Clinical Chemistry 60:10
1273–1275 (2014)

Opinion

Improving the 510(k) FDA Process for Cardiac Troponin Assays: In Search of Common Ground

Fred S. Apple,[1,2*] Judd Hollander,[3] Alan H.B. Wu,[4] and Allan S. Jaffe[5]

We met recently with the leadership of the Food and Drug Administration's (FDA's)[6] Division of Chemistry and Toxicology Devices to discuss concerns about the heterogeneity of analytical and clinical protocols used in studies for clearance of cardiac troponin assays. We, as experts, are frequently asked to help with the evaluation of new cardiac troponin assays and are aware of variability between the specific protocols used, which are difficult to understand, but which likely reflect differences in the various companies' interpretations of what elements are mandated by the FDA. We advocated to the FDA the use of standardized study protocols to reduce complexity and permit better comparisons among methods and provided suggestions to achieve these goals. Attending from the FDA's Division of Chemistry and Toxicology Devices in the Office of In Vitro Diagnostics and Radiological Health were the Division Director, the Branch Chief of Cardio-Renal Devices, Medical Officers, and Reviewers.

Although the FDA seemed supportive, it must be made clear that the opinions expressed here are those of the authors and do not represent those of the FDA. It was our impression that the FDA was in favor of uniform protocols, especially if developed by national organizations; they even expressed a willingness to participate. The FDA indicated, and we concurred, a need to evaluate protocols within the context of the sponsor's specific claims. The FDA leadership stated that it does not mandate the number of participants needed in a study, the specific criteria for diagnosis of acute myocardial infarction (AMI), or approaches used in reference interval studies. Rather, the FDA emphasized that manufacturers should present properly designed and powered studies to support their claims. The FDA indicated that it will provide feedback on study design before study implementation. Our impression was that once a protocol is finalized, the FDA felt strongly that deviations from the original design should not occur. This article presents important issues for manufacturers to discuss with the FDA, along with our suggestions for unifying study protocols.

We provided recommendations to the FDA on several points: (*a*) the number of reference individuals for determination of a 99th percentile upper reference limit; (*b*) limit of quantification; (*c*) total imprecision requirements; (*d*) enrollment of subjects for diagnostic studies; (*e*) patient adjudication processes; and (*f*) clinical endpoints and time limits to assess outcomes. A primary focus was to ensure that the suggested protocols also apply to high-sensitivity cardiac troponin assays.

First we focused on the determination of the 99th percentile upper reference limit. It is clear that more rigorous screening of the reference population results in lower values *(1)*. We suggested a balance between the practical extent of evaluations and the depth of prescreening. IFCC guidelines *(2)* suggest that a minimum of 300 men and 300 women, appropriately distributed by race, ethnicity, and age, including individuals $>$ 60 years, are required to determine sex-specific values. We proposed the use of health questionnaires along with measured biomarkers such as N-terminal pro-B–type natriuretic peptide and estimated glomerular filtration rate to screen for eligibility. We suggested the creation of a common specimen bank for normal reference studies with adequate numbers of aliquoted samples to enable widespread distribution.

We advocated the use of whole numbers (nanograms per liter) for high-sensitivity cardiac troponin assays to avoid mistakes related to expressing the results with a large number of zeroes *(2)*. Because even values of high-sensitivity cardiac troponin assays within the reference interval contain prognostic information *(3)*, we suggested that concentrations should be reported to the limit of quantification (20% CV concentration) to facilitate risk stratification. We advocated reporting the 10% CV concentration as well

[1] Department of Laboratory Medicine and Pathology, Hennepin County Medical Center and [2] Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN; [3] Department of Emergency Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA; [4] Department of Laboratory Medicine, University of California, San Francisco, CA; [5] Cardiovascular Division in the Department of Internal Medicine and CCLS Division in the Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.

* Address correspondence to this author at: Hennepin County Medical Center, Clinical Labs P4, 701 Park Avenue, Minneapolis, MN 55415. Fax 612-904-4229; e-mail apple004@umn.edu.

Received July 16, 2014; accepted July 17, 2014.
Previously published online at DOI: 10.1373/clinchem.2014.229286

[6] Nonstandard abbreviations: FDA, Food and Drug Administration; AMI, acute myocardial infarction; LoD, limit of detection; ED, emergency department; ECG, electrocardiogram.

(2, 4). This imprecision value should be present at the 99th percentile for all high-sensitivity cardiac troponin assays *(2)*. We suggested defining the limit of detection (LoD) with Clinical Laboratory Standards Institute guidelines *(5)*. Assuming the analytical LoD is at a concentration with ≤20% CV, the percentage of measureable normal individuals with concentrations higher than LoD should be reported. This provides 1 measure of analytical sensitivity. We supported the IFCC recommendations *(2)* that high-sensitivity cardiac troponin assays be defined by the ability to (*a*) measure ≥50% of normal individuals above the LoD and (*b*) have a ≤10% CV at the 99th percentile for sex-specific values. We advocated that the FDA ask companies to make quality control materials at the 99th percentile value; they concurred with this as a shortcoming.

We next transitioned to clinical issues pertaining to cardiac troponin. In the emergency department (ED), cardiac troponin values are used to detect myocardial injury and distinguish acute presentations from chronic structural diseases *(6)*; with the use of high-sensitivity cardiac troponin assays, this practice will become more common *(7)*. AMI is only 1 reason for acute cardiac injury. In the ED, clinicians try to exclude acute cardiac injury rapidly while making sure it is not missed. The former is important because when EDs are overwhelmed, outcomes are negatively impacted *(8)*. Because chest pain is a common complaint, rapid decisions in this group would have a major impact on patient flow and outcomes. High-sensitivity cardiac troponin assays will likely decrease the time for ruling out AMI in low-risk patients (40% of the population) to 2 to 3 h *(9, 10)*. Acute cardiac injury is diagnosed with a combination of clinical presentation, electrocardiogram (ECG), imaging studies, and cardiac troponin measures. Key to this determination is a changing pattern of cardiac troponin values *(4, 6, 10)*. However, many published studies in this area are flawed *(11)*. We did not advocate that criteria for cardiac troponin changes over time become a regulatory requirement, but suggested that the FDA mandate a consistent approach toward this determination. We suggested that FDA assay clearance also be allowed for detection of cardiac injury as well as AMI since it is often difficult to determine the exact cause of cardiac troponin release in the ED. This suggestion is consistent with the universal definition of MI.

In general, the FDA clears cardiac troponin assays to aid in the diagnosis of AMI. We suggested that acute cardiac injury might be a better metric owing to the ambiguities in defining the exact cause of cardiac injury. It is often difficult to determine a yes or no answer in every patient, especially in the ED. Such attempts may lead to misclassifications or leave some patients in an ambiguous category that manufacturers believe is frowned on by the FDA. The FDA did not object to the concept of considering a claim for acute cardiac injury if manufacturers propose appropriate studies and endpoints to support that claim.

The concept of using only analytical comparisons and concordance around the 99th percentiles to clear a cardiac troponin assay as a biomarker of myocardial injury was discussed. At least 1 assay has a claim "to aid in the assessment of myocardial damage" *(12)*. We questioned whether this assay could be used as a predicate by other manufacturers seeking a cardiac injury claim, as is the case with other tests, without the need for clinical adjudication. It was our impression that the FDA was resolute that clinical outcomes were essential because cardiac troponin assays are not standardized, and it would be difficult to determine, for discrepancies, which assay was correct without clinical information.

It was indicated that with high-sensitivity cardiac troponin assays, a rising cardiac troponin pattern would likely be seen in about 20% of ED patients *(7)*. Thus, the number of patients needed to give a study the appropriate statistical power might be reduced. The FDA pointed out that they do not dictate the number of study participants, but rather that manufacturers need to substantiate their enrollment protocols with appropriately powered statistics to demonstrate equivalence to previously cleared assays. The FDA acknowledged that with high-sensitivity cardiac troponin assays, a larger number of patients with non-acute coronary syndrome myocardial injury will be detected, thereby decreasing the clinical specificity of these assays for AMI *(7, 10)*. We were of the impression that often the FDA expects all patients to be categorized as either having AMI or not having AMI despite the ambiguities described above. The FDA clarified that the adjudication plan depends on the claims being pursued and the study design to support them. It was our impression that if a manufacturer's claim for its assay was to be used to aid in the diagnosis of AMI, that the FDA expects the manufacturer to determine the conditions that led to the increased cardiac troponin values in patients not diagnosed with AMI, by use of the adjudication approach, and to include this information in the clinical labeling. We requested that the FDA consider using only 1 adjudicator for determining a "no AMI" diagnosis in patients with no increases of cardiac troponin, a normal ECG, and negative imaging findings. The FDA responded that typically >1 adjudicator is used to minimize bias, and those considering this approach should discuss this point with the agency.

Finally, length and nature of follow-up for adverse outcomes for risk stratifications was addressed. We requested that the FDA consider the use of a 30-day endpoint for risk assessment in acute coronary syndromes, which is supported by current guidelines *(13)*. For outcomes in patients with increased cardiac troponin without acute coronary syndromes, longer times for event

reporting, perhaps up to 6 months, appear more appropriate. The FDA stated that although it does not mandate the type of follow-up, it recommends that the follow-up approach be accurate, consistent for all subjects, and clinically meaningful. The FDA indicated that it had recommended follow-up for longer time periods on the basis of information provided by their panel experts, who were not identified. The FDA specifically objected to the idea that 1-year follow-up with ECGs was essential.

It is time to have uniformity among protocols in how cardiac troponin assays are analytically and clinically validated to facilitate between assay comparisons. We believe this could occur if companies worked together along with the clinical and laboratory communities to develop scientifically robust and consistent approaches. We hope our dialogue with the FDA will facilitate its involvement in this process.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: F.S. Apple, *Clinical Chemistry*, AACC; J. Hollander, *Annals of Emergency Medicine*.
Consultant or Advisory Role: F.S. Apple, Instrumentation Laboratory and Phillips; J. Hollander, Instrument Laboratories and Radiometer; A. Wu, Konica Minolta; A.S. Jaffe, Beckman, Alere, Trinity, ET Healthcare, theheart.org, Abbott, Radiometer, Ortho Dx, Critical Dx, and Amgen.
Stock Ownership: None declared.
Honoraria: F.S. Apple, Abbott Laboratories; A. Wu, Beckman, Mitsubishi, and Abbott.
Research Funding: F.S. Apple, Roche, Abbott, Siemens, Radiometer, Trinity, and Ortho Clinical Diagnostics; J. Hollander, Trinity, Abbott, Alere, Siemens, and Roche.
Expert Testimony: None declared.
Patents: A. Wu, Patent number 7,838,250.

References

1. Collinson PO, Heung YM, Gaze D, Boa F, Senior R, Christenson R, et al. Influence of population selection on the 99th percentile reference value for cardiac troponin assays. Clin Chem 2012;58:219–25.
2. Apple FS, Collinson PO, for the IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. Clin Chem 2012:58:54–61.
3. deLemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503–12.
4. Thygesen K, Johannes M, Katus H, Plebani M, Venge P, Collinson P, et al. The Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010;31:2197–204.
5. CLSI. Protocols for determination of limits of detection and limits of quantitation; approved guideline. Wayne (PA): CLSI; 2012. EP17-A.
6. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman R, White HD; Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. J Am Coll Card 2012;60:1581–98; Circulation 2012;126:2020–35; Eur Heart J 2012;33:2252–7.
7. Korley FK, Schulman SP, Sokoll LJ, Stolbach AI, deFilippi AP, Bayram JM, et al. Troponin elevations only detected with a high sensitivity assay: clinical correlations and prognostic significance. Acad Emerg Med 2014;21:727–35.
8. Pines JM, Pollack CV Jr, Diercks DB, Chang AM, Shofer FS, Hollander JE. The association between emergency department crowding and adverse cardiovascular outcomes in patients with chest pain. Acad Emerg Med 2009;16:617–25.
9. Cullen L, Miller C, Parsonage WA, Wildi K, Greenslade JH, Twerenbold R, et al. Validation of high-sensitivity troponin I in a 2-h diagnostic strategy to assess 30-day outcomes in emergency-department patients with possible acute coronary syndromes. J Am Coll Cardiol 2013;62:1242–9.
10. Korley FK, Jaffe AS. Preparing the United States for high-sensitivity cardiac troponin assays. J Am Coll Cardiol 2013;61:1753–8.
11. Jaffe AS, Moeckel M, Giannitsis E, Huber K, Mair J, Mueller C, et al. In search for the Holy Grail: suggestions for studies to define delta changes to diagnose or exclude acute myocardial infarction: a position paper from the study group on biomarkers of the Acute Cardiovascular Care Association. Eur Heart J Acute Cardiovasc Care [Epub ahead of print 2014 Jul 9].
12. TropI: instructions for use. http://apps.orthoclinical.com//IFU/ContentPages/displayDoc.aspx?hidebanner=Y&cPath=TropIES_GEM1309_WW_EN_I.pdf (Accessed June 2014).
13. Hollander JE, Blomkalns AL, Brogan GX, Diercks DB, Field JM, Garvey JL, et al. Standardized reporting guidelines for studies evaluated risk stratification of ED patients with potential acute coronary syndromes. Ann Emerg Med 2004;44:589–98.