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


For more information on this project, visit http://www.cadth.ca/en/products/optimal-use/high-sensitivity-troponin

Introduction

Acute coronary syndrome (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.\(^1\) When patients with chest pain present at an emergency department, investigations are rapidly conducted to rule out ACS. STEMI is diagnosed by specific electrocardiogram (ECG) findings and is associated with a high risk of cardiac death. NSTEMI and unstable angina are typically caused by myocardial ischemia but of differing severity depending on the presence of myocardial infarction (MI), and they 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 jointly redefined myocardial necrosis to incorporate cardiac troponin assays as a diagnostic determinant.\(^4\) In 2007, the European Society of Cardiology, the American College of Cardiology, and the American Heart Association updated the definition of MI and advocated a “rise and/or fall” of cardiac troponin 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 cardiac troponin levels, after the first measurement, has been reduced to three to six hours in the third universal definition of MI (2012).\(^5\) Therefore, in patients with suspected MI but without ECG STEMI criteria, the troponin level is the discriminating criterion between NSTEMI and unstable angina.

In Canada, there are two cardiac troponin tests available: cardiac troponin T and cardiac troponin I. In 2012, the manufacturer of the troponin T reagent started to remove the conventional reagent and replace it with a high-sensitivity troponin T assay reagent. High-sensitivity troponin I is not yet available, but its introduction to the market is expected in the near future. In the emergency medicine community, this change is generating concern. A higher-sensitivity assay, with its increased ability to detect small differences in cardiac troponin levels over time, will potentially result in earlier identification of those individuals experiencing an MI (as well as possibly identifying those who can be safely discharged from the emergency department with no further investigations).\(^7\) However, high-sensitivity assays are associated with lower specificity, which could result in higher rates of clinically relevant false-positive tests — that is, situations where patients are incorrectly identified as having NSTEMI. The use of high-sensitivity troponin T assays, therefore, could lead to additional investigations and more vascular interventions, resulting in additional costs to the health care system while causing increased anxiety to patients. Because of the changing landscape of cardiac troponin tests, there is a need to independently compare the performance of high-sensitivity troponin T with cardiac troponin T, cardiac troponin I, and high-sensitivity troponin I, as well as to determine the comparative clinical and economic impact of using these tests.
Objective
The objective of the report was to answer the following research questions:
1. What is the diagnostic test performance of high-sensitivity troponin T and high-sensitivity troponin I assays compared with each other as well as with cardiac troponin T and sensitive cardiac troponin I assays in patients with suspected ACS symptoms in the emergency department?
2. What is the clinical effectiveness of high-sensitivity troponin T and high-sensitivity troponin I assays compared with each other as well as with cardiac troponin T and sensitive cardiac troponin I assays in patients with suspected ACS symptoms in the emergency department?
3. What is the cost-effectiveness of high-sensitivity troponin T and high-sensitivity troponin I assays compared with each other as well as with cardiac troponin I assays in patients with suspected ACS symptoms in the emergency department?

A panel of experts convened by the Canadian Agency for Drugs and Technologies in Health (CADTH) developed:
- recommendations on the use of cardiac troponin for the rapid diagnosis of ACS in the emergency department based on this clinical and economic evaluation
- CADTH Rapid Response reports summarizing and appraising information on point-of-care troponin testing and current clinical practice guidelines
- a CADTH Environmental Scan describing current Canadian test use.

This clinical and cost-effectiveness evaluation, along with the recommendations, will inform the purchasing and the clinical use of the most optimal cardiac troponin assay, depending on the individual institutional context. For institutions electing to use high-sensitivity troponin T or high-sensitivity troponin I, information regarding the lower specificity of these new assays will also be provided.

Methods

Literature Search
The literature search was performed by an information specialist using a peer-reviewed search strategy. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized controlled clinical trials, comparative studies, and economic evaluations. Conference abstracts were included in the search results. The initial search was completed on May 16, 2012 and regular alerts were established to update the search until March 11, 2013.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters). Google was used to search for additional web-based materials, including conference abstracts. These searches were supplemented by reviewing the bibliographies of key papers and via contacts with appropriate experts and industry members.

Clinical Review
Two reviewers independently screened the titles and abstracts for relevance using a predefined checklist. They selected articles for inclusion in the review based on examination of the full-text publications according to selection criteria established a priori.
The methodological quality of the included diagnostic studies was assessed using the revised tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). The QUADAS-2 is a tool that evaluates the risk of bias in four domains: the selection of patients, the index test, the reference standard, and the flow and timing of the study. The tool also addresses concerns about the applicability of tests and signaling questions to help identify potential biases.

Each of the diagnostic accuracy measures were estimated for the comparison between four possible tests: high-sensitivity cardiac troponin T assay, high-sensitivity cardiac troponin I assay, cardiac troponin T assay, and cardiac troponin I assay. The analysis of the diagnostic performance involved two steps. First, the direct comparison that compares the test (such as high-sensitivity cardiac troponin I) to the reference standard for diagnosis of acute myocardial infarction (AMI) for each study was generated. Then, the results of similar tests (high-sensitivity cardiac troponin I for AMI) were pooled to create one estimate. In the absence of head-to-head evidence of tests such as high-sensitivity cardiac troponin T versus high-sensitivity cardiac troponin I, indirect comparisons were conducted to provide a comparative estimate between the two tests.

**Economic Evaluation**

The published literature of economic evaluations comparing troponin tests for patients presenting with chest pain was sparse. There was no identified cost-effectiveness study that evaluated cardiac troponin I or high-sensitivity cardiac troponin I, and there was no identified Canadian-based study. Therefore, a primary economic evaluation was conducted.

A cost-utility analysis was conducted, with treatments compared for the incremental cost per quality-adjusted life-year (QALY) gained. Secondary outcomes are the number of NSTEMI patients treated and the number of NSTEMI patients treated early. The comparators considered in this analysis were high-sensitivity cardiac troponin T, high-sensitivity cardiac troponin I, and conventional cardiac troponin I. Conventional cardiac troponin T was not considered as an appropriate treatment comparator because it is no longer available in Canada. The analysis was taken from the perspective of a publicly funded health care system and employed a lifetime horizon.

A proportion of the patients entering the model will have a positive troponin test, while a proportion of patients will have a negative troponin test. Among patients with a positive troponin test, a proportion will be true-positives representing patients that have NSTEMI, while a proportion of patients will be false-positives representing patients without NSTEMI. Similarly, patients who have a negative troponin test can either be 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 troponin test being evaluated, based on the data from the studies included in the systematic review. In addition, the proportion of non-NSTEMI patients that are diagnosed as unstable angina or non-ACS was a clinical input variable in the model. As part of the calculations of long-term QALYs, patients who do not have NSTEMI are assigned age and gender utility values of the general population for every year. Patients who have an NSTEMI are assigned lower utility values based on age-specific decrements.

Costs considered in the model include the cost of each troponin test, the cost of hospitalization for NSTEMI, the cost of hospitalization for unstable angina, and the cost of hospitalization for patients who are admitted but do not have NSTEMI (false-positives). 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.

**Results**

**Clinical Review**

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

As expected, despite different assays and different cut-off points, the sensitivity values of high-sensitivity cardiac troponin tests were consistently higher than those of cardiac troponin tests. However, there was a trade-off between sensitivity and specificity. Conventional cardiac troponin tests had lower sensitivity but relatively higher specificity values; whereas, high-sensitivity cardiac troponin tests had higher sensitivities but lower specificities, when compared with the final diagnosis of AMI (the reference standard).

Among the four types of cardiac troponin tests (high-sensitivity troponin T, high-sensitivity troponin I, cardiac troponin T, cardiac troponin I) performed at the time of emergency department presentation, high-sensitivity troponin I yielded the highest sensitivity for diagnosis of AMI, and cardiac troponin T had the highest specificity.

Although no statistically significant differences were found between various diagnostic thresholds of any of the cardiac troponin tests, the comparison of the pooled estimates of diagnostic accuracy and their confidence intervals suggested that all four types of cardiac troponin tests were consistently more sensitive at the limit of detection (LoD) threshold, with the following patterns being detected:

- cardiac troponin T:
  LoD = 99th percentile > 10% CV
- cardiac troponin I:
  LoD > 10% CV > 99th percentile.

No similar patterns were found for summary estimates of specificity.

Although non-significant, the aforementioned results indicating a higher sensitivity for cardiac troponin I at 10% CV, as compared with 99th percentile threshold, is counter-intuitive. For sensitive cardiac troponin I assays, 99th percentile concentrations appear to be lower than 10% CV concentrations; therefore, 99th percentile should have a higher sensitivity. There are several possible explanations for this result. We pooled data for each threshold from different studies, none of which primarily intended to assess the comparability of various thresholds of cardiac troponin tests. As well, LoD and 99th percentile cut-off points might be determined differently by different authors. 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 cardiac troponin tests, both of which compared high-sensitivity troponin T with cardiac troponin I. The results of our indirect comparisons, derived from a limited number of studies, suggest the following:

At the 99th percentile cut-off point —

- High-sensitivity troponin T is, overall, significantly less accurate, clinically more sensitive, and less specific than high-sensitivity troponin I, cardiac troponin T, and cardiac troponin I.
- High-sensitivity troponin I is significantly more accurate than high-sensitivity troponin T (but not cardiac troponin T or cardiac troponin I); more sensitive than cardiac troponin T (but not cardiac troponin I); significantly less sensitive than high-sensitivity troponin T; and
more specific than high-sensitivity troponin T, cardiac troponin T, and cardiac troponin I.

At the 10% CV cut-off point —
• High-sensitivity troponin T is, overall, significantly less accurate than cardiac troponin T and cardiac troponin I, more sensitive than cardiac troponin T, less sensitive than cardiac troponin I, and less specific than both cardiac troponin T and cardiac troponin I.
• No data were available on high-sensitivity troponin I.

At the LoD cut-off point —
• High-sensitivity troponin T is, overall, significantly less accurate than cardiac troponin I (but not cardiac troponin T), more sensitive than cardiac troponin T (but not cardiac troponin I), and less specific than both cardiac troponin T and cardiac troponin I.
• Overall diagnostic accuracy of high-sensitivity troponin I could not be calculated because of insufficient data.

Our review also suggested that high-sensitivity troponin T had a higher-sensitivity value regardless of the timing of the assessment, whereas cardiac troponin T had a lower sensitivity in the early hours after the onset of symptoms but a comparable sensitivity after three to six hours. The limited evidence in this review indicated that patients’ risk of MI at baseline or their previous history of ischemic heart disease had no effect on the sensitivity of high-sensitivity troponin T. However, the findings of the individual studies indicated that high-sensitivity troponin T could act as a more specific test in patients with low-to-moderate risk of MI at baseline (compared with high risk) and in patients with a negative history of ischemic heart disease (compared with a positive history of ischemic heart disease). Based on the results of the reviewed studies, a positive high-sensitivity troponin T was associated with higher mortality rates during hospitalization and after discharge when compared with cardiac troponin T or cardiac troponin I assays, suggesting that high-sensitivity troponin T 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 cardiac troponin test result might have on long-term mortality or recurrence of MI, if test results factored in treatment decisions. In addition, the review found no information on the effects of troponin tests on quality of life, readmission rates, and emergency department time until the diagnosis of MI.

**Economic Evaluation**
The base-case economic analysis estimated the incremental cost-effectiveness ratio of high-sensitivity troponin T compared with cardiac troponin I to be $119,377 per QALY. The testing strategy of high-sensitivity troponin I was extendedly dominated by cardiac troponin I and high-sensitivity troponin T in our analysis and, therefore, would not be considered cost-effective when considering all three treatment options together. This means that if a decision-maker’s maximum willingness to pay for a QALY is less than $119,377, then cardiac troponin I would be considered cost-effective. If a decision-maker’s willingness to pay for a QALY is equal or greater than $119,377, then high-sensitivity troponin T would be considered cost-effective. The effectiveness measure that contributed to relative cost-effectiveness of the three tests was diagnostic accuracy in both sensitivity and specificity of MI at emergency department presentation. In the pooled estimate used in this analysis, the sensitivity of high-sensitivity troponin I was only slightly higher than that of cardiac troponin I (0.82 versus 0.81). The sensitivity of high-sensitivity troponin T was estimated to be 0.88. This likely contributed to
high-sensitivity troponin I 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; and 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
cardiac troponin test. This suggests that the
base-case cost-effectiveness findings may not
be robust.

The cost per assay was based on information
provided by manufacturers. Specific prices for
high-sensitivity troponin T and high-sensitivity
troponin I were not directly provided, but they
were based on statements that they were about
equivalent to the costs of conventional assays.
However, a sensitivity analysis on the cost per
high-sensitivity troponin T assay indicated that
findings were not sensitive to the cost per high-
sensitivity troponin T assay.

Subgroup analyses found high-sensitivity
troponin T to be more cost-effective in younger
patients than in older patients. Additionally,
high-sensitivity troponin T 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 cardiac troponin test
that requires the purchase of a new analyzer.

Limitations
The clinical review had a number of limitations.
The inclusion criteria were limited to the
comparative studies, which included at least one
high-sensitivity and one cardiac troponin test
with or without a non–cardiac-troponin
reference standard. Our search excluded studies
comparing only a high-sensitivity or a cardiac
troponin assay with a non–cardiac-troponin
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. In addition, the inclusion
criteria might have led to the exclusion of
potentially relevant studies that did not have
more than one cardiac troponin group but might
contain useful data on some of the unanswered
questions in this review, such as diagnostic
accuracy of repeated cardiac troponin
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 cardiac troponin
tests. In addition, there were few studies that
used the same brand of high-sensitivity and
cardiac troponin tests. Furthermore, in all of the
included diagnostic studies, both high-sensitivity
and cardiac troponin 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 cardiac troponin assays,
even the indirect analyses do not provide
information that is specific for each of the
cardiac troponin products. Rather, they
aggregate the results of all assays of the same
type.

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 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, a definitive conclusion regarding the potential impact of cardiac troponin tests on morbidity and mortality in patients with chest pain who undergo high-sensitivity cardiac troponin tests in the emergency department, as compared with those who receive cardiac troponin assays, could not be provided. In addition, the impact of high-sensitivity versus conventional cardiac troponin tests on quality of life and readmission rates remains unknown because none of the included studies addressed these outcomes.

For the economic evaluation, it was assumed that all patients presenting with ischemic chest pain to an emergency department would be treated the same regardless of their medical history. In reality, decisions on whether to admit a patient after a positive cardiac troponin test would likely depend on the perceived pretest probability of NSTEMI and whether the patient had a known previous condition that might cause chronic cardiac troponin elevation. Also, the economic analysis did not account for the capital costs of the analyzers needed to conduct the various assays.

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

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

The clinical review found insufficient evidence to determine whether multiple high-sensitivity cardiac troponin test measurements can increase the diagnostic accuracy of the tests for AMI or ACS in the emergency department. The questions regarding the effects of high-sensitivity cardiac troponin 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 cardiac troponin test and to select the best diagnostic thresholds for different cardiac troponin tests.

The economic analysis found that when evaluating the cost-effectiveness of cardiac troponin I, high-sensitivity troponin I, and high-sensitivity troponin T, high-sensitivity troponin T would be considered the most cost-effective testing strategy if willingness to pay for a QALY is $119,377 or more, otherwise cardiac troponin I would be the most cost-effective test. However, there was much uncertainty in results when model assumptions were changed, and the evaluation considered only the cost-effectiveness of cardiac troponin tests in diagnosing NSTEMI in the emergency department.

CADTH’s panel of experts made the following recommendations:

- When considering the selection of a cardiac troponin assay, conventional cardiac troponin I is recommended in institutions using clinical algorithms based on conventional troponin data.
- At this time, it is recommended that institutions using conventional cardiac troponin I not change their assay.
- At this time, it is recommended that institutions using high-sensitivity cardiac troponin T not change their assay.

References


CADTH Technology Overviews contains articles that are based on CADTH Technology Reports and other CADTH reports on health technologies. The information presented in these publications is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this publication should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice.

While CADTH has taken care in the preparation of this publication to ensure that its contents are accurate, complete, and up to date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this publication or in any of the source documentation.

CADTH Technology Overviews and the information it provides is prepared and intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter presented in this publication may be different in other jurisdictions and, if used outside of Canada, it is at the user’s risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this publication will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this publication, subject to the limitations noted above. The statements and conclusions in this publication are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government.

Production of CADTH Technology Overviews is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Prince Edward Island, Saskatchewan, and Yukon.

Copyright © CADTH 2013. You are permitted to reproduce this document for non-commercial purposes, provided it is not modified when reproduced and appropriate credit is given to CADTH. You may not otherwise copy, modify, translate, post on a website, store electronically, republish, or redistribute any content from this document in any form or by any means without the prior written permission of CADTH.

Please contact CADTH’s Vice-President of Corporate Services at corporateservices@cadth.ca with any inquiries about this notice or other legal matters relating to CADTH’s services.

Cite as: Canadian Agency for Drugs and Technologies in Health. CADTH Technology Overviews, 2013; 3(2).

ISSN: 1481-4501 (online)