Higher sensitivity troponin levels in the community: What do they mean and how will the diagnosis of myocardial infarction be made?

Harvey D. White, DSc, FCSANZ
Auckland, New Zealand

Troponins are the preferred markers for risk stratification of patients with acute coronary syndromes and for making the diagnosis of myocardial infarction (MI). They guide the selection of antithrombotic therapy and selection of an invasive strategy. They are also indicative of myocyte necrosis in a number of other clinical situations such as pulmonary embolism, myopericarditis, heart failure, and renal failure.

In this issue of the Journal (Am Heart J 2010;159:972-8), Otsuka et al report the first study evaluating high-sensitivity (hs) troponins in a healthy population and correlate levels with cardiovascular disease (CVD) risk factors and the Framingham risk score. The hsTroponin T levels were measured in 1,072 middle-aged (aged between 35 and 63, mean age 44 years) Japanese men working at a company making precision instruments. Individuals with a history or presence of CVD were excluded, as was a patient who had received hemodialysis.

Detectable levels, using a lower limit of detection of hsTroponin T of 0.002 ng/mL, were found in 80.9% of participants. It is noted that a recent analytical validation article has defined the detection limit as a 0.003 ng/mL. Also, it is better to use whole numbers to avoid errors, due to possible confusion of decimal places, and to use SI units. Therefore, the lower limit of detection used in this study should be 2 ng/L.

A hsTroponin level of 20 ng/L was the highest value measured. As hsTroponin T measures 23 ng/L higher than the contemporary fourth-generation troponin T test the comparative cutpoint of 0.03 μg/L for the diagnosis of MI with the fourth-generation troponin T based on the 99th percentile becomes 0.053 μg/L or 53 ng/L. In this study this level was not found with the contemporary fourth-generation troponin T assay in any participant.

The hsTroponin T levels were associated with several CVD risk factors including age, blood pressure, estimated glomerular filtration rate, current smoking, left ventricular hypertrophy, and C-reactive protein (CRP) levels. Surprisingly, diabetes was not an independent determinant of hsTroponin T levels. Using the Framingham risk prediction score, individuals in the highest tertile of hsTroponin T had 3.98 odds ratio of the lower tertile for a ≥20% 10 year CVD risk.

This study shows that hsTroponin T may be used to identify individuals at higher risk in primary prevention and that hsTroponin T could be added to a primary risk assessment model, which would require validation. However, these results may not apply to older individuals, females, or other ethnic groups.

The significant increased odds ratio for Framingham risk was only for the highest hsTroponin tertile (≥5 ng/L) versus the lowest tertile (≥2 ng/L) and not the middle versus the lowest tertile. This could indicate that there may be a level of detectable troponins that is not prognostically important.

The authors also compared detectable (>2 ng/L) versus undetectable hsTroponin T levels and found no increased CVD risk suggesting that it may not be the troponin levels that increase risk but that other factors may be responsible, either causing the troponin elevation or increasing cardiovascular risk, such as the presence of comorbidities.

The association of hsTroponin T with elevated CRP levels is intriguing, indicating that inflammation may be important as a cause of the troponin elevations. Interestingly, CRP only correlated with Framingham risk factors if troponins were also increased with the combination of hsCRP >0.1 mg/L and hsTroponin T <5 ng/L showing no increased risk in adjusted models.

Elevated troponin levels in the community

Several previous studies have shown that increased troponin concentrations in individuals without known CVD are related to an increased risk of death. In the population-based Dallas Heart Study in 3,557 individuals, hsTroponin T values ≥0.01 μg/L were found in 0.7% of the population. Troponin levels were elevated in those with left ventricular hypertrophy, heart failure, chronic kidney disease, or diabetes. In the Rancho Bernardo Study of 957 elderly individuals (152 with heart disease) with a mean age of 77 years, 4% had elevated hsTroponin T ≥0.01 ng/mL. In this group, cardiovascular mortality for 6.8 years was increased 2-fold. The current study is the
first study evaluating troponin levels in a community environment by using a hsTroponin assay able to measure levels that were previously undetectable.

**Higher sensitivity troponin assays**

These assays are much more sensitive than contemporary assays but have the trade-off that they will be less specific for the diagnosis of MI. They have several advantages over contemporary assays. They fulfill the guideline requirements of a 99th percentile value of an apparently healthy reference population, with a coefficient of variation (CV) ≤ 10%. Although use of the 99th percentile has been recommended for a number of years, perhaps, only 40% of hospitals in the United States are using the 99th percentile for the diagnosis of MI.

Several studies have shown that hsTroponins facilitate the earlier diagnosis of MI. In a study of 57 patients with negative fourth-generation hsTroponin T levels on admission and retrospectively confirmed unstable angina or evolving non-ST-segment elevation MI, 61.5% had hsTroponin T levels detected at admission, rising to 100% at 6 hours.

**Higher sensitivity troponins and prognosis**

hsTroponin T has been shown to have prognostic value in patients with heart failure and patients with stable coronary artery disease with normal systolic function. In the PEACE (Prevention of Events with Angiotensin-Converting Enzyme Inhibition) trial, hsTroponin T was detected in 97.7% of patients who had stable coronary artery disease with the hsTroponin T assay. The hsTroponin levels were associated with risk factors including diabetes and CRP. There was a strong and graded relationship with cardiovascular death and heart failure on follow-up for 5.2 years. Surprisingly, given the relationship of troponins to plaque rupture and coronary artery thrombus formation, there was no relationship with MI. The lack of relationship may have been influenced by the strict definition of MI used in this study that required an elevation in troponin levels to >2× the upper limit of normal.

**Mechanism of elevation of troponin levels**

The concept that troponins may normally be present in the blood of healthy individuals is challenged by 2 issues. First, whether elevated levels are due to analytical issues and second whether the individuals are truly normal. The first issue is crucial. The analytical performance of the hsTroponin T used in the study by Otsuka, which achieved a 4-fold lowering of the analytical sensitivity, complies with the Universal definition of MI recommendations for the use in the diagnosis of MI. The second issue is very important when patients are selected for defining the 99th percentile for a normal population.

The mechanisms for the presence of low levels of troponins in normal individuals are unclear. There could be unrecognized underlying heart disease such as hypertension causing left ventricular hypertrophy and various causes of diastolic dysfunction such as diabetes, or silent ischemia. Some elevations may be due to undetected heart failure and, if renal failure has not been excluded, to renal dysfunction. In view of the findings of the PEACE trial, showing no relation of hsTroponin T levels to the risk of MI, recurrent minor plaque ruptures as a major cause seems unlikely. It is also possible that the presence of troponins in the blood is a normal physiologic situation, relating to physiologic myocardial cell turnover and apoptosis of the normal and aging heart.

**Diagnosis of MI**

The Universal definition of MI criteria for the diagnosis of MI is pivoted on elevated troponins, in an ischemic setting, with either ischemic symptoms or ischemic electrocardiographic changes, and a rise and/or fall in troponin levels. The cutpoint requires a troponin level greater than the 99th percentile of a healthy population as measured with an assay with an imprecision CV of ≤ 10%. Until recently, very few commercial assays have been able to detect troponin levels with the required precision. These assays require new cutpoints for the diagnosis of MI, based on the 99th percentile and a ≤ 10% CV. Also a definition of rise and/or fall is required to distinguish “normal,” or chronic background troponin levels from acute changes. The Universal definition of MI group recommended a 20% change from the baseline value to be diagnostic of reinfarction with the current troponin assays. This limit was based on 3 times the imprecision (3 SD) of the cut-off concentrations.

After the introduction of hsTroponins, there will be many individuals, outside an ischemic setting or without the myriad of other causes of troponin elevations, who will have detectable values. This situation is analogous to patients with renal disease, who have background elevated levels of contemporary troponin assay levels, where the National Academy of Clinical Biochemists recommends that a 20% change in an ischemic setting is indicative of MI.

**Biologic variation**

Measurement of the biologic variation of troponin levels in healthy individuals without evidence of CVD allows determination of reference change values that can be used to interpret serial test results. The reference
change value includes the analytical imprecision and the intraindividual biologic variability.

In a study of a new hsTroponin I assay, the intraindividual short-term variation in 17 healthy individuals with hourly measurements for 4 hours was a 46% increase or a 32% decrease in several samples. In a study testing various percent changes, a ≥30% Δ change with a sensitive troponin I assay was the optimal Δ change for specificity and risk assessment.

hsTroponin T and higher sensitivity troponin I’s have different release and clearance kinetics, and biologic variations may be different. Therefore, separate studies will need to be performed for different assays. Also, data that are not obtained from a selected population, for example, an emergency department population may be different than that obtained from healthy individuals in the community.

When hsTroponin T values are around the 99th percentile level, in the setting of ischemia, appropriate use of information about biologic variation could be used to diagnose MI, if the observed changes are greater than the biologic variation (Figure 1). A higher Δ change will improve specificity. Alternative approaches are to use analytical variability or receiver operating curves and clinical outcomes to determine the optimal Δ change. The outcomes of patients with an MI diagnosed on the basis of biologic variation and other approaches will need to be assessed.

Conclusion
The new higher sensitivity assays will enable the more rapid diagnosis of MI but will also increase the frequency of elevations not due to an acute coronary syndrome. It is important that there is a rising and/or falling pattern of troponin levels to distinguish between increased levels caused by a chronic, nonischemic pathophysiology from presentation of an acute MI. This will become especially critical when most community individuals will have detectable troponin levels with the new higher sensitivity tests.

If the new higher sensitivity assays can measure small changes in troponin levels within the normal range with acceptable imprecision, then our ability to distinguish...
patients with an acute MI from those with "normal" levels or those with chronic disease states will improve.

The study by Otsuka et al answers the question as to whether hsTroponins can define individuals at higher risk in the community, but it has not addressed the question as to whether hsTroponins in a normal population can define individuals at higher risk of clinical events such as death, MI, or stroke. The study has helped with our incomplete understanding of what constitutes normal community troponin levels. However, a clinically meaningful troponin cutpoint for primary prevention has not been defined by this study, and the results provide no information to guide physician selection of therapies to improve patient management.

Additional basic and clinical studies are required to elucidate the cellular mechanisms for the release of troponins and the impact on patient outcomes to aid our understanding of what elevated troponin levels mean in apparently healthy individuals.

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Disclosures
Conflicts of interest: no conflict of interest to declare.

References
1. White HD. Will new higher-precision troponins lead to clarity or confusion? Curr Opin Cardiol 2008;23:292-5.