ADDING VALUE TO LABORATORY TESTING:
USE OF LABORATORY GUIDELINES TO HARMONISE
BEST PRACTICE – TROPONIN POC ASSAYS

Jill Tate on behalf of
AACB Troponin POC Working Party
AACB
Troponin POC Working Party

- Louise Cullen (ED cardiology physician)
- Rita Horvath (evidence-based methodology)
- Gus Koerbin (Troponin)
- Cameron Martin (POC Co-ordinator)
- Paul Simpson (POC)
- Fernando San Gil (POC)
- Jill Tate (Troponin – IFCC WG-TnI)
- Philip Tideman (Cardiologist)
- Rosy Tirimacco (POC – IFCC Task Force chair)
Background

- iCCnet (CHSA) conducted ACS study to investigate:
  - Sensitivity/specificity/NPV/PPV for rule-in/ rule-out
    - hsTnT and 3 POC cTn assays
  - AND timing for safe rule-out of ACS using POC
    - sample times: 1, 3, 4, 6, 8, 12 hours
- Clinical concerns about accelerated diagnostic pathway (ADP) for ACS being used with POC assays in EDs in Queensland.
- NSW Health Pathology aiming for harmonised POC testing algorithms for ACS assessment.
Aims and scope of guideline and target groups

- Recommendations aim to cover both clinical & laboratory aspects of using POC troponin assays in assessment of ACS and to achieve harmonisation of testing practices.
- Document is based on currently available evidence, and consensus & comments of key stakeholders involved in management of ACS patients.
- Recommendations targeted at:
  - Clinicians requesting and interpreting cTn tests in patients presenting with symptoms of ACS
  - Healthcare professionals (both in clinical & lab settings) providing a POC cTn testing service
  - Manufacturers of POC troponin devices.
Process to harmonise troponin practices

- Expert group formed to develop consensus recommendations.
- Seek evidence:
  - Local data – iCCnet, NSW Health Pathology, Pathology QLD
  - Literature
- Discussion to reach consensus.
- Writing of recommendations & dissemination for commenting:
  - AACB 2015 ASC & AACB 2015 POC SES feedback
  - Sought comments from RCPA, NSW Health Pathology, Pathology QLD, ACEM, CSANZ, NSW Cardiac Network
- Revision of recommendations.
- Make available recommendations and supplement with:
  - Responses to comments
  - Tools, e.g. local algorithms, case studies.
iCCnet: 806 patients presenting to Chest Pain Centre 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.

Data courtesy: Rosy Tirimacco, Phil Tideman, Paul Simpson
0035 (95 min from symptom onset until admission)

<table>
<thead>
<tr>
<th></th>
<th>0 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
<th>6 h</th>
<th>8 h</th>
<th>12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsTnT</td>
<td>16</td>
<td>20</td>
<td>21</td>
<td>26</td>
<td>37</td>
<td>60</td>
<td>105</td>
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<tr>
<td>AQT90-TnT</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>18</td>
<td>35</td>
<td>69</td>
</tr>
<tr>
<td>AQT90-TnI</td>
<td>21</td>
<td>16</td>
<td>23</td>
<td>33</td>
<td>68</td>
<td>110</td>
<td>200</td>
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<td>h232</td>
<td>50</td>
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<td>50</td>
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<td>75</td>
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Data courtesy: Rosy Tirinamco, Phil Tideman, Paul Simpson
Clinical recommendations - I

- Focus on the impact of different analytical performance of cTn assays on their clinical performance and diagnostic pathways, irrespective of testing at the POC or in the laboratory.
- Present data show that current POC assays are less analytically sensitive than most laboratory cTn assays.
- Results of current cTn assays (POC or laboratory) are **NOT** directly comparable and values **CANNOT** be transferred between assays unless there is evidence of such comparability.
- Clinical users of POC and laboratory cTn results need to be aware of the limitations of their cTn assays in use in management of patients to avoid adverse effects on patient management and for patient safety.
Serial cTn measurements should be performed for all patients presenting with symptoms suggestive of ACS, unless the patient has been reliably ACS symptom-free for 12 h when a single sample is appropriate.

Recommended timing of samples using ADPs using highly sensitive lab-based cTn assay is obtaining:
- 1st sample at admission and 2nd sample at 2-3 h post admission to an ED.

Evidence is scarce to support ADPs using POC assays
- To safely discharge patients from ED, when using less sensitive cTn assays, the 2nd sample should be collected at 6-8 h post admission.
A timed myocardial infarction protocol was used by 55.3% (94 sites), but not by 29.4% (50 sites) and 15.3% (26 sites) did not know.

Timing of blood draw was 0 and 6 h at 29.6% of sites, but earlier (timing: 0 and 2 h; 0 and 3 h; 0 and 4 h; 0, 1 and 2 h) at 23.2% of sites.
<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 POC cTnI</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>99&lt;sup&gt;th&lt;/sup&gt; perc. = 20 ng/L (no CV given by Aldous – IFCC website table lists 17% CV at 20 ng/L)</td>
<td>Architect cTnI 28 ng/L; 0h &amp; 6-12h; ADP clinical pathway Cardio3 0h vs 2h</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. 7</td>
</tr>
<tr>
<td></td>
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<td>As above then Cardio3 2h +ECG + TIMI score cut-off of 0</td>
<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></td>
<td>As above then Cardio3 2h +ECG + TIMI score cut-off of 1</td>
<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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<tr>
<td>Alere Cardio3 POC cTn</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>99&lt;sup&gt;th&lt;/sup&gt; 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>
<td>Diercks et al. 23</td>
</tr>
</tbody>
</table>
Clinical recommendations - III

- Serial testing should be performed using the same cTn assay and platform.

- For individual patients transported to a different hospital location where a different cTn assay is used, recommended that initial sample is taken and accompanies patient to new destination.

- If initial sample is tested by POC assay and 2nd sample by a lab-based assay, retest 1st sample during laboratory working hours and use same sampling time as recommended when two laboratory results available.

- If initial sample cannot be retested, then use time frame from when patient is symptom-free. If this is >12 h then a single sample is appropriate.
Laboratory recommendations

- **Preanalytical**
  - e.g. processes to avoid micro-clots

- **Analytical**
  - cTn assays “clinically usable” & fit-for-purpose with ≤20% CV at 99th percentile
  - Interferences, method comparison of POC vs. lab assay

- **Postanalytical**
  - Test name
  - Reporting units – aim for harmonised “ng/L”
  - Education to users of assay

- **Governance**
  - Input from stakeholders
  - Audit and review of assay performance & clinical use.
**Long term troponin imprecision – is your assay fit-for-purpose?**

<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>Referenc</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% - E 2010 (N=5 analysers) CV: 6.0% - 10.7% - E 170 (N=3 analysers) CV: 2.9% - 5.8% - e 411 (N=2 analysers) CV: 5.7% - 9.3% - e 601 (N=1 analyser) CV: 3.9%</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>
<td>Saenger et al. 15</td>
</tr>
<tr>
<td>hs-TnT (ng/L)</td>
<td>Roche Elecsys 2010</td>
<td>LOW QC (N=91): Mean 26.5 ng/L HIGH QC (N=91): Mean 2053 ng/L</td>
<td>One site; more than one reagent lot and calibrator lot used</td>
<td>ICCnet data</td>
</tr>
<tr>
<td>hs-Tnl (ng/L)</td>
<td>Abbott Architect 4100/ 8200/ 16200 STAT</td>
<td>LOW serum pool (N= 495 - 831): - 4100 (N=1 analyser): Mean 4.7 ng/L CV 19% - 8200 (N=1 analyser): Mean 4.2 ng/L CV 15% - 16200 (N=2 analysers): Mean 5.0 ng/L CV 15% Overall 95% of low QC results are 3.2 – 6.2 ng/L Change of 3 ng/L (not 2 ng/L) at &lt;6 ng/L within acceptable CV for clinical use. MEDIUM serum pool (N= 498 - 842): - 4100 (N=1 analyser): Mean 36.8 ng/L CV 8% - 8200 (N=1 analyser): Mean 36.0 ng/L CV 8% - 16200 (N=2 analysers): Mean 36.0 ng/L CV 7%</td>
<td>Three sites and 4 analysers; multiple reagent and calibrator lots used; precision data collated over 12 months</td>
<td>Kavsak et al. 16</td>
</tr>
<tr>
<td>cTnT (ng/L)</td>
<td>Radiometer AQT90 FLEX TnT</td>
<td>LOW QC (N=143): Mean 43.5 ng/L MEDIUM QC (N=144): Mean 643 ng/L HIGH QC (N=137): Mean 9947 ng/L</td>
<td>One site; more than one reagent lot and calibrator lot used</td>
<td>ICCnet data</td>
</tr>
<tr>
<td>cTnI (ng/L)</td>
<td>Radiometer AQT90 FLEX Tnl</td>
<td>LOW QC (N=140): Mean 36.0 ng/L MEDIUM QC (N=132): Mean 303 ng/L HIGH QC (N=132): Mean 1364 ng/L</td>
<td>One site; more than one reagent lot and calibrator lot used</td>
<td>ICCnet data</td>
</tr>
<tr>
<td>cTnI (µg/L)</td>
<td>Abbott i-STAT</td>
<td>QC (N=21): Mean 0.41 µg/L</td>
<td>Seven sites; 12 cartridge lots used; QC assayed at each site 3 times over 14 weeks</td>
<td>Pathology Queensland data</td>
</tr>
</tbody>
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Tools – local algorithms for POC troponin testing

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

Abbott i-STAT Troponin I Testing Protocol
To be used with Acute Coronary Syndrome Assessment and Treatment Guidelines

- Troponin I on presentation (Time 1)
  - >0.04 µg/L
  - ≤0.04 µg/L
  - Repeat i-STAT Tnt; Collect second sample at 3-6 hours after presentation (Time 2)
  - High-risk stratification
    - Yes
    - No
    - AMI not likely
    - Clinical assessment and further Tnt testing if AMI suspected

Notes about the i-STAT method:
- At the 0.04 µg/L cut off the i-STAT Tnt has a precision of approximately 56.5% C.V.
- At the 0.06 µg/L cut off the CV is verified 10% by the manufacturer.
- At the current time the i-STAT instrument cannot report in µg/L.
- *Change (Delta Tnt)* consistent with an acute change in Tnt >24% at above 0.10 µg/L Tnt and 29.02 µg/L at 0.01 µg/L, or ≤20% at >0.10 µg/L.
Recommendations to come out of guideline – for discussion

- General consensus in Australia to harmonise cTn test names.
- cTn results released from POC devices should be clearly differentiated from cTn results reported from the laboratory using an assay with different analytical sensitivity.
  - e.g. ‘Troponin T – POC’ vs. ‘Troponin T – Highly sensitive’.
- Clinical and laboratory communities should standardise on cTn units of measurement in Australia namely “ng/L” and report values in whole numbers.
  - Disadvantage – same units could be seen then as interconvertible results between assays of differing sensitivity – so a lot of clinical education is required and a clear distinction of what assay sensitivities or methods are reported.
- Question for Audience: Is my lab able to implement the guideline recommendations? – what are the logistical issues?
Acknowledgements

- Data from iCCnet, NSW Health Pathology, Pathology Queensland
- Public commenting phase:
  - RCPA – Graham Jones
  - Private pathology – Grahame Caldwell
  - NSW Health Pathology – Chemical Pathology Clinical Stream: Michael Whiley, Fred San Gil, Rita Horvath, Gus Koerbin
  - Pathology Queensland – Chemical Pathology, Kobus Ungerer
  - Australasian College of Emergency Medicine - Dr Yusef Nagree, Prof Anthony Lawler
  - The Cardiac Society of Australia and New Zealand – Quality Standards Committee, Dr Derek Chew
  - NSW Cardiac Network – Dr Matthew Bragg (ED Director, Bowral and District Hospital)
- AACB Troponin POC Working Party