**Rapid diagnostic strategies using high sensitivity troponin assays - what is the evidence and how should they be implemented?**

Paul Collinson1, Ahmed Dakshi2, Aleem Khand2

1Departments of Clinical Blood Sciences and Cardiology, St George’s University Hospitals NHS Foundation Trust and St George’s University of London, Cranmer Terrace London SW17 0QT, UK

2Liverpool University hospital NHS foundation trust, Liverpool, L9 7AL, UK

Corresponding author: Professor Paul Collinson1, email: [paul.collinson@stgeorges.nhs.uk](mailto:paul.collinson@stgeorges.nhs.uk)

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**Abstract:** The introduction of high sensitivity measurement of cardiac troponin T (hs cTnT) and cardiac troponin I (hs cTnI) has given the laboratory the ability to measure very low levels of cardiac troponin. The limit of detection of these assays is well below the 99th percentile. These low levels can also be measured with small values of imprecision. A range of algorithms combining presentation measurement with very small repeat sample intervals, repeats at 1-2 hours have been developed. These are able to predict with acceptable accuracy the diagnosis that would be achieved with continued repeat sampling out to 6-12 hours from presentation. In this article we review the evidence for the diagnostic accuracy of these approaches and the practical aspects of implementation into routine clinical practice.

Introduction

There are two criteria which define a high sensitivity cardiac troponin (hs-cTn) assay. First, the 10% coefficient of variation (CV) is at or below the 99th percentile of the method. In practice the 10% CV is often well below the 99th percentile. Second, that the assay can measure or quantify troponin, above the LOD, in 50% or more of the reference population, in both males and females(1). The reference population has a profound effect on the value of the 99th percentile. 99th percentiles are progressively lower as the criteria to exclude occult cardiac disease become more stringent(2). In addition, the ability to detect troponin in 50% of the reference population values can be compromised, particularly in females as troponin concentrations in healthy female controls are lower than males(3).

The introduction of hs cTn should be seen as evolution rather than revolution as progressive improvement of analytical sensitivity and reduction of imprecision is a characteristic of immunoassay development. There has been variation in the pace of development between troponin assays.. The change from the 4th generation cardiac troponin T (cTnT) assay to the fifth generation hs-cTn assay was marked by a significant improvement in assay sensitivity. This increase in analytic sensitivity was less marked with troponin I assays, as compared to troponin T, generally as analytic sensitivity in earlier generation troponin I assays was already quite significant (4) and the impact of the shift to hs-cTn less dramatic. The clinical impact of hs-cTn arises from two assay features, first the ability to measure very low values of cTn and the second to measure these values with very low imprecision. The ability to measure very low values means that the earliest phase of troponin release can be measured reliably. The ability to measure with low imprecision means that serial measurements at very low cTn values across short time intervals become possible. It is therefore possible to accurately reflect the release curve of troponin much earlier. These two features have resulted in the development of rapid diagnostic strategies for early detection of myocardial infarction based on single and rapid serial troponin measurement (5;6), updating previous strategies based on rapid serial measurement of creatine kinase and its MB fraction(7).

Rapid diagnostic algorithms for confirmation and exclusion of myocardial infarction.

The definition of myocardial infarction (MI) has always required a cTn value that exceeds the 99th percentile and undergoes a significant. Rapid algorithms are not primarily diagnostic but predictive. They are based on the findings that early troponin measurements can be used to predict subsequent values taken 3-6 hours later. There is an inference that very low value troponin, such as below LOD, can rule out MI as the likelihood of a subsequent troponin rise to beyond 99th percentile is very remote. High values rule in MI. Values remaining stable at a value below the 99th over 1-2 hours are likely to remain so and rule out MI.. Therefore, these algorithms categorise patients into rule-in, rule-out and intermediate. It is important to understand how hs-cTn assays can be used in this context. There are two components to rapid diagnostic algorithms, admission measurement and serial measurement using a short repeat sampling interval (1-3 hours).

Presentation high sensitive troponin value interpretation and inference is predicated on three characteristics of hs-cTn and the pathophysiology of coronary atherosclerosis and plaque rupture.. First, that a rise in troponin exceeding the 99th percentile that might previously have been borderline or not detected using a non high sensitivity assay, can now be reliably measured(8). The second is the finding that very low troponin values are associated with a very low probability of underlying cardiac disease and even atherosclerosis in the absence of overt cardiac disease (9-12). This translates into a low risk that the patient admitted with chest pain and a very low troponin is likely to have underlying ischaemic heart disease as the cause. Rule out thresholds are close to or at the limit of detection of the assay hence around the 5th percentile. Finally, and often overlooked is prior probability of disease, the use Bayesian analysis, The incidence of MI in chest pain populations of MI is in the range 3-20%. When prior probability is low, diagnostic sensitivities of 95% will translate into an impressive negative predictive value of >99%.

Serial measurement is contingent on short term intra-individual variation and the ability to perform measurements with low degrees of analytical imprecision. Short term biological variation of cTn is very low(13) so serial measurement over short time frames allows early detection of change to confirm or exclude evolving myocardial injury.

The evidence base for accelerated diagnostic programs for suspected acute coronary syndromes (ACS) and interpretation of troponin kinetics.

 Rapid diagnosis was proposed by the ESC, initially based on hs cTn measurements on admission and 3 hours from admission(14) and subsequently, measurement on admission then 1-2 hours from admission(15;16). A number of criticisms of these guidelines have been made(17) of which the lack of a proper evidence based review is the most serious(18). As part of the National Institute of Health and Care Excellence (NICE) update of the use of hs cTn a comprehensive evidence review as well as economic modelling was undertaken(19;20). The tables from the review have been published(20). A modified and updated version concentrating on rapid diagnostic pathways is shown in table 1. Strategies for implementation of hs-cTn for rapid diagnosis can be divided into three types, although these are not mutually exclusive. Admission measurement, often referred to as “one and done” was originally proposed by Body for single sample rule out(5). This strategy has the strongest evidence base from meta-analysis of large scale observational studies(21) and most importantly from two randomised controlled trials (RCT)(22;23). When combined with risk scoring, the use of a single low troponin value excludes up to 50% of chest plain patients without MI depending on the series(24-26). A refinement proposed as part of the ESC guidelines is to use a single high hs cTn cut off to rule in MI. However, the diagnostic efficiency of this strategy is questionable(27).

The second strategy is to utilise serial measurement with the first sample measured on presentation and the second measured 1-2 hours from admission, combined with calculation of the change between values, the delta. A value remaining below an optimised decision threshold (typically not the 99th percentile) combined with a low delta value allows rapid rule out MI. A high delta value rules in MI. In practice, admission measurement with rule out (and rule in) can then be followed by serial testing at 1-2 hours. Intermediate values (not ruled out or ruled in) require further testing. The third option is a composite approach using admission measurement followed by serial measurement at 3 hours but using the 99th percentile(28). Here, rule out MI is either on admission measurement alone or both values remain below the 99th percentile with a low delta value. A high delta with a rise to a value exceeding the 99th percentile rules in MI.

All of the proposed strategies consider the question of diagnosis or exclusion of non ST elevation myocardial infarction (NSTEMI). The problem is that patients present with chest pain and only a minority have ischaemic heart disease (8%, angina, 9% MI)(29). Another important complicating factor is competing causes of acute myocyte injury leading to troponin elevation; non-ischaemic causes are in totality greater than NSTEMI(30). They also do not address the problem of chronic myocardial injury. Practical strategies for use of hs cTn measurement in routine clinical practice need to consider all of these factors. One example of such an approach is illustrated in figure 1.

Practical aspects of implementation

The published analytical performance of the existing hs cTn methods mean that in theory all should reach the analytical goals required for measurement close to the limit of detection of the assay and serial measurements over short time intervals. However, local verification of analytical performance is desirable as not all instrumentation may necessarily achieve what is theoretically possible(31). This can be remedied and usually requires close working with the manufacturer.

Presentation sample draw and single sample rule out of low risk individuals should be standard practice as it is strongly evidence based and will allow immediate discharge of a significant proportion of chest pain patients.

Patients not in this group, irrespective of the first troponin level, require serial testing over 1-3 hours to determine which of three categories they fall into. Where all cTn values are below the 99th percentile without a significant delta, myocardial injury is excluded. Discharge is then dictated by clinical suspicion of unstable angina or exclusion of serious non-ischaemic pathology. and the patient can be discharged. A significant delta value indicates acute myocardial injury (which will include MI) and requires hospital admission and assessment. The higher the troponin and the larger the delta value, the greater the probability the patient will have sustained an NSTEMI. Those with cTn above the 99th percentile but with minimal change require further assessment that the likelihood of acute injury is low but the troponin elevation requires explanation and possibly investigation. The use of the term “troponitis” is entirely inappropriate(32).

The challenge with short time serial measurement is the turnaround time that is possible with central laboratory analysis. Very few laboratories can provide detailed information on turnaround time measured from blood draw to provision of results. Most simply detail time from sample receipt to result availability. Although laboratories aim for a 60 minute turnaround time there is likely variation in total turnaround time this is unlikely to be achieved consistently irrespective of timing of troponin sampling. This challenges the concept of the 0/1 hour ESC algorithm. Results for the first sample may not be available before the time for the second sample draw. The ESC guidelines(16) recommend (section 3.3.4.3) the second sample should be taken at 1 hour in the absence of the presentation sample result. This will have two consequences. First 2 samples will be taken on all patients, which increases the cost and reduces the convenience of presentation sampling. Second, it is appropriate to await the results of the second sample, even if the presentation sample supports discharge, thus delaying discharge.

Pragmatically, the use of a 0-2 hour strategy or a combined strategy based on 0-3 hour sampling would seem to be a solution. The UK Advanced Access Collaborative has sponsored a series of studies aimed at the implementation of rapid diagnosis based on hs-cTn. These case studies are available to read via the NEQAS cardiac biomarker website (https://www.ukneqas-cm.org.uk/). The results of these studies suggest that implementation of presentation sampling is usually straightforward but serial measurements is more complex and a 0-2 hour strategy was easier to implement. It is unlikely that a 0-1 strategy can be successfully implemented without the provision of hs-cTn by point of care testing (POCT).

Does rapid diagnosis make a difference?

There is evidence from randomised controlled trials (RCT)s of POCT that rapid diagnosis provision of cTn results can improve patient flow but the findings are not consistent and depend on local pathways(33;34). The RCT of presentation sampling of cTn demonstrated safety but did not result in significant changes in length of stay(22). The single RCT of 0-1 hour testing versus conventional testing did show a reduction in length of stay but the comparison was not with diagnosis based on the 99th percentile(35) and there are concerns about long-term outcomes in those who had rapid diagnosis and discharge(36). Additionally, rapid diagnosis in this study did not appear cost-effective(37), similar to findings with rapid diagnosis based on POCT(38). Comparison of the modified 0-3 hour algorithm with usual care also demonstrated reduction in length of stay(23). There was therefore evidence that provision of rapid diagnosis will reduce length of stay. In addition COVID has emphasised risks of prolonged ER or hospital study. A reduction of potential exposure to Covid 19, or other infections, provides a powerful incentive for accelerated safe discharge.

In conclusion, rapid diagnostic pathways based on hs-cTn should be part of the repertoire of all UK laboratories. Single sample rule out on admission using hs-cTn is theoretically achievable with all hs-cTn methods currently available. The optimal serial testing strategy will depend on part on local circumstances. A RCT between strategies is likely to provide the most robust economic analysis of accelerated diagnostic pathways in practice.

Table 1 Summary of studies of rapid diagnosis. (RCT, Randomised controlled trial. NPV, Negative Predictive Value. hs cTn, High Sensitivity Cardiac Troponin. hs-cTnT, High Sensitivity

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| **0-1-hour vs 0/3-hour RCT** | | | | | | |
| **Name** | **Publication date** | **Country** | **Sample size**  **(prevalence)** | **hs-cTn** | **Discharge %** | **NPV** |
| RAPID TnT  Chew et al(35) | 2019 | Multi-centre/Australia | Total:3,378  0/1hour:1,646  (MI 0.5%) | hs-TnT | 45.1% (0/1hr) vs 32.3% (0/3hr) | 99.6% (0/1hr) 30-day death/MI |

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| **0-1-hour Prospective studies hs-TnT** | | | | | | |
| **Name** | **Publication date** | **Country** | **Sample size**  **(prevalence)** | **hs-cTn** | **Rule out %** | **NPV (Sensitivity)** |
| Andersen et al (39) | 2021 | Denmark | 1003  (MI 8.8%) | hs-cTnI | 47% | 100% (100%) |
| Allen et al(40) | 2021 | Multi-centre/USA | 1,430  (MI 11.4%) | hs-TnT | 57.8%  +Low HEART score: 30.8% | 97.2% (96.1 %)  +Low HEART score:98.4%  MACE/DEATH 30 days |
| Twerenbold et al(41) | 2019 | Multi-centre/Argentina, Switzerland | 2,296 (MI 9.8%) | hs-TnT | 62% | 99.8%  MACE/DEATH 30 days |
| Rapid CPU  Stoyanov et al(42) | 2020 | Single centre/Germany | 1,282 (MI 13.1%) | hs-TnT | 62.8% | 99.9%  30 day all cause death |
| Twerenbold et al(43)  APACE/BACC | 2018 | Multicentre | 4,368 (MI 17%)  3,500 | hs-TnT  hs-TnI Abbott architect | 57%  44% | 99.8% for AMI (cTnT)  99.7% for AMI (cTnI) |
| Mueller et al  TRAPID-AMI(44) | 2016 | Multicentre | 1,282 (MI 17%) | hs-TnT | 63.4% | 99.1% for AMI (96.7%) |
| Pickering et al(45) | 2016 | Multicentre (Australia/Canada/New Zealand) | 2,222 (MI 9.7%) | hs-TnT  hs-TnI (Abbott Architect) | 64.1%  54.2% | 99.8% for AMI (97.1%)  99.5% for AMI (98.8%) |
| Reichlin et al(46) | 2015 | Multicentre | 1,320 (MI 17.3%) | hs-TnT | 59.5% | 99.9% for AMI (99.6%) |
| Reichlin et al(47) | 2012 | Multicentre | Overall MI 17%  Derivation:436  Validation:436 | hs-TnT | N/A  60% | Derivation: 100% (100%)  Validation: 100% (100%) for AMI  99.8% for 30 day death |

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| **0-1-hour prospective studies hs-TnI** | | | | | | |
| **Name** | **Publication date** | **Country** | **Sample size** | **hs-TnI** | **% Rule out** | **NPV(sensitivity)** |
| HIGH US  Nowak et al al(48) | 2020 | Multi-centre/United states of America | 2,113  (MI 11.8%) | Siemens Atellica | 50.4% | 99.7% for AMI  (98.7%)  99.8% for 30-day AMI/death |
| Neumann et al(49) | 2016 | Single centre/Hamburg, Germany | Derivation:  BACC: 1,040  (17.7%)  Validation:  ADAPT:1,748  (14.2%)  APACE:2,261  (19.0%) | Abbott Architect | BACC 39%  NA for validation sets | BACC  Admission 97.1% (92.2%)  0-1h 99.0% (97.6%)  Validation:  ADAPT:  99.6% (admission)  99.7% for 0/2 hour for AMI  APACE:  98.6% admission  99.2% 0-1h  for AMI |
| Jaeger et al(50) | 2016 | Multicentre | Derivation: 750 (18.1%)  Validation:750 (12.9%) | Siemens Vista | 47.8%  57.1% | Derivation 98.9% (97.1%)  Validation:100%  (100%)  For AMI |
| Maria Rubini Gimenez et al(51) | 2015 | Multicentre | 1811 (18.0%)  Derivation:906  Validation:905 | Abbott Architect | 55.7%  50.5% | Derivation:99.2% (97.6%)  For AMI  Validation: 99.6% (98.8%)  For AMI |

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| **0-2-hour prospective studies hs-cTn** | | | | | | |
| **Name** | **Publication date** | **Country** | **Sample size** | **hs-cTn** | **NPV for 30-day MACE** |
| Meller et al(52) | 2015 | Multicentre | Derivation: 1,085  Validation: 1,590 | hs-TnT  +ECG findings+TIMI score. | 100%  99.1% |
| Than et al(53) | 2014 | Single centre RCT | 542  271 ADP  272 Conventional | hs-TnI  Abbott  +TIMI score+ECG findings | Conventional 100%  ADP 99.8% |
| Cullen et al(54) | 2013 | Multicentre | Primary cohort:1,635  Secondary cohort: 909 | hs-TnI Abbott | 100%(+TIMI score=0)  99.7% (+TIMI score ≤1)  99.7% (+TIMI score ≤1) |
| ADAPT trial  Than et al(55) | 2012 | Multicentre | 1, 975 | TnI Abbot /TnI Beckman Coulter (conventional sensitive) | 99.7% (TIMI 0, non-ischemic ECG) |
| Aldous et al(56) | 2012 | Multicentre (Subset of ASPECT) | 1,000 | hs-cTnT | 99.3% (+non-ischemic ECG/TIMI 0) |

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| **Rapid rule out (1 sample) studies** | | | | | | | | |
| Name | Publication date | Site | Type of study | Sample size (MI%) | hs-cTn | Cut off | Rule out % | NPV (Sensitivity) |
| HISTORIC  Anand et al(23) | 2021 | Multi-centre/Scotland | RCT | 31,492  (NA) | hs-TnI Abbott Architect | 5ng/L | 71% | 99.7% 30-day safety outcome. |
| Allen et al(40) | 2021 | Multicentre/USA | Prospective observational | 1,430  (MI 11.4%) | hs-TnT | 6ng/L | 32.8%  20.1%:  (Low HEART SCORE) | 98.3% (96.2%) 30 day MACE  +low HEART score: 99.0% for 30-day MACE. |
| Body et al(25) | 2020 | Multicentre UK | Prospective observational | 999 (13.1%) | hs-cTnI Siemens Atellica | 5ng/L | 50.4% | 99.8% (99.2%) |
| LoDED  Carlton et al(57) | 2020 | Multicentre/United Kingdom | RCT | 629  (NA) | hs-TnT/hs-TnI Abbott Architect,Beckmann | 5ng/L | 45% | 100% for 30-day MACE |
| Sandoval et al (58) | 2017 | Single centre | Prospective observational | 1631(10.4%) | Hs cTnI Abbott Architect | 5 ng/L | 50% | 98.9% (94.7%) for acute AMI  98.5% (94.9%) for 30 days AMI/cardiac death |
| Sandoval et al (59) | 2017 | Multicentre/US and Scotland | Prospective observational | Derivation: 1647  (10.4%)  Validation:  2198  (NA) | hs-TnI Abbott Architect | 1.9 ng/L | 27%  22% | Derivation  99.1% (99.0%) for AMI  99.6% for 30 days AMI/cardiac death  Validation:  98.8% (99.3%) for AMI  99.1% for 30 days AMI/cardiac death |
| Chew et al(60) | 2017 | Single centre/ England | Prospective observational | 1642  (NA) | hs-TnT | 5ng/L  + non-ischemic ECG | 36.9% | 99.8% for 6 weeks MACE |
| Carlton et al(61) | 2016 | Multicentre | Prospective observational | 3155  (9.2%) | hs-TnI Abbott Architect | 1.2ng/L | 18.8% | 99.5% (99.0%) for 30 day AMI |
| Shah et al(24) | 2015 | Multicentre/Scotland | Prospective observational | Derivation: 4870  (20%)  Validation:  1126  (23%)  308  (NA) | hs-TnI Abbott Architect | 5ng/L | 47.5%  41.7%  40.3% | Derivation: 99.6% NPV for AMI/subsequent AMI/cardiac death at 30 days  Validation:  99.3% NPV  99.8% NPV |
| Bandstein et al(62) | 2014 | Single centre/Sweden | Prospective observational | 14,636  (5.4%) | hs-TnT | 5ng  +Non-ischaemic ECG | 60.7% | 99.8% for MI  100% for death  At 30 days |
| Maria Rubini Gimenz et al(63) | 2013 | Multicentre | Prospective observational | 2072  (21.4%)  1180  (19.9%)  1567  (19.8%)  1151  (18.8%) | hs-TnT  hs-TnI (Siemens Vista)  hs-TnI (Abbott Architect)  hs-TnI  (Beckman) | 5 ng/L  0.5 ng/L  1.9 ng/L  2 ng/L | 26.5%  13.9%  12.6%  11.5% | 98.6% (98.2%)  98.8% (99.2%)  100% (100%)  99.5% (99.2%)  MI at presentation |
| Body et al(64) | 2011 | Single centre/Uk | Prospective observational | Derivation  703 (18.5%)  Validation  915  (NA) | hs-TnT | 3ng/L | 27.7%  17.5% | 100% (100%)  99.4% (98.8%) |

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| **Ultra-rapid rule out pathway (0-30 minutes)** | | | | | | | |
| **Name** | **Publication date** | **Country** | **Sample size** | **hs-cTn** | **cut off** | **Discharge %** | **NPV** |
| Nowak et al REACTION US(65) | 2018 | Single centre/USA | 569  (7.7%) | hs-TnT | 6 ng/L  8 ng/L delta <3 ng/L | 28.8%  41% | 100% (100%) for AMI |

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