Higher sensitivity troponin assays: Quo vadis?

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This editorial refers to ‘Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35’ by M.S. Sabatine et al. on page 162.

Central to the universal definition of myocardial infarction (MI) is the recommendation that cardiac troponin (cTn; I or T) is the biomarker of choice for detection of myocardial necrosis because of its high clinical sensitivity and almost absolute myocardial tissue specificity. The guidelines are based on the assays presently available. However, predicated on data suggesting that there is additional information below the levels that are presently being measured, manufacturers have begun to develop much more sensitive cTn assays that allow measurement of concentrations in the range of pg/ml rather than ng/ml. These assays should permit accurate measurement of most if not all normal subjects with an optimal level of analytical imprecision (coefficient of variation ≤10%).

Preliminary observations using levels now measurable and based on values below the present 99th percentile of the current assays suggest that more sensitive assays will result in an increased diagnosis of MI and that these patients are at substantial risk post-infarction. Recent data indicate that these previously undetectable levels are also associated with worse outcomes in patients with an acute coronary syndrome, especially if these low level elevations continue post-event, in those with heart failure, and stable angina pectoris, and even elderly apparently healthy population cohorts. These concentrations have also been found to be associated with cardiovascular high-risk features, higher carotid artery plaque burden, and impaired cardiac performance.

The introduction of troponin assays with still higher sensitivity will also probably allow for still earlier detection of MI as recently documented when a more sensitive contemporary assay is substituted for an earlier, less sensitive iteration. It should be clear that these novel assays are not those presently in contemporary use; they require substantial additional analytical and clinical validation prior to clinical use. Several such advanced high-sensitivity generations of cTn assays are being developed by manufacturers. The article by Sabatine and colleagues makes clear how much more sensitive these novel assay are by showing that the values measured are below the level of detection of well-established contemporary cTn assays.

The question as to whether such ‘high-performance’ assays might be able to indicate the presence of myocardial ischaemia in the absence of myocardial necrosis is suggested by the study of Sabatine et al. Previous data with a high-sensitivity assay did not find changes of cTnT in the presence of stress-induced reversible perfusion defects on nuclear scans 4 h post-stress. In contrast, Sabatine et al. report that a single molecule detection technology using a monoclonal cTnT capture antibody and a fluorescence-tagged affinity-purified goat detecting antibody does detect cTnT elevations. The technology depends on laser excitation causing the emission of a single fluorescent molecule that may be detected as a single digital event. This configuration enables very high analytical sensitivity. Using this Singulex cTn assay, the authors demonstrate minute changes of cTnT that are associated with the presence and severity of perfusion defects in nuclear stress tests of patients with possible myocardial ischaemia. Receiver operating characteristic (ROC) analysis determined that an increase of cTnT concentration of 1.3 pg/ml was the only independent predictor of perfusion defects (OR 3.54, P = 0.007). This cut-off value was superior to traditional indicators of myocardial ischaemia, including angina pectoris or stress-induced ST depression ≥2 mm. The level of precision necessary to make these observations is reported to be present, but we are not totally convinced, especially if consideration of biological variability is added. Recent data suggest this may be as high as 70%.

These findings were generated in a highly selected cohort, and thus may not translate into a general population with lower pre-test probability of coronary artery disease. The unusual nature of the cohort is made clear by the surprisingly low frequency of positive ECG stress tests (37%). Based on their data, Sabatine et al. cast doubt on the prevailing hypothesis that cTn is only released following irreversible myocyte death, and claim that cTns may be released from myocardial cells after stress-induced reversible myocardial ischaemia. This, as the authors acknowledge, remains hypothetical since the methodology...
applied does not give any information on the integrity of myocardial cells in the working human heart after moderate or severe myocardial ischaemia leading to troponin I release.

Whether the analytical precision of this and/or other highly sensitive assays is sufficient to yield robust data in less selected patients is uncertain. Before applying these sensitive assays in clinical practice, therefore, several caveats must be stated. First, all these new highly sensitive assays are potentially troubled by difficulties in assay standardization and precision at these low levels, which correspond to detection of only a few molecules in the blood specimen. At these low levels, biological variability of baseline values becomes an issue. In addition, the normal range determination will depend critically on what is selected as a normal reference population, and the possibility of analytical confounds is high with this level of sensitivity.

For the diagnosis of MI, the universal definition guidelines recommend that a cTn value must not only exceed the 99th percentile threshold in the setting of ischaemia but should ideally show a typical rise and/or fall. Based on analytical but not biological variability, a rise of >20% has been considered adequate for the diagnosis of an acute MI. The recent biological variability data suggest that the increment required to be sure one has a significant change is probably higher. The relative change values for use in serial troponin testing was calculated as 70% for increasing and -41% for resolving troponin values. Testing these values and the assay performance in chest pain patients in emergency departments will be crucial before we begin utilization of the ‘high-performance’ assays. In addition, we will need data to know whether at these very low cut-off values we should continue to treat patients with aggressive anti-coagulation, IIB/IIIA anti-platelet agents and an invasive strategy according to ACS guidelines. Until these data become available, these new assays should not be implemented for clinical use.

The present study by Sabatine et al. is one of several studies that give glimpses into the new era of highly sensitive assays. The data highlight a variety of still unresolved issues. These demand scientific scrutiny and have to be resolved before single or serial cTn values from these ‘high-performance’ assays can be taken as proof of myocardial injury or necrosis, and/or used clinically. The remarkable work of Sabatine et al. is a starting point for yet another round of biomarker trials focused on these critical analytical and clinical issues.

Conflict of interest: A.S.J. reports having been a consultant to most of the major diagnostic companies including consultant to Singulex who made the assay used in the study by M.S. Sabatine et al.

References