AHA/CDC Scientific Statement

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

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I. Introduction

In 1998, the American Heart Association convened Prevention Conference V to examine strategies for the identification of high-risk patients who need primary prevention. Among the strategies discussed was the measurement of markers of inflammation.[1] The Conference concluded that "many of these markers (including inflammatory markers) are not yet considered applicable for routine risk assessment because of: (1) lack of measurement standardization, (2) lack of consistency in epidemiological findings from prospective studies with endpoints, and (3) lack of evidence that the novel marker adds to risk prediction over and above that already achievable through the use of established risk factors." The National Cholesterol Education Program Adult Treatment Panel III Guidelines identified these markers as emerging risk factors,[1a] which could be used as an optional risk factor measurement to adjust estimates of absolute risk obtained using standard risk factors. Since these publications, a large number of peer-reviewed scientific reports have been published relating inflammatory markers to cardiovascular disease (CVD). Several commercial assays for inflammatory markers have become available. As a consequence of the expanding research base and availability of assays, the number of inflammatory marker tests ordered by clinicians for CVD risk prediction has grown rapidly. Despite this, there has been no consensus from professional societies or governmental agencies as to how these assays of markers of inflammation should be used in clinical practice.

On March 14 and 15, 2002, a workshop titled "CDC/AHA Workshop on Inflammatory Markers and Cardiovascular Disease: Applications to Clinical and Public Health Practice" was convened in Atlanta, Ga, to address these issues. The goals of this workshop were to determine which of the currently available tests should be used; what results should be used to define high risk; which patients should be tested; and the indications for which the tests would be most useful. These determinations should assist the clinician in selecting tests judiciously and appropriately and should assist healthcare payers in making decisions about the support of such tests in clinical practice.

To achieve this goal, the workshop set down five objectives:

(1) To review the scientific evidence from diverse sources to examine the association between several inflammatory markers (high-sensitivity C-reactive protein [hs-CRP], serum amyloid A [SAA], white blood cell [WBC] count, fibrinogen, etc) and CVDs, including the strength, consistency, independence, and generalizability of the data.

(2) To consider the clinical chemistry and various assays of inflammatory markers, to identify which may be the best assays to use in identifying persons at risk.

(3) To identify areas in which questions persist in order to foster additional research on inflammatory markers and CVD.

(4) To recommend which tests should be performed for which patients and in which clinical settings, for the purpose of risk stratification, therapeutic monitoring, and other clinical applications, on the basis of the scientific evidence.

(5) To explore the public health implications of an association between inflammatory markers and CVD.

This conference was jointly sponsored by the Centers for Disease Control and Prevention and the American Heart Association. Specifically, the National Center for Chronic

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Disease Prevention and Health Promotion and the National Center for Environmental Health provided financial and organizational support. The American Heart Association, its Expert Panel on Population and Prevention Science, and its Councils on Atherosclerosis, Thrombosis, and Vascular Biology; Clinical Cardiology; and Epidemiology and Prevention coordinated the workshop, with support from unrestricted educational grants from industry sponsors (see Acknowledgments). The writing group, endorsed by the Science Advisory and Coordinating Committee of the American Heart Association, included representation from the above-mentioned agencies and organizations, as well as the American Association for Clinical Chemistry and the American College of Cardiology.

The workshop consisted of 1½ days of presentations and discussions of topics relevant to inflammatory markers and CVD. The first half of the workshop consisted of state-of-the-art lectures by recognized authorities in the field. The second half consisted of three concurrent discussion groups on the issues related to laboratory science, clinical science, and population science. The recommendations of this workshop are derived from these discussion groups. The invited lectures and discussion group findings will be published in a separate document. A complete list of participants, organized by discussion group, is listed at the end of this publication (Appendix 1).

This document uses the major findings and conclusions of the Workshop to develop a statement that has been fully reviewed and approved by The Science Advisory and Coordinating Committee of AHA and the CDC. It crafts a statement that considers the best available evidence for an association between inflammatory markers and CVD. In this consideration, the US Surgeon General's criteria for inference of causality were used in examination of the evidence—namely, the strength, temporality, dose-response relationship, biological plausibility, and consistency of the evidence were reviewed.[1b] The quality of scientific evidence for an association was assessed,[2] and the American College of Cardiology/American Heart Association classification of recommendations and levels of evidence were used (see Appendix 2). Moreover, consideration of recommendations for the use of inflammatory markers as screening tools also employed an evidence-based approach.[3] This included evidence from properly designed, randomized trials that intervention in screening-positive persons benefited the patients, and it included consideration of the potential benefits, harm, differences in performance between different groups of people, use in various screening strategies, and cost-effectiveness.

II. Evidence for Inflammation as a Key Pathogenetic Mechanism in Atherosclerosis

A role for inflammation has become well established over the past decade or more in theories describing the atherosclerotic disease process.[4,5] From a pathological viewpoint, all stages, ie, initiation, growth, and complication of the atherosclerotic plaque,[6,7] might be considered to be an inflammatory response to injury. The major injurious factors that promote atherogenesis—cigarette smoking, hypertension, atherogenic lipoproteins, and hyperglycemia—are well established. These

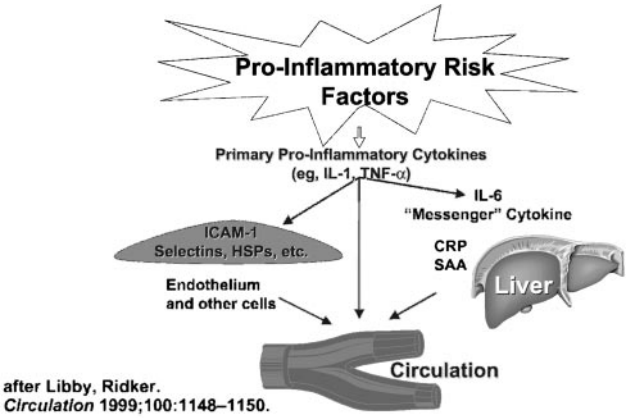

Figure 1. The inflammatory cascade. IL indicates interleukin; ICAM, intercellular adhesion molecule; and HSP, heat shock protein.

risk factors give rise to a variety of noxious stimuli that elicit secretion of both leukocyte soluble adhesion molecules, which facilitate the attachment of monocytes to endothelial cells, and chemotactic factors, which encourage the monocytes' migration into the subintimal space. The transformation of monocytes into macrophages and the uptake of cholesterol lipoproteins are thought to initiate the fatty streak. Further injurious stimuli may continue the attraction and accumulation of macrophages, mast cells, and activated T cells within the growing atherosclerotic lesion. Oxidized low-density lipoproteins may be one of several factors that contribute to loss of smooth muscle cells through apoptosis in the atherosclerotic plaque cap, and secretion of metalloproteinases and other connective tissue enzymes by activated macrophages may break down collagen, weakening the cap and making it prone to rupture. This disruption of the atherosclerotic plaque then exposes the atheronecrotic core to arterial blood, which induces thrombosis. Thus, virtually every step in atherogenesis is believed to involve cytokines, other bioactive molecules, and cells that are characteristic of inflammation.

These pathophysiological insights provide potential targets for measurement as a means to identify and monitor the ongoing inflammatory process (Figure 1). Potential targets for measurement include proinflammatory risk factors such as oxidized low-density lipoproteins, proinflammatory cytokines (eg, interleukin-1, tumor necrosis factor-α), adhesion molecules (eg, intercellular adhesion molecule-1, selectins), inflammatory stimuli with hepatic effects (eg, interleukin-6) or the products of the hepatic stimulation, such as SAA, C-reactive protein (CRP), and a host of other acute-phase reactants. Finally, other indicators of cellular responses to inflammation, such as elevated leukocyte count, might be evaluated. It should be pointed out that this inflammatory cascade may have sources other than an atherosclerotic coronary artery, including atherosclerosis in other arteries, as well as systemic inflammation (eg, connective tissue diseases) and local infections (eg, gingivitis, prostatitis, bronchitis, urinary tract infections, gastric inflammation). These systemic inflammations may result in elevated levels of inflammatory markers that may be incorrectly attributed to

TABLE 1. Inflammatory Markers for Consideration as Predictors of Cardiovascular Risk

Adhesion molecules
Cytokines
Acute-phase reactants
Fibrinogen
SAA
CRP
WBC count
Other (eg, erythrocyte sedimentation rate)

atherosclerotic CVD. Nonetheless, increasing recognition of the inflammatory component of atherogenesis provides the biological plausibility for the *potential* use of inflammatory markers as indicators of atherogenesis or as predictors of atherosclerotic complications.

III. Characteristics Desirable in a CVD Risk Predictor

Understanding of the inflammatory cascade in Figure 1 allows the consideration of a number of inflammatory markers as *potentially* useful predictors of prevalent or incident CVD (Table 1). Such markers, however, may not be useful in the clinical arena unless they possess additional characteristics.[8] These include: (1) the ability to standardize the assay and to control the variability of the measurement; (2) independence from established risk factors; (3) association with CVD clinical end points in observational studies and clinical trials; (4) the presence of population norms to guide interpretation of results; (5) ability to improve the overall prediction beyond that of traditional risk factors; (6) generalization of results to various population groups; and (7) acceptable cost of the assays. The use of the marker is also affected by the type of relationship with CVD (eg, linear, nonlinear, dichotomous). These characteristics then can be examined in the inflammatory markers currently under consideration.

Several features of the relationship between inflammatory markers and CVD end points should be taken into account. First, is the assayed substance a risk factor or a risk marker (Figure 2)? In other words, does the analyte measure a step in the causal pathway leading to atherosclerosis or the disease process itself? Next, which CVD end points are being considered? Inflammatory markers may relate differently to prevalent atherosclerotic disease than to acute or chronic syndromes in the coronary, cerebral, or peripheral arterial beds. Third, does the ability of the marker to predict CVD end points differ over the timeframe of the events, ie, short term versus long term? Fourth, does measurement of the marker indicate efficacy of therapy or changing prognosis? Finally, is the use of the test cost-effective? Namely, can the incremental cost of the test be justified by reductions in other costs or improvements in outcomes? Conversely, are there indirect costs of a positive test that are prohibitive?

IV. Laboratory Tests Available to Assess Inflammation

A sizable number of studies have examined the inflammation–CVD association through measurement of a variety of

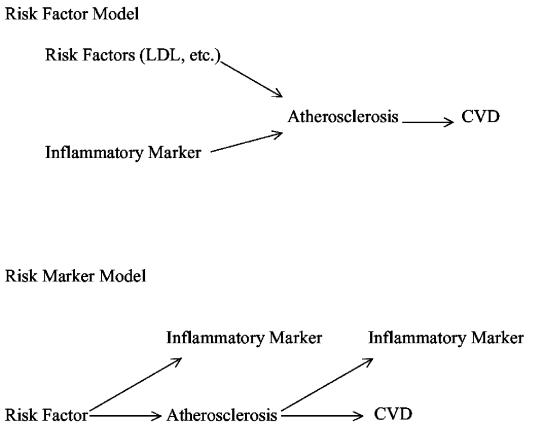

Figure 2. Alternative models for the role of inflammatory markers in CVD: risk factor or risk marker?

analytes. Only some of these assays, however, are currently employable in clinical settings, after consideration of the stability of the analyte, the commercial availability of assays, the standardization of those assays to allow comparison of results, and the precision of the assays as measured by the coefficient of variation. Table 2 summarizes the currently available assays for inflammatory markers. Several markers are only stable when frozen, which limits their use to research settings. Likewise, only the acute-phase reactants (fibrinogen and CRP) and WBC count have widely available assays. CRP has a proficiency-testing program from the College of American Pathologists. A program to standardize CRP testing is underway at the Centers for Disease Control and Prevention. Most of the acute-phase reactant assays have acceptable coefficients of variation.

These comparisons of the various inflammatory markers favor CRP from the clinical chemistry perspective. It needs to be emphasized that the assays considered in Table 2 were for hs-CRP with acceptable precisions down to or below 0.3 mg/L. It is within these lower, previously "normal" ranges that the hs-CRP levels seem to have predictive abilities for CVD events. Although new assays of other inflammatory markers, with precision, standardization, and other characteristics that are superior to those of the current assays, may become available, the hs-CRP assay represents the best candidate at this time.

V. Evidence for Association of Inflammatory Markers With CVD: Clinical and Epidemiological Studies

A. Prediction of Incident CVD Events: Primary Prevention

Several older prospective epidemiological studies have documented an association between inflammatory markers such as WBC count and fibrinogen[9–11] and CVD. In general, these analyses have shown gradation of risk across the measured ranges. Multivariate adjustment for other risk factors did not remove the association between CVD incidence and WBC count or fibrinogen. These data, along with newer studies of hs-CRP and SAA, regardless of their utility in current clinical

TABLE 2. Assays of Inflammatory Markers for Potential Clinical Use*

Analyte	Stability	Assay Availability	World Health Organization Standards Available?†	Interassay Precision
Soluble adhesion molecules (eg, E-selectin, P-selectin, intracellular adhesion molecule-1, vascular cell adhesion molecule-1)	Unstable (unless frozen)	Limited	No	CV<15%
Cytokines (eg, interleukin-1β, -6, -8, and -10 and tumor necrosis factor-α)	Unstable (unless frozen)	Few	Yes (Reference 1)	CV<15%
Acute-phase reactants				
Fibrinogen	Unstable‡ (unless frozen)	Many	Yes§ (Reference 2)	CV<8%
SAA	Stable	One	Yes (Reference 3)	CV<9%
hs-CRP	Stable	Many	Yes (Reference 4)	CV<10%
WBC count	Stable	Many	Yes	CV<3%

*Courtesy of William Roberts, MD, PhD. CV indicates coefficient of variation.

†Information on specific standards is available at the following World Health Organization web site: http://www.who.int.biologicals.

‡In correctly anticoagulated blood, stable for at least 12 hours on ice or several hours at room temperature.

§World Health Organization standard available only for mass assay, not for functional assays most commonly in use.

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practice, add consistency to the inflammatory marker–CVD association.

Newer analyses have examined analytes such as hs-CRP, SAA, and other acute-phase reactants or cytokines. Many of the newer studies did not measure these factors in all patients but rather performed nested case-control studies. This study design is valid in terms of estimation of relative risk and temporality of the level of marker predating the CVD events, and often uses strict matching criteria to limit confounding. However, it does not allow incidence of clinical CVD events to be measured in various strata. Rather, relative odds estimate relative risks across various strata of inflammatory markers. A similar number of large prospective studies corroborate the findings of the nested case-control studies, however.[12–23]

A meta-analysis of prospective population-based studies has compared persons in the lower tertile of hs-CRP with those in the upper tertile.[15,16] With a good consistency between studies, a relative odds of 2.0 (95% CI 1.6–2.5) for major coronary events was observed for the upper tertile with the lowest tertile used as a reference. These prospective studies include men,[17,18] women,[19,20] and the elderly.[21–23] Large population-based studies such as the study from the MONICA (MONItoring trends and determinants in CArdiovascular disease) Augsberg Center in Germany,[12] the Atherosclerosis Risk in Communities Study,[24] the Women's Health Study,[13] the Honolulu Heart Study,[14] and the NHANES (National Health And Nutrition Examination Survey) studies (cross-sectional[25,26]) are also represented. In general, most studies show a dose-response relationship between the level of hs-CRP and risk of incident coronary disease. Recent studies also suggest association with incidence of sudden death[27,28] and peripheral arterial disease.[29] The strength of the association, however, has been modest in some studies.[24–26] It should be noted that studies of other, newer inflammatory markers such as interleukin-6 and SAA show similar results.[20,30] A notable characteristic of all these studies is their limitation to white North American or European populations, with the exception of Japanese-American men in the Honolulu Heart Study.[14,31] Data are limited for persons of African, South Asian, or Native American descent, who may be at particularly high risk for CVD, and for other racial/ethnic groups. Race and ethnicity did not appear to be an effect modifier of the hs-CRP–stroke association in one study.[25]

The ability of hs-CRP to add to the predictive capacity of other, established risk factors has been examined in several studies. Through stratification or multivariable statistical adjustment, hs-CRP retains an independent association with incident coronary events after adjusting for age, total cholesterol, HDL cholesterol, smoking, body mass index, diabetes, history of hypertension, exercise level, and family history of coronary disease.[13,32,33] In some studies, the magnitude of the relative risk in the upper percentiles of hs-CRP is attenuated after this adjustment, including loss of statistical significance.[34] Recent studies demonstrate the capability of elevated hs-CRP to predict coronary events in women after adjusting for risk factors used in the Framingham risk score,[13] and in the elderly with extensive adjustment for CVD risk factors and measures of subclinical atherosclerosis.[21] Relatively few studies have adjusted for body mass index or for measures of diabetes or glucose metabolism.

Inflammatory markers such as hs-CRP have not been good predictors of the extent of atherosclerotic disease, showing poor correlations with results of tests that quantify the extent

of atherosclerosis, such as Doppler ultrasound scans of carotid arteries[35] and electron beam computerized tomography for coronary calcium.[36,37] Nonetheless, some studies suggest a positive correlation,[38–41] and more research is required to fully define the relationship between inflammatory markers and atherosclerotic mass. Inflammatory markers may measure other characteristics than atherosclerotic mass. These characteristics may include the activity of lymphocyte and macrophage populations within plaque or the degree of plaque destabilization and ongoing ulceration or thrombosis.

B. Prediction of Recurrent CVD Events and Death: Secondary Prevention

A growing number of studies have examined inflammatory markers as predictors of recurrent CVD and death in different settings, including the short-term risk, long-term risk, and risk after revascularization procedures such as percutaneous coronary intervention (PCI), including the risk of restenosis. Although several markers have been studied, the strongest association with prognosis has been with fibrinogen and hs-CRP. hs-CRP consistently predicts new coronary events in patients with unstable angina and acute myocardial infarction.[42–51] Most of these studies have been long term, but some in-hospital survivorship studies[52–54] have also shown an association.

For patients with acute coronary syndromes, cutpoints for elevated hs-CRP different than those for prediction in asymptomatic patients may be useful. For example, a level of >10 mg/L in acute coronary syndromes may have better predictive qualities, whereas a level of >3 mg/L may be more useful in patients with stable coronary disease.

Many analyses have adjusted for other prognostic factors, demonstrating continued predictive capacity with hs-CRP. In acute coronary syndromes, hs-CRP predicts recurrent myocardial infarction independent of troponins, which suggests it is not merely a marker for the extent of myocardial damage.[52–54] Recent data also suggest that hs-CRP may be a marker for risk of restenosis after PCIs,[55,56] but all studies are not in agreement with these results.[57] Elevated hs-CRP levels also seem to predict prognosis and recurrent events in patients with stroke[58,59] and peripheral arterial disease.[60] These data suggest that hs-CRP may have a role in risk stratification of patients with established CVD, although more data are needed that compare the prognostic value of elevated levels of hs-CRP with other prognostic measures currently in use.

C. Sources of Variability of Inflammatory Markers

Generally, the precision and reproducibility of inflammatory marker assays such as the acute-phase reactants have been acceptable (Table 2). For example, the coefficient of variation of hs-CRP assays is generally <10% from the 0.3- to 10-mg/L range.[61] Considerable within-individual variability exists, however, for both hs-CRP and fibrinogen.[62,63] In general, although CRP is an acute-phase reactant and as such has higher within-subject variability than an established risk factor such as serum cholesterol, it also has a broader distribution in the population. The final result is that, in a manner similar to cholesterol, two separate measurements of hs-CRP are adequate to classify a person's risk level and to account for the increased within-individual variablility.[63,64] The distribution of the logarithm of hs-CRP level is a normal distribution, and the nontransformed values are skewed toward the higher values, with most populations showing >95% of subjects with hs-CRP values of <10 mg/L. There seems to be population-to-population consistency in this, though as previously stated, data for racial and ethnic populations are limited (eg, NHANES III).

TABLE 3. Patient Characteristics and Conditions Associated With Increased or Decreased Levels of hs-CRP

Increased Levels	Decreased Levels
Elevated blood pressure	
Elevated body mass index	Moderate alcohol consumption
Cigarette smoking	Increased activity/endurance exercise
Metabolic syndrome/diabetes mellitus	Weight loss
Low HDL/high triglycerides	Medications
Estrogen/progestogen hormone use	Statins
Chronic infections (gingivitis, bronchitis)	Fibrates
Chronic inflammation (rheumatoid arthritis)	Niacin

Sources of variation of inflammatory markers have been studied to varying degrees.[62–64] There seems to be little seasonal or diurnal variation with hs-CRP.[65] Several factors have been identified as being associated with increased or decreased levels of hs-CRP (Table 3); this list is likely incomplete. For example, body weight and the metabolic syndrome are consistently associated with elevated hs-CRP, and weight loss is associated with reduction in hs-CRP levels, with some authors suggesting that hs-CRP is merely a marker for obesity and insulin resistance.[66–74] This association of hs-CRP with these conditions is poorly defined from a mechanism standpoint, and is possibly due to coassociation with prevalent vascular disease. Individuals with evidence of active infection, systemic inflammatory processes, or trauma should not be tested until these conditions have abated. An hs-CRP level of >10 mg/L, for example, should be discarded and repeated in 2 weeks to allow acute inflammations to subside before retesting.

D. Studies of Use of Inflammatory Markers in Clinical Practice

Despite the ability of some inflammatory markers to predict incident or recurring events, various analyte characteristics and within-individual variation seem to limit the analytes to hs-CRP and possibly fibrinogen. The specific clinical settings in which hs-CRP or other factors would be most useful, however, need to be defined by careful clinical investigations, including clinical trials. As noted, the levels of inflammatory markers do not seem to correlate well with extent of angiographically defined atherosclerosis,[51] and therefore seem to be of little value in selection of patients for coronary artery procedures. Inflammatory markers may have greater potential as a means to augment risk assessment in the identification of persons who should be considered for lipid-lowering, antiplatelet, or other cardioprotective drug therapies, as well as

TABLE 4. Recommendations for Clinical and Public Health Practice

	Procedure Should Be Performed (Class I)	Conflicting Evidence/Opinion: Weight in Favor of Usefulness/Efficacy (Class IIa)	Conflicting Evidence/Opinion: Usefulness/Efficacy Less Well Established (Class IIb)	Procedure Should Not Be Performed (Class III)
Population Science				1. The entire adult population should not be screened for hs-CRP for purposes of cardiovascular risk assessment. (Class III, Level of Evidence C)
Clinical Practice				
		1. Measurement of hs-CRP is an independent marker of risk and, in those judged at intermediate risk by global risk assessment (10 to 20% risk of CHD per 10 years), at the discretion of the physician, 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. Measurement of hs-CRP 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. hs-CRP levels may be useful in motivating patients to improve lifestyle behaviors. The benefits of this strategy remain uncertain. (Class IIb, Level of Evidence C)	
		4. Patients with persistently unexplained, marked elevation of hs-CRP (>10mg/L) after repeated testing should be evaluated for noncardiovascular etiologies. (Class IIa, Level of Evidence B)		
				5. Other inflammatory markers (cytokines, other acute-phase reactants) should not be measured for the determination of coronary risk in addition to hs-CRP. (Class III, Level of Evidence C)
		6. In patients with stable coronary disease or acute coronary syndromes, hs-CRP measurement may be useful as an independent marker of prognosis for recurrent events, including death, MI, and restenosis after PCI. The benefits of therapy based on this strategy remain uncertain. (Class IIa, Level of Evidence B)		

TABLE 4. Continued

	Procedure Should Be Performed (Class I)	Conflicting Evidence/Opinion: Weight in Favor of Usefulness/Efficacy (Class IIa)	Conflicting Evidence/Opinion: Usefulness/Efficacy Less Well Established (Class IIb)	Procedure Should Not Be Performed (Class III)
				7. Application of secondary prevention measures should not depend on hs-CRP determination. (Class III, Level of Evidence A) 8. Application of management guidelines for acute coronary syndromes should not be dependent on hs-CRP levels. (Class III, Level of Evidence A) 9. Serial testing of hs-CRP should not be used to monitor effects of treatment. (Class III, Level of Evidence C)
Laboratory Testing				
		1. Of current inflammatory markers identified, hs-CRP has the analyte and assay characteristics most conducive to use in practice. (Class IIa, Level of Evidence B) 2. Measurement of markers should be done twice (averaging results), optimally two weeks apart, fasting or nonfasting in metabolically stable patients. If hs-CRP level is >10 mg/L, test should be repeated and patient examined for sources of infection or inflammation. (Class IIa, Level of Evidence B) 3. hs-CRP levels, using standardized assays, categorize patients as follows: **Relative Risk Category and Average hs-CRP Level** Low <1 mg/L Average 1.0 to 3.0 mg/L High >3.0 mg/ L (Class IIa, Level of Evidence B)		
	4. hs-CRP results should be expressed as mg/L only. (Class I, Level of Evidence C)			

for increased emphasis on therapeutic lifestyle changes. If the patient is already targeted for these treatments according to current guidelines (eg, secondary prevention), then a level of inflammatory marker is less useful. A better potential use may be in those patients at baseline risk for whom an additional risk predictor may provide support for or against additional lifestyle or drug therapies.[75–77] Post hoc analyses from two randomized controlled trials (AFCAPS/TexCAPS [Air Force/Texas Coronary Atherosclerosis Prevention Study] trial of lovastatin versus placebo[77] and the Physicians' Health Study of aspirin versus placebo[76]) both suggest that persons with elevated hs-CRP levels have a larger absolute risk reduction in the intervention groups, which supports the potential utility of hs-CRP to target patients for primary preventive interventions.

One potential use for markers that might be considered is that of monitoring of the effects of therapy, such as an HMG-CoA reductase inhibitor. For example, if the marker does not fall, treatment might be intensified. HMG-CoA reductase inhibitors do seem to reduce hs-CRP levels,[78] but the response is very heterogeneous, with many nonresponders and a few hyper-responders contributing to the reduction in mean hs-CRP level. Unfortunately, it is not known if the responders with lowered hs-CRP levels have a greater reduction in risk than the nonresponders. Conversely, despite recent indications of possible increased risk with the use of estrogen in hormone replacement therapy (HRT)[79] and the finding that hs-CRP is increased with estrogen use,[80] it is not yet possible to conclude that an increased hs-CRP brought about by estrogen use is an indicator of increased CVD risk.

Thus, a role of these markers in the monitoring of therapy has not been established.

VI. Recommendations for Use of Inflammatory Markers in Clinical and Public Health Practice

The writing group examined the currently available evidence in the topic areas of laboratory, clinical, and population sciences in order to derive recommendations for use of inflammatory markers in clinical practice. The recommendations were classified, and the evidence for each recommendation was then rated according to the system used by the American College of Cardiology/American Heart Association (Appendix 2, Table 5). Table 4 summarizes the recommendations, with Quality of Evidence of Class I constituting enough evidence that clinicians and practitioners should use inflammatory markers in laboratory, clinical, and public health practices. Quality of Evidence of Class IIa and Evidence Level of A or B constitutes enough evidence that clinicians and practitioners might reasonably use inflammatory markers. Conversely, Quality of Evidence Class III supports a recommendation against the use for that specific purpose.

From the laboratory medicine/clinical chemistry perspective, the first question is: "If inflammatory markers are to be used, which test should be recommended?" Current evidence supports the use of hs-CRP as the analyte of choice, after consideration of the various analytes' stabilities; the analytes' assay precision, accuracy, and availability; and the availability of standards for proper assay calibration (Table 2). Additional analytes, improved assays, or evidence for benefits of combinations of assays may in the future be found to have advantages, but further research is needed (see Research Recommendations). Therefore, the measurement of alternative or additional analytes is not recommended at this time (Clinical Practice Recommendation No. 5 in Table 4).

The next question is: "How should hs-CRP be measured?" The hs-CRP assay, to reduce within-individual variability, should be performed in a metabolically stable person without obvious inflammatory or infectious conditions. Results for hs-CRP should be expressed as mg/L only. Two assays, averaged, fasting or nonfasting, and optimally 2 weeks apart, provide a more stable estimate of level of this marker. If a level of >10 mg/L is identified, there should be a search initiated for an obvious source of infection or inflammation, which could obscure any prediction of coronary risk that might be attributed to the elevated level. That result of >10 mg/L should then be discarded and the hs-CRP measured again in 2 weeks.

The cutpoints of low risk (<1.0 mg/L), average risk (1.0 to 3.0 mg/L), and high risk (>3.0 mg/L) correspond to approximate tertiles of hs-CRP in the adult population. The high-risk tertile has an ≈2-fold increase in relative risk compared with the low-risk tertile. These tertiles are based on distributions of hs-CRP samples from >15 populations involving >40 000 persons gathered for the purpose of this workshop, allowing adequate definition of the population distribution. In general, the high-risk category includes the skewed tail of the distribution.

After the identification of hs-CRP as the current analyte of choice, the next question is: "When and in whom should this inflammatory marker be measured?" Key to this discussion are the purpose for its measurement and the likelihood that further diagnostic and therapeutic plans might change on the basis of the test results. No clinical trials have been completed in which a population has been randomly allocated to screening for hs-CRP and compared with a control population not allocated to hs-CRP screening and both groups followed up prospectively to determine the benefits and harms of the screening. In particular, there continue to be few data on the cost-effectiveness of screening with inflammatory markers, taking into account further testing and treatment of persons classified as having high risk for CVD or the possibility of reduced testing and treatment of persons classified as being at low risk. Evidence-based practice does not require clinical trial evidence but rather requests that evidence currently available be taken into account in the formulation of recommendations. Such trials, however, are a recognized area for needed research (see Research Recommendations).

The best evidence to date supports the use of hs-CRP as an independent predictor of increased coronary risk. Although evidence for benefit or harm is not conclusive (Quality of Evidence IIb, Level C) for using this marker in all patients and in typical practice settings as part of a global risk assessment, the Writing Group endorses (at Evidence Level B) the optional use of hs-CRP to identify patients without known CVD who may be at higher absolute risk than estimated by major risk factors. Specifically, those patients at intermediate risk (eg, 10% to 20% risk of coronary heart disease (CHD) over 10 years), in whom the physician may need additional information to guide considerations of further evaluation (eg, imaging, exercise testing) or therapy (eg, drug therapies with lipid-lowering, antiplatelet, or cardioprotective agents), may benefit from measurement of hs-CRP. Those who have a 10-year risk of >20% are designated as CHD risk equivalents and already qualify for intensive medical interventions. This recommendation assumes the assessment of traditional cardiovascular risk factors and the calculation of an absolute risk score before measurement of hs-CRP.[75] The Writing Group discourages use of hs-CRP as an alternative to major risk factors for risk assessment. Treatment of patients with elevated hs-CRP on the basis of the hs-CRP alone has limited data to support it at the present time, and would require a prospective clinical trial to prove efficacy. The further assessment of patients with highly elevated hs-CRP (>10 mg/L) for noncardiovascular causes of inflammation was also endorsed. Thus, clinical judgment is required whether to adjust risk within this risk category by measurement of hs-CRP.

An interesting but untested use for hs-CRP is to motivate persons with moderate to high risk levels to improve their lifestyles (eg, smoking cessation, dietary modification, exercise, weight loss) or to comply with drug therapies. Limited data support the effectiveness of this particular application at the present time, and it would require a randomized, controlled trial to prove efficacy.

Measurement of hs-CRP also may be useful in the estimation of prognosis in patients who need secondary preventive care, such as those with stable coronary disease or acute

coronary syndromes and those who have undergone PCI. This information may be useful in patient counseling because it offers motivation to comply with proven secondary preventive interventions. Such prognostication may lead to more aggressive diagnostic testing or treatment options. However, current guidelines for secondary prevention generally recommend, without measuring hs-CRP, the aggressive application of secondary preventive interventions. Thus, secondary preventive care and acute coronary syndrome interventions should not depend on hs-CRP levels because the evidence for their effectiveness is already strong (Recommendations 7 and 8), so the utility of hs-CRP in secondary prevention seems to be more limited. Moreover, little evidence supports the use of serial testing for hs-CRP as a means to measure disease activity or to monitor therapy (Recommendation 9). Thus, the role of hs-CRP in secondary prevention likely is limited because of the reduced likelihood that it will alter management.

Finally, the entire adult population should not be screened for hs-CRP for purposes of cardiovascular risk assessment. Little evidence supports a recommendation for widespread screening for hs-CRP as a public health measure (Class III, Level of Evidence C). Such a recommendation would have to be based on additional evidence from studies of potential benefits and harm for such a screening initiative.[81]

VII. Recommendations for Research

A. Basic/Laboratory Sciences

The recognition that the inflammatory response is a key mechanism in the pathogenesis of atherosclerosis and its related clinical syndromes has provided a new paradigm with important implications for CVD research at the basic, clinical, and population levels. A discussion of the needs for further elucidation of basic mechanisms by which inflammation leads to clinical disease is beyond the scope of this report. One issue of relevance, however, is the current designation of inflammatory markers as risk markers in distinction to risk factors. A risk factor is associated with a disease by virtue of its participation in the causal pathway leading to the disease. A risk marker is statistically associated with the disease but need not be causally linked; in fact, it may be a measure of the disease process itself (Figure 2). In the case of inflammatory markers, the association might reflect a response to other, established risk factors (eg, obesity, diabetes, hyperlipidemia, cigarette smoking) or due to inflammatory processes as part of atherosclerotic disease. Given the lack of association between hs-CRP levels and the extent of atherosclerosis quantified by imaging technologies, the risk marker model seems to concur best with current evidence. Some evidence, however, also implicates a possible role for hs-CRP in the causation of atherosclerosis.[82–85] Furthermore, it is biologically plausible that CRP has a role in plaque instability as an explanation for the close relationship between hs-CRP and clinical syndromes as compared to its relationship to the extent of atherosclerosis.[5–7] Additional investigation of the role of hs-CRP and other inflammatory markers in atherogenesis is needed to fully understand this issue.

Further clinical chemistry and laboratory medicine research is needed to assure optimal measurement of the presence, level, and perhaps type of inflammation in an individual patient. As identified in Table 2, additional analytes hold promise as inflammatory markers but are currently limited by their instability, lack of available assays applicable to clinical rather than research settings, lack of precision, and lack of available standards. Fibrinogen levels, for example, have long been independently associated with incident coronary disease in numerous studies. Newer assays of fibrinogen that use immunologic methods need to be investigated to determine if they predict CVD as effectively as the previous functional assays and if they offer potential benefits from standardization and improved precision.

Another area in need of investigation is the use of combinations of inflammatory markers in the classification of CVD risk. Different analytes might be measured concurrently or sequentially to improve the sensitivity or specificity of the screening process. Another need is to identify markers or combinations of markers with greater specificity for atherosclerotic risk. Current assays are not specific for atherosclerosis and thus are not useful in the setting of other systemic inflammatory or infectious processes.

Despite the endorsement of hs-CRP as the current analyte of choice, there remains much to learn about optimizing its application to risk assessment. There needs to be continued standardization and performance testing for hs-CRP assays that are available to the clinical practice of medicine, including performance criteria for these assays, so that only assays with adequate precision and accuracy are recommended. There need to be additional comparisons of hs-CRP assays between serum samples and those plasma samples collected in heparin or in EDTA. Finally, additional work needs to be invested in the examination of CVD risk at various hs-CRP levels to better refine the cutpoints used for cardiovascular risk prediction and to assign levels of absolute risk to each stratum.

B. Clinical Sciences

An important conclusion from Table 4 is the striking lack of Level A evidence (derived from multiple randomized clinical trials). This endorses the need for not only additional investigation of the hs-CRP–CVD association but also the study of the application of these markers to cost-effective medical care. Thus, most current evidence has been derived from observational studies or post hoc analyses of randomized trials in which the intervention was not hs-CRP screening and the interventions were not intended to alter inflammation.

Therefore, randomized clinical trials need to be performed to test whether risk categorization by hs-CRP leads to (1) therapeutic risk reductions in additional patients who are not currently identified or (2) a reduction in the number of patients in need of treatment by identifying low-risk groups that heretofore had been recommended for further diagnostic testing or aggressive interventions. Furthermore, experimental studies need to be carried out to determine whether reductions in hs-CRP levels from nonpharmacological and pharmacological interventions are associated with reductions in CVD risk. These studies should then clarify strategies,

based on hs-CRP levels, for additional treatment planning, further diagnostic testing, and change in recommended targets for treatments (such as LDL cholesterol or blood pressure levels). The importance of hs-CRP reductions that have been observed with lipid-lowering drugs and other cardioprotective agents needs to be much better understood. Similarly, the meaning of a continued elevation of hs-CRP levels after acute or chronic management of acute coronary syndromes needs to be elucidated. Should such patients undergo further imaging or more aggressive therapy? Experimental rather than exclusively observational study designs likely are essential to sort out many of these issues.

Several specific issues need resolution over the short term to assure optimal benefits from current recommendations. First, can hs-CRP be used quantitatively as part of estimation of absolute risk for coronary disease? Recent data suggest that an hs-CRP level, with the prior probability from a Framingham risk score, be used to increase or reduce the risk estimated for women.[13] Additional studies are needed to improve the precision of the absolute risk estimates. Multipliers were developed by the Framingham Heart Study for fibrinogen, for example.[10] Second, postmenopausal HRT increases hs-CRP.[80,86,87] Recent evidence suggests that an elevated hs-CRP identifies an increased coronary risk in women on HRT, although it is not yet known whether elevations in hs-CRP due to HRT are important predictors of risk.[15,80] Finally, does drug therapy with antiinflammatory drugs such as aspirin, COX-II inhibitors, or other therapies administered at the time of hs-CRP measurement alter the predictive value of the level of the marker?[88]

Behavioral studies, including clinical trials, need to establish the utility of inflammatory markers in increasing patients' motivation to adhere to lifestyle modifications or to comply with pharmacotherapy for the primary or secondary prevention of CVD. This will be especially important if additional studies suggest that monitoring hs-CRP or other markers can be used to gauge disease activity or some other prognostically meaningful aspect of disease.

Finally, the cost-effectiveness of hs-CRP testing should be evaluated in clinical studies, preferably as an end point of clinical trials. Cost-effectiveness studies of diagnostic strategies often are not performed, but important questions need to be answered to assure wise utilization of resources. Are additional healthcare costs reduced or increased through the measurement of hs-CRP? Alternatively, can risk stratification be improved so low-risk patients can be better identified and managed less expensively through the addition of hs-CRP to an initial laboratory-based assessment (eg, lipid profile)?

C. Population Science

Critically needed is a firm understanding of the distribution of inflammatory markers in the entire population and in important population subgroups such as children, the elderly, and racial/ethnic groups. This might best be accomplished by pooling existing population study data, or the standardized analysis of samples from these studies, to describe the factors affecting hs-CRP levels. A major and urgent need is for population-based hs-CRP data as CVD risk predictors in African Americans, Hispanic Americans, Native Americans, and persons of Asian and South Asian (Indian subcontinent) heritage. Current "normal" values are derived almost exclusively from European or European-American reference populations, leaving open the chance for over- or underclassification of risk in these other large population groups.

Similarly, the meaning of elevated hs-CRP levels in children and young adults needs to be evaluated.[89] Given the models in Figure 2, it is unlikely that these young people have much atherosclerotic burden. The finding of an elevated hs-CRP in these individuals nonetheless may provide an early warning for later risk.

The pooling of data or the standardized assay of blood samples from large population-based prospective studies likely is needed to more robustly describe the relationship between inflammatory markers and CVD end points, including the calculation of absolute risk (incidence) for various strata of hs-CRP, which is not possible from nested case-control studies. This also would facilitate adjustment for established cardiovascular risk factors to better define independent predictive value and the relative risk for each hs-CRP stratum. Equally importantly, this pooling will allow the consistency of the association of elevated hs-CRP to be described in age, race, and disease subgroups, which would be important for its clinical utility. Finally, larger sample sizes will allow the interactions, if any, between hs-CRP levels and established risk factors to be evaluated and factored into risk-prediction equations.

VIII. Summary

This working group sought to translate the rapidly growing body of evidence for inflammation as a key process in atherosclerosis into clinical and public health practice. Basic science and epidemiological studies have developed an impressive case that atherogenesis is essentially an inflammatory response to a variety of risk factors and the consequences of this response lead to the development of acute coronary and cerebrovascular syndromes. Although several cytokines, acute-phase reactants, and cellular responses to inflammatory stimuli potentially might be predictive of clinical disease, the laboratory tests to assess inflammation are limited to those that are employable in clinical settings, have commercially available assays that can be standardized, and have adequate precision. On the basis of these considerations, it is most reasonable to limit current assays of inflammatory markers to hs-CRP, measured twice, either fasting or nonfasting, with the average expressed in mg/L, in metabolically stable patients. Relative risk categories (low, average, high) correspond to approximate tertiles of values ($<$1.0, 1.0 to 3.0, and $>$3.0 mg/L, respectively), based on an aggregation of population studies.

hs-CRP has been studied in nested case-control and prospective studies, which have shown graded, dose-response relationships to clinical CVD that remain after adjustment for other risk factors, with moderately strong associations between the lower and upper tertiles (RR $\approx$2.0). hs-CRP seems to add predictive value above that of currently established risk factors. The evidence, however, is not entirely consistent across published studies, and in particular, additional prospective studies are needed to more precisely define risk at various strata and to assure consistency in other age, sex, and race-ethnicity groups.

On the basis of the available evidence, the Writing Group recommends against screening of the entire adult population for hs-CRP as a public health measure. The Writing Group does conclude that it is reasonable to measure hs-CRP as an adjunct to the major risk factors to further assess absolute risk for coronary disease primary prevention. At the discretion of the physician, the measurement is considered optional, based on the moderate level of evidence (Evidence Level C). In this role, hs-CRP measurement appears to be best employed to detect enhanced absolute risk in persons in whom multiple risk factor scoring projects a 10-year CHD risk in the range of 10% to 20% (Evidence Level B). However, the benefits of this strategy or any treatment based on this strategy remain uncertain. The finding of a high relative risk level of hs-CRP (>3.0 mg/L) may allow for intensification of medical therapy to further reduce risk and to motivate some patients to improve their lifestyle or comply with medications prescribed to reduce their risk. Individuals at low risk (<10% per 10 years) will be unlikely to have a high risk (>20%) identified through hs-CRP testing. Individuals at high risk (>20% risk over 10 years) or with established atherosclerotic disease generally should be treated intensively regardless of their hs-CRP levels, so the utility of hs-CRP in secondary prevention appears to be more limited.

In patients with stable coronary disease or acute coronary syndromes, hs-CRP measurement may be useful as an independent marker for assessing likelihood of recurrent events, including death, myocardial infarction, or restenosis after percutaneous coronary intervention. However, secondary preventive interventions with proven efficacy should not be dependent on hs-CRP levels. Further, serial testing of hs-CRP should not be used to monitor effects of treatment.

These recommendations should not be interpreted to mean that the scientific evidence is fully adequate. Randomized trials in which inflammatory marker testing was the primary intervention have not been performed to provide Level A evidence, nor have cost-effectiveness analyses been completed to assess additional costs or cost savings through the use of such tests. The currently available evidence was assessed in the formulation of these recommendations. A long list of recommendations for further research reflects the need to clarify numerous issues. Nonetheless, basic and epidemiological studies suggest that this will be a fertile topic for investigations and will help define the most effective and efficient use of inflammatory markers in the prediction of CVD.

Appendix 1

List of Participants

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Appendix 2

TABLE 5. American College of Cardiology/American Heart Association Classification of Recommendations and Levels of Evidence

Classification of Recommendations
Class I
Conditions for which there is evidence and/or general agreement that a given procedure is useful and effective.
Class II
Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa
Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb
Usefulness/efficacy is less well established by evidence/opinion.
Class III
Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful.
Levels of Evidence
Level of Evidence A
Data derived from multiple randomized clinical trials.
Level of Evidence B
Data derived from a single randomized trial or nonrandomized studies.
Level of Evidence C
Consensus opinion of experts.

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