Benchmarks for the Assessment of Novel Cardiovascular Biomarkers

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The investigation of novel circulating serum and plasma biomarkers in patients with cardiovascular disease has been accelerating at a remarkable pace. For example, a Medline search that uses the terms “biomarkers” and “acute coronary syndromes” (ACS) reveals an approximate tripling in the number of published reports during the 2-year interval from 2003 to 2004 compared with the period from 2001 to 2002, and this number more than doubled from 2005 to 2006. Although this expanding body of research has established firm evidence for the value of biomarkers, such as for diagnosis and risk assessment among patients with suspected ACS, it has also deluged the clinical and research communities with candidate biomarkers, very few of which are likely to survive the test of time as useful clinical tools. It is thus increasingly important for researchers, manufacturers, regulators, and clinicians to critically appraise the value of new biomarkers as they emerge as candidates for further investigation and possible clinical application. The superb report by Wollert and colleagues in the present issue of *Circulation* on growth differentiation factor-15 (GDF-15) as a biomarker for prognostic assessment in ACS provides an opportunity to outline a basic set of benchmarks against which new markers can be evaluated.

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Criteria for the Appraisal of Novel Biomarkers

Assessment of the clinical potential of a novel biomarker may be structured around 3 fundamental questions (Figure): (1) Can the clinician measure it? (2) Does it add new information? (3) Does it help the clinician to manage patients?

Can the Clinician Measure the Biomarker?

To be clinically useful, analytical methods must be available that allow reliable measurement, optimally with capability for high throughput tests, prompt turnaround time, and reasonable cost. Evaluation of these properties requires that each new biomarker and its assay(s) undergo a thorough examination of preanalytical (eg, conditions of measurement, sample handling, sample type), and analytical performance. Although it would seem necessary for these steps to be completed early in the development of a biomarker, they are often undertaken after initial epidemiological studies bring attention to the new biochemical test. For example, after promising experimental and epidemiological data established links between soluble CD40 ligand and atherothrombosis, further investigation has revealed important and potentially confounding influences of sample handling (timing of processing, temperature, and centrifugation steps) and sample type on its measured concentration.

Does the Biomarker Add New Information?

The pivotal criterion with regard to the potential clinical value of a candidate biomarker is the consistency and strength of the association between the biomarker and the outcome or disease of interest, and the extent to which it is an improvement on (either adding to or replacing) established tools. Because of obvious influences in decisions about reporting and publication of first-time observations, the first publication of data with a new marker is often dramatically “positive.” External validation is thus a critical step on the path toward clinical integration. For prognostic application in patients with ACS, for example, a reasonable benchmark is consistent findings from multiple studies that utilize prospectively collected samples among patients with well-characterized clinical outcomes in which the biomarker is independently associated with the risk of death or death and nonfatal clinical events. Although validation in at least 2 adequately-sized clinical studies should be viewed as a minimum, most biomarkers recommended for routine clinical use in ACS by professional society guidelines have demonstrated consistent risk relationships in 10 or more studies. Notably, if specific decision-limits are recommended for a biomarker, then these thresholds must be validated in multiple datasets.

No simple criterion exists for the magnitude of the risk relationship that will translate into clinical value. Moreover, there is debate about the optimal metrics by which to assess the incremental value of a new clinical risk indicator when added to established tools. Although we recognize the limitations of using a single criterion, we and others have sometimes used a 2-fold higher relative risk as an informal initial litmus test in early decisions to pursue additional investigation of a prognostic biomarker. However, many established risk indicators used in cardiovascular disease have a more modest strength of association. As an example,
for assessment of the risk of a first coronary event, the relative odds across tertiles of systolic blood pressure have been shown to be 1.5, with an area under the receiver operating characteristic curve of 0.64. Nevertheless, systolic blood pressure is entrenched in clinical care because the associated risk is modifiable and is used to direct therapeutic interventions. In addition, some biomarkers may have particular value in subsets of patients for whom traditional tools have limitations or their results are ambiguous. Therefore, our current approach is to use all the available information (preanalytical and analytical performance, unadjusted and adjusted relative risks, area under the receiver operating curve, reclassification of risk, and performance in subgroups), as well as any data about a potential to modify the risk associated with the biomarker, in order to make an integrated assessment of the possible value of a biomarker. Use of one measure alone, such as the c statistic, may underestimate the clinical value of a biomarker. Both the settings in which the biomarker was studied and the outcomes analyzed must be considered in the assessment of the consistency of data and in the formulation of any recommendations for clinical use or regulatory approval. For example, the relationship between the inflammatory biomarker C-reactive protein and outcome in patients with ACS depends on the timing of measurement and the end point of interest. When measured early after presentation, C-reactive protein is associated with short-term and long-term mortality risk but shows a more modest relationship, if any, with the risk of recurrent ischemic events. When measured remotely after ACS, after the acute-phase response to the ACS has
resolved, however, a relationship between C-reactive protein and recurrent myocardial infarction emerges.\textsuperscript{12} Finally, other physiological characteristics that influence clearance or biological variability of the marker should be determined.

**Will It Help the Clinician to Manage Patients?** Biomarkers have a variety of possible clinical applications that may enhance the care of patients with cardiovascular disease.\textsuperscript{2} Broadly, they may be used for (1) early detection of otherwise subclinical disease; (2) diagnostic assessment of an acute or chronic clinical syndrome; (3) risk stratification of patients with a suspected or confirmed diagnosis; (4) selection of an appropriate therapeutic intervention; and (5) monitoring the response to therapy (Figure). Each of these potential uses merits consideration in the evaluation of a new biomarker’s value. As a first general principle, those conditions or aspects of care for which available tools have important limitations present the greatest opportunity for a new biomarker to impact care. For example, the challenges of accurately diagnosing heart failure have accelerated integration of the natriuretic peptides as an aid to the assessment of patients with shortness of breath.

As a second general principle, those applications that directly influence medical decision making are the most likely to earn recognition for their clinical value. Because cardiac troponin is useful both for diagnosis and for selection of patients who are most likely to benefit from specific treatments, such as administration of glycoprotein IIb/IIIa receptor inhibitors, this biomarker has become a cornerstone of care for patients with suspected ACS.\textsuperscript{1,7} At present, many newer markers, some of which have been granted regulatory approval for clinical use (eg, myeloperoxidase), have been shown to be independently associated with prognosis but have limited data about therapeutic intervention. The information gleaned from those prognostic markers that have not yet been shown to influence specific therapeutic decisions may still be used to guide triage, to inform patients and their families, and to identify those patients at highest risk who have the most to gain in absolute terms from all evidence-based interventions. Selective use of such biomarkers is reasonable in patients for whom a more complete assessment of the absolute risk is desired by the clinician.\textsuperscript{1} Nevertheless, recommendations for routine measurement in all patients with ACS are not likely to emerge unless data that support the benefit of specific therapeutic interventions become available.

**Pathobiological Considerations**

A thorough understanding of the pathobiology of a putative novel marker is not essential to the establishment of its diagnostic or prognostic performance. However, pathophysiological information may be very useful in providing support for the validity of the epidemiological observations, as well as direct research that pertains to possible diagnostic and therapeutic applications. Previous work\textsuperscript{13} has also provided proof-in-principle that “multimarker” approaches that integrate information from pathophysiologically distinct processes may enhance risk stratification in ACS.\textsuperscript{2} We believe that knowledge of the biology of the marker will help ensure that all of its potential applications (and problems) are fully considered.

**How Does GDF-15 Match up to These Benchmarks for Performance?**

The study by Wollert et al represents part of a carefully orchestrated initial evaluation of a promising new biomarker for risk assessment in ACS.\textsuperscript{3} GDF-15, a member of the transforming growth factor-\(\beta\) cytokine superfamily, is secreted by cardiomyocytes during ischemia and reperfusion. The authors evaluated the prognostic performance of an assay that used a polyclonal antibody against GDF-15, for which they have previously described the analytical performance.\textsuperscript{14} From what is known from these studies, there are no definite barriers to the development of an immunoassay appropriate to clinical use in either serum or plasma. Full characterization of the implications of preanalytical perturbations in sample handling still needs to be conducted.

The authors report a strong association between GDF-15 and death at 1 year that was consistent across a variety of relevant subgroups and was independent of most major clinical indicators of mortality risk in patients with ACS, which included age, gender, delay to treatment, diabetes, previous myocardial infarction, history of heart failure, and ST-segment depression. The authors also compared the prognostic performance of GDF-15 relative to other established and novel markers, which showed that the adjusted risk was numerically greater for each standard deviation increase in GDF-15 than for N-terminal pro-B-type natriuretic peptide. Moreover, these 2 markers provided complementary information with regard to mortality. Together these data provide a robust initial assessment of GDF-15, with compelling evidence for a relationship with mortality risk that is independent of other clinical risk indicators. Although this study was conducted in 2 phases, with an initial pilot study followed by a larger validation study in the same trial population, GDF-15 needs to be examined in other cohorts of patients with ACS, including less selected populations. In addition to external validation, the potential of GDF-15 to guide decisions about treatment must be explored to understand its implications for patient care. Hypotheses about potential interactions with treatment may need to be deferred until the pathophysiology of this protein is better understood.

Wollert et al hypothesize that the circulating concentrations of GDF-15 may reflect a unique pathophysiological axis not represented by available markers of necrosis, inflammation, or hemodynamic stress. The functions of this protein are incompletely characterized, however, and a deeper understanding of its role in the pathobiology of ACS is needed. Moreover, the absence of a decline in concentration over 72 hours of serial sampling is surprising, given its proposed responsiveness to ischemic injury, and merits additional study.

**Conclusions**

Steady progress in the discovery of new biomarkers and evolution toward more sophisticated clinical applications offer promising possibilities to enhance the care of patients. At the same time, the remarkable increase in the pace of
reports about new biomarkers demands even greater attention to their rigorous individual and comparative assessment. Gauged by our benchmarks, the report by Wollert et al provides a strong basis for additional investigation of GDF-15.4

Disclosures
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Brigham and Women’s Hospital holds patents related to use of inflammatory markers in cardiovascular disease.

References

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