Concentrations of C-Reactive Protein and B-Type Natriuretic Peptide 30 Days after Acute Coronary Syndromes Independently Predict Hospitalization for Heart Failure and Cardiovascular Death: Just Another Brick in the Wall?

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In this issue of Clinical Chemistry, Scirica and colleagues have examined the role of C-reactive protein (CRP)2 as a risk predictor of heart failure and cardiac death after admission with suspected acute coronary syndromes (1). They highlight the important fact that heart failure after acute myocardial infarction (AMI) is a significant predictor of an adverse prognosis. Indeed, the success of cardiologists in myocardial salvage post-AMI is producing a cohort of patients who have survived but with a damaged myocardium and who will, inexorably, progress to heart failure. Heart failure is a growing cause of morbidity, mortality, and cost in health care systems throughout the world. The study was performed within the context of an interventional trial. It is therefore worth examining how it fits into the body of knowledge about CRP and heart failure and if it supports the notion that it is now prime time for high-sensitivity CRP (hsCRP) measurement.

Pentraxins as Inflammatory Markers for Routine Clinical Practice

The pentraxins are a superfamily of conserved proteins characterized by a cyclic multimeric structure. The classical short pentraxins are CRP and serum amyloid P component, acute-phase proteins. Long pentraxins have an unrelated, long amino-terminal domain coupled to the carboxy-terminal pentraxin domain. CRP was originally isolated as a protein that binds to the C-polysaccharide of the cell wall of pneumococci. It is a pentraxin composed of 5 23-kDa subunits that plays a key role in the innate immune response and is produced mainly by hepatocytes after stimulation by cytokines, of which interleukin-6 (IL-6) appears the major inducer. hsCRP concentrations increase 6 h after acute stimuli, reaching a peak (up to 100-fold above baseline) within 48 h. With abrupt cessation of stimuli, values decrease exponentially at a rate close to the half-life of CRP (18–20 h) (2). Population-based cutoffs have been proposed for risk stratification (3). No diurnal variation, age, or sex dependence was demonstrated in initial studies (4, 5), but these findings have been questioned. The Dallas Heart Study compared hsCRP concentrations between different race and sex groups and found race and sex effects (5).

The evidence that CRP is a risk predictor is extensive and consistent for populations with and without prior cardiovascular disease. hsCRP measurement predicts risk of cardiovascular events, death, and risk of developing cardiac failure (2). hsCRP predicts risk of developing heart failure in patients with stable coronary disease (6) and in patients presenting with acute coronary syndromes (7). hsCRP is also a prognostic marker across all stages of heart failure. In asymptomatic intervals, hsCRP elevation was associated with evidence of systolic dysfunction on cardiac magnetic resonance imaging in males but not in females (8). Higher hsCRP concentrations occurred in patients with higher New York Heart Association functional class and were related to higher rates of readmission and mortality (9). As a marker of a poor prognosis in patients with established heart failure, hsCRP elevation appears to be associated with diastolic dysfunction (10). Aldosterone blockade with spironolactone does not reduce hsCRP (11), nor does treatment with an angiotensin-converting enzyme inhibitor (6).

Assessment of the additional independent prognostic value of hsCRP measurement is not easy. In acute coronary syndrome patients, hsCRP adds to the ability of B-type natriuretic peptide (BNP) to predict...
risk, but studies tend to include risk of heart failure as part of a composite endpoint. Importantly, Scirica et al. (1) show hsCRP to be an independent risk predictor for heart failure alone. When hsCRP is examined in other categories of patients with vascular disease, BNP (measured as the N terminus of the prohormone, NT-proBNP) and hsCRP are independent predictors of CHF risk after stroke or transient ischemic attack (12). hsCRP adds additional prognostic risk stratification to BNP measurement in some (13) but not all (14) studies of patients with established heart failure.

Is hsCRP Ready for Prime Time?

A biomarker must fulfill a number of criteria to achieve routine clinical use, and must fulfill them all. Is this test APT?

1. ANALYTICAL SUITABILITY: THE THREE P’S
Population aspects of the test are known: effect of age and sex and influence of comorbid conditions.

Preanalytical factors are defined: collection conditions, anticoagulant requirements, preanalytical sample handling, and stability in storage. The marker needs to be measurable in the routine clinical laboratory without special handling conditions.

Performance: the ability to measure the biomarker with precision and accuracy; analysis must be simple and have a rapid turnaround time. Ideally, it should be implemented on existing laboratory equipment rather than requiring additional apparatus.

2. PLAUSIBILITY
Clinical plausibility: sensitivity and specificity for the medical condition of interest in clinically appropriate populations—this means populations where the test will actually be used in routine clinical practice. Many studies on biomarkers evaluate them in clinical trial sample banks or highly selected patient groups. This does not constitute an appropriate environment to evaluate test performance, as the disease prevalence is inappropriately high. Such studies allow proof of concept but need to be followed by prospective evaluation in a clinically representative population. There are very few prospective observational studies of biomarkers performed using routine clinical populations with no exclusion criteria and well-documented final diagnoses and outcomes. Such studies are essential before any biomarker can be used in clinical routine.

Biological plausibility for the putative clinical role: the pathobiology of the marker needs to be understood.

3. TREATMENT EFFECTIVENESS: EVIDENCE-BASED MEDICINE
This is the most important criterion—the “so what?” question. Any new biomarker must either offer a significant improvement in diagnostic efficiency or result in a change in treatment. Ideally, it should do both. In addition, it will have to demonstrate cost-effectiveness. A new test will have to demonstrate that it will result in cost reduction, either directly or by reduction in patient episode cost, or produce improved health care outcomes when assessed against a formal measure such as quality-adjusted life years.

Of all the available new (and not so new) biomarkers, measurement of hsCRP comes closest to clinical application. It meets many of the criteria listed above. Despite this, measurement of hsCRP is a class IIa recommendation in the National Academy of Clinical Biochemistry (NACB) acute coronary syndrome biomarker recommendations and is not included in any of the recent NACB guidelines for biomarkers in patients with heart failure. One reason for lack of acceptance of hsCRP as a marker in heart failure is that although measurements are prognostic, clinicians are rather more interested in biomarkers for diagnosis. The second and most critical step is that hsCRP measurement cannot be related to any treatment strategy.

Is this changed by the Scirica et al. report (as well as other recent studies)? The answer is: a bit. Scirica and colleagues again used a clinical trial population, something that they acknowledge as a limitation. There is a useful contribution, as the effect of statin treatment can be evaluated. There appeared to be no difference in benefit of statin between high and low hsCRP groups on the risk of subsequent heart failure, although overall risk was reduced with high-intensity statin treatment. More importantly, the recent JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), which randomized patients to statin treatment or placebo on the basis of hsCRP elevation, for the first time linked hsCRP to therapy and showed a positive outcome (15). Discussion will continue, as a low hsCRP treatment arm was not included in the JUPITER trial design for reasons the authors can justify. The evidence is now reasonable for a change in practice for primary prevention and for addition of hsCRP measurement to conventional risk stratification in intermediary risk groups, with treatment initiation in the high hsCRP group. Beyond that, not yet.

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