All troponin assays are equal but some assays are more equal than others (with apologies to George Orwell).

Measurement of cardiac troponin (cTn) using ‘high sensitivity’ cTn (hs-cTn) assays is supported by evidence-based medicine and is incorporated into the guidelines of the European Society of Cardiology as well as the Fourth Universal Definition of Myocardial Infarction (2018). The majority of diagnostic companies have launched or are in the process of launching cTn assays into routine clinical practice and for use in research trials, which meet the criteria for high sensitivity. A high sensitivity assay is defined analytically by the ability to measure at least 50% of a reference population and an imprecision (coefficient of variation (%CV)) <10% at the 99th percentile upper reference limit (URL). In clinical practice, the imprecision of measurement at the 99th percentile for most assays is typically much lower, <5%, and the limit of detection of the assay (the concentration which can be reliably distinguished from background noise) is very low.

The advent of hs-cTn assays moving globally into routine clinical and research use is associated with a number of challenges. For front-line clinicians, there needs to be acceptance that these assays are exceptionally sensitive tools for the detection of myocardial injury but as has always been the case, myocardial injury does not always equate with myocardial infarction (MI). Indeed, with hs-cTn assays, MI subsumes only a modest percentage of the increases observed. For laboratory medicine, there are challenges with service delivery based on the use of diagnostic algorithms incorporating an admission measurement with repeat measurement at 1–3 hours post-admission. For journals, including readers, editors and their reviewers, there is also the challenge of understanding and educating hs-cTn users on the nature of the improved analytics of hs-assays, how they differ from existing assays and how to implement them into routine clinical practice and validate their performance. The challenges therefore are to use agreed definitions and terminology and to provide sufficiently detailed information on analytical methodology to allow intelligent interpretation of clinical and research studies. Such information is often missing from the published literature despite the pleas of editors of journals with a more analytic focus.

There have been a multiplicity of articles addressing the clinical challenges of hs-cTn. This topic remains an area in need of continuing education. There is widespread clinical use of hs-cTn measurements in the assessment of patients presenting with symptoms of ischaemia, chest pain or equivalent. However, because there are groups of patients such as the elderly, diabetics and women who can present atypically or even relatively silently, often the diagnostic algorithm is used for any ‘pain between knees and nose’ or perhaps if the ‘patient looks a bit poorly’. However, there are other challenges which appear to relate to a basic misunderstanding of what a hs-cTn assay really is and the meaning of the Fourth Universal Definition of Myocardial Infarction (2018) in terms of the 99th percentile URL derived from an apparently healthy reference population.

The definition of an abnormal hs-cTn in terms of the 99th percentile is a slight aberration in terms of normal laboratory medicine practice. The 95th percentile interval, hence from 2.5th to 97.5th percentiles, is the norm. When MI was redefined, the definition moved from a classification based on the ECG and conventional ‘cardiac enzymes’ of twice the upper limit of normal (where the probability of an abnormal result in a reference population is only 0.0044%) to one where the probability is now 1%. Hence there was a desire to make the decision limit more exacting, that is, 1% rather than 2.5%.

A recent published paper, which has generated much publicity and comment, illustrates the caution which must be exercised in performing studies on hs-cTn and cardiac biomarkers in general, understanding the analytical performance of an assay, and publishing and interpreting the results. The study itself (Is the Current Threshold for Diagnosis of ‘Abnormality’, Including Non ST Elevation Myocardial Infarction, Using Raised Highly Sensitive Troponin Appropriate for a Hospital Population), the CHARIOT study, was a large prospective study measuring hs-cTn in the serum of unselected admissions to a hospital. It illustrates some of the apparent misunderstandings of the concept of hs-cTn assays both at the analytical and clinical levels.

There are some straightforward factual inaccuracies. First, the authors claim that they used hs-cTn assays but in fact, the assays used only met the criteria of a contemporary (sensitive) assay.
Acute chest pain or other symptoms suggestive of myocardial ischemia

Clinical history*

\[ \text{cTn*} \longrightarrow \text{ECG*} \]

No myocardial ischemia or injury
Consider other diagnosis

Evidence of myocardial ischemia and/or injury

Coronary angiography* & other imaging techniques

Type 1 AMI
Unstable Angina
Secondary Myocardial Injury (Type 2 AMI)
(Type 3-5 AMI)
Non-ischaemic myocardial injury – acute
Myocardial injury - chronic

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It is important to remember that hs-cTn assays are extremely sensitive for myocardial injury, and that myocardial injury does not always (in fact most often), does not equate acute MI. The diagnosis of MI remains clinical but the diagnostic process should be circular rather than linear, as illustrated in Figure 1. The first question is, whether the changes are acute or chronic. A repeat measurement and examination of the change (delta) value will answer this. The second question is whether the clinical change is compatible with an acute ischaemic injury or is likely secondary to another pathology. The advent of the high sensitivity cTn assay is, in fact, a great breakthrough as it allows very early and very accurate rule-out and rule in for acute myocardial injury and acute MI. Robust data confirm this can be done with a minimum risk of adverse events at 30 days. Also, and paradoxically, it reduces the number of analytical false-positive diagnoses around the diagnostic 99th percentile URL (minimal analytical noise). The use of high sensitivity assays has unequivocally been shown to be more efficient for patient care through early triage and improved diagnostic accuracy especially in women but it can only be achieved if we understand the principles of...
their use properly, including how to properly calculate the 99th percentile URL.

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References


