Cardiac troponins in blood are the most sensitive and specific biochemical markers of myocardial damage and are paramount for classification, risk stratification, and customized therapy in patients with acute coronary syndromes (1, 2). Despite the overt advantages, some important obstacles to troponin analysis and interpretation have remained, such as assay standardization, interference, preanalytical variability, and imprecision (3).

Introduction of the 99th percentile reference limit for the diagnosis of myocardial infarction by the European Society of Cardiology/American College of Cardiology (ESC/ACC) Consensus Committee (4, 5) has largely been driven by the demonstration that even the lowest detectable amounts of cardiac troponins in blood are associated with increased cardiac risk (6–8). Conversely, patients with any detectable troponins benefit from early coronary or pharmacologic intervention (6–8). Implementation of the new definition of acute myocardial infarction is not trivial because it will almost double the number of patients with a diagnosis of acute myocardial infarction (9–11). Therefore, to avoid misclassification arising from assay imprecision, the consensus committee proposed that the 99th percentile reference limit should be measured with a total imprecision (CV) <10%. However, many troponin and creatine kinase MB (CKMB) assays have not been validated in large clinical trials, and the relative performance of commercially available assays is not transparent. Until now, clinicians and laboratory physicians have had to rely on the manufacturers’ claims and package inserts (12, 13). There are, however, some caveats with such claims and inserts. Frequently, package inserts still suggest the 97.5 percentiles or do not provide adequate information. There is strong market competition, and it should be kept in mind that several assays have never been evaluated in the peer-reviewed literature.

In this issue of Clinical Chemistry, Apple et al. (14) evaluate the detection limits and analytical imprecision of different widely used commercial assays for cardiac troponins and CKMB mass. The authors carefully collected a very large reference population according to NCCLS standards (15), which consisted of 696 healthy adults. The authors mainly determined the 99th percentile and analytical imprecision of each method. Thus, for the first time, Apple et al. (14) provide an objective platform to compare assays directly with each other independently of the manufacturers’ information. In addition, the sample size of the reference population allowed them to look for ethnic, age, and gender differences at the lower end of the troponin and CKMB mass ranges.

Interestingly, Apple et al. (14) found little divergence between manufacturers’ claims and their own laboratory findings. The authors confirmed the large diversity of troponin assays with respect to 99th percentile reference values and total imprecision. Not surprisingly, none of the troponin assays except for the Tosoh AIA 600 II cardiac troponin I test met the precision requirements of the new definition of acute myocardial infarction.

Differences among assay calibrators largely explain the divergence of the concentrations at the lower limit of detection and the 99th percentile. Thus, lower detectable troponin concentrations do not automatically mean higher clinical sensitivity. Therefore, all assays, including the Tosoh AIA 600II, must document their clinical performance.

Measurements at the lowest concentration range bear some unexpected caveats. The first caveat is that the reason for and the role of lowest detectable troponin concentrations in apparently healthy persons remains unclear. Moving the decision limits to lower concentrations will enforce the need to differentiate background noise from subclinical cardiac pathology. Currently, the next (fourth) generation troponin T assay is being tested for analytical and clinical performance. Preliminary data suggest a fivefold reduction of the lower detection limit with adequate precision. Thus, it is tempting to speculate that differentiation between “background noise” and “subclinical cardiac pathology” will become an ever more challenging task.

The second caveat, which is probably linked to the first, is that the authors address the issue of age-, gender-, and race-dependent differences in 99th percentile reference values. Some troponin and CKMB mass assays showed significantly higher 99th percentile cutoffs for males than for females and for blacks than for Caucasians. In addition, age-dependent increases in the 99th percentile reference concentrations were found with all CKMB mass assays. Thus, regardless of the reason for troponin or CKMB mass release, these data suggest the need for specific cutoff values that consider age, gender, and ethnic differences, at least for some troponin and CKMB mass assays.

In summary, the study by Apple et al. (14) provides a platform for objective comparison of troponin and CKMB mass assay performance. The data underscore the need for introduction of improved troponin assays that comply with the new definition and precision requirements. Although the present study made an important step, enormous efforts are still needed to resolve assay differences and to provide tools for comparison of assays using predetermined cut-points such as the 99th percentile or the 10% CV limit.

References
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