Some experts propose C-reactive protein (CRP) as a screening tool for prediction of cardiovascular disease (CVD). Many epidemiologic studies show positive associations between elevated CRP levels and incident CVD. Assessment of the value of new prognostic tests, however, must rely on understanding of test characteristics rather than on associations measured by relative risks. In the case of CRP, test characteristics must be judged in the context of currently available CVD risk prediction algorithms. In this review of literature published before January 2006, the authors describe what is known about the additional utility of CRP in risk prediction. They find no definitive evidence that, for most individuals, CRP adds substantial predictive value above that provided by risk estimation using traditional risk factors for CVD. Use of CRP may add to risk estimation in a limited subset of individuals who are at intermediate predicted risk according to the Framingham risk score. The authors propose that many questions still must be addressed before CRP is incorporated into risk prediction algorithms and before universal screening with CRP can be recommended.

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Differences between Association and Predictive Utility

Countless studies report “strong, independent” associations between novel risk markers and CVD. Typically, these studies find unadjusted odds ratios for disease in the range of 2.0 to 3.0, and occasionally a bit higher, for individuals with the highest compared with the lowest levels of the factor. After adjustment for age, sex, and other established CVD risk factors, the relative risks (which may be reported as rate ratios, odds ratios, or hazards ratios, depending on the study design) for the association are typically attenuated to within the range of 1.5 to 2.0. Such findings indicate that an “independent” association exists between the marker and disease, provided one assumes that the multivariable model adjusted for all important confounding. However, whether such an association indicates clinical utility for measuring the factor is an entirely different issue.

Decisions about the predictive utility of new tests should not focus on associations and relative risks. The consequences of decision making based solely on significant associations would include screening for and treating hundreds of risk markers and risk factors. Rather, we should base decisions about the additional utility of a new test for risk prediction on the test’s performance (that is, sensitivity, specificity, predictive values, and clinical likelihood ratios) in the context of existing predictors. Useful ways to examine potential additional utility in the context of existing predictors include examination of the calibra-
than a randomly selected person from the unaffected population has limitations (14), one can think of the c-statistic as a measure of test performance. To date, most investigators have published their findings as AUCs. Although the c-statistic and the AUC are equivalent functions of the power of a diagnostic test for discriminating between persons with and without disease, it indicates the probability, across the entire spectrum of cutoff values for the test, that a given individual with disease (or who develops disease) will have a higher value on the test than an individual who does not have (or will not develop) disease. A perfect test has an AUC of 1.0; a test that is no better than chance has an AUC of 0.5.

Receiver-operating characteristic (ROC) curve: A graphical representation of the areas under receiver-operating characteristic curves for defining a positive and a negative test result.

Sensitivity: The probability that a test result is positive given that disease is present; also known as the true-positive rate. This is the AUC.

Specificity: The probability that a test result is negative given that disease is absent; also known as the true-negative rate.

Thus, only unusually strong, independent risk factors can markedly improve risk discrimination in the population as a whole; most new risk factors do not achieve this level of added risk above standard risk factors. It is true that 2 prediction strategies may yield the same c-statistic but have different utility. A given strategy may have a higher sensitivity at a given specificity, or vice versa. Thus, examination of the 2 receiver-operating characteristic curves and consideration of where the maximal clinical benefit lies are useful to determine the overall utility of a test in the population and for subgroups.

The observation that single risk factors predict CVD risk poorly can be explained by the fact that CVD is a complex disease with multiple antecedents. Accordingly, investigators developed multivariable risk prediction algorithms to predict the absolute and relative risks for occurrence of CVD and coronary heart disease (CHD) events over the next decade (17–20). The Framingham risk score (20, 21), which uses age, sex, total and high-density lipoprotein cholesterol levels, blood pressure, smoking, and diabetes as variables to predict risk, is widely recommended. When a model containing these traditional risk factors was applied to several diverse epidemiologic cohorts, the AUC ranged from 0.66 to 0.83 in men and from 0.72 to 0.88 in women (17). Thus, despite some contrary claims (22–24), traditional risk factors, when considered in combination, provide valuable approximations of CVD risk that are superior to approximations based on single risk factors (17, 25). Given the improvement in risk discrimination provided by multivariable models, these multivariable risk estimates are the logical standard to which new risk factors must be added and compared.

The National Cholesterol Education Program’s Third Adult Treatment Panel (21) used a modified form of the Framingham risk score as its risk prediction tool. The panel suggested thresholds of 10-year risk on which treatment decisions regarding lipid-lowering therapy should be based, in order to match the intensity of therapy to the magnitude of absolute risk. In the panel’s scheme, individuals with a predicted 10-year risk for CHD less than 10%...
are considered to be at low risk, those with a risk of 10% to 20% are considered to be at intermediate risk, and those with a risk greater than 20% (or with existing CHD or CHD risk equivalents) are considered to be at high risk. The focus is on identifying individuals at highest risk in order to initiate drug therapy. At present, an estimated 66% of U.S. adults are at low risk, 21% are at intermediate risk, and 13% are at high risk (26).

**Utility of CRP in CVD Risk Prediction**

Having established some of the issues related to the utility of a novel marker in risk prediction, we now consider the specific case of CRP. We searched for relevant English-language literature archived in MEDLINE from 1966 through December 2005 using the terms *C-reactive protein* or *CRP* in combination with *coronary* or cardiovascular. We also combined the preceding terms with the terms sensitivity, specificity, likelihood ratio, c-statistic, receiver operating characteristic, or ROC and supplemented the 2 MEDLINE searches by examining bibliographies from key articles and systematic reviews. We selected population-based studies, including cohort, case–cohort, case–control, and nested case–control studies, which examined the prospective risk for incident CHD or CVD on the basis of CRP measurements. We excluded studies examining the role of CRP for risk stratification after onset of cardiovascular events or in the setting of acute coronary events.

**Question 1: Is CRP Associated with CVD?**

Several large prospective cohort studies show that higher levels of CRP are associated with increased risk for CVD. These studies typically reported age-adjusted relative risks for CVD in the range of 2.0 to 3.0 for the highest compared with the lowest strata of CRP. Danesh and colleagues (27) recently reported a meta-analysis of 22 prospective studies published between 1996 and 2003 that examined CRP as a predictor for CVD events. Participants in these studies had a mean age at entry of 57 years and were followed for a mean of 12 years; 7068 participants developed CHD. All the studies used high-sensitivity CRP assays, and almost all adjusted for smoking and at least some other CHD risk factors. For the highest compared with the lowest tertile of CRP, the combined multivariable-adjusted odds ratio for coronary heart disease was 1.58 (95% CI, 1.48 to 1.68). Studies published since this meta-analysis continue to show similar adjusted relative risks for CRP (28–32). For example, in the Women’s Health Study, women in the top 10% compared with the bottom 10% of CRP levels had multivariable-adjusted relative risks of only 2.1 (28). Thus, CRP is consistently, although weakly, associated with CHD after adjustment for established risk factors.

**Question 2: What Magnitude of Multivariable Relative Risk Would Substantially Improve the C-Statistic with Addition of CRP to Traditional Risk Factors?**

To answer this question, we expanded an analysis approach suggested by Pepe and colleagues (16) to examine the change in c-statistic associated with the addition of a new variable to an existing risk score. Assuming that the correlation coefficient between CRP and the Framingham risk score is 0.3 (33), a multivariable-adjusted odds ratio of 3.4 for the highest versus the lowest quartile of CRP levels would be required to increase the c-statistic from 0.80 to 0.85, a moderate improvement. A more marked improvement in AUC from 0.80 to 0.90 would require a multivariable-adjusted odds ratio of 6.9. C-reactive protein and almost all other novel risk factors that have been described in the clinical literature in the past decade do not approach these levels of multivariable relative risk.

These data indicate that any new or “novel” risk factor will need to be very strongly associated with CVD and very poorly correlated with the traditional risk factors in the Framingham risk score if it is to provide substantial improvement in risk discrimination. However, much of the univariate association between CRP and CVD can be explained through the correlation of CRP with other risk factors, including age, smoking, obesity, diabetes, alcohol intake, hormone replacement therapy use, fibrinogen, and other thrombotic and inflammatory markers (34, 35). Studies show significant correlations of CRP with burden of established risk factors (34, 35) and with the metabolic syndrome (36), and CRP level also correlates significantly with the Framingham risk score (33). A recent study using the National Health and Nutrition Examination Survey III sample found that the risk for elevated CRP level attributable to the presence of any elevated or borderline traditional CVD risk factors was 78% in men and 67% in women (37). These data suggest that an elevated CRP level is in large measure attributable to traditional CVD risk factors, providing insight into its limited additional clinical utility in multivariable risk models.

**Question 3: Does CRP Add to Existing Algorithms for Risk Prediction?**

Most studies of CRP and risk prediction have reported only relative risk findings. As of January 2006, only 1 study had published sensitivity and specificity values, 7 studies had published data on changes in c-statistics, and none had published likelihood ratios to indicate the utility of CRP when added to established risk factors or risk prediction algorithms. Thus, we urge publication of findings on other test characteristics of CRP added to traditional risk factors in future studies.

The Table shows comparisons of c-statistics with and without CRP included in the multivariable model, from studies that have reported these data (27, 29, 31, 36, 38–40). None of these studies showed substantial improvements in risk discrimination when CRP was considered in
the context of the full range of traditional risk factors for CVD. The largest improvement in c-statistic with addition of CRP to the Framingham risk score was observed in a cohort of 3435 men from southern Germany, age 45 to 74 years (40). In that study, the c-statistic increased only 1.5% when CRP was added to the Framingham risk score, from 0.735 to 0.750. In the Women’s Health Study (a prospective study of 27,939 healthy women, of whom only approximately 2% had CVD events over 8 years), CRP alone yielded a c-statistic of 0.64 for prediction of CVD (38). This level of c-statistic is similar to that seen for most risk factors when considered alone. When CRP was included in a multivariable model that did not include low-density lipoprotein cholesterol for predicting 8-year risk for CVD, the c-statistic of 0.81 indicated a relatively high degree of discrimination for risk estimation. However, when low-density lipoprotein cholesterol was substituted for CRP in the multivariable model, the c-statistic also was 0.81 (38).

In the Rotterdam Study, involving 7983 healthy men and women, 157 participants had incident myocardial infarctions during follow-up. These 157 participants were compared with 500 randomly selected controls in a nested case-control study. When CRP was added to the Framingham risk function, using the upper 20% of the CRP distribution as the cutoff for a positive test result, sensitivity of prediction increased modestly from 31.2% to 39.5% and specificity increased from 84.4% to 87.0%. However, as shown in the Table, addition of CRP did not significantly improve the c-statistics of the Framingham risk function alone in this study (39) or most others (27, 29, 31, 36).

**Question 4: Does a Low CRP Level Markedly Reduce Risk for People Who Are Predicted To Be at High Risk according to Established CVD Risk Factors?**

The preceding questions have examined CRP as a tool for risk prediction from the perspective of the entire population. It is possible that CRP might add more predictive value by further stratifying or reclassifying risk among certain subgroups. To address this question, some studies have stratified participants on their risk predicted by the Framingham equations and examined whether CRP levels substantially change the magnitude of risk within these strata. This approach reduces the inherent predictive value of the continuous Framingham risk score by turning it into a categorical variable, but it may help to determine whether CRP adds value in some subgroups.

For example, in the Women’s Health Study (38), the investigators stratified participants into 4 levels of absolute predicted CVD risk over the ensuing 10 years, using the Framingham coronary risk score. Women were also stratified into groups based on CRP levels: low (<1.0 mg/L), intermediate (1.0 to 3.0 mg/L), and high (>3.0 mg/L). As shown in the Figure, the greatest contribution in stratifying risk came from the traditional risk factors in the Framingham risk function, with those middle-risk and high-risk women having a substantially larger benefit from CRP as an additional risk factor. The largest improvement in c-statistic with addition of CRP was observed in women with the highest absolute risk of developing CVD over the ensuing 10 years (41). The c-statistic increased from 0.68 to 0.70 for this group. The c-statistic also increased from 0.54 to 0.56 for women at intermediate absolute risk (42). The c-statistic for women at lowest absolute risk remained unchanged (0.30) (42) and was actually slightly lower with the addition of CRP (0.30 to 0.28) for women at highest absolute risk (42). Thus, CRP added more predictive value to the Framingham risk function among women at higher absolute risk of CVD over 10 years (41).
mingham equation (with risks varying more than 20-fold), regardless of CRP level. Women in the highest stratum of absolute Framingham-predicted CVD risk (≥10%) and who had intermediate or high CRP levels were at substantially greater risk than the rest of the cohort. Women with high predicted risk but low levels of CRP did have somewhat lower risk than those with intermediate and high levels of CRP (Figure). However, risk among these women with high levels of traditional risk factors but low CRP levels was still greater than 10 times higher than that of the referent group (38), a finding observed in other studies in men (40). Thus, CRP slightly modulated the predicted risk, but not to the extent of changing the management of the patient. In other words, addition of CRP did not cause reclassification of high-risk women into the low-risk category, where the recommendations for lipid-lowering therapy would definitely change (21). Furthermore, no data exist to indicate that the substantial risk factor burden present in the highest-risk women should go untreated merely because of a low CRP level.

**Question 5: Does a High CRP Level Markedly Increase Risk for People Who Are Predicted To Be at Low Risk according to Established CVD Risk Factors?**

Several studies have observed that, among individuals predicted to be at low risk according to traditional risk factors, high CRP levels do not indicate substantially higher CVD event rates (38–40). For example, in the Women’s Health Study, among women in the 2 lowest strata of Framingham-predicted 10-year risk (0% to 4%), high levels of CRP did not substantially increase the risk for CVD (Figure) (38). Thus, high CRP levels accompanied by low levels of traditional CVD risk factors do not identify individuals at high risk; thus, treatment recommendations would not change despite knowledge of the CRP level. The answers to questions 4 and 5 indicate that, for individuals at low or high predicted cardiovascular risk on the basis of traditional risk factors, CRP does not change the overall magnitude of observed risk, and it has little or no value for deciding which patients merit preventive treatments.

**Question 6: Does CRP Modulate Risk Prediction for People Predicted To Be at Intermediate Risk?**

Available data indicate that CRP, like other novel risk markers (41), may add to risk discrimination in the subset of individuals at intermediate predicted risk for CHD by Framingham risk score. For example, men in the MONICA (MONItoring of trends and determinants in CArdiovascular disease) Augsburg cohort study (40) with predicted risk in the intermediate range of 15% to 19% and with elevated CRP levels had observed 10-year event rates greater than those in some men predicted to be at high risk in the absence of CRP data. These results suggest that such individuals should receive intensive primary prevention therapy, as if they are in reality at “high risk.” Current clinical practice guidelines already suggest the option of treatment for patients at this level of predicted risk, in the absence of CRP measurement, but it is also true that some patients and physicians would prefer to have the additional assurance that high risk is present before committing to long-term drug therapies (21).

**Question 7: Can One Use Uniform Criteria for CRP To Predict Risk in Different Population Subgroups?**

Data from several studies suggest that current clinical cut-points recommended for high-sensitivity CRP assays cannot be applied universally. Median CRP levels vary widely, with African-American and Hispanic persons having median CRP levels 2 to 3 times those in Chinese persons (42–44). Median levels of CRP for Chinese persons are 1.0 mg/L or less (that is, more than half of these patients have CRP levels in the low-risk range), whereas the median levels of CRP for African-American persons are 3.0 mg/L or greater (more than half have high-risk CRP levels) (42–44).

The potential for substantial misclassification of risk by CRP exists if uniform cut-points are used across all ethnicities. For example, in 1 multiethnic cohort study (43), 65.7% of middle-aged Chinese individuals had CRP levels of 1.0 mg/L or less and only 6.3% had CRP levels greater than 3.0 mg/L, compared with 42.7% and 25.0%, respectively, among white persons. These differences were observed even though the Chinese participants had higher levels of triglycerides, hemoglobin A1c, insulin, plasminogen activator inhibitor-1, and systolic blood pressure. In the same multiethnic study, 51.6% of participants with Framingham-predicted risk less than 10% nonetheless had CRP levels in the intermediate or high range (revealing substantial misclassification by CRP), and most such individuals were of South Asian or aboriginal extraction. Conversely, 15.9% of participants with predicted risk greater

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**Figure. Multivariable relative risk for cardiovascular disease (CVD), based on level of C-reactive protein (CRP) and level of absolute predicted 10-year Framingham coronary heart disease risk in the Women’s Health Study.**

Data are from reference 38.
C-reactive protein (CRP) is a nonspecific marker of inflammation that, in healthy individuals, has been shown to be associated with future incidence of CVD.

Inflammation has emerged as a key mediator of atherogenesis and triggering of CVD events.

CRP, when examined critically, does not improve risk discrimination enough to recommend its routine adoption for population screening.

CONCLUSIONS

Inflammation is a major mechanism in the process of atherogenesis and in triggering of clinical CVD events. Some experts propose that CRP, a nonspecific marker of inflammation, is a new tool that improves CVD risk estimation and that it should be used as a routine clinical risk assessment test. However, as with almost all novel risk factors that have been described for cardiovascular risk, CRP, when examined critically, does not improve risk discrimination enough to recommend its routine adoption for population screening.

In 2003, the Centers for Disease Control and Prevention and the American Heart Association published a scientific statement on the applications of screening with markers of inflammation (5). The panel made the following class IIa recommendation: “Measurement of hs[high-sensitivity]-CRP...i n those judged at intermediate risk by global risk assessment (10 to 20% risk for CHD per 10 years), at the discretion of the physician, may help direct further evaluation and therapy in the primary prevention of CVD. The benefits of such therapy based on this strategy remain uncertain.” The panel also concluded that “the entire adult population should not be screened for hs-CRP for purposes of cardiovascular risk assessment.”

Three years later, we agree with the panel’s recommendation. Specific individuals may benefit from knowledge of their CRP level, but many questions still must be answered before we accept it as a standard CVD risk factor, incorporate it into risk prediction algorithms, and use it for universal screening. Until we understand whether and how

Key Summary Points

Novel risk markers for cardiovascular disease (CVD) are often said to add independent predictive value for risk prediction, based on the finding of a significant relative risk after adjustment for traditional risk factors.

However, the utility of novel risk markers for screening and risk prediction should be judged not by relative risks but by test characteristics such as sensitivity, specificity, predictive values, likelihood ratios, model calibration, c-statistics, and areas under receiver-operating characteristic curves.

Inflammation has emerged as a key mediator of atherogenesis and triggering of CVD events.

C-reactive protein (CRP) is a nonspecific marker of inflammation that, in healthy individuals, has been shown to be associated with future incidence of CVD.

Few studies have reported test characteristics for CRP, particularly in the context of traditional risk prediction algorithms such as the Framingham risk score.

In the overall adult population, CRP appears to add little to risk prediction that uses the Framingham risk score. Likewise, among subgroups of individuals predicted to be at high (>20%) or low (<10%) risk by Framingham, CRP levels contribute little further risk discrimination. Among those predicted to be at intermediate 10-year risk (10% to 20%) by Framingham, CRP levels greater than 3.0 mg/L may indicate high risk and need for more intensive preventive therapy.

Many questions remain before CRP can be accepted as a standard CVD risk factor, incorporated into risk prediction algorithms, or used for universal screening.

Future studies of CRP and other novel CVD risk markers should focus on test characteristics, not just relative risks, in order to better define their utility for risk prediction when added to traditional CVD risk factors.

than 20% had low CRP levels (43). Therefore, use of uniform cut-points to define CVD risk is probably not appropriate across diverse populations. Somewhat similar criticisms may be leveled at other continuous risk factors, such as cholesterol and blood pressure. However, therapies aimed at directly reducing those risk factors have proven benefit in reducing CVD events regardless of subgroup.

Question 8: Does Decreasing CRP Level Itself Reduce Events?

Measurement of novel risk markers can be clinically useful if data from prospective controlled trials demonstrate that targeting individuals with elevated levels and specifically lowering the factor in question reduce events. We currently lack data testing the primary hypothesis that institution of therapies, such as statins or aspirin, solely on the basis of CRP levels will decrease future CVD events. It also remains unclear whether reductions in CRP levels and CVD events observed with statin medications are due (directly and indirectly) to changes in lipids alone or to direct effects of statins on inflammation and CRP levels. Primary data do not exist to document that lowering of CRP level itself reduces event rates. Although widely publicized as showing that CRP reduction improves outcomes over and above the improvement provided by reduction of low-density lipoprotein cholesterol levels in secondary prevention of CHD, recent data from an analysis of the PROVE-IT (PRavastatin Or atorVastatin Evaluation and Infection Therapy) trial (45) add no new information to this debate. Unfortunately, the authors did not report baseline CRP levels or change in CRP levels between initiation of statin therapy and initial measurement of CRP 30 days later. They also did not report on or adjust for important potential confounders (46–48). Other data examining CRP levels in cholesterol-lowering primary prevention trials have not yet demonstrated that independent lowering of CRP levels itself reduces events (49).
we should incorporate CRP into clinical practice, it should remain, at most, a “tiebreaker” test, measured selectively in individuals at intermediate risk for CVD when the merits of beginning drug therapy for other risk factors are unclear. Future evaluations of CRP should focus not on measurement of associations but on test characteristics such as likelihood ratios and the additional utility of CRP over and above traditional risk factor measurement.

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