ. Usefulness of lowering low-density lipoprotein cholesterol to <70 mg/dl and usefulness of C-reactive protein in patient selection. Am J Cardiol 2003;92:1224–7.
83. Horne BD, Muhlestein JB, Carlquist JF, et al. Statin therapy, lipid levels, C-reactive protein and the survival of patients with angiographically severe coronary artery disease. J Am Coll Cardiol 2000; 36:1774–80.
84. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. Circulation 2003;108:2292–7.
85. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. Circulation 2004;109:1955–9.
86. Scirica BM, Morrow DA. Is C-reactive protein an innocent bystander or proatherogenic culprit? The verdict is still out. Circulation 2006;113:2128–34.

87. Jialal I, Devaraj S, Venugopal SK. C-reactive protein: risk marker or mediator in atherothrombosis? Hypertension 2004;44:6–11.
88. Torzewski J, Torzewski M, Bowyer DE, et al. C-reactive protein frequently colocalizes with the terminal complement complex in the intima of early atherosclerotic lesions of human coronary arteries. Arterioscler Thromb Vasc Biol 1998;18:1386–92.
89. Han KH, Hong KH, Park JH, et al. C-reactive protein promotes monocyte chemoattractant protein-1—mediated chemotaxis through upregulating CC chemokine receptor 2 expression in human monocytes. Circulation 2004;109:2566–71.
90. Venugopal SK, Devaraj S, Yuhanna I, Shaul P, Jialal I. Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. Circulation 2002;106:1439–41.
91. Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. Blood 1993;82:513–20.
92. Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. Circulation 2000;102:1000–6.
93. Pasceri V, Cheng JS, Willerson JT, Yeh ET, Chang J. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. Circulation 2001;103:2531–4.
94. Bisoendial RJ, Kastelein JJ, Levels JH, et al. Activation of inflammation and coagulation after infusion of C-reactive protein in humans. Circ Res 2005;96:714–6.
95. Danenberg HD, Szalai AJ, Swaminathan RV, et al. Increased thrombosis after arterial injury in human C-reactive protein-transgenic mice. Circulation 2003;108:512–5.
96. Lange LA, Carlson CS, Hindorff LA, et al. Association of polymorphisms in the CRP gene with circulating C-reactive protein levels and cardiovascular events. JAMA 2006;296:2703–11.
97. Chen K, Fanghong L, Li J, et al. Induction of leptin resistance through direct interaction of C-reactive protein with leptin. Nat Med 2006;12:425–30
98. Pepys MB, Hirschfield GM, Tennent GA, et al. Targeting C-reactive protein for the treatment of cardiovascular disease. Nature 2006;440:1217–21.
99. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003;290:898–904.
100. Blake GJ, Ridker PM, Kuntz KM. Potential cost-effectiveness of C-reactive protein screening followed by targeted statin therapy for the primary prevention of cardiovascular disease among patients without overt hyperlipidemia. Am J Med 2003;114:485–94.
101. Lloyd-Jones DM, Liu K, Tian L, Greenland P. Narrative review: assessment of C-reactive protein in risk prediction for cardiovascular disease. Ann Intern Med 2006;145:35–42.