

# C-reactive protein for the prediction of cardiovascular risk: Ready for prime-time?

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C-reactive protein (CRP) is an acute phase reactant that increases during the host response to tissue injury, including that caused by infection, trauma, malignant disease and chronic inflammatory conditions.<sup>1</sup> In recent years, increasing attention has been paid to elevated levels of CRP as a potential risk factor for atherosclerosis.<sup>2</sup> An evolving body of epidemiological and laboratory evidence indicates that the screening of CRP levels may be a useful test for predicting the risk of atherosclerotic cardiovascular disease.<sup>3</sup>

Media awareness of CRP as a risk factor is growing as well. A recent cover story on CRP in a widely read periodical, emblazoned with the headline “The Heart Test That Could Save Your Life,” further described CRP as an “easy, new way to help predict your risk of heart attack and stroke.”<sup>4</sup> We critically examined the evidence regarding CRP levels as a test for predicting the risk of cardiovascular disease. In particular, we focused on the factors that contribute to the usefulness and validity of any screening test (Table 1). Our evaluation of the literature finds insufficient support for the widespread use of a CRP screening test as a strategy for determining the risk of cardiovascular disease.

The utility of any test depends on its ability to discriminate between individuals who have (or are at risk of) disease and healthy, disease-free individuals. This ability is often expressed in terms of the sensitivity, specificity and predictive

values (positive and negative) of the test.<sup>5</sup> These properties depend on the prevalence of disease in the population being tested and the distribution of competing (similar) conditions.<sup>6</sup> When applied to populations with a low prevalence of disease, even highly accurate tests may have a poor positive predictive value. Since about 75% of the adult population is at low to moderate risk of cardiovascular disease, relying solely on *any* single screening test in isolation (including CRP) will likely generate an excess of false-positive results.<sup>7</sup>

Unfortunately, while a number of studies have indicated that an elevated CRP level confers a higher risk for cardiovascular disease, few studies have reported values for sensitivity and specificity. By extracting data from one such study<sup>8</sup> and calculating predictive values, Levinson and Elin determined that a CRP concentration in the highest quartile had a positive predictive value of only 0.86% for the development of cardiovascular disease.<sup>9</sup> This was due, at least in part, to extensive overlap in the distributions of CRP values between cases and controls.

Another desirable attribute of a screening test for cardiovascular disease risk is the ability to confer predictive value conjointly and incrementally with that of a validated global risk prediction strategy.<sup>10</sup> In the field of cardiovascular disease prediction, a number of global risk scores are in widespread use, with one of the most validated and time-honoured being the Framingham Risk Score.<sup>11</sup> Indeed,

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**Table 1: Evidence base regarding the validity and usefulness of testing C-reactive protein levels to predict cardiovascular risk**

Characteristic	Data sources	Magnitude of support*	Comments
Reliability	Cross-sectional	Interassay +++ Within-subject + Between-subject +	Multiple determinants of CRP variability within the population
Accuracy	Case-control	Sensitivity ++ Specificity +	Few studies report absolute risk per quartile or measures of test performance
Additive value (to global risk scoring)	Cohort, case-control	+ to ++	Conflicting data
Generalizability	Cohort	?	Limited information
Ability to motivate patients	No data	?	Limited information
Improved patient outcomes	Retrospective subgroup analyses of RCTs	++	No prospective data

Note: CRP = C-reactive protein, RCT = randomized controlled trial.  
\*+ = minimal, ++ = moderate, +++ = strong, ? = unknown.

global risk scores (such as Framingham) have been incorporated into a number of national treatment guidelines by organizations dedicated to the prevention and treatment of cardiovascular disease.<sup>12-14</sup>

Two studies, with conflicting data, shed light on the ability of the CRP level to provide incremental information to the Framingham Risk Score.<sup>15,16</sup> The Women's Health Study followed 27 939 asymptomatic women for a mean of 8 years to monitor the development of cardiovascular events.<sup>15</sup> The risk of cardiovascular disease appeared to be modulated by CRP concentration at each level of Framingham-estimated risk. However, as with many other studies of CRP and the risk of cardiovascular disease, only the relative risks of different strata of CRP concentration were provided, making it impossible to predict a given participant's absolute risk of cardiovascular disease.

Conflicting information on the incremental value of CRP is provided by the Rotterdam Study, a population-based cohort of 7983 men and women aged 55 years and older.<sup>16</sup> The investigators conducted a nested case-control study comparing 157 participants who had myocardial infarctions during follow-up with 500 randomly selected control subjects. The addition of the CRP level to the Framingham risk function did not improve the area under the receiver operating characteristic curve or increase the sensitivity or specificity of the Framingham risk function. Indeed, the addition of traditional cardiovascular disease risk factors to the univariate analysis relating CRP levels to the risk of infarction substantially attenuated the relation.

Perhaps the ultimate determinant of the usefulness of any screening test is whether patients are better off if the test is used. An effective and valuable screening test for atherosclerosis would safely and inexpensively identify patients at elevated risk of the disease, ideally early in the natural history of the condition (in the presymptomatic phase), affording the opportunity to intervene and prevent the ensuing illness. This is particularly critical in coronary artery disease, where nearly half of initial presenting cases are fatal myocardial infarctions or sudden cardiac death.<sup>17</sup> Early and widely available screening could therefore have an enormous impact on people with this disease.

In the case of CRP measurement, there is indirect, retrospective evidence that this screening test could be used to target preventive therapy to those at higher risk. Ridker and colleagues conducted a post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study, a primary prevention trial of lovastatin in 6605 people with no history of atherosclerotic cardiovascular disease.<sup>18</sup> The investigators measured baseline CRP levels in 5742 participants. The risk of acute coronary events was related to CRP concentration, with a 17% increase in adjusted risk with each increasing quartile of CRP (95% confidence interval [CI] 3%–33%). Moreover, having a CRP level above the study median predicted benefit from lovastatin, irrespective of the low-density lipoprotein cholesterol level. Similar analyses have been reported on the ability of CRP

levels to predict benefit from ASA in primary prevention and pravastatin in secondary prevention.<sup>19,20</sup>

However, these studies were retrospective subgroup analyses of trials that were not designed to test a strategy of CRP-guided intervention. The ultimate test for the usefulness of CRP measurement would come from a controlled trial that randomly assigns patients to testing or no testing, directly measuring the harms and benefits of such an approach, with rigorous blinding of both patients and physicians. This strategy could also provide a direct appraisal of the cost-effectiveness of CRP screening in comparison with the use of a validated global risk score, such as the Framingham equation.

The applicability of CRP testing to special populations has not been established. Nearly all studies have been carried out with relatively homogenous white cohorts in North America and Western Europe. Limited data are available for ethnic groups that may be at particularly high risk of cardiovascular disease, such as African, South Asian and Aboriginal populations. Other risk prediction tools such as Framingham have been extrapolated with difficulty to groups beyond their derivation cohort, which has resulted in some misclassification of risk.<sup>21-23</sup> It is therefore essential that studies of CRP testing take place in these populations before screening can be applied with confidence to all groups.

The evidence base supporting the inclusion of CRP in vascular disease risk assessment is tenuous, incomplete and conflicting. Few studies report critical indices of test validity (e.g., sensitivity, specificity and predictive value); moreover, there are no prospective trials on the issue of whether screening improves patient outcomes. Until these issues are addressed — preferably through rigorous clinical trials employing randomization and blinding — calls for the widespread adoption of CRP measurement as a screening test must be regarded as premature.

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