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High-Sensitivity Troponin in Suspected Acute Coronary Syndrome: What General Cardiologists Need to Know

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Take Home Messages

- **High sensitivity troponin (hscTn) assays increase diagnostic yield** and improve outcomes in non-ischaemic myocardial injuries, but not in those with a final diagnosis of AMI.
- **Assay choice matters** operationally (cross-reactivity with hs-cTnT in skeletal myopathy; macrotroponin artefact with cTnI), but **there is no definitive RCT** proving clinical superiority of T vs I.
- **0/1-hour algorithms** are safe and efficient with hs-cTn; they detect more early MIs, but real-world gains in length of stay are modest.
- Troponin release kinetics cannot reliably distinguish aetiology.
- A rule out threshold below the **Limit of detection (LoD)** is a powerful tool to streamline care while preserving safety. Some have postulated using it to refine the diagnosis of unstable angina.

Road to high-sensitivity troponin

Previously, the MB fraction of creatinine kinase (CK-MB) was considered the biomarker with the greatest diagnostic accuracy for acute myocardial infarction (AMI). (1) The introduction of cardiac troponin (cTn) assays reclassified a quarter of patients with CK-MB-defined 'unstable angina' as AMI. (2) This was clinically meaningful: mortality and reinfarction risk were 6 times higher in patients with an elevated cTn despite normal CK-MB, and these patients benefited from intensified medical therapy (3)

The Fourth Universal Definition of AMI incorporates cTn as a necessary criteria (**Table 1**) (4) with major guidelines recommending the use of hscTn assays(5,6). High-sensitivity detect concentrations well below previous Limits of Quantiation (LoQ) (**Table 1)** and can identify dynamic changes within the reference range. Notably, very low or undetectable values, within the normal range have a fraction of the risk of major adverse cardiac events (MACE) compared with those within the normal range. (7) These advances have challenged the clinical relevance of 'unstable angina', prompting calls for biomarker-based redefinition.(1)(7)

The cluster randomised HIGH-STEACS trial demonstrated that switching to hscTn assay reclassified 17% of patients with an undetectable conventional cTn as having a 'myocardial injury', (**Table 1**) a third of whom were diagnosed with a type 1 MI (8). (9) Reclassification increased the rate of coronary angiography and revascularisation. Surprisingly, the trial found no reduction in AMI or cardiac death with use of the hscTn assay. Long term outcomes improved

mainly among those with non-ischaemic myocardial injury, highlighting the assay's value beyond AMI diagnosis. (10)

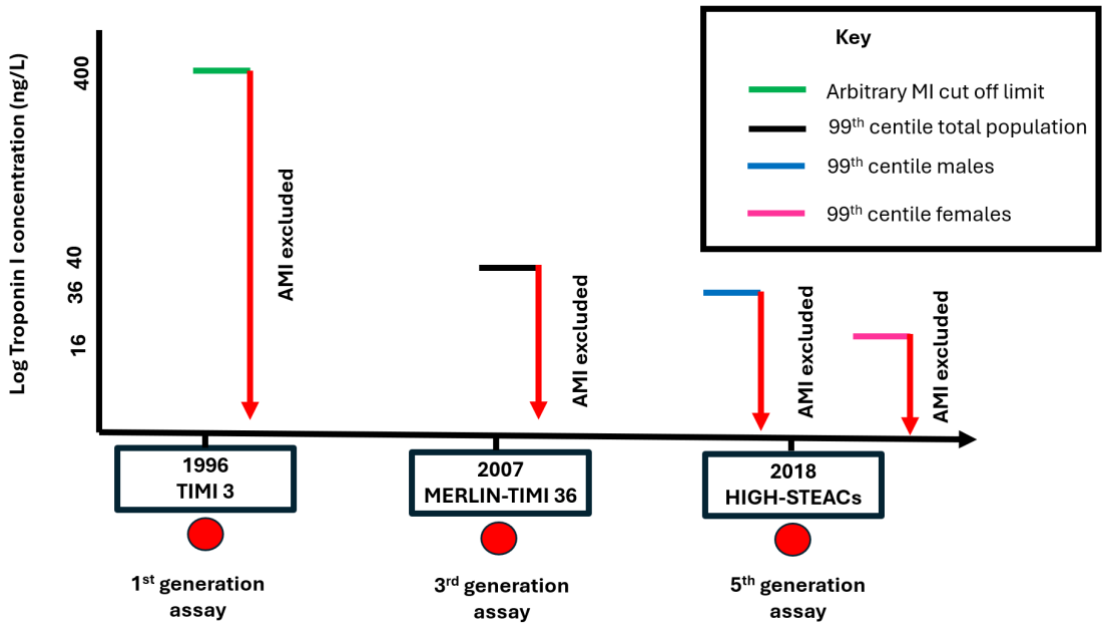

Figure 1. Original Figure illustrating the increasing sensitivity of cTn across different generations of the assay. Shown are the AMI cut off for 3 different landmark trials in cardiology. TIMI 3a trial compared the use of tPA in with placebo in patients with unstable angina or non q wave AMI. Merlin-TIMI 36 compared ranolazine to placebo in patients with NSTEMI. HIGH-STEACs compared a hscTn assay to a non-hscTn assay. Of interest, many of the patients enrolled in TIMI 3 with unstable angina would be reclassified as having an AMI using modern hscTn.

Troponin T (cTnT) versus Troponin I (cTnI): what matters clinically?

cTnT binds to tropomyosin, whilst cTnI inhibits the actin and myosin interaction. (11) Both are cardiac-specific, yet false positive hs-cTnT results may occur in skeletal myopathy due to assay cross-reactivity – rare with hs-cTnI(12). Conversely, cTnI more often forms macrotroponin complexes, causing artefactual elevation.(13)

Whilst the majority of cTn release in myocardial injury occurs from a 'structural pool' within the cardiac sarcomere, some is derived from an 'early release' pool within the cardiomyocyte cytosol. In addition to myocyte necrosis it is speculated apoptosis, exocytosis of intracellular blebs and normal cardiomyocyte turnover may contribute to release of circulating cTn. (11) Even brief balloon occlusion, insufficient for necrosis, can raise circulating hs-cTn within 30 minutes, with larger increases for cTnI than cTnT at comparable injury levels. (14)

Elimination kinetics differ slightly: cTnI appears to peak earlier (10.9 versus 12 hours)(15) and clears faster, (15,16) though both remain elevated for days due to half-lives of 11-20hours. (16) Though cTn appears to rise more rapidly in type 1 AMI, troponin kinetics and peak concentrations cannot reliably distinguish between causes of elevated troponin. (17) No randomised controlled trial (RCT) compares cTnT and cTnI directly, though observational data suggest cTnI may be more accurate, while cTnT may have superior prognostic value.(18)

When should we sample—0/1 h or 0/3 h?

The ESC 2020 guidance endorsed the 0/1h algorithms, reflecting the ability of hs-cTn to detect very small changes early after symptom onset.(19) Supporting evidence largely came from observational analyses retrospectively comparing 0/1 and 0/3h strategies – designs prone to measurement and temporal bias. (20–22)

In the RAPID-TnT RCT, a 0/1h strategy was non-inferior for 30-day safety and shortened discharge time by an hour. However, it compared hs-TnT at 0/1h with a conventional assay at 0/3h, confounding assay type with timing.(23) Long-term results suggested that the 0/1h was associated with an increased risk of death/MI in patients with a cTn value <29ng/L, suggesting increased sensitivity to detect small troponin rises within a 0/1h framework did not improve safety. (24) In MACROS-2, using a hscTnT in both arms, the 0/1h algorithm was non-inferior to the 0/3h pathway for safety and slightly improved sensitivity for type 1 MI, reducing median stay by just 39 minutes. (25)

"Very troponin-negative" chest pain (LoD strategy)

Observational studies show that patients with initial hs-cTn value below the LoD have one sixth the risk of AMI or cardiac death compared with those with detectable levels within the normal range. (26) In a Swedish registry of >100,000 cases, those below LoD had even lower one-year mortality than the age-matched general population. (27)

RCTs evaluating LoD-based discharge confirm its safety and efficacy. (28,29) The HISTORIC trial randomised >30,000 patients to standard care (0/6/12h troponin sampling) versus an accelerated pathway discharging patients if hs-cTnI<5g/L after ≥2h of chest pain or <3ng/L delta over 3h. Although not statistically, non-inferior, event rates were lower in the accelerated arm, supporting LoD-guided early discharge as safe and efficient.(28)

Conclusions

As cardiac troponin assays have become more sensitive, their use has grown increasingly complex. High sensitivity assays improve accuracy for myocardial infarction and intensify treatment, yet their greatest value may be in detecting non-coronary cardiac injury. Although rapid diagnostic algorithms are safe, their efficiency gains are modest. The next step may be moving high sensitivity PoC testing prehospitally, enabling earlier triage, better resource use, and more personalised care.

Disclosures

No disclosures

Table 1. Table of definitions

Term	Definition
First WHO definition AMI (1971)	**Requires 2 of the following:** • Typical symptoms • Typical ECG pattern i.e. the development of Q waves An initial increase and subsequent decrease in serum enzymes attributed to myocardial necrosis
Current 4th Universal Definition AMI (2018) (Inclusive of types 1, 2 and 3)	**Acute myocardial injury** with clinical evidence of acute myocardial ischaemia and with a detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile of the healthy reference population **and at least 1 of**: • Symptoms of myocardial ischaemia • New ischaemic ECG changes • Development of pathological Q waves • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality consistent with ischaemia Identification of coronary thrombus by angiography or autopsy
Acute Myocardial Injury	Evidence of elevated cTn values with at least 1 value above the 99th percentile of the healthy reference population. **Acute** if there is a rise and/or fall of cTn values.
Unstable Angina (ESC 2023)	Myocardial ischaemia at rest or on minimal exertion **in the absence of cardiomyocyte injury/necrosis.**
Hstroponin	An cTn assay which is able to detect cTn in at least 50% of the normal reference population **and** that has a coefficient of variation (CoV) of <10% at the 99th centile of the normal reference population
Limit of blank (LoB)	The highest apparent concentration of an analyte expected in a sample where none of that analyte is truly present. **Formula:** mean of a 'blank' sample x 1.645 SD of the 'blank' sample.
Limit of Quantiation (LoQ)	Lowest concentration where the assay maintains a <10% coefficient of variation for repeated measurements.
Limit of detection (LoD)	The lowest concentration of an analyte that can be reliably distinguished from a blank sample. (where 95% of the frequency distribution is above the LoB)
Normal reference range	cTn which are above the LoD and below the 99th percentile of the normal reference population
Macrotroponin	Complex of circulating cTn with autoantibodies (usually IgG) in the blood. This can cause persistently high/false positive troponin results. More common in autoimmune conditions such as Rheumatoid arthritis.

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Table 2. Summary of Troponin RCTs Trial (year, journal)	Design	Major result	Clinical Takeaway
RATPAC (2011, BMJ)(30)	Multicentre RCT (n=2,400) comparing point of care (POC) (non-hs) (0, 90 mins) versus central laboratory (cTn)	4h discharge proportion (32 versus 13%) no increase in 3 month MACE (3 versus 2%). POC cost/patient £1,217 versus £1,007	POC testing compared with laboratory cTn increases proportion discharged within 4 hours with no evidence increased MACE. Unlikely to be cost effective.
HEART Pathway (2015, Circ)	Single centre RCT (n= 282) randomised to use of HEART pathway with 0, 3h troponin sampling versus 'usual care'	Primary outcome: use of cardiac testing – 68.8% versus 56.7%. Secondary outcomes. Reduced length of stay (LOS) 21.9h versus 9.9h. No MACE observed in either group in those discharged.	Use of HEART score in addition to standard care reduces downstream cardiac testing and LOS. Studied not powered to detect MACE.
HIGH-STEACS (2018, Lancet)(31)	Stepped-wedge cluster RCT. HscTnI versus cTnI.(10 sites). (n=48,282)	17% cTnI group reclassified as having myocardial injury. 1/3rd of whom diagnosed with MI. No reduction in 1 year death/MI (5.8% versus 6.1%). Reduced LOS (10.1 versus 8.8h)	Hstroponin Improves diagnostic sensitivity and reduces LoS, but does not improve death or MI.
RAPID-TnT (2019, Circ)(23)	Multicentre RCT (n=3,378,) ESC 0/1 with hscTnT versus 0/3h with cTnT	Reduced LoS (4.6h versus 4h), non-inferior for death/MI (0.3% vs 0.4%).	Small improvement in LoS with 0,1h pathway with 0/1h pathway. 0/1h pathway **and** hscTnT non-inferior to 0/3h pathway using cTnT
LODED (2020, Heart)(29)	Multi-centre RCT (n=629). Single sample LoD (<6h chest pain) and normal ECG strategy versus 'usual care'	Reduced LoS (6.5h versus 5.6h). No difference in 30 day MACE (0.3% versus 0.3%)	Single sample <LoD rule out strategy is safe and reduces LoS
HISTORIC (2021, Circ)(28)	Stepped-wedge cluster RCT (7 hospitals, n=31,492). Early rule out >2h pain and hscTnI<5 versus 'usual care'	Reduced LoS (8.9h versus 7.3h). 30 day death/MI (0.3% versus 0.4%) – underpowered to reach no inferiority margin	Very low/LoD troponin rule out reduces LoS and may be safe
ARTICA (2024, Eur Heart J)(32)	Pre-hospital RCT Netherlands (n=863). POC hscTnI<LoD (Abbot) rule out pre-hospital versus ED transfer. Recruited low risk chest pain.	No increase 1 year MACE (1.7% versus 1.4%). Cost saving 700 euro/patient	Safe and economical to use PoC hscTnI rule out MI pre-hospital in low risk chest pain patients
MACROS (2025, presented ESC)(25)	RCT (2 centres, n=3,543) 0/1 versus 0/3h pathway both using hscTnT	No Difference in % discharged within 4 hours (21.8% versus 19.2%), LoS reduced (273mins versus 312mins). No difference in 30 day MACE (0.8% versus 1.1%)	ESC 0/1h pathway equivalent to 0/3h pathway in safety with only small gains in efficiency of discharge

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