REVIEW

CME CREDIT

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Using C-reactive protein to assess cardiovascular disease risk

ABSTRACT

C-reactive protein (CRP), a marker of inflammation, is directly involved in atherogenesis, and elevated CRP levels (as measured by highly sensitive assays) are associated with increased cardiovascular risk. We welcome the recent joint guidelines on CRP testing from the Centers for Disease Control and Prevention and the American Heart Association; however, whereas the guidelines suggest measuring the CRP level only in patients at intermediate risk, we advocate measuring it as well in patients at high risk.

KEY POINTS

CRP measured by a highly sensitive assay (hs-CRP) is the inflammatory marker of choice to assess cardiovascular risk.

An hs-CRP level of less than 1.0 mg/L is considered to denote low risk, 1.0 to 3.0 mg/L intermediate risk, and more than 3.0 mg/L high risk.

Patients with intermediate-risk or high-risk CRP levels gain the largest absolute risk reduction with aggressive risk-lowering therapy.

C-REACTIVE PROTEIN (CRP) has gained official recognition as a cardiac test, now that the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) have issued guidelines for measuring inflammatory markers such as CRP in assessing the risk of cardiovascular disease.[1]

In this paper we:

- Briefly review the basic and clinical data that established an association between CRP levels and cardiovascular risk
- Summarize the recent CDC-AHA guidelines on CRP testing
- Offer our own recommendations (which differ somewhat from the CDC-AHA guidelines) on how to use CRP measurement to guide therapy
- Discuss some of the ongoing randomized trials being conducted to assess the clinical benefit of reducing CRP levels.

BASIC AND CLINICAL EVIDENCE SUPPORTING CRP MEASUREMENT

Inflammation plays a fundamental role in atherothrombosis, from its initiation through progression.[2] CRP, a measure of inflammation, is a mediator as well as a marker of atherothrombosis.

CRP as a mediator of atherothrombosis

Numerous basic science studies have provided evidence that CRP plays a direct pathogenic role in arterial disease. Specifically, CRP can:

- Activate complement[3]
- Enhance T-cell-mediated endothelial cell destruction[4,5]
- Induce expression of adhesion molecules, such as vascular cell adhesion molecule-1 and E-selectin[4]

FIGURE 1

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CRP was a stronger predictor of risk than LDL in healthy women

- Stimulate macrophages to produce tissue factor[6]
- Attenuate nitric oxide production[7,8]
- Increase the expression and activity of plasminogen activator inhibitor-1 in human endothelial cells[9]
- Inhibit angiogenesis
- Promote intima-medial thickening in children.[10]

CRP levels correlate with risk

More than a dozen prospective epidemiologic studies[11–21] demonstrated that elevated CRP levels predict cardiovascular events in people without a history of cardiovascular disease (reviewed by Ridker,[22] FIGURE 1). Events predicted include myocardial infarction,[23] stroke, peripheral arterial disease, and sudden cardiac death.[11,12,24,25]

Furthermore, elevated CRP levels predict recurrent ischemia and death in patients with stable and unstable angina,[26–28] those undergoing coronary intervention,[29] and those presenting with an acute myocardial infarction.[30] The long-term prognostic value of the CRP level is as strong as that of exercise stress testing.

In both stable and unstable angina, elevated CRP levels predict future events independently of findings on coronary angiogra-

FIGURE 2

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phy. The association between CRP levels and future cardiovascular events has also been found to be independent of age, smoking, cholesterol levels, diabetes, and other major cardiac risk factors.

For example, CRP levels may identify people at increased risk whose low-density lipoprotein (LDL) cholesterol levels are not elevated. Ridker et al[31] recently showed that CRP levels were a stronger predictor of risk than LDL cholesterol levels in more than 27,000 healthy American women followed over a mean of 8 years.

In addition, the CRP level adds prognostic information when it is combined with the LDL cholesterol level or Framingham Risk Score (FIGURE 2).[22,31]

The association cuts across national and cultural lines: CRP levels also predict coronary risk in other populations, such as South Asians.

Also of note: CRP reflects the metabolic syndrome and can predict the development of type 2 diabetes mellitus and symptomatic peripheral arterial disease.[1,9,32]

Weight loss, diet, exercise, smoking cessation, statins, thiazolidinediones all lower CRP

CDC-AHA GUIDELINES ON CRP TESTING

On March 14 and 15, 2002, the CDC-AHA "Workshop on Inflammatory Markers and Cardiovascular Disease: Application to Clinical and Public Health Practice" convened in Atlanta, Georgia, to address the growing evidence linking inflammatory markers to cardiovascular disease.[1]

The goals of this workshop were to identify the best available test, to define who should be tested (ie, in what conditions the test would be useful), and to specify how to interpret the test results.

CRP is the inflammatory marker of choice

The guidelines identify CRP (as measured by a high-sensitivity [hs] assay) as the inflammatory marker of choice for cardiovascular risk stratification. Although a number of other inflammatory markers such as serum amyloid A, white blood cell count, and fibrinogen have been investigated, the "hs-CRP" level has the most stability, assay precision, accuracy, and availability.

Who should be tested?

The CDC-AHA Writing Group endorsed the optional use of hs-CRP testing in patients at intermediate risk, ie, a 10% to 20% risk of coronary heart disease over 10 years.

The 10-year risk of a coronary event is calculated on the basis of the patient's age, total cholesterol level, smoking status, high-

density lipoprotein (HDL) cholesterol level, and systolic blood pressure. This scoring system has been published,[33] and is also available online at **www.nhlbi.nih.gov/guidelines/cholesterol/profmats.htm.**

According to the Writing Group, patients with a 10-year risk greater than 20% would not benefit from hs-CRP measurement, since they already have a level of risk equivalent to that of a person with known coronary heart disease and require aggressive medical therapy.

Therefore, physicians who may need more information to guide their decision in regards to further diagnostic testing or therapy may use the hs-CRP level as an additional tool. However, at this time, treatment solely on the basis of the hs-CRP level is not recommended.

The hs-CRP assay also may be used for prognostic purposes in secondary prevention. However, secondary preventive care and acute coronary interventions should not depend on the hs-CRP level. Therefore, the Writing Group sees the utility of hs-CRP in secondary prevention as somewhat limited at this time. Furthermore, it discouraged the use of serial testing for hs-CRP as a way to monitor therapy or to measure disease activity.

The guidelines state that the hs-CRP assay should not be performed for the purpose of risk stratification in people with underlying inflammatory or infectious conditions.

How to interpret the results

An hs-CRP level of less than 1.0 mg/L is considered to denote low risk, 1.0 to 3.0 mg/L intermediate risk, and greater than 3.0 mg/L high risk. These cut points are based on the distribution of hs-CRP levels in more than 40,000 persons from more than 15 populations.

To reduce variability in a patient's levels, two fasting or nonfasting assays should be performed at least 2 weeks apart and the results averaged, which should give a stable result.

If the average of the two levels is greater than 10 mg/L, a search for an inflammatory or infectious disease should be initiated. This result should be disregarded for coronary risk stratification purposes, and the hs-CRP level should be measured again in approximately 2 weeks.

Patients at intermediate risk who have elevated CRP levels should undergo aggressive risk modification. Modification of many of these risk factors will also lead to a reduction in CRP levels. However, at this time no randomized trial has shown a decrease in clinical outcomes when CRP is reduced. Therefore, treatment of elevated hs-CRP solely on the basis of the hs-CRP levels is not recommended by the CDC-AHA Writing Group.

OUR RECOMMENDATIONS

The CDC-AHA guidelines[1] are a dramatic advance in risk assessment, but we would go farther. Specifically, we advocate hs-CRP testing in all patients at intermediate risk *or high risk* for cardiovascular disease.

Furthermore, we believe hs-CRP should be measured in conjunction with cholesterol testing, and the results should be used to help clinicians in risk stratification in both primary *and secondary* prevention.[34]

The utility of CRP testing in patients with myocardial infarction, stable angina, or unstable angina has been reviewed recently in the *Cleveland Clinic Journal of Medicine*.[35] Elevated hs-CRP levels in these settings identify patients with higher inflammatory burdens who are at higher risk of future ischemic events.

No one knows yet whether lowering CRP per se reduces clinical events

An elevated CRP level provides additional prognostic value to traditional cardiac risk factors. Therefore, in a high-risk patient, an elevated hs-CRP level should even further alert both the physician and the patient to the need for aggressive risk-lowering strategies.

Historic analogies

This view may not yet be mainstream, but advances in medicine come slowly.

To use a historical analogy, when the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure issued its first report in 1977,[36] a systolic blood pressure of 159 mm Hg was not classified as hypertension, and the recommended follow-up was in 6 to 9 months. In contrast, in the Committee's sixth report 20 years later,[37] the same systolic blood pressure was classified as stage 1 hypertension, and the recommended follow-up was in 2 months. The Committee's seventh report,[38]

published in May 2003, is even more aggressive: a systolic pressure of 120 to 139 or a diastolic pressure of 80 to 89 now is classified as "prehypertensive."

Similarly, in the first report of the National Cholesterol Education Program (NCEP), published in 1988, the optimal LDL cholesterol level in patients with coronary artery disease was defined as less than 130 mg/dL.[39] It took 14 years to lower this value to 100 mg/dL,[33] and now many experts strongly advocate lowering it even further.[34,40]

Better prediction may promote healthier lifestyles

Multiple deleterious lifestyles and behaviors contribute to most deaths from cardiovascular causes.[41] Furthermore, people with healthy lifestyles and few risk factors have a lower mortality rate from heart disease.[42]

For example, the Nurses' Health Study demonstrated that women who maintain a desirable body weight, do not smoke, exercise regularly, and consume a moderate amount of alcohol have a 84% lower risk of cardiovascular disease compared with women with higher-risk behaviors.[43] Yet the prevalence rates of obesity and diabetes are increasing.[44]

We propose a randomized trial of CRP-guided therapy

Compliance with lifestyle recommendations is directly related to the absolute risk perceived by the patient. Thus, the addition of hs-CRP to traditional risk factors will provide an improved prediction tool, which should be shared with patients for better compliance with lifestyle and behavioral changes.

MANY INTERVENTIONS LOWER CRP

Many interventions such as weight loss, diet, exercise, and smoking cessation all lead to reduced CRP levels.[22,45–47]

Many drugs such as statins and thiazolidinediones also lead to a significant reduction in CRP levels.[14,19,48,49]

In two recent randomized trials, Cholesterol And Recurrent Events (CARE)[48] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),[14] the benefit associated with statin use in those with elevated CRP was much greater than in those with low CRP levels, indicating that patients with elevated CRP levels may benefit more from statin therapy.[50]

Unfortunately, as yet no randomized trials have been published that show that reducing CRP levels per se will reduce clinical events or deaths. Therefore, we must be cautious when interpreting observational studies that have shown a reduction in CRP with different interventions.

FUTURE DIRECTIONS

Despite the extensive basic and clinical data linking inflammation to atherogenesis and the strong association between CRP concentrations and cardiovascular risk, randomized trials that test the arterial inflammation hypothesis are lacking. The most important question is whether lowering CRP levels by suppressing inflammation will translate into fewer clinical events.

CRP-guided therapy in secondary prevention

Recently, we proposed a randomized study of usual care vs CRP-guided therapy in patients with a history of cardiovascular events and an elevated baseline CRP level.[46] We propose to test aspirin, statins, angiotensin-converting enzyme (ACE) inhibitors, clopidogrel, fibrates, and thiazolidinediones in a stepwise fashion. All patients will receive aspirin, a statin, and an ACE inhibitor as indicated. If CRP levels remain elevated, additional medications will be introduced for a 2-week period and CRP levels will be rechecked. If the added agent has no effect on CRP, it will be discontinued.

We believe this approach of using serial CRP measurements to guide therapy will allow formulation of a rational therapeutic strategy instead of an approach of reflex "polypharmacy" for each patient. The above approach will help to decide whether combinations of drug therapy really lead to an incremental decrease in morbidity and mortality.

CRP in primary prevention

The results of the AFCAPS/TexCAPS trial of lovastatin and the Physicians' Health Study of aspirin vs placebo suggest that patients with elevated CRP levels gain the largest absolute

risk reduction from these drugs. Furthermore, CRP levels have a strong prognostic value in people with "normal" LDL cholesterol levels.

Hence, a large-scale prevention trial of 15,000 patients without high LDL levels but with elevated CRP levels began in early 2003.[50] This trial, called Justification for the Use of Statins in Primary Prevention, an Intervention Trial Evaluating Rosuvastatin (JUPITER), will randomize patients to receive rosuvastatin or placebo. This study will help answer whether suppression of inflammatory burden will translate into decreased clinical events.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial is ongoing. Patients at high risk of a first coronary event or who have already had an event are being randomized to receive either clopidogrel or placebo, in addition to aspirin.[51] Levels of hs-CRP are being measured to ascertain the effect of clopidogrel on CRP and how this correlates with clinical event reduction.

In addition, randomized clinical trials must be conducted to assess the utility of CRP as a motivational tool to encourage patients to adhere to lifestyle modifications or to comply with pharmacotherapy for prevention of clinical events.

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