Clinical Chemistry 47:3
403–411 (2001)

Review

High-Sensitivity C-Reactive Protein: A Novel and Promising Marker of Coronary Heart Disease

Nader Rifai[1,2,4*] and Paul M. Ridker[2,3,5]

Background: **Coronary heart disease remains the leading cause of morbidity and mortality in the industrialized world. Clinical and laboratory studies have shown that inflammation plays a major role in the initiation, progression, and destabilization of atheromas. C-Reactive protein (CRP), an acute phase reactant that reflects low-grade systemic inflammation, has been studied in a variety of cardiovascular diseases.**

Approach: **Findings from prospective clinical trials were examined to determine the prognostic utility of CRP in acute coronary syndromes, and observations from epidemiological studies were reviewed to determine the ability of CRP to predict future first coronary events. The analytical considerations of CRP measurement in these clinical applications were also examined.**

Content: **In patients with established coronary disease, CRP has been shown to predict adverse clinical events. In addition, prospective studies have consistently shown that CRP is a strong predictor of future coronary events in apparently healthy men and women. The relative risk associated with CRP is independent of other cardiovascular disease risk factors. High-sensitivity CRP (hs-CRP) assays are needed for risk assessment of cardiovascular disease. Such assays are currently available but may require further standardization because patients' results will be interpreted using population-based cutpoints. Preventive therapies to attenuate coronary risk in individuals with increased hs-CRP concentrations include aspirin and statin-type drugs.**

Summary: **hs-CRP has prognostic utility in patients with acute coronary syndromes and is a strong independent predictor of future coronary events in apparently healthy subjects.**

Coronary heart disease (CHD)[6] is the major cause of death in the developed world. Atherosclerosis, the underlying cause of most CHD, is a process that starts early in life and progresses slowly and silently for decades. The clinical manifestation usually occurs in the form of myocardial infarction (MI), stroke, angina, or sudden death between ages 50 and 60 years in men and between 60 and 70 years in women. Cholesterol screening has been used as a tool to identify individuals who are at increased risk of developing future coronary events. Although this approach has been useful, it fails to identify almost one-half of the 1.3 million individuals who develop MI in the US each year who have either normal or only moderately increased serum cholesterol concentrations.

Laboratory and clinical evidence has demonstrated that atherosclerosis is not simply a disease of lipid deposits. Rather, systemic inflammation also plays a pivotal role in atherothrombotic inception and progression *(1–3)*. Mononuclear cells, macrophages, and T lymphocytes are prominent in atheromatous plaques in the arterial wall *(4–7)*. Furthermore, the shoulder region of a plaque, the most vulnerable site for rupture in acute coronary syndromes, is heavily infiltrated with inflammatory cells *(8–10)*. Cytokines, which cause the de novo hepatic production of acute phase reactants such as C-reactive protein (CRP) *(11)*, have been shown to increase in acute coronary syndromes even in the absence of myocardial necrosis *(12)*. Therefore, CRP has been examined as a surrogate marker of other inflammatory mediators such as interleukin-6 and tumor necrosis factor-α to better understand the inflammatory component of atherosclero-

[1] Department of Laboratory Medicine, Children's Hospital, [2] Center for Cardiovascular Disease Prevention, Divisions of Preventive Medicine, and [3] Cardiovascular Diseases, Brigham and Women's Hospital, and Departments of [4] Pathology and [5] Medicine, Harvard Medical School, Boston, MA 02115.

*Address correspondence to this author at: Children's Hospital, Department of Laboratory Medicine, 300 Longwood Ave., Boston, MA 02115. Fax 617-713-4347; e-mail rifai@tch.harvard.edu.

Received September 14, 2000; accepted December 15, 2000.

[6] Nonstandard abbreviations: CHD, coronary heart disease; MI, myocardial infraction; hs-CRP, high-sensitivity C-reactive protein; RR, relative risk; 95% CI, 95% confidence interval; CARE, Cholesterol and Recurrent Events; MRFIT, Multiple Risk Factors Intervention Trial; PHS, Physicians' Health Study; PVD, peripheral vascular disease; WHS, Women's Health Study; TC, total cholesterol; HDL-C and LDL-C, HDL- and LDL-cholesterol.

sis *(13, 14)*. Current knowledge, however, suggests that the CRP concentration might reflect the vulnerability of the atheromatous lesion and the likelihood of a plaque to rupture *(2, 3, 15)*. This acute phase reactant has been studied over the last several years in a wide variety of atherosclerotic diseases *(12, 16–20)*. Its prognostic utility in acute coronary syndromes *(12, 16–20)* and its ability to predict future coronary events in apparently healthy men and women *(21–30)* have been demonstrated. The development of high-sensitivity CRP (hs-CRP) assays has been instrumental in exploration of the role of this acute phase reactant in predicting first cardiovascular events. Prospective studies have consistently demonstrated a positive association between hs-CRP and future coronary events. For hs-CRP to make the transition from clinical research to the routine clinical setting, however, several important issues must be satisfactorily addressed: (*a*) the availability of population-based cutpoints for interpretation and risk assessment; (*b*) the existence of potential therapeutic modalities; and (*c*) the reliability of the analytical systems used for measurement.

hs-CRP as a Prognostic Indicator in Acute Coronary Syndromes

Several studies have demonstrated that hs-CRP, measured at either presentation or discharge, may have prognostic value in patients with acute coronary syndromes. Some reports have also examined the risk stratification of patients by hs-CRP alone or in combination with cardiac troponins.

Liuzzo et al. *(12)* showed that in 31 patients with severe unstable angina and no evidence of myocardial necrosis, as documented by the absence of increased cardiac troponin T, hs-CRP concentrations >3 mg/L at admission were associated with an increased incidence of recurrent angina, coronary revascularization, MI, and cardiovascular death. The same group later demonstrated that hs-CRP >3 mg/L at discharge in 53 unstable angina patients was associated with increased readmission for recurrent instability and MI *(16)*. In a similar study of unstable angina, Ferreiros et al. *(18)* concluded that the prognostic value of hs-CRP measured at discharge was better than that determined at admission in predicting adverse outcome at 90 days. Furthermore, hs-CRP was the strongest independent predictor of adverse events in multivariate analysis. Data from the Thrombolysis In Myocardial Infarction 11A (TIMI 11A), a study of unstable angina and non-Q-wave MI, showed that markedly increased hs-CRP (15.5 mg/L) at presentation in 437 patients was a good predictor of 14-day mortality in that population *(19)*. Furthermore, hs-CRP helped to identify those patients with negative cardiac troponin T (qualitative rapid bedside method with cutoff of <0.2 μg/L) who were at increased risk of mortality *(19)*. Morrow et al. *(19)* concluded from that study that a strategy for risk stratification using both cardiac troponin T and hs-CRP should be considered. Similar conclusions were reported in a follow-up report by the same group using serum amyloid A, another acute phase reactant, instead of hs-CRP *(31)*. A recent report by de Winter et al. *(17)* showed that hs-CRP concentrations >5 mg/L at admission in 150 patients with non-ST-elevation acute coronary syndromes were associated with an increased incidence of major cardiac events within 6 months, regardless of cardiac troponin I values.

hs-CRP as a Predictor of Future Coronary Events

Over the last 6 years, several prospective studies have demonstrated that hs-CRP is a predictor of future cardiovascular morbidity and mortality among individuals with known cardiovascular disease. Data from the European Concerted Action on Thrombosis and Disabilities (ECAT) Angina Pectoris Study Group, a study of 2121 men and women with stable and unstable angina, demonstrated that each standard deviation increase in hs-CRP was associated with a 45% increase in the relative risk (RR) of nonfatal MI or sudden cardiac death [95% confidence interval (95% CI), 1.15–1.83] *(20)*. Similarly, in the Cholesterol and Recurrent Events (CARE) trial, hs-CRP was a predictor of recurrent coronary events in men and women who had already suffered a MI *(32)*. Those with hs-CRP concentrations in the highest quintile had an 80% higher chance of developing another coronary event within the 5-year study period (RR = 1.77; 95% CI, 1.1–2.9). Therefore, hs-CRP has the potential to be used in the stratification of patients into high- and low-risk groups.

Perhaps of greater clinical importance is the demonstration that hs-CRP concentrations predict first MI and stroke. To date, 10 prospective studies, 6 in the US and 4 in Europe, have consistently shown that hs-CRP is a powerful predictor of future first coronary event in apparently healthy men and women (Fig. 1). Findings from the Multiple Risk Factors Intervention Trial (MRFIT) demonstrated a direct positive association between hs-CRP and CHD mortality in men followed over a 17-year period (RR = 2.8; 95% CI, 1.4–5.4) *(22)*. This relationship, however, was evident only among smokers. A similar association between hs-CRP and future coronary events was noted in the Cardiovascular Health Study and Rural Health Promotion Project, which included men and women over 65 years of age with subclinical cardiovascular disease *(26)*. The Physicians' Health Study (PHS) demonstrated similar positive association between hs-CRP and future coronary events in apparently healthy men *(23)*. Unlike the observation in MRFIT, however, this association was evident in both smokers and nonsmokers. This study showed that those in the highest quartile of hs-CRP had a twofold higher risk of future stroke (RR = 1.9; 95% CI, 1.1–3.3), threefold higher risk of future MI (RR = 2.9; 95% CI, 1.8–4.6), and fourfold higher risk of future peripheral vascular disease (PVD; RR = 4.1; 95% CI, 1.2–6.0) *(23, 28)*. The RRs were stable over a long period of time (≥6 years) and independent of other CHD risk factors. The European MONICA (Monitoring Trends

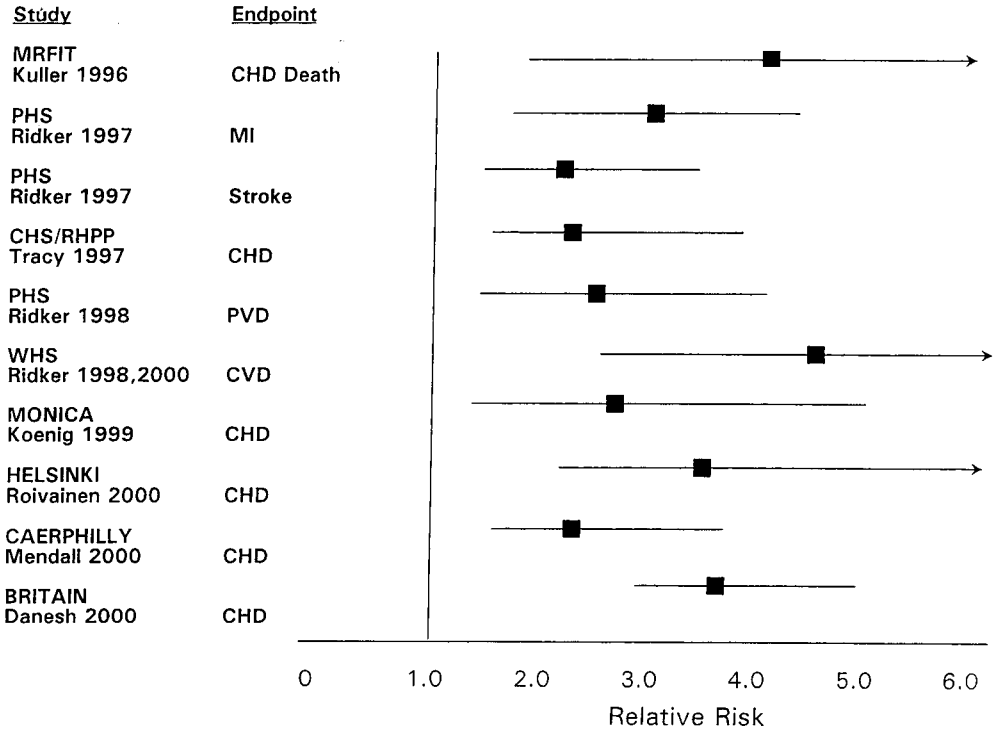

Fig. 1. Prospective studies of hs-CRP as a risk factor for future cardiovascular disease in populations of apparently healthy men and women. RR estimates (■) and 95% CIs (*lines*) are computed for those in the top compared with the bottom quartile. Data from Refs. *(21–30)*.

and Determinants in Cardiovascular Disease) Augsburg study showed that an increase of one standard deviation in the log-transformed value of hs-CRP was associated with a 50% increase in coronary risk and that subjects with hs-CRP concentrations in the highest quintile had a 2.6-fold higher risk of developing future coronary events *(21)*. A recent report from the Helsinki Heart Study confirmed these observations and demonstrated that those in the highest quartile of hs-CRP had a more than threefold higher risk of future MI or cardiac death (RR = 3.56; 95% CI, 1.93–6.57) *(27)*.

Two reports from the Women's Health Study (WHS) showed that hs-CRP is a strong predictor of future cardiovascular events in women (RR = 4.4; 95% CI, 2.2–8.9) *(24, 25)*. In stratified analyses, hs-CRP continued to be a strong predictor of future cardiovascular events even among subgroups of women with no history of hyperlipidemia, hypertension, smoking, diabetes, or family history of CHD *(25)*. The hs-CRP concentrations seen in these postmenopausal women were somewhat higher than those reported previously in men. Although no difference in hs-CRP values was noted between premenopausal women and age-matched males, recent reports showed that hormone replacement therapy (estrogen alone or estrogen and progestin) is associated with increased hs-CRP concentrations *(33, 34)*. These findings suggest that the increased hs-CRP seen in the WHS subjects may reflect the influence of hormone replacement therapy rather than the effect of gender.

Predictive Value of hs-CRP and Other Biochemical Markers for CHD Risk

The RR estimates derived from most of the above-mentioned prospective studies were independent of other recognized cardiovascular risk factors. Data from both the PHS *(35)* and WHS *(24)* showed that the predictive value of hs-CRP was significantly higher than that associated with traditional biochemical CHD risk markers [total cholesterol (TC), HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C)] or novel markers [lipoprotein(a), homocysteine, apolipoproteins AI and B]. In women, for example, the univariate RR of future cardiovascular events presented in Fig. 2 demonstrate that hs-CRP was the single strongest predictor of risk (RR = 4.4; 95% CI, 2.2–8.9). In comparison, LDL-C, a well-established marker of CHD, was a lesser predictor of future risk (RR = 2.4; 95% CI, 1.3–4.6). Furthermore, in a multivariate analysis that accounted for other CHD risk factors (obesity, hypertension, diabetes, family history), only hs-CRP and the ratio of TC to HDL-C had independent predictive value. In the same study of postmenopausal women *(24)*, hs-CRP was shown to predict risk among those with LDL-C values <1300 mg/L, a concentration deemed "desirable" by the current National Cholesterol Education Program guidelines for primary prevention. In this subgroup (mean LDL-C, 1040 mg/L), the RRs of future MI, stroke, and coronary revascularization in the lowest to the highest quartiles of hs-CRP were 1.0, 2.4, 2.9, and 4.1, respectively (95% CI for the 4th vs 1st quartile, 1.7–11.3).

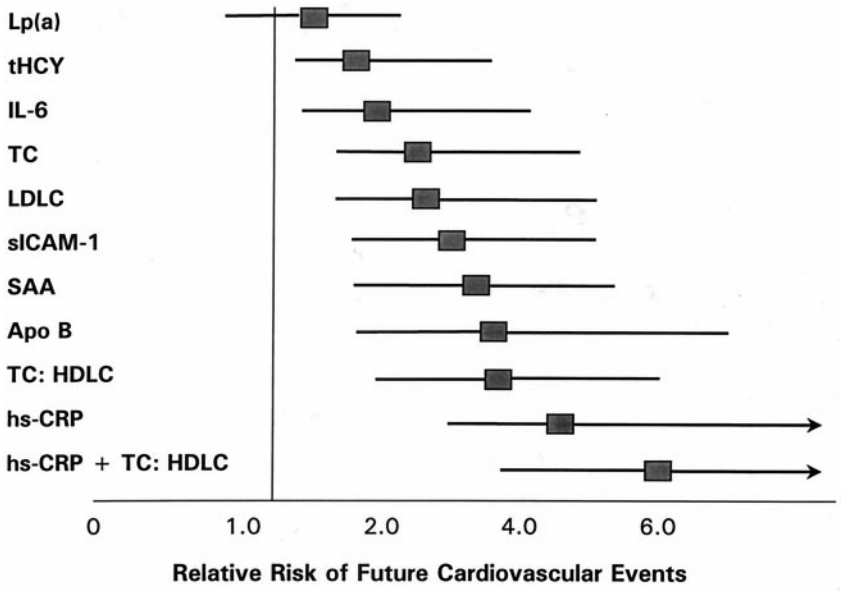

Fig. 2. RRs for future cardiovascular events among apparently healthy women in the WHS according to baseline values of several biochemical markers.

For consistency, risk estimates (■) and 95% CIs (*lines*) are computed for those in the top compared with the bottom quartile for each marker. *Lp(a)*, lipoprotein(a); *tHCY*, total homocysteine; *IL-6*, interleukin-6; *sICAM-1*, soluble intercellular adhesion molecule-1; *LDLC*, LDL-C; *SAA*, serum amyloid A; *Apo B*, apolipoprotein B; *HDLC*, HDL-C. Adapted from Ridker et al. *(24)*.

After adjustment for other CHD risk factors and concentration of HDL-C, the RR associated with hs-CRP remained highly significant (RR = 3.1; 95% CI, 1.1–8.3) and increased ~39% with each increasing quartile of hs-CRP. This study thus demonstrated that hs-CRP can identify individuals at increased risk of developing future coronary events who otherwise would be missed if only lipid measurements were used. Other examined markers of inflammation, e.g., serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule-1, showed consistent association but a slightly weaker RR of future coronary events.

The predictive value of hs-CRP in men and women increased considerably when evaluated in models that included lipid values. Data from the PHS demonstrated that, compared with those with TC and hs-CRP below the 75th percentile, those with increased TC alone had a 2.3-fold increase in risk (95% CI, 1.5–3.7), whereas those with increased hs-CRP alone had a 1.5-fold increase in risk (95% CI, 0.9–2.4) *(35)*. In contrast, the risk of developing coronary events increased 5-fold (95% CI, 2.5–9.8) among those with high concentrations of both TC and hs-CRP. Therefore, the joint effects of both risk factors are greater than the product of the individual effects of each risk factor considered alone. Furthermore, when the study participants were stratified according to quintile of hs-CRP and quintile of TC:HDL-C ratio, the RR of first coronary event in those in the highest quintiles of both hs-CRP and TC:HDL-C ratio was approximately ninefold higher than that of men in the lowest quintiles of these analytes. Data from the WHS demonstrated similar findings such that women in the highest quintile of both hs-CRP and TC:HDL-C ratio had a RR more than eightfold higher than that of women in the lowest quintiles (Fig. 3). In all of these analyses, risk prediction models that incorporated lipids were significantly better ($P < 0.001$) than those based on hs-CRP alone *(24)*.

Interpretation of hs-CRP Values

For the purpose of assessing risk of future first coronary events, hs-CRP concentration should be interpreted using cut points established by prospective clinical studies. Each patient will be classified into a quintile of risk, depending on the hs-CRP concentration. Therefore, the reporting of hs-CRP results focuses on the quintile of risk and not on the actual mass concentration.

The within-person biologic variability of hs-CRP is low over a long period of time *(36)*. Laboratory measurements on paired samples obtained from 236 subjects at baseline and 5 years later showed that an individual's log-normalized hs-CRP concentrations are highly correlated ($r = 0.60$). Somewhat comparable correlation coefficients were noted for TC ($r = 0.37$), LDL-C ($r = 0.32$), HDL-C ($r = 0.74$), and triglycerides ($r = 0.49$) over the 5-year follow-up period. This finding lends further support to the fact that hs-CRP is a good and biologically stable predictor of future MI despite the fact that it is an acute phase reactant, providing that the patient is not suffering from an active infection or using a drug that affects hs-CRP concentration. hs-CRP values >15 mg/L (~99th percentile of the general population) indicate an active inflammation; patients should be advised to have a repeat measurement in 2–3 weeks or after the infection in resolved.

As indicated earlier, models containing both hs-CRP and TC or the TC:HDL-C ratio were better able to predict future first coronary events than those containing hs-CRP alone. The RRs of future first coronary events for men and women as well as lipid concentrations were computed in quintiles from the PHS and WHS databases, respectively,

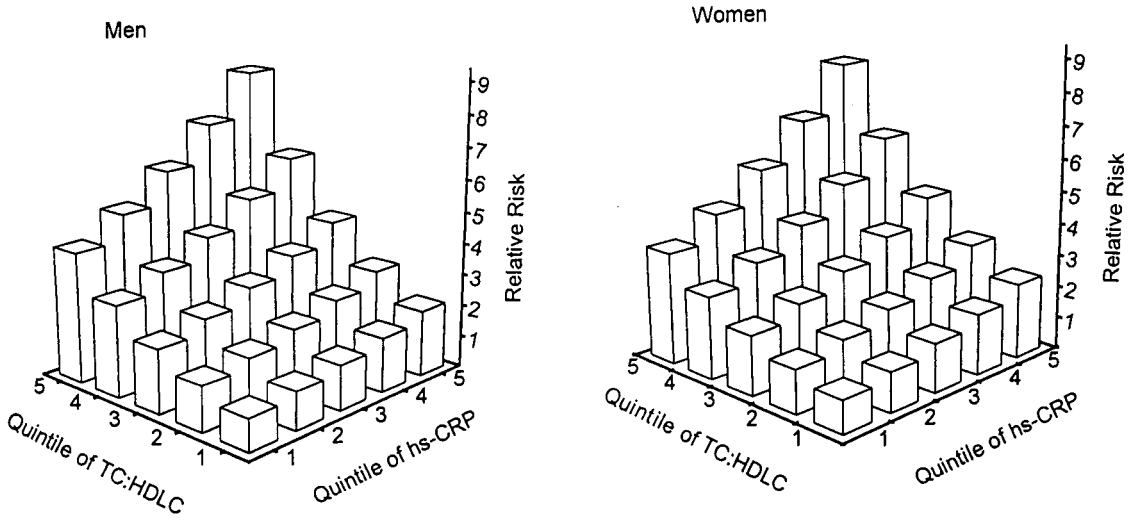

Fig. 3. RRs of first coronary event among apparently healthy men (*left*) and women (*right*) associated with different hs-CRP concentrations and TC:HDL-C ratios.

Adapted from Ridker and co-workers *(23, 24)*.

and are presented in Fig. 3. Because the computed RRs did not vary significantly between men and women, a single risk assessment algorithm is suggested for both genders (Table 1) *(37)*. The hs-CRP concentrations were derived from ongoing population-based surveys. It is important to note that it is not necessary in this case to report the actual hs-CRP concentration to the clinician but only the patient's RR. The clinical laboratory should play an active role in the interpretation and implementation of this clinical application. Providing incomplete information or just the actual hs-CRP concentration will only frustrate and prevent the clinician from correctly interpreting the data and managing the patient.

Potential Preventive Therapies

Although no specific therapies have been developed to decrease hs-CRP and there is no direct evidence that risk of future cardiovascular events is diminished by reducing hs-CRP, studies have shown that aspirin *(23)* and pravastatin *(32)* are effective in decreasing the incidence of future coronary events in those with increased hs-CRP concentration. These studies suggest that the two examined drugs possess antiinflammatory characteristics.

Among apparently healthy men in the PHS with increased hs-CRP (>2.1 mg/L), aspirin use decreased the risk of future MI by almost 60% *(23)*. In contrast, aspirin use was associated with a much smaller, although statistically significant, 14% decrease in future MI among men with low hs-CRP (<0.55 mg/L). Although the magnitude of reduction in future risk of MI depended on the concentration of hs-CRP, it is important to note that all subjects benefited from aspirin use. These findings suggest that aspirin was acting not only as an antiplatelet agent but also as an antiinflammatory drug.

Similar findings were also noted with pravastatin use in the CARE study *(32)*. As indicated earlier, CARE is a prospective study of men and women with average lipid concentrations who have suffered an MI. Participants

Table 1. RR estimates for future coronary events in men and women associated with quintiles of hs-CRP and TC:HDL-C ratio.[a]

			Quintile of hs-CRP, mg/L				
	Men	Women	1 (<0.7)	2 (0.7–1.1)	3 (1.2–1.9)	4 (2.0–3.8)	5 (3.9–15.0)
Quintile of TC:HDL-C ratio							
1	**<3.4**	**<3.4**	1	1.2	1.4	1.7	2.2
2	**3.4–4.0**	**3.4–4.1**	1.4	1.7	2.1	2.5	3
3	**4.1–4.7**	**4.2–4.7**	2	2.5	2.9	3.5	4.2
4	**4.8–5.5**	**4.8–5.8**	2.9	3.5	4.2	5.1	6
5	**>5.5**	**>5.8**	4.2	5	6	7.2	8.7

[a] RR estimates and TC:HDL-C ratio were derived from the PHS *(23)* and the WHS *(24)* databases. hs-CRP concentrations were derived from ongoing population-based surveys.

were randomized between 40 mg of pravastatin per day and placebo and followed for 5 years *(38)*. Study participants with high hs-CRP (>9.9 mg/L or 90th percentile) at baseline experienced a reduction of 54% in the incidence of recurrent coronary events compared with a reduction of 25% in those with low hs-CRP (<9.9 mg/L or 90th percentile), although baseline lipid values were almost identical in the two groups. Moreover, during the 5-year follow-up, pravastatin lowered mean hs-CRP by almost 40%. This represented a 22% difference at 5 years in median hs-CRP between the pravastatin and placebo groups. Furthermore, the magnitude of change in hs-CRP appeared to be unrelated to that of LDL-C in both the pravastatin and placebo groups. These findings suggest that pravastatin may have antiinflammatory characteristics that are independent from its lipid-lowering property. Clinical trials are currently ongoing to further explore the interaction between pravastatin, aspirin, and the inflammatory response in primary and secondary prevention settings.

Interrelationships with Other CHD Risk Factors

Several CHD risk factors appear to modulate the inflammatory response and affect hs-CRP concentration. Obesity, for example, is directly associated with increased hs-CRP concentrations, an intriguing observation considering that interleukin-6, the primary stimulant of the de novo hepatic synthesis of CRP, is secreted by adipose tissue *(39, 40)*. Therefore, the attenuation of the inflammatory response may represent a mechanism by which diet and weight loss reduce cardiovascular risk. Cigarette smoking has also been shown to increase the concentration of several inflammatory markers, including hs-CRP, interleukin-6, and soluble intercellular adhesion molecule-1. Increases of both interleukin-6 *(41)* and soluble intercellular adhesion molecule-1 *(42)* were shown to be associated with increased risk of future first coronary events in both men and women. Smoking cessation decreases these markers. Diabetic patients are reported to have increased hs-CRP values *(43)*; In this regard, links between hs-CRP and the insulin resistance syndrome have also been reported *(44)*. In addition, experimental findings suggest that increased blood pressure promotes endothelial expression of cytokines and inflammatory activation *(6, 45, 46)*. These observations suggest that perhaps better control of diabetes and hypertension may attenuate the contribution of the inflammatory response to overall cardiovascular risk. Finally, physical exercise has been shown to have a beneficial effect in terms of reducing the concentration of several inflammatory markers *(47, 48)*. Taken together, the available evidence thus supports the hypothesis that hs-CRP concentrations correlate with endothelial dysfunction *(49)*.

Analytical Considerations in the Measurement of hs-CRP

Historically, CRP has been measured in clinical laboratories by immunoturbidimetric and immunonephelometric assays designed to detect active inflammation and infection. The dynamic range of these assays spans from 3 mg/L (~90th percentile of the general population) to well over 200 mg/L. Such traditional assays, however, do not have appropriate sensitivity in the range required for the determination of cardiovascular risk in apparently healthy men and women.

To achieve the desired limit of quantification, manufacturers and investigators have continued to use immunochemical techniques in their attempts to measure hs-CRP, but with modifications to increase the detectable signal. Several approaches have been used, including the labeling of anti-CRP antibodies with either an enzyme (ELISA) or a fluorescent compound, and attaching the antibodies, either monoclonal or polyclonal, to polystyrene beads *(50–55)*. The latter approach was popular among manufacturers because it enabled the adaptation to commonly used automated analyzers in clinical chemistry laboratories. Currently, hs-CRP concentrations as low as 0.15 mg/L (<2.5th percentile of the general population) can be reliably measured. It is important to note, however, that not all hs-CRP assays possess a similar sensitivity or lower limit of quantification *(56)*. For practical considerations, it is advisable to have a single CRP assay in the clinical laboratory that is capable of measuring low and high concentrations. However, if that is impossible, clinicians should be aware of the availability of two different CRP assays and request hs-CRP for cardiovascular risk prediction purpose.

Because the hs-CRP value of an individual patient is interpreted in the context of cutpoints established by prospective clinical studies, standardization of hs-CRP assays is crucial. Poor agreement among methods will lead to misclassification and mismanagement of patients. Recent reports have indicated that the measurement of low hs-CRP concentrations is not consistent among various methods, suggesting that standardization efforts are needed *(51, 56)*. In one case where a significant bias was noted between two methods *(51)*, the manufacturers of both reagent systems claimed to have their calibrators traceable to the WHO reference materials. Unfortunately, this is not an unusual occurrence. Although manufacturers attempt to standardize their assays using the WHO calibrators, they often fail to follow the appropriate value transfer protocol from the reference materials to their own calibrators *(57)*. Invariably, this leads to suboptimal standardization.

An in-house hs-CRP ELISA method *(52)*, utilizing polyclonal antibodies from Calbiochem, was used in MRFIT, the Cardiovascular Health Study, and the Rural Health Promotion Project as well as in the early work from the PHS. The analytical performance and clinical efficacy of the ELISA assay were compared with those of an automated and commercially available latex-enhanced method (Dade Behring) *(51)* used at present in several prospective studies, including the PHS, WHS, Women's Health Initiative, Nurses' Health Study, Health Profes-

sionals' Study, and Texas/Air Force Coronary Atherosclerosis Prevention Study *(58)*. The two assays were evaluated using plasma samples from the PVD cohort of the PHS in a nested case-control design. Excellent analytical agreement between the two methods was reported (slope = 0.99; intercept = 0.36 mg/L; $r = 0.95$) *(58)*. In addition, for both methods, the calculated RRs of developing future PVD increased significantly with each increasing quartile of hs-CRP. The calculated interquartile increase in RR of PVD was 31% (95% CI, 5.2–62.2) for the ELISA and 34% (95% CI, 8.2–66.1) for the latex-enhanced method. Furthermore, all but two participants were classified into concordant quartiles or varied by only one quartile. This study demonstrated comparable clinical efficacy of the two methods and linked the earlier and the current data, thus assuring consistency among reported hs-CRP values. On the basis on this report, the US Food and Drug Administration approved the use of this latex-enhanced method in the risk assessment of cardiovascular disease. Therefore, this latex-enhanced method is usually used as the reference procedure when comparison studies of various hs-CRP assays are conducted. At present, only a few hs-CRP methods are commercially available. However, several assays are currently under development or evaluation and are expected to be available for routine clinical use in the very near future.

CONCLUSION

hs-CRP is a very promising novel biochemical marker for the prediction of future first or recurrent coronary events. American and European prospective studies have been highly consistent regarding the ability of hs-CRP to predict future CHD risk in both men and women. Potential preventive therapeutic modalities to attenuate coronary risk in those with increased hs-CRP concentrations have been suggested. The potential use of hs-CRP as a means to improve the cost-to-benefit ratio in statin therapy is currently under investigation. Although standardization of hs-CRP measurement at the lower concentration range among various methods should be addressed, a robust and Food and Drug Administration-approved method is currently available. Several other sensitive assays are under development and are expected to be commercially available soon.

References

1. Libby P, Ridker PM. Novel inflammatory markers of coronary risk: theory versus practice [Editorial; comment]. Circulation 1999; 100:1148–50.
2. Ross R. Atherosclerosis—an inflammatory disease [see comments]. N Engl J Med 1999;340:115–26.
3. Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995;91:2844–50.
4. Cybulsky MI, Gimbrone MA Jr. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. Science 1991;251:788–91.
5. Navab M, Hama SY, Nguyen TB, Fogelman AM. Monocyte adhesion and transmigration in atherosclerosis. Coron Artery Dis 1994;5:198–204.
6. Nagel T, Resnick N, Atkinson WJ, Dewey CF Jr, Gimbrone MA Jr. Shear stress selectively upregulates intercellular adhesion molecule-1 expression in cultured human vascular endothelial cells. J Clin Invest 1994;94:885–91.
7. Nakashima Y, Raines EW, Plump AS, Breslow JL, Ross R. Upregulation of VCAM-1 and ICAM-1 at atherosclerosis-prone sites on the endothelium in the ApoE-deficient mouse. Arterioscler Thromb Vasc Biol 1998;18:842–51.
8. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 1994;90:775–8.
9. van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology [see comments]. Circulation 1994;89:36–44.
10. Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques [see comments]. Lancet 1989;2:941–4.
11. Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. Adv Immunol 1983;34:141–212.
12. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina [see comments]. N Engl J Med 1994;331:417–24.
13. Rus HG, Vlaicu R, Niculescu F. Interleukin-6 and interleukin-8 protein and gene expression in human arterial atherosclerotic wall. Atherosclerosis 1996;127:263–71.
14. Sukovich DA, Kauser K, Shirley FD, DelVecchio V, Halks-Miller M, Rubanyi GM. Expression of interleukin-6 in atherosclerotic lesions of male ApoE-knockout mice: inhibition by 17β-estradiol. Arterioscler Thromb Vasc Biol 1998;18:1498–505.
15. Maseri A. Inflammation, atherosclerosis, and ischemic events—exploring the hidden side of the moon [Editorial; comment]. N Engl J Med 1997;336:1014–6.
16. Biasucci LM, Liuzzo G, Grillo RL, Caligiuri G, Rebuzzi AG, Buffon A, et al. Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. Circulation 1999;99:855–60.
17. de Winter RJ, Bholasingh R, Lijmer JG, Koster RW, Gorgels JP, Schouten Y, et al. Independent prognostic value of C-reactive protein and troponin I in patients with unstable angina or non-Q-wave myocardial infarction. Cardiovasc Res 1999;42:240–5.
18. Ferreiros ER, Boissonnet CP, Pizarro R, Merletti PF, Corrado G, Cagide A, Bazzino OO. Independent prognostic value of elevated C-reactive protein in unstable angina. Circulation 1999;100: 1958–63.
19. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, Braunwald E. C-Reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. J Am Coll Cardiol 1998;31:1460–5.
20. 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 [see comments]. Lancet 1997;349:462–6.
21. Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, 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.
22. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. Am J Epidemiol 1996;144:537–47.
23. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men [published erratum appears in N Engl J Med; see comments]. 1997;336:973–9.
24. 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.
25. 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 [see comments]. Circulation 1998;98:731–3.
26. Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol 1997;17:1121–7.
27. Roivainen M, Viik-Kajander M, Palosuo T, Toivanen P, Leinonen M, Saikku P, et al. Infections, inflammation, and the risk of coronary heart disease. Circulation 2000;101:252–7.
28. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease [see comments]. Circulation 1998; 97:425–8.
29. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses [see comments]. BMJ 2000;321:199–204.
30. Mendall MA, Strachan DP, Butland BK, Ballam L, Morris J, Sweetnam PM, Elwood PC. C-Reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. Eur Heart J 2000;21:1584–90.
31. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, Braunwald E. Serum amyloid A predicts early mortality in acute coronary syndromes: A TIMI 11A substudy. J Am Coll Cardiol 2000;35:358–62.
32. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, 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.
33. Ridker PM, Hennekens CH, Rifai N, Buring JE, Manson JE. Hormone replacement therapy and increased plasma concentration of C-reactive protein. Circulation 1999;100:713–6.
34. Cushman M, Legault C, Barrett-Connor E, Stefanick ML, Kessler C, Judd HL, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. Circulation 1999; 100:717–22.
35. 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 [see comments]. Circulation 1998;97:2007–11.
36. 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.
37. Rifai N, Ridker PM. Proposed cardiovascular risk assessment algorithm using high-sensitivity C-reactive protein and lipid screening [Opinion]. Clin Chem 2001;47:28–30.
38. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators [see comments]. N Engl J Med 1996;335:1001–9.
39. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults [see comments]. JAMA 1999;282:2131–5.
40. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-Reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999;19:972–8.
41. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH, Buring JE. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000;101:1767–72.
42. Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men [see comments]. Lancet 1998;351:88–92.
43. Ford ES. Body mass index, diabetes, and C-reactive protein among U.S. adults [see comments]. Diabetes Care 1999;22: 1971–7.
44. Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102:42–7.
45. Liu Y, Liu T, McCarron RM, Spatz M, Feuerstein G, Hallenbeck JM, Siren AL. Evidence for activation of endothelium and monocytes in hypertensive rats. Am J Physiol 1996;270:H2125–31.
46. McCarron RM, Wang L, Siren AL, Spatz M, Hallenbeck JM. Monocyte adhesion to cerebromicrovascular endothelial cells derived from hypertensive and normotensive rats. Am J Physiol 1994;267:H2491–7.
47. Manson JE, Hu FB, Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. N Engl J Med 1999;341:650–8.
48. Smith JK, Dykes R, Douglas JE, Krishnaswamy G, Berk S. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. JAMA 1999;281:1722–7.
49. 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.
50. Wilkins J, Gallimore JR, Moore EG, Pepys MB. Rapid automated high sensitivity enzyme immunoassay of C-reactive protein. Clin Chem 1998;44:1358–61.
51. Ledue TB, Weiner DL, Sipe JD, Poulin SE, Collins MF, Rifai N. Analytical evaluation of particle-enhanced immunonephelometric assays for C-reactive protein, serum amyloid A and mannose-binding protein in human serum. Ann Clin Biochem 1998;35:745–53.
52. Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. Clin Chem 1997;43: 52–8.
53. Kapyaho K, Welin MG, Tanner P, Karkkainen T, Weber T. Rapid determination of C-reactive protein by enzyme immunoassay using two monoclonal antibodies. Scand J Clin Lab Invest 1989;49: 389–93.
54. Eda S, Kaufmann J, Molwitz M, Vorberg E. A new method of

measuring C-reactive protein, with a low limit of detection, suitable for risk assessment of coronary heart disease. Scand J Clin Lab Invest Suppl 1999;230:32–5.

55. Borque L, Bellod L, Rus A, Seco ML, Galisteo-Gonzalez F. Development and validation of an automated and ultrasensitive immunoturbidimetric assay for C-reactive protein. Clin Chem 2000;46: 1839–42.

56. Roberts WL, Sedrick R, Moulton L, Spencer A, Rifai N. Evaluation of four automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Clin Chem 2000;46:461–8.

57. Johnson A, Sampson E, Blirup-Jensen S, Scvendsen P. Recommendations for the selection and use of protocols for assignment of values to reference materials. Eur J Clin Chem Clin Biochem 1996;34:279–85.

58. Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. Clin Chem 1999;45: 2136–41.