Being Rational about (Im)precision:
A Statement from the Biochemistry Subcommittee of the
Joint European Society of Cardiology/American College of
Cardiology Foundation/American Heart Association/World
Heart Federation Task Force for the Definition of
Myocardial Infarction

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We have for many years advocated for very precise cardiac troponin assays to improve the sensitivity of detection of cardiac necrosis and to decrease over time the amount of change (or delta) in cardiac troponin concentrations needed to be considered significant (1, 2). During the time period when assays were insufficiently precise at very low levels, we and others advocated using as a cutoff concentration the lowest value at which the assay achieved a 10% CV rather than the 99th percentile value (3). Guidelines have never such a recommendation, however, but instead have promoted recognition that “optimal” diagnostic performance of troponin assays was achieved by using the 99th percentile (1, 4). Over time, assay precision has improved substantially. Nevertheless, some clinicians, as well as some regulatory agencies and clinical trial groups, advocate that troponin assays that fail to meet the 10% CV criterion should not be used, a recommendation based on the mistaken impression that such assays would increase the rates of detection of increased concentrations considered to be false-positive results. This issue is a major concern for clinicians because many cardiac troponin increases are difficult to explain, and thus their detection is often considered a false-positives result. However, increases of troponin, albeit often caused by ischemia, also can be induced by nonischemic cardiac injuries such as those associated with drugs, toxins, and trauma (5).

We believe assays with imprecision up to a 20% CV may reasonably be used for diagnosis and/or risk stratification, This belief is based on the following arguments:

1. When assay validation is done properly, modest increases in imprecision above 10% (up to 25% CV) inherently increase the 99th percentile value and thus protect against false-positive values (6). In a simulation that included more than 500 000 randomly generated cardiac troponin values derived from assays in clinical use, the 99th-percentile concentrations derived from the simulation went from 0.06 µg/L at an assay imprecision of 0 to 0.063 µg/L with an assay imprecision of 10%, and to 0.07 µg/L when the imprecision was 25% (P not significant).

2. The results of these computer-simulation studies failed to show any increase in false-positive results between imprecision values of 10% and 25%. The rate was identically 0.010 across this imprecision range. When the rates of false-positive changes observed with serial samples were examined, the results were slightly different for 10% vs 25% assay imprecisions, being, respectively, 13 and 15 false positives per thousand for 2 samples, and 14 and 20 per thousand for 3 samples. It should be noted that in none of these situations would the values be very different, so none of these values would have resulted in clinical consideration of a rising and/or falling pattern (6). Even when the specific modeling approach was altered, the results were similar (7).

3. A similar study that used different modeling techniques explored the effect of assay imprecision on the ROC area under the curve for prognosis by using cardiac troponin from the Gusto IA trial (8). Increments of imprecision from 5% to 20% did not alter the areas under the curve: 0.549 at 5% CV imprecision, 0.556 at 10% CV imprecision, and 0.543 at
20% CV imprecision for cardiac troponin. These differences did not come close to approaching statistical significance.

4. It is unclear how a metric mandating a 10% CV at the 99th percentile value might be applied. In the past, when this value was deemed important and different approaches provided varying results, there was considerable controversy about how best to determine the value analytically (9–13). The areas of controversy revolved around imprecision in calculation of the 99th percentile value of the reference population and how precisely the assay imprecision could be estimated at this concentration.

5. A policy to preclude the use of assays that did not have imprecision less than 10% at the 99th percentile value might force some hospitals to change assays, and such a change has associated logistic and financial costs. In addition, this policy would make the logistics of clinical trials increasingly complex because it would preclude certain centers from participation if they did not use an assay that met this particular metric, and it might preclude end points from being counted if a study patient’s event occurred in a hospital where a “less precise” assay was being used.

6. Precision is not the only metric that is useful in assay evaluation. A sensitive assay with slightly more imprecision will correctly identify more patients at risk than an insensitive one with excellent precision. The easiest way to meet the 10% CV metric would be to increase the assay threshold, thereby decreasing its clinical sensitivity. However, such a change would identify fewer patients with disease and increase the time after myocardial injury until the first positive results were identified, thereby prolonging diagnostic evaluations to the detriment of our clinical efforts (14, 15).

On the basis of these considerations, the policy of precluding the use of assays that do not achieve a level of 10% imprecision at the 99th percentile value does not have a sound rationale. We concur that if an assay’s imprecision is >20% CV, because there are no available data regarding what effect this level of assay imprecision would have on clinical accuracy, the use of such an assay should be discouraged. We believe this concept should apply to both laboratory-based and point-of-care assay systems.

In our view, to make these decisions transparent through uniform information disclosure, regulatory agencies should demand that manufacturers of in vitro diagnostic assays provide published information concerning their assays that includes the limit of the blank, limit of detection, limit of quantification, lowest concentration that has a 20% CV (also called the functional sensitivity), and percentage CV at the 99th percentile (16). Such information will be particularly important now, when a new generation of high-sensitivity assays is just being validated (17).

We will continue to advocate for more precise cardiac-troponin assays. The effort to increase assay precision will make assays more analytically sensitive and allow for more reasonable reference delta intervals to identify those patients with acute vs chronic problems. However, the suggestion of banning assays that have slightly greater than 10% levels of imprecision (i.e. up to 20%) will not improve clinical care or research applications. On the contrary, it will confuse those who use cardiac troponin assays, be costly both financially and logistically, and result in less sensitive (see argument 6 above) and thus potentially less clinically valuable assays.

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References


