

## EDITORIAL COMMENT

## Avoiding the Imminent Plague of Troponinitis



### The Need for Reference Limits for High-Sensitivity Cardiac Troponin T\*

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The limitations of the presently used troponin assays when obtained early after presentation in patients with chest pain are well documented. Their sensitivity and specificity for acute myocardial infarction (MI) are 77% and 93% for troponin I and 80% and 91% for troponin T (1), respectively. A second draw several hours later increases the sensitivity, but the cost effectiveness of this approach is poor (1). The use of these troponin assays in hospitalized patients is fraught with peril as there are innumerable causes of “troponinitis” that are unrelated to an acute coronary syndrome. This scenario has made the inpatient consultation for troponin elevation into the bane of the consulting cardiologist. The myriad causes of troponin elevation have been recently reviewed in a consensus document (2) and include myocarditis, Takotsubo cardiomyopathy, heart failure, hypertensive urgency, trauma, cardioversion or cardiopulmonary resuscitation, atrial fibrillation with rapid ventricular response, chronic kidney disease, sepsis, and pulmonary embolism.

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More recently, the potential clinical utility of the new highly sensitive cardiac troponin T assays (hs-cTnT) have been touted (3,4). These new assays can detect cTnT concentrations 10-fold lower than current assays (5). They increase the sensitivity for acute MI but at the price of a reduction in specificity that could lead to a plague of “troponinitis” and confusion to the clinical cardiology community regarding interpretation of these values. Serial

troponins looking for a rise and fall typical of myocardial ischemia/infarction are most useful in this setting to determine whether the first measure was an indication of myocardial ischemia or not. A useful algorithm has been recently proposed for interpretation of these levels and distinguishing ischemic mechanism from nonischemic myocardial injury or other underlying structural heart disease (4).

These ultrasensitive assays have been carefully tested in the emergency department (ED) setting. In a multicenter study of 718 patients, the area under the receiver-operating characteristic curve for the correct diagnosis of acute MI (17% of the patients) ranged between 0.95 and 0.96 compared with 0.90 for standard troponin assays (6). Similarly, in a multicenter study of a sensitive troponin I assay in 1,818 consecutive patients, sensitivity and specificity for acute MI were 91% and 90%, respectively (7). In a single center study of 377 patients with chest pain and low-to-intermediate likelihood of acute coronary syndrome (ACS) (9.8% ultimately positive), the hs-cTnT assay detected 27% more ACS cases than did standard troponin assays and a level >99th percentile predicted ACS with a hazard ratio of 9.0 (8). However, in this study, because of the low prevalence of true positives, the positive predictive value was only 38%. This finding points out for the need of assessing the pre-test likelihood of disease in the patients in the ED because a single level of hs-cTnT, although sensitive, may be misleading in the wrong clinical scenario.

Elevations in these novel biomarkers have been shown to have prognostic implications in normal patient populations entered into large screening databases. In the DHS study (Dallas Heart Study) of 3,593 normal subjects 30 to 65 years of age, hs-cTnT was elevated in 25% of individuals, whereas standard troponin T was only elevated in 0.7% (9). When the patients were stratified by baseline hs-cTnT level and followed for 6.4 years, those with elevated hs-cTnT over 14 pg/ml (99th percentile) had a significantly higher all-cause mortality (up to 28.4%) compared with the rest of the study population. Similarly, CHS study (Cardiovascular Health Study) of 4,221 adults over 65 years of age without prior heart failure showed that those with the a cTnT >12.94 pg/ml had a hazard ratio of 2.5 for heart failure and 2.9 for cardiovascular death compared with those with undetectable cTnT (10). A recent study from the same database demonstrated that a baseline hs-cTnT level >12.1 pg/ml was associated with a 1.89 risk of sudden cardiac death when fully adjusted for other risk factors (11). In the ARIC (Atherosclerosis Risk in Communities) study of 9,698 individuals 54 to 74 years of age, those with levels >14 pg/ml (7.4% of the population) had a hazard ratio of 2.3 for coronary heart disease and 7.6 for fatal coronary heart disease (12). Clearly, hs-cTnT is a marker of adverse cardiovascular outcome in large populations of normal older individuals.

The paper in this issue of the *Journal* by Gore et al. (13) presents convincing data in regard to the flaws in the presently used 99th percentile for the high-sensitivity

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troponin T assay that sits at 14 pg/ml. With data from 12,618 patients culled from the DHS, ARIC, and CHS study cohorts discussed previously, they demonstrate that the 99th percentile in these studies would be 18, 22, and 36 pg/ml in the respective studies and slightly lower when patients with left ventricular hypertrophy or dysfunction, and high N-terminal brain natriuretic peptide levels were excluded. The authors (13) demonstrate that with the presently used level of 14, up to 10% of men over age 65 years would meet the criteria for acute MI if blood was drawn at baseline. This paper clearly delineates the need for age, sex, and racial cutoffs for hs-cTnT in the same way that there is such stratification for coronary calcium scores developed from the MESA (Multi-Ethnic Study of Atherosclerosis) study (14). In fact, there is a calculator using the MESA study database to calculate arterial age based on age, sex, and race (15). A similar calculator could be developed using the databases studied in the paper by Gore et al. (13) for hs-cTnT that would be useful for determining the meaning of any isolated value based on the patient's demographics.

The major downside of the analysis in the current paper by Gore et al. (13) is that it is retrospective in nature and thus not ideal to truly test these cutoffs for hs-cTnT prospectively. A prospective study in a large multiethnic population of diverse ages would be most useful. It might also be helpful, especially for understanding racial variation, to test blood from MESA study participants if it is available. As it stands now, reasonable numbers of African Americans were tested in the DHS study, but few from other racial and ethnic groups were represented in any of the cohorts tested. We, as a cardiology community, have work to do if we wish to avoid the imminent plague of troponitis that will be upon us if we are unable to interpret the hs-cTnT assays that will undoubtedly be coming to an ED and intensive care unit near us very soon.

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## REFERENCES

1. Goodacre S, Thokala P, Carroll C, et al. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health Technol Assess* 2013;17:1–188.
2. Newby LK, Jesse RL, Babb JD, et al. ACCF 2012 Expert Consensus Document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2012;60:2427–63.
3. Mohammed AA, Januzzi JL Jr. Clinical applications of highly sensitive troponin assays. *Cardiol Rev* 2010;18:12–9.
4. de Lemos JA. Increasingly sensitive assays for cardiac troponins: a review. *JAMA* 2013;309:2262–9.
5. de Lemos JA, Morrow DA, deFilippi CR. Highly sensitive troponin assays and the cardiology community: a love/hate relationship? *Clin Chem* 2011;57:826–9.
6. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;361:858–67.
7. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;361:868–77.
8. Januzzi JL, Bamberg F, Lee H, et al. High-sensitivity troponin T concentrations in acute chest pain patients evaluated with cardiac computed tomography. *Circulation* 2010;121:1227–34.
9. de Lemos JA, Drazner MH, Omland T. 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.
10. deFilippi CR, de Lemos JA, Christenson RH. Association of serial measures of cardiac troponin t using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010;304:2494–502.
11. Hussein AA, Gottdiener JS, Bartz TM, et al. Cardiomyocyte injury assessed by a highly sensitive troponin assay and sudden cardiac death in the community: the Cardiovascular Health Study. *J Am Coll Cardiol* 2013;62:2112–20.
12. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011;123:1367–76.
13. Gore MO, Seliger SL, deFilippi CR, et al. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. *J Am Coll Cardiol* 2014;63:1441–8.
14. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2006;113:30–7.
15. Munir JA, Wu H, Bauer K, et al. Impact of coronary calcium on arterial age and coronary heart disease risk estimation using the MESA arterial age calculator. *Atherosclerosis* 2010;211:467–70.

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