Health Policy Advisory Committee on Technology

Technology Brief: Update

High-sensitivity troponin assays for the diagnosis of myocardial infarction

February 2013
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Lobby 2, Level 2, Citilink Business Centre
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This brief was prepared by Dr Ann Scott, Deanne Forel, Dr Merricc Edgar-Hughes and Stef Gurgacz from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).
High-sensitivity troponin assays for the diagnosis of myocardial infarction: February 2013

Register ID
WP042

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

High-sensitivity troponin assays are widely used throughout South Australia and New Zealand. South Australia utilises high-sensitivity troponin-T assays.

Australian Therapeutic Goods Administration approval
☒ Yes ARTG number (s) 181218
☐ No
☐ Not applicable

International utilisation

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<th>Widely diffused</th>
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<td>United States</td>
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2013 Safety and effectiveness issues

One rapid systematic review and three non-randomised comparative studies were eligible for inclusion in this update.

**CADTH**¹

A rapid systematic review from the Canadian Agency for Drugs and Technologies in Health (CADTH) summarised the evidence on high-sensitivity cardiac troponin T assays, compared with conventional troponin T or I tests, published between January 2007 and January 2012 (level I diagnostic accuracy evidence, based on the highest level of evidence of included studies). Fifteen non-randomised comparative studies were identified by the literature search, which was limited to English-language papers and comparative studies or secondary analyses. A single reviewer selected and appraised the included studies and conducted the data analysis. The quality assessment of diagnostic accuracy studies (QUADAS) instrument² was used to assess the methodological quality of the included studies. The risk of bias was low for 10 of the 15 studies. Three studies were rated as having a high risk of bias owing to their retrospective data collection, while in one study the rating was uncertain because the timing of blood sampling was not reported. The remaining study was an abstract and could not be reliably assessed. Applicability was good for all studies with respect to the index test, reference test and patient selection.

All patients in the studies presented to the emergency room, intensive care unit or pain unit of the hospital with chest pain or suspected acute coronary syndrome. Blood samples were collected from patients at admission and several times within 48 hours after presentation. In all studies, the final adjudicated diagnosis was made by two cardiologists.

Twelve studies, 10 of which were prospective, compared high-sensitivity troponin T assays with standard troponin T tests. The results are summarised in Table 1. High-sensitivity troponin T tests had a higher sensitivity but a lower specificity, compared with conventional troponin T tests, for diagnosing acute coronary syndrome and acute myocardial infarction. A single retrospective study reported on the clinical impact of both tests in 1452 randomly selected patients with acute coronary syndrome. The patients who had cardiac troponin T levels that were higher than the 99th percentile cut-off in the high-sensitivity and the conventional assay groups had similar 1-year mortality rates (9.2% versus 10.7%, p=0.52). However, as the cut-off values for each of the assays differ; direct comparisons between assays are limited.
High-sensitivity troponin assays for the diagnosis of myocardial infarction: February 2013

Table 1  Comparative diagnostic validity of high-sensitivity troponin T assay compared with conventional troponin T test

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUROC</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute myocardial infarction (11 studies; n=4575)</strong></td>
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<td></td>
</tr>
<tr>
<td>High-sensitivity troponin T*</td>
<td>62% to 99%</td>
<td>49% to 89%</td>
<td>0.66 to 0.96</td>
<td>38% to 85%</td>
<td>72% to 100%</td>
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<td>Conventional troponin T†</td>
<td>8% to 88%</td>
<td>89% to 99%</td>
<td>0.79 to 0.96</td>
<td>54% to 97%</td>
<td>51% to 94%</td>
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<td><strong>Acute coronary syndrome (1 study; n=377)</strong></td>
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</tr>
<tr>
<td>High-sensitivity troponin T‡</td>
<td>69%</td>
<td>89%</td>
<td>0.79</td>
<td>38%</td>
<td>96%</td>
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<tr>
<td>Conventional troponin T§</td>
<td>35%</td>
<td>99%</td>
<td>0.79</td>
<td>72%</td>
<td>93%</td>
</tr>
<tr>
<td><strong>Unstable angina (1 study; n=377)</strong></td>
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<tr>
<td>High-sensitivity troponin T‡</td>
<td>55%</td>
<td>89%</td>
<td>0.72</td>
<td>30%</td>
<td>96%</td>
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<tr>
<td>Conventional troponin T§</td>
<td>21%</td>
<td>99%</td>
<td>0.72</td>
<td>55%</td>
<td>94%</td>
</tr>
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</table>

AUROC: area under the receiver operating characteristic curve; NPV: negative predictive value; PPV: positive predictive value

*0.014 μg/L cut-off; †0.01 μg/L to 0.04 μg/L cut-off; ‡0.013 μg/L; §0.03 μg/L.

Seven prospective, non-randomised, comparative studies assessed the validity of high-sensitivity troponin T assays compared with conventional troponin I tests. The results are summarised in Table 2. The tests were comparable in diagnosing acute coronary syndrome and acute myocardial infarction.

Table 2  Comparative diagnostic validity of high-sensitivity troponin T assay compared with conventional troponin I test

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUROC</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute myocardial infarction (6 studies; n=2396)</strong></td>
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</tr>
<tr>
<td>High-sensitivity troponin T*</td>
<td>82% to 99%</td>
<td>49% to 94%</td>
<td>0.66 to 0.96</td>
<td>38% to 85%</td>
<td>72% to 99%</td>
</tr>
<tr>
<td>Conventional troponin I†</td>
<td>75% to 96%</td>
<td>83% to 95%</td>
<td>0.61 to 0.97</td>
<td>68% to 93%</td>
<td>88% to 98%</td>
</tr>
<tr>
<td><strong>Acute coronary syndrome (1 study; n=87)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-sensitivity troponin T*</td>
<td>0.88</td>
<td></td>
<td></td>
<td>85%</td>
<td>79%</td>
</tr>
<tr>
<td>Conventional troponin I†</td>
<td>0.83</td>
<td></td>
<td></td>
<td>100%</td>
<td>57%</td>
</tr>
</tbody>
</table>

AUROC: area under the receiver operating characteristic curve; NPV: negative predictive value; PPV: positive predictive value

*0.014 μg/L cut-off; †0.016 μg/L to 0.06 μg/L cut-off.

The review noted some clinical and methodological limitations in the evidence base. The studies were quite heterogeneous in the timing of blood sampling, which varied from 0 to 48 hours after admission. In addition, the cut-off values for the assays varied substantially, which hindered inter-study comparisons and is likely to have led
to the variability of sensitivity and specificity seen in Tables 1 and 2. The review also noted a lack of cost effectiveness evidence precluding the assessment of the comparative economic impact of using high sensitivity troponin T, conventional troponin T or conventional troponin I.

Pracoñ et al\(^3\)

This study examined the use of a conventional troponin I test, Dimension Flex Troponin I (Siemens Healthcare Diagnostics, AG, Zurich, Switzerland), and the high-sensitivity Architect Troponin I (Abbott Laboratories, Abbott Park, IL, USA) in 187 consecutive patients admitted with chest pain and suspected acute coronary syndrome in June and July 2010 (level II diagnostic accuracy evidence). Blood samples were taken within 24 hours of onset or peak of symptoms. The attending physician was blinded to the results of the high-sensitivity troponin assay, as were the two cardiologists who determined the final diagnosis.

The patient cohort had a mean age of 64 (standard deviation 13.9) years and included 119 men (64%). Acute myocardial infarction was diagnosed in 84 patients (45%). For a single reading at admission, the sensitive troponin I assay had a higher area under the receiver operating characteristic curve (AUROC) (0.92, 95% confidence interval [CI] 0.87, 0.95) than the standard troponin I assay (0.86, 95% CI 0.81, 0.91) (p=0.02). At the 99\(^{th}\) percentile cut-off for the assays, the sensitive test (0.028 ng/mL cut-off) had a higher sensitivity, specificity, positive predictive value and negative predictive value for acute myocardial infarction (87%, 88%, 86% and 89%) than the conventional assay (0.07 ng/mL cut-off) (82%, 81%, 78% and 85%). The diagnostic accuracy of the sensitive assay was consistent among patient subgroups, including men, women, younger and older patients, and those with ST-elevation or non-ST elevation myocardial infarction.

Of the 12 false positive results recorded with the sensitive assay, the elevated troponin levels were attributable to a specific cause, other than myocardial infarction, in all but one patient. In contrast, among the 19 false positives identified by the standard test, there was no apparent cause identified. Thus, it is possible that these readings resulted from imprecision in the standard assay.

Reiter et al\(^4\)

This multicentre study updated the results previously presented by Reichlin et al.\(^5\) It examined the diagnostic accuracy of three high-sensitivity cardiac troponin assays in patients who were admitted to hospital between April 2006 and June 2009 with symptoms of acute myocardial infarction, with a symptom onset or peak within the previous 12 hours (level II diagnostic accuracy evidence). All patients underwent an initial clinical assessment. Levels of blood myoglobin, creatine kinase-MB and cardiac
troponin I or T were measured at presentation and six to nine hours afterwards, or as long as clinically indicated. The final adjudicated diagnosis was made by two independent cardiologists who reviewed all available medical records to the end of the 90-day follow-up period. A variety of troponin assays were used as part of the diagnostic adjudication process.

Four assays were assessed in the study: a high-sensitivity troponin T assay—Roche high-sensitive-cTnT (Roche Diagnostics, Indianapolis, IN, USA); two high-sensitivity troponin I assays—cTnI-Ultra (Siemens Healthcare Diagnostics, AG, Zurich, Switzerland) and Architect Troponin I (Abbott Laboratories, Abbott Park, IL, USA); and one conventional troponin T assay—Roche cTnT (Roche Diagnostics, Indianapolis, IN, USA). Blood samples were collected within the first hour of the patient’s admission, with additional samples being collected at one, two, three and six hours thereafter. Serial sampling was discontinued when the diagnosis was finalised.

Of the 1247 patients who were consecutively enrolled, 1098 patients had blood troponin levels measured with all four assays. Acute myocardial infarction was the final diagnosis in 173 (16%) patients, of whom 41 had ST-segment elevation and 132 did not. Pre-existing coronary artery disease was present in 401 (37%) patients.

The sensitive assays were better able to diagnose acute myocardial infarction in patients with pre-existing heart disease, as quantified by AUROC, than the standard assay (p<0.01 for all comparisons) (Table 3). However, the diagnostic accuracy was similar among the three sensitive assays (p>0.05). All assays showed lower specificity in patients with pre-existing cardiac disease than in those without. This was particularly evident with the high-sensitivity troponin T assay (p<0.001). The accuracy of diagnosing acute coronary syndrome was similarly low for the three sensitive assays (AUROC range 0.66 to 0.67) when used in patients with pre-existing disease, compared with patients who did not have extant cardiac disease (AUROC range 0.86 to 0.89, p<0.001 for all comparisons).

Among the patients who did not have acute myocardial infarction, 40 per cent had baseline troponin levels above the cut-off for the high-sensitivity troponin T test, and between 13 per cent and 15 per cent had levels above the cut-off for the high-sensitivity troponin I assays. Overall, the high-sensitivity troponin I assays outperformed the high-sensitivity troponin T test. However, the high-sensitivity troponin T assay (hazard ratio 2.3, 95% CI 1.1, 5.1, p=0.034) and the Siemens high-sensitivity troponin I test (hazard ratio 2.3, 95% CI 1.2, 4.4, p=0.009) were able to predict mortality independent of age, sex, pre-existing coronary artery disease, arterial hypertension and diabetes.
Table 3 Comparative diagnostic validity of high-sensitivity troponin assays compared with a conventional troponin T test for acute myocardial infarction

<table>
<thead>
<tr>
<th>Troponin assay</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUROC</th>
<th>PPV</th>
<th>NPV</th>
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</thead>
<tbody>
<tr>
<td>Roche high-sensitivity troponin T*</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>History of CAD</td>
<td>94%</td>
<td>59%</td>
<td>0.92</td>
<td>35%</td>
<td>97%</td>
</tr>
<tr>
<td>No history of CAD</td>
<td>94%</td>
<td>81%</td>
<td></td>
<td>45%</td>
<td>99%</td>
</tr>
<tr>
<td>Siemens high-sensitivity troponin †</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>History of CAD</td>
<td>91%</td>
<td>85%</td>
<td>0.94</td>
<td>58%</td>
<td>98%</td>
</tr>
<tr>
<td>No history of CAD</td>
<td>89%</td>
<td>91%</td>
<td></td>
<td>62%</td>
<td>98%</td>
</tr>
<tr>
<td>Abbott high-sensitivity troponin ‡</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>History of CAD</td>
<td>83%</td>
<td>87%</td>
<td>0.93</td>
<td>61%</td>
<td>96%</td>
</tr>
<tr>
<td>No history of CAD</td>
<td>85%</td>
<td>93%</td>
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<td>66%</td>
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<td>Roche conventional troponin §</td>
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<td></td>
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<tr>
<td>History of CAD</td>
<td>69%</td>
<td>97%</td>
<td>0.87</td>
<td>84%</td>
<td>93%</td>
</tr>
<tr>
<td>No history of CAD</td>
<td>83%</td>
<td>95%</td>
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<td>83%</td>
<td>95%</td>
</tr>
</tbody>
</table>

AUROC: area under the receiver operating characteristic curve; CAD: coronary artery disease; NPV: negative predictive value; PPV: positive predictive value

*0.014 ng/mL cut-off; †0.04 ng/mL cut-off; ‡0.028 ng/mL; §0.035 ng/mL.

Aldous et al

This is a secondary analysis of the results from a multicentre study of adult patients presenting to the emergency room between November 2007 and December 2010 with symptoms of cardiac ischemia without ST-segment elevation (level II diagnostic accuracy evidence). Blood troponin T levels were measured at admission and two hours later using the Elecsys Troponin T assay (Roche Diagnostics, Indianapolis, IN, USA). A conventional assay (Architect Troponin I, Abbott Laboratories, Abbott Park, IL, USA) (cut-off 0.028 μg/L) was used to measure troponin I levels at admission and six to 12 hours afterwards, if required. Diagnoses were independently adjudicated by a cardiologist who was blinded to the results of the high-sensitivity assay.

Of the 939 patients recruited, 205 (22%) had non-ST-segment elevation myocardial infarction. The median patient age was 65 (interquartile range 56 to 76) years and 60 per cent were men. Among the patients, 486 had a history of ischemic heart disease. By two hours after admission, the high-sensitivity troponin T test had a sensitivity of 92.2 per cent (95% CI 88.1, 95.0) and a specificity of 79.7 per cent (95% CI 78.6, 80.5) for diagnosing non-ST myocardial infarction (cut-off 14 ng/L). However, the substantial false negative rate of 7.8 per cent suggested that later measurements would still be required. By one year, the high-sensitivity assay was superior to the conventional assay in predicting death and heart failure, whereas the conventional assay was superior in predicting non-fatal myocardial infarction.
2013 Cost impact

No economic studies were identified by the literature search. It is important that cost-effectiveness analyses take place in order to assess the impact of the increased false positive rate associated with high-sensitivity troponin assays on the management of chest pain, in particular the cost impact of false positives on increased hospital admission and unnecessary cardiac investigation.

2013 Ethical, cultural or religious considerations

No issues were identified from the retrieved material.

2013 Other issues

A search of the clinical trial databases identified one clinical trial, conducted by the University of Erlangen-Nürnberg in Germany, which compared the accuracy of a high-sensitivity troponin T assay and a conventional troponin T test in diagnosing early myocardial necrosis in elderly patients with acute coronary syndrome without ST-segment elevation (NCT01370382). The trial, which was completed in December 2011, recruited 180 patients, but the results have yet to be published.

Of the articles included in this update, one noted a competing interest. In Aldous et al., two of the authors had received consultancy and speaker fees from various health product manufacturers, but only one author received fees from a company associated with one of the troponin assays being investigated.

Two studies were identified that investigated the use of copeptin (the C-terminal part of vasopressin) as a marker of endogenous stress, in addition to cardiac troponin, in patients with chest pain or established myocardial infarction. Potocki et al. examined this dual marker strategy in 1170 of the 1247 patients recruited by Reiter et al. The addition of copeptin measurements improved the accuracy of the conventional troponin T assay in diagnosing acute myocardial infarction in patients with pre-existing coronary artery disease (AUROC 0.94 versus 0.86, p<0.001). For the high-sensitivity assay, the improvement was less marked (AUROC 0.92 versus 0.94, p=0.11). However, the negative predictive value of both tests rose to at least 99.3 per cent when combined with copeptin measurements. Giannitsis et al. studied the addition of copeptin measurements to a high-sensitivity troponin T assay in 503 patients. This combination was more effective in ruling out non-ST-segment elevation myocardial infarction than the high-sensitivity assay alone (negative predictive value 95.8% versus 99.03%).

2013 Summary of findings

This update confirmed earlier results showing that while the high-sensitivity troponin T assays were more sensitive than conventional troponin T tests in diagnosing acute
coronary syndrome and acute myocardial infarction, they were also less specific. In addition, recent studies suggested that the high-sensitivity troponin T assays had a similar diagnostic utility to that of conventional and high-sensitivity troponin I tests. One study showed that high-sensitivity troponin I and T assays were less specific in diagnosing myocardial infarction in patients with pre-existing coronary artery disease than in those without.

Overall, the high-sensitivity troponin assays appeared to be more sensitive than conventional troponin assays, but the high-sensitivity troponin T assays may not be superior to conventional or high-sensitivity troponin I assays. Differences in the timing of the use of the test (zero to 48 hours) and the cut-off values employed for each assay made direct comparisons between the included studies difficult and may have resulted in the large variability in sensitivity and specificity. Nonetheless, the effect of high-sensitivity troponin assays on patient outcomes is still unclear as there are no data on whether high-sensitivity assay results shorten the time from symptom onset to treatment or how they change clinical management. Test-specific algorithms may also be needed to delineate the optimum time interval for conducting these tests and whether one test is superior to another in particular patient subgroups. Furthermore, it is likely that the investigation of multiple biomarker testing may affect how high-sensitivity troponin tests are utilised, depending on which diagnostic characteristics of the assays are potentiated by the addition of other markers.

2013 HealthPACT assessment

The evidence presented in the 2013 update indicates that high-sensitivity troponin assays achieve a higher sensitivity and greater negative predictive value compared with conventional troponin assays. As myocardial infarction is a life-threatening event, specificity reduction in false-negatives and therefore greater detection is of benefit to patients. However, these assays achieve lower specificity when compared to conventional assays, resulting in a higher false positive rate. Consequently, patients who experience a false positive may experience a longer hospital stay, as well as undergo unnecessary investigations or interventions. This highlights the importance of clinical protocols for the management of chest pain, as appropriate consideration of pre-test probabilities may result in less false positive results.

Due to heterogeneity in the evidence, particularly with regard to timing of testing and cut-off values for the different assays, direct comparisons of diagnostic performance were limited. In addition, the impact of using high-sensitivity troponin assays in clinical practice is unknown. Cost-effectiveness data is required to demonstrate the impact of the higher sensitivity and increased false positive rate on
the costs of managing chest pain. Based on this information no further research on behalf of HealthPACT is warranted at this time.

2013 Included studies

All evidence included for assessment in this Technology Brief has been assessed according to the revised National Health and Medical Research Council levels of evidence. A document summarising these levels may be accessed via the following link on the HealthPACT website.

Total number of included studies 4
Total number of level I diagnostic accuracy studies 1
Total number of level II diagnostic accuracy studies 3

2013 References


TECHNOLOGY BRIEF

REGISTER ID

NAME OF TECHNOLOGY   HIGH SENSITIVITY TROPNONIN 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 (ACS)

STAGE OF DEVELOPMENT (IN AUSTRALIA)

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

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☑ Yes  ARTG number 181218
☐ No
☐ Not applicable

INTERNATIONAL UTILISATION

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<th>COUNTRY</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
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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’ (Baker et al 2011). 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 (Baker et al 2011). 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 (Baker et al 2011). 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
High sensitivity troponin assays for the diagnosis of myocardial infarction (August 2011)

management of ACS (Chew et al 2011). 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 (Mathur 2002). 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 (Mathur 2002). 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 (New Zealand Health Information Service 2006). 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).
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>
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</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>
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</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>
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</thead>
<tbody>
<tr>
<td>Sensitive troponin I</td>
<td>90.7%</td>
<td>90.2%</td>
<td>96.4%</td>
<td>76.7%</td>
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<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>
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</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>
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</thead>
<tbody>
<tr>
<td>Abbott Architect Troponin I</td>
<td>94%</td>
<td>87%</td>
<td>98%</td>
<td>59%</td>
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<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>
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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).

**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.

**HEALTHPACT ASSESSMENT**

Based on the uncertainty surrounding the potential advantages and disadvantages of using high sensitivity troponin assays for the routine diagnosis of MI, it is recommended that the technology be monitored for 12 months in the hope that higher quality (preferably randomised) trials become available. (Searches of clinical trial registers indicate that additional studies are currently underway). This could provide clarity in regards to the risk/benefit profile for the use of the technology.

- Monitor

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**HEALTHPACT ACTION**

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**NUMBER OF STUDIES INCLUDED**

Total number of studies 3
Total number of Level III studies 3

**REFERENCES**


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
HEALTH PACT DECISION

☐ New and Emerging Health Technology Report
☑ Monitor
☐ Refer

☐ Full Health Technology Assessment Report
☐ Archive
☐ Decision pending

PRIORITY RATING

☐ High
☐ Medium
☐ Low