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. Those at intermediate risk, however, who comprise up to 40% of the population at risk,4 would be candidates for additional intervention.

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, 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, 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. 

This has recently been discussed in detail by Cook, and alternative statistical approaches have been suggested, such as clinical risk reclassification. 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 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 atherosclerotic 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


Keywords: Editorials  atherosclerosis  epidemiology  imaging  inflammation  risk factors
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Circulation. 2007;116:3-5
doi: 10.1161/CIRCULATIONAHA.107.707984
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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