Technology Brief

High sensitivity troponin assays for the diagnosis of myocardial infarction (v1.0)

August 2011
TECHNOLOGY BRIEF

REGISTER ID  WP042 (v1.0)

NAME OF TECHNOLOGY  HIGH SENSITIVITY TROPONIN ASSAYS

PURPOSE AND TARGET GROUP  TO MEASURE CARDIAC TROPONIN CONCENTRATION IN PATIENTS PRESENTING WITH CHEST PAIN, TO DIAGNOSE OR EXCLUDE MYOCARDIAL INFARCTION (HEART ATTACK)/ACUTE CORONARY SYNDROME

STAGE OF DEVELOPMENT (IN AUSTRALIA)

☐ Yet to emerge  ☐ Established
☐ Experimental  ☐ Established but changed indication or modification of technique
☐ Investigational  ☐ Should be taken out of use
☑ Nearly established

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☑ Yes  ARTG number 181218
☐ No
☐ Not applicable

INTERNATIONAL UTILISATION

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>LEVEL OF USE</th>
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<tbody>
<tr>
<td></td>
<td>Trials underway or completed</td>
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<td>United States of America</td>
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IMPACT SUMMARY

Troponin is a complex of three structural proteins that are integral to muscle contraction in cardiac muscle. Troponin is released when cardiac myocyte is damaged and therefore
can be used to diagnose myocardial infarction (MI) in the presence of ischaemia. The higher the concentration of troponin in the blood, the greater the damage to the cardiac muscle. Conventional troponin testing requires serial blood sampling over a six to 12 hour period, whereas high sensitivity troponin tests can measure very low concentrations of the protein, allowing diagnosis or exclusion of MI/ACS to occur earlier.

**BACKGROUND**

Chest pain may be indicative of MI; however, there are many other causes for chest pain, such as indigestion and muscle strain. Chest pain may result from poor blood supply to the heart (angina) or the sudden blockage of coronary arteries (MI). Symptoms can include pain, sweating, anxiety, nausea and shortness of breath. Managing patients with chest pain is a common and challenging clinical problem.

Current guidelines indicate that patients with MI or ACS should be identified accurately and in a timely manner so that appropriate treatment may be promptly administered. Consequently, patients presenting to the emergency department (ED) with chest pain are frequently admitted until a negative biomarker test excludes myocardial injury (Baker et al 2011). Over time, various biomarkers have been used, e.g. creatine kinase-MB (CK-MB), but in recent years cardiac contractile protein troponins have become the preferred and recommended biomarker (Masson et al 2010; Omland 2010).

The troponin complex in striated muscle tissue (such as cardiac tissue) consists of a cluster of three distinct polypeptides:

- troponin C (binds calcium ions)
- troponin T (binds tropo-myosin; facilitates contraction)
- troponin I (binds actin; inhibits actin-myosin interactions) (Baker 2011; Omland 2010).

The function of the troponin complex is to regulate sarcomere (the basic unit of a muscle cell) contraction. This is achieved when the troponin binds to thin filaments and controls the calcium-triggered interaction of actin and myosin (the two filamentous protein molecules contained in muscle cells) (Baker et al 2011; Omland 2010).

In the United States of America (USA), the National Academy of Clinical Biochemistry 2007 guidelines define MI, as detected by biomarker tests, as the ‘detection of rise and/or fall of cardiac biomarkers (preferably cardiac troponin) with at least one value above the 99th percentile of the upper reference limit’. In the United Kingdom (UK), the National Institute of Clinical Excellence (NICE) also suggests, for optimal sensitivity, that a second biomarker measurement is conducted 10 to 12 hours after the onset of symptoms in order to preclude a false negative result. High sensitivity cardiac troponin assays have the potential to improve diagnostic accuracy earlier than 10 to 12 hours post-admission,
thereby expediting discharge in patients who test negative for an acute cardiac event. Conversely, the increased sensitivity of these assays may lead to an increase in hospital admissions, due to the detection of lower, previously undetectable levels of troponin that may not necessarily be due to MI (Baker et al 2011).

The National Heart Foundation of Australia, in association with the Cardiac Society of Australia and New Zealand, has recently published updated guidelines for the management of ACS. These guidelines recommend that where available, high sensitivity troponin assays should be used in preference to conventional assays. In addition, these guidelines suggest that a positive finding identifies patients at increased risk, but does not provide definitive evidence of MI. Therefore, a positive troponin result should be followed up by a search for an alternative plausible diagnosis and/or cardiac consultation if ACS is suspected in the context of the clinical presentation (Chew et al 2011). It is important to note that a number of the authors of this guideline document declared conflicts of interest, including one author who had received speakers honoraria from Roche Diagnostics Australia.

**CLINICAL NEED AND BURDEN OF DISEASE**

Hospital admission for acute MI occurs predominantly in individuals aged 40 years and over, with almost two thirds of admissions occurring in Australians aged 65 to 90 years of age. The number of public hospital separations in Australia for patients with acute MI during 2003–2004 was 46,885, of which about two thirds were male. This equates to a rate of 519 separations per 100,000 population of Australians aged over 40 years (Mathur 2002).

In New Zealand, 51 per cent of all deaths reported in 2003 were due to acute MI. The number of public hospital separations in New Zealand for patients with acute MI in 2002 to 2003 was 11,582 (7,272 male and 4,310 female) (New Zealand Health Information Service 2006).

Importantly, published literature indicates that up to eight per cent of patients with an evolving MI are mistakenly discharged without appropriate diagnosis and care, leading to increased morbidity and mortality (Engel and Rockson 2007).

**DIFFUSION**

There are currently several troponin assays approved by the Australian Therapeutic Goods Administration (TGA), although it is possible that some of the assays have been registered under more than one number (TGA 2010; TGA 2011a; TGA 2011b; TGA 2011c). Correspondence with a representative at Roche Diagnostics revealed there is
Currently one high sensitivity troponin assay on the Australian Register of Therapeutic Goods (Table 1).

### Table 1: TGA-approved troponin assays for diagnosis of MI

<table>
<thead>
<tr>
<th>ARTG number</th>
<th>Name, manufacturer</th>
<th>Intended purpose</th>
<th>Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>181218</td>
<td>Troponin IVDs, Roche Diagnostics Australia Pty. Ltd.</td>
<td>Immunoassay for the in vitro quantitative determination of cardiac troponin T in human serum and plasma. The assay can be used as an aid in the differential diagnosis of ACS to identify necrosis, e.g. acute MI. The test is further indication for the risk stratification of patients presenting with ACS and for cardiac risk in patients with chronic renal failure. The test may also be useful for the selection of more intensive therapy and intervention in patients with elevated levels of troponin T.</td>
<td>19/03/2011</td>
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IVD: in vitro diagnostics; ACS: acute coronary syndrome; MI: myocardial infarction

Studies of high sensitivity troponin assays have been conducted in a number of centres in Australia, New Zealand, Europe and the USA. Communication with Roche Diagnostics identified that Australia hospitals and pathology laboratories have been evaluating (both from a clinical and an analytical perspective) the troponin T high sensitivity assay for the last 12-18 months and all sites are now using the troponin T high sensitivity assay routinely if they have the required instrumentation to do so. All other troponin I testing is still based on the conventional non-high sensitivity assays.

Roche Diagnostics has suggested that it is important to differentiate the officially accepted terminology ‘high sensitivity’ from marketing hype which uses terms such as ‘highly sensitive’, ‘ultra-sensitive’ or ‘super-sensitive’. Specifically, they explained that this officially accepted terminology has been recently endorsed by the American Association for Clinical Chemistry in order to separate true (specifically designed and manufactured) highly sensitive assays from conventional assays that make such claims just by reducing their clinical cut-off.

**Comparators**

The traditional approach to diagnosing patients with suspected MI is based on clinical symptoms, electrocardiographic changes (depression or elevation of the ST segment or T wave insertion) and biochemical marker detection (Hasic et al 2003). The main comparator for high sensitivity troponin assays for the detection of MI is traditional biomarker screening, using conventional non-high sensitivity troponin assays (CK-MB etc.).
For many years, measurement of cytoplasmic CK-MB was the gold standard for the assessment of myocardial injury (Masson et al 2010). CK-MB was incorrectly believed to not be released by skeletal muscle. An improved understanding of CK-MB and confirmation of the cardio-specificity of troponin T and I have led to the substitution of CK-MB with troponins as the preferred biomarkers (Hasic et al 2003).

Earlier generation troponin assays were limited by their insufficient specificity for cardiac troponin, imprecision at low values, low sensitivity within the first hours after the onset of chest pain and long result turnaround time. Some current generation troponin assays use recombinant human cardiac troponin, which in the case of troponin T enable reproducibility and standardisation of assays in a turnaround time of nine to 12 minutes (Dahdal and Dahdal 2009).

Although conventional myocyte necrosis markers have a high diagnostic value, their sensitivity is weak within the first hours after the onset of chest pain, owing to a delayed increase in circulating levels of cardiac troponins (Keller et al 2009). To address this, a new generation of sensitive assays for cardiac troponins meeting the guideline requirements in terms of reproducibility in a cardio-normal reference population is being developed. Although troponin T and troponin I exhibit unique cardiac myocyte specificity, troponin T is the only commercially available high sensitivity troponin assay. This is because cardiac troponin T assays have achieved global standardisation and cardiac troponin I assays remain non-standardised and are therefore not easily commutable between patients. Attempts are currently underway to achieve some form of standardisation between the troponin I tests.

**SAFETY AND EFFECTIVENESS ISSUES**

Three non-randomised comparative studies were eligible for inclusion in this technology brief (Aldous et al 2011; Keller et al 2009; Reichlin et al 2009).

**Study profiles**

Aldous et al (2011) recruited 332 patients out of 1,479 consecutive patients presenting with chest pain at a New Zealand hospital between November 2006 and April 2007. Patients were eligible for inclusion if the attending clinician was sufficiently suspicious of ACS that serial troponins and electrocardiograms were indicated, and if there was a sufficient serum sample to allow measurement of four different serum assays at two time points. Patients underwent serial cardiac troponin testing using second generation troponin I assays at baseline (0 hours) and follow-up (6–24 hours). After routine testing (at both time points), the remaining sample was frozen and stored for later measurement using three high-sensitivity troponin assays including Roche High Sensitivity Troponin T, Abbott Architect Troponin I, Roche Troponin T and Abbott CK-MB mass. The patients...
were investigated and treated as per standard care; hence the sensitive troponin assay results did not affect treatment. Troponin results were compared for their diagnostic utility, and sensitivity and specificity were calculated for each biomarker test. Results for the CK-MB test were not reported in detail in the study; therefore they have not been included in the safety and effectiveness section of this technology brief.

Keller et al (2009) conducted a multicentre study to determine troponin levels, as assessed by sensitive troponin assays and traditional myocardial necrosis markers, in 1,818 consecutive patients with a high pre-test probability of acute MI. All patients presented with new-onset chest pain at one of three German centres between January 2007 and December 2008. Troponin levels were measured and compared at the time of admission to hospital and at three and six hours post-admission. Primary diagnosis was based on conventional troponin assays, using Roche Troponin T or Siemens Dimension RxL Troponin I. These conventional troponin I assays were used only for the diagnosis of MI and not for comparison with the sensitive troponin I assay. The final diagnosis at discharge was based on all available clinical, laboratory and imaging findings, as adjudicated by an expert committee of two independent cardiologists who were unaware of the results of the troponin I assays and a third cardiologist when consensus could not be reached.

Finally, Reichlin et al (2009) conducted a prospective, multicentre study that examined the diagnostic performance of four troponin assays. From April 2006 to April 2008, a total of 786 consecutive patients who presented to the ED in Basel, Switzerland, with symptoms of chest pain and angina pectoris (suggestive of MI) and in whom the onset or peak symptoms occurred within 12 hours before presentation, were eligible for inclusion. All patients underwent cardiac troponin I or cardiac troponin T, CK-MB and myoglobin testing at presentation and at six to nine hours after presentation, or as long as clinically indicated. The final diagnosis for each patient was determined by two independent cardiologists who reviewed all available medical records from the time of the patient’s arrival in the ED to the end of the 60-day follow-up period. A third cardiologist was employed where consensus regarding diagnosis could not be reached. The conventional cardiac troponin assays used included Abbott AxSYM Troponin I ADV, Beckman Coulter AccuTnI and Roche Troponin T. The four sensitive tests used included Abbott Architect Troponin I, Roche High Sensitive Troponin T, Roche Troponin I and Siemens Troponin I Ultra.

**Safety**

The included studies did not report safety data.

**Effectiveness**

Aldous et al (2011) reported the adjudicated index diagnosis as seen in Figure 1.
The baseline serum sample was taken a median of four hours (interquartile range 2.0–8.6) from symptom onset and the follow-up sample was taken a median of 9.4 hours (interquartile range 6.3–13.3) from presentation. The sensitivity of the conventional troponin assay at baseline was 78.7 per cent (75.6–80.0) compared with 83.6 per cent for the Roche High Sensitivity Troponin T assay, 74.5 per cent for the Abbott Architect Troponin I assay and 62.7 per cent for the Roche Troponin T assay. Analysis of baseline troponin testing found that of the three high sensitivity troponin tests, Roche High Sensitivity Troponin T and Abbott Architect Troponin I were equivalent to one another (P > 0.1) and each significantly outperformed Roche Troponin T (P < 0.001 for both). Comparing specificities, Abbott Architect Troponin I and Roche Troponin T were both more specific than Roche High Sensitivity Troponin T (P = 0.020 and P < 0.001, respectively), and Roche Troponin T was more specific than Abbott Architect Troponin I (P = 0.019).

Test performance improved at the later sampling point for all assays. Performance was significantly improved from baseline for Roche High Sensitivity Troponin T (P = 0.049), Abbott Architect Troponin I (P = 0.005) and Roche Troponin T (P < 0.001). Roche High Sensitivity Troponin T (P = 0.004) and Abbott Architect Troponin I (P = 0.012) were more sensitive than Roche Troponin T but equivalent to each other, and Abbott Architect Troponin I (P = 0.014 for both assays). Roche Troponin T (P < 0.001) was more specific than Roche High Sensitivity Troponin T, and Roche Troponin T was more specific than Abbott Architect Troponin I (P = 0.002). The sensitivity and specificity of the high sensitivity tests at follow-up are detailed in Table 2.
Table 2: Diagnostic performance of high sensitivity troponin assays measured at arrival to ED as reported by Aldous et al (2011)

<table>
<thead>
<tr>
<th>Troponin assay</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche High Sensitivity Troponin T</td>
<td>90.9%</td>
<td>81.5%</td>
</tr>
<tr>
<td>Abbott Architect Troponin I</td>
<td>90.8%</td>
<td>88.3%</td>
</tr>
<tr>
<td>Roche Troponin T</td>
<td>82.7%</td>
<td>93.7%</td>
</tr>
</tbody>
</table>

Keller et al (2009) reported the final discharge diagnosis of acute MI in 413/1818 patients (22.7%), including 130 patients (7.2%) who presented with MI with ST-segment elevation. The diagnostic accuracy of sensitive troponin I was highest, with an area under the receiver-operating-characteristics curve of 0.95 within three hours of presentation of symptoms and 0.96 by six to 12 hours follow-up. Table 3 shows the sensitivity and specificity of sensitive troponin I versus standard troponin T tests.

Table 3: Diagnostic performance of sensitive versus standard troponin assays as reported by Keller et al (2009)

<table>
<thead>
<tr>
<th>Troponin assay</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive troponin I</td>
<td>90.7%</td>
<td>90.2%</td>
<td>96.4%</td>
<td>76.7%</td>
</tr>
<tr>
<td>Standard troponin T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99th percentile</td>
<td>72.7%</td>
<td>94.1%</td>
<td>90.7%</td>
<td>81.4%</td>
</tr>
<tr>
<td>10% coefficient variation</td>
<td>63.7%</td>
<td>97.2%</td>
<td>88.3%</td>
<td>88.8%</td>
</tr>
</tbody>
</table>

NPV: negative predictive value; PPV: positive predictive value

These findings suggest that sensitive troponin I assays are more sensitive than standard tests but less specific (the statistical significance of this was not reported). Keller et al (2009) also calculated the time it took to diagnose MI in 95 per cent to 100 per cent of patients using the sensitive troponin I assay and found that 88 per cent of MIs were detected on admission in patients presenting six hours after the onset of symptoms and 95 per cent were detected in those presenting between six and 12 hours after the onset of symptoms.

The adjudicated final diagnosis in the study by Reichlin et al (2009) is seen in Figure 2.
Cardiac troponin levels at presentation, as assessed by all of the assays, was significantly higher in patients whose final diagnosis was MI compared with those who had a different final diagnosis.

This study reports a statistically significant improvement in sensitivity in the four new troponin tests (at the cost of specificity) in comparison with conventional testing methods (Table 4). The superiority of sensitive troponin tests was more pronounced among patients with recent-onset chest pain.

**Table 4: Diagnostic performance* of sensitive versus standard troponin assays as reported by Reichlin et al (2009)**

<table>
<thead>
<tr>
<th>Troponin assay</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott Architect Troponin I</td>
<td>94%</td>
<td>87%</td>
<td>98%</td>
<td>59%</td>
</tr>
<tr>
<td>Roche High-Sensitive Troponin T</td>
<td>100%</td>
<td>14%</td>
<td>100%</td>
<td>19%</td>
</tr>
<tr>
<td>Roche Troponin I</td>
<td>92%</td>
<td>88%</td>
<td>98%</td>
<td>62%</td>
</tr>
<tr>
<td>Siemens Troponin I Ultra</td>
<td>97%</td>
<td>68%</td>
<td>99%</td>
<td>38%</td>
</tr>
<tr>
<td>Standard assay</td>
<td>83%</td>
<td>93%</td>
<td>97%</td>
<td>72%</td>
</tr>
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</table>

NPV: negative predictive value; PPV: positive predictive value.
*Diagnostic performance, in this study, is reported according to the ‘limit of detection’, which was the only variable reported for all five assays.
COST IMPACT

Comprehensive evaluation of patients presenting with chest pain is a resource-intensive and expensive process (Panteghini 2002). A large number of patients are admitted to the ED for chest pain annually. In the USA alone more than five million patients may be evaluated for chest pain annually, with an average hospital stay of two days and at a total cost of more than US$6 billion (Engel and Rockson 2007). However, as mentioned earlier, published literature indicates that up to eight per cent of patients with an evolving MI are mistakenly discharged without appropriate diagnosis and care, leading to increased morbidity and mortality (Engel and Rockson 2007). With the economic pressures in health care, it is important to optimise the efficiency of care for patients with chest pain (Panteghini 2002). The use of rapid and effective diagnostic protocols, such as those employing high sensitivity troponin assays, may have the potential to improve patient care and reduce complications. However, while the use of a high sensitivity troponin test may reduce the percentage of patients with MI who are mistakenly discharged from hospital, it may also increase the number of patients without MI who undergo unnecessary further testing. For example, a recent study in a New Zealand hospital reported that the number of positive tests more than doubled using a new highly sensitivity troponin assay; however, 90% of the new positive tests were due to causes other than type 1 acute myocardial infarction (AMI) (some were thought to be due to type 2 AMI, but the majority occurred in patients with other acute cardiac or medical problems) (Jairam et al 2011). This study suggests that indiscriminate testing using high sensitivity troponin assays may result in a greater number of patients requiring serial troponin testing and/or additional invasive tests, which in turn will have process and resource consequences for emergency departments and health services (Jairam et al 2011). The improved sensitivity of the high sensitivity test is relevant to the negative predictive value of the test. It may have value in “ruling out” ACS at an earlier time for many patients who present to Emergency Departments. However, the standard test had very good NPV and it remains to be seen whether there is positive impact on Emergency Department throughputs with use of the high sensitive test.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

There were no issues identified from the retrieved material.

OTHER ISSUES

In the study by Aldous et al (2011) the reagents used for two of the high sensitivity troponin assays were donated by the manufacturer (Roche Elecsys); however, the manufacturer played no role in the design of the study, the analysis of the data, or the preparation of (or decision to submit) the manuscript. Similarly, Reichlin et al (2009) reported that assays were donated by the manufacturers, who played no role in the design
of the study, the analysis of the data, or the preparation of (or decision to submit) the manuscript. Reichlin et al (2009) also reported that its study was supported by grants received from Abbott, Roche and Siemens, among other clinical foundations. Additionally, one of this study’s authors received research grant support from Abbott, Roche and Siemens, consulting fees from Abbott, and lecture fees from Abbot Roche and Siemens. Keller et al (2009) reported that two authors received lecture fees from troponin assay manufacturers (Siemens Healthcare Diagnostics and Abbott Diagnostics).

SUMMARY OF FINDINGS

The adjudicated final diagnosis of patients presenting with chest pain in all three included studies was MI in a proportionally small number of patients (17–33%). A large proportion of patients experienced chest pain from non-cardiac causes, and hence were false positives for acute MI. This exemplifies the importance of accurate and rapid diagnosis of MI in order to decrease the burden on the health care system, as many of these patients may be unnecessarily admitted to hospital.

Overall, the new high sensitivity troponin assays appear to be more sensitive than conventional troponin assays, particularly at earlier time points. However, specificity may be sacrificed. Moving from routine troponin to high sensitivity troponin tests has the advantage of earlier diagnosis, but has the disadvantage of increased uncertainty as to whether raised troponin levels are due to MI or other conditions. Some patients may benefit from the improved NPV of the high sensitivity test and hence earlier “rule out” of ACS, shorter assessment time and time to discharge in the Emergency Department. Whether this occurs in practice remains to be seen.

HEALTHPACT ASSESSMENT

HealthPACT noted the concerns raised by the evaluators regarding a potential conflict of interest of the authors of the studies included for assessment. Based on the uncertainty surrounding the potential advantages and disadvantages of using high sensitivity troponin assays for the routine diagnosis of MI, HealthPACT have recommended that the technology be monitored for 12-months, awaiting the potential publication of higher quality, preferably randomised, trials become available could provide clarity in regards to the risk/benefit profile for the use of the technology.

NUMBER OF STUDIES INCLUDED

<table>
<thead>
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<tbody>
<tr>
<td>Total number of Level III studies</td>
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REFERENCES


Therapeutic Goods Administration (TGA). Public Summary: summary of ARTG entry: 180970, Australian Government Department of Health and Ageing, Canberra, 2011a,

**SOURCES OF FURTHER INFORMATION**


**SEARCH CRITERIA TO BE USED**

Highly sensitive troponin OR Highly sensitive troponin test OR Highly sensitive troponin assay; Sensitive troponin OR Sensitive troponin test OR Sensitive troponin assay; Myocardial infarction OR Heart attack