Editorial

Acute Coronary Syndrome Biomarkers
The Need for More Adequate Reporting

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Improvements in our understanding of the pathophysiology of atherosclerosis and acute coronary syndromes (ACS) have led to an “explosion” in the development of assays of blood biomarkers to characterize these processes and to predict prognosis. These research assays are performed in a single-center research setting and often use plasma specimens collected in highly selected study populations on which a multitude of biomarkers has been tested in the past. All of these novel markers seem to add prognostic information to established risk indices of ACS. How can so many different analytes all be so predictive?

One reason may be that the diagnostic tools under investigation are optimized with respect to their characteristics and discriminator limits to gain optimal predictive power in the very specific study cohort. Should these tools and their decision limits be applied to a chest pain population with different characteristics, however, specificity may become a significant problem markedly affecting accuracy. Furthermore, application of these tools in a routine setting not allowing such careful sample preparation or optimization procedures may markedly reduce sensitivity.

Another reason, and we shall concentrate on this point here, is that the presently available markers are used in a less than optimal manner. However, if the lack of optimal use of the present makers is not made explicit, it may distort both the importance of the new marker and how to use established markers. Many recent reports have, in our estimation, done this but have failed to acknowledge it overtly in the manuscript, perhaps leading readers to miss this important consideration. The informed but busy clinician may be less able to discern these issues. As investigators who have worked over many years to establish reasonable criteria for the use of troponin makers, we have become concerned that the lack of clarity about these issues is not only leading to confusion about the new markers but has also further confounded clinicians about how to use the troponin assays on which we now rely. Accordingly, the purpose of this editorial is to sensitize authors, readers, and reviewers to these important issues.

The use of inappropriately high cut-off values for troponin

Initially, some companies were reluctant to use very low cut-off values because they worried that clinicians might lose faith in the assays if they started to see a large increase in the number of elevations detected compared with creatine kinase-MB. Thus, at first companies pushed the use of values like the “myocardial infarction cut-off or the receiver-operator curve–determined value which was, when data driven, often the level that equated troponin values with creatine kinase-MB values, which at the time was the gold standard. In addition, the initial troponin assays lacked the sensitivity to use very low cut-off values. However, assays have improved and, spurred by the European Society of Cardiology/American College of Cardiology redefinition of acute myocardial infarction guidelines, many groups began to use lower values. It has been clear since 1992 that any detectable level of troponin has prognostic significance in patients with acute coronary syndromes. These values were therefore used in studies that attempted to assess the impact of therapy. In a recent analysis, the Fast Revascularization during InStability in Coronary artery disease (FRISC) and Global Utilization of Streptokinase and tPA for Occluded arteries (GUSTO) groups quantitated the effects of differences in the cut-off values for cardiac troponin T in patients with ACS based on serial samples. The sensitivity of troponin T for detection of death at 30 days varied from 0.92 to 0.85 to 0.73 when the values for the 99th percentile, the 10% coefficient of variability value, and the receiver-operator curve value were used, respectively. For death plus myocardial infarction, the values were 0.89, 0.81, and 0.66, respectively, and for death at 1 year, the values were 0.87, 0.79, and 0.68, respectively. The corresponding odds ratios for these values for death or myocardial infarction at 30 days were 3.1, 2.6, and 2.2. Although the data for cardiac troponin I assay vary, the principles expounded are similar.

Thus, when studies evaluate a new marker in patients with ACS using the receiver-operator curve value, they reduce the sensitivity of troponin. This approach alone might allow a putative marker to appear to provide additional prognostic significance in instances when, had troponin been used optimally, it may not have had a significant additive benefit. At times it is difficult to discern that a higher cut-off value is being used. We believe that when such high values are used, the authors, reviewers, and editors have a responsibility to make sure that there is an adequate discussion of why that cut-off value was used and what the implications for using a more sensitive and more predictive cut-off value for troponin might have been. In most cases, the data to answer these questions are already available within the data set.
To facilitate these recommendations for all articles involving biomarkers, we would suggest consideration of the following whenever a paper concerns biochemical markers:

1. Journals might consider appointing members of their staffs to specifically scrutinize manuscripts in this area.
2. The timing and number of samples used in any analysis of blood biomarkers should be clear and there should be a discussion concerning the adequacy of the timing and numbers of samples used in the study.
3. Troponin sampling and cut-off values that are the basis for assessments of prognosis in patients with ACS should be used in the most optimal manner.
4. The characteristics, including the sensitivity and precision, of all the assays used should be reported. Such reporting should be facilitated by the publication of the International Federation of Clinical Chemistry and Laboratory Medicine paper on the sensitivity and low-end precision of troponin assays.
5. The appropriate cut-off values for the analytes being evaluated and all covariates should be listed. If alternative cut-off values are used, the rationale for their use and their effect on the data should be discussed.
6. At times, data will not be available to clarify all of these issues. If so, the implications of alternative approaches in sampling and cut-off values should be included in the discussion section.
7. Information on the characteristics of the novel assays used and their variability, precision, and normal values should be included and commented on when important for the proper use of the marker. When preserved samples are used, data concerning their reliability over time should be included.
8. Whenever possible, the incremental value of a given approach over and above other analytes should be calculated.

This is an important responsibility for both authors and journals. Unless we begin to pay attention to these important considerations, there will be continued confusion about the value of newer markers and increased difficulty in deciding how best to use markers such as troponin on which we now rely so heavily.

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