The Centers for Disease Control and Prevention/American Heart Association (CDC/AHA) Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice was convened on March 14 and 15, 2002, in Atlanta, Ga, to examine the selection and use of inflammatory markers to predict cardiovascular disease (CVD) risk. Three discussion groups on issues related to laboratory, clinical, and population science were organized. The present report contains a summary of the discussions and recommendations of the clinical practice discussion group.

**Recommendations for Clinical Practice**

1. High-sensitivity C-reactive protein (hsCRP) is an independent marker of risk that may be used at the discretion of the physician in patients judged by global risk assessment to be at intermediate risk (10% to 20% risk of coronary heart disease [CHD] per 10 years) for cardiovascular disease (CVD). hsCRP may help direct further evaluation and therapy in the primary prevention of CVD. The benefits of such therapy based on this strategy remain uncertain. (Class IIa, Level of Evidence: B)

2. hsCRP is an independent marker of risk and may be used at the discretion of the physician as part of a global coronary risk assessment in adults without known CVD. The benefits of this strategy remain uncertain. (Class IIb, Level of Evidence: C)

3. hsCRP levels may be useful in motivating patients to improve their lifestyle behaviors. The benefits of this strategy remain uncertain. (Class IIb, Level of Evidence: C)

4. Patients with persistently unexplained marked elevation of hsCRP (>10 mg/L) after repeated testing should be evaluated for noncardiovascular causes. (Class IIa, Level of Evidence: B)

5. Inflammatory markers (cytokines, other acute-phase reactants) other than hsCRP should not be measured for the determination of coronary risk. (Class III, Level of Evidence: C)

6. hsCRP measurement in patients with stable coronary disease or acute coronary syndromes (ACS) may be useful as an independent marker of prognosis for recurrent events, including death, myocardial infarction, and restenosis after percutaneous coronary intervention (PCI). The benefits of therapy based on this strategy remain uncertain. (Class IIa, Level of Evidence: B)

7. Application of secondary prevention measures should not depend on hsCRP determination. (Class III, Level of Evidence: A)

8. Application of management guidelines for ACS should not depend on hsCRP levels. (Class III, Level of Evidence: A)

9. Serial testing of hsCRP should not be used to monitor the effects of treatment. (Class III, Level of Evidence: C)

**Recommendations for Research**

1. Research should be conducted to determine the effect on cardiovascular outcomes when hsCRP measurements are used to define further the LDL threshold for initiating lipid-lowering therapy.

2. Multiple randomized clinical trials should be conducted to provide evidence on the outcomes associated with the use of hsCRP to guide the short- and long-term man-
agreement of ACS (eg, application of PCI, choice and duration of drug treatment).

3. Randomized clinical trials are needed to investigate the value of hsCRP in improving adherence to lifestyle modification and pharmacotherapies for primary and secondary prevention of CVD.

4. Further research is recommended to determine whether increased hsCRP in women on hormone replacement therapy conveys increased cardiovascular risk.

5. Clinical research is needed to determine whether long-term use of acetylsalicylic acid (or other drugs) at the time of hsCRP measurement confounds its predictive value.

**Discussion**

The Clinical Science Discussion Group focused on questions about the use of inflammatory markers to predict risk and guide therapy among patients with clinical and subclinical atherosclerotic vascular disease. At the outset of these discussions, 2 points were recognized. First, on the basis of the recommendation of the Laboratory Science Discussion Group at this conference, of the current inflammatory markers identified, hsCRP has the analyte and assay characteristics that are the most conducive for use in practice, although a variety of serum or plasma markers may be used to measure inflammation. Therefore, the deliberations and recommendations of the present discussion group were restricted to the use of hsCRP in clinical practice. It was recognized that other candidate markers such as fibrinogen may prove useful for clinical application if issues surrounding reliable assays and standardization can be resolved. Ultimately, the recommendations set forth in this report with regard to hsCRP may be extended to other markers of inflammation if certain issues about their clinical use can be resolved.

Second, although the present discussion group focused on questions relating to treatment strategies in clinical settings with patients, the immense population burden of atherosclerosis is such that recommendations about the use of inflammatory markers in patients without clinical evidence of CHD could have a broad impact on its prevalence and incidence. Therefore, our recommendations overlap with those of the Population Science Discussion Group with regard to the use of inflammatory markers as a strategy to direct therapy for the primary prevention of CVD.

The initial discussions of the present discussion group focused on the use of hsCRP as a strategy to guide therapy for the primary prevention of CVD. Central to these deliberations were the observations from key findings and recommendations of the American Heart Association (AHA) Prevention V conference,¹ which emphasized that as a first approximation of global risk is the essential first step in the process of selecting patients for further intervention or additional diagnostic tests. The determination of global risk is accomplished via a multifactorial statistical model such as that from the Framingham Heart Study, wherein established risk factors such as age, sex, smoking history, blood pressure, total serum cholesterol, HDL cholesterol (HDL-C), and family history are used to calculate the 10-year risk of a coronary event.² This strategy endorsed in the AHA Prevention V conference report is recommended as the important initial step in cardiovascular risk assessment by the Adult Treatment Panel III of the National Cholesterol Education Program (ATP III).³ Greenland et al⁴ have recommended that further use of noninvasive testing might be used, if additive, to modify treatment strategies, especially for those patients determined to be at moderate risk (ie, >20% events during a 10-year period by the ATP III–recommended global risk scoring system). The central question for the present discussion group was whether the addition of hsCRP testing after evaluating global risk might change the category of risk such that the recommended therapy would be assigned to a different target level (eg, the LDL cholesterol [LDL-C] target might change from 130 mg/dL to 100 mg/dL on the basis of an elevated hsCRP level).

Early prospective epidemiological studies have documented a relationship between inflammatory markers and CVD. The present discussion group reviewed evidence accumulated from meta-analysis of prospective population-based studies that compared people in the lower tertile of hsCRP with those in the upper tertile.⁵ ⁶ The studies were consistent in their finding with an increase in relative odds of 2.0 (95% CI 1.6 to 2.5) for major coronary events observed between the upper tertile and the lowest tertile used as a reference. Broad representation for sex and age was present in these studies for men,⁷ ⁸ women,⁹ ¹⁰ and older adults.¹¹ ¹³ Similar results may be found in most large studies including MONICA (MONitoring trends and determinants in CArdiovascular disease) Augsburg Center in Germany,¹⁴ the Atherosclerosis Risk in Communities Study,¹⁵ the Women’s Health Study,¹⁶ the Honolulu Heart Study,¹⁷ and the National Health And Nutrition Examination Survey (NHANES) studies.¹⁸ ¹⁹ In general, a consistent concentration-dependent relationship has been reported between the level of hsCRP and the risk of incident CHD. Similarly, an association between the incidence of sudden death²⁰ ²¹ and peripheral arterial disease²² has been suggested. Some studies have reported lower strength in the associated risk. Importantly, with the exception of the Japanese American men in the Honolulu Heart Study, these studies depend on data derived from white North American or European populations.¹⁷ ²³ More information is needed for individuals of African, South Asian, and Native American descent, who may be at higher risk for CVD, as well as for other racial/ethnic groups. In one study, race and ethnicity did not appear to modify the association between hsCRP and stroke.²⁴

The present discussion group was especially interested in the ability of hsCRP to add to the predictive capacity of other established risk factors. In several studies in which this has been examined via stratification or multivariable statistical adjustment for age, total cholesterol, HDL-C, smoking, body mass index, diabetes, history of hypertension, exercise level, and family history of coronary disease, hsCRP has retained an independent association with incident coronary events.¹⁶ ²⁴ ²⁵ Because of the emphasis on the global risk determination as advocated by ATP III, the discussion group felt strongly that it was essential for hsCRP or any new inflammatory marker to demonstrate additive value when compared with the predictive value of the Framingham risk model rather than...
place the emphasis on comparison to a single variable, such as LDL-C.

Importantly, the discussion group stressed recent data that demonstrated the capability of elevated hsCRP to predict coronary events in women after adjusting for risk factors used in the Framingham risk score, as well as similar observations in older adults, with extensive adjustment for CVD risk factors and measures of subclinical atherosclerosis. It was noted that relatively few studies have adjusted for body mass index or for evidence of diabetes or glucose metabolism and also that hsCRP has not provided reliable predictions of the extent of angiographically defined atherosclerosis. It was concluded, therefore, that a major role for hsCRP was to be found in the assessment of risk as an additive element to the Framingham risk assessment, and through this process, the identification of patients for more aggressive risk-reduction targets such as goals for LDL-C lowering. Because of the evidence suggesting that an increased hsCRP will elevate an intermediate risk (10% to 20% risk of CHD per 10 years) to a high risk (>20% risk of CHD per 10 years), the discussion group recommends (Class IIa) that hsCRP be measured in intermediate-risk patients to direct further evaluation and therapy in the primary prevention of CVD. At the same time, it is recognized that the benefits of such therapy based on this strategy remain uncertain. The use of hsCRP as part of the global risk assessment for patients without known CVD was recommended (Class IIb) to be used at the discretion of the physician. Again, no prospective randomized clinical evidence is available to confirm the clinical benefits of such a strategy. The discussion group felt that in both instances, the presence of an elevated hsCRP might serve to motivate patients to adhere better to preventive therapies (Class IIb); however, evidence from prospective randomized clinical trials to support this intuitive recommendation is not available. Retrospective subset analyses for statin therapy in the Cholesterol and Recurrent Events (CARE) trial and aspirin in the Physicians Health Study suggest that those with elevated hsCRP levels have a larger absolute risk reduction after treatment than do those in the placebo group. The discussion group recommended that prospective randomized clinical research studies be conducted to establish the benefits of hsCRP measurement on clinical outcomes. It was further recommended (Class IIa) that patients with persistently unexplained marked elevation of hsCRP (>10 mg/L) after repeated testing should be evaluated for noncardiovascular causes such as infection or inflammation.

The present discussion group considered the results of several studies that examined the use of hsCRP as a predictor of recurrent CVD events and death in patients with known CHD presenting with ACS, coronary revascularization procedures, or both. Transient increases in inflammatory markers have been consistently observed in unstable angina patients when compared with stable angina patients. These clinical studies support the pivotal involvement of inflammation and inflammatory mediators, including CRP, in the vulnerable plaque. It was emphasized that among patients with ACS, the levels during the acute phase are higher, with hsCRP >10 mg/L having better predictive value. Among patients with ACS, elevated hsCRP predicts recurrent myocardial infarction in a manner that is independent of troponin levels or other biomarkers. Other studies have suggested that hsCRP predicts restenosis after PCI as well as prognosis and recurrent events after stroke and peripheral artery disease. Thus, it was recommended (Class IIa) that hsCRP might be measured among patients with known CHD to define those who might receive greater clinical benefit from aggressive risk-reduction strategies. These included patients with ACS as well as those undergoing PCI. These observations notwithstanding, it was strongly emphasized by the discussion group that the application of secondary prevention measures should not depend on hsCRP (Class III), the early management of patients with ACS should not be driven by hsCRP, and the hsCRP results should not be used to monitor treatment because of significant variation in value, independent of treatment modality.

With regard to recommendations for further research, the present discussion group especially emphasized the need for randomized trials of statins, aspirin, and other preventive therapies to determine their effect in reducing cardiovascular events among patients with higher risk scores or those with clinical events such as ACS. The working group discussed the lack of evidence that serial measurement of hsCRP will reflect the effectiveness of medical therapies. Whereas it was understood by the discussion group that many physicians now use hsCRP to establish the risk of CVD, it was strongly emphasized that available evidence does not support the use of hsCRP as a guide for the treatment of acute coronary syndrome.

References


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