**High sensitivity troponin, analytical advantages, clinical benefits and clinical challenges – an update.**

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**Abstract.**

The measurement of cardiac troponin (cTn) by a high sensitivity method now represents the standard method for cTn measurement in the laboratory. High sensitivity method are not measuring a novel form of troponin but have undergone methodological improvement in assay sensitivity to allow both very low level detection and repeat measurements at low levels with very low degrees of analytical imprecision. The methods identify additional patients with myocardial injury who would benefit from evidence-based interventions. Rapid predictive algorithms utilising measurement on admission as well as short sampling periods (1-2 hours) allow much more rapid categorisation of patients to appropriate clinical pathways. The shift in the diagnosis from traditional “cardiac enzymes” to troponin based on the 99th percentile has accounted for the majority of the detection of myocardial injury in patients without acute coronary syndromes. These patients have a worse prognosis irrespective of the underlying cause of their hospital admission. The appropriate management strategy in this group, beyond managing the underlying problem, remains to be defined. Measurement of cTn in otherwise asymptomatic individuals may have a role for patient selection for preventive treatment or for patients monitoring. Clinical trials in this area are awaited.

193 words

Article highlights.

* High sensitivity cardiac troponin (hs cTn) measurement are the laboratory standard.
* Predictive algorithms based on hs cTn allow very rapid (with 2 hour) patient categorisation.
* Prognostically significant hs cTn elevations occur in a range of other clinical conditions.
* In the general population, measurement of hs cTn allows risk stratification.
* Preventive treatments utilising hs cTn measurements may have a role in the future.

**High sensitivity troponin, analytical advantages, clinical benefits and clinical challenges – an update.**

*Uptake of hs troponin assays.*

High sensitivity assays for cardiac troponin (cTn) are now available from all of the major manufacturers[1]. In Europe, most laboratories are currently using or intending to change to a high sensitivity assay. It is therefore worth assessing the “state-of-the-art” in respect to high sensitivity cardiac troponin (hs cTn) assays. The review will cover the characteristics of hs cTn assays and why they offer significant analytical advantages and clinical benefits as well as posing challenges for the laboratory, emergency physicians and cardiologists.

Definition of a high sensitivity troponin assay.

High sensitivity assays for cTn did not spring fully formed into the world like Athena from the forehead of Zeus (although similarly causing headaches to some clinicians) but represent the next stage in the evolution of cardiac troponin immunoassay performance. In part this evolution was driven by the desire of manufacturers to produce assays with better analytical characteristics than the first and second-generation assays. It was also influenced by the redefinition of myocardial infarction[2]. The redefinition required the ability to measure the 99th percentile of a healthy population and set an imprecision goal of <10% at the 99th percentile. These twin specifications predicated improvements in absolute assay sensitivity in tandem with improved imprecision. The evolution of cTn assays is shown schematically in figure 1.

A high sensitivity assay is not measuring a different form of cTn, The term “high sensitivity” relates to assay performance. A high sensitivity assay is defined as one which an imprecision of <10% at the 99th percentile and the ability to detect values above the limit of detection in 50% or more of a healthy population[3]. The definition of a “healthy population” is problematic. It affects the value of the 99th percentile itself, hence the perceived imprecision profile of the assay, and the ability to detect > 50% of the healthy population. Progressive patient selection from a random sample of an apparently healthy population by a combination of health questionnaire, disease biomarkers and cardiac imaging to produce a subset that is deemed 100% cardiac healthy will produce a shift in the 99th percentile[4;5]. This shift occurs due to exclusion of the outlier tail in the upper end of the distribution curve. A secondary effect is the reduction in the absolute percentage of individuals with measurable troponin, especially in women[6]. Hence, an assay which is designated “high sensitivity” may then not meet “high sensitivity” criteria, especially in females. A caveat must be applied here. Just because an assay is apparently not as “high sensitivity” as it is advertised does not mean its clinical performance is necessarily inadequate. Previous generation troponin assays which did not meet high sensitivity criteria were able to function adequately in routine clinical use[7]. The 99th percentile is affected by age. In patients presenting to the Emergency Department who are currently otherwise well, the 99th percentile in those > 65 years of age is substantially higher[8]. Studies have shown that there is a correlation between age and cTn levels and risk[9] even in the apparently healthy elderly[10]. However, the question as to whether this is an effect of subclinical myocardial injury or due to ageing remains. However, it remains a consideration for managing those presenting to the ED in considering what is “normal”. Finally there are statistical considerations in determining the 99th percentile. The confidence intervals around the 99th percentile are determined by the sample size and for the minimum recommended number of 300 are large[11]. Clearly, as large a sample size as possible is desirable. In addition, the choices statistical methodology will affect the value obtained[12] as well as methods of outlier exclusion[13].

*Analytical advantages and clinical benefits of high sensitivity troponin assays.*

The analytical advantages of hs cTn assays are increased analytical sensitivity, seen as a very low limit of detection (LOD) and limit of quantitation (LOQ) and an improved imprecision profile. These two analytical characteristics translate into clinical benefit.

Reduction in the LOD means that there is the ability to measure cTn at very low levels, approaching or achieving the lowest percentile found in healthy individuals. The ability to measure below the 99th percentile and within the reference interval has significantly improved the ability to detect degrees of myocardial damage previously missed. Meta-analysis comparing conventional sensitive with high sensitivity assays demonstrates superior outcome prediction. Patients with injury not detected by a conventional sensitive assay but with elevated high sensitivity troponin values showed worse outcomes than those where no injury was detected by both conventional and high sensitivity assays[14]. This is to be expected and is analogous to the findings when diagnosis based on conventional “cardiac enzymes” was compare with the first-generation troponin assays[15;16]. An implementation study of hs cTnI compared outcomes between a baseline phase reporting the same cTnI cut-off that was achieved with a conventional sensitive version of the same assay to the implementation phase which lowered the cut-off to the 99th percentile. During the baseline phase, patients with intermediate cTnI values (those between the original cut-off and the 99th percentile) were under diagnosed and undertreated with worse outcomes compared to those in the implementation phase[17].

Concerns were raised that the increased case detection following introduction of hs cTn assays would result in substantial increases in the number of patients with a diagnosis of acute myocardial infarction (AMI). Rises in caseload would then overwhelm the Emergency Department (ED) and Coronary Care Unit (CCU) with a consequent increase in need for health care interventions and increased costs. This has been shown not be the case. Compared to diagnosis based on “cardiac enzymes” there was a significant increase in patients with a diagnosis of myocardial infarction (MI) on moving to the troponin standard[18]. However, once the redefinition was accepted, subsequent introduction of hs cTn assays did not have a significant impact. Although initial reports suggested an increase in the number of patients with AMI[19], this was not confirmed in subsequent studies[20-22]. The impact on clinical care and resource utilisation seems to have been neutral or beneficial[23-25].

Assay sensitivity also allows discrimination between the 99th percentiles for males and females. The use of sex specific cut-offs increases in the case detection rate in females whilst leaving that in males largely unchanged[26] although increased case detection has also been reported in both males and females [27;28]. Coronary heart disease remains an under diagnosed and undertreated condition in females[29] and the use of gender specific 99th percentiles is endorsed by the most recent universal definition of myocardial infarction[30] and will improve case finding. However, it has been pointed out that case detection may not translate into improvement in clinical outcomes[31] although findings are not consistent[28]. Failure to improve outcome in females may be due to the limited impact of interventions at troponin levels close to the 99th percentile[32], increased diagnosis of myocardial injury rather than myocardial infarction or change in clinical practice [27;33;34]. Impact may be only on long-term outcomes with improved preventative strategy. Nevertheless, laboratory medicine practitioners should be strongly encouraged to become cardiac feminists and embrace sex specific 99th percentiles for hs cTn to improve the diagnosis and hopefully future management of under diagnosed coronary artery disease in females.

Improved assay imprecision has the effect of reducing diagnostic uncertainty at a given value of troponin. Using the conventional formula to calculate diagnostic imprecision it can be demonstrated that for a troponin of 40 ng/L the range of the results will vary (at 95% probability) from +/- 0.8 ng/L at 1% imprecision to +/-15.7 ng/L at 20% imprecision. Hence, a low value of imprecision at the 99th percentile will result in a substantial reduction in the number of borderline values above and below the 99th percentile. Reduction of scatter around the 99th percentile will have the impact of reducing diagnostic uncertainty and so reduce the number of misclassified patients[35].

The combination of the assay sensitivity plus lower imprecision has produced the most significant change in the use of troponin. There has been development of a number of decision algorithms to achieve very rapid patient categorisation with cTn measurement either on hospital admission[36] or within 1-2 hours of hospital admission[37-39]. This approach has been recommended by the European Society of Cardiology (ESC) [40;41].

It is important to appreciate that such algorithms are predictive and not diagnostic. They are aimed exclusively at patients when the initial diagnosis is uncertain and where the objective is to define the probability of a subsequent final diagnosis of non-ST elevation myocardial infarction (NSTEMI). They classify patients into three catagories. The first is a high probability group (rule in AMI) for admission and investigation. In the high probability group, it is likely that following admission and with repeat cTn measurement over 3 to 12 hours there will be a rise in cTn that will exceed the 99th percentile. The subsequent rise in troponin to above the 99th percentile would then categorise the patient as acute myocardial injury and therefore possible AMI. The second is an intermediate probability group requiring further investigation over 3-6 hours to confirm or exclude AMI. The final one is a low probability group (rule out AMI) for immediate discharge. In the low probability group, it is likely that repeat measurements over 6-12 hours would exclude AMI so that patient is at low risk if immediately discharged. These algorithms are therefore optimised for rule out and the rule in performance is less good[42] especially when prior probability of disease is low[43].

These algorithms are predicated by two assumptions. The first is that a very low troponin at hospital presentation predicts a probability that the patient will have a final diagnosis of NSTEMI of 1% or less. The second is that disease prevalence will not significantly affect performance. The incidence of NSTEMI in ED populations is from ~2-15 %[44;45]. There may therefore be a disconnect between sensitivity and negative predictive value. This will be most significant in patients presenting very early from onset of chest pain[46]. The second is that the assay will be able to detect a change in the troponin which is significant but may not necessarily exceed the 99th percentile. The ability to measure small changes over very short timeframe (1 hour) may prove to be a challenge to laboratory. Concerns have been raised that the levels of imprecision required may not be achievable in routine clinical practice[47]. It may also be the case that the required imprecision may be within normal performance variation of the assay or analyser although this may be more important for rule in diagnosis than rule out [48]. The use of multiple analysers with different imprecision profiles may affect the ability to detect a change for the scenario of all measurements on equipment with a lower performance specification or measurements split between two different instruments[49]. Other concerns have been the impact of changes in reagent lot[50].

These algorithms are a two-stage process. A single measurement is made on admission. This uses a high threshold for immediate rule in, a very low threshold for immediate rule out and an intermediary zone (between the rule in and rule out values) for repeat testing. The sample taken 1-2 hours from admission divides patients into three categories. Those with a significant change (delta value) in cTn, even if both remain below the 99th percentile, are considered to rule in for AMI. Those with a cTn value below the 99th percentile and a low delta cTn are ruled out. Patients who do not meet these criteria are classified as intermediate and require further investigation. This is illustrated schematically in figure 2.

Rapid predictive algorithms differ from the diagnostic recommendation that a significant rise in troponin could be detected using hs cTn assays with sampling on admission and at three hours with diagnosis defined by a significant change and the three hour sample exceeding the 99th percentile[40;51]. A composite approach combining a very low threshold on admission to rule out[52] combined with the use of sex-specific 99th percentiles either on admission or at three hours plus cTn delta (the High-STEACS pathway) has been proposed and evaluated[53]. Systematic review and meta-analysis shows that all of these pathways work well for rule out and are most effective when serial sampling is used[54;55]. In routine clinical practice it is very difficult to achieve a turnaround time of less than 60 minutes which may result in inappropriate retesting while waiting for the result of the first sample. Serial sampling using 0-2 and 0-3 hour pathways may be more practical and more clinically effective than 0-1 hour pathways.[42].

*Troponin elevation in non-acute coronary syndrome patients.*

It is important to recognise that troponin elevation in non-ACS patients is not a novel phenomenon due to the introduction of high sensitivity assays[56]. Two factors have combined to increase the range of clinical conditions where myocardial injury can be detected. The first is the redefinition of myocardial infarction itself. When troponin assays were introduced, diagnosis was based on the WHO definition of MI which included the use of abnormal “cardiac enzyme” values [57] designated as twice the upper reference limit[58]. This meant that the probability a “normal” result would be classified as abnormal was 0.0044%. The redefinition of MI proposed the use of cTn instead of “cardiac enzymes” as biochemical “gold standard”. This was based on the cardiospecificity of cTn and its superior prognostic ability[15;16]. However, the diagnosis was now based on the 99th percentile so automatically 1% of all “normal” troponin results are abnormal. This occurred more frequently as assay performance improved to reliably detect values at or below the 99th percentile. The second was that diagnostic discriminants for cTn were originally selected to match diagnosis achieved by WHO criteria using conventional “cardiac enzymes” as the predicate test. This produced excellent sensitivity and specificity when cTn assays were first used clinically. When the shift to the 99th percentile occurred, it immediately became apparent that troponin elevation occurred in a wide variety of clinical conditions outside ACS. Indeed, in unselected troponin testing, there are more cases of myocardial damage due to ischaemic or non-ischaemic causes than from type 1 MI[44]. This is evolution is summarised in figure 3.

A selection of clinical conditions where elevation of cTn occurs in the non-ACS population is included in the fourth redefinition of MI[30]. This document also acknowledges the fact that myocardial injury may occur due to other causes than MI (either type 1 or type 2).

The presence of elevated cTn in the non ACS population provides a challenge for clinicians and laboratory medicine practitioners. It is been suggested that these elevations are ignored or trivialised. The terms “troponitis” , “troponinitis” or “troponiaemia” have been used. Indeed, some workers have proposed arbitrarily raising the 99th percentile to define such patients as “normal”. Such an approach is fraught with hazards[59]. In all cases where cTn elevation has been documented in non-ACS populations and the patients followed up, these non-ACS cTn elevations have proved to be prognostic irrespective of the underlying cause[60]. This can be most clearly documented in patients admitted to the intensive care unit[61] and the most recent incarnation of this phenomenon is patients with Covid 19[62]. If you came home and found that half of the tiles had fallen from your roof you would not call it “tileitis” and ignore it. The two key facts to remember are that no troponin is better than any troponin and that clinical patient assessment is required. If the clinical features do not suggest ACS but there is troponin elevation the patient will still require assessment and possibly further investigation and treatment, but a cardiologist may not be the appropriate clinician.

*Utilisation and interpretation of high sensitivity troponin results in routine clinical practice.*

There is consistent over requesting of cTn measurements with the majority of requests in patients where ACS is not suspected. This can be argued both ways. Appropriate test requesting improves the diagnostic accuracy of testing[44]. However, the powerful prognostic predictive nature of cTn measurement has also meant that it is being increasingly recommended outside of suspected ACS. Measurement of cTn is now being recommended as part of the routine investigation of Covid 19 patients as a disease severity marker[63]. It is likely that the almost routine requesting for cTn measurement for patients with pain “between knees and nose” is unlikely to be reversed. It is therefore necessary to consider a rational strategy for troponin interpretation. In my own institution an audit of two months requesting from the ED (4101 requests for cardiac troponin T of which approximately 25% of requests were for chest pain?ACS ) showed that 1732/4101 (42%) were <5 ng/L, 998/4101 (24.3%) between 6 and <14 ng/L and 1371 (33.4%) >14. The majority of troponin results did not lead to further action as they were single requests. However, 1971/4101 (48.1%) fall in the range 5-50 ng/L where further evaluation might have been appropriate and 398 (9.7%) were >50 ng/L. Overall, repeat testing occurred in 769/4101 (18.8%) of which 515 fell in the range 5-50 ng/L.

Clinical patient assessment remains crucial. An initial low troponin in a patient presenting with suspected ACS but no other significant risks permits immediate discharge. If the reason for investigation was not suspected ACS, then repeat troponin measurement is also unlikely to be helpful if the result is below the 99th percentile. When a decision for repeat testing is indicated on clinical grounds, it is the combination of the second value plus the change between the two values, expressed as an absolute delta rather than a percentage delta,[64-66] which informs subsequent management. Unless there are compelling clinical features of unstable angina or definitive dynamic changes on the electrocardiogram, there is no indication for immediate initiation of potentially dangerous antithrombotic therapy. Current guidelines support that even in patients with NSTEMI cardiac catheterisation should be performed within 24 hours, not instantly[41]. Since repeat hs cTn measurements can be performed 1-2 hours after the initial sample, patient assessment should be performed with the results of retesting unless diagnosis is certain. Caution in interpretation is always required. Delta changes are most efficient diagnostically at lower troponin values and in the absence of other confounding clinical features such as uncertainties in sample timing or other comorbidities. It has been shown that only small changes may occur in up to 20% of patients with NSTEMI[67].

Interpretation of results require consideration of three factors. First, the clinical features of the patient plus the results of all other investigations which have also occurred. Clearly, an elevated troponin in the presence of a chest x-ray that indicates pneumonia or pulmonary embolus may explain an elevated troponin in the absence of a more obvious cardiac cause. Second, the magnitude of the troponin elevation. The greater the troponin elevation, the greater the probability that the cause is AMI. However, a very high troponin in the absence of supporting clinical features should suggest that the diagnosis is either not AMI, such as myocarditis, or occasionally something completely different such as assay interference[68;69]. Finally, whether a significant change (delta troponin) has occurred. Patients can then be divided into those with acute cardiac injury (one cTn value exceeds the 99th percentile with a significant delta) and chronic cardiac injury (cTn exceeds the 99th percentile but the delta change is low or absent). There is one caveat. Patients presenting late with AMI may have troponin values which bracket the peak of the release curve or are only obtained on the descent phase of the release curve. This is where the magnitude of the troponin elevation may provide value. Clinical assessment is then required to decide whether the acute cardiac injury is due to AMI or another cause. A knife in the heart will cause acute myocardial injury but is hopefully not confused with AMI. Other conditions may be more subtle. It must be emphasised that the assessment of cTn results should not proceed in a linear fashion but is circular, taking into account the cTn value and its delta, the clinical findings and the ECG. The crucial decision is to identify patients with AMI that requires intervention (type 1 MI) as there are treatments of proven efficacy. Patients with type 2 MI, have an adverse outcome[70] as do those with an uncertain diagnosis[60]. It is extremely difficult to distinguish between clinical conditions designated type 2 MI and acute myocardial injury and may be clinically meaningless[71]. Treatment strategiesfor type 1 MI are well-defined. When there is troponin elevation for anything other than type I MI it is essential that the underlying condition and/or triggering event is identified and treated, if possible. Any other strategy is likely to cause harm. This is summarised schematically in figure 4.

*High sensitivity troponin and chronic disease prediction and management.*

The ability to measure cTn down to very low levels prompted interest in the use of cTn for prognostic risk stratification in the general and apparently healthy population[72]. The landmark Dallas heart study showed association between hs cTnT levels, cardiac imaging and outcome[73]. This was followed by similar data for hs cTnI[74]. There was an early interest in the use of cardiac biomarkers and cTn in particular as a tool for risk stratification[75]. This was largely because it was appreciated that current risk models did not have adequate performance. The topic has been recently re-reviewed[76;77]. The association between cTn and cardiovascular outcomes in the general population has been confirmed in a series of meta-analyses[78-80] and large studies[81]. In addition, associations have been shown between cTn and heart failure[82] and stroke[83-85]. There appear to be differences between cTnT and cTnI [86], differences in males and females [74] and influences of age[87]. In addition, association occur in more obvious risk populations such as Type 2 diabetes mellitus[88] as well as those with less obvious but with a known cardiovascular disease risk such as psoriasis[89]. It is not just baseline values which are important. Temporal changes may be even better predictor[90]. These elevations may have a genetic basis[81;91].

Although elevation of cTn is associated with cardiovascular risk, the “so what” question must be asked. What will be the clinical role of cTn measurement and what treatment options should be used? Inclusion of troponin in risk prediction scores in addition to the conventional variables improved risk classification[92;93] although other workers have proposed biomarker combinations or inclusion of other variables[94;95]. There is evidence that interventions can affect cTn levels and modify risk, first demonstrated for lifestyle change and risk of heart failure[96]. The most common intervention for both primary and secondary prevention of cardiovascular disease is statin therapy. There have been a number of studies which have examined the potential role of cTn measurement for patient selection or patient monitoring. Studies in both primary[97] and secondary prevention[98] suggest cTn measurement can be used for improved patient selection for intervention. The most intriguing early finding in a primary prevention study was that cTn levels were reduced by statin therapy and predicted outcome irrespective of LDL cholesterol levels[99]. Similar results have been shown in secondary prevention[100]. Similarly, introduction of statin therapy is associated with changes in cTn levels[101]. However, although these findings are very promising, the studies remain observational and appropriately powered randomised controlled trials are required before routine monitoring of cTn in the population can be recommended.

*Conclusion.*

Measurement of cTn by high sensitivity methods is now the accepted laboratory standard. The role in acute disease management is well established as it facilitates very rapid assessment in the ED. There are expanding roles for cTn measurement in non-ACS patients though this remains confusing for some clinicians. The role of hs cTn measurement in the general population and for chronic disease management looks promising but is not yet ready for prime time.

Disclosures relevant to this article

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**Figure legends**

**Figure 1.**

Evolution of troponin assays showing improvement in assay sensitivity and shift in imprecision affecting percentage detection of a hypothetical reference population.

**Figure 2.**

Generic schematic showing the decision algorithm suggested by the European Society of Cardiology. Individual values for cut-offs and deltas are assay specific.

**Figure 3.**

Impact of the diagnostic classification on the discriminant limit for biomarkers for myocardial infarction as a percentage probability of abnormal. WHO = World Health Organisation; NACB = National Academy of Clinical Biochemistry of the American Association of Clinical Chemists; ESC = European Society of Cardiology; AHA = American Heart Association.

**Figure 4.**

Schematic for troponin interpretation. ECG = electrocardiogram; Δ cTn = delta cardiac troponin; hs cTn = high sensitivity cardiac troponin, MI = myocardial infarction.