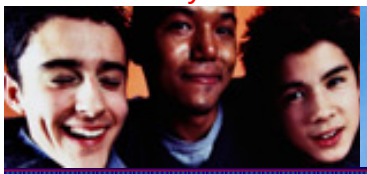

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C-REACTIVE PROTEIN: SCREENING OF CORONARY ARTERY DISEASE

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Executive Summary

Coronary artery disease (CAD), the leading cause of death in the United States, resulted in 459,841 deaths in 1998 and accounted for one of every five deaths. CAD is the leading cause of premature and permanent disability in the United States and in 1997, $10.8 billion was paid by Medicare for CAD. Numerous studies suggest that inflammatory changes in the vessel walls initiate atherosclerosis. As the disease progresses, the atherosclerotic plaques erode, become unstable, and eventually rupture. Plaque rupture causes thrombosis and the acute coronary syndromes, unstable angina (UA) and acute myocardial infarction (MI). Due to this link between chronic, low-grade inflammation and CAD, researchers have investigated serum inflammatory markers, particularly, acute-phase reactants, to determine if their appearance correlates with the presence or extent of CAD.

C-Reactive protein (CRP) is the classic acute-phase reactant. Researchers have hypothesized that CRP may provide an adjunctive method for assessment of cardiovascular risk. Several studies indicate that plasma levels of CRP are a strong independent risk predictor of future (MI), stroke, and vascular death among individuals without clinically recognized cardiovascular disease. Serum levels of this sensitive but nonspecific acute-phase reactant can increase by as much as 10,000-fold in response to tissue injury.

Studies have shown that slight elevations in baseline serum levels of CRP have a significant, dose-dependent association with increased risks for CAD morbidity and mortality in individuals with and without symptomatic CAD. Nevertheless, CRP is a nonspecific marker of inflammation, and it remains unclear whether CRP is a risk factor for CAD and a potential target for intervention, whether increased levels indicate the presence of an atherosclerotic plaque at high risk for rupture leading to thrombosis and acute MI, or whether this inflammatory marker is increased due to conditions unrelated to atherosclerosis, ie, the coexistence of a disorder associated with the acute-phase response.

The results of CRP testing must be analyzed in conjunction with the results of standard diagnostic tests,

medical history, and clinical findings. Its efficacy as a stand-alone test has not been proven. There is some evidence from epidemiological studies demonstrating that serum levels of CRP are increased in patients with MI, stable or unstable angina. Nevertheless, it remains unclear whether CRP itself is a risk factor for CAD or whether it simply reflects the extent of the acute-phase response to arterial inflammation or inflammation elsewhere in the body, or whether it is a marker of other classic CAD risk factors such as obesity or smoking.

The CRP test is a promising avenue of research but at the present time, there is no solid proof that CRP testing is superior to standard methods of risk stratification, that reducing serum CRP levels improves health outcomes or quality of life, or that CRP testing is cost-effective. Thus, the available evidence does not support the routine use of the CRP test for the diagnosis, management, or screening of patients with diagnosed disease, or in asymptomatic, healthy subjects.

Background

Coronary artery disease (CAD), the leading cause of death in the United States, resulted in 459,841 deaths in 1998 and accounted for one of every five deaths. An estimated one million Americans experienced a myocardial infarction (MI) in 2001 with 650,000 having a first attack and 450,000 having a recurrence. More than 40% of persons who have a MI during a given year will die as a result. Nearly 12.5 million people have a history of MI and/or angina pectoris (AP). Of these, an estimated seven million Americans (over 20 years of age) have a history of MI. From 1988 to 1998, the age-adjusted mortality rate from CAD decreased by 26.3%. Deaths due to CAD are most common among the elderly; 85% of people who die of MI are $\geq$65 years of age. CAD is the leading cause of premature and permanent disability in the United States, accounting for 19% of disability allowances paid by the Social Security Administration. In 1997, Medicare paid $10.8 billion for CAD.[1, 2]

AP affects nearly 6.5 million Americans. Approximately 400,000 new cases of stable AP, defined as predictable chest pain on exertion or under mental or emotional stress, and roughly 150,000 new cases of unstable AP (UA), defined as unpredictable chest pain while at rest, occur each year. Approximately 27% of men and 14% of women will develop AP within 6 years of having a diagnosed MI.[3]

The etiology of CAD is multifactorial. Although CAD can occur in patients without known risk factors, the major independent risk factors for CAD are smoking, hypertension, elevated serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL), low serum high-density lipoprotein cholesterol (HDL), elevated triglycerides, diabetes mellitus, and advancing age. Other risk factors for CAD are categorized as conditional risk factors or predisposing risk factors. Conditional risk factors are associated with an increased risk for CAD although their specific independent, causative, and quantitative contributions to the disease have not been established. These factors include: small LDL particles, elevated serum homocysteine, elevated serum lipoprotein (a), prothrombotic factors such as fibrinogen, and inflammatory markers such as C-reactive protein (CRP).[3-8]

Numerous studies suggest that atherogenesis and the development of CAD are caused by injury to the vascular endothelium, inflammation, and/or oxidative stress. Inflammatory changes in the vessel walls initiate atherosclerosis. As the disease progresses, the atherosclerotic plaques erode, become unstable, and eventually rupture. Plaque rupture causes thrombosis and the acute coronary syndromes, UA and acute MI. The site of plaque rupture in acute coronary syndromes is associated with the accumulation of lipid-laden plaques, activated lymphocytes and macrophages. Due to the possibility of a link between chronic, low-grade inflammation and CAD, researchers have investigated serum inflammatory markers, particularly, acute-phase reactants produced during the acute-phase response, to determine if their appearance correlates with the presence or extent of disease. Laboratory and experimental evidence indicate that atherosclerosis, in addition to being a disease of lipid accumulation, also represents a chronic inflammatory process. The acute-phase response is a nonspecific reaction induced by inflammation, infection, or tissue damage that results in increased production and circulating levels of various serum proteins known as acute-phase reactants.[3,6,7,9-18]

C-Reactive Protein

CRP is the classic acute-phase reactant. Researchers have hypothesized that inflammatory markers such as high-sensitivity C-reactive protein may provide an adjunctive method for assessment of cardiovascular risk. In support of this hypothesis, several studies have shown that plasma levels of CRP are a strong independent predictor of risk of future myocardial infarction, stroke, peripheral arterial disease, and vascular death among individuals without clinically recognized cardiovascular disease. In addition, among patients with acute coronary ischemia, stable angina pectoris, and a history of myocardial infarction, levels of CRP have been associated with increased vascular event rates.

The hypothesis that CRP testing might have prognostic usefulness for patients with acute myocardial infarction dates back to the 1940s, when levels of CRP were observed to increase as part of the "acute-phase response" associated with ischemia.

Serum levels of this sensitive but nonspecific acute-phase reactant can increase by as much as 10,000-fold in response to tissue injury: Levels can rise from the normal level of <5.0 mg/L to 500 mg/L within 4 to 8 hours after the event.

While the exact mechanism by which CRP levels increase in CAD patients, or in those at risk for the disease, is unknown, one group of researchers has proposed that CRP is an indirect risk factor for CAD, and that elevated serum CRP reflects one or more of the following situations:[4,11,12,14]

- Coronary vessel inflammation in response to infectious agents
- The severity of the inflammatory response in atherosclerotic vessels
- The extent of inflammation related to myocardial ischemia
- The extent of inflammation related to myocardial necrosis
- The amount and activity of circulating pro-inflammatory cytokines.

CRP and CAD

Current methods for estimating risks for CAD in individual patients have limitations, although they are reasonably accurate when applied to populations. Based on traditional risk factors, clinicians can only predict 50% to 60% of the variation in the absolute risk of a coronary event in an individual patient. The limitations of standard methods of risk assessment provided the impetus for research into novel markers of risk including CRP. Early studies examining the relationship of CRP to CAD relied on standard laboratory assays, mainly enzyme-linked immunosorbent assays (ELISAs) with lower limits of detection of 3.0 to 5.0 mg/L. While these assays have sufficient sensitivity to diagnose acute inflammation or to monitor autoimmune disease or infection, more sensitive assays are needed to detect the subtle increases in CRP that are associated with CAD. High-sensitivity CRP (hs-CRP) immunoassays that measure serum levels of CRP as low as 0.175 mg/L are now available and are deemed reliable and valid. The results of these assays indicate the presence of low-grade inflammation, which in selected patients may aid in the assessment of the risk of CAD and other vascular diseases.

Since about 1995, epidemiological studies utilizing the hs-CRP assays have evaluated whether the measurement of CRP levels would provide a means of detecting atherosclerosis in apparently healthy individuals, of assessing disease progression or risk of recurrent coronary events in patients with preexisting CAD, and of monitoring therapies or preventive interventions. CRP testing may also provide information that is additive to the predictive value of standard risk markers such as TC and other serum lipids. Nevertheless, due to its nonspecificity, CRP itself is not diagnostic, but is used in conjunction with other objective tests and clinical observations. Recently developed commercial CRP assays can be used with standard equipment in hospitals and outpatient laboratories, and thus could be used in the general clinical setting. The newer assays are automated, analytical instruments based on the nephelometric analysis of antigen antibodies. Nephelometry is the most commonly used immunochemical technique for measuring protein levels in serum and other body fluids and tissues. The test is simple to perform and involves the drawing of blood from the patient by standard venipuncture in standard 3- or 5-mL collection tubes. The samples are centrifuged and run through the analyzer. One type of assay consists of a suspension of polystyrene particles coated with murine monoclonal antibodies to CRP; the limit of detection of this assay is 0.175 mg/L CRP. The concentration of suspended particles is optimal for agglutination measurement by nephelometry. When the reagents are mixed with the serum samples, the intensity of the scattered light in the nephelometer is dependent upon the level of CRP in the sample. CRP levels are determined by comparisons with dilutions of a standard of known concentration. Another assay is a two-site chemiluminescent enzyme immunometric assay with one monoclonal and one polyclonal anti-CRP antibody; this assay has a limit of detection of 0.1 to 500 mg/L. A third assay uses a polyclonal anti-CRP antibody coated to latex particles and rate nephelometric measurements; the limit of detection of this assay is 1.0 mg/L. [3,7-10,13-14,18-22]

There are several advantages to using CRP measurements for assessing low-grade inflammation. These include: the only determinant of serum CRP level is the rate of hepatic synthesis, which closely reflects the degree of inflammation; CRP is stable in frozen plasma samples; despite marked increases in serum CRP during the acute-phase response, the long-term levels and year-to-year consistency within individuals is similar to that observed for other risk factors such as blood cholesterol; CRP assays detect

low-grade inflammation that may not be detectable by other tests.[7,8,12,14,20,22]

Evaluation of Evidence

Several studies indicate that elevated levels of CRP among apparently healthy men and women are a strong predictor of future cardiovascular events. Epidemiological data supporting the role of CRP as a biomarker for vascular risk are consistent across different study populations, including: smokers enrolled in the Multiple Risk Factor Intervention Trial;[23] elderly patients followed in the Cardiovascular Health Study; 24 women in the Women's Health Study;[8,25] and in three independent European cohorts, the MONICA Augsberg cohort,[26] the Helsinki Heart Study,[27] and the British Regional Practice study. 14 In most of these studies, the effect of CRP on vascular risk remained highly significant after adjustment for traditional risk factors typically used in global risk-assessment programs.

Clinical Research Studies

Studies on CRP testing involve four areas of prognostication and risk stratification; the prediction of recurrent events or death in patients with CAD, the effects of therapy on serum CRP levels, the impact of CRP changes on outcomes, and the prediction of a first CAD event in asymptomatic individuals. The study populations comprised of patients with preexisting, diagnosed CAD, presenting with a first CAD event, or at high risk for CAD (e.g., patients with high cholesterol) and asymptomatic individuals who at study entry were in apparent good health. Depending upon the study design, objective and the patient population, the outcomes assessed included determination of the relative risk (RR) of the following in relation to CRP levels: death due to any cause; death due to cardiac causes; recurrent CAD (stable AP, UA, or MI); restenosis following percutaneous transluminal coronary angioplasty; and effects of therapy with statins, anti-inflammatory agents such as aspirin, or antibiotics.

The studies reviewed on patients with diagnosed CAD include 12 prospective cohort studies, 3 prospective, nested case-control studies, and 2 randomized controlled trials. Their findings are summarized in Appendix III. The studies reviewed on asymptomatic populations include 1 randomized, placebo-controlled trial, 1 prospective cohort study, and 1 meta-analysis. Their findings are summarized in Appendix IV. Most of the studies evaluated the relevant outcomes before and after adjustment for potential confounding variables such as smoking, diabetes, personal or family history of CAD, blood lipids and lipoproteins, medical or surgical therapies, and other serum inflammatory markers. Some studies used commercial hs-CRP assays while others used standard laboratory assays. The limits of detection of the assays and the cutoff values employed to indicate abnormal results varied among the studies. Relative Risks (RRs) were frequently determined after stratification of the subjects.

Evidence regarding patients

A review of the available evidence from prospective studies in which CRP testing was used to predict the short- and long-term risks of a recurrent CAD event or death due to cardiac causes in patients who were followed from 90 days to 9 years revealed the following major findings:

- Mean serum CRP levels are generally elevated in CAD cases compared with CAD-free controls before and after adjustment for other CAD risk factors.
- Serum CRP levels are correlated with established cardiovascular risk factors such as smoking, age, body mass index (BMI), and diabetes, as well as with clinical variables such as prior MI and coronary artery stenosis severity. Serum CRP levels increase in women taking hormone replacement therapy.
- Elevated baseline CRP levels are independently predictive of the short- and long-term risks of recurrent MI or death in patients with UA, or a history of MI.
- One study of hypercholesteremic men with severe CAD found that the link between CRP and CAD prognosis was attenuated by other risk factors for the disease.
- Statin therapy leads to the highest reductions in serum CRP levels in CAD patients with the highest levels of CRP; however, the exact mechanisms for this and the effects on CAD outcomes are unclear.
- The increased risks of recurrent disease or death are reduced by statin therapy in CAD patients with high CRP levels; these patients may benefit from more aggressive therapy and follow-up, but whether CRP is a modifiable CAD risk factor has not been demonstrated in well-designed intervention trials.
- Elevated baseline CRP levels are associated with a higher risk for restenosis after coronary revascularization indicating that patients in this subgroup may require more aggressive therapy by stenting or drug therapy; however, there were some conflicting results with one study showing no link between CRP and the short-term risk of restenosis.
- Antibiotic therapy reduced serum CRP levels in a cohort of patients who were seropositive for Chlamydia pneumoniae; however, treatment had no significant effect on CAD outcomes during six months of follow-up. More research is needed on the role of antibiotic therapy in the outcomes of these patients.

Evidence regarding asymptomatic, initially healthy subjects

A review of the available evidence from prospective studies in asymptomatic, initially healthy subjects who were followed for three to over eight years demonstrated the following:

- Elevated baseline CRP levels, even when within the normal range, are independently predictive of the long-term risk of future CAD (eg, first MI) in apparently healthy individuals, and in some cases are the strongest predictors of risk.
- Risks for CAD or cardiovascular disease (CVD) are increased by 2- to 7-fold in individuals with the highest levels of CRP compared with those with the lowest level. Increased CRP levels can be detected several years before the clinical onset of CAD.
- In one study, short-term aspirin use reduced the risk of MI in men with the highest level of CRP. However, it remains unclear whether CRP testing accurately identifies individuals who would benefit from primary prevention efforts, eg, drug therapy, or whether long-term aspirin therapy has an effect on CRP levels, CAD risk or CAD outcomes in those who develop the disease.
- CRP levels increase in healthy postmenopausal women on hormone replacement therapy.
- CRP test results are additive to the predictive value of the standard CAD risk markers total

cholesterol (TC) and high-density lipoprotein cholesterol (HDL) for CAD in healthy men and women.

- Increased risks in individuals with elevated CRP are stable over long periods, and are independent of other CAD risk factors such as smoking and hyperlipidemia.
- The predictive value of CRP testing appears to be greatest in individuals who are at low risk according to other CAD risk factors, eg, those with normal lipid levels or nonsmokers.

Risk Estimates Associated With CRP Evaluation

Although epidemiological studies demonstrate association between low-grade inflammation and vascular risk, application of CRP testing in clinical practice requires estimates of risk across a spectrum of CRP levels. For each quintile increase in CRP, the adjusted relative risk of suffering a future cardiovascular event has been reported to increase 26% for men (95% CI 11% to 44%; P <0.005) and 33% for women (95% CI 13% to 56%; P <0.001). [8]

Potential Additive Value of CRP in Global Risk Assessment

In current strategies of global risk assessment, lipid testing is the only blood test routinely recommended. However, CRP evaluation may have the potential to improve cardiovascular risk prediction models when used as an adjunct to this approach. For example, in the Women's Health Study, the area under the receiver-operator curve (ROC) associated with CRP testing in combination with total and HDL cholesterol evaluation was significantly greater than that associated with lipid evaluation alone (P <0.001). [8,19,28] Although ROC characteristics are useful for interpreting test sensitivity and specificity, these data can be more easily understood by examining estimates of relative risk associated with combined lipid and CRP testing. Men with levels of both CRP and the total cholesterol; HDL cholesterol ratio in the top quintile represent a very-high-risk group compared with men with levels of both parameters in the lowest quintile. Also, increasing quintiles of CRP have additive predictive value at all lipid levels, including those typically associated with low to moderate risk.

CRP testing may also have potential prognostic value among "low-risk" subgroups as determined by traditional methods of global risk detection. Among postmenopausal women, CRP levels are a strong predictor of subsequent cardiovascular risk among nonsmokers, as well as among those without hypertension, diabetes, or a family history of myocardial infarction. Moreover, in an analysis of women with LDL levels below 130 mg/dL (current target for lipid reduction set by National Cholesterol Education Program guidelines for primary prevention) those with elevated levels of CRP still had markedly elevated risks of future myocardial infarction, stroke, and coronary revascularization, even after adjustment for other traditional risk factors.[8]

Further support for potential utility of CRP testing as an adjunct in global risk assessment is provided in a recent meta-analysis of population-based cohorts adjusted for smoking and most major vascular risk factors.[14] In that analysis, which in aggregate included 2557 cases with a mean follow-up of 8 years, individuals with baseline CRP levels in the top third of the distribution had a 2-fold increase in risk of future vascular events (95%CI 1.5 to 2.3; P <0.001). Importantly, no evidence was seen of heterogeneity among these studies, which indicates broad consistency in predictive value of CRP across

different population groups.[14]

Assay Characteristics of CRP Tests

Standard clinical assays for CRP typically have a lower detection limit of 3 to 8 mg/L. Thus, these assays lack sensitivity within the low-normal range and cannot be used effectively for vascular risk prediction. In recognition of this limitation, initial epidemiological studies used research-based assays designed to determine CRP levels with excellent fidelity and reproducibility across the normal range.[29,30] Several such "high-sensitivity" or "ultra-sensitive" assays for CRP are now commercially available or in development, and formal standardization programs have been undertaken to ensure comparability across CRP assays.[22,31,32]

Clinical studies demonstrate that results with one commercial CRP assay (Dade Behring Inc.) correlate well with CRP levels on the basis of early research assays. In several large-scale prospective studies, this assay has been shown to reproduce the predictive value of CRP testing for both peripheral arterial disease and for myocardial infarction and stroke. At this time, several other CRP assays are in clinical development and appear to have acceptable test characteristics. In the low-normal range needed for vascular risk detection, the variability and classification accuracy of CRP is similar to that of total cholesterol.[33] CRP levels increase with acute infection and trauma.[34] Thus, testing should be avoided within a 2- to 3-week window in patients who have had an upper respiratory infection or other acute illness. Individuals with clinical inflammatory conditions such as rheumatoid arthritis or lupus are likely to have elevations of CRP well into the clinical range; CRP evaluation for the purpose of vascular risk prediction may be of limited value in such patients. However, for most individuals, CRP levels appear to be stable over long periods of time.[35] These data support the possibility that enhanced inflammatory response and, hence, increased propensity to plaque rupture may involve important genetic determinants.

In an ongoing survey of several thousand American men and women, <2% of all CRP values have been >1.5 mg/dL, a level considered to be indicative of a clinically relevant inflammatory condition. In such cases, the CRP measure should be repeated to exclude the possibility of recent infection. If a second clinically elevated level is observed, evaluation for a previously unsuspected inflammatory condition may be needed.[36]

Many conditions may cause significant inflammation, which will result in high CRP levels. These conditions include: myocardial infarction, unstable angina, rheumatic fever, rheumatoid arthritis, systematic lupus erythematosus, tuberculosis, pneumococcal pneumonia, cancer, postoperative infection, trauma (e.g., injuries or burns) or heatstroke. Other conditions that may only cause a mild increase of CRP include: diabetes, glucose intolerance and high blood pressure (hypertension), all of which are independent risk factors for heart disease. Research indicates that if the CRP levels are elevated, a patient must stop smoking, exercise, lower blood pressure, lose weight and eat a heart-healthy diet, irrespective of the cholesterol level. In addition, cholesterol-lowering drugs called statins may fight inflammation, therefore they, too, are believed to be helpful in lowering the CRP levels.[8]

Quality of the Evidence

The bulk of the evidence is from prospective cohort studies and nested case-control studies designed to demonstrate an epidemiological link between CRP levels and CAD morbidity and mortality. While most of the studies were well-designed and their results consistent, ie, demonstrating a link between elevated CRP and increased relative risks for CAD in both symptomatic and asymptomatic populations, the extrapolation of these findings to the individual patient in the clinical setting is problematical. One reason for this is that the different studies used different analytical tests resulting in interstudy differences in CRP levels. Thus, a precise cutoff value to differentiate between low and high risk has not been defined. While CRP levels are relatively stable over time, the effect that intra-individual variability has on the determination of CRP levels for risk stratification remains unknown.[37-38]

Overall, the studies reviewed, evaluated objective outcomes of interest in well-defined populations. However, some were comprised of selected patients who participated in clinical trials, which limits the generalizability of the results. The potential for bias exists in case-control studies and is related to the retrospective collection and review of data, and problems in patient selection. The nested case-control study design, while a plausible design for evaluating multiple risk factors or biologic validity, is not conducive to calculating absolute risks. Many of the studies reviewed herein employed this design, which limited the analyses to the determination of RRs. Without the availability of the absolute risks or the data needed for their calculation, it is difficult to generalize the results from these studies to the general population. Most of the studies employed multivariate analyses to control for possible confounding and calculated confidence intervals as a measure of the precision of the likelihood estimates.[39-41]

A surrogate endpoint is defined as a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. Surrogate endpoints, in the causal chain, include measures such as LDL levels for MI or measures of subclinical disease, such as atherosclerosis on coronary angiography. A surrogate outcome is considered valid and reliable only if there is a validated causal connection between the change in the surrogate and change in the clinically important outcome. The findings are fairly consistent in epidemiological studies that changes in CRP are correlated with changes in the risk of CAD both before and after adjustment for confounders. Nevertheless, surrogate endpoints such as CRP can only be considered valid when their relationship with the clinically important outcome is firmly established in long-term randomized clinical trials showing that modifications in the surrogate are associated with modifications in the clinically important outcome. 42 In addition, for a disease risk factor to be useful in screening for the disease, the association between the two must be very strong.[43] Whether or not the association between CRP and CAD is sufficiently strong to ensure optimal performance of the CRP test for CAD screening has not been established.

Patient Selection Criteria

Due to the paucity of data on the relationship of CRP testing to health outcomes and quality of life in

CAD patients and in asymptomatic individuals, the patient selection criteria for CRP testing for CAD risk stratification and screening have not been established. The delineation of these criteria await the performance and completion of studies proving that the results of serum CRP testing assist the clinician in the selection of preventive or therapeutic interventions for CAD, and subsequently, in improved health outcomes.

Complications/Safety Issues

No complications or safety issues related to serum CRP testing have been reported in the medical literature. As with any diagnostic or screening test, a false-positive result could lead to additional procedures and therapies that are unnecessary and possibly harmful. Similarly, a false-negative result could lead to the withholding of appropriate treatment, and the possibility of morbidity or mortality.

Limitations of CRP Evaluation

Several limitations of CRP evaluation require consideration. Inflammatory markers are nonspecific, increase with acute infection or trauma, and have been shown to predict total mortality as well as cardiovascular events. CRP evaluation during times of infection or trauma and among individuals with known systemic inflammatory conditions may limit clinical utility. However, these effects have tended to lead to underestimation of the true predictive value of CRP in epidemiological studies. The utility of CRP testing across different ethnic groups also is uncertain. On the other hand, although cost effectiveness of CRP testing has not been formally evaluated, testing for CRP is inexpensive and likely to prove cost effective, particularly when compared with techniques such as electron-beam calcium scanning or magnetic resonance imaging.

Finally, the consistency of data concerning CRP in primary prevention does not imply that screening for CRP among post infarction patients will have clinical utility. After acute ischemia, levels of CRP can rise substantially such that determining an individual's underlying basal level is difficult, an effect that may result in misclassification. In addition, measures of ventricular function and infarct size are likely to have far greater predictive value among individuals who have recently suffered acute infarction. Thus, rather than generalizing results from primary prevention, carefully controlled studies of postinfarction patients that include information about ventricular function and other important prognostic factors are needed to determine whether CRP evaluation has utility in secondary prevention.

Regulatory Status of the Technology

Food and Drug Administration (FDA)
The following CRP tests used in the clinical studies have received 510(k) approval from the FDA (approval date):

- N High Sensitivity CRP Assay (Dade Behring Inc, Newark, DE) (October 25, 1999). The FDA

approved this test for the measurement of CRP in human serum and plasma for the detection and evaluation of infection, tissue injury, inflammatory disorders, and associated diseases.[44]
- The IMMULITE® C-Reactive Protein Reagent System (Diagnostic Products Corp, Los Angeles, CA) (April 6, 1999). The FDA approved this device for the measurement of CRP in human serum or plasma as an aid for evaluating the amount of injury to body tissues.[45]
- The IMMAGE Immunochemistry System C-Reactive Protein Reagent (Beckman Coulter Inc, Brea, CA) (June 12, 1998). The FDA approved this device for the quantitation of CRP levels in human serum and plasma as an aid for the evaluation of trauma, infection, inflammation, surgery, and stress.[46]
- The Ektachem Clinical Chemistry Slide C-Reactive Protein Assay (Johnson & Johnson Clinical Diagnostics Inc, Rochester, NY) (July 31, 1995).[47]

Health Care Financing Administration (HCFA)
As per searches of HCFA's Coverage Issues Manual and transmittal page, there is no national Medicare policy specific to CRP testing for CAD.[48]

Cost

The cost of one CRP test, the N High Sensitivity CRP Assay (Dade Behring Inc) is approximately $50.00.[21] No information is available on the costs of the other FDA-approved assays. No information on the aggregate average charge to patients when multiple treatments are indicated, or the aggregate charge to patients nationwide was found in searches of the medical literature.

Cost-effectiveness: No cost-effectiveness analyses on CRP testing for CAD risk assessment were identified in searches of the medical literature.

Issues of Controversy

Accuracy

Since the CRP response is nonspecific, it is essential that concomitant disorders associated with the acute-phase response be ruled out since the presence of these conditions can confound the test results. In addition, the assays have not been optimized for measuring elevations within the normal range. Assay results can be affected by the coexistence of a minor illness such as a cough or cold. An individual's level could increase up to 10.0 mg/L during subclinical illness and remain increased for days to weeks. This possibility indicates that a single CRP test may not yield valid results and that serial CRP testing should be performed to arrive at an accurate baseline value. However, there is a lack of agreement on the number and frequency of testing for CRP tests.

One group of researchers recommends that CRP testing be avoided if there is evidence of recent infection or trauma, and suggested a period of two weeks for CRP levels to return to basal levels. CRP values >15.0 mg/L are a likely indicator of acute or chronic inflammation and a repeat test is

recommended if CRP levels >5.0 mg/L are observed. [49]

Mechanisms

The exact mechanisms leading to increased serum CRP in patients with CAD and the mechanisms linking CAD risk with inflammatory markers are unclear.[9,13]

Technical issues

There is a need for additional standardization of hs-CRP assays before their widespread introduction into clinical practice for CAD risk stratification.[22] Roberts et al. (2000) evaluated the precision, linearity, and comparability of four hs-CRP assays (the Dade Behring N High Sensitivity CRP assay, the Abbott IMx, the Diagnostic Products IMMULITE, and the Beckman Coulter IMMAGE) in serum samples obtained from 322 apparently healthy blood donors. The four assays had varying results in this healthy population. The imprecision of the Dade Behring N High Sensitivity CRP assay, the Abbott IMx, the Diagnostic Products IMMULITE, and the Beckman Coulter IMMAGE methods was $\leq$7.6%, $\leq$12%, $\leq$9.8%, and $\leq$9.7% at 3.5 mg/L, respectively. The CRP level that demarcated each quartile differed among the assays. The authors concluded that since CRP results will most likely be interpreted in terms of quintiles or quartiles for risk assessment, hs-CRP assays would need to be standardized for CRP levels of 0.2 to 10 mg/L so that results obtained in large populations can be applied to individual patients. Note: The IMx assay is not FDA-approved for use in the United States.[22]

Alternatives

Comparisons of CRP With Other Novel Markers of Vascular Risk

Testing for homocysteine and lipoprotein(a), both of which are involved in atherothrombosis, has been recommended for certain high-risk groups. For example, homocysteine evaluation is recommended among those with impaired methionine metabolism due to renal failure or hypothyroidism, whereas lipoprotein(a) assessment has been recommended for those with premature atherosclerosis in the absence of other risk factors.[50,51]

Three large-scale prospective studies have compared directly the relative efficacy of homocysteine screening to CRP evaluation.[8,23,28,52-55] In each study, magnitude of risk prediction associated with CRP levels in the top quintile was greater than that associated with similar elevations of homocysteine. In one prospective cohort of women, levels of homocysteine, lipoprotein(a), several inflammatory parameters including CRP, and a full lipid panel were simultaneously measured as markers of subsequent vascular risk.[8] Data show univariate relative risk of future cardiovascular events in that cohort for women in the top versus bottom quartile for each of these parameters. As shown, CRP was the single strongest predictor of risk (RR 4.4 for the highest versus lowest quartile). In multivariate analysis, only CRP level and total HDL cholesterol ratio proved to have independent predictive value once age, smoking status, obesity, hypertension, family history, and diabetes also were accounted for.

Future of the Procedure

Increasing knowledge regarding the relationship between increased CRP levels and CAD will lead to an improved ability to predict risks of future disease in symptomatic and asymptomatic individuals, to initiate and guide therapy, to prevent clinical disease in apparently healthy individuals, and to develop new targeted therapeutic strategies. For example, possible therapeutic goals could include the inhibition of the inflammatory response or the interruption of the tissue damage associated with increased deposition of CRP within the myocardium or arterial wall.[13,15]

Conclusions

Studies have shown that slight elevations in baseline serum levels of the classic inflammatory marker CRP have a significant, dose-dependent association with increased risks for CAD morbidity and mortality in individuals with and without symptomatic CAD. Nevertheless, CRP is a nonspecific marker of inflammation, and it remains unclear whether CRP is a risk factor for CAD and a potential target for intervention, whether increased levels indicate the presence of an atherosclerotic plaque at high risk for rupture leading to thrombosis and acute MI, or whether this inflammatory marker is increased due to conditions unrelated to atherosclerosis, i.e., the coexistence of a disorder associated with the acute-phase response.

The results of CRP testing must be analyzed in conjunction with the results of standard diagnostic tests, medical history, and clinical findings. Its efficacy as a stand-alone test has not been proven. Although individuals with the highest CRP levels appear to derive the most benefits from medical therapy with aspirin or statins, no therapy has been shown in randomized controlled trials to consistently reduce CRP levels, and there is a paucity of evidence demonstrating that a reduction in CRP levels leads to decreased CAD morbidity and mortality.

There is evidence from epidemiological studies demonstrating that serum levels of CRP are increased in patients with stable AP, UA, or MI. In addition, large, prospective studies have shown a relationship between elevated serum CRP levels and future risk of CAD. Nevertheless, it remains unclear whether CRP itself is a risk factor for CAD or whether it simply reflects the extent of the acute-phase response to arterial inflammation or inflammation elsewhere in the body, or whether it is a marker of other classic CAD risk factors such as obesity or smoking.

The CRP test is a promising avenue of research for the primary and secondary prevention of CAD. At the present time, there is no solid proof that CRP testing is superior to standard methods of risk stratification, that reducing serum CRP levels improves health outcomes or quality of life, or that CRP testing is cost-effective. Thus, the available evidence does not support the routine use of the CRP test for the diagnosis, management, or screening of patients with diagnosed disease, or in asymptomatic, healthy subjects.

Recommendations

It remains unclear whether CRP is a risk factor for CAD, whether increased levels indicate the presence of an atherosclerotic plaque at high risk for rupture leading to thrombosis and acute MI, or whether CRP is increased due to conditions unrelated to atherosclerosis.

The results of CRP testing must be analyzed in conjunction with the results of standard diagnostic tests, medical history, and clinical findings; its efficacy as a stand-alone test has not been proven.

The optimal clinical role and effectiveness of CRP testing await the results of well-designed trials examining whether reductions in CRP are linked with improved health outcomes, and whether there are effective treatments for reducing CRP.

Available evidence does not support the routine use of the CRP test for the diagnosis, management, or screening of patients with diagnosed disease, or in asymptomatic, healthy subjects. There is a need for well-designed clinical trials to evaluate the clinical efficacy and effectiveness of the test as an adjunct to other standard and novel markers for CAD.

Appendix I: Methodology

Evidence evaluated for this report was obtained from a search of PreMEDLINE, MEDLINE, EMBASE, Current Contents, and HealthSTAR databases spanning the years 1966 to February 2002. Search terms included C-reactive protein, CRP, high-sensitivity C-reactive protein, coronary artery disease, arteriosclerosis, atheroma, angina pectoris, myocardial infarction, and hypercholesteremia as keywords, subject words and title words, combined with diagnosis, prognosis, risk stratification, screening, therapy, prevention, statin and revascularization. In addition, information was obtained from the AHA, the ACC, the National Institutes of Health (NIH), and the FDA.

Appendix II: Professional Organizations/Consensus/Guidelines

American Heart Association/American College of Cardiology (AHA/ACC):
An AHA/ACC statement published in 1999 on the assessment of CAD risk states that while CRP is a potential risk factor for CAD and, as such, may be a promising risk predictor, routine measurement of CRP is not recommended. Further, if CRP testing is used, high-sensitivity tests are the preferred method. While CRP appears to be related to systemic inflammation, its etiologic role in atherogenesis is uncertain.[4]

While noting that CRP levels are predictive of an adverse outcome in CAD patients, in a set of guidelines on the management of patients with USAP and non-ST-segment elevation MI that were published in 2000, the AHA/ACC stated that the available evidence does not support the routine use of this marker.[56]

American Heart Association (AHA):
The AHA states that currently available CRP tests lack sufficient sensitivity to detect the differences in CRP levels observed in recent research, and that whether CRP testing adds to available methods of risk assessment (e.g., TC or HDL-C measurement) has not been proven. The association added that most of the data on CRP testing is for men and that less is known about the efficacy of testing in women.[6]

The following abbreviations and acronyms are used in Appendix III and IV:

ACADEMIC	Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia Study
CAPTURE	Chimeric c7E3 AntiPlatelet Therapy in Unstable Angina REfractory
ECAT	European Concerted Action on Thrombosis and Disabilities Angina
IL-1	Interleukin-1
IL-6	Interleukin-6
ACE	Angiotensin-converting enzyme
LDL-C	Low-density lipoprotein cholesterol
AP	Angina pectoris
LMWH	Low-molecular-weight heparin
BMI	Body mass index
LOS	Length of stay
BP	Blood pressure
Lp(a)	Lipoprotein (a)
CABG	Coronary artery bypass graft
LV	Left ventricular
CAD	Coronary artery disease
LVEF	Left ventricular ejection fraction
LVWM	Left ventricular wall motion to Standard Treatment trial
CARE	Cholesterol And Recurrent Events trial
MONICA	MONItoring Trends and Determinants in CArdiovascular
NR	Not reported
CCU	Coronary care unit Disease Project -- Augsburg Cohort Study
NS	Not statistically significant
CHF	Congestive heart failure

OR	Odds ratio
CI	95% confidence interval
CK-MB	Creatine kinase-MB
PEPI	Postmenopausal Estrogen/Progestin Intervention Study
CSAP	Chronic stable angina pectoris
PHS	Physicians' Health Study
CVD	Cardiovascular disease
PTCA	Percutaneous transluminal coronary angioplasty
dx	Diagnosis
pt(s)	Patient(s)
RR	Relative risk
RCT	Randomized controlled trial Pectoris Study Group
SAA	Serum amyloid A
ECG	Electrocardiogram
SD	Standard deviation
ELISA	Enzyme-linked immunosorbent assay
TC	Total cholesterol
FACT	Fluvastatin Alone and in Combination Treatment Study
TNF-a	Tumor necrosis factor-a
sICAM-1	Soluble intercellular adhesion molecule-1
TnT	Troponin T
FRISC	FRagmin during InStability in Coronary Artery Disease trial
f/u	Follow-up
grp(s)	Group(s)
t-PA	Tissue plasminogen activator
HDL-C	High-density lipoprotein cholesterol
tx	Treatment
HR	Hazard ratio
USAP	Unstable angina pectoris
HRR	Hazard rate ratio

vWF	von Willebrand factor
HRT	Hormone replacement therapy
WBC	White blood cell
hs-CRP	High-sensitivity C-reactive protein
WHS	Womens' Health Study
WOSCOPS	West Of Scotland COronary Prevention Study
hx	History
IgG	Immunoglobulin G

Appendix III: Studies on the Efficacy of CRP Testing in Patients with Diagnosed Coronary Artery Disease

Authors/Study Design	Study Population	CRP Assay/Protocol/ Outcomes	Results	Conclusions/ Comments
Haverkate et al. (1997) 15 European centers ECAT Study Group Prospective cohort study To determine relationship of elevated serum CRP and SAA to CAD risk in pts w/ stable and unstable CAD F/u time, 2 yrs 1984-1987	n=2121 CAD outpts who had coronary angiography (1797 men, 324 women): n=1030 USAP n=743 CSAP n=5 atypical chest pain Exclusion criteria: MI w/in prior 2 mos; severe right heart failure or noncardiac disease likely to cause death w/in 1 yr	IMx CRP assay (Abbott Laboratories) (0.05-30.0 mg/L) (Note: This assay is not FDA-approved) Normal value: <3.0 mg/L ≤3.6 mg/L CRP (lower 4 quintiles) >3.6 mg/L CRP (5th quintile) Outcomes were all coronary events assessed by independent committee Adjustment for study center; age; sex; smoking; use of heparin,	75 coronary events (20 sudden deaths, 7 fatal MI, 48 nonfatal MI) in 41 pts w/ USAP, 29 w/ CSAP, and 5 w/ atypical chest pain. Baseline serum CRP levels associated w/ increased risk for coronary events in USAP and CSAP pts. The RR was 2x greater in the upper quintile of CRP (>3.6 mg/L) compared w/ the lower 4 quintiles (≤3.6 mg/L).	This long-term, prospective trial demonstrated that outpts w/ CSAP or USAP had slightly increased serum CRP levels that were associated w/ increased risk for sudden death and MI before and after adjustment for confounding variables. While the mechanisms are unclear, increased CRP may reflect inflammation and tissue damage w/in atheromatous lesions. Although increase in CRP was w/in normal range, it might indicate a

			diuretics, or digoxin; hypertension; BMI; serum triglyceride level; LVEF; prior MI; and number of vessels w/ >50% stenosis or occlusion	Approximately 33% of the events were in pts w/ CRP levels >3.6 mg/L at baseline. The RR was 1.45 for all pts (p=0.02) CRP levels significantly correlated w/ age, smoking, BMI, triglycerides, stenosis severity, medication use, hx of MI, and LVEF RR was 1.81 for 5th quintile and remained significant after adjustment for center, age, smoking, medications, BMI, triglycerides, and ejection fraction (p=NR). SAA levels unrelated to CAD risk.	greater risk for progressive CAD. Limitations: selected population; majority of pts were men; accuracy of assay for predicting risks unclear since median level in CAD pts was w/in normal range.

	Toss et al. (1997) University Hospital, Uppsala, Sweden Substudy of FRISC Study* Prospective cohort study To determine relationship of elevated serum CRP, TnT, and fibrinogen levels to short-term risk in pts w/ USAP F/u time, 5 mos Study timeframe NR	n=965 pts w/ unstable CAD hospitalized for chest pain and suspected acute MI or recent-onset AP (627 men, 338 women): n=290 prior MI n=376 non-Q-wave MI n=589 USAP Exclusion criteria: Men <40 yrs of age; premenopausal women; serious comorbidities; hypersensitivity to heparin	Standard CRP assay Normal value: <2.0 mg/L Blood samples obtained at median of 25 hrs after onset of last episode of chest pain Pts were randomized to tx w/ LMWH or placebo during f/u <2.0 mg/L CRP (1st tertile) 2.0-10.0 mg/L CRP (2nd tertile) >10.0 mg/L CRP (3rd tertile) Outcomes were death and death and/or new MI combined. Adjustment for age, sex, BMI, smoking, hx of diabetes, hypertension, prior MI, CHF, number of anti-anginal drugs, modified Braunwald class, degree of ischemia on baseline ECG, tertiles of CRP and fibrinogen, and TnT value.	42 (4.4%) deaths, 118 (12.3%) new MI, 138 (14.4%) died and/or had new MI. The probabilities of death during f/u were 2.2%, 3.6%, and 7.5% for the 1st - 3rd tertiles of CRP, respectively (p=0.003). The probabilities of death and/or new MI were 11.8%, 14.9%, and 16.3% in the 1st - 3rd tertiles, respectively (p=0.26). Pts who died had higher median level of CRP (15.0 vs 5.0 mg/L; p<0.001). Highest tertile of CRP associated w/ increased risk of death compared w/ lowest tertile (RR=3.46; CI, 1.51-7.92). After adjustment for risk factors including fibrinogen, CRP was independent	In pts w/ hx of unstable CAD, baseline CRP measured during hospitalization for tx of acute symptoms was significant risk factor for death during short term, but not for combined outcome of death and/or new MI. Thus, increased serum CRP may be related to poor prognosis. Limitations: selected population (only pts at high risk for subsequent events were included in LMWH trial); blood sample obtained at admission, not at discharge; effects of tx w/ LMWH on outcome are unclear.

				risk factor for death (p=0.014); however, it was not an independent risk factor for death and/or new MI. Only TnT value and number of anti-anginal drugs were correlated w/ both outcomes.	
	Ridker et al. (1998a) Substudy of CARE trial† Prospective nested case-control study To evaluate (1) relationship of elevated serum CRP and SAA to risk of recurrent MI or death; and (2) whether statin tx reduces the risk F/u time, 5 yrs	n=391 pts w/ prior MI who subsequently developed recurrent MI or died of cardiac causes. n=391 age- and sex-matched controls w/o recurrent CAD (342 men, 49 women) Inclusion criteria: prior MI at 3-20 mos before randomization; TC <240 mg/dL; LDL-C levels 115-175 mg/dL; LVEF not <25%; no CHF	hs-CRP assay (Dade-Behring) Blind assessment of prerandomization blood samples obtained at a mean of 8.9 mos after acute MI Outcomes were recurrent coronary events and effects of pravastatin tx on outcomes <0.12 mg/dL CRP (1st quintile) 0.12-0.20 mg/dL CRP (2nd quintile) 0.21-0.37 mg/dL CRP (3rd quintile) 0.38-0.66 mg/dL CRP (4th quintile) >0.66 mg/dL CRP (5th quintile)	Mean serum CRP levels higher in cases compared w/ controls (0.56 vs 0.48 mg/dL; p=0.03) The RRs for recurrent MI or death from cardiac causes generally increased w/ increasing quintile of CRP: 1.0 for 1st, 1.07 for 2nd, 1.19 for 3rd, 0.98 for 4th, and 1.77 for 5th (p=0.044); however, only the RR for the top quintile (>0.66 mg/dL) was significantly increased compared w/ bottom quintile	Persistent postinfarction inflammation as reflected by high CRP and SAA levels was associated w/ increased risks for recurrent MI and death over 5 yrs. The increased risks were independent of smoking or serum lipid levels. Limitations: retrospective analysis w/ possibility of bias; association does not prove causation.

				(CI, 1.1-2.9). The RR for recurrent MI or death was 75% higher in pts in the top quintile than those in bottom quintile. The highest risk for recurrent MI or death occurred in pts w/ the highest levels of CRP and SAA who were randomized to placebo (RR=2.81; p=0.007).	
	Ridker et al. (1999) Brigham and Women's Hospital and Harvard Medical School, Boston, MA Substudy of CARE trial† Prospective cohort study To evaluate long-term effects of pravastatin tx on serum CRP levels F/u time, 5 yrs Study timeframe NR	n=477 randomly selected participants of the CARE trial w/o recurrent CAD after acute MI Exclusion criteria: baseline or 5-yr CRP value >3 SDs above the mean (n=5, 1%) The remaining 472 pts were randomized to pravastatin (n=258) or standard tx plus placebo (n=214)	hs-CRP assay (Dade-Behring) Blind assessment of prerandomization blood samples obtained at a mean of 8.9 mos after acute MI Outcome was serum CRP level in relation to pravastatin or placebo Adjustment for age, BMI, smoking, blood pressure, and baseline lipid levels	Baseline characteristics were similar between pravastatin and placebo grps. In pravastatin grp, mean baseline CRP levels decreased by 18.4% over 5 yrs (0.38 vs 0.31 mg/dL; p=0.002). In the placebo grp, mean baseline CRP levels increased by 19.4% over 5 yrs (0.36 vs 0.43 mg/dL; p=0.04).	Pravastatin tx reduced serum CRP levels. Pravastatin may decrease inflammation and reduce the likelihood of recurrent CAD but based on these findings, it cannot be concluded that CRP is a modifiable risk factor for CAD. Limitations: findings require replication in additional studies w/ adjustment for the effects of other anti-inflammatory agents; association

				These differences persisted after adjustment for age; BMI; smoking; blood pressure; and baseline levels of HDL-C, LDL-C, TC, and triglycerides.	does not prove causative relationship between CRP and CAD.
	Buffon et al. (1999) Università Cattolica del Sacro Cuore, Rome, Italy; Ospedale Fetebenefratelli-Isola Tiberina, Rome, Italy Prospective cohort study To evaluate efficacy of CRP, SAA, and fibrinogen for predicting short- and long-term prognosis following PTCA in pts w/ USAP or CSAP F/u time, 1 yr Study timeframe NR	n=121/219 (55%) pts who underwent PTCA for a single, nonocclusive coronary artery stenosis: n=52 CSAP n=69 USAP Exclusion criteria: 98 pts were excluded due to MI w/in 3 mos; multilesion PTCA; total occlusion; previous PTCA or CABG; LVEF <30%; left bundle branch block; and comorbidities associated w/ acute-phase response	IMx CRP assay (Abbott Laboratories) (Note: This assay is not FDA-approved). Blood samples obtained immediately before procedure. <0.28 mg/dL CRP (1st tertile) <0.82 mg/dL CRP (2nd tertile) >0.88 mg/dL CRP (3rd tertile) Elevated CRP defined as >0.3 mg/Dl Adjustment for age; gender; diabetes; hypertension; smoking; USAP; CRP, SAA, and fibrinogen tertiles; target stenosis; hypercholesteremia; multivessel disease; & balloon/vessel ratio	Before PTCA, elevated serum CRP levels were found in 29% of CSAP pts and 78% of USAP pts (p<0.001). 15/121 (12%) pts had early adverse events. 2/52 (4%) CSAP pts had early adverse events (CRP levels 2.2 and 18.7 mg/dL); both in top CRP tertile. 13/69 (19%) USAP pts had early adverse events (median CRP, 2.1 mg/dL). Incidence of adverse events increased from 0% in bottom tertile to 30% in top tertile (p=0.014).	An elevated serum CRP level before PTCA for single-vessel disease is an independent risk factor for early complications and clinical restenosis w/ in 1 yr of tx. The authors concluded that CRP is a stronger predictor of an adverse outcome than USAP, demonstrating that underlying inflammation may play a more important role in prognosis than clinical instability. Limitations: small sample size; repeat coronary angiography not performed in pts w/ o clinical evidence of restenosis; not all pts available at f/

				Clinical restenosis was higher among pts w/ elevated CRP compared w/ those w/ normal levels (63% vs 27%; p<0.001). CRP tertile (RR=12.2; p<0.001), hypertension (RR=4.3; p=0.046), and female gender (RR=4.1; p=0.033) were the only independent predictors of early adverse events. CRP tertile (RR=6.2; p=0.001), SAA levels (RR=6.0; p=0.011), residual stenosis (RR=3.2; p=0.007) and acute gain (RR=0.3; p=0.01) were the only independent predictors of clinical restenosis.	u.

	Ferreirós et al. (1999) Hospital Italiano de Buenos Aires, Buenos Aires, Argentina Prospective cohort study To evaluate short-term prognostic value of CRP in pts w/ USAP F/u time, 90 days Study timeframe NR	n=194 consecutive pts w/ USAP hospitalized for acute ischemic chest pain at rest for 24 hrs (121 men, 73 women): n=63 prior MI n=70 progressive AP n=88 recent-onset AP Exclusion criteria: necessity for thrombolysis; elevated total serum CK-MB on admission or during first 24 hrs; certain subtypes of AP, serious CAD, concomitant inflammatory disease, or cancer	Standard CRP ELISA w/ detection range of 0.1-12.0 mg/dL (normal value <0.3 mg/dL) Serum CRP measured at admission, at 48 hrs, and at discharge (mean hospital LOS, 8 d). Cutoff value was defined as 1.5 mg/dL. Outcomes were incidence of death due to any cause, acute MI, and/or refractory AP during 90 days after discharge. The treating physician was blinded to the CRP results. Adjustment for age, presence of ST-segment depression on admission ECG, silent ischemia during 24-hr Holter recording, LVWM score, and other high-risk characteristics	A serum CRP level of >1.5 mg/dL at admission was unrelated to in-hospital outcome (OR=0.80; CI, 0.23-2.73; p=NS). CRP >1.5 mg/dL at discharge was predictive of death, MI, or refractory AP (OR=15.2; CI, 5.2-44.8; p<0.001). The combined outcome of refractory AP, MI, or death was related to CRP level at admission (HR=1.9; CI, 1.2-8.3; p=0.002) after adjustment for age, ECG findings, silent ischemia, LVWM score, and high-risk clinical status. By multivariate analysis, CRP level at discharge was strongest independent predictor for combined	This short-term, prospective trial showed that USAP pts w/ serum CRP levels >1.5 mg/dL at hospitalization and discharge have a worse 90-day prognosis and are nearly 2x more likely to experience refractory AP, death, or MI. CRP levels obtained at discharge were more predictive than levels obtained at admission and could be more useful for risk stratification in these pts. Persistently high or increasing CRP levels could indicate a need for more aggressive monitoring and tx. Differences in prognosis could not be accounted for by differences in tx since pts received similar medications. Limitations: short-term f/u only; findings require confirmation in larger populations.

				outcome of refractory AP, MI, or death at 90 days (HR=3.16; CI, 2.0-5.2; p<0.001). There were no differences in in-hospital tx or in the use of coronary angiography or revascularization procedures between pts w/ CRP values above and below the cutoff value. The data were confirmed in a validation set.	
	Anderson et al. (1999) University of Utah, LDS Hospital, Salt Lake City, Utah ACADEMIC Study Randomized, double-blind, placebo-controlled trial To evaluate efficacy of azithromycin for (1) reducing serum CRP, IL-1, IL-6, and TNF-a levels; and (2) reducing	n=302 CAD pts who were seropositive for C pneumoniae (IgG titers ≥1:16) (269 men, 33 women) n=183 hx of MI n=191 hx of CABG n=137 hx of PTCA or stenting	CRP assay (Johnson & Johnson Clinical Diagnostics Inc) (no details provided and normal value was undefined) Randomized to azithromycin (500 mg/d for 3 d, then 500 mg/wk for 3 mos) (n=150) or placebo (n=152) Outcomes were effects of tx on serum marker levels and incidence of CAD. Mean change	At 3 and 6 mos, mean serum CRP levels were similar between tx and placebo grps (0.92 vs 0.87 mg/dL; p=0.77 and 0.87 vs 1.0 mg/dL; p=0.14), respectively. The mean change score for CRP was significant at 6 mos in the azithromycin-treated grp	By 6 mos, azithromycin reduced serum CRP levels compared w/ placebo in CAD pts who were seropositive for C pneumoniae, but had no significant effect on clinical outcomes including CVD death, nonfatal MI, hospitalization for USAP, or unplanned revascularization. Additional, larger, long-term studies

	coronary events F/u time, 6 mos Study timeframe NR		score defined as change in serum levels between baseline and f/u levels.	compared w/ the placebo grp (-0.001 vs 0 mg/dL; p=0.017) but not at 3 mos (0.036 vs 0 mg/dL; p=0.67). Azithromycin had no effect on later outcomes (at 6 mos) including a composite CVD outcome, CVD death, nonfatal MI, hospitalization for USAP, unplanned revascularization, or nonfatal stroke (p=0.60). Azithromycin had no effect on antichlamydial antibody titers.	are needed to further evaluate this tx in CAD pts. Limitations: due to low event rate at 6 mos, the study lacked adequate statistical power to determine tx effects; interim results only; optimal dose and duration of antibiotic tx are unclear; results do not prove that this infectious agent is related to CAD pathogenesis.
	Tommasi et al. (1999) University of Perugia, Perugia, Italy Prospective cohort study To evaluate the utility of elevated serum CRP as a prognostic indicator in pts w/ first,	n=274 consecutive pts admitted to CCU w/in 12 hrs of first acute MI Exclusion criteria: inadequate ECG results; systemic disease; prior MI; delayed admission and lack of CRP measurements; or residual ischemia [210/274 (77%) pts were excluded	Standard CRP immunoassay (normal value, ≤0.5 mg/dL). Blood collected in hospital w/in mean of 8 hrs of symptom onset. All pts received nitrates and aspirin and some received beta blockers and ACE inhibitors. <0.45 mg/dL (1st quartile) 0.45-0.93	17 coronary events, including 4 cardiac deaths, 11 USAP, 2 recurrent MI occurred during f/u. Mean serum CRP level was higher in pts who died during f/u (5.09 vs 1.84 mg/dL; p=0.02) or who had AP (3.0 vs	Elevated serum CRP was significantly associated w/ a poorer prognosis and higher likelihood of recurrent disease or death w/in 1 yr of dx in pts who were discharged from the hospital after a first, uncomplicated acute MI. Pts in the top

	uncomplicated MI F/u time, mean, 13 ±4 mos 1993-1995	under these criteria] n=64 pts who comprised study grp had uncomplicated hospital stay, no residual myocardial ischemia, LVEF ≥50%; no involvement of collateral vessels; no AP; normal LV function; negative exercise test results (55 men, 9 women)	mg/dL (2nd quartile) >0.93-2.55 mg/dL (3rd quartile) >2.55 mg/dL (4th quartile) Outcomes were cardiac death, nonfatal MI, USAP, & CHF. F/u was halted if pt underwent revascularization and upon the occurrence of one ischemic event. Adjustment for age, gender, diabetes mellitus, hypertension, smoking, infarct site, stenosis severity, ejection fraction, CRP level upon admission, peripheral arterial disease, peak CK-MB value, plasma cholesterol, and fibrinolytic tx.	1.84 mg/dL; p=0.05). No difference was found for pts w/ recurrent MI (4.0 vs 1.98 mg/dL; p=NS). Mean serum CRP was higher in pts w/ any coronary event (3.61 vs 1.48 mg/dL; p<0.001) compared w/ those who had no event. The incidence of coronary events increased w/ increasing quartile of CRP and was 6%, 12%, 31%, and 56%, respectively, for the 1st − 4th quartiles (RR=3.55; CI, 1.56-8.04; p=0.006). Pts w/ a CRP level >2.55 mg/dL had a lower event-free survival rate compared w/ pts w/ levels ≤2.55 mg/dL (p=0.0051).	quartile of CRP had a 56% incidence of a coronary event during f/u. The authors noted that in this carefully selected grp, increases in CRP were most likely related to myocardial ischemia and inflammation at the atherosclerotic site since pts w/ systemic, inflammatory processes were excluded from this analysis. CRP testing may serve as a way to identify subgrps of pts w/ poor prognosis despite being at low risk according to standard clinical criteria. Limitations: a number of pts were excluded resulting in small sample size.

				In a multivariate analysis, increased serum CRP (>2.55 mg/dL) was the only independent factor for the occurrence of a coronary event (p=0.001).	
	Garcia-Moll et al. (2000) St. George's Medical School, London, UK Prospective cohort study To evaluate the efficacy of serum CRP testing for predicting the prognosis of CSAP F/u time, median, 1.6 yrs 1994-1997	n=924 CSAP pts w/ stable symptoms for ≥3 mos prior to study entry (592 men, 332 women): 0 vessel disease (n=218) 1 vessel disease (n=250) 2 vessel disease (n=261) 3 vessel disease (n=182) Exclusion criteria: recent MI, USAP, prior CABG or PTCA, kidney failure, valvular heart disease, inflammatory or connective tissue diseases; malignant arrhythmias, liver disease, any condition posing possibility of death w/in 1 yr. 13 (1.4%) pts	hs-CRP immunoassay (limits of detection, 0.2-12.0 mg/L) Blood specimens obtained prior to coronary angiography. Blinded interpretation of angiograms. Outcomes were hospitalization for USAP, need for revascularization, MI, stroke, cardiac death in relation to baseline CRP levels, and the effects of HRT on CRP levels Adjustment for stenosis severity and extent, CRP level, age, gender, prior MI, and LVEF	There were 89 events during f/u including USAP (n=53), MI (n=7), death (n=22), and stroke (n=7). Serum CRP levels were higher in pts who had coronary events compared w/ those w/o events (2.6 vs 2.3 mg/L; p=0.061). When women on HRT were excluded, the association between CRP level and incidence of a coronary event was significant (2.6 vs 2.2 mg/L; p=0.046). Only serum CRP (OR=1.68; CI, 1.04-2.72;	In this cohort of CSAP pts w/ a varying spectrum of disease severity, serum CRP levels were a significant predictor of an increased risk for a coronary event. CRP may be a useful prognostic indicator, but the clinical implications of these epidemiological findings remain unclear. Limitations: some pts excluded from analysis

		excluded from analysis due to death, other serious disease, or loss to f/u		p=0.033) and the number of diseased vessels (OR=1.58; CI, 1.27-1.97; p<0.0005) were independent predictors of a cardiac event. Serum CRP levels were increased in women on HRT (p=0.001)	
	Lindahl et al. (2000) University of Uppsala, Uppsala, Sweden FRISC Study Group* Prospective cohort study To assess relationship of serum CRP and other inflammatory markers to long-term risk of death from cardiac causes in USAP pts F/u time, mean, 37.0 mos (range 1.6-50.6) 1992-1996	n=917 USAP FRISC study participants w/ complete data on CRP, TnT, and fibrinogen levels (577 men, 340 women) At FRISC study entry, pts had USAP or chest pain suggestive of acute MI and chest pain onset w/in 72 hrs of study entry; ECG evidence of ischemia manifested as ST-segment depression and/or T-wave inversion. n=422 AP at rest w/in wk prior to chest pain n=532 w/ chest pain upon admission	Standard CRP immunoassay Median time from onset of chest pain to entry was 24 hrs <2.0 mg/L CRP (1st tertile) 2.0-10.0 mg/L CRP (2nd tertile) >10.0 mg/L CRP (3rd tertile) Outcomes were rates and adjusted and unadjusted RRs of death due to cardiac causes. Information obtained from death certificates from the Swedish National Cause of Death Register. Adjustment for age, sex, BMI, smoking, hypertension, prior MI, hx of CHF, diabetes, prior	Index event was acute MI in 358 (39%) and USAP in 599 (61%). 124 (13.5%) pts died during f/u; 92 (74%) deaths were due to cardiac causes. At entry, median serum CRP levels were higher in pts who died of cardiac causes compared w/ those who survived (13.0 mg/L vs 5.0 mg/mL; p<0.001). The CAD mortality rate was 5.7% of 314 pts w/ CRP <2.0 mg/L; 7.8% of 294 pts in 2nd tertile, and	In this cohort of USAP pts, several baseline variables were significant, independent predictors of the risk of death due to cardiac causes over a period of approximately 3 yrs. While the authors noted that myocardial necrosis may have accounted for some of the increased serum CRP levels, they added that the risk of death rose over time in those w/ CRP elevations at baseline. They concluded that inflammation causes instability in CAD, which is reflected by inflammatory

	Exclusion criteria: bleeding disorders	CSAP, prior stroke, hx of medication use for CSAP or CHF, ECG abnormalities, index event, TnT levels w/ in 24 hrs of admission, CRP and fibrinogen at study entry	16.5% of 309 pts in the top tertile (>10.0 mg/L) (p=0.29 and p=0.001, respectively, for the 2nd and 3rd tertiles). In a multivariate analysis, the HR for death due to cardiac causes was 2.3 (CI, 1.3-4.0) for pts w/ serum CRP levels >10.0 mg/L. Other independent predictors of death were advancing age, diabetes, hx of CHF, anti-anginal drug requirements at admission, ST-segment depression, and TnT level >0.06 mg/L.	markers, and that pts w/ increased CRP and other markers may require aggressive tx. Limitations: possibility of bias related to misclassification of cause of death on death certificates.

	Danesh et al. (2000) St. George's Hospital Medical School, London, UK; Royal Free and University College Medical School, London, UK; Imperial Cancer Research Fund Cancer Epidemiology Unit, Oxford, UK Prospective nested case-control study and meta-analysis To assess associations of CRP, SAA, serum albumin, and WBC count w/ CAD events F/u time, mean, 9.5 yrs 1978-1996	n=506 men who were randomly selected from 24 British towns provided blood samples and subsequently died from CAD (n=223) or had nonfatal MI (n=284) [data not reported for one participant] n=1025 age- and residence-matched men w/o cardiac events	Standard CRP immunoassay (no details provided) Blind assessment of baseline CRP and SAA Outcomes were CAD and fatal MI determined by death certificates and physician reports Risks evaluated for pts in bottom third of baseline values compared w/ those in top third <0.9 mg/L CRP (1st tertile) 0.9-2.4 mg/L CRP (2nd tertile) >2.4 mg/L CRP (3rd tertile) Adjustment for age, smoking, BP, BMI, serum TC, HDL-C, triglycerides, lipids, homocysteine, positivity for bacterial infections, and various demographic and environmental factors	Unadjusted OR=3.46 (CI, 2.59-4.62) for CAD. OR=2.13 (CI, 1.38-3.28) for CAD in men in top tertile (>2.4 mg/L) of CRP compared w/ men in bottom tertile (<0.9 mg/L) after adjustment for confounding variables, including age, town, socioeconomic variables, smoking, and other vascular risk factors. Similar adjusted ORs were obtained for SAA (1.65; CI, 1.07-2.55) while the ORs for WBC count and serum albumin were not significantly increased. Serum CRP levels were associated w/ smoking, BMI, and respiratory function (p<0.0001) and remained strong after adjustment	In this population of British men, baseline values of the four inflammatory markers were correlated w/ each other, and serum CRP and SAA levels were significantly associated w/ increased risks for CAD. The authors noted that the risk of CAD decreased after adjustment for confounding variables, which raises questions about whether CRP is an independent risk factor for the disease. In addition, none of the inflammatory markers were strongly associated w/ markers of infection or plasma homocysteine. Limitations: analysis limited to men w/ available specimens; retrospective outcome data obtained from primary physician reports & death

				for confounding variables. The baseline values of the four inflammatory markers were strongly correlated ($p<0.0001$). Serum CRP and the other markers were not significantly correlated w/ Helicobacter pylori seropositivity or Chlamydia pneumoniae IgG titers, or w/ plasma homocysteine levels or socioeconomic factors.	certificates.
	Strandberg et al. (2000) University of Helsinki, Helsinki, Finland Prospective cohort study To assess effect of statin tx on serum CRP and lipid levels in hypercholesteremic CAD pts and to determine the mechanisms of the	n=66 hyperlipidemic CAD pts w/ stable disease and no statin tx w/in 8 wks of study entry (47 men, 19 women) n=29 prior MI Note: 60 pts who had frozen samples available were included in statistical analysis	Standard immunoassay for CRP (Medix Biochemica, Espoo, Finland) (limit of detection, 0.3-30.0 mg/L) Pts treated w/ atorvastain (20 mg/d) (n=30) or simvastatin (20 mg/d) (n=30) after 8-wk, lead-in period of no tx	Median serum CRP levels at baseline and at 12 mos were 1.55 and 1.0 mg/mL, respectively ($p=0.03$). CRP level was more likely to decrease (n=36, 60%) than to increase (n=19, 31.7%) or remain unchanged (n=5, 8.3%) during tx.	In this study of hyperlipidemic pts w/ CAD, decreased serum CRP levels were significantly correlated w/ increased levels of HDL-C during 12 mos of statin tx. The authors noted these findings differ from previous study (Ridker et al., 1999) in which the changes in CRP induced by statin tx

	anti-inflammatory effects of statins F/u time, 12 mos Study timeframe NR		Blood samples obtained at baseline and at 12 mos Outcomes were correlations between changes in serum CRP levels and lipid levels during tx Adjustment for gender; age; aspirin use; statin type; and changes in BMI, triglycerides, LDL-C, and HDL-C	Mean reductions in lipids were observed: LDL-C decreased by 47.3%, and triglycerides by 7.7%. HDL-C increased by a mean of 7.1% during statin tx. The change in serum CRP level during tx correlated w/ changes in HDL-C ($p<0.001$) and apolipoprotein A1 ($p<0.001$) but not w/ changes in LDL-C or triglycerides. The change in CRP levels was not related to the statin type used during tx. In a multivariate analysis, only HDL-C and apolipoprotein A1 were significantly correlated w/ the change in CRP.	became nonsignificant by 5th yr; thus, further studies are needed to elucidate the effects of statin tx on CRP levels. The results of this study are preliminary since long-term effects are unknown, and while CRP levels decreased during statin tx, study did not examine whether decreased CRP levels led to a reduction in cardiac events. Limitations: small sample size; data missing for 9%; lack of controls and randomization.

	Packard et al. (2000) Glasgow Royal Infirmary, Glasgow, Scotland; Glasgow University, Glasgow, Scotland; SmithKline Beecham Pharmaceuticals, Harlow, UK; diaDexus, Santa Clara, CA Substudy of WOSCOPS‡ Prospective nested case-control study, 1989-1995 To evaluate the prognostic value of serum inflammatory markers of CAD, including CRP, lipoprotein-associated phospholipase A2, fibrinogen, and WBC count	n=580 hypercholesteremic men who had a coronary event n=1160 controls from the same cohort who had not had a coronary event matched for age and smoking status Original cohort consisted of 6595 men who had LDL-C levels from 174-232 mg/dL, who had no prior hx of MI, and who were randomized to pravastatin or placebo	Standard hs-CRP immunoassay (lower limit of detection, 0.1 mg/L) <0.76 mg/L (1st quintile) 0.76-1.44 mg/L (2nd quintile) 1.45-2.52 mg/L (3rd quintile) 2.53-4.59 mg/L (4th quintile) >4.59 mg/L (5th quintile) Outcomes were MI or death from cardiac causes, revascularization as a first event, or the combined outcomes of MI or death from cardiac causes, and revascularization as a first event. Revascularization was defined as PTCA or CABG. Adjustment for age; systolic BP; triglycerides; LDL-C and HDL-C; and for fibrinogen, WBC count, and CRP in conjunction w/ lipoprotein-associated phospholipase A2 (Model 1) and lipoprotein-associated phospholipase A2 (Model 2)	Mean serum CRP levels: cases, 2.36 mg/L; controls, 1.88 mg/L (p<0.001) CRP: RRs were 1.28 (CI, 1.14-1.43), 1.21 (CI, 0.94-1.55), and 1.27 (CI, 1.14-1.42) for MI or death from cardiac causes; revascularization as a first event; the combined outcomes of MI, death from cardiac causes, and revascularization as a first event, respectively (p<0.001). In Model 1, elevated CRP was an independent risk factor for a cardiac event (RR=1.21; CI, 1.06-1.39; p=0.004) as were WBC count and lipoprotein-associated phospholipase A2. In Model 2, CRP was not an independent risk factor for a	In addition to WBC count and fibrinogen levels, elevated serum CRP was a significant and independent predictor of risk of a cardiac event in this population of hypercholesteremic, middle-aged men. Risk was doubled for men in highest quintile for CRP. However, in a multivariate analysis, risk increases associated w/ elevated CRP were attenuated after adjusting for confounding variables. RR was no longer significant after accounting for WBC count. Authors concluded it is possible that CRP simply reflects the presence of atherosclerosis and that elevated levels of lipoprotein-associated phospholipase A2 were the strongest predictor of CAD in these pts. Limitations:

					cardiac event (p=0.09); however, when WBC count or WBC count and fibrinogen were omitted, the risk increase was significant (RR=1.16; CI, 1.01-1.32 and RR=1.15; CI, 1.03-1.29, respectively). The risk was approximately twice as high in the fifth quintile compared w/ the lowest quintile for CRP, WBC count, and fibrinogen. CRP was significantly correlated w/ age, BMI, systolic BP, cholesterol, triglycerides, LDL-C, fibrinogen, and the WBC count (and negatively correlated w/ HDL-C).	retrospective study cannot prove causation; population limited to men only.

	Horne et al. (2000) University of Utah, LDS Hospital, Salt Lake City, Utah Intermountain Heart Study Prospective cohort study To evaluate (1) joint predictive value of serum CRP and lipids for survival in CAD pts; and (2) assess effects of statin tx on survival in pts w/ elevated CRP F/u time, mean, 3 yrs (range 1.8-4.3) 1994-1997	n=985 pts w/ severe CAD (coronary stenosis ≥70% in ≥1 branch) confirmed by coronary angiography (683 men, 302 women): n=393 CSAP n=285 USAP n=211 acute MI n=172 statin tx	Standard CRP immunoassay; cutoff value <0.5 mg/dL Outcomes were survival and relationship among statin tx, serum CRP level, and survival <1.2 mg/dL CRP (1st tertile) 1.2-1.7 mg/dL CRP (2nd tertile) >1.7 mg/dL CRP (3rd tertile) Adjustment for age, sex, smoking, diabetes, hypertension, family hx of CAD, presenting dx, number of stenotic vessels, renal failure, clinical interventions (medical tx, PTCA, CABG, stenting, or atherectomy), LVEF, HDL-C, LDL-C, TC, and CRP	109 (11%) pts died during f/u. In a univariate analysis, risk of death was not related to levels of TC, LDL-C, HDL-C, or the TC: HDL-C ratio. Statin tx decreased the risk of death (HR=0.39; CI, 0.20-0.78; p=0.02). In a multivariate analysis, statin tx was independently protective against risk of death (HR=0.49; CI, 0.24-0.97; p=0.04). In same model, serum CRP (HR=1.6/ tertile; CI, 1.3-2.1; p=0.0002); age (HR=1.08/yr; CI, 1.05-1.10; p<0.0001); LVEF (HR=0.97/% increase; CI, 0.96-0.99; p<0.0001); and diabetes (HR=1.7; CI, 1.1-2.6; p=0.02) were independent	In this study of pts w/ severe CAD, lipid levels were not predictive of survival; however, CRP and statin tx were independent predictors of survival. Pts in the upper tertile of CRP were more likely to die during f/u. Statin tx was most beneficial to pts in the higher tertiles of CRP and may reflect anti-inflammatory properties of these drugs. Whether lower mortality rates in statin-treated pts were related to a reduction in CRP levels by statin tx remains unclear. Limitations: lack of randomization creates difficulties in ascertaining the exact role of statin tx in survival; baseline CRP levels may have been affected by myocardial injury; findings require confirmation in RCT.

				survival predictors. Statins benefited pts w/ elevated CRP by eliminating the increased mortality across increasing CRP tertiles [(statin tx, HR=0.97/ tertile CRP; p value for trend= 0.94) (no statin tx, HR=1.8/ tertile CRP; p<0.0001)].	
	Heeschen et al. (2000) Stanford University Medical School, Stanford, CA; Kerckhoff Clinic, Bad Nauheim, Germany; University Hospital Hamburg, Hamburg, Germany; Erasmus University Rotterdam, Rotterdam, Netherlands CAPTURE Trial§ Prospective cohort study To evaluate predictive value of CRP and TnT for	n=447 USAP pts enrolled in placebo grp of CAPTURE trial. All had recurrent chest pain at rest associated w/ ECG changes during tx and target lesions of ≥70% diameter stenosis (320 men, 171 women)	N Latex CRP Mono Test (Behring Diagnostics) (limit of detection, 0.2 mg/ L); cutoff value: 0.5 mg/L Blinded determination of serum CRP and TnT levels at baseline & before discharge ≤2.8 mg/L CRP (1st quintile) 2.9-5.3 mg/ L CRP (2nd quintile) 5.4-9.9 mg/L CRP (3rd quintile) 10.0-22.6 mg/L CRP (4th quintile) >22.6 mg/ L CRP (5th quintile) Outcomes were death, MI, need for urgent intervention	13 (2.9%) deaths and 47 (10.5%) MIs during 6-mo f/u. Baseline statistics: 83 pts in 1st quintile of CRP, 85 in 2nd, 94 in 3rd, 98 in 4th, and 87 in 5th. CRP was ≥10.0 mg/L in 185 pts (47%) and <10.0 mg/L in 262 (59%). For first 24- and 72-hr periods, incidences of death and MI were not related to serum CRP level when	In this grp of pts w/ refractory USAP who were scheduled for PTCA, baseline levels of CRP were not predictive of outcome at 72 hrs; however, pts w/ CRP levels >10.0 mg/L were significantly more likely to die or have an MI during 6 mos of f/u and were also more likely to experience coronary restenosis. TnT was a better predictor of immediate risk and early outcomes in these pts, but CRP was a better

	short- and long-term outcomes in USAP pts F/u time, 6 mos 1993-1995		(PTCA or CABG), symptomatic restenosis of treated lesion necessitating repeat revascularization during f/u. F/u at 24 hrs before PTCA, ≥72 hrs post-PTCA at 30 days, and at 6 mos. Adjustment for gender; age; diabetes; hypercholesteremia; hypertension; hx of angina, MI, PTCA, or CABG; ST-segment depression; T-wave inversion; TnT; CRP; and CK-MB	comparing 2nd - 5th quintiles w/ the bottom quintile. Incidences of death and MI at 30 days and at 6 mos were higher in pts in the two upper quintiles (>10.0 mg/L CRP) compared w/ pts in the bottom quintile (14.1% vs 7.6%; p=0.03 and 18.9% vs 9.5%; p=0.003, respectively, for the time periods). Risks were increased in pts in upper quintiles for MI (13.5% vs 8.4%; p=0.16) and for death (5.4% vs 1.1%; p=0.005) compared w/ those in bottom quintile. In a multivariate analysis, CRP (p=0.01), TnT (p<0.001), and age >65 yrs (p=0.02) were independent predictors of death and MI at 6 mos.	indicator of a poor prognosis at 30 days or 6 mos even in pts w/ normal TnT values. It was concluded that the difference in risk according to CRP status could help to guide medical tx. Limitations: highly selected pts participating in RCT; generalizability to other populations unclear.

				The incidence of restenosis during f/u was related to CRP level (7% vs 2.3%; p=0.03) CRP levels obtained at discharge were not significantly predictive of the outcome at 30 days or 6 mos.	
	Cortellaro et al. (2000) University of Milan, Milan, Italy Substudy of FACT Study¶ Randomized, double-blind, multicenter trial To evaluate effects of statin tx on serum CRP, fibrinogen, and t-PA inhibitor levels in CAD pts F/u time, 24 wks Study timeframe NR	n=333 FACT study CAD pts w/ mixed hyperlipidemia, triglycerides from 180-400 mg/dL, and LDL-C from 135-250 mg/dL n=217 CSAP n=205 prior MI n=119 coronary revascularization	Standard CRP immunoassay (RapiTex CRP, Dade-Behring) Randomized to one of four grps Blood samples obtained at baseline and at 12 and 24 wks. Analysis performed by technician blinded to tx grp.	Mean serum CRP levels did not change significantly between baseline values (range 4.7-5.9 mg/L) and values at 12 and 24 wks in any of the four tx grps.	Neither statin monotherapy nor combination tx resulted in a decrease in serum CRP levels in these CAD pts w/ hyperlipidemia. The methodological limitations of this study do not allow for conclusions to be drawn regarding the lack of effects of statin tx on CRP levels in this pt population, or on the role of statin tx and CRP in the secondary prevention of CAD. Limitations: lack of placebo control and short f/u time did not allow for accurate evaluation of tx effects.

	Tomoda and Aoki (2000) Tokai University Hospital, Boseidai, Isehara, Kanagawa, Japan Prospective cohort study To evaluate relationship of elevated serum CRP to outcome after acute MI F/u time, 6 mos 1994-1998	n=234 pts w/ acute MI admitted to CCU w/in 6 hrs of onset (181 men, 53 women) Exclusion criteria: typical chest pain of <30 min duration	Standard CRP immunoassay (0.1-20 mg/dL). Normal value defined as <0.3 mg/dL. Blood specimens were obtained w/in 6 hrs of symptom onset and all pts were treated by PTCA and stenting following coronary angiography. 100/234 (42.7%) had bailout stenting for dissection or suboptimal dilation. Outcomes were in-hospital events (coronary reocclusion, reinfarction, target vessel revascularization, bailout stenting, other cardiac events, and death) and late outcomes (restenosis, revascularization, and death) Adjustment for age, gender, diabetes mellitus, hypertension, hypercholesteremia, smoking, hx of acute MI, and USAP before study entry	W/in 6 hrs after the onset of the acute MI, serum CRP was ≥0.3 mg/dL in 49 pts (21%) (Grp 1) and was <0.3 mg/dL in 185 pts (79%) (Grp 2). Mean serum CRP at admission: Grp 1, 1.04 mg/dL; Grp 2, 0.14 mg/dL ($p<0.001$) Baseline characteristics similar between the two grps Incidence of in-hospital events including coronary reocclusion ($p<0.05$), target vessel revascularization ($p<0.05$), bail-out stenting ($p<0.005$), death ($p<0.01$), and major cardiac events ($p<0.005$) were increased in pts w/ elevated CRP compared w/ pts who had normal values. Major cardiac events occurred in 22.4% of those	In this study of pts who underwent PTCA and stenting for acute MI, elevated serum CRP levels on admission were significantly related to a poorer prognosis and a higher likelihood of a major cardiac event including reocclusion, need for revascularization or bail-out stenting, and death. Almost one quarter of pts w/ high CRP levels had an event compared w/ less than 5% of pts w/ normal values. CRP may be an efficacious marker for acute coronary events in pts presenting w/ acute MI who are treated w/ PTCA and stenting. Limitations: authors stated that the assay they used was not very sensitive and that a hs-CRP assay used in another study demonstrated that 70% of pts w/ acute MI had

			w/ elevated CRP levels compared w/ only 4.3% of those w/ normal values. There were no differences in the incidence of late outcomes including restenosis, target vessel revascularization, and death between the two grps (p=NS)	elevated CRP levels.

* In the Fragmin During Instability in Coronary Artery Disease (FRISC) trial, patients were randomized to treatment with low-molecular-weight heparin or to placebo for unstable coronary artery syndromes.
† The Cholesterol and Recurrent Events (CARE) trial was a randomized controlled trial to evaluate whether pravastatin prevented disease recurrence in patients with a prior history of MI.
‡ In the West of Scotland Coronary Prevention Study (WOSCOPS), pravastatin therapy reduced the incidence of coronary events and death from cardiac causes in approximately one third of the hypercholesteremic men who were enrolled (n=6595).
§ The Chimeric c7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment Trial (CAPTURE) was designed to assess outcomes in patients with refractory USAP who were randomized to abciximab or placebo at ≤24 hours before a scheduled percutaneous transluminal coronary angiography.
¶ The Fluvastatin Alone and in Combination Treatment (FACT) Study compared the efficacy and safety of fluvastatin and bezafibrate in monotherapy and in combination on serum lipids in hyperlipidemic CAD patients.

Appendix IV Studies on the Efficacy of CRP Testing in Asymptomatic Populations

Authors/Study Design	Study Population	CRP Assay/Protocol/ Outcomes	Results	Conclusions/ Comments

Ridker et al. (1998b) Brigham and Women's Hospital, Boston, MA; Harvard Medical School, Boston, MA Substudy of PHS* Prospective nested case-control study To evaluate whether serum CRP adds to the predictive value of TC and HDL-C in determining the risk of a first MI in apparently healthy men F/u time, 8 yrs 1982-1995	n=245 men w/o CAD when enrolled in PHS and who subsequently developed a first MI n=372 controls w/ o MI matched for age and smoking status	CRP assayed by ELISA (limits of detection, 0.5-2.5 mg/L) Randomized to aspirin or placebo at beginning of trial Blind assessment of blood samples ≤0.55 mg/L CRP (1st quartile) 0.56-1.14 mg/L CRP (2nd quartile) 1.15-2.10 mg/L CRP (3rd quartile) ≥2.11 mg/L CRP (4th quartile) Outcomes were risk of first MI in relation to CRP and lipid parameters Adjustment for BMI, age, diabetes, smoking, family hx of CAD, and hypertension	In univariate analysis, baseline levels of CRP (RR=1.38; CI, 1.19-1.61), TC (RR=1.62; CI, 1.39-1.90), and the TC:HDL-C ratio (RR=1.59; CI, 1.37-1.86) were associated w/ future MI (all p values were <0.0001). Risk of future MI increased by 38% for each quartile of CRP (CI, 19%-61%) (p<0.001). RRs of future MI among men w/ high levels of both CRP and TC (RR=5.0; p=0.0001) were higher than the product of the individual risks associated w/ elevations of either CRP (RR=1.5; CI, 0.9-2.4; p=0.1) or TC (RR=2.3; CI, 1.5-3.7; p=0.0003). Increased RR for elevated CRP and TC persisted after adjustment for	In this grp of initially asymptomatic men, baseline serum CRP level was independently and dose-dependently correlated w/ the risk of a future MI w/ in 8 yrs. CRP added to the predictive value of TC and HDL-C testing. The authors concluded that the CRP test may help to identify increased risks for future MI in individuals w/ normal lipid levels, and in nonsmokers. These individuals could be targeted for primary prevention (eg, dietary modification, exercise, weight loss, etc). Limitations: retrospective study cannot prove causation & poses potential biases; subjects drawn from clinical study and may not be representative of the general population; CRP levels measured

				confounding variables. Baseline CRP level was predictive of risk in men w/ low as well as high levels of TC and the TC:HDL-C ratio, in nonsmokers, and after adjustment for other risk factors.	only once at baseline; population included men only, so results are not generalizable to women.
	Koenig et al. (1999) University of Ulm Medical Center, Ulm, Germany; MEDIS Institute and Institute of Epidemiology, Neuherberg, Germany; Imperial College School of Medicine, Hammersmith Hospital, London, UK Substudy of MONICA Project¥ Prospective cohort study To evaluate whether elevated serum CRP levels are predictive of	n=936 men aged 45-64 yrs who were randomly sampled from the general population and who participated in first MONICA Project Exclusion criteria: hx of MI; hx of other diseases associated w/ acute-phase response	Standard CRP immunoassay (limits of detection, 0.05-10.0 mg/L) ≤0.577 mg/L CRP (1st quintile) ≤1.117 mg/L CRP (2nd quintile) ≤2.243 mg/L CRP (3rd quintile) ≤4.537 mg/L CRP (4th quintile) ≤90.770 mg/L CRP (5th quintile) Outcomes were first acute fatal or nonfatal MI and sudden death Adjustment for age, BMI, TC, HDL-C, smoking, alcohol, blood pressure, education, occupation, and seasonal factors	53 (5.7%) CAD events occurred including 26 fatal and 27 nonfatal MIs Mean serum CRP levels were significantly correlated w/ age, BMI, TC, smoking, alcohol, blood pressure, diabetes, and seasonal and occupational variables Unadjusted HRR=1.67 (CI, 1.29-2.17) for a 1 SD increase in log-CRP After adjustment for age, and for age and smoking, the HRRs were 1.60 (CI, 1.23-2.08) and 1.50 (CI,	In this prospective study of unselected, initially healthy men, elevated CRP was independently predictive of a future CAD event including a fatal or nonfatal MI. The authors concluded that low-grade inflammation may be involved in atherogenesis and subsequently to the occurrence of CAD. Limitations: statistical association does not prove causation

future CAD in apparently healthy men F/u time, 8.2 yrs 1984-1992			1.14-1.97), respectively Men in the highest quintile had a 2.6-fold increased risk for a future CAD event	
Danesh et al. (2000) University of Oxford, Oxford, UK; St George's Hospital Medical School, London, UK; Royal Free and University College Medical School, London, UK Meta-analysis of prospective studies of CAD and its relationship to serum levels of CRP Weighted mean f/u, 8 yrs 1997-2000	n=2557 subjects: 14 prospective studies of CRP and CAD including 11 population-based cohort studies (n=1953) and 3 prospective studies on pts w/ preexisting CAD (n=604) Weighted mean age at study entry, 58 yrs	All studies used sensitive assays and all adjusted for smoking and traditional CAD risk factors (age, gender, socioeconomic factors, etc) <0.9 mg/L CRP (1st tertile) 0.9-2.4 mg/L CRP (2nd tertile) >2.4 mg/L CRP (3rd tertile)	The combined risk ratio for CAD was 1.9 (CI, 1.5-2.3) after adjustment for confounding variables in CAD pts in the upper tertile compared w/ the bottom tertile of CRP For the 11 population-based studies, the combined risk ratio was 2.0 (CI, 1.6-2.5)	The results demonstrate that the risk of CAD is significantly, independently, and dose-dependently increased in both the general population and in CAD pts in relation to increasing serum CRP level. The risk of a future CAD event is increased by ~2-fold. Limitations: statistical association does not prove causation; specific data from individual studies were not provided making it difficult to draw inferences from findings.

* The Physicans' Health Study (PHS) was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of aspirin and beta-carotene for the primary prevention of CVD in 22,071 U.S. healthy males.

£ The Womens' Health Study (WHS) was a primary prevention trial to evaluate the efficacy of vitamin E and aspirin for primary prevention in 39,876 postmenopausal women with no prior history of MI, stroke, or transient ischemic attack.
¥ The Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Project -- Augsburg Cohort Study evaluated trends in CVD in randomly selected inhabitants aged 25 to 64 years from 1984 to 1985.
§ The Postmenopausal Estrogen/Progestin Intervention (PEPI) Study was a randomized, placebo-controlled trial that evaluated the effects of four hormone replacement therapies on CVD risk factors in 875 healthy, postmenopausal women.

Appendix V: Public Comment

This report was made available for a thirty-day public comment period. Two written public comment were received, approving the report and its recommendations.

From: "Kottke, Thomas E., M.D."
To: "'anil.kaul@state.mn.us'"
Date: 2/17/02 8:42PM
Subject: C-reactive protein: Screening for coronary artery disease

Dear Dr. Kaul:

I have reviewed the above referenced document prepared by the Minnesota Health Technology Advisory Committee and dated January 28, 2002. I find the report to be a complete and accurate analysis of the data. I agree with the recommendations in the report.

Best wishes,

Thomas E. Kottke, MD, MSPH
Project Director, CardioVision 2020
pager 47422
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visit http://www.cardiovision2020.org/
to register for Quit&Win

From: "Kullo, Iftikhar J., M.D."
To: "'anil.kaul@state.mn.us'"
Date: 3/1/02 4:38PM
Subject: CRP

Dear Doctor Kaul:

I have reviewed the HTAC evaluation entitled "C-Reactive Protein: Screening of Coronary Artery Disease". This is an excellent and balanced report on the status of high-sensitivity C-reactive protein assay in determination of risk of coronary artery disease. I agree with the reports' conclusion that markers of inflammation such as CRP have promise in improving prediction of cardiovascular events. Although available evidence does not support the routine measurement of CRP for risk prediction in otherwise asymptomatic patients, it may be useful in certain clinical situations.

Thank you for the opportunity to review the report. Please let me know if you have any other questions.

Sincerely,

Iftikhar J. Kullo, M.D.
Assistant Professor
Senior Associate Consultant
Div of Cardiovascular Medicine
Mayo Clinic

IJK/smm

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