Risk Stratification in Acute Coronary Syndrome Using Cardiac Troponin I

The interest in risk stratification of patients with acute coronary syndrome (ACS), i.e., acute myocardial infarction (MI) and unstable angina pectoris (AP), has increased considerably within recent years because of improved knowledge of pathology, progress in immunoassays of already existing biochemical markers, introduction of new biochemical markers [especially cardiac troponin I (cTnI) and T (cTnT)], and new methods of treatments.

Coronary artery disease may present clinically as stable AP or ACS. In cases of stable AP, myocardial ischemia commonly results from increases in myocardial oxygen demand that outstrip the ability of stenosed coronary arteries to increase oxygen delivery (1). In ACS, the accepted cause of acute MI is a plaque disruption, or fissuring, leading to coronary thrombosis with or without vasospasm, and thereby intermittent or persistent coronary occlusion. In patients with unstable AP, pathological postmortem investigations have documented that unstable AP leading to MI or cardiac death frequently is preceded by microinfarctions (2). This is important because patients with non-Q-wave MI tend to have smaller infarcts on presentation and rarely have total occlusion of the infarct-related vessel; it therefore is considered a relatively unstable condition associated with a lower initial mortality but a higher risk of later MI or cardiac death (3).

On the basis of the above considerations, many large-scale trials divide the patients with ACS into patients with ST-segment elevation and non-ST-segment elevation. If the patient presents with signs of evolving acute MI, i.e., an electrocardiogram (ECG) with unequivocal ST-segment elevation, then the patient in most cases is subjected to thrombolysis or primary percutaneous transluminal coronary angioplasty. However, evaluation of patients with non-ST-segment elevation is a key issue today because new treatments are focused to a great extent on this group, i.e., low-molecular-weight heparins, platelet glycoprotein IIb/IIIa antagonist, direct thrombin inhibitors, and coronary intervention in the acute as well as the subacute phase. Therefore, our diagnostic strategy of ACS is concentrated primarily on confirmation/exclusion of acute MI and the detection of minor myocardial damage (MMD) to facilitate risk stratification and treatment.

To detect MMD, it is necessary to use markers sensitive to myocardial injury and specific for myocardial tissue. Measurements of creatine kinase isoenzyme MB (CKMB), especially the new immunoassays measuring CKMB mass, have improved the diagnosis of MMD as well as being of prognostic importance. However, the greatest attention has been given to the new biochemical markers, the troponins, especially because of their high cardiospecificity, high sensitivity for MMD, and their long diagnostic time-window.

The troponins are components of the troponin regulatory complex located on the thin filament of the contractile apparatus of the myocyte. Three types of troponins exist: troponin C (TnC), TnI, and TnT. The high cardiac tissue specificity of TnI and TnT compared with TnC and other cardiac biochemical markers is well established. The evaluation of cTnI and cTnT was initially carried out in patients with acute MI (4–6). However, increased serum cTnT concentrations were also seen in approximately one-third of patients with unstable AP or in other chest pain patients in whom an acute MI had been ruled out (7). A multicenter study first suggested that increased cTnT may be a useful prognostic indicator in patients with unstable AP (8). Numerous prognostic studies on cTnT have corroborated this finding (7). However, only one commercial immunoassay is available for the measurement of cTnT. This has led to a great interest in cTnI, and in the last few years, the prognostic value of increased cTnI in patients with ACS has triggered considerable interest. However, no prognostic studies have been published with regard to the great majority of cTnI assays, and in those assays where prognostic studies have been published, only one or two of the assays have been the subject of more than one prognostic study published in a peer-reviewed journal.

The study by Morrow et al. (9) in this issue of Clinical Chemistry is welcome. This study deals with three main issues: different cTnI immunoassays, decision limits/diagnostic time-window, and risk stratification in a non-ST-segment patient population. The present study is especially important because it makes reference to a commercially available cTnI immunoassay that has been approved by the Food and Drug Administration (FDA) in the US and is waiting for a standardization of cTnI. However, a not inconsiderable number of commercial cTnI immunoassays have been approved by the FDA (16 different immunoassays from eight different companies). Add to this those not FDA approved.

As noted by Morrow et al. (9), large differences exist in the construction of cTnI assays, e.g., anti-cTnI antibody components that target different protein epitopes; interaction between the locations of these protein regions; the action of proteolytic enzymes, causing degradation of both COOH and NH2 termini of TnI; and conformational changes resulting from the association of cTnI with TnC and TnT in binary and ternary complexes (10–12). Reported results for the same sample may vary up to 20-fold among cTnI methods (12), and the diversity of these assays can therefore lead to substantial confusion concerning reference ranges, analytical interferences, coefficients of variation, diagnostic time-windows, and decision values for both diagnostic and prognostic purposes.

Both the AACC and the IFCC have set up subcommittees to establish cTnI standardization. In the meantime, the only way the clinician/clinical chemist can rely on a specific cTnI immunoassay is from publication in a peer-reviewed journal. In this respect, it is vital that all information on the specific cTnI immunoassay is given. Also bear in mind that if one looks at the international literature on CKMB as a cardiac marker, it often is difficult to figure out (a) just what the authors have measured—CKB, CKMB, or merely CK—catalytic activity (immunoinhibition or electrophoresis) or mass
concentration, (b) reference values, and (c) decision limits for myocardial injury, etc. This is despite the fact that it should be simple to provide this information. A standardization of CKMB mass has been carried out, and even so, it is still not incorporated in clinical practice.

Morrow et al. (9) show good correlation coefficients among the three assays, although it is noteworthy that there is discordance between the Dimension RxL assay and the other two assays in favor of the RxL assay in ~10% of the patients who suffered an adverse event. This again illustrates the problem with many different assays for only one marker. Furthermore, the decision limits that Morrow et al. found best for risk stratification were not the decision limits given by the manufacturers on the package inserts; this can lead to considerable confusion for others. Although the cTnT assay is from a single company, similar problems to those for the individual cTn immunoassays have existed for cTnT, because we have at present the third generation of the cTn immunoassay. The cTnT discrimination limit of myocardial injury has decreased from the initial 0.50 μg/L to as low as 0.06 μg/L (13), although the widely used discriminator concentrations are 0.10 and 0.20 μg/L.

New generations of cTn assays are being developed, which should in fact be an improvement, but they possess the risk of further diagnostic confusion. This is illustrated by Morrow et al. (9), who note only the increased sensitivity of the current generation of cTn assays but do not state the generation in question. The admission sample for early risk stratification has shortcomings unless the diagnostic time-window for the release of biochemical markers is considered. This was demonstrated recently in the GUSTO IIa study, in which 35% of the patients were cTnT positive on admission, whereas an additional 44% became positive when sampled at 8 and 16 h (14). In the study by Morrow et al. (9), only 80% had serial sampling.

Prognostically, the present study shows that patients with increased cTnI are at a two- to threefold increased risk of suffering death or acute MI within 43 days after the index event, which confirms the results of the few other cTnI prognostic studies [and similar to the increased risk in the cTnT studies (8)]. However, as noted earlier, we still have only one or two reliable prognostic studies for only a few of the cTn immunoassays. More studies for each assay are needed to implement a cTnI device in the laboratory, not only for prognostic information but also to evaluate the accuracy and reference ranges, etc., and to understand the meaning of false positives and analytical difficulties.

I fully agree with the statement by Morrow et al. (9), that until adequate cTnI standardization is possible, specific thresholds established for individual assays should not be generalized and that the clinical efficacy of each cTnI assay at a given decision limit should be established in well-conducted clinical studies. Data from these assays should not be extrapolated to other assays not evaluated in the clinical setting. This is the best we can do at present. However, beyond the need for standardization of cTnI, there is also a need for international agreement on the diagnosis of myocardial injury. In addition to the National Academy of Clinical Biochemistry (15) and IFCC (16) recommendations on biochemical markers, a large expert group that included persons from such fields as pathology, clinical chemistry/cardiology (biochemical, ECG, imaging techniques), epidemiology, social/economics, and trialists was convened at a “Heart to Heart House Policy Conference” between the European Society of Cardiology and the American College of Cardiology in June 1999 to discuss refinements of the criteria for the diagnosis of MI. We look forward to an expected report in mid-2000.

References

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