High-Sensitivity Cardiac Troponin Assays: Isn’t It Time for Equality

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There are abundant data that women who present with acute coronary events are less frequently diagnosed and have worse outcomes than men (1, 2). Part of the problem may be that women are less apt to manifest increased biomarkers when they present and perhaps for that reason, often receive less aggressive guideline-mandated care (3, 4). It may be that the reason for this is that women have lower reference values for biomarkers of cardiac injury that are rarely taken into account. This certainly was the case for creatine kinase (CK)3 MB, for which reference values in women were half of those in men but often were not taken into account (5). This appears again to be so with high-sensitivity cardiac troponin assays (6), for which the urge for “simplicity” may cause us to repeat this error. In addition, the pathogenesis of coronary artery disease is different in men than in women, with women having lower cardiac troponin values for any given extent of disease (7). Further, because women have more endothelial dysfunction and less fixed coronary disease, they are more often diagnosed with type 2 acute myocardial infarctions that are associated with lower cardiac troponin values (8). Given these facts, it appears at first glance axiomatic that sex-specific criteria will be necessary to detect all of the women in need of acute care. In addition, if we do not embrace this approach, the cutoff values derived from a mixed population of men and women will be lower than necessary for men, exacerbating the major issue related to high-sensitivity cardiac troponin assays, the lack of clinical specificity for acute myocardial infarction.

Into this landscape come 2 recent studies reported in Clinical Chemistry (9, 10). Unfortunately, neither is definitive. The first, from the Thrombolysis in Myocardial Infarction (TIMI) group (9), evaluated only the initial samples of patients enrolled in 1 of 2 randomized therapy trials. To qualify, patients had to manifest either an increased cardiac troponin or CK MB value or electrocardiographic changes. Based on the fourth-generation Roche cardiac troponin T (cTnT) assay data (an assay that is not highly sensitive), 94% of patients (3984/4215) had increased values.

The Abbott hs-cTnI assay has a low, non–peer-reviewed 99th percentile of 26 ng/L that when broken down by sex gives a cutoff of 16 ng/L for females and 34 ng/L for males. One would anticipate that the Abbott hs-cTnI assay would show markedly increased cTnI values in almost all of these patients from the TIMI group. Because the hs-cTnI assay was the gold standard, there were nearly 3 times more false-positive increases of cTnT than true negatives (485 compared to 144), a disturbing result. Perhaps some of the misclassifications may have resulted from the imprecision of the cTnT assay at values between 10 and 30 ng/L, as suggested in the validation paper on the hs-cTnT assay (11). Nonetheless, the inclusion criteria for the study and the late enrollment (mean of 13 h) made substantial increases of hs-cTnI very likely. And that is exactly what the data show. It appears that there were very few patients, regardless of sex, who had minor increases that could allow for a robust evaluation of the need for sex-specific cutoff values. There were only 40 women and 46 men with values between the overall value for all comers and the sex-specific cutoff values. Only 3 of the men who had adverse outcomes were reclassified on the basis of sex-specific values. However, there is much we do not know. Perhaps because we have only the initial hs-cTnI assay values, subsequent local laboratory cardiac troponin values made it clear that an event was occurring and treatment was then initiated, reducing subsequent events. Alternatively, perhaps these individuals did not have ischemic heart disease at all, but structural heart disease, and chronic increases were detected only with the hs-cTnI assay. Because we do not have serial samples, we cannot know whether this was or was not the case. If we suppose that to be the case, then, although cardiac troponin increases might still be of prognostic importance in the long term, they may not identify 30-day, short-term events nearly as well. Thus, this study is far from definitive in regards to whether sex-specific cutoff values will be useful. What is needed are studies similar to the one by Mills et al.
(12) in which individuals with marginal cardiac troponin increases were randomized for treatment or no treatment. It is of interest that within the data set of that study, after reanalysis using the same Abbott hs-cTnl assay, there were profound differences related to sex, and the patients would have benefited by the use of sex-specific cutoff values (13). Retrospective findings are less powerful than prospective ones, but these data suggest care is needed in interpreting the TIMI data.

The second report from Kavsak et al. (10) takes a very different approach. They measured a large number of samples from 5206 patients, including 2552 women presenting to 2 different emergency departments. The diagnoses in these patients were unclear, but in-hospital mortality was available. Increased values using the Abbott hs-cTnl assay were similar between the sexes for those who died (33 ng/L compared to 35 ng/L). In those who survived, women had lower values. The reported low 99th percentile maximized the negative predictive value for mortality; with the limit of detection value (1.2 ng/L) being even better in this regard. These results were not unexpected. Despite the fact that the illnesses in these emergency department patients were not complicated by the presence of overt heart disease, the presence of an increased high-sensitivity cardiac troponin value probably should be viewed as an indication of an adverse prognosis, which was, in fact, the case. It is also not surprising that the predictive high-sensitivity cardiac troponin values in women were lower because women are known to have lower reference interval values. Thus, these data are no more convincing to us than the TIMI group data.

We opine that better studies are needed using serial samples before we can conclude, as we believe, that sex-specific 99th percentile values are needed to optimize the clinical evaluation of both men and women. In men such values would improve specificity and in women they would improve sensitivity. Because sex-specific cutoff values are used in more than just acute ischemic heart disease, we need to think broadly about the implications. Because acute ischemic heart disease usually causes more marked increases in serial values, not many men or women are misclassified as in the study reported by the TIMI group. That still may not mean, as implied by Kavsak et al., that sex-specific cutoff values may not be necessary in more diverse groups of acutely ill patients. In addition, such sex-defined cutoffs may be essential for the evaluation of more chronic diseases states, providing the ability to predict events during primary and/or secondary prevention (14).

As clinicians and laboratorians, we are careful to recapitulate what we would argue are the errors of the past made in the interest of simplicity. Good studies with high-sensitivity cardiac troponin assays are needed, and many of the convenience samples to which we have easy access, as in the examples above, yield interesting but not definitive findings. We have given similar warnings in regard to a variety of other issues, such as calculating δ values (15). We have much to learn about high-sensitivity cardiac troponin assays, but we must define the issues by conducting better studies than the ones we have to date. And if there is ambiguity, why not err on the side of giving women who present with cardiovascular disease equal opportunity to get good outcomes by making sure all of our diagnostic and therapeutic algorithms do not inadvertently put women at a disadvantage?

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