TITLE: C-Reactive Protein Levels for Cardiovascular Disease Screening: A Review of Accuracy, Use, and Guidelines

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CONTEXT AND POLICY ISSUE:

Cardiovascular disease (CVD) accounts for the death of more Canadians than any other disease. Current Canadian guidelines for the diagnosis and treatment of dyslipidemia and the prevention of CVD recommend the calculation of the Framingham Risk Score (FRS) for the initial assessment of the majority of patients for primary prevention of cardiovascular disease. The FRS recommended in the guidelines provides an estimate of the 10-year risk of nonfatal myocardial infarction or coronary death based on the Framingham risk estimate tables which adjust for sex, age, total cholesterol, smoking status, high-density lipoprotein cholesterol level, and systolic blood pressure. Despite the use of the FRS and many known risk factors, a substantial proportion of CVD events occurs in individuals without known risk factors.

More recently, the role of inflammation in cardiovascular disease has been recognized. In an attempt to improve cardiovascular risk prediction, extensive research has taken place examining the role of plasma concentrations of circulating inflammatory markers as predictors of CVD. Of these markers, C-reactive protein (CRP) has been extensively evaluated.

CRP is an acute-phase protein synthesized primarily in the liver and is increased during the inflammatory response to tissue injury or infection. CRP has long been recognized and thought to be related to CVD, but only with the development of more sensitive assay methods has it been possible to study and identify increases in CRP within ranges significant to cardiovascular disease. The term “high-sensitivity” or “highly sensitive” CRP (hsCRP) refers to measurement of CRP in serum or plasma samples using immunoassay methods with sufficient sensitivity to measure CRP levels with accurately and reproducibly at or below 0.3 mg/L, levels sufficient to assess CVD risk. Older, less commercial assays had detection limits in the range of 2 to 10 mg/L and were only suitable for measurement of acute phase responses rather than baseline levels.
Despite several published studies on the role of CRP in cardiovascular screening, it is still not recommended for routine measurement in CVD risk assessment. Recently, results from the JUPITER trial, an RCT which used a CRP level of 2.0 mg/L to initiate statin therapy in patients without cardiovascular disease, were published. The study was planned to continue until 520 events occurred but was terminated early when an independent monitoring board found a statistically significant reduction of events in the treatment arm after 393 events. In light of this study, this report will look at the value of adding CRP to standard screening for patients at risk for CVD.

RESEARCH QUESTIONS:

1. What is the evidence for the accuracy and clinical effectiveness of using C-reactive protein for screening for patients for cardiovascular disease?

2. What is the evidence that a level of 2.0mg/L of C-reactive protein should be used for screening for cardiovascular disease?

3. What are the guidelines for use of C-reactive protein for screening for cardiovascular disease?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. Database results include articles published between 2003 and December 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews, health technology assessments, meta-analyses, and guidelines.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by evidence-based guidelines.

SUMMARY OF FINDINGS:

The literature search identified one health technology assessment, one meta-analysis, one systematic review, and three guidelines.

Health technology assessments

The Institute for Clinical Systems Improvement produced an HTA in 2003 addressing the relationships between coronary heart disease (CHD) and two markers of cardiovascular disease risk: CRP and homocysteine. Both case-control and prospective nested case-control studies were identified, and 11 prospective studies that used hsCRP were summarized. Based on the evidence examining the association of CRP levels and subsequent CHD events, the authors concluded that CRP, if measured by high-sensitivity assay (hsCRP), may have independent value as a predictor of cardiovascular risk and independent value in identifying patients with normal lipids who could benefit from treatment (Conclusion Grade II based on Class B and C
evidence) but that further study is needed to determine if decreasing CRP levels would decrease cardiovascular disease risk.

The authors also commented on the need to determine the reliability of CRP testing, the need for direct evidence from prospective trials to establish if there are effective therapies to decrease levels of CRP, and then whether a decrease in CRP would decrease cardiovascular disease risk, and finally, the need to determine accuracy of the prediction. Relative risks have been reported but positive predictive values and absolute risks have not been reported and therefore the actual risk for coronary disease in a given individual with moderate CRP elevation is unknown.

Systematic reviews and meta-analyses

Shah et al. (2008) conducted a systematic review of 31 prospective cohort studies with the objective of evaluating the predictive performance of CRP in predicting CVD events, rather than simply studying its association. The authors looked at three measures of the predictive performance of CRP: discrimination, calibration, and reclassification. They also examined the population distribution of CRP in all selected studies, and the shape of the relationship with CHD events (for example whether there is a linear relationship between CRP and CVD events or a threshold value for CRP above which increased risk was noted) to better understand the factors that could constrain performance of this marker.

The authors searched Medline and EMBASE up to and including August 2007 for all prospective studies (including cohort, nested case-control, or case-cohort studies) of initially healthy subjects evaluating the association between CRP concentration and coronary events with no threshold sample size. Studies in which total mortality was the only outcome were excluded from the systematic review. Thirty-one prospective studies with a combined 84,063 individuals and 11,252 coronary events were included in the systematic review. These studies included 12 studies of men alone, 6 studies of women alone, and 13 including both men and women.

Discrimination refers to the ability of the marker to distinguish individuals who will develop an event from those who will remain event free and was assessed using disease detection rate and the area under the receiver operating characteristic (ROC) curve (AUC). In all of the 25 studies with relevant information (40,684 individuals and 9351 cases), there was a substantial overlap of baseline CRP values among incident cases and controls. The disease detection rate, or sensitivity, was estimated and reported as the proportion of those who developed events who tested positive using CRP cut-points corresponding to pre-set false positive rates of 5% of 10%. The estimates for detection rate for a 5% false positive rate from individual studies ranged from 5.8% to 15.5%. The pooled estimates for detection rates for a 10% false positive rate were 16.43%, 16.64%, and 14.77% for studies with ≤5 years, >5 and ≤10, and >10 years of follow-up respectively. In other words, using a CRP cutoff level that would result in a 10% false positive rate, only around 15% of patients who were going to have a CVD event would be identified. Study-specific AUC values were also estimated and pooled. The pooled AUC values were 0.59, 0.59, and 0.57 for studies with ≤5 years, >5 and ≤10, and >10 years of follow-up respectively. AUC values of 0.5 would represent no discrimination, whereas values of 1 represent perfect discrimination. The values reported in this meta-analysis indicate low or moderate discrimination of CRP.

The second predictive measure examined was calibration. Calibration uses a risk model to order or stratify risk and then assesses accuracy by tests that evaluate model fit. Five studies
(16.1%; 42,141 individuals, 2430 incident cases) were identified that reported the effect of adding CRP to the calibration of risk models based on traditional risk factors. The assessment was made in different ways in the 5 studies, precluding pooled analysis, but none appeared to identify a quantitatively large improvement in model fit, though statistically significant differences were sometimes judged as being clinically important. However, the authors noted that regardless of the metric used, even when statistically significant results were found, they were of quantitatively small improvements.

The final method used to measure predictive performance was to look at reclassification, or quantifying the extent to which CRP shifts individuals between categories of CHD risk initially determined using established risk models. Only one study was found that previously reported on the ability of CRP to reclassify subjects into risk categories. In that study, only 70 of the 26,927 participants crossed the 10-year 20% CHD risk threshold following the addition of CRP. The study did not provide data on the eventual outcome of these reclassified individuals.

Finally the authors looked at the shape of the CRP-coronary event relationship. In all of the 25 studies with relevant information (40,684 individuals and 9351 cases), there was a substantial overlap of baseline CRP values among incident cases and controls. A total of twelve studies reported risk of CVD events according to quartiles of CRP concentration (OR 1.00, 1.23, 1.62, and 2.43 for Q1, Q2, Q3, and Q4 respectively), and 10 studies reported risk according to quintiles (OR 1.00, 1.50, 1.77, 2.27, 3.09 for Q1, Q2, Q3, Q4, and Q5 respectively). A linear graded association of log-CRP values with log risk of events was found in all studies. High CRP levels were associated with higher risk of CHD events, such that patients in the higher CRP quartile or quintile were at the highest risk for CHD events. Although the risk of CHD events increased with higher CRP values, the authors noted that many events still occur among individuals with low to mid-range values, pointing to the poor value of CRP measurements in predicting CHD events and to establish a threshold value.

The authors concluded that despite published data that indicates that CRP is consistently associated with CHD risk, measurement of CRP predicts cases of CHD only modestly well, providing much more limited information for risk prediction than tests of association alone might indicate.

Danesh et al. updated their previous meta-analysis for a second time in 2004. Results from a search of studies published prior to 2003 that included essentially general populations (described by the authors as cohorts not selected on the basis of pre-existing disease) with more than a year of follow-up were pooled with the results from a prospective study published by the authors in the same article. The objective, as found in the original meta-analyses, was to assess the associations of blood levels of fibrinogen, CRP, and albumin and leukocyte count with subsequent risk of CHD. Patient risk factors were measured at baseline and followed-up prospectively for subsequent coronary heart disease. All studies included used hsCRP assays and all but two reported adjustments for smoking and other established risk factors for CHD. A total of 7068 cases of patients with CHD with a weighted mean age at entry of 57 years and a weighted mean follow-up of 12 years were included in the analysis.

Comparison of individuals with CRP values in the top third with those in the bottom third at baseline yielded a combined odds ratio of 1.58 (95% CI, 1.48 to 1.68). This value is smaller than their previous meta-analysis of studies published prior to 2000 (based on 1953 cases of CHD) which had an odds ratio of about 2.0 (95% CI, 1.6-2.5). The authors also noted a tendency toward more extreme findings in studies published prior to 2000 and also performed an analysis restricted to four studies involving more than 500 patients, comprising 4107 cases of coronary
heart disease. This yielded a combined odds ratio of 1.49 (95% CI, 1.37 to 1.62, $X^2 = 10.6$, with 3 df; $P=0.01$) which is somewhat smaller than the overall odds ratio.

There was evidence of heterogeneity between the studies but with the exception of the date of publication, characteristics such as sample size, location, sampling method, sex of participants, mean duration of follow-up, and sample storage temperature did not account for much of the overall heterogeneity.

The authors concluded that in comparison with major established risk factors (such as an increased total serum cholesterol concentration and cigarette smoking), the CRP concentration was a relatively moderate predictor of the risk of coronary heart disease.

**Guidelines**

In 2006, McPherson et al. published a position statement on recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in collaboration with the Canadian Cardiovascular Society. Along with discussion of standard cholesterol screening, they issued recommendations on potential additional investigations for further evaluation of risk assessment including CRP. Based on more than 20 prospective epidemiological studies, the authors concluded that the data support the judicious use of hsCRP measurement and that it may be useful in the further definition of CAD risk for patients with a FRS between 10% and 19% (class IIb, level C). They also added in the appendix that a hsCRP level of less than 1.0mg/L indicates low risk for cardiovascular disease, between 1.0mg/L to 3.0mL indicates moderate risk and more than 3.0 mg/L indicates high risk.

In March of 2002, the Centers for Disease Control (CDC) and Prevention and the American Heart Association (AHA) jointly sponsored a workshop titled “CDC/AHA Workshop on Inflammatory Markers and Cardiovascular Disease: Applications to Clinical and Public Health Practice” to determine which of the currently available tests should be used; what results should be used to define high risk; which patients should be tested; and the indications for which the tests would be most useful. In 2003, the major findings and conclusions of the Workshop were used to publish a statement fully reviewed and approved by The Science and Advisory and Coordinating Committee of AHA and the CDC. In publication of the statement, the US Surgeon General’s criteria for inference of causality were used in examination of the evidence, the quality of scientific evidence for an association was assessed, and the American College of Cardiology/AHA classification of recommendations and levels of evidence were used. Consideration of the recommendations for the use of inflammatory markers as screening tools also employed an evidence-based approach.

The guideline states that current evidence supports hsCRP as the analyte of choice, after consideration of the various analytes’ stabilities: the analytes’ assay precision, accuracy, and availability; and the availability of standards for proper assay calibration. Additionally, the optional use of hsCRP is recommended to identify patients without known CVD who may be a higher absolute risk than estimated by major risk factors. Specifically, testing is recommended in patients at intermediate risk (e.g. 10% to 20% risk of CHD over 10 years), in whom the physician may need additional information to guide further evaluation or therapy. When testing, two assays, averaged, fasting or nonfasting, and optimally 2 weeks apart, should be done to provide a more stable estimate of level of CRP. A level above 10mg/L should initiate a search for an obvious source of infection or inflammation which may obscure any prediction of coronary risk. The result of >10mg/L should then be discarded and the hsCRP measured again in 2
weeks. Recommended cutpoints for low risk (<1.0mg/L), average risk (1.0 to 3.0 mg/L), and high risk (>3.0 mg/L) correspond to approximate tertiles of hsCRP in the adult population (Class IIa, Level of Evidence B). These tertiles are based on distributions of hsCRP samples from >15 populations involving >40 000 persons gathered for the purpose of the workshop.

Guidelines from the Association of Women’s Health, Obstetric and Neonatal Nurses published in 2003 relate to primary prevention in cardiovascular health for women. CRP was included under other therapies and emerging clinical tools with the recommendation that there is insufficient evidence to recommend population-wide routine screening of CRP levels, but women at 10 to 20% risk of CHD per 10 years should be considered for hsCRP testing at the discretion of the health care provider. The hsCRP assay should be performed following the CDC/AHA recommendations and performed on two different occasions, preferably two weeks apart, either fasting or non-fasting in clinically stable women. When hsCRP levels are >10mg/L, the patient should be tested for sources of infection.

Limitations

Despite several published studies on the role CRP for screening for CVD, summarized in one health technology assessment, one meta-analysis, and one systematic review, the evidence comes from observational studies. Though they show the potential benefit of CRP in risk prediction, they often only report measures of association (e.g. odds ratios, hazard ratios), which do not directly address the usefulness of CRP as a predictor. Shah et al. estimated the predictive value based on the observational studies but commented that there was a lack of consistent reporting of relevant data and as such had to infer the values. They also commented that further clarification would require pooling of studies on the basis of data for individual participants from prospective studies.

Evidence from RCTs would be useful to make an appropriate decision on the usefulness of CRP as a predictor for CVD disease. However, an RCT of a selective CRP inhibitor would provide the most useful evidence on the causal relationship between CRP and CVD but no such agent currently is available. Though statins decrease CRP levels, they also decrease LDL levels which reduces the ability to conclusively attribute the results of the JUPITER study to CRP reduction.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The results from one meta-analysis and one systematic review evaluating the usefulness of CRP in the prediction of future CVD events revealed a consistent association of elevated CRP levels with incidence of cardiovascular events. However, questions remain regarding the usefulness of CRP values in establishing risk due to its low corresponding role in predicting CVD risk. The included studies did not provide rationale for the use of a CRP level of 2.0 mg/L for screening for cardiovascular disease. Guidelines currently do not recommend routine use of CRP for screening patients at risk of CVD. Rather, CRP screening is recommended for clarifying disease in patients with intermediate risk scores. However, it does not appear that measurement of CRP adds value beyond measurement of well-established risk factors for cardiovascular disease. The lack of high quality evidence from RCTs and the remaining questions about the ability of CRP to assess risk of cardiovascular disease should be considered when deciding whether CRP should be used as a standard screening tool.
REFERENCES:


