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High-Sensitivity Cardiac Troponin for the Rapid Diagnosis of Acute Coronary Syndrome in the Emergency Department: A Clinical and Cost-Effectiveness Evaluation

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Nazila Assasi, MD PhD[1,2]
Gord Blackhouse, MSc[1,2]
Kaitryn Campbell, MLIS[1,2]
Robert B. Hopkins, PhD[1,2]
Ron Goeree, MA[1,2,3]

March 2013

[1] Programs for the Assessment of Technology in Health (PATH) Research Institute, St. Joseph's Healthcare Hamilton, Hamilton, Ontario.
[2] Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario.
[3] Centre for Evaluation of Medicines, St. Joseph's Healthcare Hamilton, Hamilton, Ontario.

Reviewers

These individuals kindly provided comments on this report.

External Reviewers

The project protocol and draft reports were reviewed by the following:

Peter A. Kavsak PhD, FCACB, FACB
Clinical Biochemist
Juravinski Hospital and Cancer Centre
Hamilton, ON

Robert C. Welsh, MD, FRCPC
Professor of Medicine
Mazankowski Alberta Heart Institute and the University of Alberta
Edmonton, AB

Andrew Worster, MD, CCFP(EM), MSc
Director, Emergency Medicine Research
McMaster University
Hamilton, ON

CADTH Peer Review Group, Reviewer

Joseph Beyene, BSc, MSc, PhD
Associate Professor
McMaster University
Hamilton, ON

Industry

The following manufacturers were provided with an opportunity to comment on an earlier version of this report: Roche Diagnostics (cardiac troponin assays), Siemens Diagnostics (cardiac troponin assays), Beckman Coulter Canada (cardiac troponin assays), Ortho Clinical Diagnostics (cardiac troponin assays), Abbott Diagnostics (cardiac troponin assays), Response Biomedical (cardiac troponin assays), and bioMérieux (cardiac troponin assays). All comments that were received were considered when preparing the final report.

Authorship

Nazila Assasi contributed to the protocol, screening questionnaires, data abstraction forms, and the review manager database; conducted the clinical review and write up; and reviewed the final report.

Gord Blackhouse was responsible for the conceptualization and write up of the primary economic evaluation and budget impact analysis. He wrote the economic review and provided review and comments on the clinical review.

Robert Hopkins completed the statistical analysis, and drafted the methods and results.

Kaitryn Campbell designed and executed the literature search, wrote methods, and managed references for the literature search of the report. She abstracted some clinical study data and critically appraised a number of studies.

Ron Goeree contributed to the design of the study; and oversaw data collection, analysis, and report preparation. He commented on the report and contributed to writing and report revisions.

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Conflicts of Interest

Dr. Kavsak received grants from Randox and Beckman Coulter for speaking engagements and travel, and from Roche, Beckman Coulter, Randox, Abbott, and Ortho Clinical Diagnostics for research funding. He is listed as an inventor on patents filed by McMaster University related to laboratory testing in acute cardiac care. Dr. Welsh received consulting and research grants respectively from Roche Canada and Alere.

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ABBREVIATIONS

ACC	American College of Cardiology
ACS	acute coronary syndrome
AHA	American Heart Association
AMI	acute myocardial infarction
AUC	area under the curve
CABG	coronary artery bypass graft
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	cost-effectiveness acceptability curve
cTn	cardiac troponin
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CV	coefficient of variation
DVT	deep vein thrombosis
ECG	electrocardiogram
ED	emergency department
ESC	European Society of Cardiology
hs-cTnI	high-sensitivity cardiac troponin I
hs-cTnT	high-sensitivity cardiac troponin T
HTA	health technology assessment
IHD	ischemic heart disease
LoD	limit of detection
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PE	pulmonary embolism
QALY	quality-adjusted life-year
ROC curve	receiver operating characteristic curve
STEMI	ST-segment elevation myocardial infarction
UA	unstable angina
VTE	venous thromboembolism

1 INTRODUCTION

When patients with chest pain (or other symptoms suggestive of acute coronary syndrome [ACS]) present at an emergency department (ED), investigations are rapidly conducted to rule out ACS. ACS represents a spectrum of clinical presentations of myocardial ischemia ranging from ST-segment elevation myocardial infarction (STEMI) to non-STEMI (NSTEMI) and unstable angina (UA).[1-3] STEMI is diagnosed by specific electrocardiogram (ECG) findings and portends a high risk of cardiac death. NSTEMI and UA are typically caused by myocardial ischemia, but of differing severity depending on the presence of myocardial infarction (MI), and are often clinically indistinguishable because of the similarity in symptoms and transient or non-specific ECG findings of ischemia at presentation. In 2000, the European Society of Cardiology and the American College of Cardiology (ESC/ACC) jointly redefined myocardial necrosis to incorporate cardiac troponin (cTn) assays as a diagnostic determinant. In 2007, the ESC/ACC/American Heart Association (AHA) updated the definition of MI and advocated a **"**rise and/or fall**"** of cTn during a six to nine-hour time period using the 99th percentile in a reference population as the cut-off for classifying an acute and evolving MI.[3] The time frame for the assessment of cTn, after the first measurement, has been reduced to three to six hours in the third universal of MI (2012).[4] Therefore, in patients with suspected MI, but without ECG STEMI criteria, the cTn level is the discriminating criterion between NSTEMI and UA.

In Canada, there are two cTn tests available: cardiac troponin T (cTnT) and cardiac troponin I (cTnI). As of 2012, the manufacturer of the cTnT reagent started to remove the conventional reagent and replace it with a high-sensitivity cTnT (hs-cTnT) reagent. High-sensitivity cTnI (hs-cTnI) is not yet available, but its introduction to the market is expected within the next year. In the emergency medicine community, such a change is generating concern. A higher sensitivity assay will potentially result in earlier identification of those individuals experiencing an MI (as well as possibly those who can be safely discharged from the ED with no further investigations). However, the use of high-sensitivity assays may also be associated with lower clinical specificity. Such lower specificity could potentially result in higher rates of false-positive tests; that is, situations where patients are incorrectly identified as having NSTEMI. Therefore, the use of hs-cTn assays could lead to conducting additional investigations and undertaking more vascular interventions (e.g., angiogram). These additional investigations and interventions carry the potential to increase the pressure on EDs, cardiology referrals, and possibly cardiac catheterization suites. These could result in additional costs to the health care system and cause increased anxiety to patients.

Note on terminology: Non–high-sensitivity (conventional or sensitive) cardiac troponin T and cardiac troponin I tests hereafter are denoted as conventional cTnT and cTnI, and high-sensitivity cardiac troponin tests are denoted as hs-cTnT and hs-cTnI.

Because of the changing landscape of cTn tests there is a need to independently compare the performance of hs-cTnT with cTnT, cTnI and hs-cTnI as well as determine the comparative clinical and economic impact of using these tests. Information on the economic impact of cTn tests is an important gap as no such economic evaluations were retrieved in the Rapid Response review on hs-cTnT, recently published by the Canadian Agency for Drugs and Technologies in Health (CADTH).[5] Other project scoping work seems to confirm this gap. Given the gap in economic information and the need for good quality guidance on the use of cTn tests, a full health technology assessment (HTA) along with optimal use recommendations will inform the purchasing and the clinical use of the most optimal cTn assay, depending on the individual

institutional context; and for institutions electing to use hs-cTnT or hs-cTnI, the full HTA will provide information for clinicians regarding the lower specificity of these new assays.

2 OBJECTIVES

The objective of this review is to evaluate the clinical and cost-effectiveness of hs-cTnT and hs-cTnI for the early diagnosis of ACS in the ED.

Research questions

1. What is the diagnostic test performance of hs-cTnT and hs-cTnI assays compared with each other as well as with cTnT and sensitive cTnI assays in patients with suspected ACS symptoms in ED?
2. What is the clinical effectiveness of hs-cTnT and hs-cTnI assays compared with each other as well as with cTnT and sensitive cTnI assays in patients with suspected ACS symptoms in ED?
3. What is the cost-effectiveness of hs-cTnT and hs-cTnI assays compared with each other as well as with cTnI assays in patients with suspected ACS symptoms in the ED?

3 METHODS

3.1 Literature searches

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946 to May 16, 2012) with in-process records through Ovid; Embase (1980 to week 19, 2012) through Ovid; The Cochrane Library (2012, Issue 2) and the Health Economic Evaluations Database (HEED) through Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were high-sensitivity cardiac troponin and medical emergency circumstances, acute myocardial infarction (AMI), cardiac ischemia, chest pain, or ACS.

Methodological filters were applied to limit retrieval to HTAs, systematic reviews, meta-analyses, randomized controlled trials, non-randomized controlled clinical trials, comparative studies, and economic evaluations. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year, but was limited to the English language (with the exception of French Canadian technology assessments, which are not translated). Conference abstracts were included in the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on May 16, 2012. Regular alerts were established to update the search until March 11, 2013. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters), which includes the

websites of regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. The Google search engine was used to search for additional web-based materials, including conference abstracts. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry members. See Appendix 1 for more information on the grey literature search strategy.

3.2 Selection criteria

3.2.1 Inclusion criteria

Studies suitable for inclusion were selected from those identified through the literature search, using the criteria listed below.

Population	• Patients presenting to an ED with chest pain or other symptoms suggestive of ACS.
Intervention	• hs-cTnT assay • hs-cTnI assay
Comparator	• cTnT assay • cTnI assay

Outcome	• Diagnostic Test Performance:
	  • Sensitivity
	  • Specificity
	  • Positive likelihood ratio
	  • Negative likelihood ratio
	  • Area under the curve (AUC) of the receiver operating characteristic (ROC) curve
	  • Positive predictive value
	  • Negative predictive value
	  • Rates of false-positive tests
	  • Rates of false-negative tests
	  • Accuracy
	  • ED time until diagnosis or detection of abnormal concentration.
	
	• Clinical:
	  • Thromboembolic events (e.g., venous thromboembolism [VTE]: deep vein thrombosis [DVT], or pulmonary embolism [PE])
	  • Acute cardiovascular events (e.g., ACS, AMI)
	  • Chronic/non-acute cardiovascular events (e.g., coronary artery stenosis/narrowing seen on angiogram)
	  • Revascularization procedures (e.g., angiograms, percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG])
	  • Heart failure
	  • Quality of life
	  • Death
	  • 30-day readmission rate
	  • 30-day recurrence rate

	• 30-day mortality
	• Any harm outcomes reported.
	
	• Economic:
	  • Quality of life
	  • Incremental cost-effectiveness ratio
	  • Cost per outcome unit
	  • Cost per quality-adjusted life-year (QALY).

Study Design	HTAs, systematic reviews and meta-analyses, randomized controlled trials, non-randomized studies, and economic analyses.

3.2.2 Exclusion criteria

Studies were excluded if they did not meet the selection criteria, provided the results of a qualitative or a non-comparative quantitative clinical study were not an original economic evaluation, or presented the study results in an abstract form. Duplicate publications, narrative reviews, and editorials were also excluded.

3.3 Selection method

3.3.1 Clinical review

Two reviewers independently screened the titles and abstracts for relevance using a predefined checklist (Appendix 2). Any discrepancies between reviewers were discussed until consensus was reached. Full texts of relevant titles and abstracts were retrieved, and assessed for inclusion. Two independent reviewers, using explicit predetermined criteria (Appendix 3A), made inclusion and exclusion decisions. Any discrepancies between reviewers were resolved by consensus, consulting a third reviewer when necessary.

3.3.2 Economic review

Two reviewers independently screened the titles and abstracts for relevance based on the criteria that the study appeared to potentially be an economic evaluation, and evaluated a cTn testing strategy. Any discrepancies between reviewers were discussed until consensus was reached. Full texts of relevant titles/abstracts were retrieved, and assessed for inclusion. Two independent reviewers, using explicit predetermined criteria (Appendix 3B), made inclusion and exclusion decisions. Any discrepancies between reviewers were resolved by consensus, consulting a third reviewer when necessary.

3.4 Quality assessment and data extraction

3.4.1 Clinical review

The methodological quality of the included diagnostic studies was assessed using the Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2).[6] The QUADAS-2 is a tool that evaluates the risk of bias in a selection of patients, index test, reference standard, and flow and timing of the study. The tool also addresses concerns about the applicability of tests and signaling questions to help identify potential biases.

Data from all included studies were extracted into predefined data extraction forms (Appendix 4). Relevant data were directly extracted from the text or tables. The data extraction was performed one reviewer. A second reviewer checked the abstracted data for accuracy. Any disagreements in data extraction were discussed until consensus was reached. The data extraction forms were piloted by the reviewers a priori, and a calibration exercise using a small number of studies was undertaken to ensure consistency between the reviewers.

3.4.2 Economic review

The methodological quality of cost-effectiveness studies was assessed using the guidelines for appraisal of economic studies by Drummond and Jefferson.[7]

3.5 Data analysis methods

3.5.1 Clinical review

a) Outcomes

Statistical outcomes that provided tests of differences in diagnostic test performance between types of tests included sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, AUC of the summary ROC curve, positive predictive value, negative predictive value, and diagnostic odds ratio. Details on how each of these methods was derived are provided in Appendix 5.

For clinical outcomes, it had been planned a priori in the protocol for this review to report differences between the study tests for changes in continuous measures (e.g., quality of life) as weighted mean difference and for changes in binary measures (such as thromboembolic events [e.g., VTE, DVT, PE], acute and chronic cardiovascular events, revascularization procedures, heart failure, recurrence, readmission and death), as relative risks. However, due to scarcity of studies reporting these outcomes, we could only provide a qualitative description of the reported incidence rates and hazard ratios.

b) Comparisons

Each of the diagnostic accuracy measures were estimated for the comparison between four possible tests: hs-cTnT assay, hs-cTnI assay, cTnT assay, and cTnI assay. The focus of the comparisons was:

- hs-cTnT versus cTnT
- hs-cTnI versus cTnI
- hs-cTnT versus cTnI
- hs-cTnI versus cTnT
- hs-cTnT versus hs-cTnI.

c) Direct and Indirect Comparisons

The analysis of the diagnostic performance involves two steps. In the first step, the direct comparison was generated that compares the test, such as hs-cTnI, to the reference standard for diagnosis of AMI for each study. Then the results of similar tests (hs-cTnI for AMI) were pooled to create one estimate. The pooling of the estimates was conducted with two different methods. In the preferred method, where there were at least four different studies that reported the same outcome, and the data were diverse enough to allow statistical convergence, a random effects meta-analysis for diagnostic tests was conducted in STATA with the command "midas tp fp fn tn." If there were fewer than five studies

(N < 5), then a fixed effects analysis was conducted with a simple sum of the elements in the 2x2 tables.[8] From the summarized table, the diagnostic estimates were generated.

In the absence of head-to-head evidence of tests such as hs-cTnT versus hs-cTnI, indirect comparisons were conducted to provide a comparative estimate between the two tests. The comparative estimates were compared as pairwise comparisons derived from the publicly available indirect treatment comparison software (http://www.cadth.ca/index.php/en/itc-user-guide) developed for CADTH by Wells et al. (2009).[9] The method used by the CADTH software has been referred to as the Bucher method.[10] One caveat with this analysis of the pairwise estimates, such as for sensitivity, was that the estimation was conducted under the assumption of normality which creates confidence intervals (CIs) not bounded by one, which was observed in the data. In particular, the CIs for sensitivity or specificity were never above the value 1.0. This is different than the CI for sensitivity or specificity alone, which are bounded by one because of the use of binomial CIs. The estimates from the indirect comparison were interpreted as a ratio of estimates (relative sensitivity, relative specificity, relative AUC.).[11]

d) Missing Data

There were published articles that did not report all of the statistical parameters and CIs, and wherever possible the missing parameters and CIs were derived using available information. For example, few studies reported the elements of the two-by-two contingency table; that is the number of true-positive, false-positive, true-negative, and false-negative results. Unfortunately, these latter values are required for meta-analysis of diagnostic accuracy studies.
To derive the missing information, we relied on two methods. First, given an estimate of sensitivity, specificity and positive predictive value, we could derive the prevalence of the disease cases; that is, the number of disease cases.[12]

PPV = (sensitivity*prevalence)/ ((sensitivity*prevalence + (1- specificity)*(1-prevalence)).

Second, for a given level of sensitivity and CIs, the number of disease cases can be derived to replicate the CI. This is under the assumption that the CIs were derived with binomial approximation methods. From the number of disease cases, the number of true positives and false negatives were derived. After a similar exercise for the non-disease cases, the numbers of true negatives and false positives were derived.[13] With the derived 2x2 table estimates, the estimates and CIs were recreated to ensure approximate consistency. Studies that reported estimates with few decimal places; e.g., sensitivity = 94 instead of 94.4, lead to the creation of a range of possible values in 2x2 table, and this may have led to differences in the 2x2 table from the original study. To minimize the differences, the mean predicted values of the 2x2 estimates were used.

3.5.2 Economic Review

Because of the difficulty in pooling results from economic evaluations, the economic literature is analyzed using qualitative descriptions only.

4 CLINICAL REVIEW RESULTS

4.1 Selection of primary studies

A total of 1,163 potential citations were identified by the systematic search, with 1,046 citations being excluded during the title and abstract review based on irrelevance to the questions of interest. The full text documents of the remaining 118 articles were retrieved. Of these 118 articles, 96 did not meet the eligibility criteria and were excluded. Twenty-six articles were excluded because they were published only in an abstract form. Three of the excluded studies were duplicate or older publications of the already included studies. Twenty-two articles, reporting 16 studies, met the inclusion criteria and were included in this review. Figure 1 shows the PRISMA flowchart of the process used to identify and select studies for the review and the main reasons for exclusion. The list of the excluded studies and the reasons for exclusion are provided in Appendix 6.

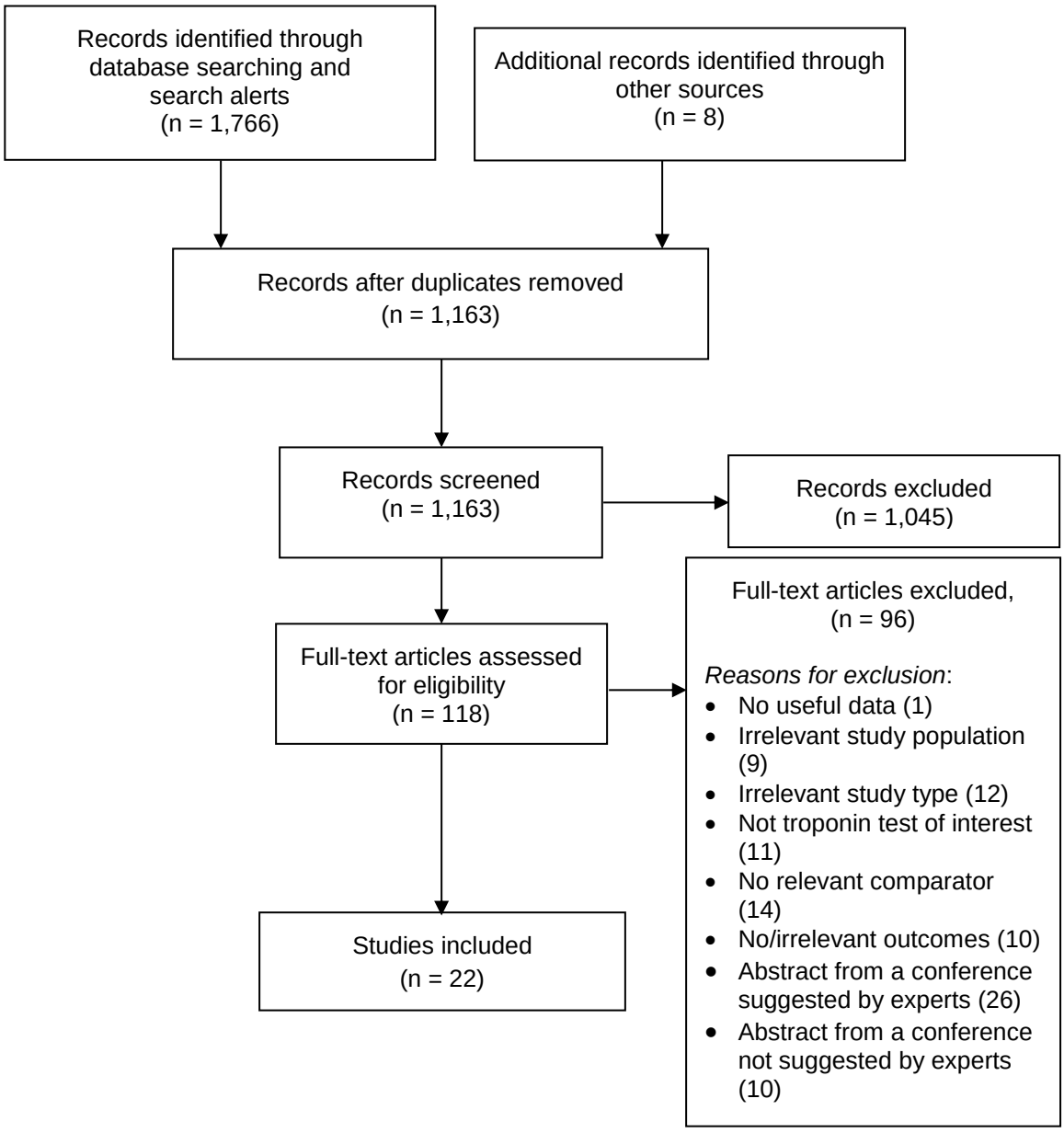
4.2 Study characteristics

An overview of the included studies is provided in Table 1. All of the included articles were published between 2009 and 2012, with the majority published in 2011 (54%). Four of the 16 included studies were conducted in Germany,[14-17] three in New Zealand,[18-20] three in the United States,[21-23] two in Canada,[24,25] one in the United Kingdom,[26] one in France,[27] and one in Sweden.[28] The APACE study was conducted in multiple countries in Europe.[29] The patients enrolled in all studies presented with chest pain to EDs or chest pain units. All studies enrolled adult patients. However, the inclusion criteria were limited to patients older than 21 years of age in three studies,[21,22,28] older than 25 years of age in one study,[26] and between the ages of 18 and 85 in one study.[16]

Fifteen of the included studies were diagnostic studies with a single cohort design, that is, all patients received all of the study tests and the reference standard, with the primary outcome of the study being diagnostic performance of cTn tests. One study[25] retrospectively selected a cohort of patients who had both hs-cTnI and AccuTnI tests performed using their “earliest presentation” blood samples. This study compared various concentrations of each test to the lowest concentration group in the same test result category, to evaluate the ability of the tests to predict death and MI. In all but one[28] of the diagnostic studies reference standard was uniformly reported to be the final diagnosis of AMI or ACS based on available clinical, laboratory and imaging information. Lindahl et al. (2010)[28] did not report the method for adjudicating of the final diagnosis, although they seem to have used the final diagnosis of AMI as the reference standard for evaluation of diagnostic accuracy of cTn tests. The final diagnoses were reported to be determined by two cardiologists (10 studies),[14-21,27,29] one cardiologist and one emergency physician (one study),[24] two unspecified physicians (one study),[23] or two investigators with MD and PhD degrees (one study).[26] Two studies did not report on the number and specialty of the adjudicator(s).[22,28] The diagnosis of AMI was based on the universal definition of MI provided by the joint task force of the ESC, ACC, AHA, and the World Heart Federation task force (2007) in four studies,[14,15,17,27] and the ESC/ACC 2000 definition of MI in three studies.[18-20] The remaining studies did not specify the definition they used for the diagnosis of AMI.

All of the studies consistently administered both high-sensitivity and cTn tests to all participants at presentation to ED. The details of the reference standard and cTn tests used, as well as times of measurement are provided in Table 1.

Figure 1: Study Selection Flow Diagram — Clinical Review



4.3 Critical Appraisal of Individual Studies

Table 2 summarizes the results of the QUADAS-2 assessments. Six studies were rated as being in a high risk of selection bias due to a failure to recruit a consecutive or random sample of patients,[15,19-21,23,25] four of those restricted their recruitment period to the morning to evening hours and excluded the patients referring to ED at night.[19-21,23] The likelihood of selection bias due to convenience sampling was discussed in one of these studies.[19] However, the authors reported they had missed only a small proportion of eligible patients who presented outside the recruitment hours. The authors of the three other studies did not discuss the restricted recruitment time as a limitation of their study.[20,21,23] One study included patients with a negative cTnT at baseline,[15] and one included patients for whom the results of cTn tests, performed on retrospectively collected blood samples, were available.[25] In six studies[16,17,22,26,28,29] it was unclear whether their exclusion criteria could have introduced any selection bias, four of them excluded pregnant patients or those with concurrent non-cardiac conditions that might have affected their cTn levels, such as renal failure or active malignancy;[16,22,26,29] and in two studies patients were recruited in a retrospective manner.[17,28]

Two studies reported blinding of the results of both high-sensitivity and cTn tests at the time of determining the final diagnosis.[18,24] In the remaining studies, the results of the cTn test (one of the index tests of interest in this review) were used to establish the diagnosis of MI or ACS (the reference standard).These studies were rated as having an unclear risk of bias in the index test domain.

None of the studies reported any specific information to assess whether the investigators were blinded to the reference standard results (final diagnosis) at the time of interpreting the results of cTn tests. This might raise a theoretical bias concern, especially for the retrospective studies. However, because in all of the studies the clinical diagnosis of MI (as the reference standard) required multiple clinical examinations and diagnostic tests, the results of which would have routinely been reported to the investigators who interpreted the results of index (cTn) tests, we decided it was impossible to blind the diagnosis process. Therefore, the risk of bias for reference standard was scored as low in all of the included studies. In addition, it was not possible to answer the question about the “appropriate interval between the index test and reference standard” because the exact time of confirmation of diagnosis (reference standard) was not reported by the authors of the included studies, due to the longitudinal nature of the clinical decision-making process.

Four studies were classified as being in high risk of bias for the flow and timing domain, in which a proportion of the recruited patients were excluded from the analysis due to technical problems, controversial management, insufficient serum sample, or missing test results.[14,15,21,26]

Overall, applicability concerns related to all three domains were low for all of the included studies. In order to be rated as applicable to the research question, the studies should have included the same patient population, same index tests (cTn assays), and same reference standard as were defined in our study questions. One study, which exclusively included patients with an objective sign of cardiac ischemia, was classified as raising higher levels of applicability concern in terms of patient selection.

Table 1: Characteristics of the Included Diagnostic Studies									
Study		**Country**	**Study Population**	**Target Condition**	**No. of Patients**	**Index Test**			**Reference Standard**
Study Group	**Author Year (study name)**					**CTn Test(s)**	**Cut-off(s) (mcg/L)**	**Time(s) of Measurement**	
G.1 (APACE)	**Reiter et al. 2012**[30]	Multinational	Adult patients presenting in ED with symptoms suggestive of MI within the last 12 hours. Subgroup analysis patients with CAD versus those without a history of CAD.	AMI, ACS	1098	Roche Elecsys hs-cTnT	0.014 (99th percentile)	0, 1, 2, 3, and 6 hours after presentation	Diagnosis by two independent cardiologists (and medical records) during a median follow-up of 3 months.
							0.003 (LoD)		
						Roche Elecsys cTnT Gen4	0.035 (10% CV)		
							0.010 (LoD)		
						Abbott Architect cTnI	0.028 (99th percentile)		
							0.010 (LoD)		
							0.032 (10% CV)		
						Siemens Centaur XP Ultra cTnI	0.040 (40 ng/L) (99th percentile)		
							0.006 (LoD)		
	Reiter et al. 2011[31]	Multinational	Subgroup analysis patients > 70 years old versus ≤ 70 years old).	AMI, ACS	1098	Roche Elecsys hs-cTnT	0.014 (99th percentile)	ED presentation	Diagnosis by two independent cardiologists (and medical records) during a median follow-up of 3 months.
							0.005 (LoD)		
						Roche Elecsys cTnT Gen4	0.035 (10% CV)		
							0.010 (LoD)		
						Abbott Architect cTnI	0.028 (99th percentile)		
							0.010 (LoD)		
							0.032 (10% CV)		
						Siemens Centaur XP Ultra cTnI	0.040 (99th percentile)		
							0.006 (LoD)		
	Hochholzer et al. 2011[32]	Multinational		AMI	1159	Roche Elecsys hs-cTnT	0.014 (99th percentile)	ED presentation	Diagnosis by two independent cardiologists who had access to all available medical records and data, but were blinded to the biomarker results used for the present analysis.
						Roche Elecsys cTnT Gen4	0.010 (LoD)		
	Reichlin et al. 2011[33]	Multinational		AMI	836	Roche Elecsys hs-cTnT	The diagnostic accuracy was reported based on absolute and relative changes in	0, 1, and 2 hours after presentation	Diagnosis by two independent cardiologists (and medical records) during a median follow-up of 3 months.
						Siemens Centaur XP			

Table 1: Characteristics of the Included Diagnostic Studies									
Study		**Country**	**Study Population**	**Target Condition**	**No. of Patients**	**Index Test**			**Reference Standard**
Study Group	**Author Year (study name)**					**CTn Test(s)**	**Cut-off(s) (mcg/L)**	**Time(s) of Measurement**	
						Ultra cTnI	cTn levels.		
	Reichlin et al. 2009[29]	Multinational		AMI	718	Roche Elecsys hs-cTnT	0.014 (99th percentile)	0, 1, 2, 3, and 6 hours after presentation	Diagnosis by two independent cardiologists (and medical records) during a median follow-up of 2 months.
							0.002 (LoD)		
						Roche Elecsys cTnT Gen4	0.035 (10% CV)		
							0.010 (LoD)		
						Roche cTnI	0.160 (99th percentile)		
							0.100 (LoD)		
							0.300 (10% CV)		
						Abbott Architect cTnI	0.028 (99th percentile)		
							0.010 (LoD)		
							0.032 (10% CV)		
						Siemens Centaur XP Ultra cTnI	0.040 (99th percentile)		
							0.006 (LoD)		
Mueller et al. 2012[14]		Germany	Patients with suspected ACS who referred to the chest pain unit. Patients were not excluded for severe renal failure or older age.	NSTEMI, Death, Death/MI	1384	Roche Elecsys hs-cTnT	0.014 (99th percentile)	At presentation and every 6 hours (up to 24 hours) if needed	Diagnosis of acute MI based on the criteria of the Joint ESC/AACF/AHA/WHF Task Force definition. Final diagnoses made by two cardiologists.
						Siemens Centaur XP Ultra cTnI	0.040 (99th percentile)		
G.2	**Kurz et al. 2011**[15]	Germany	Patients presenting to the ED with chest pain suggestive of ACS admitted to chest pain unit.	AMI	94	Roche Elecsys hs-cTnT	0.0135 (99th percentile)	At presentation	Diagnosis of MI according to ESC/ACC/AHA/WHF Task Force guidelines; NSTEMI also needed addition of cTnT changes with additional clinical symptoms Final diagnosis was made by two cardiologists.
						Roche Elecsys cTnT	0.03 (recommended threshold); 0.01 (LoD)		
	Giannitsis et al. 2010[34]	Germany		UA or evolving NSTEMI	863	Roche Elecsys hs-cTnT	0.013 (99th percentile)	0, 1 to 2 and 6 hours after presentation	
						Roche Elecsys cTnT Gen4	0.03 (10% CV)		
G.3	**Aldous et al. 2012**[18]	New Zealand	Patients who attending physician deemed sufficiently	AMI	332	Roche Elecsys hs-cTnT	0.014 (99th percentile)	0 and 6 to 24 hours after	Diagnosis by two independent cardiologists based largely on ACC
							0.005 (LoD)		

Table 1: Characteristics of the Included Diagnostic Studies									
Study		**Country**	**Study Population**	**Target Condition**	**No. of Patients**	**Index Test**			**Reference Standard**
Study Group	**Author Year (study name)**					**CTn Test(s)**	**Cut-off(s) (mcg/L)**	**Time(s) of Measurement**	
			suspicious of ACS that cTn and ECG though necessary for diagnosis.				0.013 (10% CV)	presentation	definitions.
						Roche Elecsys cTnT Gen4	0.03 (10% CV)		
							0.010 (LoD)		
							0.01 (99th percentile)		
						Abbott Architect cTnI	0.028 (99th percentile)		
							0.010 (LoD)		
							0.032 (10% CV)		
	Aldous et al. 2011[35]	New Zealand		MACE, Death	332	Roche Elecsys hs-cTnT	0.014 (99th percentile)		diagnosis by two independent cardiologists based largely on ACC definitions, and 2-year follow-up for outcomes.
						Roche Elecsys cTnT Gen4	0.032 (10% CV)		
						Abbott Architect cTnI	0.028 (99th percentile)		
Kavsak et al. 2012[24]		Canada	Patients ≥ 18 years of age with possible cardiac ischemic symptoms within 6 hours before presentation, who had a cTn test ordered by an ED physician.	Serious Adverse Cardiac Events	186	Roche Elecsys hs-cTnT	0.014 (99th percentile)	At presentation	Diagnosis by a cardiologist and an ED physician, independently, who were blinded to the biomarker data, except for cTnI.
						Beckman Coulter hs-cTnI	0.010 (99th percentile)		
						Beckman Coulter AccuTnI	0.04 (99th percentile)		
Schreiber et al. 2012[21]		US	Adult (> 21 years of age) with suspected ACS who referred to ED on weekdays between 9:00–17:00 hours, where study coordinators were available.	AMI	486	Errena Singulex hs-cTnI	0.008 (99th percentile)	0 and 1.5 hours after presentation	Diagnosis by two independent cardiologists (and medical records) during a 30 days follow-up period.
						Siemens Dimension RxL cTnI	0.070 (99th percentile)		
Bhardwaj et al. 2011 (IMAGINE)[22]		US	Patients ≥ 21 years old with symptoms thought to represent possible ACS, including chest discomfort.	ACS	318	Errena Singulex hs-cTnI	0.00628 (99th percentile)	2 to 4 hours from presentation	Diagnosis of ACS and acute MI using standard (not specified) criteria by Investigators at each site reviewing the cases.
						Roche Elecsys cTnT Standard	0.03 (10% CV)		
Body et al. 2011[26]		UK	Patients >25 years with chest pain within the previous	AMI	703	Roche Elecsys hs-cTnT	0.014 (99th percentile)	At presentation	Diagnosis by two independent investigators who had all clinical,
							0.003 (LoD)		

Table 1: Characteristics of the Included Diagnostic Studies									
Study		**Country**	**Study Population**	**Target Condition**	**No. of Patients**	**Index Test**			**Reference Standard**
Study Group	**Author Year (study name)**					**CTn Test(s)**	**Cut-off(s) (mcg/L)**	**Time(s) of Measurement**	
			24 hours and the initial treating physician suspected may be cardiac in nature.			Roche Elecsys cTnT Standard	0.010 (99th percentile)		laboratory, and imaging data available for review, but who were blinded to hs-cTnT levels.
Aldous et al. 2011[19]		New Zealand	Patients attending ED between 05:30 hours and 20:00 hours who presented within 4 hours of symptom onset and had ischemic-type pain.	AMI	358	Roche Elecsys hs-cTnT	0.014 (99th percentile)	0, 1, 2, and 24 hours after presentation	Diagnosis of MI using a predefined objective-structured adjudication process based ACC definitions 2001. Final diagnosis was made by two cardiologists.
						Abbott Architect cTnI	0.028 (99th percentile)		
Aldous et al. 2011 (ASPECT)[20]		New Zealand	Patients ≥ 18 years with at least 5 minutes of chest pain presenting to the ED between 05:30 and 20:00 hours.	AMI, ACS	1000	Roche Elecsys hs-cTnT	0.014 (99th percentile)	0 and 2 hours after presentation	Clinical symptoms, 30 days follow-up and the results of Lab-cTnI (Abbott Architect) 0, 2, and 6 to 12 hours after admission. Final diagnosis was made by two cardiologists.
						POC-cTnI	< 0.05 (99th percentile)		
Keller et al. 2011 (Prospective Biomarkers Assessment Registry)[16]		Germany	Patients between 18 and 85 years of age presenting with acute angina pectoris or equivalent symptoms (chest pain/suspected ACS).	AMI	1818	Abbott Architect hs-cTnI	0.010 (LoD)	0 and 3 hours after presentation	Diagnosis by two independent cardiologists (and medical records) during a 30 days follow-up period.
							0.032 (10% CV)		
						Abbott Architect cTnI	0.0034 (LoD)		
							0.030 (99th percentile)		
Freund et al. 2011[27]		France	Patients >18 years who presented to the ED with chest pain suggestive of ACS with onset or peak occurring within the previous 6 hours.	AMI	317	Roche Elecsys hs-cTnT	0.014 (99th percentile)	0 and 3 to 9 hours after presentation	Diagnosis by two independent cardiologists (and medical records, including cardiac cTn values and coronary angiography and discharge summary).
						Beckman Coulter AccuTnI OR Siemens Centaur XP Ultra cTnI	0.14 (Siemens), 0.06 (Beckman) (10% CV)		
Januzzi et al. 2010 (ROMICAT)[23]		US	Low to intermediate-risk patients presenting to ED weekdays between	UA, AMI, ACS	377	Roche Elecsys hs-cTnT	0.013 (99th percentile)	0 and 48 hours after presentation	Diagnosis by two independent physicians (and medical records, including Stat T cTnT) during a 6
						Roche Elecsys cTnT Gen4	0.01 (99th percentile)		

Table 1: Characteristics of the Included Diagnostic Studies									
Study		**Country**	**Study Population**	**Target Condition**	**No. of Patients**	**Index Test**			**Reference Standard**
Study Group	**Author Year (study name)**					**CTn Test(s)**	**Cut-off(s) (mcg/L)**	**Time(s) of Measurement**	
			07:00 and 19:00 with chest discomfort and clinical suspicion of ACS; age > 18 years, > 5 minutes of chest discomfort within 24 hours.				0.03 (recommended threshold)		months follow-up period.
Lindahl et al. 2010 (GUSTO-IV)[28]		Sweden	≥ 21 years of age with one or more episodes of angina lasting ≥5 minutes, within 24 hours of admission, and either a positive cTnT or cTnI test result or ≥ 0.5 mm of transient or persistent ST-segment depression.	Death/ AMI	1452	Roche Cobas hs-cTnT	0.014 (99th percentile)	0 and 6 to 24 hours after presentation	Recording mortality or rate of adjudicated MI, at 30 days.
						Roche Elecsys cTnT Gen3	0.010 (99th percentile)		
Christ et al. 2010[17]		Germany	Patients with acute chest pain of possible coronary origin alone as judged by the emergency physician on duty.	AMI	137	Roche Elecsys hs-cTnT	0.014 (99th percentile)	At presentation	Diagnosis by two independent cardiologists based on the universal definition of MI, 6 months follow-up and cardiac cTn results
							0.003 (LoD)		
						Roche Elecsys cTnT Gen4	0.01 (LoD)		
							0.035 (10% CV)		
Kavsak et al. 2009[25]		Canada	Patients presenting to ED (in 1996) with symptoms suggestive of ACS who had frozen specimens with sufficient volume for measurement of AccuTnI (in 2003) and hs-cTnI (in 2007).	ACS	383	Beckman Coulter hs-cTnI	Various	At presentation	The lowest concentration group.
						Beckman Coulter AccuTnI	Various		

ACS = acute coronary syndrome; AMI = acute myocardial infarction; cTnT = cardiac troponin T; CAD = coronary artery disease; ECG = echocardiogram; ED = emergency department; ESC = European Society of Cardiology; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; LoD = limit of detection; MACE = major adverse cardiac events; MI = myocardial infarction; No. = number; NSTEMI = non-ST-segment elevation myocardial infarction; UA = unstable angina; UK = United Kingdom; US = United States; WHF = World Heart Federation.

Table 2: Risk of Bias and Applicability in the Included Diagnosis Studies (results of QUADAS-2 quality assessment)								
Study	**Risk of Bias**				**Applicability Concerns**			**Potential Issues**
Author and Year (study name)	**Patient Selection**	**Index Test**	**Reference Standard**	**Follow and Timing**	**Patient selection**	**Index Test**	**Reference Standard**	
G.1 (APACE)[29-33]	?	?	L	L	L	L	L	• Patients with terminal kidney failure requiring dialysis were excluded. • The results of cTn tests were used in interpreting the reference standard.
Mueller 2012[14]	L	?	L	H	L	L	L	• Approximately 10% of the included patients were excluded from the analysis due to controversial management or missing test results. • The results of cTn test were used in interpreting the reference standard.
G.2[15,34]	H	?	L	H	L	L	L	• Patients with a negative initial cTnT enrolled (pop is "evolving NSTEMI"). • Patients with severe kidney disease and those undergoing PCI were excluded. • A number of patients were excluded due to technical problems (206). • The results of cTn tests were used in interpreting the reference standard.
G.3[18,35]	L	L	L	L	L	L	L	• Only included patient that had both a baseline and follow-up cTn results.
Kavsak 2012[24]	L	L	L	L	L	L	L	• Patients for whom outcome occurred before the performance of the first cTn test were excluded.
Schreiber 2012[21]	H	?	L	H	L	L	L	• Patient recruitment took place on weekdays between 9:00 and 17:00h. • The results of cTn tests were used in interpreting the reference standard. • About 5% of the included patients were excluded from the analysis due to insufficient quantity of blood for test.
Bhardwaj 2011(IMAGINE)[22]	?	?	L	L	L	L	L	• Patients receiving thrombolytic agent before 1st blood draw; those with ACS secondary to high output states; diagnosis of liver cirrhosis; renal failure requiring dialysis; and patients presenting 2 hours after relief of cardiac symptoms; chest pain after trauma to chest; acute infection; cocaine-related chest pain; pregnancy; active malignancy; acute bowel ischemia; severe peripheral vascular disease; and acute cerebral ischemia were excluded. • The results of cTn tests were used in interpreting the reference standard.
Body 2011[26]	?	?	L	H	L	L	L	• Patients with renal failure requiring dialysis, trauma with suspected myocardial contusion, or another medical condition mandating hospital admission were excluded. • The results of cTn tests were used in interpreting the reference standard.

Table 2: Risk of Bias and Applicability in the Included Diagnosis Studies (results of QUADAS-2 quality assessment)								
Study	**Risk of Bias**				**Applicability Concerns**			**Potential Issues**
Author and Year (study name)	**Patient Selection**	**Index Test**	**Reference Standard**	**Follow and Timing**	**Patient selection**	**Index Test**	**Reference Standard**	
								• A percentage of patients were excluded due to insufficient serum sample.
Aldous *2011*[19]	H	?	L	L	L	L	L	• Patient recruitment took place daily between 5:30 and 20:00h. • The results of cTn tests were used in interpreting the reference standard.
Aldous *2011 (ASPECT)*[20]	L	?	L	L	L	L	L	• Patient recruitment took place daily between 5:30 and 20:00h. • The results of cTn tests were used in interpreting the reference standard. • STEMI patients were excluded from the analysis (less likely to introduce bias, since the results will be pooled with studies with similar patient population, if possible).
Keller 2011 (Prospective Biomarkers Assessment Registry)[16]	?	?	L	L	L	L	L	• Pregnant patients, intra-venous (IV) drug abusers, patients with recent trauma or surgery, and anemic patients were excluded. • The results of cTn tests were used in interpreting the reference standard.
Freund *2011*[27]	L	?	L	L	L	L	L	• The results of cTn tests were used in interpreting the reference standard.
Januzzi 2010 (ROMICAT)[23]	H	?	L	L	L	L	L	• "Convenience sample", low to intermediate-risk patients accepted on weekdays between 7:00 and 19:00h. • Results of cTn tests were used in interpreting the reference standard.
Lindahl 2010 (GUSTO-IV)[28]	?	?	?	L	H	L	L	• The study was performed in a RCT population (retrospectively) with an objective sign of cardiac ischemia. • It is not clear if the index tests were interpreted without the knowledge of the results of the reference standard. • The results of cTn tests were used in interpreting the reference standard.
Christ 2010[17]	?	?	L	L	L	L	L	• The study was performed using retrospective data • The results of cTn tests were used in interpreting the reference standard.
Kavsak 2009[25]	H	?	L	L	L	L	L	• The study population was restricted to the patients who had both AccuTnI and hs-cTnI tests performed on retrospectively collected specimens.

? = unclear; ACS = acute coronary syndrome; ctn = cardiac troponin; G = group of studies; H = high; hs-cTnI = high-sensitivity cardiac troponin I; L= low; NSTEMI = non-ST-segment elevation myocardial infarction; RCT = randomized controlled trial; STEMI = ST-segment elevation myocardial infarction.

4.4 Data analyses and synthesis

4.4.1 Diagnostic test performance of hs-cTnT and hs-cTnI assays compared with each other as well as with conventional cTnT and sensitive cTnI assays in patients with suspected ACS symptoms in the ED?

a) Diagnostic performance of cTn assays compared with the reference standard (direct comparisons)

Diagnostic performance of a single cTn test administered at ED presentation
Overall seven studies contributed to the pooled analysis of the diagnostic accuracy of a single cTn test sample for diagnosis of AMI at the time of ED presentation.[15,16,18,19,21,26,29] Different cTn tests were considered as index tests and final diagnosis of AMI served as the reference standard in our analysis. To avoid heterogeneous data, this analysis excluded the studies if they reported on specific subgroups of patients, excluded STEMI patients from their analyses, or reported the diagnosis accuracy of the tests performed in time points other than ED presentation.

In the selected studies, cTn assays were used with different diagnostic threshold levels: limit of detection (LoD), that is the lowest concentration of cTn that can be reliably detected by a testing procedure; 99th percentile cut-off point, that is the 99th percentile of the values for a reference control group (healthy population); and 10% coefficient of variation (CV), that is the lowest concentration with an acceptable imprecision (CV < 10%). The cut-off values were different for each type of cTn test and varied from one study to another (Table 1). We only included accuracy data related to cut-off points that had been determined a priori by the investigators and used as a part of laboratory diagnostic criteria. The reported information related to the cut-off points determined in a data-dependent manner, based on ROC curve analyses, was excluded from our pooled analyses. ROC-derived thresholds maximize both sensitivity and specificity and their inclusion in a meta-analysis might result in overestimation of actual diagnostic accuracy.

Data on the performance of a single hs-cTnI, hs-cTnT, cTnI, or cTnT, carried out at ED presentation for diagnosis of AMI, were available from three,[16,21,22] five,[15,18,19,26,28] six,[16,18,19,21,26,29] and four[18,22,26,29] studies. Reichlin et al.[29] used three different cTnI assays in a single study. Therefore, data from multiple arms of this study were included in the pooled analyses related to cTnI. Table 3 presents the sensitivity and specificity measures of the cTn assays reported in these studies. The results of direct pooled analyses of cTn test versus the gold standard (final diagnosis of AMI) at the time of presentation are provided in Table 4. As it is shown in this table, among the four types of cTn assays, the highest sensitivity of a single sample for diagnosis of AMI was found for hs-cTnI at LoD threshold (1.00, 95% CI, [0.98 to 1.00]; one study;[16] n = 1,818) and the highest specificity was for cTnT at 10% CV threshold (0.97 to 95% CI, [0.96 to 0.98]; two studies;[18,29] n = 1,050). The pooled analysis also showed that the summary estimates of sensitivity for all four types of cTn assays were consistently higher at the cut-off point of LoD; whereas, no similar pattern was detected for summary estimates specificity. Data from the study by Bhardwaj et al. (2011; n = 318)[22] in which the diagnostic accuracy of hs-cTnI for ACS were compared with that of cTnT was not included in the pooled analysis of baseline measurement data because this study reported to have performed cTn tests of interest at two to four hours after ED admission. In this study, the sensitivity and specificity of hs-cTnI was reported to be 0.57 (95% CI, 0.45 to 0.67) and 0.86 (95% CI, 0.81 to 0.90) respectively. The sensitivity and specificity values for cTnT were 0.22 (95% CI, 0.14 to 0.34) and 0.97 (95% CI, 0.94 to 0.99) respectively, at two to four hours after ED admission.

b) Comparison of diagnostic thresholds of cTn assays (single measurement)

The pooled estimates of sensitivity and specificity for different cut-off points of the four types of cTn tests are also shown in summary ROC curves (Figures 2 to 5).

Due to paucity of studies utilizing hs-cTnI, we could not compute the diagnostic performance of this test at the 10% CV cut-off point. The sensitivity of hs-cTnI at LoD (1.00; 95% CI, [0.98 to 1.00], one study;[16] n = 1,818) was statistically higher than that of the 99th percentile cut-off point (0.82; 95% CI, [0.79 to 0.85], two studies;[16,21] n = 2,204) and its specificity (0.31; 95% CI, [0.28 to 0.34], one study;[16] n = 1,818) was statistically lower than that of the 99th percentile cut-off point (0.824; 95% CI, [0.790 to 0.854], two studies;[16,21] n = 2,204) (Table 4 and Figure 2).

There was no statistically significant difference between sensitivities of hs-cTnT at 99th percentile and 10% CV cut-off points. However, the sensitivity of this test at LoD (0.97; 95% CI, [0.96 to 0.98], three studies;[18,26,29] n = 1,753) was statistically higher, and its specificity at this threshold (0.326; 95% CI, [0.321 to 0.329], three studies;[18,26,29] n = 1,753) was statistically lower than those of the two other cut-off points (Table 4 and Figure 3).

The sensitivities and specificities of all three cut-off points of cTnI were statistically different, with LoD being the most sensitive (0.92; 95% CI, [0.90 to 0.93], three studies;[16,18,29]; n,= 2,868) and least specific (0.808; 95% CI, [0.804 to 0.812], three studies;[16,18,29]; n,= 2,868) and the 99th percentile threshold being the most specific (0.94, 95% CI, [0.92 to 0.96], five studies;[16,18,19,21,29] n,=,3,712) and least sensitive (0.81, 95% CI, [0.76 to 0.85], five studies;[16,18,19,21,29] n,=,3,712) among the three cut-off points (Table 4 and Figure 4).

The sensitivity of cTnT at 10% CV threshold (0.48, 95% [CI, 0.46 to 0.50], two studies;[18,29] n = 1,050) was statistically lower and its specificity (0.97, 95% CI, [0.96 to 0.98], two studies;[18,29] n = 1,050) was statistically higher than the two other cut-off points for this test (Table 4 and Figure 5). No statistically significant differences were found between the 99th percentile threshold and LoD for cTnI in terms of sensitivity and specificity.

When ROC curves were constructed for different cut-off points of each cTn assay, the AUC for cTn tests were not statistically different, based on the overlapping CIs.

c) Diagnostic performance of serial cTn tests

Due to the paucity of data on serial measurements of the cTn assays no pooled analysis was conducted to evaluate the diagnostic accuracy of combinations of consecutive cTn tests. Overall, three of the included studies reported on the performance of serial cTn assays.[14,16,27] Two of these studies reported the diagnostic accuracy of serial testing in diagnosis of AMI;[14,27] whereas, one study reported the accuracy of relative changes of cTn concentration during consecutive measurements.[16] All three studies compared hs-cTnT with cTnI.

The diagnostic accuracy measures of serial cTn testing from the available studies are summarized in Table 5. As the Table shows, the sensitivity and specificity of serial hs-cTnT ranged from 0.93[27] to 0.98[14] and from 0.41[14] to 0.82[27] respectively. The sensitivity of serial cTnI varied between 0.71[27] and 0.91[14] and its specificity between from 0.46[14] to 0.97.[27]

d) Subgroup analyses

Data on the following patient subgroups were available from the included studies. These subgroups were not pre-specified. In all of these studies different cTn (index) tests were compared with the final diagnosis of AMI (as the reference standard).

NSTEMI

Aldous et al. (2011)[20] focused their analysis on NSTEMI patient (n = 1,000), hs-cTnT was compared with point-of-care cTnI (POC-cTnI).The sensitivity and specificity of hs-cTnT for diagnosis of AMI at a cut-off point of 99th percentile were found to be 0.91 (95% CI, 0.87 to 0.94) and 0.81 (95% CI, 0.80 to 0.82) respectively. POC-cTnI showed significantly lower sensitivity (0.62, 95% CI, 0.58 to 0.66), and higher specificity (0.96; 95% CI, 0.94 to 0.97) values.

Timing of assessment

Subgroup data on timing of assessment were available for two studies.[26,29] Table 6 summarizes the diagnostic performance measures of cTn tests in the subgroup of patients with early versus late presentation. Both studies considered a three-hour period after the onset of symptoms as a cut-off point for definition of early presentation. Body et al.[26] used an additional six-hour cut-off point to distinguish between early and late presentation. As the table shows, hs-cTnT showed sensitivity and specificity values higher than 80% when it was used at a 99th percentile cut-off point, regardless of timing of assessment. The point estimates of sensitivity were perfect (1.00) in both studies when using LoD cut-off points, but specificity values were lower and variable at this threshold. By contrast, cTnT had much lower levels of sensitivity (0.44[29] to 0.66[26] in patients who presented within three hours and 0.71[26] in those who presented within six hours from the onset of chest pain), compared with those in the late presentation subgroup where the sensitivity of cTnT improved considerably (0.92 in patients who presented within three hours and 0.93 who presented within six hours from the onset of chest pain).[26] The specificity estimates for cTnT maintained between 0.82 and 0.93 in the late presentation subgroup.[26]

Reichlin et al. (2009)[29] reported the diagnostic performance of cTnI in patients who presented within three hours of their symptoms (Table 6) but did not report the results of late measurements. Based on the results of this study, the sensitivity values of cTnI assays for detection of AMI were maximized (≥ 0.85), when they were used at LoD thresholds. The specificity values were relatively stable across different cut-off points, except for Siemens-Ultra cTnI, which yielded a significantly lower specificity when using LoD (0.74; 95% CI, [0.67 to 0.80], as compared with the 99th percentile cut-off point (0.95; 95% CI, [0.90 to 0.97]).

Baseline risk stratification

One of the included studies[27] reported the diagnostic performance of cTn tests in subgroups of patients with high risk of MI at baseline (n = 59) and those with intermediate or low risk of MI at baseline (n = 258). One additional study[23] limited its patient population to low and intermediate-risk patients (n = 377). The findings of these studies are shown in Table 7. Januzzi et al. (2010)[23] reported similar sensitivity values for hs-cTnT and cTnT in low and moderate-risk patients (0.88, 95% CI, [0.47 to 1.00]). However, the comparison of the reported estimates of specificity and their CIs shows that the specificity of cTnT (0.94 with 95% CI [0.92, 0.97] and 0.97 with 95% CI, [0.95 to 0.98] for the 99th percentile and LoD thresholds respectively) was statistically higher than that of hs-cTnT (0.85; 95% CI, [0.81 to 0.89]) in patients with a low-to-moderate risk of disease.

In the study by Freund et al. (2011),[27] hs-cTnT was shown to have similar sensitivity values in high and low-risk subgroups, but the specificity of the test was statistically higher in the low-to-moderate-risk population (0.85 [95% CI, 0.79 to 0.89] versus 0.67 [95% CI, 0.49 to 0.81] in high-risk group). When compared with hs-cTnT, in both risk categories, cTnI was reported to have relatively lower sensitivity (0.77 [95% CI 0.54 to 0.92] versus 0.91.(95% CI, 0.69 to 0.98) in low risk and 0.65 [95% CI, 0.43 to 0.83] versus 0.96 [95% CI, 0.76 to 1.00] in high-risk populations),

but higher specificity values (0.97 [95% CI, 0.94 to 0.99] versus 0.85 [95% CI, 0.79 to 0.89] in the low-risk group and 0.94 [95% CI, 0.79 to 0.99] versus 0.67 [95% CI, 0.49 to 0.81] in the high- risk populations) (Table 7).

History of ischemic heart disease

One study reported on the diagnostic performance of hs-cTnT, cTnT, and two cTnI (Abbott Architect and Siemens-Ultra) assays in diagnosis of AMI, based on the patients' history of ischemic heart disease (IHD).[30] As it is demonstrated in Table 8, in both subgroups of patients with (n = 401) and without (n = 697) a history of IHD, hs-cTnT was statistically more sensitive than cTnT, according to non-overlapping CIs. However, there was no statistically significant difference between hs-cTnT and cTnI assays. When compared between the two subgroups of patients with and without a history of IHD, hs-cTnT had similar sensitivity values. However, it was statistically more specific in patients with a negative history (0.81 [95% CI, 0.78 to 0.84] versus 0.59 [95% CI, 0.54 to 0.65] in patients with a positive history). In both subgroups, cTnI assays were reported to have sensitivity and specificity values that were greater than 80%. The specificity of these assays was slightly higher in patients with no previous ischemic heart disorders.

Baseline cTn test results

The diagnostic performance of repeated cTn assays was evaluated in three studies,[16,33,34] based on the baseline cTn test results. An overview of the diagnostic accuracy estimates from these studies is presented in Table 9. One of the three studies, that excluded STEMI patients from the analysis, reported the accuracy of cTn tests in the diagnosis of NSTEMI from UA only in patients who had initially positive test results.[34] The two other studies that had AMI as the outcome of interest reported on the diagnostic performance of cTn tests in patients with a positive or negative test at baseline.[16,33] All three studies compared hs-cTnT to a cTnI assay.

Comparison of the sensitivity and specificity values estimated from data presented by Reichlin et al. (2011)[33] showed that, in patients with a positive baseline test, hs-cTnT was statistically more sensitive and less specific than Siemens cTnI-ultra, when these cTn tests were performed two hours after an initially positive cTn assay (Table 9). In patients who had negative test results at baseline; however, this study found no statistically significant difference between hs-cTnT and cTnI-Ultra assays, which were performed one or two hours after ED admission. The differences reported by the two other studies[16,34] were also non-significant in either of the subgroups.

Age groups

Reiter et al. (2011)[31] reported on the diagnostic performance of hs-cTnT, cTnT, and two cTnI (Abbott Architect and Siemens-Ultra) assays in elderly patients *(*> 70 years of age; n = 406) and those who were under 70 years of age (n = 681) (Table 10). This study found no significant difference between hs-cTnT and the cTnI assays in terms of diagnostic performance in either of the subgroups. However, as it is shown in Table 10, the sensitivity values of cTnT in both subgroups (0.59 [95% CI, 0.47 to 0.70; 10% CV threshold] for ≤ 70 years, and 0.83 [95% CI, 0.84 to 0.90; LoD threshold] or 0.76 [95% CI, 0.57 to 0.79; 10% threshold] for > 70 years age groups) were statistically lower than those of hs-cTnT (0.88 [95% CI, 0.78 to 0.94; 99th percentile threshold] for under 70, and 1.00 [95% CI, 0.96. 1.00; LoD threshold] or 0.98 [95% CI, 0.93 to 1.00; 99th percentile threshold] for 70 plus age groups). On the contrary, the specificity values of cTnT (0.98 [95% CI, 0.97 to 0.99; 10% CV threshold] for under 70, and 0.90 [95% CI, 0.86 to 0.93; LoD threshold] or 0.96 [95% CI, 0.93 to 0.98; 10% threshold] for > 70 years age groups) were statistically higher than those of hs-cTnT (0.86 [95% CI, 0.83 to 0.89; 99th percentile threshold] for under 70, and 0.01 [95% CI 0.00. 0.03; LoD threshold] or 0.49 [95% CI

0.0.44, 0.55; 99th percentile threshold] for > 70 age groups). Based on the construction of ROC curves for different diagnostic thresholds, the authors suggested that the optimum cut-off points were significantly higher in the elderly population than in younger patients.

e) Relative diagnostic accuracy of cTn assays (indirect comparisons)

Based on the 99th percentile cut-off point at ED presentation, Table 11 presents estimates of relative diagnostic accuracy for the diagnosis of AMI with the four cTn assays, using indirect comparisons. Overall diagnostic accuracy is represented by the AUC of the ROC curve. The relative sensitivity and specificity are also presented.

As shown in the table, overall relative diagnostic accuracy for hs-cTnT was statistically lower compared with both cTnT (0.942; 95% CI, 0.907 to 0.977), and cTnI (0.923, 95% CI, 0.886 to 0.961). Overall relative diagnostic accuracy for hs-cTnI is not statistically different compared with either cTnT (1.016; 95% CI, 0.993 to 1.040) or cTnI (0.996; 95% CI, 0.968 to 1.025). Comparing the high-sensitivity tests to each other finds hs-cTnI to have higher overall diagnostic accuracy compared with hs-cTnT (1.079; 95% CI, 1.038 to 1.122). Relative sensitivity for hs-cTnT was statistically higher compared with both cTnT (1.353; 95% CI, 1.272 to 1.439), and cTnI (1.089; 95% CI, 1.077 to 1.180). Relative sensitivity for hs-cTnI was found to be statistically higher compared with cTnT (1.270; 95% CI, 1.215 to 1.327), but not compared with cTnI (1.024; 95% CI, 0.949 to 1.104). Although hs-cTnT had higher relative sensitivity compared with hs-cTnI, it was not statistically significant (1.066; 95% CI, 0.998 to 1.138). Relative specificity for hs-cTnT was statistically lower compared with both cTnT (0.864; 95% CI, 0.844 to 0.886), and cTnI (0.875; 95% CI, 0.849 to 0.901). Relative specificity for hs-cTnI was found to be statistically lower compared with cTnT (0.942; 95% CI, 0.931 to 0.954) and to cTnI (0.953; 95% CI, 0.933 to 0.973). When comparing the two high-sensitivity cTn tests with each other, hs-cTnI had higher relative specificity compared with hs-cTnT (1.090; 95% CI, 1.064 to 1.116).

Based on the 10% CV cut-off point at ED presentation, Table 12 presents estimates of relative diagnostic accuracy for diagnosis of AMI with the four cTn assays, using indirect comparisons. As shown, overall relative diagnostic accuracy for hs-cTnT was statistically lower compared with cTnI (0.946; 95% CI, 0.926 to 0.967), but not compared with cTnT (0.983, 95% CI, 0.964 to 1.007). Relative sensitivity for hs-cTnT was statistically higher compared with cTnT (0.577; 95% CI, 0.534 to 0.623), but not cTnI (0.963; 95% CI 0.945 to 0.982). Relative specificity for hs-cTnT was statistically lower compared with cTnT (0.853; 95% CI, 0.824 to 0.886) and cTnI (0.905; 95% CI, 0.874 to 0.937). No data were available to compare diagnostic accuracy of hs-cTnI compared with other cTn tests.

Table 13 presents similar results using a cut-off point based on the LoD. Overall relative accuracy of hs-cTnT for diagnosis of AMI was statistically lower compared with cTnT (0.956; 95% CI, 0.934 to 0.978), and cTnI (0.940; 95% CI, 0.922 to 0.959). Relative sensitivity for hs-cTnT was statistically higher compared with both cTnT (1.469; 95% CI, 1.420 to 1.519), and cTnI (1.060, 95% CI, 1.040 to 1.080). Relative sensitivity for hs-cTnI was found to be statistically higher compared with cTnT (1.508; 95% CI, 1.459 to 1.559), but not cTnI (1.088; 95% CI 1.060 to 1.104). The relative sensitivity was higher for hs-cTnI compared with hs-cTnT (1.027; 95% CI, 1.011 to 1.042).

Relative specificity for hs-cTnT was statistically lower compared with both cTnT (0.344; 95% CI, 0.339 to 0.350) and cTnI (0.403; 95% CI, 0.398 to 0.409). Relative specificity for hs-cTnI was found to be statistically lower compared with cTnT (0.325; 95% CI, 0.294 to 0.359), but not compared with cTnI (0.381; 95% CI, 0.345 to 0.421). There was no statistically significant

difference in the relative specificity of hs-cTnT compared with hs-cTnI (1.058; 95% CI, 0.958 to 1.170).

4.4.2 What is the clinical effectiveness of hs-cTnT and hs-cTnI assays compared with each other as well as with conventional cTnT and sensitive cTnI assays in patients with suspected ACS symptoms in the ED?

a) Major cardiovascular events

Mortality data were available from five studies.[14,17,28,32,35] The incidence data reported by two studies[14,28] are presented in Table 14. Estimates of hazard ratio for death and/or MI, using Cox proportional hazard analyses, and the accuracy of cTn tests in prognosis of cardiac or all-cause mortality (with or without MI) were reported in five[14,25,28,32,35] and two[32,35] studies respectively (Tables 15 and 16).

As it is shown in Table 14 , the relative frequencies of incident MI and death during the study follow-up times were statistically higher in patients with a positive hs-cTnT than those with a positive cTnI or cTnT (except for the incidence of non-fatal MI that was not statistically different in patients with positive and negative cTnI tests).

Hazard ratios provided in Table 15 show that positive results of both high-sensitivity and cTn tests were associated with statistically higher risks of death or composite outcome of death or MI, as compared with those who had negative test results. However, the hazard ratios were two to three times higher for hs-cTnT than for cTnI or cTnT assays, suggesting that a positive hs-cTnT was a better independent prognostic factor of mortality. Christ et al.[17] found that patients with dynamic changes of 30% or more had the highest risk for death or MI ($P < 0.001$). The results of their study are not shown in the table, since the authors did not report any details of hazard data in their publication.

Based on the data published by Mueller at al. (2012; n = 1,384),[14] the frequency of patients who died after they were discharged with a negative hs-cTnT (one death) was five times smaller than the number of deaths in those who had a normal cTnI (five deaths). Similarly, the number of patients with a subsequent MI was 2.4 times lower in patients who were discharged with a negative hs-cTnT (five non-fatal MIs), compared with those who had a negative cTnI test (12 non-fatal MIs). The authors suggested that the hazard of discharging patients with normal values of cTn tests is “substantially’ lower when hs-cTnT is used, as compared with discharging based on a normal cTnI test. In the study by Hochholzer et al. (2011),[32] after adjustment for the baseline MI risk score, hs-cTnT was not a prognostic factor for incident MI ($P = 0.23$) or the composite outcome of cardiac death or non-fatal MI ($P = 0.06$) (Table 15). This study found hs-cTnT to be statistically more sensitive, but less specific than cTnT in prognosis of death alone (Table 16). Kavsak et al.(2009; n = 383)[25] compared patient subgroups who had various cTn concentrations measured by hs-cTnI or AccuTnI to those with lowest concentrations of the same cTn test, in terms of short and long-term risk of death and/or MI. As shown in Table 15, the results of their Cox proportional hazard analysis showed that patients with hs-cTnI or AccuTnI values greater than 0.04 mcg/L were in a statistically higher risk of 30-day MI and the composite outcome of death or MI at any study time point from 30 days to 10 years, when compared with patients in the lowest concentration group of the same cTn test. Neither hs-cTnI nor AccuTnI could statistically predict short-term mortality (30 days). However, an hs-cTnI value greater than 0.01 mcg/L was shown to be an independent prognostic factor for mortality at one ($P = 0.04$) or two years ($P < 0.01$). The corresponding hazard ratios for AccuTnI were not statistically significant for the prediction of death at one or two years.

The prognostic accuracy of cTn test for composite outcomes that included major cardiac events outcomes was reported in three studies[24,25,35] (Table 16). Kavsak et al. (2012; n = 186)[24] defined "serious cardiac outcomes" as the composite of MI, heart failure, and arrhythmias. They reported fairly similar AUC of the ROC curve estimates for hs-cTnT, hs-cTnI, and cTnI assays. In a different study by the same author[25] AccuTnI achieved a statistically greater AUC of the ROC curve (0.81, 95% CI, [0.73 to 0.90]) for the composite outcome of death or MI at 30 days, as compared with the AUC for hs-cTnI (0.74, 95% CI, (0.66 to 0.82); *P* = 0.05) Aldous et al. (2011)[35] included cardiac death, non-fatal MI, and revascularization in their composite outcome named MACE (major adverse cardiovascular events). In this study, the AUC of the ROC curves for hs-cTnT, cTnT, and cTnI tests were statistically predictive of two-year cumulative MACE that was significantly higher for hs-cTnT (AUC = 0.70, 95% CI, [0.63 to 0.76]) than for cTnT [AUC = 0.61, 95% CI, [0.63 to 0.76]; *P* = 0.001). However, there was no statistical difference between hs-cTnT and cTnI (AUC = 0.86, 95% CI, [0.78 to 0.95]; *P* = 0.094) in terms of diagnostic accuracy for two-year MACE. In addition, this study found no statistical differences between hs-cTnT, cTnT, and cTnI in terms of subsequent revascularization procedures, based on overlapping CIs for estimates of AUC of the ROC curve.

b) Quality of life

The review found no evidence reporting on the effects of cTn tests on quality of life outcomes.

c) Readmission rates

Readmission rates were not reported in any of the included studies.

d) ED time until diagnosis or detection of abnormal concentration

No description related to ED times between the performance of cTn tests and the diagnosis of MI or ACS was found in the included studies.

Table 3: Pooled Analysis of Sensitivity and Specificity of Troponin Tests for Diagnosis of AMI, at the Time of ED Presentation						
cTn Test (index test)[a]	**No. of Studies (comparison groups)[b]**	**Diagnostic Accuracy[c] Measures**				
		Included Studies	**Sensitivity**	**Pooled Sensitivity**	**Specificity**	**Pooled Specificity**
Cut-off Point = 99th Percentile						
hs-cTnI	2 (2)	Shreiber et al.[21]	0.83 (0.62 to 1.00)	0.82 (0.79 to 0.85)	0.82 (0.78 to 0.86)	0.90 (0.89 to 0.90)
		Keller et al.[16]	0.82 (0.77 to 0.87)		0.92 (0.90 to 0.94)	
hs-cTnT	5 (5)	Kurz et al.[15]	0.82 (NR, NR)	0.88 (0.835 to 0.92)	0.76 (NR, NR)	0.82 (0.80 to 0.84)
		Reichlin et al.[29]	0.95 (0.90 to 0.98)		0.80 (0.77 to 0.83)	
		Aldous et al.[19]	0.91 (0.83 to 0.95)		0.82 (0.80 to 0.83)	
		Body et al.[26]	0.85 (0.78 to 0.91)		0.82 (0.79 to 0.85)	
		Aldous et al.[18]	0.84 (0.77 to 0.87)		0.838 (0.81 to 0.86)	
cTnI	5 (7)	Aldous et al.[18]	0.75 (0.68 to 0.80)	0.81 (0.76 to 0.85)	0.905 (0.875 to 0.93)	0.94 (0.92 to 0.96)
		Reichlin et al.[29]	0.86 (0.79 to 0.92)		0.92 (0.90 to 0.94)	
		Reichlin et al.[29]	0.89 (0.82 to 0.94)		0.92 (0.89 to 0.94)	
		Keller et al.[16]	0.79 (0.75 to 0.84)		0.945 (0.93 to 0.957)	
		Aldous et al.[19]	0.75 (0.68 to 0.80)		0.97 (0.952, 0.983)	
		Reichlin et al.[29]	0.84 (0.76 to 0.90)		0.94 (0.91, 0.95)	
		Shreiber et al.[21]	0.75 (0.51 to 0.99)		0.97 (0.95, 0.99)	
cTnT	2 (2)	Body et al.[26]	0.75 (0.67 to 0.82)	0.65 (0.63 to 0.67)	0.95 (0.92, 0.96)	0.95 (0.94 to 0.96)
		Aldous et al.[18]	0.63 (0.57 to 0.67)		0.96 (0.93, 0.97)	
Cut-off Point = 10% CV						
hs-cTnI	0	-	-	-	-	-
hs-cTnT	1 (1)	Aldous et al.[18]	0.84 (0.77 to 0.89)	-	0.83 (0.80, 0.85)	-
cTnI	2 (3)	Aldous et al.[18]	0.89 (0.84 to 0.93)	0.87 (0.85 to 0.88)	0.88 (0.86, 0.90)	0.92 (0.91 to 0.92)
		Reichlin et al.[29]	0.85 (0.77 to 0.90)		0.93 (0.90, 0.95)	
		Reichlin et al.[29]	0.75 (0.66 to 0.82)		0.97 (0.95, 0.98)	
cTnT	2 (2)	Reichlin et al.[29]	0.72 (0.64 to 0.80)	0.48 (0.46 to 0.50)	0.97 (0.96, 0.98)	0.972(0.96 to 0.98)
		Aldous et al.[18]	0.43 (0.38 to 0.46)		0.97 (0.95, 0.989)	
Cut-off Point = LoD						
hs-cTnI	1 (1)	Keller et al[16]	1.00 (0.98 to 1.00)	-	0.31 (0.28 to 0.34)	-
hs-cTnT	3 (3)	Reichlin et al.[29]	1.00 (0.97 to 1.00)	0.97 (0.96, 0.98)	0.14 (0.12 to 0.18)	0.326 (0.321 to 0.329)
		Body et al.[26]	1.00 (0.97 to 1.00)		0.34 (0.30 to 0.38)	
		Aldous et al.[18]	0.97 (0.92 to 0.99)		0.41 (0.39 to 0.42)	
cTnI	3 (5)	Reichlin et al.[29]	0.97 (0.91 to 0.99)	0.92 (0.90, 0.93)	0.68 (0.64 to 0.72)	0.808 (0.804 to 0.812)
		Aldous et al.[18]	0.946 (0.88 to 0.97)		0.72 (0.69 to 0.73)	
		Reichlin et al.[29]	0.94 (0.88 to 0.97)		0.87 (0.84 to 0.89)	

Table 3: Pooled Analysis of Sensitivity and Specificity of Troponin Tests for Diagnosis of AMI, at the Time of ED Presentation						
cTn Test (index test)[a]	**No. of Studies (comparison groups)[b]**	**Diagnostic Accuracy[c] Measures**				
		Included Studies	**Sensitivity**	**Pooled Sensitivity**	**Specificity**	**Pooled Specificity**
		Keller et al.[16]	0.87 (0.83 to 0.91)		0.89 (0.87 to 0.90)	
		Reichlin et al.[29]	0.92 (0.86 to 0.96)		0.88 (0.86 to 0.91)	
cTnT	2 (2)	Reichlin et al.[29]	0.83 (0.76 to 0.90)	0.66 (0.64, 0.68)	0.93 (0.91 to 0.95)	0.95 (0.94 to 0.96)
		Aldous et al.[18]	0.63 (0.67 to 0.67)		0.955 (0.93 to 0.97)	

AMI = acute myocardial infarction; cTnI = cardiac troponin I; c-cTnT = cardiac troponin T; CV = coefficient of variation; DOR = diagnostic odds ratio; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; LoD = limit of detection; LR (+) = positive likelihood ratio; LR (–) = negative likelihood ratio; NR = not reported.

[a]All studies compared cTn assays (index tests) with the final diagnosis of AMI as the reference standard.

[b]Some studies included more than one type of the same cTn assay.

[c]Reference standard: diagnosis AMI by two physicians using the available clinical, laboratory and imaging information.

Table 4: Pooled Accuracy Estimates of Troponin Tests in Diagnosis of AMI, When Administered at the Time of ED Presentation

cTn Test (index test)[b]	Cut-off Point	No. of Studies	Diagnostic Accuracy[a] Measures							
			Sensitivity	Specificity	LR (+)	LR (–)	DOR	AUC of the ROC	I^2	Chi^2 *P* value
hs-cTnI	99th percentile	2	0.82 (0.79 to 0.85)	0.90 (0.89 to 0.90)	8.0 (7.1 to 8.9)	0.20 (0.16 to 0.24)	40.3	0.94 (0.91 to 0.95)	NA	NA
	10% CV	0	-	-	-	-	-	-	-	-
	LoD	1	1.00 (0.98 to 1.00)	0.31 (0.28 to 0.34)	1.5 (1.5 to 1.6)	0.00 (0.00 to 0.00)	undefined	undefined	NA	NA
hs-cTnT	99th percentile	5	0.88 (0.83 to 0.92)	0.82 (0.80 to 0.84)	5.0 (4.5 to 5.4)	0.15 (0.10 to 0.21)	33.6	0.87 (0.84 to 0.90)	70.9	0.016
	10% CV	1	0.84 (0.77 to 0.89)	0.83 (0.80 to 0.85)	4.9 (4.3 to 5.6)	0.20 (0.16 to 0.24)	24.7	0.90 (0.88 to 0.92)	NA	NA
	LoD	3	0.97 (0.96 to 0.98)	0.33 (0.32 to 0.33)	1.4 (1.4 to 1.5)	0.08 (0.05 to 0.12)	18.3	0.88 (0.87 to 0.90)	NA	NA
cTnI	99th percentile	7	0.81 (0.76 to 0.85)	0.94 (0.92 to 0.96)	13.6 (10.1 to 18.2)	0.21 (0.16 to 0.26)	65.7	0.94 (0.92 to 0.96)	76.4	0.007
	10% CV	3	0.87 (0.85 to 0.88)	0.92 (0.91 to 0.92)	10.4 (9.3 to 11.4)	0.15 (0.13 to 0.17)	70.5	0.95 (0.94 to 0.96)	NA	NA
	LoD	5	0.92 (0.90 to 0.932)	0.81 (0.80 to 0.81)	4.8 (4.6 to 5.0)	0.10 (0.08 to 0.12)	48.0	0.94 (0.93 to 0.95)	NA	NA
cTnT	99th percentile	2	0.65 (0.63 to 0.67)	0.95 (0.94 to 0.96)	13.5 (11.0 to 16.6)	0.37 (0.35 to 0.40)	36.6	0.92 (0.91 to 0.94)	NA	NA
	10% CV	2	0.48 (0.46 to 0.50)	0.97 (0.96 to 0.98)	17.3 (13.0 to 23.2)	0.53 0.51 to 0.56)	32.5	0.92 (0.90 to 0.93)	NA	NA
	LoD	2	0.66 (0.64 to 0.68)	0.95 (0.94 to 0.96)	12.5 (10.3 to 15.2)	0.36 (0.33 to 0.38)	35.1	0.92 (0.91 to 0.94)	NA	NA

AMI = acute myocardial infarction; AUC = area under the curve; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CV = coefficient of variation; DOR = diagnostic odds ratio; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; LoD = limit of detection; LR (+) = positive likelihood ratio; LR (–) = negative likelihood ratio; NA = not applicable; no. = number; ROC = receiver operating characteristic curve.

[a]Reference standard: the diagnosis AMI by two physicians using the available clinical, laboratory and imaging information.

[b]All studies compared cTn assays (index tests) with the final diagnosis of AMI as the reference standard.

Table 5: Reported Diagnostic Accuracy of Serial CTn Testing in Diagnosis of AMI									
Study	**Outcome**	**CTn Test (index test)[a]**	**Time of Measurement**	**Sensitivity**	**Specificity**	**LR (+)[b]**	**LR (–)[b]**	**DOR**	**AUC of the ROC**
Freund et a.[27]	AMI	hs-cTnT	ED presentation and 3-9 hours after	0.93 (0.89 to 1.00)	0.82 (0.77 to 0.87)	5.2 (4.0 to 6.7)	0.09 (0.03 to 0.25)	60.5	0.93 (0.88 to 0.97)
		cTnI	ED presentation and 3-9 hours after	0.71 (0.55 to 0.84)	0.97 (0.94 to 0.98)	23.7 (11.7 to 47.7)	0.30 (0.19 to 0.47)	79.2	0.94 (0.9 to 0.98)
Mueller et al.[14]	NSTEMI	hs-cTnT	ED presentation and every 6 hours there after	0.98 (0.97 to 0.99)	0.41 (0.37 to 0.44)	1.7 (1.6 to 1.8)	0.05 (0.03 to 0.08)	34.1	0.905[b] (0.683 to 0.936)
		cTnI	ED presentation and every 6 hours there after	0.91 (0.88 to 0.93)	0.46 (0.43 to 0.50)	1.7 (1.6 to 1.8)	0.20 (0.15 to 0.25)	8.6	0.788[b] (0.675 to 0.834)

AMI = acute myocardial infarction; AUC = area under the curve; c-cTnI = conventional cardiac troponin I; DOR = diagnostic odds ratio; ED = emergency department; hs-cTnT = high-sensitivity cardiac troponin T; LR (+) = positive likelihood ratio; LR (–) = negative likelihood ratio; NSTEMI = non-ST-segment elevation myocardial infarction; ROC = receiver operating characteristic curve.

[a]All studies compared cTn assays (index tests) with the final diagnosis of AMI as the reference standard.

[b]These values were not reported by the authors and were estimated using the available parameters.

Table 6: Reported Diagnostic Accuracy of Troponin Tests in Diagnosis of AMI, Based on the Time Period Between the Onset of Symptoms and ED Presentation

Author Year	Population Subgroup	CTn Test	Cut-off Point	Assessment Time	Sensitivity	Specificity	LR (+)[a]	LR (–)[a]	AUC of the ROC
Body et al. 2011[26]	Early: ≤ 3 hours from the symptom onset	hs-cTnT	99th percentile	ED presentation	0.80 (0.69 to 0.88)	0.83 (0.78 to 0.88)	4.7 (3.8 to 5.7)	0.25 (0.18 to 0.33)	0.94 (0.91 to 0.96)
			10% CV		1.00 (0.95 to 1.00)	0.64 (0.57 to 0.70)	2.8 (2.5 to 3.1)	0.00	0.94 (0.91 to 0.96)
		cTnT	99th percentile		0.66 (0.54 to 0.77)	0.95 (0.91 to 0.97)	12.1 (8.3 to 17.5)	0.36 (0.29 to 0.44)	0.86 (0.82 to 0.91)
Reichlin et al. 2009[29]	≤ 3 hours from the symptom onset	hs-cTnT	99th percentile	ED presentation	0.85 (0.66 to 0.96)	0.84 (0.78 to 0.89)	5.3 (4.3 to 6.5)	0.18 (0.11 to 0.30)	0.91 (0.87 to 0.95)[a]
			LoD		1.00 (0.87 to 1.00)	0.15 (0.11 to 0.21)	1.2 (1.1 to 1.2)	0.00	0.92 (0.87 to 0.97)
		cTnT	10% CV		0.44 (0.26 to 0.65)	0.99 (0.96 to 1.00)	46.5 (20.3 to 106.8)	0.56 (0.47 to 0.68)	0.96 (0.93 to 0.99)[a]
			LoD		0.56 (0.35 to 0.75)	0.95 (0.91 to 0.98)	11.0 (7.5 to 16.2)	0.47 (0.37 to 0.59)	0.76 (0.64 to 0.88)
		cTnI (Abbott Architect)	99th percentile		0.70 (0.50 to 0.86)	0.96 (0.92 to.0.98)	17.6 (11.7 to 26.5)	0.31 (0.23 to 0.43)	0.95 (0.91 to 0.98)[a]
			10% CV		0.70 (0.50 to 0.86)	0.96 (0.93 to 0.99)	17.6 (11.7 to 26.5)	0.31 (0.23 to 0.43)	0.95 (0.91 to 0.98)[a]
			LoD		0.85 (0.66 to 0.96)	0.90 (0.85 to 0.94)	8.5 (6.6 to 10.9)	0.17 (0.10 to 0.28)	0.93 (0.88 to 0.99)
		cTnI (Siemens-Ultra)	99th percentile		0.77 (0.56 to 0.91)	0.95 (0.90 to 0.97)	15.2 (10.6 to 21.7)	0.24 (0.17 to 0.36)	0.95 (0.91 to 0.98)[a]
			LoD		0.92 (0.75 to 0.99)	0.74 (0.67 to 0.80)	3.5 (3.1 to 4.1)	0.11 (0.05 to 0.22)	0.94 (0.90 to 0.98)
		cTnI (Roche)	99th percentile		0.63 (0.42 to 0.81)	0.96 (0.93 to 0.99)	15.9 (10.5 to 24.1)	0.39 (0.29 to 0.51)	0.93 (0.89 to 0.97)[a]
			10% CV		0.41 (0.22 to 0.61)	0.98 (0.95 to 0.99)	19.8 (10.9 to 35.9)	0.61 (0.51 to 0.72)	0.92 (0.88 to 0.96)[a]
			LoD		0.85 (0.66 to 0.96)	0.91 (0.86 to 0.95)	9.4 (7.2 to 12.2)	0.17 (0.10 to 0.27)	0.92 (0.86 to 0.99)
Body et al. 2011[26]	≤ 6 hours after the onset of the symptoms	hs-cTnT	99th percentile	ED presentation	0.83 (0.74 to 0.90)	0.83 (0.79 to 0.87)	4.8 (4.0 to 5.9)	0.21 (0.15 to 0.30)	0.94 (0.91 to 0.94)
			10% CV		1.00 (0.97 to 1.00)	0.35 (0.30 to 0.39)	1.5 (1.4 to 1.6)	0.00	0.94 (0.91 to 0.96)
		cTnT	99th percentile		0.71 (0.62 to 0.80)	0.95 (0.93 to 0.97)	15.2 (10.3 to 22.4)	0.30 (0.23 to 0.39)	0.86 (0.82 to 0.91)
Body et al. 2011[26]	Late: > 3 hours from the symptom onset	hs-cTnT	99th percentile	ED presentation	0.87 (0.76 to 0.95)	0.95 (0.92 to 0.97)	16.2 (11.6 to 22.7)	0.13 (0.06 to 0.25)	0.86 (0.82 to 0.91)
			10% CV		1.00 (0.94 to 1.00)	0.33 (0.28 to 0.38)	1.5 (1.4 to 1.6)	0.00	0.94 (0.91 to 0.96)
		cTnT	99th percentile		0.93 (0.83 to 0.98)	0.82 (0.78 to 0.86)	5.2 (4.3 to 6.2)	0.09 (0.04 to 0.18)	0.94 (0.91 to 0.96)
Body et al. 2011[26]	> 6 hours after the onset of the symptoms	hs-cTnT	99th percentile	ED presentation	0.98 (0.80 to 1.00)	0.81 (0.75 to 0.87)	5.2 (4.4 to 6.2)	0.03 (0.01 to 0.12)	0.94 (0.91 to 0.96)
			10% CV		1.00 (0.94 to 1.00)	0.32 (0.27 to 0.40)	1.5 (1.4 to 1.6)	0.00	0.61 (0.91 to 0.96)
		cTnT	99th percentile		0.92 (0.74 to 0.99)	0.93 (0.88 to 0.96)	13.2 (9.8 to 17.8)	0.09 (0.05 to 0.19)	0.86 (0.82 to 0.91)

AMI = acute myocardial infarction; AUC = area under the curve; c-cTnI = cardiac troponin I; cTnT = cardiac troponin T; CV = coefficient of variation; ED = emergency department; hs-cTnT= high-sensitivity cardiac troponin T; LoD = limit of detection; LR (+) = positive likelihood ratio; LR (–) = negative likelihood ratio; MI = myocardial infarction; ROC = receiver operating characteristic curve.
[a]These values were not reported by the authors and were estimated using the available parameters.

Table 7: Reported Diagnostic Accuracy of Troponin Tests in Diagnosis of AMI, Based on the Pretest Probability of MI									
Author Year	**Population Subgroup**	**cTn test (index test)[a]**	**Cut-off Point**	**Assessment Time**	**Sensitivity**	**Specificity**	**LR (+)[b]**	**LR (–)[b]**	**AUC of the ROC**
Freund 2011 et al. [27]	Low-to-moderate risk	hs-cTnT	99th percentile	0, and 3 to 9 hours after ED presentation	0.91 (0.69 to 0.98)	0.85 (0.79 to 0.89)	6.0 (5.3 to 6.6)	0.11 (0.06 to 0.15)	0.95 (0.90 to 1.00)[b]
		cTnI	10% CV		0.77 (0.54 to 0.92)	0.97 (0.94 to 0.99)	26.1 (24.0 to 28.1)	0.23 (0.17 to 0.3)	0.97 (0.92 to 1.00)[b]
Januzzi 2010 et al.[23]		hs-cTnT	99th percentile	4.2 hours (median) after ED presentation	0.88 (0.47 to 1.00)	0.85 (0.81 to 0.89)	5.9 (4.1 to 8.4)	0.15 (0.02 to 0.92)	0.92 (0.80 to 1.00)[b]
		cTnT	99th percentile		0.88 (0.47 to 1.00)	0.94 (0.92 to 0.97)	14.7 (9.1 to 23.8)	0.13 (0.02 to 0.83)	0.97 (0.88 to 1.00)[b]
			LoD		0.88 (0.47 to 1.00)	0.97 (0.95 to 0.98)	29.4 (15.5 to 55.6)	0.13 (0.02 to 0.81)	0.98 (0.91 to 1.00)[b]
Freund 2011 et al.[27]	High risk	hs-cTnT	99th percentile	0, and 3 to 9 hours after ED presentation	0.96 (0.76 to 1.00)	0.67(0.49 to 0.81)	2.9 (2.3 to 3.4)	0.07 (0.00 to 0.17)	0.94 (0.91 to 0.97)[b]
		cTnI	10% CV		0.65 (0.43 to 0.83)	0.94 (0.79 to 0.99)	11.7 (10.1 to 13.4)	0.37 (0.18 to 0.55)	0.91 (0.88 to 0.95)[b]

AMI = acute myocardial infarction; AUC = area under the curve; c-cTnI = cardiac troponin I; CV = coefficient of variation; ED = emergency department; hs-cTnT = high-sensitivity cardiac troponin T; LoD = limit of detection; LR (+) = positive likelihood ratio; LR (–) = negative likelihood ratio; MI = myocardial infarction; ROC = receiver operating characteristic curve.

[a]All studies compared cTn assays (index tests) with the final diagnosis of AMI as the reference standard.

[b]Calculated using available parameters, if not reported by the authors.

Table 8: Reported Diagnostic Accuracy of Troponin Tests in Diagnosis of AMI, Based on Previous History of IHD in Patients with Chest Pain Who Are Referred to ED

Author Year	Population Subgroup	cTn Test (index test)[a]	Cut-off point	Assessment Time	Sensitivity	Specificity	LR (+)[b]	LR (–)[b]	AUC of the ROC
Reiter et al. 2012[30]	Positive history of CAD	hs-cTnT	99th percentile	Serial testing	0.94 (0.85 to 0.98)	0.59 (0.54 to 0.65)	2.3 (2.0 to 2.7)	0.11 (0.06 to 0.20)	0.89 (0.86 to 0 93)[b]
		cTnT	10% CV		0.69 (0.57 to 0.79)	0.97 (0.94 to 0.99)	22.6 (12.1 to 42.4)	0.32 (0.22 to 0.44)	0.95 (0.92 to 0.99)[b]
		cTnI (Abbott Architect)	99th percentile		0.83 (0.73 to 0.91)	0.87 (0.83 to 0.91)	6.4 (4.8 to 8.6)	1.15 (0.70 to 1.89)	0.92 (0.88 to 0.96)[b]
		cTnI (Siemens-Ultra)	99th percentile		0.91 (0.82 to 0.96)	0.85 (0.80 to 0.88)	6.0 (4.6 to 7.9)	0.11 (0.05 to 0.23)	0.94 (0.91 to 0.98)[b]
	Negative history of CAD	hs-cTnT	99th percentile	Serial testing	0.94 (0.87 to 0.98)	0.81 (0.78 to 0.84)	4.9 (4.2 to 5.9)	0.07 (0.03 to 0.16)	0.95 (0.92 to 0.9)[b]
		cTnT	10% CV		0.83 (0.57 to 0.77)	0.95 (0.96 to 0.99)	16.5 (11.5 to 23.7)	0.18 (0.12 to 0.28)	0.96 (0.93 to 0.99)[b]
		cTnI (Abbott Architect)	99th percentile		0.85 (0.77 to 0.92)	0.93 (0.91 to 0.95)	12.2 (9.0 to 16.6)	0.16 (0.10 to 0.25)	0.96 (0.93 to 0.99)[b]
		cTnI (Siemens-Ultra)	99th percentile		0.89 (0.81 to 0.94)	0.91 (0.88 to 0.93)	9.8 (7.6 to 12.8)	0.12 (0.07 to 0.21)	0.96 (0.93 to 0.99)[b]

AMI = acute myocardial infarction; AUC = area under the curve; CAD = coronary artery disease; CV = coefficient of variation; cTnI = conventional cardiac troponin I; ED = emergency department; hs-cTnT = high-sensitivity cardiac troponin T; IHD = ischemic heart disease; LR (+) = positive likelihood ratio; LR (–) = negative likelihood ratio; ROC = receiver operating characteristic curve.

[a]All studies compared cTn assays (index tests) with the final diagnosis of AMI as the reference standard.

[b]Calculated using available parameters, if not reported by the authors.

Table 9: Reported Diagnostic Accuracy of Troponin Tests in Diagnosis of AMI, Based on the Results of Baseline Troponin Test								
Author Year	**Population Subgroup**	**cTn Test (index test)[a]**	**Assessment Time**	**Sensitivity**	**Specificity**	**LR (+)[b]**	**LR (–)[b]**	**AUC of the ROC**
Reichlin et al. 2011[33]	Positive test at baseline	hs-cTnT	1 hour after ED presentation (absolute change)	0.84 (0.79 to 0.88)[b]	0.86 (0.83 to 0.89)[b]	6.0 (4.9 to 7.4)	0.19 (0.14 to 0.25)	0.88 (0.83 to 0.93)
		cTnI-ultra		0.76 (0.72 to 0.80)[b]	0.89 (0.85 to 0.92)[b]	6.9 (5.1 to 9.3)	0.27 (0.23 to 0.32)	0.87(0.81 to 0.92)
		hs-cTnT	1 hour after ED presentation (relative [≥ 25%] change)	0.55 (0.49 to 0.61)[b]	0.86 (0.83 to 0.89)[b]	3.9 (3.1 to 5.0)	0.52 (0.46 to 0.60)	0.7 (0.64 to 0.77)
		cTnI-ultra		0.52 (0.48 to 0.56)[b]	0.86 (0.82 to 0.89)[b]	3.7 (2.8 to 4.9)	0.56 (0.50 to 0.62)	0.71 (0.63 to 0.79)
		hs-cTnT	2 hour after ED presentation (absolute change)	0.90 (0.86 to 0.93)[b]	0.87 (0.84 to 0.90)[b]	6.9 (5.6 to 8.6)	0.11 (0.08 to 0.16)	0.91 (0.86 to 0.96)
		cTnI-ultra		0.76 (0.72 to 0.80)[b]	0.89 (0.85 to 0.92)[b]	6.9 (5.1 to 9.3)	0.27 (0.23 to 0.32)	0.86 (0.78 to 0.94)
		hs-cTnT	2 hours after ED presentation (relative [≥ 25%] change)	0.75 (0.70 to 0.80)[b]	0.80 (0.76 to 0.83)[b]	3.8 (3.1 to 4.5)	0.31 (0.25 to 0.38)	0.79 (0.71 to 0.87)
		cTnI-ultra		0.50 (0.46 to 0.54)[b]	0.90 (0.86 to 0.93)[b]	5.0 (3.6 to 6.9)	0.55 (0.50 to 0.61)	0.74 (0.64 to 0.83)
Keller et al. 2011[16]		hs-cTnT	3 hours after ED presentation (relative [≥ 20%] change)	0.60 (0.54 to 0.66)	0.97 (0.96 to 0.98)	18.9 (13.3 to 27.0)	0.41 (0.35 to 0.48)	0.94 (0.91 to 0.96)[b]
		cTnI		0.62 (0.57 to 0.68)	0.97 (0.96 to 0.98)	25.3 (17.4 to 36.7)	0.39 (0.33 to 0.45)	0.95 (0.93 to 0.97)[b]
		hs-cTnT	3 hours after ED presentation (relative [≥ 50%] change)	0.50 (0.44 to 0.56)	0.99 (0.98 to 1.00)	55.3 (29.3 to 104.4)	0.50 (0.43 to 0.59)	0.97 (0.95 to 0.99)[b]
		cTnI		0.50 (0.44 to 0.55)	0.99 (0.98 to 0.99)	36.1 (22.1 to 59.2)	0.51 (0.44 to 0.59)	0.95 (0.93 to 0.97)[b]
Giannitis et al. 2010[34] (excluded STEMI patients)[c]		hs-cTnT	1 to 3 hours after ED presentation	1.00 (0.75 to 1.00)	0.77 (0.58 to 0.90)	4.4 (3.8 to 5.0)	0.00	NA
		cTnT		0.92 (0.61 to 0.99)	0.97 (0.83 to 0.99)	30.7 (19.2 to 49.1)	0.08 (0.06 to 0.12)	0.99 (0.98 to 1.00)[b]
		hs-cTnT	Within 6 hours after ED presentation	1.00 (0.86 to 1.00)	0.71 (0.52 to 0.86)	3.5 (3.0 to 4.0)	0.00	NA
		cTnT		1.00 (0.87 to 1.00)	0.87 (0.70 to 0.96)	7.7 (6.1 to 9.7)	0.00	NA
Reichlin et al. 2011[33]	Negative test at baseline	Hs-cTnT	1 hour after ED presentation (absolute change)	0.82 (0.57 to 0.97)[b]	0.95 (0.93 to 0.96)[b]	16.4 (10.9 to 24.6)	0.19 (0.05 to 0.67)	0.85 (0.61 to 1.00)
		cTnI-ultra		0.94 (0.69 to 0.98)[b]	0.61 (0.58 to 0.64)[b]	2.4 (2.1 to 2.8)	0.10 (0.02 to 0.68)	0.80 (0.67 to 0.94)
		hs-cTnT	1 hour after ED presentation (relative [≥ 25%] change)	0.82 (0.57 to 0.97)[b]	0.90 (0.88 to 0.92)[b]	8.2 (5.8 to 11.6)	0.20 (0.06 to 0.71)	0.83 (0.59 to 1.00)
		cTnI-ultra		0.94 (0.69 to 0.98)[b]	0.43 (0.40 to 0.46)[b]	1.6 (1.4 to 1.9)	0.15 (0.02 to 0.97)	0.70 (0.55 to 0.85)
		hs-cTnT	2 hour after ED presentation (absolute change)	1.00 (0.74 to 1.00)[b]	0.95 (0.93 to 0.96)[b]	20.0 (14.9 to 26.9)	0.00	0.98 (0.96 to 1.00)
		cTnI-ultra		0.88 (0.66 to 0.97)[b]	0.96 (0.94 to 0.97)[b]	21.9 (14.9 to 32.1)	0.13 (0.04 to 0.48)	0.89 (0.72 to 1.00)
		hs-cTnT	2 hours after ED presentation (relative [≥ 25%] change)	1.00 (0.74 to 1.00)[b]	0.86 (0.83 to 0.88)[b]	7.1 (6.0 to 8.5)	0.00	0.95 (0.91 to 0.99)
		cTnI-ultra		0.88 (0.66 to 0.97)[b]	0.87 (0.85 to 0.89)[b]	6.7 (5.2 to 8.7)	0.14 (0.04 to 0.53)	0.86 (0.69 to 1.00)
Keller et al. 2011[16]		hs-cTnT	3 hours after ED presentation (relative [≥ 20%] change)	0.92 (0.81 to 0.98)	0.97 (0.96 to 0.98)	35.0 (23.3 to 52.7)	0.08 (0.04 to 0.17)	0.99 (0.97 to 1.00)[b]
		cTnI		0.93 (0.83 to 0.98)	0.95 (0.93 to 0.96)	16.7 (12.8 to 21.8)	0.08 (0.04 to 0.14)	0.98 (0.96 to 1.00)[b]
		hs-cTnT	3 hours after ED presentation (relative [≥ 50%] change)	0.92 (0.81 to 0.98)	0.98 (0.97 to 0.99)	44.8 (28.2 to 71.1)	0.09 (0.04 to 0.18)	0.99 (0.97 to 1.00)[b]
		cTnI		0.93 (0.83 to 0.98)	0.95 (0.93 to 0.96)	17.0 (13.1 to 22.2)	0.08 (0.04 to 0.14)	0.98 (0.96 to 1.00)[b]

AMI = acute myocardial infarction; AUC = area under the curve; cTnI = cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; LR (+) = positive likelihood ratio; LR (–) = negative likelihood ratio; NA = not applicable; ROC = receiver operating characteristic curve.

[a]All studies compared cTn assays (index tests) with the final diagnosis of AMI as the reference standard.

[b]Calculated using available parameters, if not reported by the authors.

[c]The analysis evaluated the accuracy of the cTn tests in diagnosis of evolving NSTEMI from UA.

Table 10: Reported Diagnostic Accuracy of Troponin Tests in Diagnosis of AMI, Based on Age Categories of Patients with Chest Pain Referred to ED									
Author Year	**Population Subgroup**	**CTn Test (index test)[a]**	**Cut-off Point**	**Assessment Time**	**Sensitivity**	**Specificity**	**LR (+)[b]**	**LR (–)[b]**	**AUC of the ROC**
Reiter et al. 2011[31]	≤ 70 years	hs-cTnT	99th percentile	ED presentation	0.88 (0.78 to 0.94)	0.86 (0.83 to 0.89)	6.3 (5.0 to 7.9)	0.14 (0.07 to 0.27)	0.94 (0.9 to 0.96)
		cTnT	10% CV		0.59 (0.47 to 0.70)	0.98 (0.97 to 0.99)	29.5 (15.9 to 54.6)	0.42 (0.31 to 0.56)	0.9 (0.87 to 0.93)
		cTnI (Abbott Architect)	99th percentile		0.79 (0.68 to 0.87)	0.93 (0.91 to 0.95)	11.3 (8.1 to 15.7)	0.23 (0.14 to 0.36)	0.95 (0.92 to 0.97)
		cTnI (Siemens-Ultra)	99th percentile		0.87 (0.77 to 0.93)	0.92 (0.89 to 0.94)	10.9 (8.1 to 14.6)	0.14 (0.08 to 0.26)	0.95 (0.90 to 0.97)
	> 70 years	hs-cTnT	99th percentile	ED presentation	0.98 (0.93 to 1.00)	0.49 (0.44 to 0.55)	1.9 (1.7 to 2.2)	0.04 (0.01 to 0.16)	0.94 (0.90 to 0.91)
			LoD		1.00 (0.96 to 1.00)	0.01 (0.00 to 0.03)	1.0	0.0	NR
		cTnT	10% CV		0.76 (0.57 to 0.79)	0.96 (0.93 to 0.98)	19.0 (10.9 to 33.2)	0.25 (0.18 to 0.36)	0.90 (0.87 to 0.93)
			LoD		0.83 (0.74 to 0.90)	0.90 (0.86 to 0.93)	8.3 (5.9 to 11.7)	0.19 (0.12 to 0.29)	NR
		cTnI (Abbott Architect)	99th percentile		0.89 (0.81 to 0.94)	0.87 (0.83 to 0.91)	6.8 (5.1 to 9.2)	0.13 (0.07 to 0.22)	0.95 (0.92 to 0.97)
			10% CV		0.88 (0.80 to 0.94)	0.88 (0.84 to 0.91)	7.3 (5.4 to 10.0)	0.14 (0.08 to 0.23)	NR
			LoD		0.94 (0.87 to 0.98)	0.72 (0.67 to 0.78)	3.4 (2.8 to 4.0)	0.08 (0.04 to 0.18)	NR
		cTnI (Siemens-Ultra)	99th percentile		0.92 (0.85 to 0.96)	0.83 (0.79 to 0.87)	5.4 (4.2 to 7.0)	0.10 (0.05 to 0.19)	0.95 (0.90 to 0.97)
			LoD		0.99 (0.94 to 1.00)	0.30 (0.25 to 0.35)	1.4 (1.3 to 1.5)	0.03 (0.00 to 0.24)	NR

AMI = acute myocardial infarction; AUC = area under the curve; c-cTnI = cardiac troponin I; CV = coefficient of variation; ED = emergency department; hs-cTnT= high-sensitivity cardiac troponin T; LoD = limit of detection; LR (+) = positive likelihood ratio; LR (–) = negative likelihood ratio; NR = not reported; ROC = receiver operating characteristic curve.

[a]All studies compared cTn assays (index tests) with the final diagnosis of AMI as the reference standard.

[b]Calculated using available parameters, if not reported by the authors.

Table 11: Relative Diagnostic Performance of Troponin Tests for Diagnosis of AMI, When Used at a 99th Percentile Cut-off Point at the Time of ED Presentation				
	hs-cTnT	**hs-cTnI**	**cTnT**	**cTnI**
	Relative AUC of the ROC Curve			
hs-cTnT	1	0.927 (0.891 to 0.963)	0.942 (0.907 to 0.977)	0.923 (0.886 to 0.961)
hs-cTnI	1.079 (1.038 to 1.122)	1	1.016 (0.993 to 1.040)	0.996 (0.968 to 1.025)
cTnT	1.062 (1.023 to 1.102)	0.984 (0.961 to 1.007)	1	0.980 (0.954 to 1.006)
cTnI	1.084 (1.041 to 1.129)	1.004 (0.976 to 1.033)	1.021 (0.994 to 1.048)	1
	Relative Sensitivity			
hs-cTnT	1.00	1.066 (0.998 to 1.138)	1.353 (1.272 to 1.439)	1.089 (1.007 to 1.179)
hs-cTnI	0.938 (0.883 to 0.998)	1.00	1.270 (1.215 to 1.327)	1.024 (0.949 to 1.092)
cTnT	0.739 (0.695 to 0.786)	0.788 (0.749 to 0.828)	1.00	0.805 (0.753 to 0.861)
cTnI	0.918 (0.848 to 0.993)	0.978 (0.912 to 1.050)	1.242 (1.162 to 1.328)	1.00
	Relative Specificity			
hs-cTnT	1	0.918 (0.896 to 0.940)	0.864 (0.844 to 0.886)	0.875 (0.849 to 0.901)
hs-cTnI	1.090 (1.064 to 1.116)	1	0.942 (0.931 to 0.954)	0.953 (0.933 to 0.973)
cTnT	1.157 (1.129 to 1.185)	1.061 (1.048 to 1.074)	1	1.012 (0.990 to 1.033)
cTnI	1.143 (1.110 to 1.178)	1.049 (1.027 to 1.071)	0.988 (0.968 to 1.010)	1

AMI = acute myocardial infarction; AUC = area under the curve; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; ROC = receiver operating characteristic curve.

Table 12: Relative Diagnostic Performance of Troponin Tests for Diagnosis of AMI , When Used at a 10% CV Cut-off Point at the Time of ED Presentation				
	hs-cTnT	**hs-cTnI**	**cTnT**	**cTnI**
	Relative AUC of the ROC Curve			
hs-cTnT	1	NA	0.983 (0.959 to 1.007)	0.946 (0.926 to 0.967)
hs-cTnI	NA	NA	NA	NA
cTnT	1.018 (0.993 to 1.043)	NA	1	0.963 (0.945 to 0.982)
cTnI	1.057 (1.034 to 1.080)	NA	1.038 (1.019 to 1.058)	1
	Relative Sensitivity			
hs-cTnT	1	NA	1.734 (1.606 to 1.873)	0.965 (0.899 to 1.037)
hs-cTnI	NA	NA	NA	NA
cTnT	0.577 (0.534 to 0.623)	NA	1	0.557 (0.534 to 0.580)
cTnI	1.036 (0.964 to 1.113)	NA	1.797 (1.723 to 1.873)	1
	Relative Specificity			
hs-cTnT	1	NA	0.853 (0.824 to 0.883)	0.905 (0.874 to 0.937)
hs-cTnI	NA	NA	NA	NA
cTnT	1.172 (1.132 to 1.214)	NA	1	1.061 (1.049 to 1.074)
cTnI	1.105 (1.067 to 1.144)	NA	0.942 (0.932 to 0.953)	1

AMI = acute myocardial infarction; AUC = area under the curve; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; NA = not available; ROC = receiver operating characteristic curve.

Table 13: Relative Diagnostic Performance of Troponin Tests for Diagnosis of AMI, When Used at a LoD Cut-off Point at the Time of ED Presentation				
	hs-cTnT	**hs-cTnI**	**cTnT**	**cTnI**
	Relative AUC of the ROC curve			
hs-cTnT	1	undefined	0.956 (0.934 to 0.978)	0.940 (0.922 to 0.959)
hs-cTnI	undefined	undefined	undefined	undefined
cTnT	1.047 (1.023 to 1.071)	undefined	1	0.984 (0.966 to 1.002)
cTnI	1.064 (1.042 to 1.085)	undefined	1.016 (0.998 to 1.035)	1
	Relative sensitivity			
hs-cTnT	1	0.974 (0.959 to 0.989)	1.469 (1.420 to 1.519)	1.060 (1.040 to 1.080)
hs-cTnI	1.027 (1.011 to 1.042)	1	1.508 (1.459 to 1.559)	1.088 (1.068 to 1.108)
cTnT	0.681 (0.658 to 0.704)	0.663 (0.641 to 0.685)	1	0.721 (0.696 to 0.747)
cTnI	0.944 (0.926 to 0.962)	0.919 (0.902 to 0.936)	1.386 (1.338 to 1.436)	1
	Relative specificity			
hs-cTnT	1	1.058 (0.958 to 1.170)	0.344 (0.339 to 0.350)	0.403 (0.398 to 0.409)
hs-cTnI	0.945 (0.855 to 1.044)	1	0.325 (0.294 to 0.359)	0.381 (0.345 to 0.421)
cTnT	2.905 (2.861 to 2.950)	3.075 (2.783 to 3.397)	1	1.172 (1.160 to 1.184)
cTnI	2.479 (2.446 to 2.512)	2.623 (2.375 to 2.897)	0.853 (0.845 to 0.862)	1

AMI = acute myocardial infarction; AUC = area under the curve; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; LoD = limit of detection; ROC = receiver operating characteristic curve.

Table 14: Death and Incident AMI in Patients Diagnosed by cTn Tests Reported by the Included Studies						
Author Year	**cTn Test (index test)[a]**	**Outcome**	**Proportion of Outs Identified by a Positive Test (%)**	***P* Value[b]**	**Incidence of Outcome**	
					No. of Events/ No. of Test Positives (%)	***P* Value[c]**
Mueller 2012 et al.[14]	hs-cTnT	Non-fatal MI	NR	-	55/1,078 (51%)	*P* = 0.006
	cTnI		NR	-	48/989 (4.9%)	*P* = 0.177
	hs-cTnT	Cardiac death	NR	-	33/1,078 (3.1%)	*P* = 0.003
	cTnI		NR	-	31/989 (3.1%)	*P* = 0.017
	hs-cTnT	All-cause death	NR	-	105/1,078 (9.7%)	*P* < 0.001
	cTnI		NR	-	101/989 (10.2%)	*P* < 0.0001
	hs-cTnT	Cardiac death/Non-fatal MI	NR	-	84/1,078 (7.8%)	*P* < 0.001
	cTnI		NR	-	75/989 (7.6%)	*P* = 0.014
	hs-cTnT	Death/Non-fatal MI	NR	-	153/1,078 (14.2%)	*P* < 0.001
	cTnI		NR	-	143/989 (14.5%)	*P* < 0.0001
Lindahl 2010 et al.[28]	hs-cTnT	AMI (30 days)	86/94 (91%)	*P* < 0.001	NR	NR
	cTnT		74/94 (79%)			
	hs-cTnT	All-cause death (1 year)	114/123 (93%)	*P* < 0.001	NR	NR
	cTnT		93/123 (76%)			

AMI = acute myocardial infarction; cTn = cardiac troponin; cTnI = cardiac troponin I; cTnT = cardiac troponin T; hs-cTnT = high-sensitivity cardiac troponin T; MI = myocardial infarction; No. = number; NR = not reported.
[a]All studies compared cTn assays (index tests) with the final diagnosis of AMI as the reference standard.
[b]*P* value for the comparison of the outcomes diagnosed by high-sensitivity versus cTn tests.
[c]*P* value for the comparison of the risk in test-positives versus test-negatives.

Table 15: Hazard Ratios of Major Cardiac Events and Death in Patients Diagnosed by cTn Tests				
Author and Year	**cTn Test**	**Outcome**	**HR (95% CI)**	***P* Value**
Mueller 2012[14]	hs-cTnT	Death[a]	9.24 (1.27 to 67.24)[b]	*P* = 0.029[c]
		Death/MI[a]	3.51 (1.52 to 8.11)[b]	*P* = 0.003[c]
	cTnI	Death[a]	3.61 (1.43 to 9.09)[b]	*P* = 0.007[c]
		Death/MI	2.19 (1.28 to 3.78)	*P* = 0.005[c]
Aldous 2011[35]	hs-cTnT	MACE (2 years)	5.2 (1.9 to 14.5)[b]	*P* = 0.001[c]
	cTnT	MACE (2 years)	1.7 (0.9 to 3.2)[b]	*P* = 0.076[c]
	cTnI	MACE (2 years)	2.7 (1.3 to 5.4)[b]	*P* = 0.007[c]
Hochholzer 2011[32]	hs-cTnT	Death[d]	7.2 (4.4 to 12.18)[e] 2.60 (1.42 to 4.74)[b]	*P* < 0.001[c] *P* < 0.001[c]
		Incident MI[d]	2.51 (1.36 to 4.62)[e] 1.53 (0.76 to 3.08)[b]	*P* = 0.003[c] *P* = 0.23[c]
		Cardiac death/Non-fatal MI[d]	3.63 (2.17 to 6.07)[e] 1.75 (0.98 to 3.12)[b]	*P* < 0.001[c] *P* = 0.06[c]
Lindahl 2010[28]	hs-cTnT	Death (1 year)	4.29 (2.15 to 8.56)	*P* < 0.001[c]
		Death/MI (30 days)	3.57 (1.71 to 7.44)	*P* < 0.001[c]
	cTnT	Death (1 year)	2.16 (1.41 to 3.31)	*P* < 0.001[c]
		Death/MI (30 days)	2.62 (1.58 to 4.34)	*P* < 0.001[c]
Kavsak 2009[25]	hs-cTnI (> 0.04 mcg/L)	Death (30 days)	NR	*P* > 0.10[f]
		MI (30 days)	13.20 (1.73 to 99.9)[b]	*P* = 0.01[f]
		Death/MI (30 days)	7.20 (1.66 to 31.21)[b]	*P* = 0.01[f]
		Death/MI (6 months)	5.82 (2.02 to 16.75)[b]	*P* < 0.01[f]
		Death/MI (1 year)	4.58 (1.90 to 11.04)[b]	*P* < 0.01[f]
		Death/MI (2 years)	4.32 (2.00 to 9.32)[b]	*P* < 0.01[f]
		Death/MI (5 year)	1.94 (1.18 to 3.18)	*P* < 0.01[f]
		Death/MI (10 years)	1.85 (1.23 to 2.77)[b]	*P* < 0.01[f]
	hs-cTnI (0.01 mcg/L to 0.04 mcg/L)	Death (1 year)	3.64 (1.04 to 12.70)[b]	*P* = 0.04[f]
		Death (2 years)	4.06 (1.54 to 10.70)[b]	*P* < 0.01[f]
		Death/MI (30 days)	3.60 (0.76 to 16.94)[b]	*P* = 0.11[f]
		Death/MI (6 months)	3.77 (1.26 to 11.27)[b]	*P* = 0.02[f]
		Death/MI (1 year)	3.38 (1.37 to 8.33)[b]	*P* < 0.01[f]
		Death/MI (2 years)	4.01 (1.85 to 8.70)[b]	*P* < 0.01[f]
		Death/MI (5 year)	1.89 (1.15 to 3.11)[b]	*P* < 0.01[f]
		Death/MI (10 years)	1.66 (1.10 to 2.52)[b]	*P* = 0.02[f]
	AccuTnI (> 0.04 mcg/L)	Death (30 days)	NR	*P* > 0.10[g]
		MI (30 days)	26.1 (5.91 to 115.00)[b]	*P* < 0.01[g]

Table 15: Hazard Ratios of Major Cardiac Events and Death in Patients Diagnosed by cTn Tests				
Author and Year	**cTn Test**	**Outcome**	**HR (95% CI)**	***P* Value**
		Death/MI (30 days)	14.68 (4.96 to 43.48)[b]	*P* < 0.01[g]
		Death/MI (6 months)	7.78 (4.03 to 15.04)[b]	*P* < 0.01[g]
		Death/MI (1 year)	5.42 (3.09 to 9.53)[b]	*P* < 0.01[g]
		Death/MI (2 years)	4.37 (2.69 to 7.10)[b]	*P* < 0.01[g]
		Death/MI (5 year)	2.73, 1.85 to 4.03)[b]	*P* < 0.01[g]
		Death/MI (10 years)	2.34 (1.68 to 3.26)[b]	*P* < 0.01[g]
	AccuTnI (0.02 to 0.04 mcg/L)	Death (1 year)	1.56 (0.69 to 3.54)[b]	*P* = 0.29[g]
		Death (2 years)	1.64 (0.86 to 3.11)[b]	*P* = 0.13[g]
		Death/MI (30 days)	3.37 (0.89 to 12.75)[b]	*P* = 0.07[g]
		Death/MI (6 months)	2.03 (0.88 to 4.68)[b]	*P* = 0.10[g]
		Death/MI (1 year)	1.91 (0.97 to 3.77)[b]	*P* < 0.01[g]
		Death/MI (2 years)	2.09 (1.22 to 3.60)[b]	*P* = 0.01[g]
		Death/MI (5 year)	1.78 (1.18 to 2.67)[b]	*P* = 0.01[g]
		Death/MI (10 years)	1.70 (1.21 to 2.39)[b]	*P* < 0.01[g]

cTn = cardiac troponin; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CI = confidence interval; HR = hazard ratio; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; MACE = major adverse cardiovascular events (composite of cardiovascular death, non-fatal MI and revascularization); MI = myocardial infarction.
Note: *P* value for the comparison of the hazard rate in a specified hs-cTnI concentration versus the lowest concentration group (< 0.005 mcg/L).
Not: *P* value for the comparison of the hazard rate in a specified AccuTnI concentration versus the lowest concentration group (< 0.01 mcg/L).
[a]Median follow-up = 271 days.
[b]Hazard ratio adjusted for known confounding factors (in Cox proportional hazard model).
[c]*P* value for the comparison of the hazard rate in test-positives versus test-negatives.
[d]Median follow-up = 16.3 months.
[e]Unadjusted hazard ratio.

Table 16: Estimates of Diagnostic Accuracy of Troponin Tests (administered at ED presentation) for Major Cardiac Events and Death Reported in the Included Studies

Author and Year	cTn Test	Outcome	Diagnostic Accuracy Measures				
			Sensitivity	Specificity	LR (+)[a]	LR (–)[a]	AUC of the ROC
Kavsak et al. 2012[24]	hs-cTnT	Serious cardiac outcomes (MI. heart failure, arrhythmia)	0.77 (0.55 to 0.92)	0.80 (0.70 to 0.83)	3.5 (2.4 to 4.9)	0.27 (0.12 to 0.59)	0.82 (0.71 to 0.94)
	hs-cTnI		0.80 (0.56 to 0.94)	0.67 (0.58 to 0.75)	2.4 (1.8 to 3.2)	0.31 (0.14 to 0.69)	0.86 (0.76 to 0.96)
	cTnI		0.60 (0.36 to 0.81)	0.93 (0.87 to 0.96)	7.9 (4.1 to 14.9)	0.45 (0.28 to 0.72)	0.86 (0.78 to 0.95)
Aldous et al. 2011[35]	hs-cTnT	MACE (30 days)	0.79 (0.67 to 0.87)[a]	NR	NR	NR	NR
	cTnT		0.71 (0.60 to 0.81)[a]	NR	NR	NR	NR
	cTnI		0.71 (0.60 to 0.81)[a]	NR	NR	NR	NR
	hs-cTnT	MACE (2 years)	NR	NR	NR	NR	0.70 (0.63 to 0.76)[b]
	cTnT		NR	NR	NR	NR	0.61 (0.53 to 0.69)[b]
	cTnI		NR	NR	NR	NR	0.66 (0.59 to 0.73)[b]
	hs-cTnT	Cardiac death[c]	NR	NR	NR	NR	0.77 (0.71 to 0.86)
	cTnT		NR	NR	NR	NR	0.68 (0.55 to 0.80)
	cTnI		NR	NR	NR	NR	0.73 (0.64 to 0.82)
	hs-cTnT	Non-fatal MI[c]	NR	NR	NR	NR	0.66 (0.59 to 0.73)
	cTnT		NR	NR	NR	NR	0.57 (0.48 to 0.65)
	cTnI		NR	NR	NR	NR	0.61 (0.53 to 0.68)
	hs-cTnT	Revascularization[c]	NR	NR	NR	NR	0.68 (0.58 to 0.78)
	cTnT		NR	NR	NR	NR	0.61 (0.49 to 0.73)
	cTnI		NR	NR	NR	NR	0.64 (0.53 to 0.76)
Hochholzer et al. 2011[32]	hs-cTnT	Death[d]	0.78 (0.68 to 0.87)	0.66 (0.63 to 0.69)	2.3 (2.0 to 2.7)	0.33 (0.20 to 0.53)	0.79 (0.74 to 0.84)
	cTnT		0.43 (0.32 to 0.55)	0.89 (0.87 to 0.91)	4.0 (2.9 to 5.4)	0.63 (0.52 to 0.77)	0.69 (0.62 to 0.76)
Kavsak et al. 2009[25]	hs-cTnI	Death/MI (30 days)	NR	NR	NR	NR	0.74 (0.66 to 0.82)
	cTnI		NR	NR	NR	NR	0.81 (0.73 to 0.90)

AUC = area under the curve; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; LR (+) = positive likelihood ratio; LR (–) = negative likelihood ratio; MACE = major adverse cardiovascular events (composite of cardiovascular death, non-fatal MI and revascularization); MI = myocardial infarction; NR = not reported; ROC = receiver operating characteristic curve.

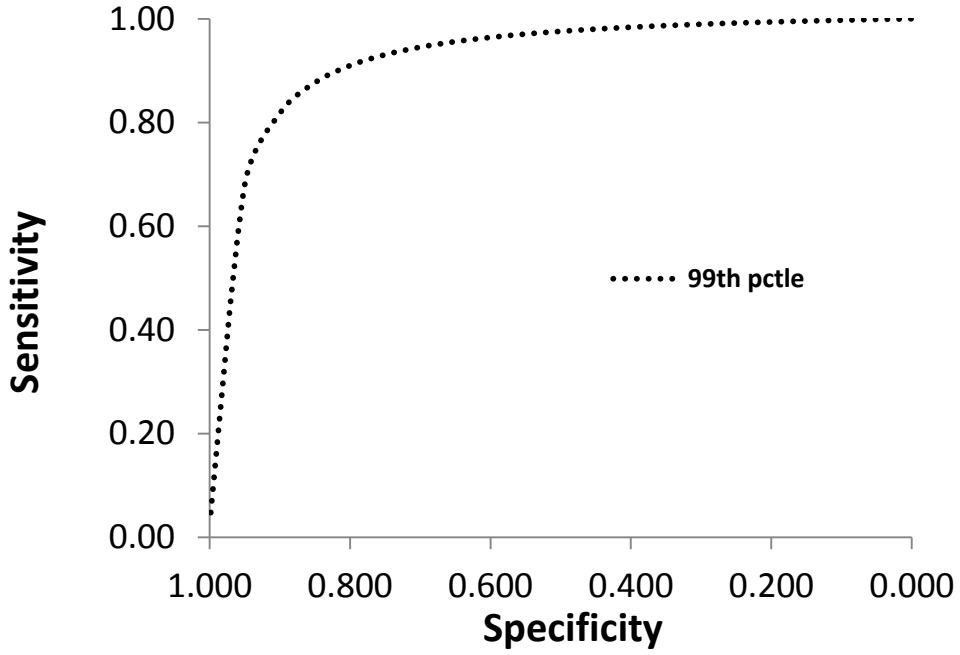
[a]Calculated using available parameters.

[b]Area under ROC curve for prediction of 30-day MACE, using serial samples [ED presentation and 6 to 24 hours after presentation], is reported to be 0.54 (95% CI, 0.47 to 0.62) for hs-cTnT; 0.56 (95% CI, 0.47 to 0.64) for cTnT; and 0.64 (95% CI, 0.53 to 0.76) for cTnI.

[c]Length of follow-up = 2 years.

[d]Median follow-up = 16.3 months.

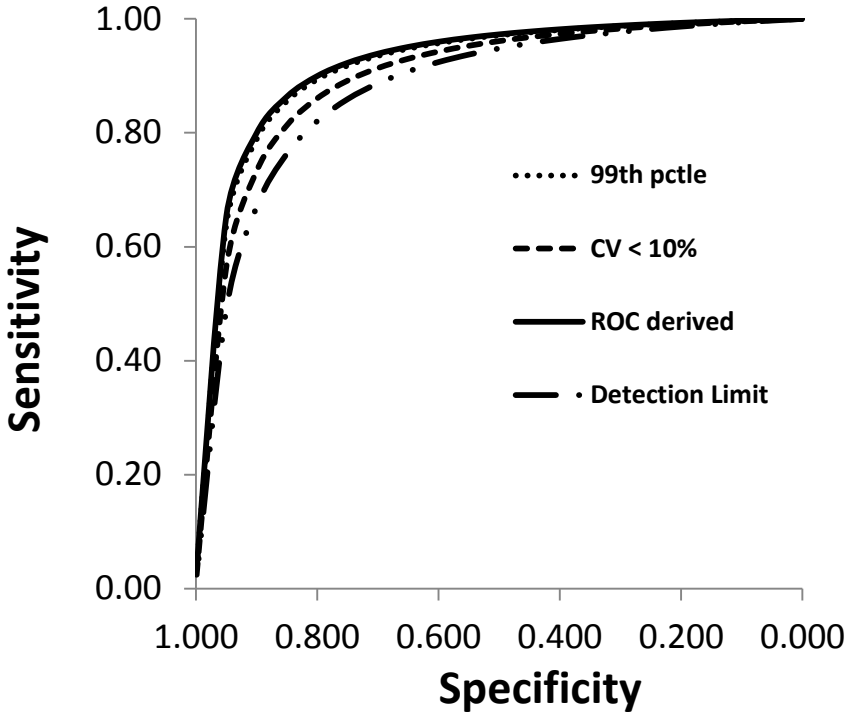
Figure 2: Summary of ROC Curve for hs-cTnI at ED Presentation



Cut-off	Studies (n)	Sensitivity	Specificity	DOR	SROC AUC
99th percentile	2	0.824 (0.790 to 0.854)	0.897 (0.889 to 0.904)	40.3	0.939 (0.912 to 0.946)
CV < 10%	0				
ROC derived	0				
Detection Limit	1	1.00 (0.98 to 1.00)	0.308 (0.278 to 0.339)	undefined	undefined

AUC = area under the curve; CV = coefficient of variation; DOR = diagnostic odds ratio; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; pctle = percentile; ROC = receiver operating characteristic curve SROC = summary receiver operating characteristic curve.

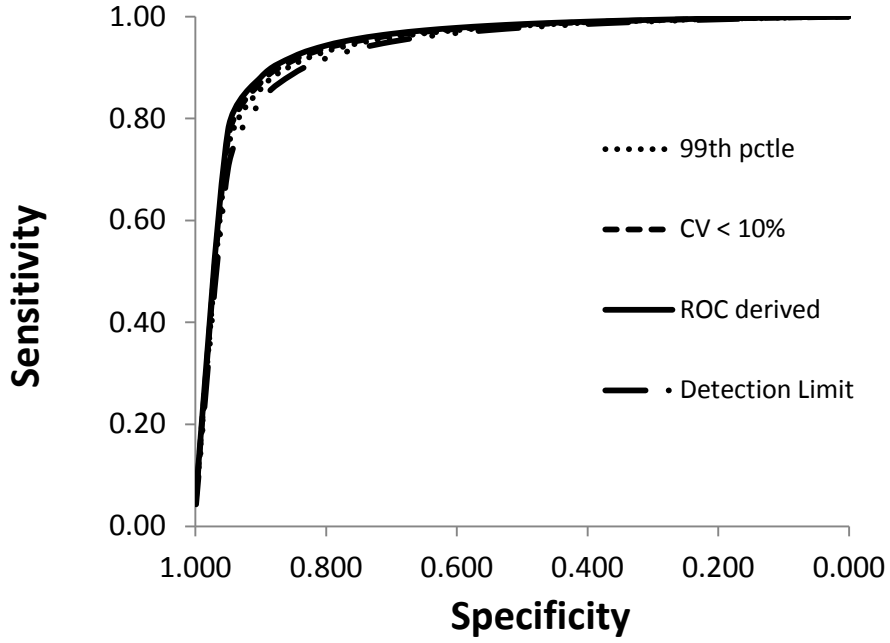
Figure 3: Summary of ROC Curve for hs-cTnT at ED Presentation



Cut-off	Studies (n)	Sensitivity	Specificity	DOR	SROC AUC
99th percentile	5	0.878 (0.825 to 0.917)	0.823 (0.804 to 0.841)	33.6	0.870 (0.838 to 0.897)
CV < 10%	1	0.836 (0.773 to 0.886)	0.829 (0.798 to 0.854)	24.7	0.901 (0.884 to 0.918)
ROC derived	1	0.844 (0.813 to 0.871)	0.869 (0.839 to 0.893)	35.9	0.923 (0.908 to 0.938)
Detection Limit	3	0.974 (0.961 to 0.983)	0.326 (0.321 to 0.329)	18.3	0.881 (0.866 to 0.897)

AUC = area under the curve; cTnI = conventional cardiac troponin I; ED = emergency department; CV = coefficient of variation; DOR = diagnostic odds ratio; pctle = percentile; ROC = receiver operating characteristic; SROC = summary receiver operating characteristic.

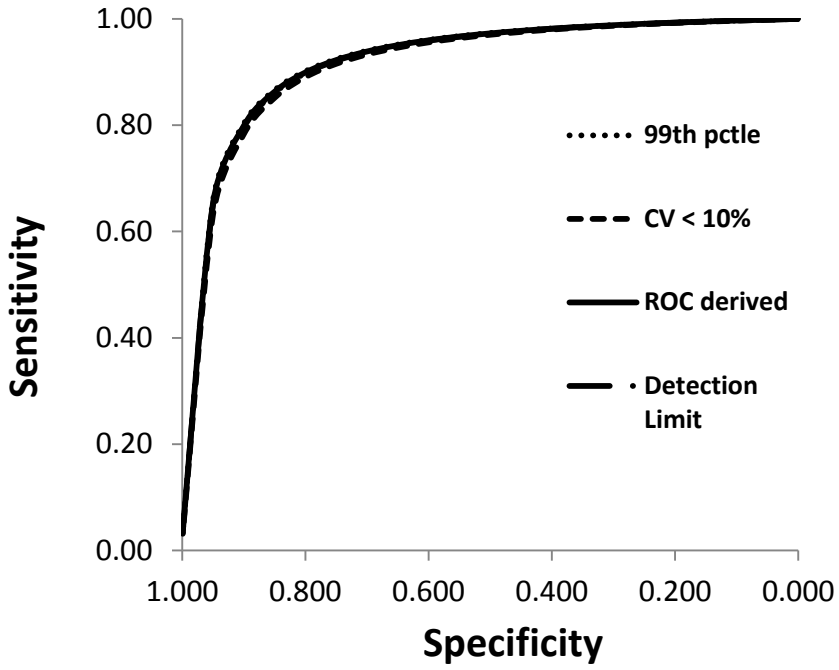
Figure 4: Summary of ROC Curve for cTnI at ED Presentation



Cut-off	Studies (n)	Sensitivity	Specificity	DOR	SROC AUC
99th percentile	7	0.806 (0.755 to 0.849)	0.941 (0.920 to 0.956)	65.7	0.943 (0.919 to 0.960)
CV < 10%	3	0.866 (0.846 to 0.884)	0.916 (0.909 to 0.923)	70.5	0.952 (0.942 to 0.963)
ROC derived	1	0.918 (0.864 to 0.954)	0.856 (0.829 to 0.874)	66.5	0.950 (0.938 to 0.963)
Detection Limit	5	0.919 (0.904 to 0.932)	0.808 (0.804 to 0.812)	48.0	0.937 (0.928 to 0.946)

AUC = area under the curve; cTnI = conventional cardiac troponin I; ED = emergency department; CV = coefficient of variation; DOR = diagnostic odds ratio; pctle = percentile; ROC = receiver operating characteristic; SROC = summary receiver operating characteristic.

Figure 5: Summary of ROC Curve for cTnT at ED Presentation



Cut-off	Studies (n)	Sensitivity	Specificity	DOR	SROC AUC
99th percentile	2	0.649 (0.627 to 0.668)	0.952 (0.943 to 0.960)	36.6	0.924 (0.911 to 0.938)
CV < 10%	2	0.482 (0.463 to 0.497)	0.972 (0.964 to 0.979)	32.5	0.917 (0.903 to 0.931)
ROC derived	1	0.627 (0.572 to 0.665)	0.955 (0.942 to 0.965)	35.7	0.923 (0.907 to 0.938)
Detection Limit	2	0.663 (0.641 to 0.683)	0.947 (0.938 to 0.955)	35.1	0.922 (0.908 to 0.936)

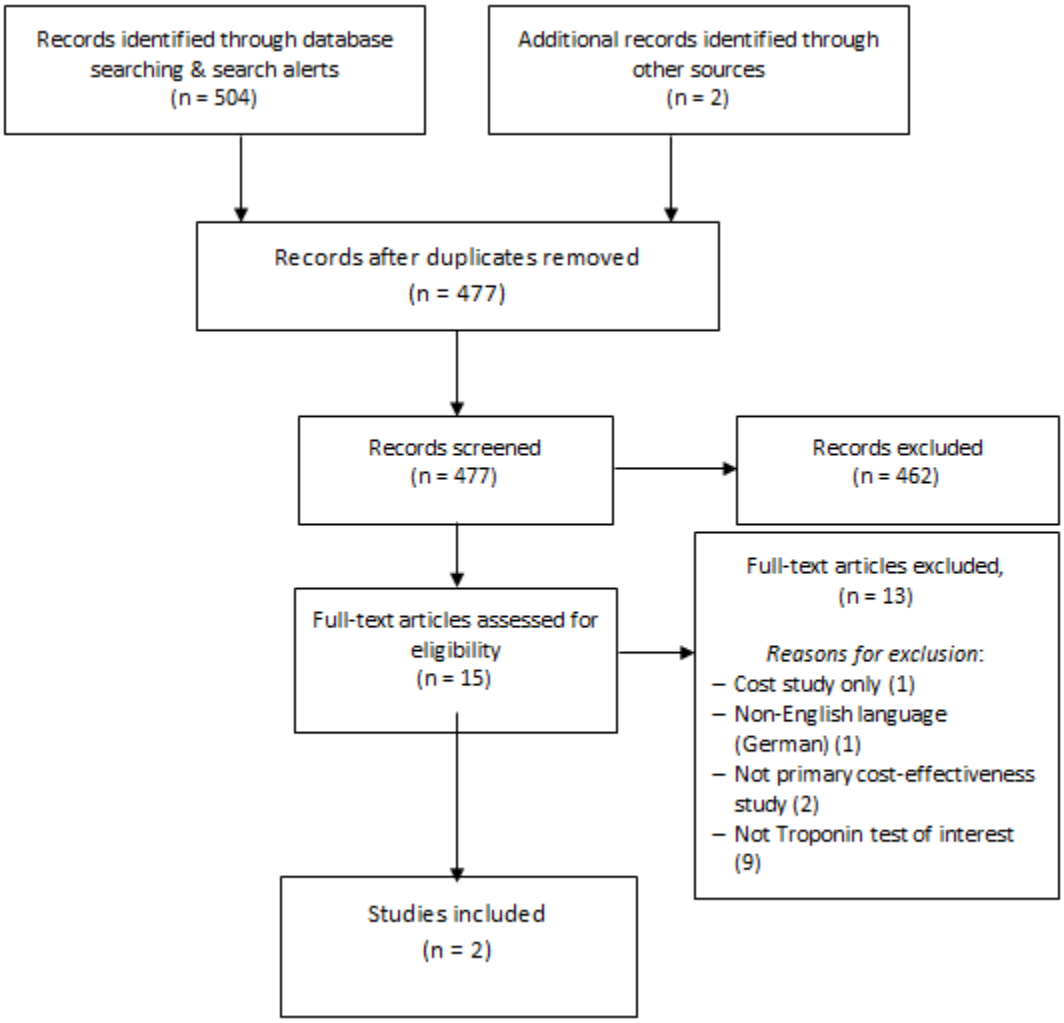
AUC = area under the curve; c-cTnT = conventional cardiac troponin T; ED = emergency department; CV = coefficient of variation; DOR = diagnostic odds ratio; hs-cTnI = high-sensitivity cardiac troponin I; pctle = percentile; ROC = receiver operating characteristic curve; SROC = summary receiver operating characteristic curve.

5 ECONOMIC REVIEW RESULTS

5.1 Selection of primary studies

A total of 433 citations were identified by the systematic search as potentially relevant economic studies. Four hundred and sixty-two studies were excluded after title and abstract screening, leaving 15 studies for full text review. Thirteen studies were excluded during full text review. Nine studies were excluded because they did not include either hs-cTnT or hs-cTnI as a comparator. Two studies were excluded because they were not primary cost-effectiveness analyses, one study was excluded because it was non-English, and one study was excluded because it evaluated costs but not effectiveness. After full text review there were two relevant economic studies to evaluate. Figure 6 shows the PRISMA flowchart of the process used to identify and select studies for the review and the main reasons for exclusion. The list of the excluded studies and the reasons for exclusion are provided in Appendix 7.

Figure 6: PRISMA Diagram for Economic Literature Search



5.2 Study characteristics

Two relevant economic evaluations were identified in the systematic review.[36,37] One was a full publication[36] while the other was published in abstract form only[37]. Both studies were model-based, cost-utility analyses and took lifelong time horizons. Both studies included cTnT and hs-cTnT as treatment comparators for the diagnosis of MI in patients presenting to the ED with chest pain.

5.3 Critical Appraisal of Individual Studies

Critical appraisal of the included studies was guided by the Drummond and Jefferson checklist.[7] Because the economic evaluation by Vaidya et al.[37] was in abstract form only, details on its methodology was not available. Therefore, no critical appraisal was conducted on this study.

The economic evaluation by Thokala et al.[36] had a number of strengths. The overall study design was transparent and appeared to be appropriate. Appropriate sensitivity analyses were conducted and conclusions made were appropriate given the findings of the evaluations. One weakness of the study was that the details of the design of an effectiveness study used as a source for a number of model inputs including the one-year probability of death and MI for treated and untreated patients was not clearly stated.

5.4 Results of the primary economic studies

Thokala et al.[36] was a UK-based evaluation that compared the cost-effectiveness of different cTn testing strategies for patients presenting to an ED with chest pain. Five different strategies were evaluated. The testing strategies included: cTnT test results on presentation (99th percentile cut-off); cTnT test results on presentation (10% CV cut-off); hs-cTnT test results on presentation (99th percentile cut-off; 4), 10-hour cTn test results only; and no cTn testing. The model included both a short-term decision tree representing the first year following the chest pain episode and a long-term model representing the remaining lifetimes of the patients. In the short-term, model patients with a negative cTn test at presentation were assumed to be discharged home while patients with a positive test were assumed to have a second cTn test 10 hours after presentation. Patients who received false-positive results were assumed to be correctly identified by the 10-hour cTn test and subsequently discharged. Patients who had false-positive cTn tests at presentation were assumed to consume resources from the time of the presentation cTn to the 10-hour cTn test. Mortality and subsequent MI at one year depended on whether MI patients were treated or not. Patients with a MI and a positive test at presentation were assumed to be treated while patients with a negative cTn test on presentation were assumed not to be treated. In the long-term part of the model, costs were assigned to patients suffering an MI. Lifetime QALYs were assigned to patients based on age and whether they had another MI within one year. Three scenarios were tested in the model based on how frequent physicians would be available to make decisions for discharging patients who were false positive on admission cTn test, but correctly diagnosed with the second cTn test. In the “doctor on demand” scenario it was assumed that patients could be discharged within one hour after the second cTn test. In the twice daily scenario, it was assumed that discharge decisions would be made twice a day, while in the once daily scenario it was assumed that ward physicians would be available only once a day to discharge patients. The sensitivity and specificity for cTnT and hs-cTnT upon presentation was based on a meta-analysis conducted by the authors .The sensitivities for cTnT and hs-cTnT used in the model was 0.80 and 0.96

respectively. The specificity of cTnT and hs-cTnT were 0.91 and 0.72 respectively. The prevalence of MI in the study population was assumed to be 7%. The probability of one-year death for treated and untreated patients was assumed to be 11% and 21% respectively. The probability of a second MI after one year was assumed to be 11% and 29% for treated and untreated patients respectively.

The economic model estimated hs-cTnT (99th percentile cut-off) to produce 0.026 more QALYs than cTnT (99th percentile cut-off). The incremental cost of hs-cTnT compared with cTnT varied from £179 to £324 depending on the scenario of doctor availability assumed. The incremental cost per QALY for hs-cTnT varied from £7,340 to £12,340 depending on the scenario assumed. The authors did not provide a conclusion of the cost-effectiveness of hs-cTnT compared with cTnT because their focus was on the cost-effectiveness of delayed 10-hour cTn testing versus other testing strategies. They did conclude that delayed cTn testing was unlikely to be cost-effective compared with making discharge decisions based on hs-cTnT at presentation.

Vaidya et al.[37] presented an economic analysis of different biochemical testing strategies for patients presenting to the ED with chest pain. Three different testing strategies were compared: cTnT; hs-cTnT; and hs-cTnT plus H-FABP (heart-type fatty acid binding protein). The analysis was European-based; however, a specific country perspective was not described in the abstract. At the time of this review the study was only presented in abstract form. Therefore, few details about the methods of the model were available other than that it was a lifetime model of the costs and consequences of the three testing strategies to diagnose MI. The incremental cost per QALY of hs-cTnT compared with cTnT was reported to be €3,478. Furthermore, the authors stated that hs-cTnT saved 16 to 17 lives per 1,000 AMI patients. The authors concluded that hs-cTnT was cost-effective versus cTnT.

6 PRIMARY ECONOMIC EVALUATION

The published literature of economic evaluations comparing cTn tests for patients presenting with chest pain was sparse. The two cost-effectiveness studies identified evaluated hs-cTnT and cTnT. Neither of these studies evaluated cTnI or hs-cTnI. Additionally, neither one of these evaluations was a Canadian-based study. Because of these limitations, a primary economic evaluation was conducted.

6.1 Methods

6.1.1 Type of economic evaluation

A cost-utility analysis was conducted, with treatments compared in terms of the incremental cost per QALY gained. A cost-utility analysis incorporates both mortality and quality of life impacts of disease and treatment. The use of the cost per QALY outcome also allows for comparison with economic evaluations of other conditions and treatments.

6.1.2 Target population

The population cohort entering the model are 65-year-old patients presenting to an ED with ischemic chest pain, without ST-segment elevation ECG who require cTn testing for diagnosis of NSTEMI. This population was chosen because it was assumed that patients with chest pain

and ST-segment elevation or other ECG changes would be treated immediately regardless of the findings of the cTn test. Therefore, the model evaluates cTn tests in terms of its ability to diagnose NSTEMI.

6.1.3 Comparators

Three comparators were considered in this analysis:

- hs-cTnT
- hs-cTnI
- cTnI

Because cTnT is no longer available in Canada, it was not considered as an appropriate treatment comparator.

6.1.4 Perspective

The analysis was taken from the perspective of a publicly funded health care system. The costs in the analysis included those of drugs that are covered in the provincial formularies for eligible patients, in-patient costs, and physician fees for services that are covered in provincial fee schedules. Indirect costs, such as productivity losses, were not considered; however, since the base-case starting age is 65 years, indirect costs such as productivity losses may be minimal.

6.1.5 Effectiveness

The primary outcome measure used in the analysis was QALYs. Secondary outcomes included were the expected number of NSTEMI patients treated early, the number of untreated NSTEMI patients, and number of false-positive hospital admissions for each comparator.

6.1.6 Time horizon

A lifetime horizon was used in the model.

6.1.7 Modelling

The model is made up of two parts. The first part of the model is a decision tree following patients from the presentation to an ED with chest pain to one year after their episode. A graphical representation of the decision tree is provided in Figure 7. The starting population of the model is patients presenting to an ED with ischemic chest pain and are suspicious of having ACS, but do not have ST-segment elevation or other abnormal ECG findings at presentation.

As shown in Figure 7, a proportion of patients will have a positive cTn test at presentation, while a proportion of patients will have a negative cTn test. A proportion of patients with a positive presentation cTn test are assumed to be admitted to hospital. In the base-case analysis it is assumed that all patients with a positive cTn test will be admitted to hospital while this assumption is varied in sensitivity analysis. Patients who have a positive cTn test at presentation but are not immediately admitted to hospital, are assumed to be observed in the ED, and retested six hours later to confirm NSTEMI. The assumption of six hours between cTn tests was based on recent consensus guidelines that state that cTn tests should be measured at first assessment and repeated three to six hours later.[4]

Patients with a negative cTn test are assumed to be observed for six hours in the ED and assumed to be retested six hours later. Patients with a negative cTn test at presentation but a positive second cTn test are assumed to be admitted to hospital for treatment. Patients with a negative cTn test at presentation and a negative second cTn test are assumed to be discharged home.

Among patients with a positive cTn test, a proportion will be true positives representing patients who have NSTEMI; while a proportion of patients will have false- positive tests, representing patients without NSTEMI. Similarly, patients who have a negative cTn test can either represent a true negative (do not have NSTEMI) or a false negative (have NSTEMI). The proportion of patients in each diagnostic category (true positives, false positives, true negatives, false negatives) are determined by both the underlying prevalence of NSTEMI and the diagnostic accuracy of the cTn test being evaluated.

A proportion of patients with NSTEMI are assumed to die in the short-term part of the model (one year). The proportions of NSTEMI patients who die differ depend on when or if NSTEMI is diagnosed and treated. For example, patients who have a positive cTn test at presentation and are treated relatively quickly are assumed to have a lower mortality rate than NSTEMI patients who are not diagnosed and treated until their second cTn test. Patients with false-negative NSTEMI test results are discharged home and are assigned higher one-year mortality than patients with NSTEMI who are admitted to hospital and treated.

Figure 8 shows a stratification of non-NSTEMI patients who is not illustrated in Figure 7. Specifically, non-NSTEMI patients are further stratified in the model as having UA or being non-ACS. Non-ACS patients who are admitted to hospital are assigned false-positive admission costs and are assumed to receive no benefit from treatment upon admission. In the base case, UA patients who have a false-positive admission are also assumed to not receive a mortality benefit from the admission. However, they are not assigned a cost of a false-positive admission as non-ACS patients are. This assumption was made recognizing that some UA patients would be hospitalized regardless of cTn results, and that they could potentially receive benefit from hospital admission as well.

In a sensitivity analysis, UA patients are assigned both the costs of a false-positive hospital admission, along with the mortality benefit assumed for treated NSTEMI patients. Non-ACS patients are assumed to have mortality rates equivalent to the general population.

The annual probability of death in the long-term part of the model is dependent on patient age, gender, and whether they had suffered an NSTEMI, had UA, or did not have any type of ACS during the short-term part of the model.

Figure 7: Short-Term cTn Model Structure

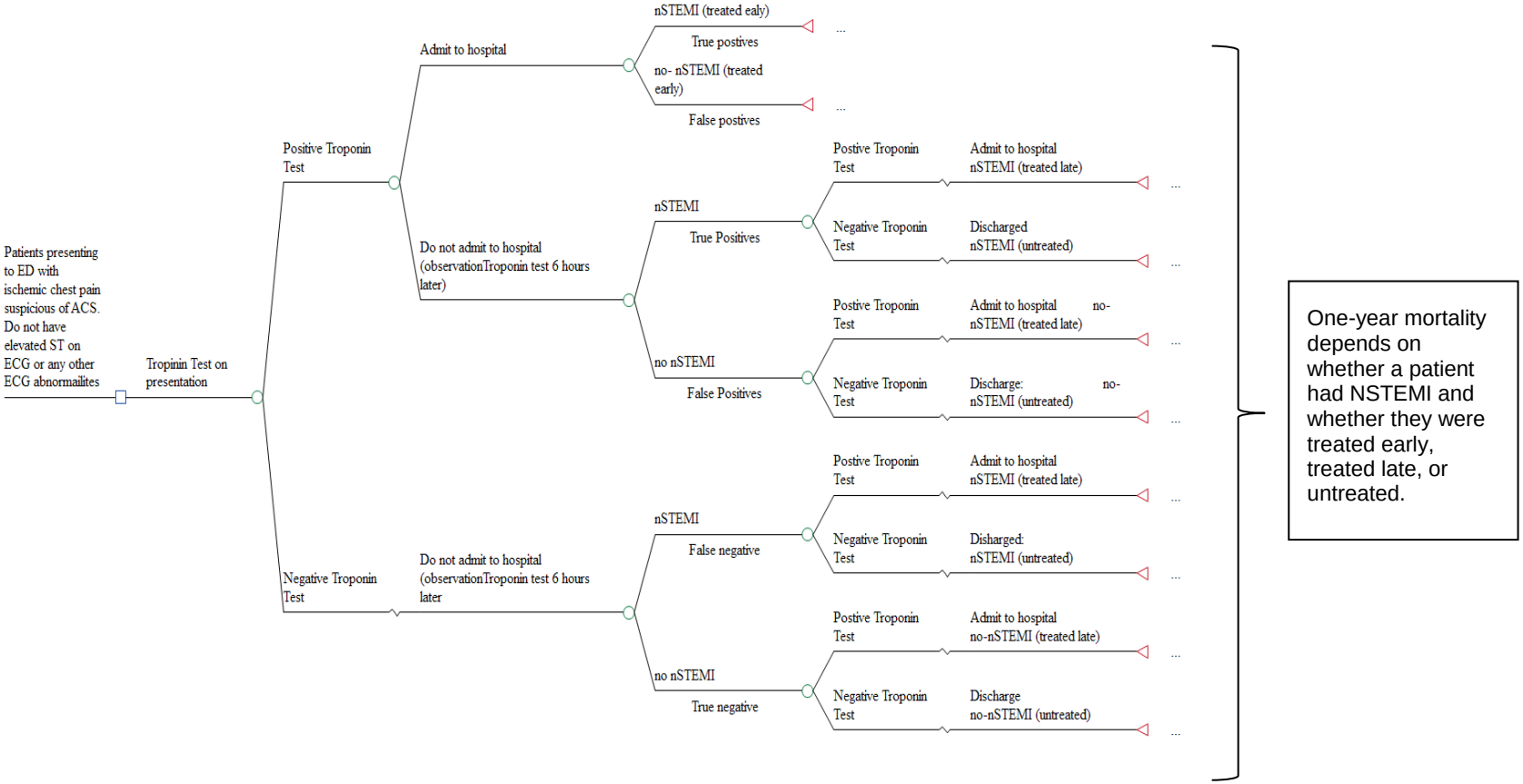
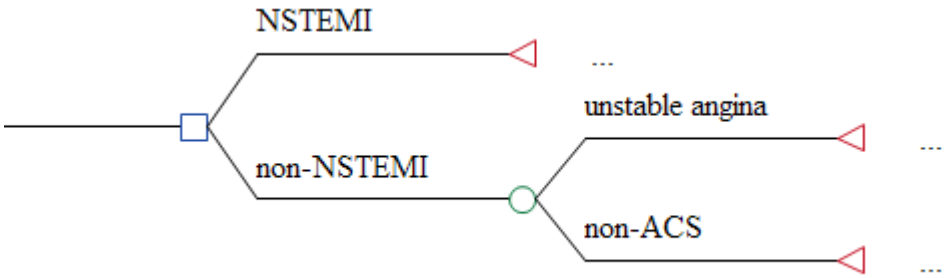


Figure 8: Defining Non-NSTEMI Patients



6.1.8 Valuing outcomes

A number of clinical variables are used to populate the model and estimate the number of expected QALYs for each cTn test comparator. Sensitivity and specificity of the tests, as well as the underlying prevalence of NSTEMI were used to estimate the diagnostic status (e.g., true positives, false positives, true negatives, false negatives) of patients during the acute chest pain episode. In addition, the proportion of non-NSTEMI patients who are diagnosed as UA or non-ACS was a clinical input variable in the model. Other clinical model variables related to morality, both for the one-year short-term part of the model along with the long-term part of the model. Additionally, utility values for patients with and without NSTEMI were also parameters used in the model to estimate QALYs. Targeted literature searches were used to identify sources for parameters that could be based on findings from the clinical systematic reviews. Details the sources and values of the clinical variables used in the model are provided in the following paragraphs.

a) Prevalence of NSTEMI

The underlying prevalence of NSTEMI among the target population of the model was based on data from studies included in the clinical systematic review. Seven studies[15,16,20-22,27,29] that reported the number of patients diagnosed with NSTEMIs were included for the estimation of NSTEMI prevalence. Three of these studies[16,27,29] included STEMI patients in their patient population while the remaining studies did not. Since the model begins with patients without STEMI on presentation ECG, STEMI patients were excluded from the total study population. One study that reported the number of patients with NSTEMI[14] was excluded from the calculation because the starting population was likely an overrepresentation of MI patients as it included patients who underwent early invasive treatment. Data from these studies were pooled using random effects meta-analysis.[38] The pooled prevalence of NSTEMI was estimated to be 0.16 (0.09 to 0.24). This was used as the base case of prevalence in the model.

b) Diagnostic Accuracy

The sensitivity and specificity for each cTn test at presentation to the ED was derived from the clinical systematic review. The values for sensitivity and specificity for each test is provided in Table 17. As shown, hs-cTnT has the highest sensitivity at presentation (0.878) along with the lowest specificity (0.823). The cTnI has the lowest sensitivity (0.806) but the highest specificity (0.941).

Table 17: Sensitivity and Specificity Values for Troponin Tests Taken at Presentation to ED (99th percentile cut-off)		
Test	**Sensitivity Mean (95% CI)**	**Specificity Mean (95% CI)**
hs-cTnT	0.878 (0.825 to 0.917)	0.823 (0.804 to 0.841)
hs-cTnI	0.824 (0.79 to 0.854)	0.897 (0.889 to 0.904)
cTnI	0.806 (0.755 to 0.849)	0.941 (0.92 to 0.956)

CI = confidence interval; cTnI = cardiac troponin I; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T.

In the model, patients with a negative cTn test at presentation are assumed to be observed and have a second cTn test six hours later. For patients with a true- negative cTn test at baseline, it was assumed that all patients will have a negative cTn test on the second cTn test.

It was assumed that 0.90 of false-negative presentation cTn tests would become true positive upon the second cTn test. This was based on data from the Body et al.[26] study, in which the diagnostic accuracy of presentation hs-cTnT were evaluated separately for patients presenting less than three hours from the onset of symptoms and for patients presenting six or more hours after presentation. The sensitivity of hs-cTnT in patients presenting less than three hours from the onset of symptoms was reported to be 0.80, while the sensitivity of hs-cTnT for patients presenting six hours or more after symptom onset was reported to be 0.98. This can imply that 0.90 of the false-negative cases would become true positives as time from symptom to testing increases (0.18/0.20).

c) Proportion of Non-NSTEMI Patients Who Are Diagnosed with UA

The proportion of non-NSTEMI patients who have UA were based on data from studies included in the clinical systematic review. Seven studies[15,16,20-22,27,29] were used to estimate the proportion of non-NSTEMI patients who were diagnosed with UA. Data from these studies were pooled using random effects meta-analysis.[38] The pooled prevalence of NSTEMI was estimated to be 0.16 (95% CI, 0.08 to 0.23). Based on these data, it was assumed that 0.16 of patients who did not have NSTEMI had UA, while 0.84 of patients without NSTEMI had no form of ACS.

d) Mortality

Short-term mortality (six months to one year) after NSTEMI varied greatly in studies identified through the targeted literature search. Abbott et al.[39] compared outcomes of STEMI and NSTEMI after PCI and reported the one-year mortality for 799 NSTEMI patients to be 5.5%. In a Finish study of 1,188 consecutive patients hospitalized for ACS, the proportion of NSTEMI patients deceased at 10 months to 27%, Allen et al.[40] estimated long-term mortality for patients with ACS. Based on the Kaplan-Meier curve presented in the study, the one-year mortality of NSTEMI patients can be estimated to be 24%.

In the base case of the model, a one-year mortality rate after NSTEMI of 16.26%. This represents the weighted average of one-year mortality reported in these studies. This baseline mortality was applied to NSTEMI patients treated early. Because the sensitivity of all assays at presentation was more than 0.50, the model would predict that most NSTEMI patients would be treated early.

The relative risk of one-year mortality between NSTEMI patients treated late compared with patients treated early was assumed to be 1.01. This was based on expert opinion. An alternative estimate of 1.035 (0.98 to 1.09) is tested in sensitivity analysis. This was based on findings reported from the Timing of Intervention in Patients With Acute Coronary Syndromes (TIMACS) study.[41] The TIMACS study reported the relative risk of death at six months to be 0.81 (0.60 to 1.11) for patients in the early intervention strategy compared with patients in the late intervention strategy. The relative risk of death was adjusted to reflect that the median difference in time to intervention in the early and late treated patients in the TIMACS study was 36 hours, while the model assumes a difference of only six hours between those patients treated early and those treated late (1.035 = 1/(0.81^(6/36)). A relative risk of 1.01 was assumed in the base case because clinical experts felt that 1.035 would be an overestimate of the impact of a six hour delay of diagnosis of NSTEMI on mortality risk.

The relative risk of one-year mortality for patients who are not treated relative to patients treated was assumed to be 1.91. This was based on the ratio of the one-year mortality for untreated MI patients (21%) to the one-year mortality for treated MI (11%) used in the economic evaluation of cTn testing strategies by Thokala et al.[36]

The relative risk of mortality after one year post NSTEMI was assumed to be 1.77 compared with that of the general population. Allen et al.[40] reported that 0.62 of NSTEMI patients in their study had died after 10 years. Based on the published Kaplan-Meier curve from this study, the one-year mortality was estimated to be 0.24. This means 0.5 of NSTEMI patients who were alive after one year in the Allen study died during years 2 to 10. The nine-year cumulative mortality for the general population using life tables was calculated as 0.283 using the mean age (71) and gender mix (40% males) of NSTEMI patients from Allen et al.[40] The resulting relative risk of death for NSTEMI patients compared with the general population was thus estimated to be 1.77 (0.5/.283).

For patients with UA, the one-year risk of mortality was assumed to be 0.062. This was the average of the 10-month mortality of UA patients reported in a Finnish study of patients hospitalized for ACS (0.026) and one-year mortality of 0.09 as measured from the Kaplan-Meier curve presented from Allen et al.[40]

The relative risk of mortality after one year for patients with UA compared with the general population was estimated to be 1.38. Allen et al. reported the multivariable adjusted relative risk of long-term death of NSTEMI compared with UA to be 1.28. The covariates adjusted for included age, prior MI, elevated creatinine, congestive heart failure at presentation, heparin, appropriate heparin therapy, appropriate aspirin therapy and revascularization therapy. This relative risk was applied to the relative risk of death of NSTEMI compared with the general population (1.38 = 1.77/1.28).

For patients who did not have NSTEMI or UA during the initial acute episode, annual mortality rates were based on Canadian life tables [42,43] without adjustment.

e) Utility Values

Utility values were applied to patients who were alive in each annual cycle in order to calculate QALYs. For patients who did not have NSTEMI during their acute episode, general population age and gender specific utility values were applied each year. These utility values were based on data published by Kind et al.[44] For patients who had NSTEMI, utility decrements were applied to general population utility values depending on the age of the patient. The decrements were based on a study[45] in which 2,950 patients who had survived an MI in the past filled out a

survey that included an EQ5D questionnaire. The average utility score was compared with that of the general population and decrements for MI survivors by age group were reported. The general population utilities used in the model are presented in Table 18. The decrements for patients with NSTEMI are provided in Table 19.

Table 18: General Population Utility Values by Age and Gender

Age Group	Males	Females
under 25	0.94	0.94
25-34	0.93	0.93
35-44	0.91	0.91
45-54	0.84	0.85
55-64	0.8	0.81
65-74	0.78	0.78
75+	0.73	0.71

Table 19: Utility Decrements for Patients with NSTEMI by Age Group

Age Group	Utility Decrement (95% CI)
45-54	–0.06 (–0.082 to –0.039)
55-64	–0.051(–0.066 to –0.035)
65-74	–0.025 (–0.04 to –0.012)
75+	–0.007(–0.027 to 0.13)

CI = confidence interval; NSTEMI = non-ST-segment elevation myocardial infarction.

6.1.9 Resource use and costs

a) Hospital Admission

The cost of a true-positive NSTEMI and false-positive hospital admission were derived using data from the Ontario Case Costing Initiative database[46] and the Ontario Schedule of Benefits for Physician Services.[47]

The cost of a false-positive hospitalization was assumed to be $2,136 in the model. This was based on the assumption that a false-positive hospitalization would be two days in duration. The assumption of a two-day length of stay for a false-positive hospitalization was based on expert opinion. A daily in-patient cost of $974 was assumed. This was based on the average cost ($3,799) and length of stay (3.9 days) for an UA admission.[46] One internal medicine consultation fee ($157)[47] and one internal medicine subsequent visit fee ($31)[47] was included in the false-positive admission cost estimate.

The cost of a true-positive NSTEMI hospitalization was estimated to be $11,387. This cost was estimated in a number of steps. First, selecting case mix groups (CMGs) from the OCCI database, average in-patient costs were derived for MI admissions with CABG (CMGs 166,170,171,170), MI with PCI (CMG 175), and MI without CABG or PCI (CMGs 143,144). Next, physician fees were estimated for each type of MI hospitalization using the Ontario Schedule of Benefits and added to the in-patient costs. Finally, an overall MI cost was calculated by weighing the costs by the proportion of NSTEMI patients who would receive a CABG, PCI, or neither procedure. Based on data for NSTEMI patients presented by Goldberg et al.,[48] it was assumed that 0.308 of patients would receive PCI while 0.093 would receive CABG during their hospitalization.

b) ED Costs

For patients who are not admitted to hospital after results of presentation cTn test, additional ED costs of $144.64 were applied. This included the cost of a repeat ECG ($36.40) and additional six hours of ED time. The hourly cost of ED was derived from one report that stated the average cost per ED visit in Ontario was $148 [49] and another that stated that the average time spent in the ED during an episode was 8.2 hours.[50] The cost of an ECG was based on data provided by a hospital in southwestern Ontario and from the Ontario Schedule of Benefits.[47]

c) CTn Tests

Manufacturers were contacted regarding the costs of troponin assays. Not all manufacturers provided pricing information. A manufacturer of both hs-cTnT and cTnT indicated that the price per assay was around $3.00 for both types of assays. One manufacturer of cTnI stated that the cost of hs-cTnI would be comparable with their current cTnI and other tests available in Canada. Another manufacturer of cTnI provided a price list which showed the cost per assay for cTnI ranging from $3.05 per assay to $12.50 per assay. The median cost of all cTnI assays in the price list was $6.75.

Based on this information, a cost of $3.00 was assigned per hs-cTnT assay. A cost of $6.75 was assigned per hs-cTnI and cTnI assay.

6.1.10 Discount rate

In accordance with CADTH guidelines,[51] a 5% discount was applied to costs and QALYs.

6.1.11 Variability and uncertainty

The variability and uncertainty in the model were assessed in several ways. Patient variability was assessed by conducting one-way sensitivity analyses based on age and gender. Joint model parameter uncertainty was assessed using probabilistic sensitivity analysis and presented as cost-effectiveness acceptability curves (CEACs). In the probabilistic sensitivity analysis, beta distributions were applied to sensitivity and specificity variables, along with prevalence and utility variables. Gamma distributions were applied to cost variables, while log normal distributions were assigned to the relative risk variables. In addition, key model parameters were varied in one-way sensitivity analysis. These included the prevalence of NSTEMI, the one-year mortality post NSTEMI, the relative risk of mortality for patients treated late, the cost of a false-positive hospital admission, the proportion patients with initial positive tests who would be hospitalized, the proportion of false-negative presentation cTn tests that would become true positives after a second test, and the proportion of non-NSTEMI cases that would be UA.

6.2 Results

6.2.1 Analysis and results

Table 20 presents the base-case results of the economic model. As shown, among the four test strategies, the model predict hs-cTnT to have the highest expected costs ($2,186), followed by hs-cTnI ($2,082) and cTnI ($2,018). The ordering of strategies in terms of costs is related to the specificity of each test at baseline. Tests with lower specificity will have more false-positive hospitalizations resulting in higher overall costs.

The expected discounted number of QALYs was highest for hs-cTnT (8.1399), followed by hs-cTnI (8.1389) and cTnI (8.1385). The ordering of strategies in terms of QALYs is directly related to the sensitivity of each test at baseline. That is, tests with higher sensitivities at ED presentation result in more patients being treated earlier and less patients being untreated, reducing mortality from NSTEMI.

Table 20: Base-Case Model Results

Testing Strategy	Costs	QALYs	Treated Early	Untreated	False-Positive Admission
hs-cTnT	$2,186	8.1399	0.142	0.002	0.125
hs-cTnI	$2,082	8.1389	0.133	0.003	0.073
cTnI	$2,018	8.1385	0.130	0.003	0.041

cTnI = cardiac troponin I; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; QALY = quality-adjusted life-year.

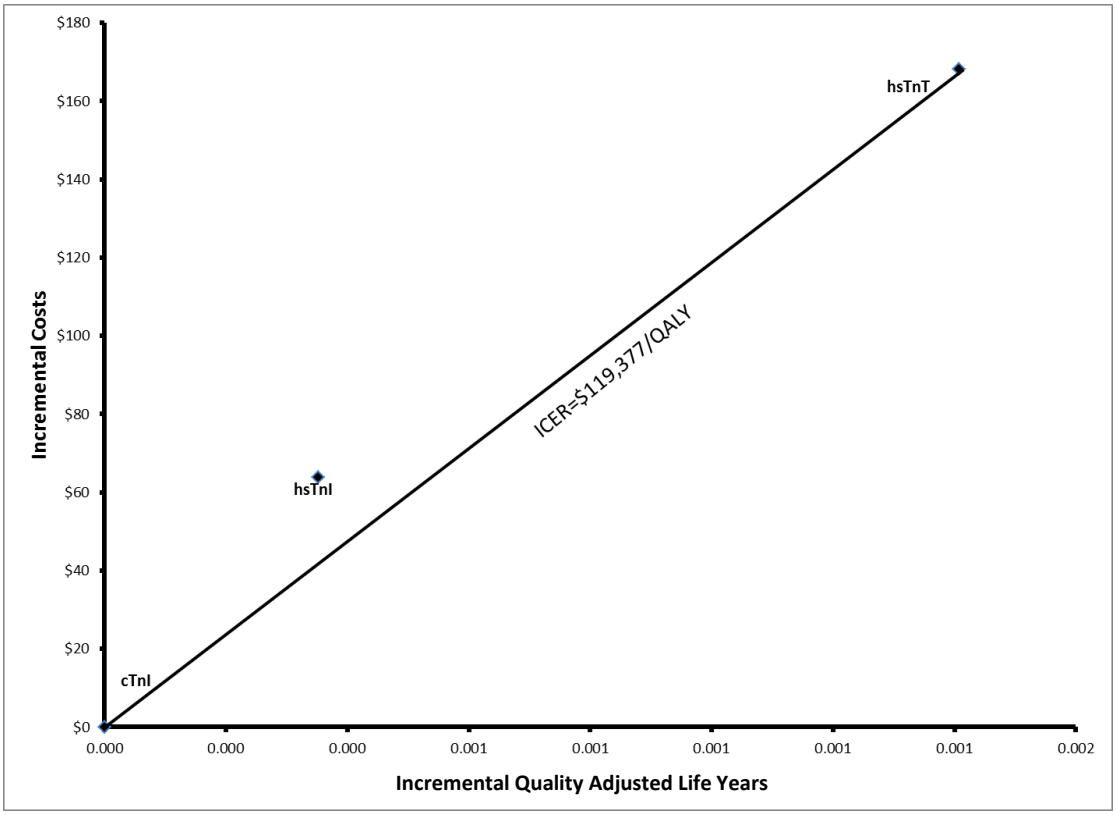
Table 21 presents incremental costs and QALYs of each strategy relative to cTnI, which had the lowest expected costs and QALYs. The incremental costs and QALYs of each strategy relative to cTnI are plotted in Figure 9. The figure also shows the efficiency frontier for the incremental cost per QALY outcome. The two strategies that make up the efficiency frontier are cTnI and hs-cTnT. The hs-cTnI testing strategy is extendedly dominated by a combination of cTnI and hs-cTnT. Because hs-cTnI is extendedly dominated and not on the frontier, it would not be considered to be cost-effective, regardless of the value placed on gaining an incremental QALY. The incremental cost per QALY moving from cTnI to hs-cTnT is estimated to be $119,377. Therefore, cTnI would be considered the cost-effective test if a decision-maker's maximum willingness-to-pay per QALY is less than $119,377. If the maximum willingness-to-pay per QALY is $119,377 or higher, then hs-cTnT would be considered the cost-effective test.

Table 21: Base-Case Incremental Costs, QALYs, and Cost Per QALY

Testing Strategy	Incremental Costs	Incremental QALYs	$/QALY
hs-cTnT	$168	0.001408	$119,377
hs-cTnI	$64	0.000352	Dominated
cTnI	$0	0.000	Reference

cTnI = cardiac troponin I; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; QALY = quality-adjusted life-year.

Figure 9: Base-Case Efficiency Frontier



a) Results of variability analysis

Table 22 presents one-way sensitivity analysis on cost-effectiveness results by patient age and gender. For each sensitivity analyses, the incremental cost per QALY of moving from one testing strategy on the efficiency frontier to the testing strategy is presented. Because hs-cTnI was dominated in all analyses, and therefore not part of the efficiency frontier, it is not shown in the table. Among males, the incremental cost per QALY of hs-cTnT compared with cTnI varies from $85,400 for 50-year-olds to $361,400 for 85-year-olds. Among females, the incremental cost per QALY of hs-cTnT varies from $78,700 for a 50-year-old to $299,900 for an 85-year-old. The cost per QALY increases with age because an older patient will have lower overall life expectancy. Therefore, less QALYs are accumulated in patients who benefit from treatment due to the higher sensitivity of hs-cTnT. As shown, for all sensitivity analyses based on age and gender, hs-cTnI is dominated (extendedly), and therefore, is not part of the efficiency frontier.

Table 23 presents cost-effectiveness results stratified by pretest probability. One study[27] reported diagnostic accuracy separately for patients they classified as having either a low/moderate pretest probability of MI or a high pretest probability of MI. The study evaluated hs-cTnT and cTnI, but not hs-cTnI For low-to-moderate risk patients Freund et al.[27] reported the sensitivity for hs-cTnT and cTnI to be 0.91 and 0.77 respectively. Specificity for hs-cTnT and cTnI was reported to be 0.85 and 0.97 respectively. For patients classified as having high pretest probability of MI, the sensitivity was found to be 0.65 for cTnI and 0.96 for hs-cTnT. Specificity for this patient group was 0.65 for hs-cTnT and 0.88 for cTnI. After adjusting for NSTEMIs, the proportion of patients with NSTEMI was 0.09 in the low/moderate patient group and 0.28 in the high-risk patient group. If these parameters are used in the model, the incremental cost-effectiveness of hs-cTnT compared with cTnI is $121,500 for patients with low-

to-moderate risk and $65,300 for patients with high pretest probability of MI. Because data were not available for hs-cTnI in these subgroups, they were not included in the analysis.

Table 22: Sensitivity Analysis on Patient Gender and Age			
	Efficiency Frontier $/QALY		
	cTnI	**hs-cTnT**	**hs-cTnI**
Male Age			
50	reference	$85,400	dominated
55	reference	$95,800	dominated
65	reference	$128,400	dominated
75	reference	$202,700	dominated
85	reference	$361,400	dominated
Female Age			
50	reference	$78,700	dominated
55	reference	$86,000	dominated
65	reference	$110,200	dominated
75	reference	$168,600	dominated
85	reference	$299,000	dominated

cTnI = cardiac troponin I; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; QALY = quality-adjusted life-year.

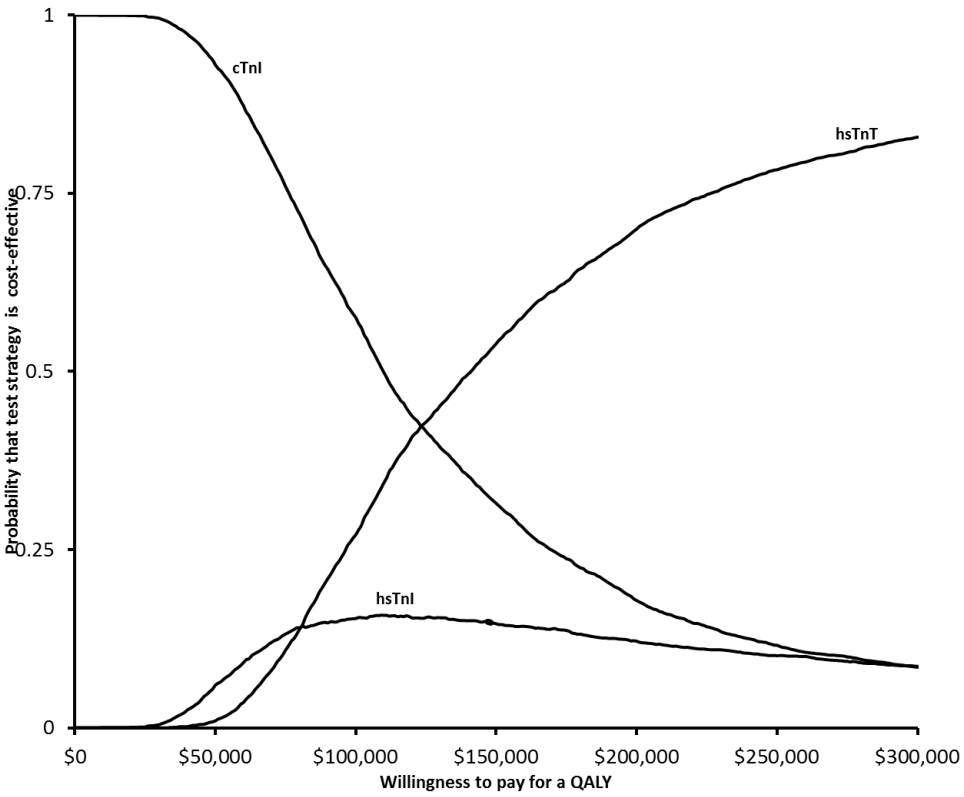
Table 23: Sensitivity Analysis on Pretest Probability			
	Efficiency Frontier $/QALY		
	cTnI	**hs-cTnT**	**hs-cTnI**
Pretest probability			
low-moderate	reference	$121,500	not analyzed
high	reference	$65,300	not analyzed

cTnI = cardiac troponin I; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; QALY = quality-adjusted life-year.

6.2.2 Results of uncertainty analysis

The joint parameter uncertainty of the model was assessed using probabilistic sensitivity analysis. This uncertainty is expressed using CEACs. CEACs for the three treatment strategies are presented in Figure 10. The CEACs show the probability that each testing comparator is cost-effective as a function of the amount a decision-maker is willing to pay for a unit of an outcome of interest (e.g., QALY). Among the three testing strategies, cTnI has the highest probability of being cost-effective for willingness-to-pay values up to $124,000. For willingness-to-pay values greater than $124,000 per QALY, hs-cTnT had the highest probability of being the cost-effective test. The probability that hs-cTnT is cost-effective at willingness-to-pay values of $50,000 per QALY, $75,000 per QALY, and $100,000 per QALY, was estimated to be 0.01, 0.11, and 0.27 respectively.

Figure 10: Cost-Effectiveness Acceptability Curves



In addition to probabilistic sensitivity analysis, a number of one-way sensitivity analyses were conducted on key model variables. These sensitivity analyses are presented in Table 24 and Table 25.

A sensitivity analysis was also conducted by changing several structural assumptions of the model. These include incorporating cTnT as a treatment comparator and assuming patients with UA are assigned both false-positive hospital costs and treatment benefits. Results from these structural sensitivity analyses are provided in Table 26.

The prevalence rate assumed in the model has a large impact on cost-effectiveness results. If an NSTEMI prevalence rate of 0.05 is assumed, then incremental cost per QALY of hs-cTnT becomes $415,800. If a prevalence rate of 0.10 is assumed in the model, the incremental cost-effectiveness ratio of hs-cTnT becomes $201,000 per QALY.

If the baseline one-year mortality is 0.10, the cost per QALY of hs-cTnT becomes $194,200 per QALY compared with cTnI that, if the one-year mortality is assumed to be 0.20, the cost per QALY of hs-cTnT becomes $97,100. In the base-case analysis, the model assumed a 1.01 relative risk of one-year mortality for NSTEMI for patients treated late compared with those treated earlier. If the relative risk of mortality is assumed to be 1.035 based upon the data from

Mehta et al.,[41] the cost per QALY of hs-cTnT becomes $94,200. If the relative risk is assumed to be 1.05 the cost-effectiveness of hs-cTnT becomes $83,600.

In the base case it assumed that the cost of a hs-cTnT assay is $3. If instead the cost per assay is $10, the cost per QALY of hs-cTnT becomes $127,900. If the cost per assay of hs-cTnT is $20, the cost per QALY of hs-cTnT becomes $140,100. If the cost per assay of hs-cTnT is $30, the cost per QALY of hs-cTnT becomes $146,100.

In the base case it was assumed that untreated NSTEMI patients would have a 1.91 relative risk of death at one-year compared with treated NSTEMI patients. If it is instead assumed the relative risk of death for untreated patient is 1.2, the cost per QALY of hs-cTnT compared with cTnI becomes $402,900. If the relative risk of death for untreated NSTEMI patients is assumed to be 1.6, the cost per QALY of hs-cTnT becomes $172,400. If the relative risk of mortality is assumed to be 2.2, the cost per QALY becomes $92,800.

The cost of a false-positive hospital admission is assumed to be $2,136 in the base-case analysis. This is based on a 48-hour admission and at a per day UA hospitalization cost. If instead a cost of $1,000 per false-positive admission is used in the model, the cost per QALY of hs-cTnT becomes $52,200. If the cost per false-positive admission is $3,000, the incremental cost per QALY of hs-cTnT becomes $170,500.

In the base-case analysis it is assumed that 0.9 of all false-negative presentation cTn tests would become true positives upon a second cTn test. If it assumed that all false-negative cTn tests become true positive on subsequent testing, the cost per QALY of hs-cTnT becomes $1,100,000. This less favourable cost per QALY occurs because if all false-negative presentation cTn results become true positives, all tests regardless of their sensitivity upon presentation will result in no NSTEMI patients being untreated. If the proportion of false-negative presentation cTn tests that become true positives is assumed to be 0.8, the cost per QALY of hs-cTnT becomes $67,800. In the base-case, it is assumed that all patients with a positive cTn test at presentation to the ED will be admitted to hospital. If it is assumed that less than 100% of all cTn positive patients are admitted to hospital, the incremental cost-effectiveness of hs-cTnT compared with cTnI becomes more favourable. If only 0.60 of patients with positive presentation cTn tests are assumed to be immediately admitted to hospital, the cost per QALY of hs-cTnT becomes $81,600.The larger proportion of non-NSTEMI patients who are assumed to have UA the more favourable the cost-effectiveness of hs-cTnT is compared hs-cTnI. Based on a published study,[46] utility decrements were applied to patients with NSTEMI based on age. If only half the baseline utility decrements are applied, the cost per QALY of hs-cTnT becomes $118,000. If three times the baseline utility decrements are applied, the incremental cost per QALY becomes $125,600.

The model was evaluated assuming the upper 95% CI values for sensitivity and specificity for all tests. In this sensitivity analysis all comparators comprised the efficiency frontier. The cost per QALY moving from cTnI to hs-cTnI is $70,900, while the cost per QALY moving from hs-cTnI to hs-cTnT is $170,300.

The model was also evaluated assuming the lower 95% CI values for sensitivity and specificity for all tests. In this sensitivity analysis hs-cTnI was extendedly dominated. The cost per QALY of hs-cTnT relative to cTnI is $122,800 in this sensitivity analysis.

As shown in Table 26, if cTnT is included in the analysis, cTnT becomes the cost-effectiveness test if willingness to pay for a QALY is less than $177,400. If willingness to pay for a QALY is equal to or greater than $177,400 then hs-cTnT is the cost-effective test. In this analysis the pooled sensitivity and specificity for cTnT at presentation was assumed to be 0.65 and 0.95 respectively (see Table 4).

If false-positive costs and treatment benefits are assigned to patients with UA who do not have NSTEMI, the cost per QALY of hs-cTnT becomes $22,500.

Table 24: One-Way Sensitivity Analysis on Key Model Variables

		Efficiency Frontier $/QALY		
		cTnI	**hs-cTnT**	**hs-cTnI**
NSTEMI Prevalence Rate (base-case = 0.16)				
0.05		Reference	$415,800	Dominated
0.1		Reference	$201,000	Dominated
0.2		Reference	$93,600	Dominated
0.3		Reference	$57,800	Dominated
One-Year Post NSTEMI Mortality Rate (base-case = 0.16)				
0.05		Reference	$388,300	Dominated
0.1		Reference	$194,200	Dominated
0.2		Reference	$97,100	Dominated
0.3		Reference	$64,800	Dominated
Relative Risk of Mortality NSTEMI Treated Late Versus Early (base-case = 1.01)				
1		Reference	$133,700	Dominated
1.01		Reference	$119,400	Dominated
1.02		Reference	$107,900	Dominated
1.035		Reference	$94,200	Dominated
1.04		Reference	$90,400	Dominated
1.05		Reference	$83,600	Dominated
Relative Risk of Mortality NSTEMI Untreated Versus Treated (base-case = 1.91)				
1.2		Reference	$402,900	Dominated
1.4		Reference	$241,400	Dominated
1.6		Reference	$172,400	Dominated
1.8		Reference	$134,000	Dominated
2.0		Reference	$109,700	Dominated
2.2		Reference	$92,800	Dominated
Cost of False-Positive Admission (base-case = $2,136)				
500		Reference	$22,700	Dominated
1000		Reference	$52,200	Dominated
1500		Reference	$81,800	Dominated
2000		Reference	$111,400	Dominated
3000		Reference	$170,500	Dominated
4000		Reference	$229,700	Dominated

cTnI = cardiac troponin I; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; NSTEMI = non-ST-segment elevation myocardial infarction; QALY = quality-adjusted life-year.

Table 25: One-Way Sensitivity Analysis on Key Model Variables			
	Efficiency Frontier $/QALY		
	cTnI	**hs-cTnT**	**hs-cTnI**
Cost of hs-cTnT assay (base-case = $3)			
$5	Reference	$121,900	Dominated
$10	Reference	$127,900	Dominated
$15	Reference	$134,000	Dominated
$20	Reference	$140,100	Dominated
$30	Reference	$146,100	Dominated
Proportion of False-Negative First Test Becoming True Positive (base-case = 0.9)			
1	Reference	$1,100,000	Dominated
0.8	Reference	$67,800	Dominated
0.6	Reference	$39,900	Dominated
0.4	Reference	$30,200	Dominated
0.2	Reference	$25,400	Dominated
Proportion of Initial Positive Tests That Are Admitted to Hospital (base-case = 1.0)			
1	Reference	$119,400	Dominated
0.8	Reference	$100,900	Dominated
0.6	Reference	$81,600	Dominated
0.4	Reference	$61,400	Dominated
0.2	Reference	$40,400	Dominated
Proportion of non-NSTEMI That Are UA (base-case = 0.16)			
0.1	Reference	$128,200	Dominated
0.2	Reference	$113,200	Dominated
0.4	Reference	$83,200	Dominated
0.6	Reference	$53,200	Dominated
Relative Utility Decrement for MI Patients Compared with Base-Case			
Half base-case	Reference	$118,000	Dominated
Base-case	Reference	$119,400	Dominated
2 times base-case	Reference	$122,500	Dominated
3 times base-case	Reference	$125,600	Dominated
Use upper 95% CIs for presentation cTn sensitivity and specificity for all tests			
	Reference	$122,800	Dominated
Use lower 95% CIs for presentation cTn sensitivity and specificity for all tests			
	Reference	$170,300	$70,900

CI = confidence interval; cTnI = cardiac troponin I; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; QALY = quality-adjusted life-year; UA = unstable angina.

Table 26: One-Way Sensitivity Analysis on Model Structural Assumptions				
		Efficiency Frontier $/QALY		
	cTnT	**cTnI**	**hs-cTnT**	**hs-cTnI**
Include cTnT as a Treatment Comparator				
	reference	dominated	$177,400	Dominated
Include False Hospitalization Cost and Treatment Benefit of Patients with UA				
	Not applicable	Reference	$22,500	Dominated

cTnI = cardiac troponin I; cTnT = cardiac troponin T; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; QALY = quality-adjusted life-year; UA = unstable angina.

7 DISCUSSION

7.1 Summary of Main Findings

The clinical review attempted to compare the diagnostic performance and all relevant clinical outcomes among high-sensitivity and conventional cTn tests in chest pain patients who present to the ED.

The results of this systematic review showed that the diagnostic performance of cTn tests varied across studies. This might be due to variability in study populations (various eligibility criteria), methods of clinical diagnosis of AMI, or diagnostic cut-off points used for cTn tests.

As expected, despite different assays and different cut-off points, the sensitivity values of high-sensitivity cTn tests were consistently higher than those of cTn tests. However, there was a trade-off between sensitivity and specificity. Conventional cTn tests had lower sensitivity but relatively higher specificity values; whereas, high-sensitivity cTn tests had higher sensitivities but lower specificities, when compared with the final diagnosis of AMI (the reference standard). The included studies demonstrated that among the four types of cTn tests (hs-cTnT, hs-cTnI, cTnT, cTnI) performed at the time of ED presentation, hs-cTnI yielded the highest sensitivity for diagnosis of AMI and cTnT had the highest specificity. Although construction of the pooled ROC curves revealed no statistically significant differences between various diagnostic thresholds of any of the cTn tests, the comparison of the pooled estimates of diagnostic accuracy and their CIs suggested that all four types of cTn tests were consistently more sensitive at the LoD threshold, with the following patterns being detected:

- hs-cTnT: LoD > 99th percentile = 10% CV
- hs-cTnI: LoD > 99th percentile; 10% CV (data not available)
- cTnT: LoD = 99th percentile > 10% CV
- cTnI: LoD > 10% CV > 99th percentile.

No similar patterns were found for summary estimates of specificity.

Although non-significant, the above pooled results indicating a higher sensitivity for cTnI at 10% CV, as compared with 99th percentile threshold, is counter-intuitive. For sensitive cTnI assays, 99th percentile concentrations appear to be lower than 10% CV concentrations. Therefore, 99th percentile should have a higher sensitivity. Several possible explanations for this result might be suggested. We pooled data for each threshold from different studies (five studies for 99th percentile and two studies for 10% CV). None of these studies primarily intended to assess the comparability of various thresholds of cTn tests. Two studies that included both 99th percentile and 10% CV thresholds for cTnI assays reported contradictory results. In the study by Reichlin et al.,[29] for Abbott Architect cTnI the sensitivity values were comparable with the 99th percentile (0.86, 95% CI, 0.79 to 0.92) and 10% CV thresholds (0.85; 95% CI, 0.77 to 0.90). This study reported the sensitivity of Roche cTnI to be higher with the 99th percentile cut-off point (0.84; 95% CI, 0.76 to 0.90) than the 10% CV (0.75; 95% CI, 0.66 to 0.82). In contrast, in the study by Aldous et al.,[18] Abbott Architect cTnI showed a higher sensitivity with a 10% CV cut-off point (0.89; 95% CI, 0.0.84 to 0.93), as compared with 99th percentile (0.75; 95% CI, 0.68 to 0.80). Another reason for being cautious in interpreting the above patterns is that LoD and 99th percentile cut-off points might be determined differently by different authors. For example, some refer to this threshold as limit of the blank, which is lower than the LoD.[52] Furthermore, the definitions for a healthy reference population used to define 99th percentile cut-off points might vary across the included studies.

The review identified two studies reporting on the diagnostic accuracy of serial cTn tests, both of which compared hs-cTnT with cTnI. The limited evidence from these studies indicated sensitivity values in the range of 0.93 to 0.98 for hs-cTnT and 0.71 to 0.91 for cTnI. The specificity values ranged from 0.41 to 0.82 for hs-cTnT and from 0.46 to 0.97 for cTnI.

The results of our indirect comparisons, derived from a limited number of studies, suggest the following:

At the 99th percentile cut-off point:

- hs-cTnT is overall significantly less accurate, clinically more sensitive, and less specific than hs-cTnI, cTnT and cTnI
- hs-cTnI is significantly more accurate than hs-cTnT (but not cTnT and cTnI), more sensitive than cTnT (but not cTnI), significantly less sensitive than hs-cTnT, and more specific than hs-cTnT, cTnT and cTnI.

At the 10% CV cut-off point:

- hs-cTnT is overall significantly less accurate than cTnT and cTnI, more sensitive than cTnT and cTnI but significantly less sensitive than hs-cTnI, and less specific than both cTnT and cTnI (but not hs-cTnI)
- no data were available on hs-cTnI.

At the LoD cut-off point:

- hs-cTnT is overall significantly less accurate than cTnI (but not cTnT), more sensitive than cTnT (but not cTnI), and less specific than both cTnT and cTnI
- overall diagnostic accuracy of hs-cTnI could not be calculated due to insufficient data.

Our review also suggested that hs-cTnT had a higher sensitivity value regardless of timing of the assessment; whereas, cTnT had a lower sensitivity in the early hours after the onset of symptoms, but a comparable sensitivity after three to six hours.[26] The limited evidence in this review showed that patients' risk of MI at baseline or their previous history of IHD had no effect on sensitivity of hs-cTnT. However, the findings of the individual studies indicated that hs-cTnT could act as a more specific test in patients with low-to-moderate risk of MI at baseline (compared with patients at high-risk)[27] and in patients with a negative history of IHD (compared with the ones with a positive history of IHD).[30]

Based on the results of the reviewed studies, a positive hs-cTnT was associated with higher mortality rates during hospitalization and after discharge, when compared with cTnT or cTnI assays, suggesting that hs-cTnT can be a better prognostic factor of mortality. Similar results were reported for composite outcomes that included MI and/or death. However, none of the included studies reported on the effects that a high-sensitivity or cTn test results might have on long-term mortality or recurrence of MI, if test results factored in treatment decisions. In addition, the review found no information of the effects of troponin tests on quality of life, readmission rates, and ED time until the diagnosis of MI.

The base-case economic analysis estimated the incremental cost-effectiveness ratio of hs-cTnT compared with cTnI to be $119,377 per QALY. This means that if a decision-maker's maximum willingness to pay for a QALY is less than $119,377, then cTnI would be considered cost-effective. If a decision-maker's willingness to pay for a QALY is equal or greater than $119,377 then hs-cTnT would be considered cost-effective. Probabilistic analysis revealed that among the three testing strategies evaluated, hs-cTnT had the highest probability of being cost-effective for

willingness-to-pay thresholds equal or greater than $124,000 per QALY. The testing strategy of hs-cTnI was extendedly dominated by cTnI and hs-cTnT in our analysis, and therefore, would not be considered cost-effective when considering all three treatment options together. The effectiveness measure that contributed to relative cost-effectiveness of the three tests was diagnostic accuracy in terms of both sensitivity and specificity of MI at ED presentation. In the pooled estimate used in this analysis, the sensitivity of hs-cTnI was only slightly higher than that of cTnI (0.82 versus 0.81). The sensitivity of hs-cTnT was estimated to be 0.88. This likely contributed to hs-cTnI being extendedly dominated in the analysis.

The incremental cost-utility ratio was sensitive to a number of key model assumptions including NSTEMI prevalence; NSTEMI one-year mortality; mortality differences between patients treated early, late, and not at all. Additionally, results were sensitive to assumptions on the proportion of initial positive-results patients who would be admitted to hospital, the cost of a false-positive hospitalization, and the proportion of initial patients with false-negative results who would have true-positive test results with the second cTn test. This suggests that the base-case cost-effectiveness findings may not be robust.

The cost per each assay was based on information provided by manufacturers. Specific prices for hs-cTnT and hs-cTnI were not directly provided. Instead, they were based on statements that they were about equivalent to the costs of conventional assays. However, a sensitivity analysis on the cost per hs-cTnT assay indicated that findings were not sensitive to the cost per hs-cTnT assay.

Subgroup analyses found hs-cTnT to be more cost-effective in younger patients than in older patients. Additionally, hs-cTnT was found to be more cost-effective in patients with higher pretest probability of MI than those with lower pretest probability of MI.

The economic evaluation did not account for the capital costs of analyzers needed to conduct the various assays. These capital costs can be substantial and laboratories are often bound by time specific contracts with manufacturers. Therefore, there may be constraints on switching to a different cTn test that requires the purchase of a new analyzer.

7.2 Strengths and Limitations

7.2.1 Strengths

The clinical review provides a comprehensive review of available comparative evidence on accuracy and clinical outcomes of high-sensitivity and cTn tests for diagnosis of AMI or ACS. The review also highlights the limitations of the existing evidence by appraising the quality of the included studies. In addition to the direct comparison cTn tests to the reference standard (final diagnosis of AMI) in terms diagnostic accuracy estimates, we also indirectly compared the relative accuracy of different cTn tests in the diagnosis of AMI.

7.2.2 Limitations

a) A number of limitations exist in this HTA:
In the clinical review, the inclusion criteria were limited to the comparative studies, which included at least one high-sensitivity and one cTn test with or without a non-cTn reference standard. Our search excluded studies comparing only a high-sensitivity or a cTn assay with a non-cTn reference standard. However, the possibility that this exclusion could result in some

useful data for indirect meta-analysis having been missed cannot be ruled out. Data from a larger number of studies would helpful to perform a more efficient indirect meta-analysis. It has been reported that four times the amount of studies are needed to achieve the same precision for an indirect comparison as would be needed for a direct comparison.[53] In addition, the above-mentioned inclusion criteria might have led to the exclusion of potentially relevant studies that did not have more than one cTn group, but might contain useful data on some of the unanswered questions in this review, such as diagnostic accuracy of repeated cTn measurements as compared with the single measurement, quality of life outcomes, readmission rates, or the most effective timing of administration.

Our search found no head-to-head studies comparing the diagnostic performance of high-sensitivity with conventional cTn tests. In addition, there were insufficient studies that used the same brand of high-sensitivity and cTn tests. Furthermore, in all of the included diagnostic studies, both high-sensitivity and cTn tests were compared with the clinical diagnosis of AMI as the reference standard. As a result, direct comparisons of the high-sensitivity versus conventional tests were not possible. In addition, because the included studies used various cTn assays (in terms of manufacturer, platform, etc.), even the indirect analyses do not provide information that is specific for each of cTn products (e.g., Beckman Coulter hs-cTnI versus Errena Singulex hs-cTnI). Rather, they aggregate the results of all assays of the same type (e.g., all hs-cTnI assays).

Many studies did not report the definition base on which they diagnosed AMI. Therefore, it was not possible to determine whether the final diagnosis of MI (reference standard), which was made clinically, was similar across the studies. A number of studies recorded the final diagnosis at the time of hospital discharge; whereas, others followed up with the patients beyond discharge to confirm the diagnosis. The length of follow-up also differed from study to study. These methodological diversities might increase the risk of detection bias. In addition, 4 of 15 included studies (27%) were found to be at risk of selection bias due to their failure to enroll the study participants in a consecutive or random manner.

Another limitation of the clinical review is that few studies reported longer-term cardiovascular outcomes or mortality. As a result, this review was not able to provide a definitive conclusion regarding the potential impact of cTn tests on morbidity and mortality in patients with chest pain who undergo high-sensitivity cTn tests in ED, as compared with those who receive cTn assays. In addition, the impact of high-sensitivity versus conventional cTn tests on quality of life and readmission rates remains unknown because none of the included studies addressed these outcomes.

A number of subgroup analyses were presented in the clinical review. However, it should be noted that these subgroups were not pre-specified.

The economic evaluation had a number of limitations. As with all economic models, a simplification of reality was necessary. It was assumed that all patients presenting with ischemic chest pain to an ED would be treated the same regardless of their medical history. In reality, decisions on whether to admit a patient after a positive cTn test would likely depend on the perceived pretest probability of NSTEMI and whether the patient had a known previous condition that might cause chronic cTn elevation.

Another limitation of the economic analysis was that it did not account for the capital costs of the analyzers needed to conduct the various assays.

Another major limitation of the economic analysis was that it was solely based on the various cTn tests and how they can be used to diagnose NSTEMIs and did not take into account the tests' role in other types of ACS, namely STEMI and UA. Patients with STEMI were not included in the analysis because it was assumed that patients with a ST-segment elevation would be admitted to hospital from the ED regardless of the findings from the cTn test. Though there may be prognostic value in cTn results for all types of ACS, there was insufficient information from published studies to incorporate it into the model.

7.3 Generalizability of Findings

A number of studies excluded patients at high risk, such as those with terminal kidney disorders or chest trauma. This heterogeneity of inclusion and exclusion criteria among the included studies can result in limited patient generalizability.

8 CONCLUSIONS

Current evidence suggests that the overall diagnostic accuracy of high-sensitivity cTn tests is not statistically better than that of cTn tests in the diagnosis of AMI in chest pain patients referring to ED. Based on the results of our indirect comparisons, the overall diagnostic accuracy of hs-cTnT at 99th percentile is statistically lower than that of both cTnT and cTnI. There were insufficient studies and a lack of direct comparisons to reliably estimate the relative diagnostic accuracy of hs-cTnT and hs-cTnI. However, our indirect meta-analyses reveal that although hs-cTnI provides less clinical sensitivity than hs-cTnT, it can be overall more specific and more accurate than hs-cTnT. The review also suggests that hs-cTnT can be a better predictor of death and other major cardiovascular adverse events, when compared with cTn tests.

The clinical review found insufficient evidence to determine whether multiple high-sensitivity cTn test measurements can increase the diagnostic accuracy of the tests for AMI or ACS in ED. The questions regarding the effects of high-sensitivity cTn tests on quality of life and readmission rates, as well as the most effective cut-off point and timing of administration, remain unanswered. Well-designed prospective studies, using standard definitions for the diagnosis of AMI and ACS, are still required to determine the most beneficial cTn test and select the best diagnostic thresholds for different cTn tests.

The economic analysis found that when evaluating the cost-effectiveness of cTnI, hs-cTnI and hs-cTnT, hs-cTnT would be considered the most cost-effective testing strategy if willingness to pay for a QALY is $119,377 or more, otherwise cTnI would be the most cost-effective test. However, there was a lot of uncertainty in results when model assumptions were changed and the evaluation only considered the cost-effectiveness of cTn tests in diagnosing NSTEMI in the ED.

9 REFERENCES

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase Ovid MEDLINE Ovid MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 16, 2012
Alerts:	Monthly search updates began May 16, 2012 and ran until March 11, 2013.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; non-randomized controlled clinical trials; comparative studies; economic evaluations.
Limits:	English Humans (for clinical studies)

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.dm	Embase=Device Manufacturer; contains the full name of the manufacturer of a drug or device discussed in an article
.dv	Embase=Device Trade Name; contains the medical device trade names assigned to the records
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.jw	Journal Word; contains individual words from every journal name
.kw	Medline=Keyword Heading; contains the Keyword Headings assigned by indexers at NLM to describe the content of an article Embase=Key Word; contains keywords defined by the author of the article
.mp	Medline=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier Embase=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword
.pt	Publication type

MULTI-DATABASE STRATEGY	
Line #	**Searches**
	Medical Emergency Circumstances, Acute Myocardial Infarction, Cardiac Ischemia, Chest Pain, or Acute Coronary Syndrome Concept
1	exp Ambulances/ use prmz
2	Early Diagnosis/ use prmz
3	Emergencies/ use prmz
4	Emergency Medical Services/ use prmz
5	Emergency Medical Technicians/ use prmz
6	Emergency Medicine/ use prmz
7	exp Emergency Service, Hospital/ use prmz
8	exp Emergency Treatment/ use prmz
9	Evidence-Based Emergency Medicine/ use prmz
10	Time Factors/ use prmz
11	Triage/ use prmz
12	((acute or urgent*) adj2 care).ti,ab,kw.
13	(ambulance* or emergencies or emergency* or first response or first responder* or out-of-hospital or paramedic* or prehospital or pre-hospital).ti,ab,kw.
14	(earl* or rapid*).ti.
15	((earl* or rapid*) adj (diagnos* or detect*)).ab,kw.
16	(trauma center* or trauma centre* or triage or rescue personnel).ti,ab,kw.
17	Ambulance/ use emez
18	Early Diagnosis/ use emez
19	Emergency/ use emez
20	Emergency Care/ use emez
21	Emergency Health Service/ use emez
22	Emergency Medicine/ use emez
23	Emergency Medical Services Education/ use emez
24	Emergency Nurse Practitioner/ use emez
25	Emergency Nursing/ use emez
26	Emergency Patient/ use emez
27	Emergency Physician/ use emez
28	Emergency Surgery/ use emez
29	Emergency Treatment/ use emez
30	Emergency Ward/ use emez
31	Evidence Based Emergency Medicine/ use emez
32	First Aid/ use emez
33	Rescue Personnel/ use emez
34	Time/ use emez
35	Acute Coronary Syndrome/ use prmz
36	(Chest Pain/ or Heart Failure/ or Heart Injuries/ or Myocardial Infarction/) and acute*.mp.
37	((coronary syndrome? or (heart adj2 infarct*) or (myocardial adj2 infarct*) or (myocardium adj2 infarct*) or chest pain?) and acute*).ti,ab,kw.
38	((cardiac* or myocardial injur*) and acute*).ti.
39	Acute Coronary Syndrome/ use emez
40	Acute Heart Failure/ use emez
41	Acute Heart Infarction/ use emez
42	(Heart Failure/ or Heart Infarction/ or exp Heart Injury/ or Thorax Pain/) and acute*.mp.
43	or/1-42
	High-Sensitivity Cardiac CTn Concept
44	Troponin/
45	Troponin I/
46	Troponin T/

MULTI-DATABASE STRATEGY	
Line #	**Searches**
47	(troponin* or cTn* or TnI* or TnT*).ti,ab,kw,dm,dv.
48	or/44-47
49	(high sensitivity or highsensitivity or high sensitive or highsensitive or HS or highly sensitive or highlysensitive or ultra high* or ultrahigh* or ultra sensitiv* or ultrasensitiv* or new assay* or newer assay* or emerging assay* or new sensitive or increased sensitivity or next generation or new generation or newer generation or better sensitivity).ti,ab,kw,dm,dv.
50	more sensitiv*.ti,ab,kw,dm,dv.
51	or/49-50
52	48 and 51
53	(cTnIhs* or cTnI-hs* or cTnIultra* or cTnI-ultra* or TnIultra* or TnI-ultra* or hs-cTnI* or hs-TnI* or hscTnI* or hs-cTnI*).ti,ab,kw,dv.
54	(cTnThs* or cTnT-hs* or cTnTultra* or cTnT-ultra* or hs-cTnT* or hs-TnT* or hscTnT* or hs-cTnT*).ti,ab,kw,dv.
55	(Architect* adj10 (troponin* or cTn* or TnI* or TnT*)).ti,ab,kw,dm,dv.
56	(Access* and Beckman* and (AccuTnI* or troponin* or cTn* or TnI* or TnT*)).ti,ab,kw,dm,dv.
57	(Vista* and (troponin* or cTn* or TnI* or TnT*)).ti,ab,kw,dm,dv.
58	((Cobas e601 or Cobas e411 or Elecsys) adj10 (troponin* or cTn* or TnI* or TnT*)).ti,ab,kw,dm,dv.
59	or/52-58
	Clinical Studies
60	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
61	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
62	Multicenter Study.pt.
63	Randomized Controlled Trial/
64	Randomized Controlled Trials as Topic/
65	Controlled Clinical Trial/
66	Controlled Clinical Trials as Topic/
67	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/
68	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/
69	Clinical Trials/
70	Multicenter Study/ or Multicenter Study as Topic/
71	Randomization/
72	Random Allocation/
73	Random Sampling/
74	Double-Blind Method/
75	Double Blind Procedure/
76	Double-Blind Studies/
77	Single-Blind Method/
78	Single Blind Procedure/
79	Single-Blind Studies/
80	Placebos/
81	Placebo/
82	Control Groups/
83	Control Group/
84	Cross-Over Studies/ or Crossover Procedure/
85	(random* or sham or placebo*).ti,ab,hw.
86	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
87	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
88	(control* adj3 (study or studies or trial*)).ti,ab,hw.
89	(clinical adj3 (study or studies or trial*)).ti,ab,hw.

MULTI-DATABASE STRATEGY	
Line #	**Searches**
90	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti,ab,hw.
91	(phase adj3 (study or studies or trial*)).ti,ab,hw.
92	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw.
93	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw.
94	(allocated adj "to").ti,ab,hw.
95	trial.ti.
96	Epidemiologic Methods/
97	Epidemiologic Studies/
98	Cohort Studies/
99	Longitudinal Studies/
100	Prospective Studies/
101	Follow-Up Studies/
102	Retrospective Studies/
103	Case-Control Studies/
104	Cross-Sectional Study/
105	Evaluation Studies.pt.
106	Evaluation Studies as Topic/
107	Comparative Study.pt.
108	Observational Study/
109	Cohort Analysis/
110	exp Case Control Study/
111	Cross-sectional Study/
112	Quasi Experimental Study/
113	exp Longitudinal Studies/
114	Prospective Studies/
115	Retrospective Studies/
116	Followup Studies/
117	Pretesting/
118	exp Program Evaluation/
119	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.
120	(cohort adj7 (study or studies or design or analysis or analyses)).ti,ab,hw.
121	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab,hw.
122	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,hw.
123	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab,hw.
124	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab,hw.
125	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,hw.
126	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.
127	(population adj3 (study or studies or analysis or analyses)).ti,ab,hw.
128	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.
129	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,hw.
130	((natural adj experiment) or (natural adj experiments)).ti,ab,hw.
131	(quasi adj (experiment or experiments or experimental)).ti,ab,hw.
132	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.
133	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,hw.
134	((comparison or comparative*) adj3 (study or studies or analysis or analyses)).ti,ab,hw.
135	((before-after or (before* adj after)) adj3 (study or studies or design?)).mp.

MULTI-DATABASE STRATEGY	
Line #	**Searches**
136	((follow up or followup) and (base line* or baseline*)).ti,ab,hw.
137	exp "Sensitivity and Specificity"/
138	False Positive Reactions/
139	False Negative Reactions/
140	Diagnostic Techniques, Cardiovascular/
141	Troponin/du
142	Troponin T/du
143	Troponin I/du
144	Validation Studies.pt.
145	sensitivit*.ti,ab.
146	specificity.ti,ab.
147	predict*.ti,ab.
148	distinguish*.ti,ab.
149	differentiat*.ti,ab.
150	enhancement.ti,ab.
151	identif*.ti,ab.
152	detect*.ti,ab.
153	diagnos*.ti,ab.
154	accura*.ti,ab.
155	precision.ti,ab.
156	prognos*.ti,ab.
157	false positive*.ti,ab.
158	false negative*.ti,ab.
159	exp Diagnosis/
160	Diagnostic Procedures/
161	Acute Coronary Syndrome/di or Acute Heart Failure/di or Acute Heart Infarction/di or Chest Pain/di or Heart Failure/di or Heart Infarction/di or Heart Injury/di or Heart Injuries/ or Myocardial Infarction/di or Thorax Pain/di
162	or/60-161
163	exp animals/
164	exp animal experimentation/
165	exp models animal/
166	exp animal experiment/
167	nonhuman/
168	or/163-167
169	exp humans/
170	exp human experiment/
171	or/169-170
172	168 not 171
173	43 and 59 and 162
174	173 not 172
175	Diagnostic Techniques, Cardiovascular/
176	biomarker*.ti.
177	Cardiovascular System Examination/
178	or/175-177
179	Meta-Analysis.pt.
180	Meta-Analysis/ or Systematic Review/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/
181	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
182	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or

MULTI-DATABASE STRATEGY	
Line #	**Searches**
	overview*))).ti,ab.
183	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
184	(data synthes* or data extraction* or data abstraction*).ti,ab.
185	(handsearch* or hand search*).ti,ab.
186	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
187	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
188	(meta regression* or metaregression* or mega regression*).ti,ab.
189	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
190	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
191	(cochrane or health technology assessment or evidence report).jw.
192	Meta Analysis/ or Systematic Review/ or Biomedical Technology Assessment/
193	or/179-192
194	43 and (59 or 178) and 193
195	174 or 194
196	limit 195 to English
197	remove duplicates from 196
	Economic Studies
198	*Economics/
199	*Economics, Medical/
200	*Economics, Pharmaceutical/
201	exp "Costs and Cost Analysis"/
202	exp Health Care Costs/
203	exp Decision Support Techniques/
204	Economic Value of Life/
205	exp Models, Economic/
206	Markov Chains/
207	Monte Carlo Method/
208	Decision Trees/
209	Uncertainty/
210	exp "Quality of Life"/
211	Quality-Adjusted Life Years/
212	exp Health Care Cost/
213	exp Health Economics/
214	exp Economic Evaluation/
215	exp Pharmacoeconomics/
216	exp Economic Aspect/
217	Quality Adjusted Life Year/
218	(econom* or cost or costly or costing or costed or price or prices or pricing or priced or discount or discounts or discounted or discounting or expenditure or expenditures or budget* or afford* or pharmacoeconomic or pharmaco-economic*).ti,ab.
219	(cost* adj1 (util* or effective* or efficac* or benefit* or consequence* or analy* or minimi* or saving* or breakdown or lowering or estimate* or variable* or allocation or control or illness or sharing or life or lives or affordabl* or instrument* or technolog* or day* or fee or fees or charge or charges)).ti,ab.
220	(decision adj1 (tree* or analy* or model*)).ti,ab.
221	((value or values or valuation) adj2 (money or monetary or life or lives or costs)).ti,ab.
222	(qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab.
223	(sensitivity analys*s or "willingness to pay" or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc*).ti,ab.

MULTI-DATABASE STRATEGY	
Line #	**Searches**
224	(unit-cost or unit-costs or markov).ti,ab.
225	or/198-224
226	43 and (59 or 178) and 225
227	limit 226 to English
228	remove duplicates from 227

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
The Cochrane Library Issue 2-3, 2012	Same MeSH and keywords, used as per Medline search, excluding study types, Human, and language restrictions. Syntax adjusted for Cochrane Library databases.
Health Economic Evaluations Database (HEED)	Same keywords used as per Medline search, excluding study types, Human, and language restrictions. Syntax adjusted for HEED.

Grey Literature

Dates for Search:	June 2012; focused update March 11, 2013
Keywords:	Included terms for high-sensitivity cardiac troponin
Limits:	English (with the exception of French Canadian technology assessments which are not translated)

The following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/resources/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economic
- Databases (free)
- Internet Search
- Open Access Journals.

Conferences and Meetings

1. American Association for Clinical Chemistry Annual Meeting Abstracts: http://www.aacc.org/events/2012am/abstracts/pages/default.aspx#

2. Canadian Society of Clinical Chemists Annual Conference: http://www.cscc.ca/en/conferences.html

3. International Federation of Clinical Chemistry and Laboratory Medicine, IFCC-WorldLab & IFCC EuroMedLab Congresses: http://www.ifcc.org/ifcc-congresses-and-conferences/ifcc-worldlab-congresses/

4. American Heart Association (AHA): http://my.americanheart.org/professional/Sessions/ScientificSessions/Archive/Archive-Scientific-Sessions_UCM_316935_SubHomePage.jsp

APPENDIX 2: TITLE AND ABSTRACT SCREENING CHECKLIST

Reviewer: _____ **Date:** _____

Ref ID: _____ **First Author (year):** _____

	Include	Exclude
1. What is the STUDY POPULATION in this article?	□ Patients presenting in the ED with chest pain □ Patients with suspected ACS or AMI □ Can't tell	□ Patients in non-ED hospital setting, i.e., regular hospital wards, intensive care unit (ICU), coronary care unit (CCU). □ Community-based/non-institutional care settings.
2. What is the INTERVENTION?	□ hs-cTnT □ hs-cTnI	□ Conventional/sensitive (i.e., non–high-sensitivity) cardiac assays.
3. What is the TYPE OF STUDY reported in this article?	□ Randomized controlled trial □ Non-randomized controlled trial □ Meta-analysis/ systematic review or health technology assessment □ Comparative observational study □ Economic evaluation □ Can't decide	□ Before after trial □ Non-comparative observational study □ Qualitative study
Include for full text review	□ **Yes**	□ **No**

APPENDIX 3: FULL TEXT SCREENING CHECKLIST

A. Clinical Review

1. Did this article include patients presenting in the ED with chest pain who are SUSPECTED to have ACS or AMI?

- □ Yes (include)
- □ No (exclude)
- □ Maybe (include)

2. Is the article the PRIMARY REPORT of the FINAL results from a:

- □ Randomized controlled trial (include)
- □ Non-randomized controlled trial (include)
- □ Meta-analysis/ systematic review or health technology assessment (include)
- □ Comparative observational study (include)
- □ All other study types (exclude)
- □ Can't decide (include)

3. What COMPARATOR is used in the study?

- □ Conventional cTnT assay (include)
- □ Sensitive cTnI assay (include all non–point-of-care assays or Siemens Stratus CS point-of-care assay)
- □ Cardiac ischemia biomarkers other than cTn (exclude)
- □ No comparator (exclude)

4. Include if the OUTCOME of interest in the study is one of the following:

- □ Diagnostic Test Performance (including sensitivity, specificity, positive or negative likelihood ratios, positive or negative predictive values, AUC ROC, rates of false-positive or negative tests, and test accuracy)
- □ Thromboembolic events (e.g., VTE, DVT, PE)
- □ Acute cardiovascular events (e.g., ACS, AMI)
- □ Chronic/non-acute cardiovascular events (e.g., coronary artery stenosis/narrowing on angiogram)
- □ Revascularization procedures (e.g., angiograms, PCI, CABG)
- □ ED time until diagnosis or detection of abnormal concentration
- □ Heart failure
- □ Quality of life
- □ Death
- □ 30-day readmission rate
- □ 30-day recurrence rate
- □ 30-day mortality
- □ Any harm outcomes reported
- □ None of the above (exclude)

5. Final Decision

- □ **Include**
- □ **Exclude**
- □ **Non-English /Unable to translate**

Reason for Exclusion:

- □ Inappropriate study population
- □ Not study types of interest
- □ Not primary report of study
- □ Study description only
- □ No intervention of interest
- □ No/inappropriate control group
- □ No relevant outcomes

B. Economic Review

Author (Year) _____ REF ID _____

Level 2 Screening Questions	Circle One	
Q1. Is this a Primary economic evaluation?	Yes	No
Q2. Are costs measured?	Yes	No
Q3. Is effectiveness measured	Yes	No
Q4. Does the study evaluate laboratory testing for patients admitted to an ED suspected of having MI or ACS?	Yes	No
Q5. Is one of treatment comparators: a) hs-cTnT (Roche Cobas E, Roche Elecsys) or b) hs-cTnI (Abbott Architect, Beckman Access, Siemens Vista)	Yes Yes	No No
Q6. Is one of the treatment comparators: a) hs-cTnT (Roche Cobas E, Roche Elecsys) or b) hs-cTnI (Abbott Architect, Beckman Access, Siemens Vista) or c) Sensitive cTnT (Roche Cobas H232, Roche, Elecsys TnT Gen 4, Roche Cardiac Reader cTnT) or d) Sensitive cTnI (Abbott AxSYM ADV, Abbott Architect, Alere Triage Cardio2, Alere Triage Cardio3, Beckman Access AccuTnI, bioMérieux Vidas Ultra, Ortho Vitros ECi ES, Siemens Centaur XP Ultra, Siemens Dimension RxL, Siemens Dimension Vista, Siemens Immulite 2500, Siemens Stratus CS)	Yes Yes Yes Yes	No No No No
Include study for review	Yes	No

APPENDIX 4: DATA ABSTRACTION FORM

STUDY	
Ref ID	
Author	
Publication year	
Country	
Funding	

METHODOLOGY	
Study type	**☐RCT ☐ non-RCT**
Study design	
Setting	
Total sample size	
Number of eligible	
Number of randomized	
Number completed the study	
Number evaluated	
Sampling procedure	
Randomization procedure	

INCLUSION/EXCLUSION	
Inclusion criteria	
Exclusion criteria	

INTERVENTION/COMPARATOR				
	hs-cTnT **□ reference standard** **□ index test**	**hs-cTnI** **□ reference standard** **□ index test**	**Comparator 1** **□ reference standard** **□ index test**	**Comparator 2**
Product/Manufacturer				
Sample size				
Time since chest pain onset				
Time since ED admission				

POPULATION CHARACTERISTICS					
		hs-cTnT	hs-cTnI	Comparator 1	Comparator 2
Mean age, year (SD)					
Gender (% female)					
Ethnicity (% white)					
Prior diagnosis of IHD					
Cardiac treatments 1.----------(%) 2.----------(%) 3.----------(%)					
Cardiac risk factors	BMI				
	Waist to hip ratio				
	Smoking (% current)				
	Smoking (% former)				
Pre-existing conditions	Hypertension (%)				
	Diabetes (%)				
	Hyperlipidemia (%)				
	Pre-existing angina				
	Previous MI				
ECG Results	ST-segment elevation (%)				
	ST depression (%)				
	T inversion (%)				
	Left to right bundle branch block (%)				
	Other----------				
Other biomarkers (unit) 1.----------( ) 2.----------( ) 3.---------- ( )					

REPORTED OUTCOMES	
Primary	
Secondary	
Timing of Assessment (days)	

RESULTS				
Outcome	**hs-cTnT**	**hs-cTnI**	**Comparator 1**	**Comparator 2**
Diagnostic Test Performance				
sensitivity				
Specificity				
Positive likelihood ratio				
Negative likelihood ratio				
Positive predictive value				
Negative predictive value				
Area under ROC Curve				
% False-positive tests				
% False-negative tests				
Test accuracy				
Thromboembolic events (%)				
VTE **DVT** **PE**				
Acute cardiovascular events				
ACS **AMI**				
Revascularization procedures (e.g., angiograms, PCI, CABG) (%)				
Heart failure (%)				
30-day readmission rate (%)				
30-day recurrence rate (%)				
30-day mortality (%)				
Overall mortality (%)				
Adverse events: ---------- (%)				

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMI = body mass index; CABG = coronary artery bypass graft; DVT = deep vein thrombosis; ECG = electrocardiogram; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; ID = identification; IHD = ischemic heart disease; PCI = percutaneous coronary intervention; PE = pulmonary embolism; RCT = randomized controlled trial; ROC = receiver operating characteristic; SD = standard deviation; VTE = venous thromboembolism.

APPENDIX 5: DETAILS OF OUTCOME MEASURES/TESTS OF ACCURACY

	+ Test 2	– Test 2	Total
+ Test 1	True Positive (A)	False Positive (B)	A + B
– Test 2	False Negative (C)	True Negative (D)	C + D
Total	A + C	B + D	A + B + C + D

True positives (A) will be identified when the positive Test 1 agrees with the positive Test 2. False positives (B) will be identified when the positive Test 1 disagrees with the negative Test 2. False negatives (C) will be identified when the negative Test 1 disagrees with the positive Test 2.

True negative (D) will be identified when the negative Test 1 agrees with the negative Test 2.

From this 2 x 2 table, several tests of accuracy can be made with CIs.[54]

Sensitivity: TP/(TP+FN): the proportion of persons with the disease who are correctly identified by a test. i.e., a test with a high-sensitivity is useful for ruling out a disease if a person tests negative.

Confidence interval: $p \pm Z * \sqrt{\frac{p*(1-p)}{TP+FN}}$

Specificity: TN/(TN+FP). The proportion of persons without a disease who are correctly identified by a test. High specificity is important when the treatment or diagnosis is harmful to the patient.

Confidence interval: $p \pm Z * \sqrt{\frac{p*(1-p)}{TN+FP}}$

Positive Predictive Value (PPV): TP/(TP+FP): the proportion of patients with positive test results who are correctly diagnosed.

Confidence interval: $p \pm Z * \sqrt{\frac{p*(1-p)}{TP+FP}}$

Negative Predictive Value (NPV): TN/(TN+FN): proportion of patients with negative test results who are correctly diagnosed.

Confidence interval: $p \pm Z * \sqrt{\frac{p*(1-p)}{TN+FN}}$

Positive Likelihood Ratio (LR+): Indicates how much more likely it is to get a positive test in the diseased as opposed to the non-diseased group.

Confidence interval: $LR+ = \exp(\ln \frac{sensitivity}{1-specificity} \pm 1.96 * \sqrt{\frac{1-sensitivity}{TP} + \frac{specificity}{FP}})$

Negative Likelihood Ratio (LR-): Indicates how much more likely it is to get a negative test in the non-diseased as opposed to the diseased group.

Confidence interval: $LR- = \exp(\ln \frac{1-sensitivity}{specificity} \pm 1.96 * \sqrt{\frac{sensitivity}{FN} + \frac{1-specificity}{TN}})$

Receiver Operating Characteristic Curve Analysis

AUC analysis will be performed for the patient level analysis. Because the estimates of sensitivity and specificity will be constructed for the full patient population, only one estimate of sensitivity and one estimate of specificity will be generated. With only one estimate, the sensitivity/specificity graphical methods to derive AUC are not applicable. Instead, the accepted method of estimating AUC will be determined by the non-parametric Wilcoxon approximation of the 2x2 table (which is statistically equivalent to the AUC generated with the trapezoid rule, and the Mann-Whitney U Test).

The degree of precision of the estimate of the AUC estimated will be reported by generating the standard error and 95% CI around the estimate.

AUC: represents the probability that a randomly chosen diseased subject is correctly diagnosed with greater suspicion than a randomly chosen non-diseased subject.

$$\text{Wilcoxon AUC} = \frac{TN \times TP + 0.5 \times TN \times FN + 0.5 \times FP \times TP}{N_N \times N_A}$$

Standard error (Hanley and McNeil method):

$$SE(A) = \sqrt{\frac{A(1-A) + (N_A - 1) * (Q_1 - A^2) + (N_N - 1) * (Q_2 - A^2)}{N_A * N_N}}$$

where A = AUC, area under the curve

N_A = number of positive disease cases

N_N = number of negative disease cases

$$Q1 = \frac{TN \times [TP^2 + TP \times FN + \frac{1}{3} \times FN^2] + FP \times [\frac{1}{3} \times TP^2]}{N_N \times N_A^2}$$

$$Q2 = \frac{FN \times [\frac{1}{3} \times TN^2] + TP \times [TN^2 + TN \times TP + \frac{1}{3} xFP^2]}{N_A \times N_N^2}$$

Example:

Overall			Total
	CICA: D+	CICA: D-	
64 CT: + test	183	22	205
64 CT: - test	2	219	221
Total	185	241	426

TP = 183, FP= 22, FN = 2, TN = 219

D+: disease positive, D–: disease negative (absent)

AUC = (219 x 183 + 0.5 x 219 x 2 + 0.5 x 22 x 183) / (185 x 241) = 0.9490
Similarly, Q1 = 0.9287, Q2 = 1.5051, SE = 0.0581.
95% CI = (0.9490 – 1.96*0.0581, 0.9490 + 1.96* 0.0581) = (0.8351, 1)

Kappa-coefficient:
Cases of disagreement between the two observers will be resolved by consensus, and the inter-observer variability in identifying disease will be calculated and expressed using the Cohen's kappa-coefficient (κ).

According to Landis and Koch,[55] a kappa (*κ)* value of 0 indicated poor agreement; 0.01 to 0.20, slight agreement; 0.21 to 0.40, fair agreement; 0.41to 0.60, moderate agreement; 0.61 to 0.80, good agreement and 0.81 to 1.00, excellent agreement.

		Rater # 1		
		Positive	Negative	Total
Rater # 2	Positive	P11	P12	P1 (rater 2)
	Negative	P21	P22	P2 (rater 2)
	Total	P1 (rater 1)	P2 (rater 1)	1

In percentages:
Po = Probability of Observed Agreement = P11 + P22
Pe = probability of Expected Agreement = P1 (rater 1) * P1 (rater 2) + P2 (rater 2) * P2 (rater 2)
Kappa = (Po – Pe)/(1 – Pe).

Example with counts:

		Rater # 1		
		Positive	**Negative**	**Total**
Rater # 2	Positive	48	6	54
	Negative	8	30	38
	Total	56	36	92

Kappa = ((48/92+30/92) - (56/92*54/92 +36/92 * 38/92))/(1- (56/92*54/92 – 36/92*38/92)= 0.6837.

APPENDIX 6: LIST OF STUDIES EXCLUDED FROM THE CLINICAL REVIEW AND THE REASONS FOR EXCLUSION

No useful data:

1. Lippi G, Cervellin G, Aloe R, Montagnana M, Salvagno GL, Guidi GC. Non-commutability of results of highly sensitive troponin I and T immunoassays. Biochem Med (Zagreb). 2012;22(1):127-9.

Irrelevant study population:

1. Bahrmann P, Heppner HJ, Christ M, Bertsch T, Sieber CC. Early detection of Non-ST-Elevation Myocardial Infarction in geriatric patients by a new high-sensitive cardiac Troponin T assay. Aging Clin Exp Res. 2011.
2. Correia LC, Sodre FL, Lima JC, Sabino M, Brito M, Garcia G, et al. Prognostic value of high-sensitivity troponin I versus troponin T in acute coronary syndromes. Arq Bras Cardiol. 2012.
3. Jairam S, Jones P, Samaraie L, Chataline A, Davidson J, Stewart R. Clinical diagnosis and outcomes for troponin T 'positive' patients assessed by a high sensitivity compared with a 4th generation assay. Emerg Med Australas. 2011;23(4):490-501.
4. Korosoglou G, Lehrke S, Mueller D, Hosch W, Kauczor H-U, Humpert PM, et al. Determinants of troponin release in patients with stable coronary artery disease: insights from CT angiography characteristics of atherosclerotic plaque. Heart. 2011;97(10):823-31.
5. Melki D, Lind S, Agewall S, Jernberg T. Diagnostic value of high sensitive troponin T in chest pain patients with no persistent ST-elevations. Scand Cardiovasc J. 2011;45(4):198-204.
6. Ndrepepa G, Braun S, Schulz S, Byrne RA, Pache J, Mehilli J, et al. Comparison of prognostic value of high-sensitivity and conventional troponin T in patients with non-ST-segment elevation acute coronary syndromes. Clin Chim Acta. 2011;412(15-16):1350-6.
7. Truong QA, Bayley J, Hoffmann U, Bamberg F, Schlett CL, Nagurney JT, et al. Multi-marker strategy of natriuretic peptide with either conventional or high-sensitivity troponin-T for acute coronary syndrome diagnosis in emergency department patients with chest pain: From the "Rule Out Myocardial Infarction Using Computer Assisted Tomography" (ROMICAT) trial. Am Heart J. 2012;163(6):972-9.
8. Venge P, Johnston N, Lindahl B, James S. Normal plasma levels of cardiac troponin I measured by the high-sensitivity cardiac troponin I Access prototype assay and the impact on the diagnosis of myocardial ischemia. J Am Coll Cardiol. 2009;54(13):1165-72.
9. Weber M, Bazzino O, Navarro Estrada JL, De MR, Salzberg S, Fuselli JJ, et al. Improved diagnostic and prognostic performance of a new high-sensitive troponin T assay in patients with acute coronary syndrome. Am Heart J. 2011;162(1):81-8.

Irrelevant study type:

1. A sensitive troponin I method for early diagnosis of acute myocardial infarction. Biomark Med. 2010;4(3):342.
2. Using sensitive cardiac troponin methods for early diagnosis of acute myocardial infarction. Biomark Med. 2010;4(3):342-3.
3. Apple FS. A new season for cardiac troponin assays: it's time to keep a scorecard. Clin Chem. 2009;55(7):1303-6.
4. Body R, Carley S, McDowell G. High-sensitivity troponin < 3 ng/L ruled out acute myocardial infarction. Ann Intern Med. 2012;156(4):JC2-9.

5. Ceriani E, Rusconi AM. Highly sensitive troponin and diagnostic accuracy in acute myocardial infarction. Intern Emerg Med. 2012 Jul 6.
6. Jarausch J. Diagnostic and prognostic information provided by a high sensitivity assay for cardiac troponin T. J Med Biochem. 2010;29(4):274-81.
7. Olatidoye AG, Wu AH, Feng YJ, Waters D. Prognostic role of troponin T versus troponin I in unstable angina pectoris for cardiac events with meta-analysis comparing published studies. Am J Cardiol . 1998;81(12):1405-10.
8. Reichlin T, Mueller C. Serial changes in highly sensitive cardiac troponin improve the early diagnosis of acute myocardial infarction. *Evid Based Med*. 2012.
9. Shand J, Menown I, McEneaney D. A timely diagnosis of myocardial infarction. Biomark Med. 2010;4(3):385-93.
10. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J. 2012 Jun 21.
11. Vasikaran SD, Macdonald SP, Sikaris KA. High-sensitivity cardiac troponin assays for risk stratification and for the diagnosis of acute myocardial infarction. Ann Clin Biochem. 2012;49(Pt:3):3-10.
12. Welsford M. ACP Journal Club. Sensitive cardiac troponin assays were more accurate than a standard troponin assay for early diagnosis of AMI. Ann Intern Med. 2009;151(12):JC6-12.

Not a troponin test of interest:

1. Almas A, Parkash O, Hameed A, Islam M. Emergency evaluation of acute chest pain. J Coll Physicians Surg Pak. 2010;20(2):74-8.
2. Balk EM, Ioannidis JPA, Salem D, Chew PW, Lau J. Accuracy of biomarkers to diagnose acute cardiac ischemia in the emergency department: a meta-analysis. Ann Emerg Med. 2001;37(5):478-94.
3. Bock JL, Singer AJ, Thode J. Comparison of emergency department patient classification by point-of-care and central laboratory methods for cardiac troponin I. Am J Clin Pathol. 2008;130(1):132-5.
4. Casals G, Filella X, Bedini JL. Evaluation of a new ultrasensitive assay for cardiac troponin I. Clin Biochem. 2007;40(18):1406-13.
5. Hetland O, Dickstein K. Cardiac troponins I and T in patients with suspected acute coronary syndrome: a comparative study in a routine setting. Clin Chem. 1998;44(7):1430-6.
6. Hjortshoj S, Venge P, Ravkilde J. Clinical performance of a new point-of-care cardiac troponin I assay compared to three laboratory troponin assays. Clin Chim Acta. 2011;412(3-4):370-5.
7. Nusier MK, Ababneh BM. Diagnostic efficiency of creatine kinase (CK), CKMB, troponin T and troponin I in patients with suspected acute myocardial infarction. J Health Sci. 2006;52(2):180-5.
8. Pracon R, Kruk M, Jakubczak B, Demkow M, Bilinska ZT. Superior early diagnostic performance of a sensitive cardiac troponin assay as compared to a standard troponin test in the diagnosis of acute myocardial infarction. Kardiol Pol. 2012;70(2):131-8.
9. Saadeddin SM, Habbab MA, Siddieg HH, Al Seeni MN, Tahery AB, Sobki SH, et al. Evaluation of 6 cardiac troponin assays in patients with acute coronary syndrome. Saudi Med J. 2003;24(10):1092-7.
10. Venge P, Lagerqvist B, Diderholm E, Lindahl B, Wallentin L. Clinical performance of three cardiac troponin assays in patients with unstable coronary artery disease (a FRISC II substudy). Am J Cardiol. 2002;89(9):1035-41.
11. Wong PSC, Rao G, Innasimuthu A, Saeed Y, Robinson A, Robinson D. Validation of a prediction score to distinguish patients with acute myocardial infarction from other causes of raised troponin T. Eur Heart J. 2010;31(1):678.

No relevant comparator:

1. Aldous SJ, Richards AM, Cullen L, Than MP. Early dynamic change in high-sensitivity cardiac troponin T in the investigation of acute myocardial infarction. Clin Chem. 2011;57(8):1154-60.
2. Boden H, Ahmed T, Hoogslag G, Bootsma M, Cannegieter S, Cobbaert C, et al. The value of serum troponin-T to predict infarct size in patients with first ST elevation myocardial infarction treated with primary percutaneous coronary intervention in the era of high sensitive troponin assays. J Am Coll Cardiol. 2012;59(13 Suppl 1):E403.
3. Cullen LA, Greenslade JH, Brown AFT, Hammett CJK, Than MP, Chu KH, et al. Comparison of 2 and 6 hour time intervals in the diagnosis of acute myocardial infarction. Eur Heart J. 2011;32(1):725.
4. Ferraro S, Boracchi P, Santagostino M, Marano G, Vendramin C, Rossi L, et al. Ultra-sensitive troponin I levels to exclude acute myocardial infarction from myocardial injury. Clin Chem Lab Med. 2012;50(1):159-66.
5. Gassenmaier T, Buchner S, Birner C, Jungbauer CG, Resch M, Debl K, et al. High-sensitive troponin I in acute cardiac conditions: Implications of baseline and sequential measurements for diagnosis of myocardial infarction. Atherosclerosis. 2012;222(1):116-22.
6. George J, Jack D, Mackle G, Callaghan TS, Wei L, Lang CC, et al. High sensitivity troponin T provides useful prognostic information in non-acute chest pain. QJM. 2012;105(2):159-66.
7. Giavarina D, Carta M, Fortunato A, Wratten ML, Hartmann O, Soffiati G. Copeptin and high sensitive troponin for a rapid rule out of acute myocardial infarction? Clin Lab. 2011;57(9-10):725-30.
8. Heinisch C, Twerenbold R, Reiter M, Reichlin T, Meissner J, Arenja N, et al. Early diagnosis of acute myocardial infarction using the combination of a high-sensitive cardiac troponin assays and copeptin - Insights from a multicenter study. Eur Heart J. 2010;31(1):51-2.
9. Irfan A, Reichlin T, Twerenbold R, Reiter M, Balmelli C, Meissner J, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Eur Heart J. 2011;32(1):990.
10. Kelly A-M. Performance of a sensitive troponin assay in the early diagnosis of acute myocardial infarction in the emergency department. Emerg Med Australas. 2011;23(2):181-5.
11. Meune C, Balmelli C, Twerenbold R, Reichlin T, Reiter M, Haaf P, et al. Patients with acute coronary syndrome and normal high-sensitivity troponin. Am J Med. 2011;124(12):1151-7.
12. Paoloni R, Kumar P, Janu M. Pilot study of high-sensitivity troponin T testing to facilitate safe early disposition decisions in patients presenting to the emergency department with chest pain. Intern Med J. 2010;40(3):188-92.
13. Ray P, Freund Y, Chenevier-Gobeaux C, Allo JC, Boddaert J, Riou B. Diagnostic performance of high-sensitivity troponin in emergency elderly patients. Eur Geriatr Med. 2011;2(Suppl 1):S119-20.
14. Reichlin T, Twerenbold R, Hochholzer W, Reiter M, Meissner J, Potocki M, et al. Clinical use of a high-sensitive cardiac troponin assay in patients with suspected myocardial infarction. Eur Heart J. 2010;31(1):51.

No/irrelevant outcomes:

1. Braga F, Dolci A, Valente C, Boido A, Moretti A, Guzzetti S, et al. Impact of the implementation of highly sensitive cardiac troponin T assay in a university hospital setting. Biochim Clin. 2011;35(4):301-6.
2. Chenevier-Gobeaux C, Meune C, Blanc MC, Cynober L, Jaffray P, Lefevre G. Analytical evaluation of a high-sensitivity troponin T assay and its clinical assessment in acute coronary syndrome. Ann Clin Biochem. 2011;48(5):452-8.

3. DeFilippi CR, Gandotra P, Gantzer ML, Henderson S, Heckendorf J, Christenson R. Characteristics of chest pain patients without acute coronary syndromes stratified by a "hyper-sensitive" troponin I assay. J Am Coll Cardiol. 2010;55(10 Suppl 1):A118.
4. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem. 2010;56(2):254-61.
5. Haaf P, Drexler B, Reichlin T, Twerenbold R, Reiter M, Meissner J, et al. High sensitivity cardiac troponin in the distinction of acute myocardial infarction from acute cardiac non-coronary artery disease. Circulation. 2012;126(1):31-40.
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APPENDIX 7: LIST OF STUDIES EXCLUDED FROM THE ECONOMIC REVIEW AND REASONS FOR EXCLUSION

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APPENDIX 8: BUDGET IMPACT ANALYSIS

Budget Impact Analysis of Switching from Conventional to High-Sensitivity Troponin Assays in the ED for the Diagnosis of ACS

The Budget Impact Analysis (BIA) was prepared after the Optimal Use Recommendations for cardiac troponin were made. As such, the BIA was not considered in the making of the recommendations and did not undergo stakeholder feedback.

Methods

A budget impact analyses was conducted to evaluate the financial implications of implementing the HTERP recommendations. For the analysis, it was assumed that all EDs in Canada would switch from conventional troponin assays to high-sensitivity troponin assays for the diagnosis of ACS. This assumption was made, in the absence of knowing how many hospitals are considering the selection of a troponin assay.

A number of different steps were taken to complete the analysis. First, the total number of annual ED visits for suspected ACS in Canada was estimated. Second, the current distribution of types of troponin assays (conventional troponin T, high-sensitivity troponin T, conventional troponin I, and high-sensitivity troponin I) used in Canada was determined. Third, the cost per each assay type (conventional troponin T, high-sensitivity troponin T, conventional troponin I, and high-sensitivity troponin I) was estimated. Finally, the annual budget impact of switching from conventional to high-sensitivity assays was calculated by multiplying the total number of annual assays conducted in the ED for diagnosis of ACS by the cost differential between conventional and high-sensitivity assays accounting for the proportion of EDs in Canada that are already using high-sensitivity assays. Sensitivity analysis were conducted varying the price differential between conventional and high-sensitivity assays, the number of assays conducted per ED visit for suspected ACS, the proportion of ED visits that result in hospital admission, and the proportion of hospitals that would switch to high-sensitivity troponin assays.

The annual number of ED visits for suspected ACS in Canada was estimated from a number of sources. A report on the burden of ACS in Canada[1] reported that there were 109,109 hospitalizations for ACS across Canada in fiscal year 2009. This analysis was based on data from the Canadian Institute for Health Information (CIHI). Only a fraction of ED visits for suspected ACS will result is a hospital admission. Therefore in the absence of direct data, in order to indirectly calculate the total number of ED visits for suspected ACS, the proportion of ED visits that result in hospitalization needs to be estimated. Data from an Institute for Clinical Evaluative Sciences (ICES) on ED utilization in Ontario[2] were combined with data from the burden of ACS report[1] to make this estimate. Based upon data presented in the ICES, the proportion of all ED visits in Ontario that are for cardiovascular diagnoses or chest pain was calculated to be 0.078. The total number of ED visits in Ontario was reported to be 3,700,000. This implies the total of annual ED visits in Ontario for suspected ACS to be 288,674 (3,700,000 x 0.078). The report on the burden of ACS in Canada[1] reported the total number of ACS hospitalizations in Ontario to be 48,365. Combining these data implies that the proportion of ED visits that result in a hospitalization is 0.133 (48,365/288,674). Applying this proportion to the total number of annual ACS hospitalizations in Canada results in an estimate of the number of ED visits for suspected ACS to be 818,847 (109,109/0.133).

It was assumed that all patients presenting to the ED with suspected ACS will receive a troponin test at presentation. Some patients will receive more than one test while in the ED. The analysis assumes an average of 1.5 troponin tests would be conducted per patient visit. This assumption is varied in sensitivity analyses.

The current distribution of the types of troponin assays used in EDs in Canada employed in the analysis was based on an Environmental Scan conducted by CADTH.[3] In the Environmental Scan, hospitals and other health centres were surveyed about their current troponin use. Based on the survey, 0.08 of

respondents currently use conventional troponin T, 0.15 of respondents use high-sensitivity troponin T, while 0.77 of respondents use conventional troponin I.

The price of each type of assay was determined through correspondence with various manufacturers. Based on this correspondence, the cost per conventional troponin T and high-sensitivity troponin T were assumed to be $3. The cost of both conventional troponin I and high-sensitivity troponin I was assumed to be $6.75. Therefore, the incremental cost per assay moving from conventional troponin T to high-sensitivity troponin T was assumed to be $0, while the incremental cost of switching from conventional troponin T to high-sensitivity troponin I was assumed to be $3.75 per assay. The incremental cost of switching from conventional troponin I to high-sensitivity troponin I was assumed to be $0, while the incremental cost of moving from conventional troponin I to high-sensitivity troponin T was assumed to be a savings of $3.75. Given some uncertainty around the cost of the assays, the price differential between conventional and high-sensitivity troponin assays was assessed in sensitivity analyses.

Note: The analysis does not account for the capital costs of the analyzers needed to conduct the various assays. These capital costs can be substantial and laboratories are often bound by time-specific contracts with manufacturers.

Results

Based upon the assumptions previously described, Table 1 presents the base-case annual budget impact of switching from conventional to high-sensitivity assays. If the 8% of EDs using conventional troponin T switch to high-sensitivity troponin T, the annual budget impact is $0. This is because based on information provided by manufacturers it was assumed that conventional troponin T and high-sensitivity troponin T assays cost the same. The annual budget impact of all conventional troponin T users switching to high-sensitivity troponin I is estimated to be $368,481. The budget impact of all 77% of centres using conventional troponin I switching to high-sensitivity troponin T is a savings of $3,546,629. This savings is due to the base-case assumption that each high-sensitivity troponin T assay is $3.75 cheaper than conventional troponin I assays.

Table 1: Base-case Annual Budget Impact of Switching from Conventional to High-Sensitivity Troponin Assays

	Estimated Annual Budget Impact
Currently Using cTnT	
Switch to hs-cTnT	$0
Switch to hs-cTnI	$368,481
Currently Using cTnI	
Switch to hs-cTnT	-$3,546,629
Switch to hs-cTnI	$0

cTnI = conventional troponin I; cTnT = conventional troponin T; hs-cTnI = high-sensitivity troponin I: hs-cTnT = high-sensitivity troponin T.

Table 2 presents a sensitivity analysis of budget impact by varying the price differential between conventional and high-sensitivity troponin assays. In this sensitivity analysis it was assumed that the price differential would be the same regardless of which type of high-sensitivity test (i.e., high-sensitivity troponin T, high-sensitivity troponin I) EDs are switching to. As shown, if high-sensitivity tests were $3 more expensive than conventional tests, switching from conventional troponin T costs $294,785 annually, while EDs switching from conventional troponin I costs $2.8 million. If the price differential was $15, the cost of the current conventional troponin T users switching to high-sensitivity tests is $1.47 million; while the cost of current conventional troponin I switching to high-sensitivity tests is $14.19 million.

Table 2: Sensitivity Analysis of Budget Impact by Incremental Cost of High-Sensitivity Troponin Assays Compared With Conventional Assays					
	Incremental Cost of High-Sensitivity Compared With Conventional Assay				
	$0	**$3**	**$5**	**$10**	**$15**
Currently Using cTnT					
Switch to hs-cTnT	$0	$294,785	$491,308	$982,616	$1,473,924
Switch to hs-cTnI	$0	$294,785	$491,308	$982,616	$1,473,924
Currently Using cTnI					
Switch to hs-cTnT	$0	$2,837,303	$4,728,839	$9,457,677	$14,186,516
Switch to hs-cTnI	$0	$2,837,303	$4,728,839	$9,457,677	$14,186,516

cTnI = conventional troponin I; cTnT = conventional troponin T; hs-cTnI = high-sensitivity troponin I: hs-cTnT = high-sensitivity troponin T.

No published estimates of the annual number of ED visits in Canada for suspected ACS were identified. Therefore, the number of ED visits was calculated by applying a multiplier to the number of ACS hospitalizations in Canada. This multiplier was based on the inverse of the proportion of ED visits for suspected ACS that results in hospital admission. In the base case, it was assumed that 0.13 of all ED visits for suspected ACS would result in a hospital admission. Therefore, a multiplier of 7.69 (1/0.13) was applied to published estimates of the number of ACS hospitalizations in Canada to derive the number of ED visits for suspected ACS. Table 3 presents a sensitivity analysis on budget impact by the assumed proportion of ED visits that result in hospital admission. As shown, if the proportion was assumed to be 0.10, the budget impact of switching from conventional troponin T to high-sensitivity troponin I is estimated to be $490,991; while the budget impact of moving from conventional troponin I to high-sensitivity troponin T is estimated to result in a savings of $4.73 million. If the proportion of ED visits for suspected ACS that result in a hospitalization was assumed to be 0.25, the estimated budget impact of moving from conventional troponin T to high-sensitivity troponin I is $196,396. The estimated savings from moving from conventional troponin I to high-sensitivity troponin T is $1.89 million.

Table 3: Sensitivity Analysis of Budget Impact by Proportion of ED Visits for Suspected ACS Leading to Hospital Admissions				
	Proportion of ED Visits for Suspected ACS Leading to Hospital Admissions			
	0.1	**0.15**	**0.2**	**0.25**
Currently Using cTnT				
Switch to hs-cTnT	$0	$0	$0	$0
Switch to hs-cTnI	$490,991	$327,327	$245,495	$196,396
Currently Using cTnI				
Switch to hs-cTnT	–$4,725,784	–$3,150,522	–$2,362,892	–$1,890,313
Switch to hs-cTnI	$0	$0	$0	$0

ACS = acute coronary syndrome; ED = emergency department; cTnI = conventional troponin I; cTnT = conventional troponin T; hs-cTnI = high-sensitivity troponin I: hs-cTnT = high-sensitivity troponin T.

In the base-case analysis, it was assumed that each patient seen in the ED for suspected ACS would receive 1.5 troponin tests while in the ED. Table 4 presents the budget impact varying the number of troponin tests received while in the ED. If it is assumed that each patient receives only one troponin test, the budge impact of switching from conventional troponin T to high-sensitivity troponin I is $245.654. The annual savings by switching from conventional troponin I to high-sensitivity troponin T becomes $2.3 million. If it is assumed that each patient receives four troponin tests while in the ED, the budget impact of switching from conventional troponin T to high-sensitivity troponin I is $982,616. The budget impact of switching from conventional troponin I to high-sensitivity troponin T is a savings of $9.46 million.

Table 4: Sensitivity Analysis of Budget Impact by Proportion of ED Visits for Suspected ACS Leading to Hospital Admissions				
	Number of Troponin Assays per ED Visit			
	1	**2**	**3**	**4**
Currently using cTnT				
Switch to hs-cTnT	$0	$0	$0	$0
Switch to hs-cTnI	$245,654	$491,308	$736,962	$982,616
Currently using cTnI				
Switch to hs-cTnT	–$2,364,419	–$4,728,839	–$7,093,258	–$9,457,677
Switch to hs-cTnI	$0	$0	$0	$0

ACS = acute coronary syndrome; ED = emergency department; cTnI = conventional troponin I; cTnT = conventional troponin T; hs-cTnI = high-sensitivity troponin I: hs-cTnT = high-sensitivity troponin T.

In the base case, it was assumed that all centres currently using conventional troponin assays would switch to high-sensitivity assays. However, the decision to switch assays may be based on several factors including whether a centre is currently in a purchase cycle for equipment needed to analyze the assays. Table 5 presents budget impact varying the proportion of current conventional troponin users that would switch to high-sensitivity assays. If 10% of current conventional assay users switch, the budget impact of switching from conventional troponin T to high-sensitivity troponin I is $36,848. The budget impact of current conventional troponin I users switching to high-sensitivity troponin T is a savings of $354,663. If 0.75 of current conventional assay users switch, the budget impact of switching from conventional troponin T to high-sensitivity troponin I is $276,361. The budget impact of current conventional troponin I users switching to high-sensitivity troponin T is a savings of $2.66 million.

Table 5: Sensitivity Analysis on the Proportion of EDs Using Conventional Assays That Would Switch to High-Sensitivity Troponin Assays				
	Proportion of EDs That Would Switch to High-Sensitivity Troponin Assays			
	10%	**25%**	**50%**	**75%**
Currently Using cTnT				
Switch to hs-cTnT	$0	$0	$0	$0
Switch to hs-cTnI	$36,848	$92,120	$184,240	$276,361
Currently Using cTnI				
Switch to hs-cTnT	–$354,663	–$886,657	–$1,773,314	–$2,659,972
Switch to hs-cTnI	0	0	0	0

ED = emergency department; cTnI = conventional troponin I; cTnT = conventional troponin T; hs-cTnI = high-sensitivity troponin I; hs-cTnT = high-sensitivity troponin T.

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