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Inflammatory markers and the risk of recurrent coronary events: the importance of dynamic risk assessment

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Article p. 50

During the past decade considerable interest has focused on markers of inflammation in general, and C-reactive protein (CRP) specifically, in an attempt to improve cardiovascular risk prediction. Multiple prospective epidemiological studies have shown an association between increased levels of inflammatory markers and the risk of incident myocardial infarction (MI), stroke, peripheral arterial disease, and sudden cardiac death [1–5]. These data were supported by laboratory and experimental evidence that have demonstrated that atherothrombosis, in addition to being a disease of lipid accumulation, also represents a chronic inflammatory process [6, 7]. Despite this, however, a recent report from the Framingham Heart Study has shown that for assessing risk in individual persons the use of the multiple contemporary biomarkers adds only moderately to standard risk factors for the prediction of cardiovascular risk [8]. Thus, in outpatient settings, the primary use of CRP has been recommended as an adjunct for cardiovascular risk assessment mainly in patients at intermediate risk, as defined by the Framingham Risk Score [9].

In post-MI patients the role and potential utility of inflammatory risk markers is even less certain. This may possibly be due to the fact that in the contemporary era of aggressive coronary revascularization and management with lipid lowering therapies in this population, it is more difficult to identify the incremental prognostic yield of inflammatory markers. Furthermore, in the post-MI period there are multiple potential stimuli for production of markers of inflammation that may mask the relatively minor increases in the levels of these markers that occur as a result of vascular inflammation. Inflammatory markers have been investigated in a secondary setting in several studies, and have been shown to predict risk of both recurrent ischemia and death among patients with acute coronary syndromes [10, 11], and among those in the chronic phase after acute MI [12–14]. However, in all prior analyses, markers of inflammation were univariate predictors of risk, and the impact of these markers was reduced when adjustment was made for the presence of important confounding factors that have a closer association with outcome in the postinfarction period. In a report by Lindahl et al. [10], CRP measurements during the acute MI phase were associated with long-term mortality, but no adjustment was made for left ventricular dysfunction. Similarly, Tommasi et al. [13] reported that increased CRP levels obtained during the acute MI phase correlate with subsequent outcome, despite the fact that CRP levels may correlate with infarct size in the early post-MI period.

The association of inflammatory markers, including CRP and serum amyloid A (SAA), with recurrent coronary events was assessed in the prospective multicenter THROMBOgenic risk-factor (THROMBO) study that was initiated in our institute [14]. The study enrolled 1045 stable postinfarction patients in whom lipid, hemostatic and inflammatory factors were measured 2 months after the index MI. All patients were assessed for recurrent cardiac events during a subsequent 2-year follow-up period. Consistent with prior studies of inflammatory markers in a secondary prevention

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setting, unadjusted Cox analysis in THROMBO revealed an increasing risk of recurrent coronary events with increasing quartile levels of CRP and SAA. However, after multivariate adjustment, none of the analyzed inflammatory markers was identified as a significant predictor for recurrent coronary events during the 2-year follow-up period.

In this issue of the journal, Marcinkowski et al. [15] provide an interesting, and potentially important, contribution to the controversial field of the role of inflammatory markers as predictors of risk in a secondary setting. The study was carried out in 107 patients with a first MI who were followed up for 18 months. Similar to THROMBO, the end point of this study comprised of cardiac death, nonfatal reinfarction or unstable angina pectoris. However, there are several important differences between this study and THROMBO that might have led to different findings. First, despite a relatively small sample size, 90% of the patients in the study by Marcinkowski et al. [15] experienced ST-elevation MI, making this study cohort a higher-risk population than in THROMBO, with a higher event rate during follow-up. This may have facilitated a comprehensive analysis of the association between inflammatory markers and recurrent coronary events. Second, while serum levels of CRP and SAA were assessed in THROMBO only at the 2-month follow-up visit, Marcinkowski et al. [15] employed a more dynamic risk-assessment, in which serum levels of several inflammatory markers (including CRP, fibrinogen, soluble intercellular adhesion molecule 1, erythrocyte sedimentation rate, and white blood cell count) were obtained at 2 time-points after the index MI — at an early phase (10 days) and at a later post-recovery phase (10 weeks). The study demonstrates that obtaining levels of inflammatory markers close to the acute postinfarction phase does not contribute significantly to risk prediction, possibly due to the fact that increased levels of these biomarkers during the acute phase are closely related to infarct size and tissue injury, whereas among patients in whom inflammatory markers remain elevated from day 10 through week 10 there is a significant increase in the risk of recurrent coronary events. These findings further stress the importance of dynamic risk-assessment in post-MI patients. Repeated measures facilitate assessment of time-dependent changes in markers of coronary risk. Thus, early changes in levels of inflammatory markers are probably more closely associated with the index event than with subsequent risk, whereas long-term changes in the levels of these markers may be more closely associated with outcome. Most randomized trials today evaluate variables that are obtained during enrollment or the index event and do not take into account effect of long-term changes in risk factors. The findings of Marcinkowski et al. [15] suggest that continuous risk-assessment of the quantitative changes in risk markers over time yields the possibility of greater positive or negative predictive accuracy of event rates. It is possible that longer-term follow-up of changes in levels of inflammatory markers in this population will further improve dynamic risk-assessment of outcome and response to therapy. This, possibility, however, needs to be evaluated in future studies.

Despite the interesting findings by Marcinkowski et al. [15] several important limitations of this study should be mentioned. Of the 22 patients who experienced the study's composite end point, the overwhelming majority (16 patients; 72%) had unstable angina, whereas more severe end points such as cardiac death and reinfarction occurred in only one and five patients, respectively. Thus, it is possible that the association between levels of inflammatory markers at 10 weeks and recurrent events is significant only when the end point of recurrent ischemia is assessed. Future studies, with a larger sample size and a longer-term follow-up period, are needed to validate if the findings persist after adjustment for "classic" risk factors such as age and infarct size when more severe end points (e.g. cardiac death, reinfarction, or heart failure events) are assessed. It should also be noted that study patients had variable follow-up periods, and that end point events occurred at different time-points. Thus, the usage of logistic regression analysis may not be applicable when censored data are analyzed. Importantly, Marcinkowski et al. [15] were careful to validate the consistency of their results using Cox analysis, which is a more suitable statistical methodology for this study.

The results of the study by Marcinkowski et al. [15] provide supportive evidence that evaluation of inflammatory markers relatively late in the postinfarction period may be important for long-term risk-stratification, and stress the importance of continuous profiling and risk-assessment in postinfarction patients. These findings should be incorporated in the design of future trials that evaluate the role of inflammatory markers as predictors of outcome in post MI patients.

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