

Neopterin and Cardiovascular Disease: Growing Evidence for a Role in Patient Risk Stratification

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Compelling evidence has emerged in recent years regarding the implications of inflammation in the pathogenesis of atherosclerosis and its complications (1). The growing appreciation of the role of inflammation in atherogenesis, atheromatous plaque growth, and plaque disruption has triggered interest as to whether circulating inflammatory biomarkers may help to identify subjects at risk of future cardiovascular events. Of all currently available biomarkers, high-sensitivity C-reactive protein (hsCRP)⁴ appears to have the best profile as an independent predictor of increased coronary risk (2). Despite being a nonspecific acute-phase reactant, hsCRP has been shown in large epidemiological and clinical studies to be an independent predictor of cardiovascular events (3), i.e., myocardial infarction, stroke, and death in patients with angina (4) and apparently healthy subjects. Because hsCRP is not a specific marker of vascular inflammation, however, the search for highly sensitive and specific markers of risk continues unabated.

Evidence from our group (5–8) and others (9, 10) in recent years indicates that neopterin, an immune modulator produced by activated macrophages, may be useful for cardiovascular risk stratification in patients with coronary artery disease. In this issue of *Clinical Chemistry*, Grammer et al. (11) report the results of the LURIC (Ludwigshafen Risk and Cardiovascular Health) study regarding the prognostic role of circulating neopterin. They found neopterin to be an independent predictor for both all-cause and cardiovascular mortality in patients with and without coronary artery disease. These findings are important, as they extend previous observations by other authors regarding the prognostic role of neopterin. This study—with a median follow-up period of 8 years, the longest of all ne-

opterin follow-up studies—showed that increased neopterin concentrations predict cardiovascular death and death from all causes, independently of coronary artery disease extension and severity. This finding is consistent with results of previous studies (5–8, 10, 12, 13) and indicates that increased neopterin concentrations are a marker of atheromatous plaque activity rather than simply an estimation of the anatomical extent of coronary artery disease. Interestingly, the study of Grammer et al. also confirms and expands previous findings by our group (5) that increased neopterin concentrations are an independent predictor of death in patients with minor nonobstructive coronary artery disease.

Inflammation plays an important role in atheromatous plaque vulnerability and disruption, and we have previously documented an association between high neopterin concentrations and the presence of vulnerable-complex plaques (12). Moreover, Adachi et al. (14) reported neopterin to be a “stimulus” for plaque inflammation and instability. Indeed, increased circulating concentrations of neopterin have been also shown by Zouridakis et al. (13) to be independently associated with rapid angiographic coronary artery stenosis progression in patients with chronic stable angina. Data from our previous work (5–8, 12, 13) and recent data from others (9–11) indicate that neopterin concentrations identify a “vulnerable” phenotype among patients with both stable coronary artery disease and acute coronary syndromes.

An important aspect of the study of Grammer et al. is that they have carried out a head-to-head comparison between neopterin and hsCRP. In their study, neopterin remained independently associated with all-cause mortality even after adjustment for conventional cardiovascular risk factors, angiographic coronary artery disease, and hsCRP concentrations. Of importance, hazard ratios for adverse outcomes were greater for high neopterin compared with high CRP levels. Another important contribution of the Grammer et al. study is the assessment of N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) in conjunction with neopterin and hsCRP. Interestingly, the predictive role of neopterin, but not that of hsCRP, remained significant—albeit weakened—after entering the variable NT-pro-BNP in the different models. Unfortunately, Grammer et al. (11) do not provide information re-

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⁴ Nonstandard abbreviations: hsCRP, high-sensitivity C-reactive protein; LURIC, Ludwigshafen Risk and Cardiovascular Health; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

garding the relationship between neopterin and left ventricular ejection fraction, an established marker of death in patients with coronary artery disease. We have reported a negative correlation between neopterin concentrations and left ventricular ejection fraction in patients with chronic stable angina (6).

Neopterin not only may be a marker for clinical outcome but could also play a pathogenic role in coronary artery disease. This molecule is produced mainly by activated macrophages, which have been shown to play a key part in atheromatous plaque disruption. Neopterin can interfere with intracellular signaling pathways known to be influenced by oxidative stress. It stimulates nuclear factor- κ B translocation to the nucleus, thus promoting the expression of proinflammatory genes and the production of adhesion molecules, tissue factor, and many other proteins implicated in atherogenesis, atheromatous plaque disruption, and disease progression.

In previous articles (15, 16), we have referred to neopterin as the “forgotten” inflammatory biomarker, as this molecule is hardly ever taken into account in review articles dealing with biomarkers of cardiovascular risk, despite substantial evidence for its predictive role. The study by Grammer et al. in this issue of *Clinical Chemistry* (11) and the recent article of Ray et al. (10) showing a strong predictive role for neopterin, however, are likely to increase awareness as to the potential value of neopterin in the clinical setting. Further research is required to establish the true role of neopterin in clinical practice and whether this molecule plays any role in the pathogenesis of atherosclerosis and coronary artery disease progression.

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