10 Frequently Asked Questions about High Sensitivity Cardiac Troponin I

1. How specific is cardiac troponin I (cTnI)?

Troponin I is a regulatory molecule that sits on the tropomyosin-actin complex in both cardiac and skeletal myocytes. Cardiac troponin I (cTnI) differs from skeletal muscle troponin I in having a unique N-terminal amino acid sequence as well as several unique internal amino acid sequences, and is only expressed by cardiac myocytes. Thus, cTn is the preferred biomarker for diagnosis of acute myocardial infarction (AMI) and myocardial injury.

2. What is a high-sensitivity cardiac troponin (hs-cTn) assay?

hs-cTn assays measure the same molecule as current methods but demonstrate superior analytic sensitivity and precision. hs-cTnI assays can accurately quantify cTn in blood at ~10 fold lower concentrations than current methods. The International Federation of Clinical Chemistry (IFCC) and American Association for Clinical Chemistry (AACC) defines a hs-cTn assay as being able to detect cTn below the 99th percentile upper reference limit (URL) and above the limit of detection (LoD) in at least 50% of healthy subjects. hs-cTn assays also must have an analytic imprecision ≤10% coefficient of variability (CV) at the 99th% URL.

3. What do all those laboratory terms above mean?

- 99th% URL – The 99th highest value among 100 healthy subjects as defined by no history of cardiac disease and absent cardiac risk factors such as diabetes, heart failure, hypertension, renal disease and hyperlipidemia. 99th% URL values are usually determined in reference cohorts of 300 – 700 healthy subjects. For the new Abbott hs-cTnI assay the 99th% URLs are sex-specific: 17 ng/L for females and 35 ng/L for males.
- LoD – The limit of detection is defined as the lowest concentration of cTn that can be detected with 95% confidence from a sample with no troponin. For the new hs-cTnI assay, the LoD is 2 ng/L.
- Analytic imprecision – analytical precision of an assay is the random dispersion in repeat test results on a single sample. This is defined as the coefficient of variation (CV) where %CV = mean/standard deviation × 100. As troponin concentrations decrease the %CV (imprecision) will increase. For the new hscTnI the CV at 35 ng/L is 3%.
- LoQ – The limit of quantitation for hs-cTn assays is the concentration of cTn where the %CV is less than 20%. This is the lowest value the FDA allows to be reported for hs-cTn and for the new hs-cTnI assay the LOQ is 4 ng/L.

4. Why are the units for hs-cTn assays (ng/L) different from the current assays (ng/mL)?

The current units for cTnI are ng/mL and the lower limit of quantitation (LoQ) is 0.03 ng/mL. The LoQ for the new hs-cTnI method is 4 ng/L which would be 0.004 ng/mL in the current units. Changing to ng/L, instead of ng/mL, enables hs-cTnI value reporting to be integer-based, thereby avoiding challenges related to reporting and communication values with many zeroes. For example, a current value of 0.1 ng/mL will be 100 ng/L when reported from the new hs-cTnI assay.

5. What is the accepted definition for acute myocardial infarction?

The Fourth Universal Definition of Myocardial Infarction was published in August 2018. It states, *"The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL".* Detection of an elevated cTn value above the 99th percentile upper reference limit (URL) is defined as "myocardial injury." Myocardial injury may only be considered to be secondary to an acute myocardial infarction when there is (i) a rise and/or fall of cTn values with serial testing and (ii) other supportive clinical evidence of myocardial ischemia. The document also emphasizes the benefits of using hs-cTn assays. To summarize the clinical approach it states that patients presenting with chest pain are evaluated clinically, including the prompt acquisition of a 12-lead electrocardiogram (ECG). Patients demonstrating ST-segment elevation on a 12-lead ECG may be eligible for emergent reperfusion therapies, including primary percutaneous coronary interventions. Those without ST elevation may be experiencing non-ST-elevation myocardial infarction (NSTEMI), unstable angina, or non-ischemic causes of myocardial injury or be normal. Serial testing for cTn will differentiate NSTEMI patients from those with other causes of chest pain by demonstrating a significant change in cTn (delta) together with ischemic symptoms and clinical risk factors.

6. How does the high sensitivity assays enhance the clinical utility?

The increased sensitivity of the troponin assay (i) allows earlier detection of myocardial injury, and (ii) enables the detection of even lesser amount of cardiac injury – often undetected by conventional assays. This allows shorter serial testing intervals and the implementation of Accelerated Diagnostic Protocols (ADPs) that will facilitate the rapid triage of chest pain patients and shorter emergency department lengths of stay.

7. Why is the enhanced precision of the hs-cTnI assay for lower values so important?

Precision minimizes analytic variation and allows the reporting of reliable and reproducible delta values used in ADPs.

8. So what is an Accelerated Diagnostic Protocol (ADP) using hs-cTnI assays?

Serial testing protocols using current cTn assays were obliged to test at 4 – 6 hr intervals because the methods were not sensitive or precise enough to detect small changes over shorter time intervals. Fortuitously, the excellent sensitivity and precision of hscTnI assays allows the development of accelerated diagnostic protocols (ADPs) for ruling in or ruling out myocardial infarction in an emergent setting. These protocols rely on both absolute values above and below the sex-specific 99th% URL and the detection of changes (deltas) at several predefined time points. These ADPs have demonstrated very high negative predictive values (~ 99.5%) in numerous large studies. For instance, patients may be classified as low risk for AMI when the time since onset of symptoms is greater than 2 hrs, hs-cTnI value is less than the LOQ (< 4ng/L), and clinical risk factors, as determined by particular ADP (e.g., The Heart Pathway), are favorable. Similarly, patients are considered low risk when the 2 hr value is less than the 99th% sex-specific URL and the delta between the 0 and 2 hr values is < 5 ng/L. Accelerated classification as high risk for AMI occurs when values are above the sex specific 99th% and deltas > 10 ng/L. The full

ADP endorsed by Division of cardiology, Department of emergency medicine, and laboratory medicine at BJH is shown in figure 1.

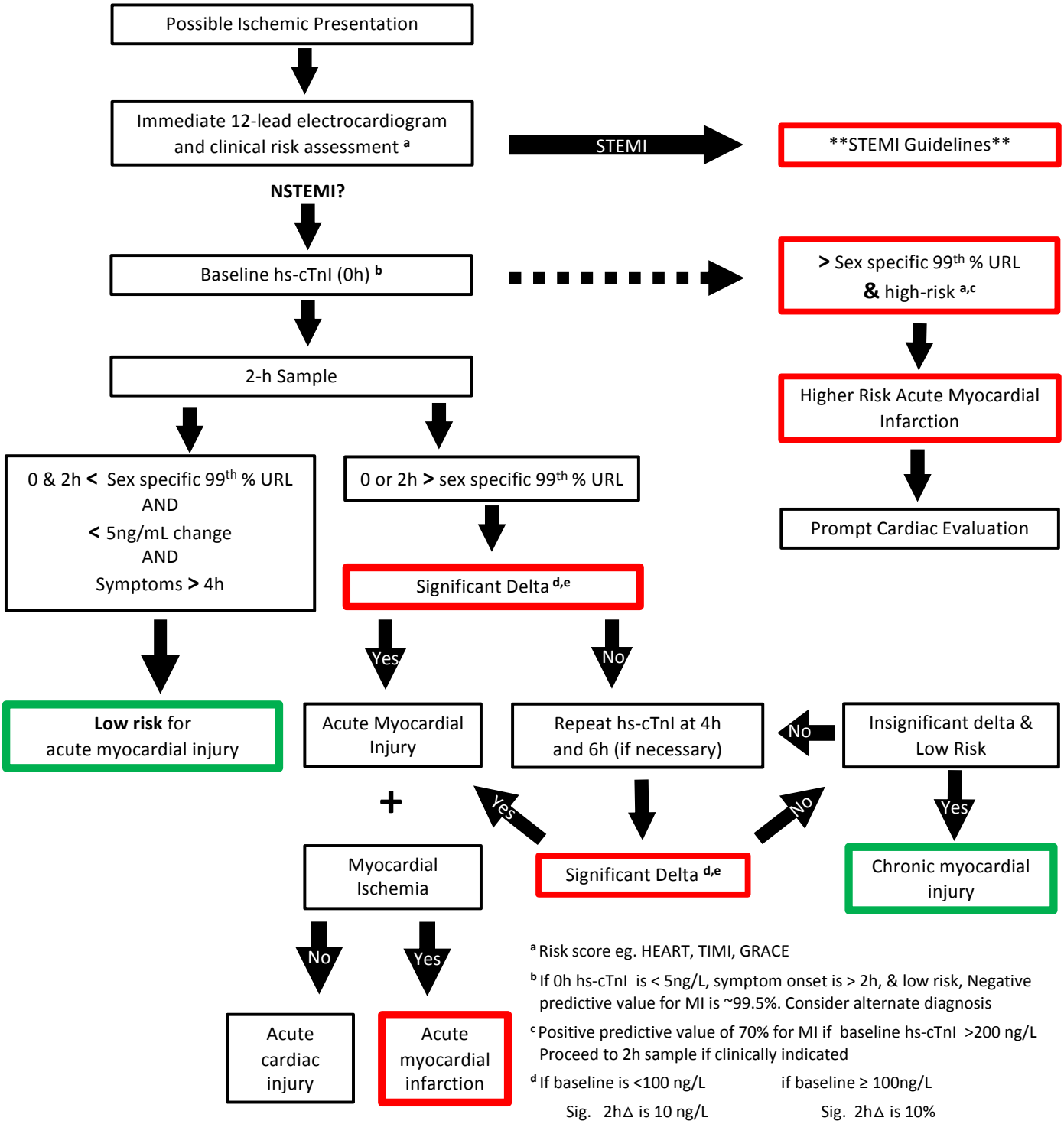
9. Are there other causes for an elevated cTnI besides AMI?

Yes. Patients with chronic comorbidities that cause non-ischemic cardiac injury will often have hs-cTn values above the 99th%, but usually < 100 - 150 ng/L. Thus, the initial differential at these hs-cTnI concentrations must be kept broad and include conditions responsible for insidious and acute causes of myocardial injury: heart failure, chronic kidney disease, myocarditis, cardiotoxic drugs, cardiomyopathy, amyloidosis and sepsis, all of which can result in non-ischemic cardiac injury. Unlike AMI, these comorbidities will not result in significant deltas when serial hscTnI testing is performed over several hours, unless their onset is acute rather than chronic.

10. What caveats should I be aware of?

It is important to note that acute MI, patients presenting early (within the first 2 hours of chest-pain symptoms) may have values below the LoQ. Finally, late presenters may not exhibit increasing cTn values as their cTn concentrations have "plateaued" but not yet started to decrease.

High Sensitivity Troponin I Algorithm



99th % URL
Male: 35 ng/L
Female: 17 ng/L

[a] Risk score eg. HEART, TIMI, GRACE

[b] If 0h hs-cTnI is < 5ng/L, symptom onset is > 2h, & low risk, Negative predictive value for MI is ~99.5%. Consider alternate diagnosis

[c] Positive predictive value of 70% for MI if baseline hs-cTnI >200 ng/L Proceed to 2h sample if clinically indicated

[d] If baseline is <100 ng/L

Sig. 2hΔ is 10 ng/L
Sig. 4hΔ is 15ng/L
Sig. 6hΔ is 20ng/L

if baseline ≥ 100ng/L

Sig. 2hΔ is 10%
Sig. 4hΔ is 15%
Sig. 6hΔ is 20%

*At least one cTnI must be elevated for rules to apply

[e] If samples are collected >10-20h after onset of acute chest pain, troponin may have peaked and delta criteria may not apply. Declining troponin can be significant (ie. old MI). Same criteria are used with negative delta.