Editorial

Cardiovascular Biomarkers

Added Value With an Integrated Approach?

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In primary prevention, traditional risk factors are a useful first step in the determination of who could be at risk for cardiovascular events. In the era of “global risk assessment” scores such as the Framingham score, the Prospective Cardiovascular Münster (PROCAM) score, or the European Society of Cardiology Systematic Coronary Risk Evaluation (SCORE), which are derived from multivariable statistical models, should be used. However, it has been noted that a considerable number of at-risk patients cannot be identified on the basis of traditional risk factors alone. This has prompted the search for novel markers of cardiovascular risk to help improve risk prediction. Such markers could either represent various blood biomarkers relevant to the pathophysiology of atherothrombosis (eg, markers of the inflammatory response, coagulation markers, markers of platelet aggregation, lipoproteins, or lipid-related variables), genetic markers, or markers of subclinical disease, which may also aid in improved risk prediction. Determination of global risk on the basis of traditional risk factors allows categorization into high (10-year risk, >20%), low (10-year risk, <10%), or intermediate risk (10-year risk, 10% to 20%). Subjects at high risk should be recommended lifestyle changes or prescribed a statin. Subjects at intermediate risk would be reevaluated 3 to 5 years later. Those at intermediate risk, however, who comprise up to 40% of the population at risk, would be candidates for additional testing to increase or decrease their actual risk. A large panel of blood biomarkers are available for this purpose, but most of them are not yet applicable in clinical practice for various reasons.

Emerging Blood Biomarkers

Atherosclerosis is characterized by a nonspecific local inflammatory process that is accompanied by a systemic response. Thus a number of prospective studies in initially healthy subjects have convincingly demonstrated an independent association between even slightly elevated concentrations of various systemic markers of inflammation and important cardiovascular end points. At this time, the largest database exists for C-reactive protein (CRP), the classic acute-phase protein. The measurement procedure is well standardized and automated, and high-sensitive assays with sufficient precision are available. On the basis of substantial evidence of a contribution of inflammation to atherothrombogenesis, a recent American Heart Association/Centers for Disease Control and Prevention consensus report has recommended the measurement of CRP in asymptomatic subjects at intermediate risk for future coronary events (10-year risk, 10% to 20%). However, there are other emerging biomarkers like lipoprotein-associated phospholipase A₂ (Lp-PLA₂), an enzyme that is produced by monocytes/macrophages, T-cells, and mast cells and has been found to generate proinflammatory and proatherogenic molecules. Because Lp-PLA₂, in contrast to CRP, does not correlate with most other risk factors, there is an additive effect of CRP and Lp-PLA₂ in risk prediction. This may also apply to combinations of other biomarkers, though evidence so far is limited. In the future, we might see a biomarker profile that covers various aspects of the complex pathophysiology of the atherothrombotic process, and potentially, we would be able to focus on biological patterns or systems rather than on single biomarkers. To date, however, there is no sound evidence to suggest such a procedure for clinical practice, and there is even an ongoing discussion of whether any of the emerging blood biomarkers alone contributes incremental information over and above the information gained from available “global risk” scores.

Markers of Subclinical Atherosclerotic Disease

There is mounting evidence that markers of subclinical disease (eg, intima-media thickness as assessed by high-resolution carotid ultrasound; coronary calcium determined with multislice computed tomography; or ankle-brachial index, a strong marker of atherosclerotic burden) may also contribute to improved risk prediction. However, the clinical utility of multislice computed tomography needs to be further tested, and measurement of carotid intima-media thickness may be burdened by considerable interobserver variability when it is used in routine clinical practice. Thus, similar to blood biomarkers, the potential incremental value of such surrogate markers of clinical atherosclerotic complications is not unequivocally evident. Still, from a theoretical viewpoint the combination of blood biomarkers and markers of subclinical disease seems an attractive approach because this may integrate information on structural or functional vascular wall pathology and systemic “activity” of the disease (Figure).

However, for markers of subclinical disease as well as for blood biomarkers, controversy exists with regard to which parameter represents the most useful one and for which time period of the atherosclerotic process, and which combination of markers may be most appropriate for decision making. Finally, analytical and cost considerations deserve further study.
Statistical Methodology: Limitations in Assessment of Incremental Diagnostic Information

A great deal of such uncertainty is based on the limited availability of adequate statistical tools to demonstrate the incremental value of an emerging biomarker in addition to global risk scoring. We have realized that evidence of just some moderately strong association in epidemiological studies is insufficient to assess the true clinical utility of a new candidate marker. Most frequently, $c$ statistics and area under the receiver-operating characteristic curve have been used. Risk estimates that would be needed here to show a clinically important increase in the area under the curve are usually not seen in cardiovascular medicine. $^{18}$ Thus, disappointingly, only a few studies have shown a statistically significant improvement in the area under the curve, which, however, in most cases was too small to be considered clinically relevant. The aggregate experience from a number of such studies demonstrates that once there is a single strong predictor of risk in the model, which may be even age alone, it is extremely difficult to show a relevant contribution of any additional variable to model prediction. This has recently been discussed in detail by Cook, $^{18}$ and alternative statistical approaches have been suggested, such as clinical risk reclassification. $^{19}$ This procedure attempts to improve risk prediction by development and validation of algorithms that more precisely allocate an individual to a risk category by use of a model that has incorporated a new risk variable in addition to conventional risk factors, compared with a basic model that contains conventional risk factors alone. Such approach focuses particularly on those subjects at intermediate risk to either reclassify an individual into the low- or high-risk category.

Integration of Biochemical and Bioimaging Markers: The Solution?

In the presence of such complex background, Cao and colleagues $^{20}$ present important data from the Cardiovascular Health Study in this issue of Circulation. The investigators simultaneously measured carotid intima-media thickness, plaque characteristics, and CRP, and related all 3 variables to the 12-year incidence of cardiovascular disease (CVD) events and all-cause mortality in 5888 elderly subjects. Main results showed that all parameters were correlated with one another,
yet each parameter independently predicted risk of CVD events and mortality in multivariable models, which included all 3 measures and traditional risk factors. Being in the top tertile of the carotid intima-media thickness distribution was more predictive for various events than having CRP > 3 mg/L or than being in the high-risk group on the basis of carotid plaque characteristics. Elevated CRP was a particularly useful predictor in the presence of subclinical atherosclerosis with a 72% increase in risk for CVD and 52% increase in total mortality. Cumulative event rates suggested a possible additive interaction for composite CVD and all-cause mortality with an excess risk attributable to the interaction of CRP and subclinical atherosclerosis of 54% for CVD death and 79% for all-cause mortality. By contrast, CRP did not add predictive power in the absence of carotid atherosclerosis. Finally, both CRP and subclinical atherosclerosis added only modest incremental information to risk prediction when adjusted for the effect of conventional risk factors with either c statistics or area under the curve derived from receiver-operating characteristic analysis.

**Conclusions**

First, global risk assessment, with traditional risk factors, still represents the rational basis for cardiovascular risk stratification. Second, although theoretically attractive, currently available biomarkers, even the combination of a robust systemic marker of “disease activity” with a marker that provides information on structural changes of the arterial vasculature, which must be seen as a surrogate/precursor of clinical disease, does not appreciably improve risk prediction. However, the Cardiovascular Health Study cohort was an elderly population and results may not be generalizable to younger individuals with low risk, in whom CRP may work in the absence of significant atherothrombotic burden. Also, the statistical tools used, as mentioned earlier, may be debatable. Third, in the future, despite such somewhat disappointing information regarding single markers, the clinical application of multimarker panels, for which the possibilities of model improvement are greater, may still prove to be a promising approach, provided that such variables show low correlations with conventional risk factors and with each other but provide strong associations with clinical events. Such emerging markers will have to be rigorously evaluated in large cohorts for their clinical efficacy and effectiveness with innovative statistical analytical tools. The world of proteomics and metabolomics, together with advanced imaging modalities such as functional molecular imaging, may offer such promising candidates.

**Disclosures**

None.

**References**


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