C-Reactive Protein, Inflammation, & Cardiovascular Disease

Part 3: New Developments in Evaluating the Role of CRP as a Marker for Cardiovascular Disease

In Parts 1 and 2 of this series we reviewed evidence indicating an association between inflammation and cardiovascular disease; more specifically, we demonstrated the value of C-reactive protein (CRP) as an indicator of cardiovascular risk. In Part 3, we bring to light the latest developments regarding CRP and its value in identifying cardiovascular disease.

History

In 1948, the fatality rate of heart disease in the USA was 146.2 deaths per 100,000 people. By 1963, that rate had risen to 220.3 deaths per 100,000. Since then, the mortality rate has dropped steadily: In 1996, it reached a low of 87 deaths per 100,000 and is continuing to decline.

This decrease can be directly correlated to one of the most significant studies ever undertaken: The Framingham Heart Study. Set up in 1948, this study recruited more than 2,000 men and women in an effort to determine why 1 in 4 males living in Framingham, Massachusetts, of age 55 or older, developed heart disease. In 1971, the study added more than 5,000 sons and daughters of the original participants and it's still growing. It represents one of the most comprehensive studies in epidemiology ever undertaken in medicine: More than 1,000 research papers have been published from the data collected in Framingham.

The results of this study defined the way we look at heart disease: Well-known risk factors of cardiovascular disease, such as smoking, high cholesterol, diabetes, and obesity, were first identified in the Framingham study. Physicians now had a framework with which to evaluate their patients.

The rate of death from cardiovascular disease has dropped as a direct result of finding these causal factors. The Framingham study, however, has not identified measurable markers to assist in the primary and secondary prevention of the varied ischemic syndromes. The risk factors identified in the Framingham study account for only 50% of all myocardial infarctions (MI). This suggests that our ability to predict the risk of heart disease is still evolving and that novel, specific markers of cardiovascular risk remain to be identified.(1)

As reported in Parts 1 and 2 of this series, a growing body of evidence suggests that inflammation may be involved in the development of heart disease. In autopsy reports the atherosclerotic plaques of unstable angina patients contain more inflammatory cells than do patients with chronic stable angina (CSA). These inflammatory cells, which include macrophages, lymphocytes, and mast cells, may release proinflammatory cytokines (e.g., interleukin-1, interleukin-6, tumor necrosis factor-a), which may destabilize and rupture existing plaques.

Despite the link between inflammation and cardiovascular disease, assays for the suspect inflammatory cells and the cytokines they release are not readily available in a clinical setting. CRP, on the other hand, is an apt candidate marker of inflammation as it has a serum half-life of 19 hours, it's very stable in blood samples and several highly sensitive assays are readily available.

A recent study conducted at the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital in Boston by Dr. Paul Ridker evaluated over 28,000 participants in the Women's Health Study. They found that over an eight year span 77% of the cardiovascular events occurred in women with low-density lipoprotein-cholesterol (LDL-C) levels in the low risk range.(2) The corresponding CRP levels showed a significant correlation with reported cardiac events. Dr. Ridker theorizes that since CRP levels may rise more than 10 years prior to a cardiac event, this may give doctors a phenomenal window of opportunity to measure possible cardiac risk.

Studies such as Dr. Ridker's and additional supporting evidence have prompted the American Heart Association and the Centers for Disease Control and Prevention to issue new guidelines on the use of CRP as a test for coronary artery inflammation. As reported recently in the Wall Street Journal,(3) the new CDC guidelines recommend that patients whose risk levels are elevated from other tests should be tested for CRP. They caution that the CRP test is not a replacement for existing tests nor should it be used as a general screening tool for the entire population. This is the first time in 20 years that a new tool has been recommended to assess the risk of heart disease by the nation's leading professional medical health organizations.

What led to this new guideline? Following are some of the lastest reports of CRP's use in evaluating cardiovascular risk in the primary and secondary prevention of heart disease.

Studies in healthy patients

A 2002 report from the Framingham study correlated CRP levels with carotid atherosclerosis.(4) In a cohort of 3,173 men and women they found higher levels of carotid stenosis (>25%) among the highest quartile of CRP readings. Elevated CRP levels were associated with a risk factor of 1.6 among the men and 3.9 among the women; and after adjustment for other cardiovascular risk factors, this association proved much stronger in women and remained significant. When CRP was correlated with internal carotid intima-media thickness (IMT), the results were similar and also gender specific. When related to coronary artery calcification, however, the correlation was significant for both men and women after adjustment for other cardiovascular risk factors. The correlation between CRP and IMT is particularly interesting as IMT has been shown to be a very strong predictor of future cardiovascular events with a risk factor of 3.15 for MI and stroke.(5,6)

CRP has also shown a significant correlation with sudden cardiac death (SCD). SCD is defined as unexpected death, usually due to cardiac arrhythmias in apparently healthy individuals. This type of mortality is responsible for more than half of all cardiac-related deaths in developed countries. In the Physicians Health Study, which

involved 15,000 participants and spanned a 17-year period, 97 SCD events were reported and a strong correlation was found with high CRP levels.(7) Subjects with the highest CRP levels (mean 4.4 mg/ml) showed an almost three-fold increase in risk, while all 97 SCD victims had significantly elevated CRP levels (1.7 mg/ml) as compared with controls (1.0 mg/ml). Interestingly, these results were independent of other measurements such as homocysteine, triglycerides, total cholesterol, LDL-C, and high-density lipoprotein-cholesterol (HDL-C). In addition, the CRP levels were found to be elevated up to nine years prior to SCD.

A third and very interesting study was conducted by Rifai et al, at the Harvard Medical School.(8) A cohort of 643 women were enrolled who subsequently developed cancer or cardiovascular disease and were matched with 643 healthy women over a period of 58 months. Blood samples were collected and baseline CRP levels determined. CRP showed no association with the incidence of cancer, but correlated very strongly with the development of cardiovascular disease. The lowest to the highest quartiles of CRP measuremens showed relative cardiovascular risk levels of 1.0, 2.9, 3.4, and 5.6. Of note, this study showed higher CRP quartiles than did previous studies completed by the author. Because this study included MI, stroke, cardiovascular mortality, and coronary revascularization, the author suggests that CRP may be a stronger marker for events resulting from atherosclerotic plaque rupture and acute thrombosis rather than events primarily associated with lesional stenosis. This is consistent with the hypothesis that inflammation is strongly associated with plaque vulnerability.

Studies in patients with known coronary heart disease

Not only is CRP a strong predictor of cardiac risk in apparently healthy individuals, but it has demonstrated utility in the prognosis of patients who have experienced a cardiac event. Retterstol et al. studied a cohort of 247 patients who had experienced MI over a ten-year period.(9) Cardiac mortality was compared with CRP

measurements and found to correlate significantly. After adjusting for serum cholesterol, fibrinogen, smoking and hypertension, the relative risk for cardiac death doubled with increasing CRP levels and patients in the highest quartile were at six times the risk as compared with the lowest quartile. They concluded that CRP is a strong predictor of mortality in patients who have experienced MI and that inflammation appears to be a critical prognostic factor.

A similar study was conducted by Speidi et al, (10) at the University of Vienna, Austria. The authors followed 125 patients with angiographically proven and stable coronary artery disease (CAD) over a 72-month period; each patient had acute signs of coronary syndromes upon hospital admittance. The cohort was divided into three tertiles according to CRP levels, with the highest tertile indicating a >3.8-fold increase in the likelihood of developing a cardiac event. Figure 1 shows the probability of a cardiac event occurring for each of the three tertiles. It is apparent that the probability of a cardiac event increases with increasing CRP levels. In addition, Speidi et al. also evaluated CRP levels as they relate to the number of diseased vessels involved in each patient's disease. Figure 2 shows that higher CRP values correlated with greater numbers of affected vessels (defined as >70% narrowing of the lumen).

CRP and the cardiac troponins

The troponin subunits I (TnI) and T (TnT) are relatively new cardiac markers and are used to detect cardiac damage and to determine long-term risk after or during a cardiac event. As such, TnI and TnT are not used to screen healthy patients for risk of a future cardiac event.

Of late, many studies have evaluated the efficacy of measuring CRP in combination with TnI and TnT in patients who have suffered a cardiac event. Although the significance of this relationship is still being defined, several recent studies have provided some insight.

Heeschen et al. evaluated 447 patients with

unstable angina (UA) measuring serum TnT and CRP levels.(11) After coronary intervention, patients were assessed at 72 hours and again at a six months. TnT showed strong predictive value for short-term mortality and MI (17.4% vs. 4.2%), whereas CRP did not (10.3% vs. 8.0%). CRP did, however, demonstrate strong predictive value for mortality and MI at the six-month follow-up visit. (18.9% vs. 9.5%).

In a similar study by de Winter et al., CRP and TnI were measured upon admission in UA and non-Q-wave myocardial infarction (NQMI) patients.(12) The results were kept blinded, and after a six-month follow-up period the reported incidence of major cardiac events within the cohort was determined. The results showed that elevated CRP levels (>5.0mg/L) occurring with simultaneous TnI elevations (>0.4 ug/L) correlated with the highest incidence of a major cardiac event. Patients with elevated CRP values had a higher incidence of cardiac events than those with normal CRP levels, regardless of whether or not TnI was elevated. Event-free survival was excellent in patients with normal CRP and TnI values, and was the poorest in patients with abnormal values for both analytes. Similar studies support this and have implied that CRP may be an important prognostic marker as CRP elevations may detect risk when TnI or TnT levels are normal.(13,14,15)

An elegant study by Sabatine et al. compared mortality at 30-day and six-month follow-up periods in 450 patients presenting with non-ST elevated acute coronary syndrome (ACS) (16) Baseline measurements were made to determine levels of CRP, TnI, and B-type natriuretic peptide (BNP). Interestingly, the 30-day risk of mortality nearly doubled with the addition of each elevated biomarker (Figure 3). Similar correlations were found with the incidence of MI, congestive heart failure, and a composite of both (Table 1). The authors commented that this is not surprising because each marker may represent different pathobiologies of the ACS process: Troponins measure necrosis; CRP, inflammation; and BNP, left ventricular overload. The simultaneous measurements of these three markers undoubtedly add unique prognostic information for the clinician.

Preventive measures

Several recent studies suggest that abnormal CRP levels may be indicative of existing coronary heart disease (CHD) or may predict the likelihood of developing CHD. Many of these studies have outlined therapeutic and behavioral modalities which may lower CRP values and thus lower the risk of developing CHD.
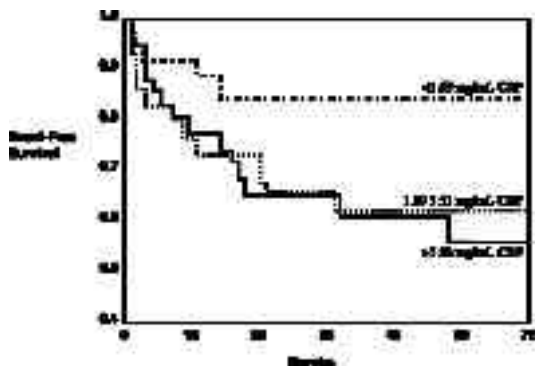

Figure 1. Kaplan-Meier survival plots for death, myocardial infarction, and need for revascularization procedures according to tertiles of CRP,
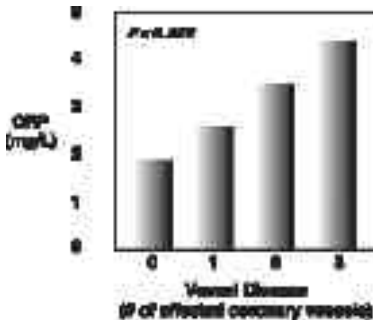

Figure 2. Median values of CRP according to the number of affected coronary vessels (> 70% narrowing of the lumen).
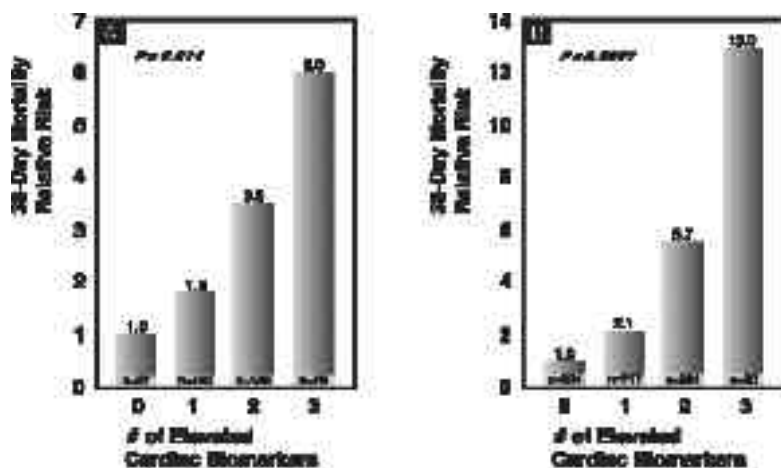
Figure 3. Relative 30-day mortality risks in OPUS-TIMI 16 (A) and TACTICS-TIMI 18 (B) in patients stratified by the number of elevated cardiac biomarkers.

Elevated Cardiac Biomarkers

Endpoints	0	1	2	3	P value[2] for Trend
30-day					
Death	1.0	1.8	3.5	6.0	0.014
MI	1.0	3.5	4.3	11.1	0.0006
CHF	1.0	1.8	2.7	6.9	0.007
D/MI	1.0	5.3	7.2	16.3	0.0001
D/MI/CHF	1.0	6.2	8.2	17.9	0.0001
10-Month					
Death	1.0	0.9	2.3	5.1	0.001
MI	1.0	2.0	2.3	3.9	0.004
CHF	1.0	1.8	3.9	8.5	0.0009
D/MI	1.0	1.8	2.3	4.6	0.0001
D/MI/CHF	1.0	1.9	2.5	4.7	0.0001

D: Death; MI: Myocardial Infarction; CHF: Congestive Heart Failure

Table 1: Relative risk of death, MI, and CHF in OPUS-TIMI 16

Some of the most popular therapeutic options for this purpose are members of the statin family. The statins are a group of medications known as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. They are prescribed for individuals with average or elevated LDL-C or below average HDL-C. Studies have shown that statins have a positive effect on lowering cholesterol and CRP levels.

Data from the Cholesterol and Recurrent Events (CARE) trial tested the effect of statin therapy. The study showed that in 472 post-MI patients the level of CRP decreased 17.4% compared to 4.2% for placebo over a five-year period. In the Pravastatin Inflammation/CRP Evaluation (PRINCE) study, 1,702 participants with no history of CHD and 1,182 with known CHD received 40 mg/day of pravastatin. After six months, the first group lowered their CRP values an average of 16.9% and similar results were seen for the post-MI cohort. In addition to these results using pravastitin, lower CRP levels have also been observed using simvastatin and atorvastatin when given for a relatively short time frame of six weeks.(17)

In addition to statins, there are many new studies which describe methods available to the general public to reduce CRP levels and the associated risk of CHD. One method is taking a small amount of aspirin each day. A recently published study showed that among 304 CHD patients admitted to the hospital 174 were taking aspirin before admission. This group showed lower TnI and CRP levels throughout a 12-month period. The risk of a further cardiac event showed a decrease from a probability of 2.64 for the untreated group down to 0.98 for the treated group. The authors hypothesized that the modification of the acute phase inflammatory response to MI may be the major mechanism in lowering risk.(18)

Another method of reducing CRP levels and risk of CHD is weight loss. A recently completed study at the University of Vermont enrolled 61 obese, post-menopausal women. Twenty five completed a weight loss program with an average loss of about 32 pounds. Their average drop in plasma CRP levels compared to baseline was 32.3%.(19)

Other lifestyle changes affecting CRP include moderate alcohol consumption and endurance training. Both of these were shown to lower CRP levels.(20,21)

CRP as a risk factor for coronary heart disease

As was discussed earlier in the context of the Framingham study, existing risk factors only account for approximately one half of all cases of documented CHD. Indeed the Framingham study was instrumental in constructing a framework for the medical community to follow in preventing CHD. It does not, however, provide a construct which can be applied to all cases and does not offer a measureable, reproducible marker which consistently detects CHD risk. There is, therefore, a strong impetus to identify a reliable marker to predict CHD.

Does CRP fit as a new CHD risk factor? To date, research suggests that CRP does fulfill most of the necessary requirements. The association of CRP levels with CHD is very strong and is independent of other risk factors, and the consistency of results from many population-based studies has been remarkable. Furthermore, CRP determinations can be additive in their predictive ability, with a strong correlation between high CRP levels and high total cholesterol levels.(22) CRP levels are also responsive to therapeutic modalities, which can be applied to the primary care setting and may prove effective in reducing the incidence of CHD prior to more expensive secondary treatments.(23)

That CRP is relatively stable in plasma or serum facilitates its evaluation in a clinical setting, and several accurate, reproducible, and inexpensive assays are readily available. In addition, an international standard is available and widely used.

CRP is a systemic marker of inflammation and, as such, is not specific for cardiac inflammation as compared to the exquisite specificity of TnI and TnT. Strong associations between CRP levels and CHD have been shown, but whether CRP is causal or merely an indicator has not been determined. In addition, proper exclusion criteria for interpretation have not been defined and cut-off values for the primary and secondary care settings have not been agreed upon.

The future is bright for CRP testing in CHD risk assessment, but CRP values can only be interpreted with full knowledge of the clinical state of the patient by physical exam and pertinent laboratory tests.

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