Recommendations for Use of Point-of-Care (POC) Troponin Assays in Assessment of Acute Coronary Syndrome

Endorsed by:

Australasian Association of Clinical Biochemists (AACB)
Royal College of Pathologists of Australasia (RCPA)
The Integrated Cardiovascular Clinical Network CHSA
New South Wales Health Pathology
Pathology Queensland
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Recommendations for Use of Point-of-Care (POC) Troponin Assays in Assessment of Acute Coronary Syndrome

Endorsed by:
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PREAMBLE

Background and Rationale
Surveys conducted in Europe 1-3 and in Australia 4 have reported on the lack of harmonisation of all aspects of troponin measurement in the routine laboratory and at the point-of-care (POC), including pre-analytical sample collection and haemolysis, decision limits, and optimal sampling times, in addition to guideline recommendations for troponin use in diagnostic pathways for patients presenting with chest pain to the Emergency Department. Harmonised analytical and clinical recommendations are needed in the assessment of acute coronary syndrome (ACS). As an example, laboratories in Australia that are using the Architect high sensitive troponin I assay (hs-TnI) or the Cobas or Elecsys high sensitive troponin T assay (hs-TnT) have agreed upon harmonised decision limits (personal communications, LC, JT, RH).

Aims and Scope
This document is based on the currently available evidence and consensus and comments of key stakeholders involved in the management of ACS patients. The recommendations aim to cover both the clinical and laboratory aspects of using POC troponin assays in the assessment of ACS.

Clinical recommendations will highlight the importance of understanding:
- Differences between laboratory-based and POC troponin assays and their impact on interpretation of test results and clinical decision making;
- Timed serial measurements on patients presenting with symptoms suggestive of ACS to ensure safety and that acute myocardial infarction (AMI) is not missed;
- Interpretation of troponin results in the clinical context;
- Importance of clinical acumen when interpreting all troponin results.

Laboratory recommendations will highlight:
- Limitations of POC troponin assays;
- Delineation of troponin assays as to whether they are “clinically usable”;
- Assay performance specifications.

Target group
The recommendations are intended for:
- Clinicians requesting and interpreting troponin tests in patients presenting with symptoms of ACS
- Health care professionals, both in clinical and laboratory settings, providing a POC troponin testing service
- Manufacturers of POC troponin devices
Format and tools for implementation

The recommendations are presented in two formats:
1/ executive summary outlining the key clinical and laboratory recommendations;
2/ comprehensive document explaining the recommendations and the evidence behind them (Appendix 3), and the process of the development of the document (Appendix 1).

The recommendations are supplemented with the below tools to facilitate implementation:
o Executive summary of key recommendations for clinical and laboratory staff
o Diagnostic algorithms for different POC troponin assays (see Appendix 2 for examples)
o Educational materials including a slide presentation of the recommendations and case studies

The educational materials are available on the AACB website at:

References


EXECUTIVE SUMMARY: KEY RECOMMENDATIONS

1. Clinical Recommendations

I. This guideline provides recommendations for the use of POC Troponin test results in the management of ACS patients.

II. The following recommendations take into account the impact of the analytical performance of currently available Tn assays on their clinical use and interpretation. The recommendations regarding use of POC troponin assays are based on laboratory data showing that current POC assays are less analytically sensitive than most laboratory assays (labelled as ‘high sensitivity’ or ‘sensitive’ assays) for troponin.

III. The results of various troponin assays, whether they are available in POC or laboratory formats, are NOT directly comparable and values CANNOT be transferred between assays unless there is evidence of such comparability.

IV. Clinical users of POC and laboratory-based troponin assays need to be aware of the limitations of the actual troponin assay used in the management of their patients in order to avoid adverse effects on patient management and for patient safety.

V. Troponin results must always be interpreted in the clinical context. Biomarkers are only one component of clinical information to be used with ECG(s) and clinical history for risk stratification according to clinical guidelines. Elevated troponin results alone do not rule in the diagnosis of ACS as elevated troponin can occur in non-ACS conditions (causes of non-ACS troponin elevations are shown in Table 1).

VI. Serial troponin measurements should be performed for all patients presenting to an ED with symptoms suggestive of ACS, unless the patient has been reliably ACS symptom-free for 12 hours when a single sample is appropriate.

VII. Serial testing should be performed using the same troponin assay and platform. We recommend to re-baseline the troponin value for individual patients if transported to a different hospital location where a different troponin assay is used. Example scenarios are:

- Baseline Troponin I done at presentation but second location uses troponin T assay, or vice versa;
- Baseline troponin I done by a POC device but second location uses a different laboratory-based troponin I assay or one with higher analytical sensitivity;
- Baseline troponin T done by a POC device but second location uses a different laboratory-based troponin T assay or one with higher analytical sensitivity.
At the second location collect a new baseline sample and a second sample at 2-3 hours (if testing with a highly sensitive troponin assay) and 6-8 hours (if testing with a less analytically sensitive assay) unless the patient has been symptom-free for >12 hours, when a single sample is appropriate.

VII. In general quantitative troponin delta change has not been determined for use with POC assays as POC assays are less precise at low troponin concentration (see local algorithms for examples).

VIII. When a laboratory is used, results should be available as soon as possible, with a goal of within 60 minutes after the sample is received in the laboratory. Otherwise POC testing could be considered although the laboratory-based troponin assay is the preferred testing option when available.

2. Laboratory Recommendations

2.1 Analytical

I. It is the laboratory’s responsibility to inform clinicians about the limitations of POC troponin vs. laboratory-based troponin assays in terms of analytical performance which impacts their clinical utility.

   − All current troponin POC assays are analytically less sensitive for the detection of the troponin molecule.
   − Troponin is measurable above the limit of detection in <10% of the healthy population with POC devices.
   − POC assays are less analytically sensitive at earlier time points (<6 hours after the onset of symptoms) compared with highly sensitive and sensitive assays.

II. POC troponin assays are “clinically usable” based on a scorecard performance approach.

III. Both laboratory-based and POC troponin assays may be affected by analytical interferences including heterophilic antibodies, immunoglobulin complexes, fibrin clots, etc. These may interfere with troponin measurement in some assays and cause false-positive or false-negative values.

IV. POC troponin methods should be validated for clinical concordance, or at least compared against the local laboratory-based sensitive or highly sensitive troponin assay where patients may be referred. In this way POC results can be assessed against laboratory results, but not used for monitoring unless the differences are larger than the variation between assays.

V. Analytical performance specifications for POC troponins should ideally be driven by data coming from direct studies investigating the impact of analytical performance of the test on clinical outcomes related to the management of patients at risk of ACS; or, for practical reasons, from indirect outcome studies investigating the impact of analytical performance on clinical classification or decisions related to the management of ACS patients.

2.2 Preanalytical (sample collection and processing)

I. Troponin testing should only be performed by operators who have attained the required competency standards and where the POC system is accredited within a quality framework.

II. False negative and false positive troponin results due to micro-clots and haemolysis are relatively common in Emergency Department samples. Educational examples (Appendix 4) are available at the AACB website at: http://www.aacb.asn.au/resources/recommendations-for-use-of-troponin-poc
III. A general approach to reducing micro-clots is: Mix blood tubes immediately after collection to avoid formation of micro-clots that may not be visible on testing but which may cause incorrect troponin values.

IV. Avoid haemolysed samples by:
   − Use of trained collectors
   − Do not collect blood from the site of insertion of an intravenous cannula
   − Do not use very fine bore needles
   − Do not collect blood into syringe and then transfer it into a vacuum tube.

2.3 Postanalytical

2.3.1 Test name:
I. The naming of generations of troponin assays has been inconsistent and largely market-driven. Highly sensitive assays measure the same protein as the sensitive assays, and even more sensitive cardiac troponin assays will certainly be developed, thus making any ‘high sensitivity’ designation obsolete.

II. For the purpose of reporting of results, if the analytical performance of a new assay is significantly different from a previous troponin assay the test name should indicate this, e.g. ‘Troponin T – Highly sensitive’.

III. We recommend there is a general consensus in Australia regarding troponin test names for the same manufacturer’s assay to allow for harmonised reporting of troponin in the electronic medical record.

IV. Troponin results released from POC devices should be clearly differentiated from troponin results reported from the laboratory using an assay with different analytical sensitivity (e.g. ‘Troponin T – POC’ vs ‘Troponin T – Highly sensitive’).

2.3.2 Reporting units:
I. The international consensus is that troponin should be reported in ng/L unitage and expressed as whole numbers. Highly sensitive troponin assays generally use units of ng/L, whereas results from less sensitive assays have usually been reported in µg/L to two or more decimal points. As a consequence, the reporting of these more sensitive assays produces results that may be a thousand-fold different compared to results by other less sensitive assays, and thus has the potential for confusion and medical error, e.g. 4000 ng/L is 4.000 µg/L and 4 ng/L is 0.004 µg/L.

II. To improve patient safety we recommend that the clinical and laboratory communities standardise on troponin units of measurement in Australia namely “ng/L” and report values in whole numbers. This will allow for harmonised reporting of troponin in the electronic medical record.

2.3.3 Education to users about assay:
I. Various healthcare professionals request and measure troponin. It is essential that there is a comprehensive education process communicated to all users.

II. Supporting information detailing troponin assay utility and comparing the local assay to others in use should be provided.

III. General educational materials including a slide presentation of the recommendations and case studies are available on the AACB website at: http://www.aacb.asn.au/resources/recommendations-for-use-of-troponin-poc
2.4 Governance

2.4.1 Input from stakeholders:

I. Introduction of a more sensitive troponin assay requires close communication between the laboratory, Emergency Department, cardiologists, and other relevant clinicians. Ideally decisions regarding assay performance, clinical cut-off, and turnaround time of results should be decided on by all the stakeholders.

II. Discussion regarding the likelihood of the impact of a more sensitive assay on the increase in patients with elevated troponin and patient classifications is essential prior to assay implementation.

2.4.2 Audit and review of assay performance and clinical use:

I. There should be a review process to ensure ongoing performance and correct laboratory use of troponin assays.

II. Review by the site doing the assay is required to determine its performance, e.g. imprecision close to the troponin cut-off concentration.

III. Laboratories should collaborate with the clinical team and regularly review and audit the clinical use of the assay.

3. Literature references


1. Clinical Recommendations

I. This guideline provides recommendations for the use of POC Troponin test results in the management of ACS patients.

II. The following recommendations take into account the impact of the analytical performance of currently available Tn assays on their clinical use and interpretation. The recommendations regarding use of POC troponin assays are based on laboratory data showing that current POC assays are less analytically sensitive than most laboratory assays (labelled as ‘high sensitivity’ or ‘sensitive’ assays) for troponin.

III. There are many different assays available both for POC and laboratory-based troponin testing. Importantly, the results of various assays are NOT directly comparable and values CANNOT be transferred between assays unless there is evidence of such comparability.

IV. Clinical users of POC and laboratory-based troponin assays need to be aware of the limitations of the actual troponin assay used in the management of their patients in order to avoid adverse effects on patient management and for patient safety.

V. Troponin results must always be interpreted in the clinical context. Biomarkers are only one component of clinical information to be used with ECG(s) and clinical history for risk stratification according to clinical guidelines.\
- Elevated troponin results alone do not rule in the diagnosis of ACS as elevated troponin can occur in non-ACS conditions (causes of non-ACS troponin elevations are shown in Table 1).
- Normal troponin results (at 0 and 3 hours after admission of patient to the Emergency Department [ED]) do not rule out ACS where there is a high clinical suspicion; in such cases further troponin testing may be indicated at 6 hours or at 12 hours post admission to ED (slowly evolving AMIs may not elevate troponin until >12 hours after admission and unstable angina (UA) will not be detected).\
- Less sensitive troponin assays may require a longer time period to show a clinically significant elevation in troponin.

VI. Serial troponin measurements should be performed for all patients presenting to an ED with symptoms suggestive of ACS, unless the patient has been reliably ACS symptom-free for 12 hours when a single sample is appropriate.
- The reason a second sample has NOT been tested should be clearly justified and documented.
- The baseline should be the time of the first blood draw rather than from time of onset of symptoms.
- Recommended timing of samples using accelerated diagnostic pathways, using laboratory-based highly sensitive assays, is obtaining the first sample at admission to ED and the second sample at 2-3 hours later.
- In order to safely discharge patients from the ED, it is recommended when using less sensitive (e.g. POC) troponin assays that a sample is collected at 6-8 hours after the first blood draw. Few POC troponin assays have been studied and reported as part of an accelerated, integrated assessment process that includes a combination of clinical assessment, ECGs and POC troponin.

VII. Serial testing should be performed using the same troponin assay and platform. We recommend to re-baseline the troponin value for individual patients if transported to a different hospital location where a different troponin assay is used. Example scenarios are:
- Baseline troponin I done at presentation but second location uses troponin T assay, or vice versa;
- Baseline troponin I done by a POC device but second location uses a different laboratory-based troponin I assay or one with higher analytical sensitivity;
- Baseline troponin T done by a POC device but second location uses a different laboratory-based troponin T assay or one with higher analytical sensitivity.

At the second location collect a new baseline sample and a second sample at 2-3 hours (if testing with a highly sensitive troponin assay) and 6-8 hours (if testing with a less analytically sensitive assay) unless the patient has been symptom-free for >12 hours, when a single sample is appropriate.

VIII. In general quantitative troponin delta change has not been determined for use with POC assays as POC assays are less precise at low troponin concentration (see local algorithms for examples).

XI. When a laboratory is used, results should be available as soon as possible, with a goal of within 60 minutes after the sample is received in the laboratory. Otherwise POC testing could be considered although the laboratory-based troponin assay is the preferred testing option when available.

X. Local algorithms for use of POC troponin testing are shown in Appendix 2.

Table 1: Causes of elevated cardiac troponins

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<th>Causes of Elevated Cardiac Troponins</th>
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<tr>
<td>Acute Myocardial Infarction</td>
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<tr>
<td>Tachy or bradyarrhythmias</td>
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<td>Aortic dissection or severe aortic valve disease</td>
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<tr>
<td>Severe hypo or hypertension, e.g. haemorrhagic shock, hypertensive emergency</td>
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<tr>
<td>Acute or chronic heart failure</td>
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<tr>
<td>Hypertrophic cardiomyopathy</td>
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<td>Coronary vasculitis, e.g. SLE, Kawasaki syndrome</td>
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<tr>
<td>Coronary artery spasm, e.g. cocaine</td>
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<tr>
<td>Severe pulmonary embolism or pulmonary hypertension</td>
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<td>Dialysis dependent renal failure</td>
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2. Laboratory Recommendations

2.1 Analytical

I. It is the laboratory’s responsibility to inform clinicians the limitations of POC troponin vs. laboratory-based troponin assays in terms of analytical performance which impacts their clinical utility.
   - All current troponin POC assays are analytically less sensitive for the detection of the troponin molecule and troponin is measurable above the limit of detection in <10% of the healthy population with POC devices.
   - Studies using the i-STAT POC assay have shown that by lowering the decision cut-off to half of that of the 99th percentile troponin concentration of the reference population distribution that more AMIs are detected (example of analytical sensitivity of i-STAT cTnI POC vs. AccuTnI and Architect cTnI lab-based assays is shown in Figure 1). 13
   - Current POC assays are less diagnostically sensitive at earlier time points (<6 hours after the onset of symptoms) compared with highly sensitive and sensitive assays (see Figures 2-5).
   - The increased analytical sensitivity of highly sensitive assays allows for the second sample to be collected at an earlier time point.

II. Table 2 shows the analytical characteristics of commercial POC troponin assays declared by the manufacturer. Generally POC troponin assays are “clinically usable” based on a scorecard performance approach related to the management of patients at risk of ACS. 9 This means that imprecision at the 99th percentile troponin concentration is >10 % CV and ≤20 % CV. For example:
   - I-STAT POC Troponin I assay is clinically usable at a cut-off 0.04 µg/L with an imprecision of approx. 20 % CV reported (Pathology Queensland local data collated over several months).
   - AQT90 Troponin T assay is also “clinically usable” at a cut-off of 0.02 µg/L cTnT with an imprecision of 11 % CV (NSW Health Pathology local data).

III. All troponin assays should be verified for analytical imprecision using the manufacturer’s QC and ideally, also, a low concentration QC sample or patient pool at close to the 99th percentile cTn concentration. Figures 6A-E show the analytical imprecision that can be obtained close to the 99th percentile cTn concentration for the highly sensitive hs-TnT and hs-TnI assays vs. POC troponin assays.
   - Note that the laboratory-based highly sensitive Roche hs-TnT (Fig. 6A) and Abbott Architect hs-TnI (Fig. 6B) assays have lower imprecision than the three POC troponin assays, AQT90 Troponin I (Fig. 6C), AQT90 Troponin T (Fig. 6D) and i-STAT cTnI (Fig. 6E).
   - Regarding imprecision of highly sensitive troponin assays over a multiple number of analysers, Saenger et al. reported hs-TnT precision on 11 Roche Elecsys and Cobas analysers over 21 days at 14 ng/L (2SD: 3 ng/L)15; Kavsak et al. reported hs-TnI precision for 4 Architect analysers over 12 months at 5 ng/L (2SD: 2 ng/L), and at 36 ng/L (2SD: 6 ng/L) [Table 3]. 16
   - For POC troponin assays less long term precision information is available at concentrations close to or below the 99th percentile concentration. Local precision data using one AQT90 analyser are: cTnT at 44 ng/L (2SD: 7 ng/L) and cTnI at 36 ng/L (2SD: 7 ng/L) [Table 3]. Using 7 i-STAT analysers and 12 cartridge reagent lots over 14 weeks, the QC with a mean cTnI of 0.41 µg/L gave 2SD of 0.06 µg/L.

IV. Both laboratory-based and POC troponin assays may be affected by analytical interferences including heterophilic antibodies, immunoglobulin complexes, fibrin clots, etc. These may interfere with troponin measurement in some assays and cause false-positive or false-negative values.

V. POC troponin methods should be validated for clinical concordance, or at least compared against the local laboratory-based sensitive or highly sensitive troponin assay where patients may be referred. In this way POC results can be assessed against laboratory results, but not used for monitoring unless the differences are larger than the variation between assays.
VI. Analytical performance specifications for POC troponins should ideally be driven by data coming from direct studies investigating the impact of analytical performance of the test on clinical outcomes related to the management of patients at risk of ACS; or from indirect outcome studies investigating the impact of analytical performance on clinical classification or decisions related to the management of ACS patients.

VII. Appendix 3 shows diagnostic sensitivity and specificity for troponin POC and high sensitive studies reported in recent literature.

2.2 Preanalytical (sample collection and processing)

I. Troponin testing should only be performed by operators who have attained the required competency standards and where the POC system is accredited within a quality framework.

I. False negative and false positive troponin results due to micro-clots and haemolysis are relatively common in Emergency Department samples. Note false positives are reported to occur in some POC studies. Ter Avesta et al. reported that 3/261 samples tested by AQT90 Troponin T assay were false positive. Local studies confirm that false positive results occur on AQT 90, i-STAT and h232 analysers at a frequency of an average of 2 per 300 samples most likely due to pre-analytical sample handling (local data from NSW Health, Pathology Queensland, iCCnet SA). Refer to Appendix 4 for case studies which are available at the AACB website at: http://www.aacb.asn.au/resources/recommendations-for-use-of-troponin-poc

II. A general approach to reducing micro-clots is: Mix blood tubes immediately after collection to avoid formation of micro-clots that may not be visible on testing but which may cause incorrect troponin values.

III. Avoid haemolysed samples by:

− Use of trained collectors
− Do not collect blood from the site of insertion of an intravenous cannula
− Do not use very fine bore needles
− Do not collect blood into syringe and then transfer it into a vacuum tube.

2.3 Postanalytical

2.3.1 Test name:

I. The naming of generations of troponin assays has been inconsistent and largely market-driven. Highly sensitive assays measure the same protein as the sensitive assays, and even more sensitive cardiac troponin assays will certainly be developed, thus making any ‘high sensitivity’ designation obsolete.

II. For the purpose of reporting of results, if the analytical performance of a new assay is significantly different from a previous troponin assay the test name should indicate this, e.g. ‘Troponin T – Highly sensitive’.

III. We recommend there is a general consensus in Australia regarding troponin test names for the same manufacturer’s assay to allow for harmonised reporting of troponin in the electronic medical record.

IV. Troponin results released from POC devices should be clearly differentiated from troponin results reported from the laboratory using an assay with different analytical sensitivity (e.g. ‘Troponin T – POC’ vs ‘Troponin T – Highly sensitive’).
2.3.2 Reporting units:

I. The international consensus is that troponin should be reported in ng/L (or pg/mL) unitage and expressed as whole numbers. In Australasia highly sensitive troponin assays generally use units of ng/L, whereas results from less sensitive assays have usually been reported in µg/L to two or more decimal points. As a consequence, the reporting of these more sensitive assays produces results that may be a thousand-fold different compared to results by other less sensitive assays, and thus has the potential for confusion and medical error, e.g. 4000 ng/L is 4.000 µg/L and 4 ng/L is 0.004 µg/L.

II. To improve patient safety we recommend that the clinical and laboratory communities standardise on troponin units of measurement in Australia namely “ng/L” and report values in whole numbers. This will allow for harmonised reporting of troponin in the electronic medical record.

2.3.3 Education to users about assay: 

I. Various healthcare professionals request and measure troponin. It is essential that there is a comprehensive education process communicated to all users.

II. Supporting information detailing troponin assay utility and comparing the local assay to others in use should be provided.

III. General educational materials including a slide presentation of the recommendations and case studies are available on the AACB website at: http://www.aacb.asn.au/resources/recommendations-for-use-of-troponin-poc

2.4 Governance

2.4.1 Input from stakeholders: 

I. Introduction of a more sensitive troponin assay requires close communication between the laboratory, Emergency Department, cardiologists, and other relevant clinicians. Ideally decisions regarding assay performance, clinical cut-off, and turnaround time of results should be decided on by all the stakeholders.

II. Discussion regarding the likelihood of the impact of a more sensitive assay on the increase in patients with elevated troponin and patient classifications is essential prior to assay implementation.

2.4.2 Audit and review of assay performance and clinical use: 

I. There should be a review process to ensure ongoing performance and correct laboratory use of troponin assays.

II. Review by the site doing the assay is required to determine its performance, e.g. imprecision close to the troponin cut-off concentration.

III. Laboratories should collaborate with the clinical team and regularly review and audit the clinical use of the assay.
Table 2: Analytical characteristics of commercial Point-of-Care troponin (cTn) assays declared by the manufacturer (modified from IFCC troponin table) 18

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<tr>
<th>Commercial cTn Assays: Company/platform(s)/assay</th>
<th>LoB (µg/L)</th>
<th>LoD (µg/L)</th>
<th>99th % (µg/L)</th>
<th>% CV at 99th per.</th>
<th>10 % CV (µg/L)</th>
<th>Acceptance criterion (^a)</th>
</tr>
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<tbody>
<tr>
<td>Abbott i-STAT cTnI</td>
<td>0.02</td>
<td>0.08</td>
<td>16.5</td>
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<td>Alere Triage Cardio 3 cTnI</td>
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<td>Radiometer AQT90 TnI</td>
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<td>12.3</td>
<td>0.027</td>
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<tr>
<td>Radiometer AQT90 TnT</td>
<td>0.0080</td>
<td>0.017</td>
<td>15.2</td>
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<tr>
<td>Roche Cobas h232 TnT</td>
<td>0.05</td>
<td>NAD(^b)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>Clinically usable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Commercial cTn Assays: Company/platform(s)/assay</th>
<th>LoB (ng/L)</th>
<th>LoD (ng/L)</th>
<th>99th % (ng/L)</th>
<th>% CV at 99th per.</th>
<th>10 % CV (ng/L)</th>
<th>Acceptance criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott i-STAT cTnI</td>
<td>Analyser values are only given in µg/L not ng/L</td>
<td></td>
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<tr>
<td>Alere Triage Cardio 3 cTnI</td>
<td>2</td>
<td>10</td>
<td>22</td>
<td>17.0</td>
<td>37</td>
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<tr>
<td>Radiometer AQT90 TnI</td>
<td>9.5</td>
<td>23</td>
<td>12.3</td>
<td>12.3</td>
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<td>Clinically usable</td>
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<tr>
<td>Radiometer AQT90 TnT</td>
<td>8</td>
<td>17</td>
<td>15.2</td>
<td>15.2</td>
<td>26</td>
<td>Clinically usable</td>
</tr>
<tr>
<td>Roche Cobas h232 TnT</td>
<td>50</td>
<td>NAD(^b)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>Clinically usable</td>
</tr>
</tbody>
</table>

LoB, limit of blank; LoD, limit of detection determined according to CLSI EP17-A guideline; NAD, the 99th percentile (per.) concentration of the troponin value distribution of a reference population is indeterminate; NA, data are not available; \(^a\) Acceptance criterion: % CV at 99th percentile: guideline acceptable ≤10 %; clinically usable >10 to ≤20 %; not acceptable >20 %; \(^b\) Cobas h232 TnT next generation assay to be introduced in 2016 has a LoD of 40 ng/L and CV of 10.7 % at 63 ng/L (personal communication, RT, PS).

NB: The international consensus is that troponin should be reported in ng/L (or pg/mL) unitage and expressed as whole numbers. This issue requires further harmonisation in Australasia.
Figure 1: Analytical sensitivity of POC troponin I assay (i-Stat) and sensitive troponin I assays (Beckman Coulter AccuTnI and Abbott Architect cTnI).
A new 0.04 µg/L (40 ng/L) i-Stat cut-off is presented by the horizontal lines. The vertical lines present the 99th percentile cut-off values of the comparative methods; N=172 (data are from Pathology Queensland study). Even at the lowered i-Stat cut-off, a number of samples will have a negative i-Stat result and a positive laboratory cTnI (i.e. false negatives by POC testing; also see Schneider et al. 13).
Figure 2: Serial troponin measurements by POC assays compared with high sensitive hs-TnT assay and diagnostic sensitivity for 806 patients presenting to Chest Pain Centre (South Australia) with symptoms suggestive of ACS. A positive result for AMI was defined as the baseline and/or the second time point giving a result above the 99th percentile of the assay.

![Sensitivity Graph](image)

Figure 3: Serial troponin measurements by POC assays compared with high sensitive hs-TnT assay and diagnostic specificity for 806 patients presenting to Chest Pain Centre (South Australia) with symptoms suggestive of ACS. A positive result for AMI was defined as the baseline and/or the second time point giving a result above the 99th percentile of the assay. Note that the diagnostic specificity and Positive Predictive Value are higher for hs-TnT when a cTnT value above the 99th percentile combined with a delta cTnT change of ≥7 ng/L is used, in keeping with the Universal Definition of AMI guidelines, which requires there be a rise and/or fall of cTn over time (see Appendix 3).

![Specificity Graph](image)
Figure 4: Serial troponin measurements by POC assays compared with high sensitive hs-TnT assay. Negative Predictive Value for 806 patients presenting to Chest Pain Centre (South Australia) with symptoms suggestive of ACS. A positive result for AMI was defined as the baseline and/or the second time point giving a result above the 99th percentile of the assay.

Figure 5: Serial troponin measurements by POC assays compared with high sensitive hsTnT assay. Positive Predictive Value for 806 patients presenting to Chest Pain Centre (South Australia) with symptoms suggestive of ACS. A positive result for AMI was defined as the baseline and/or the second time point giving a result above the 99th percentile of the assay. Note that the diagnostic specificity and Positive Predictive Value are higher for hs-TnT when a cTnT value above the 99th percentile combined with a delta cTnT change of ≥7 ng/L is used, in keeping with the Universal Definition of AMI guidelines, which requires there be a rise and/or fall of cTn over time (see Appendix 3).
**Figures 6A-E:** Precision of high sensitive troponin (hs-cTn) and POC cTn assays determined close to the 99th percentile cTn concentration. Laboratory data and manufacturer’s data are plotted vs. the analytical imprecision (2SD) determined from replicate measurements of patient sample pools. Depending on the cTn concentration of pools, linear regression slopes may vary between laboratory and manufacturer’s data; only data close to the 99th percentile cTn concentration are shown. Dotted lines represent the imprecision (2SD) at the 99th percentile determined from the laboratory data. Note that the laboratory-based high sensitive Roche hs-TnT (Fig. 6A) and Abbott Architect hs-TnI (Fig. 6B) assays have lower analytical imprecision than the three POC cTn assays, AQT90 Troponin I (Fig. 6C), AQT90 Troponin T (Fig. 6D) and i-STAT cTnI (Fig. 6E). POC cTn assays when tested by routine laboratories gave comparable precision to that specified by the manufacturer, i.e., they are ‘fit for purpose’.

**Roche hs-TnT Assay**
Manufacturer’s data: 99th percentile 14.0 ng/L; imprecision (2SD) is 2.8 ng/L. Laboratory data: imprecision (2SD) at 14.0 ng/L is 2.5 ng/L. On repeat analysis, 14.0 ng/L cTnT by hs-TnT is from 11.5 to 16.5 ng/L. Assay is fit for purpose.

**Abbott hs-TnI Assay**
Manufacturer’s data: 99th percentile 26.2 ng/L; imprecision (2SD) is 2.1 ng/L. Laboratory data: imprecision (2SD) at 26.2 ng/L is 2.3 ng/L. On repeat analysis, 26.2 ng/L cTnI by hs-TnI is from 23.9 to 28.5 ng/L. Assay is fit for purpose.
Radiometer AQT90 Troponin T Assay
Manufacturer's data: 99th percentile 17 ng/L; imprecision (2SD) is 5 ng/L.
Laboratory data: imprecision (2SD) at 20 ng/L cTnT is 4 ng/L.
On repeat analysis, 20 ng/L cTnT is from 16 to 24 ng/L.
Assay is fit for purpose.

Radiometer AQT90 Troponin I Assay
Manufacturer's data: 99th percentile 23 ng/L; imprecision (2SD) is 6 ng/L.
Laboratory data: imprecision (2SD) at 23 ng/L is 5 ng/L.
On repeat analysis, 23 ng/L cTnI is from 18 to 28 ng/L.
Assay is fit for purpose.

Abbott i-STAT Troponin I Assay
Manufacturer's data: 99th percentile 0.08 µg/L; imprecision (2SD) is 0.03 µg/L.
Laboratory data: imprecision (2SD) at 0.04 µg/L cTnI is 0.01 ng/L.
On repeat analysis, 0.04 µg/L cTnI is from 0.03 to 0.05 µg/L.
Assay is fit for purpose.
Note that the present i-STAT assay reports only in µg/L to 2 decimal places.
<table>
<thead>
<tr>
<th>Assay (unit)</th>
<th>Manufacturer/analyser(s)</th>
<th>Precision for serum pools or manufacturers’ quality controls (QC)</th>
<th>Notes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-TnT (ng/L)</td>
<td>Roche Elecsys 2010/cobas e 411 /E 170 / cobas e 601</td>
<td>LOW serum pool: CV range at 14.2 ng/L: 2.9% - 10.7% (2SD: 0.8 - 3.0 ng/L)</td>
<td>CV: 6.0% - 10.7% (2SD: 1.7-3.0 ng/L)</td>
<td>Multi-site study of 8 labs and 11 analysers; up to 3 reagent lots used; study conducted over 21 days with 4 calibrations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- E 2010 (N=5 analysers)</td>
<td>CV: 6.0% - 10.7% (2SD: 1.7-3.0 ng/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- E 170 (N=3 analysers)</td>
<td>CV: 2.9% - 5.8% (2SD: 0.8-1.7 ng/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- e 411 (N=2 analysers)</td>
<td>CV: 5.7% - 9.3% (2SD: 1.6-2.6 ng/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- e 601 (N=1 analyser)</td>
<td>CV: 3.9% (2SD: 1.1 ng/L)</td>
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<tr>
<td>hs-TnT (ng/L)</td>
<td>Roche Elecsys 2010</td>
<td>LOW QC (N=91): Mean 26.5 (2SD: 3.7) ng/L;</td>
<td>CV 7.0%</td>
<td>One site; more than one reagent lot and calibrator lot used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIGH QC (N=91): Mean 2053 (2SD: 193) ng/L;</td>
<td>CV 4.7%</td>
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</tr>
<tr>
<td>hs-Tnl (ng/L)</td>
<td>Abbott Architect 4100/ 8200/ 16200 STAT</td>
<td>LOW serum pool (N= 495 - 831):</td>
<td>Mean 4.7 (2SD: 1.8) ng/L;</td>
<td>CV 19%</td>
</tr>
<tr>
<td></td>
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<td>- 4100 (N=1 analyser): Mean 4.7 (2SD: 1.8) ng/L;</td>
<td>CV 19%</td>
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<tr>
<td></td>
<td></td>
<td>- 8200 (N=1 analyser): Mean 4.2 (2SD: 1.3) ng/L;</td>
<td>CV 15%</td>
<td></td>
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<tr>
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<td></td>
<td>- 16200 (N=2 analysers): Mean 5.0 (2SD: 1.5) ng/L;</td>
<td>CV 15%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>MEDIUM serum pool (N= 498 - 842):</td>
<td>Mean 36.8 (2SD: 5.9) ng/L;</td>
<td>CV 8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 4100 (N=1 analyser): Mean 36.8 (2SD: 5.9) ng/L;</td>
<td>CV 8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 8200 (N=1 analyser): Mean 36.0 (2SD: 5.8) ng/L;</td>
<td>CV 8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 16200 (N=2 analysers): Mean 36.0 (2SD: 5.0) ng/L;</td>
<td>CV 7%</td>
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<tr>
<td>cTnT (ng/L)</td>
<td>Radiometer AQT90 FLEX TnT</td>
<td>LOW QC (N=143): Mean 43.5 (2SD: 6.8) ng/L;</td>
<td>CV 7.9%</td>
<td>One site; more than one reagent lot and calibrator lot used</td>
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<tr>
<td></td>
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<td>MEDIUM QC (N=144): Mean 643 (2SD: 67) ng/L;</td>
<td>CV 5.2%</td>
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<tr>
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<td></td>
<td>HIGH QC (N=137): Mean 9947 (2SD: 1200) ng/L;</td>
<td>CV 6.0%</td>
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<tr>
<td>cTnl (ng/L)</td>
<td>Radiometer AQT90 FLEX Tnl</td>
<td>LOW QC (N=140): Mean 36.0 (2SD: 7.2) ng/L;</td>
<td>CV 10.1%</td>
<td>One site; more than one reagent lot and calibrator lot used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEDIUM QC (N=132): Mean 303 (2SD: 28) ng/L;</td>
<td>CV 4.6%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>HIGH QC (N=132): Mean 1364 (2SD: 121) ng/L;</td>
<td>CV 4.4%</td>
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<tr>
<td>cTnl (µg/L)</td>
<td>Abbott i-STAT</td>
<td>QC (N=21): Mean 0.41 (2SD: 0.06) µg/L;</td>
<td>CV 7.2%</td>
<td>Seven sites; 12 cartridge lots used; QC assayed at each site 3 times over 14 weeks</td>
</tr>
</tbody>
</table>
Appendix 1: Methods for developing the recommendations

Membership of the AACB Troponin Point-of-Care Working Party:
Rosy Tirimacco, Jill Tate, Paul Simpson, Andrea Rita Horvath, Louise Cullen, Fernando San Gil, Cameron Martin, Gus Koerbin, Phil Tideman

The recommendations have been conceived through a consensus process by a group of experts who have included an Emergency Physician (LC), a Cardiologist (PT), a Pathologist (RH), and Scientists (GK, CM, FSG, PS, JT, RT) who routinely analyse and use troponin testing at the POC and in the routine laboratory. There was no IVD Industry involvement in deriving the recommendations.

The recommendations were developed after reviewing the relevant evidence available in the literature up to December 2015 (Appendix 3 shows the diagnostic sensitivity and specificity of troponin POC studies from the recent literature) and by examining the results of a recent 2014-2015 clinical trial of patients presenting to the Chest Pain Centre in South Australia. This study investigated the clinical utility of POC troponin (Roche Cobas h232, Radiometer AQT90 Troponin T and Troponin I) versus high sensitivity laboratory troponin (hs-TnT).

Strength of recommendations:
The local clinical trial data verify the findings of the literature and add strength to the recommendations for serial testing and the timing of samples for current POC assays. The literature and trial data on POC troponin testing strongly support the recommendation that using current POC assays patients presenting with symptoms of ACS cannot be excluded at early time points, unlike the use of high sensitive troponin assays (see Figures 2-5).

Next update of document:
The next update is due in 3 years (2018) or earlier if new evidence becomes available that warrants review and modification of the recommendations.

Conflicts of Interest:
LC – Has received research support and speakers fees from Alere, Abbott Diagnostics, Beckman Coulter, Roche, Radiometer Pacific, and Siemens.
RH – Roche Diagnostics and Radiometer Australia have partially funded the troponin trial performed in NSW.
GK – Has received research support from Abbott Diagnostics.
CM – none
FSG – none
PS – Roche Diagnostics and Radiometer Australia funded the troponin trial performed in SA.
JT – none
PT - Roche Diagnostics and Radiometer Australia funded the troponin trial performed in SA.
RT - Roche Diagnostics and Radiometer Australia funded the troponin trial performed in SA.
The following organisations and individuals have reviewed and/or commented on the public consultation draft of the recommendations:

- Australasian Association of Clinical Biochemists (AACB)
- Royal College of Pathologists of Australasia (RCPA)
- Australasian College of Emergency Medicine (ACEM) – Council of Advocacy, Practice and Partnerships
- The Integrated Cardiovascular Clinical Network CHSA
- New South Wales Health Pathology
- Pathology Queensland
- Dr Grahame Caldwell (Private Pathology)
- Dr Matthew Bragg (ED Director, Bowral and District Hospital, NSW Cardiac Network)
- The Cardiac Society of Australia and New Zealand (CSANZ) – Quality Standards Committee

The comments received have been reviewed and answered by the guideline development group (accessible at: http://www.aacb.asn.au/resources/recommendations-for-use-of-troponin-poc) and the final recommendations include all relevant suggestions. The final draft of the recommendations has been endorsed by the above organisations.

DISCLAIMER:

The Australasian Association of Clinical Biochemists (AACB) and the Royal College of Pathologists of Australasia (RCPA) have developed these recommendations as a tool to assist laboratories in the reporting and management of high risk results. Each recommendation includes indicators of the strength of the recommendation ("needs to", "should" and "may"), which reflect the consensus views of the expert working party. The use of these recommendations is subject to the judgement of individual laboratory practices.

The AACB and RCPA have made all reasonable efforts to ensure the quality of the recommendations. However subject to any warranties, terms or conditions which may be implied by law and which cannot be excluded, the recommendations are provided on an "as is" basis. The AACB and RCPA do not warrant or represent that the recommendations are complete, accurate, error-free, or up-to-date for all possible clinical scenarios or local circumstances. Users are responsible for evaluating the suitability, accuracy, currency, completeness and fitness for purpose of the recommendations. Any decision not to follow these recommendations and the settings where this applies should be documented by the laboratory.

Except as set out in this paragraph, the AACB and RCPA exclude: (i) all warranties, terms and conditions relating in any way to; and (ii) all liability (including for negligence) in respect of any loss or damage (including direct, special, indirect or consequential loss or damage, loss of revenue, loss of expectation, unavailability of systems, loss of data, personal injury or property damage) arising in any way from or in connection with the recommendations or any use thereof. Where any statute implies any term, condition or warranty in connection with the provision or use of the recommendations, and that statute prohibits the exclusion of that term, condition or warranty, then such term, condition or warranty is not excluded. To the extent permitted by law, the AACB and RCPA’s liability under or for breach of any such term, condition or warranty is limited to the resupply or replacement of services or goods.

December 2016
Appendix 2: Local Algorithms for Point-of-Care Troponin Testing

The intent of the local algorithms is to provide information and they are only meant as a guide. The Working Party notes that there are differences between algorithms at present, for example reporting units, decision limits, etc.

ICCnet (Country Health South Australia) and NSW Health Pathology

### AQT Troponin T Testing Protocol

To be used with the Acute Coronary Syndrome Assessment and Treatment Guidelines

- Troponin T on presentation
  - >17 ng/L
  - ≤17 ng/L
- Time >6 hours: Repeat Troponin T
  - >17 ng/L
  - ≤17 ng/L
- High-risk ACS
- Clinical Assessment

### Causes of elevated cardiac troponins

- Acute Myocardial Infarction
- Tachy or bradyarrhythmias
- Aortic dissection or severe aortic valve disease
- Severe hypo or hypertension, eg haemorrhagic shock, hypertensive emergency
- Acute or chronic heart failure
- Hypertrophic cardiomyopathy
- Coronary vasculitis, eg SLE, Kawasaki synd.
- Coronary artery spasm, eg cocaine
- Severe pulmonary embolism or pulmonary hypertension
- Dialysis dependent renal failure
- Cardiac Contusion or surgery
- Rhabdomyolysis with cardiac involvement
- Myocarditis, severe sepsis
- Cardiotoxic agents, eg anthracyclines, CO poisoning
- Severe burns affecting >30% body surface
- Severe acute neurological conditions, eg stroke, trauma
- Infiltrative diseases, eg amyloidosis, sarcoidosis
- Extreme exertion, eg marathon running
- Frequent defibrillator Shocks
AQT Troponin I Testing Protocol
To be used with the Acute Coronary Syndrome Assessment and Treatment Guidelines

Troponin I on presentation

>23 ng/L

≤23 ng/L

Time >6 hours: Repeat Troponin I

>23 ng/L

≤23 ng/L

High-risk ACS

Clinical Assessment

Causes of elevated cardiac troponins
- Acute Myocardial Infarction
- Tachy or bradyarrhythmias
- Aortic dissection or severe aortic valve disease
- Severe hypo or hypertension, eg haemorrhagic shock, hypertensive emergency
- Acute or chronic heart failure
- Hypertrophic cardiomyopathy
- Coronary vasculitis, eg SLE, Kawasaki synd.
- Coronary artery spasm, eg cocaine
- Severe pulmonary embolism or pulmonary hypertension
- Dialysis dependent renal failure
- Cardiac Contusion or surgery
- Rhabdomyolysis with cardiac involvement
- Myocarditis, severe sepsis
- Cardiotoxic agents, eg anthracyclines, CO poisoning
- Severe burns affecting >30% body surface
- Severe acute neurological conditions, eg stroke, trauma
- Infiltrative diseases, eg amyloidosis, sarcoidosis
- Extreme exertion, eg marathon running
- Frequent defibrillator Shocks
Abbott i-STAT Troponin I Testing Protocol
To be used with Acute Coronary Syndrome Assessment and Treatment Guidelines

TnI on presentation (Time 1)

>0.04 µg/L

≤0.04 µg/L

Repeat i-STAT TnI: Collect second sample at 3-6 hours after presentation (Time 2)

High-risk stratification

TnI >0.04 µg/L WITH a typical rise and/or fall of TnI.
“Change (Delta TnI)”: TnI (Time 2 – Time 1) is ≥0.02 µg/L at ≤0.10 µg/L, or >20% at >0.10 µg/L

No

AMI not likely

Yes

Clinical assessment and further TnI testing if AMI suspected

Notes about the i-STAT method
• At the 0.04 µg/L cut off the i-STAT TnI has a precision of approximately 16.5% CV.
• At the 0.08 µg/L cut off the CV is verified 10% by the manufacturer.
• At the current time the i-STAT instrument can only report in µg/L.
• “Change (Delta TnI)” consistent with an acute change in TnI is: >20% at above 0.10 µg/L TnI and ≥0.02 µg/L at 0.10 µg/L and below [Pretorius CJ et al. Eur Heart J Acute Cardiovasc Care. 2014 Jun;3(2):149-57].

Causes of elevated cardiac troponins
• Acute Myocardial Infarction
• Tachy or bradyarrhythmias
• Aortic dissection or severe aortic valve disease
• Severe hypo or hypertension, eg haemorrhagic shock, hypertensive emergency
• Acute or chronic heart failure
• Hypertrophic cardiomyopathy
• Coronary vasculitis, eg SLE, Kawasaki synd.
• Coronary artery spasm, eg cocaine
• Severe pulmonary embolism or pulmonary hypertension
• Dialysis dependent renal failure
• Cardiac Contusion or surgery
• Rhabdomyolysis with cardiac involvement
• Myocarditis, severe sepsis
• Cardiotoxic agents, eg anthracyclines, CO poisoning
• Severe burns affecting >30% body surface
• Severe acute neurological conditions, eg stroke, trauma
• Infiltrative diseases, eg amyloidosis, sarcoidosis
• Extreme exertion, eg marathon running
• Frequent defibrillator Shocks

Cameron Martin – Pathology Queensland -Statewide Point of Care 07 3646 8426

December 2016
Cobas h232 Troponin T Testing Protocol
To be used with the Acute Coronary Syndrome Assessment and Treatment Guidelines

Troponin T on presentation
>100 ng/L
50-100 ng/L
<50 ng/L

Time 8-12 hours: Repeat Troponin T
>100 ng/L
50-100 ng/L
<50 ng/L

High-risk ACS
Consider for high-risk ACS. Further investigation required
Clinical Assessment

Causes of elevated cardiac troponins
- Acute Myocardial Infarction
- Tachy or bradyarrhythmias
- Aortic dissection or severe aortic valve disease
- Severe hypo or hypertension, eg haemorrhagic shock, hypertensive emergency
- Acute or chronic heart failure
- Hypertrophic cardiomyopathy
- Coronary vasculitis, eg SLE, Kawasaki synd.
- Coronary artery spasm, eg cocaine
- Severe pulmonary embolism or pulmonary hypertension
- Dialysis dependent renal failure
- Cardiac Contusion or surgery
- Rhabdomyolysis with cardiac involvement
- Myocarditis, severe sepsis
- Cardiotoxic agents, eg anthracyclines, CO poisoning
- Severe burns affecting >30% body surface
- Severe acute neurological conditions, eg stroke, trauma
- Infiltrative diseases, eg amyloidosis, sarcoidosis
- Extreme exertion, eg marathon running
- Frequent defibrillator Shocks
## Appendix 3: Diagnostic sensitivity and specificity for Point-of-Care (POC) and high sensitive troponin (cTn) studies from the recent literature

<table>
<thead>
<tr>
<th>cTn Assay</th>
<th>Subject group</th>
<th>Sample collection timing</th>
<th>cTn decision limit</th>
<th>Decision criteria</th>
<th>Outcome parameter</th>
<th>Study sensitivity (95% CI) (%)</th>
<th>Study specificity (95% CI) (%)</th>
<th>Study PPV (95% CI) (%)</th>
<th>Study NPV (95% CI) (%)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alere Cardio3</td>
<td>960 patients presenting to ED, non-traumatic chest pain; 220 (22.9%) AMI (196 NSTEMI)</td>
<td>0h and 2h post presentation</td>
<td>99th perc. = 20 ng/L (no CV given)</td>
<td>Architect cTnI 28 ng/L; 0h &amp; 6-12h; ADP clinical pathway</td>
<td>MACE 30d</td>
<td>0h: 87.7 (83.6-91.1)</td>
<td>0h: 93.1 (91.9-94.1)</td>
<td>0h: 79.1 (75.3-82.1)</td>
<td>0h: 96.2 (95.0-97.3)</td>
<td>Aldous et al.</td>
</tr>
<tr>
<td>POC cTnI</td>
<td></td>
<td></td>
<td></td>
<td>Cardio3 0h vs 2h</td>
<td></td>
<td>2h: 93.6 (89.9-96.2)</td>
<td>2h: 90.2 (89.0-90.9)</td>
<td>2h: 73.8 (70.9-75.9)</td>
<td>2h: 98.0 (96.7-98.8)</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>As above then</td>
<td></td>
<td>0h: 99 (98.0-100)</td>
<td>19.0 (18.4-19.0)</td>
<td>28.1 (27.5-28.1)</td>
<td>100 (96.7-100)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>As above then</td>
<td></td>
<td>100 (95.4-99.4)</td>
<td>37.3 (36.5-37.7)</td>
<td>33.1 (32.2-33.5)</td>
<td>98.6 (96.2-99.5)</td>
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<tr>
<td>Alere Cardio3</td>
<td>858 (of 1107) patients presenting to ED with suspected ACS. Serial measurements were tested in 18 EDs (MIDAS study - 9.6% AMI)</td>
<td>0h, 90 min, 3h, 6h (680 of 858 patients had complete data across all 4 times)</td>
<td>99th perc. = 0.05 ug/L</td>
<td>cTnI and cTnT assays with varying local decision limits; AHA/ACC criteria for AMI</td>
<td>None given</td>
<td>3h: 84.1 (74.4-91.3)</td>
<td>3h: 93.4 (91.4-95.1)</td>
<td>3h: 57.5 (48.1-66.5)</td>
<td>3h: 98.2 (97.0-99.1)</td>
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<td>POC cTnI</td>
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<td>Architect cTnI 28 ng/L; 0h &amp; 6-12h; ADP clinical pathway</td>
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<td>6h: 87.5 (77.9-93.3)</td>
<td>6h: 92.6 (90.2-94.4)</td>
<td>6h: 58.3 (48.9-67.2)</td>
<td>6h: 98.4 (97.0-99.2)</td>
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<td>Architect hs-TnI 0h vs 2h</td>
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<td>99.0 (94.4-99.4)</td>
<td>3h: 93.4 (91.4-95.1)</td>
<td>3h: 57.5 (48.1-66.5)</td>
<td>3h: 98.2 (97.0-99.1)</td>
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<td>Architect hs-TnI 2h +ECG + TIMI score cut-off of 0</td>
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<td>28.1 (27.5-28.1)</td>
<td>33.1 (32.2-33.5)</td>
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<td>100 (98.0-100)</td>
<td>19.0 (18.4-19.0)</td>
<td>28.1 (27.5-28.1)</td>
<td>100 (96.7-100)</td>
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<td>As above then</td>
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<td>98.3 (95.4-99.4)</td>
<td>37.3 (36.5-37.7)</td>
<td>33.1 (32.2-33.5)</td>
<td>98.6 (96.2-99.5)</td>
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<td>Abbott</td>
<td>960 patients presenting to ED, non-traumatic chest pain; 220 (22.9%) AMI (196 NSTEMI)</td>
<td>0h and 2h post presentation</td>
<td>99th perc. = 26.2 ng/L (4.7% CV)</td>
<td>Architect cTnI 28 ng/L; 0h &amp; 6-12h; ADP clinical pathway</td>
<td>MACE 30d</td>
<td>0h: 90.0 (86.1-93.1)</td>
<td>0h: 93.9 (92.8-94.8)</td>
<td>0h: 81.5 (77.9-84.3)</td>
<td>0h: 96.9 (95.7-97.9)</td>
<td>Aldous et al.</td>
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<td>2h: 95.0 (91.5-97.3)</td>
<td>2h: 92.5 (91.4-93.1)</td>
<td>2h: 78.9 (76.0-80.7)</td>
<td>2h: 98.4 (97.3-99.1)</td>
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<td>Architect cTnI 28 ng/L; 0h &amp; 6-12h; ADP clinical pathway</td>
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<td>100 (98.0-100)</td>
<td>19.7 (19.1-19.7)</td>
<td>28.2 (27.7-28.2)</td>
<td>100 (96.8-100)</td>
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<td>Architect hs-TnI 2h +ECG + TIMI score cut-off of 0</td>
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<td>98.7 (96.0-919.7)</td>
<td>38.9 (38.0-39.2)</td>
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<td>99.0 (96.8-99.7)</td>
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<td>Medience</td>
<td>169 patients presenting with symptoms of ACS; 19 (11.2%) AMI</td>
<td>0h, 3h and 6h post- presentation</td>
<td>99th perc. = 29 ng/L (5% CV)</td>
<td>MI according to 2007 Universal Definition of MI; &gt;99th clinical symptoms of ischaemia; 1 cTn &gt;99th perc. (Vitros cTnI)</td>
<td>None given</td>
<td>0h: 53 (29-76)</td>
<td>0h: 86 (79-91)</td>
<td>0h: 32 (17-51)</td>
<td>0h: 93 (88-97)</td>
<td>Palamalai et al.</td>
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<td>Pathfast (POC)</td>
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<td>3h: 89 (67-100)</td>
<td>3h: 82 (84-94)</td>
<td>3h: 39 (28-66)</td>
<td>3h: 98 (91-98)</td>
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<td>cTnI</td>
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<td>6h: 95 (74-100)</td>
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<td>6h: 99 (96-100)</td>
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<td>Max: 95 (74-100)</td>
<td>Max: 78 (71-84)</td>
<td>Max: 35 (22-50)</td>
<td>Max: 99 (95-100)</td>
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</table>
| Radiometer AQT90 (POC) cTnI | 169 patients presenting with symptoms of ACS; 19 (11.2%) AMI | 0h, 3h and 6h post-presentation | 99th perc. = 23 ng/L (17% CV) | assay 34 ng/L | None given | 0h: 26 (9-51) | 3h: 63 (38-84) | Max: 68 (43-97) | 0h: 93 (87-96) | 3h: 91 (85-95) | Max: 89 (82-93) | 0h: 31 (11-59) | 3h: 48 (28-69) | Max: 43 (25-63) | 0h: 91 (85-95) | 3h: 95 (90-98) | Max: 96 (91-98) | Palamalai et al. 13

| Radiometer AQT90 (POC) cTnI | 458 patients referred with chest pain by GP or ambulance service; suspected of ACS; 104 (23%) AMI | 0h, 6-9h, 12-24h post-presentation | 99th perc. = 39 ng/L (no CV given) | MI according to 2007 Universal Definition of MI b; clinical symptoms of ischaemia; cTnI >99th perc. (Vitros cTnI assay 34 ng/L) | None given | 1st sample: 58 (47-69) | 2nd sample: 85 (75-92) | 1st sample: 94 (91-96) | 2nd sample: 91 (87-94) | 1st sample: 71 (58-81) | 2nd sample: 71 (61-80) | 1st sample: 90 (86-93) | 2nd sample: 96 (93-98) | Hjortshoj et al. 19

| Radiometer AQT90 (POC) cTnI | 806 patients (39 with AMI) | 0h, 2h, 3h, 4h, 6h, 8h and 12h post-presentation | 99th perc. = 23 ng/L | MI according to 2007 Universal Definition of MI b; clinical symptoms of ischaemia; hsTnT >14 ng/L; clinical history & further investigations (echocardiography, stress testing, coronary angiography, ultrasound, x-ray) | Followed up at 7d, 30d, & 12mo for CV events, significant bleeding | 2h: 89.7 (75.8-97.1) | 3h: 89.5 (75.2-97.1) | 4h: 94.4 (81.3-99.3) | 6h: 97.1 (84.7-99.9) | 8h: 100.0 (89.7-100.0) | 12h: 100.0 (89.1-100.0) | 2h: 91.1 (88.8-93.1) | 3h: 91.1 (88.7-93.1) | 4h: 91.0 (88.6-93.1) | 6h: 91.6 (89.1-93.7) | 8h: 90.3 (87.7-92.7) | 12h: 89.8 (86.6-92.5) | 2h: 35.0 (25.7-45.2) | 3h: 35.8 (26.2-46.3) | 4h: 36.6 (26.8-47.2) | 6h: 39.8 (29.2-51.1) | 8h: 39.5 (29.2-50.7) | 12h: 41.6 (30.4-45.4) | 2h: 99.4 (98.5-99.8) | 3h: 99.4 (98.4-99.8) | 4h: 99.7 (98.9-100.0) | 6h: 99.8 (99.0-100.0) | 8h: 100.0 (99.2-100.0) | 12h: 100.0 (99.1-100.0) | South Australian iCCnet Study

| Abbott i-STAT (POC) cTnI | 169 patients presenting with symptoms of ACS; 19 (11.2%) AMI | 0h, 3h and 6h post-presentation | 99th perc. = 80 ng/L (16% CV) | MI according to 2007 Universal Definition of MI b; clinical symptoms of ischaemia; cTnI >99th perc. (Vitros cTnI assay 34 ng/L) | None given | 0h: 32 (13-57) | 3h: 68 (43-87) | Max: 74 (49-91) | 0h: 92 (86-96) | 3h: 90 (84-94) | Max: 88 (82-93) | 0h: 33 (13-59) | 3h: 46 (28-66) | Max: 44 (26-62) | 0h: 91 (86-95) | 3h: 96 (91-98) | Max: 96 (92-99) | Palamalai et al. 13

| Abbott i-STAT (POC) cTnI and Radiometer AQT90 (POC) cTnI | Comparative study of 195 patients presenting to a suburban ED in Melbourne by i-STAT and AQT90 cTnI; 13 (6.7%) AMI | 0h for 195 patients; later timed sample for 6 of these patients | Lowered i-STAT cut-off to 50% of 99th perc. to 40 ng/L; Lowered AQT90 cTnI cut-off from 24 to 12 ng/L | Architect cTnI 28 ng/L; clinical symptoms; ECG; Universal Definition of MI b | Clinical audit | i-STAT cTnI: True Positive rate (sensitivity) increased from 34% to 80.9% by changing the cut-off from 80 to 40 ng/L. False Positive rate only increased from 0% to 3.7%. | AQT90 cTnI: True Positive rate (sensitivity) increased from 51% to 76.5% by changing the cut-off from 24 to 12 ng/L. False Positive rate only increased from 3.7% to 7.1%. | Concluded: used reporting below 99th percentile of normals to improve sensitivity of POC cTn assay and identify additional AMI patients without losing the specificity required to identify appropriate pts for discharge from ED. | Schneider et al. 20

| Abbott i-STAT Retrospective Presentation | i-STAT 99th | Death | i-STAT: 43 | i-STAT: 85 | i-STAT: 33 | i-STAT: 89 | Venge et al. 28
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Study Group</th>
<th>Sample or Presentation Timing</th>
<th>Delta cTnT</th>
<th>MACE</th>
<th>Mi</th>
<th>MI Followed Up</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td><strong>Roche Elecsys hs-TnT</strong></td>
<td>960 patients presenting to ED, non-traumatic chest pain; 220 (22.9%) AMI (196 NSTEMI)</td>
<td>0h and 2h post presentation</td>
<td>99th perc. = 14 ng/L (&lt;10% CV)</td>
<td>MACE 30d</td>
<td>Architect cTnI 28 ng/L; 0h &amp; 6-12h; ADP clinical pathway</td>
<td>hs-TnT 0h vs 2h</td>
<td>Architect cTnI 28 ng/L; 0h &amp; 6-12h; ADP clinical pathway</td>
<td>hs-TnT 2h + ECG + TIMI score cut-off of 0</td>
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<tr>
<td><strong>Roche hs-TnT</strong></td>
<td>806 patients (39 with AMI)</td>
<td>0h, 2h, 3h, 4h, 6h, 8h and 12h post-presentation</td>
<td>99th perc. = 14 ng/L</td>
<td>MI according to 2007 Universal Definition of MI; clinical symptoms of ischaemia; hs-TnT &gt;14 ng/L; clinical history &amp; further investigations (echocardiography, stress testing, coronary angiography, ultrasound, x-ray)</td>
<td>Followed up at 7d, 30d, &amp; 12mo for CV events, significant bleeding</td>
<td>99th perc. = 14 ng/L AND delta cTnT of 7 ng/L</td>
<td>MI according to 2007 Universal Definition of MI; clinical symptoms of ischaemia; hs-TnT &gt;14 ng/L; clinical history &amp; further investigations (echocardiography, stress testing, coronary angiography, ultrasound, x-ray)</td>
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<td>MI according to 2007 Universal Definition of MI; clinical symptoms of ischaemia; hs-TnT &gt;14 ng/L; clinical history &amp; further investigations (echocardiography, stress testing, coronary angiography, ultrasound, x-ray)</td>
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<tr>
<td>Roche Cobas h232 (POC) cTnT</td>
<td>Danish paramedic study of 985 patients; 200 (20%) with AMI; median symptom duration of 70 min (35-180)</td>
<td>Pre-hospital sample median time 88 min (58-131)</td>
<td>cTnT &gt;50 ng/L</td>
<td>ECG, symptoms of prolonged chest pain, suggestive of AMI</td>
<td>Survival analysis done</td>
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<td>8h: 88.6</td>
<td>(73.3-96.8)</td>
<td>12h: 93.9</td>
<td>(90.6-95.4)</td>
<td>12h: 50.8</td>
<td>(37.7-63.9)</td>
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<td>12h: 93.9</td>
<td>(79.8-99.3)</td>
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<th>Roche Cobas h232 (POC) cTnT</th>
<th>806 patients (39 with AMI) 0h, 2h, 3h, 4h, 6h, 8h and 12h post-presentation</th>
<th>cTnT decision limit 50 ng/L (no 99th perc. is available)</th>
<th>MI according to 2007 Universal Definition of MI 2; clinical symptoms of ischaemia; hs-TnT &gt;14 ng/L; clinical history &amp; further investigations (echocardiography, stress testing, coronary angiography, ultrasound, x-ray)</th>
<th>Followed up at 7d, 30d, &amp; 12mo for CV events, significant bleeding</th>
<th>South Australian iCCnet Study</th>
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<tbody>
<tr>
<td>2h: 79.5</td>
<td>(63.5-90.7)</td>
<td>3h: 89.5</td>
<td>(85.2-97.1)</td>
<td>4h: 91.9</td>
<td>98.9 (97.8-99.5)</td>
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<td>3h: 89.5</td>
<td>(85.2-97.1)</td>
<td>4h: 91.9</td>
<td>(78.1-98.3)</td>
<td>6h: 88.6</td>
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<td>4h: 91.9</td>
<td>(78.1-98.3)</td>
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<td>(73.3-96.8)</td>
<td>8h: 88.6</td>
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<td>6h: 88.6</td>
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<td>12h: 97.0</td>
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<td>12h: 97.0</td>
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<td>99.9 (98.0-99.8)</td>
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<td>12h: 97.0</td>
<td>(84.2-99.9)</td>
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<td>99.9 (98.6-100.0)</td>
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<th>Radiometer AQT90 (POC) cTnT</th>
<th>806 patients (39 with AMI) 0h, 2h, 3h, 4h, 6h, 8h and 12h post-presentation</th>
<th>99th perc. = 17 ng/L</th>
<th>MI according to 2007 Universal Definition of MI 2; clinical symptoms of ischaemia; hs-TnT &gt;14 ng/L; clinical history &amp; further investigations (echocardiography, stress testing, coronary angiography, ultrasound, x-ray)</th>
<th>Followed up at 7d, 30d, &amp; 12mo for CV events, significant bleeding</th>
<th>South Australian iCCnet Study</th>
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<tr>
<td>2h: 86.6</td>
<td>(69.5-94.1)</td>
<td>3h: 92.1</td>
<td>(78.6-98.3)</td>
<td>4h: 94.4</td>
<td>98.9 (97.8-99.7)</td>
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<td>3h: 92.1</td>
<td>(78.6-98.3)</td>
<td>4h: 94.4</td>
<td>(81.3-99.3)</td>
<td>6h: 97.1</td>
<td>99.5 (98.7-99.9)</td>
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<td>4h: 94.4</td>
<td>(81.3-99.3)</td>
<td>6h: 97.1</td>
<td>(84.7-99.9)</td>
<td>8h: 97.1</td>
<td>99.7 (98.9-100.0)</td>
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<td>6h: 97.1</td>
<td>(84.7-99.9)</td>
<td>8h: 97.1</td>
<td>(84.7-99.9)</td>
<td>12h: 96.9</td>
<td>99.9 (98.9-100.0)</td>
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<td>8h: 97.1</td>
<td>(84.7-99.9)</td>
<td>12h: 96.9</td>
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<td>99.9 (98.6-100.0)</td>
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<td>12h: 96.9</td>
<td>(83.8-99.9)</td>
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ACS, acute coronary syndrome; ADP, Accelerated Diagnostic Pathway; AHA/ACC, American Heart Association/American College of Cardiology; AMI, acute myocardial infarction; ECG, electrocardiograph; MACE, major adverse cardiac events; NPV, Negative Predictive Value; PPV, Positive Predictive Value; ROC AUC – Receiver Operating Curve Area under Curve; TIMI score, The Thrombolysis In Myocardial Infarction score; a Venge P et al. evaluated prognostic performances of assays and found that i-STAT and Stratus CS identified significantly fewer of the deaths than those identified by the lab-based assays. 24
Appendix 4: Educational materials

Educational materials include a slide presentation of the recommendations and case studies and are available on the AACB website at: http://www.aacb.asn.au/resources/recommendations-for-use-of-troponin-poc

Appendix 5: Glossary of terms

Highly sensitive (hs) cTn assay – refers to a more analytically sensitive assay than current contemporary cTnI and cTnT assays. Evidence for application of the term to an assay may be:

1) Ability to yield reliable, valid measurements in more than 80% of samples from healthy subjects;
2) Troponin concentration corresponding to a CV of <10% is significantly lower than the 99th percentile value of the healthy reference population; and
3) Clinical studies in chest pain and ACS patients using these assays should show increased prognostic ability over contemporary assays in detection of cardiac events.

Limit of Detection (LoD) – refers to the lowest amount of troponin detected with 99% probability, using an estimation procedure partly based on nonparametric statistics. LoD is the lowest troponin concentration likely to be reliably distinguished from the Limit of Blank (LoB) which is the highest measurement result for a sample that contains no troponin (blank sample).

Limit of Quantitation (LoQ) – for clinical application of troponin the most important assay characteristic is LoQ, defined as the lowest amount of troponin that can be quantitatively determined with stated acceptable (i.e. “clinically meaningful”) imprecision and bias. The allowable analytical performance should be defined and applied to the concentration corresponding to the 99th percentile upper reference limit that, to be clinically usable, cannot be lower than the LoQ of the troponin assay. Necessarily LoQ is ≥ LoD.

The (99th percentile) URL of a healthy reference population – if troponin concentrations from a healthy reference population are ranked in centiles from least to greatest, the upper reference limit (URL) is given by the 99th centile. A sample size of at least 300 individuals per sex- and age-matched reference population should avoid the effect of outliers and achieve a 95% probability that at least 99% of the population will have a troponin concentration representative of health. Different studies using manufacturer’s troponin methods and platforms have shown variability of the 99th percentile concentration depending on the reference population used, the skewness of the distribution and the number of outliers. Clinicians should refer to their local laboratory for information about the analytical performance of the troponin assay and the clinical decision limit in use at their site.
References


