



Canadian Agency for
Drugs and Technologies
In Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL



TITLE: Assessment of High Sensitivity Cardiac Troponin T Assay for the Rapid Diagnosis of Acute Coronary Syndrome and Acute Myocardial Infarction in the Emergency Room: A Review of the Clinical and Economic Evidence

DATE: 03 February 2012

CONTEXT AND POLICY ISSUES

The acute coronary syndromes (ACS) encompass a spectrum of unstable coronary artery disease from unstable angina to transmural myocardial infarction. Their common aetiology is the formation of thrombus on an inflamed and complicated atheromatous plaque.¹ Acute myocardial infarction (AMI) reflects a state of acute myocardial necrosis.¹ It was estimated that in 2004 there were 1,565,000 hospitalizations for primary or secondary diagnosis of an acute coronary syndrome (ACS), 669,000 for unstable angina and 896,000 for myocardial infarction in USA.^{2,3} Despite the reduction of coronary heart disease mortality over the past 40 years, hospital admissions for acute coronary syndromes (ACS) continue to increase.⁴ The rapid and reliable diagnosis of acute myocardial infarction is a major unmet clinical need.⁵ Failure to identify patients with ACS is a serious clinical problem.⁶

Cardiac troponin is a central to, and the marker of choice for the diagnosis of, acute myocardial infarction and risk assessment in acute coronary syndrome.^{5,7-9} Conventional cardiac troponin includes cardiac Troponin T (cTnT) and cardiac troponin I (cTnI).¹⁰⁻¹³ The limit of detection of cTnT is 0.01 µg/L.^{6,10,14} The recommended positive cut-off (99th percentile in a healthy population) for the diagnosis of ACS/AMI is 0.030 µg/L.^{6,15} There are several cTnI assays available on the market^{8,16-19} including Abbott Architect troponin I 3rd generation (TnI 3), Roche Troponin I and Siemens Troponin ultra. The limits of detection for Abbott Architect troponin I 3rd generation (TnI 3), Roche Troponin I and Siemens Troponin I ultra are 0.01 µg/L, 0.1 µg/L and 0.06 µg/L respectively.¹⁶ The recommended cut-off values (99th percentile) for Abbott Architect troponin I 3rd generation (cTnI 3), Roche Troponin I and Siemens Troponin ultra were 0.028 µg/L, 0.16 µg/L and 0.04 µg/L respectively.¹⁶ Since the existing conventional cardiac troponin assays do not meet clinical needs, the drive to improve the analytical sensitivity and specificity for the diagnosis of ACS and AMI has led to the development of new high sensitive cardiac troponin T (hs-cTnT) based on humanised monoclonal antibodies.²⁰

Recently developed hs-cTnT has a detect limit of 0.003 µg/L.²¹⁻²³ The recommended 99th percentile cut-off point of hs-cTnT is 0.014 µg/L.⁶ It has been suggested that undetectable hs-

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cTnT at presentation has very high negative predictive value, which may be considered to rule out AMI.^{15,21} It was also reported that the hs-cTnT assay increases the number of non-ST elevation myocardial infarction (NSTEMI) diagnoses and enables earlier detection of evolving NSTEMI. A doubling of the hs-cTnT concentration within 3 h in the presence of a second concentration in the 99th percentile or higher is associated with a positive predictive value of 100% and a negative predictive value of 88%.²⁴ Concentrations of hs-cTnT >0.014 µg/L improve the prediction of death but not subsequent AMI in unselected patients presenting with acute chest pain.¹⁰ When AMI is defined by hs-TnT, it improves the early diagnostic accuracy compared with conventional troponins.²⁵ Furthermore, by measuring hs-TnT, it seems possible to exclude AMI already within the first few hours from admission.²¹

The aim of this review is to evaluate the evidence of the validity of hs-cTnT, cTnT and cTnI in the risk stratification of ACS in patients with chest pain or suggested ACS in emergency room (ER).

RESEARCH QUESTIONS

1. What is the comparative sensitivity and specificity of conventional cardiac troponin T (cTnT) and high sensitivity cardiac troponin T (hs-cTnT) when evaluating patients presenting to the ER with chest pain?
2. What is the comparative sensitivity and specificity of cardiac troponin I (cTnI) and hs-cTnT when evaluating patients presenting to the ER with chest pain?
3. What is the comparative clinical impact of using hs-cTnT, cTnT, or cTnI?
4. What is the comparative economic impact of using hs-cTnT, cTnT, or cTnI?

KEY MESSAGE

High sensitivity cardiac troponin T (cTnT) showed a higher sensitivity but lower specificity in the diagnosis of acute coronary syndrome and acute myocardial infarction compared with conventional cTnT. High sensitivity cTnT was found to have similar diagnostic value compared with cardiac troponin I (cTnI). The long term comparative clinical impact and the cost effectiveness of using high sensitivity cTnT, conventional cTnT and cTnI remain to be established.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and economic studies. Where possible, retrieval was limited to the human

population. The search was also limited to English language documents published between January 1, 2007 and January 6, 2012.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications, and evaluated the full-text publications for the final article selection, according to the selection criteria present in Table 1.

Table 1: Selection Criteria

Population	Patients presenting in ER with chest pain Patients with ACS and AMI
Intervention	High Sensitivity Cardiac Troponin T (hs-cTnT) Assay
Comparator	Conventional Cardiac Troponin T (cTnT) Assay; Cardiac Troponin I (cTnI) Assay
Outcomes	Assay sensitivity and specificity, rates of false positive and negative tests Clinical outcomes: cardiovascular events (e.g. ACS, AMI), need for revascularization procedures (e.g. angiograms, PCI), quality of life, death, any harm outcomes reported Economic: early discharge from ER, hospital admission, LOS, second ER visit, hospital re-admission, cost of test, cost of ACS/AMI case.
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials (RCTs), non-randomized studies, economic evaluations

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria.

Critical Appraisal of Individual Studies

QUADAS checklists^{26,27} were used to assess the methodological quality for the included non-randomized studies. No systematic reviews, randomized controlled trials or economic evaluations were identified for critical appraisal.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 515 citations. Upon screening titles and abstracts, 465 citations were excluded, and 50 potentially relevant articles were retrieved for full-text review. Of the 50 potentially relevant reports, 35 did not meet the inclusion criteria. Fifteen were included in this review.^{5,7,9,15,20-22,24,25,28-33} The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 1). Fourteen^{5,9,15,20-22,24,25,28-33} were observational studies assessing the comparative accuracy and validity of hs-

cTnT compared with cTnT or/and cTnI in adult patients with chest pain or suspected ACS in ER or intensive care unit (ICU) or hospital. One study⁷ reported the comparative clinical impact (such as mortality and MI) of using hs-cTnT and cTnT.

Summary of Study Characteristics

Twelve non-randomized studies^{5,9,15,21,24,25,28-31,33} were identified assessing the validity of hs-cTnT compared with cTnT. Seven^{5,20,21,29-32} prospective studies were found assessing the validity of hs-cTnT compared with cTnI. One retrospective study⁷ including 1,452 patients was identified assessing the comparative clinical impact of using hs-cTnT and cTnT. All patients were presented to the ER, ICU or pain unit of the hospital due to chest pain or suspected ACS. The blood samples for hs-cTnT and cTnT assay were collected at admission and several times within 48 hours after admission. In all included studies, final adjudicated diagnosis (such as ACS, AMI or unstable angina) was made by two cardiologists. No evidence was identified for the comparative economic impact of using hs-cTnT, cTnT, or cTnI. The main characteristics of the included studies are summarized in Appendix 2.

What is the comparative sensitivity and specificity of cTnT and hs-cTnT?

Among the 12 studies comparing hs-cTnT with cTnT, ten^{5,15,21,24,25,28-31,33} were prospective studies. One²² was retrospective and one⁹ was a cross-sectional study. All trials were conducted in adults. One³¹ focused on an elderly population (age >70 years old). Two^{9,15} were from the USA. Four studies^{22,24,25,33} were conducted in Germany. Three studies^{5,28,31} were from Switzerland, two^{29,30} from New Zealand and one²¹ from Norway. Seven studies^{9,15,22,24,25,28,33} compared hs-cTnT with cTnT and the remaining five^{5,21,29-31} compared hs-cTnT with both cTnT and cTnI individually. Sample size ranged from 94²⁴ to 1,159.²⁸ The main outcomes reported were area under receiver operating characteristic curve (AUROC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The AUROC is an estimate of the probability of a true diagnosis. An AUC of 1.0 (100%) indicates a test can classify a patient with perfect accuracy, while an AUC of 0.5 indicates a test has a 50% chance of correct classification.

What is the comparative sensitivity and specificity of cTnI and hs-cTnT?

All seven^{5,20,21,29-32} studies were prospective and conducted in adults. One³¹ focused on an elderly population (age >70 years old). Two^{5,31} were from Switzerland, three^{20,29,30} from New Zealand, one²¹ from Norway and one³² from France. Two^{20,32} compared hs-cTnT with cTnI and the remaining five^{21,24,29-31} compared hs-cTnT with cTnT and cTnI. Sample size ranged from 87³² to 718.⁵ The main outcomes reported were area under receiver operating characteristic curve (AUROC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

What is the comparative clinical impact of using hs-cTnT, cTnT, or cTnI?

Only one retrospective study⁷ including 1,452 patients were identified assessing the comparative clinical impact of using hs-cTnT and cTnT. The reported outcomes were mortality and myocardial infarction at 30 days and mortality during one year follow-up.

What is the comparative economic impact of using hs-cTnT, cTnT, or cTnl?

No evidence was identified for the comparative economic impact of using hs-cTnT, cTnT, or cTnl.

Summary of Critical Appraisal

The risk of bias and applicability concerns of all included studies in the report are summarized in Appendix 3.

Overall, the risk of bias was low in 10 studies.^{5,9,15,20,21,28-31,33} Three studies^{7,22,24} were rated as high because the patient selection was from retrospective cohorts. One²⁵ was rated uncertain because the blood sample timing was not reported. One study³² was unable to be assessed because it was presented in an abstract. The reference tests in all included studies were cTnT or cTnl. All index tests (hs-cTnT) were clearly reported. There is no concern about the applicability on index test, reference test and patient selection.

Summary of FindingsWhat is the comparative sensitivity and specificity of cTnT and hs-cTnT?

The main findings of the included studies are summarized below and in Appendix 5.

For the diagnosis of AMI

Eleven^{5,9,15,21,22,24,28-31,33} studies reported the comparative diagnostic validity of hs-cTnT for AMI compared with cTnT. For hs-cTnT (cut-off value of 0.014 µg/L), the reported AUROCs ranged from 0.66 to 0.96. The sensitivity ranged from 61.5% to 99% and the specificity ranged from 49% to 89%. The positive predictive value ranged from 38% to 85% and the negative predictive value was 72.1% to 100%. For cTnT (cut-off value from 0.01 µg/L to 0.04 µg/L), the reported AUROCs ranged from 0.79 to 0.96. The sensitivity ranged from 7.69% to 88% and the specificity range was 89 to 99%. The positive predictive value ranged from 54.2% to 97.3% and the negative predictive value were 50.9 to 94.4%.

For the diagnosis of ACS

In the cross-sectional study, Januzzi⁹ assessed the validity of hs-cTnT versus cTnT in the diagnosis of ACS. The author reported that the AUROC, sensitivity, specificity, PPV and NPV were 0.79, 69%, 89%, 38% and 96% respectively for hs-cTnT (cut off: 0.013 µg/L) and 0.79, 35%, 99%, 72% and 93% (cut off: 0.03 µg/L) respectively for cTnT.

For the diagnosis of unstable angina

Januzzi⁹ also reported that the AUROC, sensitivity, specificity, PPV and NPV for the diagnosis of unstable angina were 0.72, 55%, 89%, 30% and 96% respectively for hs-cTnT (cut off: 0.013 µg/L) and 0.72, 21%, 99%, 55% and 94% (cut off: 0.03 µg/L) respectively for cTnT.

What is the comparative sensitivity and specificity of cTnI and hs-cTnT?

Seven^{5,20,21,29-32} non-randomized studies were identified assessing the validity of hs-cTnT compared with cTnI. The cut off value for the diagnosis of ACS were $\geq 99\%$ percentile 0.014 $\mu\text{g/L}$ for hs-cTnT and from 0.016 $\mu\text{g/L}$ to 0.06 $\mu\text{g/L}$ for cTnI (depending on the manufacturer of cTnI). Most of the studies reported all of the following outcomes: area under receiver operating characteristic Curve (AUROC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The main findings were summarized below and in Appendix 5.

For the diagnosis of AMI

Six^{5,20,21,29-31} studies reported the comparative diagnostic validity of hs-cTnT for AMI compared with cTnI. For hs-cTnT, the reported AUROCs ranged from 0.66 to 0.96. The sensitivity ranged from 81.6% to 99%. The specificity ranged from 49% to 94%. The positive predictive value ranged from 38% to 85% and the negative predictive value was 72.1% to 99%. For cTnI, the reported AUROCs ranged from 0.61 to 0.97. The sensitivity varied from 75% to 96%. The specificity ranged from 83% to 95%. The positive predictive value ranged from 68% to 93% and the negative predictive value was from 87.9% to 98%.

For the diagnosis of ACS

In the abstract, Zuily³² assessed the validity of hs-cTnT versus cTnI in the diagnosis of ACS. The author reported that the AUROC, PPV and NPV were 0.88, 85%, and 79% respectively for hs-cTnT (cut off: 0.014 $\mu\text{g/L}$) and 0.83, 100% and 57.1% (cut off: 0.014 $\mu\text{g/L}$) respectively for cTnI.

What is the comparative clinical impact of using hs-cTnT, cTnT, or cTnI?

In an retrospective study, Lindahl⁷ assessed the hs-cTnT assay compared with the third-generation cTnT assay in serum samples collected 48 hours from 1,452 randomly selected ACS patients. The author reported the death/AMI rates during a 30 day follow-up period were 7.9 and 8.7 respectively for hs-cTnT positive patients (cut off: 0.014 $\mu\text{g/L}$) and cTnT positive patients (cut off: 0.01 $\mu\text{g/L}$) respectively. The mortality rate at one year follow-up were 10.4 and 10.7 respectively for hs-cTnT and cTnT respectively. The author also found that the 16% of the patients that had levels higher than the 99th percentile cutoff for hs-cTnT (0.014 $\mu\text{g/L}$) but less than that for cTnT (0.01 $\mu\text{g/L}$) had a similar 1-year mortality as the 60% that were positive for both assays (9.2% versus 10.7%, $P = 0.52$) and a higher 1-year mortality compared with the 24% that were negative for both assays (9.2% versus 2.6%, $P = 0.001$). For death or acute myocardial infarction at 30 days, the group that was positive only for hs-cTnT had an intermediate risk compared with the groups negative or positive for both assays (2.4%, 5.2%, and 8.7%; $P < 0.001$). The author concluded that the hs-cTnT assay, compared with the cTnT assay, identified more patients with myocardial damage and who were at an increased risk for new cardiac events.

What is the comparative economic impact of using hs-cTnT, cTnT, or cTnI?

No evidence was identified to assess the comparative economic impact of using hs-cTnT, cTnT, or cTnI.

Limitations

Although the overall methodological risk of bias of the included studies was low except for three^{7,22,24} rated as high risk because of the patient were retrospectively selected, several limitations (clinical and methodological heterogeneities) should be emphasized in the interpreting the body evidence presented in this review. Firstly, across the included studies, the timing for taking blood samples used for testing the cardiac troponins varied from 0 to 48 hours after presentation. Secondly, the cut off value for the assays, especially for cTnI, varied from study to study depending the on the manufacturer. These clinical heterogeneities in terms of sampling time, cutoff value limit the ability to make direct comparison of the diagnostic validity of hs-cTnT with cTnT or cTnI across the included studies. Thirdly, the one study⁷ identified for evaluating the clinical impact (such as mortality) of hs-cTnT versus cTnT was not from a randomized controlled trial. In addition, it was followed up for one year, which may be insufficient to evaluate long term outcomes. Moreover, there was no cost economic analysis. Finally, a small number of studies (2 of 15) were conducted in North America (USA); the analyses were conducted in different countries, so their findings may not be transferable to the Canadian setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

High sensitivity cTnT showed a higher sensitivity but lower specificity in the diagnosis of AMI and ACS compared with conventional cTnT. The comparative validity of hs-cTnT and cTnI in the diagnosis of AMI and ACS were similar. Limited and low quality evidence showed similar one-year mortality in patients with hs-cTnT greater than the 99th percentile ($>0.014 \mu\text{g/L}$) compared with those with cTnT greater than 99th percentile ($>0.03 \mu\text{g/L}$). However, the above findings must be interpreted with caution due to clinical and methodological heterogeneities in the included studies. Well-designed clinical trials are needed to evaluate the comparative clinical impact of using hs-cTnT, cTnT and cTnI for diagnosis of AMI and ACS. Moreover, a comprehensive economic evaluation that compares the cost-effectiveness of hs-cTnT with cTnT or cTnI in the Canadian context is required to determine the cost-effectiveness in Canada.

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health

Tel: 1-866-898-8439

www.cadth.ca

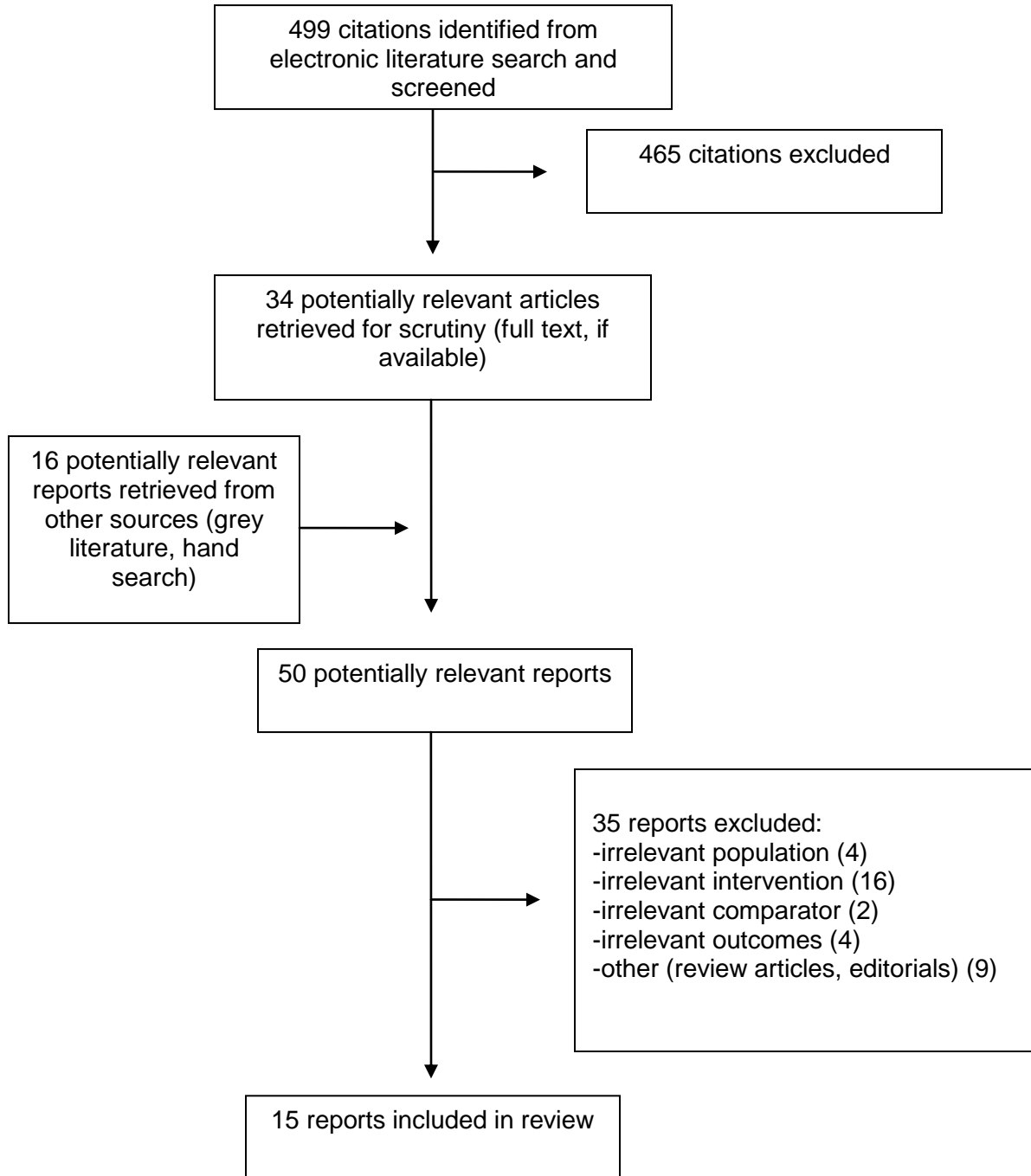
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Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies on Clinical Effectiveness and Safety

First Author, Publication Year, Country	Study Design, Length of Study	Patient Characteristics, Sample Size	Intervention	Comparators	Main Outcomes
Aldous, ²⁰ 2011, New Zealand	Non-randomized study, prospective, 2.5 years	Adult patients with chest pain attending in ED N=385	hsTnT	Tnl	AMI AUROC Sensitivity, Specificity, PPV NPV
Body, ¹⁵ 2011, USA	Non-randomized study, prospective, Following up 6 months	Adult patients with chest pain attending in ED N=703	hsTnT	cTnT	AMI All-cause mortality AUROC Sensitivity, Specificity, PPV NPV
Hochholzer, ²⁸ 2011, Switzerland and Spain	Non-randomized study, prospective, 3 years and Following up 1 year	Adult patients with chest pain attending in ED N=1159	hsTnT	cTnT	AMI All-cause Mortality AUROC Sensitivity, Specificity, PPV NPV
Ndrepepa, ²⁵ 2011, Germany	Non-randomized study, prospective, Following up 4 years	Adult patients with suspected NSTEMI-ACS N=447	hsTnT	cTnT	Mortality AUROC
Aldous, ²⁹ 2011 New Zealand	Non-randomized study, prospective, Following up 2 years	Adult patients with suspected ACS N=327	hsTnT	cTnT cTnl	MACE Cardiac mortality Non-fatal AMI Revascularization AUROC
Aldous, ³⁰ 2011, New Zealand	Non-randomized study, prospective, Following up 2 years	Adult patients with suspected ACS N=327	hsTnT	cTnT cTnl3	AMI AUROC Sensitivity, Specificity, PPV NPV
Melki, ²¹ 2011, Norway	Non-randomized study, prospective, 1.5 years	Adult patients with chest pain with no persistent ST elevation N=233	hsTnT	cTnT cTnl	AMI AUROC Sensitivity, Specificity, PPV NPV
Reiter, ³¹ 2011, Switzerland and Spain	Non-randomized study, prospective, 3 years,	Elderly (>70 years old) patients with suggested AMI in ED N=406	hsTnT	cTnT cTnl-ultra cTnl	AMI AUROC Sensitivity, Specificity, PPV

First Author, Publication Year, Country	Study Design, Length of Study	Patient Characteristics, Sample Size	Intervention	Comparators	Main Outcomes
	Follow up: 3 months				NPV
Zuily, ³² 2011, France	Non-randomized study, prospective, 5 months, Follow up: 3 months (Only abstract available)	Adult patients with suspected ACS admitted in ICU N=87	hsTnT	cTnI	ACS AUROC PPV NPV
Christ, ²² 2010, Germany	Non-randomized study, retrospective, 6 months,	Adult patients with chest pain attending in ED N=137	hsTnT	cTnT	AMI AUROC Sensitivity, Specificity, PPV NPV
Kurz, ³³ 2011, Germany#	Non-randomized study, prospective, 7 months,	Adult patients with suspected NSTEMI-ACS admitted to chest pain unit N=94	hsTnT	cTnT	AMI AUROC Sensitivity, Specificity, PPV NPV
Lindahl, ⁷ 2010, Sweden	Non-randomized study, retrospective, Follow-up: 30 days and 12 months for mortality	Adult patients with suspected NSTEMI-ACS, N=1452	hsTnT	cTnT cTnI	Mortality/AMI Mortality
Giannitsis, ²⁴ 2010, Germany#	Non-randomized study, retrospective, 7 months	Adult patients with suspected NSTEMI-ACS admitted to chest pain unit N=94	hsTnT	cTnT	AMI AUROC Sensitivity, Specificity, PPV NPV
Reichlin, ⁵ 2009, Switzerland	Non-randomized study, prospective, 7 months	Adult patients with suspected NSTEMI in ED N=718	hsTnT	cTnT cTnI-ultra cTnI (Abbott-Achitect) cTnI (Roche)	AMI AUROC Sensitivity, Specificity, PPV NPV
Januzzi, ⁹ 2010, USA	Non-randomized study, cross-sectional	Adult patients with Chest pain ED N=377	hsTnT	cTnT	ACS AMI Unstable angina AUROC Sensitivity, Specificity, PPV NPV

ACS=acute coronary syndrome; AE=adverse events; AMI=acute myocardial infarction; AUROC=area under receiver operating characteristic curve; cTnI= conventional troponin I; cTnI3= 3rd generation cTnI; cTnT=conventional cardiac troponin T; ED=emergency department; hsTnT=high-sensitivity troponin T; ICU=intensive care unit; MACE = major adverse cardiac events; NPV=negative predictive value; NSTEMI-ACS=non-ST-segment elevation acute coronary syndromes; NSTEMI=non-ST-segment elevation myocardial infarction; PPV=positive predictive value; The data reported in Kurt³³ and Giannitsis²⁴ were from the same study.

Appendix 3: Critical Appraisal of Included Studies with QUADAS checklists^{26,27}

First Author, Publication Year, Country	Risk bias				Applicability concerns		
	Patient Selection	Index test	Reference test*	Flow and time	Patient Selection	Index test	Reference test
Aldous, ²⁰ 2011, New Zealand	L	L	L	L	L	L	L
Body, ¹⁵ 2011, USA	L	L	L	L	L	L	L
Hochholzer, ²⁸ 2011, Switzerland and Spain	L	L	L	L	L	L	L
Ndrepepa, ²⁵ 2011, Germany	L	L	L	?	L	L	L
Aldous, ²⁹ 2011 New Zealand	L	L	L	L	L	L	L
Aldous, ³⁰ 2011, New Zealand	L	L	L	L	L	L	L
Melki, ²¹ 2011, Norway	L	L	L	L	L	L	L
Reiter, ³¹ 2011, Switzerland and Spain	L	L	L	L	L	L	L
Zuily, ³² 2011, France	Abstract. QA was not done						
Christ, ²² 2010, Germany	H	L	L	L	H	L	L
Kurz, ³³ 2011, Germany	L	L	L	L	L	L	L
Lindahl, ⁷ 2010, Sweden	H	L	L	L	H	L	L
Giannitsis, ²⁴ 2010, Germany	H	L	L	L	H	L	L
Reichlin, ⁵ 2009, Switzerland	L	L	L	L	L	L	L
Januzzi, ⁹ 2010, Germany	L	L	L	L	L	L	L

*Reference test was clinical diagnosis of AMI or ACS
 L=low risk; H=high risk; ?=unclear;

Appendix 4: Main Study Findings and Authors' Conclusions

First Author, Publication Year, Country	Main results		Author's Conclusions
	Intervention (hs-cTnT)	Comparator (cTnT or cTnl)	
Aldous, ²⁰ 2011, New Zealand	within 2 hrs: ≥99% percentile 0.014 µg/L AUROC: 81.6% Sensitivity: 95.1% Specificity:75.6% PPV: 53.8% NPV:98.3%	cTnl At 2 h: ≥99% percentile 0.028 µg/L AUROC: 93.2% Sensitivity: 86.6% Specificity:95% PPV: 82.6% NPV:96.3%	"hsTnT taken at 0 and 2 h after presentation, together with ECG results, could identify patients suitable for early stress testing with a false negative rate for AMI of 1.2%. Further trials of such an approach are warranted. The specificity of hsTnT for diagnosing AMI could be improved by the use of a delta of ≥20%, but at the cost of major reductions in sensitivity." (p. 1)
Body, ¹⁵ 2011, USA	From <3 to > 6 hrs: cutoff: 99% percentile 0.014 µg/L AUROC: 0.94 Sensitivity: 85.4% Specificity:82.4% PPV: 52.4% NPV:96.1%	cTnT From <3 to > 6 hrs: ≥99% percentile 0.01 µg/L AUROC: 0.86 Sensitivity: 75.2% Specificity:94.6% PPV: 75.8% NPV:94.4%	"Undetectable hs-cTnT at presentation has very high negative predictive value, which may be considered to rule out AMI, identifying patients at low risk of adverse events. Pending further validation, this strategy may reduce the need for serial testing and empirical treatment, enabling earlier reassurance for patients and fewer unnecessary evaluations and hospital admissions" (p. 1332)
Hochholzer, ²⁸ 2011, Switzerland and Spain	0 hrs: cutoff: 99% percentile 0.014 µg/L <u>For death during 1 year follow up</u> AUROC: .0.79 for Sensitivity: 79% Specificity:66% PPV: 14% NPV:98% <u>For AMI:</u> AUROC: NR Sensitivity: 57% Specificity:64% PPV: 6% NPV:96%	cTnT 0 hrs: cutoff: 99% percentile 0.014 µg/L <u>For death during 1 year follow up</u> AUROC: NR Sensitivity: 43% Specificity:89% PPV: 22% NPV:96% <u>For AMI:</u> AUROC: NR Sensitivity: 17% Specificity:81% PPV: 5% NPV:96%	"Concentrations of hs-cTnT >0.014 µg/L improve the prediction of death but not subsequent AMI in unselected patients presenting with acute chest pain" (p. 1318)
Ndrepepa, ²⁵ 2011, Germany	Sampling time: NR : cutoff: 99% percentile 0.014 µg/L # of NSTEMI: 268 (60%) <u>For 4 year mortality</u> AUROC: 0.691 (P=0.004, vs cTnT)	cTnT Sampling time: NR cutoff: 99% percentile 0.01 µg/L # of NSTEMI: 201(45%) <u>For 4 year mortality</u> AUROC: 0.639	"The use of hsTnT instead of cTnT increased the proportion of patients with NSTEMI among patients with NSTEMI-ACS and significantly improved risk stratification regarding long-term mortality." (p. 1350)
Aldous, ²⁹ 2011 New Zealand	0-24 hrs cutoff: 99% percentile 0.014µg/L AUROC <u>For MACE:</u> 0.69 Cardiac mortality: 0.77 Non-fatal AMI:0.66 Revascularization:	cTnT 0-24 hrs cutoff: 99% percentile 0.01 µg/L AUROC <u>For MACE:</u> 0.61 Cardiac mortality: 0.68	"hsTnT outperformed contemporary Tnl and TnT assays for the prediction of MACE at two years. Those with levels below the LOD for hsTnT identified a group of patients at very low risk for adverse events." (p. 249)

First Author, Publication Year, Country	Main results		Author's Conclusions
	Intervention (hs-cTnT)	Comparator (cTnT or cTni)	
	0.68	Non-fatal AMI:0.57 Revascularization: 0.61 cTni 0-24 hrs cutoff: 99% percentile 0.028 µg/L AUROC For MACE: 0.65 Cardiac mortality: 0.73 Non-fatal AMI:0.61 Revascularization: 0.64	
Aldous, ³⁰ 2011, New Zealand	0-24 hrs cutoff: 99% percentile 0.014µg/L for AMI AUROC: 0.92 Sensitivity: 83.6% Specificity:83.6% PPV:71.9% NPV:91.2%	cTnT 0-24 hrs cutoff: 99% percentile 0.01 µg/L for AMI AUROC: 0.80 Sensitivity: 62.7% Specificity:95.5% PPV:97.3% NPV:83.8% cTnI 3 (3rd generation) 0-24 hrs cutoff: 99% percentile 0.028 µg/L for AMI AUROC: 0.88 Sensitivity: 74.5% Specificity:90.5% PPV:79.6% NPV:87.9%	"hsTnT was superior to cTnT but equivalent to cTnI (3 rd generation) for the diagnosis of AMI. Serial troponin measurement increased test performance. hsTnT was the most likely to be raised at baseline in those with AMI. A delta troponin increases specificity but reduces sensitivity." (p. 241)
Melki, ²¹ 2011, Norway	0-2 hrs cutoff: 99% percentile ≥ 0.014µg/L for AMI AUROC: 0.95-0.96 Sensitivity: 97-99% Specificity,74-71% PPV: 78-77% NPV: 97-99%	cTnT 0-2 hrs cutoff: 99% percentile ≥0.04µg/L for AMI AUROC: 0.93-0.96 Sensitivity: 79-88% Specificity:94-92% PPV:93-92-% NPV:82-88% cTnI 0-2 hrs cutoff: 99% percentile ≥0.06µg/L for AMI AUROC: 0.94-.097 Sensitivity: 90-96% Specificity:92-89%	"When acute MI is defined by a high sensitive troponin assay, the use of hs-TnT improves the early diagnostic accuracy compared with conventional troponins. By measuring hs-TnT it seems possible to exclude acute MI already within the first few hours from admission." (p. 198)

First Author, Publication Year, Country	Main results		Author's Conclusions
	Intervention (hs-cTnT)	Comparator (cTnT or cTnl)	
		PPV:92-89 % NPV:91-96%	
Reiter, ³¹ 2011, Switzerland and Spain	0-6 hrs cutoff: 99% percentile ≥ 0.014µg/L for AMI AUROC:0.94 Sensitivity: 98% Specificity: 49% PPV: 38% NPV 99%	cTnT 0-6 hrs cutoff: 99% percentile ≥ 0.028µg/L for AMI AUROC:NR Sensitivity: unknown Specificity: unknown PPV: unknown NPV unknown cTnl-ultra 0-6 hrs cutoff: 99% percentile ≥ 0.04µg/L for AMI AUROC:0.95 Sensitivity: 92% Specificity: 83% PPV: 64% NPV 97% cTnl 0-6 hrs cutoff: 99% percentile ≥ 0.028µg/L for AMI AUROC:0.95 Sensitivity: 89% Specificity: 87% PPV: 69% NPV 96%	“Sensitive cTn assays have high diagnostic accuracy also in the elderly. Mild elevations are common in elderly non-AMI patients. Therefore the optimal cut-off levels are substantially higher in elderly as compared with younger patients. Furthermore, hs-cTnT assays yielded different prognostic value.” (p. 1379)
Zuily, ³² 2011, France	(data reported in abstract) 0-6 hrs cutoff: 99% percentile ≥ 0.014µg/L for ACS AUROC: 0.88 PPV: 84.6% NPV: 79%	cTnl (data reported in abstract) 0-6 hrs cutoff: 99% percentile ≥ 0.014 µg/L for ACS AUROC: 0.83 PPV: 100% NPV: 57.1%	“Serial assay of hs-cTnT in this study contributed valuable information for diagnosis of ACS.” (p. 116)
Christ, ²² 2010, Germany	0-6 hrs cutoff: 99% percentile 0.014µg/L for AMI AUROC: 0.91 Sensitivity: 95%	cTnT 0-6 hrs cutoff: 99% percentile 0.04µg/L for AMI AUROC: 0.89 Sensitivity: 65%	“The introduction of hs-cTnT assay displays an excellent diagnostic performance for the workup of patients with chest pain at the time of their initial presentation. Even small increases of hs-cTnT indicate increased risk for death or myocardial infarction during follow-up.” (p. 1134)

First Author, Publication Year, Country	Main results		Author's Conclusions
	Intervention (hs-cTnT)	Comparator (cTnT or cTnl)	
	Specificity:61.5% PPV:29.7% NPV:98.6%	Specificity:90.6% PPV:54.2% NPV:93.8%	
Kurz, ³³ 2011, Germany	0-24 hrs cutoff: 99% percentile 0.014µg/L for NSTEMI AUROC: 0.82 Sensitivity: 82% Specificity:76.1% PPV:85% NPV:72.1%	cTnT 0-24 hrs cutoff: 99% percentile 0.03µg/L for NSTEMI AUROC: NR Sensitivity: NR Specificity: NR PPV:85% NPV:NR	"A baseline sample of hs-cTnT allows an earlier prediction of non-STEMI than the less sensitive and precise fourth generation cTnT assay. Probably, this excellent performance of TnTs at baseline and follow-up could obviate the need for other early markers of necrosis in future." (p. 209)
Lindahl, ⁷ 2010, Sweden	At 48 hrs cutoff: 99% percentile 0.014µg/L Mortality/AMI at 30 days: 7.9% Mortality at 1 year: 10.4% Positive results among 94 death/MI at 30 days 86(91%) Positive results among 123 death at 1 year 114 (93%)	cTnT At 48 hrs cutoff: 99% percentile 0.01 µg/L Mortality/AMI at 30 days: 8.7% Mortality at 1 year 10.7% Positive results among 94 death/MI at 30 days 74(79%) Positive results among 123 death at 1 year 93(76%)	"The new hs-cTnT assay, compared with the old cTnT assay, identified more patients with myocardial damage and who were at an increased risk for new cardiac events." (p. 224)
Giannitsis, ²⁴ 2010, Germany	cutoff: 99% percentile 0.014µg/L for NSTEMI <u>At baseline</u> Sensitivity: 61.5% Specificity:77.4% PPV:69.6% NPV:70.6% <u>At 3 hrs</u> Sensitivity: 100% Specificity:76.7% PPV:65% NPV:100% <u>At 6 hrs</u> Sensitivity: 100% Specificity:70.1% PPV: 73.4% NPV:100%	cTnT cutoff: 99% percentile 0.01 µg/L for NSTEMI <u>At baseline</u> Sensitivity: 7.69% Specificity:90.3% PPV:40% NPV:50.9% <u>At 3 hrs</u> Sensitivity: 91.7% Specificity:96.8% PPV:91.7% NPV:96.8% <u>At 6 hrs</u> Sensitivity: 100% Specificity:87.1% PPV: 86.7%	"The high-sensitivity cTnT assay increases the number of NSTEMI diagnoses and enables earlier detection of evolving NSTEMI. A doubling of the hs-cTnT concentration within 3 h in the presence of a second concentration >or=99th percentile is associated with a positive predictive value of 100% and a negative predictive value of 88%." (p. 642)

First Author, Publication Year, Country	Main results		Author's Conclusions
	Intervention (hs-cTnT)	Comparator (cTnT or cTnI)	
		NPV:100%	
Reichlin, ⁵ 2009, Switzerland	0-6hrs cutoff: 99% percentile 0.014µg/L for NSTEMI AUROC: 0.96 Sensitivity: 95% Specificity:80% PPV:50% NPV:99%	<p>cTnT 0-6hrs cutoff: 99% percentile 0.01 µg/L for NSTEMI AUROC: 0.90 Sensitivity: unknown Specificity: unknown PPV:: unknown NPV: unknown</p> <p>cTnI-ultra 0-6hrs cutoff: 99% percentile 0.004µg/L for NSTEMI AUROC: 0.96 Sensitivity: 89% Specificity:92% PPV:68% NPV:98%</p> <p>cTnI (Abbott-Architect) 0-6hrs cutoff: 99% percentile 0.028µg/L for NSTEMI AUROC: 0.96 Sensitivity: 86% Specificity:92% PPV:69% NPV:97%</p> <p>cTnI (Roche) 0-6hrs cutoff: 99% percentile 0.016µg/L for NSTEMI AUROC: 0.94 Sensitivity: 84% Specificity:94% PPV:73% NPV:97%</p>	“The diagnostic performance of sensitive cardiac troponin assays is excellent, and these assays can substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of chest pain.” (p. 858)
Januzzi, ⁹ 2010, Germany	4 hrs cutoff: 99% percentile 0.013µg/L for ACS AUROC: 0.79 Sensitivity: 69%	<p>cTnT 4 hrs cutoff: 99% percentile 0.03 µg/L for ACS</p>	“Among low- to intermediate-risk patients with chest pain, hs-cTnT provides good sensitivity and specificity for ACS. Elevation of hs-cTnT identifies patients with myocardial injury and significant structural heart disease, irrespective of the diagnosis of ACS.” (p. 1227)

First Author, Publication Year, Country	Main results		Author's Conclusions
	Intervention (hs-cTnT)	Comparator (cTnT or cTnI)	
	Specificity:89% PPV:38% NPV:96% <u>For AMI</u> AUROC: 0.86 Sensitivity: 88% Specificity:85% PPV:11% NPV:100% <u>for unstable angina</u> AUROC: 0.72 Sensitivity: 55% Specificity:89% PPV:30% NPV:96%	AUROC: 0.79 Sensitivity: 35% Specificity:99% PPV:72% NPV:93% <u>for MI</u> AUROC: 0.86 Sensitivity: 88% Specificity:97% PPV:39% NPV:100% <u>for unstable angina</u> AUROC: 0.72 Sensitivity: 21% Specificity:99% PPV:55% NPV:94%	

ACS=acute coronary syndrome; AE=adverse events; AMI=acute myocardial infarction; AUROC=area under receiver operating characteristic curve; cTnI= conventional troponin I; cTnI3= 3rd generation cTnI; cTnT=conventional cardiac troponin T; ED=emergency department; hsTnT=high-sensitivity troponin T; ICU=intensive care unit; MACE = major adverse cardiac events; NPV=negative predictive value; NSTEMI=non-ST-segment elevation acute coronary syndromes; NSTEMI=non-ST-segment elevation myocardial infarction; PPV=positive predictive value; The data reported in Kurt³³ and Giannitsis²⁴ were from the same study.