

High-Sensitivity Troponin Assays: Boon or Bane for the Cardiologist?

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The Troponin Era

The advent of the “troponin era” has its roots in the redefinition of acute myocardial infarction (AMI) by the joint committee of European and American cardiologists in 2000.¹ Troponin was identified as the preferred serologic biomarker for acute coronary syndrome (ACS). Since then, troponin assays have continued to evolve with improved sensitivity and reproducibility, leading to a renewal of guidelines in 2007 and 2012.²

With increasing sensitivity of troponin assays, cutoff levels were lowered. A 99th percentile upper reference limit (URL) refers to the troponin concentration at the 99th percentile of a reference population. The use of the 99th percentile URL increases the ability of these assays to detect both early AMI and structural cardiac abnormalities. The first-generation troponin assays were not sufficiently sensitive to detect troponins in reference to “healthy” individuals and thus the cutoffs were set at levels at which the assays coefficient of variation (CV) were 10%. These early assays were thus not sensitive for early myocardial necrosis but highly specific, resulting in its use as a dichotomy tool for ACS rule-in. However, this should not be confused with newer generation high-sensitivity troponin (hsTn) assays, which are assays that have a CV of 10% or less at the 99th percentile URL and are able to detect cardiac troponin levels in at least 50% of the reference normal population.³

hsTn assays have only been available since 2010, with commercial availability still limited to a small number of hsTn assays. They are now able to measure tenfold lower concentrations with higher precision as compared to first generation assays.³ Is the increased sensitivity afforded by hsTn a boon for the cardiologist, or a bane that could result in greater confusion for the physician interpreting these assays?

Role of Troponins in Clinical Practice

The universal definition of myocardial infarction (MI) is the detection of a rise and/or fall of cardiac troponins

with at least one value above the 99th percentile URL in addition to at least one of the following: 1) symptoms of ischaemia; 2) new electrocardiogram (ECG) changes of ST-T segments, new left bundle branch block or development of pathological Q waves; 3) imaging evidence of new regional wall motion abnormality or loss of viable myocardium; and/or 4) identification of an intracoronary thrombus by angiography or autopsy.² They are separated into 5 types of MI according to aetiology (Table 1). The only aetiology of interest to a cardiologist in the emergency department (ED) is type 1 AMI due to spontaneous plaque rupture. The need to ascertain the type of MI has been, in part, due to the hsTn assays' ability to detect even the smallest amount of ongoing myocardial necrosis, leading to further confusion as a physician attempts to diagnose “troponinitis”. Forty-three percent of all troponin assays ordered for inpatients will flag positive. However, only 28% will ultimately be labelled as AMI.⁴ A positive test now demands greater physician discretion.

There is, however, an upside to the advent of hsTn. The optimum sensitivity of older standard troponin assays for AMI occurs 10 to 12 hours after the onset of symptoms. This results in the need for hospital admission and observation while serial testing is completed. hsTn assays are able to overcome this because they can detect much lower levels

Table 1. Types of Myocardial Infarction

Type 1	Spontaneous MI
Type 2	MI secondary to ischaemic imbalance
Type 3	MI resulting in death without biomarkers
Type 4a	MI related to PCI
Type 4b	MI related to stent thrombosis
Type 5	MI related to CABG

CABG: Coronary artery bypass graft; MI: Myocardial infarction; PCI: Percutaneous coronary intervention

Source: Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959-69.

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of troponin, allowing for earlier recognition of AMI. They are precise, and have small CV levels even at 99th percentile in reference populations, and are specific for myocardial necrosis. Increased values and changes in values over time also correlate well with risk of future adverse cardiac events.⁵ In landmark studies, non-ST-elevation myocardial infarction (NSTEMI) can be ruled out as early as 4 hours after symptom onset, allowing shorter inpatient stay for patients without raised levels of troponin and earlier intervention for those with a confirmed AMI.⁶ The historically conservative approach to avoid missing a potential ACS has led clinicians to admit many more patients than are subsequently found to have an MI. This further compounds the crowding in the ED, which is associated with adverse outcomes for both patients with and without AMI.⁷ Follow-on studies with hsTn demonstrate low-level troponin elevations within 60 to 180 minutes of the AMI, allowing for earlier diagnosis and faster rule-out of AMI.^{8,9} Two large prospective ED trials showed that hsTn assays are more accurate than standard troponin assays in the successful diagnosis of AMI within 3 hours of symptom onset.¹⁰ This potentially reduces the duration of stay at the ED and should increase the number of patients successfully discharged from the ED. A modelling study found that early hsTn testing was financially beneficial in almost all cases.¹¹

Chest pain is the second most common symptom and leading cost of malpractice dollars spent in the ED. The European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) guidelines from 2014 have acknowledged the use of hsTn assays and made recommendations on the use of a fast track protocol. The guidelines state that hsTn assays have a NPV of greater than 95% for AMI on admission. Adding on a second repeat test at 3 hours can increase this to 100%.¹²

hsTn assays are strong prognostic markers for cardiovascular death and recurrent ischaemic events in AMI, with studies showing their superiority over standard assays in predicting cardiovascular death at 1-year follow-up.¹³ Elevated troponin levels also correlate with an adverse prognosis in several stable chronic disease states.¹⁴ Examples include heart failure, atrial fibrillation, renal failure, pulmonary embolism and sepsis.

Limitations of High-Sensitivity Troponins

Lack of an Industry Standard

The variability in hsTn characteristics between manufacturers prevents comparisons between assays and clinical centres.⁵ The appropriate hsTn cutoff for clinical use is far from settled, with no consensus yet as to the population from which to derive this value, preventing consistent interpretation.¹⁵

Lower Specificity of hsTn for AMI

The main counterpoint to the increased sensitivity of hsTn assays is a lower specificity to rule-in AMI. Reported specificity for hsTn assays is 80% to 85%, compared to 97% for standard troponin assays.¹⁶ Serial sampling to detect assay level changes (delta value) is required to improve assay specificity. ESC guidelines recommend a greater than 20% relative change in patients with an initially elevated hsTn level to diagnose AMI. However, the delta of 20% is based on older generation assays. The situation with hsTn assays is more complex, as both biological variation and assay dependent imprecision can result in wide ranging relative changes.¹⁶ Further studies are required before the use of delta values, relative or absolute, can be adopted. Applying the existing definition of a 20% increase from baseline to hsTn assays may under-detect AMI.

Non-specific as to Aetiology of Myocardial Necrosis

Troponins are highly specific for myocardial necrosis, but are not so with regards to the aetiology. Cardiologists are primarily concerned with elevations due to plaque rupture as to the aetiology, since this has implications on the decision for and timing of coronary intervention. Whilst HsTn is a useful tool with increased sensitivity for the detection of type 1 MIs, this comes at the cost of over-diagnosis.¹⁷

Future Directions

Outcome data will steadily come from centres adopting the “early rule-out protocols” with hsTn assays. This will allow the analysis of optimal timing of samples to be taken after presentation to ED and the optimal cutoffs for both ruling out and ruling in of AMI. A comparison between clinical effectiveness of different protocols will advance the continuing refinement of workflows at the ED to exclude AMI. It has yet to be demonstrated prospectively whether patients discharged under the hsTn early rule-out protocols have longer term safety comparable to those receiving conventional screening. A key issue is that a miss rate will remain regardless of the assay’s sensitivity—what is an acceptable percentage miss rate? This underscores the dilemma a triaging physician constantly faces.

Further research is needed to determine the 99th percentile value for hsTn assays, the influence of variables such as age and gender on these thresholds, and appropriate delta values for the definition of MI.

Conclusion

hsTn assays hold the promise of earlier diagnosis and improved clinical outcomes for patients presenting with chest pain and possible AMI. Its value lies in the potential

for use in the ED, thereby cutting costs and reducing waiting time in already overcrowded hospitals. However, the question is now a matter of specificity. HsTn assays do not differentiate myocardial necrosis due to plaque rupture from other causes. The assumption that all elevated hsTn implies a type 1 MI can lead to confusion and frustration in both the ED and inpatient settings.

In conclusion, the diagnosis of type 1 MI is not made solely on biochemical investigations, and must also involve ECG changes, symptoms and pretest probability. Hence, the usage of hsTn assays should be in tandem with clinical parameters. An emphasis on concurrent clinical assessment would allow the clinician to use and interpret these assays appropriately. This, together with a consensus on testing and assessment strategies, will go a long way to moderate the current variations with the use of hsTn in clinical practice.

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REFERENCES

1. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-69.
2. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Eur Heart J* 2012;33:2551-67.
3. Apple FS, Collinson PO. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem* 2012;58:54-61.
4. Saaby L, Poulsen TS, Hosbond S, Larsen TB, Pyndt Diederichsen AC, Hallas J, et al. Classification of myocardial infarction: frequency and features of type 2 myocardial infarction. *Am J Med* 2013;126:789-97.
5. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, 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.
6. Aldous SJ, Richards MA, Cullen L, Troughton R, Than M. A new improved accelerated diagnostic protocol safely identifies low-risk patients with chest pain in the emergency department. *Acad Emerg Med* 2012;19:510-6.
7. 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.
8. Than M, Cullen L, Aldous S, Parsonage WA, Reid CM, Greenslade J, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol* 2012;59:2091-8.
9. Meller B, Cullen L, Parsonage WA, Greenslade JH, Aldous S, Reichlin T, et al. Accelerated diagnostic protocol using high-sensitivity cardiac troponin T in acute chest pain patients. *Int J Cardiol* 2015;184:208-15.
10. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;361:858-67.
11. Thokala P, Goodacre SW, Collinson PO, Stevens JW, Mills NL, Newby DE, et al. Cost-effectiveness of presentation versus delayed troponin testing for acute myocardial infarction. *Heart* 2012;98:1498-503.
12. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012;33:2252-7.
13. Aldous SJ, Richards M, Cullen L, Troughton R, Than M. Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain. *CMAJ* 2012;184:E260-8.
14. Melki D, Lugnegard J, Alfredsson J, Lind S, Eggers KM, Lindahl B, et al. Implications of Introducing High-Sensitivity Cardiac Troponin T Into Clinical Practice: Data From the SWEDEHEART Registry. *J Am Coll Cardiol* 2015;65:1655-64.
15. Koerbin G, Abhayaratna WP, Potter JM, Apple FS, Jaffe AS, Ravalico TH, et al. Effect of population selection on 99th percentile values for a high sensitivity cardiac troponin I and T assays. *Clin Biochem* 2013;46:1636-43.
16. Wu AH, Lu QA, Todd J, Moecks J, Wians F. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. *Clin Chem* 2009;55:52-8.
17. Januzzi JL Jr. What to expect when measuring high-sensitivity troponin: practical advice for clinicians. *J Am Coll Cardiol* 2015;65:1665-7.