Risk Stratification in Secondary Prevention
Advances in Multimarker Profiles, or Back to Basics?

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Prevention and risk management of atherosclerotic vascular disease remain major health challenges. Coronary heart disease (CHD) and other cardiovascular diseases remain the primary causes of mortality and morbidity in developed countries. Improvement of risk stratification by identification of new biomarkers has been extensively investigated in both primary and secondary clinical settings in the past decade. A substantial number of biomarkers, representing various stages of atherogenesis and impaired cardiac function, have been evaluated against modifiable traditional risk factors, such as cholesterol, blood pressure, smoking status, and diabetes.1-4 However, whether these various biomarkers add incremental prognostic information to that provided by traditional risk factors is still controversial, and the clinical implications of “high” biomarker levels have yet to be determined. A multimarker strategy of combining biomarkers may theoretically help clinicians to stratify subjects into risk categories, but data on this subject are scarce.5,6

In this issue of Circulation, Blankenberg and coauthors7 evaluate the prognostic value of multiple biomarkers compared with that of traditional risk factors on cardiovascular events in a large subgroup of the Heart Outcomes Prevention Evaluation (HOPE) study. The biomarkers examined cover a broad range of inflammation and endothelial activation, including C-reactive protein (CRP) and cellular adhesion molecules, as well as the cardiac neurohormone N-aminoterminal of the prohormone brain natriuretic peptide (NT-proBNP). The well-known HOPE study was a randomized, clinical trial investigating ramipril and vitamin E in patients with CHD, peripheral vascular disease, diabetes, or previous stroke. A total of 3199 patients with available blood samples for subsequent biomarker analyses were enrolled in the subgroup examined by Blankenberg et al. Patients were followed up with respect to recurrent cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality as the primary end points of the HOPE study. As expected from existing literature among high-risk populations, age, gender, smoking status, LDL/HDL cholesterol ratio, systolic blood pressure, presence or absence of diabetes, and plasma glucose were all individually associated with the primary end point and included in a basic model. Among the inflammatory biomarkers, interleukin-1Ra, interleukin-18, and soluble intracellular adhesion molecule-1 were independently associated with the primary end point, although the predictive values were modest. Analyses of an optimal cutoff point revealed that only high CRP levels (>6 mg/L) were independently associated with primary outcome. For NT-proBNP, the risk of recurrent cardiovascular events was increased by >2-fold in patients with levels in the highest versus the lowest tertiles. NT-proBNP was also independently associated with myocardial infarction but not with stroke, which is surprising and the exact opposite finding of previous reports on B-type natriuretic peptides and cardiovascular events.5,8 Blankenberg and colleagues7 also tested whether these biomarkers improved the discriminative value of their basic model with traditional risk factors by using receiver-operating characteristic curves. A primary finding of their study is that the addition of inflammatory biomarkers, alone or in combination, did not change the area under the curve, whereas addition of NT-proBNP did increase area under the curve from 0.65 to 0.71 (P<0.001). The authors concluded that traditional risk factors outperformed biomarkers, reflecting inflammation and endothelial dysfunction with respect to risk of recurrent cardiovascular events, with NT-proBNP being the only biomarker providing incremental prognostic information.

Blankenberg and colleagues’ multimarker HOPE substudy addresses an important and highly clinically relevant question as to the clinical usefulness of various biomarkers in risk stratification in patients with high cardiovascular risk. The simultaneous measurement of a large number of biomarkers provides an opportunity to investigate and compare their predictive ability in the same cohort. On pathophysiological examination, the various biomarkers in the present study reflect different mechanisms of development of atherosclerotic cardiovascular disease. The proinflammatory cytokines tumor necrosis factor-α and the interleukins stimulate several important steps in the development of endothelial dysfunction. The mechanisms of this cytokine stimulation include recruitment of inflammatory cells and upregulation of expression of various endothelial adhesion molecules. The cellular adhesion molecules soluble vascular cell adhesion molecule-1 and soluble intracellular adhesion molecule-1 promote adhesion and migration of circulating leukocytes to the vascular wall. Adhesion and migration are involved in the early phase of lipid accumulation and development of atherosclerosis. Increased levels in plasma are potential biomarkers of activated and vulnerable endothelium. Nevertheless,
although these molecules are of substantial interest from a pathophysiological point of view, their predictive value with regard to cardiovascular disease among different populations, including the HOPE substudy, has not been impressive.\textsuperscript{3,7} By contrast, CRP is generally accepted as the primary inflammatory biomarker, although the clinical implications of CRP measurements are still a matter of debate. Thus, CRP may only be a moderate predictor of CHD compared with traditional modifiable risk factors such as total cholesterol and smoking.\textsuperscript{1} The potential clinical usefulness of CRP in secondary prevention has been investigated in different populations by using post hoc analyses, with conflicting results. In the study by Blankenberg et al\textsuperscript{7} and in recent published data from the AtheroGene study,\textsuperscript{9} CRP did not add incremental prognostic information to that provided by traditional risk factors. In contrast, others have reported that CRP levels after statin therapy have prognostic impact in patients with CHD.\textsuperscript{10} A possible explanation for the discrepancies in these findings could be the close interrelations between high CRP levels and abnormal CHD traditional risk factors, as recently demonstrated in the third National Health and Nutrition Examination Survey.\textsuperscript{11} Therefore, the risk of potential residual confounding is substantial in post hoc analyses of CRP as a prognostic marker. In addition, as indicated in the Blankenberg et al study,\textsuperscript{7} only high CRP levels above the 70% to 80% percentile may have prognostic impact. Accordingly, in the recently published 2006 update of American Heart Association/American College of Cardiology guidelines for secondary prevention in patients with cardiovascular disease,\textsuperscript{12} recommendations emphasize that clinicians should remain focused on aggressive management of traditional modifiable risk factors such as smoking, blood pressure, LDL cholesterol levels, sedentary lifestyle, and obesity. These guidelines are based on substantial evidence, including large, randomized trials on lipid reduction, and they provide new treatment goals, such as that LDL cholesterol preferably should be <70 mg/dL.\textsuperscript{12} In other words, the majority if not all of these patients should be treated with statin therapy, underlining that the clinical utility of CRP measurements may be limited in secondary prevention.

Only a single biomarker, NT-proBNP, was able to improve risk stratification beyond that of traditional risk factors in the multimarker study by Blankenberg et al.\textsuperscript{7} B-type natriuretic peptides are markers of impaired cardiac function. The physiologically active BNP and the inactive NT-proBNP are released from the ventricular myocardium in response to increased wall stretch and pressure overload from the prohormone proBNP. In clinical settings, B-type natriuretic peptides are increasingly used as diagnostic markers in patients with suspected acute or chronic heart failure because these peptides can rule out heart failure with a very high negative predictive value of approximately 98% to 99%.\textsuperscript{13,14} In addition, high prognostic values of B-type natriuretic peptides have been a consistent finding among different populations from the community\textsuperscript{4,8} and in patients with stable and unstable CHD.\textsuperscript{15–17} On the basis of these reports, the US Food and Drug Administration approved NT-proBNP measurements for risk stratification in patients with stable CHD in December 2005. However, although B-type natriuretic peptides may have potential as risk biomarkers in both primary and secondary settings, important questions still need to be answered before BNP or NT-proBNP measurements can be recommended in general risk stratification. Thus, their ability to classify risk in individual subjects has yet to be established. Classification power of a biomarker, or the ability to improve risk stratification, can be evaluated by the use of receiver-operating characteristic curves,\textsuperscript{19} as discussed in a recent extensive Circulation review article.\textsuperscript{19} The study by Blankenberg et al\textsuperscript{7} supports the potential role for B-type natriuretic peptides in risk stratification by demonstrating a modest but highly significant improvement of the discriminative capability of traditional risk factors. The recently published ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study among patients admitted to an emergency department observed similar improvement in discriminative value after NT-proBNP was added to the basic clinical models.\textsuperscript{14} With respect to the definition of a possible risk threshold for abnormal values of BNP and NT-proBNP levels, this issue remains controversial. As for LDL cholesterol, B-type natriuretic peptide levels appear to be a continuum of risk; that is, the lower the better, and we have not seen the end of the line yet. Plasma levels of the B-type natriuretic peptides are predominantly influenced by age, kidney function, left ventricular ejection fraction, and, presumably, body mass index. Consequently, available data demonstrate that different cutoff levels may be useful according to the population examined. Although B-type natriuretic peptide levels are modifiable by therapy such as angiotensin-converting enzyme inhibitors and \(\beta\)-blockers, whether increased BNP or NT-proBNP levels should be a specific therapeutic target for intervention remains to be investigated in detail. In this context, high unexplained variation would disqualify these peptides for monitoring patients. New data from our group demonstrate that the unexplained variation of both BNP and NT-proBNP plasma levels is low, being only 15% and 8%, respectively, in patients with stable chronic heart failure,\textsuperscript{20} suggesting potential clinical utility of these peptides in therapeutic management.

In conclusion, extensive research in biomarkers moves on and provides new important knowledge on the pathogenesis and complex mechanisms behind the development of cardiovascular disease. Given that the predominantly available evidence is in prevention and treatment of traditional modifiable risk factors, biomarkers should be carefully evaluated through appropriate analyses against these basic risk models. In this context, new models that will improve risk stratification may be created in the near future. Finally, whether high CRP or NT-proBNP levels have potential as therapeutic targets by improving prognosis will be addressed in ongoing randomized clinical trials, in both primary and secondary settings.

Disclosures

None.

References


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